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(71) Applicants: **STICHTING HET NEDERLANDS KANKER INSTITUUT-ANTONI VAN LEEUWEN-HOEK ZIEKENHUIS** [NL/NL]; Plesmanlaan 121, NL-1066 CX Amsterdam (NL). **AGENDIA N.V.** [NL/NL]; Science Park 406, NL-1098 XH Amsterdam (NL).

(72) Inventors: **LINN, Sabine**; c/o Plesmanlaan 121, NL-1066 CX Amsterdam (NL). **SEVERSON, Tesa**; c/o Plesmanlaan 121, NL-1066 CX Amsterdam (NL). **PEETERS, Justine Kate**; c/o Science Park 406, NL-1098 XH Amsterdam (NL). **SIMON, Iris**; c/o Science Park 406, NL-1098 XH Amsterdam (NL).

(74) Agent: **JANSEN, C.M.**; V.O., Johan de Wittlaan 7, NL-2517 JR Den Haag (NL).

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(54) Title: METHODS FOR MOLECULAR CLASSIFICATION OF BRCA-LIKE BREAST AND/OR OVARIAN CANCER

(57) Abstract: The invention relates to a method of assigning treatment to a breast and/or ovarian cancer patient. More specifically, the invention relates to a method for classification of breast and/or ovarian cancer as BRCA-like or sporadic-like by determining a level of expression of a set of genes and comparing said level of expression to a reference. A patient that is classified as BRCA-like is treated with a DNA-damage inducing agent.



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METHODS FOR MOLECULAR CLASSIFICATION OF BRCA-LIKE BREAST AND/OR OVARIAN CANCER

Field of the invention

- 5 The invention relates to the field of oncology. More specifically, the invention relates to a method for typing breast and/or ovarian cancer cells. The invention provides means and methods for classification of breast and/or ovarian cancer cells.

Background of the invention

- 10 Maintenance of DNA integrity depends on homologous recombination, a conservative mechanism for error-free repair of double strand breaks (DSBs). In the absence of homologous recombination, alternative error-prone mechanisms such as non-homologous end joining are invoked, leading to genomic instability (Karran, 2000. *Curr Opin Genet Dev* 10: 144-50; Khanna and Jackson, 2001. *Nat Genet* 27: 247-54; van Gent et al., 2001. *Nat Rev Genet* 2: 196-206). This instability is thought to predispose to familial breast and/or ovarian cancer in patients carrying germ line mutations in BRCA1 or BRCA2, genes involved in homologous recombination. Absence of homologous recombination offers a potential drug target for therapies that lead to DSBs during the DNA replication phase, when homologous recombination is the dominant DSB repair mechanism.
- 20 Examples of these therapies are bifunctional alkylating agents, which cause DNA interstrand crosslinks resulting in direct DSBs in the DNA; platinum compounds, which give rise to mainly DNA intrastrand crosslinks resulting in DSBs during DNA replication; and poly(ADP-ribose)polymerase (PARP)-inhibitors (Bryant et al., 2005. *Nature* 434: 913-7; Fong et al., 2009. *N Engl J Med* 361: 123-34), which inhibit repair of single-strand DNA breaks also resulting in DSBs during replication. Recent evidence is indeed showing that BRCA1/-2-mutated breast cancers are particularly sensitive to such agents (Fong et al., 2009. *N Engl J Med* 361: 123-134; O'Shaughnessy et al., 2009. *J Clin Oncol* 27: 3; Silver et al., 2010. *J Clin Oncol* 28: 1145-1153; Tutt et al., 2010. *Lancet* 376: 235-44). This sensitivity is likely not restricted to BRCA1/-2-mutated breast cancers.

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- It is thought that up to 30% of sporadic (germline BRCA-wild type) breast cancers have defects in homologous recombination repair, a phenotype which is often referred to as 'BRCAness' (Turner et al., 2004. *Nat Rev Cancer* 4: 814-819). In order to identify sporadic breast cancers sensitive to agents which (directly or indirectly) induce DSBs,
- 35 many studies have focused on BRCA1-mutated breast cancers, since this group of tumors

is relatively homogenous, clustering within the basal-like, hormone-receptor and HER2-receptor negative (triple-negative (TN)) molecular subtype ('t Veer et al., 2002. Nature 415: 530; Sorlie et al., 2003. Proc Natl Acad Sci USA 100: 8418). Consequently, multiple trials with DSB-inducing agents have been performed in patients with TN breast cancer and indeed have shown excellent responses or improved outcome not only in mutation carriers (O'Shaughnessy et al., 2009. J Clin Oncol (Meeting Abstracts) 27:3; Silver et al., 2010. J Clin Oncol 28: 1145-1153).

BRCA2-mutated breast cancers show a similar distribution over the breast cancer subtypes as sporadic tumors (~70% estrogen-receptor (ER)- or progesterone-receptor (PR)-positive) (Lakhani et al., 2002. J Clin Oncol 20: 2310), and have not been studied extensively with a similar approach.

Adjuvant systemic treatment decisions for early breast and/or ovarian cancer are generally based on results of large randomized clinical trials conducted in the general breast cancer population, not taking into account the molecular heterogeneity of the disease (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005. Lancet 365: 1687-717). With this approach some treatment strategies that are highly beneficial to a small percentage of the general breast and/or ovarian cancer population may have been discarded in the past, such as intensified alkylating therapy (Fisher et al., 1999. J Clin Oncol 17: 3374-88; Nieto and Shpall, 2009. Curr Opin Oncol 21: 150-7). To investigate this, we hypothesized that a small subgroup of breast and/or ovarian cancer patients, with tumors that resemble BRCA-mutated breast and/or ovarian cancer, might derive substantial benefit from intensified therapy with a DNA-damage inducing agent, such as an alkylating agent.

Summary of the invention

The present inventors have developed a gene profile, termed 'BRCAness' profile that is indicative of the presence of a BRCA mutation in a breast and/or ovarian cancer cell, for example a sporadic breast cancer cell.

In one aspect, the invention provides a method of assigning treatment to a breast and/or ovarian cancer patient, the method comprising determining a level of expression for at least two genes that are selected from Table 1 in a relevant sample from the cancer patient, especially a breast and/or ovarian cancer patient or a ovarian cancer patient,

whereby the sample comprises expression products from a cancer cell of the patient; comparing said determined level of expression of the at least two genes to the level of expression of the at least two genes in a template; typing said sample as being BRCA-like or not, based on the comparison of the determined levels of expression; and

- 5 assigning DNA-damage inducing treatment to a breast and/or ovarian cancer patient of which the sample is classified as BRCA-like. Said relevant sample preferably is a breast cancer sample and/or an ovarian cancer sample.

- 10 In a preferred method according to the invention, the sample is typed by determining a level of RNA expression for at least two genes that are selected from Table 1 and comparing said determined RNA level of expression to the level of RNA expression of the at least two genes in a reference.

- 15 In one embodiment, said DNA-damage inducing treatment preferably comprises an alkylating agent, platinum salt and/or an inhibitor of poly(ADP-ribose) polymerase (PARP; collectively termed PARP inhibitor). Preferred DNA-damage inducing treatment comprises a nitrogen mustard alkylating agent, N,N'-triethylenethiophosphoramidate and carboplatin.

- 20 In another embodiment, said DNA-damage inducing treatment preferably comprises a PARP inhibitor, preferably 2-[(2R)-2-Methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide dihydrochloride benzimidazole carboxamide (ABT-888).

- 25 An DNA-damage inducing treatment, comprising a PARP inhibitor, preferably ABT-888, preferably further comprises a tyrosine kinase inhibitor. Said tyrosine kinase inhibitor preferably is (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide (Neratinib).

- 30 In a preferred method according to the invention, a level of expression of at least five genes from Table 1 is determined, more preferred a level of expression of all 77 genes from Table 1, in a relevant sample from the breast and/or ovarian cancer patient.

- 35 The level of expression of at least two genes from Table 1 in a relevant sample from the breast and/or ovarian cancer patient is compared to template, wherein the template preferably is a measure of the average level of said at least two genes in at least 10

independent individuals. Said at least 10 independent individuals are preferably suffering from breast and/or ovarian cancer.

It is further preferred that a method according to the invention is combined with a method of determining a metastasizing potential of the sample from the patient including, for example, a 70 gene Amsterdam profile (MammaPrint ®; (van 't Veer et al., 2002. Nature 415: 530) and other multigene expression tests such as a 21 gene signature (Oncotype DX®; Paik et al., 2004. New Engl J Med 351: 2817) and EndoPredict (Filipits et al., 2011. Clinical Cancer Research 17: 6012). A method of determining a metastasizing potential of the sample is a 70 gene Amsterdam profile. It is further preferred that a method according to the invention is combined with a method of determining the molecular subtype of the samples, for example with BluePrint (Krijgsman et al., 2011. BCRT 133: 37-47) or other multigene tests for determining molecular subtypes such as PAM50 (Chia et al., 2012. Clin Cancer Res 18: 4465-4472).

Brief description of the drawings

Figure 1

Overview of the strategy for generating the BRCAness signature.

5 Figure 2

Supervised hierarchical clustering of gene expression in triple negative breast tumors. Top differentially expressed genes in the triple negative cohort (ANOVA FDR < 0.0001) reveal two groups: one enriched for BRCA1-like status and one for sporadic-like status. Sample column: black is BRCA1-like and white indicates sporadic-like.

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Figure 3.

Survival analysis. We visualized the 10 year breast cancer specific survival (univariate) of the cohort with respect to BRCA1-like status using the Kaplan-Meier method. Multivariate survival analysis was performed using the Cox proportional hazards model.

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Figure 4

Scatter plot showing the AUC value (y-axis), indicative for to the identification of BRCA1-like patients, for groups of the top ranked genes (ANOVA). The x-axis displays the number of genes within the group. The red circles indicates the groups with the least errors in training of the model (N=2, 72, 77).

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Figure 5

Heatmap showing the standardized (median centered at zero) gene expression of BRCA1 and the Claudin genes represented on the Agilent chip. The samples are ordered by their BRCA1-like (DNA copy number) status (black) as depicted on the LHS of the heatmap.

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Detailed description of the invention

The term BRCA, as is used herein, refers to the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2). BRCA1 and BRCA2 are human genes that are known as tumor suppressor genes. Mutation of these genes has been linked to hereditary breast and ovarian cancer. In normal cells, BRCA1 and BRCA2 help ensure the stability of the cell's genetic material (DNA) and help prevent uncontrolled cell growth. Mutation of these genes has been linked to the development of hereditary breast and ovarian cancer. According to estimates of lifetime risk, about 12 percent of women (120 out of 1,000) in the general population will develop breast and/or ovarian cancer sometime during their lives compared with about 60 percent of women (600 out of 1,000) who have inherited a harmful mutation in BRCA1 or BRCA2.

Activation of BRCA after DNA damage occurs via activation of ataxia telangiectasia mutated serine-protein kinase (ATM) or ataxia telangiectasia and Rad3 related protein kinase (ATR). These kinases phosphorylate BRCA1 directly or indirectly (via cell cycle checkpoint kinase 2 (CHK2). ATM and ATR also phosphorylate histones (H2AX), which then co-localize together with some proteins to form nuclear foci at DNA damage sites. The foci may further include the tumor protein p53-binding protein 1 (53BP1) and the nuclear factor with BRCT domains protein 1 (NFB1), which take part in activation of CHK2. The so called MRN complex, consisting of double-strand break repair protein (Mre11), Rad50, and Nijmegen breakage syndrome 1 protein (Nibrin), is a part of these foci as well.

The term BRCA mutation, as is used herein, refers to a mutation in BRCA1 and/or BRCA2, preferably BRCA1, and/or in one or more other genes of which the protein product associates with BRCA1 and/or BRCA2 at DNA damage sites, including ATM, ATR, Chk2, H2AX, 53BP1, NFB1, Mre11, Rad50, Nibrin, BRCA1-associated RING domain (BARD1), Abraxas, and MSH2. A mutation in one or more of these genes may result in a gene expression pattern that mimics a mutation in BRCA1 and/or BRCA2. The BRCAness profile, therefore, is indicative of the presence of a mutation in one or more of these genes in a breast and/or ovarian cancer cell.

The term BRCAness, or BRCA-like, refers to a sporadic breast and/or ovarian cancer sample that phenotypically resembles a mutation BRCA1 and BRCA2, preferably BRCA1. For example, the term BRCAness or BRCA-like refers to sporadic breast and/or

ovarian cancers in which a BRCA1-like Comparative Genomic Hybridization (CGH) pattern is detected (Lips et al., 2011. Ann Oncol 22: 870-876; Vollebergh et al., 2011. Ann Oncol 22: 1561-1570), but in which no mutation of BRCA1 could be detected. Similarly, the term BRCAness or BRCA-like also refers to sporadic breast and/or ovarian cancers that show a correlation with the BRCAness profile, but in which no mutation of BRCA1 could be detected.

The term functionally inactivated, as used herein, refers to a genetic alteration that diminishes or abolishes the activity a BRCA-dependent DNA repair mechanism. Said alteration is an insertion, a point mutation, or, preferably, two or more point mutations, or a deletion in one of more genes of which the expression product is involved, preferably required, in the BRCA-dependent DNA repair mechanism. Said genes include BRCA1 and BRCA2.

The present invention therefore provides a method of assigning treatment to a breast and/or ovarian cancer patient, the method comprising determining a level of expression for at least two genes that are selected from Table 1 in a relevant sample from the breast and/or ovarian cancer patient, whereby the sample comprises expression products from a cancer cell of the patient; comparing said determined level of expression of the at least two genes to the level of expression of the at least two genes in a template; typing said sample as being BRCA-like or not, based on the comparison of the determined levels of expression; and assigning treatment comprising a DNA-damage agent to a breast and/or ovarian cancer patient of which the sample is classified as BRCA-like. The method for assigning treatment may assist in the selection of an optimal treatment of said patient by the treating physician.

Methods of classifying a sample from a breast and/or ovarian cancer patient according to the presence or absence of a BRCAness profile in a breast and/or ovarian cancer cell comprise determining the level of expression of genes from the gene profile, as indicated in Table 1. The methods of the invention allow classifying a breast and/or ovarian cancer sample into a "BRCAness" category; in cases where no mutation in BRCA1 and/or BRCA2 could be identified or no mutation analysis was performed. Therefore, the BRCAness profile allows the functional classification of a BRCA-like phenotype in a breast and/or ovarian cancer sample, in contrast to the genotypical classification that is provided by the analysis of genetic mutations in BRCA1 and/or BRCA2. As is indicated

hereinabove, the BRCAness profile can also be used to classify a sample from a breast and/or ovarian cancer patient in which the BRCA-dependent DNA repair mechanism is functionally inactivated by alteration of one or more genes encoding other components of the BRCA-dependent DNA repair mechanism.

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The term BRCAness, or BRCA-like, refers to the phenotypic characterization of a sample from breast and/or ovarian cancer patient that is or resembles a phenotype that is the result of genetic aberrations including aberrations in BRCA1 and/or BRCA2 genes. Said BRCAness or BRCA-like phenotype is preferably characterized by the BRCAness profile.

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It was found that breast and/or ovarian cancer patients with a BRCAness or BRCA-like phenotype have an improved response to treatment comprising a DNA-damage agent, compared to a breast and/or ovarian cancer patient without a BRCA-like phenotype.

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BRCA1 is required for proper function of a homologous recombination (HR)-mediated DNA repair pathway and deficiency results in genomic instability. BRCA mutated tumors have a specific pattern of alterations, which has been used to develop a BRCA-like classifier to distinguish between BRCA-like breast and/or ovarian cancers and breast and/or ovarian cancers with or without a mutation in BRCA1 and/or BRCA2. The genes depicted in Table 1 were identified in a multistep analysis of samples from breast cancer patients. In a first step, 128 breast cancer samples were classified according to the presence of mutations in BRCA1 as well as a specific pattern of chromosomal aberrations according to a Multiplex Ligation-dependent Probe Amplification (MLPA) assay, to identify both BRCA1-like mutated breast cancers and sporadic cases (Lips et al., 2011. Breast Cancer Research 13: R107). A total of 61 breast cancer samples were identified to have a BRCA1-like CGH profile (8 of which actually presented with a BRCA1 mutation), A total of 67 breast cancer samples were scored as sporadic-like using the MLPA assay (of which 4 did contain mutations in BRCA1 (BRCA-)),

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Subsequently, genes were identified of which the relative level of expression is indicative for either the sporadic-like phenotype or the BRCA1-like phenotype, as determined using the MLPA assay. The term relative is used to indicate that the level of expression was compared to the level of expression in a template, in this case pooled breast cancer samples. The expression of each of the genes depicted in Table 1 correlates with one of the two phenotypic subtypes. This correlation is represented as a fold change/ratio (BRCA-like/Sporadic-like), with a positive number indicating upregulation in BRCA-like

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and a negative number indicating downregulation in BRCA-like. For example, upregulation of GABBR2, PROM1 and/or ROPN1B is indicative of a BRCA-like phenotype, while downregulation of these genes is indicative of a Sporadic-like phenotype.

