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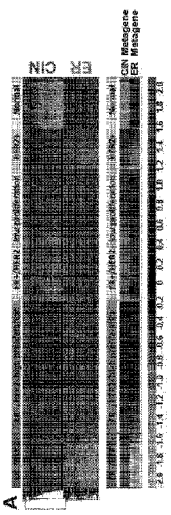

FIG. 1

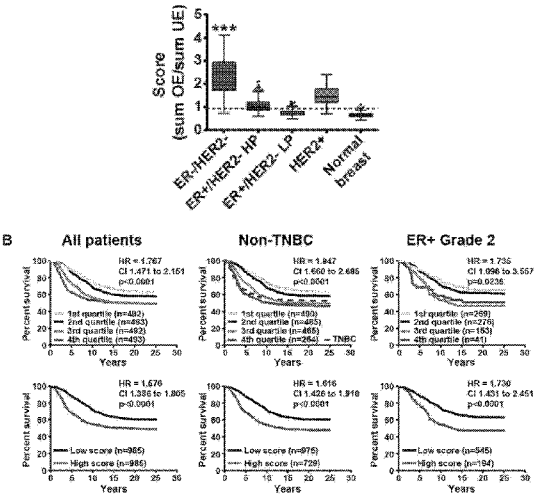

FIG. 1 cont'd

(57) Abstract: The invention provides methods of determining the aggressiveness, prognosis and response to therapy for particular cancers, which include comparing the expression levels of one or a plurality of differentially expressed genes from one or more 5 functional metagenes, including a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune system metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein 10 Synthesis/Modification metagene and a Multiple Networks metagene. The method disclosed herein may be particularly suitable as a companion diagnostic for cancer therapies.

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TITLE

DETERMINING CANCER AGGRESSIVENESS, PROGNOSIS AND RESPONSIVENESS TO TREATMENT

FIELD

THIS INVENTION relates to cancer. More particularly, this invention relates to methods of determining the aggressiveness of cancers, prognosis of cancers and/or predicting responsiveness to anti-cancer therapy.

BACKGROUND

Hormone receptors (ER and PR) and HER2 are standard biomarkers used in clinical practice to aid the histopathological classification of breast cancer and management decisions. Hormone receptor (HR)- and HER2- positive tumors benefit from tamoxifen and anti-HER2 therapies, respectively. On the other hand, there are currently no targeted drug therapies for management of triple negative breast cancer (TNBC), which lacks expression of HR/HER2. TNBCs are more sensitive to chemotherapy than HR-positive tumors because they are generally more proliferative, and pathological complete responses (pCR) after chemotherapy are more likely in TNBC than in non-TNBC[1,2]. Paradoxically, TNBC is associated with poorer survival than non-TNBC, due to more frequent relapse in TNBC patients with residual disease[1,2]. Only 31% of TNBC patients experience pCR after chemotherapy[3], emphasizing the need for targeted therapies.

Transcriptome profiling has been used to dissect the heterogeneity of breast cancer into five intrinsic 'PAM50' subtypes; Luminal A, Luminal B, Basal-like, HER-2 and normal-like subtypes that relate to clinical outcomes[4-8]. Several gene signatures have been developed to predict outcome or response to treatment including: MammaPrint[9], OncotypeDx[10,11], Theros[12-15]. These commercial signatures rely on models that select genes based on clinical phenotypes such as tumor response or survival time. Notwithstanding their clinical utilities, these models fail to identify core biological mechanisms for the phenotypes of interest. Recently, an approach based on biological function-driven gene coexpression signatures, "attractor metagenes", has been applied to the prediction of survival in certain cancers. However such approaches are at an early stage and much work needs to be done to develop this attractor metagene analysis in relation to cancers in general and also for specific cancers.

SUMMARY

The present invention relates to the comparison of expression levels of a plurality of differentially expressed genes from one or a plurality of functional metagenes, including a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune system metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene; wherein the comparison of expression level of a plurality of genes in these metagenes is used to facilitate determining the aggressiveness of certain cancers. This comparison may also, or alternatively, assist in providing a cancer prognosis for a patient. The invention also relates to predicting the responsiveness of a cancer to an anti-cancer treatment by determining an expression level of one or a plurality of genes associated with one or a plurality of the aforementioned twelve functional metagenes.

The invention further relates to the comparison of expression levels of a specific signature of differentially expressed proteins to facilitate or assist in determining the aggressiveness of a particular cancer, a prognosis for a cancer patient and/or predicting responsiveness to an anti-cancer treatment. One or both of these comparisons may also be integrated with the aforementioned comparison of the expression levels of the plurality genes from one or a plurality of the aforementioned functional metagenes in determining cancer aggressiveness, prognosis and/or treatment.

In a first aspect, the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein

Synthesis/Modification metagene and a Multiple Networks metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In a second aspect, the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis.

In one embodiment of the above aspects, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one of the aforesaid metagenes. In an alternative embodiment, the one or plurality of overexpressed genes and/or one or the plurality of underexpressed genes are selected from a plurality of the aforesaid metagenes.

Suitably, for the method of the above aspects the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-

Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene comprise one or a plurality of genes listed in Table 21.

In a third aspect, the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level

In a fourth aspect, the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis.

In one embodiment of the third and fourth aspects, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected

from one of the aforesaid metagenes. In an alternative embodiment, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from a plurality of the aforesaid metagenes.

Suitably, the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene comprise one or a plurality of genes listed in Table 22.

In particular embodiments of the method of the third and fourth aspects, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are from one or a plurality of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene.

In a fifth aspect, the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In a sixth aspect, the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes

associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a more favourable cancer prognosis.

In certain embodiments, the genes associated with chromosomal instability are of a CIN metagene. Non-limiting examples include genes selected from the group consisting of *ATP6V1C1, RAP2A, CALM1, COG8, HELLS, KDM5A, PGK1, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPI, PIR, MCM10, MELK, FOXM1, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPREl, ACOT7, NAEl, SHMT2, TCP1, TXNRD1, ADM, CHAF1A and SYNCRIP*. Preferably, the genes are selected from the group consisting of: *MELK, MCM10, CENPA, EXOl, TTK* and *KIF2C.*

In certain embodiments, the genes associated with estrogen receptor signalling are of an ER metagene. Non-limiting examples include genes selected from the group consisting of: *BTG2, PIK3IP1, SEC14L2, FLNB, ACSF2, APOM, BIN3, GLTSCR2, ZMYND10, ABAT, BCAT2, SCUBE2, RUNX1, LRRC48, MYBPC1, BCL2, CHPT1, ITM2A, LRIG1, MAPT, PRKCB, RERE, ABHD14A, FLT3, TNN, STC2, BATF, CD1E, CFB, EVL, FBXW4, ABCB1, ACAA1, CHAD, PDCD4, RPL10, RPS28, RPS4X, RPS6, SORBS1, RPL22 and RPS4XP3.* Preferably, the genes are selected from the group consisting of: *MAPT* and *MYB.*

In certain embodiments, the method of the fifth and sixth aspects further including the step of comparing an expression level of one or a plurality of other overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1*, and/or an expression level of one or a plurality of other underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH,*

KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the other overexpressed genes compared to the other underexpressed genes indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the other overexpressed genes compared to the other underexpressed genes indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

In one embodiment, the one or plurality of other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN and ZNF593.*

In one embodiment, the one or plurality of other underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1 -AS1* .

Suitably, the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling is integrated with the comparison of the expression level of the one or plurality of other overexpressed genes and/or the expression level of the one or plurality of other underexpressed genes to derive a first integrated score.

In a seventh aspect, the invention provides a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed

genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In an eighth aspect, the invention provides a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFCl* and *STAUl,* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

In one embodiment of the seventh and eighth aspects, the one or plurality of overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFCl, PML, STAUl, TXN* and *ZNF593.*

In one embodiment of the seventh and eighth aspects, the one or plurality of underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In particular embodiments, the method of the first, second, third, fourth, fifth, sixth, seventh and eighth aspects further includes the step of comparing an

expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the overexpressed proteins compared to the underexpressed proteins indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the overexpressed proteins compared to the underexpressed proteins indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

Suitably, the comparison of the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins is to thereby derive an integrated score. In one particular embodiment, the comparison of the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins is integrated with:

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(iii) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1* and/or the expression level of the underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH,*

KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3 to derive a fourth integrated score; or

(iv) the comparison of the expression level of the overexpressed genes and/or an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene, to derive a fifth integrated score; or

(v) the comparison of the expression level of the overexpressed genes and/or the expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene, to derive a sixth integrated score.

wherein the second, third, fourth, fifth and/or sixth integrated score is indicative of, or correlates with, the aggressiveness and/or prognosis of the cancer in the mammal.

In particular embodiments, the second, third, fourth, fifth and/or sixth integrated score are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation.

In a preferred embodiment, the first, second and/or third integrated scores are derived, at least in part, by exponentiation wherein the comparison of the expression level of the other overexpressed genes and the expression level of the other underexpressed genes is raised to the power of

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling; and/or

(ii) the comparison of the expression level of the overexpressed proteins and/or the expression level of the underexpressed proteins.

In a ninth aspect, the invention provides a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In a tenth aspect, the invention provides a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

In an eleventh aspect, the invention provides method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method

including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene, wherein an altered or modulated relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

Suitably, for the present aspect the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene comprise one or a plurality of genes listed in Table 21.

In a twelfth aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein an altered or modulated relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment of the eleventh and twelfth aspects, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one of the metagenes. In an alternative embodiment, the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from a plurality of the metagenes.

Suitably, the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene comprise one or a plurality of genes listed in Table 22.

In particular embodiments, the one or plurality of overexpressed genes and the one or plurality of underexpressed genes are from one or a plurality of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene.

According to the method of the eleventh and twelfth aspects, the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes includes comparing an average expression level of the one or plurality of overexpressed genes and/or an average expression level of the one or plurality of underexpressed genes. This may include calculating a ratio of the average expression level of the one or plurality of overexpressed genes and the average expression level of the one or plurality of underexpressed genes. Suitably, the ratio provides an aggressiveness score which is indicative of, or correlates with, cancer aggressiveness and a less favourable prognosis. Alternatively, the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes includes comparing the sum of expression levels of the one or plurality of overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes. This may include calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes.

In a thirteenth aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of determining an expression level of one or a plurality of genes associated with chromosomal instability in one or a plurality of non-mitotic cancer cells of the mammal, wherein a higher expression level indicates or correlates with relatively increased responsiveness of the cancer to the anti-cancer treatment

Suitably, the one or plurality of genes associated with chromosomal instability are selected from the group consisting of: *TTK, CEP55, FOXM1* and *SKIP2* and/or any CIN genes listed in Table 4.

In a fourteenth aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In certain embodiments, the genes associated with chromosomal instability are of a CIN metagene. Non-limiting examples include genes selected from the group consisting of: *ATP6V1C1, RAP2A, CALM1, COG8, HELLS, KDM5A, PGK1, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPI, PIR, MCM10, MELK, FOXM1, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPRE1, ACOT7, NAE1, SHMT2, TCP1, TXNRD1, ADM, CHAF1A and SYNCRIP*. Preferably, the genes are selected from the group consisting of: *MELK, MCM10, CENPA, EXOl, TTK* and *KIF2C.*

In certain embodiments, the genes associated with estrogen receptor signalling are of an ER metagene. Non-limiting examples include genes selected from the group consisting of: *BTG2, PIK3IP1, SEC14L2, FLNB, ACSF2, APOM, BIN3, GLTSCR2, ZMYND10, ABAT, BCAT2, SCUBE2, RUNX1, LRRC48, MYBPC1, BCL2, CHPT1, ITM2A, LRIG1, MAPT, PRKCB, RERE, ABHD14A, FLT3, TNN, STC2, BATF, CD1E, CFB, EVL, FBXW4, ABCB1, ACAA1, CHAD, PDCD4, RPL10,*

RPS28, RPS4X, RPS6, SORBSl, RPL22 and RPS4XP3. Preferably, the genes are selected from the group consisting of: *MAPT* and *MYB.*

Suitably, the method of this aspect further includes the step of comparing an expression level of one or a plurality of other overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and/or an expression level of one or a plurality of other underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of other overexpressed genes compared to the one or plurality of other underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment, the one or plurality of other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN* and *ZNF593.*

In one embodiment, the one or plurality of other underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In certain embodiments, the comparison of the expression level of the one or plurality of other overexpressed genes and/or the expression level of the one or plurality of other underexpressed genes is integrated with the comparison of the expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or the expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling to derive a first integrated score, which is indicative of, or correlates with, responsiveness of the cancer to the anti-cancer treatment. By way of example, the first integrated score may be derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation. Preferably, the integrated score is derived by exponentiation,

wherein the comparison of the expression level of the one or plurality of other overexpressed genes and the expression level of the one or plurality of other underexpressed genes is raised to the power of the comparison of the expression level of the one or plurality of overexpressed genes associated with chromosomal instability and the expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

In a fifteenth aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CDIB, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment, the one or plurality of overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN* and *ZNF593.*

In one embodiment, the one or plurality of underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

Suitably, the method of the eleventh, twelfth, thirteenth, fourteenth and fifteenth aspects further includes the step of comparing an expression level of a one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKTl, NFKBl, HER2, ASNS and COL6A1, and/or an expression level of

one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

Suitably, the comparison of the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins is to thereby derive an integrated score. In one particular embodiment, the comparison of the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins is integrated with:

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(iii) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1* and/or the expression level of the underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CDIB, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3* to derive a fourth integrated score; or

(iv) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development

metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene, to derive a fifth integrated score; or

(v) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene, to derive a sixth integrated score.

wherein the second, third, fourth, fifth and/or sixth integrated score is indicative of, or correlates with, responsiveness of the cancer to the anti-cancer treatment.

In particular embodiments the first, second, third, fourth, fifth and/or sixth integrated score are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation.

In a preferred embodiment, the first, second and/or third integrated scores are derived, at least in part, by exponentiation wherein the comparison of the expression level of the other overexpressed genes and/or the expression level of the other underexpressed genes is raised to the power of

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling; and/or

(ii) the comparison of the expression level of the overexpressed proteins and/or the expression level of the underexpressed proteins.

In a sixteenth aspect, the invention provides method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMADl, GATA3, ITGA2,

AKT1, NFKB 1, HER2, ASNS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD 50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

Suitably, the anticancer treatment of the eleventh, twelfth, thirteenth, fourteenth, fifteenth and sixteenth aspects is selected from the group consisting of endocrine therapy, chemotherapy, immunotherapy and a molecularly targeted therapy. In certain embodiments, the anticancer treatment comprises an anaplastic lymphoma kinase (ALK) inhibitor, a BCR-ABL inhibitor, a heat shock protein 90 (HSP90) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a poly (ADP-ribose) polymerase (PARP) inhibitor, retinoic acid, a B-cell lymphoma 2 (Bcl2) inhibitor, a gluconeogenesis inhibitor, a p38 mitogen-activated protein kinase (MAPK) inhibitor, a mitogen-activated protein kinase kinase 1/2 (MEKl/2) inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitor, an insulin-like growth factor 1 receptor (IGF1R) inhibitor, a phospholipase C-γ (PLCγ) inhibitor, a c-Jun N-terminal kinase (JNK) inhibitor, a p21-activated kinase-1 (PAK1) inhibitor, a spleen tyrosine kinase (SYK) inhibitor, a histone deacetylase (FDDAC) inhibitor, a fibroblast growth factor receptor (FGFR) inhibitor, an X-linked inhibitor of apoptosis (XIAP) inhibitor, a polo-like kinase 1 (PLK1) inhibitor, an extracellular-signal-regulated kinase 5 (ERK5) inhibitor and combinations thereof.

Suitably, the method of the eleventh, twelfth, thirteenth, fourteenth, fifteenth and sixteenth aspects further includes the step of administering to the mammal a therapeutically effective amount of the anticancer treatment. Preferably, the anticancer treatment is administered when the altered or modulated relative expression level indicates or correlates with relatively increased responsiveness of the cancer to the anti-cancer treatment.

In a seventeenth aspect, the invention provides a method of predicting the responsiveness of a cancer to an immunotherapeutic agent in a mammal, said method including the step of comparing an expression level of one or a plurality of

overexpressed genes selected from the group consisting of *ADORA2B, CD36, CETN3, CFDP1, KCNG1, LAMA3, NAE1, MAP2K5, PGK1, SF3B3, STAU1 and TXN* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting *oiAPOBEC3A, BTN2A2, BCL2, CAMK4, FBXW4, CAMSAP1, CARHSP1, GSK3B, HCFC1R1, PSEN2, MYB and ZNF593,* , in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the immunotherapeutic agent.

Suitably, the immunotherapeutic agent is an immune checkpoint inhibitor. Preferably, the immune checkpoint inhibitor is or comprises an anti-PDl antibody or an anti-PDLl antibody.

In an eighteenth aspect is provided a method of predicting the responsiveness of a cancer to an epidermal; growth factor receptor (EGFR) inhibitor in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *NAE1, GSK3B, TAF2, MAPRE1, BRD4, STAU1, TAF2, PDCD4, KCNG1, ZNRD1-AS1, EIF4B, HELLS, RPL22, ABAT, BTN2A2, CD1B, ITM2A, BCL2, CXCR4,* and *ARNT2* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting *oiCDIC, CD1E, CD1B, KDM5A, BATF, EVL, PRKCB, HCFC1R1, CARHSP1, CHAD, KIR2DL4, ABHD5, ABHD14A, ACAA1, SRPK3, CFB, ARNT2, NDUFC1, BCL2, EVL, ULBP2, BIN3, SF3B3, CETN3, SYNCRIP, TAF2, CENPN, ATP6V1C1, CD55* and *ADORA2B* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the EGFR inhibitor.

In a nineteenth aspect is provided a method of predicting the responsiveness of a cancer to a multikinase inhibitor in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *SCUBE, CHPT1, CDC1, BTG2, ADORA2B* and *BCL2,* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *NOP2, CALR, MAPRE1, KCNG1, PGK1, SRPK3,*

RERE, ADM, LAMA3, KIR2DL4, ULBP2, LAMA4, CA9, and *BCAP31,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the multikinase inhibitor.

Suitably, for the method of the seventeenth, eighteenth and nineteenth aspects, a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a relatively increased responsiveness of the cancer to the immunotherapeutic agent, EGFR inhibitor or multikinase inhibitor; and/or a lower relative expression level of the one or aplurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a relatively decreased responsiveness of the cancer to the immunotherapeutic agent, EGFR inhibitor and/or multikinase inhibitor.

In some embodiments, the method of the seventeenth, eighteenth and nineteenth aspects further includes the step of administering to the mammal a therapeutically effective amount of the immunotherapeutic agent, the EGFR inhibitor or the multikinase inhibitor respectively. Preferably, the immunotherapeutic agent, the EGFR inhibitor or the multikinase inhibitor is administered when the altered or modulated relative expression level indicates or correlates with relatively increased responsiveness of the cancer to the immunotherapeutic agent, the EGFR inhibitor or the multikinase inhibitor respectively.

Suitably, for the methods of the aforementioned aspects, the step of comparing an expression level of one or a plurality ofoverexpressed genes or proteins and an expression level of one or a plurality of underexpressed genes or proteins, includes comparing an average expression level of the one or plurality of overexpressed genes or proteins and an average expression level of the one or plurality of underexpressed genes or proteins. This may include calculating a ratio of the average expression level of the one or plurality of overexpressed genes or proteins and the average expression level of the one or plurality of underexpressed genes or proteins. Suitably, the ratio provides an aggressiveness score which is indicative of, or correlates with, cancer aggressiveness and a less favourable prognosis. Alternatively, the step of comparing an expression level of one or a

plurality of overexpressed genes and an expression level of one or a plurality of underexpressed genes or proteins , includes comparing the sum of expression levels of the one or plurality of overexpressed genes or proteins and the sum of expression levels of the one or plurality of underexpressed genes or proteins. This may include calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes or protein and the sum of expression levels of the one or plurality of underexpressed genes or proteins.

In certain embodiments of the aforementioned methods, the mammal is subsequently treated for cancer.

In a twentieth aspect, the invention provides a method for identifying an agent for use in the treatment of cancer including the steps of:

(i) contacting a protein product of ***GRHPR, NDUFCl, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COGS, CFDPl*** and/or ***KCNGl*** with a test agent; and

(ii) determining whether the test agent, at least partly, reduces, eliminates, suppresses or inhibits the expression and/or an activity of the protein product.

Suitably, the agent possesses or displays little or no significant off-target and/or nonspecific effects.

Preferably, the agent is an antibody or a small organic molecule.

In a twenty first aspect, the invention provides an agent for use in the treatment of cancer identified by the method of the eighteenth aspect.

In a twenty second aspect, the invention provides a method of treating a cancer in a mammal, including the step of administering to the mammal a therapeutically effective amount of an agent identified by the method of the eighteenth aspect.

Preferably, for the invention of the twentieth, twenty first and twenty second aspects, the cancer has an overexpressed gene selected from the group consisting of ***GRHPR, NDUFCl, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COGS, CFDPl, KCNGl*** and any combination thereof.

Suitably, the method of the aformentioned aspects further includes the step of determining, assessing or measuring the expression level of one or plurality of the overexpressed genes, the underexpressed genes, the overexpressed proteins and/or the underexpressed proteins described herein.

Suitably, the mammal referred to in the aforementioned aspects and embodiments is a human.

In certain embodiments of the invention of the aforementioned aspects, the cancer includes breast cancer, lung cancer inclusive of lung adenocarcinoma and lung squamous cell carcinoma, cancers of the reproductive system inclusive of ovarian cancer, cervical cancer, uterine cancer and prostate cancer, cancers of the brain and nervous system, head and neck cancers, gastrointestinal cancers inclusive of colon cancer, colorectal cancer and gastric cancer, liver cancer inclusive of hepatocellular carcinoma, kidney cancer inclusive of renal clear cell carcinoma and renal papillary cell carcinoma, skin cancers such as melanoma and skin carcinomas, blood cell cancers inclusive of lymphoid cancers and myelomonocytic cancers, cancers of the endocrine system such as pancreatic cancer and pituitary cancers, musculoskeletal cancers inclusive of bone and soft tissue cancers, although without limitation thereto. By way of example, breast cancer includes aggressive breast cancers and cancer subtypes such as triple negative breast cancer, grade 2 breast cancer, grade 3 breast cancer, lymph node positive (LN^+) breast cancer, HER2 positive ($HER2^+$) breast cancer and ER positive (ER^+) breast cancer, although without limitation thereto.

Unless the context requires otherwise, the terms *"comprise", "comprises"* and *"comprising"*, or similar terms are intended to mean a non-exclusive inclusion, such that a recited list of elements or features does not include those stated or listed elements solely, but may include other elements or features that are not listed or stated.

The indefinite articles '*a*' and '*an*' are used here to refer to or encompass singular or plural elements or features and should not be taken as meaning or defining "one" or a "single" element or feature.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: **Correlation of breast cancer subtypes and the aggressiveness gene list.** The METABRIC dataset was visualized according to the expression of the 206 genes (Table 4) in the aggressiveness gene list. The aggressiveness score for each tumor was calculated as the ratio of the CIN metagene (average value for CIN genes expression) to the ER metagene (average value for ER genes expression). (A) The expression of the aggressiveness gene list according to the GENIUS histological classification. Box plot shows the aggressiveness score of the histological subtypes. (B) The overall survival of patients in the METABRIC dataset was analyzed

according to the aggressiveness score (upper row: by quartiles; lower row: by median) in all patients, non-TNBC patients and in patients with ER+ Grade 2 tumors. The hazard ratio (HR) and confidence interval (CI) and p-value for comparisons of upper quartile vs. lower quartiles (upper row) and at the dichotomy across the median (high vs. low) are shown (Log-rank Test, GraphPad® Prism). The number of patients (n) in each group is shown in brackets.

Figure 2: Network analysis of the aggressiveness gene list. (A) Ingenuity pathway analysis was performed using direct interactions on the 206 genes in the aggressiveness gene list (red is overexpressed and green is underexpressed). One network of high direct interactions was identified. **(B)** The genes in the network in A were investigated for their correlation with the aggressiveness score and overall survival (Table 5) and eight genes (MAPT, MYB, MELK, MCM10, CENPA, EXOl, TTK and KIF2C) with the highest correlation were still connected in a direct interaction network. **(C)** The overall survival of patients in the METABRIC dataset was analyzed according to score from the 8 genes in C (upper row: by quartiles; lower row: by median) in all patients, non-TNBC patients and in patients with ER+ Grade 2 tumors.

Figure 3: Survival of patients stratified by the 8-genes score in the METABRIC dataset. The overall survival of patients in the METABRIC dataset was analyzed according to the 8-genes score in selected settings in all patients **(A)** or in ER-positive patients only **(B). (A)** TP53 mutation was compared in high vs. low 8-genes score (split by the median). The expression of the proliferation marker Ki67 was divided by dichotomy across the median and patients in each of these groups were then stratified according to their 8-genes score (split by quartiles). Disease stages (Stage I - Stage III) were stratified by the median 8-genes score. **(B)** ER^+ Grade 3, ER+ lymph node negative (LN-) and ER+ LN+ tumors were stratified by the quartiles.

Figure 4: The 8-genes score associates with survival of breast cancer patients. Four published datasets were used to validate the 8-genes score as a predictor of survival. The 8-genes score was calculated for tumors in each of the datasets and the survival of patients was stratified according to the median 8-genes score; **(A)** GSE2990[15], **(B)** GSE3494[65], **(C)** GSE2034[66] and **(D)** GSE25066[53]. The hazard ratio (HR) and confidence interval (CI) and p-value for comparisons high vs. low 8-genes score are shown in the Kaplan-Meier survival curves (Log-rank Test, GraphPad®

Prism). The number of patients (n) is shown in brackets. The table in each panel show multivariate survival analysis in the using Cox-proportional hazard model including all available conventional indicators.

Figure 5: Therapeutic targets in the aggressiveness gene list. (A) The TNBC cell lines, MDA-MB-231, SUM159PT and Hs578T were treated with control siRNA (Scrambled, Sc CTRL) or siRNA targeting the specified genes and the survival of these cells was compared on day 6. Data shown is the average from the three cell lines where each cell line was treated in triplicate. * $p< 0.05$, ** $p<0.01$ and *** <0.001 from One-Way ANOVA analysis performed using GraphPad® Prism. Data for individual cell lines is shown in Table 5. (B) A panel of breast cancer cell lines was used to prepare lysates for immunoblotting of TTK. Tubulin was used as the loading control. (C) Dose response curves for the treatment of breast cancer cell lines in the absence or presence of escalating doses of the TTK inhibitor (TTKi) AZ3146. The survival of cells was measured using the CellTitre® MTS/MTA assay carried out 6 days after treatment. Percentage survival (n = 3 per dose) was calculated as the percentage of the signal from treated cells to that from control cells. (D) The concentration of TTK required to affect the survival of 50% of the cells (IC50) was measured by GraphPad® Prism from the dose response curves in C for each cell line.

Figure 6: TTK protein expression associates with breast cancer survival. The overall survival of patients in a large cohort of breast cancer patients (n=409) was stratified according to TTK staining by IHC (scores 0-3). Kaplan-Meier survival curves are shown for all patients **(A)** with four TTK staining (categories 0-3) and (B) two categories (0-2 vs. 3). Log-rank Test and p-value were used for survival curves. (C) The distribution of high TTK staining (category 3) across histological subgroups and mitotic indices. Data shown is the mitotic index (median + range) measured as the number of mitotic cells in 10 high power fields (hpf). The number of tumors with high TTK staining to the total number of tumors in the cohort is shown on the right. High TTK expression distributed across subtypes and did not associate with mitotic index.

Figure 7: TTK associates with aggressive subtypes and is a therapeutic target. (A) Kaplan-Meier survival curves are shown for Grade 3 tumors, lymph node positive patients (LN^+) and LN^+ patients with grade 3 tumors. Log-rank Test and p-value were used for these survival curves. For patients with TNBC, and HER2, survival was statistically significant using the Gehan-Breslow-Wilcoxon test (p-

values marked by asterisks) which gives more weight to deaths at early time points. The poorer survival of patients with high Ki67 tumors and high TTK staining was a trend but did not reach significance. Survival curves and statistical analyses were performed using GraphPad® Prism. **(B)** TNBC and non-TNBC cell lines were treated for 6 days with the specified concentrations of docetaxel (doc) alone, TTK inhibitor (TTKi) alone of the combinations. The survival of cells was measured using the MTS/MTA assay as described in Methods. *** $p < 0.001$ comparing the combination to single agents and to non-TNBC cell lines from Two-Way Anova in GraphPad® Prism. **(C)** MDA-MB-231 cells were treated with docetaxel or TTKi alone or in combination and collected at 96 hours to perform apoptosis assays by flow cytometry. Early apoptotic cells were defined as annexin V+/7-AAD-.

Figure 8: Global gene expression meta-analysis of genes deregulated in TNBC, metastatic events and death at 5 years in Oncomine™. (A) TNBC in 8 datasets were compared to non-TNBC, **(B)** tumors with metastatic events at 5 years were compared to those with no metastatic events at 5 years in 7 datasets and **(C)** tumors leading to death at 5 years were compared to those that did not lead to death at 5 years were compared in 7 datasets. The datasets used in the comparisons are stated in the legends and the key for the heatmap coloring is also included. The heatmap key denotes the top or bottom x % placement of a gene according to gene rank which is based on the p-value.

Figure 9: The derivation of the 206 aggressiveness gene list. (A and **B)** are Venn diagrams for the top overexpressed genes and bottom underexpressed genes shared between TNBC and/or metastasis and death at 5 years analyses in Oncomine™. **(C** and D) The Venn diagrams from A and B were crossed with genes which were deregulated in TNBC in comparison to adjacent normal breast tissue from the METABRIC dataset. The genes marked in bold in panels C and D are the 206 genes which constitute the unfiltered aggressiveness gene list.

Figure 10: Common genes between the 206 aggressiveness gene list and metagene attractors. Venn diagrams show common genes (in bold) between the 206 aggressiveness gene list and the chromosomal instability (CIN), lymphocyte-specific and ER attractors (Cheng et al 2013a, Cheng et al 2013b). The table below lists the shared genes. The 6 overexpressed genes (marked in red) and 2 underexpressed genes (marked in green) which constitute the 8-genes signature in this study are shown. Gene set enrichment analysis of the remaining 140 genes which

were only present in the 206 gene signature reveal that these genes function in cell cycle.

Figure 11: Correlation of breast cancer subtypes and the aggressiveness gene list. The METABRIC dataset was visualized according to the expression of the 206 genes in the aggressiveness gene list. The aggressiveness score for each tumor was calculated as the sum of normalized z-score expression values of overexpressed genes divided by that of underexpressed genes. **(A** and **B)** The expression of the aggressiveness gene list was visualized according to PAM50 intrinsic subtypes and the integrative clusters classification. Box plots show the aggressiveness score of these subtypes. The shaded lines in box plots mark the median value for the aggressiveness score. *** $p < 0.001$ One-Way ANOVA using GraphPad® Prism. Kaplan-Meier curves are of overall survival of patients in the METABRIC dataset stratified according to the quartiles (left plot) or the median (middle plot) of the aggressiveness score in ER+ patients with Grade 3 tumors. Tumors of the five PAM50 intrinsic subtypes which show high aggressiveness score (higher than the median) did not show statistical difference in overall survival (right plot). The hazard ratio (HR) and the 95% confidence interval (CI) and the p-value are reported using the Log-rank Test.

Figure 12: Survival of the PAM50 breast cancer subtypes in the METABRIC dataset according to the aggressiveness score. The survival of patients in the METABRIC dataset annotated based on the PAM50 subtypes was analyzed by dichotomy across the median aggressiveness score from the 206 gene list **(A)** and the reduced 8 gene list **(B).** The p-value are reported using the Log-rank Test in GraphPad® Prism and show that all tumors with the different PAM50 subtypes but high aggressiveness score did not show a difference in patient survival (left graphs), whereas the PAM50 subtypes showed significantly different survival only in low aggressiveness score setting.

Figure 13: TTK staining association with patient survival. The overall survival of patients in a large cohort of breast cancer patients (n=409) was stratified according to TTK staining by IHC (scores 0-3). Kaplan-Meier survival curves are shown for all patients (with four TTK staining categories 0-3 and two categories (0-2 vs. 3) with 10 and 20 years follow up. Log-rank Test and p-value were used for survival curves of all patients. There were no statistical differences in the survival of patients with

Grade 1, Grade 2 or hormone positive tumors when stratified by TTK expression. Survival curves and statistical analyses were performed using GraphPad® Prism.

Figure 14: Criteria used for assigning 'prognostic subgroups' in this study.

Figure 15: Panel 1: Overall survival curves of lung cancer patients split by ten (10) CIN and two (2) ER genes as a signature; patients are low or high according to the median of the signature; Panel 2: Survival curves for lung adenocarconima split by ten (10) CIN genes and two (2) ER genes as a signature; patients are low or high according to the median of the signature; Panel 3: Survival curves for lung adenocarconima (10 years) split by ten (10) CIN genes and two (2) ER genes as a signature; patients are low or high according to the median of the signature; Panel 4: Survival curves for lung adenocarconima split by six (6) CIN genes and two (2) ER genes as a signature; patients are low or high according to the median of the signature; and Panel 5: Survival curves for lung adenocarconima (10 years) split by six (6) CIN genes and two (2) ER genes as a signature; patients are low or high according to the median of the signature.

Figure 16: (A) RNA-Seq data from the breast cancer cohort of The Cancer Genome Atlas (TCGA) data. **(B)** Recurrence-free survival of breast cancer patients in the TCGA stratified by the Aggressiveness score compared to the OncotypeDx recurrence score. **(C)** Comparison of copy number variations (CNVs) of breast tumours with high aggressiveness score to those with low aggressiveness score.

Figure 17: (A) RNA-Seq data from all cancers of The Cancer Genome Atlas (TCGA) data. **(B)** Recurrence-free survival of all cancer patients in the TCGA stratified by the Aggressiveness score compared to the OncotypeDx recurrence score.

Figure 18: Recurrence-free survival or overall survival of cancer patients with different cancer types in the TCGA data patients stratified by the 8-genes aggressiveness score.

Figure 19: Outline of Example 2. Meta-analysis was performed in Oncomine™ using breast cancer datasets irrespective of subtypes or gene expression array platforms used. The global gene expression profiles of breast tumors that led to metastatic or death event within 5 years were compared to those that did not and the top overexpressed (OE) and underexpressed genes (UE) in these comparisons were selected. The commonly deregulated genes in the primary tumors that led to metastatic and death events (depending on the annotation of each dataset) were then interrogated using the online tool KM-Plotter™ (n>4000 patients with some overlap

with the datasets in Oncomine™). Only genes which associated with relapse-free survival (RFS), distant metastasis-free survival (DMFS) or overall survival (OS) of basal-like breast cancer (BLBC) or ER-negative (ER) breast cancer were selected. The 96 genes from this training were then shortlisted to 28 genes by selecting the most significant and persistent across the different outcomes (RFS, DMFS and OS). The 28-gene signature was then validated in large cohorts of breast cancer gene expression studies including The Cancer Genome Atlas (TCGA) dataset the Research Online Cancer Knowledgebase (ROCK) dataset and the homogenous TNBC dataset for prognostication of ER-, TNBC and BLBC subtypes. Finally, the TN signature was then investigated for association with pathological complete response (pCR) after neoadjuvant chemotherapy in studies which performed gene expression profiling prior to therapy.

Figure 20: The 28-gene TN signature associates with RFS, DMFS and OS of BLBC and ER- breast cancer. The 21 overexpressed and 7 underexpressed genes were used as a signature in the online tool KM-Plotter. The signature (the average expression of the 21 overexpressed genes and the inverted expression of the 7 underexpressed genes) stratified the RFS, DMFS and OS; low: under the median of the expression of the signature and high: over the median of the expression of the signature. The hazard ratio (HR) and log-rank p-value (p) for the univariate survival analyses were generated by KM-Plotter. n = number of patients.

Figure 21: The prognostication by the TN score outperforms standard clinicothapological indicators in TNCBC, BLBC and ER- breast cancer subtypes. Two datasets, **(A)** the TNBC dataset and (B&C) the ROCK dataset, were analyzed for the TN signature and the TN score was calculated as the ratio of the average expression of the 21 overexpressed genes to that of the 7 underexpressed genes. This score was calculated for each tumor and the median TN score over the entire dataset was used to classify tumors as high (above the median) or low (below the median) for the TN score. (A) RFR of TNBC patients in the TNBC cohort stratified by dichotomy across the median TN score in the cohort. Table under the survival curve shows univariate and multivariate survival analysis for the TN score and other available clinical indicators recorded in the dataset. The TN score outperformed all the clinical indicators in the multivariate analysis. **(B)** RFS and DMFS of BLBC in the ROCK dataset stratified by dichotomy across the median TN score in the dataset. The table under the survival curves shows multivariate survival

analysis for the TN score against other available clinical indicators recorded in the dataset. The TN score outperformed all the clinical indicators in the multivariate analysis of BLBC cases. **(C)** The RFS and DMFS of ER- negative breast cancer were stratified by the TN score (data not shown) and the table shows the multivariate survival analysis that the TN score outperforms clinical indicators in ER$^-$ breast cancer cases.

Figure 22: The TN score stratifies the overall survival of ER- breast cancer patients in the TCGA dataset. The gene expression data using the Illumina HiSeq RNA-seq arrays from the TCGA breast cancer data (n = 1106) were used to calculate the TN score for all tumors. Tumors were classified as high or low for the TN score by dichotomy across the median TN score. The overall survival (OS) of ER- breast cancer cases with high TN score were compared to those with low TN score. The table below the survival curve shows that the TN score is more significant than other clinical indicators in univariate survival analysis and it is the only significant prognostic indicator in multivariate survival analysis.

