MOLECULAR DIAGNOSTIC TEST FOR CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention claims the priority benefit of U.S. Provisional Patent Application 61/383,201 filed September 15, 2010 and U.S. Provisional Patent Application 61/490,039 filed May 25, 2011, both of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a molecular diagnostic test useful for diagnosing cancers from different anatomical sites that includes the use of a common DNA damage repair deficiency subtype. The invention includes the use of a 44-gene classification model that is used to identify this DNA damage repair deficiency molecular subtype. One application is the stratification of response to, and selection of patients for breast cancer therapeutic drug classes, including DNA damage causing agents and DNA repair targeted therapies. Another application is the stratification of ovarian cancer patients into those that respond and those that do not respond to DNA damage causing agents. The present invention provides a test that can guide conventional therapy selection as well as selecting patient groups for enrichment strategies during clinical trial evaluation of novel therapeutics. DNA repair deficient subtypes can be identified from fresh/frozen (FF) or formalin fixed paraffin embedded (FFPE) patient samples.

BACKGROUND

The pharmaceutical industry continuously pursues new drug treatment options that are more effective, more specific or have fewer adverse side effects than currently administered drugs. Drug therapy alternatives are constantly being developed because genetic variability within the human population results in substantial differences in the effectiveness of many drugs. Therefore, although a wide variety of drug therapy options are currently available, more therapies are always needed in the event that a patient fails to respond.

Traditionally, the treatment paradigm used by physicians has been to prescribe a first-line drug therapy that results in the highest success rate possible for treating a disease. Alternative drug therapies are then prescribed if the first is ineffective. This paradigm is clearly not the best treatment method for certain diseases. For example, in diseases such as cancer, the first treatment is often the most important and offers the best opportunity for successful therapy,

so there exists a heightened need to chose an initial drug that will be the most effective against that particular patient's disease.

It is anticipated that there will be 207,090 new female breast cancer diagnoses in the US this year and 39,840 female breast cancer related deaths (American Cancer Society: Cancer Facts and Figures 2010). Standard chemotherapy typically includes direct DNA damaging agents such as anthracyclines and alkylating agents as well as antimetabolites and antimicrotubule agents.

Ovarian cancer is the leading cause of death among all gynecological cancers in western countries. This high death rate is due to the diagnosis at an advanced stage in most patients. Epithelial ovarian cancer (EOC) constitutes 90% of ovarian malignancies and is classified into distinct histologic categories including serous, mucinous, endometrioid, clear cell, transitional, mixed, and undifferentiated subtypes. There is increasing evidence that these differed histologies arise from different aetiologies. The current standard treatment for ovarian cancer is debulking surgery and standard platinum taxane based cytotoxic chemotherapy. However, not all patients respond to this, and of those that do, approximately 70% will experience a recurrence. Specific targeted therapies for ovarian cancer based on histological or molecular classification have not yet reached the marketplace. Similarly for other types of cancer, there is still no accurate way of selecting appropriate cytotoxic chemotherapeutic agents.

The advent of microarrays and molecular genomics has the potential for a significant impact on the diagnostic capability and prognostic classification of disease, which may aid in the prediction of the response of an individual patient to a defined therapeutic regimen. Microarrays provide for the analysis of large amounts of genetic information, thereby providing a genetic fingerprint of an individual. There is much enthusiasm that this technology will ultimately provide the necessary tools for custom-made drug treatment regimens.

Currently, healthcare professionals have few mechanisms to help them identify cancer patients who will benefit from chemotherapeutic agents. Identification of the optimal first-line drug has been difficult because methods are not available for accurately predicting which drug treatment would be the most effective for a particular cancer's physiology. This deficiency results in relatively poor single agent response rates and increased cancer morbidity and death. Furthermore, patients often needlessly undergo ineffective, toxic drug therapy.

Molecular markers have been used to select appropriate treatments, for example, in breast cancer. Breast tumors that do not express the estrogen and progesterone hormone receptors as well as the HER2 growth factor receptor, called "triple negative", appear to be responsive to PARP-1 inhibitor therapy (Linn, S. C., and Van 't Veer, L., J. Eur J Cancer *45 Suppl 1*, 11-26 (2009); O'Shaughnessy, J., et al. N Engl J Med *364*, 205-214 (2011). Recent

studies indicate that the triple negative status of a breast tumor may indicate responsiveness to combination therapy including PARP-1 inhibitors, but may not be sufficient to indicate responsiveness to individual PARP-1 inhibitors.(O'Shaughnessy et al., 2011).

Furthermore, there have been other studies that have attempted to identify gene classifiers associated with molecular subtypes to indicate responsiveness of chemotherapeutic agents (Farmer*et al.*Nat Med *15*, 68-74 (2009); Konstantinopoulos, P. A., *et al.*, J Clin Oncol *28*, 3555-3561 (2010)). However, to date there does not exist a diagnostic test that works across cancer diseases to accurately define a molecular subtype that demonstrates a deficiency in DNA damage repair, that can also predict sensitivity to any drug that directly or indirectly targets DNA damage repair across diseases.

What is therefore needed is a test that identifies DNA repair deficient tumors with sufficient accuracy to allow the stratification of patients into those who are likely to respond to chemotherapeutic agents that damage DNA, and those who should receive alternative therapies.

What is also needed is a molecular subtype classifier that is predictive of therapeutic responsiveness across different cancer types with sufficient accuracy.

SUMMARY OF THE INVENTION

In one aspect, the present invention refers to a method of predicting responsiveness of an individual to a DNA-damage therapeutic agent comprising

a. measuring expression levels of at least five biomarkers in a test sample obtained from the individual, wherein the at least five biomarkers are selected from the biomarkers in Table 2B;
b. deriving a combined test score that captures the expression levels;
c. providing a threshold score comprising information correlating the combined test score and responsiveness;
d. and comparing the combined test score to the threshold score; wherein responsiveness is predicted when the combined test score exceeds the threshold score.

In another aspect, the present invention refers to a method of diagnosing an individual for having a cancer associated with a DNA damage response deficiency (DDRD) comprising

a. measuring expression levels of at least five biomarkers in a test sample obtained from the individual, wherein the at least five biomarkers are selected from the biomarkers in Table 2B;
b. deriving a combined test score that captures the expression levels;
c. providing a threshold score comprising information correlating the combined test score and a diagnosis of the cancer;
d. and comparing the combined test score to the threshold score; wherein the individual is diagnosed as having the cancer when the test score exceeds the threshold score.

In another aspect, the present invention refers to a method of detecting a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and detection of the cancer;

d. and comparing the test score to the threshold score; wherein the cancer with DNA damage response deficiency related immune signalling is detected when the test score exceeds the threshold score.

In another aspect, the present invention refers to a method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent appropriate for treatment of the individual is selected when the test score exceeds the threshold score.

In another aspect, the present invention refers to a method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274,

CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent that targets tumors with abnormal DNA damage response is selected when the test score exceeds the threshold score.

In another aspect, the present invention refers to a method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent that inhibits expression of at least one of the biomarkers is selected when the test score exceeds the threshold score.

In another aspect, the present invention refers to the use of a therapeutic agent in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of the present invention.

In another aspect, the present invention refers to the use of a therapeutic agent that targets tumors with abnormal DNA damage response in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of the present invention.

In another aspect, the present invention refers to the use of a therapeutic agent that inhibits expression of at least one of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC,

PPP1R1A, and AL137218.1 in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of the present invention.

In another aspect, the present invention refers to the use of a therapeutic agent in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

In another aspect, the present invention refers to the use of a therapeutic agent that targets tumors with abnormal DNA damage response in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

In another aspect, the present invention refers to the use of a therapeutic agent that inhibits expression of at least one of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1 in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

The disclosure is directed to methods of using a collection of gene product markers expressed in cancer such that when some or all of the transcripts are over or under-expressed, they identify a subtype of cancer that has a deficiency in DNA damage repair. Designation of this subtype can be considered a diagnostic test as it is not related to any specific drug but rather describes the biology of the cancer in a manner that has utility in screening and selecting

appropriate cancer therapies. The disclosure also provides methods for indicating responsiveness or resistance to DNA-damage therapeutic agents. In different examples, this gene or gene product list may form the basis of a single parameter or a multiparametric predictive test that could be delivered using methods known in the art such as microarray, Q-PCR, immunohistochemistry, ELISA or other technologies that can quantify mRNA or protein expression.

In addition, the biological pathway described herein is a feature of cancer itself, similar to grade and stage, and as such, is not limited to a single cancer disease type. Therefore, the collection of genes or gene products may be used to predict responsiveness of cancer therapeutics across different cancer types in different tissues. In one example, these genes or gene products are useful for evaluating both breast and ovarian cancer tumors.

The disclosure described herein is not limited to any one drug; it can be used to identify responders and non responders to any of a range of drugs that directly or indirectly affect DNA damage and/or DNA damage repair e.g. neoadjuvant 5-fluorouracil, anthracycline and cyclophosphamide based regimens such as FEC (5-fluorouracil/epirubicin/cyclophosphamide) and FAC (5-fluorouracil/Adriamycin/cyclophosphamide). In specific examples, it is useful for evaluating paclitaxel, fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide (T/FAC) neoadjuvant treatment in breast cancer. In other examples, it is useful for evaluating platinum or platinum plus taxol treatment in ovarian cancer.

The present disclosure relates to prediction of response to drugs using different classifications of response, such as overall survival, progression free survival, radiological response, as defined by RECIST, complete response, partial response, stable disease and serological markers such as, but not limited to, PSA, CEA, CA125, CA15-3 and CA19-9. In specific examples, this disclosure can be used to evaluate pathological complete response in breast cancer treated with FEC or FAC either alone or in the context of standard treatment, or RECIST and serum CA125 levels in ovarian cancer.

In another example, the present disclosure relates to the identification of a DNA damage response deficiency (DDRD) molecular subtype in breast and ovarian cancer. This molecular subtype can be detected by the use of two different gene classifiers – one being 40 genes in length and one being 44 genes in length. The DDRD classifier was first defined by a classifier consisting of 53 probesets on the Almac Breast Disease Specific Array (DSA™). So as to validate the functional relevance of this classifier in the context of its ability to predict response to DNA-damaging containing chemotherapy regimens, the classifier needed to be re-defined at a gene level. This would facilitate evaluation of the DDRD classifier using microarray data from independent datasets that were profiled on microarray platforms other than the Almac Breast DSA™. In order to facilitate defining the classifier at a gene level, the genes to which the Almac Breast DSA™ probesets map to needed to be defined. This involved the utilization of publicly available genome browser databases such as Ensembl and NCBI Reference Sequence. Results are provided only for the 44-gene DDRD classifier model, as this model supersedes that of the 40-gene DDRD classifier model. These results demonstrate that the classifier model is an effective and significant predictor of response to chemotherapy regimens that contain DNA damaging therapeutics.

The identification of the subtype by both the 40-gene classifier model and the 44-gene classifier model can be used to predict response to, and select patients for, standard breast and ovarian cancer therapeutic drug classes, including DNA damage causing agents and DNA repair targeted therapies.

In another example, the present disclosure relates to kits for conventional diagnostic uses listed above such as qPCR, microarray, and immunoassays such as immunohistochemistry, ELISA, Western blot and the like. Such kits include appropriate reagents and directions to assay the expression of the genes or gene products and quantify mRNA or protein expression.

The disclosure also provides methods for identifying DNA damage response-deficient (DDRD) human tumors. It is likely that this description of examples can be used to identify patients that are sensitive to and respond, or are resistant to and do not respond, to drugs that damage DNA directly, damage DNA indirectly or inhibit normal DNA damage signaling and/or repair processes.

The disclosure also relates to guiding conventional treatment of patients. The disclosure also relates to selecting patients for clinical trials where novel drugs of the classes that directly or indirectly affect DNA damage and/or DNA damage repair.

The present disclosure and methods accommodate the use of archived formalin fixed paraffin-embedded (FFPE) biopsy material, as well as fresh/frozen (FF) tissue, for assay of all transcripts in the invention, and are therefore compatible with the most widely available type of biopsy material. The expression level may be determined using RNA obtained from FFPE tissue, fresh frozen tissue or fresh tissue that has been stored in solutions such as RNAlater®.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 provides a diagram representing the hierarchical analysis of ER-negative (A) and ER-positive (B) BRCA1/2 mutant and sporadic wildtype control breast samples. Probeset cluster groups are annotated on the right-hand side and pathway analysis of each probeset cluster group is annotated on the left-hand side of each image. The legend for each image indicates a sample's mutational status as well as the signature group each sample was assigned to for classifier generation.

FIG. 2 provides a diagramofbox plots comparing the AUC performance of each classification model under a 10 repeats of 5-fold cross validation for (A) the combined sample set, (B) the ER-negative sample set and (C) the ER-positive sample set. (D) Sensitivity plus specificity plot of the cross validation predictions used to select threshold. The maximum sensitivity plus specificity is 1.682 with a corresponding signature score of ~0.37.

FIG. 3 provides a diagram of a ROC curve of the classification performance for predicting BRCA status using the 44-gene classifier model, estimated by cross validation. The AUC is

~0.68 following application the classifier model. The 95% confidence limits have been estimated from bootstrap with 1000 iterations.

FIG. 4 provides a diagram of a ROC curve of the classification performance of the 44-gene classifier model in a combined analysis of three independent datasets: FEC, FAC1 and FAC2 (Bonnefoi et al., 2007; Iwamoto*et al.*,J Natl Cancer Inst 103, 264-272 (2011); Lee, J. K., et al. Clin Cancer Res *16*, 711-718 (2010)for predicting response to anthracycline-based chemotherapy. The AUC is ~0.78 following application of the classifier model. The 95% confidence limits have been estimated from bootstrap with 1000 iterations.

FIG. 5 provides a diagram of a ROC curve of the classification performance of the 44-gene classifier model in a combined analysis of three independent datasets in response in T/FAC treated samples(Hess*et al.*, J Clin Oncol *24*, 4236-4244 (2006); Lee et al., 2010; Tabchy, A., *et al.*Clin Cancer Res *16*, 5351-5361 (2010). The AUC is ~0.61 following application of the classifier model respectively. The 95% confidence limits were determined using 1000 bootstrap iterations.

FIG. 6 provides a diagram of a ROC curve of the classification performance of the 44-gene classifier model within 259 serous ovarian cancer samples in response in platinum and taxol treated samples from the in-house Almac Diagnostics ovarian dataset. The AUC is ~0.68 following application of the classifier model. The 95% confidence limits were determined using 1000 bootstrap iterations.

FIG. 7 provides a histogram representation of the 44-gene DDRD classifier scores in bone marrow samples taken from healthy donors and patients with Fanconi Anaemia mutations. The AUC is 0.90 following application of the classifier model. The 95% confidence limits were determined using 1000 bootstrap iterations.

FIG. 8 provides a figure correlating the 44-gene classifier model with therapeutic response in BRCA1 mutant and wildtype cell-lines. (A) Western blot analysis confirming increased expression of BRCA1 in the HCC1937-BR cells compared with the HCC1937-EV cells. (B) Mean 44-gene model (DDRD) classifier score (±SEM) within the control vector-only transfected HCC1937 (HCC1937-EV) and HCC1937 with returned exogenous expression of BRCA1 (HCC1937-BR) cell-lines. Histogram representation of cell-viability of HCC1937

parental and HCC1937-BR cells under constant exposure to a range of concentrations of PARP inhibitor KU0058948 (C) and cisplatin (D).

DETAILED DESCRIPTION OF THE INVENTION

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

All publications, published patent documents, and patent applications cited in this application are indicative of the level of skill in the art(s) to which the application pertains. All publications, published patent documents, and patent applications cited herein are hereby incorporated by reference to the same extent as though each individual publication, published patent document, or patent application was specifically and individually indicated as being incorporated by reference.

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

A major goal of current research efforts in cancer is to increase the efficacy of perioperative systemic therapy in patients by incorporating molecular parameters into clinical therapeutic decisions. Pharmacogenetics/genomics is the study of genetic/genomic factors involved in an individual's response to a foreign compound or drug. Agents or modulators which have a stimulatory or inhibitory effect on expression of a marker of the invention can be administered to individuals to treat (prophylactically or therapeutically) cancer in a patient. It is ideal to also consider the pharmacogenomics of the individual in conjunction with such treatment. Differences in metabolism of therapeutics may possibly lead to severe toxicity or therapeutic failure by altering the relationship between dose and blood concentration of the pharmacologically active drug. Thus, understanding the pharmacogenomics of an individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

The invention is directed to a unique collection of gene or gene product markers

(hereinafter referred to as "biomarkers")expressed in a cancer tissue. In different aspects, this biomarker list may form the basis of a single parameter or multiparametric predictive test that could be delivered using methods known in the art such as microarray, Q-PCR, immunohistochemistry, ELISA or other technologies that can quantify mRNA or protein expression.

The present invention also relates to kits and methods that are useful for prognosis following cytotoxic chemotherapy or selection of specific treatments for cancer. Methods are provided such that when some or all of the transcripts are over or under-expressed, the expression profile indicates responsiveness or resistance to DNA-damage therapeutic agents. These kits and methods employ gene or gene product markers that are differentially expressed in tumors of patients with cancer. In one embodiment of the invention, the expression profiles of these biomarkers are correlated with clinical outcome (response or survival) in archival tissue samples under a statistical method or a correlation model to create a database or model correlating expression profile with responsiveness to one or more DNA-damage therapeutic agents. The predictive model may then be used to predict the responsiveness in a patient whose responsiveness to the DNA-damage therapeutic agent(s) is unknown. In many other embodiments, a patient population can be divided into at least two classes based on patients' clinical outcome, prognosis, or responsiveness to DNA-damage therapeutic agents, and the biomarkers are substantially correlated with a class distinction between these classes of patients. The biological pathways described herein are common to cancer as a disease, similar to grade and stage, and as such, the classifiers and methods are not limited to a single cancer disease type.

Predictive Marker Panels/Expression Classifiers

A unique collection of biomarkers as a genetic classifier expressed in a cancer tissue is provided that is useful in determining responsiveness or resistance to therapeutic agents, such as DNA-damage therapeutic agents, used to treat cancer. Such a collection may be termed a "marker panel", "expression classifier", or "classifier".

The biomarkers useful in the present methods are identified in Table 1. These biomarkers are identified as having predictive value to determine a patient response to a therapeutic agent, or lack thereof. Their expression correlates with the response to an agent, and more specifically, a DNA-damage therapeutic agent. By examining the expression of a collection of the identified biomarkers in a tumor, it is possible to determine which therapeutic agent or combination of agents will be most likely to reduce the growth rate of a cancer, and in some embodiments,

breast or ovarian cancer cells. By examining a collection of identified transcript gene or gene product markers, it is also possible to determine which therapeutic agent or combination of agents will be the least likely to reduce the growth rate of a cancer. By examining the expression of a collection of biomarkers, it is therefore possible to eliminate ineffective or inappropriate therapeutic agents. Importantly, in certain embodiments, these determinations can be made on a patient-by-patient basis or on an agent-by-agent basis. Thus, one can determine whether or not a particular therapeutic regimen is likely to benefit a particular patient or type of patient, and/or whether a particular regimen should be continued.

Table 1A

Sense genes (166)		Antisense of known genes (24)		
Gene Symbol	EntrezGene ID	Almac Gene ID	Almac Gene symbol	SEQ ID NO:
ABCA12	26154		N/A	
ALDH3B2	222		N/A	
APOBEC3G	60489		N/A	
APOC1	341		N/A	
APOL6	80830		N/A	
ARHGAP9	64333		N/A	
BAMBI	25805		N/A	
BIK	638		N/A	
BIRC3	330	AS1_BIRC3	Hs127799.0C7n9_at	1
BTN3A3	10384		N/A	
C12orf48	55010		N/A	
C17orf28	283987		N/A	
C1orf162	128346		N/A	
C1orf64	149563		N/A	
C1QA	712		N/A	
C21orf70	85395		N/A	
C22orf32	91689		N/A	
C6orf211	79624		N/A	
CACNG4	27092		N/A	
CCDC69	26112		N/A	
CCL5	6352		N/A	
CCNB2	9133		N/A	
CCND1	595		N/A	
CCR7	1236		N/A	
CD163	9332		N/A	
CD2	914		N/A	
CD22	933		N/A	
CD24	100133941		N/A	
CD274	29126		N/A	
CD3D	915		N/A	
CD3E	916		N/A	
CD52	1043		N/A	
CD53	963		N/A	
CD79A	973		N/A	
CDH1	999		N/A	
CDKN3	1033		N/A	
CECR1	51816		N/A	
CHEK1	1111		N/A	
CKMT1B	1159		N/A	

CMPK2	129607		N/A	
CNTNAP2	26047		N/A	
COX16	51241		N/A	
CRIP1	1396		N/A	
CXCL10	3627		N/A	
CXCL9	4283		N/A	
CYBB	1536		N/A	
CYP2B6	1555		N/A	
DDX58	23586		N/A	
DDX60L	91351		N/A	
ERBB2	2064		N/A	
ETV7	51513		N/A	
FADS2	9415		N/A	
FAM26F	441168		N/A	
FAM46C	54855		N/A	
FASN	2194		N/A	
FBP1	2203		N/A	
FBXO2	26232		N/A	
FKBP4	2288		N/A	
FLJ40330	645784		N/A	
FYB	2533		N/A	
GBP1	2633		N/A	
GBP4	115361		N/A	
GBP5	115362	AS1_GBP5	BRMX.5143C1n2_at	2
GIMAP4	55303		N/A	
GLRX	2745		N/A	
GLUL	2752		N/A	
GVIN1	387751		N/A	
H2AFJ	55766		N/A	
HGD	3081		N/A	
HIST1H2BK	85236		N/A	
HIST3H2A	92815		N/A	
HLA-DOA	3111		N/A	
HLA-DPB1	3115		N/A	
HMGB2	3148		N/A	
HMGB3	3149		N/A	
HSP90AA1	3320		N/A	
IDO1	3620		N/A	
IFI27	3429		N/A	
IFI44	10561		N/A	
IFI44L	10964	AS1_IFI44L	BRSA.1606C1n4_at	3
IFI6	2537		N/A	
IFIH1	64135		N/A	
IGJ	3512	AS1_IGJ	BRIH.1231C2n2_at	4
IKZF1	10320		N/A	
IL10RA	3587		N/A	
IL2RG	3561		N/A	
IL7R	3575		N/A	
IMPAD1	54928		N/A	
IQGAP3	128239	AS1_IQGAP3	BRAD.30779_s_at	5
IRF1	3659		N/A	
ISG15	9636		N/A	
ITGAL	3683		N/A	
KIAA1467	57613		N/A	
KIF20A	10112		N/A	
KITLG	4254		N/A	
KLRK1	22914		N/A	
KRT19	3880		N/A	
LAIR1	3903		N/A	
LCP1	3936		N/A	

LOC100289702	100289702		N/A	
LOC100294459	100294459	AS1_LOC100294459	BRSA.396C1n2_at	6
LOC150519	150519		N/A	
LOC439949	439949		N/A	
LYZ	4069		N/A	
MAL2	114569		N/A	
MGC29506	51237		N/A	
MIAT	440823		N/A	
MS4A1	931		N/A	
MX1	4599	AS1_MX1	BRMX.2948C3n7_at	7
NAPSB	256236		N/A	
NCKAP1L	3071		N/A	
NEK2	4751		N/A	
NLRC3	197358		N/A	
NLRC5	84166		N/A	
NPNT	255743		N/A	
NQO1	1728		N/A	
OAS2	4939		N/A	
OAS3	4940		N/A	
PAQR4	124222		N/A	
PARP14	54625		N/A	
PARP9	83666		N/A	
PIK3CG	5294		N/A	
PIM2	11040		N/A	
PLEK	5341		N/A	
POU2AF1	5450		N/A	
PP14571	100130449		N/A	
PPP2R2C	5522		N/A	
PSMB9	5698		N/A	
PTPRC	5788		N/A	
RAC2	5880		N/A	
RAMP1	10267		N/A	
RARA	5914		N/A	
RASSF7	8045		N/A	
RSAD2	91543		N/A	
RTP4	64108		N/A	
SAMD9	54809		N/A	
SAMD9L	219285		N/A	
SASH3	54440		N/A	
SCD	6319		N/A	
SELL	6402		N/A	
SIX1	6495	AS1_SIX1	Hs539969.0C4n3_at	8
SLAMF7	57823		N/A	
SLC12A2	6558		N/A	
SLC9A3R1	9368	AS1_SLC9A3R1	Hs396783.3C1n4_at	9
SPOCK2	9806		N/A	
SQLE	6713		N/A	
ST20	400410		N/A	
ST6GALNAC2	10610		N/A	
STAT1	6772	AS1_STAT1	BRMX.13670C1n2_at	10
STRA13	201254		N/A	
SUSD4	55061		N/A	
SYT12	91683		N/A	
TAP1	6890		N/A	
TBC1D10C	374403		N/A	
TNFRSF13B	23495		N/A	
TNFSF10	8743		N/A	
TOB1	10140	AS1_TOB1	BRAD.30243_at	11
TOM1L1	10040		N/A	
TRIM22	10346		N/A	

UBD	10537	AS1_UBD	BRMX.941C2n2_at	12
UBE2T	29089		N/A	
UCK2	7371		N/A	
USP18	11274		N/A	
VNN2	8875		N/A	
XAF1	54739		N/A	
ZWINT	11130		N/A	
		AS1_C1QC	BRMX.4154C1n3_s_at	13
		AS1_C2orf14	BRAD.39498_at	14
		AS1_EPSTI1	BRAD.34868_s_at	15
		AS1_GALNT6	5505575.0C1n42_at	16
		AS1_HIST1H4H	BREM.1442_at	17
		AS1_HIST2H4B	BRHP.827_s_at	18
		AS2_HIST2H4B	BRRS.18322_s_at	19
		AS3_HIST2H4B	BRRS.18792_s_at	20
		AS1_KIAA1244	Hs632609.0C1n37_at	21
		AS1_LOC100287927	Hs449575.0C1n22_at	22
		AS1_LOC100291682	BRAD.18827_s_at	23
		AS1_LOC100293679	BREM.2466_s_at	24

Table 1B

Novel genes	
Gene symbol	**SEQ ID NO:**
BRAD.2605_at	25
BRAD.33618_at	26
BRAD.36579_s_at	27
BRAD1_5440961_s_at	28
BRAD1_66786229_s_at	29
BREM.2104_at	30
BRAG_AK097020.1_at	31
BRAD.20415_at	32
BRAD.29668_at	33
BRAD.30228_at	34
BRAD.34830_at	35
BRAD.37011_s_at	36
BRAD.37762_at	37
BRAD.40217_at	38
BRAD1_4307876_at	39
BREM.2505_at	40
Hs149363.0CB4n5_s_at	41
Hs172587.9C1n9_at	42
Hs271955.16C1n9_at	43
Hs368433.18C1n6_at	44
Hs435736.0C1n27_s_at	45
Hs493096.15C1n6_at	46
Hs493096.2C1n15_s_at	47
Hs592929.0CB2n8_at	48
Hs79953.0C1n23_at	49
BRMX.2377C1n3_at	50

All or a portion of the biomarkers recited in Table 1 may be used in a predictive biomarker panel. For example, biomarker panels selected from the biomarkers in Table 1 can be

generated using the methods provided herein and can comprise between one, and all of the biomarkers set forth in Table 1 and each and every combination in between (e.g., four selected biomarkers, 16 selected biomarkers, 74 selected biomarkers, etc.). In some embodiments, the predictive biomarker set comprises at least 5, 10, 20, 40, 60, 100, 150, 200, or 300 or more biomarkers. In other embodiments, the predictive biomarker set comprises no more than 5, 10, 20, 40, 60, 100, 150, 200, 300, 400, 500, 600 or 700 biomarkers. In some embodiments, the predictive biomarker set includes a plurality of biomarkers listed in Table 1. In some embodiments the predictive biomarker set includes at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% of the biomarkers listed in Table 1. Selected predictive biomarker sets can be assembled from the predictive biomarkers provided using methods described herein and analogous methods known in the art. In one embodiment, the biomarker panel contains all 203 biomarkers in Table 1. In another embodiment, the biomarker panel contains 40 or 44 biomarkers in Table 1 or 2.

Predictive biomarker sets may be defined in combination with corresponding scalar weights on the real scale with varying magnitude, which are further combined through linear or non-linear, algebraic, trigonometric or correlative means into a single scalar value via an algebraic, statistical learning, Bayesian, regression, or similar algorithms which together with a mathematically derived decision function on the scalar value provide a predictive model by which expression profiles from samples may be resolved into discrete classes of responder or non-responder, resistant or non-resistant, to a specified drug or drug class. Such predictive models, including biomarker membership, are developed by learning weights and the decision threshold, optimized for sensitivity, specificity, negative and positive predictive values, hazard ratio or any combination thereof, under cross-validation, bootstrapping or similar sampling techniques, from a set of representative expression profiles from historical patient samples with known drug response and/or resistance.

In one embodiment, the biomarkers are used to form a weighted sum of their signals, where individual weights can be positive or negative. The resulting sum ("decisive function") is compared with a pre-determined reference point or value. The comparison with the reference point or value may be used to diagnose, or predict a clinical condition or outcome.

As described above, one of ordinary skill in the art will appreciate that the biomarkers included in the classifier provided in Table 1 will carry unequal weights in a classifier for responsiveness or resistance to a therapeutic agent. Therefore, while as few as one sequence may be used to diagnose or predict an outcome such as responsiveness to therapeutic agent, the

specificity and sensitivity or diagnosis or prediction accuracy may increase using more sequences.

As used herein, the term "weight" refers to the relative importance of an item in a statistical calculation. The weight of each biomarker in a gene expression classifier may be determined on a data set of patient samples using analytical methods known in the art.

In one embodiment the biomarker panel is directed to the 40 biomarkers detailed in Table 2A with corresponding ranks and weights detailed in the table or alternative rankings and weightings, depending, for example, on the disease setting. In another embodiment, the biomarker panel is directed to the 44 biomarkers detailed in Table 2B with corresponding ranks and weights detailed in the table or alternative rankings and weightings, depending, for example, on the disease setting. Tables 2A and 2B rank the biomarkers in order of decreasing weight in the classifier, defined as the rank of the average weight in the compound decision score function measured under cross-validation. Table 2C present the probe sets that represent the genes in Table 2A and 2B with reference to their sequence ID numbers. Table 2D presents the antisense probe sequences that were present on the array for the genes in the signatures.