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A sample comprising RNA expression products from a cancer cell of a breast and/or ovarian cancer patient is provided after the removal of all or part of a breast and/or ovarian cancer sample from the patient during surgery biopsy. For example, a sample comprising RNA may be obtained from a needle biopsy sample or from a tissue sample comprising breast and/or ovarian cancer cells that was previously removed by surgery. The surgical step of removing a relevant tissue sample, in this case a breast and/or ovarian cancer sample, from an individual is not part of a method according to the invention.

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15 A sample from a breast and/or ovarian cancer patient comprising RNA expression products from a tumor of the patient can be obtained in numerous ways, as is known to a skilled person. For example, the sample can be freshly prepared from cells or a tissue sample at the moment of harvesting, or it can be prepared from samples that are stored at -70°C until processed for sample preparation. Alternatively, tissues or biopsies can be stored under conditions that preserve the quality of the protein or RNA. Examples of these preservative conditions are fixation using e.g. formaline and paraffin embedding, RNase inhibitors such as RNAsin® (Pharmingen) or RNasequre® (Ambion), aqueous solutions such as RNAlater® (Assuragen; US06204375), Hepes-Glutamic acid buffer mediated Organic solvent Protection Effect (HOPE; DE10021390), and RCL2 (Alphelys; 20 WO04083369), and non-aqueous solutions such as Universal Molecular Fixative (Sakura Finetek USA Inc.; US7138226).

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RNA may be isolated from a breast tissue sample comprising breast and/or ovarian cancer cells by any technique known in the art, including but not limited to Trizol 30 (Invitrogen; Carlsbad, California), RNAqueous® (Applied Biosystems/Ambion, Austin, Tx), Qiazol® (Qiagen, Hilden, Germany), Agilent Total RNA Isolation Kits (Agilent; Santa Clara, California), RNA-Bee® (Tel-Test, Friendswood, Texas), and Maxwell™ 16 Total RNA Purification Kit (Promega; Madison, Wisconsin). A preferred RNA isolation procedure involves the use of Qiazol® (Qiagen, Hilden, Germany). RNA can be extracted

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from a whole sample or from a portion of a sample generated by, for example section or laser dissection.

The level of RNA expression of a signature gene according to the invention can be
5 determined by any method known in the art. Methods to determine RNA levels of genes are known to a skilled person and include, but are not limited to, Northern blotting, quantitative Polymerase chain reaction (qPCR), also termed real time PCR (rtPCR), microarray analysis and RNA sequencing. The term qPCR refers to a method that allows
10 amplification of relatively short (usually 100 to 1000 basepairs) of DNA sequences. In order to measure messenger RNA (mRNA), the method is extended using reverse transcriptase to convert mRNA into complementary DNA (cDNA) which is then amplified by PCR. The amount of product that is amplified can be quantified using, for example, TaqMan® (Applied Biosystems, Foster City, CA, USA), Molecular Beacons, Scorpions® and SYBR® Green (Molecular Probes). Quantitative Nucleic acid sequence
15 based amplification (qNASBA) can be used as an alternative for qPCR.

A preferred method for determining a level of RNA expression is microarray analysis. For microarray analysis, a hybridization mixture is prepared by extracting and labelling of RNA. The extracted RNA is preferably converted into a labelled sample comprising
20 either complementary DNA (cDNA) or cRNA using a reverse-transcriptase enzyme and labelled nucleotides. A preferred labelling introduces fluorescently-labelled nucleotides such as, but not limited to, cyanine-3-CTP or cyanine-5-CTP. Examples of labelling methods are known in the art and include Low RNA Input Fluorescent Labelling Kit (Agilent Technologies), MessageAmp Kit (Ambion) and Microarray Labelling Kit
25 (Stratagene).

A labelled sample may comprise two dyes that are used in a so-called two-colour array. For this, the sample is split in two or more parts, and one of the parts is labelled with a first fluorescent dye, while a second part is labelled with a second fluorescent dye. The
30 labelled first part and the labelled second part are independently hybridized to a microarray. The duplicate hybridizations with the same samples allow compensating for dye bias.

More preferably, a sample is labelled with a first fluorescent dye, while a reference, for
35 example a sample from a breast and/or ovarian cancer pool or a sample from a relevant

cell line or mixture of cell lines, is labelled with a second fluorescent dye (known as dual channel). The labelled sample and the labelled reference are co-hybridized to a microarray. Even more preferred, a sample is labelled with a single fluorescent dye and hybridized to a microarray without a reference (known as single channel).

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The labelled sample is hybridized against the probe molecules that are spotted on the array. A molecule in the labelled sample will bind to its appropriate complementary target sequence on the array. Before hybridization, the arrays are preferably incubated at high temperature with solutions of saline-sodium buffer (SSC), Sodium Dodecyl Sulfate (SDS) and bovine serum albumin (BSA) to reduce background due to nonspecific binding, as is known to a skilled person.

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The arrays are preferably washed after hybridization to remove labelled sample that did not hybridize on the array, and to increase stringency of the experiment by reducing cross hybridization of the labelled sample to a partial complementary probe sequence on the array. An increased stringency will substantially reduce non-specific hybridization of the sample, while specific hybridization of the sample is not substantially reduced. Stringent conditions include, for example, washing steps for five minutes at room temperature 0.1x Sodium chloride-Sodium Citrate buffer (SSC)/0.005% Triton X-102. More stringent conditions include washing steps at elevated temperatures, such as 37 degrees Celsius, 45 degrees Celsius, or 65 degrees Celsius, either or not combined with a reduction in ionic strength of the buffer to 0,05x SSC or 0,01x SSC as is known to a skilled person.

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Image acquisition and data analysis can subsequently be performed to produce an image of the surface of the hybridised array. For this, the slide can be dried and placed into a laser scanner to determine the amount of labelled sample that is bound to a target spot. Laser excitation yields an emission with characteristic spectra that is indicative of the labelled sample that is hybridized to a probe molecule. In addition, the amount of labelled sample can be quantified.

The level of expression, preferably mRNA expression levels of genes depicted in Table 1, are compared to levels of expression of the same genes in a template. A preferred template comprises an RNA sample from an individual suffering from breast and/or ovarian cancer, more preferred from multiple individuals suffering from breast and/or

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ovarian cancer. It is preferred that said multiple samples are pooled from more than 10 individuals, more preferred more than 20 individuals, more preferred more than 30 individuals, more preferred more than 40 individuals, most preferred more than 50 individuals. A most preferred template comprises a pooled RNA sample that is isolated from tissue comprising breast and/or ovarian cancer cells from multiple individuals suffering from breast and/or ovarian cancer. Said pooled RNA samples preferably are isolated from multiple individuals that were known to suffer from known BRCA- breast and/or ovarian cancer or that were known to suffer from Sporadic breast and/or ovarian cancer.

Typing of a sample can be performed in various ways. In one method, a coefficient is determined that is a measure of a similarity or dissimilarity of a sample with said template, preferably BRCA- breast and/or ovarian cancer and/or sporadic breast and/or ovarian cancer. A number of different coefficients can be used for determining a correlation between the RNA expression level in an RNA sample from an individual and a template. Preferred methods are parametric methods which assume a normal distribution of the data.

The levels of expression of genes from the BRCAness signature in a sample of a patient are preferably compared to the levels of expression of the same genes in a sporadic breast and/or ovarian cancer sample and in a BRCA1- breast and/or ovarian cancer sample, or in a collection of sporadic breast and/or ovarian cancer samples and in a collection of BRCA1- breast and/or ovarian cancer samples. Said comparison may result in an index score indicating a similarity of the determined expression levels in a sample of a patient with the expression levels in a sporadic breast and/or ovarian cancer sample and in a BRCA1- breast and/or ovarian cancer sample. For example, an index can be generated by determining a fold change/ratio between the median value of gene expression across all BRCA-like samples and the median value of gene expression across all sporadic-like samples. The significance of this fold change/ratio as being significant between the two respective groups can be tested primarily in an ANOVA (Analysis of variance) model. Univariate p-values can be calculated in the model and after multiple correction testing (Benjamini & Hochberg, 1995, JRSS, B, 57, 289-300) can be used as a threshold for determining significance that the gene expression shows a clear difference between the groups. Multivariate analysis may also be performed in adding covariates such as hormone expression, tumor stage/grade/size into the ANOVA model. Significant

genes can be imputed into a prediction model such as Diagonal Linear Discriminant analysis (DLDA) to determine the minimal and most reliable group of gene signals that can predict the factor (BRCA-like status, response to therapy etc). Internal cross validation can be performed using the “leave-one-out “method to determine reliability and stability of these genes as being predictive in the model. An independent validation gene expression dataset is needed to further validate the gene signature.

An index can also be determined by Pearson or Cosine correlation, or by a coefficient of the linear diagonals, between the expression levels of the genes in a sample of a patient and the expression levels in a sample of a sporadic breast and/or ovarian cancer and the average expression levels in BRCA1 breast and/or ovarian cancer samples. The resultant scores/coefficients can be used to provide an index score. Said score may vary between +1, indicating a perfect similarity, and -1, indicating a reverse similarity. Preferably, an arbitrary threshold is used to type samples as sporadic-like or BRCA-like breast and/or ovarian cancer. More preferably, samples are classified as sporadic-like or BRCA-like breast and/or ovarian cancer based on the respective highest similarity measurement. A similarity score is preferably displayed or outputted to a user interface device, a computer readable storage medium, or a local or remote computer system.

The result of a comparison of the determined expression levels with the expression levels of the same genes in at least one template is preferably displayed or outputted to a user interface device, a computer readable storage medium, or a local or remote computer system. The storage medium may include, but is not limited to, a floppy disk, an optical disk, a compact disk read-only memory (CD-ROM), a compact disk rewritable (CD-RW), a memory stick, and a magneto-optical disk.

The expression data are preferably normalized. Normalization refers to a method for adjusting or correcting a systematic error in the measurements of detected label. Systemic bias results in variation by inter-array differences in overall performance, which can be due to for example inconsistencies in array fabrication, staining and scanning, and variation between labelled RNA samples, which can be due for example to variations in purity. Systemic bias can be introduced during the handling of the sample in a microarray experiment. In a preferred method according to the invention, the level of expression is preferably normalized using pre-processing methods such as quantile normalization.

To reduce systemic bias, the determined RNA levels are preferably corrected for background non-specific hybridization and normalized using, for example, Feature Extraction software (Agilent Technologies). Other methods that are or will be known to a person of ordinary skill in the art, such as a dye swap experiment (Martin-Magniette et al., *Bioinformatics* 21:1995-2000 (2005)) can also be applied to normalize differences introduced by dye bias. Normalization of the expression levels results in normalized expression values.

Conventional methods for normalization of array data include global analysis, which is based on the assumption that the majority of genetic markers on an array are not differentially expressed between samples [Yang et al., *Nucl Acids Res* 30: 15 (2002)]. Alternatively, the array may comprise specific probes that are used for normalization. These probes preferably detect RNA products from housekeeping genes such as glyceraldehyde-3-phosphate dehydrogenase and 18S rRNA levels, of which the RNA level is thought to be constant in a given cell and independent from the developmental stage or prognosis of said cell.

Said normalization preferably comprises previously mentioned global analysis “median centering”, in which the “centers” of the array data are brought to the same level under the assumption that the majority of genes are not changed between conditions (with median being more robust to outliers than the mean). Said normalization preferably comprises Lowess (LOcally WEighted Scatterplot Smoothing) local regression normalization to correct for both print-tip and intensity-dependent bias (for dual channel arrays) or “quantile normalization” (which transforms all the arrays to have a common distribution of intensities) for single channel arrays

In a preferred embodiment, genes are selected of which the RNA expression levels are largely constant between individual tissue samples comprising cancer cells from one individual, and between tissue samples comprising cancer cells from different individuals. It will be clear to a skilled artisan that the RNA levels of said set of normalization genes preferably allow normalization over the whole range of RNA levels. An example of a set of normalization genes is provided in WO 2008/039071, which is hereby incorporated by reference.

Said reference is preferably a RNA sample from a relevant cell line or mixture of cell lines. The RNA from a cell line or cell line mixture can be produced in-house or obtained

from a commercial source such as, for example, Stratagene Human Reference RNA. A further preferred reference is an RNA sample isolated from a tissue of a healthy individual, preferably comprising breast cells. A preferred reference comprises RNA isolated and pooled from normal adjacent tissue from cancer patients, preferably breast
5 and/or ovarian cancer patients. As an alternative, a static reference can be generated which enables performing single channel hybridizations for this test. A preferred static reference is calculated by measuring the median/mean background-subtracted level of expression (for example green-median/MeanSignal or red-median/MeanSignal) of a gene across 1-5 hybridization replicates of a probe sequence.

10

A breast and/or ovarian cancer patient is a patient that suffers, or is expected to suffer, from breast and/or ovarian cancer. The term "breast cancer" includes ductal carcinoma in situ, lobular carcinoma in situ, ductal carcinoma, inflammatory carcinoma and/or lobular carcinoma. A method according to the invention preferably further comprises
15 assessment of clinical information, such as tumor size, tumor grade, lymph node status and family history. Clinical information may be determined in part by histopathological staging. Histopathological staging involves determining the extent of spread through the layers that form the lining of the duct or lobule, combined with determining of the number of lymph nodes that are affected by the cancer, and/or whether the cancer has
20 spread to a distant organ. A preferred staging system is the TNM (for tumors/nodes/metastases) system, from the American Joint Committee on Cancer (AJCC). The TNM system assigns a number based on three categories. "T" denotes the size of the tumor, "N" the degree of lymphatic node involvement, and "M" the degree of metastasis. The method described here is stage independent and applies to all breast
25 cancers.

The term ovarian cancer refers to a cancerous growth arising from the ovary. More than 90% of all ovarian cancers are classified as "epithelial" and are believed to arise from the surface (epithelium) of the ovary. Carriers of mutations in BRCA1 and BRCA2 genes
30 account for 5%–13% of ovarian cancers. Ovarian cancer can be also be staged according to the AJCC/TNM system.

A DNA-damage inducing agent that is used in a method of the invention preferably comprises induces damage in the genomic DNA of a cell. Said genomic DNA damage
35 includes base modifications, single strand breaks and, preferably, crosslinks, such as

intrastrand and interstrand cross-links. A preferred genotoxic agent is selected from an alkylating agent such as nitrogen mustard, e.g. cyclophosphamide, mechlorethamine or mustine, uramustine and/or uracil mustard, melphalan, chlorambucil, ifosfamide; nitrosourea, including carmustine, lomustine, streptozocin; an alkyl sulfonate such as busulfan, an ethylenimine such as N,N,N'-triethylenethiophosphoramidate (thiotepa) and analogues thereof, a hydrazine/triazine such as dacarbazine, altretamine, mitozolomide, temozolomide, altretamine, procarbazine, dacarbazine and temozolomide; an intercalating agent such as a platinum-based compound like cisplatin, carboplatin, nedaplatin, oxaliplatin and satraplatin; anthracyclines such as doxorubicin, daunorubicin, epirubicin and idarubicin; mitomycin-C, dactinomycin, bleomycin, adriamycin, mithramycin, and poly ADP ribose polymerase (PARP)-inhibitors such as 3-aminobenzamide, AZD-2281, AG014699, ABT-888, and BMN-673. A further preferred DNA-damage inducing agent is provided by radiation, including ultraviolet radiation and gamma radiation.

A BRCA-like patient is preferably treated with a DNA damage-inducing agent. A preferred DNA damage-inducing agent comprises one or more alkylating agents, one or more platinum-based compounds and/or one or more PARP inhibitors. A further preferred DNA-damage inducing agent comprises one or more alkylating agents, one or more platinum-based compounds and one or more PARP inhibitors. A most preferred DNA-damage inducing agent comprises a nitrogen mustard alkylating agent, thiotepa and/or carboplatin. A most preferred DNA-damage inducing agent comprises cyclophosphamide, thiotepa and carboplatin.