Figure 23: The TN score associates with pCR after chemotherapy in ER$^-$HER2$^-$ breast cancer. Gene expression datasets which profiled tumors prior to neoadjuvant chemotherapy and recorded pathological complete responses (pCR) vs. no pCR or residual disease (RD) were analyzed for the TN signature and the TN score was calculated for each tumor. Tumors were classified as high or low TN score by dichotomy across the median TN score in each dataset. Only ER-HER2- cases were used in the data shown in the Figure. **(A)** Graphs showing the percentage of cases achieving (red bars) or not achieving (black bars) pCR in low and high TN score subgroups. Fisher's exact test was used to analyze the 2x2 contingency tables and the p-value from this test was reported when statistical significance was observed. The dotted line marks the 31% pCR rate reported in literature for TNBC. Each dataset is labeled with the accession number and the chemotherapy regimen used, namely: GSE18728, GSE50948, GSE20271, GSE20194, GSE22226, GSE42822 and GSE23988. Chemotherapy abbreviation: **5-FU,** Adriamycin, Cyclophosphamide, Taxane, X : Xeloda, Methotrexate, Epirubicin. (B) The dataset GSE22226 from the ISPY-1 trial was used to compare the TN score and pCR in the prediction of ER$^-$ patient survival after neoadjuvant chemotherapy as this dataset also recorded RFS. pCR strongly associated with RFS (first panel) as previously reported. the TN score (next three panel) was not only predictive of survival in the these patients but could

also stratified the survival of patients achieving or not achieving pCR, indicated the TN score as an independent prognostic factor for pCR after neoadjuvant chemotherapy.

Figure 24: Drug sensitivity of cancer cell lines according to the TN score. The large published study by Garnett et al. was investigated where the TN score was calculated for each cell line in the study as described in Methods. The cell lines were classified as high or low TN score according to the median TN score to compare the sensitivity of low TN score cell lines (white boxes) and high TN score cell lines (red boxes). Graphs were prepared using GraphPad® Prism showing sensitivity as -logl0[IC50] in boxes (with median marked by a line) and whiskers (marking the 1st and 3rd quartiles and outliers as dots according to Tukey method for plotting the whiskers and outliers). Unpaired two-tailed t test was used for statistical analysis.

Figure 25: The iBCR score stratifies the survival of all breast cancer patients irrespective of ER status in the ROCK dataset. The TN and Agro scores were calculated for each tumor in the ROCK dataset (n=1570, Affymetrix) and then the iBCR score was calculated as the TN score to the power of the Agro score. The RFS of all patients and the RFS of ER- or ER+ patients only was compared between high score and low score by dichotomy across the median score for each of the scores. The iBCR score was prognostic in all patients as well as ER- and ER+ subsets with better separation between low score and high score tumors (increased hazard ratio [HR] and limits of the 95% confidence intervals and decreased log rank p-value). Graphs and the univariate survival analysis using the log rank test were performed using GraphPad® Prism.

Figure 26: The iBCR score stratifies the survival of all breast cancer patients irrespective of ER status in the TCGA dataset. The TN. Agro and the iBCR scores were calculated for each tumor in the TCGA dataset (n=1 106, Illumina RNA-Seq). The RFS of all patients and the RFS of ER- or ER+ patients only was compared between high score and low score. As in the results in the ROCK dataset in Figure 7, The iBCR score was prognostic in all patients as well as ER- and ER+ subsets with better separation between low score and high score tumors.

Figure 27: The iBCR score associates with RFS and pCR after chemotherapy in the ISPY-1 trial. The dataset GSE22226 from the ISPY-1 trial was used to compare the Agro, TN and the integrated iBCR score in the prognosis and association with pCR after chemotherapy (Adriamycin, Cyclophosphamide and Taxane) in ERTTER2-

and ER+ breast cancer subtypes. Tumors were classified as high or low score by dichotomy across the median of each score in the entire dataset. High iBCR score ERTTER2- tumors were less likely to achieve pCR and these patients had poor survival. High iBCR ER+ patients were more likely to achieve pCR but since a small number of ER+ patients achieved (10/62 [16%]), the survival of high iBCR ER+ patients remained poor. Note that the Agro score identifies all but two ER-HER2- tumors as high score, thus the data from this group should not be interpreted. Also note that the Agro score is highly prognostic of survival and association with pCR in ER+ whereas the TN score is not in these patients. The integration of these two scores in the iBCR score has overcame the limitation of each of these subtype-specific scores.

Figure 28: The iBCR score associates with pCR after chemotherapy in breast cancer. Gene expression datasets with pCR annotation after chemotherapy were used as described in Figure 5 to calculate the Agro and TN scores and the integrated iBCR score. Tumors were classified as high or low score by dichotomy across the median of each score in each dataset. **(A)** ERTTER2- cases with graphs showing the percentage of cases achieving (red bars) or not achieving (black bars) pCR in low and high score subgroups. **(B)** ER+ cases were analyzed as in A. Fisher's exact test was used to analyze the 2x2 contingency tables and the p-value from this test was reported when statistical significance was observed. Each dataset is labeled with the accession number and the chemotherapy regimen used, namely: GSE18728, GSE50948, GSE20271, GSE20194, GSE22226, GSE42822 and GSE23988. Chemotherapy abbreviation: **5-FU,** Adriamycin, Cyclophosphamide, Taxane, X: Xeloda, Methotrexate, Epirubicin.

Figure 29: The iBCR score stratifies the survival of tamoxifen-treated ER+ patients. The Agro and TN scores and the iBCR score were calculated in two datasets of gene expression profiling prior to tamoxifen therapy: **A&B.** GSE6532 with 327 patients. 137 untreated and 190 tamoxifen-treated; **C:** GSE17705 with 298 patients treated with tamoxifen for 5 years. **(A)** ER+ NO patients with high iBCR score have poor RFS compared low iBCR score counterparts. **(B)** RFS of all ER+ patients and NO and Nl subsets stratified by the Agro and iBCR scores. **(C)** DMFS survival of all ER+ and NO and Nl subsets stratified by the Agro and iBCR scores. The hazard ratios and log-rank p-values are more significant for the iBCR score than the Agro score although the Agro score was significantly prognostic.

Figure 30: Drug sensitivity of cancer cell lines according to the iBCR score. The large published study by Garnett et al. was investigated where the iBCR score was calculated for each cell line from the Agro and TN scores. The cell lines were classified as high or low iBCR score according to the median iBCR score to compare the sensitivity of low iBCR score cell lines (white boxes) and high TN score cell lines (red boxes). Results according to low and high Agro score were also included. Graphs were prepared using GraphPad® Prism and unpaired two-tailed t test was used for statistical analysis (n.s. not significant).

Figure 31: Global gene expression meta-analysis of genes deregulated in primary breast tumors with metastatic events or death at 5 years in Oncomine™. (A) tumors with metastatic events at 5 years were compared to those with no metastatic events at 5 years in 7 datasets and **(B)** tumors leading to death at 5 years were compared to those that did not lead to death at 5 years were compared in 7 datasets. The datasets used in the comparisons are stated in the legends and the key for the heatmap coloring is also included. The heatmap key denotes the top or bottom x % placement of a gene according to gene rank which is based on the p-value.

Figure 32: The TN signature outperforms all published signatures for TNBC/BLBC. Relapse-free survival of basal-like breast cancer patients (BLBC) was investigated in the online database KM-Plotter (Affymetrix platform) according to the TN signature in comparison to published TNBC signatures. Hazard ratios (HR) and logrank p-values were generated by KM-Plotter. **(A)** the TN score vs. signatures **(B)** from Karn et al. (PLoS One, 201 1); from Rody et al. (Breast Cancer Res, 201 1) **(C)** IL8, **(D)** VEGF, and **(E)** B-cell metagenes; **(F)** from Yau et al. (Breast Cancer Res, 2010); **(G)** from Yu et al. (Clin Cancer Res, 2013); **(H)** from Lee et al. (PLoS One, 2013 and **(I)** from Hallet et al. (Sci Rep, 2012).

Figure 33: The TN score stratified the survival of ER$^-$ patients in the Agilent TCGA data. The original TCGA dataset using the Agilent microarrays (n=597) were analyzed for the TN score where patients were assigned as low, intermediate or high for the TN score according to tertiles. The RFS of ER- patients only were then compared according to these tertiles. The stratification was significant according to a log-rank survival test ($P<0.0001$). High TN score group vs. low TN score group had a hazard ratio (95% confidence interval) of 3.484 (1.035 to 11.23) with a log rank p-value of 0.0179.

Figure 34: The prognostication by the TN score in ER- and BLBC is not affected by systemic treatment. The online KM-Plotter tool was used to investigate the stratification of RFS, DMFS and OS of ER- breast cancer (top two rows) and BLBC (bottom two rows) in systemically untreated patients (untreated) or in patients who were treated systemically (treated). The HR, the 95% confidence intervals and the log-rank p values were provided by KM-Plotter as well as the number of patients at risk.

Figure 35: Sensitivity of cancer cell lines to anticancer drugs according to the TN score in the Cancer Cell Line Encyclopedia (CCLE) study. The gene expression data of the cancer cell lines in the study were analyzed to calculate the TN score for each cell line and were assigned to low or high TN score by dichotomy across the median. The IC_{50} for each of the 24 drugs used in the CCLE study was compared between high and low TN score cell lines and the data shown are those with statistical differences based on unpaired two-tailed *t*-test performed using GraphPad® Prism.

Figure 36: Integration of the TN and Agro scores by addition or subtraction. The ROCK dataset was used to study the integration of the TN and Agro score with the aim to develop a test that is breast cancer subtype independent. **(A)** The raw Agro and TN scores for ER+ (black dots) and ER- (red dots) in the ROCK dataset (each dot represent one patient, n = 1570 in total). The two scores are scattered and a method of integration that can retain the information from each score in the relevant breast cancer subtype is necessary. Such methods are tested in this Figure and Figure 38. **(B)** Addition method. First column shows the TN score in ER+ tumors with low (white boxes) and high (red boxes) Agro score subgroups (top panel). In the bottom panel, the Agro score in ER- tumors with low (white boxes) and high (red boxes) TN score subgroups. This data shows that the TN score is similar for ER+ tumors with low and high Agro scores and that the Agro score is similar for ER- tumors with low and high TN scores. The lack of statistical differences (independence) suggested that integration is possible. The second column shows the linear correlation between the TN score and Agro score when they were added in each patient for ER+ (top panel) and ER- (bottom panel) patients. In the third column, the TN and Agro scores were plotted against the produced summed score showing that the information from each score is retained in the final summed score for both ER+ (top panel) and ER- (bottom panel) patients.. The last column shows the overlap of data from ER+ and ER-

patients shown separately in the second and third columns. **(C)** Identical analysis as that done in B but the integration was tested by subtraction of the TN and Agro score. The linearity of the relationship between the summed score and each of the single scores (TN and Agro score) indicated that information from each score is represented in the final score. The performance of these two methods (addition or subtraction) was tested for association with survival as shown in Figure 37.

Figure 37: Comparison of different integration methods of the TN and Agro scores for prognostication in ER- **and** ER+ **RFS in the** ROCK **dataset.** The methods of integration by addition or subtraction (from Figure 36) or multiplication or division (Figure 38) were tested for the association of the produced integrated score in the ROCK dataset in ER- or ER+ breast cancer. As shown in the figure, only the addition or multiplication methods were prognostic in ER- breast cancer and the multiplication was more significant in ER+ breast cancer compared to the addition. These two methods are reasonable as subtraction or division methods would reduce the value of one of the scores. Two additional methods were tested, raising one score to the power of the second score since the relationships observed when multiplication and division methods showed exponential or power curves. As shown in the last column (shaded and marked in red box), raising the TN score to the power of the Agro score should superior prognostication in both ER- and ER+ breast cancer subtypes. In fact, the prognostication of this integrated score was better than each of the score in their respective subtypes. The method was therefore used to calculate the integrated Breast Cancer Recurrence (iBCR) score.

Figure 38: Integration of the TN and Agro scores by division or multiplication. The ROCK dataset was used to study the integration of the TN and Agro as these scores were scattered when plotted against each other (panel A in Figure 36). **(A)** The box plots in the first column are identical to those in Figure 36. The shaded boxes in panel A describe integration by division (top row) or multiplication (bottom row) of the TN and Agro scores. The division produced a power curve and the multiplication produced an exponential curve for the relationship between the TN and Agro scores after dividing them or multiplying them by each other in both ER+ (black dots) and ER- (red dots). The overlay in the last column shows that the differences between ER+ and ER- patients for the scores is retained. These two methods were tested for survival association in Figure 37 and the multiplication method was suitable. (B) As power and exponential curves were observed in the

division and multiplication methods in A, it was reasonable to test integration by raising one score to the power of the second score. As shown in the top row in the overlay or individual plots, the integration by raising the TN score to the power of the Agro score produced a linear relationship in both ER- (red dots) and ER+ (black dots) patients. This method of integration outperformed all other methods when tested for survival association as shown in Figure 37.

Figure 39: The iBCR score is prognostic in TNBC patients. In addition to the validation of the iBCR score in the ROCK dataset (Affymetrix) and the TCGA dataset (Illumina dataset) of mixed subtypes of breast cancer, the iBCR score was investigated in the homogenous TNBC dataset. As shown in the right panel, the iBCR was as prognostic (with slight improvement) compared to the TN score. This further validates the development of the integrated score to be a prognostic test in breast cancer irrespective of ER status, unlike previous limited signatures.

Figure 40: Survival of tamoxifen-treated ER+ patients according to the Agro score vs. Oncotype Dx. (A) RFS and DMFS of node negative (top) and node positive (bottom) ER+ patients treated with tamoxifen in the published study (Loi *et al, Clin Oncol,* 2007) stratified by the Agro Score (high vs. intermediate vs. low by tertiles). **(B)** DMFS of node negative or positive ER+ patients treated with tamoxifen for 5 years from the published study (Symmans *et al, J Clin Oncol,* 2010) was stratified by the tertiles of the Agro Score. **(C)** RFS and DMFS of node negative (top) and node positive (bottom) ER+ patients treated with tamoxifen in the published study (Loi *et al, Clin Oncol,* 2007) stratified by the risk groups of the OncotypeDx Recurrence Score. **(D)** DMFS of node negative or positive ER+ patients treated with tamoxifen for 5 years from the published study (Symmans *et al, J Clin Oncol,* 2010) was stratified by the risk groups of the OncotypeDx Recurrence Score.

Figure 41: Comparison of the Agro Score and MammaPrint in the KM-Plotter tool. Distant metastasis-free survival according to the Agro Score (high vs. low) or according to MammaPrint (high vs. low) in all breast cancer patients, ER+, ER+ lymph node negative (LN-) or ER+ lymph node positive (LN+) patients. The KM-Plotter online tool (n = 4142 patients). The Agro score outperformed the MammaPrint signature in all patient subsets particularly for ER+ node positive patients.

Figure 42: Sensitivity of cancer cell lines to anticancer drugs according to the iBCR score in the Cancer Cell Line Encyclopedia (CCLE) study. The gene

expression data of the cancer cell lines in the study were analyzed to calculate the TN score for each cell line and were assigned to low or high iBCR score by dichotomy across the median. The IC_{50} for each of the 24 drugs used in the CCLE study was compared between high and low iBCR score cell lines and the data shown are those with statistical differences based on unpaired two-tailed *t*-test performed using GraphPad® Prism. As this analysis was also done for the TN score (Figure 35), results from analysis of the Agro score are also shown in the top row.

Figure 43: High copy number variations (CNVs) in high Agro score tumors compared to low Agro score tumors. The breast cancer tumors in the TCGA dataset were classified as high or low for the Agro score based on the gene expression data (Illumina HiSeq RNA-seq). **(A)** The TCGA copy number variations (segmented and after deletion of germline CNV) were visualized using the UCSC Genome Browser to compare patients who were classified from gene expression data as high Agro score patients (top panel) to those classified as low Agro score patients (bottom panel). **(B)** Presentation of the distribution of clinical indicators such as ER, PR and HER2 status and others. **(C)** The difference in the CNVs profile of high Agro score patients to the low Agro score patients showing gains (red) and losses (green) of whole chromosome arms in the high Agro score patients, suggesting aneuploidy.

Figure 44: High Agro and iBCR score cell lines are more sensitive to Aurora kinase inhibitors. Two studies which treated breast cancer cell lines with Aurora kinase inhibitors were analyzed based on the Agro, TN and the iBCR score for these cell lines. As shown in Figure, high Agro score and particularly high iBCR score cell lines were more sensitive to Aurora kinase inhibitors (ENMD-2076: IC50 1.4 μM vs. 5.9 μM for high vs. low iBCR Score cell lines, p=0.0125 f-test; AMG 900: IC50 0.3 nM vs. 0.7 nM for high vs. low iBCR score cell lines, p=0.0308 *t*-test).

Figure 45: The iBCR is prognostic in the pan-cancer TCGA data for overall and relapse-free survival. The pan-cancer TCGA data were analyzed for the iBCR gene signature using the UCSC Genome Browser and the data for this signature, survival data and cancer types were downloaded from the browser. Tumors, irrespective of cancer types, were classified into quartiles based on the iBCR signature expression and the overall and relapse free survival were compared across these quartiles. As shown in the top row, overall and relapse-free survival was stratified by the iBCR signature in this pan-cancer dataset. In the far right panel in the top row, the distribution of tumors in each cancer type across the iBCR signature quartile is

shown. Cervical cancer for example displays high iBCR signature in the majority of cases whereas on the opposite side, thyroid cancer displays low iBCR signature in all the cases. The lower panels show the stratification of overall survival according to the iBCR score from the pan-cancer dataset where the stratification was statistically significant in log-rank univariate survival analysis. In addition to the breast cancer data shown in paper, the iBCR signature was prognostic in adrenocortical cancer, endometrioid cancer, kidney clear cell cancer, bladder cancer, lower grade glioma and melanoma. The iBCR was also prognostic in lung adenocarcinoma as shown in Figure 46.

Figure 46: The iBCR signature is prognostic in lung adenocarcinoma (LUAD). The iBCR signature was tested for prognostication in lung cancer in two large datasets. (A&B) KM-Plotter (Affymetrix data) was used to investigate overall survival of lung adenocarcinoma **(A)** and squamous cell carcinoma **(B).** The iBCR signature shows a strong prognostic value in lung adenocarcinoma (LUAD). **(C)** Multivariate survival analysis was performed in KM-Plotter for the iBCR signature in lung cancer in comparison to available clinical indicators; histological type (lung adenocarcinoma vs. small cell lung cancer) and stage of disease. The iBCR signature outperformed these standard clinical indicators. **(D&E)** The TCGA data for LUAD (Illumina HiSeq RNA-seq data) were stratified by quartiles or tertiles for the iBCR signature expression to test the association of the iBCR signature with overall survival (D) and relapse-free survival (E), respectively. LUAD patients with high iBCR signature had poorest survival and suffered earlier recurrence and death compared to patients with lower iBCR signature expression. It should be noted that the TCGA data for squamous cell lung carcinoma were also investigated and there was no statistical significance for the association of the iBCR signature and survival, in agreement with the very weak association seen from the KM-Plotter data.

Figure 47: The sensitivity of breast cancer cell lines treated with 24 drugs according to the iBCR score. Breast cancer cell lines (10 cell lines) were cultured in the absence or presence of escalating doses of 24 small molecular anti-cancer drugs. This published study was re-analyzed to compare the sensitivity (calculated as the -logIC50) between high iBCR score cell lines (5 cell lines: BT-549, MDA-MB-231, MDA-MB-436, MDA-MB-468 and BT-20) to low iBCR score cell lines (5 cell lines: Hs.578T, BT-474, MCF-7, T-47D, and ZR-75-1). The iBCR scores were calculated from the Agro and TN scores using the published gene expression dataset for 51

breast cancer cell lines (Neve *et al, Cancer Cell,* 2006). High iBCR score cell lines (red bars) were more sensitive than low iBCR score cell lines (white bars) to 13 drugs (shaded in grey) targeting 9 different kinases. Statistical comparison was performed in GraphPad® Prism using two tailed unpaired i-test.

Figure 48: Proteins and phosphoproteins associated with the iBCR mRNA gene signature. The iBCR score based on the mRNA expression of the 43 genes was used to stratify the patients in the TCGA breast cancer dataset as low, intermediate or high iBCR score. The reverse phase protein arrays (RPPA) from the TCGA breast cancer dataset (n=747 patients) were then compared between the three groups of patients according to the iBCR mRNA signature. **(A)** Overall survival of ER+ patients according to the iBCR mRNA signature. **(B)** Significantly up- or down-regulated proteins and phosphoproteins in ER+ patients in the low, intermediate and high iBCR score groups. **(C)** Overall survival of ER- according to the iBCR mRNA signature. **(D)** Significantly up- or down-regulated proteins and phosphoproteins in ER- patients in the low, intermediate and high iBCR score groups.

Figure 49: Prognostication of breast cancer patient survival by integrated mRNA and protein iBCR signature. The deregulated proteins and phosphoproteins in the three iBCR mRNA score groups were investigated for association with survival. Eight downregulated proteins and nine upregulated proteins were highly prognostic as a protein signature (iBCR protein signature). **(A)** Stratification of overall survival based on the iBCR protein signature (top row) and the integrated iBCR mRNA and protein signature (bottom row) in all breast cancer patients, ER+ and ER- cases. **(B)** Univariate and multivariate survival analysis using the Cox-proportional hazard model showing that the combined iBCR mRNA/Protein signature outperforms all clinicopathological indicators.

Figure 50: Proteins and phosphoproteins associated with the iBCR mRNA gene signature. (A) Stratification of lung adenocarcinoma overall survival based on the iBCR mRNA gene signature in the TCGA dataset (n=472 patients). **(B)** Comparison of proteins phosphoprotein levels between the tumors in the four quartiles of the iBCR mRNA gene signature. **(C)** Stratification of overall survival of lung adenocarcinoma patients based on six proteins deduced from panel (n=212 patients). **(D)** The combined iBCR mRNA/Protein signature stratifies the overall survival of lung adenocarcinoma patients (n=212 patients). **(E)** Multivariate Cox-proportional

hazard model for survival analysis showing that the combined iBCR mRNA/Protein score outperforms all clinicopathological indicators in lung adenocarcinoma.

Figure 51: The iBCR test is prognostic in Kidney renal clear cell carcinoma (KIRC) (left vertical panel), Skin cutaneous melanoma (SKCM) (middle vertical panel) and Uterine corpus endometrioid carcinoma (UCEC) (right vertical panel). (A) Stratification of overall survival based on the iBCR mRNA gene signature. **(B)** Stratification of overall survival based on iBCR protein signature. **(C)** Stratification of overall survival based on the combined iBCR mRNA/protein signature.

Figure 52: The iBCR test is prognostic in Ovarian adenocarcinoma (OVAC) (left vertical panel), Head & Neck squamous cell carcinoma (HNSC) (middle vertical panel) and Colon/Rectal Adenocarcinoma (COREAD) (right vertical panel). (A) Stratification of overall survival based on the iBCR mRNA gene signature. **(B)** Stratification of overall survival based on iBCR protein signature. **(C)** Stratification of overall survival based on the combined iBCR mRNA/protein signature.

Figure 53: The iBCR test is prognostic in Lower Grade Glioma (LGG) (left vertical panel), Bladder urothelial carcinoma (BLCA) (middle vertical panel) and Lung squamous cell carcinoma (LUSC) (right vertical panel). (A) Stratification of overall survival based on the iBCR mRNA gene signature. **(B)** Stratification of overall survival based on iBCR protein signature. **(C)** Stratification of overall survival based on the combined iBCR mRNA/protein signature.

Figure 54: The iBCR test is prognostic in **(A)** Kidney renal papillary cell carcinoma (KIRP). **(B)** Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), **(C)** Liver hepatocellular carcinoma (LIHC), **(D)** Pancreatic ductal adenocarcinoma (PDAC). For these cancer types, the TCGA datasets did not include RPPA arrays; only the iBCR mRNA gene expression test was used.

Figure 55: Protein-protein interaction of the iBCR mRNA/protein signature. The components of the iBCR test were analysed using the STRING database. The iBCR test (65 components) was significantly enriched (P=5.6E-14) for protein-protein interactions (129 interactions). The confidence of interactions is denoted by increasing thickness of the connecting blue lines. It is noteworthy that the components on the top right which do not show interactions contain several novel

genes that are not well characterised. The iBCR test is enriched for several biological functions related to the hallmarks of cancer (refer to Table 20).

Figure 56: The iBCR test as a companion diagnostic for immunotherapy. (A) Twelve genes from the iBCR test, particularly from the TN component, associated significantly with progression free survival of follicular lymphoma patients treated with pidilizumab + rituximab immunotherapy. The expression profile of the 12 genes in the tumours prior to treatment is shown (red indicates overexpression and green indicates underexpression). White and black boxes denote progression free survival or not, respectively. **(B)** A score was calculated based on the iBCR signature as the ratio of expression of the overexpressed genes to that of underexpressed genes. The survival of patients based on dichotomy across the median score was compared. The hazard ratio (HR) and the log-rank p-value for the survival comparison between low and high score tumors is shown in panel. **(C)** Eight patients were profiled pre- and post-treatment and the expression profiles of the 12 genes from the iBCR test were visualised in these patients. A trend for inversion of expression was observed and this was most evident for patient no. 9 who remained free of disease progression. (D) One gene was statistically significant in all patients post-treatment compared to that before treatment. This gene showed a marked different post-treatment vs. pre-treatment for patient no. 9. (E) Survival curve for the same patient group calculated from the gene signature labelled "Follicular Lymphoma" in Table 23. All conventions as per (B) above. Relapse-free survival of patients based on dichotomy across the median score is shown.

Figure 57: Network analysis of the genes from the meta-analysis of gene expression datasets.

Figure 58: Functional metagenes associate with breast cancer patient survival.

Figure 59: The iBCR test as a companion diagnostic for EGFR inhibition and multikinase inhibition. (A) Seventeen genes (see Table 23) from the iBCR test associated significantly with survival of colorectal cancer patients treated with the EGFR inhibitor cetuximab. (B) Sixteen genes (see Table 23) from the iBCR test associated significantly with overall survival of triple negative breast cancer patients treated with the EGFR inhibitor cetuximab combined with cisplatin. (C) Nineteen genes (see Table 23) from the iBCR test associated significantly with progression-free survival of lung cancer patients treated with the EGFR inhibitor erlotinib. (D) Twenty genes (see Table 23) from the iBCR test associated significantly with

progression-free survival of lung cancer patients treated with the multikinase inhibitor sorafenib.

DETAILED DESCRIPTION

The present invention is at least partly predicated on the discovery that there are genes that are associated with tumor aggressiveness and poor clinical outcome based on meta-analysis of published gene expression profiling. More particularly, the overexpression and/or underexpression of these genes (see Table 21) was found to be associated with poor survival in breast cancer. Network analysis using the Ingenuity Pathway Analysis (IPA®) software identified a number of networks or metagenes within these survival-associated genes that possess distinct biological functions as outlined in Table 21. A smaller subset of genes from each network or metagene which consistently associated with patient survival were then selected. The list of these genes and their corresponding functions are shown in Table 22. These genes were divided into six functional metagenes or networks.

The present invention is also at least partly predicated on the discovery that there are genes that are commonly de-regulated in particular subgroups that exemplify aggressive clinical behavior in triple-negative breast cancer (TNBC). More particularly, this is evident in TNBC compared to non-TNBC and normal breast, tumors associated with distant metastasis and/or death compared to their respective counterparts. Initially, a list of 206 recurrently deregulated genes was found to be particularly enriched for chromosomal instability (CIN) and estrogen receptor signaling (ER) metagenes. An aggressiveness score based on the ratio of the expression level of a CIN metagene relative to an ER metagene has been shown to identify aggressive tumors regardless of molecular subtype and clinico-pathologic indicators. Furthermore, depletion of proteins involved in kinetochore binding or chromosome segregation could be therapeutic and significantly reduced the survival of TNBC cell lines *in vitro*, particularly with regard to TTK. TTK inhibition with small molecule inhibitor affected the survival of TNBC cell lines. Also, *TTK* mRNA and protein levels were associated with aggressive tumor phenotypes. Mitosis-independent expression of TTK protein was prognostic in TNBC and other aggressive breast cancer subgroups, suggesting that protection of CIN/aneuploidy drives aggressiveness and treatment-resistance. The combination of TTK inhibition

with chemotherapy was effective *in vitro* in the treatment of cells that overexpress TTK, thus providing a therapeutic treatment for the protected CIN phenotype.

Additionally, the present invention is at least partly predicated on the discovery of a second signature of altered gene expression, including 21 overexpressed genes and 7 underexpressed genes, that is highly prognostic in patients with ER^- breast cancer, TNBC and basal-like breast cancer (BLBC). Indeed, integration of this 28 gene signature with the aforementioned aggressiveness score or gene signature produces an integrated score which is prognostic in breast cancer independent of ER status. Furthermore, the integrated score was prognostic in cancer broadly irrespective of the cancer type, as well as in specific types of cancer in addition to breast cancer, such as lung adenocarcinoma. Moreover, the 28 gene signature and the integrated score were both shown to be predictive of response to chemotherapy in breast cancer patients, as well as identify those ER^+ lymph node positive breast cancer patients who would benefit from endocrine therapy. Altered expression of the signatures described herein was also predictive of sensitivity in cancer cell lines and clinically to a range of anticancer therapeutics, and in particular, molecularly targeted inhibitors.

The inventors of the present invention have also identified a protein signature that is highly prognostic in a range of cancers, including breast cancer and lung adenocarcinoma. Furthermore, this protein signature may be integrated with the aforementioned 28 gene signature and aggressive gene signature to provide a robust prognostic indicator in cancer that was shown to outperform known clinicopathological indicators.

In one aspect, the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein

Synthesis/Modification metagene and a Multiple Networks metagene, wherein: a higher relative expression level of the plurality of the overexpressed genes compared to the plurality of the underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the plurality of the overexpressed genes compared to the plurality of the underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In a futher aspect, the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene, wherein: a higher relative expression level of the plurality of overexpressed genes compared to the plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the plurality of overexpressed genes compared to the plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis.

In one embodiment of the above aspects, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from one of the metagenes. In an alternative embodiment, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from a plurality of the metagenes.

Suitably, for the method of the above aspects the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene

and/or the Multiple Networks metagene comprise one or more genes listed in Table 21.

In another aspect, the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein: a higher relative expression level of the plurality of the overexpressed genes compared to the plurality of the underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the plurality of the overexpressed genes compared to the plurality of the underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level

In yet another aspect, the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein: a higher relative expression level of the plurality of overexpressed genes compared to the plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the plurality of overexpressed genes compared to the plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis.

Suitably, the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication

metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene comprise one or more genes listed in Table 21.

In particular embodiments of the method of the two aforementioned aspects, the plurality of overexpressed genes and the plurality of underexpressed genes are from one or more of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene. According to the method of the above aspects, the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes includes comparing an average expression level of the plurality of overexpressed genes and an average expression level of the plurality of underexpressed genes. This may include calculating a ratio of the average expression level of the plurality of overexpressed genes and the average expression level of the plurality of underexpressed genes. Suitably, the ratio provides an aggressiveness score which is indicative of, or correlates with, cancer aggressiveness and a less favourable prognosis. Alternatively, the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes includes comparing the sum of expression levels of the plurality of overexpressed genes and the sum of expression levels of the plurality of underexpressed genes. This may include calculating a ratio of the sum of expression levels of the plurality of overexpressed genes and the sum of expression levels of the plurality of underexpressed genes.

For the purposes of this invention, by *"isolated"* is meant material that has been removed from its natural state or otherwise been subjected to human manipulation. Isolated material may be substantially or essentially free from components that normally accompany it in its natural state, or may be manipulated so as to be in an artificial state together with components that normally accompany it in its natural state. Isolated material may be in native, chemical synthetic or recombinant form.

As used herein a *"gene"* is a nucleic acid which is a structural, genetic unit of a genome that may include one or more amino acid-encoding nucleotide sequences

and one or more non-coding nucleotide sequences inclusive of promoters and other 5' untranslated sequences, introns, polyadenylation sequences and other 3' untranslated sequences, although without limitation thereto. In most cellular organisms a gene is a nucleic acid that comprises double-stranded DNA.

Non-limiting examples of genes are set forth herein, particularly in Tables 4, 21 and 22, which include Accession Numbers referencing the nucloetide sequence of the gene, or its encoded protein, as are well understood in the art.

The term *"nucleic acid"* as used herein designates single- or double-stranded DNA and RNA. DNA includes genomic DNA and cDNA. RNA includes mRNA, RNA, RNAi, siRNA, cRNA and autocatalytic RNA. Nucleic acids may also be DNA-RNA hybrids. A nucleic acid comprises a nucleotide sequence which typically includes nucleotides that comprise an A, G, C, T or U base. However, nucleotide sequences may include other bases such as inosine, methylycytosine, methylinosine, methyladenosine and/or thiouridine, although without limitation thereto.

Also included are, "*variant*" nucleic acids that include nucleic acids that comprise nucleotide sequences of naturally occurring (e.g., allelic) variants and orthologs *(e.g.,* from a different species). Preferably, nucleic acid variants share at least 70% or 75%, preferably at least 80% or 85% or more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with a nucleotide sequence disclosed herein.

Also included are nucleic acid fragments. A *"fragment"* is a segment, domain, portion or region of a nucleic acid, which respectively constitutes less than 100% of the nucleotide sequence. A non-limilting example is an amplification product or a primer or probe. In particular embodiments, a nucleic acid fragment may comprise, for example, at least 10, 15, 20, 25, 30 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475 and 500 contiguous nucleotides of said nucleic acid.

As used herein, a *"polynucleotide"* is a nucleic acid having eighty (80) or more contiguous nucleotides, while an *"oligonucleotide"* has less than eighty (80) contiguous nucleotides. A *"probe"* may be a single or double-stranded oligonucleotide or polynucleotide, suitably labeled for the purpose of detecting complementary sequences in Northern or Southern blotting, for example. A *"primer"* is usually a single-stranded oligonucleotide, preferably having 15-50 contiguous nucleotides, which is capable of annealing to a complementary nucleic acid

"template" and being extended in a template-dependent fashion by the action of a DNA polymerase such as *Taq* polymerase, RNA-dependent DNA polymerase or Sequenase™. A *"template"* nucleic acid is a nucleic acid subjected to nucleic acid amplification.

It will be appreciated that the *"overexpressed'* genes or proteins referred to herein are genes or proteins that are expressed at a higher level in a cancer cell or tissue compared to a corresponding normal or otherwise non-cancerous cell or tissue or reference/control level or sample.

It will be appreciated that the *"underexpressed'* genes or proteins referred to herein are genes or proteins that are expressed at a lower level in a cancer cell or tissue compared to a corresponding normal or otherwise non-cancerous cell or tissue or reference/control level or sample.

In certain embodiments, the *"overexpressed'* and *"underexpressed'* genes referred to herein may form, or be components of, a metagene.

As used herein, a *"metagene"* is a grouping, cohort or network of a plurality of different genes that display a common, shared or aggregate expression profile, expression level or other expression characteristics that associate with, or are indicative of, a particular function or phenotype. Non-limiting examples include a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene. Table 21 provides non-limiting examples of genes that are components of the aforementioned twelve metagenes. Further non-limiting examples include a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene. Table 22 provides non-limiting examples of genes that are components of the aforementioned six metagenes.

In particular embodiments, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from one of the metagenes. In this regard, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from the same metagene. By way of example, the plurality of

overexpressed genes or the plurality of underexpressed genes may be only from one of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and the Multiple Networks metagene. In a further example, both the plurality of overexpressed genes and the plurality of underexpressed genes may be only from one of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and the Multiple Networks metagene.

Alternatively, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from a plurality of the metagenes described herein.

By *"aggressiveness"* and *"aggressive"* is meant a property or propensity for a cancer to have a relatively poor prognosis due to one or more of a combination of features or factors including: at least partial resistance to therapies available for cancer treatment; invasiveness; metastatic potential; recurrence after treatment; and a low probability of patient survival, although without limitation thereto.

Cancers may include any aggressive or potentially aggressive cancers, tumours or other malignancies such as listed in the NCI Cancer Index at http://www.cancer.gov/cancertopics/alphalist, including all major cancer forms such as sarcomas, carcinomas, lymphomas, leukaemias and blastomas, although without limitation thereto. These may include breast cancer, lung cancer inclusive of lung adenocarcinoma, cancers of the reproductive system inclusive of ovarian cancer, cervical cancer, uterine cancer and prostate cancer, cancers of the brain and nervous system, head and neck cancers, gastrointestinal cancers inclusive of colon cancer, colorectal cancer and gastric cancer, liver cancer, kidney cancer, skin cancers such as melanoma and skin carcinomas, blood cell cancers inclusive of lymphoid cancers and myelomonocytic cancers, cancers of the endocrine system such as pancreatic

cancer and pituitary cancers, musculoskeletal cancers inclusive of bone and soft tissue cancers, although without limitation thereto.

In certain embodiments, cancers include breast cancer, bladder cancer, colorectral cancer, glioblastoma, lower grade glioma, head & neck cancer, kidney cancer, liver cancer, lung adenocarcinoma, acute myeloid leukaemia, pancreatic cancer, adrenocortical cancer, melanoma and lung squamous cell carcinoma.

Breast cancers include all aggressive breast cancers and cancer subtypes such as triple negative breast cancer, grade 2 breast cancer, grade 3 breast cancer, lymph node positive (LN^+) breast cancer, HER2 positive ($HER2^+$) breast cancer and ER positive (ER^+) breast cancer, although without limitation thereto.

As used herein, *"triple negative breast cancer"* (TNBC) is an often aggressive breast cancer subtype lacking or having significantly reduced expression of estrogen receptor (ER) protein, progesterone receptor (PR) protein and HER2 protein. TNBC and other aggressive breast cancers are typically insensitive to some of the most effective therapies available for breast cancer treatment including HER2-directed therapy such as trastuzumab and endocrine therapies such as tamoxifen and aromatase inhibitors.

As used herein, a gene expression level may be an absolute or relative amount of an expressed gene or gene product inclusive of nucleic acids such as RNA, mRNA and cDNA and protein.

As would be appreciated by the skilled artisan, the present invention need not be limited to comparing the expression level of the overexpressed genes and/or proteins with the expression level of the underexpressed genes and/or proteins provided herein. Accordingly, in particular embodiments, the expression level of the overexpressed and/or underexpressed genes and/or proteins is compared to a control level of expression, such as the level of gene and/or protein expression of a "housekeeping" gene in one or more cancer cells, tissues or organs of the mammal.

In further embodiments, the expression level of the overexpressed and/or underexpressed genes and/or proteins is compared to a threshold level of expression, such as a level of gene and/or protein expression in non-aggressive cancerous tissue. A threshold level of expression is generally a quantified level of expression of a particular gene or set of genes, including gene products thereof. Typically, an expression level of a gene or set of genes in a sample that exceeds or falls below the threshold level of expression is predictive of a particular disease state or outcome.