Table 2A
Gene IDs and EntrezGene IDs for 40-gene DDRD classifier model with associated ranking and weightings

DDRD classifier 40 gene model			
Rank	**Genes Symbol**	**EntrezGene ID**	**Weights**
1	GBP5	115362	0.022389581
2	CXCL10	3627	0.021941734
3	IDO1	3620	0.020991115
4	MX1	4599	0.020098675
5	IFI44L	10964	0.018204957
6	CD2	914	0.018080661
7	PRAME	23532	0.016850837
8	ITGAL	3683	0.016783359
9	LRP4	4038	-0.015129969
10	SP140L	93349	0.014646025
11	APOL3	80833	0.014407174
12	FOSB	2354	-0.014310521
13	CDR1	1038	-0.014209848
14	RSAD2	91543	0.014177132
15	TSPAN7	7102	-0.014111562
16	RAC2	5880	0.014093627
17	FYB	2533	0.01400475
18	KLHDC7B	113730	0.013298413
19	GRB14	2888	0.013031204
20	KIF26A	26153	-0.012942351
21	CD274	29126	0.012651964

22	CD109	135228	-0.012239425
23	ETV7	51513	0.011787297
24	MFAP5	8076	-0.011480443
25	OLFM4	10562	-0.011130113
26	PI15	51050	-0.010904326
27	FAM19A5	25817	-0.010500936
28	NLRC5	84166	0.009593449
29	EGR1	1958	-0.008947963
30	ANXA1	301	-0.008373991
31	CLDN10	9071	-0.008165127
32	ADAMTS4	9507	-0.008109892
33	ESR1	2099	0.007524594
34	PTPRC	5788	0.007258669
35	EGFR	1956	-0.007176203
36	NAT1	9	0.006165534
37	LATS2	26524	-0.005951091
38	CYP2B6	1555	0.005838391
39	PPP1R1A	5502	-0.003898835
40	TERF1P1	348567	0.002706847

Table 2B
Gene IDs and EntrezGene IDs for 44-gene DDRD classifier model with associated ranking and weightings

DDRD Classifier - 44 Gene Model (NA:genomic sequence)			
Rank	**Gene symbol**	**EntrezGene ID**	**Weight**
1	CXCL10	3627	0.023
2	MX1	4599	0.0226
3	IDO1	3620	0.0221
4	IFI44L	10964	0.0191
5	CD2	914	0.019
6	GBP5	115362	0.0181
7	PRAME	23532	0.0177
8	ITGAL	3683	0.0176
9	LRP4	4038	-0.0159
10	APOL3	80833	0.0151
11	CDR1	1038	-0.0149
12	FYB	2533	-0.0149
13	TSPAN7	7102	0.0148
14	RAC2	5880	-0.0148
15	KLHDC7B	113730	0.014
16	GRB14	2888	0.0137

17	AC138128.1	N/A	-0.0136
18	KIF26A	26153	-0.0136
19	CD274	29126	0.0133
20	CD109	135228	-0.0129
21	ETV7	51513	0.0124
22	MFAP5	8076	-0.0121
23	OLFM4	10562	-0.0117
24	PI15	51050	-0.0115
25	FOSB	2354	-0.0111
26	FAM19A5	25817	0.0101
27	NLRC5	84166	-0.011
28	PRICKLE1	144165	-0.0089
29	EGR1	1958	-0.0086
30	CLDN10	9071	-0.0086
31	ADAMTS4	9507	-0.0085
32	SP140L	93349	0.0084
33	ANXA1	301	-0.0082
34	RSAD2	91543	0.0081
35	ESR1	2099	0.0079
36	IKZF3	22806	0.0073
37	OR2I1P	442197	0.007
38	EGFR	1956	-0.0066
39	NAT1	9	0.0065
40	LATS2	26524	-0.0063
41	CYP2B6	1555	0.0061
42	PTPRC	5788	0.0051
43	PPP1R1A	5502	-0.0041
44	AL137218.1	N/A	-0.0017

Table 2C

Probe set IDs and SEQ Numbers for genes contained in 40- and 44-gene signature

Probe set IDs and SEQ Numbers for genes contained in 40 and 44 gene signature		
Gene Symbol	**Probe Set ID**	**SEQ ID NO.**
FYB	BRAD.10849_at	83
CLDN10	BRAD.10890_at	84
PPP1R1A	BRAD.11026_at	85
PI15	BRAD.12809_at	86
MFAP5	BRAD.14326_s_at	87

ESR1	BRAD.15436_s_at	88
FYB	BRAD.15833_s_at	89
ESR1	BRAD.19080_s_at	90
TERF1P1	BRAD.2707_at	91
PRICKLE1	BRAD.27716_s_at	92
LATS2	BRAD.28628_s_at	93
IKZF3	BRAD.28643_at	94
MX1	BRAD.28663_s_at	95
CD274	BRAD.29038_at	96
FAM19A5	BRAD.30917_at	97
LATS2	BRAD.31470_at	98
EGFR	BRAD.32716_at	99
EGFR	BRAD.33042_at	100
EGFR	BRAD.33341_at	101
ANXA1	BRAD.33405_at	102
EGFR	BRAD.33431_at	103
KLHDC7B	BRAD.35695_at	104
IKZF3	BRAD.35710_at	105
PTPRC	BRAD.37907_at	106
TERF1P1	BRAD.40353_at	107
EGFR	BRAD.40654_s_at	108
FYB	BRAD.4701_at	109
PTPRC	BRAD.5967_at	110
EGFR	BRAD.7701_at	111
ESR1	BREM.1048_at	112
EGFR	BREM.1129_at	113
NAT1	BREM.1226_at	114
FOSB	BREM.1262_at	115
OR2I1P	BREM.130_at	116
ADAMTS4	BREM.1689_s_at	117
CYP2B6	BREM.2334_at	118
EGFR	BREM.2382_at	119
ETV7	BREM.532_at	120
ANXA1	BRHP.106_s_at	121
ESR1	BRIH.10647C1n2_at	122
EGFR	BRIH.1453C1n2_at	123
EGR1	BRIH.1518C1n4_at	124
ANXA1	BRIH.2770C3n31_at	125
NAT1	BRIH.365C1n2_at	126
IFI44L	BRIH.5410C1n7_at	127
MX1	BRIH.5478C1n2_s_at	128
ESR1	BRIH.5650C1n2_at	129
CD109	BRIH.5952C1n2_s_at	130
CXCL10	BRIH.7359C1n3_s_at	131
FYB	BRIHRC.10930C1n2_s_at	132
AC138128.1	BRMX.13731C1n18_at	133
TERF1P1	BRMX.25436C1n2_at	134
GBP5	BRMX.25712C1n2_at	135
EGR1	BRMX.3079C1n3_at	136
EGR1	BRMX.3079C2n3_at	137
ESR1	BRPD.10690C1n5_at	138
FYB	BRPD.4019C1n3_s_at	139
GBP5	BRPD.5301C1n2_s_at	140
NLRC5	BRRS.12588_at	141
GBP5	BRRS.13369_s_at	142
RSAD2	BRRS.13576_at	143
PTPRC	BRRS.13647_at	144
PTPRC	BRRS.13648_s_at	145
CD109	BRRS.13767_at	146
SP140L	BRRS.13859_at	147

KLHDC7B	BRRS.13881_at	148
APOL3	BRRS.14465_s_at	149
PRICKLE1	BRRS.15053_at	150
CLDN10	BRRS.16228_s_at	151
EGFR	BRRS.16746_s_at	152
EGFR	BRRS.16747_at	153
PRAME	BRRS.16948_s_at	154
TERF1P1	BRRS.17863_s_at	155
TERF1P1	BRRS.17909_s_at	156
AL137218.1	BRRS.18137_at	157
KIF26A	BRRS.18652_s_at	158
FYB	BRRS.2573_s_at	159
CXCL10	BRRS.2644_at	160
CD2	BRRS.2783_s_at	161
EGR1	BRRS.2935_at	162
IDO1	BRRS.3099_at	163
ITGAL	BRRS.3131_at	164
LRP4	BRRS.3220_at	165
MX1	BRRS.3319_at	166
MX1	BRRS.3319_s_at	167
RAC2	BRRS.3645_s_at	168
MFAP5	BRRS.4126_s_at	169
NAT1	BRRS.455_at	170
CDR1	BRRS.4562_at	171
ANXA1	BRRS.487_s_at	172
GRB14	BRRS.4891_s_at	173
TSPAN7	BRRS.4996_at	174
CYP2B6	BRRS.524_s_at	175
ADAMTS4	BRRS.5356_at	176
EGFR	BRRS.5451_at	177
OLFM4	BRRS.6371_at	178
FOSB	BRRS.6611_at	179
PPP1R1A	BRRS.6619_at	180
PPP1R1A	BRRS.6619-22_at	181
IFI44L	BRRS.6684_at	182
CD274	BRRS.7616_at	183
LATS2	BRRS.7901_at	184
ESR1	BRRS.81_at	185
ESR1	BRRS.81-22_at	186
FAM19A5	BRRS.8480_s_at	187
PI15	BRRS.8711_at	188
ETV7	BRRS.8900_s_at	189
EGR1	BRSA.1686C1n5_at	190
RAC2	BRSA.8072C1n2_s_at	191
SP140L	Hs369056.20C1n2_at	192
EGFR	Hs488293.0CB1n69_at	193
ANXA1	Hs494173.0CB4n15_at	194
GBP5	Hs513726.0C2n39_s_at	195
TERF1P1	Hs514006.0C1n8_at	196
TERF1P1	Hs522202.0C1n6_at	197
PRICKLE1	Hs524348.0CB1n97_at	198
PRICKLE1	Hs524348.2C1n5_s_at	199
NLRC5	Hs528836.0C1n3_s_at	200
TERF1P1	Hs591893.1C1n4_s_at	201
RSAD2	Hs7155.0CB1n102_at	202

Table 2D
Almac IDs and Almac Gene symbol and SEQ ID numbers
for antisense probe sets in 40-gene signature

(D) Almac IDs and Almac Gene symbol and SEQ ID numbers for antisense probe sets in 40 gene signature				
Gene Symbol	EntrezGene ID (40)	Almac Gene ID (32)	Almac Gene symbol	SEQ ID NO:
ADAMTS4	9507			
ANXA1	301			
ANXA1	301	AS1_ANXA1	BRAD.33405_at	51
APOL3	80833			
CD109	135228			
CD2	914			
CD274	29126			
CD274	29126	AS1_CD274	Hs584242.2C1n64_at	52
CDR1	1038			
CDR1	1038	AS1_CDR1	BRRS1RC_NM_004065_at	53
CLDN10	9071			
CLDN10	9071	AS1_CLDN10	BRRS.8182_at	54
CXCL10	3627			
CXCL10	3627	AS1_CXCL10	BRMX.13815C1n5_at	55
CYP2B6	1555			
EGFR	1956			
EGFR	1956	AS1_EGFR	BRMX.2637C1n26_at	56
EGFR	1956	AS2_EGFR	BRAD.36737_at	57
EGFR	1956	AS3_EGFR	BRAD.3853_at	58
EGFR	1956	AS4_EGFR	BRAD1_19760734_at	59
EGR1	1958			
EGR1	1958	AS1_EGR1	BRMX.2797C4n2_at	60
ESR1	2099			
ESR1	2099	AS1_ESR1	BRMX.10399C1n5_at	61
ESR1	2099	AS2_ESR1	BRMX.8912C1n3_at	62
ETV7	51513			
FAM19A5	25817			
FOSB	2354			
FOSB	2354	AS1_FOSB	BRMX.13731C1n18_at	63
FYB	2533			
FYB	2533	AS1_FYB	BRAD.25947_at	64
GBP5	115362			
GBP5	115362	AS1_GBP5	BRMX.5143C1n2(2)_at	65
GRB14	2888			
IDO1	3620			
IFI44L	10964			
IFI44L	10964	AS1_IFI44L	Hs633116.0C1n30_at	66
IFI44L	10964	AS2_IFI44L	BRSA.1606C1n4(2)_at	67
ITGAL	3683			
ITGAL	3683	AS1_ITGAL	BRAD.41047_at	68
ITGAL	3683	AS2_ITGAL	BRAD.4420_at	69
KIF26A	26153			
KLHDC7B	113730			
KLHDC7B	113730	AS1_KLHDC7B	Hs137007.0C1n9_at	70
LATS2	26524			
LATS2	26524	AS1_LATS2	BRSA.18050C1n3_at	71
LRP4	4038			
MFAP5	8076			

MX1	4599			
MX1	4599	AS1_MX1	BRMX.2948C3n7(2)_at	72
MX1	4599	AS2_MX1	Hs43047.0C4n40_at	73
MX1	4599	AS2_MX1	Hs926.1C10n7_at	74
NAT1	9			
NLRC5	84166			
NLRC5	84166	AS1_NLRC5	Hs528836.0CB6n98_s_at	75
OLFM4	10562			
OLFM4	10562	AS1_OLFM4	BRMX.7284C1n6_at	76
PI15	51050			
PI15	51050	AS1_PI15	BRAD1_19751014_at	77
PPP1R1A	5502			
PRAME	23532			
PTPRC	5788			
RAC2	5880			
RAC2	5880	AS1_RAC2	BRMX.13502C1n6_at	78
RSAD2	91543			
SP140L	93349			
SP140L	93349	AS1_SP140L	BRMX.1111C4n3_at	79
SP140L	93349	AS2_SP140L	Hs369056.9C26n3_at	80
TERF1P1	348567			
TERF1P1	348567	AS1_TERF1P1	BRMX.24432C1n2_at	81
TERF1P1	348567	AS2_TERF1P1	BRRS.17773_at	82
TSPAN7	7102			

In different embodiments, subsets of the biomarkers listed in Table 2A and Table 2B may be used in the methods described herein. These subsets include but are not limited to biomarkers ranked 1-2, 1-3, 1-4, 1-5, 1-10, 1-20, 1-30, 1-40, 1-44, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 36-44, 11-20, 21-30, 31-40, and 31-44 in Table 2A or Table 2B. In one aspect, therapeutic responsiveness is predicted in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to at least one of the biomarkers GBP5, CXCL10, IDO1 and MX1 and at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36. As used herein, the term "biomarker" can refer to a gene, an mRNA, cDNA, an antisense transcript, a miRNA, a polypeptide, a protein, a protein fragment, or any other nucleic acid sequence or polypeptide sequence that indicates either gene expression levels or protein production levels. In some embodiments, when referring to a biomarker of CXCL10, IDO1, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, or AL137218.1, the biomarker comprises an mRNA of CXCL10, IDO1, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4,

SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, or AL137218.1, respectively. In further or other embodiments, when referring to a biomarker of MX1, GBP5, IFI44L, BIRC3, IGJ, IQGAP3, LOC100294459, SIX1, SLC9A3R1, STAT1, TOB1, UBD, C1QC, C2orf14, EPSTI, GALNT6, HIST1H4H, HIST2H4B, KIAA1244, LOC100287927, LOC100291682, or LOC100293679, the biomarker comprises an antisense transcript of MX1, IFI44L, GBP5, BIRC3, IGJ, IQGAP3, LOC100294459, SIX1, SLC9A3R1, STAT1, TOB1, UBD, C1QC, C2orf14, EPSTI, GALNT6, HIST1H4H, HIST2H4B, KIAA1244, LOC100287927, LOC100291682, or LOC100293679, respectively.

In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarkers GBP5, CXCL10, IDO1 and MX1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker GBP5 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 or 39. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker CXCL10 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 or 39. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker IDO1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 or 39. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker MX-1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 or 39.

In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to at least two of the biomarkers CXCL10, MX1, IDO1 and IFI44L and at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarkers CXCL10, MX1, IDO1 and IFI44L and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker CXCL10 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 or 43. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker MX1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 or 43. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker IDO1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 or 43. In a further aspect, therapeutic responsiveness is predicted, or a cancer diagnosis is indicated, in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker IFI44L and one of at least N additional biomarkers selected from the list of biomarkers in Table 2B, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 29, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 or 43.

In other embodiments, the probes listed in Table 2C (SEQ ID NOs:83-202), or subsets thereof, may be used in the methods described herein. These subsets include but are not limited to a subset of SEQ ID NOs corresponding to one or more of GBP5, CXCL10, IDO1, MX1, IF144l, CD2, PRAME, ITGAL, LRP4, and APOL3. In other embodiments, the probes correspond to all of the biomarkers CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1. It should be understood that each subset can include multiple probes directed to the same biomarker. For example, the probes represented by SEQ ID NOs: 135, 140, 142 and 195 are all directed to GBP5. Accordingly, a subset containing probes directed or corresponding to GBP5 includes one or more of SEQ ID NOs: 135, 140, 142 and 195. A subset containing probes directed to or corresponding to CXCL10 includes one or more of SEQ ID NOs: 131 and 160.

Measuring Gene Expression Using Classifier Models

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

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

"Down-regulation", "down-regulated", "under-expression", "under-expressed", and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a

biological sample that is less than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

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

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

In certain embodiments, the expression profile obtained is a genomic or nucleic acid expression profile, where the amount or level of one or more nucleic acids in the sample is determined. In these embodiments, the sample that is assayed to generate the expression profile employed in the diagnostic or prognostic methods is one that is a nucleic acid sample. The nucleic acid sample includes a population of nucleic acids that includes the expression information of the phenotype determinative biomarkers of the cell or tissue being analyzed. In

some embodiments, the nucleic acid may include RNA or DNA nucleic acids, e.g., mRNA, cRNA, cDNA etc., so long as the sample retains the expression information of the host cell or tissue from which it is obtained. The sample may be prepared in a number of different ways, as is known in the art, e.g., by mRNA isolation from a cell, where the isolated mRNA is used as isolated, amplified, or employed to prepare cDNA, cRNA, etc., as is known in the field of differential gene expression. Accordingly, determining the level of mRNA in a sample includes preparing cDNA or cRNA from the mRNA and subsequently measuring the cDNA or cRNA. The sample is typically prepared from a cell or tissue harvested from a subject in need of treatment, e.g., via biopsy of tissue, using standard protocols, where cell types or tissues from which such nucleic acids may be generated include any tissue in which the expression pattern of the to be determined phenotype exists, including, but not limited to, disease cells or tissue, body fluids, etc.

The expression profile may be generated from the initial nucleic acid sample using any convenient protocol. While a variety of different manners of generating expression profiles are known, such as those employed in the field of differential gene expression/biomarker analysis, one representative and convenient type of protocol for generating expression profiles is array-based gene expression profile generation protocols. Such applications are hybridization assays in which a nucleic acid that displays "probe" nucleic acids for each of the genes to be assayed/profiled in the profile to be generated is employed. In these assays, a sample of target nucleic acids is first prepared from the initial nucleic acid sample being assayed, where preparation may include labeling of the target nucleic acids with a label, e.g., a member of a signal producing system. Following target nucleic acid sample preparation, the sample is contacted with the array under hybridization conditions, whereby complexes are formed between target nucleic acids that are complementary to probe sequences attached to the array surface. The presence of hybridized complexes is then detected, either qualitatively or quantitatively. Specific hybridization technology which may be practiced to generate the expression profiles employed in the subject methods includes the technology described in U.S. Pat. Nos. 5,143,854; 5,288,644; 5,324,633; 5,432,049; 5,470,710; 5,492,806; 5,503,980; 5,510,270; 5,525,464; 5,547,839; 5,580,732; 5,661,028; 5,800,992; the disclosures of which are herein incorporated by reference; as well as WO 95/21265; WO 96/31622; WO 97/10365; WO 97/27317; EP 373 203; and EP 785 280. In these methods, an array of "probe" nucleic acids that includes a probe for each of the biomarkers whose expression is being assayed is contacted with target nucleic acids as described above. Contact is carried out under hybridization conditions, e.g., stringent hybridization conditions as described above, and unbound nucleic acid is then removed. The resultant pattern of hybridized nucleic acids provides information regarding

expression for each of the biomarkers that have been probed, where the expression information is in terms of whether or not the gene is expressed and, typically, at what level, where the expression data, i.e., expression profile, may be both qualitative and quantitative.

Creating a Biomarker Expression Classifier

In one embodiment, the relative expression levels of biomarkers in a cancer tissue are measured to form a gene expression profile. The gene expression profile of a set of biomarkers from a patient tissue sample is summarized in the form of a compound decision score and compared to a score threshold that is mathematically derived from a training set of patient data. The score threshold separates a patient group based on different characteristics such as, but not limited to, responsiveness/non-responsiveness to treatment. The patient training set data is preferably derived from cancer tissue samples having been characterized by prognosis, likelihood of recurrence, long term survival, clinical outcome, treatment response, diagnosis, cancer classification, or personalized genomics profile. Expression profiles, and corresponding decision scores from patient samples may be correlated with the characteristics of patient samples in the training set that are on the same side of the mathematically derived score decision threshold. The threshold of the linear classifier scalar output is optimized to maximize the sum of sensitivity and specificity under cross-validation as observed within the training dataset.

The overall expression data for a given sample is normalized using methods known to those skilled in the art in order to correct for differing amounts of starting material, varying efficiencies of the extraction and amplification reactions, etc. Using a linear classifier on the normalized data to make a diagnostic or prognostic call (e.g. responsiveness or resistance to therapeutic agent) effectively means to split the data space, i.e. all possible combinations of expression values for all genes in the classifier, into two disjoint halves by means of a separating hyperplane. This split is empirically derived on a large set of training examples, for example from patients showing responsiveness or resistance to a therapeutic agent. Without loss of generality, one can assume a certain fixed set of values for all but one biomarker, which would automatically define a threshold value for this remaining biomarker where the decision would change from, for example, responsiveness or resistance to a therapeutic agent. Expression values above this dynamic threshold would then either indicate resistance (for a biomarker with a negative weight) or responsiveness (for a biomarker with a positive weight) to a therapeutic agent. The precise value of this threshold depends on the actual measured expression profile of all other biomarkers within the classifier, but the general indication of certain biomarkers remains fixed, i.e. high values or "relative over-expression" always contributes to either a

responsiveness (genes with a positive weight) or resistance (genes with a negative weights). Therefore, in the context of the overall gene expression classifier, relative expression can indicate if either up- or down-regulation of a certain biomarker is indicative of responsiveness or resistance to a therapeutic agent.

In one embodiment, the biomarker expression profile of a patient tissue sample is evaluated by a linear classifier. As used herein, a linear classifier refers to a weighted sum of the individual biomarker intensities into a compound decision score ("decision function"). The decision score is then compared to a pre-defined cut-off score threshold, corresponding to a certain set-point in terms of sensitivity and specificity which indicates if a sample is above the score threshold (decision function positive) or below (decision function negative).

Effectively, this means that the data space, i.e. the set of all possible combinations of biomarker expression values, is split into two mutually exclusive halves corresponding to different clinical classifications or predictions, e.g. one corresponding to responsiveness to a therapeutic agent and the other to resistance. In the context of the overall classifier, relative over-expression of a certain biomarker can either increase the decision score (positive weight) or reduce it (negative weight) and thus contribute to an overall decision of, for example, responsiveness or resistance to a therapeutic agent.

The term "area under the curve" or "AUC" refers to the area under the curve of a receiver operating characteristic (ROC) curve, both of which are well known in the art. AUC measures are useful for comparing the accuracy of a classifier across the complete data range. Classifiers with a greater AUC have a greater capacity to classify unknowns correctly between two groups of interest (e.g., ovarian cancer samples and normal or control samples). ROC curves are useful for plotting the performance of a particular feature (e.g., any of the biomarkers described herein and/or any item of additional biomedical information) in distinguishing between two populations (e.g., individuals responding and not responding to a therapeutic agent). Typically, the feature data across the entire population (e.g., the cases and controls) are sorted in ascending order based on the value of a single feature. Then, for each value for that feature, the true positive and false positive rates for the data are calculated. The true positive rate is determined by counting the number of cases above the value for that feature and then dividing by the total number of cases. The false positive rate is determined by counting the number of controls above the value for that feature and then dividing by the total number of controls. Although this definition refers to scenarios in which a feature is elevated in cases compared to controls, this definition also applies to scenarios in which a feature is lower in cases compared to the controls (in such a scenario, samples below the value for that feature would be counted). ROC curves can be generated for a single feature as well as for other single outputs, for example, a combination

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

The interpretation of this quantity, i.e. the cut-off threshold responsiveness or resistance to a therapeutic agent, is derived in the development phase ("training") from a set of patients with known outcome. The corresponding weights and the responsiveness/resistance cut-off threshold for the decision score are fixed *a priori* from training data by methods known to those skilled in the art. In a preferred embodiment of the present method, Partial Least Squares Discriminant Analysis (PLS-DA) is used for determining the weights. (L. Ståhle, S. Wold, J. Chemom. 1 (1987) 185-196; D. V. Nguyen, D.M. Rocke, Bioinformatics 18 (2002) 39-50). Other methods for performing the classification, known to those skilled in the art, may also be with the methods described herein when applied to the transcripts of a cancer classifier.

Different methods can be used to convert quantitative data measured on these biomarkers into a prognosis or other predictive use. These methods include, but not limited to methods from the fields of pattern recognition (Duda et al. Pattern Classification, 2nd ed., John Wiley, New York 2001), machine learning (Schölkopf et al. Learning with Kernels, MIT Press, Cambridge 2002, Bishop, Neural Networks for Pattern Recognition, Clarendon Press, Oxford 1995), statistics (Hastie et al. The Elements of Statistical Learning, Springer, New York 2001), bioinformatics (Dudoit et al., 2002, J. Am. Statist. Assoc. 97:77-87, Tibshirani et al., 2002, Proc. Natl. Acad. Sci. USA 99:6567-6572) or chemometrics (Vandeginste, et al., Handbook of Chemometrics and Qualimetrics, Part B, Elsevier, Amsterdam 1998).

In a training step, a set of patient samples for both responsiveness/resistance cases are measured and the prediction method is optimised using the inherent information from this training data to optimally predict the training set or a future sample set. In this training step, the used method is trained or parameterised to predict from a specific intensity pattern to a specific predictive call. Suitable transformation or pre-processing steps might be performed with the measured data before it is subjected to the prognostic method or algorithm.

In a preferred embodiment of the invention, a weighted sum of the pre-processed intensity values for each transcript is formed and compared with a threshold value optimised on the training set (Duda et al. Pattern Classification, 2nd ed., John Wiley, New York 2001). The weights can be derived by a multitude of linear classification methods, including but not limited to Partial Least Squares (PLS, (Nguyen et al., 2002, Bioinformatics 18 (2002) 39-50)) or

Support Vector Machines (SVM, (Schölkopf et al. Learning with Kernels, MIT Press, Cambridge 2002)).

In another embodiment of the invention, the data is transformed non-linearly before applying a weighted sum as described above. This non-linear transformation might include increasing the dimensionality of the data. The non-linear transformation and weighted summation might also be performed implicitly, e.g. through the use of a kernel function. (Schölkopf et al. Learning with Kernels, MIT Press, Cambridge 2002).

In another embodiment of the invention, a new data sample is compared with two or more class prototypes, being either real measured training samples or artificially created prototypes. This comparison is performed using suitable similarity measures, for example, but not limited to Euclidean distance (Duda et al. Pattern Classification, 2nd ed., John Wiley, New York 2001), correlation coefficient (Van't Veer, et al. 2002, Nature 415:530) etc. A new sample is then assigned to the prognostic group with the closest prototype or the highest number of prototypes in the vicinity.

In another embodiment of the invention, decision trees (Hastie et al., The Elements of Statistical Learning, Springer, New York 2001) or random forests (Breiman, Random Forests, Machine Learning 45:5 2001) are used to make a prognostic call from the measured intensity data for the transcript set or their products.

In another embodiment of the invention neural networks (Bishop, Neural Networks for Pattern Recognition, Clarendon Press, Oxford 1995) are used to make a prognostic call from the measured intensity data for the transcript set or their products.

In another embodiment of the invention, discriminant analysis (Duda et al., Pattern Classification, 2nd ed., John Wiley, New York 2001), comprising but not limited to linear, diagonal linear, quadratic and logistic discriminant analysis, is used to make a prognostic call from the measured intensity data for the transcript set or their products.

In another embodiment of the invention, Prediction Analysis for Microarrays (PAM, (Tibshirani et al., 2002, Proc. Natl. Acad. Sci. USA 99:6567-6572)) is used to make a prognostic call from the measured intensity data for the transcript set or their products.

In another embodiment of the invention, Soft Independent Modelling of Class Analogy (SIMCA, (Wold, 1976, Pattern Recogn. 8:127-139)) is used to make a predictive call from the measured intensity data for the transcript set or their products.

Therapeutic agents

As described above, the methods described herein permit the classification of a patient as responsive or non-responsive to a therapeutic agent that targets tumors with abnormal DNA repair (hereinafter referred to as a"DNA-damage therapeuticagent"). As used herein "DNA-damagetherapeutic agent" includes agents known to damage DNA directly, agents that prevent DNA damage repair, agents that inhibit DNA damage signaling, agents that inhibit DNA damage induced cell cycle arrest, and agents that inhibit processes indirectly leading to DNA damage. Some current such therapeutics used to treat cancer include, but are not limited to, the following DNA-damage therapeuticagents.

1) DNA damaging agents:
    a. Alkylating agents (platinum containing agents such as cisplatin, carboplatin, and oxaliplatin; cyclophosphamide; busulphan).
    b. Topoisomerase I inhibitors (irinotecan; topotecan)
    c. Topisomerase II inhibitors (etoposide;anthracylcines such as doxorubicin and epirubicin)
    d. Ionising radiation

2) DNA repair targetcd therapies
    a. Inhibitors of Non-homologous end-joining (DNA-PK inhibitors, Nu7441, NU7026)
    b. Inhibitors of homologous recombination
    c. Inhibitors of nucleotide excision repair
    d. Inhibitors of base excision repair (PARP inhibitors, AG014699, AZD2281, ABT-888, MK4827, BSI-201, INO-1001, TRC-102, APEX 1 inhibitors, APEX 2 inhibitors, Ligase III inhibitors
    e. Inhibitors of the Fanconi anemia pathway

3) Inhibitors of DNA damage signalling
    a. ATM inhibitors (CP466722, KU-55933)
    b. CHK 1 inhibitors (XL-844,UCN-01, AZD7762, PF00477736)
    c. CHK 2 inhibitors (XL-844, AZD7762, PF00477736)

4) Inhibitors of DNA damage induced cell cycle arrest
    a. Wee1 kinase inhibitors
    b. CDC25a, b or c inhibitors

5) Inhibition of processes indirectly leading to DNA damage
   a. Histone deacetylase inhibitors
   b. Heat shock protein inhibitors (geldanamycin, AUY922),

Diseases and Tissue Sources

The predictive classifiers described herein are useful for determining responsiveness or resistance to a therapeutic agentfor treating cancer. The biological pathway described herein is a feature of cancer itself, similar to grade and stage, and as such, is not limited to a single cancer disease type.Therefore, the collection of genes or gene products may be used to predict responsiveness of cancer therapeutics across different cancer types in different tissues. In one embodiment, this collection of genes or gene products is useful for evaluating both breast and ovarian cancer tumors.

As used herein, cancer includes, but is not limited to, leukemia, brain cancer, prostate cancer, liver cancer, ovarian cancer, stomach cancer, colorectal cancer, throat cancer, breast cancer, skin cancer, melanoma, lung cancer, sarcoma, cervical cancer, testicular cancer, bladder cancer, endocrine cancer, endometrial cancer, esophageal cancer, glioma, lymphoma, neuroblastoma, osteosarcoma, pancreatic cancer, pituitary cancer, renal cancer, and the like.