A further preferred DNA-damage inducing agent comprises a PARP inhibitor such as 3-aminobenzamide, 4-(3-(1-(cyclopropanecarbonyl)piperazine-4-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (AZD-2281), 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-pyrrolo[4,3,2-ef][2]benzazepin-6-one phosphate (1:1) (AG014699), 2-[(2R)-2-Methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide dihydrochloride benzimidazole carboxamide (ABT-888), (8S,9R)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one (BMN-673), 8-Fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (AG 014699) and (S)-2-(4-(piperidin-3-yl)phenyl)-2H-indazole-7-carboxamide hydrochloride (MK-4827). A most preferred PARP inhibitor is ABT-888.

DNA-damage inducing treatment comprising a PARP inhibitor, preferably MK-4827, preferably further comprises a tyrosine kinase inhibitor. Said tyrosine kinase inhibitor preferably is a receptor tyrosine kinase inhibitor such as gefitinib, erlotinib, EKB-569, lapatinib, CI-1033, cetuximab, panitumumab, PKI-166, AEE788, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, vandetanib, cediranib, afatinib, motesanib, CUDC-101, imatinib mesylate and (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide (Neratinib; Puma Biotechnology), N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-2-butenamide (BIBW2992; Afatinib, Tomtovok, Tovok) and 4-[[1-[(3-Fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]carbamic acid (3S)-3-morpholinylmethyl ester hydrochloride (AC480; Bristol Myers Squibb / Ambit Biosciences).

Methods for providing a DNA-damage inducing agent to an individual in need thereof suffering from breast and/or ovarian cancer are known in the art. For example, cisplatin may be administered at 2 to 3 mg/kg every 3 to 4 weeks or at 20 mg/m²/day for 5 days every 3 to 4 weeks; at 40 mg-120 mg/m² every 3 to 4 weeks. Cisplatin is preferably administered by injection or infusion, preferably by intravenous, intra-arterial or intraperitoneal injection or infusion.

For example, anthracyclins such as doxorubicin, daunorubicin, epirubicin and idarubicin are routinely administered at 40–75 mg/m², every 3 weeks for treatment of breast and/or ovarian cancer.

For example, gamma radiation is administered in a dose that depends on the tumour type, whether radiation is given alone or with chemotherapy, before or after surgery, the success of surgery as is known to the skilled person. For example, radiation dose ranging from 20-70 Gy is administered in a fraction schedule of 1.8-2 Gy per fraction. The typical treatment schedule is 5 days per week.

Said DNA-damage inducing agent is preferably administered at a high dosage, for example at 4000-6000 mg/m² cyclophosphamide, 300-480 mg/m² thiotepa and 1200-1600 mg/m² carboplatin.

Said DNA-damage inducing agent is preferably administered after a series of conventional chemotherapeutic administrations comprising, for example, 5-fluorouracil, epirubicin and cyclophosphamide. Said conventional therapy may comprise 5-fluorouracil (250-500mg/m²), epirubicin (60-90mg/m²), and cyclophosphamide (250-500mg/m²), which is administered every three weeks for two-five courses. Said DNA-damage inducing agent is preferably combined with radiotherapy and, in case of hormone receptor positive breast and/or ovarian cancer, an anti-oestrogen drug such as, for example, tamoxifen.

In a preferred method according to the invention, a level of RNA expression of at least five genes from Table 1 is determined, more preferred a level of RNA expression of at least ten genes from Table 1, more preferred a level of RNA expression of at least twenty genes from Table 1, more preferred a level of RNA expression of at least thirty genes from Table 1, more preferred a level of RNA expression of at least forty genes from Table 1, more preferred a level of RNA expression of at least fifty genes from Table 1, more preferred a level of RNA expression of all seventy-seven genes from Table 1.

In a preferred method according to the invention, a level of RNA expression of OGN (NM_033014; fold change -3.21) and PTGDS (NM_000954; fold change -3.15344) is determined, more preferred of OGN (NM_033014; fold change -3.21), PTGDS (NM_000954; fold change -3.15344), MFAP4 (NM_002404; fold change -3.07539), SLC40A1 (NM_014585; fold change -2.75694) and HDC (NM_002112; fold change -2.70381) is determined; more preferred of OGN (NM_033014; fold change -3.21), PTGDS (NM_000954; fold change -3.15344), MFAP4 (NM_002404; fold change -3.07539), SLC40A1 (NM_014585; fold change -2.75694), HDC (NM_002112; fold change -2.70381), CFD (NM_001928; fold change -2.69412), AMICA1 (NM_153206; fold change -2.67956), ITM2A (NM_004867; fold change -2.65539) and CLEC10A (NM_182906; fold change -2.63642) is determined.

In a further preferred method according to the invention, a level of RNA expression of AMICA1 (NM_153206; p-value 4.95E-13) and HDC (NM_002112; p-value 5.1E-11) is determined, more preferred of AMICA1 (NM_153206; p-value 4.95E-13), HDC (NM_002112; p-value 5.1E-11) CLEC10A (NM_182906; p-value 1.34E-10), BASP1 (NM_006317; p-value 1.41E-10) and ITM2A (NM_004867; p-value 2.85E-10) is determined; more preferred of AMICA1 (NM_153206; p-value 4.95E-13), HDC (NM_

002112; p-value 5.1E-11) CLEC10A (NM_182906; p-value 1.34E-10), BASP1 (NM_006317; p-value 1.41E-10), ITM2A (NM_004867; p-value 2.85E-10), LRMP (NM_006152; p-value 4.95E-10), CFD (NM_001928; p-value 5.06 E-10), CMFG (NM_001928; p-value 7.42E-10), ADRB2 (NM_000024; p-value 7.85E-10) and GIMAP7 (NM_153236; p-value 2.19E-9) is determined.

In a further preferred method according to the invention, a level of RNA expression of ROPN1 (NM_017578; fold change 7.2108) and VGLL1 (NM_016267; fold change 5.46003) is determined, more preferred of ROPN1 (NM_017578; fold change 7.2108), VGLL1 (NM_016267; fold change 5.46003), ELF5 (NM_198381; fold change 4.96581), TTYH1 (NM_020659; fold change 4.82047) and PROM1 (NM_001145850; fold change 5.09199) is determined, more preferred of ROPN1 (NM_017578; fold change 7.2108), VGLL1 (NM_016267; fold change 5.46003), ELF5 (NM_198381; fold change 4.96581), TTYH1 (NM_020659; fold change 4.82047), PROM1 (NM_001145850; fold change 5.09199), GABBR2 (NM_005458; fold change 4.00791), TFCEP2L1 (NM_014553; fold change 3.91009), PLEKHB1 (NM_021200; fold change 3.40457), NRTN (NM_004558; fold change 3.39604), and PHGDH (NM_006623; fold change 3.21109) is determined.

In a further preferred method according to the invention, a level of RNA expression of NRTN (NM_004558; p-value 3.35E-14) and PLEKHB1 (NM_021200; p-value 3.39E-11) is determined, more preferred of NRTN (NM_004558; p-value 3.35E-14), PLEKHB1 (NM_021200; p-value 3.39E-11), TTK (NM_003318; p-value 5.26E-11), PHGDH (NM_006623; p-value 1.07E-10) and CENPA (NM_001809; p-value 1.51E-10) is determined, more preferred of NRTN (NM_004558; p-value 3.35E-14), PLEKHB1 (NM_021200; p-value 3.39E-11), TTK (NM_003318; p-value 5.26E-11), PHGDH (NM_006623; p-value 1.07E-10), CENPA (NM_001809; p-value 1.51E-10), VGLL1 (NM_016267; p-value 1.61E-10), TMEM38A (NM_024074; p-value 1.97E-10), ROPN1 (NM_017578; p-value 2.93E-10), DSC2 (NM_024422; p-value 3.79E-10) and ROPN1B (NM_001012337; p-value 5.01E-10) is determined.

In an further preferred method, a level of RNA expression of genes that are upregulated in a BRCA-like cancer, compared to a sporadic cancer (indicated as +), and a level of RNA expression of genes that are downregulated in a BRCA-like cancer, compared to a sporadic cancer (indicated as -), are determined, said genes comprising ROPN1 (NM_017578; fold change 7.2108) and OGN (NM_033014; fold change -3.21); ROPN1

(NM_017578; fold change 7.2108), VGLL1 (NM_016267; fold change 5.46003), OGN (NM_033014; fold change -3.21) and PTGDS (NM_000954; fold change -3.15344); ROPN1 (NM_017578; fold change 7.2108), VGLL1 (NM_016267; fold change 5.46003), ELF5 (NM_198381; fold change 4.96581), TTYH1 (NM_020659; fold change 4.82047), PROM1 (NM_001145850; fold change 5.09199), OGN (NM_033014; fold change -3.21), PTGDS (NM_000954; fold change -3.15344), MFAP4 (NM_002404; fold change -3.07539), SLC40A1 (NM_014585; fold change -2.75694) and HDC (NM_002112; fold change -2.70381), of ROPN1 (NM_017578; fold change 7.2108), VGLL1 (NM_016267; fold change 5.46003), ELF5 (NM_198381; fold change 4.96581), TTYH1 (NM_020659; fold change 4.82047), PROM1 (NM_001145850; fold change 5.09199), GABBR2 (NM_005458; fold change 4.00791), TFCEP2L1 (NM_014553; fold change 3.91009), PLEKHB1 (NM_021200; fold change 3.40457), NRTN (NM_004558; fold change 3.39604), PHGDH (NM_006623; fold change 3.21109), OGN (NM_033014; fold change -3.21), PTGDS (NM_000954; fold change -3.15344), MFAP4 (NM_002404; fold change -3.07539), SLC40A1 (NM_014585; fold change -2.75694), HDC (NM_002112; fold change -2.70381), CFD (NM_001928; fold change -2.69412), AMICA1 (NM_153206; fold change -2.67956), ITM2A (NM_004867; fold change -2.65539) and CLEC10A (NM_182906; fold change (-2.63642)).

A further preferred set of genes that are upregulated in a BRCA-like cancer, compared to a sporadic cancer (indicated as +), and set of genes that are downregulated in a BRCA-like cancer, compared to a sporadic cancer (indicated as -), comprise AMICA1 (NM_153206; p-value 4.95E-13) and NRTN (NM_004558; p-value 3.35E-14), AMICA1 (NM_153206; p-value 4.95E-13), HDC (NM_002112; p-value 5.1E-11), NRTN (NM_004558; p-value 3.35E-14) and PLEKHB1 (NM_021200; p-value 3.39E-11), AMICA1 (NM_153206; p-value 4.95E-13), HDC (NM_002112; p-value 5.1E-11) CLEC10A (NM_182906; p-value 1.34E-10), BASP1 (NM_006317; p-value 1.41E-10), ITM2A (NM_004867; p-value 2.85E-10), NRTN (NM_004558; p-value 3.35E-14), PLEKHB1 (NM_021200; p-value 3.39E-11), TTK (NM_003318; p-value 5.26E-11), PHGDH (NM_006623; p-value 1.07E-10) and CENPA (NM_001809; p-value 1.51E-10), and AMICA1 (NM_153206; p-value 4.95E-13), HDC (NM_002112; p-value 5.1E-11) CLEC10A (NM_182906; p-value 1.34E-10), BASP1 (NM_006317; p-value 1.41E-10), ITM2A (NM_004867; p-value 2.85E-10), LRMP (NM_006152; p-value 4.95E-10), CFD (NM_001928; p-value 5.06 E-10), CMFG (NM_001928; p-value 7.42E-10), ADRB2 (NM_000024; p-value 7.85E-10), GIMAP7 (NM_153236; p-value 2.19E-9), NRTN (NM_004558; p-value 3.35E-14), PLEKHB1 (NM_021200; p-value 3.39E-11), TTK

(NM_003318; p-value 5.26E-11), PHGDH (NM_006623; p-value 1.07E-10), CENPA (NM_001809; p-value 1.51E-10), VGLL1 (NM_016267; p-value 1.61E-10), TMEM38A (NM_024074; p-value 1.97E-10), ROPN1 (NM_017578; p-value 2.93E-10), DSC2 (NM_024422; p-value 3.79E-10) and ROPN1B (NM_001012337; p-value 5.01E-10).

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Yet a further preferred set of genes comprises AMICA1 (p-value 4.95E-13; fold change -2.80197) and NRTN (p-value 3.35E-14; fold change 3.67281); more preferred AMICA1 (p-value 4.95E-13; fold change -2.80197), HDC (p-value 5.10E-11; fold change -2.85068), NRTN (p-value 3.35E-14; fold change 3.67281) and PLEKHB1 (p-value 3.39E-11; 3.30942); more preferred AMICA1 (p-value 4.95E-13; fold change -2.80197), HDC (p-value 5.10E-11; fold change -2.85068), CLEC10A (p-value 1.34E-10; fold change -2.77256), NRTN (p-value 3.35E-14; fold change 3.67281), PLEKHB1 (p-value 3.39E-11; 3.30942) and TTK (p-value 5.26E-11; fold change 2.39315); more preferred AMICA1 (p-value 4.95E-13; fold change -2.80197), HDC (p-value 5.10E-11; fold change -2.85068), CLEC10A (p-value 1.34E-10; fold change -2.77256), LRMP (p-value 4.95E-10; fold change -2.20204), NRTN (p-value 3.35E-14; fold change 3.67281), PLEKHB1 (p-value 3.39E-11; 3.30942), TTK (p-value 5.26E-11; fold change 2.39315) and ROPN1 (p-value 2.93E-10; fold change 7.63253); more preferred AMICA1 (p-value 4.95E-13; fold change -2.80197), HDC (p-value 5.10E-11; fold change -2.85068), CLEC10A (p-value 1.34E-10; fold change -2.77256), LRMP (p-value 4.95E-10; fold change -2.20204), ADRB2 (p-value 7.85E-10; fold change -2.29795), NRTN (p-value 3.35E-14; fold change 3.67281), PLEKHB1 (p-value 3.39E-11; 3.30942), TTK (p-value 5.26E-11; fold change 2.39315), ROPN1 (p-value 2.93E-10; fold change 7.63253) and ROPN1B (p-value 5.01E-10; fold change 6.13033), more preferred AMICA1 (p-value 4.95E-13; fold change -2.80197), HDC (p-value 5.10E-11; fold change -2.85068), CLEC10A (p-value 1.34E-10; fold change -2.77256), LRMP (p-value 4.95E-10; fold change -2.20204), ADRB2 (p-value 7.85E-10; fold change -2.29795), ATP8A1 (p-value 8.93E-09; fold change -2.02829), LILRB5 (p-value 2.39E-08; fold change -2.3384), MIAT (p-value 1.89E-08; fold change -2.35646), TBC1D10C (p-value 6.20E-09; fold change -2.30803), NRTN (p-value 3.35E-14; fold change 3.67281), PLEKHB1 (p-value 3.39E-11; 3.30942), TTK (p-value 5.26E-11; fold change 2.39315), ROPN1 (p-value 2.93E-10; fold change 7.63253), ROPN1B (p-value 5.01E-10; fold change 6.13033), ELF5 (p-value 9.64E-10; fold change 5.25485), FAM64A (p-value 4.10E-09; fold change 2.42828), KRTCAP3 (p-value 5.21E-09; fold change 2.80703), PROM1 (p-value 6.77E-09; fold change 4.6813) and TPX2 (p-value 1.29E-09; fold change 2.28201).

A preferred method according to the invention further comprises determining a metastasizing potential of the sample from the patient, and assigning treatment comprising a DNA-damage inducing agent to a breast and/or ovarian cancer patient of whom the sample is classified as BRCA-like and having a high metastasizing potential (poor prognosis). Said metastasizing potential is preferably determined by molecular expression profiling. Molecular expression profiling may be used instead of clinical assessment or, preferably, in addition to clinical assessment. Molecular expression profiling may facilitate the identification of patients who may be safely managed without adjuvant chemotherapy. A preferred molecular expression profiling is described in WO2002/103320, which is incorporated herein by reference. WO2002/103320 describes a molecular signature comprising at least 5 genes from a total of 231 genes that are used for determining a risk of recurrence of the breast and/or ovarian cancer. A further preferred molecular signature that is described in WO2002/103320 provides a molecular signature comprising a subset of 70 genes from the 231 genes, as depicted in Table 6 of WO2002/103320. Further preferred molecular signatures include a 21-gene recurrence score (Paik et al. N Engl J Med. 2004. 351:2817-2826) and Mammostrat™ (The Molecular Profiling Institute). A most preferred method for determining a metastasizing potential of breast cancer is a 70 gene profile (MammaPrint®) as described in Table 6 of WO2002/103320, which is incorporated herein by reference.

As an alternative, or in addition, a method according to the invention may be combined with other signatures, for example a signature for determining a molecular subtyping of the breast cancer, for example BluePrint Molecular Subtyping Profile, which classifies breast cancer into Basal-type, Luminal-type and ERBB2-type cancers as is described in US patent application 13/546,755, which is incorporated herein by reference. Other preferred tests for determining molecular subtypes include PAM50 (Chia et al., 2012. Clin Cancer Res 18: 4465-4472).