The nature and numerical value (if any) of the threshold level of expression will vary based on the method chosen to determine the expression the one or more genes or proteins used in determining, for example, a prognosis, the aggressiveness and/or response to anticancer therapy, in the mammal. In light of this disclosure, any person of skill in the art would be capable of determining the threshold level of gene/protein expression in a mammal sample that may be used in determining, for example, a prognosis, the aggressiveness and/or response to anticancer therapy, using any method of measuring gene or protein expression known in the art, such as those described herein. In one embodiment, the threshold level is a mean and/or median expression level (median or absolute) of the overexpressed and/or underexpressed genes and/or proteins in a reference population, that, for example, have the same cancer type, subgroup, stage and/or grade as said mammal for which the expression level is determined. Additionally, the concept of a threshold level of expression should not be limited to a single value or result. In this regard, a threshold level of expression may encompass multiple threshold expression levels that could signify, for example, a high, medium, or low probability of, for example, progression free survival.

By *"protein"* is meant an amino acid polymer. The amino acids may be natural or non-natural amino acids, D- or L- amino acids as are well understood in the art. As would be appreciated by the skilled person, the term "protein" also includes within its scope phosphorylated forms of a protein *{i.e.,* phosphoproteins).

Also provided are protein "variants" such as natrually occurring (eg allelic variants) and orthologs. Preferably, protein variants share at least 70% or 75%, preferably at least 80% or 85% or more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence disclosed herein.

Also provided are protein fragments, inclusive of peptide fragments thqat comprise less than 100% of an entire amino acid sequence. In particular embodiments, a protein fragment may comprise, for example, at least 10, 15, 20, 25, 30 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375 and 400 contiguous amino acids of said protein.

A *"peptide"* is a protein having no more than fifty (50) amino acids.

A *"polypeptide"* is a protein having more than fifty (50) amino acids.

It would be appreciated that in addition to comparing the expression levels of one or more genes or proteins, the methods of the present invention may further include the step of determining, assessing, evaluating, assaying or measuring the expression level of one or more of the overexpressed genes, the underexpressed genes, the overexpressed proteins and/or the underexpressed proteins described herein. The terms *"determining"*, *"measuring"*, *"evaluating"*, *"assessing"* and *"assaying"* are used interchangeably herein and may include any form of measurement known in the art, such as those described hereinafter.

Determining, assessing, evaluating, assaying or measuring nucleic acids such as RNA, mRNA and cDNA may be performed by any technique known in the art. These may be techniques that include nucleic acid sequence amplification, nucleic acid hybridization, nucleotide sequencing, mass spectroscopy and combinations of any these.

Nucleic acid amplification techniques typically include repeated cycles of annealing one or more primers to a "template" nucleotide sequence under appropriate conditions and using a polymerase to synthesize a nucleotide sequence complementary to the target, thereby "amplifying" the target nucleotide sequence. Nucleic acid amplification techniques are well known to the skilled addressee, and include but are not limited to polymerase chain reaction (PCR); strand displacement amplification (SDA); rolling circle replication (RCR); nucleic acid sequence-based amplification (NASBA), Q-β replicase amplification; helicase-dependent amplification (HAD); loop-mediated isothermal amplification (LAMP); nicking enzyme amplification reaction (NEAR) and recombinase polymerase amplification (RPA), although without limitation thereto. As generally used herein, an *"amplification product"* refers to a nucleic acid product generated by a nucleic acid amplification technique.

PCR includes quantitative and semi-quantitative PCR, real-time PCR, allele-specific PCR, methylation-specific PCR, asymmetric PCR, nested PCR, multiplex PCR, touch-down PCR and other variations and modifications to "basic" PCR amplification.

Nucleic acid amplification techniques may be performed using DNA or RNA extracted, isolated or otherwise obtained from a cell or tissue source. In other embodiments, nucleic acid amplification may be performed directly on appropriately treated cell or tissue samples.

Nucleic acid hybridization typically includes hybridizing a nucleotide sequence (typically in the form of a probe) to a target nucleotide sequence under appropriate conditions, whereby the hybridized probe-target nucleotide sequence is subsequently detected. Non-limiting examples include Northern blotting, slot-blotting, *in situ* hybridization and fluorescence resonance energy transfer (FRET) detection, although without limitation thereto. Nucleic acid hybridization may be performed using DNA or RNA extracted, isolated, amplified or otherwise obtained from a cell or tissue source or directly on appropriately treated cell or tissue samples.

It will also be appreciated that a combination of nucleic acid amplification and nucleic acid hybridization may be utilized.

Determining, assessing, evaluating, assaying or measuring protein levels may be performed by any technique known in the art that is capable of detecting cell- or tissue-expressed proteins whether on the cell surface or intracellularly expressed, or proteins that are isolated, extracted or otherwise obtained from the cell of tissue source. These techniques include antibody-based detection that uses one or more antibodies which bind the protein, electrophoresis, isoelectric focussing, protein sequencing, chromatographic techniques and mass spectroscopy and combinations of these, although without limitation thereto. Antibody-based detection may include flow cytometry using fluorescently-labelled antibodies that bind the protein, ELISA, immunoblotting, immunoprecipitation, *in situ* hybridization, immunohistochemistry and immuncytochemistry, although without limitation thereto. Suitable techniques may be adapted for high throughput and/or rapid analysis such as using protein arrays such as a TissueMicroArray™ (TMA), MSD MultiArrays™ and multiwell ELISA, although without limitation thereto.

In certain embodiments, a gene expression level may be assessed indirectly by the measurement of a non-coding RNA, such as miRNA, that regulate gene expression. MicroRNAs (miRNAs or miRs) are post-transcriptional regulators that bind to complementary sequences in the 3' untranslated regions (3' UTRs) of target mRNA transcripts, usually resulting in gene silencing. miRNAs are short RNA molecules, on average only 22 nucleotides long. The human genome may encode over 1000 miRNAs, which may target about 60% of mammalian genes and are abundant in many human cell types. Each miRNA may alter the expression of hundreds of individual mRNAs. In particular, miRNAs may have multiple roles in negative regulation *(e.g.,* transcript degradation and sequestering, translational

suppression) and/or positive regulation *(e.g.,* transcriptional and translational activation). Additionally, aberrant miRNA expression has been implicated in various types of cancer.

In this regard, an average expression level, or alternatively a sum of the expression levels, may be calculated for the plurality of overexpressed genes and for the plurality of underexpressed genes, to thereby produce or calculate a ratio.

Accordingly, determining cancer aggressiveness and/or a prognosis for a cancer patient in certain embodiments of the present invention further includes determining the ratio of the expression level *(e.g.* an average or sum of the expression level) of the plurality of overexpressed genes to the expression level *(e.g.* an average or sum of the expression level) of the plurality of underexpressed genes.

In another aspect of the invention relates to a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes associated with chromosomal instability and an expression level of a plurality of underexpressed genes associated with estrogen receptor signalling in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the plurality of overexpressed genes associated with chromosomal instability compared to the plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level expression level of the plurality of overexpressed genes associated with chromosomal instability compared to the plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In yet another aspect of the invention relates to a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes associated with chromosomal instability and an expression level of a plurality of underexpressed genes associated with estrogen receptor signalling in the mammal, wherein: a higher relative expression level of the plurality of overexpressed genes associated with chromosomal instability compared to the plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the plurality

of overexpressed genes associated with chromosomal instability compared to the plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a more favourable cancer prognosis.

Non-limiting examples of genes in a chromosomal instability (CIN) metagene include *ATP6V1C1, RAP2A, CALM1, COG8, HELLS, KDM5A, PGK1, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPI, PIR, MCM10, MELK, FOXM1, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPREl, ACOT7, NAEl, SHMT2, TCP1, TXNRD1, ADM, CHAF1A and SYNCRIP* genes, although without limitation thereto; and an estrogen receptor signalling (ER) metagene may comprise *BTG2, PIK3IP1, SEC14L2, FLNB, ACSF2, APOM, BIN3, GLTSCR2, ZMYNDIO, ABAT, BCAT2, SCUBE2, RUNX1, LRRC48, MYBPC1, BCL2, CHPT1, ITM2A, LRIG1, MAPT, PRKCB, RERE, ABHD14A, FLT3, TNN, STC2, BATF, CDIE, CFB, EVL, FBXW4, ABCB1, ACAA1, CHAD, PDCD4, RPL10, RPS28, RPS4X, RPS6, SORBS1, RPL22 and RPS4XP3* genes, although without limitation thereto. Table 4 provides further examples of genes that are components of a CIN metagene or that are components of an ER metagene.

An average expression level may be calculated for the CIN metagene and for the ER metagene, to thereby produce or calculate a ratio.

Alternatively, a sum of expression levels may be calculated for the CIN metagene and for the ER metagene, to thereby produce or calculate a ratio.

In certain embodiments, a higher or increased ratio of the average or sum of expression levels of a CIN metagene relative to an ER metagene is associated with, correlates with or is indicative of, higher or increased cancer aggressiveness.

Thus, some embodiments of the invention provide an *"aggressiveness score"* which is the ratio of CIN metagene expression level *(e.g.* average or sum of expression of CIN genes) to an ER metagene expression level *(e.g* average or sum of expression of ER genes).

Accordingly, embodiments of the aforementioned aspects of the invention include determining, assessing or measuring an expression level of a plurality of overexpressed genes associated with chromosomal instability and determining, assessing or measuring an expression level of a plurality of underexpressed genes associated with estrogen receptor signalling. In this regard, reference is made to Table 4 which provides a listing of 206 genes that include genes associated with chromosomal instability and genes associated with estrogen receptor signalling.

Preferably, the chromosomal instability genes are of a CIN metagene, comprising genes such as *ATP6V1C1, RAP2A, CALM1, COG8, HELLS, KDM5A, PGK1, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPI, PIR, MCM10, MELK, FOXM1, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPRE1, ACOT7, NAE1, SHMT2, TCP1, TXNRDl, ADM, CHAF1A and* SYNCRIP, although without limitation thereto. In one preferred embodiment, the chromosomal instability genes are selected from the group consisting of MELK, *MCM10, CENPA, EXOl, TTK* and *KIF2C.* Preferably, the estrogen receptor signalling genes are of an ER metagene comprising genes such as *BTG2, PIK3IP1, SEC14L2, FLNB, ACSF2, APOM, BIN3, GLTSCR2, ZMYND10, ABAT BCAT2, SCUBE2, RUNX1, LRRC48, MYBPC1, BCL2, CHPT1, ITM2A, LRIG1, MAPT, PRKCB, RERE, ABHD14A, FLT3, TNN, STC2, BATF, CD1E, CFB, EVL, FBXW4, ABCB1, ACAA1, CHAD, PDCD4, RPL10, RPS28, RPS4X, RPS6, SORBSl, RPL22 and RPS4XP3,* although without limitation thereto. In one preferred embodiment, the estrogen receptor signalling genes are selected from the group consisting of *MAPT* and *MYB.*

In certain embodiments, the method of the aforementioned two aspects further includes the step of comparing an expression level of one or more other overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and an expression level of one or more other underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CDIA, CDIB, CDIC, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more other overexpressed genes compared to the one or more other underexpressed genes indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the one or more other overexpressed genes compared to the one or more other underexpressed genes indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

In one embodiment, the one or more other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN* and *ZNF593.*

In one embodiment, the one or more other underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In this regard, an average expression level, or alternatively a sum of the expression levels, may be calculated for the one or more other overexpressed genes and for the one or more other underexpressed genes, to thereby produce or calculate a ratio.

Accordingly, determining cancer aggressiveness and/or a prognosis for a cancer patient in certain embodiments of the present invention further includes determining the ratio of the expression level *{e.g.* an average or sum of the expression level) of the one or more other overexpressed genes to the expression level *{e.g.* an average or sum of the expression level) of the one or more other underexpressed genes.

Detection and/or measurement of expression of the one or more other overexpressed genes and the one or more other underexpressed genes may be performed by any of those methods or combinations thereof described herein *{e.g* measuring mRNA levels or an amplified cDNA copy thereof and/or by measuring a protein product thereof), albeit without limitation thereto.

Suitably, the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling is integrated with the comparison of the expression level of the one or more other overexpressed genes and the expression level of the one or more other underexpressed genes to derive a first integrated score. In particular embodiments, this may include deriving the first integrated score, at least in part, by addition, subtraction, multiplication, division and/or exponentiation.

By way of example, the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling may be added to, subtracted from, multiplied by, divided by and/or raised

to the power of the comparison of the expression level of the one or more other overexpressed genes and the expression level of the one or more other underexpressed genes to derive the first integrated score. Alternatively, the comparison of the expression level of the one or more other overexpressed genes and the expression level of the one or more other underexpressed genes may be added to, subtracted from, multiplied by, divided by and/or raised to the power of the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling to derive the first integrated score.

In a particular preferred embodiment, the first integrated score is derived by exponentiation, wherein the comparison of the expression level of the one or more other overexpressed genes and the expression level of the one or more other underexpressed genes is raised to the power of the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling.

As would be appreciated by the skilled person, the other overexpressed and underexpressed genes described herein may not necessarily be associated with chromosomal instability and estrogen receptor signalling respectively.

In a further aspect, the invention provides a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or more overexpressed genes, wherein the one or more overexpressed genes are selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and an expression level of one or more underexpressed genes, wherein the one or more underexpressed genes are selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed genes compared to

the one or more underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAPl, CARHSPl, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN* and *ZNF593.*

In one embodiment, the one or more underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In yet another aspect, the invention provides a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or more overexpressed genes, wherein the one or more overexpressed genes are selected from the group consisting of *CAMSAPl, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSPl, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and an expression level of one or more underexpressed genes, wherein the one or more underexpressed genes are selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAPl, CARHSPl,*

CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN and *ZNF593.*

In one embodiment, the one or more underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In particular embodiments, the method of the aforementioned aspects further includes the step of comparing an expression level of one or more overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB 1, HER2, ASNS and COL6A1, and an expression level of one or more underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

As would be appreciated by the skilled artisan, the expression level of one or more of the overexpressed proteins and/or one or more of the underexpressed proteins described herein may include one or more phosphorylated forms of said proteins *{i.e.,* a phosphoprotein). In one embodiment, EIF4EBP1 is or comprises one or more phosphoproteins selected from the group consisting of pEIF4EBPl ^{S65}, pEIF4EBPl ^{T37}, pEIF4EBPl ^{T46} and pEIF4EBPl ^{T70}. In one embodiment, EGFR is or comprises one or more phosphoproteins selected from the group consisting of pEGFR^{Y1068} and pEGFR^{Y1173}. In one embodiment, HER3 is or comprises pHER3^{Y1289}. In one embodiment, AKTl is or comprises one or more phosphoproteins selected from the group consisting of pAKTl ^{S473} and pAKTl ^{X308}. In one embodiment, NFKBl is or comprises pNFKBl ^{S536}. In one embodiment, HER2 is or comprises pHER2^{Y1248}. In one embodiment, ESR1 is or comprises pESRl ^{S118}. In one embodiment, PEA15 is or comprises pPEA15^{S116}. In one embodiment, RPS6 is

or comprises one or more phosphoproteins selected from the group consisting of pRPS6^{S235}, pRPS6^{S236}, pRPS6^{S240} and pRPS6^{S244}.

An average or sum of the expression levels may be calculated for the overexpressed genes, the underexpressed genes, the overexpressed proteins and/or the underexpressed proteins, to thereby produce or calculate a ratio.

Thus, in certain embodiments of the present invention determining cancer aggressiveness and/or a prognosis for a cancer patient includes determining (i) the ratio of the expression level *(e.g.* an average or sum of the expression level) of the one or more overexpressed genes to the expression level *(e.g.* an average or sum of the expression level) of the one or more underexpressed genes; and/or (ii) the ratio of the expression level *(e.g.* an average or sum of the expression level) of the one or more overexpressed proteins to the expression level *(e.g.* an average or sum of the expression level) of the one or more underexpressed proteins.

Detection and/or measurement of expression of the overexpressed proteins and the underexpressed proteins may be performed by any of those methods or combinations thereof hereinbefore described, albeit without limitation thereto.

Suitably, the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins is to thereby derive an integrated score. In one particular embodiment, the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins is integrated with:

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(iii) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1* and the expression level of the underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C,*

NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CDIB, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3 to derive a fourth integrated score; or

(iv) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or more of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene, to derive a fifth integrated score; or

(v) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or more of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene, to derive a sixth integrated score.

In particular embodiments, the second, third, fourth, fifth and/or sixth integrated scores are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation. By way of example, the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins may be added to, subtracted from, multiplied by, divided by and/or raised to the power of (i) the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling; or (ii) the first integrated score. Alternatively, the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling or the first integrated score may be

added to, subtracted from, multiplied by, divided by and/or raised to the power of the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins.

In a further aspect, the invention provides a method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or more overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and an expression level of one or more underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

In a related aspect, the invention provides a method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or more overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and an expression level of one or more underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

In particular embodiments of the two aforementioned aspects, one or more of the overexpressed proteins and/or one or more of the underexpressed proteins are or comprise a phosphoprotein hereinbefore described.

An average or sum of the expression levels may be calculated for the one or more overexpressed proteins and the one or more underexpressed proteins, to thereby produce or calculate a ratio as hereinbefore described.

This information with respect to the aggressiveness and/or prognosis of a patient's cancer may prove useful to a physician and/or clinician in determining the most effective course of treatment. A determination of the likelihood for a cancer relapse or of the likelihood of metastasis can assist the physician and/or clinician in determining whether a more conservative or a more radical approach to therapy should be taken. As such, a prognosis may provide for the selection and classification of patients who are predicted to benefit from a given therapeutic regimen.

Accordingly, another aspect of the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene, wherein an altered or modulated relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

As would be understood by the skilled person, the relative expression level of a gene or protein may be deemed to be *"altered"* or *"modulated"* when the expression level is higher/increased or lower/deer eased when compared to a control or reference sample or expression level, such as a threshold level. In one embodiment, a relative expression level may be classified as high if it is greater than a mean and/or median relative expression level of a reference population and a relative expression

level may be classified as low if it is less than the mean and/or median relative expression level of the reference population. In this regard, a reference population may be a group of subjects who have the same cancer type, subgroup, stage and/or grade as said mammal for which the relative expression level is determined.

Suitably, for the present aspect the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene comprise one or more genes listed in Table 21.

In a related aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes and an expression level of a plurality of underexpressed genes in one or more cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or more metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein an altered or modulated relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment of the two aforementioned aspects, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from one of the metagenes. In an alternative embodiment, the plurality of overexpressed genes and/or the plurality of underexpressed genes are selected from a plurality of the metagenes.

Suitably, the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene comprise one or more genes listed in Table 22.

In particular embodiments, the plurality of overexpressed genes and the plurality of underexpressed genes are from one or more of a Carbohydrate/Lipid

Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene.

In a related aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of determining an expression level of one or more genes associated with chromosomal instability (CIN) in one or more cancer cells of the mammal, wherein a higher expression level indicates or correlates with relatively increased responsiveness of the cancer to the anti-cancer treatment.

As will be described in more detail, overexpression of some CIN genes may be predictive of the responsiveness of a cancer to an anti-cancer treatment, particularly although not exclusively when overexpressed by non-mitotic cancer cells. In this context, by "non-mitotic" means that the cancer cell is not in the mitotic or "M phase" of the cell cycle. Preferably, the non-mitotic cancer cells are in interphase. Broadly, any overexpressed CIN gene set forth Table 4 may be predictive of the responsiveness of a cancer to an anti-cancer treatment. In particular embodiments, the CIN gene is selected from the group consisting of: *TTK, CEP55, FOXM1* and *SKIP2.* In a particularly preferred embodiment, the CIN gene is selected from the group consisting of: *TTK, CEP55, FOXM1* and *SKIP2* and the cancer is breast cancer. In this regard, the inventors have shown that "bulk" measurements of extracted CIN gene mRNA or encoded protein do not provide a useful indication of whether overexpression of the CIN gene may be predictive of the responsiveness of a cancer to an anti-cancer treatment. More particularly, detection of CIN gene expression by individual cancer cells, particularly non-mitotic or interphase cancer cells, provides a more powerful indication of the responsiveness of a cancer to an anti-cancer treatment.

As previously described, detection and/or measurement of expression of the CIN gene may be performed by measuring RNA *(e.g* mRNA or an amplified cDNA copy thereof) or by measuring a protein product of a CIN gene. In a particularly preferred embodiment, a protein product of a CIN gene is detected or measured by immunohistochemistry. Typically, although not exclusively, a preferred

immunohistochemistry method includes binding an antibody to the protein product of a CIN gene expressed by a cell or tissue and subsequent detection of the bound antibody. By way of example only, the antibody may be unlabelled, directly labelled with an enzyme such as horseradish peroxidase, alkaline phosphatase or glucose oxidase or directly labelled with biotin or digoxigenin. In embodiments where the antibody is unlabelled, a secondary antibody (labelled such as described above) may be used to detect the bound antibody. Biotinylated antibodies may be detected using avidin complexed with an enzyme such as horseradish peroxidase, alkaline phosphatase or glucose oxidase. Suitable enzyme substrates include diaminobanzidine (DAB), permanent red, 3-ethylbenzthiazoline sulfonic acid (ABTS), 5-bromo-4-chloro-3-indolyl phosphate (BCIP), nitro blue tetrazolium (NBT), 3,3',5,5'-tetramethyl benzidine (TNB) and 4-chloro-l-naphthol (4-CN), although without limitation thereto.

In a further aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of a plurality of overexpressed genes associated with chromosomal instability and an expression level of a plurality of underexpressed genes associated with estrogen receptor signalling in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the overexpressed genes associated with chromosomal instability compared to the underexpressed genes associated with estrogen receptor signalling indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In certain embodiments, the genes associated with chromosomal instability are of a CIN metagene. Non-limiting examples include genes selected from the group consisting of: *ATP6V1C1, RAP2A, CALM1, COG8, HELLS, KDM5A, PGK1, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPI, PIR, MCM10, MELK, FOXM1, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPRE1, ACOT7, NAE1, SHMT2, TCP1, TXNRD1, ADM, CHAF1A and SYNCRIP.* In one preferred embodiment, the chromosomal instability genes are selected from the group consisting of *MELK, MCM10, CENPA, EXOl, TTK* and *KIF2C.*

In certain embodiments, the genes associated with estrogen receptor signalling are of an ER metagene. Non-limiting examples include genes selected from the group consisting of: *BTG2, PIK3IP1, SEC14L2, FLNB, ACSF2, APOM,*

BIN3, GLTSCR2, ZMYND10, ABAT, BCAT2, SCUBE2, RUNX1, LRRC48, MYBPC1, BCL2, CHPT1, ITM2A, LRIG1, MAPT, PRKCB, RERE, ABHD14A, FLT3, TNN, STC2, BATF, CD1E, CFB, EVL, FBXW4, ABCB1, ACAA1, CHAD, PDCD4, RPL10, RPS28, RPS4X, RPS6, SORBSl, RPL22 and RPS4XP3. In one preferred embodiment, the estrogen receptor signalling genes are selected from the group consisting of *MAPT* and *MYB.*

Suitably, the method of this aspect further includes the step of comparing an expression level of one or more other overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and an expression level of one or more other underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3* in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more other overexpressed genes compared to the one or more other underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment, the one or more other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1 , KCNG1 , MAP2K5, ND UFC1 , PML, STA Ul , TXN* and *ZNF593* .

In one embodiment, the one or more other underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In certain embodiments, the comparison of the expression level of the one or more other overexpressed genes and the expression level of the one or more other underexpressed genes is integrated with the comparison of the expression level of the plurality of overexpressed genes associated with chromosomal instability and the expression level of the plurality of underexpressed genes associated with estrogen receptor signalling to derive a first integrated score as described herein, which is

indicative of, or correlates with, responsiveness of the cancer to the anti-cancer treatment.

In another related aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or more overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1,* and an expression level of one or more underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3,* in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, TXN* and *ZNF593.*

In one embodiment, the one or more underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1.*

In particular embodiments, the method of the five aforementioned aspects further includes the step of comparing an expression level of one or more overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKT1, NFKB 1, HER2, ASNS and COL6A1, and an expression level of one or more underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or more cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or more overexpressed proteins compared to the one or

more underexpressed proteins indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

In particular embodiments, one or more of the overexpressed proteins and/or one or more of the underexpressed proteins are or comprise a phosphoprotein hereinbefore described.

An average or sum of the expression levels may be calculated for the overexpressed genes, the underexpressed genes, the overexpressed proteins and/or the underexpressed proteins, to thereby produce or calculate a ratio, as hereinbefore described.

Detection and/or measurement of expression of the overexpressed proteins and the underexpressed proteins may be performed by any of those methods or combinations thereof hereinbefore described, albeit without limitation thereto.

Suitably, the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins is to thereby derive an integrated score. In one particular embodiment, the comparison of the expression level of the one or more overexpressed proteins and the expression level of the one or more underexpressed proteins is integrated with:

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(iii) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFC1* and *STAU1* and the expression level of the underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C,*

NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CDIB, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3 to derive a fourth integrated score; or

(iv) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or more of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene, to derive a fifth integrated score; or

(v) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or more of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene, to derive a sixth integrated score,

wherein the second, third, fourth, fifth and/or sixth integrated score is indicative of, or correlates with, responsiveness of the cancer to the anti-cancer treatment.

In particular embodiments, the second, third, fourth, fifth and/or sixth integrated scores are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation, as hereinbefore described.

In a further related aspect, the invention provides a method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or more overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMADl, GATA3, ITGA2, AKTl, NFKBl, HER2, ASNS and COL6A1, and an expression level of one or more underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1,

YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more overexpressed proteins compared to the one or more underexpressed proteins indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

In particular embodiments, one or more of the overexpressed proteins and/or one or more of the underexpressed proteins are or comprise a phosphoprotein hereinbefore described.

It will be appreciated from the foregoing that the invention provides methods that determine the aggressiveness of a cancer, facilitate providing a cancer prognosis for a patient and/or predict the responsiveness of a cancer to an anti-cancer treatment. Particular, broad embodiments of the invention include the step of treating the patient following determining the aggressiveness of the cancer, providing a cancer prognosis and/or predicting the responsiveness of the cancer to anti-cancer treatment. Accordingly, these embodiments relate to using information obtained about the aggressiveness of the cancer, the cancer prognosis and/or the predicted responsiveness of the cancer to anti-cancer treatment to thereby construct and implement an anti-cancer treatment regime for the patient. In a preferred embodiment, this is personalized to a particular patient so that the treatment regime is optimized for that particular patient.

Cancer treatments may include drug therapy, chemotherapy, antibody, nucleic acid and other biomolecular therapies, radiation therapy, surgery, nutritional therapy, relaxation or meditational therapy and other natural or holistic therapies, although without limitation thereto. In particular embodiments, the cancer therapy may target aneuploidy or aneuploid tumours and/or chromosomal instability.

Generally, drugs, biomolecules *(e.g* antibodies, inhibitory nucleic acids such as siRNA) or chemotherapeutic agents are referred to herein as "anti-cancer therapeutic agents". In some embodiments relating to breast cancer, the anti-cancer treatment may include HER2-directed therapy such as trastuzumab and endocrine therapies such as tamoxifen and aromatase inhibitors. In other or alternative embodiments, the therapy may include administration of inhibitors of CIN genes or CIN gene products, such as one or more of those listed in Table 4. It will be appreciated that inhibition of the CIN gene product TTK using the specific inhibitor AZ3146 was effective against TNBC cell lines. Furthermore, siRNA-mediated

knockdown of the CIN genes *TTK, TPX2, NDC80* and *PBK* was effective against TNBC cell lines.

In certain embodiments, the cancer treatment may be directed at genes or gene products other than those listed in Tables 4, 10, 21 and/or 22. By way of example, the cancer treatment may target genes or gene products such as PLK1[71,72] or others[73-76] to thereby target aneuploid tumours or tumour cells.

Suitably, when considering (i) the relative expression of one or more of the overexpressed genes of the 29 gene signature *(i.e., CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFCl* and *STAUl)* when compared to one or more of the underexpressed genes of the 30 gene signature (i.e., *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBSl and SRPK3);* (ii) the relative expression of one or more of the overexpressed proteins (i.e., DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMAD1, GATA3, ITGA2, AKTl, NFKBl, HER2, ASNS and COL6A1) when compared to one or more of the underexpressed proteins (i.e., VEGFR2, FIER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6); and/or (iii) the first, second, third and/or fourth integrated score, the anticancer therapeutic agent is selected from the group consisting of a chemotherapy, an endocrine therapy, immunotherapy and a molecularly targeted therapy. In certain embodiments, the anticancer treatment comprises an ALK inhibitor *(e.g.,* TAE684), an Aurora kinase inhibitor (e.g., Alisertib, AMG-900, BI-847325, GSK-1070916A, ilorasertib, MK-8745, danusertib), a BCR-ABL inhibitor *(e.g.,* Nilotinib, Dasatinib, Ponatinib), a HSP90 inhibitor *(e.g.,* Tanespimycin (17-AAG), PF04291 13, AUY922, Luminespib, ganetespib, Debio-0932), an EGFR inhibitor *(e.g.,* Afatinib, Erlotinib, Lapatinib, cetuximab), a PARP inhibitor *(e.g.,* ABT-888, AZD-2281), retinoic acid *(e.g.,* all-trans retinoic acid or ATRA), a Bcl2 inhibitor *(e.g.,* ABT-263), a gluconeogenesis inhibitor *(e.g.,* metformin), a p38 MAPK inhibitor *(e.g.,* BIRB0796, LY2228820), a MEKl/2 inhibitor *(e.g.,* trametinib, cobimetinib, binimetinib, selumetinib, pimasertib, refametinib, TAK-733), a mTOR inhibitor *(e.g.,* BEZ235, JW-7-25-1), a PI3K inhibitor *(e.g.,* Idelalisib, buparlisib/apelisib, copanlisib, GSK-2636771,

pictilisib, AMG-319, AZD-8186), an IGF1R inhibitor *(e.g.,* BMS-754807, dalotuzumab, ganitumab, linsitinib), a PLCγ inhibitor *{e.g.,* U73122), a JNK inhibitor *(e.g.,* SP600125), aPAKl inhibitor *(e.g.,* IPA3), a SYK inhibitor *(e.g.,* BAY613606), a HDAC inhibitor *(e.g.,* Vorinostat), an FGFR inhibitor *(e.g.,* Dovitinib), a XIAP inhibitor *(e.g.,* Embelin), a PLK1 inhibitor *(e.g.,* Volasertib, P-937), an ERK5 inhibitor *(e.g.,* XMD8-92), a MPS1/TTK inhibitor *(e.g.,* BAY-1 161909) and any combination thereof.

By way of example, patients with a high relative expression level of one or more overexpressed genes, such as those of the 2 1 gene signature, when compared to one or more underexpressed genes, such as those of the 7 gene signature, a high relative expression level of one or more overexpressed proteins when compared to one or more underexpressed proteins and/or a high integrated score described herein are more likely to respond favourably, such as a pathological complete response, when treated with chemotherapy. In this regard, non-limiting examples of chemotherapy include a pyrimidine analogue *(e.g.,* 5-fluorouracil, capecitabine), a taxane *(e.g.,* paclitaxel), an anthracycline *(e.g.,* doxorubicin, epirubicin), an anti-folate drug *(e.g.,* the dihydrofolate reductase inhibitor methotrexate), an alkylating agent *(e.g.,* cyclophosphamide) or any combination thereof. It would be appreciated that the chemotherapy may be administered as adjuvant, neoadjuvant and/or as standard therapy, alone or in combination with other anticancer therapeutics.

Additionally, in certain embodiments, patients with a high relative expression level of one or more overexpressed genes, such as those of the 29 gene signature, when compared to one or more underexpressed genes, such as those of the 30 gene signature, a high relative expression level of one or more overexpressed proteins when compared to one or more underexpressed proteins and/or a high integrated score described herein may be more likely to respond favourably to *(i.e.,* be more sensitive to) inhibition of HSP90, EGFR, IGF1R, mTOR, PI3K, p38 MAPK, PLCy, JNK, PAK1, ERK5, XIAP, PLK1 and/or MEK1/2 and may be less likely to respond favourably to *(i.e.,* be less sensitive to) anticancer treatment with an ALK inhibitor, a BCR-ABL inhibitor, a PARP inhibitor, retinoic acid, a Bcl2 inhibitor, a gluconeogenesis inhibitor, a p38 MAPK inhibitor, an FGFR inhibitor, a SYK inhibitor, a HDAC inhibitor and/or an IGF1R inhibitor.

It will also be understood that the gene and protein signatures described herein may be used to identify those poorer prognosis patients, such as those with

larger and/or higher grade tumours, who may benefit from one or more additional anticancer therapeutic agents to the typical or standard anti-cancer treatment regime for that particular patient group. By way of example, ER^+ breast cancer patients with or without lymph node involvement with a high integrated score, and hence a relatively poor prognosis, are more likely to respond favourably to or benefit from chemotherapy and/or endocrine therapy. This may include an improved survival and/or reduced likelihood of tumour recurrence and/or metastasis for these patients.

In certain embodiments, for patients with a high relative expression level of the overexpressed genes of the 21 gene signature when compared to the underexpressed genes of the 7 gene signature and/or a high integrated score, the cancer treatment may be directed at those genes or gene products listed in Tables 13, 15, 16 and 17.

Additionally, for patients with a high relative expression level of the overexpressed proteins when compared to the underexpressed proteins and/or a high integrated score the cancer treatment may be directed at one or more of those proteins listed in Table 19.

It would be appreciated that those methods described herein for predicting the responsiveness of a cancer to an anti-cancer treatment, such as an immunotherapeutic agent, may further include the step of administering to the mammal a therapeutically effective amount of the anticancer treatment. In a preferred embodiment, the anticancer treatment is administered when the altered or modulated relative expression level indicates or correlates with relatively increased responsiveness of the cancer to the anti-cancer treatment.

Methods of treating cancer may be prophylactic, preventative or therapeutic and suitable for treatment of cancer in mammals, particularly humans. As used herein, *"treating"*, *"treat"* or *"treatment"* refers to a therapeutic intervention, course of action or protocol that at least ameliorates a symptom of cancer after the cancer and/or its symptoms have at least started to develop. As used herein, *"preventing"*, *"prevent"* or *"prevention"* refers to therapeutic intervention, course of action or protocol initiated prior to the onset of cancer and/or a symptom of cancer so as to prevent, inhibit or delay or development or progression of the cancer or the symptom.

The term *"therapeutically effective amount"* describes a quantity of a specified agent sufficient to achieve a desired effect in a subject being treated with that agent. For example, this can be the amount of a composition comprising one or

more agents that binds one or more of the overexpressed and/or underexpressed genes or gene products thereof described herein, necessary to reduce, alleviate and/or prevent a cancer or cancer associated disease, disorder or condition. In some embodiments, a *"therapeutically effective amount"* is sufficient to reduce or eliminate a symptom of a cancer. In other embodiments, a *"therapeutically effective amount"* is an amount sufficient to achieve a desired biological effect, for example an amount that is effective to decrease or prevent cancer growth and/or metastasis.

Ideally, a therapeutically effective amount of an agent is an amount sufficient to induce the desired result without causing a substantial cytotoxic effect in the subject. The effective amount of an agent useful for reducing, alleviating and/or preventing a cancer will be dependent on the subject being treated, the type and severity of any associated disease, disorder and/or condition *(e.g.*, the number and location of any associated metastases), and the manner of administration of the therapeutic composition.

Suitably, the anti-cancer therapeutic agent is administered to a mammal as a pharmaceutical composition comprising a pharmaceutically-acceptable carrier, diluent or excipient.

By *"pharmaceutically-acceptable carrier, diluent or excipient"* is meant a solid or liquid filler, diluent or encapsulating substance that may be safely used in systemic administration. Depending upon the particular route of administration, a variety of carriers, well known in the art may be used. These carriers may be selected from a group including sugars, starches, cellulose and its derivatives, malt, gelatine, talc, calcium sulfate, liposomes and other lipid-based carriers, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline and salts such as mineral acid salts including hydrochlorides, bromides and sulfates, organic acids such as acetates, propionates and malonates and pyrogen-free water.

A useful reference describing pharmaceutically acceptable carriers, diluents and excipients is Remington's Pharmaceutical Sciences (Mack Publishing Co. N.J. USA, 1991), which is incorporated herein by reference.

Any safe route of administration may be employed for providing a patient with the composition of the invention. For example, oral, rectal, parenteral, sublingual, buccal, intravenous, intra-articular, intra-muscular, intra-dermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular,

transdermal and the like may be employed. Intra-muscular and subcutaneous injection is appropriate, for example, for administration of immunotherapeutic compositions, proteinaceous vaccines and nucleic acid vaccines.

Dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. These dosage forms may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of the therapeutic agent may be effected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be effected by using other polymer matrices, liposomes and/or microspheres.

Compositions of the present invention suitable for oral or parenteral administration may be presented as discrete units such as capsules, sachets or tablets each containing a pre-determined amount of one or more therapeutic agents of the invention, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association one or more agents as described above with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the agents of the invention with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

The above compositions may be administered in a manner compatible with the dosage formulation, and in such amount as is pharmaceutically-effective. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial response in a patient over an appropriate period of time. The quantity of agent(s) to be administered may depend on the subject to be treated inclusive of the age, sex, weight and general health condition thereof, factors that will depend on the judgement of the practitioner.

In particular embodiments of the hereinbefore described methods, the cancer is breast cancer and the one or more overexpressed proteins are selected from the group consisting of DVL3, VEGFR2, INPP4B, EIF4EBP1, EGFR, HER3, SMAD1,

NFKBl and HER2 and the one or more underexpressed proteins are selected from the group consisting of ASNS, MAPK9, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6.

In particular embodiments of the hereinbefore described methods, the cancer is lung cancer, such as lung adenocarcinoma, wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1, TXN, KCNG1, BCAP31, GSK3B, FOXM1, ZNF593, EXOl, KIF2C, TTK, MELK, CENPA, TPX2, CA9, GRHPR, HCFC1R1,CEP55, MCMIO, CENPN* and *CARHSP1,* and the one or more underexpressed genes are selected from the group consisting of *BTN2A2, MTMR7, ZNRD1-AS1, MAPT* and *BTG2;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, PAI-1, Ku80, GATA3, ITGA2 and AKTl, and the one or more underexpressed proteins are selected from the group consisting of ESR1.