In one embodiment, the methods described herein refer to cancers that are treated with chemotherapeutic agents of the classes DNA damaging agents, DNA repair target therapies, inhibitors of DNA damage signalling, inhibitors of DNA damage induced cell cycle arrest and inhibition of processes indirectly leading to DNA damage, but not limited to these classes. Each of these chemotherapeutic agents is considered a "DNA-damage therapeutic agent" as the term is used herein.

"Biological sample", "sample", and "test sample" are used interchangeably herein to refer to any material, biological fluid, tissue, or cell obtained or otherwise derived from an individual. This includes blood (including whole blood, leukocytes, peripheral blood mononuclear cells, buffy coat, plasma, and serum), sputum, tears, mucus, nasal washes, nasal aspirate, breath, urine, semen, saliva, meningeal fluid, amniotic fluid, glandular fluid, lymph fluid, nipple aspirate, bronchial aspirate, synovial fluid, joint aspirate, ascites, cells, a cellular extract, and cerebrospinal fluid. This also includes experimentally separated fractions of all of the preceding. For example, a blood sample can be fractionated into serum or into fractions containing particular types of blood cells, such as red blood cells or white blood cells (leukocytes). If desired, a sample can be a combination of samples from an individual, such as a combination of a tissue and fluid sample. The term "biological sample" also includes materials

containing homogenized solid material, such as from a stool sample, a tissue sample, or a tissue biopsy, for example. The term "biological sample" also includes materials derived from a tissue culture or a cell culture. Any suitable methods for obtaining a biological sample can be employed; exemplary methods include, e.g., phlebotomy, swab (e.g., buccal swab), and a fine needle aspirate biopsy procedure. Samples can also be collected, e.g., by micro dissection (e.g., laser capture micro dissection (LCM) or laser micro dissection (LMD)), bladder wash, smear (e.g., a PAP smear), or ductal lavage. A "biological sample" obtained or derived from an individual includes any such sample that has been processed in any suitable manner after being obtained from the individual.

In such cases, the target cells may be tumor cells, for example colon cancer cells or stomach cancer cells. The target cells are derived from any tissue source, including human and animal tissue, such as, but not limited to, a newly obtained sample, a frozen sample, a biopsy sample, a sample of bodily fluid, a blood sample, preserved tissue such as a paraffin-embedded fixed tissue sample (i.e., a tissue block), or cell culture.

Methods and Kits

Kits for Gene Expression Analysis

Reagents, tools, and/or instructions for performing the methods described herein can be provided in a kit. For example, the kit can contain reagents, tools, and instructions for determining an appropriate therapy for a cancer patient. Such a kit can include reagents for collecting a tissue sample from a patient, such as by biopsy, and reagents for processing the tissue. The kit can also include one or more reagents for performing a biomarker expression analysis, such as reagents for performing RT-PCR, qPCR, northern blot, proteomic analysis, or immunohistochemistry to determine expression levels of biomarkers in a sample of a patient. For example, primers for performing RT-PCR, probes for performing northern blot analyses, and/or antibodies for performing proteomic analysis such as Western blot, immunohistochemistry and ELISA analyses can be included in such kits. Appropriate buffers for the assays can also be included. Detection reagents required for any of these assays can also be included. The appropriate reagents and methods are described in further detail below.

The kits featured herein can also include an instruction sheet describing how to perform the assays for measuring biomarker expression. The instruction sheet can also include instructions for how to determine a reference cohort, including how to determine expression levels of biomarkers in the reference cohort and how to assemble the expression data to establish

a reference for comparison to a test patient. The instruction sheet can also include instructions for assaying biomarker expression in a test patient and for comparing the expression level with the expression in the reference cohort to subsequently determine the appropriate chemotherapy for the test patient. Methods for determining the appropriate chemotherapy are described above and can be described in detail in the instruction sheet.

Informational material included in the kits can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or the use of the reagents for the methods described herein. For example, the informational material of the kit can contain contact information, e.g., a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about performing a gene expression analysis and interpreting the results, particularly as they apply to a human's likelihood of having a positive response to a specific therapeutic agent.

The kits featured herein can also contain software necessary to infer a patient's likelihood of having a positive response to a specific therapeutic agent from the biomarker expression.

a) Gene expression profiling methods

Measuring mRNA in a biological sample may be used as a surrogate for detection of the level of the corresponding protein in the biological sample. Thus, any of the biomarkers or biomarker panels described herein can also be detected by detecting the appropriate RNA. Methods of gene expression profiling include, but are not limited to, microarray, RT-PCT, qPCR, northern blots, SAGE, mass spectrometry.

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

miRNA molecules are small RNAs that are non-coding but may regulate gene expression. Any of the methods suited to the measurement of mRNA expression levels can also be used for the corresponding miRNA. Recently many laboratories have investigated the use of miRNAs as biomarkers for disease. Many diseases involve widespread transcriptional

regulation, and it is not surprising that miRNAs might find a role as biomarkers. The connection between miRNA concentrations and disease is often even less clear than the connections between protein levels and disease, yet the value of miRNA biomarkers might be substantial. Of course, as with any RNA expressed differentially during disease, the problems facing the development of an in vitro diagnostic product will include the requirement that the miRNAs survive in the diseased cell and are easily extracted for analysis, or that the miRNAs are released into blood or other matrices where they must survive long enough to be measured. Protein biomarkers have similar requirements, although many potential protein biomarkers are secreted intentionally at the site of pathology and function, during disease, in a paracrine fashion. Many potential protein biomarkers are designed to function outside the cells within which those proteins are synthesized.

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

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

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

The foregoing assays enable the detection of biomarker values that are useful in methods for predicting responsiveness of a cancer therapeutic agent, where the methods comprise detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Tables 1 or 2, wherein a classification, as described in detail below, using the biomarker values indicates whether the individual will be responsive to a therapeutic agent. While certain of the described predictive biomarkers are useful alone for predicting responsiveness to a therapeutic agent, methods are also described herein for the grouping of multiple subsets of the biomarkers that are each useful as a panel of two or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. It will be appreciated that N can be selected to be any number from any of the above-described ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

b) Microarray methods

In one embodiment, the present invention makes use of "oligonucleotide arrays" (also called herein "microarrays"). Microarrays can be employed for analyzing the expression of biomarkers in a cell, and especially for measuring the expression of biomarkers of cancer tissues.

In one embodiment, biomarker arrays are produced by hybridizing detectably labeled polynucleotides representing the mRNA transcripts present in a cell (e.g., fluorescently-labeled

cDNA synthesized from total cell mRNA or labeled cRNA) to a microarray. A microarray is a surface with an ordered array of binding (e.g., hybridization) sites for products of many of the genes in the genome of a cell or organism, preferably most or almost all of the genes. Microarrays can be made in a number of ways known in the art. However produced, microarrays share certain characteristics. The arrays are reproducible, allowing multiple copies of a given array to be produced and easily compared with each other. Preferably the microarrays are small, usually smaller than 5 cm^2, and they are made from materials that are stable under binding (e.g., nucleic acid hybridization) conditions. A given binding site or unique set of binding sites in the microarray will specifically bind the product of a single gene in the cell. In a specific embodiment, positionally addressable arrays containing affixed nucleic acids of known sequence at each location are used.

It will be appreciated that when cDNA complementary to the RNA of a cell is made and hybridized to a microarray under suitable hybridization conditions, the level of hybridization to the site in the array corresponding to any particular gene will reflect the prevalence in the cell of mRNA transcribed from that gene/biomarker. For example, when detectably labeled (e.g., with a fluorophore) cDNA or cRNA complementary to the total cellular mRNA is hybridized to a microarray, the site on the array corresponding to a gene (i.e., capable of specifically binding the product of the gene) that is not transcribed in the cell will have little or no signal (e.g., fluorescent signal), and a gene for which the encoded mRNA is prevalent will have a relatively strong signal. Nucleic acid hybridization and wash conditions are chosen so that the probe "specifically binds" or "specifically hybridizes' to a specific array site, i.e., the probe hybridizes, duplexes or binds to a sequence array site with a complementary nucleic acid sequence but does not hybridize to a site with a non-complementary nucleic acid sequence. As used herein, one polynucleotide sequence is considered complementary to another when, if the shorter of the polynucleotides is less than or equal to 25 bases, there are no mismatches using standard base-pairing rules or, if the shorter of the polynucleotides is longer than 25 bases, there is no more than a 5% mismatch. Preferably, the polynucleotides are perfectly complementary (no mismatches). It can be demonstrated that specific hybridization conditions result in specific hybridization by carrying out a hybridization assay including negative controls using routine experimentation.

Optimal hybridization conditions will depend on the length (e.g., oligomer vs. polynucleotide greater than 200 bases) and type (e.g., RNA, DNA, PNA) of labeled probe and immobilized polynucleotide or oligonucleotide. General parameters for specific (i.e., stringent) hybridization conditions for nucleic acids are described in Sambrook et al., supra, and in Ausubel et al., "Current Protocols in Molecular Biology", Greene Publishing and Wiley-

interscience, NY (1987), which is incorporated in its entirety for all purposes. When the cDNA microarrays are used, typical hybridization conditions are hybridization in 5xSSC plus 0.2% SDS at 65C for 4 hours followed by washes at 25°C in low stringency wash buffer (1xSSC plus 0.2% SDS) followed by 10 minutes at 25°C in high stringency wash buffer (0.1SSC plus 0.2% SDS) (see Shena *et al.*, Proc. Natl. Acad. Sci. USA, Vol. 93, p. 10614 (1996)). Useful hybridization conditions are also provided in, e.g., Tijessen, Hybridization With Nucleic Acid Probes", Elsevier Science Publishers B.V. (1993) and Kricka, "Nonisotopic DNA Probe Techniques", Academic Press, San Diego, Calif. (1992).

c) Immunoassay methods

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

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

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

Exemplary assay formats include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, fluorescent, chemiluminescence, and fluorescence resonance energy transfer (FRET) or time resolved-FRET (TR-FRET) immunoassays. Examples of procedures for

detecting biomarkers include biomarker immunoprecipitation followed by quantitative methods that allow size and peptide level discrimination, such as gel electrophoresis, capillary electrophoresis, planar electrochromatography, and the like.

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

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

Clinical Uses

In some embodiments, methods are provided for identifying and/or selecting a cancer patient who is responsive to a therapeutic regimen. In particular, the methods are directed to identifying or selecting a cancer patient who is responsive to a therapeutic regimen that includes administering an agent that directly or indirectly damages DNA. Methods are also provided for identifying a patient who is non-responsive to a therapeutic regimen. These methods typically include determining the level of expression of a collection of predictive markers in a patient's tumor (primary, metastatic or other derivatives from the tumor such as, but not limited to, blood, or components in blood, urine, saliva and other bodily fluids)(e.g., a patient's cancer cells), comparing the level of expression to a reference expression level, and identifying whether expression in the sample includes a pattern or profile of expression of a selected predictive biomarker or biomarker set which corresponds to response or non-response to therapeutic agent.

In some embodiments a method of predicting responsiveness of an individual to a DNA-damage therapeutic agent comprises the following steps: obtaining a test sample from the individual; measuring expression levels of one or more biomarkers in the test sample, wherein the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1,

IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3; deriving a test score that captures the expression levels; providing a threshold score comprising information correlating the test score and responsiveness; and comparing the test score to the threshold score; wherein responsiveness is predicted when the test score exceeds the threshold score. One of ordinary skill in the art can determine an appropriate threshold score, and appropriate biomarker weightings, using the teachings provided herein including the teachings of Example 1.

In other embodiments, the method of predicting responsiveness of an individual to a DNA-damage therapeutic agent comprises measuring the expression levels of one or more biomarkers in the test sample, wherein the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1. Tables 2A and 2B provide exemplary gene signatures (or gene classifiers) wherein the biomarkers consist of 40 or 44 of the gene products listed therein, respectively, and wherein a threshold score is derived from the individual gene product weightings listed therein. In one of these embodiments wherein the biomarkers consist of the 44 gene products listed in Table 2B, and the biomarkers are associated with the weightings provided in Table 2B, a test score that exceeds a threshold score of 0.3681 indicates a likelihood that the individual will be responsive to a DNA-damage therapeutic agent.

A cancer is "responsive" to a therapeutic agent if its rate of growth is inhibited as a result of contact with the therapeutic agent, compared to its growth in the absence of contact with the therapeutic agent. Growth of a cancer can be measured in a variety of ways, for instance, the size of a tumor or the expression of tumor markers appropriate for that tumor type may be measured.

A cancer is "non-responsive" to a therapeutic agent if its rate of growth is not inhibited, or inhibited to a very low degree, as a result of contact with the therapeutic agent when compared to its growth in the absence of contact with the therapeutic agent. As stated above, growth of a cancer can be measured in a variety of ways, for instance, the size of a tumor or the expression of tumor markers appropriate for that tumor type may be measured. The quality of being non-responsive to a therapeutic agent is a highly variable one, with different cancers exhibiting different levels of "non-responsiveness" to a given therapeutic agent, under different conditions. Still further, measures of non-responsiveness can be assessed using additional criteria beyond growth size of a tumor, including patient quality of life, degree of metastases, etc.

An application of this test will predict end points including, but not limited to, overall survival, progression free survival, radiological response, as defined by RECIST, complete response, partial response, stable disease and serological markers such as, but not limited to, PSA, CEA, CA125, CA15-3 and CA19-9.

Alternatively, non-array based methods for detection, quantification and qualification of RNA, DNA or protein within a sample of one or more nucleic acids or their biological derivatives such as encoded proteins may be employed, including quantitative PCR (QPCR), enzyme-linked immunosorbent assay (ELISA) or immunohistochemistry (IHC) and the like.

After obtaining an expression profile from a sample being assayed, the expression profile is compared with a reference or control profile to make a diagnosis regarding the therapy responsive phenotype of the cell or tissue, and therefore host, from which the sample was obtained. The terms "reference" and "control" as used herein in relation to an expression profile mean a standardized pattern of gene or gene product expression or levels of expression of certain biomarkers to be used to interpret the expression classifier of a given patient and assign a prognostic or predictive class. The reference or control expression profile may be a profile that is obtained from a sample known to have the desired phenotype, e.g., responsive phenotype, and therefore may be a positive reference or control profile. In addition, the reference profile may be from a sample known to not have the desired phenotype, and therefore be a negative reference profile.

If quantitative PCR is employed as the method of quantitating the levels of one or more nucleic acids, this method quantifies the PCR product accumulation through measurement of fluorescence released by a dual-labeled fluorogenic probe (i.e. TaqMan® probe).

In certain embodiments, the obtained expression profile is compared to a single reference profile to obtain information regarding the phenotype of the sample being assayed. In yet other embodiments, the obtained expression profile is compared to two or more different reference profiles to obtain more in depth information regarding the phenotype of the assayed sample. For example, the obtained expression profile may be compared to a positive and negative reference profile to obtain confirmed information regarding whether the sample has the phenotype of interest.

The comparison of the obtained expression profile and the one or more reference profiles may be performed using any convenient methodology, where a variety of methodologies are known to those of skill in the array art, e.g., by comparing digital images of the expression profiles, by comparing databases of expression data, etc. Patents describing ways of comparing expression profiles include, but are not limited to, U.S. Pat. Nos. 6,308,170 and 6,228,575, the

disclosures of which are herein incorporated by reference. Methods of comparing expression profiles are also described above.

The comparison step results in information regarding how similar or dissimilar the obtained expression profile is to the one or more reference profiles, which similarity information is employed to determine the phenotype of the sample being assayed. For example, similarity with a positive control indicates that the assayed sample has a responsive phenotype similar to the responsive reference sample. Likewise, similarity with a negative control indicates that the assayed sample has a non-responsive phenotype to the non-responsive reference sample.

The level of expression of a biomarker can be further compared to different reference expression levels. For example, a reference expression level can be a predetermined standard reference level of expression in order to evaluate if expression of a biomarker or biomarker set is informative and make an assessment for determining whether the patient is responsive or non-responsive. Additionally, determining the level of expression of a biomarker can be compared to an internal reference marker level of expression which is measured at the same time as the biomarker in order to make an assessment for determining whether the patient is responsive or non-responsive. For example, expression of a distinct marker panel which is not comprised of biomarkers of the invention, but which is known to demonstrate a constant expression level can be assessed as an internal reference marker level, and the level of the biomarker expression is determined as compared to the reference. In an alternative example, expression of the selected biomarkers in a tissue sample which is a non-tumor sample can be assessed as an internal reference marker level. The level of expression of a biomarker may be determined as having increased expression in certain aspects. The level of expression of a biomarker may be determined as having decreased expression in other aspects. The level of expression may be determined as no informative change in expression as compared to a reference level. In still other aspects, the level of expression is determined against a pre-determined standard expression level as determined by the methods provided herein.

The invention is also related to guiding conventional treatment of patients. Patients in which the diagnostics test reveals that they are responders to the drugs, of the classes that directly or indirectly affect DNA damage and/or DNA damage repair, can be administered with that therapy and both patient and oncologist can be confident that the patient will benefit. Patients that are designated non-responders by the diagnostic test can be identified for alternative therapies which are more likely to offer benefit to them.

The invention further relates to selecting patients for clinical trials where novel drugs of the classes that directly or indirectly affect DNA damage and/or DNA damage repair.

Enrichment of trial populations with potential responders will facilitate a more thorough evaluation of that drug under relevant criteria.

The invention still further relates to methods of diagnosing patients as having or being susceptible to developing a cancer associated with a DNA damage response deficiency (DDRD). DDRD is defined herein as any condition wherein a cell or cells of the patient have a reduced ability to repair DNA damage, which reduced ability is a causative factor in the development or growth of a tumor. The DDRD diagnosis may be associated with a mutation in the Fanconi anemia/BRCA pathway. The DDRD diagnosis may also be associated with breast cancer or ovarian cancer. These methods of diagnosis comprise the steps of obtaining a test sample from the individual; measuring expression levels of one or more biomarkers in the test sample, wherein the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3; deriving a test score that captures the expression levels; providing a threshold score comprising information correlating the test score and a diagnosis of the cancer; and comparing the test score to the threshold score; wherein the individual is determined to have the cancer or is susceptible to developing the cancer when the test score exceeds the threshold score. One of ordinary skill in the art can determine an appropriate threshold score, and appropriate biomarker weightings, using the teachings provided herein including the teachings of Example 1.

In other embodiments, the methods of diagnosing patients as having or being susceptible to developing a cancer associated with DDRD comprise measuring expression levels of one or more biomarkers in the test sample, wherein the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1. Tables 2A and 2B provide exemplary gene signatures (or gene classifiers) wherein the biomarkers consist of 40 or 44 of the gene products listed therein, respectively, and wherein a threshold score is derived from the individual gene product weightings listed therein. In one of these embodiments wherein the biomarkers consist of the 44 gene products listed in Table 2B, and the biomarkers are associated with the weightings provided in Table 2B, a test score that exceeds a threshold score of 0.3681 indicates a diagnosis of cancer or of being susceptible to developing a cancer.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

Tissue processing, hierarchical clustering, subtype identification and classifier development

Tumor Material

The genes determined to be useful in the present methods (Table 2) were identified from gene expression analysis of a cohort of 107 macrodissected breast tumor FFPE tissue samples sourced from the Mayo Clinic Rochester. Ethical approval for this study was obtained from the Institutional Review Board and the Office of Research Ethics Northern Ireland.

This cohort of samples can be further described as follows:

- 47 samples were wild-type for BRCA1 and BRCA2 i.e. expressed biologically functional BRCA1 and BRCA2 proteins. These samples shall henceforth be referred to as sporadic controls.
- 31 samples were BRCA1 mutant i.e. did not express biologically functional BRCA1 protein.
- 29 samples were BRCA2 mutant i.e. did not express biologically functional BRCA2 protein.

Gene Expression Profiling

Total RNA was extracted from the macrodissected FFPE tumor samples using the Roche High Pure RNA Paraffin Kit (Roche Diagnostics GmbH, Mannheim, Germany). Total RNA was amplified using the NuGEN WT-Ovation™ FFPE System (NuGEN Technologies Inc., San Carlos, CA, USA). The amplified single-stranded cDNA was then fragemented and biotin labeled using the FL-Ovation™ cDNA Biotin Module V2 (NuGEN Technologies Inc.). It was then hybridized to the Almac Breast Cancer DSA™. The Almac's Breast Cancer DSA™ research tool has been optimised for analysis of FFPE tissue samples, enabling the use of valuable archived tissue banks. The Almac Breast Cancer DSA™ research tool is an innovative microarray platform that represents the transcriptome in both normal and cancerous breast tissues. Consequently, the Breast Cancer DSA™ provides a comprehensive representation of the transcriptome within the breast disease and tissue setting, not available using generic microarray

platforms. Arrays were scanned using the Affymentrix Genechip® Scanner 7G (Affymetrix Inc., Santa Clara, CA).

Data Preparation

Quality Control (QC) of profiled samples was carried out using MAS5 pre-processing algorithm. Different technical aspects were addressed: average noise and background homogeneity, percentage of present call (array quality), signal quality, RNA quality and hybridization quality. Distributions and Median Absolute Deviation of corresponding parameters were analyzed and used to identify possible outliers.

Almac's Ovarian Cancer DSA™ contains probes that primarily target the area within 300 nucleotides from the 3' end of a polynucleotide. Therefore standard Affymetrix RNA quality measures were adapted – for housekeeping genes intensities of 3' end probesets along with ratios of 3' end probeset intensity to the average background intensity were used in addition to usual 3'/5' ratios. Hybridization controls were checked to ensure that their intensities and present calls conform to the requirements specified by Affymetrix.

Tumor samples from the BRCA1/2 mutant and sporadic control training set were split into 2 datasets based on the transcript levels of ESR1 (Estrogen receptor 1). mRNA expression level $E_{.avg}$ for each sample was determined by the average expression of all ESR1 probe sets (BRAD.15436_s_at, BRAD.19080_s_at, BREM.1048_at, BRIH.10647C1n2_at, BRIH.5650C1n2_at, BRPD.10690C1n5_at, BRRS.81_at and BRRS.81-22_at). The mRNA median expression ($E_{.med.all}$) was calculated for all samples. Samples were considered ER positive when $E_{.avg} - E_{.med.all} > 0.5$ and ER negative when $E_{.avg} - E_{.med.all} < 0.5$.

Pre-processing was performed in expression console v1.1 with Robust Multi-array Analysis (RMA) (Irizarry et al., 2003) resulting in 2 data matrices of ER positive and ER negative samples composed of 56 and 51 samples respectively. An additional transformation was performed to remove the variance associated with array quality as described by Alter (Alter et al., 2000).

Feature selection

A combined background & variance filter was applied to each data matrix to identify the most variable probesets. The background filter is based on the selection of probe sets with expression E and expression variance var_E above the thresholds defined by background standard deviation σBg (from the Expression Console software) and quantile of the standard normal distribution $z_a$at a specified significance a probesets were kept if:

$E > \log_2((z_a \sigma_{Bg}))$; $\log_2((\mathrm{var}_E) > 2\ [\log_2(\sigma_{Bg}) - E - \log_2(\log(2))]$

where the significance threshold was $a = 6.3.10^{-5}$, see Table 1 for the list of selected probesets and their gene annotations.

Hierarchical clustering analysis

Hierarchical clustering techniques were applied to microarray data from 199 epithelial serous ovarian tumors analysed using the Ovarian Cancer DSA™ (disease specific array) platform (FIG. 1). Raw expression data was preprocessed using the standard Robust Multichip Algorithm (RMA) procedure. Non-biological systematic variance in the data set was identified and removed. Those probesets whose expression levels varied significantly from tumor to tumor were identified. These probesets formed the intrinsic list.

2-D cluster analysis (tumor, probeset) was performed to establish tumor relationships based on the intrinsic list. Hierarchical agglomerative clustering was applied (Pearson correlation distance and Ward's linkage). Optimal partition number was selected using the GAP index (Tibshirani et al., 2002, J. R. Stat. Soc., 63:411-423). All probesets available in the subclusters were mapped to genes names.

Functional analysis of gene clusters

To establish the functional significance of the probeset clusters, probesets were mapped to genes (Entrez gene ID) and an enrichment analysis, based on the hypergeometric function (False Discovery Rate applied (Benjamini and Hochberg, 1995, J. R. Stat. Soc. 57:289:300)), was performed.Over-representation of biological processes and pathways were analysed for each gene group generated by the hierarchical clustering for both ER-positive and ER-negative samples using Metacore™ single experiment analysis workflow from GeneGo®. Antisense probesets were excluded from the analysis. Hypergeometric p-values were assessed for each enriched functional entity class. Functional entity classes with the highest p-values were selected as representative of the group and a general functional category representing these functional entities was assigned to the gene clusters based on significance of representation (i.e. p-value).

Genes in clusters enriched for the IFN/DD general functional terms were grouped into a DNA-damage response-deficiency (DDRD) sample group and used for the classifier generation. The sample clusters from ER-positive and ER-negative datasets represented by the IFN/DD

general functional terms were selected for classification and labelled as DDRD. Those not represented by these functional terms were labelled as non-DDRD.

Classifier development at a probeset level

Following the identification of a class of tumors that form the DDRD subgroup, computational classification of these tumors vs. all the others in the tumor cohort (non-DDRD) was performed, with reference to the functional DDRD gene list (Table 1), to identify a refined gene classification model that classifies the DDRD subgroup.This was evaluated using all combinations of the following options (a total of 18):

- Three sample sets
  - Combined sample set of ER-negative and ER-positive samples (combined sample set)
  - ER-negative samples alone
  - ER-positive samples alone
- Two feature sets
  - Full feature list with 75% variance/intensity filtering and forced inclusion of the DDRD list. Here 75% of the probesets with the lowest combined variance and intensity were removed, based on the average rank of both. When used, the term "VarInt" refers to this option.
  - DDRD list only. When used, the term "List only" refers to this option.
- Three classification algorithms
  - PLS (Partial Least Squares) (de Jong, 1993)
  - SDA (Shrinkage Discriminate Analysis)(Ahdesmaki and Strimmer, 2010)
  - DSDA (Diagonal SDA)(Ahdesmaki and Strimmer, 2010)

The AUC was used to assess the performance of the different models. Iterative Feature Elimination (IFE) was implemented throughout the development of each model, where the maximum AUC was the main criteria in selecting an optimal number of features over cross validation. In cases where there was no visible AUC difference across features, the minimum feature length was selected.

Classifier development at a gene level

To facilitate validation of the classifier across multiple array platforms, the selected probeset classifier was regenerated at the gene level. A redevelopment of the probeset classifier at a gene level required two separate steps:

1. The expression intensities of the unique genes in the probeset classifier were estimated from the median of the probesets mapping to each gene, excluding anti-sense probesets.
2. The classifier parameters used for classification were re-estimated

A threshold was chosen based on the maximum sensitivity and specificity over all cross validation predictions.

Similarly the gene level defined expression intensities for the 10 top genes (or any number of features present in current 44 gene signature) could be used to re-develop the classifier based on only these 10 genes (or any number of features present in current 44 gene signature) by re-estimating classification parameters in cross-validation in the training data set as well as to re-establish the threshold by assessing and maximising the sensitivity and specificity obtained from all cross-validation predictions. The methodology would be similar to the method used when working from a larger feature set (described above) except there will be no feature selection involved: the features will remain the same but will be assigned new weights.

Calculating classifier scores for validation data sets

Public Datasets

The datasets used in for this analysis are namely: FAC1 [GEO accession number GSE20271, (Tabchy et al., 2010)], FAC2 [GEO accession number GSE22093, (Iwamoto et al., 2011)], FEC [GEO accession number GSE6861, (Bonnefoi et al., 2007)], T/FAC1 [http://bioinformatics.mdanderson.org/pubdata.html, (Hess et al., 2006)], T/FAC2 [GEO accession number GSE16716, (Lee et al., 2010)] and T/FAC3 [GEO accession number GSE20271, (Tabchy et al., 2010)]. It must be noted that there is an overlap in 31 samples between the FAC1 and FAC2 datasets. These samples were removed from the FAC2 dataset and as such were only included once in the combined analysis of the FAC1, FAC2 and FEC datasets. In addition, sample GSM508092 was removed from FAC1 as it is a metastatic lymph node sample.

All datasets were pre-processed using RMA (Irizarry et al., 2003). For each validation set, the probesets that map to the classifier genes were determined, excluding anti-sense

probesets (if applicable). Annotation for Affymetrix X3P and U133A arrays are available from the Affymetrix website. The median intensity over all probesets mapping to each gene in the classifier was calculated, resulting in a gene intensity matrix. The classifier was then applied to this data matrix to produce a classifier score/prediction for each sample.

Calculating performance metrics

To calculate NPV and PPV, the prevalence of each end point (BRCA status/Response) was estimated using the proportions of each class in the corresponding data set.

Univariate and Multivariate analysis

Univariate and multivariate analysis was carried out to assess respectively the association between the DDRD classifier and response, and to determine if the association, if any, was independent to known clinical predictors. The p-values presented Table 4, for univariate analysis were calculated using logistic regression in MATLAB. For the multivariate analysis we used step-wise logistic regression (Dupont, 2009), where the p-values represent the log-likelihood of the variable. The log-likelihood is a measure of the importance of the variable's fit to the model, thus highlighting it's independence as a predictor relative to the other predictors. In both univariate and multivariate analysis, a p-value < 0.05 was used as the criterion for significance. Furthermore, samples with unknown clinical factors were excluded in this assessment.

Results

Selection of samples for classifier generation

The objective of this study was to characterize at a transcriptomic level a set of genes that would be capable of determining responsiveness or resistance of a pathogenic cell to DNA-damage therapeutic agents. With this in mind, those samples within the Almac breast cancer dataset that best represented this biology were to be selected and compared to the remaining samples for classifier generation (see next section). It was decided that the samples from sample cluster two within the ER-ve sample set were the most relevant samples for this selection as these showed the greatest proportion of BRCA mutant samples (64%) and they exhibited the most dominant biology (IFN/immune response). From within the ER+ve sample set, the samples from sample cluster two and three were selected as these sample clusters had 73% and 67% BRCA mutant tumors respectively. In addition, the most dominant biology within these clusters

was related to cell cycle, DNA damage response and IFN/immune response. Immune signaling and cell-cycle pathways have been reported to be modulated in response to DNA-damage (Jackson, S. P., and Bartek, J., Nature 461, 1071-1078 (2009); Rodier, F., *et al.*, Nat Cell Biol *11*, 973-979 (2009); Xu, Y.,Nat Rev Immunol6, 261-270 (2006), andthese subgroups were combined to form a putative DDRD subgroup. Those samples within cluster two of the ER-ve sample set (described below) and clusters two and three of the ER+ve sample set (described below) were class labelled DDRD (DNA damage response deficient) (see FIG. 1A) whilst the samples within sample clusters one and three of the ER-ve sample set and sample clusters one, four, five and six of the ER+ve sample set were class labeled non-DDRD(see FIG. 1B).