Examples

Example 1

Materials and methods

5

Patient samples

128 triple negative breast cancer samples (fresh frozen) with long-term follow-up were collected from two European cancer centers. BRCA1 mutation and promoter methylation was determined by next generation sequencing and methylation -specific multiplex
10 ligation-dependent probe amplification (MS-MLPA) and BRCA1-like classification by MLPA [Lips et al., 2011. Breast Cancer Research 13: R107]. In addition we collected full genome expression data for all patients and mutation data for 21 known DNA repair genes. Differential gene expression was examined between tumors that classify as BRCA1-like with no mutation or methylation for mutations or dysregulation in another
15 gene or genes involved in DNA repair, which may be responsible for the BRCA1-like phenotype.and sporadic-like.

Gene expression preprocessing methods:

i) Exploratory biological analysis

20 The RNA quality was assessed by a Bioanalyzer and samples with RIN above 5 were selected for further analysis. RNA was amplified and labeled and hybridized to the Agendia customised Agilent whole genome microarrays according to the manufacturers protocol's.

Raw fluorescence intensities were quantified using Feature Extraction software (Agilent
25 Technologies, Santa Clara, CA, USA) according to the manufacturer's protocols. Quality of the microarray process is monitored by an internal Agendia QC model using QCs that are related to background issues, general array signal intensity, intensity of signature genes, product specific normalization genes, and array uniformity and control genes (positive and negative) (will provide reference to a paper). Only those samples that
30 passed QC check were analysed further.

The Microarray expression dataset (N=128) was imported into R/Bioconductor software (www.bioconductor.org) where feature Signal intensities were pre-processed according to the LIMMA module (green channel only, R statistics) with background subtraction.

35 ii) BRCAness signature development

Gene Expression Normalization

After background subtraction of the single channel data, a value of 10 was added to all probe intensities. All probe intensities that were still smaller than 1 are assumed to be technical artifacts and set as missing values. The log2 transformed probe intensities are normalized using quantile normalization [Bolstad et al., 2003. Bioinformatics 19: 185] from the R package limma in Bioconductor. Principal component analysis (PCA) showed a batch effect for biobank in triple negative. To adjust for these batches we applied ComBat [Johnson et al., 2006. Biostatistics 8: 118] without non-batch covariates. Genes with multiple probes were summarized by their first principal component or most variable probe, as described in the next section.

Gene Summarization

Prior to summarization, missing values are filled in by 10 nearest neighbor imputation using the R package impute from Bioconductor. A gene is summarized by the first principal component of a correlating subset of its probes (all probes having a correlation higher than 0.5 with at least one other probe), or by its most variable probe if no such subset exists. When summarizing by first principal component, its sign is adjusted such that the largest element of the first loading is positive, and it is scaled to be as variable as the most variable probe. When summarizing by most variable probe, it is mean centered and missing values are restored.

For some genes, the probes do not show one single concordant signal, as might happen when they target splice variants or when a probe is defective. This discordance was measured by doing PCA and then subtracting the absolute value of the summation of the first principal component from the sum of absolute values of the first principal component. If this discordance measure is larger than 0.1, multiple signals might be present and we do not summarize the gene but keep its probes separate in further analysis. There were 43 genes (167 probes) that were seen as 'discordant' in the TN).

Clustering and visualization:

For clustering and visualization purpose in Partek genomics Suite, missing values were imputed with the median value for the gene across all samples. The data was shifted so each sample had a median of 0.0. Clustering was performed using both PCA and Hierarchical Clustering (Pearson Dissimilarity, average linkage)

Differential expression between classes was assessed using ANOVA models in Partek genomics Suite with the significant genes selected univariately with $P < 0.0001$ and a fold change > 2 , or a fold change < -2 .

5 Supervised analysis- differentially expressed genes:

All data was filtered to have genes with variance > 1 across all samples.

Differential expression between classes was assessed using ANOVA models in Partek genomics Suite with the significant genes selected univariately to have any change in 'BRCA1-like' relative to 'Sporadic-like' with FDR (step up) < 0.00001 , Fold change > 2 or

10 Fold change < -2 .

Supervised analysis-BRCAness signature development:

Top variable genes (variance > 1 across all samples) were used for the model input. Genes were further filtered to include those also present in the validation set ($N=2049$). The

15 Classification model was Linear Diagonal Discriminant Analysis (LDDA) with equal prior probabilities.

Gene features selected (from the top variable genes) using a univariate ANOVA examining the BRCA1-like/Sporadic-like status. Multiple groups of variables were
20 tested from 1 to 100 in increments of 1. 1-level cross validation was predicted on the BRCA1-like status with the maximum number of partitions ("full leave-one-out") with data randomly reordered.

The significant number of genes in the model was selected based on the Area under
25 Curve (AUC).

Results

A 'BRCAness' signature was developed using whole genome gene expression data. The signature has been developed on fresh frozen (FF) breast tumors that were categorized
30 as either 'BRCA1-like' or 'Sporadic' using MLPA (Lips et al., 2011. Breast Cancer Research 13: R107). This prediction model endeavors to predict 'BRCA-like' tumors with a validated high sensitivity/specificity rate.

This model was built using 128 FF Triple Negative breast cancer samples (see Figure 1).

35 In this patient cohort, 8 (13%) of the 128 TN patients had a BRCA1 mutation. Fifty

three patients were classified as BRCA1-like. Using whole genome expression analysis, we identified a set of highly significant differentially expressed genes between the BRCA1-like and sporadic-like tumors whose functions are defined as cell cycle control and DNA recombination and repair. Supervised hierarchical clustering of gene expression for this set of genes in triple negative breast tumor is shown in Figure 2. We determined no significant differences in mutation frequency of 21 random DNA repair genes between the two classes. Breast cancer specific survival analysis (BCSS) reveals patients with a BRCA1-like tumor have a significantly worse prognosis (HR = 2.25, p = 0.046, CI = 1.05 – 4.97)(see Figure 3).

BRCAness signature development

In an unsupervised analysis, 185 genes were found to be differentially expressed and were plotted using hierarchical clustering. Many of these genes were found to be involved in cell cycle control and DNA recombination and repair.

In a supervised classification model of Linear Diagonal Discriminant Analysis (LDDA) , 77-gene signature was developed to identify BRCAness patients.

Whether the BRCAness signature is related to the Claudin-low subtype has also been explored [[Heerma van Voss et al., 2013. ASCO abstract <http://meetinglibrary.asco.org/content/117999-132>; Prat et al., 2010. Breast Cancer Res. 12: R68]. Heerma van Voss et al. have proposed the dysregulation of the Claudin proteins in BRCA1 related tumors. As is shown in Figure 4, this is not the case for the expression of the Claudin genes in relation to the BRCA1-like status.

As is indicated in Figure 5, the top 2, top 72 and top 77 genes were selected as potential signature genes.

Example 2

A validation set comprising 53 samples was used to test the signature. This validation set had been hybridized on the Illumina microarray platform . The data for each sample was scaled to the same median as the test set.

Tables 3-6 are presented for both the training and the 53 validation samples. The top 3 significant results(2, 72 and 77 genes) are presented in Tables 3, 4 and 5, respectively.

Table 6 provides the results of other gene sets on the training and the 53 validation samples. For each set of genes, both results for the training dataset and the validation dataset are indicated.

- 5 Following this, a smaller number of genes were analyzed to see if there could be a ‘minimum set’ of genes that could still give the same significance in validation. The sensitivity for a lower number of genes remained the same (or even slightly higher), however the specificity dropped.
- 10 As this signature is also developed in FF a higher number of genes may be more appropriate to facilitate the conversion of the signature to FFPE. In validation of this signature, we have focused on the 77 gene panel. In the validation set, the sensitivity was 0.9200 and the specificity was 0.6071.
- 15 An update of the patient information provided in Table 5B for the validation data set resulted in a sensitivity of 0.9565, a specificity of 0.6296, a Positive Predictive Value of 0.6875, a Negative Predictive Value of 0.9444, a Matthews Correlation Coefficient of 0.6086, and an Area Under Curve of 0.7931 for the 77 gene signature.

20 **Conclusion**

Our data show that patients with BRCA1-like tumors have a significantly worse prognosis. Although not all of these tumors are BRCA1 mutant, they do possess differentially expressed genes that are involved in cell cycle control and DNA recombination and repair and therefore may be more susceptible to specific treatments such as PARP inhibitors. A BRCAness gene signature has been developed that is able to effectively identify a group of patients that are BRCA1-like and may better respond to DNA-damage inducing agents comprising one or more alkylating agents, one or more platinum-based compounds and/ or one or more PARP inhibitors.

30 **Example 3**

Methods

115 HER2 negative patients (HER2-) were considered in this analysis. The BRCAness classification was computed using the 77 gene panel BRCAness gene signature. Patients were treated with oral PARP inhibitor veliparib (ABT-888) in combination with

carboplatin and chemotherapy (V/C) (71 patents), or with chemotherapy alone (44 patients).

The association between BRCAness classification and response in the V/C and control arms alone (Fisher Exact test), and relative performance between arms (biomarker x treatment interaction, likelihood ratio test) was determined using a logistic model. The BRCAness signature was assessed in the context of a subset of patients that were negative for progesterone receptor, estrogen receptor and HER2 (triple negative; TN). Statistical calculations are descriptive (e.g. p-values are measures of distance with no inferential content).

Results

Of the 115 patients assessed, 56 were classified as BRCA-like using the 77 gene panel BRCAness gene signature. 16% of BRCA-like patients were progesterone receptor and estrogen receptor positive (hormone receptor positive; HR+) and HER2-.

The distribution of pathological complete response (pCR) rates among BRCAness signature dichotomized groups stratified by hormone receptor status is indicated in Table 7.

The BRCAness signature classification associated with patient response in the V/C arm (OR = 6.8, $p=0.0005$) but not in the control arm (OR = 0.75, $p=1$). There is a significant biomarker x treatment interaction in the V/C arm relative to control arm = 9.3, $p=0.018$), which remains significant upon adjusting for HR status ($p=0.016$).

When the BRCA1-like patients were added to the graduating TN subset, the OR associated with V/C is 4.9, which is comparable to that of the TN signature (OR: 4.4), while increasing the prevalence of biomarker-positive patients by ~8%. Evaluation of the BRCAness signature in the context of the graduating signature is pending.

Conclusion: Although the sample size was small, the analysis suggests the BRCAness signature shows promise for predicting response to veliparib/carboplatin combination therapy, relative to control. This signature will contribute to the selection criteria of PARP inhibitor trials.

Table 1

Gene symbol	mRNA reference	Systematic Name	Sequence	P-value	Fold-Change (BRCAness)	Seq ID NO
ABCA6	NIM_080284	Homo sapiens ATP-binding cassette, sub-family A (ABC1), member 6 (ABCA6), mRNA [NIM_080284]	ATTAGTAAAGTCACCCAAAGAGTCAGGCACCTGGGTATTGTGGAAATAAACTATATAAAC	1.07E-08	-2.17231	1
ACTR3B	NIM_020445	Homo sapiens ARP3 actin-related protein 3 homolog B (yeast) (ACTR3B), transcript variant 1, mRNA [NIM_020445]	ATAGAAGATGATGGTTTGTTCGGTGAGTGTGGATGAAATACTCTCTTGCCACCATTTGT	1.59E-09	2.55945	2
ADRB2	NIM_000024	Homo sapiens adrenergic, beta-2-, receptor, surface (ADRB2), mRNA [NIM_000024]	CTCTATTGCTCACACGGGGTATTTTAGGCAGGGATTGAGGAGCAGCTTCAGTTGTTT	7.85E-10	-2.29795	3
AMICA1	NIM_153206	Homo sapiens adhesion molecule, interacts with CXADR antigen 1 (AMICA1), transcript variant 2, mRNA [NIM_153206]	CTCCTGTGGGCAGGGTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAACCAA	4.95E-13	-2.80197	4
ATP8A1	NIM_006095	Homo sapiens ATPase, aminophospholipid transporter (APLT), class 1, type 8A, member 1 (ATP8A1), transcript variant 1, mRNA [NIM_006095]	CTATGCAGTGTATGTGTCATTTGGCCTTTTGTGAATGTGCATGTTTAAACTGCAAAATTT	8.93E-09	-2.02829	5
AURKB	NIM_004217	Homo sapiens aurora kinase B (AURKB), mRNA [NIM_004217]	AATAGCAGTGGGACACCCGACATCTTAACGGGCACCTCACAAATTGATGACTTTGAGATT	3.71E-08	2.192	6
B3GNT5	NIM_032047	Homo sapiens UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5 (B3GNT5), mRNA [NIM_032047]	AAATGTCAACAAAGGGGAAAATAAACTATCAGCTTGGATGGTCACTTGAATAGAGAGATGGT	1.97E-08	1.99447	7
BASP1	NIM_006317	Homo sapiens brain abundant, membrane attached signal protein 1 (BASP1), mRNA [NIM_006317]	TCAATGCCAATCCTCCATTCTCTCTCCAGATATTTTGGGAGTGACAAACATTCTCTC	1.41E-10	-2.05825	8
C10orf35	NIM_145306	Homo sapiens chromosome 10 open reading frame 35 (C10orf35), mRNA [NIM_145306]	GGAGCAGGACTTGGGCTTAGGGCAGGTGGAAAAAATTCAGACTTTTTTAGCAGCTGTTT	9.70E-10	2.00989	9
CCNA2	NIM_001237	Homo sapiens cyclin A2 (CCNA2), mRNA [NIM_001237]	AAGTTTATAGATGCTGACCCCATACCTCAAGTATTGCCCATCAGTTATTGCTGGAGCTGC	1.36E-08	2.04841	10
CDC20	NIM_001255	Homo sapiens cell division cycle 20 homolog (S. cerevisiae) (CDC20), mRNA [NIM_001255]	GGTAATGATAAATTGGTCAATGTGTGGCCTAGTGCTCTCTGGAGAGGGTGGGCTGGGTTCTCT	1.77E-08	2.33461	11

CDCA3	NM_031299	Homo sapiens cell division cycle associated 3 (CDCA3), mRNA [NM_031299]	ACATACGACAGGGTAAGCGGCCTTCACCCCTAAGTGAAATGTTAGTGAACTAAAGGAA	8.32E-10	2.38825	12
CDCA5	NM_080668	Homo sapiens cell division cycle associated 5 (CDCA5), mRNA [NM_080668]	TCACCAGATGATGCAGAGTTGAGATCATCATTCGCAAGTTCTCTGTTCTCTGAGGAACATA	3.15E-08	2.0278	13
CDCA7	NM_031942	Homo sapiens cell division cycle associated 7 (CDCA7), transcript variant 1, mRNA [NM_031942]	ATTACTTGATATGTAAACCATTTGCTGTGTCATTCATGTTTGTGATGCATAATTGGACCT	4.11E-09	2.67162	14
CDCA8	NM_018101	Homo sapiens cell division cycle associated 8 (CDCA8), mRNA [NM_018101]	CCCAGGCTTGAAGGCACATGGCTTTCTCATGTAGGGCTCTCTGTGGTATTGTTATTATT	1.03E-08	2.13825	15
CDT1	NM_030928	Homo sapiens chromatin licensing and DNA replication factor 1 (CDT1), mRNA [NM_030928]	CACCTTGACTTCAGTATTCTGACCTCCTAAACCTCTAATAAAGTCATGCTTACAGCCACT	1.10E-08	2.18541	16
CENPA	NM_001809	Homo sapiens centromere protein A (CENPA), transcript variant 1, mRNA [NM_001809]	CATGACTAGATCCAATGGATTCTGCGATGCTGTCTGGACTTTGCTGCTCTGAACAGTAT	1.51E-10	2.39079	17
CENPF	NM_016343	Homo sapiens centromere protein F, 350/400ka (mitosin) (CENPF), mRNA [NM_016343]	AAAGTTTGGAAAGCACTGATCAGCTGTTAGCATTGCCATTCCTCTACTGCAATGTAATAAG	3.84E-08	2.27088	18
CEP55	NM_018131	Homo sapiens centrosomal protein 55KDa (CEP55), transcript variant 1, mRNA [NM_018131]	GTAAACCAAAAACTTTTAAATTTCTTCAGGTTTTCTAACATGCTTACCCTGGGCTACTG	2.73E-09	2.13814	19
CFD	NM_001928	Homo sapiens complement factor D (adipsin) (CFD), mRNA [NM_001928]	GGCCTGAAGGTCAGGGTCAACCAAGCAACAAAGTCCCGAGCAATGAAGTCATCCACTCCT	5.06E-10	-2.78936	20
CHAF1B	NM_005441	Homo sapiens chromatin assembly factor 1, subunit B (p60) (CHAF1B), mRNA [NM_005441]	CCTGGCATCTCGTGAAAGTGACACACACTTCATGAGGGGACTCCTTTTCAATAAGAATA	1.30E-08	1.91542	21
CITED4	NM_133467	Homo sapiens Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4 (CITED4), mRNA [NM_133467]	ACAGCCCGAACCCGTGGAGCAATGCCCTGTCTGGCCTCAAAACCAAAATAAAACTGGGT	8.92E-09	2.44312	22
CLEC10A	NM_182906	Homo sapiens C-type lectin domain family 10, member A (CLEC10A), transcript variant 1, mRNA [NM_182906]	AGGACTCTTCTCAGGACTCCTCGCAGACCCGCTCTGGGAGAGAGAAATAAGCACTGGGAGA	1.34E-10	-2.77256	23
DSC2	NM_024422	Homo sapiens desmocollin 2 (DSC2), transcript variant Dsc2a, mRNA [NM_024422]	CCATCCTTGCAATATTGTTGGGCATAGCATGCTCTTTTGATCTCTGTTTACGCTGGTCT	3.79E-10	2.30894	24