In particular embodiments of the hereinbefore described methods, the cancer is kidney cancer, such as renal clear cell carcinoma, wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *EIF3K, ADORA2B, KCNG1, BCAP31, EXOSC7, FOXM1, CD55, ZNF593, KIF2C, TTK, MELK, CENPA, TPX2, CEP55, PML, CENPN* and *CARHSP1,* and the one or more underexpressed genes are selected from the group consisting of *BCL2* and *MAPT;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, PAI-1 and EIF4EBP1, and the one or more underexpressed proteins are selected from the group consisting of HER3, MAPK9, ESR1 and RAD50.

In particular embodiments of the hereinbefore described methods, the cancer is melanoma, such as skin cutaneous melanoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *EIF3K, ADORA2B, GSK3B, EXOSC7, FOXM1, EXOl, KIF2C, CENPA, TPX2, CAMSAP1, MCMIO* and *ABHD5* and the one or more underexpressed genes are selected from the group consisting of *BCAP31, BTN2A2, SMPDL3B, MTMR7, ME1* and *BTG2;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of PAI-1, EIF4EBP1, EGFR, HER3 and Ku80 and the one or more

underexpressed proteins are selected from the group consisting of ASNS, MAPK9 and ESRl.

In particular embodiments of the hereinbefore described methods, the cancer is endometrial cancer, such as uterine corpus endometrioid carcinoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1, EIF3K, KCNG1, BCAP31, GSK3B, EXOSC7, FOXM1, ZNF593, EXOl, KIF2C, MAP2K5, TTK, MELK, GRHPR,* and *PML,* and the one or more underexpressed genes is *MYB;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, INPP4B, EIF4EBP1 and ASNS and the one or more underexpressed proteins are selected from the group consisting of MAPK9, ESR1 and YWHAE.

In particular embodiments of the hereinbefore described methods, the cancer is ovarian adenocarcinoma and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1, EIF3K, TXN, ADORA2B, KCNG1, GSK3B, STAU1, MAP2K5,* and *HCFC1R1,* and the one or more underexpressed genes are selected from the group consisting of *BTN2A2,* and *ZNRD1-AS1,* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of PAI-1 and VEGFR2 and the one or more underexpressed proteins are selected from the group consisting of ASNS, MAPK9, ESR1, YWHAE and PGR.

In particular embodiments of the hereinbefore described methods, the cancer is head and neck cancer, such as head and neck squamous cell carcinoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1, TXN, ADORA2B, KCNG1, CD55, ZNF593, NDUFC1,* and *HCFC1R1,* and the one or more underexpressed genes are selected from the group consisting of *BTN2A2,* and *MTMR7;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of PAI-1, INPP4B, EGFR, HER3, SMADl, GATA3, ITGA2 and COL6A1 and the one or more underexpressed proteins are selected from the group consisting of VEGFR2 and ASNS.

In particular embodiments of the hereinbefore described methods, the cancer is colorectal cancer, such as colorectal adenocarcinoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *EIF3K, TXN, CD55, NDUFCl, HCFC1R1,* and *PML,* and the one or more underexpressed genes are selected from the group consisting of *BTN2A2, SMPDL3B,* and *MET,* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, PAI-1, INPP4B, EIF4EBP1, EGFR and HER3 and the one or more underexpressed proteins are selected from the group consisting of ASNS, MAPK9, YWHAE, RAD50 and PEA15.

In particular embodiments of the hereinbefore described methods, the cancer is glioma, such as lower grade glioma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of TXN, *BCAP31, STAU1, PML, CARHSP1,* and *BTN2A2;* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, PAI-1, VEGFR2, Ku80, SMAD1 and NFKB1 and the one or more underexpressed proteins are selected from the group consisting of ESR1, YWHAE and PGR.

In particular embodiments of the hereinbefore described methods, the cancer is bladder cancer, such as urothelial carcinoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *ADORA2B, KCNG1, STAU1, MAP2K5,* and *CAMSAP1,* and the one or more underexpressed genes are selected from the group consisting of *GNB2L1, EIF3K, TXN, BCAP31, EXOSC7, CD55, NDUFCl, GRHPR, CETN3, BTN2A2, SMPDL3B,* and *ERC2,* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, VEGFR2, Ku80, SMAD1 and AKT1 and the one or more underexpressed proteins is ASNS.

In particular embodiments of the hereinbefore described methods, the cancer is lung cancer, such as lung squamous cell carcinoma, and wherein:

(i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1, ZNF593,* and *SMPDL3B,* and the one or more underexpressed genes are selected from the group consisting of *GSK3B, MAP2K5, NDUFCl, CAMSAPI, ABHD5,* and *MET,* and/or

(ii) the one or more overexpressed proteins are selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EGFR and GATA3 and the one or more underexpressed proteins is ASNS.

In particular embodiments of the hereinbefore described methods, the cancer is adrenocortical carcinoma, and wherein:

the one or more overexpressed genes are selected from the group consisting of *GNB2L1, EIF3K, TXN, ADORA2B, KCNG1, BCAP31, FOXM1, ZNF593, EXOl, KIF2C, MAP2K5, TTK, MELK, CENPA, TPX2, GRHPR, CEP55, MCMIO,* and *CENPN,* and the one or more underexpressed genes are selected from the group consisting of *MTMR7, BCL2, MAPT, MYB,* and *STC2.*

In particular embodiments of the hereinbefore described methods, the cancer is kidney renal papillary cell carcinoma and wherein:

the one or more overexpressed genes are selected from the group consisting of *GNB2L1, ADORA2B, KCNG1, GSK3B, FOXM1, CD55, EXOl, KIF2C, STAU1, TTK, MELK, CENPA, TPX2, CA9, CEP55,* and *MCMIO,* and the one or more underexpressed genes are selected from the group consisting of *SMPDL3B,* and *BCL2.*

In particular embodiments of the hereinbefore described methods, the cancer is pancreatic ductal adenocarcinoma and wherein:

the one or more overexpressed genes are selected from the group consisting of *EIF3K, ADORA2B, GSK3B, EXOSC7, FOXM1, CD55, EXOl, STAU1, CAMSAP1,* and *CETN3* and the one or more underexpressed genes are selected from the group consisting of *BTN2A2, SMPDL3B, MTMR7, ME1, BCL2,* and *ERC2.*

In particular embodiments of the hereinbefore described methods, the cancer is liver hepatocellular carcinoma and wherein:

the one or more overexpressed genes are selected from the group consisting of *GNB2L1, TXN, EXOSC7,* and *CA9,* and the one or more underexpressed genes is *MTMR7.*

In particular embodiments of the hereinbefore described methods, the cancer is cervical squamous cell carcinoma and/or endocervical adenocarcinoma and wherein:

the one or more overexpressed genes are selected from the group consisting of *STAU1, CA9,* and *ME1* and the one or more underexpressed genes are selected from the group consisting *oiEIF3K, TXN, BCAP31, EXOSC7,* and *ZNRD1-AS1.*

Furthermore, in certain embodiments, patients with a high relative expression level of one or more overexpressed genes, such as those of the 29 gene signature, when compared to one or more underexpressed genes, such as those of the 30 gene signature, a high relative expression level of one or more overexpressed proteins when compared to one or more underexpressed proteins and/or a high integrated score as described herein may be more likely to respond favourably to immunotherapy.

Accordingly, one aspect provides a method of predicting the responsiveness of a cancer to an immunotherapeutic agent in a mammal, said method including the step of comparing an expression level of one or more overexpressed genes selected from the group consisting of *ADORA2B, CD36, CETN3, KCNGl, LAMA3, MAP2K5, NAEl, PGKl, STAU1, CFDP1, SF3B3* and *TXN,* and an expression level of one or more underexpressed genes selected from the group consisting of *APOBEC3A, BCL2, BTN2A2, CAMSAP1, CAMK4, CARHSP1, FBXW4, GSK3B, HCFC1R1, MYB, PSEN2* and *ZNF593,* in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the immunotherapeutic agent.

In one embodiment the one or more overexpressed genes are selected from the group consisting of *ADORA2B, CETN3, KCNGl, MAP2K5, STAU1* and *TXN,* and/or an expression level of one or more underexpressed genes are selected from the group consisting of *BTN2A2, CAMSAP1, CARHSP1, GSK3B, HCFC1R1,* and *ZNF593.*

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *ADORA2B, CD36, KCNGl, LAMA3, MAP2K5, NAEl, PGKl, STAU1, CFDP1,* and *SF3B3* and/or an expression level of one or more underexpressed genes are selected from the group consisting of *APOBEC3A, BCL2, BTN2A2, CAMK4, FBXW4, PSEN2* and, *MYB.*

It would be understood for particular embodiments of the present aspect that one or more other overexpressed genes and/or one or more other underexpressed genes from one or more of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene,

an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene. such as those listed in Table 21, may be included in the step of comparing an expression level of one or more overexpressed genes and an expression level of one or more underexpressed genes.

Insofar as they relate to cancer, immunotherapy or immunotherapeutic agents use or modify the immune mechanisms of a subject so as to promote or facilitate treatment of a cancer. In this regard, immunotherapy or immunotherapeutic agents used to treat cancer include cell-based therapies, antibody therapies *(e.g.,* anti-PDl or anti-PDLl antibodies) and cytokine therapies. These therapies all exploit the phenomenon that cancer cells often have subtly different molecules termed cancer antigens on their surface that can be detected by the immune system of the cancer subject. Accordingly, immunotherapy is used to provoke the immune system of a cancer patient into attacking the cancer's cells by using these cancer antigens as targets.

Non-limiting examples of immunotherapy or immunotherapeutic agents include adalimumab, alemtuzumab, basiliximab, belimumab, bevacizumab, BMS-936559, brentuximab, certolizumab, cituximab, daclizumab, eculizumab, ibritumomab, infliximab, ipilimumab, lambrolkizumab, mepolizumab, MPDL3280A muromonab, natalizumab, nivolumab, ofatumumab, omalizumab, pembrohzumab, pexelizumab, pidilizumab, rituximab, tocilizumab, tositumomab, trastuzumab, ustekinumab, abatacept, alefacept and denileukin diftitox. In particular preferred embodiments, the immunotherapeutic agent is an immune checkpoint inhibitor, such as an anti-PDl antibody *(e.g.,* pidilizumab, nivolumab, lambrolkizumab, pembrohzumab), an anti-PDLl antibody *(e.g.,* BMS-936559, MPDL3280A) and/or an anti-CTLA4 antibody *(e.g.,* ipilimumab).

As would be appreciated by the skilled artisan, immune checkpoints refer to a variety of inhibitory pathways of the immune system that are crucial for maintaining self-tolerance and for modulating the duration and/or amplitude of an immune response in a subject. Cancers can use particular immune checkpoint pathways as a major mechanism of immune resistance, particularly against T cells that are specific for tumour antigens. Accordingly, immune checkpoint inhibitors include any agent that blocks or inhibits the inhibitory pathways of the immune system. Such inhibitors

may include small molecule inhibitors or may include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. By way of example, immune checkpoint receptors or receptor ligands that may be targeted for blocking or inhibition include, but are not limited to, CTLA-4, 4-IBB (CD137), 4-1BBL (CD137L), PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, TIM3, B7H3, B7H4, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-Hl; MEDI4736), MK-3475 (PD-1 blocker), nivolumab (anti-PDl antibody), pidilizamab (CT-01 1; anti-PDl antibody), BY55 monoclonal antibody, AMP224 (anti-PDLl antibody), BMS-936559 (anti-PDLl antibody), MPLDL3280A (anti-PDLl antibody), MSB0010718C (anti-PDLl antibody) and yervoy/ipilimumab (anti-CTLA-4 checkpoint inhibitor), albeit without limitation thereto.

In one embodiment, the method of predicting the responsiveness of a cancer to an immunotherapeutic agent, may further include the step of administering to the mammal a therapeutically effective amount of the immunotherapeutic agent.

In a related aspect is provided a method of predicting the responsiveness of a cancer to an EGFR inhibitor in a mammal, said method including the step of comparing an expression level of one or more overexpressed genes selected from the group consisting оï NAEI, *GSK3B, TAF2, MAPRE1, BRD4, STAU1, TAF2, PDCD4, KCNG1, ZNRD1-AS1, EIF4B, HELLS, RPL22, ABAT, BTN2A2, CD1B, ITM2A, BCL2, CXCR4,* and *ARNT2and* an expression level of one or more underexpressed genes selected from the group consisting *of CDIC, CD1E, CD1B, KDM5A, BATF, EVL, PRKCB, HCFC1R1, CARHSP1, CHAD, KIR2DL4, ABHD5, ABHD14A, ACAA1, SRPK3, CFB, ARNT2, NDUFC1, BCL2, EVL, ULBP2, BIN3, SF3B3, CETN3, SYNCRIP, TAF2, CENPN, ATP6V1C1, CD55* and *ADORA2B* in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the EGFR inhibitor.

It would be appreciated that the EGFR inhibitor may be any known in the art, including monoclonal antibody and small molecule inhibitors thereof, such as those

hereinbefore described. In particular embodiments, the EGFR inhibitor is or comprises erlotinib and/or cetuximab.

In certain embodiments, the cancer is or comprises lung cancer, colorectal cancer or breast cancer.

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *NAE1, GSK3B,* and *TAF2* and/or the one or more underexpressed genes are selected from the group consisting of *CD1C, CD1E, CDIB, KDM5A, BATF, EVL, PRKCB, HCFC1R1, CARHSP1, CHAD, KIR2DL4, ABHD5, ABHD14A, ACAA1, SRPK3,* and *CFB.*

In one embodiment, the one or more overexpressed genes are selected from the group consisting of *MAPRE1, BRD4, STAU1, TAF2, GSK3B, PDCD4, KCNG1, ZNRD1-AS1, EIF4B* and *HELLS* and/or the one or more underexpressed genes are selected from the group consisting of *ARNT2, NDUFC1, BCL2, ABHD14A, EVL, ULBP2,* and *BIN3.*

In one embodiment, the one or more overexpressed genes are selected from the group consisting *oiRPL22, ABAT, BTN2A2, CDIB, ITM2A, BCL2, CXCR4,* and *ARNT2* and/or the one or more underexpressed genes are selected from the group consisting of *SF3B3, CETN3, SYNCRIP, TAF2, CENPN, ATP6V1C1, CD55* and *ADORA2B.*

In a related aspect is provided a method of predicting the responsiveness of a cancer to a multikinase inhibitor in a mammal, said method including the step of comparing an expression level of one or more overexpressed genes selected from the group consisting of *SCUBE, CHPT1, CDC1, BTG2, ADORA2B* and *BCL2,* and an expression level of one or more underexpressed genes selected from the group consisting of *NOP2, CALR, MAPRE1, KCNG1, PGK1, SRPK3, RERE, ADM, LAMA3, KIR2DL4, ULBP2, LAMA4, CA9,* and *BCAP31,* in one or more cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the EGFR inhibitor.

Multikinase inhibitors typically work by inhibiting multiple intracellular and/or cell surface kinases, some of which may be implicated in tumor growth and metastatic progression of a cancer, thus decreasing tumor growth and replication. It would be appreciated that the multikinase inhibitor may be any known in the art,

including small molecule inhibitors, such as those hereinbefore described. Non-limiting examples of multikinase inhibitors include sorafenib, trametinib, dabrafenib, vemurafenib, crizotinib, sunitinib, axitinib, ponatinib, ruxolitinib, vandetanib, cabozantinib, afatinib, ibrutinib and regorafenib. In a particular embodiment, the multikinase inhibitor is or comprises sorafenib.

In one embodiment, the cancer is or comprises lung cancer.

Suitably, with regard to predicting the responsiveness of a cancer to an immunotherapeutic agent, an EGFR inhibitor or a multikinase inhibitor, a higher relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with a relatively increased responsiveness of the cancer to the agent or inhibitor; and/or a lower relative expression level of the one or more overexpressed genes compared to the one or more underexpressed genes indicates or correlates with a relatively decreased responsiveness of the cancer to the agent or inhibitor.

In a further aspect, the invention provides a method for identifying an agent for use in the treatment of cancer including the steps of:

(i) contacting a protein product of *GRHPR, NDUFC1, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COGS, CFDP1* and/or *KCNG1* with a test agent; and

(ii) determining whether the test agent, at least partly, reduces, eliminates, suppresses or inhibits the expression and/or an activity of the protein product.

Suitably, the cancer is of a type hereinbefore described, albeit without limitation thereto. Preferably, the cancer has an overexpressed gene selected from the group consisting of *GRHPR, NDUFC1, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COGS, CFDP1* and *KCNG1* and any combination thereof,

Suitably, the agent possesses or displays little or no significant off-target and/or nonspecific effects.

Preferably, the agent is an antibody or a small organic molecule.

In embodiments relating to antibody inhibitors, the antibody may be polyclonal or monoclonal, native or recombinant. Well-known protocols applicable to antibody production, purification and use may be found, for example, in Chapter 2 of Coligan *et al,* CURRENT PROTOCOLS IN IMMUNOLOGY (John Wiley & Sons NY, 1991-1994) and Harlow, E. & Lane, D. *Antibodies: A Laboratory Manual,* Cold Spring Harbor, Cold Spring Harbor Laboratory, 1988, which are both herein incorporated by reference.

Generally, antibodies of the invention bind to or conjugate with an isolated protein, fragment, variant, or derivative of the protein product of one or more of *GRHPR, NDUFC1, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COG8, CFDP1* and *KCNG1*. For example, the antibodies may be polyclonal antibodies. Such antibodies may be prepared for example by injecting an isolated protein, fragment, variant or derivative of the protein product into a production species, which may include mice or rabbits, to obtain polyclonal antisera. Methods of producing polyclonal antibodies are well known to those skilled in the art. Exemplary protocols which may be used are described for example in Coligan *et al*, CURRENT PROTOCOLS IN IMMUNOLOGY, ***supra,*** and in Harlow & Lane, 1988, ***supra.***

Monoclonal antibodies may be produced using the standard method as for example, described in an article by Kohler & Milstein, 1975, Nature **256,** 495, which is herein incorporated by reference, or by more recent modifications thereof as for example, described in Coligan ***et al.,*** CURRENT PROTOCOLS IN IMMUNOLOGY, *supra* by immortalizing spleen or other antibody producing cells derived from a production species which has been inoculated with one or more of the isolated protein products and/or fragments, variants and/or derivatives thereof.

Typically, the inhibitory activity of candidate inhibitor antibodies may be assessed by *in vitro* and/or *in vivo* assays that detect or measure the expression levels and/or activity of the protein products of one or more of *GRHPR, NDUFC1, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COG8, CFDP1* and *KCNG1* in the presence of the antibody.

In embodiments relating to small organic molecule inhibitors, this may involve screening of large compound libraries, numbering hundreds of thousands to millions of candidate inhibitors (chemical compounds including synthetic, small organic molecules or natural products, for example) which may be screened or tested for biological activity at any one of hundreds of molecular targets in order to find potential new drugs, or lead compounds. Screening methods may include, but are not limited to, computer-based ("in silico") screening and high throughput screening based on in vitro assays.

Typically, the active compounds, or "hits", from this initial screening process are then tested sequentially through a series of other in vitro and/or in vivo tests to further characterize the active compounds. A progressively smaller number of the "successful" compounds at each stage are selected for subsequent testing, eventually

leading to one or more drug candidates being selected to proceed to being tested in human clinical trials.

At the clinical level, screening a test agent may include obtaining samples from test subjects before and after the subjects have been exposed to a test compound. The levels in the samples of the protein product of the overexpressed genes may then be measured and analysed to determine whether the levels and/or activity of the protein products change after exposure to a test agent. By way of example, protein product levels in the samples may be determined by mass spectrometry, western blot, ELISA and/or by any other appropriate means known to one of skill in the art. Additionally, the activity of the protein products, such as their enzymatic activity, may be determined by any method known in the art. This may include, for example, enzymatic assays, such as spectrophotometric, fluorometric, calorimetric, chemiluminescent, light scattering, microscale thermophoresis, radiometric and chromatographic assays.

It would be appreciated that subjects who have been treated with test agents may be routinely examined for any physiological effects which may result from the treatment. In particular, the test agents will be evaluated for their ability to decrease cancer likelihood or occurrence in a subject. Alternatively, if the test agents are administered to subjects who have previously been diagnosed with cancer, they will be screened for their ability to slow or stop the progression of the cancer as well as induce disease remission.

In a particular embodiment, the invention may provide a *"companion diagnostic"* whereby the one or more genes that are detected as having elevated expression are the same genes that are targeted by the anti-cancer treatment.

In a related aspect, the invention provides an agent for use in the treatment of cancer identified by the method hereinbefore described.

Suitably, the cancer is of a type hereinbefore described, albeit without limitation thereto. Preferably, the cancer has an overexpressed gene selected from the group consisting of *GRHPR, NDUFC1, CAMSAP1, CETN3, EIF3K, STAU1, EXOSC7, COG8, CFDP1, KCNG1* and any combination thereof.

In another related aspect, the invention provides a method of treating a cancer in a mammal, including the step of administering to the mammal a therapeutically effective amount of an agent hereinbefore described.

In this regard, test agents that are identified of being capable of reducing, eliminating, suppressing or inhibiting the expression level and/or activity of a protein product of *GRHPR, NDUFCl, CAMSAPl, CETN3, EIF3K, STAUl, EXOSC7, COGS, CFDPl* and/or *KCNGl* may then be administered to patients who are suffering from or are at risk of developing cancer,. For example, the administration of a test agent which inhibits or decreases the activity and/or expression of the protein product of one or more of the aforementioned genes may treat the cancer and/or decrease the risk cancer, if the increased activity of the biomarker is responsible, at least in part, for the progression and/or onset of the cancer.

Suitably, the cancer is of a type hereinbefore described, albeit without limitation thereto. Preferably, the cancer has an overexpressed gene selected from the group consisting of *GRHPR, NDUFCl, CAMSAPl, CETN3, EIF3K, STAUl, EXOSC7, COGS, CFDPl, KCNGl* and any combination thereof.

All computer programs, algorithms, patent and scientific literature referred to herein is incorporated herein by reference.

For the present invention, the database accession number or unique identifier provided herein for a gene or a protein, such as those presented in Tables 4, 5, 10, 15, 16, 17 and 18, as well as the gene and/or protein sequence or sequences associated therewith, are incorporated by reference herein.

So that preferred embodiments of the invention may be fully understood and put into practical effect, reference is made to the following non-limiting examples.

EXAMPLE 1

Materials and Methods

Meta-analysis of global gene expression in TNBC

We performed a meta-analysis of global gene expression data in the Oncomine™ database[19] (Compendia Bioscience, MI) using a primary filter for breast cancer (130 datasets), sample filter to use clinical specimens and dataset filters to use mRNA datasets with more than 151 patients (22 datasets). Patients of all ages, gender, disease stages or treatments were included. Three additional filters were applied to perform three independent differential analyses: (1) triple negative (TNBC cases vs. non-TNBC cases, 8 datasets[49-56]; (2) metastatic event analysis at 5 years

(metastatic events vs. no metastatic events, 7 datasets[53,54,57-61]) and (3) survival at 5 years (patients who died vs. patients who survived, 7 datasets[49,54,56,58,61-63]). Deregulated genes were selected based on the median p-value of the median gene rank in overexpression or underexpression patterns across the datasets (Figure 8). The union of these three deregulated gene lists resulted in a gene list of deregulated genes in aggressive breast cancers (Figure 9). The METBRIC dataset[21] was used as the validation set for further analysis. The normalized z-score expression data of the METABRIC dataset was extracted from Oncomine™ and imported into BRB-ArrayTools[64] (V4.2, Biometric Research Branch, NCI, Maryland, USA) with built in R Bioconductor packages. Survival curves for the METABRIC dataset were constructed using GraphPad® Prism v6.0 (GraphPad Software, CA, USA) and the Log-rank (Mantel-Cox) Test was used for statistical comparisons of survival curves.

Ingenuity Pathway Analysis and derivation of the eight gene list

Pathway analysis was performed using the Ingenuity Pathway Analysis® (Ingenuity Systems®, CA). For pathway analysis in IPA®, we used only direct relationships. After pathway analysis, we set to identify the minimum gene list that recapitulates the aggressiveness 206 gene list. We used the METABRIC dataset to perform statistical filtering in the BRB-ArrayTools software to derive the minimum gene list as follows: (1) the correlation of each gene in the CIN metagene and the ER metagene to the metagene itself was determined by quantitative trait analysis using the Pearson's correlation coefficient (univariate p-value threshold of 0.001); (2) the association of each gene with overall survival using univariate Cox proportional hazards model (univariate test p-value < 0.001); and (3) the fold-change of gene expression between high aggressiveness score tumors and low aggressiveness score tumors was calculated for each gene. We selected genes with Pearson's correlation coefficient > 0.7 to the metagenes, strongest survival association and more than 2-fold deregulation between high and low agressiveness score tumors. The METABRIC dataset and four publically available datasets were used to validate the 8-genes score. The four datasets (GSE25066[53], GSE3494[65], GSE2990[15], GSE2034[66]) were analyzed as described previously[67].

Cell culture and drug treatments

Breast cancer cell lines were obtained from ATCC™ (VA, USA) and cultured as per ATCC™ instructions. All cell lines were regularly tested for mycoplasma and authenticated using STR profiling. For the siRNA screen, siRNA

solutions (Shanghai Gene Pharma, China) were used to transfect cells (MDA-MB-231, SUM159PT and Hs578T) with 10 nM of respective siRNA using Lipofectamine® RNAiMAX (Life Technologies, CA, USA). For drug treatments, docetaxel and the TTK inhibitor AZ3146 were purchased from Selleck Chemicals LLC (TX, USA) and diluted in DMSO. Six days after siRNA knockdown or after drug treatments the survival of cells in comparison to control was determined using the CellTiter 96® Assay as per manufacturer instructions (Promega Corporation, WI, USA). For immunoblotting, standard protocols were used and membranes were probed with antibodies against TTK (anti-MPSl mouse monoclonal antibody [Nl] abl 1108 (Abeam, Cambridge), and γ-tubulin (Sigma-Aldrich®) then developed using chemiluminescence reagent plus (Milipore, MA, USA). Flow cytometry to quantify apoptosis was performed using Annexin V-Alexa$_{488}$ and 7-AAD (Life Technologies) as per manufacturer instruction using BD FACSCanto II™ flow cytometer (BD Biosciences, CA, USA).

Breast cancer tissue microarrays, immunohistochemical and survival analysis

The Brisbane Breast Bank collected fresh breast tumor samples from consenting patients; the study was approved by the local ethics committees. Tissue microarrays (TMAs) were constructed from duplicate cores of formalin-fixed, paraffin-embedded (FFPE) breast tumor samples from patients undergoing resection at the Royal Brisbane and Women's Hospital between 1987 and 1994. For biomarker analysis, whole tumor sections or TMAs (depending on the marker) were stained with antibodies against ER, PR, Ki67, HER2, CK5/6, CK14, EGFR and TTK (Table 8), and scored by trained Pathologists. The Vectastain® Universal ABC kit (Vector laboratories, CA) was used for signal detection according to the manufacturer's instructions. Stained sections were scanned at high resolution (ScanScope Aperio, Leica Microsystems, Wetzlar, Germany), and then images were segmented into individual cores for analysis using Spectrum software (Aperio). Survival and other clinical data were collected from the Queensland Cancer Registry and original diagnostic Pathology reports, and in addition we performed an internal histopathological review (SRL) of representative tumor sections from each case, stained with H&E. For analysis of HER2-amplification TMAs were analyzed using HER2 CISH. Criteria for assigning prognostic subgroups in this study are summarized in Figure 14.

Other statistical analysis

Statistical analyses were prepared using GraphPad® Prism v6.0. The types of tests used are stated in Figure Legends. Univariate and multivariate Cox proportional hazards regression analyses were performed using MedCalc for Windows, version 12.7 (MedCalc Software, Ostend, Belgium).

Results

Meta-analysis of gene expression profiles in TNBC

We performed a meta-analysis of published gene expression data, irrespective of platform, using the Oncomine™ database[19] (version 4.5). We compared the expression profiles of 492 TNBC cases vs. 1382 non-TNBC cases in 8 datasets and found 1600 overexpressed and 1580 underexpressed genes in the TNBC cases (cutoff median p-value across the 8 datasets < lxl 0^{-5} from a Student's i-test, Figure 8). We also compared the expression profiles of primary breast cancers from 512 patients who developed metastases vs. 732 patients who did not develop metastases at 5 years (7 datasets in total) to identify 500 overexpressed and 480 underexpressed genes in the metastasis cases (cutoff median p-value across the 7 datasets < 0.05 from a Student's i-test, Figure 8). Finally, we compared the expression profiles of 232 primary breast tumors from patients who died within 5 years vs. 879 patients who survived in 7 datasets and found 500 overexpressed and 500 underexpressed genes in the poor survivors (cutoff median p-value across the 7 datasets < 0.05 from a Student's i-test, Figure 8). The union of these analyses - genes deregulated in TNBC and in tumors that metastasized or resulted in death within 5 years - generated a gene list of 305 overexpressed and 341 underexpressed genes (Figure 9A&B). The deregulated genes from our analyses did not consider deregulation in comparison to normal breast tissue. To identify cancer-related genes, we used the METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) dataset[21] as a validation dataset. Of the 305 overexpressed and 341 underexpressed genes identified in the meta-analysis, 117 overexpressed and 89 underexpressed genes (206 genes) were deregulated in TNBC (250 cases) vs. 144 adjacent normal tissue (1.5 fold-change cutoff; Figure 9C&D).

Clinicopathological features of the aggressiveness gene list

We compared the 206 genes from the above analysis, we called the "aggressiveness gene list" (Table 4), to the recently described metagene attractors[16,17] and found that 45 of the overexpressed genes were in the CIN metagene, whereas 19

of the underexpressed genes were in the ER metagene (Figure 10). The expression of the aggressiveness gene list was visualized in the METABRIC dataset, stratified according to the histological subtypes by the GENUIS classification[22]. As shown in Figure 1A, ER7HER2$^-$ (TNBC), in comparison to adjacent normal breast tissue, showed the highest upregulation of CIN genes (red in the heat map) and downregulation of ER signaling genes (green in the heat map). Tumors of other subtypes showed a range of deregulation of these genes. To quantify these trends, we calculated the "aggressiveness score" as the ratio of the CIN metagene (average of expression of CIN genes) to the ER metagene (average of expression of ER genes). The aggressiveness score was highest for ER7HER2$^-$ (TNBC), followed by HER2$^+$ then ER$^+$ tumors (box plot in Figure 1). We also analyzed the aggressiveness score in the five intrinsic breast cancer subtypes predefined by the PAM50 classification[8] and the ten integrative clustering (intClust) subtypes defined by combined clustering of gene expression and copy number data subtypes[21] (Figure 11). The aggressiveness score was highest in the basal-like and the intClust 10 subtypes which are enriched for TNBC and have poor prognosis.

Interestingly, tumors of various subtypes scored higher than the median aggressiveness score (line in box plots in Figure 1 and Figure 11). To this end, we examined the overall survival of patients in the METABRIC dataset stratified by quartiles and also dichotomized by the median of the aggressiveness score. Tumors with high aggressiveness score had worse survival than those with low aggressiveness score. The survival of patients with non-TNBC tumors with high aggressiveness score had poor survival that was similar to TNBC patients (Figure IB). Among ER$^+$ tumors we found that high aggressiveness score predicted poor survival in both Grade 2 (Figure IB) and Grade 3 (Figure 11) tumors. Tumors with high aggressiveness score showed poor survival regardless of the PAM50 intrinsic breast cancer subtypes (Figure 11). The PAM50 classifier was prognostic only in low aggressiveness score tumors (Figure 12).

One network of direct interactions in the aggressiveness gene list associates with patient survival

We performed network analysis on the aggressiveness gene list using the Ingenuity Pathway Analysis (IPA®) and found a network with direct interactions between 97 of the 206 deregulated genes (Figure 2A). To find the minimal genes that represent the aggressiveness genes and this network, the 97 genes in this network

were analyzed for their correlation with the CIN or ER metagenes and overall survival in the METABRIC dataset (Table 5). We selected genes according to the following criteria: (1) highest correlation with the metagenes (Pearson's correlation coefficient > 0.7); (2) association with overall survival (Cox proportional hazards model, $p < 0.001$), and (3) more than 2-fold deregulation with least standard deviation of expression between high and low aggressiveness score tumors. These analyses identified two genes from the ER metagene *(MAPT* and *MYB)* and six genes from the CIN metagene *(MELK, MCM10, CENPA, EXOl, TTK* and *KIF2C).* These 8 genes were maintained in a directly connected network (Figure 2B). The classification of tumors (high vs. low across the median) from these eight genes, again representing the ratio of CIN and ER metagenes, predicted the classification from the 206 genes with 95% sensitivity and 97% specificity by prediction of microarray (PAM) analysis (data not shown). Importantly, a high score from these eight genes identified poor survival in all patients, non-TNBC patients and ER^+ Grade 2 (Figure 2C).

Next, we explored the 8-genes score for prognosis in several molecular and histological settings in the METABRIC dataset. The survival of patients with tumors with wild-type TP53 were stratified by the 8-genes score (Figure 3A). Patients with mutant TP53, which were mainly of high score, showed worse survival than those with wild-type TP53, suggesting that TP53 mutation is an independent prognostic factor. Patients with tumors with low or high expression of the proliferation marker Ki67 were stratified by the 8-genes score suggesting that the 8-genes score is independent of proliferation (Figure 3A). We also found that the 8-genes score stratified the survival of patients from all stages of disease (Stage I - Stage III, Figure 3A). We focused on ER^+ and found that, as in the case of ER^+ Grade 2 tumors (Figure 2C); the 8-genes score stratified the survival of patients with ER^+ Grade 3 tumors (Figure 3B). Importantly, the 8-genes score identified ER^+LN^- and ER^+LN^+ patients who had poor survival similar to ER^-LN^- and ER^-LN^+ patients, respectively (Figure 3B). High 8-genes score identified poor survival of patients with tumors of all PAM50 subtypes and the prognostication by PAM50 classification was only evident in low 8-genes score tumors (Figure 12).

The 8-genes aggressiveness score in multivariate survival analysis

To exclude the possibility that the aggressiveness score - calculated using the 206 genes or the 8 genes - was redundant; we performed multivariate Cox-proportional hazards model analysis in the METABRIC dataset (with Illumina

platform) in comparison to conventional clinical variables and current gene signatures. As detailed in Table 1, the aggressiveness scores significantly associated with patient survival when compared with conventional variables and outperformed MammaPrint[9], OncotypeDx[10,11], proliferation/cell cycle[16,20] and CIN[20] signatures. Moreover, our aggressiveness scores outperformed the CIN4 classier[23] which was recently developed from the CIN signature.

We validated the six CIN and two ER genes in univariate survival association using the online tool Kaplan-Meier (KM)-plotter[24] (Tables 6 & 7) which has the gene expression and survival data of more than 2000 patients (but are not part of the METABRIC dataset). We found that the collective expression of the six overexpressed genes *(MELK, MCM10, CENPA, EXOl, TTK* and *KIF2C)* significantly associated with relapse free survival (RFS) and distant metastasis free survival (DMFS) in all patients, ER^+ patients, lymph node negative (LN^-) or positive (LN^+) patients (Table 6). The two underexpressed genes *(MAPT* and *MYB)* also significantly associated with RFS and DMFS in these patient groups (Table 7).

More importantly, we performed multivariate survival analysis of the 8-genes score in four datasets (with Affymetrix platform from the Gene Expression Omnibus [GEO]; GSE2990, GSE3494, GSE2034 and GSE25066). Again, the score was significantly associated with survival in a multivariate Cox-proportional hazards model in every dataset tested (Figure 4). Altogether, we found that in multiple datasets that used different platforms, the 8-genes score identified patients with poor survival independently of other clinico-pathologic indicators and outperforming current signatures.

Therapeutic targets in the aggressiveness gene list

The overexpressed genes in the CIN metagene are involved in or regulate mitosis, spindle assembly and checkpoint, kinetochore attachment, chromosome segregation and mitotic exit. Thus it is not surprising that several of the overexpressed genes are targets for molecular inhibitors, such as CDK1[25,26] and AURKA/AURKB[27] and have been trialed pre-clinically and clinically[28]. To this end, we performed siRNA depletion against 25 genes of the CIN metagene in three TNBC cell lines, MDA-MB-231, SUM159PT and Hs578T. We found that knockdown of four genes *(TTK, TPX2, NDC80* and *PBK)* consistently affected the survival of these cells (Figure 5A and Table 5). The knockdown of *TTK* showed the worst survival and since it was in the 8-genes score we selected TTK for further studies. We found

that TTK protein was higher in TNBC cell lines compared to the near-normal MCF10A cell line, and luminal/HER2 cell lines (Figure 5B). Next, we used the specific TTK inhibitor (TTKi), AZ3146, against a panel of breast cancer cell lines and found that TNBC cell lines were more sensitive to the TTKi (Figure 5C).

TTK expression in aggressive tumors and potential for combination therapy

To further study the potential of TTK as therapeutic target, we investigated TTK expression at the mRNA and protein levels in breast cancer patients. We analyzed the correlation of *TTK* mRNA expression, dichotomized at the median, with clinicopathological indicators in the METABRIC dataset of 2000 patients (Table 2). High *TTK* mRNA expression associated with younger age of tumor diagnosis, larger tumor size, higher tumor grade, higher Ki67 expression, TP53 mutations, an ER/PR negative tumor phenotype, HER2 positivity and TNBC. Based on PAM50 subtyping, high *TTK* mRNA was associated with luminal B, HER2-enriched and basal-like tumors.

We also analyzed TTK expression in a cohort of breast cancer patients (406 patients) by IHC. TTK and its activity is detected at all stages of the cell cycle, however, it is upregulated during mitosis[29]. Thus, we observed TTK staining in non-mitotic cells to define high TTK levels (score of 3) in order to exclude the bias of elevated TTK level during mitosis. Similar to *TTK* mRNA, high TTK protein level (Table 3) associated with high tumor grade, high Ki67 expression and TNBC status (particularly basal TNBC). Moreover, in agreement with the *TTK* mRNA associations with the PAM50 intrinsic subtypes, high TTK protein was observed in HER2-positive and proliferative $ER^+/HER2^-$ tumors (most related to luminal B) but low TTK protein in non-proliferative $ER^+/HER2^-$ tumors (most related to luminal A). In addition to these associations with aggressive phenotypes, we also found that high TTK protein significantly associated with aggressive histological features including ductal histology, pushing tumor border, lymph node involvement, nuclear pleomorphism, lymphocytic infiltration and higher mitotic scores (Table 3). Altogether, like the high aggressiveness score from the 206 or 8 genes, high level of TTK mRNA and protein span across breast cancer subtypes marking aggressive behavior.