ER-ve sample set: Within the ER-ve sample set, the hierarchical cluster analysis defined three sample clusters and six probeset cluster groups. Probeset cluster three was identified as the most significant biology within the ER-ve sample set and was enriched for interferon and immune response signaling.

ER+ve sample set: Within the ER+ve sample set, the hierarchical analysis defined six sample groups and six probeset cluster groups. Probeset cluster five was identified as the most significant biology within the ER+ve sample set and was enriched for extracellular matrix remodeling. The next most significant probeset cluster within the ER+ve sample set is probeset cluster six and again was enriched for interferon and immune response signaling.

Development and validation of the DDRD classifier model

Following the identification of a class of tumors, that form the DDRD subgroup, computational classification of these tumors vs. all others in the tumor cohort with reference to the functional DDRD (IFN/DNA damage) gene list was performed to identify a refined gene classification model, which classifies the DDRD subgroup.

The classification pipeline was used to derive a model using the set of combined ER-ve and ER+ve breast cancer samples. The classification pipeline has been developed in accordance with commonly accepted good practice [MAQC Consortium, Nat Biotechnol 2010]. The process will, in parallel: 1) derive gene classification models from empirical data; and 2) assess the classification performance of the models, both under cross-validation. The performance and success of the classifier generation depends on a number of parameters that can be varied, for instance the choice of classification method or probe set filtering. Taking this into account, two feature sets were evaluated (i) the full feature list with 75% variance/intensity filtering (with

forced inclusion of the DDRD (IFN/DNA damage) list, Table 1) and (ii) the DDRD (IFN/DNA damage) list only; and three classification algorithms were evaluated, namely PLS (Partial Least Squares); SDA (*Shrinkage Discriminate Analysis*) and DSDA (*Diagonal SDA*). *Iterative Feature* Elimination (IFE) was used throughout model development, which is an iterative procedure removing a fraction of the worst-ranked features at each iteration; stopping when only a minimum number of features remain. The Area under the Receiver Operating Characteristics Curve (AUC-ROC), denoted AUC, was used to assess the classification performance, as this measure is independent of cut-off between groups and prevalence rates in the data. It is also one of the recognized measurements of choice for classification performance. As such, the best number of features for each model was chosen based on the average AUC under cross-validation.

A cross comparison of the models was made, by first selecting the best number of features for each model based on the highest average AUC, and then using box-plots to visualize the performance for each model. This is demonstrated in FIG. 2. From left to right, the first three plots represent the PLS, SDA and DSDA classifiers respectively that were developed using an initial filtering of probe sets to remove 75% with the lowest average variance and intensity (forcing the inclusion of the gene list). The next three plots respectively represent the PLS, SDA and DSDA classifiers developed using the DDRD (IFN/DNA damage) list only.

From FIG. 2, it is clear that the 'PLS VarInt' classification model, comprising 53 probe sets, is the highest performing model, with a significantly higher AUC than the majority of the other 5 models. This model was then taken forward to the next phase for validation on independent external data sets, to assess the ability of the DDRD classification scores to stratify patients with respect to response and prognosis.

A non-orthodox approach to validating the classification model was taken, due to the fact that the validation data sets where either public or internal data with different array platforms. Commonly used approaches are not designed to be applicable to alternative array platforms, and as such a phased approach for classification model development and independent validation was followed:

1. Phase I - Model generation at the probe set level, selecting the best model under cross validation for classifying the DDRD subgroup (described previously)

2. Phase II - Transformation of the probe set level classification model to a gene level classification model

3. Phase III - Validation of re-developed gene classification model using external data sets

Having selected a candidate model to progress to the validation stage, this model needed to be re-built at the gene level (Phase II). This involved mapping the probe sets in the classification model to the gene level and recalculating the weights for each gene. The 53 probe sets in the selected model mapped to 40 genes listed in Table 2A and subsequently mapped to 44 genes listed in Table 2B when the accuracy of the annotation pipeline was improved through further analysis.

In the re-development of the gene classification model, to ensure that all information relating to the gene is used, the median intensity of all probe sets associated with each gene (Table 2C) is used as the gene expression value. This was calculated for all samples, resulting in a gene expression data matrix, as opposed to a probe set expression data matrix that was used in Phase I for model development and selection. To stabilize the intensities across different batches, the median of all probe sets for each sample was subtracted from the corresponding intensity of each gene for that sample.

New weights were calculated for each gene using PLS regression, resulting in the final gene classifier models (40-gene and 44-gene classifier models) that may be used for validation on external data sets from different array platforms (Phase III).

In Phase III, the validation of the classifier using data sets that may be from other array platforms, the following steps were taken:

1. The probe sets that map to the genes in the classifier are determined, excluding anti-sense probe sets (if applicable)
2. The median intensity over all probe sets relating to each gene in the classifier is calculated resulting in a reduced gene intensity matrix
    a. If no probe sets exist for the gene on the particular array platform, the observed average from the training data will be used as a replacement
3. The median value of all probe sets for each sample is calculated and subtracted from the reduced gene intensity matrix
4. The value for each gene is multiplied by the "weight" of that gene in the signature.
5. The values obtained in point 4 for each of the genes in the signature are added together to produce a signature score for that sample.
6. The classifier produces a score for each sample, which can then be used to stratify patients from say, more likely to respond to less likely to respond.

Example 2

In silico validation of the 44-gene DDRD classifier model

The performance of the 44-gene DDRD classifier model was validated by the Area Under the ROC (Receiver Operator Characteristic) Curve (AUC) within the original Almac breast dataset and three independent datasets. The AUC is a statistic calculated on the observed disease scale and is a measure of the efficacy of prediction of a phenotype using a classifier model (Wray et. al., PLoS Genetics Vol 6, 1-9). An AUC of 0.5 is typical of a random classifier, and an AUC of 1.0 would represent perfect separation of classes. Therefore, in order to determine if the 44-gene DDRD classifier model is capable of predicting response to, and selecting patients for, standard breast and ovarian cancer therapeutic drug classes, including DNA damage causing agents and DNA repair targeted therapies, the hypothesis is that the AUCs following application within these datasets should be above 0.5 with the lowest confidence interval also above 0.5.

Assessment of 44-gene classifier model's ability to separate BRCA mutant from sporadic tumors

The classifier scores for predicting DDRD status were utilized to assess the ability of the model to separate BRCA mutant samples from sporadic samples. This analysis was performed to assess the relationships between the classifier model and BRCA mutation status. BRCA mutant tumors display a high degree of genomic instability due to a deficiency in DNA damage response by virtue of the loss of functional BRCA1/2. As such, the hypothesis is that the DDRD classifier models should be able to separate BRCA mutant samples from BRCA wildtype sporadic samples.

FIG. 3 shows that the 44-gene classifier models separate the BRCA mutants from the sporadic samples with an AUC of ~0.68, where the lower confidence interval is ~0.56 for both models (Table 3A); showing that the performance is significantly better than a random classifier. As such, this analysis confirms that the 44-gene DDRD classifier model is capable of identifying samples with high genomic instability due to an inability to repair DNA damage.

Application of classifier model to independent microarray clinical datasets

Independent breast microarray clinical datasets

(1) Assessment of the 44-gene DDRD classifier model's predictive power to DNA-damaging chemotherapy

To assess the ability of the 44-gene DDRD classifier model to predict response to DNA-damaging chemotherapeutics, it was applied to data combined from three publicly available datasets. In each study, breast cancer patients were treated with neoadjuvant 5-fluorouracil, anthracycline, and cyclophosphamide-based regimens, drugs that directly damage DNA. The first (Tabchy *et al.*, 2010) and second (Iwamoto *et al.*, 2011) datasets had response data for 87 and 50 ER-positive and ER-negative primary breast tumor samples respectively following neoadjuvant treatment with fluorouracil, doxorubicin and cyclophosphamide (FAC). The third dataset (Bonnefoi *et al.*, Lancet Oncol *8*, 1071-1078(2007)) had response data for 66 ER-negative primary breast tumor samples following neoadjuvant 5-fluorouracil, epirubicin and cyclophosphamide (FEC) treatment. Each study used pathological complete response (pCR) or residual disease (RD) as endpoints. As each dataset was relatively small, the data was combined to increase the power of the analysis.

The analysis revealed that that the 44-gene DDRD classifier model was significantly associated with response to anthracycline-based chemotherapy (relative risk (RR) = 4.13, CI = 1.94-9.87; AUC = 0.78, CI = 0.70-0.85, P = 0.001; Table 3B, FIG. 4). The negative predictive value (NPV) of the classifier was considerably higher than the positive predictive value (PPV) (0.90 versus 0.44, Table 3B), indicating that DDRD-negative tumors were unlikely to respond to DNA-damaging chemotherapy.

Stepwise logistic regression was used to determine the ability of the 44-gene DDRD classifier model to predict response in the combined datasets when adjusting for clinical variables (Table 4). The 44-gene DDRD classifier model was determined to be the most significant clinical variable in univariate analysis. Multivariate analysis confirmed that the 44-gene DDRD classifier model's predictive value was independent of stage, grade and notably ER status.

Negativity for estrogen, progesterone and HER2 receptors has been suggested as a biomarker of abnormal DDR and thus response to DNA-damaging and DNA repair targeted therapies (Foulkes et al., 2010). However, this approach excludes the 20% of BRCA1 and the 40% of BRCA2 mutant tumors that are reported to be ER-positive (Foulkes et al., 2004; Tung et al., 2010). In contrast, by virtue of the analysis approach we adopted, the 44-gene DDRD classifier detects the DDRD subgroup in both ER-positive and ER-negative tumors, as validated by the multivariate analysis of the 44-gene DDRD classifier's predictive value within the combined analysis of FEC and FAC datasets, demonstrating its independence from ER status.

Clinically, this is an important aspect of the translational application of the DDRD classifier as it suggests it can be applied to all breast cancer patients, irrespective of ER status, to determine their predicted responsiveness to DNA-damaging therapeutics.

(2) Assessment of 44-gene DDRD classifier model's predictive power to taxane-containing chemotherapy regimens

The ability of the 44-gene DDRD classifier model to predict response to chemotherapy regimens that contained non-DNA-damaging agents such as taxanes was assessed. Data was combined from 3 datasets with response data following neoadjuvant treatment with paclitaxel and FAC (T/FAC) for 321 primary breast cancer patients, where response was defined as pCR (Hess et al., 2006; Lee et al., 2010; Tabchy et al., 2010). Whilst the 44-gene DDRD classifier model was both associated with response (AUC = 0.61, CI = ~0.52-0.69, Table 3B, FIG. 5), this performance was significantly reduced compared to that within the FAC/FEC only treated samples. In addition, multivariate analysis indicated the DDRD classifier was not independent from other clinical parameters (P = 0.21) in its ability to predict response to T/FAC (Table 4). This suggests that the subgroup detected by the DDRD classifier is more sensitive to DNA-damaging only regimens rather than regimens also containing anti-microtubule agents.

Independent ovarian microarray clinical datasets

It was decided to explore the performance of the 44-gene DDRD classifier model in another disease area. As such, the performance of the classifier models was assessed within a set of 259 FFPE primary ovarian cancer samples with serous histology. These samples were from patients that received either adjuvant platinum treatment or adjuvant platinum and taxane treatment and were profiled on the Ovarian cancer DSA™. Response data was determined by RESIST and/or the serum marker CA125 levels. Applying the 44-gene DDRD classifier model to these samples proved to separate the responders from the non-responders significantly, with an AUC of ~0.68 and a lower confidence limit of approx 0.59 (FIG. 6). The 44-gene DDRD classifier model detects dysfunction of the Fanconi Anemia/BRCA pathway.

The Fanconi anemia/BRCA (FA/BRCA) pathway, which includes BRCA1 and BRCA2, plays an integral role in DNA repair and can be lost in breast cancer either due to mutation or epigenetic silencing (Kennedy and D'Andrea, 2006). It was therefore determined if the 44-gene DDRD classifier model could detect abrogation of members of this pathway in addition to BRCA1 and BRCA2. A public dataset was identified with microarray data generated from the

bone marrow of 21 FA patients carrying a range of mutations in the FA/BRCA pathway and 11 healthy controls with a functional FA/BRCA pathway (Vanderwerf, S. M., *et al.*, Blood *114*, 5290-5298 (2009). The 44-gene DDRD classifier model significantly distinguished between the FA/BRCA mutant and normal samples with an AUC of 0.90 (CI = 0.76-1.00, P<0.001, FIG. 7), demonstrating a strong correlation between the DDRD classifier and dysfunction of the FA/BRCA pathway through multiple mechanisms.

Summary of *in silico* validation of 44-gene DDRD classifier model

The *in silico* validation of the 44-gene DDRD classifier model has shown the following:

(a) The 44-gene DDRD classifier model is able to significantly separate BRCA mutant breast tumor samples from wildtype BRCA (sporadic) breast tumor samples. This implies that the DDRD classifier model is capable of detecting biology related to tumors with a high level of genomic instability, such as BRCA mutant tumors. These tumors typically respond better to DNA damaging chemotherapeutic regimens.

(b) The 44-gene DDRD classifier model is able to significantly separate defined responders (those that demonstrated pCR) from the non-responders (those that did not demonstrate pCR) in a combination of three independent breast datasets following neoadjuvant treatment with FAC and FEC (Bonnefoi et al., 2007; Iwamoto et al., 2011; Tabchy et al., 2010) and T/FAC (Hess et al., 2006; Lee et al., 2010; Tabchy et al., 2010). The 44-gene DDRD classifier model was found to be independent of other clinical factors and the most significant independent predictor of response in the FAC/FEC combined analysis. These studies were carried out using fresh frozen (FF) samples and using two different microarray platforms, namely the Affymetrix X3P microarray and the Affymetrix U133A microarray. These results validate the performance of the 44-gene DDRD classifier model within independent breast datasets utilizing a different sample material (FF instead of FFPE) and utilizing microarray data from two different microarray platforms.

(c) The 44-gene DDRD classifier model is able to significantly separate responders from non-responders within an independent Almac ovarian dataset following adjuvant treatment with platinum or platinum/taxane based therapy. This data was generated using FFPE samples profiled upon the Almac Ovarian DSA™.

(d) The 44-gene DDRD classifier model is able to significantly distinguish between FA/BRCA mutant and normal samples using bone marrow tissue samples, demonstrating

a strong correlation between the DDRD classifier and dysfunction of the FA/BRCA pathway through multiple mechanisms.

In summary, the DDRD classifier model has been independently validated and demonstrated robustness in performance across three different disease areas (breast, ovarian and FA), demonstrated ability to separate responders from non-responders to four different chemotherapeutic regimens (FAC, FEC, T/FAC and platinum/taxane) in two different sample types (FFPE and FF) utilizing data from four different microarray platforms (Almac Breast DSA™ and Almac Ovarian DSA™, Affymetrix X3P microarray and Affymetrix U133A microarray). It has been demonstrated that the DDRD is an independent predictor of response to DNA-damage therapeutic agents and can predict mutations in the FA/BRCA pathways. This plasticity and repeatability of performance implies that the biology identified within the DDRD subgroup identified via the 44-gene classifier model is significantly and robustly related to predicting response to DNA damage causing agents and as such supports the claim of this invention which is to identify a subtype that can be used to predict response to, and select patients for, standard breast and ovarian cancer therapeutic drug classes, including drugs that damage DNA directly, damage DNA indirectly or inhibit normal DNA damage signaling and/or repair processes.

Table 3:
Performance metrics and independence assessment of the 44-gene DDRD classifier model in breast datasets

Numbers in brackets denote the 95% confidence limits from +/- 2SD from cross-validation (A) or bootstrapping with 1000 repeats (B). AUC=Area Under the Receiver Operating Characteristics Curve; ACC=Accuracy; SENS=Sensitivity; SPEC=Specificity; PPV=Positive Predictive value; NPV=Negative Predictive Value; RR=Relative Risk, pCR=pathological complete response, RD=residual disease.

(A) Prediction of BRCA mutation status using the 44-gene DDRD classifier model										
Data set	**No.**	**Treat-ment**	**Clinical Outcome**	**AUC (CI)**	**ACC (CI)**	**SENS (CI)**	**SPEC (CI)**	**PPV (CI)**	**NPV (CI)**	**RR (CI)**
Train-ing	107	N/A	BRCA mutant V wildtype	0.68 (0.56-0.78)	0.70 (0.57-0.76)	0.58 (0.48-0.65)	0.79 (0.64-0.86)	0.78 (0.63-0.85)	0.60 (0.49-0.65)	1.93 (1.23-2.55)
(B) Prediction of pCR using 44-gene DDRD classifier model										
Data set	**No.**	**Treat-ment**	**Clinical Outcome**	**AUC (CI)**	**ACC (CI)**	**SENS (CI)**	**SPEC (CI)**	**PPV (CI)**	**NPV (CI)**	**RR (CI)**
FAC1 FAC2 and FEC	203	FEC and FAC	pCR V RD	0.78 (0.70-0.85)	0.76 (0.64-0.83)	0.82 (0.69-0.92)	0.58 (0.52-0.62)	0.44 (0.36-0.48)	0.90 (0.81-0.95)	4.13 (1.94-9.87)
T/ FAC	321	T/FAC	pCR V RD	0.61 (0.53-0.69)	0.53 (0.43-0.62)	0.49 (0.38-0.60)	0.67 (0.64-0.70)	0.29 (0.22-0.35)	0.83 (0.80-0.87)	1.72 (1.05-2.65

Table 4
Univariate and Multivariate Analysis of the 44-gene DDRD classifier model

Comparison of the 44-gene DDRD classifier model to standard pathological parameters in independent validation sets. The predictive value of the DDRD classifier model as well as significant clinical parameters were evaluated in a univariate and multivariate analysis using logistic regression models with *p*-values coming from a log-likelihood test.

Univariate and Multivariate Analysis of the 44-gene DDRD classifier model		
FAC1, FAC2 and FEC	**Univariate**	**Multivariate**
Variable	**P value**	**P value**
DDRD classifier	0.0000	0.0014
ER	0.0004	0.0249
Stage	0.0459	0.0492
Grade	0.0100	0.0468
T/FAC	**Univariate**	**Multivariate**
Variable	**P value**	**P value**
DDRD classifier	0.0129	0.2100
ER	0.0000	0.0000
Stage	0.3626	0.0359
Grade	0.0000	0.0115

Example 3

In vitro validation of the 44-gene DDRD classifier model

In order to assess the biology underlying the genes contained within the 44-gene classifier model, a number of studies were carried out *in vitro* using a panel of breast cell-lines.

Methods

Maintenance of cell-lines

The HCC1937 parental, HCC1937-EV and HCC1937-BR cell-lines were kindly donated by Professor Paul Harkin from Queen's University College Belfast (QUB). The cell-lines were routinely maintained in RPMI-1640 medium supplemented with 50 U penicillin/ml, 50μg streptomycin/ml, 2mM glutamine, 1mM Sodium Pyruvate and 20% (v/v) fetal bovine serum (FBS). The HCC1937-EV and HCC937-BR cell-lines also required 0.2ml/mg geneticin. Cell-lines were cultured at 37°C with a humidified atmosphere of 5% CO_2.

Clonogenic assays – determination of PARP-1 inhibitor sensitivity

For measurement of sensitivity to PARP-1 inhibitor (KU0058948), exponentially growing cells were seeded into 6-well plates. Twenty-four hours following seeding the cells were exposed to medium containing increasing doses of drug. Cell medium was replenished every 4-5 days. After 12-14 days the cells were fixed in methanol, stained with crystal violet and counted. The percentage survival of control for a given dose was calculated as the plating efficiencies for that dose divided by the plating efficiencies of vehicle-treated cells. Survival curves and half maximal inhibitory concentration (IC_{50}) values were calculated using GraphPad Prism.

Cell viability assay – determination of cisplatin sensitivity

For measurement of sensitivity to cisplatin, exponentially growing cells were seeded into 96-well plates. 24 hours following seeding the cells were exposed to medium containing increasing doses of cisplatin. Cells were incubated in the presence of drug for 96 hours following which time the viability of the cells was assessed using the Promega CellTitre-Glo

luminescent cell viability assay. The sensitivity of the cells was calculated as the percentage of vehicle (DMSO) control. Survival curves and half maximal inhibitory concentration (IC_{50}) values were calculated using GraphPad Prism.

Results

The DDRD subgroup can be identified within breast cancer cell-line models

A preclinical model system was used to confirm that the 44-gene DDRD classifier was a measure of abnormal DDR. The HCC1937 breast cancer cell-line is DDRD due to a BRCA1 mutation (Tomlinson et al., 1998). The 44-gene classifier was applied to HCC1937 empty vector control cells (HCC1937-EV) and HCC1937 cells in which BRCA1 functionality was corrected (HCC1937-BR) (FIG. 7A). The DDRD 44-gene classifier score was found to be higher within HCC1937-EV relative to HCC1937-BR cells, with average scores of 0.5111 and 0.1516 respectively (FIG. 7B). Consistent with the DDRD 44-gene classifier scores, the HCC1937 BRCA1 mutant cell-line was more sensitive to the PARP-1 inhibitor KU0058948 (FIG. 7C) and cisplatin (FIG. 7D) relative to the BRCA1 corrected cell-line. These preclinical data suggest that the DDRD 44-gene classifier measures immune signalling in DDRD-positive tumor cells and correlates with response to both a DNA-damaging agent (cisplatin) and a DNA repair targeted agent (PARP-1 inhibitor).

The DDRD 44-gene classifier detects dysfunction of the Fanconi Anemia/BRCA pathway

The Fanconi anemia/BRCA (FA/BRCA) pathway, which includes BRCA1 and BRCA2, plays an integral role in DNA repair and can be lost in breast cancer either due to mutation or epigenetic silencing (Kennedy, R. D., and D'Andrea, A. D., J Clin Oncol *24*, 3799-3808 (2006)). It was determined if the DDRD 44-gene classifier could detect abrogation of members of this pathway in addition to BRCA1 and BRCA2. A public dataset was identified with microarray data generated from the bone marrow of 21 FA patients carrying a range of mutations in the FA/BRCA pathway and 11 healthy controls with a functional FA/BRCA pathway (Vanderwerf et al., 2009). The DDRD 44-gene classifier significantly distinguished between the FA/BRCA mutant and normal samples with an AUC of 0.90 (CI = 0.76-1.00, $P<0.001$), demonstrating a strong correlation between the DDRD classifier and dysfunction of the FA/BRCA pathway through multiple mechanisms.

Conclusion

The DDRD 44-gene classifier score was significantly higher in the BRCA1 mutant, and thus DDRD, HCC1937 breast cancer cell-line relative to an isogenic BRCA1 corrected cell-line. As the 44-gene classifier score correlates with DDR dysfunction within these cells, it demonstrates that the immune signalling detected by the DDRD classifier is intrinsic to the cell and not a function of lymphocytic infiltrate. BRCA1 and BRCA2 represent part of the FA/BRCA DDR network, which contains a number of other proteins that have been reported to be mutant or under-expressed in approximately 33% of breast cancer (Kennedy, R. D., and D'Andrea, A. D., J Clin Oncol *24*, 3799-3808 (2006).As described previously, the DDRD 44-gene classifier significantly separated bone marrow samples from patients with FA mutations from normal controls. This suggests that the DDRD classifier is capable of detecting any abnormality within the pathway rather than specifically BRCA1 or BRCA2 dysfunction. It is possible that the DDRD 44-gene classifier may identify tumors with DDR-deficiency due to other mechanisms such as PTEN loss, cell-cycle checkpoint dysfunction or increased reactive oxygen species due to metabolic disturbance. Due to constitutive DNA-damage, these tumors are likely to respond to DNA repair targeted therapies such as PARP-1 or CHK1/2 inhibitors.

SEQUENCE LISTING

Hs127799.0C7n9_at (SEQ ID NO:1)

GGGACCAAGGTGGAGATCAAACGTAAGTGCACTTTCCTAATGCTTTTTCTTATAAGG
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BRMX.5143C1n2_at (SEQ ID NO:2)

TTTATTGGTCTTCAGATGTGGCTGCAAACACTTGAGACTGAACTAAGCTTAAAACAC
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BRSA.1606C1n4_at (SEQ ID NO:3)

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BRIH.1231C2n2_at (SEQ ID NO:4)

TCCTTATGGGGCCCGGTATGTGGGCTCCATGGTGGCTGATGTTCATCGCACTCTGGT
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GCCACCACTGGGAAGGAGGCCGTGTTAGACGTCATTCCCACAGACATTCACCAGAG
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CTGGACCTTTTGTCTCACACAGCAGTACCCTGACCTGCTGTGCACCTTACATTCCTA
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BRAD.30779_s_at (SEQ ID NO:5)
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TACAAAAATTAGCCGGGCGTGGTGGCCCACGCCTGTAATCCCAGCTACTCGGGAGG
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BRSA.396C1n2_at (SEQ ID NO:6)
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BRMX.2948C3n7_at (SEQ ID NO:7)
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Hs539969.0C4n3_at (SEQ ID NO:8)
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Hs396783.3C1n4_at (SEQ ID NO:9)
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BRMX.13670C1n2_at (SEQ ID NO:10)
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BRMX.941C2n2_at (SEQ ID NO:12)
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CGAGGGCAGGGAGGAAGTGGCAAGAATAACATTTGTGAAGATGTCCAGGTGAGAA
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BRMX.4154C1n3_s_at (SEQ ID NO:13)

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ACCAGTCGGGTTGCCAGCAAAGCAGTGGATGCAAGACTTGCCCTCCAGGAGCTTAC
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BRAD.39498_at (SEQ ID NO:14)
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BRAD.34868_s_at (SEQ ID NO:15)
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TCCCAGGCTCTCAACAGGGGAGAGTGTGGTGTTTCCTGCAGGCCAGGCCAGCTGCC
TCCGCGTGATCAAAGCCACACTCTGGGCTCCAGAGTGGGGATGACATGCACTCAGC
TCTTGGCTCCACTGGGATGGGAGGAGAGGACAAGGGAAATGTCAGGGGCGGGGAG
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TGAAAACCTCTCCTCATGTTCTGCTTTCGATTCGTTAAGAGAGCAACATTTTACCCA
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Hs505575.0C1n42_at (SEQ ID NO:16)
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BREM.1442_at (SEQ ID NO:17)
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BRRS.18792_s_at (SEQ ID NO:20)
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GCATGGCCTTCTGAAGCTGCTGGCCGTACGTCTGGAGCATGAAGAACTGGATGATC
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Hs632609.0C1n37_at (SEQ ID NO:21)
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CCAGGAGGATTGCTTGAGTCTAGGAGTTCAAGACCGGTCTGGGCAACATGGTGAAA
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Hs449575.0C1n22_at (SEQ ID NO:22)
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BRAD.18827_s_at (SEQ ID NO:23)
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BREM.2466_s_at (SEQ ID NO:24)
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BRAD.2605_at (SEQ ID NO:25)
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BRAD.33618_at (SEQ ID NO:26)
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CCCCACTGATAGGAAGGTCCTAGGCTGCCGTGGGCCCTGGGGATGTGTGCTTCATTG
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BRAD.36579_s_at (SEQ ID NO:27)
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BRAD1_5440961_s_at (SEQ ID NO:28)
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GTGGTTTCATTCCAATTTCCTGTATATCGGAATCATCACCATCTGTGTATGTGTGATT
GAGGTGTTGGGGATGTCCTTTGCACTGACCCTGAACTGCCAGATTGACAAAACCAG
CCAGACCATAGGGCTATGATCTGCAGTAGTCCTGTGGTGAAGAGACTTGTTTCATCT
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BRAD1_66786229_s_at (SEQ ID NO:29)
GCCTGGGACGCTGCTGCTGTTCAGGAAACGATGGCAGAACGAGAAGCTCGGGTTGG
ATGCCGGGGATGAATATGAAGATGAAAACCTTTATGAAGGCCTGAACCTGGACGAC
TGCTCCATGTATGAGGACATCTCCCGGGGCCTCCAGGGCACCTACCAGGATGTGGG
CAGCCTCAACATAGGAGATGTCCAGCTGGAGAAGCCGTGACACCCCTACTCCTGCC

AGGCTGCCCCCGCCTGCTGTGCACCCAGCTCCAGTGTCTCAGCTCACTTCCCTGGGA
CATTCTCCTTTCAGCCCTTCTGGGGGCTTCCTTAGTCATATTCCCCCAGTGGGGGGTG
GGAGGGTAACCTCACTCTTCTCCAGGCCAGGCCTCCTTGGACTCCCCTGGGGGTGTC
CCACTCTTCTTCCCTCTAAACTGCCCCACCTCCTAACCTAATCCCCCCGCCCCGCTGC
CTTTCCCAGGCTCCCCTCACCCCAGCGGGTAATGAGCCCTTAATCGCTGCCTCTAGG
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CACTTAGTGATAATAAATTCTTCCCAACTGCA

BREM.2104_at (SEQ ID NO:30)
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CCATCCTGTGCACCCTGGTCTTCCTGATCCGGTACATGTTCCGCCACAAGGGCACCT
ACCATACCAACGAAGCAAAGGGGGCGGAGTCGGCAGAGAGCGCGGACGCCGCCAT
CATGAACAACGACCCCAACTTCACAGAGACCATTGATGAAAGCAAAAAGGAATGG
CTCATTTGAGGGGTGGCTACTTGGCTATGGGATAGGGAGGAGGGAATTACTAGGGA
GGAGAGAAAGGGACAAAAGCACCCTGCTTCATACTCTTGAGCACATCCTTAAAATA
TCAGCACAAGTTGGGGGAGGCAGGCAATGGAATATAATGGAATATTCTTGAGACTG
ATCACAAAAAAAAAAAAACCTTTTTAATATTTCTTTATAGCTGAGTTTTCCCTTCTGTA
TCAAAACAAAATAATACAAAAAATGCTTTTAGAGTTTAAGCAATGGTTGAAATTTG
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BRAG_AK097020.1_at (SEQ ID NO:31)
ATGTCCAAAAAGATACAGAAGAACTAAAGAGCTGTGGTATACAAGACATATTTGTT
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CAGCAATGTGGAATTATCACCCATCATCATCCAATCGCAGATGGAGGGACTCCTGA
CATAGCCAGCTGCTGTGAAATAATGGAAGAGCTTACAACCTGCCTTAAAAATTACC
GAAAAACCTTAATACACTGCTATGGAGGACTTGGGAGATCTTGTCTTGTAGCTGCTT
GTCTCCTACTATACCTGTCTGACACAATATCACCAGAGCAAGCCATAGACAGCCTGC
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GAGTTTCGGGACAAATTAGCTGCACATCTATCATCAAGAGATTCACAATCAAGATC
TGTATCAAGATAAAGGAATTCAAATAGCATATATATGACCATGTCTGAAATGTCAG
TTCTCTAGCATAATTTGTATTGAAATGAAACCACCAGTGTTATCAACTTGAATGTAA
ATGTACATGTGCAGATATTCCTAAAGTTTTATTGAC