ELF5	NM_198381	Homo sapiens E74-like factor 5 (ets domain transcription factor) (ELF5), transcript variant 1, mRNA [NM_198381]	TCTCAGGTCAGATGTTAAACGTTTATAAACCGGAAATGTCCTAACCAACTCTGTAATGG	9.64E-10	5.25485	25
EXO1	NM_003686	Homo sapiens exonuclease 1 (EXO1), transcript variant 3, mRNA [NM_003686]	AAGCATCCAGAAGAGAAAGCATCATATGCGGAGAACCAAGCCGGGTACAGATCAAACT	1.72E-08	2.21367	26
FAM64A	NM_019013	Homo sapiens family with sequence similarity 64, member A (FAM64A), mRNA [NM_019013]	AGGAGGGTAGCCCTGTTCAAGAGCAATTTCTGCCCTTTGTAATATTTAAGAAACCTG	4.10E-09	2.42828	27
FOXM1	NM_202002	Homo sapiens forkhead box M1 (FOXM1), transcript variant 1, mRNA [NM_202002]	GGTAGGATGACCTGGGGTTTCAATTGACTTCTGCTCCTGCTTTAGTTTGTAGTAAGAGG	6.38E-09	2.28481	28
FUCA1	NM_000147	Homo sapiens fucosidase, alpha-L-1, tissue (FUCA1), mRNA [NM_000147]	TTCTCTGATAACCTACTTGCTTACTCAATGCGCTTTAAGCCAAGTCACCCGTGTCCTATG	5.54E-09	-1.91098	29
GABBR2	NM_005458	Homo sapiens gamma-aminobutyric acid (GABA) B receptor, 2 (GABBR2), mRNA [NM_005458]	GAGGAATTTCTCGTACCCTACTGTCATGGTATCGATGATTTTAAATAAATTTGTGCAAAATTG	1.37E-08	4.53168	30
GIMAP5	NM_018384	Homo sapiens GTPase, IMAP family member 5 (GIMAP5), mRNA [NM_018384]	TCATGTTCTAATAATCACCAATTCAGACTCAGATCCTCGTGGTCTATGGAGCATGCTGC	1.13E-08	-1.9587	31
GIMAP7	NM_153236	Homo sapiens GTPase, IMAP family member 7 (GIMAP7), mRNA [NM_153236]	TTTGGGAAGTCAGCCATGAAGCACATGGTCACTCTGTTCACTCGCAAGAAAGAGTTGGAG	2.19E-09	-2.26543	32
GMFG	NM_004877	Homo sapiens glia maturation factor, gamma (GMFG), mRNA [NM_004877]	CTCCAAGAAAAGTTGCTTTCTTTCGTGATCTCTGGGCTGGGGACTGAAATTCCTGATGT	7.42E-10	-1.86818	33
HDC	NM_002112	Homo sapiens histidine decarboxylase (HDC), mRNA [NM_002112]	CCGAGGGTAGACAGGCAGCTTCTGTGGTTCAGCTTGACATGATATATACACAGAAAT	5.10E-11	-2.85068	34
HIST1H1A	NM_005325	Homo sapiens histone cluster 1, H1a (HIST1H1A), mRNA [NM_005325]	CTGCTAAAGCTAAGGCTGTAAACCACCAAGCGGCCAAGGCTAGGGTGACGAAGCCAAAGA	1.53E-08	2.91491	35
HORMAD1	NM_032132	Homo sapiens HORMA domain containing 1 (HORMAD1), mRNA [NM_032132]	AGGTCTAAAGAAAGTCCAGATCTTTCTATTCTCATTTCTCAGGTTGAGCAGTTAGTCAAT	3.31E-08	3.50544	36
HRASLS	NM_020386	Homo sapiens HRAS-like suppressor (HRASLS), mRNA [NM_020386]	TTGGAGGAGGAAAAAGAAACCTGGGGTGAACTACTATTTTTCAGTGCATCTTACTGTTCC	2.16E-09	3.25731	37
IQGAP3	NM_178229	Homo sapiens IQ motif containing GTPase activating protein 3 (IQGAP3), mRNA [NM_178229]	ATCTACCAACTTCTGTACTGTGTCCTTCTGATGTTAATAAAAAAGCAGCTGTACTCCC	8.23E-09	1.98991	38

ITM2A	NM_004867	Homo sapiens integral membrane protein 2A (ITM2A), mRNA [NM_004867]	CTAGTTGCTGTGGAGGAAATCGTGATGTTAGTAACCTTGGCACTCTTATTTACCAACTT	2.85E-10	-2.79709	39
KCNK5	NM_003740	Homo sapiens potassium channel, subfamily K, member 5 (KCNK5), mRNA [NM_003740]	CTGTGAAATGTTTAAATGAACCATGTTGTTGCTGGTTGCTCTGGCATCGGCACACTGTA	3.44E-08	2.54732	40
KLF2	NM_016270	Homo sapiens Kruppel-like factor 2 (lung) (KLF2), mRNA [NM_016270]	GAGACAGGTGGGCATTTTGGGCTACTCTGTTGTTTATTAAGATTGCTGGGTTGGT	1.15E-08	-1.86066	41
KRTCAP3	NM_173853	Homo sapiens keratinocyte associated protein 3 (KRTCAP3), mRNA [NM_173853]	GCTAGAGGAAATGACAGAGCTCGAATCTCTAAATGTAAAGGACAGGAAAAATGACAGCT	5.21E-09	2.80703	42
LILRB5	NM_006840	Homo sapiens leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 5 (LILRB5), transcript variant 2, mRNA [NM_006840]	CTAGATTCTGCAGTCAAGAGTACTAAATATCTCTTGCAATTTTGAAATGAAGCCACAGACT	2.39E-08	-2.3384	43
LRMP	NM_006152	Homo sapiens lymphoid-restricted membrane protein (LRMP), mRNA [NM_006152]	AGGTTCTCAGAAATGACCGTAAGATAGCTTACATTTCTCTTTTGGCCTTATCTCCCAA	4.95E-10	-2.20204	44
MCM10	NM_182751	Homo sapiens minichromosome maintenance complex component 10 (MCM10), transcript variant 1, mRNA [NM_182751]	TGCTCTTACATTATGTGGAGCCCTGTGATAGAAAATATGAAAAATCTCATATATTTTT	6.82E-09	2.27218	45
MCM2	NM_004526	Homo sapiens minichromosome maintenance complex component 2 (MCM2), mRNA [NM_004526]	TTTGGGTGGGATGCCTTGCCAGTGTGCTTACTTGTGTTGCTGAACATCTTGCACCTCGG	4.00E-09	1.89845	46
MELK	NM_014791	Homo sapiens maternal embryonic leucine zipper kinase (MELK), mRNA [NM_014791]	GGAAAGTGACAATGCAATTTGAATTAGAAAGTGTGCCAGCTTCAAAAACCCGATGTGGTGG	2.91E-08	2.3082	47
MFAP4	NM_002404	Homo sapiens microfibrillar-associated protein 4 (MFAP4), mRNA [NM_002404]	AAATTACACCTGGAGTCAGGTGCAGAGGGAACCTTGATTTTACAGGCTCATTTTGAT	3.10E-09	-3.17716	48
MIAT	NR_003491	Homo sapiens myocardial infarction associated transcript (non-protein coding) (MIAT), non-coding RNA [NR_003491]	TGGCTGAGATGATACCCGACCTCTAGGGAAATTCCTAGAGTAACTTCTAGGAAATGTCA	1.89E-08	-2.35646	49
NRTN	NM_004558	Homo sapiens neurturin (NRTN), mRNA [NM_004558]	TGGACGCGCAGCGCTACCACACGCGTGCACGAGCTGTGGCGCGCAGTGCCTGCG	3.35E-14	3.67281	50
OGN	NM_033014	Homo sapiens osteoglycin (OGN), transcript variant 1, mRNA [NM_033014]	AACTAATGATCACAGCTATTATACTACTTCTCTGTTATTTTGTGTGATGCCTCATTTCC	8.77E-09	-3.70339	51

PADI2	NM_007365	Homo sapiens peptidyl arginine deiminase, type II (PADI2), mRNA [NM_007365]	AGAGCTGAAAAACCAAGTGCCTATTGAGGGTGTCTGTCTGGAGACTTAGAGTTTGTCA	6.23E-09	2.83004	52
PHGDH	NM_006623	Homo sapiens phosphoglycerate dehydrogenase (PHGDH), mRNA [NM_006623]	TTGTCCAAGGCACTACACCTGTACTGCGAGGGGCTCAATGGAGCTGTCTTCAGGCCAGAA	1.07E-10	2.95348	53
PLCB4	NM_000933	Homo sapiens phospholipase C, beta 4 (PLCB4), transcript variant 1, mRNA [NM_000933]	CCTTATCTGTAAACAGTGGAGTTAGACTACATACTTTTGGCACTAACATCTCATGAAA	2.00E-08	2.1783	54
PLEKHB1	NM_021200	Homo sapiens pleckstrin homology domain containing, family B (evectins) member 1 (PLEKHB1), transcript variant 1, mRNA [NM_021200]	TAAAGCTCCCTGTAAATGGGGGCTCCATTAGTTCTGCTGCCGAGACTAATAAAGATTG	3.39E-11	3.30942	55
PROM1	NM_001145850	Homo sapiens prominin 1 (PROM1), transcript variant 6, mRNA [NM_001145850]	TTTTGCGGTAAAACTGGCTAAGTACTACTCGTGAATGGATTGCGGAGGCGGTGACGATG	6.77E-09	4.6813	56
PSAT1	NM_058179	Homo sapiens phosphoserine aminotransferase 1 (PSAT1), transcript variant 1, mRNA [NM_058179]	TACCATCTTCCATAGGTAGAGAGAAAGTTGATTGGTTGTTTCAATTATGCC	2.59E-09	2.92479	57
PTCRA	NM_138296	Homo sapiens pre T-cell antigen receptor alpha (PTCRA), mRNA [NM_138296]	ACAGGGGCATTAGGGAGCAGATGACTGAGAACATAAAAAAGAACTTAAATGACACAGC	2.13E-08	-2.02765	58
PTGDS	NM_000954	Homo sapiens prostaglandin D2 synthase 21kDa (brain) (PTGDS), mRNA [NM_000954]	CAAAGCAACCTGCCCACTCAGGCTTCATCTGCACAATAAACTCCGGGAAGCAAGTCAGT	2.88E-09	-3.30008	59
RAD51AP1	NM_006479	Homo sapiens RAD51 associated protein 1 (RAD51AP1), transcript variant 2, mRNA [NM_006479]	GGTTGGGAGAATCACAGCTTTACAAGGGTGTATTATATTGATTGTTTATATTGAGG	5.08E-09	2.09804	60
ROPN1	NM_017578	Homo sapiens ropporin, rhophilin associated protein 1 (ROPN1), mRNA [NM_017578]	GAATGACTTTACCCAAAACCCAGGGTTCAGCTGGAGTAAAGCACAAATTTTGGCAATT	2.93E-10	7.63253	61
ROPN1B	NM_001012337	Homo sapiens ropporin, rhophilin associated protein 1B (ROPN1B), mRNA [NM_001012337]	TGGCAATTTTAAAGGAAGATACAGAGGTGATTGTACTTCAGAAATGATAAACCATATACC	5.01E-10	6.13033	62
RPL39L	NM_052969	Homo sapiens ribosomal protein L39-like (RPL39L), mRNA [NM_052969]	GAGAGAAGCAAGCATCTTTCCTCTTTGGAGTAGGAAATTCAGACTTGAAAAAGTGGTGT	1.86E-09	1.83988	63
SCML4	NM_198081	Homo sapiens sex comb on midleg-like 4 (Drosophila) (SCML4), mRNA [NM_198081]	CATTTTGATTAAACTTTAAGCAGGACAGATTGCTGAAGCCATGATATTAAAGGTTTGAC	2.20E-08	-2.67377	64

SLC40A1	NM_014585	Homo sapiens solute carrier family 40 (iron-regulated transporter), member 1 (SLC40A1), mRNA [NM_014585]	CTCATGTTATCATCATTAGTGAATCTGTGTTGTAGAACATGAGGGTGTAAAGCCTTCAGCCT	3.12E-09	-2.86082	65
SLC7A8	NM_182728	Homo sapiens solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 (SLC7A8), transcript variant 2, mRNA [NM_182728]	TTTTTTGTAAGTTGATGCCTTACTTTTGGATAAATATTTTGAAGCTGGTATTCTAT	9.52E-09	-2.29559	66
SUV39H2	NM_024670	Homo sapiens suppressor of variegation 3-9 homolog 2 (Drosophila) (SUV39H2), mRNA [NM_024670]	ATTTGCCAAATGATTACCGATGCTCTGAAAAAGGGGGTCACTGGGTCTCATAGACTGAT	2.32E-09	1.87415	67
TBC1D10C	NM_198517	Homo sapiens TBC1 domain family, member 10C (TBC1D10C), mRNA [NM_198517]	GGAAGGGGTTGGCTGAGTCAAGGGACCCAGAGGGCACCAGGAATAAAATCTTCTTGAAC	6.20E-09	-2.30803	68
TBC1D9	NM_015130	Homo sapiens TBC1 domain family, member 9 (with GRAM domain) (TBC1D9), mRNA [NM_015130]	AAACATCCGGATGATGGGCAAGCCCTCACCTCGGCCAGTCACTATGAAATCTCGGCCAT	1.92E-08	-2.16865	69
TFCP2L1	NM_014553	Homo sapiens transcription factor CP2-like 1 (TFCP2L1), mRNA [NM_014553]	GATGGTGGCTAAATTTTAAATTCCTCAAAAGTGTAGGAGGCTAATATGTCTCTTAAGTTC	2.97E-08	3.56367	70
TMEM38A	NM_024074	Homo sapiens transmembrane protein 38A (TMEM38A), mRNA [NM_024074]	TTACAGAAATCTGGCAGCAGCTCCAGTCAAGAAATGTCACCTGGTGGCATGATATCTTA	1.97E-10	2.2764	71
TPX2	NM_012112	Homo sapiens TPX2, microtubule-associated, homolog (Xenopus laevis) (TPX2), mRNA [NM_012112]	AGAGAACCCATTTCTCAGACTTTTACTACCCGTGCTGAGAAAGCATACTTGACAACT	1.29E-09	2.28201	72
TRIM2	NM_015271	Homo sapiens tripartite motif-containing 2 (TRIM2), transcript variant 1, mRNA [NM_015271]	GATGCTTAAAAAATTTCTAAAGATGAATTTGTGTGGCAGTGATTGGTCTGTTTGTGGAGAA	5.65E-09	2.3576	73
TTK	NM_003318	Homo sapiens TTK protein kinase (TTK), transcript variant 1, mRNA [NM_003318]	TGTTTGGTCTTAGGATGATTTTGTACTATATGACTTACGGGAAAAACACCATTTTCAGCA	5.26E-11	2.39315	74
TTYH1	NM_020659	Homo sapiens tweety homolog 1 (Drosophila) (TTYH1), transcript variant 1, mRNA [NM_020659]	GGCTCTGACCCCTGATCTCAACTCGTGGCAGTCACTTAAGTGGAAAAAGGGTTGATTTAAATA	2.16E-08	4.69134	75
UGT8	NM_003360	Homo sapiens UDP glycosyltransferase 8 (UGT8), transcript variant 2, mRNA [NM_003360]	TGCCGCTGTCCATCAGATCTCCTTTTGTACAGATTTTTTACTGGATATGCTTGTGCT	1.12E-08	2.48001	76
VGLL1	NM_016267	Homo sapiens vestigial like 1 (Drosophila) (VGLL1), mRNA	AGACACGGCAGCAAGATCCCTCGCATATTGTTCCAGATAAAATGAAAGCTGCTCACAC	1.61E-10	5.4559	77