We examined the association of TTK protein level with patient survival and found that breast tumors with high TTK staining (category 3) had worse survival than other staining groups at 5 years (Figure 6A&B) and 10 and 20 years (Figure 13).

Importantly, high TTK staining (category 3) was not restricted to a particular histological subgroup or to tumors with high mitotic index (Figure 6C). Next, we focused on prognostication of aggressive subgroups (Grade 3, lymph node positive, TNBC, HER2 or high Ki67) and found that high TTK protein level identified exceptionally aggressive tumors that lead to poor survival of less than 2 years (Figure 7A). Finally, to exploit our finding that TTK, as a part of the aggressiveness score, was associated with aggressive breast tumors and that TTK inhibition was effective in TNBC cell lines that overexpress this protein (Figure 5), we investigated the therapeutic potential of combining TTK inhibition with chemotherapy. We found that TTKi synergized with docetaxel at very low (sub-lethal doses) in the treatment of TNBC cell lines which overexpress TTK in comparison to cell lines which do not (Figure 7B) and that this combination induced apoptotic cell death (Figure 7C).

CIN metagene and ER metagenes in lung adenocarcinoma

There is also reason to believe that the metagene signature may work for other cancers, such as lung cancer. FIG. 15 provides overall survival curves of lung cancer patients split by ten (10) CIN genes that include the aforementioned six (6) (genes as well as ***CENPN, CEP55, FOXM1*** and ***TPX2***; and the two (2) ER genes ***MAPT*** *and* ***MYB*** as a signature; patients are low or high according to the median of the signature. The signature outperformed tumour grade and disease stage and remained significant when adjusted for AJCC T (size) and N (lymph node) stages (tumour size (T stage) and lymph node status (N stage) in multivariate Cox regression analysis in lung cancer patients (Table 9). In particular, the signature was prognostic in lung adenocarcinoma. The prognostication of lung adenocarcinoma was significant even when including a minimal gene set of 6 CIN genes and 2 ER genes.

In Figure 16A we show the global gene expression (by RNAseq) of the breast cancer patients in the TCGA dataset. From these data the 8-genes score (Aggressiveness score) and the OncotypeDx (Recurrence score) were investigated for association with survival. The 8-genes score stratified breast cancer survival better than the OncotypeDx (Figure 16B). Further, the 8-genes score (Aggressiveness score) identified tumours with high genomic copy number variations involving whole chromosome arms deletions and duplications reflecting aneuploidy (Figure 16C).

We also find that the 8-genes score (Aggressiveness score) stratifies the survival of all cancers collectively in the TCGA data better than the OncotypeDx (Figure 17) and that the 8-genes score (Aggressiveness score)was prognostic in each of the tested cancers (Figure 18). Similarly, as in breast cancer (Figure 16C), the 8-genes score (Aggressiveness score) identified tumors of all cancer types with high genomic copy number variations involving whole chromosome arms deletions and duplications reflecting aneuploidy (data not shown). These cancer types include breast cancer, bladder cancer, colorectral cancer, glioblastoma, lower grade glioma, head & neck cancer, kidney cancer, liver cancer, lung adenocarcinoma, abute myeloid leukaemia, pancreatic cancer and lung squamous cell carcinoma.

Discussion

This meta-analysis of gene expression in the Oncomine™ database identified a list of 206 was enriched with two core biological functions/metagenes; chromosomal instability (CIN) and ER signaling. We calculated the aggressiveness score, the ratio of CIN to ER metagenes, which associated with overall survival of breast cancer. A core of eight genes (six CIN genes and two ER signaling genes) was representative and recapitulated the correlations with outcome from the 206 genes. The score from the six CIN genes to the 2 ER signaling genes, 8-genes score, associated with survival in several breast cancer datasets. Our aggressiveness scores outperformed conventional variable and published signatures in multivariate survival analysis. Particularly in ER^+ tumors, some cases have survival as poor as that of the aggressive $HER2^+$ and TNBC subtypes. Our data suggest that the interplay of cancer-related biological functions, namely CIN and ER signaling, are better predictors of phenotypes than single genes or single functions. This notion is in line with recent studies showing that the interaction of biologically-driven predictors provide better prognosis [16,17,30]. Recently, all ER^- tumors were described to have a high level of CIN metagene, however, it was not clear that ER^+ tumors could be described as low CIN tumors [16]. In our study, we clarify that ER^+ disease contains a considerable fraction of tumors that have high level of CIN genes and that the relationship between CIN and ER genes is a powerful predictor of survival in these patients.

The fidelity of chromosome segregation is ensured by the proper attachment of the microtubules from the mitotic spindle to the kinetochores of chromosomes in a tightly regulated process and CIN refers to the missegregation of whole

chromosomes thus producing aneuploidy[31]. Using aneuploidy as a surrogate marker for CIN, Carter et al developed a gene signature and found that this "CIN signature" predicts clinical outcome in multiple cancers[20]. More recently, a minimal gene set that captures the CIN signature, CIN4 *(AURKA, FOXM1, TOP2A* and *TPX2)* was described as the first clinically applicable qPCR derived measure of tumor aneuploidy from FFPE tissue. Since Grade 2 tumors heterogeneous characteristics in terms of clinical outcome, the significance of the CIN4 classier is the stratification of Grade 2 tumors into good and poor prognosis groups[23]. Our aggressiveness scores were prognostic in all tumor grades and disease stages (stages I-III and lymph node negative and positive) and outperformed the CIN signature and the CIN4 classier in multivariate survival analysis in the METABRIC dataset. Strikingly, but in agreement with previous studies[32,33], the prognostication using the CIN metagene and our aggressiveness scores from gene expression levels were restricted to ER^+ disease but not in the TNBC or HER2 subtypes. This may be explained that ER^- tumors have a high level of CIN metagene as per our results and published previously[16]. However, our results with TTK protein level clearly demonstrate that TNBC, HER2, high grade, lymph node positive and proliferative tumors contain subgroups with high TTK levels exclusive of mitotic cells and have poorer survival than those with low TTK expression or TTK expression in mitotic cells. We propose that there are two types of high expression of CIN genes that may not be clearly differentiated by mRNA expression studies. One form of elevated CIN genes relates to high level of mitosis and proliferation whereas the second form that we measured by IHC exclusive of mitotic cells is driven by another aggressive phenotype; protection of aneuploidy and genomic instability. The recent study of the CIN4 classifier lends support to our proposition. In this study, using flow cytometry to measure aneuploidy by DNA content, the authors found that a substantial proportion of tumors with high CIN4 scores have a normal DNA ploidy and that a significant proportion of aneuploid cases had low CIN4 score[23].

Chromosome missegregation and aneuploidy enhance genetic recombination and defective DNA damage repair[34] to drive a "mutator phenotype" required for oncogenesis[35]. Genomic instability caused by deregulated mitotic spindle assembly checkpoint (SAC) and aneuploidy has been termed "non-oncogene addiction"[36,37]. It is tempting to suggest that CIN and aneuploidy are exploited by breast cancer stem cells which are high in TNBC[38] due to the link between cancer stem cells, aneuploidy

and therapy resistance[39,40]. This is supported by studies that implicate several genes involved in the SAC and chromosome segregation in tumor initiation, progression and cancer stem cells, e.g. AURKA in ovarian cancer[41], MELK/FOXM1 in glioblastoma[42,43], MELK[44] and MAD2[45] in breast cancer and SKP2 in several cancers[46]. The role of CIN genes to protecting aneuploidy could provide an insight to the paradox that TNBC show a better response to chemotherapy due to higher level of proliferation, yet these tumors have poorer outcome. We propose that resistance in TNBC could be attributed to the ability of aneuploid cells to adapt and drive recurrence. At least *in vivo,* chemotherapy has been shown to induce the proliferation quiescent aneuploid cells as a mechanism for therapy resistance[39]. We envisage that the high level of the CIN metagene in TNBC, particularly genes involved in chromosome segregation, is protective of this state. Indeed, one study found that a high level of TTK is protective of aneuploidy in breast cancer cells and its silencing reduces the tumorigenicity of breast cancer cell lines *in vivo*[47]. Our results from the patient cohort demonstrate that high TTK protein expression exclusive of mitosis was indeed prognostic aggressive tumors and support the concept that protection from aneuploidy and genomic instability is an aggressive phenotype that drives poor outcome.

Our results with the TTK molecular inhibitor, in agreement with published studies using siRNA depletion[47,48], supports the idea of targeting chromosomal segregation in tumors with a high CIN phenotype as a therapeutic strategy. We also suggest that while TTK is high in TNBC as previously described[47,48], a considerable proportion of non-TNBC tumors that display aggressive features also show an elevated level of CIN genes, and would benefit from such targeted therapies. To our knowledge the combination of sub-lethal doses of taxanes with TTK inhibition has not been investigated so far in breast cancer, but in other cancers[33,50-53]. Our results reveal that TTK inhibition indeed sensitizes breast cancer cells with high TTK to docetaxel.

Referring particularly in FIGS 16-18, as well as the 8-genes score (Aggressiveness score) being prognostic for the survival of cancer patients after treatment, the aggressiveness score also identifies tumors with high copy number variations involving whole chromosome arms reflecting aneuploid status. Thus, the aggressiveness score may also serve as a companion diagnostic for drugs that target aneuploidy by means of targeting genes listed in Table 4, inclusive of the 8 genes

used to produce the aggressiveness score (such as χχK6[7-70]) or by other drugs that target the aneuploidy state (such as PLK1[71,72] or others[73-76]).

In conclusion, our study emphasizes that classification of breast cancer based on biological phenotypes facilitates understanding the drivers of oncogenic phenotypes and therapeutic potentials. Importantly, our studies demonstrate that IHC assessment of CIN genes, exemplified by TTK here; provide better characterization and understanding for the contribution of CIN to tumor aggressiveness and prognosis.

Throughout this specification, the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. Various changes and modifications may be made to the embodiments described and illustrated herein without departing from the broad spirit and scope of the invention.

All computer programs, algorithms, patent and scientific literature referred to herein is incorporated herein by reference in their entirety.

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Table 1: Univariate and multivariate survival analysis of the aggressiveness score in the METABRIC dataset

	Univariate Cox-proportional hazards model		Multivariate Cox-proportional hazards model (stepwise)	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
206 genes score (high, low)	1.6173 (1.4174 - 1.8454)	O.0001	1.5188 (1.3227 - 1.7440)	0.0001
8 genes score (high, low)	1.5853 (1.2883 - 1.8103)	<0.0001	1.4~<3() (1.2198 - 1(344)	<').0oo1
Lymph node (+, -)	1.8594 (1.6289 - 2.1224)	O.OOOl	1.6807 (1.4610 - 1.9334)	0.0001
Tumor size (T1, T2, T3)	1.4.54 (1.2i131- 1] 080)	<ii0i1	1.i666 (1.1642 - 1.(.04 1)	0.0001
HER2 status (+, -)	1.4565 (1.2537 - 1.6920)	0.0001	1.1983 (1.0183 - 1.4101)	0.0302
Tumor grade (1, 2, 3)	1.3500 (1.2095 - 1.5067)	0.000 1	ns	ns
Ki67 (+, -)	1.4184 (1.2399 - 1.6226)	0.0001	ns	ns
Mitotic Prediction (high, low)	1.3320 (1.1669 - 1.5204)	0.000 1	ns	ns
CIN4 (high, low)	1.5310 (1.3413 - 1.7476)	0.0001	ns	ns
CIS 75 (high, low)	1.5004 (1.3132 - 1.^143)	0.000 1	ns	ns
Cell Cycle (high, low)	1.5018 (1.3145 - 1.7158)	0.0001	ns	ns
ER status (+, -)	1.3016 (1.1167 - 1.5170)	0.0008	ns	ns
OncoTypeDx (L, I, H)	1.2672 (1.0909 - 1.4720)	0.0021	ns	ns
Treatment (yes, no)	1.1646 (0.9753 - 1.2639)	0.0939		
Age (<40, >40)	1.1235 (0.8480 - 1.4886)	0.4196		

HR: Hazard Ratio. CI: confidence interval. ns: not significant. OncoTypeDx scores are low (L, < 18), intermediate (I, 18-31), high (H >31). All variables were included in the multivariate Cox-proportional hazards model analysis and by stepwise model, only significant co-variants were included in the final analysis shown in Table.

Table 2: Correlation of *TTK* mRNA level and clinico-pathological indicators in the METABRIC dataset

Comparison		TTK Low	TTK high	X^2
Tumor size				
	<2cm	346 (18%)	280 (14%)	p<1.0E-6
	>2cm <5cm	509 (26%)	685 (35%)	p=3.2E-5
	>5cm	60 (3%)	92 (5%)	p=1.25E-2
Tumor Grade				
	Grade 1	137 (7%)	33 (2%)	p<1.0E-6
	Grade 2	479 (25%)	296 (16%)	p<1.0E-6
	Grade 3	251 (13%)	706 (37%)	p<1.0E-6
Ki67 expression				
	Low	826 (39%)	242 (11%)	
	High	237 (11%)	831 (39%)	p<1.0E-6
Immunohistochemical subtypes				
ER negative		71 (4%)	369 (19%)	p<1.0E-6
ER positive		827 (42%)	681 (35%)	
PR negative		306 (15%)	637 (32%)	p<1.0E-6
PR positive		617 (31%)	432 (22%)	
HER2 negative		802 (40%)	744 (37%)	
HER2 positive		118 (6%)	323 (16%)	p<1.0E-6
non-TNBC		885 (45%)	840 (43%)	
Triple negative (TNBC)		29 (1%)	221 (11%)	p<1.0E-6
Intrinsic subtypes				
Luminal A		552 (28%)	169 (9%)	p<1.0E-6
Luminal B		142 (7%)	350 (18%)	p<1.0E-6
HER2-enriched		40 (2%)	200 (10%)	p<1.0E-6
Normal-like		161 (8%)	41 (2%)	p<1.0E-6
Basal-like		26 (1%)	305 (15%)	p<1.0E-6
Age (years)				
	<50	137 (8%)	259 (13%)	p=8.68E-4
	50-74	485 (24%)	549 (27%)	ns
	75-100	282 (14%)	253 (13%)	ns
TP53 mutation				
	Wildtype	390 (96%)	331 (40%)	
	Mutant	14 (2%)	85 (10%)	p<1.0E-6

X2: Chi square test performed using GraphPad® Prism. ns not significant

Table 3: Associations between TTK protein expression and clinico-pathological indicators

Parameter	TTK (0-1)	TTK (2)	TTK (3)	P value[#]
Histological type				
Ductal NOS	147(60.7 %)	67(27.7 %)	28 (11.6 %)	
Lobular	43(76.8 %)	10 (17.9 %)	3 (5.4 %)	
Mixed ducto-lobular	31(88.6 %)	4 (11.4 %)	0 (0.0 %)	0.0265
Metaplastic	9(56.3 %)	7 (43.8 %)	0 (0.0 %)	
Tubular/cribiform	8(80.0 %)	2 (20.0 %)	0 (0.0 %)	
Other special types (incl mixed)	37(66.1 %)	14 (25.0 %)	5 (8.9 %)	
Overall grade				
1	43(76.8 %)	13(23.2 %)	0 (0.0 %)	
2	162(77.5 %)	41 (19.6 %)	6 (2.9 %)	<0.0001
3	73(47.7 %)	50 (32.7 %)	30 (19.6 %)	
Mitotic score				
1	193(79.8 %)	44(18.2 %)	5 (2.1 %)	
2	33(61.1 %)	18 (33.3 %)	3 (5.6 %)	<0.0001
3	52(43.0 %)	42 (34.7 %)	27 (22.3 %)	
Nuclear pleomorphism score				
1-2	164(75.2 %)	49(22.5 %)	5 (2.3 %)	<0.0001
3	115(57.2 %)	55 (27.4 %)	31 (15.4 %)	
Tubule score				
1	10(76.9 %)	3(23.1 %)	0 (0.0 %)	
2	52(69.3 %)	20 (26.7 %)	3 (4.0 %)	ns
3	216(65.5 %)	81 (24.5 %)	33 (10.0 %)	
Lymph node status				
Positive	77(62.1 %)	41(33.1 %)	6 (4.8 %)	0.0056
Negative	81(73.0 %)	18 (16.2 %)	12 (10.8 %)	
Tumor size				
<2 cm	112(68.3 %)	40(24.4 %)	12 (7.3 %)	
2-5 cm	104(66.2 %)	38 (24.2 %)	15 (9.6 %)	ns
>5 cm	19(61.3 %)	6 (19.4 %)	6 (19.4 %)	
Lymphovascular invasion				
Absent	214(67.3 %)	77(24.2 %)	27 (8.5 %)	ns
Present	63(63.6 %)	27 (27.3 %)	9 (9.1 %)	
Lymphocytic infiltrate				
Absent	119(78.3 %)	28(18.4 %)	5 (3.3 %)	
Mild	115(63.9 %)	47 (26.1 %)	18 (10.0 %)	0.0007
Moderate	36(53.7 %)	23 (34.3 %)	8 (11.9 %)	
Severe	7(41.2 %)	6 (35.3 %)	4 (23.5 %)	
Central scarring/fibrosis				
Absent	254(67.7 %)	90(24.0 %)	31 (8.3 %)	ns
Present	25(56.8 %)	14 (31.8 %)	5 (11.4 %)	
Tumor border				
Infiltrative	250(69.1 %)	88(24.3 %)	24 (6.6 %)	
Pushing (<50%)	11(36.7 %)	11 (36.7 %)	8 (26.7 %)	0.0003
Pushing (>50%)	16(64.0 %)	5 (20.0 %)	4 (16.0 %)	
Ki67 expression (20% threshold)				
Low	240(71.6 %)	77(23.0 %)	18 (5.4 %)	<0.0001
High	14(25.9 %)	23 (42.6 %)	17 (31.5 %)	
Prognostic subgroups				
HER2+	21(51.2 %)	14(34.1 %)	6 (14.6 %)	
HR+/HER2-neg (Ki67-high)	6(24.0 %)	13 (52.0 %)	6 (24.0 %)	
HR+/HER2-neg (Ki67-low)	196(76.0 %)	53 (20.5 %)	9 (3.5 %)	<0.0001
TN (basal-like)	23(41.8 %)	20 (36.4 %)	12 (21.8 %)	
TN (non-basal)	10(71.4 %)	1 (7.1 %)	3 (21.4 %)	

TMAs were scored by two independent assessors according to the following categories: 0, negative; 1, weak and focal staining (pooled with negative cases for this analysis); 2, moderate-strong focal staining (collectively <50% of tumour cells); 3 = moderate-strong diffuse staining (>50% of tumour cells). Regarding % cells stained, we disregarded mitotic cells to assess mitosis-independent TTK expression. [#]Chi square test (GraphPad® Pr sm. ns: not significant)

Table 4: The aggressiveness genelist (206 genes)

Input	Approved Name	HGNC ID	Location
ADIRF	adipogenesis regulatory factor	HGNC:24043	10q23.31
AFF3	AF4/FMR2 family, member 3	HGNC:6473	2q11.2-q12
AGO2	argonaute RISC catalytic component 2	HGNC:3263	8q24.3
AGR3	anterior gradient 3 homolog (Xenopus laevis)	HGNC24167	7p21. 1
AHNAK	AHNAK nucleoprotein	HGNC:347	11q12-q13
ALD113A2	aldehyde dehydrogenase 3 family, member A2	11G\(_:403	17pl l.2
AMLN	antiliin. actin bjiticluig protein	HfiNC:140S2	7p15-p14
APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	HGNC: 17352	22ql3. 1-ql3.2
AQP9	aquaporin 9	HGNC:(.4i	1Sq
AVT1ftN1C2	ATPase, H+ transporting, lysosomal 42kDa, V I subunit C2	HGNC: 18264	2p25. i
AUNIP	nufotn kinase A and nuclear interacting protein	HGNC:28363	1p36.11
ALRlvA	aurora kinase A	HGNC: 11393	20ql3
AUKKB	atin ua kinase B	H(i\i :11390	17p13.i
AZGP1	alpha-2 -glycoprotein 1, zinc -binding	11G\(_:910	7q22. 1
BBiS1	Bardet-Biedl syndrome 1	HGNC:966	11q13
BCL2	B-cell CLL/lymphoma 2	HGNC: 990	18q21.3
BIRC5	baculoviral IAP repeat containing 5	HGNC:593	17q25.3
BLM	Bloom syndrome, RecQ helicase-like	HGNC:1058	15q26.1
BTG2	BTG family, member 2	HGNC:1131	1q32
BUB1	BUB1 mitotic checkpoint serine/threonine kinase	HGNC: 1148	2q13
BYSL	bystin-like	HGNC:1157	6p21.1
C10orf32	chromosome 10 open reading frame 32	HGNC235 16	10q24.33
C18orf56	chromosome 18 open reading frame 56	HGNC:29553	18p11.32
ClorflUo	chromosome 1 open reading frame 106	HGNC:25599	lq32. 1
C3orf21	chromosome 3 open reading frame 21	H(i\i :15494	1q25
C7orf63	chromosome 7 open reading frame 63	HGNC26107	7q21.13
CA9	carbonic anhydrase IX	HGNC:1373	9p13.3
CARD10	caspase recruitment domain family, member 10	HGNC: 16422	22ql3. 1
CASC1	cancer susceptibility candidate 1	HGiNC:29SW	12p12.1
CCDC170	coiled-coil domain containing 170	HGNC:21 177	6q25. 1
CCDC17A	coiled-coil domain containing 176	H(i\i :19855	14q24.3
CCNA2	cyclin A2	11G\(_:157S	4q27
CCNB2	cyclin B2	HGNC:1,¾«t	15q21.3
CCNE1	cyclin E1	HGNC: 1589	19ql2
CCNG2	cyclin G2	HG\{ :1593	4q21.22
CD1O3	CD 163 molecule	HGNC: 163 1	12pl3
CDC20	cell division cycle 20	HGiNC:1723	1p34,1
LDL25A	cell division cycle 25A	HGNC: 1725	3p21
CDC25B	cell division cycle 25B	H(i\ C :-2<>	2(p13
CDC45	cell division cycle 45	HGNC: 1739	22ql l.21

CDCA3	cell division cycle associated 3	HGNC:14624	12p13.31
LDLA5	cell division cycle associated 5	HGNC: 14626	1 lql3. 1
CDCA7	cell division cycle associated 7	HGNC:14628	2q31.1
CDCA8	cell division cycle associated 8	HGNC:14629	1p34.3
LDK1	cyclin-dependent kinase 1	HGNC:1780	10q21.2
CDKN2A	cyclin-dependent kinase inhibitor 2A	HGNC: 1787	9p21
CEM'A	centromere protein A	HGNC:1851	2p23.3
LENPE	centromere protein E, 312kDa	HGNC: 1856	4q24-q25
t:EN1'N	centromere protein N	HGNC:30873	16q23.2
CENPW	centromere protein W	HGNC:21488	6q22.32
(3EP55	centrosomal protein 55kDa	HGNC:19761	10q24.1
CHEKl	checkpoint kinase 1	HGNC: 1925	11q24.2
CIRB?	cold inducible RNA binding protein	HGNC:1982	19p13.3
LkAP2L	cytoskeleton associated protein 2-like	HGNC:26877	2ql3
CKSIB	CDC28 protein kinase regulatory subunit 1B	HGNC:19083	1q21.2
LKS2	CDC28 protein kinase regulatory subunit 2	HGNC:2000	9q22
(3 1.1(3 6	chloride intracellular channel 6	HGNC:[illegible]	21q21.12
LML2	COX assembly mitochondrial protein 2 homolog (S. cerevisiae)	HGNC:24447	16q23.2
CMYA5	cardiomyopathy associated 5	HGNC:14305	5q14.1
CPEB2	cytoplasmic polyadenylation element binding protein 2	HGNC:21745	4p15.33
(3ST3	!!!!¾ atin C	HGNC:24775	20p11.2
LSTB	cystatin B (stefin B)	HGNC:2482	21q22.3
L TS V	cathepsin V	HGNC:2538	9q22.33
(3YB5I)1	cytochrome b5 domain containing 1	HGNC:26516	17p13.1
(3\ BRI)1	cytochrome b reductase 1	HGNC:20797	2q31
DACHI	dachshund homolog 1 (Drosophila)	HGNC:2663	13q22
DAPK1	death-associated protein kinase 1	HGNC:2674	9q34.1
DLPDLl	DEP domain containing 1	HGNC:22949	Ip3 1.2
l)K(3 1	dyskeratosis congenita 1, dyskerin	HGNC:2890	Xq28
DLGAP5	discs, large (Drosophila) homolog-associated protein 5	HGNC:16864	14q22.3
DNAJC12	DnaJ (Hsp40) homolog, subfamily C, member 12	HGNC:28908	10q21.3
DNALI1	dynein, axonemal, light intermediate chain 1	HGNC:14353	1p35.1
E(1 2	enoyl-(3oA delta isomerase 2	HGNC:[illegible]	6p24.3
ELOVL5	ELOVL fatty acid elongase 5	HGNC:21308	6p21.1-p12.1
ESRl	estrogen receptor 1	HGV 3436	6q24-q27
Exo i	exonuclease 1	HGNC:35 11	Iq42-q43
FAM198B	family with sequence similarity 198, member B	HGNC:25312	4q¾2.1
FAM214A	family with sequence similarity 214, member A	HGNC:25609	15q21.2-q21.3
FAM64A	family with sequence similarity 64, member A	HGNC:25483	17p13.2
FAM83D	family with sequence similarity 83, member D	HGNC: 16122	20
FOXA1	forkhead box A1	HGNC:5021	14q12-q13
FOXMI	forkhead box M1	HGNC:3818	12pl3

FPR3	formyl peptide receptor 3	HGNC:3828	19q13.3-q13.4
GAPDH	glyceraldehyde-3 -phosphate dehydrogenase	HGNC:4141	12p13.3 1
GFRA1	GDNF family receptor alpha 1	HGNC:4243	10q25-q26
GGH	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	HGNC4248	8q12.3
GLI3	GLI family zinc finger 3	HGNC:4319	7p13
GLYAT1L2	glycine-N-acyltransferase -like 2	HGNC:24178	11q12.1
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	HGNC:28959	3p22.3
GPSM2	G-protein signaling modulator 2	HGNC:29501	1p13.3
GSTM1	glutathione S-transferase mu 1	HGNC:4632	1p13.3
GSTM3	glutathione S-transferase mu 3 (brain)	HGNC:4635	1p13.3
GTPBP4	GTP binding protein 4	HGNC:21505	1p34.1
GTSE1	G-2 and S-phase expressed 1	HGNC: 13698	22q13.2-q13.3
HUWE1	HECT, UBA and WWE domain containing 1, E3 ubiquitin protein ligase	HGNC:25444	2q1 7.1
HRASLS	HRAS-like suppressor	HGNC: 14922	3q29
HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4	HGNC:5213	5q2
HSD17B8	hydroxysteroid (17-beta) dehydrogenase 8	HGNC:3554	6p2L3
IGF2R	insulin-like growth factor 2 receptor	HGNC:5471	2q33-q34
IGFBP4	insulin-like growth factor binding protein 4	HGNC: 5473	17q12-q2U
IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)	HGNC:6021	5q11.2
IL8	interleukin 8	HGNC:6025	4q13-q21
IMPA2	inositol(myo)-1(or 4)-monophosphatase 2	HGNC:6051	18p11.2
IRAK1	interleukin-1 receptor-associated kinase 1	HGNC:6112	Xq28
KCNG1	potassium voltage-gated channel, subfamily G, member 1	HGNC:6245	20q13
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	HGNC:6284	10q22
KCTD3	potassium channel tetramerization domain containing 3	HGNC:21305	1q41
KIF13B	kinesin family member 13B	HGNC: 14405	8p21
KIF14	kinesin family member 14	HGNC:19181	1q32
KIF20A	kinesin family member 20A	HGNC: 9787	5q3 1
KIF23	kinesin family member 23	HGNC:6392	15q23
KIF2C	kinesin family member 2C	HGNC:6393	1p34.1
KIF5C	kinesin family member 5C	HGNC:6325	2q23
KR16A	keratin 6A	HGNC:6443	12q13. 13
LAD1	ladinin 1	HGNC:6472	1q21.1-q32.3
LAPTM4B	lysosomal protein transmembrane 4 beta	HGNC: 13646	8q22. 1
LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	HGNC:6560	7p22.3
LMNB2	lamin B2	HGNC:6638	19p13.3
LOC100290690	-	-	-
LRIG1	leucine-rich repeats and immunoglobulin-like domains 1	HGNC: 17360	3p14
LRP8	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	HGNC:6700	1p32.3
LYPD6	LY6/PLAUR domain containing 6	HGNC:28751	2q23.2

MAD2L1	\ tAD2 mitotic an esi deficient-like 1	HGNC:6763	4q27
MAPT	microtubule-associated protein tau	HGNC:6893	17q21
Mi M1«	m m chro no so me ttiamlettattce complex co dp o ne n 10	HGNC:18043	10p13
MCM2	minichromosome maintenance complex component 2	HGNC:6944	3q21
MCM4	minichromosome maintenance complex component 4	HGNC:6947	8q12-q13
MCM6	minichromosome maintenance complex component 6	HGNC:6949	2q14-q21
MCM7	minichromosome maintenance complex component 7	HGNC:6950	7q21.3-q22.1
MEIS3P1	Meis homeobox 3 pseudogene 1	HGNC:7002	17p12
MELK	maternal embryonic leucine zipper kinase	HGNC:16870	9p13.1
MLPH	melanophilin	HGNC:29643	2q37.2
MST1	macrophage stimulating 1 (hepatocyte growth factor-like)	HGNC:7380	3p21
MTHFD1L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	HGNC:21055	6q25.1
MX2	myxovirus (influenza virus) resistance 2 (mouse)	HGNC:7533	21q22.3
MYB	v-myb avian myeloblastosis viral oncogene homolog	HGNC:7545	6q22-q23
NCAPG	non-SMC condensin I complex, subunit G	HGNC:24304	4p15.32
NDC80	NDC80 kinetochore complex component	HGNC:16909	18p11.31
NFIA	nuclear factor I/A	HGNC:7784	1p31.3-p31.2
NME5	NME/NM23 family member 5	HGNC:7853	5q31.2
NOP2	NOP2 nucleolar protein	HGNC:7866	12p13
NOSTRIN	nitric oxide synthase trafficker	HGNC:20203	2q31.1
NUAK1	NUAK family, SNF1-like kinase, 1	HGNC:28870	12q23.3
NRIP1	nuclear receptor interacting protein 1	HGNC:8001	21q11.2
NUP62	nucleoporin 62kDa	HGNC:8058	19q13.33
NUP93	nucleoporin 93kDa	HGNC:28958	16q13
NUSAP1	nucleolar and spindle associated protein 1	HGNC:18538	15q15
OGN	osteoglycin	HGNC:8126	9q22
PDCD4	programmed cell death 4 (neoplastic transformation inhibitor)	HGNC:8763	10q24
PFKP	phosphofructokinase, platelet	HGNC:8878	10p15.3-p15.2
PHYHD1	phytanoyl-CoA dioxygenase domain containing 1	HGNC:23396	9q34.13
PIP	prolactin-induced protein	HGNC:8993	7q32-qter
PLAT	plasminogen activator, tissue	HGNC:9051	8p12-p11.21
PLCH1	phospholipase C, eta 1	HGNC29185	3q25
PNP	purine nucleoside phosphorylase	HGNC:7892	14q11.2
PNPLA7	patatin-like phospholipase domain containing 7	HGNC:24768	9q34.3
PRC1	protein regulator of cytokinesis 1	HGNC:9341	15q26.1
PSMA2	proteasome (prosome, macropain) subunit, beta type, 2	HGNC9539	1p34.2
PTGER3	prostaglandin E receptor 3 (subtype EP3)	HGNC:9595	1p31.2
PTPRT	protein tyrosine phosphatase, receptor type, T	HGNC:9682	20q12-q13

PTTG1	pituitary tumor-transforming 1	HGNC:9690	5q35.1
QDPR	quinoid dihydropteridine reductase	HGNC:9752	4p15.31
RAB27B	RAB27B, member RAS oncogene family	HGNC:9767	18q21.2
RABEP1	rabaptin, RAB GTPase binding effector protein 1	HGNC:17677	17p13.2
RAD51AP1	RAD51 associated protein 1	HGNC:16956	12p13.2-p13.1
RBM38	RNA binding motif protein 38	HGNC:15818	20q13.31
RERG	RAS-like, estrogen-regulated, growth inhibitor	HGNC:15980	12p13.1
RFC4	replication factor C (activator 1) 4, 37kDa	HGNC:9972	3q27
RIPK2	receptor-interacting serine-threonine kinase 2	HGNC:10020	8q21
RNASE4	ribonuclease, RNase A family, 4	HGNC:10047	14q11
RPP40	ribonuclease P/MRP 40kDa subunit	HGNC:20992	6p25.1
RPS23	ribosomal protein S23	HGNC:10410	5q14.2
S100A8	S100 calcium binding protein A8	HGNC:10498	1q12-q22
SCUBE2	signal peptide, CUB domain, EGF-like 2	HGNC:30425	11p15.3
SH3BGRL	SH3 domain binding glutamic acid-rich protein like	HGNC:10823	Xq13.3
SKP1	S-phase kinase-associated protein 1	HGNC:10899	5q31
SKP2	S-phase kinase-associated protein 2, E3 ubiquitin protein ligase	HGNC:10901	5p13
SLC16A10	solute carrier family 16 (aromatic amino acid transporter), member 10	HGNC:17027	6q21-q22
SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	HGNC:11005	1p34.2
SLC39A6	solute carrier family 39 (zinc transporter), member 6	HGNC:18607	18q12.2
SLC40A1	solute carrier family 40 (iron-regulated transporter), member 1	HGNC:10909	2q32
SLC7A5	solute carrier family 7 (amino acid transporter light chain, L system), member 5	HGNC:11063	16q24.3
SOD2	superoxide dismutase 2, mitochondrial	HGNC:11180	6q25
SOX11	SRY (sex determining region Y)-box 11	HGNC:11191	2p25
SRD5A1	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	HGNC:11284	5p15.31
SRPK1	SRSF protein kinase 1	HGNC:11305	6p21.31
STC2	stanniocalcin 2	HGNC:11374	5q35.2
STIL	SCL/TAL1 interrupting locus	HGNC:10879	1p32
STK32B	serine/threonine kinase 32B	HGNC:14217	4p16
SYTL4	synaptotagmin-like 4	HGNC:15588	Xq21.33
TAT	tyrosine aminotransferase	HGNC:11573	16q22.1
TBC1D9	TBC1 domain family, member 9 (with GRAM domain)	HGNC:21710	4q31.1
TEAD4	TEA domain family member 4	HGNC:11717	12p13.3-p13.2
TFF1	trefoil factor 1	HGNC:11755	21q22.3
TFF3	trefoil factor 3 (intestinal)	HGNC:11757	21q22.3
TMEM26	transmembrane protein 26	HGNC:28550	10q21.3
TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	HGNC:1249	20q11.2
TRIP13	thyroid hormone receptor interactor 13	HGNC:12307	5p15
TROAP	trophinin associated protein	HGNC:12327	12q13.12

ττκ	TTK protein kinase	HGNC: 12401	6ql3-q21
TUBA4V	tubulin, alpha 4a	HGNC:12409	2q36.3
UBE2C	ubiquitin-conjugating enzyme E2C	HGNC: 15937	20ql3.12
USB1	U6 snRNA biogenesis 1	HGNC:25693	16q13
\'GLL1	vestigial like Ï (Drosophila)	HGNC:20985	Xq26.3
XBP1	X-box binding protein 1	HGNC:12801	22q12.1
YEATS2	YEATS domain containing 2	HGNC:25489	3q27.3

Table 5: Degregulated genes from Ingenuity Pathway Analysis and correlation with aggressiveness score

			Pearson correlation coefficient with respective nietagene				High vs. Low score
	Symbol	UniqueID	Correlation coefficient	Parametric p-value	FDR	Permutation p-value	Fold-change
ER Metagene	*MAPT*	*ILMN_2310814*	*0.755*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*4.55*
	MYB	*ILMN_1711894*	*0.718*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*3.33*
	BCL2	ILMN_2246956	0.682	< 1e-07	< 1e-07	< 1e-07	-2.86
	STC2	ILMN_1691884	0.65	< 1e-07	< 1e-07	< 1e-07	-4.55
	BTG2	ILMN_1770085	0.544	< 1e-07	< 1e-07	< 1e-07	-2.38
	CLIC6	ILMN_1699665	0.403	< 1e-07	< 1e-07	< 1e-07	-3.45
	ESR1	ILMN_1678535	0.842	< 1e-07	< 1e-07	< 1e-07	-12.99
	FOXA1	ILMN_1766650	0.78	< 1e-07	< 1e-07	< 1e-07	-5.56
	XBP1	ILMN_1809433	0.741	< 1e-07	< 1e-07	< 1e-07	-2.56
	TFF3	ILMN_1811387	0.73	< 1e-07	< 1e-07	< 1e-07	-10.75
	DACH1	ILMN_1755741	0.684	< 1e-07	< 1e-07	< 1e-07	-3.85
	TFF1	ILMN_1722489	0.645	< 1e-07	< 1e-07	< 1e-07	-10.00
	PTPRT	ILMN_1698885	0.637	< 1e-07	< 1e-07	< 1e-07	-2.63
	PLAT	ILMN_1738742	0.557	< 1e-07	< 1e-07	< 1e-07	-2.38
	GSTM3	ILMN_1736184	0.5	< 1e-07	< 1e-07	< 1e-07	-2.00
	RPS23	ILMN_1772459	0.467	< 1e-07	< 1e-07	< 1e-07	-2.00
	GSTM1	ILMN_2391861	0.384	< 1e-07	< 1e-07	< 1e-07	-2.00
	ITPR1	ILMN_1789505	0.546	< 1e-07	< 1e-07	< 1e-07	-1.85
	SKP1	ILMN_1711766	0.689	< 1e-07	< 1e-07	< 1e-07	-1.75
	IGFBP2	ILMN_1725193	0.38	< 1e-07	< 1e-07	< 1e-07	-1.72
	GLI3	ILMN_1771962	0.486	< 1e-07	< 1e-07	< 1e-07	-1.61
	AHNAK	ILMN_1714567	0.551	< 1e-07	< 1e-07	< 1e-07	-1.59
	NRIP1	ILMN_1718629	0.548	< 1e-07	< 1e-07	< 1e-07	-1.59
	TAT	ILMN_1791678	0.304	< 1e-07	< 1e-07	< 1e-07	-1.56
	PDCD4	ILMN_1768004	0.44	< 1e-07	< 1e-07	< 1e-07	-1.54
CIN Metagene	*MELK*	*ILMN_1731184*	*0.9*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.29*
	MCM10	*ILMN_2413898*	*0.868*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.22*
	CENPA	*ILMN_1801257*	*0.909*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.2*
	EXO1	*ILMN_1673721*	*0.885*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.15*
	TTK	*ILMN_1788166*	*0.837*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.15*
	KIF2C	*ILMN_1685916*	*0.888*	*< 1e-07*	*< 1e-07*	*< 1e-07*	*2.13*
	CENPN	ILMN_1720526	0.814	< 1e-07	< 1e-07	< 1e-07	2.04
	CEP55	ILMN_1747016	0.891	< 1e-07	< 1e-07	< 1e-07	2.03
	FOXM1	ILMN_2344971	0.869	< 1e-07	< 1e-07	< 1e-07	2.01
	TPX2	ILMN_1796949	0.88	< 1e-07	< 1e-07	< 1e-07	2.01
	AURKB	ILMN_1684217	0.884	< 1e-07	< 1e-07	< 1e-07	2.25
	AURKA	ILMN_1680955	0.854	< 1e-07	< 1e-07	< 1e-07	2.09