BRAD.20415_at (SEQ ID NO:32)
GGTTTCCTTCCCAGGACAGCTGCAGGGTAGAGATCATTTTAAGTGCTTGTGGAGTTG
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GATTAGCTCTGCAGAGTGTCTTGGTTGAGAGAATAACCTCATAGTACCAACATGAC
ATGTGACTTGGAAAGAGACTAGAGGCCACACTTGATAAATCATGGGGCACAGATAT
GTTCCCACCCAACAAATGTGATAAGTGATTGTGCAGCCAGAGCCAGCCTTCCTTCAA
TCAAGGTTTCCAGGCAGAGCAAATACCCTAGAGATTCTCTGTGATATAGGAAATTT
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TCTCCTGGAAATAGGTCTGTCCACTCCTGGTCATTGGTGGATGTTAAACCCATATTC
CTTTCAACTGCTGCCTGCTAGGGAAAACTGCTCCTCATTATCATCACTATTATTGCTC
ACCACTGTATCCCCTCTACTTGGCAAGTGGTTGTCAAGTTCTAGTTGTTCAATAAAT
GTGTTAATAATGCTTAAAAAAAAAAAAAAAAAA

BRAD.29668_at (SEQ ID NO:33)
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CTAGGAAAATGCGCATCTTAATGACTCTTTGTAAAGAGAGGCATTTCTTACAACTGT
GATGTTTGCTTACATAAAAGTTACCTCATAAGTTAATTCTAACTTTTATTCTTGAATT
TTATTTCATTTCAATAGCTTGTTTCATTTGCACGCCTTTGTATTTTGATTGACCTGTA

GAATGGATGTTAGGAAACTCAAAATTGAACACAGTGAAACAAATGGTATTTGAAGA
AATGTAATATCTTTTATATTCTATTTATGATATCCATAATCAAATGAGATTATTTTAC
CACATAAATGTTTTAAATATCAGATTTTTAGTTTGCAGTTTTAGGAAAATGCTTTAG
ATAGAAAAGGTTCTTATGCATTGAATTTGGAGTACTACCAACAATGAATGAATTTAT
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TCAGGTCAGTTTGTTTTGAAACTGAAATTGGAAATAAATCTGGAAATGTTTTGTTGC
ACTAAAATAATAAAATGAATTGTACTG

BRAD.30228_at (SEQ ID NO:34)
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AGCAAGGCAGCCGTGCTGTTCTAGTTCCTCTCCATCCGCCACCTCCCCTCCCGCTGC
CCCAGAAGTTTCTATCATTCCATGGAGAAAGCTGTGTTCCAATGAATCCTACCTCTT
GCCCAGTCCCAGGCAGAGTAAGCAGGGCCCACCTAGGGACCAAGAAAGAGTAGGA
AGAAGGGGACGAGCCGGGAGCAAAACCACCTCAGACACCCGGGCCTTCTCAGCCTT
CTCCCCGCGGCCAGCTGGGTCTCCGGGGACCCTGGGCCCTGGGCCGCCCATTCCTGG
CCCTCCCGCTGCATCTCAGACCTGACACCCAACGGGGGGATGTGGTGGCCTGTGCC
CACCTTCTCTCCCTCCTCCCGACCCGCCCCCTCGCCCCCACCCCTGTGTGTTTCGCCA
GTTAAGCACCTGTGACTCCAGTACCTACTACTGGTTTTGGGTTGGTTGTTCTGTCTTT
TTTTTAATTAAATAAAAACATTTTTAAAATGTT

BRAD.34830_at (SEQ ID NO:35)
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TGCCACGCCGCCCTAAAAGCACACTCATCCCCTCACTTGCCGCGTCGCCCTCCCAGG
CTCTCAACAGGGGAGAGTGTGGTGTTTCCTGCAGGCCAGGCCAGCTGCCTCCGCGT
GATCAAAGCCACACTCTGGGCTCCAGAGTGGGGATGACATGCACTCAGCTCTTGGC
TCCACTGGGATGGGAGGAGAGGACAAGGGAAATGTCAGGGGCGGGGAGGGTGACA
GTGGCCGCCCAAGGCCCACGAGCTTGTTCTTTGTTCTTTGTCACAGGGACTGAAAAC
CTCTCCTCATGTTCTGCTTTCGATTCGTTAAGAGAGCAACATTTTACCCACACACAG
ATAAAGTTTTCCCTTGAGGAAACAACAGCTTTAAAAGAAAAAGAAAAAAAAAGTCT
TTGGTAAATGGCAAAAAAAAAAAAAAAAAAAAAAAA

BRAD.37011_s_at (SEQ ID NO:36)
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CACGCACACACACACACACACACTCACTGCGGAGAACCTTGTGCCTGGCTCAGAGC
CAGTCTTTTTGGTGAGGGTAACCCCAAACCTCCAAAACTCCTGCCCCTGTTCTCTTC
CACTCTCCTTGCTACCCAGAAATCATCTAAATACCTGCCCTGACATGCACACCTCCC
CTGCCCCACCAGCCCACTGGCCATCTCCACCCGGAGCTGCTGTGTCCTCTGGATCTG
CTCGTCATTTTCCTTCCCTTCTCCATCTCTCTGGCCCTCTACCCCTGATCTGACATCCC
CACTCACGAATATTATGCCCAGTTTCTGCCTCTGAGGGAAAGCCCAGAAAAGGACA
GAAACGAAGTAGAAAGGGGCCCAGTCCTGGCCTGGCTTCTCCTTTGGAAGTGAGGC
ATTGCACGGGGAGACGTACGTATCAGCGGCCCCTTGACTCTGGGGACTCCGGGTTT
GAGATGGACACACTGGTGTGGATTAACCTGCCAGGGAGACAGAGCTCACAATAAA
AATGGCTCAGATGCCACTTCAAAGAAAAAAAAAA

BRAD.37762_at (SEQ ID NO:37)
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GACATGGGCAGAGCAATGGTGGCCAGGCTCGGGCTGGGGCTGCTGCTGCTGGCACT
GCTCCTACCCACGCAGATTTATTCCAGTGAAACAACAACTGGAACTTCAAGTAACTC
CTCCCAGAGTACTTCCAACTCTGGGTTGGCCCCAAATCCAACTAATGCCACCACCAA

GGTGGCTGGTGGTGCCCTGCAGTCAACAGCCAGTCTCTTCGTGGTCTCACTCTCTCT
TCTGCATCTCTACTCTTAAGAGACTCAGGCCAAGAAACGTCTTCTAAATTTCCCCAT
CTTCTAAACCCAATCCAAATGGCGTCTGGAAGTCCAATGTGGCAAGGAAAAACAGG
TCTTCATCGAATCTACTAATTCCA

BRAD.40217_at (SEQ ID NO:38)
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TGGGAGATCCCAGAGTTTCCTTTCCCTCTTGGCCATATTCTGGTGTCAATGACAAGG
AGTACCTTGGCTTTGNCACATGTCAAGGCTGAAGAAACAGTGTCTCCAACAGAGCT
CCTTGTGTTATCTGTTTGTACATGTGCATTTGTACAGTAATTGGTGTGACAGTGTTCT
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TATTCCTAAGTCCTAACTCCTCCTTGTGGTGTTGGATTTGTAAGGCACTTTATCCCTT
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GATTGTCACTTTTTGTACCTGCATTAATTTAATAAAATATTCTTATTTATTTTGTTAN
NTNGTANANNANNATGTCCATTTTCTTGTTTATTTTGTGTTTAATAAAATGTTCAGTT
TAACATCCCANNNGAGAAAGTTAAAAAA

BRAD1_4307876_at (SEQ ID NO:39)
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CTTCCTCCTACTCACCATCAGCCTCCTGGTTATGGTACAGATACAAACTGGACTCTC
AGGACAAAACGACACCAGCCAAACCAGCAGCCCCTCAGCATCCAGCAACATAAGC
GGAGGCATTTTCCTTTTCTTCGTGGCCAATGCCATAATCCACCTCTTCTGCTTCAGTT
GAGGTGACACGTCTCAGCCTTAGCCCTGTGCCCCCTGAAACAGCTGCCACCATCACT
CGCAAGAGAATCCCCTCCATCTTTGGGAGGGGTTGATGCCAGACATCACCAGGTTG
TAGAAGTTGACAGGCAGTGCCATGGGGGCAACAGCCAAAATAGGGGGGTAATGAT
GTAGGGGCCAAGCAGTGCCCAGCTGGGGGTCAATAAAGTTACCCTTGTACTTGCAA
AAAAAAAAAAAAAAAAA

BREM.2505_at (SEQ ID NO:40)
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TTGCAGTTACACTAAAAGGTGACCAATCATGGTCACCAAATCAGCTGCTACTACTCC
TGTAGGAAGGTTAATGTTCATCATCCTAAGCTATTCAGTAATAACTCTACCCTGGCA
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AAATATTTCCCTCACCTTTCCCATCTTCCAAGGGTATAAGGAATCTTTCTGCTTTGGG
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TTTAAAGAATGCTCTTTACTTCATGGACTTCCACTGCCATCCTCCCAAGGGGCCCAA
ATTCTTTCAGTGGCTACCTACATACAATTCCAAACACATACAGGAAGGTAGAAATA
TCTGAAAATGTATGTGTAAGTATTCTTATTT

Hs149363.0CB4n5_s_at (SEQ ID NO:41)
GGGAAATCAGTGAATGAAGCCTCCTATGATGGCAAATACAGCTCCTATTGATAGGA
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GAGTTTGCTAATACAATGCCAGTCAGGCCACCTACGGTGAAAAGAAAGATGAATCC
TAGGGCTCAGAGCACTGCAGCAGATCATTTCATATTGCTTCCGTGGAGTGTGGCGA
GTCAGCTAAATGGCAGGGGCAGCAAGATGGTGTTGCAGACCCAGGTCTTCATTTCT
CTGTTGCTCTGGATCTCTGGTGCCTACGGGGACATCGTGATGACCCAGTCTCCAGAC
TCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAAGTGCAAGTCCAGCCAGAG
TATTTTATATAGGTCCAACAACAAGAACTACTTAGCTTGGTACCAGCAGAAAGCAG

GACAGCCTCCTAAATTGTTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTG
ACCGATT

Hs172587.9C1n9_at (SEQ ID NO:42)
AACGAAAGTCTAGCCTTTCGTACCCGTATATATAAAGACACCCCTGTTCTGATTGGA
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CATCTCCTGCATGTAGACCAAATATTAAAACTTTCCTCCGTCCATCTTTAACTGCTG
GTGTTTTCAACCCTTTCCCCTCTGTGCCATGTTTCTAGCTTTTATTTAAAACGTACTTT
GGTTTTCCTTGGCAAAATTGTGTCTAGCTACTAGGATGACGTGTCTTAATTTTTTTTT
AAATGTTGGCGCTGAAACTGGCTTTGATCAACGTTTTAAAAAGACGCGCGCTAGTT
GTGATTGGCCAAGTGATTTCTTCTTACCCTCTTAAGTTTAGAAAGGTTAATTTCATAT
CTTGATTTGTCTATTTAAACTTGGAGATATTTTCAATAATTTGTTCCAAATGCACCAT
GACTATTAACTCATAAGTAACAATATGAAACCTGATGTTAAGCTACATGAACACAT
TTAATTTCACCACAATATGACATCCTCATATGAAAGCACTCTCTTATCTTTTACAAGT
TCAACTGGTATTTGTGTAATCTGCTGT

Hs271955.16C1n9_at (SEQ ID NO:43)
TGCTACCATGCCTGACTAGTTTTTGTATTTTTAGTAGAGACAGGGTTTGACCATATT
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TGCTAGGGTTACNAGGTGTGAACCACCATGCCTAACTATCGTTGCTACTTTCTATTG
GAAGAGAAGGCAGCCCTGATTTAGTCTGTTTACAGTCTGCATTATGTGGAGAATAG
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CTTTGTCTCTTGACAACTGTTAACTGAGAACAGGGCCCTTGCTCCTCTAGGTGTGCA
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GCTGCTTGAATTTTCATCATNANCCTCCACNCCTTNCACCTNCNNGNNAAAAAAAA
AGCGTGCAGGAAGTAGCATTTCAGATCCTTCTCCACCACCTCTGCTTCCCTTCTCCCT
TCTTTTCCTCCTTGCAGCATTCCCTTTAGTACNAGGGAGGGATGGTGGTTGAAAATG
GGGGGAATGATGTTGCTCAGAAAAAAAAAAAA

Hs368433.18C1n6_at (SEQ ID NO:44)
ATAATGCTGGAAACAGAAGCACCAAACTGATTGTGCAATTACTCCTTTTGTAGAAG
AGGCCAAAATCCTCCTCCTCCTTCCTTTCTCCTATATTCACTCCTCCAGGATCATAAA
GCCTCCCTCTTGTTTATCTGTGTCTGTCTGTCTGATTGGTTAGATTTGGCTNCCCTTC
CAAGCTAATGGTGTCAGGTGGAGAACAGAGCAACCTTCCCTCGGAAGGAGACAATT
CGAGGTGCTGGTACATTTCCCTTGTTTTCTATGTTCTTCTTTCTAGTGGGTCTCATGT
AGAGATAGAGATATTTTTTTGTTTTAGAGATTCCAAAGTATATATTTTTAGTGTAAG
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TCTCGTGGTCTGTGTCTGTGAACCAGGGCAGGTAATTGTGACACTGCATCTCATAGA
ACTCTGCCTGCCCAGATTTTTGTGTGCTCACCTCAATGGGTGAAAAATAAAGTCTGT
GTAAACTGTTAAAAAAAAAAAAAAAAAAA

Hs435736.0C1n27_s_at (SEQ ID NO:45)
TCCTCAGACCCAGTAATTCCACCCCTAGGAATCCAGCTTACACACACAAGAAAGAA
AAGATAAATGTACAAGGTTAGTCACTGCACAGTGAGACAGCAAAAGATTAGAAAG
AACCCAAGTGATTATTGATCTGGGTTTTATTCCTTTATAGCCCAACCATATGATGGA
ATACTATAATGTTGTAAAAATGGGTTAAGAGTTCTTTATGAATTGGTGTGGAAACAT
CGCCAAGATATGAAAGCCAAATGCAGAAAAATATATGTGGTATGCTATTATCTATG
TGAAAAAGACATTACTATTCTCTGGAAGGATAAACACAAATTTGAGAATGGTGGAT
ATCTGGGGTGAGAGGTATCCTTTTCACTGTTCTTTAAAAGTTTTGNNATTTTGGTGTT
TGCCTATTCAAAAAAATGGTTAAAATCAGTTGCCACCAATTAAAAATTAGGAGAAT
GCATATAAAGAANNNAANTTCCTGTTAAAAAAAAAAAAAAAAAAAA

Hs493096.15C1n6_at (SEQ ID NO:46)
GCCCATAGTCCCATCTTTTTACAGGCATTTTTTACACCTGGAGCAGCCAGAGGACGC
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TCTTTAACATGGTTCTTCTGATTCAGTCCGGCCAATTAAATCTAAATCCACCCCTGA
AAGCCATCTGGTGTGGATAACAAGCCCACAAATGAGCAGTCAGCTTTTTGTGCCCTT
TAGGGCCTGGGACAACCACGGGATCTAAAAGGGGCTGGAACTAGAGGTCTTGAGCT
CCTGTTCCTAAAATCATCTTCATCCTATATCTGCAGCCTTCTCCTGCCACGGCATGCA
CCCACACATGCGAGCCTCCCGGGTACTGTCATCCTGAATTCTGAGACCATCCAGCAC
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CAGGACAAGGGACATGGAAGGCTGCAATTTAAGAGTCTAAAAGGTTTTAGAATCCT
GAAGGAGGTTTAACAAGCTGAATTGAAGAATAATACCTTTCTCAACTGGAGAGAAT
TTACATGATTGCATTATTGTTAAAATTAACA

Hs493096.2C1n15_s_at (SEQ ID NO:47)
ATCATTTAGTTGAATCATTATAAGTCTAGGACTGTCTGTAGATGTAAATTTGTTAAG
AATTAGGACTCAAGAGTAGAATTCCTTTAATCCACATAGACTTACAATGGTGCTGTG
CACATGGAGCCCCTAAATCATTGCTGACTGAGTAGATTTCCCAGGGTAAGCCCAAG
AAGTTACTCCTAGAAGGGGCTGGTAGGGGAAAGAGCCAACATCCCACATGCCTGCC
CACTTTGGGTCTGGTCCCAAGAAACAAACTCCAGTGGCCTCGAAAATTTAATATTGC
TGTCAGAAGGGCCTCCCCTTCAAAGGAACAGGTCCTGATAGCTCTTGTTATATGCAA
AGTGGAAAGGTAACGTGACTGTTCTCTGCATTTCCTGCCTTTCAATTGAGTGAAGAC
AGACAGATGATTTATTGGGCATTTCCTAGCCTCCCCTTCACCATAGGAAACCAGACT
GAAAAAAAGGTGCAAATTTTAAAAAGATGTGTGAGTATCTTGAGGGGGCTGGGGG
AGAATTCCTGTGTACCACTAAAGCAAAAAAAGAAAACTCTCTAACAGCAGGACCTC
TGATCTGGAGGCATATTGACCATAAATTTACGCCA

Hs592929.0CB2n8_at (SEQ ID NO:48)
TTTTTCTGAGCAACATCATTCCCCCCATTTTCAACCACCATCCCTCCCTGGTACTAAA
GGGAATGCTGCAAGGAGGAAAAGAAGGGAGAAGGGAAGCAGAGGTGGTGGAGAA
GGATCTGAAATGCTACTTCCTGCACGCTTTTTTTCTTCTTGGAGGTGGAAGGAGTGG
AGGATGATGATGAAAATTCAAGCAGCATGTACTAGACGGCAGAGCAGCATGAGCT
ACATCCACACTGTGCAAAGTCCTTAATGTGCACACCTAGAGGAGCAAGGGCCCTGT
TCTCAGTTAACAGTTGTCAAGAGACAAAGACAGGTTGTCCTGCTGGGTTAACTGGC
AAGGAAAGTTTTAGGGACTATGATGGCTCTCTATTCTCCACATAATGCAGACTGTAA
ACAGACTAAATCAGGGCTGCCTTCTCTTCCAATAGAAAGTAGCAACGATAGTTAGG
CATGGTGGTTCACACCTTGTAACCCTAGCACTTCGTGGGCAG

Hs79953.0C1n23_at (SEQ ID NO:49)
ATCAGAACAATTTCATGTTATACAAATAACATCAGAAAAATATCTTAAATTATATGG
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TACTAGGCATTATAGTAGTGCTAGGCACTATAGTAATGCTGGGGTATAAACAAGAA
TAAAACAAAATAAGTTCCTTATTTCAGGTAACTTACAGTATAGGTCAGTGGTTCTTA
GCTTGCTTTTTAATTATGAATTCCTTTGAAAGTCTAGTAAAATAATCCAACACCATT
ATTCCCCATTGCACATACCCCCAGATGTTTTAGACATATTTTCAATTGCTCCATGGA
CCTTAAGAAAACTTGGTTGGTGTGCAGTTTGGTGTATTATGGGTAAGACTGGACCTG
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CAGACCACTTAAACCTCTCTTTAGTCTTCTCTGTAGAATGATGATAATACCATCTAA
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AAAAAGCAACGTGTTTATAATGGTAAAAAA

BRMX.2377C1n3_at (SEQ ID NO:50)
TGGGAATCATGAACTCCTTCGTCAACGACATCTTCGAACGCATCGCGGGTGAGGCTT
CCCGCCTGGCGCATTACAACAAGCGCTCGACCATCACCTCCAGGGAGATCCAGACG
GCCGTGCGCCTGCTGCTGCCCGGGGAGTTGGCCAAGCACGCCGTGTCCGAGGGCAC
CAAGGCCGTCACCAAGTACACCAGCGCTAAGTAAACTTGCCAAGGAGGGACTTTCT
CTGGAATTTCCTGATATGACCAAGAAAGCTTCTTATCAAAAGAAGCACAATTGCCTT
CGGTTACCTCATTATCTACTGCAGAAAAGAAGACGAGAATGCAACCATACCTAGAT
GGACTTTTCCACAAGCTAAAGCTGGCCTCTTGATCTCATTCAGATTCCAAAGAGAAT
CATTTACAAGTTAATTTCTGTCTCCTTGGTCCATTCCTTCTCTCTAATAATCATTTACT
GTTCCTCAAAGAATTGTCTACATTACCCATCTCCTCTTTTGCCTCTGAGAAAGAGTA
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GTACCTTAATAAATTTGTATGCCTTTTCTCTT

BRAD.33405_at (SEQ ID NO:51)
GAAAGTGATAATACAGAAAGGTGGGGCTGGTGTAGGGNTNAAGNCAGGATGCTTT
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NAAGANCGTNATGAGATCAATGCNGATGAGNCACTTAGAAGNAGCAATTAGTTAG
GCAAAGGGAAGTGAATGTGNAGGAGGAACAAGCATTCCAGGCAAGAAGAACACCC
TATCGAAAAGCCTGGAAGCAAAACATTAGTGAGGCTACCTTTCATAAATTGCTTTCT
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AGGACTTGTGAAATACATATTCGAGGAAAAACTATGCACAAGGCCGTGCATTTAAA
AATAAACTCCCTAAGGCTGGGGTGAAACCTGCTACGGTCTGCGCAAGTTGACTGTT
AATGAATTTGATTCTCAGGTGTGAGTGATTAAAAGAACACTGATCATGTCATTTTCT
TTTTGGTCACTAATTCCCTCCCTCCCTTCTCTTTCTTTTCTTTTTTCTTTTCTTTTCTTT
TTCTTTCTTTCTTCCCGACAGAGAAAGACTCCATCTC

Hs584242.2C1n64_at (SEQ ID NO:52)
TAAGATGTTTAAGTATATCCAACCGTCCCAGACCACATTGGCCTATTTCCTCCTCTT
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ATTGTAATAATACATTTTCTTGTTAATCTCCTCATTATACTATGAGCTCCTTGAGGAC
AGGTACTTTGTCTTGCTCACATCTGTAGATTCAATGCCTGGCACAGCGATTGATATT
GCAAGGGCACTTAATAAATGGTTTTTGAATAAAAGAATTGCTTAAAGTAAAATATA
GCTGTAAATTGTATTATAAAAGGACAGTGGGTGGCAGTCTGAGGTCTGCTATTTACT
GGTTTGGGCAAGTTACTTAATCTGTTTGCTTCCTCAGCTGTACGATGGGTAAAATAA
TAGTGGTTATCACAACAGGGTGGTTACAGCGATGAAATGAGATTATGTGTGTAGGC
TACCACATAATTGTAAAGCTGATATTTAAATGGAACAGATACTGCACAGACACTTG
AGGTCTGAGAATAAGATTAGGTCAACCAGAGTATTAATGGGTTAAATAAAGGTGAC
ATCCTATGCAACCAACGGTTTGATCTTTATGCT

BRRS1RC_NM_004065_at (SEQ ID NO:53)
GTCTTCCAGTCAGTCAGTGTCTTCCAGAAAAATCTACGTCTTCCACCAAATCCAGGT
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TTCCTGAAGATCCACGTCTTCCAGAAAATCCATGTCTTCCAGAAAATCCATGTCTTC
CAGTAACCTCCCAGTCTTCCAGAAAATCCACGTCTTCCCAACAATCCAAGTCTTCCG
GATAATTTGGGTCTTCCTGAAAATCTACGTCTTCCAAAAAAGCCATGTCTTCCAGAA
AATCCACATCTTCCAATGGCCTCCAGGTCTTCCAGACTATCCATGTCTTCCAGAAAA
TCCTTGTCTTCCCTTAAATCTATAGCTTCCAAAAAATCCGGGTCTTCCAGGAAATCC
GTGTCTTCCAGCAAGTCCACGTCTTCCAACAAAGCCATGTCTTCCAGACTATCCATG
TCTTCCAGAAAATCCTTGTCTTCCCTCAAATCCATAGCTTCCGAAAAATCCAGGTCT
TCCAGGAAATCCGTGTCTTCCAGCAAATCCACGTCTTCCAACAAAGCCATGTCTTCC
ATCAAATTAATGTCTTCCAGCCTACTTGTG

BRRS.8182_at (SEQ ID NO:54)
AGCATCGTTTATGAAAACAACTAAATATTCACTAATGGTGCCAGTGGAATAAATCA
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GCTTTTTCAACAATCTACTGAGTGGCCATGGGCATGTGGATATGGCCATGAATGAGC
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AAAAAGATTTACCTTTTTAAATAAATGTTGTAGAATACTTAAAAAAAAACAAACTAG
AATTTGCCTGTGTGCAGCCAGTAACATGTCTATTTAACCTGGACACCTTTTGAGGAA
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GAATGAAAAGAAACATAAGGAGTGGGTACAAAGACTTCTATCTATGAATGATTAAA
AAGGCTAGAGTACGAATACTTCTTGAACCTTTGGTACTAAATGCTTTTCATGTTCTA
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AAGCCAAAAAAAAAAAAAAAAAAAAAAAAAA

BRMX.13815C1n5_at (SEQ ID NO:55)
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TTGAAAACCATTCAGCACATTTATCTTATGTAACATGCAGAGCATATATCTATCTGT
ATTTTTAAAATTTTCCTGTTACTCATTGATACATAGTACTTAATTACATGTTATTCCA
TGTACACTGAAAACAATATAGGAAATATATACATCTAAGACTTCTACTTTGTACAGT
CTTTCATTAAATAAGAATACTTACACATACATTTTCAGATATTTCTACCTTCCTGTAT
GTGTTTGGAATTGTATGTAGGTAGCCACTGAAAGAATTTGGGCCCCTTGGGAGGAT
GGCAGTGGAAGTCCATGAAGTAAAGAGCATTCTTTAAAAAGCAGATTTGATTGCAT
ACCTTTTAGTTATTTGAGATTCTGAGAATTCTGATAAACCCCAAAGCAGAAAGATTC
CTTAGTACCCTTGGAAGATGGGAAAGGTGAGGGAAATATTTGAAGCAGGGTCAGAA
CATCCACTAAGAACATAGCACCTCAGTAGAGCTTACATTATAGTGCCAGGGTAGAG
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BRMX.2637C1n26_at (SEQ ID NO:56)
TCCATCAGGGCACGGTAGAAGTTGGAGTCTGTAGGACTTGGCAAATGCATTCTTTCA
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GATCAACTCACGGAACTTTGGGCGACTATCTGCGTCTATCATCCAGCACTTGACCAT
GATCATGTAGACATCGATGGTACATATGGGTGGCTGAGGGAGGCGTTCTCCTTTCTC
CAGGATGGAGGAGATCTCGCTGGCAGGGATTCCGTCATATGGCTTGGATCCAAAGG
TCATCAACTCCCAAACGGTCACCCCGTAGCTCCAGACATCACTCTGGTGGGTATAGA
TTCTGTGTAAAATTGATTCCAATGCCATCCACTTGATAGGCACTTTGCCTCCTTCTGC
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GACATGCTGCGGTGTTTTCACCAGTACGTTCCTGGCTGCCAGGTCGCGGTGCACCAA
GCGACGGTCCTCCAAGTAGTTCATGCCCTTTGCGATCTGCACACACCAGTTGAGCAG
GTACTGGGAGCCAATATTGTCTTTGTGCCAA

BRAD.36737_at (SEQ ID NO:57)
CTGTCCAGAATGTAGAGGACAGACCCATGGGAACTTCAAAATTCCCCTCTCAATNC
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AACAAGGAAAGAGGCTGGTAAAACTGCATTTTGCACAAAAGTGTTGATTCAACATG
AAGTCAAATAATATGTTCTAATGAAACCACACCTCTCACACACATATCCTTTCTCTC
AAACCTCGGTGTTACTCTGGCCAAAAGTCTTAGGTTTCTTGAAGTGTTTGTGGAAGA
GTAGATGGAGTTTTATTTAACATTATCAAGAAATCCAAGCTGCAGACCCCACACAT
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BRAD.3853_at (SEQ ID NO:58)
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TCTAAGCGGATTTTATTCTGCAGGTCCTTTTAACATAATGAGTAATATTTGTGTTGG
GAATGACTGAGAAGAAATTTCATAATGATGTGAAGATCTACCTGTAAATAGTTCCT
CTGTCGTATGCTGGTATTTATATTCTAGCATCTCAACAGTGCTGATGGTCACTCATCT
TGGAGTTCCCTGAATTTTTTTTTTTTTTTCAAAACTCCTGTAATGTTACATTACCCAT
ACTTTTGTTGTTGCTGCTGTTGTTGTTGTTTTGAGACGGAGTGTCGCTCTGTCGCCCA
GGCTGGAGTGCANGTNGNNCCGCGCCCGGCACATGACTGCATACTTTCAAGGAGAG
GACTCAGAGCTTTTATTTATTTAAAGAAACTTGAAAGGAGGAAAGTGGATTAAGAA
AAAAAAAA

BRAD1_19760734_at (SEQ ID NO:59)
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AGGTAACATTGTACAGCTTTCAACAGTGGATCAGAACATAGATGTCTCTTCTAATTC
ACAAGTACCAATGGCTCAATTAATTTAAGGGACATTTTCTGAGTTGTGTGATTTCAC
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TGTAGGAAGAGTTAAAGGATGTGAAGTAGTCATTTTACTTATTCATAACACATTTTA
GGGAAAATTGTGCTGTTGCTGTTGGGGAGAAAGTTAAAGCTATCAACTATAACCTG
GACTCCAGTCCAATTTTTCACATCTGGTTGCTACTTTTAAAAAGGATCATTTTAATTT
TTAAATGCAGAATGTGTTGCACTTTACCTTTGACATTCCAGGTTTCCTCATGGTCATT
TAGAAAAATAAAGCAGGAAATTCTAATGCCTTAGCATCTACTTTAATAAGATGTTTG
CATTTATAAAAATAACAAGAAACTGA

BRMX.2797C4n2_at (SEQ ID NO:60)
TTTAATTTTTTGGAAGGATATACACCACATATCCCATGGGCAATAAAGCGCATTCAA
TGTGTTTATAAGCCAAACAGTCACTTTGTTTAAGCAAACACAAGTACAAAGTAAAA
TAGAACCACAAAATAATGAACTGCATGTTCATAACATACAAAAATCGCCGCCTACT
CAGTAGGTAACTACAACATTCCAACTCCTGAATATATTTATAAATTTACATTTTCAG
TTAAAAAAAATAGACTTTTGAGAGTTCAGATTTTGTTTTAGATTTTGTTTTCTTACATT
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TTCCCCCCAAATCATCACTCNCCTGCCCCCCTTAAGGGCTAGAGGGTGAGGCATGTC
CCTCACAATTGGCACATGGTNCAAGGCCATCAGGCAAGGGNGCATTCACACAAAAG
GGCACCAGG