		[NM_016267]			
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Table 2

hgnc_symbol	Sequence	SEQ ID NO
ABCA6	ATTAGTAAAGTACCCAAAGAGTCAGGCACTGGGTATTGTGAAATAAAACTATATAAAC	1
ACTR3B	ATAGAAGATGATGGTTGTTGTCGGTGAGTGTGGATGAAATACTTCCTTGACCATTGT	2
ACTR3B	CCCGGAAGTGGATCAAACAGTACACGGGTATCAATGCGATCAACCAGAAGAAGTTTGTTA	78
ACTR3B	TAGAGAAAACAACATTAGAAAATGGCGAAAATCGTTAGTCCAGGGAGAGAAATGTGGGG	79
ACTR3B	ATAGAAGATGATGGTTGTTGTCGGTGAGTGTGGATGAAATACTTCCTTGACCATTGT	80
ADRB2	CTCTTATTGCTCACACGGGGTATTTTAGCAGGGATTGAGGAGCAGCTTCAGTTGTTT	3
AMICA1	CTCCTGTGGCAGGGTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAACCAA	4
ATP8A1	CTATGCAGTGTATGTGTCATTGGCCTTTTGTGAATGTGCATGTTTAAACTGCAAAATT	5
AURKB	GTCTGTGTATGATAGGGGAAAGAAGGATCCCTAACTGTTCCCTTATCTGTTTTCTACC	6
AURKB	AATAGCAGTGGGACACCCGACATCTTAACGCGCACTTCACAATTGATGACTTTGAGATT	81
B3GNT5	TGGTGCTCCAGTGTAGGGCTATCTTTTAAAAATGTCAACAAAGGGAAAAATAAACTATC	7
B3GNT5	AAATGTCAACAAAGGGAAAAATAAACTATCAGCTTGGATGGTCACTTGAATAGAAGATGGT	82
BASP1	TTCAGTCAACTTTACCAAGAAGTCCTGGATTCCAAGATCCGCGTCTGAAAAGTGCAGTAC	8
BASP1	TCAATGCCAATCCTCCATTCTCTCTCCAGATATTTTGGGAGTGACAAACATTCTCTC	83
C10orf35	GGAGCAGGACTTGGGCTTAGGGCAGGTGGAAAAAATCCAGACTTTTTTAGCACTGTTTT	9
CCNA2	AAGTTTGATAGATGCTGACCCATACCTCAAGTAITTGCCATCAGTTATTGCTGGAGCTGC	10
CCNA2	AAGTTTGATAGATGCTGACCCATACCTCAAGTAITTGCCATCAGTTATTGCTGGAGCTGC	84
CDC20	ATCCACCAAGGCATCCGCTGAAGACCAACCCATCACCTCAGTTGTTTTTATTTTCTAA	11
CDC20	GGTAATGATAACTTGGTCAATGTGTGGCCTAGTCTCCTGGAGAGGGTGGCTGGTTCCT	85
CDCA3	ACACTACGACAGGGTAAGCGGCCCTTACCCCTAAGTGAAAAATGTTAGTGAACATAAGGAA	12
CDCA3	AGGAATGGCTTGTCTTAGACTCCTCCTCAGCTACCAAACTGGGACTCACAGCTTTAT	86
CDCA5	TCACCAGATGATGCAGAGTTGAGATCATCATTTGCAAAAGTTCTCTGTTCTCTGAGGAACTAA	13

CDCA7	GCTGTGCCATTCAATGTTTGATGCATAAATTGGACCTTGAATCGATAAGTGTAATACAGC	14
CDCA7	GCATAATATCTGGAATAATTGCTGCTGCTTCTACTTCTCAAATCTTTCTGTAAAGT	87
CDCA7	ATTTACTTGCCATATGTAACCAATTGCTGTGCCATTCAATGTTTGATGCATAATTGGACCT	88
CDCA8	CCCAGGCTTGAAGGCACATGGCTTTCTCATGTAGGGCTCTCTGTGGTATTTGTTATTAT	15
CDCA8	CCCAGGCTTGAAGGCACATGGCTTTCTCATGTAGGGCTCTCTGTGGTATTTGTTATTAT	89
CDT1	CACCTTGACTTCAGTATTTCTGACCTCTAAACTCTAATAAAGTCATGCTTACAGCCACT	16
CENPA	TAGTTTGTGAGTTACTCATGTGACTATTTGAGGATTTTGAAAACATCAGATTTGCTGTGG	17
CENPA	GGGGATGAATAGAAAACCTGTAAGCTTTGATGTTCTGGTTACTTCTAGTAAATTCCTGTC	90
CENPA	CATGACTAGATCCAATGGATTCTGCGATGCTGTCTGGACTTTGCTGTCTGAACAGTAT	91
CENPF	CAGGACTTCTCTTTAGTCAGGGCATGCTTTATTAGTGAGGAGAAAACAATTCCTTAGAAG	18
CENPF	GCTGGAGATAGACCTTTTAAAGTCTAGTAAAGAAAGAGCTCAATAATTCATTGAAAAGCTAC	92
CENPF	AAAGTTTGAAGCACTGATCACCTGTTAGCATTGCCATTCTCTACTGCAATGTAATAG	93
CEP55	GACCGTCAACATGTGCAGCATCAATTGCATGTAATTTCTAAGGAGCTCCGAAAAGCAAGA	19
CEP55	GTAACCAAAAACTTTTAAATTTCTTCAGGTTTTCTAACATGCTTACCCTGGGCTACTG	94
CEP55	GTAACCAAAAACTTTTAAATTTCTTCAGGTTTTCTAACATGCTTACCCTGGGCTACTG	95
CFD	GGCTGAAGGTCAGGGTCACCCAAGCAACAAAGTCCCGAGCAATGAAGTCATCCACTCCT	20
CHAF1B	CCTGGCATCTCGTGAAAGTGCACACACTTCATGGAGGACTCCTTTTCAATAAGAATTA	21
CITED4	ACAGCCGAACCCGTGGAGCAATGCCCTGTCTGGCTCCAAACCAAAATAAACTGGGT	22
CLEC10A	AGGACTCTTCTCAGGACCTCCTCGCAAGACCGCTCTGGGAGAGAAATAAGCACTGGGAGA	23
DSC2	CCATCCTTGCAATATTGTTGGGCATAGCATTGCTCTTTTGCATCCTGTTTACGCTGGTCT	24
DSC2	CAAAATTTAGGACACTAGCAGAAGCATGCATGAAGAGATGAGTGTGTTCTAATAAGTCTCT	96
ELF5	TCTCAGGTCCAGATGTTAAACGTTTATAAAACCGGAAATGTCCTAACAACTCTGTAATGG	25
ELF5	TCTCAGGTCCAGATGTTAAACGTTTATAAAACCGGAAATGTCCTAACAACTCTGTAATGG	97
EXO1	AAGCATCCAGAAAGAGAAAGCATATAATGCCGAGAACACGCGGGTTACAGATCAAACT	26
EXO1	AAGCATCCAGAAAGAGAAAGCATATAATGCCGAGAACACGCGGGTTACAGATCAAACT	98
FAM64A	AGGAGGGGTAGCCCTGTTCAAGAGCAATTTCTGCCCTTTGTAAATTTAAGAAACCTG	27
FAM64A	AAGAAACCAAGCATGTGACTTTCTTAGATAAACACTGCTTTCTCATAATAAAGACTATTTGC	99
FAM64A	AAACAGCATATGAGTTAAAAGATTTTACAACTGGGCTTTGATTTGATGTGAGCTGG	100
FAM64A	GAATTCAGCATCTCCAGAAAGCTGTCCCAAGAGCTAGATGAAGCCATTATGGCGGAAGAGA	101
FOXM1	GGTAGGATGACCTGGGGTTTCAATTGACTTCTGTTCTTCTGTTTGTAGTTTGATAGAAGG	28

FOXM1	GGTAGGATGACCTGGGGTTTCAATTGACTTCTGTTCCTTGCTTTTAGTTTGATAGAAGG	102
FUCA1	TTCTGATAAACCTACTTGCTTACTCAATGCCTTTAAGCCAAAGTCACCCGTGTTGCCTATG	29
GABBR2	GAGGAATTTCTGTACCCCTACTGCATGGTATCGAATTTTAAATAAATGTTGCAAATTTG	30
GIMAP5	TCAATGTTCTAATAATCACCAATTCAGACTCAGATCCTCGTGGTCTATGGAGCATGCTGC	31
GIMAP7	TTTGGGAAGTCAGCCATGAAGCACATGGTCATCTTGTTCACTCGCAAAGAAGAGTTGGAG	32
GIMAP7	TTTGGGAAGTCAGCCATGAAGCACATGGTCATCTTGTTCACTCGCAAAGAAGAGTTGGAG	103
GMFG	CTCCAAGAAAAGTTGCTTCTTTCGTTGATCTCTGGGCTGGGACTGAATTCCTGATGT	33
HDC	CCGAGGGTAGACAGGCAGCTTCTGTGGTTCAGCTTGACATGATATATAACACAGAAAT	34
HIST1H1A	CTGCTAAAGCTAAGGCTGTAAACCCCAAGCGGCCAAGGCTAGGGTGACGAAGCCAAAGA	35
HORMAD1	AGGTCTAAAGAAAGTCCAGATCTTTCTATTTCTCATTCTCAGGTTGAGCAGTTAGTCAAT	36
HORMAD1	CCCAGATTACCAGCCTCCCGGTTTTAAGGATGGTGATTGTGAAGGAGTTATATTGAAGG	104
HRASLS	GTGGCCTATAACTTACTTGTCACAACACTGTGAACATTTGTGACATTGCTTCGCTATGGA	37
HRASLS	TTGGGAGGAGGAAAAGAACCTCGGGGTGAATACTTATTTTTCAGTGCATCATTTACTGTTCC	105
IQGAP3	ATCTACCCAACTTCTGTACTGTTGCCCTTCTGATGTTAATAAAGCAGCTGTTACTCCC	38
ITM2A	CTAGTTGCTGTGGAGGAAATTCGTGATGTTAGTAACCTTGGCATCTTTATTACCAACTT	39
KCNK5	CTGTCTCCAGGTAGGTGACCAGAGAACTTGAGCGAAGCTCAAGCCTCTCAACTCAAGG	40
KCNK5	CTGTGAAATGTTTTAATGAACCATGTTGTTGCTGGTGTCTGGCATCGCGCACACTGTA	106
KCNK5	CTGTGAAATGTTTTAATGAACCATGTTGTTGCTGGTGTCTGGCATCGCGCACACTGTA	107
KLF2	GAGACAGGTGGGCATTTTGGGCTACCTGGTTCGTTTTTATAAGATTTTGTCTGGGTTGGT	41
KRTCAP3	GCTAGAGGAAATGACAGAGCTCGAATCTCCTAAATGTAAAAGGCGAGGAAAATGAGCAGCT	42
LILRB5	CTAGATTCTGCAGTCAAAGATGACTAATATCCTTGCAATTTTGAATGAAGCCACAGACT	43
LRMP	AGGTTCTCAGAATGACCGTAAGATAGCTTACATTTCTCTCTTTTGGCCTTTATCTCCCAA	44
MCM10	CCTCCTGTGACTCTGGAAGCAAGGATTGGCTGTGATTTGTCCATTGATTCCTGATTGA	45
MCM10	TGCTCTTACATTATTGTGGAGCCCTGTGATAGAAATATGAAAATCTCATATATTTTTT	108
MCM2	TTTGGGTGGGATGCCCTGCCAGTGTGCTTACTTGGTGTCTGAACATCTGCCACCTCCG	46
MCM2	TTTGGGTGGGATGCCCTGCCAGTGTGCTTACTTGGTGTCTGAACATCTGCCACCTCCG	109
MELK	GATACAGCCTACATAAAGACTGTTATGATCGCTTTGATTTTAAAGTTCAATGGAACTACC	47
MELK	GGAAAGTGACAATGCAATTTGAATTAGAAGTGTGCCAGCTTCAAAAACCCGATGTGGTGG	110
MFAP4	AAATTACACCTGGAGTCAGGTGCAGAAGGGGAACCTTGATTTTACAGGCCCTCATTTTGAT	48
MIAT	CAACAAAGGAGCGTCACTTGGATTTTGTTCATCCATGAATGTAGCTGCTCTGTGTGA	49

MIAT	TGGTGAGATGATACCCGACCCCTCTAGGGAAATCTTAGAGTAACTTCTAGGAAATGTCA	111
NRTN	TGGACGCGCACAGCCGCTACACACGGTGCACGAGCTGTCGGCGCGGAGTGC	50
OGN	GGTACATGTTCCAAAACTTTGAAAAAGCTAAATGTTTCCCATGATCGCTCATTTCTTT	51
OGN	AACTAATGATCACAGCTATTATACTACTTTCTCGTTATTTTGTGTCATGCCTCATTTCC	112
PAD12	TCTAAGGCTTTCCCAATGATGTCGGTAAATTTCTGATGTTTCTGAAGTTCCCGGACTCA	52
PAD12	GCTGAAGGTCTGCTTCCAGTACCTAAACCGAGGCGATCGCTGGATCCAGGATGAAATTGA	113
PAD12	AGAGCTGAAAAACACCAAGTGCCTATTTGAGGGTGTCTGTCTGGAGACTTAGAGTTTGTCA	114
PHGDH	ACCCACCCACTGTGATCAATAGGGAGAGAAAAATCCACATCTTGGGCTGAACGCGGGCCT	53
PHGDH	TTGGTCCAAGGCACTACACCTGTACTGCAGGGGCTCAATGGAGCTGTCTTCAGGCCAGAA	115
PLCB4	CCTTATCTGTAAACAGTGGAGTTAGACTACATATCTTTTGGCACTAACATCTCATGAAA	54
PLCB4	ACAGATCTAGTGAACATTAGTTTACCTACATGGTGGCTGAAAAATCCAGAAGTAACTAAG	116
PLEKHB1	TAAAGTCCCTGTAAATGGGGGCTCCATTAGTTCTGCTGCCGAGACTAATAAAGATTTG	55
PROM1	TGGGGTGTGTTCCCATTTGGATGCAATTTCTATCAAAACTCTATCAAAATGTGATGGCTAG	56
PROM1	TTTTTGGGTAAACTGGTAAGTACTATCGTCGAATGGATTTCGGAGGACGTGTACGATG	117
PSAT1	TACCAATCTTTCCATAGGTAGAAGAGAAAAAGTTGATTGGTTGTTTCAATTATGCC	57
PSAT1	GATGCATCAGCTATGAACACATCTAACCCAGGATATACTCTGTTCTTGAACAACATACAA	118
PTCRA	ACAGGGGCATTTAGGGAGCAGATGACTGAGAACATTAATAAAGAACTTAAATGACACAGC	58
PTGDS	CAAAGCAACCCTGCCACTCAGGCTTCATCCTGCACAATAAACTCCGGAAGCAAGTCAGT	59
RAD51AP1	GGTTGGGAGAATCACAGCTTTACAAGGGTGTTTATATTTGATTTGTGTTTATATTTGAGG	60
ROPN1	GAATGACTTTACCCAAAACCCAGGGTTTCAGCTGGAGTAAAGCACAAATTTGGCAAATTT	61
ROPN1	GAATGACTTTACCCAAAACCCAGGGTTTCAGCTGGAGTAAAGCACAAATTTTGGCAAATTT	119
ROPN1B	TGGCAATTTTAAAGGAAGATACAGAGGTGATTGTACTTCAGAATGATAAACCCATATACC	62
RPL39L	GAGAGAAGCAAGCATCTTTGCCTCTTTGGAGTAGGAAATTCAGACTTGAAAAAGTGGTGT	63
SCML4	TCACCTTGCACTGTCTGGAACAACTTGAATATTTTACGCCGTGAAAGAAAAAGGAAAAAA	64
SCML4	CATTTTGCAATTAACCTTTAAGCAGGACAGATTGCTGAAGCCATGATATTTAAGGTTTGAC	120
SLC40A1	CTCATGTTATCATCATTTAGTGATCTGTGTTGTAGAACATGAGGGGTGAAGCCTTCAGCCT	65
SLC40A1	CTCATGTTATCATCATTTAGTGATCTGTGTTGTAGAACATGAGGGGTGAAGCCTTCAGCCT	121
SLC7A8	TTTTTTGTAAAGTTGATGCCTTACTTTTTGGATAAATAATTTTGAAGCTGGTATTTCTAT	66
SLC7A8	TTTTTTGTAAAGTTGATGCCTTACTTTTTGGATAAATAATTTTGAAGCTGGTATTTCTAT	122
SLC7A8	CCTGTCTATTTCTGGGTGTTTACTGGCAACACAAAGCCCAAGTGTTCAGTGACTTCATT	123