	CCNE1	ILMN_2374425	0.813	< 1e-07	< 1e-07	< 1e-07	2.64
	CDC45	ILMN_1670238	0.861	< 1e-07	< 1e-07	< 1e-07	2.22
	PTTG1	ILMN_2042771	0.846	< 1e-07	< 1e-07	< 1e-07	2.15
	BIRC5	ILMN_2349459	0.822	< 1e-07	< 1e-07	< 1e-07	2.28
	CCNB2	ILMN_1801939	0.89	< 1e-07	< 1e-07	< 1e-07	2.39
	CDCA5	ILMN_1683450	0.89	< 1e-07	< 1e-07	< 1e-07	2.49
	CDC20	ILMN_1663390	0.873	< 1e-07	< 1e-07	< 1e-07	3.22
	UBE2C	ILMN_2301083	0.861	< 1e-07	< 1e-07	< 1e-07	2.75
	SLC7A5	ILMN_1720373	0.749	< 1e-07	< 1e-07	< 1e-07	3.75
	BUB1	ILMN_2202948	0.896	< 1e-07	< 1e-07	< 1e-07	1.97
	CDCA8	ILMN_1709294	0.87	< 1e-07	< 1e-07	< 1e-07	1.96
	PRC1	ILMN_1728934	0.817	< 1e-07	< 1e-07	< 1e-07	1.96
	CCNA2	ILMN_1786125	0.888	< 1e-07	< 1e-07	< 1e-07	1.95
	CDCA3	ILMN_1737728	0.859	< 1e-07	< 1e-07	< 1e-07	1.95
	HJURP	ILMN_1703906	0.861	< 1e-07	< 1e-07	< 1e-07	1.9
	KIF20A	ILMN_1695658	0.844	< 1e-07	< 1e-07	< 1e-07	1.9
	NCAPG	ILMN_1751444	0.848	< 1e-07	< 1e-07	< 1e-07	1.89
	CHEK1	ILMN_1664630	0.853	< 1e-07	< 1e-07	< 1e-07	1.85
	SKP2	ILMN_1665538	0.709	< 1e-07	< 1e-07	< 1e-07	1.83
	MCM4	ILMN_1737205	0.75	< 1e-07	< 1e-07	< 1e-07	1.79
	CDK1	ILMN_1747911	0.776	< 1e-07	< 1e-07	< 1e-07	1.75
	LMNB2	ILMN_1708101	0.799	< 1e-07	< 1e-07	< 1e-07	1.74
	RAD51AP1	ILMN_1670353	0.818	< 1e-07	< 1e-07	< 1e-07	1.74
	TROAP	ILMN_1700337	0.784	< 1e-07	< 1e-07	< 1e-07	1.73
	DLGAP5	ILMN_1749829	0.86	< 1e-07	< 1e-07	< 1e-07	1.7
	MAD2L1	ILMN_1777564	0.709	< 1e-07	< 1e-07	< 1e-07	1.7
	GTSE1	ILMN_1771039	0.858	< 1e-07	< 1e-07	< 1e-07	1.69
	CENPE	ILMN_1716279	0.858	< 1e-07	< 1e-07	< 1e-07	1.67
	MCM2	ILMN_1681503	0.764	< 1e-07	< 1e-07	< 1e-07	1.66
	MCM6	ILMN_1798654	0.792	< 1e-07	< 1e-07	< 1e-07	1.6
	BLM	ILMN_1709484	0.792	< 1e-07	< 1e-07	< 1e-07	1.57
	KIF14	ILMN_1808071	0.808	< 1e-07	< 1e-07	< 1e-07	1.55
	KIF23	ILMN_1811472	0.824	< 1e-07	< 1e-07	< 1e-07	1.55
	BYSL	ILMN_1682792	0.741	< 1e-07	< 1e-07	< 1e-07	1.52
	CDC25A	ILMN_1711005	0.773	< 1e-07	< 1e-07	< 1e-07	1.52
	GTPBP4	ILMN_1742577	0.755	< 1e-07	< 1e-07	< 1e-07	1.67
	SRPK1	ILMN_1798804	0.763	< 1e-07	< 1e-07	< 1e-07	1.62
	CKS2	ILMN_1756326	0.717	< 1e-07	< 1e-07	< 1e-07	1.6
	NDC80	ILMN_1664511	0.765	< 1e-07	< 1e-07	< 1e-07	1.46
	RFC4	ILMN_1724489	0.759	< 1e-07	< 1e-07	< 1e-07	1.45
	MCM7	ILMN_1663195	0.704	< 1e-07	< 1e-07	< 1e-07	1.64
	S100A8	ILMN_1729801	0.517	< 1e-07	< 1e-07	< 1e-07	8.16
	KRT6A	ILMN_2219002	0.474	< 1e-07	< 1e-07	< 1e-07	3.27

	PFKP	ILMN_1805737	0.595	< 1e-07	< 1e-07	< 1e-07	2.87
	SOD2	ILMN_2336781	0.565	< 1e-07	< 1e-07	< 1e-07	2.69
	IL8	ILMN_2184373	0.357	< 1e-07	< 1e-07	< 1e-07	2.27
	CDC25B	ILMN_2338323	0.594	< 1e-07	< 1e-07	< 1e-07	2.01
	CKS1B	ILMN_2041046	0.691	< 1e-07	< 1e-07	< 1e-07	1.75
	GAPDH	ILMN_1802252	0.685	< 1e-07	< 1e-07	< 1e-07	1.61
	SLC16A10	ILMN_1782938	0.45	< 1e-07	< 1e-07	< 1e-07	1.45
	VGLL1	ILMN_1719753	0.524	< 1e-07	< 1e-07	< 1e-07	3.16
	CDKN2A	ILMN_1717714	0.591	< 1e-07	< 1e-07	< 1e-07	1.91
	RIPK2	ILMN_1758939	0.674	< 1e-07	< 1e-07	< 1e-07	1.7
	TUBA4A	ILMN_1784300	0.399	< 1e-07	< 1e-07	< 1e-07	1.66
	PSMB2	ILMN_1764794	0.633	< 1e-07	< 1e-07	< 1e-07	1.52
	NOP2	ILMN_1723158	0.617	< 1e-07	< 1e-07	< 1e-07	1.52
	IRAK1	ILMN_2379130	0.625	< 1e-07	< 1e-07	< 1e-07	1.51
	DKC1	ILMN_1671257	0.692	< 1e-07	< 1e-07	< 1e-07	1.5
	DAPK1	ILMN_1708340	0.432	< 1e-07	< 1e-07	< 1e-07	1.43
	TEAD4	ILMN_1705301	0.554	< 1e-07	< 1e-07	< 1e-07	1.42

Cox proportional hazards model, Wald Statistic p-value cutoff univariate test: 0.001 10000 random permutations,

Cell survival after siRNA depletion in vitro

Parametric p-value	FDR	Permutation p-value	Hazard Ratio	SD of log intensities	MDA-MB-231	Sum159PT	Hs578T
5.00E-07	*1.47E-06*	*< 1e-07*	*-1.112347052*	*1.567*			
0.0008816	*1.28E-03*	*8.00E-04*	*-1.091703057*	*1.258*			
< 1e-07	< 1e-07	< 1e-07	-1.209189843	1.043			
2.86E-05	5.55E-05	< 1e-07	-1.074113856	1.938			
2.45E-05	4.95E-05	< 1e-07	-1.154734411	1.03			
< 1e-07	< 1e-07	< 1e-07	-1.111111111	2.214			

< 1e-07	< 1e-07	< 1e-07	-1.207729469	1.076			
6.00E-07	1.62E-06	< 1e-07	-1.133786848	1.358			
2.43E-05	4.95E-05	< 1e-07	-1.204819277	0.736			
5.66E-05	9.98E-05	< 1e-07	-1.096491228	1.625			
5.50E-06	1.21E-05	< 1e-07	-1.242236025	0.723			
< 1e-07	*< 1e-07*	*< 1e-07*	*1.274*	*0.799*	91 ± 3% (n=3)	46 ± 4 (n=5)	92 ± 3 (n=3)
7.00E-07	*1.84E-06*	*< 1e-07*	*1.221*	*0.791*	98 ± 6% (n=3)	68 ± 8 (n=6)	83 ± 2 (n=3)
1.00E-07	*3.46E-07*	*< 1e-07*	*1.253*	*0.762*	155 ± 17% (n=3)	100 ± 1 (n=3)	52 ± 2 (n=3)
< 1e-07	*< 1e-07*	*< 1e-07*	*1.267*	*0.767*			
4.00E-07	*1.25E-06*	*< 1e-07*	*1.222*	*0.799*	51 ± 1% (n=3)	34 ± 6 (n=6)	19 ± 1 (n=3)
< 1e-07	*< 1e-07*	*< 1e-07*	*1.271*	*0.756*			
5.00E-06	1.13E-05	< 1e-07	1.204	0.779			
1.00E-07	3.46E-07	< 1e-07	1.26	0.75	87 ± 4% (n=3)	37 ± 1 (n=6)	57 ± 1 (n=3)
1.00E-07	3.46E-07	< 1e-07	1.247	0.744	66 ± 1% (n=3)	72 ± 2 (n=5)	62 ± 2 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.326	0.782	57 ± 7% (n=3)	64 ± 1 (n=3)	24 ± 3 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.256	0.836			
< 1e-07	< 1e-07	< 1e-07	1.273	0.873			
3.30E-06	7.81E-06	< 1e-07	1.182	0.878			
< 1e-07	< 1e-07	< 1e-07	1.246	0.882			
< 1e-07	< 1e-07	< 1e-07	1.259	0.958			
5.00E-07	1.47E-06	< 1e-07	1.184	0.965	100 ± 26% (n=3)	79 ± 3 (n=6)	100 ± 1 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.232	0.966			
< 1e-07	< 1e-07	< 1e-07	1.271	0.998			
< 1e-07	< 1e-07	< 1e-07	1.184	1.194	98 ± 5% (n=3)	101 ± 1 (n=6)	110 ± 1 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.208	1.239			
3.29E-05	6.06E-05	< 1e-07	1.109	1.299			
< 1e-07	< 1e-07	< 1e-07	1.279	0.726	91 ± 4%	76 ± 2	83 ± 3

					(n=3)	(n=6)	(n=3)
2.00E-07	6.69E-07	< 1e-07	1.267	0.692			
< 1e-07	< 1e-07	< 1e-07	1.269	0.893			
< 1e-07	< 1e-07	< 1e-07	1.3	0.709			
4.00E-07	1.25E-06	< 1e-07	1.232	0.765			
< 1e-07	< 1e-07	< 1e-07	1.301	0.693			
< 1e-07	< 1e-07	< 1e-07	1.322	0.806			
< 1e-07	< 1e-07	< 1e-07	1.271	0.784			
0.0001213	1.96E-04	2.00E-04	1.23	0.603			
0.0008164	1.20E-03	6.00E-04	1.191	0.612	76 ± 3% (n=3)	45 ± 6 (n=6)	63 ± 3 (n=3)
6.00E-07	1.62E-06	< 1e-07	1.24	0.764			
9.00E-07	2.18E-06	< 1e-07	1.214	0.84			
1.08E-05	2.28E-05	< 1e-07	1.284	0.583			
6.12E-05	1.06E-04	< 1e-07	1.194	0.728	83 ± 4% (n=3)	65 ± 4 (n=6)	91 ± 2 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.378	0.717	86 ± 7% (n=3)	55 ± 7 (n=6)	68 ± 10 (n=3)
8.00E-07	2.04E-06	< 1e-07	1.311	0.595	106 ± 3% (n=3)	62 ± 5 (n=6)	54 ± 1 (n=3)
4.80E-06	1.11E-05	< 1e-07	1.188	0.884			
< 1e-07	< 1e-07	< 1e-07	1.464	0.52			
< 1e-07	< 1e-07	< 1e-07	1.374	0.601			
9.00E-07	2.18E-06	< 1e-07	1.264	0.704			
0.0007066	1.07E-03	3.00E-04	1.205	0.587			
9.41E-05	1.57E-04	1.00E-04	1.282	0.491			
6.00E-07	1.62E-06	< 1e-07	1.36	0.51			
< 1e-07	< 1e-07	< 1e-07	1.381	0.577			
8.50E-06	1.83E-05	< 1e-07	1.363	0.466			
7.55E-05	1.28E-04	1.00E-04	1.297	0.472			
					56 ± 4% (n=3)	65 ± 1 (n=3)	28 ± 2 (n=3)
					119 ± 6% (n=3)	90 ± 1 (n=3)	39 ± 5 (n=3)
2.59E-05	5.13E-05	< 1e-07	1.063	2.187			
5.27E-05	9.47E-05	< 1e-07	1.098	1.328			
0.000120	1.96E-	< 1e-07	1.133	1.029			

5	04							
0.0002994	4.76E-04	1.00E-04	1.123	0.999				
0.0003927	6.05E-04	2.00E-04	1.101	1.239				
3.25E-05	6.06E-05	< 1e-07	1.174	0.818				
0.0007626	1.14E-03	5.00E-04	1.153	0.768		105 ± 7% (n=3)	94 ± 1 (n=3)	84 ± 4 (n=3)
0.0003141	4.91E-04	1.00E-04	1.196	0.66				
3.31E-05	6.06E-05	< 1e-07	1.278	0.548				
				CENPF		88 ± 4% (n=3)	86 ± 3 (n=6)	70 ± 3 (n=3)
				MYBL1		73 ± 5% (n=3)	83 ± 1 (n=3)	47 ± 4 (n=3)
				GPSM2		87 ± 4% (n=3)	80 ± 4 (n=5)	60 ± 6 (n=3)
				ANP32E		95 ± 2% (n=3)	79 ± 8 (n=6)	94 ± 4 (n=3)
				TOP2A		122 ± 8% (n=3)	73 ± 1 (n=3)	69 ± 5 (n=3)
				TYMS		75 ± 8% (n=3)	71 ± 2 (n=5)	68 ± 4 (n=3)
				PBK		59 ± 2% (n=3)	55 ± 7 (n=6)	46 ± 1 (n=3)
				ASPM		94 ± 6% (n=3)	37 ± 1 (n=6)	65 ± 2 (n=3)

Table 6: Association of the 6 overexpressed genes in the 8-genes score with RFS and DMFS at 5 and 10 years

Patient subgroup and cut-off		RFS			
		5 years		10 years	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value
All	Median	2.52 (2.17 - 2.93)	<1.00E-16	2.16 (1.90 - 2.47)	<1.00E-16
	Quartile	3.03 (2.48 - 3.70)	<1.00E-16	2.48 (2.09 - 2.89)	<1.00E-16
	Tertile	2.83 (2.35 - 3.41)	<1.00E-16	2.70 (2.24 - 3.27)	<1.00E-16
ER+	Median	2.67 (2.25 - 3.17)	<1.00E-16	2.28 (1.96 - 2.65)	<1.00E-16
	Quartile	2.90 (2.29 - 3.67)	<1.00E-16	2.54 (2.18 - 3.23)	<1.00E-16
	Tertile	2.87 (2.34 - 3.53)	<1.00E-16	2.51 (2.11 - 2.99)	<1.00E-16
LN-	Median	2.78 (2.19 - 3.48)	<1.00E-16	2.25 (1.84 - 2.74)	2.20E-16
	Quartile	2.76 (2.00 - 3.80)	1.10E-10	2.51 (1.91 - 3.29)	5.10E-12
	Tertile	2.93 (2.21 - 3.87)	4.30E-15	2.53 (2.00 - 3.19)	1.00E-15
LN+	Median	2.20 (1.57 - 3.08)	2.40E-06	1.88 (1.40 - 2.52)	1.90E-05
	Quartile	3.19 (1.87 - 5.44)	6.60E-06	2.56 (1.67 - 3.94)	8.10E-06
	Tertile	2.45 (1.61 - 3.37)	1.70E-05	2.05 (1.45 - 2.91)	4.00E-05

Patient subgroup and cut-off		DMFS			
		5 years		10 years	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value
All	Median	2.87 (2.17 - 3.79)	8.90E-15	2.37 (1.87 - 3.01)	1.90E-13
	Quartile	3.64 (2.41 - 5.52)	5.80E-11	3.43 (2.41 - 4.88)	3.30E-12
	Tertile	3.53 (2.48 - 5.04)	8.70E-14	2.93 (2.18 - 3.90)	3.70E-14
ER+	Median	3.45 (2.49 - 4.74)	1.30E-13	2.63 (2.00 - 3.45)	4.20E-13
	Quartile	3.41 (2.21 - 5.27)	8.80E-09	3.27 (2.26 - 4.71)	2.20E-11
	Tertile	3.87 (2.62 - 5.74)	8.10E-13	3.07 (2.24 - 4.20)	2.30E-13
LN-	Median	4.84 (2.53 - 9.26)	1.40E-07	2.80 (2.00 - 3.93)	4.20E-10
	Quartile	4.86 (2.02 - 9.37)	2.70E-10	4.46 (2.61 - 7.60)	1.80E-09
	Tertile	3.98 (2.61 - 6.07)	4.20E-12	3.76 (2.46 - 5.74)	4.50E-11
LN+	Median	2.12 (1.59 - 3.80)	9.40E-03	2.18 (1.28 - 3.62)	3.00E-03
	Quartile	2.87 (1.18 - 7.44)	1.50E-02	2.87 (1.31 - 6.29)	6.00E-03
	Tertile	3.51 (1.50 - 8.21)	2.00E-03	2.88 (1.47 - 5.65)	1.40E-03

p-values are from Log rank test from KM-plotter

Table 7: Association of the 2 overexpressed genes in the 8-genes score with RFS and DMFS at 5 and 10 years

Patient subgroup and cut-off		RFS			
		5 years		10 years	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value
All	Median	0.53 (0.46 – 0.61)	<1.00E-16	0.59 (0.52 – 0.67)	5.60E-16
	Quartile	0.53 (0.35 – 0.81)	<1.00E-16	0.59 (0.52 – 0.68)	8.20E-14
	Tertile	0.49 (0.43 – 0.57)	<1.00E-16	0.57 (0.50 – 0.65)	<1.00E-16
ER+	Median	0.60 (0.51 – 0.71)	2.10E-09	0.65 (0.56 – 0.76)	2.60E-08
	Quartile	0.62 (0.48 – 0.79)	1.30E-04	0.69 (0.54 – 0.86)	1.30E-03
	Tertile	0.54 (0.45 – 0.66)	6.00E-10	0.63 (0.52 – 0.76)	5.60E-07
LN-	Median	0.61 (0.49 – 0.76)	9.00E-06	0.71 (0.58 – 0.86)	4.20E-04
	Quartile	0.56 (0.44 – 0.72)	3.50E-06	0.63 (0.50 – 0.79)	6.00E-05
	Tertile	0.53 (0.42 – 0.66)	2.30E-08	0.62 (0.50 – 0.76)	4.60E-06
LN+	Median	0.58 (0.42 – 0.80)	9.70E-04	0.70 (0.52 – 0.93)	1.30E-02
	Quartile	0.59 (0.43 – 0.84)	3.00E-03	0.70 (0.53 – 0.98)	3.50E-02
	Tertile	0.57 (0.41 – 0.78)	4.00E-04	0.68 (0.50 – 0.93)	9.70E-03

Patient subgroup and cut-off		DMFS			
		5 years		10 years	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value
All	Median	0.59 (0.47 – 0.74)	2.50E-06	0.59 (0.47 – 0.74)	2.50E-06
	Quartile	0.58 (0.46 – 0.74)	4.40E-06	0.58 (0.46 – 0.74)	4.40E-06
	Tertile	0.57 (0.46 – 0.71)	4.90E-07	0.57 (0.46 – 0.71)	4.90E-07
ER+	Median	0.62 (0.48 – 0.81)	3.00E-04	0.62 (0.48 – 0.81)	3.00E-04
	Quartile	0.56 (0.39 – 0.82)	2.40E-03	0.56 (0.39 – 0.82)	2.40E-03
	Tertile	0.57 (0.42 ~0.78)	3.m -04	0.57 (0.42 ~0.78)	3.00E-04
LN-	Median	0 ¾ – 1.00) ~	4.60E-02	¾ 54 – 1.00)	4.60E &
	Quartile	0.64 (0.46 – 0.89)	7.00E-03	0.64 (0.46 – 0.89)	7.00E-03
	Tertile	0.60 (0.44 – 0.81)	1.00E-03	0.60 (0.44 – 0.81)	1.00E-03
LN+	Median	0.58 (0.35 – 0.96)	3.20E-02	0.58 (0.35 – 0.96)	3.20E-02
	Quartile	0.49 (0.29 – 0.83)	6.90E-03	0.49 (0.29 – 0.83)	6.90E-03
	Tertile	0.56 (0.34 – 0.92)	2.10E-02	0.56 (0.34 – 0.92)	2.10E-02

p-values are from Log rank test from KM-plotter

Table 8: details of antibodies and iininunohistochemistry conditions used for breast cancer TMA analysis in this study

Antibody	Clone	Species	Source	Dilution	Antigen Retrieval*	Cellular Localization	Cut-off used for classification as 'positive'
ER	6F11	Mouse	Novocastra	1:100	Citrate	Nucleus	> 1%
PR	1A6	Mouse	Novocastra	1:200	Citrate	Nucleus	> 1%
HER2	CB11	Rabbit	Dako	1:200	Citrate	Cell Membrane	3+ (>30%)
CK5/6	D5/16 B4	Mouse	Chemicon	1:400	Citrate	Membrane + Cytoplasm	Any positivity
CK14	LL002	Mouse	Novocastra	1:40	Citrate	Membrane + Cytoplasm	Any positivity
EGFR	31G7	Mouse	Invitrogen	1:100	EDTA	Cell Membrane	Any positivity
Ki-67	MIB-1	Mouse	Dako	1:200	Citrate	Nucleus	Any positivity (20% cells stained classed as 'Ki67-high')
TTK	N1	Mouse	Abcam	1:100	EDTA	Cytoplasm	0 Negative 1 weak and focal staining 2 moderate-strong focal staining (collectively <50% tumor cells) 3 moderate-strong diffuse staining (>50% tumor cells) *Regarding estimating % of cells stained, we disregarded mitotic cells to assess mitosis-independent expression of TTK*

*Antigen retrieval in O.OIM citric acid buffer (pH 6.0) at 125 °C for 5 min in a pressure cooker, or in 0,001 M Tris/EDTA; pH 8.8, at 105°C for 15 min in a pressure cooker.

Table 9: Multivariate analyses

Covariants	P value	Hazard Ratio	Covariants	P value	Hazard Ratio	Covariants	P value	Hazard Ratio
Grade	0.7045	1.04 (0.86 - 1.25)	Stage	0	1.46 (1.26 - 1.68)	AJCC stage T	0.0002	1.35 (1.16 - 1.58)
10CIN 2ER signature	0.0002	1.59 (1.25 - 2.04)	10CIN 2ER signature	0	2.2 (1.73 - 2.79)	AJCC stage N	0	1.73 (1.5 - 1.99)
						10CIN 2ER signature	0.0075	1.35 (1.08 - 1.69)

EXAMPLE 2

Materials and Methods

Meta-analysis of global gene expression in TNBC

We performed a meta-analysis of global gene expression data in the Oncomine™ database [37] (Compendia Bioscience, Ann Arbor, MI) using a primary filter for breast cancer (130 datasets), sample filter to use clinical specimens and dataset filters to use mRNA datasets with more 151 patients (22 datasets). Two additional filters were applied to perform two independent differential analyses. The first differential was metastatic event analysis at 5 years (metastatic events vs. no metastatic events, 7 datasets [51, 56-61]) and the second differential analysis was survival at 5 years (patients who died vs. patients who survived, 7 datasets [39, 57, 59, 61-64]). Deregulated genes were selected based on the median **p-value** of the median gene rank in overexpression or underexpression patterns across **the** datasets for each of the two differential analyses.

Deriving the 28-signattire (the TN signature)

The online tool KM-Plotter [38] which collates gene expression data from Affymterix platform for more than 4000 breast cancer patients were used for developing the 28-gene signature. From the deregulated genes in **primary** tumors which led to metastatic or death events within 5 years discovered in the meta-analysis in Oncomine™, 166 genes were common in both survival events. These genes were then interrogated one by one in KM-Plotter restricting the univariate **survival** analysis to ER- or **BLBC** subtypes. Genes which significantly associated with relapse-free survival (RFS), distant metastasis-free **survival** (DMFS) or overall survival (OS) in either ER- or BLBC **subtypes** were short selected. The 96 genes that were significant in this filtering where then sorted for their level of significance as well as the prevalence of significance across the different survival outcomes (RES, DMFS and OS) and across ER- and BLBC subtypes. Based on this sorting, six groups of gene lists were obtained with different levels of survival association (Table 14). Each of these groups were then used as a metagene and the average expression of genes in each group was investigated for association with survival in KM-Plotter in ER- and BLBC subtypes. Based on these analysis, four groups were selected and two were excluded. **Furthermore,** for two groups, the top 4 and 3 genes were found to be more prognostic than the rest of the group and these were selected. In total, the 7

genes (which their downregulation associates with poor survival) from these two groups and 21 genes (which their upregulation associates with poor survival) in the other two groups were selected to test for association with survival in KM÷Plotter. These 28 genes showed the highest association with survival as a gene signature compared to any single gene in the original list or any groups from this list. These 28 genes were selected as the triple negative (TN) signature and was subjected to validation as described below.

Validation of the TN signature in breast cancer cohorts

Three large breast caneer gene expression datasets were used for validation. The Research Online Cancer Knowledgebase (ROCK) dataset [40] (GSE47561; n~1570 patients) and the homogenous TNBC dataset [32] (GSE31519; n=579 TNBC patients) were obtained from Gene Expression Omnibus (GEO) and the data was imported into BRB~ArrayToo]s [65] (V4.2, **Biometrics** Research Branch, NCI, **Maryland,** USA) with built in R Bioconductor packages. The Cancer Genome Atlas (TCGA) dataset [39]; using the Illumina HiSeq RNA-Seq arrays **(n=1.106** patients) **or the** Agilent custom arrays (Agilent G4502A-07-3) on 597 patients of the 1106 total patients, were obtained from the UCSC Genome Browser [66, 67]. The TN signature was investigated in each of these datasets where a score was devised to quantify the signature; the TN score = average expression of the 21 genes whose overexpression associated with poor survival ÷ average expression of the 7 genes whose underexpression associated with poor survival. The TN score **for** each tumor in each dataset was calculated and tumors were assigned as high or low TN score tumors by dichotomy across the median TN score in each dataset. In some cases, tertiles of the TN score in each dataset. were used to classify tumors as high, **intermediate** or low TN score tumors and in other cases the quartiles of the TN score were used to classify tumors in the 1st, 2nd, **3rd** or 4th **quartiles,** The survival of patients **in** high (over the median, last tertile of the 4th quartile) vs. low TN score groups was compared. Survival analyses were constructed using GraphPad* Prism v6.0 (GraphPad Software, CA, USA) and the Log-rank (Mantel-Cox) Test was used for statistical comparisons of survival curves.

Association of the TN score and signatures with pathological complete responses (pCK) after neoadjuvant chemotherapy and response to endocrine therapy

Datasets which performed gene expression profiling prior to neoadjuvant chemotherapy or endocrine therapy alone were obtained from GEO. The datasets

used in this study for neoadjuvant **chemotherapy** and recorded pathological complete response **(pCR)** include: GSE18728 **[42],** GSE50948 [43], GSE20271 **[44],** GSE20194 [45], GSB22226 [41, 46], GSE42822 [47] and GSE23988 [48]. For datasets which **performed** gene expression profiling prior to endocrine therapy **(tamoxifen)** and recorded patient survival include: GSE6532 [25] and GSE 17705 [51]. These datasets using the Affymeuix gene expression array platforms were imported into BRB-ArrayTools and normalized as described previously [68]. Each tumor in the datasets were assigned as high or low score for our signatures as described **in** the previous sections. The rate of pCR after chemotherapy or the survival of patients after endocrine therapy were compared between high score tumors and low score tumors using GraphPad ® Prism.

Global gene expression profiles comparison by class comparison

Global gene expression comparison was carried out to compare tumors with high TN or **iBCR** scores to those with low TN or iBCR scores to characterize additional differences between these tumors and identify deregulated genes which could be suitable as for drug targeting. These comparisons were carried out in the large cohort of 1570 patients in the ROCK **data-set** and **BRB-ArrayTools** was used to perform the Class Comparison test. The two classes were high vs. low score tumors and the parameters selected in this plugin in ArrayTools were as follows: Type of univariate test used = Two-sample T-test; Class variable = TN score (high **or** low) or iBCR score (high or low); fold-change cutoff = 1.5 fold; Permutation p-values for significant genes were **computed** based on 10000 random permutations and Nominal significance level of each univariate test: 0.05. The results from these analyses are shown in Tables 13 and 15-17.

Integration of the Agro and TN signatures in the integrated Breast Cancer Recurrence (iBCR) score

We previously published the Aggressiveness (Agro) signature and score also from meta-analysis and extensive validation and show that this signature is prognostic in ER+ breast cancer [36]. To test whether the Agro signatures could be integrated with the TN signature (prognostic in ER- breast cancer) to produce an integrated test that is independent of ER status, several integration methods **were** investigated. The hypothesis behind the integration methods was to identify a direct relationship that can describe the relationship between the TN and Agro scores in both **ER-** and ER+ breast cancer subtypes that is also in direct relationship with the integrated score. In

other words, the integrated score would retain the information from each the **Agro** and TN scores relevant to their prognostic value in ER^+ and ER^- breast cancers, respectively, The ROCK dataset was used to test the different methods of integration and the performance of these methods in the stratification of survival of ER* and ER^- breast cancer. The addition or subtraction of the scores produced a direct relationship between the **TN** and Agro score and the produced integrated score (Figure 36). These two methods were then analyzed for prognostication of ER* and **ER^-** subtypes in the ROCK dataset and only the addition method retained prognostication in **ER^-** breast cancer (Figure 37). **Similarly,** multiplying and dividing the **TN** and Agro scores were tested and an exponential and power curve relationships described the relation between the two scores and with the integrated score (Figure 38). Again, these two methods were tested from prognostication in the ROCK dataset and only the multiplication method retained prognostication in ER^- breast cancer (Figure 37). Because the multiplication and division methods produced exponential and power curves for the relationship between the scores, integration by raising one score to the power **of** the other score appeared reasonable. Exponential and power curves are the result of power equations. Indeed, integration by raising the TN score to the power of the Agro score was highly prognostic in both **ER*** and **ER^-** breast cancers (Figures 37 and 38). This integrated score, the integrated Breast Cancer Recurrence (iBCR) score was in fact more prognostic in **ER*** and **ER^-** patients in the ROCK dataset than the single Agro and TN scores, respectively. The iBCR score was validated in the ROCK and homogenous TNBC datasets (Affymetrix platform), the **TOGA** dataset (Illumina RNA-Seq platform) and the ISPY-I trial dataset (GSE22226 **[41,** 46], Agilent platform), illustrating the platform-independence of the iBCR score which is driven by the platform independence of tire Agro and TN signatures as they were discovered from meta-analysis irrespective of array platforms used from independent studies,

Mining drug screen studies

Two large studies which treated large panels of cancer cell lines with large panels of anticancer drugs were investigated **to** determine whether cell lines with high Agro, TN or iBCR scores show different sensitivity to particular anticancer drugs in comparison to cancer cell lines with low Agro, TN or iBCR scores. Briefly, the datasets of gene expression profiling from Genentech (niRNA Cancer Cell Line Profiles **GSE10843),** Pfizer (Pfizer Molecular Profile Data for Cell Line GSE34211) and Broad Institute/Novartis (Cancer Cell Line Encyclopedia [COLE] GSE3613)

were obtained from GEO and imported into ArrayTools as described earlier. The Agro, TN and iBCR scores for all the cell lines profiled were calculated and cell lines were assigned as high or low for each of the scores based on dichotomy across the median in each dataset. For cell lines which were profiled **in** more than one dataset, the average scores were used. Using this data, the sensitivity of cancer cell lines with high and low Agro, TN or iBCR scores was compared to those with low scores to anticancer drugs was investigated in two studies [49, 50]. Drugs which had significantly different IC50 in high score cell lines compared to low score cell lines are described herein. Statistical significance was detennined from unpaired two-tailed t-test using GraphPad® Prism.

Other statistical analysis

Univariate and multivariate Cox proportional hazards regression analyses were performed using MedCalc for Windows, version 12.7 (MedCalc Software, Qstend, Belgium),

Results

Meta-analysis of gene expression profile in Oneomim™

We **performed** a meta-analysis of published gene expression data, irrespective of **platform** or breast cancer subtype, using the Oncomine™ database [37] (version 4,5). We were able to compared the expression profiles of primary breast tumors from 512 patients who developed metastases vs. 732 patients who did not develop metastases at 5 years (7 datasets in total) to identify 500 overexpressed genes and 500 underexpressed genes in the metastasis cases (cutoff median p-value across the datasets < **0.05 from** a **Student's** /-test. Figure 31). We also compared the expression profiles of 232 primary breast tumors from patients who died **within** 5 years vs. 879 patients who survived in 7 datasets and found 500 overexpressed genes and 500 underexpressed genes in the poor survivors (cutoff median **p-value** across the datasets < 0.05 from a Student's /-test, Figure 31). Since several datasets were annotated for one of these outcomes but not both, we rationalized that the union of **these** analyses is more appropriate particularly that death is the most likely outcome in metastatic **disease.** The union of the over- and expressed genes in tumors that associated with metastasis and those that associated with death **within 5** years revealed common 101 overexpressed and 65 underexpressed genes (Figure 19). These 166 deregulated genes were then subjected to training using the online tool

KM-plotter [38] to derive a 28 gene signature as described in methods below followed by validation of this signature, the TN signature, in several large cohorts of breast cancer gene expression datasets (Figure 19).

***The** TN signature is prognostic in **TNBC,** BLBC **and** ESC breast cancer subtypes*

The 166 deregulated genes in primary breast tumors that associated with poor outcome discovered from the Oncomine™ meta-analysis were interrogated using KM-Plotter. The overexpression of 31 genes and the underexpression of 65 genes associated with RFS, DMFS or OS of BLBC or ER- breast cancer (Table 14). Based on the level of significance in univariate survival analysis and the prevalence of this significance across the different disease outcomes (RES, DMFS and OS), a list of 21 overexpressed and 7 underexpressed genes (Table 1) were shortlisted as a signature with the strongest association with survival in both BLBC and ER- breast cancer subtypes (Figure 20).

The 28-gene signature, the TN signature, was then validated in multivariate survival analysis in two breast cancer cohorts, the homogenous TNBC dataset [32] and the Research Online Cancer Knowledgebase (ROCK) dataset [40]. We devised a score to quantify trends in the TN signature, the TN score, which is calculated as the ratio of the average expression of the 21 overexpressed genes to that of the 7 underexpressed genes. Dichotomy across the median TN score stratified the survival of TNBC (Figure 21A), BLBC (Figure 21B) and ER- (Figure 21C) patients and outperformed all standard clinicopafJioiogical indicators. These analyses indicated that the TN score is an independent prognostic factor that identified TNBC, BLBC or ER- patients with poor survival irrespective to tumor size and grade, patient age, lymph node status or treatment. The TN signature also **outperformed** all previously published signatures that are prognostic in ER-, TNBC or BLBC subtypes [30-35] (Figure 32),

While the discovery of the signature in Oncomine™ included datasets using the Affymterix, Alumina and Agilent platforms, the training and validation above was limited **to** the Affymterix platform. Thus, we validated the TN score in The Cancer Genome Atlas (TCGA) dataset [39] which used the Alumina HiSeq RNA-seq platform. As shown in Figure 22, the RFS of ER- patients in the TCGA dataset was stratified by TN score and this stratification **outperformed** that by standard clinicopathological indicators. The original TCGA publication used Agilent custom arrays (Agilent G4502A-07-3) on 597 patients and we analyzed the prognosis of the

TN score in this data. The **TN** score stratified the survival of **ER**- patients in the Agilent TCGA data (Figure 33). Altogether, the prognostic value of the TN signature/score was validated in large, independent cohorts of breast cancer in TNBC, BLBC and **ER**- breast cancer subtypes irrespective of the gene expression array platforms used.