BRMX.10399C1n5_at (SEQ ID NO:61)
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CCTCAATGATGGTTAAAACTGATTCTGAACCAAAGGTAAACAGGGTTCCTCCCCAT
GCCTTGGAGAGCTCCAGTCTGCAGAAAGCTAATGAAGCCCTTGAAGCAGTATCTTG
TCTTCCATCCACACTTTATTGAAATGCTTTTGAATCTTATTGTGTTGTAATTACATAC
TATAGAAAACTCCGCCAACCTCTATTTCAAGGTTTGGGCCCATGACTCTCGCTAAAA
CATTTCAGTTCCATTTTCCAGAACATACCATTTCTAAATGCATCTGTGAGGGCCCTC
CACAAGTATTTTCAGTCCACATTTCAGAAAACTTGAAAGTGACGCAGGTTCCTGACT
TAGTTGATGGTGGGTAAAGGGAATGCCATTATGAGTGGTGGAGGTTGTTTTCTTTTT
TCTTGCCATATTCTCAGCATAATATTTGAAACCTACAAAAGAAGTTTGATAATATAA
CTGTATATTTTATGCCTGCACTAGTGGAGGA

BRMX.8912C1n3_at (SEQ ID NO:62)
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ACACATTAAGATACGCCAGAGTGACAGGGACATTAAATAAATCAAGTATCCATGAA
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CTGTTTCCTTCCCTTCTCTCTTTGCCCTCAACCTTTCCTTCCCTCTTATCCATGGGAAT
GACTCTAGGAATCCTGTTGAGTGTATGTGTGTGCGTGTTCTTTTCTTTTTCTCTCATG
AATATTACACTTTTATTAGCCAGCTATACTTGTGTTGATGAAAAAGACAAAATGGAA
TTTTGTTTTCCTTTAACAATCAAGTATGAATGGTCTGCTTACAGGATGTCCCTTCTTG
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BRMX.13731C1n18_at (SEQ ID NO:63)
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GGGGATGGACGGAAGGGAGACCGAGGAAAGGCTTTCGGGAGTGGGGACATTATCC
CCCCAGAGGTGTGCTGCCCCACCCAGCTGCACCCCACAATCTGGCCAACTCATTTCA
CAGTATAAATCACTCCAGCAGGACGGCATCACAGCAGCCCCTGCTGCCTGAAATCA
GAGCGGCCCAACGAGGAAGGCCAGGAGGGTCGGCTGGCAGGGGGCAGGGTCTTGG
GATAACACTGTCATCAGAAACAAGGCTGGGGGCTGATTTCGGGGTGGGGAGCCTTA
GGAGGCCAGAAATTCCAATCAGAGCCAGTTTTTCTGGGAGGGAGTGGCTAGACAGT
CAAGGAAGGACGTTCACATTTCAAAAGAAGTCGGGTGGGGGGATGAGATTATTCTA
GGGGGGCATCGAATTCCCTTTAAGGGGGGGGCTCACTTCTGCCCAGAGTAAAGAGG
ATCTCACACCATGGAAATGTGCCAACTTTTTTGTACAAAGT

BRAD.25947_at (SEQ ID N:64)
CTTCCATTCCTCATGATTTTAGGGTTATCCTCATTCAGATCTACTCTAGTTATAATAG
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CTTGTTTTAGACTCTTCTACAGTTTAGACTTCAATGTGCATACTAAATGCATAACATT
CGTATCAAATAATTAACATTTATATACAATTAACAAATAAGGACAAATTTTATACAA
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CAGCACTGCCTTTTTAAAAGACAGGTCACTTGAATAGAGAATATAAGATATAACCA
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CCTTTTTCTTTTATTTTTATTTTTTGAAGGAGGATTATTTACTGGTGGTCTAAAAGAA
GTACCTTCAACTTCTTCATAATTGTAGCCAAAGCGGAAATGGAATATTTAATAATTC
TTACATCTCACTAATGTAGTCTTCTG

BRMX.5143C1n2(2)_at (SEQ ID NO:65)
AATAATTATAAAGTTTATTTAAATGTTGATTGTCCCAAGGTCTACAGTTTCTTTTCTG
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GAGTAAAACACATGGATCATCGTTATTAACAGTCCTCTGGGCGTGCTGGAGCTCACT
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CATCTGTTGTTCCTGCATTTTCTGTTGCTCTGCCAGCCAATTTTGTTTGGCTATCTCC
ATTTAACTCACTTGTTCCTGATGGAGTCTCTCCCTCTCCTGCATCATTTGCTCGTTCT
GCCTTTGAATCGCCGCCAACCTTTGCGCTTCAGCCTTTTCAGCTTCTGCTTTCACTTG
TGCCTCTGAGGAGAAAAAGATAATC

Hs633116.0C1n30_at (SEQ ID NO:66)
GTGTCAACATTTATGCTCCTAAAGGATGTTGGGTCAAATGAAATGTTCCTCATTGTT
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TAAGGGCACTCTGTGTTACCCCTTTAAACAAAATAAAGAAGTCCTACATTCTGCCCA
GATTTTTTTCAGGCTCCACCAAAGGGTTGGGTGAATTATGGCCCAAAAGTTGGTGAG
GATGATGGTGAACCTTCAATCACCTTCAGTCTCCCAACCAACAATGGTCATGGCTTG
TTTTCTCCCTGGATTACATGGAGAAAATCATGCCCTACTTTTTGGACCTGTTGCTTCT
ACATTTGTATGGTAACTGTGAAACCATCCTAATGAACAGCAAACATTAACCACTAC
ATAAAATGTAGACTTTGAATAAAAACACAGCTAAGTACTAACCAGCTTGCCCTTTA

AGCCAATTCCCTGTAGCTACTTACAGCACGACTGTTAGCTCCTTTCCTTATAGTTTCT
TACTGCCTTAAAGTCACATAGATGTGGTCACAAGGCACTAACTTCCCTTAGTTATTT
CTATAAGATAATATATGTAACGTTGGCA

BRSA.1606C1n4(2)_at (SEQ ID NO:67)
AGTGCAGAGAGGATGAGAATATCCTTCATGGGGTCCAGTTCCAAATCTGAAGCATA
ATTTCCAACCATCAAAATATTGGAAATAGGAATGCCTAGCATTTTATGGACATTCAT
GACCCGGCTTTGAGAAGTCATAGATCTACTCATGTTTAAAAAGTTGTCTTGAAGAAC
CTCACTGCAATCATCCACTTTAGTAAGCAAGGCCACATATGCTATACCACAGTTTAA
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GAGTTGATGTCTAAGACATAAGCCACACAGTGAATCCTGTCCTTCAGAGATGGAGA
GGTGATAAAAGTAGAATGCTCAGGTGTAATTGGTTTACGGGAATTAAACTGTTATA
AAAACATAAGGTAACATTCAGAAATCAGAGAGCCTCTGTTTAACCCTTAAAGACAC
AATTAATGCTTCTAATACTGTAACTACTGATCTCCCTCTTTCTCCTCAGCTACTCTTT
CCCCAAACAGTAGCACCTCCTCTTTACTTCCTTTCTCACTGGGGGGCATAATGCCAC
CAACTTTTTTGTACAAAGTTCCCTTTTTAATG

BRAD.41047_at (SEQ ID NO:68)
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TTTCAGTGTCATTTAATATCTGTGATGGCAATCCCTACTCAAAGCTCTTTGTTTTCAG
TGTTCCTGTATTGCTCTTTTGTTAATCCCTTAATATAAAAGTAAATAATAACCCAGTT
GGCATATTATTTTGATGACATTAAATTGGGGAGAATAGATACTGTGATTTTTGAAGC
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TCTATTTTTTTATTTTTTTTCAGATGGAGTCTTGCTCTGTCTTCTATCCAGGCTGAGGC
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TGCACTCCAGCCTGGGTGACAGAGCAAGATGCCATCTCTTAAAAAAAAAAAAAAAAA
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BRAD.4420_at (SEQ ID NO:69)
GTTAATATCTTTTTCGTTTATTGTCTGTCTCTGAAGGTAGGGACTTTGCCTCATTTAC
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AATAAATGATTTTTTTCTCTGGAAATTGTCAAAATCTGCATGAGGTGTATCAGGCCA
GCCATTGTCAGCCTCAGTTTAGAGGCAAGGAAATAGGTTCAGAAAGGTTCAAGGAC
GTGCTGAAGTCACAGGGCGAGGCAGCAGCAGAGAGCCTGCTTGTTGAGAGCCAAGT
CTTATGGGACTTGCCTCCTTCTCTCCCACTGAGGCTGGGGACACCAGGTGGCCCAGA
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TCTAACACTCTTGGGACCATAAAAAATGGAACAAGTCTGGGCATGGTAACTCACGC
CTGTAATCACAGTATTTTGAGAGGCTGAGGTGGGAGGATCACTTGTGGCCAGGAGT
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Hs137007.0C1n9_at (SEQ ID NO:70)
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GGGCTTCTGGAGGGGCTGGGAGAGCCCCACAAGGCTGCAGAGGGTGGTGAGCCCG
GAGTGGGCCTGGCCTGGTGTGGGCTGGGGGTATGGGCAGGAGCTGCAGACAGCAG
GGCTGCACCAGCGGACCAGTTTCAGAGGCAAGGGTTCTAGGCCCTTGAGAATCCAC
AGTGCCAAACAGACCCAGATAGCTACGGGGTTGGTACCTGGGGAGGCCTTAGGACA
GGCAGAAAGTCCCAGAGGCGAGGGCGTTGCCTGGGGACGTTTTTGCTCCCTGTCCT

GCTGACAGAGCATAGGAAGTGTGAATGTTTTCTACCCCCTCCTCTCTCGGCTCAGCA
GAGCTCCAGCGAGCCAAGTCCTTGTCTGTGGAGACGCATCAGTCCCTGGCTCTAGG
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AGGTACGGAATTGAGTCAGGAAACAGTCTGGGTGTGGAGTGAG

BRSA.18050C1n3_at (SEQ ID NO:71)
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CATTGAGCAGAGTGTTATCNNNNNNNNNNNNNACATTATTGCACAGAGATTTCTCA
TCAATGTTCTTCAGTTTTTATGTCTTTTCCTAAATGTGAATAAGTGCTATGGATAAAA
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GTAAGAAAAAATGGATATAAACAAAATAAGTGCTCTTTCTAAACTGTACTAAATTT
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TGAGTCCTGTTTTCAAAAGTGTCCTGTTTGGGTTTTCTTGGTGAAGAGCAGAATTTC
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BRMX.2948C3n7(2)_at (SEQ ID NO:72)
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TGTCGCTCCGCTCCTTCAGGAGCCAGCTGTAGGTGTCCTTGTCCTGCAGGAGCTGCA
GCATGGCCTTCTGAAGCTGCTGGCCGTACGTCTGGAGCATGAAGAACTGGATGATC
AAAGGGATGTGGCTGGAGATGCGCTTGCTGGCCTCCTGGTGATAGGCCATCAGGTG
CTGAAAGATCTCCTCCATGGAAGAGTCTGTTGCCGAGCTGGACTGGAAAGCCCCAA
AATCCCAGGATTTCTTCTTCTTTTCTTCTTCCAGCTCCTTCTCTCTGACCTTCTGCAAT
GCACCCCTGTATACCTGGTCCTGGCAGTAGACAATCTGTTCCATCTGGAAGTGGAGG
CGGATCAGCTTCTCACCTTCTCTCTCTTGTTCTGCTCTAATGTCTTCAATTTTGGACTT
GGCGGTTCTGTGGAGGTTAAAAAACTCTTCAAAATTTTTTATCGCCAACTTTTTTGT
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Hs43047.0C4n40_at (SEQ ID NO:73)
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GACTTTTCTCGGCATTAAAAAAATCTAGTACCTCTCTTGGCCAGAACCCCTAATTTT
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Hs926.1C10n7_at (SEQ ID NO:74)
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CCAAGCATACAGCCACAGTTTACCGTTGGAGGGATCTTTCCACGGAGGTAAACAGT
GCTGTTTTCTCCAAGTGCCAGAACAAAAACACAACAGCACACACACAATGAGATGG
TTTGGCTCTGTGTCCCCAACCAAATCTCATCTCAAATTGTGTTTGGCTCTGTGTCCCC

AACCAAATCTCATCTCAAATTGTGTTTGGCTCTGTGTCCCCATCCAAATCTCATCTCA
AATTGTAATCCCCATGTGTCAAGAGAGCAACCTGGTGGGAGGTGACTAGGTCATGG
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Hs528836.0CB6n98_s_at (SEQ ID NO:75)
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AAGTACTCAGCAGCAGCACCTCCAGGTCCAGAGGCACCTCCAGCTGCATGCACACA
CAATGAATGAAAGACTGCCAGGTGTCCGAACCCTGGACATGCAGCTTGTTGAGTTG
CAGGATGACTCTCTGTTCAGGGTCCAAGGTCTCGTTCCTGGAATCCAGGTCCGTGTT
GGGGAGGAAGAACTTCATCTTGGCGTTCAGCCATTCTGGGTCTTTGGTGAGCAGCCT
CACAAGACAGCTCCACAGGTTCTTGTTGCCGAGCTGGAGGCCAACGGGGTCCATGA
GGAGCCAGCCTTGGTCTCCTCGTTCATGATAGGTGCTCTAGGGTCCCCACGGAGAG
GGTCTCATGGGTGTCTGGGCTATGTGTGCCTTGAGCTGGATTGACAGGTTGTTTCCA
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BRMX.7284C1n6_at (SEQ ID NO:76)
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CAGCTGTATGACCAGTTTTTCCATCTCCTTCACTTCTACCTTGATCAGCTCGAAGTCC
AGTTCAGTGTAAGAAATGGTATCCTTCTCCATGATGTCAATTCGGACAGTTAGGTTT
AACAGTTTCTTTTCATACACACTAATTAATTGGACATATTCCCTCACTTTAGAAAGTT
CTTTCTCAAACTTCTGAGAAAGAACATGAGCTGTGAATTCCAAGCGTTCCACTCTGT
CCACGGGAAAGGTGGTGTCTGGCAGGGAAACAGAGCACTGGCAGGTCCCACGGTC
ATCCACGGAGCCGGTGAAATTGGAAAACAACTGGGACACAGAACCTCCGCTGCCTA
AGCTGCGGCTGGAGCTGGAGCCCGACCTGGAGCTGGAGCTGAAGCTGGAGCTGGA
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CCAAATCCCCTGCAGCTTGGCCAAGGAAGCCAA

BRAD1_19751014_at (SEQ ID NO:77)
TCTTTTATTGAAAGAAAAAACAATACAATGGACTTTAAAAAGCTACATTTGTTATGG
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TCACAACATCAGAGGCACCATTTTTGCCACAGAATTAGGTAATGAATAAAACTTCTC
CAAATTAATCTGTTTAAAAAATATCTAAAATGGTACAGTATATTTGAGGATTATATA
AATATGTGAGACATATTTAGATATTTTTTAAAAATAGTGTTTATATATATGCATCAC
AATCTTCTCTAATTCTCAAAATATTATGGCACCAAAATTCTGTTTGTCAAATAAAAC
ACAAGATGCTGTAATATGTATCCAAGCACCAGCTTAGCACAGTATTTAATTCTCCCC
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GAAATAATTTAGGCCCTCAAATTTTTTTTTTATTAGCTGATTGTTTTTAGAGAAAAA
AGAGGGAGCTAAACCATTTACATTAATGTTGCTCTGTGTGATAGAATCAATCCTAGG
GCTCAGAGAAGATATTCCTAGGCACTGGAGA

BRMX.13502C1n6_at (SEQ ID NO:78)
TCAAACTTGAATCNTTTAAATTTATTTTCTGCTTAAGCAGGTTTGAGTTGGGTTTTCT
ATTTGCAATAGCAAAAGTCCTGACTGGCAAGGTTTAAAAGTTTGAAGACTCTCACA
GGTAAGTGCAGCTCAGGATCCTGTGAGTGCAGCAGAAAGTCTTAAGAAATGGCAGG
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CTTCTGAGACACTCATTTTTGCTGGGTAGAGGAACTCTCTGGGCAAGCAGGACCATC
GATATTAGAGCAGCTGGCCTCAGGAGGGGAGTAAGAGCCCCATCCCTGAAGGTACA

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GTGGGACTGGAGTGAACGGGTACC

BRMX.1111C4n3_at (SEQ ID NO:79)
TTTTTTCTTCTTTTCCTCTTGGGTTTTCCCAAAGTAGAGTTGTTTGCAATATCCACAG
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GTTAAATGTCTTCTCCAGTTCACTGAGAACATTGTACACCACTCTTTGTACAGGGAC
CAGGTTTCTACAAGAATCTTCAGAATCTTCAAACATTTTATTTGTGATGAGTTCCCG
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CTTATGTCTTTTGAAGTGCTTGAATACAGTGTCATAGACAAGTCCCTCATCTACATC
CTGGTCTTCCGTGAACAGCCTGGCTCGGAAGGTCCTACGCCCACGGACTCTCACTGA
TTGCTAGCACAGCAGTCTGAGCCAA

Hs369056.9C26n3_at (SEQ ID NO:80)
CCTTCCCCATTTCTCACTTTCCACAGGTGGGATGTGGCAGTCCTCATGGAAGACTCT
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CCAAGTTTCTCATCTAGAAGGTAAAACAGTGTCCACGTCACTGGGAATCACAAGAT
TCAGGAAGGCCACCCCTCTGGGCATCTAGAACACACTGCTTATGTGTGAGCCTGTAT
AGACAGGCATATGCTTCTCCCTGGGATATGAAGGAAAAATATGGCATGGAGATTTC
AGAACAAATCCTGGTCTGCAGTGAAGTTCAGGAGGAAGGGGTATATGTCAGAATAA
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AGAGGATGATCTTATAGGAATCTGAATAATTGTATTATGCTGCAGATAAAACCAGG
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GAGACCCAGAGAATTACATATGATGGAATAACCTTCTAAGATATCATCACATCCCA
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BRMX.24432C1n2_at (SEQ ID NO:81)
GTGGCTGTTGCTGGCCCCACCTCCGCTTATGTCCTTAACATGCCTCAGGTGGTTCAT
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CTTCACAGGCTAAAGGTGCTTCATAACCTTGTTCATGTATTGAGGTTCTGTTGGCTCT
TGTAATGGTAATTTCACATGTGGGCAGTTGTTCATATTGATGTTTCTATAGGGGTAT
GATAGCTGGAGAGGTCTGCGCCACTGTCTTGCTCTGCCTTGATCANNNNNNNNNNN
NAACAAGAATTTGTCTCCTCCTAGTTTTTCTTTTTCTCTTAACCGACCTAGGTTTAGC
CTTTTAATCCTTCTCCCTCCTCTGCTTCTAATGTCATTGTTTCTTTGTATGCCTATCAT
ATCTACATGCTACATGACCTTCAGCTGG

BRRS.17773_at (SEQ ID NO:82)
AGTTTTAAGGAAAAATTGTATGATTTAAAAGATTATAAAACTTTATTACTGGGCTAT
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GGATATTTTTGTATCATATGTACGATGATAATTTATAGGGTATTTTAAATGATGTTTT
TTAGCCTCCTTAAGTTTTAAGTGGATCTTGCAAATGAAAACAAGTATTATTGAGTTT
GACATACTCAAATTGCCCAAATATCAGCTGTTTAAACAACCAAGTCATCATTGATAC
TTTAGTAAAGGTTAGTAAATGTCATCAAAGGCTTATTTGCAGTTTACAGTTTTTATT
ACTTAGGAGACTTAAGGAGTACCTGCCAGGTTTGTCCATGCTAATGCTACGATTTTG
TTTTTGTAGTTCAACCATATTTTGTATGGAGATACTTTGAGGCTCTGTAAATTTCTGG
TTACTCCTCAGAACCCACTAGATTTAGCATTTCATGGATGACTTGTGTTTGAACAAT

TATTACTATAATGGTTGCCAGATGATTATTTTCTTATTCTCTTCTTTGTTCTACATGG
AGAAATAAAACCAATAAATAAGGGAGA

BRAD.10849_at (SEQ ID NO:83)
GTGCCAATGTGAAGTCTGGATTTTAATTGGCATGTTATTGGGTATCAAGAAAATTAA
TGCACAAAACCACTTATTATCATTTGTTATGAAATCCCAATTATCTTTACAAAGTGT
TTAAAGTTTGAACATAGAAAATAATCTCTCTGCTTAATTGTTATCTCAGAAGACTAC
ATTAGTGAGATGTAAGAATTATTAAATATTCCATTTCCGCTTTGGCTACAATTATGA
AGAAGTTGAAGGTACTTCTTTTAGACCACCAGTAAATAATCCTCCTTC

BRAD.10890_at (SEQ ID NO:84)
AATGCTTATGTCTAAAAGAGCTCGCTGGCAAGCTGCCTCTTGAGTTTGTTATAAAAG
CGAACTGTTCACAAAATGATCCCATCAAGGCCCTCCCATAATTAACACTCAAAACT
ATTTTTAAAATATGCATTTGAAGCATCTGTTGATTGTATGGATGTAAGTGTTCTTAC
ATAGTTAGTTATAT

BRAD.11026_at (SEQ ID NO:85)
CTGGGCACCTCTGGGACAGCAAAAAAAACTGCAGAATGCATCCCTAAAACTCACGA
GAGAGGCAGTAAGGAACCCAGCACAAAAGAACCCTCAACCCATATACCACCACTG
GATTCCAAGGGAGCCAACTCGGTCTGAGAGAGGAGGAGGTATCTTGGGATCAAGAC
TGCAGTTTGGGAATGCATGGACACCGGATTTGTTTCTTA

BRAD.12809_at (SEQ ID NO:86)
ACCATGTTCATCTTGTCCTCCAAGTTATGGGGGATCTTGTACTGACAATCTGTGTTTT
CCAGGAGTTACGTCAAACTACCTGTACTGGTTTAAATAAGTTTACCTTTTCCTCCAG
GAAATATAATGATTTCTGGGAACATGGGCATGTATATATATATATGGAGAGAGAAT
TTTGCACATATTATACATATTTTGTGCTAATCTTGTTTTCCTCTTAGTATTCCTTTGTA
TAAATTAGTGTTTGTCTAGCATGTTTGTTTAATCCTTT

BRAD.14326_s_at (SEQ ID NO:87)
GATGGCTGGTCTGCCCCCTAGGAGACTCCGTCGCTCCAATTACTTCCGACTTCCTCC
CTGTGAAAATGTGGATTTGCAGAGACCCAATGGTCTGTGATCATTGAAAAAGAGGA
AAGAAGAAAAAATGTATGGGTGAGAGGAAGGAGGATCTCCTTCTTCTCCAACCATT
GACAGCTAACCCTTAGACAGTATTTCTTAAACCAATCCTTTTGCAATGTCCAGCTTT
TACCCCTA

BRAD.15436_s_at (SEQ ID NO:88)
GGCATGGAGCATCTGTACAGCATGAAGTGCAAGAACGTGGTGCCCCTCTATGACCT
GCTGCTGGAGATGCTGGACGCCCACCGCCTACATGCGCCCACTAGCCGTGGAGGGG
CATCCGTGGAGGAGACGGACCAAAGCCACTTGGCCACTGCGGGCTCTACTTCATCG
CATTCCTTGCAAAAGTATTACATCACGGGGGAGGCAGAGGGTTTCCCTGCCACAGT
CTGAGAG

BRAD.15833_s_at (SEQ ID NO:89)
GAAATTAGAGTCCTATATTCAACTAAAGTTACAACTTCCATAACTTCTAAAAAGTGG
GGAACCAGAGATCTACAGGTAAAACCTGGTGAATCTCTAGAAGTTATACAAACCAC
AGATGACACAAAAGTTCTCTGCAGAAATGAAGAAGGGAAATATGGTTATGTCCTTC
GGAGTTACCTAGCGGACAATGATGGAGAGATCTATGATGATATTGCTGATGGCTGC
ATCTATGACAATGACT

BRAD.19080_s_at (SEQ ID NO:90)

TTAGATTTCCAGCTTGTCACCTTCAAGGTTACCTTGTGAATAGGACTTTTTTGAGCTA
TTTCTATCCAGTTGACTATGGATTTTGCCTGTTGCTTTGTTTCCACCAACTCTCCCTG
AAGATGAGGCGCACAGACAGACAACTCACAGGCAAGAACAGCCTGGTCCATCTTG
AAAGATTCTCAAGACTATTCTCCACAAG

BRAD.2707_at (SEQ ID NO:91)
TGTTTAAAAATGTTGTGGGTACATAGTATGTGTTGTGGGTACATCGTATGTGTTGTG
GGTACATAGTATNGTGGGGTCCATGAGATGTTTTGATACAGGCATGCAATGTGAAA
TAAGCACATCATGGGGAATGGGGTATCCCTCCCCTCAAGCGTTTATCCTTCAAGTTA
TAAAAAATTCAATTACAGTCTTAGTTATGTCAAAATGTAC

BRAD.27716_s_at (SEQ ID NO:92)
ACCAGAATTTATGGATGAACTGATTGCTTATATTTTAGTCAGGGTTTATAAATGTAG
ATGGTCAAATTTACATTGCCTAGTGATGGAAAATTCAACTTTTTTTGATTTTTTTTTC
CAATATTAAAAAAGGCTCTGTATGCATGGTGGG

BRAD.28628_s_at (SEQ ID NO:93)
AAGATTCCTGTGTACTGGTTTACATTTGTGTGAGTGGCATACTCAAGTCTGCTGTGC
CTGTCGTCGTGACTGTCAGTATTCTCGCTATTTTATAGTCGTGCCATGTTGTTACTCA
CAGCGCTCTGACATACTTTCATGTGGTAGGTTCTTTCTCAGGAACTCAGTTTAACTA
TTATTTATTGATATATCATTACCTTTGAAAAGCTTCTACTGGCACAATTTATTAT

BRAD.28643_at (SEQ ID NO:94)
TCTCCTCTCATCTGCATTTCTCAGAAATGCCCTCCCTGCCCAGTGGTGACTTTCCCTC
GTCACTCCTATGGAGTTCTACCTGGAGCCCAGCCATGTGTGGAACTGTGAAGTTTAC
TCCTCTGTAAAGATGGTTTAAAGAAAGTCAGCTTCTGAAATGTAACAATGCTAACCC
TTGCTGGAACCCTGTAAGAAATAGCCCTGCTGATAGTTTTCTAGGTTTATCATGTTT
GATTTTTACACTGAAA

BRAD.28663_s_at (SEQ ID NO:95)
GAATTTTTCTCTATTTCCAGCACGCTGATTTGATTTAAAAATGTAATAAGACCAAGA
GTTGGAGTAAAGGGATATTCATTCCATGTTAAAAGTGGCTTCATAGCTACTGACAA
ATGTCTGAACTATTGTCGTGCCCTTCAAAACTGGAGTTTTCTAAAATAATCTTATTTT
TATACTTGTATGTTCCAGCAATTTAAGATATATACCATTGAAAGGGAAAT

BRAD.29038_at (SEQ ID NO:96)
GGCTGAGCAAGGCACATAGTCTACTCAGTCTATTCCTAAGTCCTAACTCCTCCTTGT
GGTGTTGGATTTGTAAGGCACTTTATCCCTTTTGTCTCATGTTTCATCGTAAATGGCA
TAGGCAGAGATGATACCTAATTCTGCATTTGATTGTCACTTTTTGTACCTGCATTAAT
TTA

BRAD.30917_at (SEQ ID NO:97)
AACGCAGGCCGCTTTATTCCTCTGTACTTAGATCAACTTGACCGTACTAAAATCCCT
TTCTGTTTTAACCAGTTAAACATGCCTCTTCTACAGCTCCATTTTTGATAGTTGGATA
ATCCAGTATCTGCCAAGAGCATGTTGGGTCTCCCGTGACTGCTGCCTCATCGATACC
CCATTTAGCTCCAGAAAGCAAAGAAAACTCGAGTAACACTTGTTTGA

BRAD.31470_at (SEQ ID NO:98)
TCATCTCCGTATTCTTCAGCTTCATCCAAAACTGACTTAGAAGCCTCCCTTGACCCTC
ACCTGACTATTCACAGGTTATAGCACTTTATGTTTTTCAGTTCTGTTATTTTAATTGG
TGCCTCTGTTTGTGATCTTTAAGAACATAAAATTCTGGCAAGTAACTATTTGCTA

BRAD.32716_at (SEQ ID NO:99)
CACTTTGCAGCCTTGAGAGGTGCAGAAGAGACACCGAGGGGTTCACCACCAGAGCC
ACCATTGTCAGAGAGGCGTCCAGCTGTGTCCACCTGGGACTCTGCCTTCAGGGCTTC
TTGCCTGGCTGGGAGCTGCACAGGCAGACTCCTGGGACGGTGTGCCGACAGCTCTG
GGCACCCCCTTCTAGGATCTGATTCCTGAGGAATCACAATGTGGATTTCACAATCAC
TTCCAGTGTCTTTTGCCAACCTCTGTGAACAGATGT

BRAD.33042_at (SEQ ID NO:100)
AAGTTTGCACAGTTCTAGACACGATAAATACATGTGAAATCACACAACTCAGAAAA
TGTCCCTTAAATTAATTGAGCCATTGGTACTTGTGAATTAGAAGAGACATCTATGTT
CTGATCCACTGTTGAAAGCTGTACAATGTTACCTATTTATTTGCAGACATCCTTTGG
AAACAAATAGGTAGATTTGCAACAAATAAAGAGTGGAGTACAGCTGCTGACATTAC
CTTGTATATTCATGCCTTTATG

BRAD.33341_at (SEQ ID NO:101)
GACTGCACAGCAGCAAGACAGATTGCCATGGAGCATGTTGTGCCCAACTAGGGACA
GCGCAGATAGATTCTGTAATTTGCCTAACAATGTCTATAGGATGATCCCATTTGTCA
AAAAAAAAANNGAACTGGGCTTTATTGATGTCACCTAAATGCACCTAAACTTCTTTT
TTGCCCCATGCTCTTCTGTACTCTTGATCTTTCCCCAAATTTTTAAAAACATGACACT
CATTCCCTTATTTTTCCTACTTAG

BRAD.33405_at (SEQ ID NO:102)
TTAATTGCTTTCTCTCACCAGGGAAGGTGTGGGAAGGACTTGTGAAATACATATTCG
AGGAAAAACTATGCACAAGGCCGTGCATTTAAAAATAAACTCCCTAAGGCTGGGGT
GAAACCTGCTACGGTCTGCGCAAGTTGACTGTTAATGAATTTGATTCTCAGGTGTGA
GTGATTAAAAGAACACTGATCATGTCATTTTCTTTTTGGTCACTAATTCCCTCC

BRAD.33431_at (SEQ ID NO:103)
GTCATCCAGAGTTATAATGGCCCATTATCTAATGGTCAGAGTTTACTTAGGCTTTCA
CTACTTCCACTGCCCACTTGAAACAGGGAAAAATATTTTCCCCCCGCGCTGTGAGTG
TGCTATTTAGAGCTGACCACAAGCGGGGGGAAGAGAGGATGGCTCGGATGCTGCAT
TTCCACTGAGAACACAAGGCTGGCAAAGCTTGTCTGCTGCCCAGCAAGCACTTCAG
GCTCACACCATTTTAGGTTCACTTTAAGTAGTTTCTCAAT