SUV39H2	ATTTGCCAAATGTATTACCGATGCCTCTGAAAAGGGGGTCACTGGGTCTCATAGACTGAT	67
TBC1D10C	GGAAAGGGTTGGCTGAGTCAAGGGACCCAGAGGGCACCAGGAATAAAATCTTCTTGAAC	68
TBC1D9	AAACATCCGGATGATGGGCAAGCCCTCACCTCGGCCAGTGACTATGAAATCTCGGCCAT	69
TBC1D9	CTGGATGTTTAGCTTCTTACTGCAAAAACATAAGTAAACAGTCAACTTTACCATTTCCG	124
TBC1D9	TGTCACAGAGAAATCTGAAAGTAGCAGCAAAAGACAGAGGGCTCATGACAGGTTTTGCTTT	125
TFCP2L1	GATGGTGGGCTAAATTTTAAATTTCAAAAGTGTAGGAGGCTAATATTGCTTCTAAGTTC	70
TFCP2L1	GATGGTGGGCTAAATTTTAAATTTCAAAAGTGTAGGAGGCTAATATTGCTTCTAAGTTC	126
TMEM38A	TTACAGAAATCCTGGCAGCAGCTCCAGTCAAGAAATGTCACTGGTGGCATGATATCTTA	71
TPX2	AGAGAACCCATTCTCCAGACTTTTACCTACCCGTGCCTGAGAAAGCATACTTGACAACT	72
TPX2	AGAGAACCCATTCTCCAGACTTTTACCTACCCGTGCCTGAGAAAGCATACTTGACAACT	127
TRIM2	GATGCTTAAAAACTTTCTAAAGATGAATTGTGTGGCAGTGATTGGTCTGTTTGTGGAGAA	73
TRIM2	GATGCTTAAAAACTTTCTAAAGATGAATTGTGTGGCAGTGATTGGTCTGTTTGTGGAGAA	128
TTK	TGTTTGGTCCTTAGGATGATTTTGTACTATATGACTTACGGGAAAAACACCATTTTCAGCA	74
TTK	TGTTTGGTCCTTAGGATGATTTTGTACTATATGACTTACGGGAAAAACACCATTTTCAGCA	129
TTYH1	GGCTCTGACCCCTGATCTCAACTCGTGGCACTAACTTGGAAAAGGGTTGATTTAAAAATA	75
UGT8	TGCCGTGTCCATCAGATCTCCTTTTGTGCAGTATTTTTACTGGATATTGCCTTTGTGCT	76
VGLL1	AGACACGGCAGCAAGACATCCCTGCATATTGTTCCAGATAAAAAATGAAAAGCTGCTCACAC	77

Table 3

3A Top 2 genes in training data set

Real\Predicted	0	1
0	58	9
1	12	49
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	61	
Actual Negative (N):	67	
Predicted Positive (P'):	58	
Predicted Negative (N'):	70	
True Positive (TP):	49	
False Positive (FP):	9	
False Negative (FN):	12	
True Negative (TN):	58	
Sensitivity (TP/(TP+FN)):	0.8033	
Specificity (TN/(FP+TN)):	0.8657	
Positive Predictive Value (TP/(TP+FP)):	0.8448	
Negative Predictive Value (TN/(FN+TN)):	0.8286	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.6712	
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.8345	

5

3B Top 2 genes in validation data set

Real\Predicted	0	1
0	0	28
1	0	25
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	25	
Actual Negative (N):	28	
Predicted Positive (P'):	53	
Predicted Negative (N'):	0	
True Positive (TP):	25	
False Positive (FP):	28	
False Negative (FN):	0	
True Negative (TN):	0	
Sensitivity (TP/(TP+FN)):	1.0000	
Specificity (TN/(FP+TN)):	0.0000	
Positive Predictive Value (TP/(TP+FP)):	0.4717	
Negative Predictive Value (TN/(FN+TN)):		
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):		
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.5000	

Table 4

4A Top 72 genes in training data set

Real\Predicted	0	1
0	51	16
1	7	54
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	61	
Actual Negative (N):	67	
Predicted Positive (P'):	70	
Predicted Negative (N'):	58	
True Positive (TP):	54	
False Positive (FP):	16	
False Negative (FN):	7	
True Negative (TN):	51	
Sensitivity (TP/(TP+FN)):	0.8852	
Specificity (TN/(FP+TN)):	0.7612	
Positive Predictive Value (TP/(TP+FP)):	0.7714	
Negative Predictive Value (TN/(FN+TN)):	0.8793	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.6486	
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.8232	

5 4B Top 72 genes in validation data set

Real\Predicted	0	1
0	17	11
1	2	23
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	25	
Actual Negative (N):	28	
Predicted Positive (P'):	34	
Predicted Negative (N'):	19	
True Positive (TP):	23	
False Positive (FP):	11	
False Negative (FN):	2	
True Negative (TN):	17	
Sensitivity (TP/(TP+FN)):	0.9200	
Specificity (TN/(FP+TN)):	0.6071	
Positive Predictive Value (TP/(TP+FP)):	0.6765	
Negative Predictive Value (TN/(FN+TN)):	0.8947	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.5487	
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.7636	

Table 5

5A Top 77 genes in training data set

Real\Predicted	0	1
0	51	16
1	8	53
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	61	
Actual Negative (N):	67	
Predicted Positive (P'):	69	
Predicted Negative (N'):	59	
True Positive (TP):	53	
False Positive (FP):	16	
False Negative (FN):	8	
True Negative (TN):	51	
Sensitivity (TP/(TP+FN)):	0.8689	
Specificity (TN/(FP+TN)):	0.7612	
Positive Predictive Value (TP/(TP+FP)):	0.7681	
Negative Predictive Value (TN/(FN+TN)):	0.8644	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.6313	
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.8150	

5 5B Top 77 genes in validation data set

Real\Predicted	0	1
0	17	11
1	2	23
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	25	
Actual Negative (N):	28	
Predicted Positive (P'):	34	
Predicted Negative (N'):	19	
True Positive (TP):	23	
False Positive (FP):	11	
False Negative (FN):	2	
True Negative (TN):	17	
Sensitivity (TP/(TP+FN)):	0.9200	
Specificity (TN/(FP+TN)):	0.6071	
Positive Predictive Value (TP/(TP+FP)):	0.6765	
Negative Predictive Value (TN/(FN+TN)):	0.8947	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.5487	
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.7636	

Table 6

6A Top 30 genes in training data set

Positive Outcome	1
Negative Outcome	Outcome(s) other than 1
Actual Positive (P):	25
Actual Negative (N):	28
Predictive Positive (P'):	40
Predictive Negative (N'):	13
True Positive (TP):	25
False Positive (FP):	15
False Negative (FN):	0
True Negative (TN):	13
Sensitivity (TP/(TP+FN)):	1.0000
Specificity (TN/(FP+TN)):	0.4643
Positive Predictive Value (TP/(TP+FP)):	0.6250
Negative Predictive Value (TN/(FN+TN)):	1.0000
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.5387
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.7321

5 6B Top 58 genes in training data set

Positive Outcome	1
Negative Outcome	Outcome(s) other than 1
Actual Positive (P):	25
Actual Negative (N):	28
Predictive Positive (P'):	36
Predictive Negative (N'):	17
True Positive (TP):	23
False Positive (FP):	13
False Negative (FN):	2
True Negative (TN):	15
Sensitivity (TP/(TP+FN)):	0.9200
Specificity (TN/(FP+TN)):	0.5357
Positive Predictive Value (TP/(TP+FP)):	0.6389
Negative Predictive Value (TN/(FN+TN)):	0.8824
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.4874
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.7279

6C Top 50 genes in training data set

Positive Outcome	1
Negative Outcome	Outcome(s) other than 1
Actual Positive (P):	25
Actual Negative (N):	28
Predicted Positive (P'):	39
Predicted Negative (N'):	14
True Positive (TP):	23
False Positive (FP):	16
False Negative (FN):	2
True Negative (TN):	12
Sensitivity (TP/(TP+FN)):	0.9200
Specificity (TN/(FP+TN)):	0.4286
Positive Predictive Value (TP/(TP+FP)):	0.5897
Negative Predictive Value (TN/(FN+TN)):	0.8571
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.3947
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.6743

6D Top 40 genes in training data set

5

Positive Outcome	1
Negative Outcome	Outcome(s) other than 1
Actual Positive (P):	25
Actual Negative (N):	28
Predicted Positive (P'):	38
Predicted Negative (N'):	15
True Positive (TP):	24
False Positive (FP):	14
False Negative (FN):	1
True Negative (TN):	14
Sensitivity (TP/(TP+FN)):	0.9600
Specificity (TN/(FP+TN)):	0.5000
Positive Predictive Value (TP/(TP+FP)):	0.6316
Negative Predictive Value (TN/(FN+TN)):	0.9333
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	0.5098
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.7300

6E 77 genes in training data set for 3 sets of non overlapping random genes. All yielded the same results.

Real\Predicted	0	1
0	30	37
1	36	25
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	61	
Actual Negative (N):	67	
Predictive Positive (P'):	62	
Predictive Negative (N'):	66	
True Positive (TP):	25	
False Positive (FP):	37	
False Negative (FN):	36	
True Negative (TN):	30	
Sensitivity (TP/(TP+FN)):	0.4098	
Specificity (TN/(FP+TN)):	0.4478	
Positive Predictive Value (TP/(TP+FP)):	0.4032	
Negative Predictive Value (TN/(FN+TN)):	0.4545	
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):	-0.1423	
Area Under Curve (((TP/(TP+FN)) + (TN/(FN+TN)))*0.5):	0.4288	

5

6F 77 genes in validation data set for 3 sets of non overlapping random genes. All yielded the same results.

10

Real\Predicted	0	1
0	28	0
1	0	25
Positive Outcome	1	
Negative Outcome	Outcome(s) other than 1	
Actual Positive (P):	25	
Actual Negative (N):	28	
Predictive Positive (P'):	53	
Predictive Negative (N'):	0	
True Positive (TP):	25	
False Positive (FP):	28	
False Negative (FN):	0	
True Negative (TN):	0	
Sensitivity (TP/(TP+FN)):	1.0000	
Specificity (TN/(FP+TN)):	0.0000	
Positive Predictive Value (TP/(TP+FP)):	0.4717	
Negative Predictive Value (TN/(FN+TN)):		
Matthews Correlation Coefficient ((TP*TN-FP*FN)/sqrt(P*N*P'*N')):		
Area Under Curve (((TP/(TP+FN)) + (TN/(FP+TN)))*0.5):	0.5000	

Table 7
Distribution of pCR rates among BRCAness signature dichotomized groups stratified by HR status

	V/C (n=71)		Control (n=42)	
	Sporadic-like (32)	BRCA1-Like (39)	Sporadic-like (26)	BRCA1-Like (16)
TN (n=58)	4 / 6	18 / 32	2 / 6	3 / 14
HR+HER2- (n=55)	1 / 26	4 / 7	4 / 20	0 / 2

CLAIMS

1. A method of assigning treatment to a breast and/or ovarian cancer patient, the method comprising:
 - 5 determining a level of expression for at least two genes that are selected from Table 1 in a relevant sample from the breast and/or ovarian cancer patient, whereby the sample comprises expression products from a cancer cell of the patient;
comparing said determined level of expression of the at least two genes to the level of expression of the at least two genes in a template;
 - 10 typing said sample as being BRCA-like or not, based on the comparison of the determined levels of expression; and
assigning DNA-damage inducing treatment to a breast and/or ovarian cancer patient of which the sample is classified as BRCA-like.
- 15 2. The method according to claim 1, whereby the sample is typed by determining a level of RNA expression for at least two genes that are selected from Table 1 and comparing said determined RNA level of expression to the level of RNA expression of the at least two genes in a template.
- 20 3. The method according to claim 1, whereby the DNA-damage inducing treatment comprises alkylating agents, platinum salts and/or PARP inhibitors.
4. The method according to claim 1, whereby the DNA-damage inducing treatment comprises a nitrogen mustard alkylating agent, N,N'-triethylenethiophosphoramidate
25 and carboplatin.
5. The method according to claim 1, whereby the DNA-damage inducing treatment comprises a PARP inhibitor.
- 30 6. The method according to claim 5, whereby the PARP inhibitor is 2-[(2R)-2-Methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide dihydrochloride benzimidazole carboxamide (ABT-888).
7. The method according to claim 5 or 6, whereby the treatment further comprises a
35 tyrosine kinase inhibitor.

8. The method according to claim 7, whereby the tyrosine kinase inhibitor is (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide (Neratinib).

5 9. The method according to claim 1, whereby a level of expression of at least five genes from Table 1 is determined.

10. The method according to claim 1, wherein the template is a measure of the average level of said at least two genes in at least 10 independent individuals.

10

11. The method according to claim 1, comprising determining a level of expression for all 77 genes from Table 1 in a relevant sample from the breast and/or ovarian cancer patient.

15 12. The method according to claim 1, further comprising determining a metastasizing potential of the sample from the patient.

13. The method according to claim 12, whereby the metastasizing potential is determined by a 70 gene Amsterdam profile.

20

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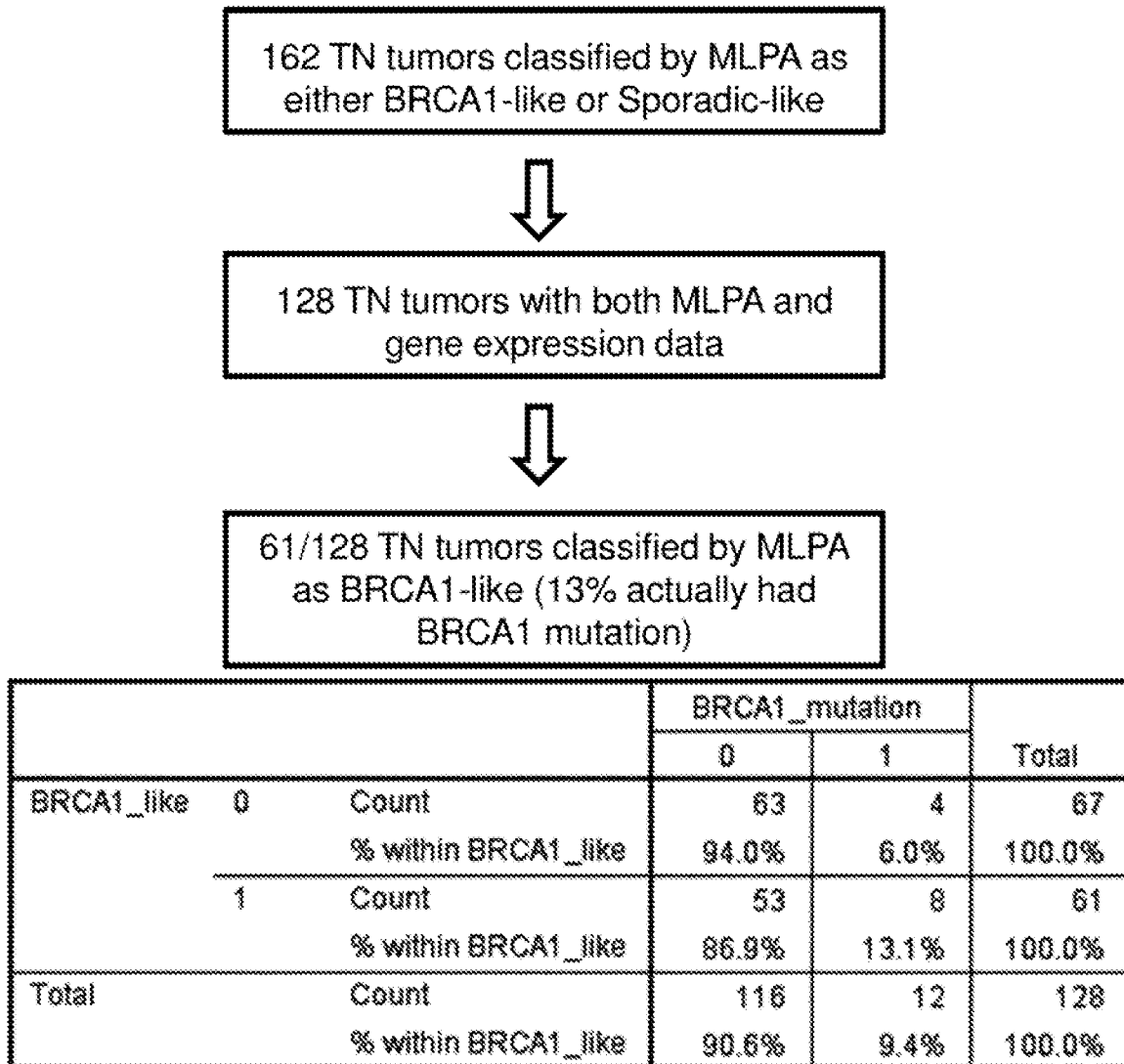