The TN score and the likelihood of pCR after chemotherapy

Chemotherapy is a standard therapy for EE- breast cancer and the only mode of therapy for ER-HER2- (TNBC) breast cancer. Although, pathological complete response (pCR) differs by receptor status, it remains highly predictive of survival within the different breast cancer subtypes **[41],** Given the association of the TN score with outcome in TNBC, BLBC and ER- breast cancer, we questioned whether this score is also associated with pCR after chemotherapy. To this end, we analyzed publically available datasets of neoadjuvant chemotherapy trials which recorded pCR and performed pre-treatment gene expression profiling. As shown in Figure 23A, pCR after chemotherapy in ER-/HER2- patients was less likely after TX (GSEl 8728), AT/CMF (GSE50948) or FAC (GSE20271) chemotherapy regimens when these patients had a high TN score. TFAC chemotherapy regimen was less likely to produce pCR in high TN score tumors in one study (GSE20194) but without a significant association in a second study (GSE20271). ER-HER2- tumors with high TN score had a trend to lower response to AC/T chemotherapy (GSE22226 AC/T). In contrast, pCR was achieved in 57% and 60% of ER-HER2- tumors **with** high TN score after treatment with the FEC/TX (GSE42822) and FAC/TX (GSE23988) regimens, respectively. Altogether, the rate of pCR **stratified** by the TN score was significantly different in either the low or high TN score tumor from the reported general 31% pCR rate in TNBC [9] (dotted line in Figure 23A). In one dataset, the ISPY-1 trial (GSE22226), the relapse-free **survival** (RFS) was also recorded. As shown in Figure 23B, pCR was a strong predictor of RFS in **ER-HER2-** breast cancer as previously published [41]. The TN score was not only a strong predictor of RFS after chemotherapy, but also could stratify the survival of patients who achieved pCR further in addition to the stratification of patients who did not achieve pCR to good and poor prognosis groups (Figure 23B). This data indicates that the TN score is independent and has additional value to monitoring pCR after neoadjuvant chemotherapy in ER-HER2- (TNBC) breast cancer patients. To further illustrate the utility of the TN score, we analyzed ER- and BLBC patient outcome in KM-plotter

for systemieally untreated and treated patients separately. As summarized in Table 11 (Figure 34 for survival curves), the **TN** signature was prognostic in either systemieally untreated or treated ER- and BLBC subtypes.

Therapeutic targets based on the TN signature

The overexpressed genes in the TN signature contains novel genes which have limited literature describing their function, particularly in cancer. These genes includes *GRHPR, NDUFC1, CAMSAPl, CETN3, EIF3K, STAU!, EXOSC7* and *KCNGl,* These genes are novel candidates for future studies to investigate the effect of their knockdown on the survival of ER- or TNBC breast cancer cell lines. In addition, we took two approaches to identify possible therapeutic strategies envisioned by the TN signature to benefit the poor survival of patients identified by this signature. First, we compared the global gene expression profile of TNBC/BLBC tumors with high TN score to those with low TN score. Secondly, we analyzed published pre-clinical studies which **treated** cancer cell lines with panels of moleeularly targeted drugs to determine whether cell lines with high TN score display sensitive to particular drugs. In the first approach, a class **comparison** between the global gene expression profiles of BLBC or **ER-** tumors with high TN score to those with low TN score was carried out in the ROCK dataset. In comparison to low TN score BLBC tumors, high TN score BLBC tumors overexpressed 171 probes and underexpressed 251 probes (Table 15). **In** a similar analysis, high TN score ER- tumors overexpressed 307 probes and underexpressed 332 probes (Table 16). Of the overexpressed probes, 87 probes (82 genes) were commonly overexpressed in high TN score BLBC and ER- breast cancer compared to low TN score counterparts. Of the 87 probes, 39 probes were prognostic in BLBC and ER- breast cancer (marked in bold in Table 15). More importantly, the 87 probes include genes which encode several kinases, enzymes and ion channels which could be targets or current for future drug development for the treatment of the high TN score tumors that have poor outcome.

In the second approach, published studies which surveyed panels of molecular drugs against cancer cell lines were analyzed. The Cancer Cell Line Encyclopedia (CCLE) study [50] investigated the pharmacological profiles for 24 anticancer drugs across 479 cancer cell lines which were also profiled with gene expression arrays. We calculated the TN score for each cell line in this study and compared the sensitivity of these cell lines to the anticancer drugs according to the TN score. Cancer cell lines

with high TN score were less **sensitive** to inhibition of ALK **(TAE684)** and **BCR**-ABL (Nilotinib) but more sensitive to the **inhibition** of HSP90 (Tanespimycm [17-AAGj) and EGFR (Erlotinih or Lapatinib) (Figure 35). **In** a similar method, we also analyzed a second large study. Garnet! et al. [49], which tested 130 drugs against more than **600** cancer cell lines. As shown in Figure 24, ceil lines with high TN score were less sensitive to inhibition of PARP (ABT-888), retinoic acid (ATRA), Bcl2 (ABT-263), **DHFR** (methotrexate), glucose (metformin) and p38MAPK (**BIRB** 0796). Two IGF1R inhibitors showed different results; high TN score cell lines were less sensitive to the OSI-906 inhibitor but more sensitive to the BMS-536924 inhibitor. As shown in Figure 24, cell lines with high TN score were also sensitive to HSP90 inhibition (17-AAG and Elesclomol) in agreement with the findings from the CCLE study (Figure 35), High TN score cell lines were also more sensitive to mTOR/PI3K (BEZ235) and MEK (RDEA-1 19) inhibition.

Integration of the TN score and the aggressiveness score

We have recently published the aggressiveness gene signature/score **(Agio** score) [36] from a meta-analysis in Oncomine™ and validated that this score is prognostic in ER^+ breast cancer at the gene level. **ER**- breast cancer, BLBC and TNBC almost consistently express high level of the Agro score thus this signature was not prognostic in these subtypes. We further showed that one of these genes, TTK/MPSl, is upregulated in TNBC cell lines and some ER- negative cell lines, and that TTK is a therapeutic target in these cell lines. Moreover, we showed that the **TTK** protein level by immunohistoehemistTy (IHC) is prognostic in very aggressive subgroups of breast cancer including high grade, proliferative tumors, **lymph** node positive, TNBC and $HER2^+$ subtypes [36]. The integration of the TN gene signature (prognostic in ER-/BLBC/TNBC) and the Agro gene signature (prognostic in **ER^+)** would allow one integrated signature and score which will be prognostic in breast cancer irrespective of subtypes. As detailed **in** the methods section, the addition, subtraction, multiplication or division of the TN and Agro scores were investigated in the ROCK dataset to identify a direct **relationship** that would retain the information provided from each of the scores, A linear relationship was observed by the addition or subtraction of the TN and Agro scores (Figure 36), but only the integration by addition was prognostic in ER- patients (Figure 37). On the other hand, the multiplication and division of the TN and Agro score produced exponential and power curves relationships, respectively (Figure 38). Only the multiplication of the

scores was prognostic in ER- breast cancer (Figure 37). Since multiplication and division produced exponential and power curves for the relationship between the **TN** and **Agro** score, we also tested integration by one score raised to the power **of** the second score. Indeed, the TN score raised to the power of Agro score was highly prognostic in ER- and ER+ patients in the ROCK dataset (Figure 37). This method to integrate the **TN** and Agro scores, the integrated breast cancer recurrence (iBCR) score, was prognostic in all patients, ER- and ER+ patients in the ROCK dataset (Figure 25) and the TCGA dataset (Figure 26). Moreover, the iBCR score was as prognostic as the TN score in the homogenous TNBC dataset [32] (Figure 39), supporting the iBCR score as prognostic test in breast cancer.

The iBCR score and the likelihood of pCR after chemotherapy

The association of the iBCR score with patient sun'ival and the likelihood of pCR after chemotherapy was investigated in the ISPY-1 trial (GSE22226). The RFS of **ER-/HER2-** patients was stratified by iBCR score better than the TN score alone (Figure 27). High iBCR score ER7HER2- patients were less likely to achieve pCR (Figure 27), which could explain the poorer sun'ival of these patients. In ER* breast cancer, the iBCR score stratified the RFS patients similarly to the Agro score. Although higher likelihood pCR was observed in high iBCR score ER* tumors (Figure 27), this subgroup had poor RFS. This can be explained by the small number **of ER*** patients who achieved pCR (**10/62** [16%] vs. **10/34** [29%] in ERHER2-). These results provide further validation and evidence for the value of the iBCR score as a single test which incorporates the Agro score (prognostic in ER*) and the TN score (prognostic in **ER-**). The results in Figure 25 from the ROCK dataset (Affymetrix platform), Figure 26 from the TCGA dataset (Illumina platform) and Figure 27 from the ISPY-1 trial (Agilent platform) also provide evidence for the robustness of the Agro and TN scores and **the** derived iBCR score across independent studies across the **three** major gene expression array platforms.

Next, the association of the iBCR score with pCR was investigated in other neoadjuvant chemotherapy datasets **in** both ER-HER2- and **ER*** patients. pCR was less likely in high iBCR ER-/HER- patients after TX (GSE18728) chemotherapy regimen and not different to low iBCR ER-/HER2- patients when treated with AT/CMF (GSE50948). In the other datasets, pCR was more likely in high iBCR score ER-/HER2- patients after treatment with FAC (GSE20271), TFAC (GSE20271

and GSE20194), EEC/TX (GSE42822) and EAC/TX (GSE23988) neoadjuvant chemotherapy regimens (Figure 28A),

As shown in the summary from these four studies in Table 12, of the total 183 ER$^-$ HER2$^-$ patients, 120 patients (65.6%) had high iBCR score and of these 54 patients (29.5%) achieved pCR while 66 patients (36.1%) did not achieve pCR. The larger number of patients with high iBCR score that did not achieving pCR (66/120, 55%) and that recurrence may be observed on high iBCR score patients after pCR (55/120, 45%) could explain the poorer survival of high iBCR score ER$^-$HER2$^-$ patients (40-50% survival at 10 years in Figure 25 and Figure 26), Based on these studies and that chemotherapy is the mainstay in the treatment of ER7HER2$^-$ breast cancer, low iBCR score patients may be spared from additional treatments particularly if they achieve pCR after chemotherapy. On tire other hand, high iBCR ER-HER2- patients and particularly those who do not achieve pCR should be offered additional therapy which could be based on the unregulated genes in the Agro or TN signatures or based on other overexpressed genes in these tumors (Tables 15 and 16) or from the pre¬clinical analysis we performed from drug sensitivity studies (Figures 24 and 3.5).

High iBCR score in ER$^+$ was associated with higher likelihood of pCR after AT/CMF (GSE50948), TX (GSE18728), TFAC (GSE20271 and GSE20194) and FAC/TX (GSE23988) neoadjuvant chemotherapy regimens (Figure 38B), Despite this higher pCR likelihood, high iBCR ER+ patients have poorer survival (Figures 25 and 26) which could be explained by the small number of ER+ patients who achieve pCR (of the 207 ER$^+$ patients in the above five studies, 5 [2.5%] with low iBCR and 20 [9.7%] with high iBCR score achieved pCR). Thus, for ER$^+$ breast cancer where a decision about including chemotherapy with the standard endocrine therapy in the treatment planning may be informed by the iBCR score. The value of the iBCR score in the treatment planning of ER+ patients is tire described next section.

The iBCR score and the treatment of ER$^+$ breast cancer

ER$^+$ breast cancer patients are treated with endocrine therapy, particularly tamoxifen. When these patients are lymph node positive (N1), adjuvant chemotherapy is also included. For lymph node negative (NO) ER$^+$ patients, decision to include chemotherapy is less certain as good prognosis patients (small and lower grade tumors) would be over-treated if chemotherapy is included whereas poorer prognosis patients (larger and higher grade tumors) would be under-treated if chemotherapy is not included. This clinical decision has been the motivation for the development of

Oncotype Dx® recurrence score, the **Ma*imaPrint®** and more recently the **PAM5D** risk of recurrence score. We have previously published that the Agro score outperformed the Oncotype Dx and the MammaPrint tests in multivariate survival analysis in the METABRIC dataset of 2000 patients [36]. This finding is further supported by direct comparison of the Agro score to Oncotype Dx (Figure 40) and **MammaPrint** (Figure 41) in all ER^+ patients and **in** the NO and Nt subsets. For the iBCR score, as shown in Figure 29A, this score was prognostic in ER^+ NO patients who were not treated with tamoxifen indicating that high iBCR ER^+ **NO** patients should be treated with tamoxifen. When ER+ NO or Nl patients are treated with tamoxifen, the iBCR score can still identify patients who have poor RFS (Figure 29B) and DMFS (Figure 29C), Thus, ER+ NO or Nl patients with high iBCR score may benefit from the inclusion of adjuvant chemotherapy in their treatment as these patients may experience better pCR (Figure 28B). Nonetheless, as pCR rate in ER^+ is not high, high iBCR score ER+ patients, **particularly** Nl, should be offered additional targeted therapies. The type of targeted therapies for these patients **is** suggested in the next section.

***The** iBCR score predicts therapies for ER/HER2⁻ and ER^+ and breast cancer subtypes*

The overexpressed genes in the Agro and TN signature contain targetable genes which could be useful for therapeutic intervention against the high iBCR tumors which have poor survival alter the **standard** treatments. Similar to the analysis performed for the TN signature above, we took two approached to identify additional possible targets in the high iBCR score breast tumors. In the first approach, a class comparison between the global gene expression profiles of ER^+ or **ER⁻** tumors with high iBCR score to those with low iBCR score was carried out in the ROCK dataset. The produced gene-list (1178 probes, data not shown) was then filtered by comparison to normal breast tissue which was also profiled in this dataset. In comparison to low iBCR score tumors and normal breast tissue, high iBCR score tumors overexpressed 204 probes (181 genes) and underexpressed 124 probes (116 genes) (Table 17). Of the 181 overexpressed genes, 134 genes were specifically upreguiated in high iBCR score ER^+ vs. normal breast and low iBCR ER^+ and 95 genes were specifically upreguiated in high iBCR score ER^- vs. normal breast and low iBCR ER^-. As shown in Table 13, 49 genes were uniquely upreguiated in high iBCR score ER- tumors compared to low score **iBCR** score ER^- tumors and normal

breast tissue. Similar compaiison revealed that high iBCR score ER^+ tumors have unique upregulation of 86 genes. High iBCR score ER^- and ER^+ tumors commonly overexpressed 46 genes in compaiison to low score **iBCR** counterparts and normal breast tissue. These genes encode several kinases, enzymes and ion channels which could be targets for current or future drug development for the treatment of the high iBCR score tumors with poor outcome. Of the downregulated probes, a particularly **interesting** hit was the miero-RNA (miRNA) hsa-mir-568 (9.3- and **2.2-fold** downregulated in high iBCR score ER^- vs. normal breast and low iBCR score ER^-, respectively; 5,6- and 2,9-fold downregulated in high iBCR score BR^+ vs. **normal** breast and low iBCR score ER^+, respectively). This downregulated miRNA in the high iBCR score tumors targets several of the upregulated genes in these tumors, particularly those which are upregulated compared to **normal** breast tissue (Table 18). This miRNA could be a genomic-based treatment against high iBCR **score** breast cancers.

In the second approach, again similar to the above analysis for the TN score, published studies of drug screens were analyzed for the association of the iBCR score with sensitivity of cancer cell lines to anti-cancer drugs. In the CCLE study (Figure **42),** cancer cell lines with high iBCR score were less sensitive to inhibition of ALK (TAE684) and BCR-ABL (Nilotinib) similar to results from the TN score. In addition, high iBCR cell lines were less sensitive to inhibition of FGFR (TKI258) and **IGF1R** (AEW541), High iBCR score cell lines were more sensitive to the inhibition of HSP90 (Tanespimycin [17-AAG]) (Figure 42). In the second large study by Garnett et al. [49], high iBCR score cell lines were more sensitive to low iBCR score cell lines to 8 anticancer drugs (Figure 30). These include inhibitors of HSP90 (17AAG), mTOR/PI3K (BEZ235) and IGFIR (BMS-536924) as also observed in the TN score results. Additionally, high iBCR score cell lines were more sensitive to inhibition of PI3K (GDC0941), mTQR (jW-7-25-1), XIAP (Embelin) and PLKl (B1-2536) which also matched results from Agro score results (Figure 30). The Agro score also identified sensitivity **to** inhibition of RSK **(CMI),** MEK (PD0325901) and DNA damage (Bleomycin). Similar to results from high TN score, high iBCR score cell lines were also less sensitive to the inhibition of PARP (ABT-888 and AZD-2281), retinoic acid (ATRA), Bcl2 (ABT-263), DHFR (methotrexate) and glucose (metformin). Additionally, high iBCR score cell lines were less sensitive to inhibition of SYK (BAY 613606), HDAC (Vorinostat) and BCR-ABL (Nilotinib)

and p38MAPK (BIRB 0796). High Agro score cell lines were less sensitive to an **additional** drug against GSK3A/B (SB216763). Altogether, the TN score (Figures 24 and 35) and the Agro score and the combined iBCR score (Figures 30 and 42) associate with sensitivity to several anticancer drugs and future experimental validation would establish these scores as companion diagnostic for these drugs and benefit breast cancer patients by directing these drugs to the high score patients with poor survival.

Sensitivity of breast cancer cell lines to targeted inhibitors according to the iBCR score

Breast cancer cell lines (10 cell lines); **BT-549,** MDA-MB-231, MDA-MB-436, MDA-MB-468, **BT-20,** Hs.578T, BT-474, MCF-7, **T-47D,** and ZR-75-1, were cultured in the absence or presence of escalating doses of 24 anti-cancer drugs. The survival of cells was determined six days in comparison to untreated cells using the MTS/MTA assay. The response of the cell lines to the drugs was analyzed in GraphPad® Prism using a dose response curve to calculate the $\log_{10}$ of IC50 (1C50 is the dose required to kill **50%** of the cells). Sensitivity was presented as the -l©gio[IC5QL This drug screen which we published previously (Al-Ejeh *et* ***al, Oncotarget,*** 2014) was re-analyzed according to the iBCR score. The gene expression datasets of 51 breast cancer cell lines by Neve et al. ***(Cancer Cell,*** 2006), was analyzed to calculate the Agro and TN scores for each cell line to calculate the iBCR score. Each cell line was assigned as low of high iBCR score by dichotomy across the median of all the cell lines in the Neve et al. dataset. Based on the low or high iBCR score classification, the sensitivity of the 10 cell lines used in our screen was compared between high iBCR score cell lines (5 cell lines) to low iBCR score cell lines (5 cell lines). As shown in Figure 47, high iBCR score cell lines were significantly more sensitive to **the-** inhibition of p38MAPK (LY222882Q), PLCu (IJ73122), JNK (SP600125), PAK1 (IPA3), MEK (AS703026 and AZD6244), **ERK5** (XMD 8-92 and **BIX02188),** HSP90 (17-AAG, PF04291 13 and AUY922), IGF1R (GSK1904529A) and EGFR (Afatinib). The results from our screen are in agreement with the higher sensitivity of high iBCR score cancer cell lines to HSP90, IGF1R and MEK inhibitors we identified from the two previously published large cell line studies.

Discussion

Our meta-analysis of gene expression datasets in the Oncomine™ database has previously identified a signature, the Aggressiveness signature (Agra signature), which was prognostic in ER+ breast cancer. We validated one of the genes in this signature, TTK/MPS1, by IHC and found that TTK positivity in interphase cells (exclusive of mitotic ceils) was prognostic in highly aggressive breast cancers such as high grade, high grade and lymph node positive and highly proliferative (Ki67 positive) cases [36]. In this study, we used our meta-analysis approach to identify a second signature, the triple negative signature (TN signature), which was highly prognostic in **ER\.** TNBC and BLBC subtypes. The TN signature **outperformed** all standard clincopatholical indicators in multivariate survival analysis and also outperformed published signatures in ER- breast cancer. We were also able to integrate the Agro signature (prognostic in **ER+** breast cancer) to produce the integrated Breast Cancer Recurrence (iBCR) test. The two signatures and the iBCR were validated in large independent cohorts of breast cancer studies irrespective of the gene expression arrays used indicating the experimenter/technology independence of our signatures. Importantly, both the Agro and TN signatures and the iBCR test associated with response and outcome after endocrine therapy for ER+ and neoadjuvant chemotherapy for **ER-** and ER+ breast cancers. Moreover, by comparison of the global gene expression profiles of high iBCR score tumors to low iBCR score tumors, we were able to identify several overexpressed targets which can be used for the targeted therapy of these poor prognosis patients who are not really benefiting from the current treatment standards. In addition, mining of large preclinical studies of drug screens against cancer cell lines showed that the signatures and iBCR score predict higher sensitivity of cell lines to particular drugs. Thus, the signatures and the iBCR test could be used as a companion diagnostic to direct targeted therapies to those patients who would benefit from these treatments to increase their low survival rates. Altogether, our studies have not only extensively illustrated the potential of our signatures in personalized medicine, but may also shed light for future studies to understand the underlying mechanisms for the aggressiveness of tumors that the iBCR test identified that lead to poor survival

To date, there is an unmet medical need for the prognostication of ER- breast cancer and the development of effective therapies against these tumors particularly when lacking **HER2** expression. Chemotherapy remains to be the only standard therapy in these patients and the response rate after chemotherapy in the neoadjuvant setting is

reported as 31%· in ER HER2 (TNBC) patients [9]. Identifying patients who would truly benefit from chemotherapy would aid clinicians to determine patients who may require longer or additional treatment regimens including investigational clinical trial enrolment. Our signatures and the iBCR score predict higher pCR after chemotherapy in patients who have high scores compared to those with low score. The low score patients have better survival and may not require additional therapy. On the other hand, despite the higher pCR in high score patients, this patient subgroup still has poor survival and recurrences were present even after achieving pCR in high score patients when we analyzed the data from the ISPY-1 trial. Our results from comparative analysis and mining pre-clinical drug screens identified several targets and sensitivity to drugs in development. Thus, ER- and particularly TNBC patients with high scores for our signatures/iBCR test may benefit from the inclusion of therapies envisioned by these signatures to increase their survival rates. Such clinical development will depend on future prospective validation of our signatures and the iBCR test in clinical trials and pie-clinical studies.

In ER+ breast cancer, three commercial tests exist for clinical decisions to spare or include adjuvant chemotherapy with the standard endocrine therapy; Oncotype Dx®, MammaPrint^ and Prosigna*. These have been validated for ER+ lymph node negative (NO) breast cancer patients treated with endocrine therapy whether patients with high risk according to these tests are recommended for adjuvant chemotherapy. Our signatures and tire iBCR test outperformed these tests in a direct comparison in ER+ NO patient-survival after tamoxifen therapy. Moreover, our tests also predicted the response of ER+ patients to chemotherapy and importantly could predict sensitivity to targeted therapies. The current commercial tests do not have this capability. Importantly, our signatures and the iBCR test was also prognostic in the subgroup with unmet need, ER+ lymph node positive breast cancer (ER+ Nl), The survival of these patients was stratified to poor and good prognosis groups by our signatures and iBCR test which also informed whether these patients are benefiting from endocrine therapy. Clinical validation of our signatures and the iBCR test along with validation of drug sensitivity predictions would aid the development of new treatment regimens for ER+ patients who are at high risk of relapse or metastatic spread after the current treatment standards.

The comparison of aggressive ER- tumors identified by our signatures to their counterparts and to normal breast tissue identified several kinases, enzymes (redox

particularly) and potassium channels which could inform new directions in developing targeted treatments against **ER**- breast cancer. On the other hand, for aggressive ER+ tumors identified by our signatures, although targets were not restricted to cell cycle and proliferation, these functions were notably enriched. This high proliferation profile could explain the higher pCR **in,** these tumors after chemotherapy as proliferative tumors would be more responsive to chemotherapeutics. Nonetheless, we have previously clarified that the overexpressed genes **in** the Agro signature, thus the **iBCR** test, are genes that are involved in kinetochore binding and chromosome segregations and that the signature is prognostic even in proliferative tumors (high Ki67 expression) [36]. Deregulation of genes involved in chromosome segregation would produce aneuploidy and chromosomal instability **(CIN)** [52], At least *in viva,* **chemotherapy** has been shown to induce the proliferation **quiescent** aneuploid cells as a mechanism for therapy resistance [53]. In support of the notion that high Agro score is related **to** aneuploidy, analysis of the copy number variations (CNVs) TCGA data **showed** that high Agro score tumours, compared **to** low Agro score tumors, have **high** level **of** CNVs, particularly those involving whole chromosomes or chromosome arms (Figure 43), Thus, although proliferation may be a characteristic of high Agro/iBCR score ER+ tumors, these tumors appear to be aneuploid. In line with this notion, the sensitivity of high Agro/iBCR score cell lines to *VLK1* and HSP90 inhibition (Figure 3(5) and aurora kinase inhibitors (Figure 44) support that high Agro/iBCR scores predict sensitivity to anti-aneuploid therapy. PLK1 and Aurora kinases are classical targets in aneuploidy and **HSP**90 inhibition has been reported to selectively kill aneuploid cancer cells [54]. HSP90 sensitivity was also found for high TN score tumors and interestingly, we have previously identified HSP90 as a target in TNBC by kinome profiling of breast cancer. We showed that HSP90 inhibition in combination therapy is effective *in vitro* and *in vivo [55].* We propose that anti-aneuploid drugs should be effective against ER+ tumors with high Agro/iBCR scores including PLK1, Aurora kinase and HSP90 inhibitors and that HSP90 inhibition should be effective in high TN/ifiCR score ER- tumors. While **other** therapies envisioned by our signatures and the iBCR test should also be investigated, the above targets represent first line targets for initial validation and development.

In conclusion, our meta-analysis in Oneomine™ and extensive subsequent validation and analysis have developed novel signatures and an integrated genomic test for the

prognosis of breast cancer and prediction of response to standard treatments irrespective of ER status. The novel signatures and their integration also have the potential as companion diagnostic tests for several classes of targeted therapies- in breast cancer patients who suffer poor survival. Future validation and clinical development of our signatures and the iBCR test holds a great potential and impact on personalized and precision medicine for breast cancer. Finally, it should be noted that the iBCR test has value in the prognosis of several other cancers (Figure 45) and particularly in lung adenocarcinoma (Figure 46), thus our approach and novel signatures may extend benefit to other cancer types..

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Table 10: The 28-gene signature discovered from a meta-analysis of gene expression data in breast cancer in Oneomine™

Gene Symbol	Affymetrix probe	Entrez	Gene name
↑ABHD5	213935_at	51099	abhydrolase domain containing 5; 1-acylglycerol-3-phosphate O-acyltransferase
↑ADORA2B	205891_at	136	adenosine A2b receptor
↑BCAP31	200837_at	10134	B-cell receptor-associated protein 31
↑CA9	205199_at	768	carbonic anhydrase IX
↑CAMSAP1	212711_at	157922	calmodulin regulated spectrin-associated protein 1
↑CARHSP1	218384_at	23589	calcium regulated heat stable protein 1, 24kDa
↑CD55	201926_s_at	1604	CD55 molecule, decay accelerating factor for complement (Cromer blood group)
↑CETN3	209662_at	1070	centrin, EF-hand protein, 3
↑EIF3K	221494_x_at	27335	eukaryotic translation initiation factor 3, subunit K
↑EXOSC7	212627_s_at	23016	exosome component 7
↑GNB2L1	200651_at	10399	guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1
↑GRHPR	214864_s_at	9380	glyoxylate reductase/hydroxypyruvate reductase
↑GSK3B	209945_s_at	2932	glycogen synthase kinase 3 beta
↑HCFC1R1	218537_at	54985	host cell factor C1 regulator 1 (XPO1 dependent)
↑KCNG1	214595_at	3755	potassium voltage-gated channel, subfamily G, member 1
↑MAP2K5	211370_s_at	5607	mitogen-activated protein kinase kinase 5
↑NDUFC1	203478_at	4717	NADH dehydrogenase (ubiquinone) 1, subcoinplex unknown, 1, 6kDa
↑PML	206503_x_at	5371	promyelocytic leukemia
↑STAU1	208948_s_at	6780	staufen, RNA binding protein, homolog 1 (Drosophila)
↑TXN	216609_at	7295	thioredoxin
↑ZNF593	204175_at	51042	zinc finger protein 593
↓BTN2A2	205298_s_at	10385	butyrophilin, subfamily 2, member A2
↓ERC2	213938_at	26059	ELKS/RAB6-interacting/CAST family member 2
↓IGH	211649_x_at	3492	immunoglobulin heavy locus
↓ME1	211204_at	4199	malic enzyme 1, NADP(+)-dependent, cytosolic
↓MTMR7	217292_at	9108	myotubularin related protein 7
↓SMPDL3B	205309_at	27293	sphingomyelin phosphodiesterase, acid-like 3B
↓ZNRD1-↓AS1	215985_at	80862	ZNRD1 antisense RNA 1

Table 11: The TN signature is prognostic in ER- and BLBC irrespective of systemic therapy.

		Untreated			Treated		
		HR	CI 95%	p-vahie	HR	CI 95%	p-value
ER-	RFS	2,02	1.25 - 3.26	3.20E-03	2.59	1.84 - 3.60	I.70E-08
	DMFS	4.10	1.44 - 11.7	4,20E-03	1,89	1.04 - 3.43	3.40E-02
	OS	1.77	0.65 - 4.83	***0.26***	3.82	1,43 - 10.18	3.90E-03
BLBC	RFS	2.48	1.46 - 4.21	5.10E-04	2.88	!!!i 4 –! .28!!!	4..50E-08
	DMFS	5.54	1.66 - 18.48	I.70E-03	3.14	1.38 – 7.19	4.20E-03
	OS	2.42	!!!!!Ill!!!i	*0.11*	4.89	1.65 - 14.46	1..50E-03

The 28-gene signature was used **as** described in Figure 2 in the **online** tool KM-plotter but restricting the analysis oil **ER-** or **f LBC** patients who were untreated systemically or systemically treated. The survival **curves** for RFS. DMFS and **OS** are shown in Figure **34;** only **the** hazard ratio (**HR**)**;** the 95% confidence interval (CI 95%) **and** the log-rank p-value from **these** curves **are** reported in the Table:.

Table 12: The likelihood of pCR in ER-HER2- patients according to the iBCR score

	pCR	no pCR	Sum
Low Score	12 (6.6%)	51 (27.9%)	63 (34.4%)
High Score	54 (29.5%)	66 (36.1%)	120 (65.6%)
Total	66 (36.1%)	117 (63.1%)	183 (100%)

ER-/HER2- patients stratified by low and high iBCR scores from four studies were compared for achieving or not achieving pCR after four chemotherapy regimens: FAC (GSE20271), TFAC (GSE20271 and GSE30194), FEC/TX (GSE42822) and FAC/TX (GSE23988)

Table 13: Upregulated genes in high iBCR score tumors compared to low iBCR tumors and normal breast tissue

High iBCR score ER- vs. low iBCR score ER- and normal breast			High iBCR score ER+ vs. low iBCR score ER+ and normal breast				Common in high iBCR score ER-/+ vs. low iBCR score and normal		
ACE2	HMGB3		ACP1	ENO1	MCM4		ASPM	HN1	
ADM	IL8		APOBEC3B	EPRS	MCM6	RANBP1	AURKA	KCNK1	
AR	IMPA2		ATAD2	EXOSC4	MCM7	RECQL4	BIRC5	KIF4A	
BNIP3	KYNU		AURKB	FADS1	MRPL13	RFC2	BUB1	MKI67	
C1orf106	LBP		BOP1	FANCI	MRPL15	RMDN1	BUB1B	MLF1IP	
CALML5	LRP8		CACYBP	GINS2	MSH6	RSAD2	CCNB1	MMP1	
CBS	MAGEA3	TDO2	CALU	GTSE1	MYBL2	SHMT2	CCNB2	MTFR1	
CCL18	MAGEA6	TMEM45A	CCNA2	H2AFZ	NCAPG	SMC4	CCNE2	NDC80	YKT6
CD24	ME1	TMSB15A	CCT2	HELLS	NDUFS8	SPAG5	CDC20	NEK2	ZWINT
CLIC3	MMP12	VEGFA	CDCA3	HMMR	NUDT21	SQLE	CDC6	NUSAP1	
CORO1C	PFKP	VGLL1	CEBPG	HSPH1	NUTF2	STIP1	CDK1	PDXK	
CP	PHLDA2		CKS1B	KIAA0101	OIP5	TACC3	CDKN3	PHB	
CRISP3	PTPN12		CXCL10	KIF11	PBK	TBCE	CENPF	PRC1	
DDC	QPRT		CXCL11	KIF14	PCNA	TIMM17A	CKS2	PTTG1	
ECT2	S100A7		DERL1	KIF20A	PGK1	TMPO	CNIH4	RRM2	
EZH2	S100A9		DHFR	KPNA2	PLOD2	TSN	CNTNAP2	S100A8	
FABP7	SCD		DNPH1	KPNA4	PRAME	TYMS	DDA1	S100P	
FAR2	SLC7A5		DONSON	LAPTM4B	PSMA7	UBE2S	DLGAP5	SPP1	
GABBR2	SOD2		DSCC1	LMNB1	PSMC3	UCK2	DTL	TK1	
GALNT3	SOX11		EIF4EBP1	LSM4	RACGAP1	WHSC1	ESRP1	TOP2A	
GMPS	SRD5A1		EIF5A	LY6E	RAD21	ZWILCH	GINS1	TRIP13	
GPSM2	ST14		EMC8	MAD2L1	RAD54B		HIST1H2BG	UBE2C	

Table 14. Univariate survival analysis of genes from the Oncomine Inetanalysis in the KM-Plotter online tool in BLBC and ER- breast cancer. Deriving the 28-gene signature.

		Basal-like breast cancer					
		RFS		DMFS		OS	
Gene Name	Affy Probe ID	HR	P	HR	P	HR	P
BTN2A2	205298_s_at	0.41	6.00E-12	0.34	7.20E-05	0.4	1.10E-03
IGHA1	211649_x_at	0.55	6.80E-06	0.39	1.50E-04	0.48	8.40E-03
MTMR7	217292_at	0.73	1.70E-02	0.50	1.10E-03	0.44	7.20E-03
ME1	211204_at	0.65	2.30E-03	0.38	2.10E-03	0.66	2.00E-01
BRI3	221004_s_at	0.59	9.00E-04	0.44	3.30E-03	0.34	1.60E-04
RBM38	212430_at	0.55	3.20E-04	0.48	4.20E-03	0.47	6.00E-03
GGA2	210658_s_at	0.65	1.10E-03	0.48	4.40E-03	0.6	7.90E-02
DDX11	208149_x_at	0.66	1.70E-03	0.46	7.50E-03	0.5	2.40E-02
ESPL1	38158_at	0.55	7.30E-06	0.50	8.60E-03	0.4	1.00E-03
CALR	214315_x_at	0.55	5.80E-06	0.50	9.20E-03	0.62	9.80E-02
CCL13	206407_s_at	0.58	4.70E-05	0.52	1.10E-02	0.87	6.50E-01
FANCA	203805_s_at	0.60	2.20E-04	0.54	1.70E-02	0.45	3.70E-03
NUP205	222382_x_at	0.52	3.00E-03	0.54	1.70E-02	0.56	3.90E-02
PDK3	221957_at	0.64	6.50E-04	0.55	2.10E-02	0.54	2.60E-02
MX2	204994_at	0.52	6.70E-07	0.56	2.80E-02	0.62	9.10E-02
SIRPA	202895_s_at	0.63	3.70E-04	0.58	4.10E-02	0.77	3.70E-01
FBXO41	221945_at	0.59	1.10E-04	0.53	4.20E-02	0.6	1.80E-01
COX5A	217451_at	0.75	3.60E-02	0.58	4.60E-02	0.73	2.70E-01
NOP2	214427_at	0.65	1.80E-03	0.61	5.90E-02	0.57	4.30E-02
C1QB	202953_at	0.60	1.30E-04	0.64	9.60E-02	0.66	1.50E-01
NCRNA00171	215985_at	0.59	2.40E-04	0.44	1.50E-03	0.75	3.50E-01
SMPDL3B	205309_at	1.04	7.80E-01	0.48	4.90E-03	0.61	8.80E-02
ERC2	213938_at	0.67	2.60E-03	0.50	6.80E-03	0.53	2.40E-02
DCLRE1C	219678_x_at	0.57	1.70E-05	0.52	1.10E-02	0.8	4.40E-01
FOXK2	203064_s_at	0.72	1.80E-02	0.69	1.50E-02	0.59	5.80E-02
PTCD3	217895_at	0.70	7.80E-03	0.53	1.70E-02	0.83	5.10E-01
GART	210005_at	0.56	2.10E-05	0.55	2.30E-02	0.64	1.30E-01
NF1	204325_s_at	0.70	1.20E-02	0.55	3.70E-02	0.9	7.30E-01
ASF1B	218115_at	0.70	8.00E-03	0.58	4.00E-02	0.66	1.40E-01
MLLT10	205408_at	0.63	5.70E-04	0.59	4.20E-02	0.92	7.60E-01
C11orf41	214772_at	0.70	7.90E-03	0.60	4.90E-02	0.82	4.80E-01
KIF18B	222039_at	0.58	6.10E-04	0.63	1.30E-01	0.5	3.70E-02
RECQL5	221686_s_at	0.59	3.30E-04	0.64	1.50E-01	0.54	5.40E-02
PKMYT1	204267_x_at	0.69	5.60E-03	0.66	1.10E-01	0.59	6.20E-02
TRAPPC10	208184_s_at	0.64	5.80E-04	0.64	9.00E-02	0.63	1.10E-01
ATAD5	220223_at	0.66	1.70E-03	0.68	1.40E-01	0.65	1.30E-01
RHBDD3	217622_at	0.60	1.20E-04	0.63	9.90E-02	0.68	1.80E-01
SLCO1A2	211481_at	0.62	4.60E-04	0.62	9.10E-02	0.69	2.10E-01
MARS	213672_at	0.73	2.00E-02	0.47	7.60E-03	0.75	3.20E-01