BRAD.35695_at (SEQ ID NO:104)
TGGACAGTGGACGTCTGTCACCCAAGAGAGTTGTGGGAGACAAGATCACAGCTATG
AGCACCTCGCACGGTGTCCAGGATGCACAGCACAATCCATGATGCGTTTTCTCCCCT
TACGCACTTTGAAACCCATGCTAGAAAAGTGAATACATCTGACTGTGCTCCACTCCA
ACCTCCAGCCTGGATGTCCCTGTCTGGGCCCTTTTTCTGTTTTTTATTCTATGTTCAG
CACCACTGGCACCAAATACATTT

BRAD.35710_at (SEQ ID NO:105)
TCCATGGCAACAGTCCCAACATGTTTGAGACTTCAGCTAAAGGAATGGATGTATNN
NGGNGTGTAGTCTTCAGTATATCACTGTATTTCCGTAATACTAGACTCNAAGNTATG
CNAGATNGNTTATTCCCTTNGTGAANNNGGAGTTGCTCATTACGTTCTTGAAATATC
GCACATCCTGTTGGTTCTTCAAAGGAAGCCTTTCCACCAGATTAGTGTTCAAGTCTT
TGCAGAGGAGACCAACTTTT

BRAD.37907_at (SEQ ID NO:106)
AAGGCTATGCTTTCAATCTCCTACACAAATTTTACATCTGGAATGATCTGAAGGTTC
TTCAAAGACATTCAAAATTAGGCTTTTTTATGTCCTGTTTTAAGTGAAAATATTTATT

CTTCTAAGGGTCCATTTTATTTGTATTCATTCTTTTGTAAACCTCTTTACATTTCTCTT
TACATTTTATTCTTTGCCCAAATCAAAAGTGATTCCT

BRAD.40353_at (SEQ ID NO:107)
CTTAGCATTAGAACACTCAGTAATCATATGAATTGTGCATTTGTTTGTTTTGCTTAAC
TCTTTCTGTTTGTTTATGTTTGGGGTTTTATTGTTGTTGTTTCACTTTTCTCCCATCTCT
TCCTGACTTGGTCAAATCCAAAGGAATNTTCCAAATTGTGGGGAGCAAGGCATCTG
AAATGGCTAAAAC

BRAD.40654_s_at (SEQ ID NO:108)
ATGCTATATGCTGTATCCCACCTTTCTCTGAATGTTACATTTTCTCCCCTATCCCAGG
CTGCATCTAAGAAAACTCAAAGGGAATATGCTATCTATCTTTTCCGAGCAATGAAA
GCTCTNGGGTTTTTTCCTTGCTTTTCAGGGCACNATACTTCTCTTTCTTCCTGGTTAG
ACAGGATAAGTTCTGAGTCCCNTGGTATCATCAGCTTACTTCTTCTCTGTTAAATATT
CACA

BRAD.4701_at (SEQ ID NO:109)
GTGGTCTTCCTCTGAATATTAGCAGAAGTTTCTTATTCAAAGGCCTCCTCCCAGAAG
AAGTCAGTGGGAAGAGATGGCCAGGGGAGGAAGTGGGTTTATTTTCTGTTGCTATT
GATAGTCATTGTATTACTAGAAATGAACTGTTGATGAATAGAATATATTCAGGACA
ATTTGGTCAATTCCAATGCAAGTACGGAAACTGAGTTGTCCCAAATTGATGTGACA
GTCAGGCTGTTTCATCTTTTTTG

BRAD.5967_at (SEQ ID NO:110)
TATCCTATTACTGTACTTAGTTGGCTATGCTGGCATGTCATTATGGGTAAAAGTTTG
ATGGATTTATTTGTGAGTTATTTGGTTATGAAAATCTAGAGATTGAAGTTTTTCATTA
GAAAATAACACACATAACAAGTCTATGATCATTTTGCATTTCTGTAATCACAGAATA
GTTCTGCAATATTTCATGTATATTGGAATTGAAGTTCAATTGAATTTTATCTGTATTT
AGTAAAAATTAACTTTAGCTTTGATACTAATGAATAAAGCTGGGTTT

BRAD.7701_at (SEQ ID NO:111)
GGGATTTTGAGCTATCATCTCTGCACATGCTTAGTGAGAAGACTACACAACATTTCT
AAGAATCTGAGATTTTATATTGTCAGTTAACCACTTTCATTATTCATTCACCTCAGG
ACATGCAGAAATATTTCAGTCAGAACTGGGAAACAGAAGGACCTACATTCTGCTGT
CACTTATGTGTCAAGAAGCAGATGATCGATGAGGCAGGTCAGTTGTAAGTGAGTCA
CATTGTAGCATTAAATTCT

BREM.1048_at (SEQ ID NO:112)
TTGAATAGATCATCAGTGGCCACTGATGTAATTAATCATGTCTATGTAATGAAGCTG
CCATAAAAAAACCCAGGAGGACAGTGTTGAGAGAGCTTCTAGGTTGGTGAACACTTG
GGGGTGTCTGGAAGACAGCCCACCTGGAGAGGACACGGAGGCTCTTCGCACCTTCC
CCCATACCTGGCTCTCTCCATCTCTTCATTTGTCCATCTGTATCTTTTTCATTATATTA
TCCTTGATAATAAACTGGTAAATATAAGTGTTTCCCTAAGTTCTATGAGCCACCAT

BREM.1129_at (SEQ ID NO:113)
AGGCCTCTGATTGCACTTGTGTAGGATGAAGCTGGTGGGTGATGGGAACTCAGCAC
CTCCCCTCAGGCAGAAAAGAATCATCTGTGGAGCTTCAAAAGAAGGGGCCTGGAGT
CTCTGCAGACCAATTCAACCCAAATCTCGGGGGCTCTTTCATGATTCTAATGGGCAA
CCAGGGTTGAAACCCTTATTTCTAGGGTCTTCAGTTGTACAAGACTGTGGGTCTGTA
CCAGAGCCCCCGTCAGAGTAGAATAAAAGGCTGGGTAGGGTAGAGATTCCCATGTG
CAGTGGAG

BREM.1226_at (SEQ ID NO:114)
ATACGTTTTTCACTTTCTGACCAGGACCATGCCTGTGGAGTAGATGTTGACAAGAAA
CACTGACCAGATCAAAATGTGTCTCAAGGAGAATGGCACAATTTTGTGCAAATGAA
TCAAGGAAGTCTTATTGCACAAGAGTATCCTGGAACCCAGTGCAATTGATTTTTTAG
AAAAATATATCACATAGGGGAAAAAAACTGGAATATGTTGAAGGAGACGTATATA
ATATTTAGCATCCAGATTGATGACTTCTGCCCTAACTATGCAATG

BREM.1262_at (SEQ ID NO:115)
CGCTTGAACCTGGAAAGTGGACATTGCAGTGAGCTGAGATTGTGCCACTGCACTCC
AGCCTGGGCAACACAGCGAGACTCTGTCTCAAAAAAAAAAAAAAAAAGAAAGAAAA
AAAAGAGAAAACTCAGAGATTCGTGGAGACTGGAACCACGGGTGTGGAGAGAGGG
GTTAGTAGAGACCAGATTCTGCAGGTACTATAATGACATTCCCAGGCTAAGGAGTT
TAGATCTT

BREM.130_at (SEQ ID NO:116)
ATCTACACCCTCAGGAATAAGAAAGTGAAGGGGGCAGCGAGGAGGCTGCTGCGGA
GTCTGGGGAGAGGCCAGGCTGGGCAGTGAGTAGTTGGGGAGGGGAGAAAGTATTA
AGCCAGAACCCAAGGATGGAAATACCCCTTAGTGAGTCAGTTTAGACTTCAGGCTG
TTCATTTTTGTATGATAATCTGCAAGATTTGTCCTAAGGAGTCCAATGGGGGATATG
TTTTCCTCCCGTGAGGAAATGTTTAGTTCTTGAGGGAAAAATCCCTAAATCCTCTAT
ATA

BREM.1689_s_at (SEQ ID NO:117)
GGGTAGCAAGTTCACCACAGTGTTAATGGGGGTCCCAAGGTATTCTTCCCCCAGGC
CTAGGTATAGGGCTATTACTCCTCTCTGCTCCAGGTGTAGACATACATTTACATT

BREM.2334_at (SEQ ID NO:118)
TGGAGGGTGAAATTCTGATAGACTTGAGGCTTTGAGATGTGGTCCTGGGGTGGAGC
AAGACAAGAAAAGTACTGGAGATTGGGGTTTGAGGAGTCTATGCAATTATTTTTAT
TTTTAAAAATCTTTGTGGCTACATAGCAGGTGTATATATTTATGTGGTAAGTGAGAT
ATTTCGATACAGACATACAATGTATAATCACAGGCATACAATGTAGACAGGCATAA
AGTGTATAGTCAC

BREM.2382_at (SEQ ID NO:119)
AATGTGAAACTGCTCCATGAACCCCAAAGAATTATGCACATAGATGCGATCATTAA
GATGCGAAGCCATCGAGTTACCACCTGGCATGCTTAAACTGTAAAGAGTGGGTCAA
AGTAAACTGAATTGGAAAATCCAAAGTTATGCAGAAAAACAATAAAGGAGATAGT
AAAAAGGGTTAACGAGCCAGTCCAGGGGAAGCGAAGAAGACAAAAAGAGTCCTTT
TCTGGGCCAAGTTTGATAAATTAGGCCTCCCGACCCTTTGCTCTGTTGCTTTATCAAC
TCTACTCGGCAATAACAAT

BREM.532_at (SEQ ID NO:120)
GATTAAGAACAGTTTTTTCAACAAATAGTGTTGGGACAATGGGTGTCCACATGCAA
AAGAATAAAGTTGTCCCCTTACCTTACACCATCTCCAAAAATTAACTCAAAATATGT
CAAAGACATAAACGTAAGAGCTAAAACTGTAAAACTCCTAGAATAAAACATAGGA
GTAAATCTTCATGACCTTGGATTAGGCCATTGTGTCTTAAATATAACACCAAAAGAA
TAAGTAATAAAAAAATAGATAAATTGAACTCCATCAAAATTAAAAGCCTTTGTGCT
TCATAGGACACCA

BRHP.106_s_at (SEQ ID NO:121)
TCTCAAGCTATGATCAGAAGACTTTAATTATATATTTTCATCCTATAAGCTTAAATA
GGAAAGTTTCTTCAACAGGATTACAGTGTAGCTACCTACATGCTGAAAAATATAGC

CTTTAAATCATTTTTATATTATAACTCTGTATAATAGAGATAAGTCCATTTTTTAAAA
ATGTTTTCCCCAAACCATAAAACCCTATACAAGTTGTTCTAGTAACAATACATGAGA
AAGATGTCTATGTAGCTGAAAATAAAATGACGTCACAAGAC

BRIH.10647C1n2_at (SEQ ID NO:122)
TCTTTCTTTTCCAGACAACTTTGAATGGAGAGGAGCAAATTAGTCTTTTGGTTTAATT
CTGTCTCAGTTTGCTTATCTAAAGAAAGGAAAACAGAGTGGCTACACTTGTTTAGAA
CCATATGCATACTCCAGAGAAAGATGCTCTATTAATCCAAAAAAATACAGCCACTT
GAAACCAGCCAAAGCGAAAGTGTAAGGGACTTCATGGAAAGGAGGCAGTTCACCA
AAGTATTGAGGGGTTTTATATTTTAAACTCCGCCAGTGAATTGACGTGTTATGTCAC
TTAC

BRIH.1453C1n2_at (SEQ ID NO:123)
GAATTTATTGGAGCATGACCACGGAGGATAGTATGAGCCCTAAAAATCCAGACTCT
TTCGATACCCAGGACCAAGCCACAGCAGGTCCTCCATCCCAACAGCCATGCCCGCA
TTAGCTCTTAGACCCACAGACTGGTTTTGCAACGTTTACACCGACTAGCCAGGAAGT
ACTTCCACCTCGGGCACATTTTGGGAAGTTGCATTCCTTTGTCTTCAAACTGTGAAG
CATTTACAGAAACGCATCCAGCAAGAATATTGTCCCTTTGAGCAGAAAT

BRIH.1518C1n4_at (SEQ ID NO:124)
TCCCCGGTTACTACCTCTTATCCATCCCCGGCCACCACCTCATACCCATCCCCTGTGC
CCACCTCCTTCTCCTCTCCCGGCTCCTCGACCTACCCATCCCCTGTGCACAGTGGCTT
CCCCTCCCCGTCGGTGGCCACCACGTACTCCTCTGTTCCCCCTGCTTTCCCGGCCCAG
GTCAGCAGCTTCCCTTCCTCAGCTGTCACCAACTCCTTCAGCGCCTCCACAGGGCTT
TCGGACATGACAGCAACCTTTTCTCCCAGGACAATTGAAATTTGC

BRIH.2770C3n31_at (SEQ ID NO:125)
ATGAAGACTTGGCTGATTCAGATGCCAGGGCCTTGTATGAAGCAGGAGAAAGGAGA
AAGGGGACAGACGTAAACGTGTTCAATACCATCCTTACCACCAGAAGCTATCCACA
ACTTCGCAGAGTGTTTCAGAAATACACCAAGTACAGTAAGCATGACATGAACAAAG
TTCTGGACCTGGAGTTGAAAGGTGACATTGAGAAATGCCTCACAGCTATCGTGAAG
TGCGCCACAAGCAAACCAGCTTTCTTTGCAGAGAAGCTTCATCAAGCCATGAAAGT
ATGTACCATTCT

BRIH.365C1n2_at (SEQ ID NO:126)
TGCCTTGTGTCTTCCGTTTGACGGAAGAGAATGGATTCTGGTATCTAGACCAAATCA
GAAGGGAACAGTACATTCCAAATGAAGAATTTCTTCATTCTGATCTCCTAGAAGAC
AGCAAATACCGAAAAATCTACTCCTTTACTCTTAAGCCTCGAACAATTGAAGATTTT
GAGTCTATGAATACATACCTGCAGACATCTCCATCATCTGTGTTTACTAGTAATCAT
TTTGTTCCTT

BRIH.5410C1n7_at (SEQ ID NO:127)
GGTATAGCATATGTGGCCTTGCTTACTAAAGTGGATGATTGCAGTGAGGTTCTTCAA
GACAACTTTTTAAACATGAGTAGATCTATGACTTCTCAAAGCCGGGTCATGAATGTC
CATAAAATGCTAGGCATTCCTATTTCCAATATTTTGATGGTTGGAAATTATGCTTCA
GATTTGGAACTGGACCCCATGAAGGATATTCTCATCCTCTCTGCACTGAGGCAGATG
CTGCGGGCTGCAGATGATTTTTTAGAAGATTTGCCTCTTGAGGAAACTGGTGCATTT

BRIH.5478C1n2_s_at (SEQ ID NO:128)
TGCTTATCCGTTAGCCGTGGTGATTTAGCAGGAAGCTGTGAGAGCAGTTTGGTTTCT
AGCATGAAGACAGAGCCCCACCCTCAGATGCACATGAGCTGGCGGGATTGAAAGAT
GCTGTCTTCGTACTGGGAAAGGGATTTTCAGCCCTCAGAATCGCTCCACCTTGCAGC

TCTCCCCTTCTCTGTATTCCTAGAAACTGACACATGCTGAACATCACAGCTTATTTCC
TCATT

BRIH.5650C1n2_at (SEQ ID NO:129)
TAGGCACCACATGGGATCCTTGTTCTTCCTCCTTGTAAGCAGTAATTGAAATCAGTT
TGGCAGCCTGGTTTACAGTGACCATGGTGGCTTGTCTCCCGTGCTCTTACCTCACTCT
GTTGATGTTGTAAAACCTCCAGCTAACTTCATGGGGTGGCTGACCCACGTTGCTCAT
TTATTCATTCAACACATATTCATTGACCATCTACTCTATGCCAGGTATTGTTATCAGC
ACTGGGAATAGATCAGTGAACTATTGATCTATTTGTCTAA

BRIH.5952C1n2_s_at (SEQ ID NO:130)
CTCAGTTCTGGTCCTTCAAGCCTGTATGGTTTGGATTTTCAGTAGGGGACAGTTGAT
GTGGAGTCAATCTCTTTGGTAC

BRIH.7359C1n3_s_at (SEQ ID NO:131)
CTGAGGTGCTATGTTCTTAGTGGATGTTCTGACCCTGCTTCAAATATTTCCCTCACCT
TTCCCATCTTCCAAGGGTATAAGGAATCTTTCTGCTTTGGGGTTTATCAGAATTCTCA
GAATCTCAAATAACTAAAAGGTATGCAATCAAATCTGCTTTTTAAAGAATGCTCTTT
ACTTCATGGACTTCCACTGCCATCCTCCCAAGGGGCCCAAATTCTTTCAGTGGCTAC
CTACATACAATTCCAAACACATACAG

BRIHRC.10930C1n2_s_at (SEQ ID NO:132)
TAACAAATCATCAACTTCCACTGGTCAATATATAGATTTTGGGTGTCTGAGGCCCCA
AGATTAGATGCCACTAATCTCCAAAGATTCCCTCCAA

BRMX.13731C1n18_at (SEQ ID NO:133)
GCAGGGTCTTGGGATAACACTGTCATCAGAAACAAGGCTGGGGGCTGATTTCGGGG
TGGGGAGCCTTAGGAGGCCAGAAATTCCAATCAGAGCCAGTTTTTCTGGGAGGGAG
TGGCTAGACAGTCAAGGAAGGACGTTCACATTTCAAAAGAAGTCGGGTGGGGGGAT
GAGATTATTCTAGGGGGGCATCGAATTCCCTTTAAGGGGGGGGCTCACTTCTGCCCA
GAGTAAAGAGGATCTCACACCATGGAAAT

BRMX.25436C1n2_at (SEQ ID NO:134)
TAGTTATACTTACACACTCCTCTCATGTTGTCTATGGAGTGGTGGATGCTGCAGGGA
GGGTGACATCCTAGTTAGTCCTAAGAGCCAGACTGCCTGAAGCTCACTATAACAAG
TCCTGCCTTGGGGAAGAAGGAAGTGTGTCTCTGTGAACCTCCCACCTGGGCCGAAA
GGGAGGCCACTCTCTCTGCTGCCTCTCCCCAACCTTGGCCTTCTGTGCTCCTAGTGA
ACCTCTCACCCCCTGCCTACAGCCTCGAATCTCAGACCATGATGACCTCTGGTCACC
CTGAATCAGAGCTTT

BRMX.25712C1n2_at (SEQ ID NO:135)
GTAAAATTCCTATGTCAGCACCCTAATGAGACAAATGACATCCTAATTCTTCCCCTT
GGCTTGCCAGTTTGTAGGTACTAGTTTTTCAGAAGTTACTCTAAAATATTTCTGATTG
CAGCTCCTTCCTAAAGAGCAGTATGAGCAGCATGTGGTTATTTATGTATTCACTCTT
TTCTCCTACTTCTGTGGTGACCTGGAACAAATTCTCTTATGTATGTAAAGATTGGAC
AGCCCACCTGATTCCGATGTCACTTAGATACACTGTTTTTGTATCAGCCTCTTCTCTT
AGAAA

BRMX.3079C1n3_at (SEQ ID NO:136)
GATTGTTGGCCAATAGACCTTCCACTCCAGTAGAGAGGGAGGACTTGGCTCTGAGA
ACCTCCATCTGACCTAAGAGGAAACCTCCTCTCCTATGGCCATCTCCTCCTCCTGTC

CTTTAAGTCCTCTGTGGTTACTATATCTCCTTTTCCCTTTCTTACCCTTTCGCTTAGCA
ATTTCAAT

BRMX.3079C2n3_at (SEQ ID NO:137)
AAGTTCTTTGGGATAGAGGGTGAAGAACTTGGGACATGGGCTGTTTCAGGGCAGCT
GAAGTTCAAAGGGGAATAGGTAATTGGGGGGAAGGGGGGAAGTTGGGGCAGAAAG
GGATTGTTGGGCCAATAGGACCTTTCCACT

BRPD.10690C1n5_at (SEQ ID NO:138)
AGGATTATACTTCAGTCCCTGCTTTACATTTATTTCTTAAAGAAGCTTCTGGTAAATT
AGAGCAATAGCATCGGCTTAGTTTAGTGTTGTTCTGTTGGACTAAGGATATCAGTTC
TATCCGTATGGTCGGGCCTAAAGCCTGGGAAATATTTAATGAAGGNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNATAACAAATAACAAAACAAAAACCA
AGCCATTTCCCTTTATAGTAAGA

BRPD.4019C1n3_s_at (SEQ ID NO:139)
ACAGAAGCCATTGCCTCCCTTGTTTACCTTGGGTCCACCTCCACCAAAACCCAACAG
ACCACCAAATGTTGACCTGACGAAATTCCACAAAACCTCTTCTGGAAACAGTACTA
GCAAAGGCCAGACGTCTTACTCAACAACTTCCCTGCCACCACCTCCACCATCCCATC
CGGCCAGCCAACCACCATTGCCAGCATCTCACCCATCACAACCACCAGTCCCAAGC
CTACCTCCCAGAAACATTAAACCTCCGTTTGAC

BRPD.5301C1n2_s_at (SEQ ID NO:140)
GCACAGCTCAGCACAACATTCCAAGCTCAAAATAGAAGCCTTCTCAGTGAGCTCCA
GCACGCCCAGAGGACTGTTAATAACGATGATCCATGTGTTTTACTCTAAAGTGCTAA
ATATGGGAGTTTCCTTTTTTTTACTCTTTGTCACTGATGACACAACAGAAAAGAAAC
TGTAGACCTTGGGACAATCAACATTTAAA

BRRS.12588_at (SEQ ID NO:141)
CCTGCCCTGGAAGTAATCTTGCTGTCCTGGAATCTCCTCGGGGATGAGGCAGCTGCC
GAGCTGGCCCAGGTGCTGCCGAAGATGGGCCGGCTGAAGAGAGTGGACCTGGAGA
AGAATCAGATCACAGCTTTGGGGGCCTGGCTCCTGGCTGAAGGACTGGCCCAGGGG
TCTAGCATCCAAGTCATCCGCCTCTGGAATAACCCCATTCCCTGCGACATGGCCCAG
CACCTGAAGAGCCAGGAGCCCAGGCTGGACTTTGCCTTCTTTGACAACCAGCCC

BRRS.13369_s_at (SEQ ID NO:142)
GCACAGCTCAGCACAACATTCCAAGCTCAAAATAGAAGCCTTCTCAGTGAGCTCCA
GCACGCCCAGAGGACTGTTAATAACGATGATCCATGTGTTTTACTCTAAAGTGCTAA
ATATGGGAGTTTCCTTTTTTTTACTCTTTGTCACTGATGACACAACAGAAAAGAAACT
GTAGACCTTGGGACAATCAACATTTAAA

BRRS.13576_at (SEQ ID NO:143)
GAGAGTTCAACTAAGAAAGGTCACATATGTGAAAGCCCAAGGACACTGTTTGATAT
ACAGCAGGTATTCAATCAGTGTTATTTGAAACCAAATCTGAATTTGAAGTTTGAATC
TTCTGAGTTGGAATGAATTTTTTTCTAGCTGAGGGAAACTGTATTTTTCTTTCCCCAA
AGAGGAATGTAA

BRRS.13647_at (SEQ ID NO:144)
CTCGATTATTCCCTGTACAATATTTAAAATTTATTGCTTGATACTTTTGACAACAAAT
TAGGTTTTGTACAATTGAACTTAAATAAATGTCATTAAAATAAATAAATGCAATATG
TATTAATATTCATTGTATAAAAATAGAAGAATACAAACATATTTGTTAAATATTTAC
ATATGAAATTTAATATAGCTATTTTTATGGAATTTTTCATTGATATGAAAAATATGA

TATTGCATATGCATAGTTCCCATGTTAAATCCCATTCATAACTTTCATTAAAGCATTT
ACTTTGA

BRRS.13648_s_at (SEQ ID NO:145)
GCAAATAAATTCATACATAGTACATACAAAATAAGAGAAAAAATTAAATTGCAGAT
GGTTAAATATCACATCACTTAACTGATGTTACTGAAAATGTATTTTCCTGCATAATC
ATATGGTTGACAGTATGCATTAAGAAGGTAAGTAAAACAATGAAGACAATTTTGAT
TTAATATGGTAATGCACAATTCCAACTAACGTACATTCAACAGATCATGAAATTGG
GTTATT

BRRS.13767_at (SEQ ID NO:146)
TTGCCTTCTAAATATACTGAAATGATTTAGATATGTGTCAACAATTAATGATCTTTT
ATTCAATCTAAGAAATGGTTTAGTTTTTCTCTTTAGCTCTATGGCATTTCACTCAAGT
GGACAGGGGAAAAAGTAATTGCCATGGGCTCCAAAGAATTTGCTTTATGTTTTTAG
CTAT

BRRS.13859_at (SEQ ID NO:147)
CCTGGCCACTCGCAAGACCTTTTATCTGAAAACCAGCCAAGCTTTATTCACGACACA
CTTCTTCCCTTCACTCTCCCACTTCTGTGGTCAACTCCCTGCAGAACTCCCAAACTGC
CGTTCTTTTCGATAGCTCACGATGGTGTATGAGTGTCAATCATCTGACCCTTCTTGG
AGTCTCATATTTCGTGGAAC

BRRS.13881_at (SEQ ID NO:148)
CTGAGGACCGGCTGCAGACCTCACTCTGAGTGGCAGGCAGAGAACCAAAGCTGCTT
CGCTGCTCTCCAGGGAGACCCTCCTGGGATGGGCCTGAGAGGCCGGGGCTCAGGGA
AGGGGCTGGGATCGGAACTTCCTGCTCTTGTTTCTGGACAACTTTCCCCTTCTGCTTT
AAAGGTTGTCGATTATT

BRRS.14465_s_at (SEQ ID NO:149)
AGTGTGATGGATCCCCTTTAGGTTATTTAGGGGTATATGTCCCCTGCTTGAACCCTG
AAGGCCAGGTAATGAGCCATGGCCATTGTCCCCAGCTGAGGACCAGGTGTCTCTAA
AAACCCAAACATCCTGGAGAGTATGCGAGAACCTACCAAGAAAAACAGTCTCATTA
CTCATATACAGCAGGCAAAGAGACAGAAAATTAACTGAAAAGCAGTTTAGAGACT
GGGGGAGGCCGGATCTCTAGAGCCATCCTG

BRRS.15053_at (SEQ ID NO:150)
GCGTTACAGATGGACGTAGCTGCCTTGGTTTTCCAGTCCTCAAGGGAATACTGAAG
ATGCTGACTGAAGGGGATTGGATGTTGATTTTAGAAGATGGAGAACTCCAGCCACC
TTTGTAAAGCACTAGTGTTTGTCATTTATGTAAGTCAGGTCGGCTCAGGTCTTGATA
GTCCGTCTTGGTGTGAGGCATGC

BRRS.16228_s_at (SEQ ID NO:151)
CACAGTAATGTCGAAACTAGGCCTTTGAACCAAGGCAGTCTAGGGTAAAATATAGT
TTCAAAGTATGAATAAGAATTGGTATTTGTGTTATCTTTGAGTAAGAAACTGTCCGA
TATGAATCACAACGTGGGTGAATGTAGTATTTTCCTGAAGTGTG

BRRS.16746_s_at (SEQ ID NO:152)
GGCCATGAACATCACCTGCACAGGACGGGGACCAGACAACTGTATCCAGTGTGCCC
ACTACATTGACGGCCCCCACTGCGTCAAGACCTGCCCGGCAGGAGTCATGGGAGAA
AACAACACCCTGGTCTGGAAGTACGCAGACGCCGGCCATGTGTGCCACCTGTGCCA
TCCAAACTGCACCTACGGG

BRRS.16747_at (SEQ ID NO:153)
ATCACAGGTTTGAGCTGAATTATCACATGAATATAAATGGGAAATCAGTGTTTTAG
AGAGAGAACTTTTCGACATATTTCCTGTTCCCTTGGAATAAAAACA

BRRS.16948_s_at (SEQ ID NO:154)
AGTTTCAGACAAATGTTCAGTGTGAGTGAGGAAAACATGTTCAGTGAGGAAAAAAC
ATTCAGACAAATGTTCAGTGAGGAAAAAAAGGGGAAGTTGGGGATAGGCAGATGT
TGACTTGAGGAGTTAATGTGATCTTTGGGGAGATACATCTTATAGAGTTAGAAATA
GAATCTGAATTTCTAAAGGGAGATTCTGGCTTGGGA

BRRS.17863_s_at (SEQ ID NO:155)
AACTTAAGCTGAATGTGTAATGGATTTGTCTATAGTTTTACATATTTGGAAGCATTT
TAAAATAGGTTTTAATCTTACATAAAATTACTTTTATACTTGTGTTAACATTTTCTTC
TGTGCCTTTTGGGTAATTTAATTTCTGTTATGAATTTCTGGTGCCTATGAGCTAGCTA
TCACCTACCTGAAAGGTGCTTAGAGGTGAAGGTACTGTTTCTAAAAACACATCACT
GTGACACCTTTCTATCCTCACATTTTCAAGCTTGCCTCTTTTCT

BRRS.17909_s_at (SEQ ID NO:156)
GTGACTGCTTATGAAGGGTTATTGCTCAGCTAAGTATTTCTGAATGAGTCTTAGGTC
TGTTGGCCTTCAATCTCTACCGAAACCCTGAGAACTTGATGATGCTTTTGTTTTCTGA
GAATCGTTTCAGTGTGCTGG

BRRS.18137_at (SEQ ID NO:157)
CATTTGCTGCAACTCTCAGTGGTAAGAATGATTAAGTGCAGCTATAGGAGAATACTT
CCATTGGCATGCCACCTGCGTAAAACACACAATTTTGTTAAGATATACAATAAAATT
ATTATGCTAATAGCAAATATTTTATGTAGCTCACTATGTTCCATGTAGTCTTCTAAGT
GCTTCATGTTAGTCCCCAGTTAAACACCTGGTTTTGGAAGGCTGAG

BRRS.18652_s_at (SEQ ID NO:158)
GTGAGCCTGCCAGCGTTTGCGACGTCCCCGCACGACAGGCTCATACTTTCTGAGGAT
CGTGCATAGCATAGGACGTCTGAACCTTTGTACAAATGTGTAGATGACATCTTGCTA
CAGCTTTTATTTGTGAAT

BRRS.2573_s_at (SEQ ID NO:159)
GTAAATTCAATACAATGTCAGTTTTTAAAAGTCAAAGTTAGATCAAGAGAATATTTC
AGAGTTTTGGTTTACACATCAAGAAACAGACACACATACCTAGGAAAGATTTACAC
AATAGATAATCATCTT