FIG. 1

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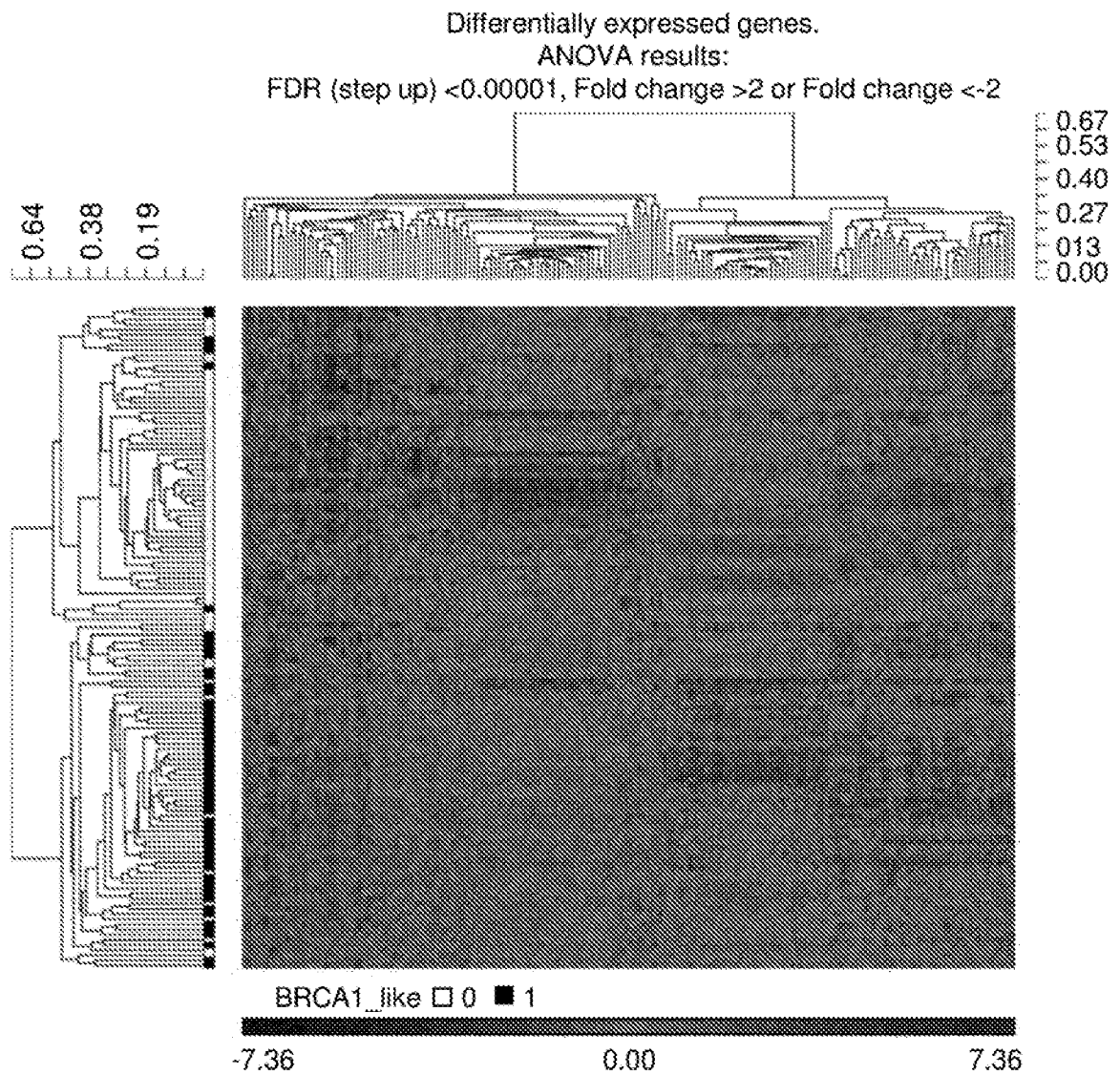
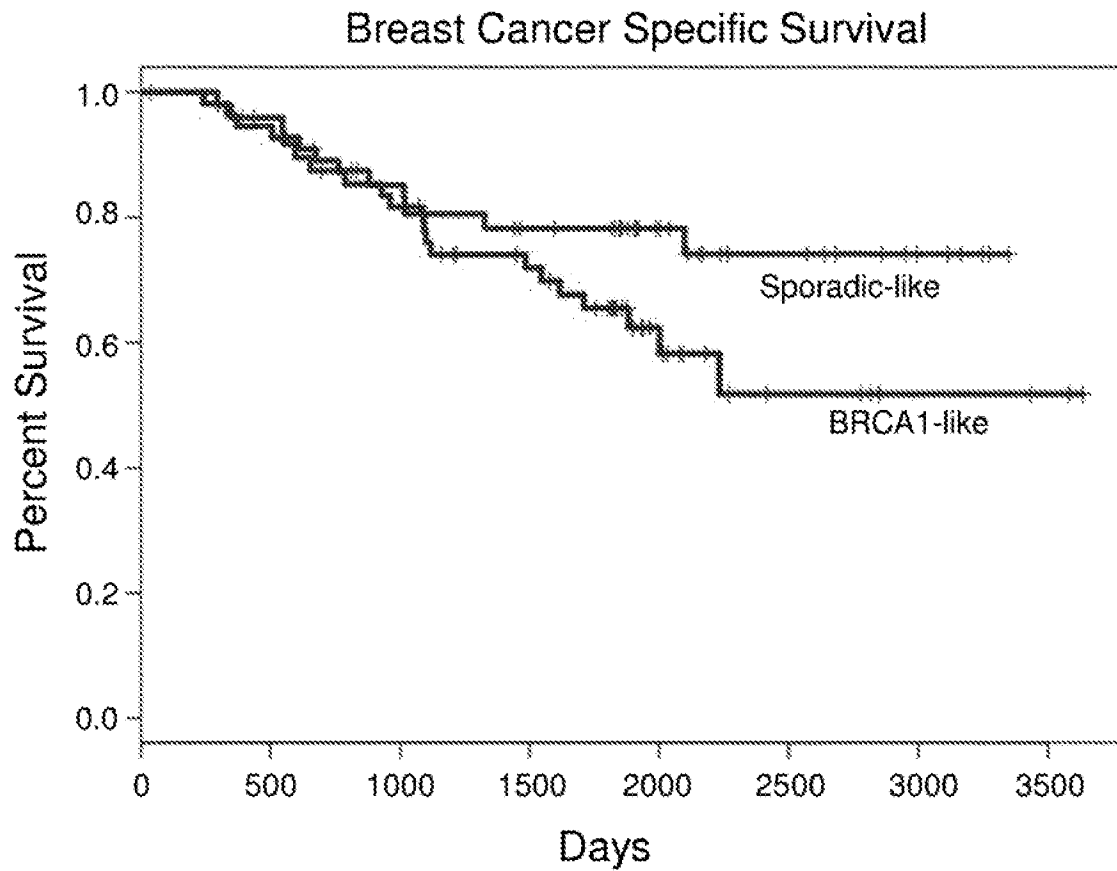


FIG. 2

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**Multivariate Analysis***

Hazard ratio = 2.65

95% CI = 0.71 – 10.0

 $P = 0.151$

*Including tumor size, number of positive lymph nodes, therapy, year of diagnosis and age at diagnosis.

Analysis is stratified for biobank.

FIG. 3

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Claudin gene expression in BRCA1-like tumors

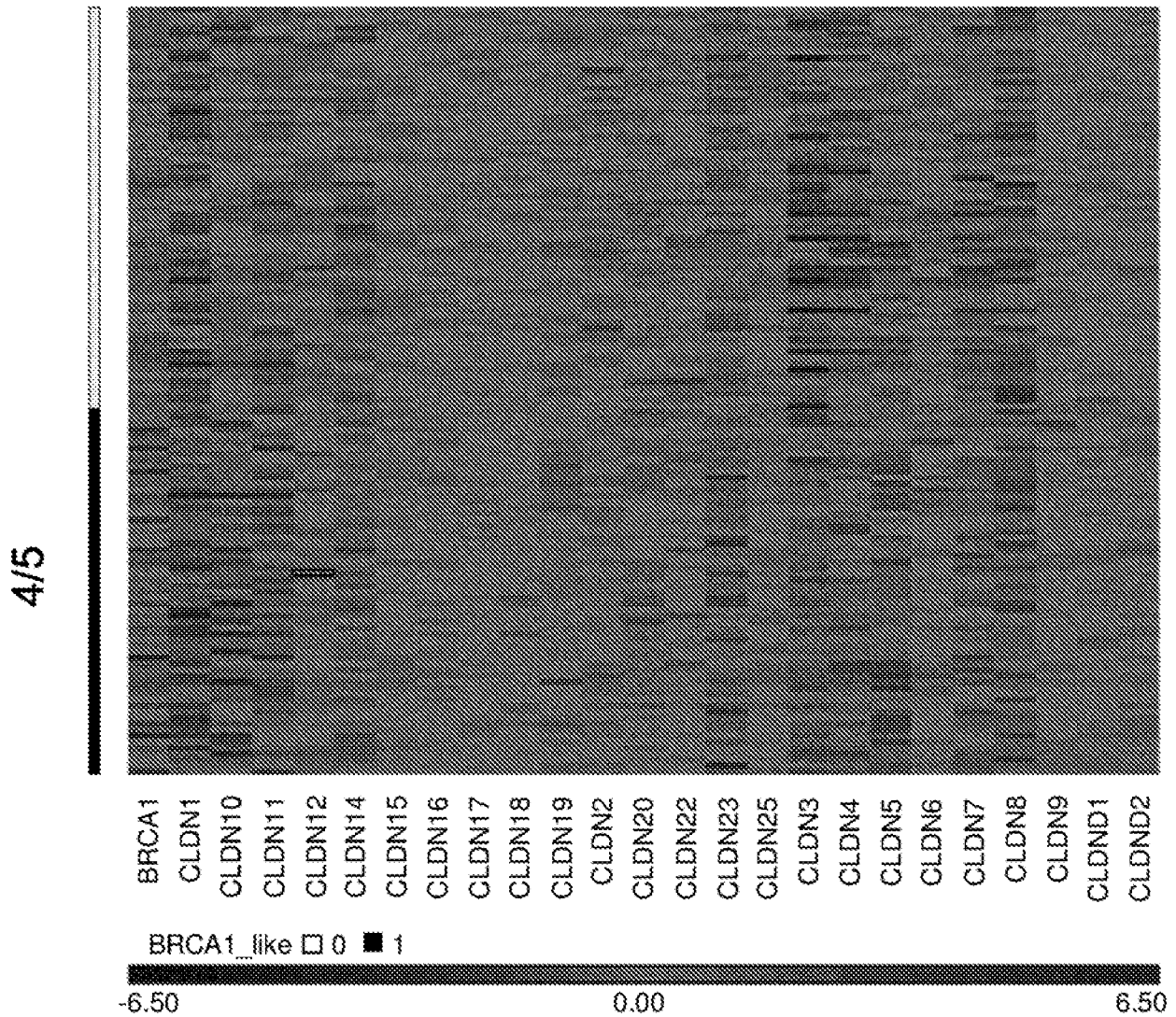


FIG. 4

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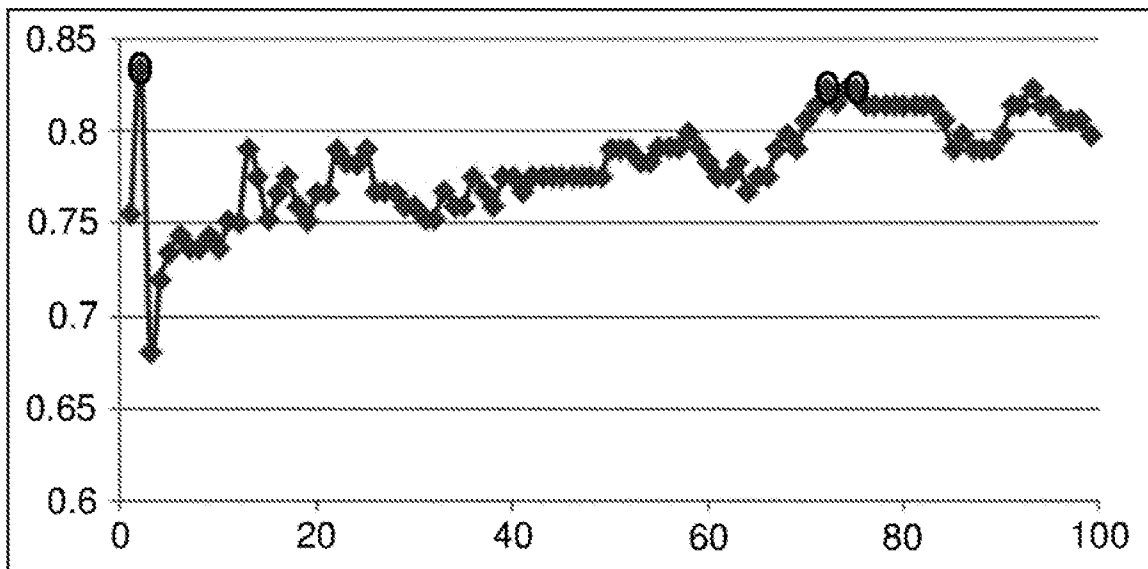


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050813

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12Q1/68

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/153345 A2 (BETH ISRAEL HOSPITAL [US]; CANNISTRA STEPHEN [US]; KONSTANTINOPOULOS P) 8 December 2011 (2011-12-08) page 11, paragraph 2 - page 12, paragraph 2 claims 1-17 page 9, paragraph 2 tables 1-4	1-13
X	WO 2012/045019 A2 (MYRIAD GENETICS INC [US]; TIMMS KIRSTEN [US]; FLAKE DARL [US]; POTTER) 5 April 2012 (2012-04-05) claims 4, 9,10,21 paragraphs [0008], [0054], [0106] tables 2,3 ----- -/--	1-13

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

26 February 2015

Date of mailing of the international search report

05/03/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
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Bruma, Anja

INTERNATIONAL SEARCH REPORT

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PCT/NL2014/050813

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	& P. A. KONSTANTINOPOULOS ET AL: "Gene Expression Profile of BRCAness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer", 14 June 2010 (2010-06-14), XP055172061, Retrieved from the Internet: URL:http://jco.ascopubs.org/content/28/22/3555/T5.expansion.html [retrieved on 2015-02-25] the whole document	1-13
X	& P. A. KONSTANTINOPOULOS ET AL: "Gene Expression Profile of BRCAness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer", 14 June 2010 (2010-06-14), XP055172061, Retrieved from the Internet: URL:http://jco.ascopubs.org/content/28/22/3555/T5.expansion.html [retrieved on 2015-02-25] the whole document	1-13
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X	----- WO 2013/075059 A1 (UNIV VANDERBILT [US]) 23 May 2013 (2013-05-23) claims 1-2,31-34 page 48, paragraph 2 - page 49, paragraph 2 ----- -/--	1-13

INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2014/050813

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	MARIEKE A VOLLEBERGH ET AL: "Genomic instability in breast and ovarian cancers: translation into clinical predictive biomarkers", CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHÄUSER-VERLAG, BA, vol. 69, no. 2, 16 September 2011 (2011-09-16), pages 223-245, XP019993251, ISSN: 1420-9071, DOI: 10.1007/S00018-011-0809-0 the whole document	1-13
A	NICHOLAS TURNER ET AL: "Opinion: Hallmarks of 'BRCAness' in sporadic cancers", NATURE REVIEWS CANCER, vol. 4, no. 10, 1 October 2004 (2004-10-01), pages 814-819, XP055085873, ISSN: 1474-175X, DOI: 10.1038/nrc1457 the whole document	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2014/050813

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