BRRS.2644_at (SEQ ID NO:160)
ACTGTACAAAGTATAAGTCTTAGATGTATATATTTCCTATATTGTTTTCAGTGTACAT
GGAATAACATGTAATTAAGTACTATGTATCAATGAGTAACAGGAAAATTTTAAAAA
TACAGATAGATATATGCTCTGCATGTTACATAAGATAAATGTGCTGAATGGTTTTCA
AATAAAAATGAGGTACTCTCCTGGAAATATTAAGAAAGACTATCTAAATGTTGAAA
GA

BRRS.2783_s_at (SEQ ID NO:161)
GAGGACCGAGCACAGAAATCTTAGAGATTTCTTGTCCCCTCTCAGGTCATGTGTAGA
TGCGATAAATCAAGTGATTGGTGTGCCTGGGTCTCACTACAAGCAGCCTATCTGCTT
AAGAGACTCTGGAGTTTCTTATGTGCCCTGGTGGACACTTGCCCACCATCCTGTGAG
TAAAAGTGAA

BRRS.2935_at (SEQ ID NO:162)
TCTGAACTCTCAAAAGTCTATTTTTTTAACTGAAAATGTAAATTTATAAATATATTC
AGGAGTTGGAATGTTGTAGTTACCTACTGAGTAGGCGGCGATTTTTGTATGTTATGA
ACATGCAGTTCATTATTTTGTGGTTCTATTTTACTTTGTACTTGTGTTTGCTTAAACA
AAGTGACTGTTTGGCTTATAAACACATTGAATGCGCTTTATTGCCCATGGGATATGT
GGTGTATATCCTTCCAAAAAATTAAAACGAAAATAAAGTAGCTGCGATTGG

BRRS.3099_at (SEQ ID NO:163)
ATTCCTGTCATTACCCATTGTAACAGAGCCACAAACTAATACTATGCAATGTTTTAC
CAATAATGCAATACAAAAGACCTCAAAATACCTGTGCATTTCTTGTAGGAAAACAA
CAAAAGGTAATTATGTGTAATTATACTAGAAGTTTTGTAATCTGTATCTTATC

BRRS.3131_at (SEQ ID NO:164)
CAGGACCCATCACGCCTGTGCAGTGGCCCCCACAGAAAGACTGAGCTCAAGGTGGG
AACCACGTCTGCTAACTTGGAGCCCCAGTGCCAAGCACAGTGCCTGCATGTATTTAT
CCAATAAATGTGAAATTCTGTCC

BRRS.3220_at (SEQ ID NO:165)
AAAGTGGCATTTTCTTGATTGGAAAGGGGGAAGGATCTTATTGCACTTGGGCTGTTC
AGAATGTAGAAAGGACATATTTGAGGAAGTATCTATTTGAGCACTGATTTACTCTGT
AAAAAGCAAAATCTCTCTGTCCTAAACTAATGGAAGCGATTCTCCCATGCTCATGTG
TAATGGTTTTAACGTTACTCACTGGAGAGATTGGACTTTCTGGAGTTATTTAACCAC
TATGTTCAG

BRRS.3319_at (SEQ ID NO:166)
TTTATAATGTCCCTTCACAAACCCAGTGTTTTAGGAGCATGAGTGCCGTGTGTGTGC
GTCCTGTCGGAGCCCTGTCTCCTCTCTCT

BRRS.3319_s_at (SEQ ID NO:167)
CACCCTCAGATGCACATGAGCTGGCGGGATTGAAGGATGCTGTCTTCGTACTGGGA
AAGGGATTTTCAGCCCTCAGAATCGCTCCACCTTGCAGCTCTCCCCTTCTCTGTATTC
CTAGAAACTGACACATGCTGAACATCACAGCTTATTTCCTCATTT

BRRS.3645_s_at (SEQ ID NO:168)
AAATTTAATTTTCTACGCCTCTGGGGATATCTGCTCAGCCAATGGAAAATCTGGGTT
CAACCAGCCCCTGCCATTTCTTAAGACTTTCTGCTGCACTCACAGGATCCTGAGCTG
CACTTACCTGTGAGAGTCTTCAAACTTTTAAACCTTGCCAGTCAGGACTTTTGCTATT
GCA

BRRS.4126_s_at (SEQ ID NO:169)
CTACTCCTTACAGTCTCTAGAATTAAATGTACTCATTTAGACAACATATTAAATGCA
TATTTTAGCCACTTTAGAGAAACCTCATAGGCACAGAGTTTCCAAGATTAATTTTAA
GAATATCTTCACGAACTTGACCCTCCTACTCCACATTGCAACATTTCCATCAGACAG
CATTTCAATTCCAGTATTAT

BRRS.455_at (SEQ ID NO:170)
GTCATCATATATAATTAAACAGCTTTTTAAAGAAACATAACCACAAACCTTTTCAAA
TAATAATAATAATAATAATAAAAAATGTATTTTAAAGATGGCCTGTGGTTATCTTGG
AAATTGGTGATTTATGCTAGAAAGCTTTTAATGTTGGTTTATTGTTGAATTCCTAGA
A

BRRS.4562_at (SEQ ID NO:171)
CATGGATTAGCTGGAAGATCTGTATTTGATGGAAGACCTTGAAATTATTGGAAGAC
ATGGATTTCCTGGAAGACGTGGATTTTCCTGGAAGATCTGGATTTGGTGGAAGACC
AGTAATTGCTGGAAGACTGGATTTGCTGGAAGACTTGATTTACTGGAAGACTTGGA
GCTTCTTGGAAGACATGGATTGTCCGGAAGACATGGATTGTCTGGAAGATGTGGAT
TTTCTGGAAGCTCAG

BRRS.487_s_at (SEQ ID NO:172)
GTGGAGGAAACTAAACATTCCCTTGATGGTCTCAAGCTATGATCAGAAGACTTTAA
TTATATATTTTCATCCTATAAGCTTAAATAGGAAAGTTTCTTCAACAGGATTACAGT
GTAGCTACCTACATGCTGAAAAATATAGCCTTTAAATCATTTTTATATTATAACTCT
GTATAATAGAGATAAGTCCATTTTTTAAAAATGTTTTCCCCAAACCATAAAACCCTA
TACAAGTTGTTCTAGTAACAATACATGA

BRRS.4891_s_at (SEQ ID NO:173)
TCAATAAGGGCGTTCTTCCTTGCAAGTTGAAACATTATTGTGCTAGGATTGCTCTCT
AGACAAGCCAGAAGTGACTTATTAAACTATTGAAGGAAAAGGACTCAAGAAAAAT
AATAAAAGACCATAAATAAGGGCGAAAACATTACCATGTGAAAAGAATGTATTTCA
CCTGCAAGTTACAAAAAAATAGTTTGTGCATTGCAAATAAGCAAAGACTTGGATTG
ACTTTACATTCATC

BRRS.4996_at (SEQ ID NO:174)
AAGCTGTGTTGTTGCTTCTTGTGAAGGCCATGATATTTTGTTTTTCCCCAATTAATTG
CTATTGTGTTATTTTACTACTTCTCTCTGTATTTTTTCTTGCATTGACATTATAGACAT
TGAGGACCTCATCCAAACAATTTAAAAATGAGTGTGAAGGGGGAACAAGTCAAAAT
ATTTTTAAAAGATCTTCAAAAATAATGCCTCTGTCTAGCATGCCAACAAGAATGCAT

BRRS.524_s_at (SEQ ID NO:175)
TGCCTGTTGTAGACCACAGTCACACACTGCTGTAGTCTTCCCCAGTCCTCATTCCCA
GCTGCCTCTTCCTACTGCTTCCGTCTATCAAAAAGCCCCCTTGGCCCAGGTTCCCTG
AGCTGTGGGATTCTGCACTGGTGCTTTGGATTCCCTGATATGTTCCTTCAAA

BRRS.5356_at (SEQ ID NO:176)
GTCAGACAGATGTGGTTGCATCCTAACTCCATGTCTCTGAGCATTAGATTTCTCATT
TGCCAATAATAATACCTCCCTTAGAAGTTTGTTGTGAGGATTAAATAATGTAAATAA
AGAACTAGCATAACACTCAAAAA

BRRS.5451_at (SEQ ID NO:177)
TCTGTGTGTGCCCTGTAACCTGACTGGTTAACAGCAGTCCTTTGTAAACAGTGTTTT
AAACTCTCCTAGTCAATATCCACCCCATCCAATTTATCAAGGAAGAAATGGTTCAGA
AAATATTTTCAGCCTACAGTTATGTTCAGTCACACACACATACAAAATGTTCCTTTT
GCTTTTAAAGTAATTTTTGACTCCCAGATCAGTCAGAGCCCCTACAGCATTGTTAA

BRRS.6371_at (SEQ ID NO:178)
GTTTAAGCCTGGAACTTGTAAGAAAATGAAAATTTAATTTTTTTTTCTAGGACGAGC
TATAGAAAAGCTATTGAGAGTATCTAGTTAATCAGTGCAGTAGTTGGAAACCTTGCT
GGTGTATGTGATGTGCTTCTGTGCTTTTGAATGACTTTATCATCTAGTCTTTGTCTAT
TTTTCCTTTGATGTTCAAGTCCTAGTCTATAGGATTGGCAGTTTAA

BRRS.6611_at (SEQ ID NO:179)
GACTGAGGGATCGTAGATTTTTACAATCTGTATCTTTGACAATTCTGGGTGCGAGTG
TGAGAGTGTGAGCAGGGCTTGCTCCTGCCAACCACAATTCAATGAATCCCCGACCC

CCCTACCCCATGCTGTACTTGTGGTTCTCTTTTTGTATTTTGCATCTGACCCCGGGGG
GCTGGGACAGATTGGCAATGGGCCGTCCCCTCTCCCCTTGGTTCTGCACTGTTGCCA
ATAAAAAGCTCTTAA

BRRS.6619_at (SEQ ID NO:180)
GGAGGGAAGGCAAGATTCTTTCCCCCTCCCTGCTGAAGCATGTGGTACAGAGGCAA
GAGCAGAGCCTGAGAAGCGTCAGGTCCCACTTCTGCCATGCAGCTACTATGAGCCC
TCGGGGCCTCCTCCTGGGCCTCAGCTTGCCCAGATACATACCTAAATATATATATAT
ATATATGAGGGAGAACGCCTCACCCAGATTTTATCATGCTGGAAAGAGTGTATGTA
TGTGAAGATGCTTGGTCAACTTGTACCCAGTGAACACACAAA

BRRS.6619-22_at (SEQ ID NO:181)
GGAGGGAAGGCAAGATTCTTTCCCCCTCCCTGCTGAAGCATGTGGTACAGAGGCAA
GAGCAGAGCCTGAGAAGCGTCAGGTCCCACTTCTGCCATGCAGCTACTATGAGCCC
TCGGGGCCTCCTCCTGGGCCTCAGCTTGCCCAGATACATACCTAAATATATATATAT
ATATATGAGGGAGAACGCCTCACCCAGATTTTATCATGCTGGAAAGAGTGTATGTA
TGTGAAGATGCTTGGTCAACTTGTACCCAGTGAACACACAAA

BRRS.6684_at (SEQ ID NO:182)
TATTCTTCTATAACACTCTATATAGAGCTATGTGAGTACTAATCACATTGAATAATA
GTTATAAAATTATTGTATAGACATCTGCTTCTTAAACAGATTGTGAGTTCTTTGAGA
AACAGCGTGGATTTTACTTATCTGTGTATTCACAGAGCTTAGCACAGTGCCTGGTAA
TGAGCAAGCATACTTGCCATTACTTTTCCTTCCCA

BRRS.7616_at (SEQ ID NO:183)
CCTAATTTGAGGGTCAGTTCCTGCAGAAGTGCCCTTTGCCTCCACTCAATGCCTCAA
TTTGTTTTCTGCATGACTGAGAGTCTCAGTGTTGGAACGGGACAGTATTTATGTATG
AGTTTTTCCTATTTATTTTGAGTCTGTGAGGTCTTCTTGTCATGTGAGTGTGGTTGTG
AATGATTTCTTTTGAAGATATATTGTAGTAGATGTTACAATTTTGTCGCCAAACTAA
ACTTGCTGCTTAATGATTTGCTCACATCTAGTAAA

BRRS.7901_at (SEQ ID NO:184)
GGACACTTTTGAAAACAGGACTCAGCATCGCTTTCAATAGGCTTTTCAGGACCTTCA
CTGCATTAAAACAATATTTTTAAAAATTTAGTACAGTTTAGAAAGAGCACTTATTTT
GTTTATATCCATTTTTTCTTACTAAATTATAGGGATTAACTTTGACAAATCATGCTGC
TGTTATTTTCTACATTTGTATTTTATCCATAGCACTTATTCACATTTAGGAAAA

BRRS.81_at (SEQ ID NO:185)
CAGTTTCTGTTCTCTCACAGGTGATAAACAATGCTTTTTGTGCACTACATACTCTTCA
GTGTAGAGCTCTTGTTTTATGGGAAAAGGCTCAAATGCCAAATTGTGTTTGATGGAT
TAATATGCCCTTTTGCCGATGCATACTATTACTGATGTGACTCGGTTTTGTCGCAGCT
TTGCTTTGTTTAATGAAACACACTTGTAAACCTCTTTTGCACTTTGAAAAAGAATCC
AGCGGGATGCTCGAGCACCTGTAAACAATTTTCTCAACCTATTTG

BRRS.81-22_at (SEQ ID NO:186)
CAGTTTCTGTTCTCTCACAGGTGATAAACAATGCTTTTTGTGCACTACATACTCTTCA
GTGTAGAGCTCTTGTTTTATGGGAAAAGGCTCAAATGCCAAATTGTGTTTGATGGAT
TAATATGCCCTTTTGCCGATGCATACTATTACTGATGTGACTCGGTTTTGTCGCAGCT
TTGCTTTGTTTAATGAAACACACTTGTAAACCTCTTTTGCACTTTGAAAAAGAATCC
AGCGGGATGCTCGAGCACCTGTAAACAATTTTCTCAACCTATTTG

BRRS.8480_s_at (SEQ ID NO:187)

AGCAAGTGTAGACACCTTCGAGGGCAGAGATCGGGAGATTTAAGATGTTACAGCAT
ATTTTTTTTTCTTGTTTTACAGTATTCAATTTTGTGTTGATTCAGCTAAATTATGAAA

BRRS.8711_at (SEQ ID NO:188)
GTCTCACATATTTATATAATCCTCAAATATACTGTACCATTTTAGATATTTTTTAAAC
AGATTAATTTGGAGAAGTTTTATTCATTACCTAATTCTGTGGCAAAAATGGTGCCTC
TGATGTTGTGATATAGTATTGTCAGTGTGTACATATATAAAACCTGTGTAAACCTCT
GTCCTTATGAACCATAACAAATGTAGCTTTTTA

BRRS.8900_s_at (SEQ ID NO:189)
CAGCCCCACCCCTGTAAATGGAATTTACCAGATGAAGGGAATGAAGTCCCTCACTG
AGCCTCAGATTTCCTCACCTGTGAAATGGGCTGAGGCAGGAAATGGGAAAAAGTGT
TAGTGCTTCCAGGCGGCACTGACAGCCTCAGTAACAATAAAAACAA

BRSA.1686C1n5_at (SEQ ID NO:190)
TCAGCTGCCCTGAAACAGCCCATGTCCCAAGTTCTTCACCTCTATCCAAAGAACTTG
ATTTGCATGGATTTTGGATAAATCATTTCAGTATCATCTCCATCATATGCCTGACCCC
TTGCTCCCTTCAATGCTAGAAAATCGAGTTGGCAAAATGGGGTTTGGGCCCCTCAGA
GCCCTGCCCTGCACCCTTGTACAGTGTCTGTGCCATGGATTTCGTTTTTCTTGGGGTA
CTCTTGATGTGAAGATAATTTGCA

BRSA.8072C1n2_s_at (SEQ ID NO:191)
GAGTGTCTCAGAAGTGTGCTCCTCTGGCCTCAGTTCTCCTCTTTTGGAACAACATAA
AACAAATTTAATTTTCTACGCCTCTGGGGATATCTGCTCAGCCAATGGAAAATCTGG
GTTCAACCAGCCCCTGCCATTTCTTAAGACTTTCTGCTCCACTCACAGGATCCTGAG
CTGCACTTACCTGTGAGAGTCTTCAAACTTTTAAACCTTGCCAGTCAGGACTTTTGC
TATTGCA

Hs369056.20C1n2_at (SEQ ID NO:192)
GAGGGACGTCAGAAAATCAGTGCATTGTGGAGTCACTTTTCTGATAAAGGGCACAT
CAGACTGCAAATGGTCCAGACAGCCAGATTCAGGACACTGATGAGTTTCTGGGGTC
ACCATAGCATCCCTGGAGTCAGCTGCTCTGCAGCCTGAAGGAGGGCTGACAGTGTG
GAGTCACTGCTATTACTTAATGAAATTATATAGAAATTCTATAATGATTATGTAATT
GCATAATGAAAACTCTCCATATCAGAGTTCAGAATATCTCCCAATTTCCAGTACAGA
ATATTATCCATAAC

Hs488293.0CB1n69_at (SEQ ID NO:193)
GACAGCAATAACTTCGTTTTAGAAACATTCAAGCAATAGCTTTATAGCTTCAACATA
TGGTACGTTTTAACCTTGAAAGTTTTGCAATGATGAAAGCAGTATTTGTACAAATGA
AAAGCAGAATTCTCTTTTATATGGTTTATACTGTTGATCAGAAATGTTGATTGTGCA
TTGAGTATTAAAAAATTAGATGTATATTATTCATTGTTCTTTACTCATGAGTACCTTA
TAATAATAATAATGTATTCTTTGTTAACAATGCCATGTTGGTACTAGTTATTAATCAT
ATC

Hs494173.0CB4n15_at (SEQ ID NO:194)
GGCAGGATATTGTAAGCCTTGAAAAAGAATTAGGCAGGATATCGGAAGCCCTGATT
AGATTCTATCCTAAGAGCAACAGAAGATCACTGACAGTGTTTTAAATAGATAGACT
AGTTTATTAGATTTGCAGTTTAGAAGTTCCCTTTTTTTTGTAATTATTGGACAGTGTAG
AGACCGGATGGTGAGAGATGAGTTAGGAAGTTGTGACAGCTCTCTATACCTACCGC
TAATGTAGAGGATTATTTATTTTCATTTCATTACCATTCGTGT

Hs513726.0C2n39_s_at (SEQ ID NO:195)
GTAATATGTTTATAATCCTTTAGATCTTATAAATATGTGGTATAAGGAATGCCATAT
AATGTGCCAAAAATCTGAGTGCATTTAATTTAATGCTTGCTTATAGTGCTAAAGTTA
AATGATCTTAATTCTTTGCAATTATATATGAAAAATGACTGATTTTTCTTAAAATAT
GTAACTTATATAAATATATCTGTTTGTACAGATTTTAACCATAA

Hs514006.0C1n8_at (SEQ ID NO:196)
GTATCCTTGAACTGGAAACCATCCACGATCGAGTATCGAGTCATTCAACACTATCAA
TTCCTGGGTGACTTTTTGAAAAAGTAGTATCTCTTGTTGCAAGAAATGCTCCATCTG
TGAGTCCATGTCTCTCACTGGAATTGGATGGAAGTGGTGAATTTCAGCCAAAGTGG
CCAAAGAAATCCTGTTCCTGTGATTCTGACGTCATCAGCCTCTGCACCTCTGTCTTCC
CTTCTGCCACATGTTGCCTGTTCTCCGTGACTTTGGTAAGA

Hs522202.0C1n6_at (SEQ ID NO:197)
GAGAGAGTGATCACGCTGCTGTGCCCACCTATGCGGTAGACCTTGTTCCTGGGTTGG
GAGATGTTTTATGATCAGGGTGCAGTAGAAAGAGCACACTAGTAGCAGTAAAGAGA
GGTGACCCTGGCTGCAGTTCTGCCTCTAACTTCCTGAGTGACCTCAGGCTAGTCACA
CAGTGACTGCTCCCCACATTTCTTTTTGTAAGCTGCAAGGATTGAATCAGACAATAG
CCTCTAAGTTTCTTCTGAACTCTCATACTCAGGGATGCCAA

Hs524348.0CB1n97_at (SEQ ID NO:198)
TTCCCTCCCACTAATTTGTTGGCCTTTAACAGCAATTTTGAAAACTGGGTCTTCTGGT
TATGTTTTTGTTTTAAAATCTTTAAATTAGAGGATGCTGTGCCATTGAGTACTTTAAG
TTAATATGAGGTTCTGGTTCAAGGAAAACTTACGTTGGATCTGAACCAATGAGCAG
ATATTTTGATATGTGCCACTCTTGCATATACATCTCAGTCCTAACTAAAGGTTCTAGT
GGCATCCAGGACCTTTAGGGAGGCATTT

Hs524348.2C1n5_s_at (SEQ ID NO:199)
CACTGCGTCTGGCAATAATGTAACTTTGAAGCTTAAAAATTAATCCCAGTTTGTAGC
AATAACAGAAGACTATCTACAACGGAAGAAAGAAGCAACTGCCTTACAGTTCTGTA
AAGAATTGGCAAGAAAATAAAGCCTATAGTTGCC

Hs528836.0C1n3_s_at (SEQ ID NO:200)
CCCTTACTTACATACTAGCTTCCAAGGACAGGTGGAGGTAGGGCCAGCCTGGCGGG
AGTGGAGAAGCCCAGTCTGTCCTATGTAAGGGACAAAGCCAGGTCTAATGGTACTG
GGTAGGGGGCACTGCCAAGACAATAAGCTAGGCTACTGGGTCCAGCTACTACTTTG
GTGGGATTCAGGTGAGTCTCCATGCACTTCACATGTTACCCAGTGTTCTTGTTACTTC
CAAGGAGAACCAAGAATGGCTCTGTCACACTCGAAGCCAGGTTTGATC

Hs591893.1C1n4_s_at (SEQ ID NO:201)
CCTCCTTTCTAAATGCAGCGACCTGTGTTCTTCAGCCCTATCCCTTTCTATTCCTCTG
ACCCCGCCTCCTTTCTAAATGCAGCGACCTCTGTTCTTCAGCCCTATCCCTTTCTATT
CCTCTGACCCCGCCTCCTTTCTAAATGCAGCGACCTCTG

Hs7155.0CB1n102_at (SEQ ID NO:202)
GGCGTCGGCGCCTAGGGCGAAGTGAGCCAGGGTGCAGTCGGGAAGCTCCAGGACG
AAGCGGCGCGGCGGAGCCATGGCCCCAGCGCAGACCCCGCGCCGCCCGAGCAGCG
GCCCCGACAGTGGCCCGCGCAGGAGCCGGCGGGCGAAGGCCATGGGCGCCTCAGC
GACGCCGCCCTCGGCCCCGCCTCGGAAACGAAACCTGGCGGGAGCCAGGCGCCGGC
GGGAAACGAAACCCGGAGGGAGCCAGGCGCCAGCGGGAAACGAAAGCGAAGCGT

CLAIMS

We claim:

1. A method of predicting responsiveness of an individual to a DNA-damage therapeutic agent comprising
    a. measuring expression levels of at least five biomarkers in a test sample obtained from the individual, wherein the at least five biomarkers are selected from the biomarkers in Table 2B;
    b. deriving a combined test score that captures the expression levels;
    c. providing a threshold score comprising information correlating the combined test score and responsiveness;
    d. and comparing the combined test score to the threshold score; wherein responsiveness is predicted when the combined test score exceeds the threshold score.

2. The method of claim 1, wherein the at least five biomarkers are selected from the group consisting of *CDR1*, *FYB*, *TSPAN7*, *RAC2*, *KLHDC7B*, *GRB14*, *AC138128.1*, *KIF26A*, *CD274*, *CD109*, *ETV7*, *MFAP5*, *OLFM4*, *PI15*, *FOSB*, *FAM19A5*, *NLRC5*, *PRICKLE1*, *EGR1*, *CLDN10*, *ADAMTS4*, *SP140L*, *ANXA1*, *RSAD2*, *ESR1*, *IKZF3*, *OR2I1P*, *EGFR*, *NAT1*, *LATS2*, *CYP2B6*, *PTPRC*, *PPP1R1A*, and *AL137218.1*.

3. The method of claim 2, wherein the combined test score captures the expression levels of all 44 biomarkers of Table 2B, and wherein responsiveness is predicted when the combined test score exceeds a threshold score calculated using the weights of Table 2B.

4. The method of any one of claims 1-3, wherein the DNA-damage therapeutic agent comprises one or more substances selected from the group consisting of: a DNA damaging agent, a DNA repair targeted therapy, an inhibitor of DNA damage signalling, an inhibitor of DNA damage induced cell cycle arrest, a histone deacetylase inhibitor, and a heat shock protein inhibitor.

5. The method of claim 4, wherein the DNA-damage therapeutic agent comprises one or more of an anthracycline, a cisplatin, a carboplatin, a cyclophosphamide, an oxaliplatin, a busulphan, an irinotecan, a topotecan, an etoposide, a doxorubicin, an epirubicin, and an ionising radiation.

6. The method of claim 4, wherein the DNA-damage therapeutic agent comprises one or more of a DNA-PK inhibitor, Nu7441, Nu7026, an inhibitor of homologous recombination, an inhibitor of

nucleotide excision repair, a PARP inhibitor, AG014699, AZD2281, ABT-888, MK4827, BSI-201, INO-1001, TRC-102, an APEX 1 inhibitor, an APEX 2 inhibitor, a Ligase III inhibitor, and an inhibitor of the Fanconi anemia pathway.

7. The method of any one of claims 1-6, wherein the individual is suspected of having or has been diagnosed as having a cancer.

8. The method of claim 7, wherein the cancer is selected from the group consisting of melanoma, colon cancer, breast cancer, and ovarian cancer.

9. The method of claim 8, wherein the cancer is breast cancer and the DNA-damage therapeutic agent comprises a combination of a 5-fluorouracil, an anthracycline and a cyclophosphamide.

10. The method of claim 9, wherein the anthracycline is epirubicin.

11. The method and claim 9, wherein the anthracyline is doxorubicin.

12. The method of claim 9, wherein a taxane is to be co-administered with the DNA-damage therapeutic agent.

13. The method of claim 8, wherein the cancer is ovarian cancer and the DNA-damage therapeutic agent comprises a platinum-containing agent.

14. The method of claim 13, wherein the DNA-damage agent is to be co-administered with a taxane.

15. The method of any one of claims 7-14, wherein the cancer is associated with one or more mutations in the Fanconi anemia/BRCA pathway.

16. A method of diagnosing an individual for having a cancer associated with a DNA damage response deficiency (DDRD) comprising

    a. measuring expression levels of at least five biomarkers in a test sample obtained from the individual, wherein the at least five biomarkers are selected from the biomarkers in Table 2B;
    b. deriving a combined test score that captures the expression levels;
    c. providing a threshold score comprising information correlating the combined test score and a diagnosis of the cancer;

d. and comparing the combined test score to the threshold score; wherein the individual is diagnosed as having the cancer when the test score exceeds the threshold score.

17. The method of claim 16, wherein the at least five biomarkers are selected from the group consisting of CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

18. The method of claim 17, wherein the combined test score captures the expression levels of all 44 biomarkers of Table 2B, and wherein the individual is diagnosed as having the cancer when the combined test score exceeds a threshold score calculated using the weights of Table 2B.

19. The method of any one of claims 16-18, wherein the cancer is selected from melanoma, colon cancer, breast cancer, and ovarian cancer.

20. The method of claim 19, wherein the cancer is associated with one or more mutations in the Fanconi anemia/BRCA pathway.

21. A method of detecting a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and detection of the cancer;

d. and comparing the test score to the threshold score; wherein the cancer with DNA damage response deficiency related immune signalling is detected when the test score exceeds the threshold score.

22. The method of claim 21, wherein the one or more biomarkers are:

a. *CXCL10* and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. IDO1 and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of CXCL10, MX1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1; or

c. selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3.

23. A method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent appropriate for treatment of the individual is selected when the test score exceeds the threshold score.

24. A method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from

the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent that targets tumors with abnormal DNA damage response is selected when the test score exceeds the threshold score.

25. A method of selecting an appropriate therapy to treat a cancer with DNA damage response deficiency related immune signalling in an individual comprising:

a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers comprise at least one biomarker selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. deriving a test score that captures the expression levels;

c. providing a threshold score comprising information correlating the test score and selection of the appropriate therapy;

d. and comparing the test score to the threshold score; wherein a therapeutic agent that inhibits expression of at least one of the biomarkers is selected when the test score exceeds the threshold score.

26. The method of any one of claims 23 to 25, wherein the one or more biomarkers are:

a. CXCL10 and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. IDO1 and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of CXCL10, MX1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1; or

c. selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3.

27. The method of any one of claims 21 to 26, wherein the cancer is melanoma, leukemia, brain cancer, prostate cancer, liver cancer, ovarian cancer, stomach cancer, colorectal cancer, throat cancer, breast cancer, skin cancer, lung cancer, sarcoma, cervical cancer, testicular cancer, bladder cancer, endocrine cancer, endometrial cancer, esophageal cancer, glioma, lymphoma, neuroblastoma, osteosarcoma, pancreatic cancer, pituitary cancer or renal cancer.

28. Use of a therapeutic agent in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of claim 21 or claim 22.

29. Use of a therapeutic agent that targets tumors with abnormal DNA damage response in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of claim 21 or claim 22.

30. Use of a therapeutic agent that inhibits expression of at least one of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1 in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined according to the method of claim 21 or claim 22.

31. Use of a therapeutic agent in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune

signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

32. Use of a therapeutic agent that targets tumors with abnormal DNA damage response in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

33. Use of a therapeutic agent that inhibits expression of at least one of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1 in the manufacture of a medicament for treating a cancer in an individual, wherein the cancer displays DNA damage response deficiency related immune signalling as determined by the level of expression of one or more biomarkers selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

34. The use according to any one of claims 28 to 33, wherein the one or more biomarkers are:

a. CXCL10 and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5,

OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1;

b. IDO1 and at least 2, at least 3, or at least 4 additional biomarkers selected from the group consisting of CXCL10, MX1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, APOL3, CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR2I1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1; or

c. selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3.

35. The use according to any one of claims 28 to 34, wherein the cancer is melanoma, leukemia, brain cancer, prostate cancer, liver cancer, ovarian cancer, stomach cancer, colorectal cancer, throat cancer, breast cancer, skin cancer, lung cancer, sarcoma, cervical cancer, testicular cancer, bladder cancer, endocrine cancer, endometrial cancer, esophageal cancer, glioma, lymphoma, neuroblastoma, osteosarcoma, pancreatic cancer, pituitary cancer or renal cancer.

36. The method of claim 1 or 16, wherein the at least five biomarkers are selected from CXCL10, MX10, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3.