CD163	216233_at	0.57	2.10E-05	0.63	8.30E-02	0.76	3.20E-01
LOC100131613	210928_at	0.61	4.10E-04	0.80	4.30E-01	0.63	1.30E-01
PPIL2	206064_s_at	0.67	3.80E-03	0.69	1.90E-01	0.76	4.00E-01
FAM49B	217535_at	0.59	1.20E-04	0.68	1.60E-01	0.8	4.50E-01
MRPS12	213840_s_at	0.66	2.50E-03	1.23	4.30E-01	1.4	2.30E-01
GCH1	204224_s_at	0.66	1.70E-03	0.66	1.20E-01	1.14	6.80E-01
LAD1	203287_at	0.66	2.60E-03	0.82	4.90E-01	0.78	3.70E-01
DHTKD1	209916_at	0.62	3.00E-04	0.87	5.90E-01	0.74	2.80E-01
GTPBP2	221050_s_at	0.64	6.50E-04	0.80	3.90E-01	0.87	6.30E-01
TSKS	220544_at	0.66	2.00E-03	0.94	8.10E-01	0.68	2.20E-01
AIMIL	220290_at	0.64	9.10E-04	0.76	3.00E-01	0.95	8.40E-01
NUP62	207740_s_at	0.59	4.90E-05	0.77	3.20E-01	0.95	8.70E-01
C21orf45	219004_s_at	0.63	4.10E-04	1.30	4.10E-01	0.94	8.50E-01
TYRO3	211431_s_at	0.69	5.60E-03	0.84	5.20E-01	0.92	7.70E-01
SSX3	215881_x_at	0.63	9.20E-04	0.94	8.20E-01	0.8	4.80E-01
MTDH	212251_at	0.70	6.90E-03	1.14	6.40E-01	0.9	7.30E-01
P2RY6	208373_s_at	0.67	2.90E-03	0.91	7.30E-01	0.89	6.80E-01
C1orf38	207571_x_at	0.70	1.70E-02	0.95	8.60E-01	0.82	5.40E-01
CR1	217552_x_at	0.65	8.70E-04	0.98	9.40E-01	1.22	5.00E-01
ZNF710	39891_at	0.66	1.90E-03	0.90	6.90E-01	0.92	7.60E-01
LRP8	208433_s_at	0.60	8.50E-04	0.98	9.60E-01	0.78	5.70E-01
SLC35A2	207440_at	0.58	5.00E-05	0.97	9.20E-01	1.11	7.10E-01
SRPK3	206216_at	0.70	8.10E-03	1.02	9.50E-01	0.89	6.80E-01
PPP3R1	204506_at	0.72	1.50E-02	0.90	7.00E-01	1	9.90E-01
FCGR3B	204007_at	0.69	4.60E-03	0.97	9.20E-01	1.07	8.00E-01
CD68	203507_at	0.62	3.10E-04	1.01	9.80E-01	0.99	9.70E-01
STAU1	208948_s_at	1.46	4.90E-03	1.95	9.40E-03	1.76	4.40E-02
EXOSC7	212627_s_at	1.68	1.10E-04	1.83	2.20E-02	1.71	5.50E-02
BCAP31	200837_at	1.59	8.10E-04	1.81	3.40E-02	1.49	1.60E-01
GNB2L1	200651_at	1.75	1.80E-05	2.15	3.20E-03	2.07	8.70E-03
ADORA2B	205891_at	1.58	7.30E-03	2.17	2.90E-02	2.87	6.60E-03
ABHD5	213935_at	1.28	4.60E-02	1.92	1.20E-02	1.92	2.00E-02
MAP2K5	211370_s_at	1.37	2.20E-02	1.84	3.40E-02	1.88	3.70E-02
KCNG1	214595_at	1.88	1.20E-03	2.78	2.30E-02	1.87	1.40E-01
CAMSAP1	212711_at	1.32	3.50E-02	1.84	1.80E-02	1.11	7.20E-01
EIF3K	221494_x_at	1.45	8.00E-03	1.59	9.30E-02	1.86	3.20E-02
CD55	201926_s_at	1.35	2.80E-02	1.99	1.30E-01	1.93	2.30E-02
CARHSP1	218384_at	1.63	2.70E-03	1.16	5.80E-01	1.01	9.80E-01
GSK3B	209945_s_at	2.02	6.10E-07	1.49	1.30E-01	1.55	1.30E-01
CA9	205199_at	1.40	2.30E-02	2.29	5.30E-03	1.99	2.90E-02
PML	206503_x_at	1.48	1.30E-02	2.16	3.70E-02	2.11	6.20E-02
TXN	216609_at	1.54	1.50E-03	2.16	3.80E-03	1.32	3.30E-01
HCFC1R1	218537_at	1.51	3.60E-03	1.19	5.70E-01	1.55	1.60E-01
NDUFC1	203478_at	1.42	1.00E-02	1.35	2.70E-01	1.19	5.50E-01
CETN3	209662_at	1.43	7.00E-03	1.12	6.60E-01	1.23	4.60E-01
GRHPR	214864_s_at	1.31	4.60E-03	1.62	6.20E-02	1.59	1.00E-01

ZNF593	204175_at	1.30	4.90E-02	0.92	7.40E-01	1.19	5.50E-01
DYNC1LI2	203590_at	1.84	2.60E-04	1.68	6.70E-02	1.62	1.60E-01
CALM1	200655_s_at	1.85	5.80E-06	1.49	1.30E-01	1.47	1.80E-01
C7orf10	219655_at	1.66	2.60E-04	1.40	2.00E-01	1.32	3.20E-01
C16orf80	217957_at	1.82	9.00E-04	2.38	5.60E-02	1.07	8.50E-01
HNRNPAB	201277_s_at	1.63	4.80E-04	1.67	6.00E-02	1.02	9.50E-01
PRRG1	205618_at	1.59	6.80E-03	1.44	2.40E-01	1.79	1.10E-01
EIF3B	211501_s_at	1.57	4.00E-03	1.33	3.30E-01	1.48	2.20E-01
PGK1	217356_s_at	1.55	8.60E-03	1.63	1.70E-01	1.32	3.90E-01
HIF1A	200989_at	1.56	7.60E-03	0.87	6.60E-01	2.15	1.30E-01
ETFA	201931_at	1.65	2.10E-04	1.30	3.50E-01	1.21	5.20E-01

ER- breast cancer						Sorting	
RFS		DMFS		OS			
HR	P	HR	P	HR	P	Avg P	Count of Sig. p val
0.45	6.50E-13	0.44	1.[illegible]3E-04	0.55	1.[illegible]OE-01	1.85E-02	5
0.59	2.40E-3[illegible]	0.5 1	8.50[illegible]-04	0.59	2.00E-02	4.90E-03	6
0.8	5.00E-02	0.75	1.70E-01	0.67	9.60E-02	5.69E-02	4
0.73	5.90E-03	0.65	4.10[illegible]-[illegible]2	**0.8.8**	6.Q0E-01	1.42E-01	4
0.58	4.20E-05	0.45	2.20E-04	0.36	8.4[illegible]E-06	7.72E-04	6
0.58	3.5[illegible]E-06	0.65	3.50E-02	0.68	9.60E-02	2.36E-02	5
0,65	1.[illegible]0[illegible]-04	0.59	1.20E-02	0.73	2.[illegible]0E-01	5.[illegible]1E-02	4
0.67	4.40E-04	0.67	7.10E-02	0.82	4.20E-01	8.74E-02	4
0.58	1.[illegible]0[illegible]-[illegible]5	0.58	8.[illegible]0[illegible]-[illegible]3	0.6	2.30E-02	6.88E-03	6
0[illegible].57	4.70E-[illegible]7	0,66	4.[illegible]0[illegible]3-[illegible]3	0.74	2.00E-0 1	5.82E-02	4
0.5[illegible]3	[illegible].[illegible]0[illegible]-[illegible]8	0.42	[illegible].30E-[illegible]2	0.58	[illegible].4[illegible]3-[illegible]5	1.13E-01	5
0.62:	3.20[illegible]-05	0,69	6.S0E-02	0.68	8.40E-02	2.S8E-02	4
0,67	3.[illegible]0[illegible]E-04	0.74	1.40E-01	0.79	3.00E-01	8.32E-02	4
0.65	[illegible].0[illegible]E-04	0.6	[illegible].40E-[illegible]2	0.64	[illegible].9[illegible]E-02	1.85E-02	6
0.55	[illegible].[illegible]0[illegible]-08	0.67	5.10E-02	0.64	5.10E-02	3.68E-02	5
0.6	6.60E-06	0,64	3.20[illegible]-[illegible]3	0.82	4.20 E-O[illegible]	1.44E-0 1	4
0.62	5.[illegible]0[illegible]-05	0.64	5.[illegible]0E-02	0.69	1.50E-01	7.14E-02	4
0.73	7.30E-[illegible]3	0.58	1.10E-02	0.79	3.2QE-01	U5E-01	4
0.67	3.20[illegible]-03	0.69	7.70E-02	0.69	1.IOE-0 1	4.90E-02	4
0.64	9.50E-05	0.58	[illegible].[illegible]0[illegible]-03	0.54	6.[illegible]0[illegible]-03	4.32E-02	4
0.63	1.80E-04	0,67	l.OOE-O1	0.93	7.80E-01	2.05E-0 1	3
1.01	9.50E-01	0.56	[illegible].[illegible]0[illegible]-03	0.63	4.4[illegible]-[illegible]2	3.12E-0 !	3
0.82	1.00E-01	0.79	2,5[illegible]E-[illegible]I	**0.86**	5.20E-01	1.51E-01	3
0.64	5.10E-05	0.8 1	3.00E-01	1.05	8.50E-0 1	2.67E-0 1	3
0,75	1.40[illegible]-0:	0.8 !	3.00E-O1	0.74	1.90E-01	9.92E-02	3
0.76	1.40E-02	0.76	1.90E-0I	1.08	7.40E-0 1	2.46E-0 !	3
0.6	3.90E-06	0.69	6.80E-02	0.86	5.30E-01	1.25E-01	3
0.69	1.80E-03	0.7	9.40E-02	0.87	5.50E-0 1	2.37E-0 1	3
0.71	2.2[illegible]E-03	0.77	2.00E-[illegible]0I	**0.88**	5.80E-01	1,62E-01	3
0.65	1.60E-04	0.74	1.40E-0 !	1.02	9.40E-0 1	3.14E-0 1	3

0.76	1.40E-02	0.83	3.70E-01	0.94	7.90E-01	2.85E-01	3
0.61	7.70E-05	0.84	4.60E-01	1.07	8.20E-01	2.41E-01	3
0.69	1.90E-03	1	1.00E+00	0.87	5.70E-01	2.96E-01	3
0.74	8.80E-03	0.9	6.20E-01	0.89	6.00E-01	2.34E-01	2
0.65	9.50E-05	0.8	2.70E-01	0.83	4.30E-01	1.50E-01	2
0.73	5.90E-03	0.92	6.70E-01	1.05	8.30E-01	2.96E-01	2
0.66	2.10E-04	0.88	5.30E-01	0.85	5.00E-01	2.18E-01	2
0.63	8.40E-05	0.72	1.40E-01	0.82	4.00E-01	1.40E-01	2
0.83	1.00E-01	0.87	4.90E-01	1.18	4.60E-01	2.33E-01	2
0.58	1.20E-06	0.8	2.70E-01	1.06	8.10E-01	2.47E-01	2
0.63	1.30E-04	0.75	2.10E-01	0.74	2.30E-01	1.67E-01	2
0.72	5.90E-03	0.97	8.70E-01	1.2	4.40E-01	3.18E-01	2
0.7	1.70E-03	0.78	2.50E-01	0.9	6.50E-01	2.52E-01	2
0.62	5.20E-05	0.88	5.40E-01	1.25	3.30E-01	2.55E-01	2
0.72	4.10E-03	0.71	1.20E-01	1.12	6.70E-01	2.66E-01	2
0.71	4.60E-03	1.03	8.80E-01	0.87	5.60E-01	3.85E-01	2
0.64	7.00E-05	0.91	6.40E-01	0.99	9.60E-01	4.12E-01	2
0.67	2.90E-04	1.14	5.30E-01	1.18	4.60E-01	3.35E-01	2
0.63	9.30E-05	0.92	7.20E-01	0.75	2.90E-01	3.40E-01	2
0.55	2.30E-07	0.69	7.10E-02	0.83	4.20E-01	2.72E-01	2
0.6	5.10E-06	0.88	5.50E-01	1.05	8.20E-01	4.27E-01	2
0.65	1.20E-04	1.16	5.40E-01	0.96	8.80E-01	4.47E-01	2
0.77	1.90E-02	1.24	3.10E-01	1.26	3.10E-01	3.22E-01	2
0.65	2.20E-04	1.02	9.40E-01	0.91	7.10E-01	4.92E-01	2
0.7	1.80E-03	1.08	7.20E-01	1.04	8.80E-01	4.96E-01	2
0.63	4.10E-05	0.73	1.20E-01	0.8	3.50E-01	3.14E-01	2
0.59	9.40E-06	0.73	1.50E-01	0.75	2.30E-01	3.00E-01	2
0.65	1.30E-04	0.85	4.20E-01	1.03	9.00E-01	4.60E-01	2
0.69	8.60E-04	0.99	9.70E-01	1.18	4.90E-01	4.85E-01	2
0.58	2.20E-05	1.05	8.70E-01	0.83	5.70E-01	4.95E-01	2
0.67	3.20E-04	1.08	7.20E-01	1.11	6.80E-01	5.05E-01	2
0.76	1.30E-02	1.16	4.70E-01	1.14	5.70E-01	4.49E-01	2
0.69	1.20E-03	0.83	3.70E-01	1.01	9.60E-01	5.06E-01	2
0.61	8.30E-06	0.7	7.80E-02	0.86	5.00E-01	3.84E-01	2
0.68	7.00E-04	1.1	6.30E-01	1.14	5.80E-01	5.27E-01	2
1.46	1.20E-03	1.78	5.20E-03	1.88	7.00E-03	1.20E-02	6
1.56	8.50E-05	1.4	5.20E-02	1.64	2.90E-02	2.64E-02	6
1.59	9.90E-05	1.83	6.20E-03	1.66	3.10E-02	3.87E-02	5
1.68	3.30E-06	1.42	8.70E-02	1.33	2.10E-01	5.15E-02	4
1.14	3.00E-01	1.43	1.20E-01	1.96	1.30E-02	7.93E-02	4
1.15	2.10E-01	1.2	3.80E-01	1.56	5.00E-02	1.20E-01	4
1.25	5.70E-02	1.47	9.10E-02	1.25	4.10E-01	1.09E-01	4
1.56	2.20E-03	1.83	2.60E-02	1.58	1.20E-01	5.21E-02	4
1.33	1.20E-02	1.88	1.90E-03	1.28	2.80E-01	1.78E-01	4
1.35	1.00E-02	1.22	3.40E-01	1.29	2.70E-01	1.26E-01	3
1.2	1.20E-01	1.6	3.60E-02	1.36	2.00E-01	8.95E-02	3

1.7	9.30E-06	1.59	3.30E-02	1.78	5.50E-03	2.67E-01	3
1.87	2.50E-07	1.55	3.90E-02	1.16	5.30E-01	1.38E-01	3
1.11	3.90E-01	1.44	8.90E-02	1.44	1.20E-01	1.09E-01	3
1.23	9.70E-02	1.17	5.10E-01	1.04	8.70E-01	2.65E-01	2
1.38	4.70E-03	1.43	8.80E-02	1.43	8.30E-02	8.52E-02	2
1.47	6.60E-04	1.29	2.60E-01	1.35	1.00E-02	1.67E-01	2
1.32	1.30E-02	0.94	7.80E-01	1	9.90E-01	4.36E-01	2
1.51	3.20E-04	1.06	7.70E-01	1.39	1.50E-01	3.41E-01	2
1.18	1.50E-01	1.14	5.40E-01	1.42	1.50E-01	1.68E-01	1
1.2	1.00E-01	0.81	3.10E-01	1.1	6.70E-01	4.03E-01	1
1.77	4.40E-06	1.66	3.10E-02	1.52	1.40E-01	6.64E-02	3
1.92	3.80E-08	1.49	6.00E-02	1.61	5.80E-02	7.13E-02	3
1.72	4.90E-06	1.63	1.90E-02	1.34	2.00E-01	1.23E-01	3
1.5	3.10E-03	1.35	2.50E-01	0.92	7.50E-01	3.18E-01	3
1.68	2.20E-05	1.89	5.00E-03	1.24	3.50E-01	2.28E-01	3
1.33	3.00E-02	1.3	2.60E-01	1.53	1.10E-01	1.26E-01	2
1.4	9.30E-03	1.32	2.30E-01	1.36	2.20E-01	1.69E-01	2
1.36	2.80E-02	1.4	2.10E-01	1.24	4.20E-01	2.04E-01	2
1.39	2.30E-02	0.73	2.30E-01	2.03	1.20E-01	1.95E-01	2
1.59	1.50E-04	1.18	4.80E-01	1.04	8.70E-01	3.70E-01	2

Top 4 genes in the module		
	BLBC	
RFS	-2.33	4.30E-11
DMFS	**-3.57**	**6.30E-07**
OS	**-3.57**	**5.70E-06**
	ER negative	
RFS	-2.22	6.50E-13
DMFS	**-2.70**	**7.80E-07**
OS	**-2.78**	**5.10E-06**

Rest of the genes in module		
	BLBC	
RFS	-2.78	1.90E-14
DMFS	-2.63	1.30E-04
OS	-2.63	4.60E-04
	ER negative	
RFS	-2.38	3.30E-15
DMFS	-2.08	2.40E-04
OS	-2.13	7.10E-04

Using top 4 genes from first module and top 3 genes from the second module		
		BTN2A2
		IGHA1
	BLBC	**MTMR7**
RFS	**-2.86**	**1.10E-16**
DMFS	**-5.00**	**7.80E-10**
OS	**-4.76**	**1.50E-08**
	ER negative	
RFS	**-2.50**	**1.00E-16**
DMFS	**-3.13**	**2.40E-08**

ME1
NCRNA00171
SMPDL3B
ERC2

*Only top 3 genes as a module had sig p value **both** DMFS and OS in **both** BLBC and ER-*		
	BLBC	
RFS	-2.13	1.60E-08
DMFS	*-1.89*	*1.90E-02*
OS	*-2.63*	*9.60E-04*
	ER negative	
RFS	-1.82	1.20E-07
DMFS	*-1.54*	*4.50E-02*
OS	*-1.75*	*2.00E-02*

	BLBC	
RFS	-2.04	2.60E-07
DMFS	1.06	0.86
OS	0.71	0.25
	ER negative	
RFS	-2.00	3.40E-09
DMFS	0.95	0.82
OS	0.89	0.66

OS	**-3.45**	**1.20E-07**

	BLBC	
RFS	2.38	9.70E-10
DMFS	3.23	5.00E-05
OS	2.98	2.00E-04
	ER negative	
RFS	2.1	2.80E-10
DMFS	1.94	1.50E-03
OS	1.86	6.70E-03

	BLBC	
RFS	1.51	2.10E-03
DMFS	1.48	1.40E-02
OS	1.58	0.1
	ER negative	
RFS	1.4	3.30E-03
DMFS	1.18	0.41
OS	1.27	0.3

	BLBC	
RFS	2	3.10E-04
DMFS	1.64	0.19
OS	1.18	0.66
	ER negative	
RFS	2.06	1.60E-05
DMFS	1.93	0.07
OS	1.38	0.38

			STAU1
			FXOSC7
			BCAP31
			GNB2L1
			ADORA2B
			ABHD5
			MAP2K5
	BLBC		**KCNG1**
RFS	**2.79**	**2.00E-14**	**CAMSAP1**
DMFS	**4.1**	**6.00E-07**	**EIF3K**
OS	**3.81**	**5.00E-06**	**CD55**
	ER negative		**CARHSP1**
RFS	**2.41**	**2.00E-14**	**GSK3B**
DMFS	**2.41**	**2.00E-05**	**CA9**
OS	**2.37**	**1.50E-04**	**PML**
			TXN
			HCFC1R1
			NDUFC1
			CETN3
			GRHPR
			ZNF593

Table 15. Class comparison of the global gene expression profiles of high TN score BLBC tumors to low TN score BLBC tumors in the ROCK dataset (highlighted probe set indicates common in high TN score BLBC and ER- breast tumours and bold probe set indicates common and prognostic in BLBC and ER- breast cancer).

Parametric p-value	FDR	Permutation p-value	Fold-change for high TN score vs. Low TN score	Probe Set	Symbol	Name	EntrezID
4.22E-05	0.0174	< 1e-07	2.9	**203108_at**	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
4.60E-04	0.0436	0.0005	2.5	**213693_s_at**	MUC1	mucin 1, cell surface associated	4582
1.03E-04	0.0249	< 1e-07	2.4	219956_at	GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6)	11226
1.88E-02	0.221	0.0172	2.3	204268_at	S100A2	S100 calcium binding protein A2	6273
2.35E-02	0.244	0.0239	2.3	204351_at	S100P	S100 calcium binding protein P	6286
7.09E-03	0.137	0.0054	2.1	**203021_at**	SLPI	secretory leukocyte peptidase inhibitor	6590
5.95E-03	0.126	0.0046	2.1	**207847_s_at**	MUC1	mucin 1, cell surface associated	4582
1.83E-03	0.0746	0.002	2.1	**202489_s_at**	FXYD3	FXYD domain containing ion transport regulator 3	5349
6.71E-05	0.0214	< 1e-07	2.0	**201468_s_at**	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
2.47E-05	0.0167	< 1e-07	2.0	204818_at	HSD17B2	hydroxysteroid (17-beta) dehydrogenase 2	3294
1.76E-03	0.0737	0.0019	2.0	**212444_at**	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
2.56E-03	0.085	0.0028	1.9	218309_at	CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	55450
7.04E-04	0.0509	0.0004	1.9	209803_s_at	PHLDA2	pleckstrin homology-like domain, family A, member 2	7262
5.08E-05	0.0195	< 1e-07	1.9	**201286_at**	SDC1	syndecan 1	6382
1.65E-03	0.0716	0.0013	1.9	210519_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
1.23E-02	0.18	0.012	1.9	209160_at	AKR1C3	aldo-keto reductase family 1, member C3	8644

4.27E-02	0.321	0.0403	1.8	**209800_at**	KRT16	keratin 16	3868
1.13E-03	0.0602	0.0008	1.8	201951_at	ALCAM	activated leukocyte cell adhesion molecule	214
5.40E-04	0.0475	0.0003	1.8	210239_at	IRX5	iroquois homeobox 5	10265
2.92E-03	0.09	0.003	1.8	221024_s_at	SLC2A10	solute carrier family 2 (facilitated glucose transporter), member 10	81031
1.92E-03	0.0755	0.0018	1.8	**203860_s_at**	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
2.71E-02	0.261	0.0282	1.8	218211_s_at	MLPH	melanophilin	79083
4.52E-03	0.111	0.0044	1.8	**201242_s_at**	ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	481
1.19E-03	0.0614	0.0009	1.8	220230_s_at	CYB5R2	cytochrome b5 reductase 2	51700
2.38E-03	0.0823	0.0028	1.8	218959_at	HOXC10	homeobox C10	3226
5.29E-03	0.12	0.0039	1.8	219959_at	MOCOS	molybdenum cofactor sulfurase	55034
2.58E-03	0.0851	0.0022	1.8	219580_s_at	TMC5	transmembrane channel-like 5	79838
1.98E-03	0.076	0.0012	1.8	**204595_s_at**	STC1	stanniocalcin 1	6781
3.06E-03	0.0914	0.0022	1.8	200862_at	DHCR24	24-dehydrocholesterol reductase	1718
3.44E-02	0.291	0.0339	1.7	211657_at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
8.94E-03	0.154	0.0078	1.7	210652_s_at	TTC39A	tetratricopeptide repeat domain 39A	22996
2.16E-03	0.0787	0.0021	1.7	201467_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
2.45E-02	0.248	0.0218	1.7	209699_x_at	AKR1C2	aldo-keto reductase family 1, member C2	1646
1.02E-02	0.165	0.0111	1.7	203215_s_at	MYO6	myosin VI	4646
8.95E-04	0.0547	0.0008	1.7	204284_at	PPP1R3C	protein phosphatase 1, regulatory subunit 3C	5507
4.66E-02	0.332	0.0457	1.7	203453_at	SCNN1A	sodium channel, non-voltage-gated 1 alpha subunit	6337
4.38E-04	0.0435	0.0005	1.7	206326_at	GRP	gastrin-releasing peptide	2922
2.35E-03	0.0821	0.0025	1.7	219127_at	PRR15L	proline rich 15-like	79170
3.86E-02	0.306	0.0346	1.7	214580_x_at	KRT6C		
1.94E-03	0.0756	0.0018	1.7	203058_s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
8.03E-03	0.146	0.0067	1.7	**209373_at**	MALL	mal, T-cell differentiation protein-like	7851
5.88E-04	0.0488	0.0006	1.7	**213285_at**	TMEM30B	transmembrane protein 30B	161291
8.97E-03	0.154	0.0098	1.7	**205110_s_at**	FGF13	fibroblast growth factor 13	2258

4.44E-04	0.0435	0.0005	1.7	**221042_s_at**	CLMN	calmin (calponin-like, transmembrane)	79789
1.44E-02	0.193	0.0151	1.7	214079_at	DHRS2	dehydrogenase/reductase (SDR family) member 2	10202
3.70E-02	0.302	0.0377	1.7	204913_s_at	SOX11	SRY (sex determining region Y)-box 11	6664
9.09E-04	0.0547	0.0014	1.6	209260_at	SFN	stratifin	2810
5.49E-03	0.121	0.0057	1.6	203946_s_at	ARG2	arginase, type II	384
1.01E-03	0.0571	0.0012	1.6	221589_s_at	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	4329
8.30E-04	0.0537	0.0005	1.6	**222258_s_at**	SH3BP4	SH3-domain binding protein 4	23677
8.16E-03	0.147	0.0083	1.6	205968_at	KCNS3	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	3790
8.44E-03	0.15	0.0094	1.6	**203180_at**	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	220
2.13E-03	0.0786	0.003	1.6	**201596_x_at**	KRT18	keratin 18	3875
1.60E-03	0.0707	0.0022	1.6	219232_s_at	EGLN3	egl nine homolog 3 (C. elegans)	112399
4.28E-04	0.0435	0.0003	1.6	**208710_s_at**	AP3D1	adaptor-related protein complex 3, delta 1 subunit	8943
9.84E-04	0.0569	0.0009	1.6	**218273_s_at**	PDP1	pyruvate dehyrogenase phosphatase catalytic subunit 1	54704
1.83E-04	0.0306	0.0003	1.6	**209945_s_at**	GSK3B	glycogen synthase kinase 3 beta	2932
3.77E-03	0.101	0.0046	1.6	**203407_at**	PPL	periplakin	5493
3.03E-02	0.275	0.0263	1.6	207802_at	CRISP3	cysteine-rich secretory protein 3	10321
1.65E-02	0.205	0.0179	1.6	205594_at	ZNF652	zinc finger protein 652	22834
1.72E-02	0.21	0.0165	1.6	210372_s_at	TPD52L1	tumor protein D52-like 1	7164
2.32E-02	0.242	0.0222	1.6	**203803_at**	PCYOX1	prenylcysteine oxidase 1	51449
2.10E-02	0.233	0.0239	1.6	**209875_s_at**	SPP1	secreted phosphoprotein 1	6696
6.66E-03	0.133	0.0077	1.6	213577_at	SQLE	squalene epoxidase	6713
2.54E-05	0.0167	< 1e-07	1.6	**201926_s_at**	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	1604
7.46E-03	0.141	0.0065	1.6	**213397_x_at**	RNASE4		
2.15E-03	0.0786	0.0025	1.6	**219468_s_at**	CUEDC1	CUE domain containing 1	404093
3.26E-03	0.094	0.0034	1.6	36711_a	MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	23764
3.75E-03	0.101	0.0039	1.6	**205709_s_at**	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1	1040
1.72E-	0.21	0.016	1.6	**220161_**	EPB41	erythrocyte membrane	54566

02		4		s_at	L4B	protein band 4.1 like 4B	
2.33E-03	0.0816	0.0026	1.5	202068_s_at	LDLR	low density lipoprotein receptor	3949
1.80E-03	0.074	0.0009	1.5	201849_at	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3	664
3.09E-03	0.0916	0.0033	1.5	219496_at	SOWAHC	sosondowah ankyrin repeat domain family member C	65124
6.63E-05	0.0214	< 1e-07	1.5	203042_at	LAMP2	lysosomal-associated membrane protein 2	3920
2.70E-03	0.0874	0.0027	1.5	222158_s_at	DESI2	desumoylating isopeptidase 2	51029
9.04E-03	0.155	0.0091	1.5	204044_at	QPRT	quinolinate phosphoribosyltransferase	23475
3.81E-05	0.0173	< 1e-07	1.5	204175_at	ZNF593	zinc finger protein 593	51042
5.28E-04	0.0472	0.0006	1.5	221526_x_at	PARD3	par-3 partitioning defective 3 homolog (C. elegans)	56288
6.97E-03	0.136	0.0074	1.5	202984_s_at	BAG5	BCL2-associated athanogene 5	9529
6.84E-05	0.0214	0.0002	1.5	219377_at	GAREM	GRB2 associated, regulator of MAPK1	64762
1.49E-04	0.0299	0.0003	1.5	202733_at	P4HA2	prolyl 4-hydroxylase, alpha polypeptide II	8974
5.37E-03	0.12	0.005	1.5	221577_x_at	GDF15	growth differentiation factor 15	9518
5.73E-04	0.0486	0.0004	1.5	209146_at	MSMO1	methylsterol monooxygenase 1	6307
6.05E-05	0.0201	0.0001	1.5	202929_s_at	DDT	D-dopachrome tautomerase	1652
7.09E-03	0.137	0.0083	1.5	213506_at	F2RL1	coagulation factor II (thrombin) receptor-like 1	2150
4.00E-07	0.00223	< 1e-07	1.5	202562_s_at	C14orf1	chromosome 14 open reading frame 1	11161
8.53E-04	0.054	0.0008	1.5	202314_at	CYP51A1		
1.47E-03	0.0676	0.0014	2.3	212094_at	PEG10	paternally expressed 10	23089
2.70E-03	0.0874	0.0018	2.2	219225_at	PGBD5	piggyBac transposable element derived 5	79605
3.43E-02	0.29	0.0339	2.0	213680_at	KRT6B	keratin 6B	3854
5.29E-03	0.12	0.0044	1.9	202286_s_at	TACSTD2	tumor-associated calcium signal transducer 2	4070
1.41E-03	0.0667	0.0015	1.9	202669_s_at	EFNB2	ephrin-B2	1948
9.41E-03	0.159	0.0091	1.9	204750_s_at	DSC2	desmocollin 2	1824
2.18E-02	0.236	0.0207	1.9	221690_s_at	NLRP2	NLR family, pyrin domain containing 2	55655
7.15E-04	0.0512	0.0008	1.9	211538_s_at	HSPA2	heat shock 70kDa protein 2	3306
4.95E-04	0.046	0.0002	1.8	206125_s_at	KLK8	kallikrein-related peptidase 8	11202
9.06E-03	0.155	0.009	1.8	205428_s_at	CALB2	calbindin 2	794
3.04E-02	0.275	0.034	1.8	202376_at	SERPINA3	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	12

2.65E-02	0.26	0.0262	1.8	205595_at	DSG3	desmoglein 3	1830
1.58E-03	0.0704	0.0014	1.8	204614_at	SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	5055
2.67E-04	0.0353	0.0003	1.8	201324_at	EMP1	epithelial membrane protein 1	2012
3.19E-02	0.281	0.0378	1.7	203628_at	IGF1R	insulin-like growth factor 1 receptor	3480
3.61E-03	0.0993	0.0036	1.7	214595_at	KCNG1	potassium voltage-gated channel, subfamily G, member 1	3755
1.91E-02	0.223	0.0205	1.7	209602_s_at	GATA3	GATA binding protein 3	2625
1.98E-03	0.076	0.0025	1.7	204059_s_at	ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	4199
1.94E-04	0.0317	0.0002	1.7	205809_s_at	WASL	Wiskott-Aldrich syndrome-like	8976
1.15E-05	0.0128	< 1e-07	1.7	204032_at	BCAR3	breast cancer anti-estrogen resistance 3	8412
3.60E-03	0.0993	0.0029	1.7	219995_s_at	ZNF750	zinc finger protein 750	79755
1.35E-03	0.0655	0.0016	1.7	212451_at	SECISBP2L	SECIS binding protein 2-like	9728
1.20E-04	0.0275	< 1e-07	1.7	203566_s_at	AGL	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase	178
1.30E-03	0.0644	0.0019	1.7	204058_at	ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	4199
1.49E-02	0.196	0.0155	1.6	218678_at	NES	nestin	10763
4.14E-02	0.315	0.0456	1.6	208900_s_at	TOP1	topoisomerase (DNA) I	7150
1.18E-03	0.0614	0.0013	1.6	208610_s_at	SRRM2	serine/arginine repetitive matrix 2	23524
1.00E-07	0.00223	< 1e-07	1.6	213526_s_at	LIN37	lin-37 homolog (C. elegans)	55957
3.34E-02	0.287	0.034	1.6	209581_at	PLA2G16	phospholipase A2, group XVI	11145
1.21E-02	0.179	0.0113	1.6	218858_at	DEPTOR	DEP domain containing MTOR-interacting protein	64798
2.63E-02	0.259	0.0258	1.6	204288_s_at	SORBS2	sorbin and SH3 domain containing 2	8470
3.97E-03	0.104	0.0038	1.6	204688_at	SGCE	sarcoglycan, epsilon	8910
1.86E-02	0.22	0.0194	1.6	217996_at	PHLDA1	pleckstrin homology-like domain, family A, member 1	22822
2.13E-04	0.0328	0.0003	1.6	209254_at	KLHDC10	kelch domain containing 10	23008
7.78E-03	0.144	0.0088	1.6	219263_at	RNF128	ring finger protein 128, E3 ubiquitin protein ligase	79589
1.05E-02	0.167	0.0083	1.6	219476_at	C1orf116	chromosome 1 open reading frame 116	79098
3.45E-02	0.291	0.0354	1.6	202600_s_at	NRIP1	nuclear receptor interacting protein 1	8204
2.73E-02	0.263	0.0249	1.6	209126_x_at	KRT6B	keratin 6B	3854
3.04E-03	0.0914	0.0031	1.6	206421_s_at	SERPINB7	serpin peptidase inhibitor, clade B (ovalbumin),	8710

						member 7	
3.35E-02	0.288	0.0341	1.6	209604_s_at	GATA3	GATA binding protein 3	2625
1.59E-03	0.0704	0.0016	1.6	212775_at	OBSL1	obscurin-like 1	23363
2.80E-02	0.266	0.026	1.6	205440_s_at	NPY1R	neuropeptide Y receptor Y1	4886
3.12E-02	0.278	0.033	1.6	204508_s_at	CA12	carbonic anhydrase XII	771
3.17E-02	0.28	0.0298	1.6	209301_at	CA2	carbonic anhydrase II	760
3.31E-02	0.286	0.0322	1.6	201860_s_at	PLAT	plasminogen activator, tissue	5327
8.35E-04	0.0537	0.0011	1.6	212294_at	GNG12	guanine nucleotide binding protein (G protein), gamma 12	55970
5.35E-04	0.0475	0.0003	1.6	201325_s_at	EMP1	epithelial membrane protein 1	2012
3.90E-02	0.307	0.0387	1.6	212992_at	AHNAK2	AHNAK nucleoprotein 2	113146
5.98E-03	0.126	0.0055	1.6	201996_s_at	SPEN	spen homolog, transcriptional regulator (Drosophila)	23013
4.43E-03	0.109	0.004	1.6	207480_s_at	MEIS2	Meis homeobox 2	4212
6.59E-03	0.133	0.0068	1.6	202454_s_at	ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	2065
4.22E-03	0.107	0.0048	1.6	212492_s_at	KDM4B	lysine (K)-specific demethylase 4B	23030
2.87E-02	0.268	0.0296	1.6	204748_at	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	5743
1.29E-02	0.183	0.0121	1.6	206307_s_at	FOXD1	forkhead box D1	2297
2.41E-02	0.247	0.0248	1.6	213110_s_at	COL4A5	collagen, type IV, alpha 5	1287
8.36E-04	0.0537	0.001	1.6	212634_at	UFL1	UFM1-specific ligase 1	23376
9.30E-03	0.157	0.0101	1.6	219681_s_at	RAB11FIP1	RAB11 family interacting protein 1 (class I)	80223
8.13E-03	0.147	0.0103	1.6	203319_s_at	ZNF148	zinc finger protein 148	7707
6.73E-04	0.0508	0.0007	1.6	204066_s_at	AGAP1	ArfGAP with GTPase domain, ankyrin repeat and PH domain 1	116987
3.68E-03	0.0999	0.004	1.6	219298_at	ECHDC3	enoyl CoA hydratase domain containing 3	79746
5.77E-03	0.124	0.0043	1.6	209720_s_at	SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	6317
3.05E-02	0.275	0.0294	1.6	210467_x_at	MAGEA12	melanoma antigen family A, 12	4111
1.88E-03	0.0755	0.0017	1.5	204029_at	CELSR2	cadherin, EGF LAG seven-pass G-type receptor 2	1952
1.09E-02	0.17	0.0114	1.5	204779_s_at	HOXB7	homeobox B7	3217
2.63E-	0.259	0.028	1.5	204686_	IRS1	insulin receptor substrate 1	3667

02		8		at			
6.28E-04	0.0493	0.001	1.5	209123_at	QDPR	quinoid dihydropteridine reductase	5860
1.04E-03	0.058	0.0009	1.5	212417_at	SCAMP1	secretory carrier membrane protein 1	9522
2.68E-03	0.0873	0.002	1.5	209719_x_at	SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	6317
9.14E-04	0.0547	0.0002	1.5	211906_s_at	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	6318
7.11E-04	0.0511	0.0007	1.5	219073_s_at	OSBPL10	oxysterol binding protein-like 10	114884
2.98E-02	0.273	0.0313	1.5	209488_s_at	RBPMS	RNA binding protein with multiple splicing	11030
6.36E-03	0.13	0.0073	1.5	203542_s_at	KLF9	Kruppel-like factor 9	687
3.76E-03	0.101	0.004	1.5	203780_at	MPZL2	myelin protein zero-like 2	10205
2.87E-02	0.268	0.0318	1.5	209443_at	SERPINA5	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5	5104
2.95E-03	0.09	0.0046	1.5	210612_s_at	SYNJ2	synaptojanin 2	8871
9.59E-03	0.16	0.0103	1.5	213030_s_at	PLXNA2	plexin A2	5362
1.19E-02	0.178	0.0124	1.5	218435_at	DNAJC15	DnaJ (Hsp40) homolog, subfamily C, member 15	29103
1.24E-02	0.181	0.0136	1.5	202998_s_at	LOXL2	lysyl oxidase-like 2	4017
2.27E-04	0.0336	0.0001	1.5	218253_s_at	EIF2D	eukaryotic translation initiation factor 2D	1939
6.56E-03	0.133	0.0062	1.5	203439_s_at	STC2	stanniocalcin 2	8614
3.01E-02	0.274	0.031	1.5	203929_s_at	MAPT	microtubule-associated protein tau	4137
4.26E-03	0.108	0.0038	1.5	204256_at	ELOVL6	ELOVL fatty acid elongase 6	79071
1.60E-04	0.0299	0.0003	1.5	218407_x_at	NENF	neudesin neurotrophic factor	29937
1.46E-03	0.0676	0.0019	1.5	221588_x_at	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	4329
1.23E-05	0.013	< 1e-07	0.3	211634_x_at			
3.61E-05	0.0173	0.0001	0.3	211635_x_at			
5.90E-04	0.0488	0.001	0.3	216491_x_at	IGHM	immunoglobulin heavy constant mu	3507
4.51E-04	0.0435	0.0007	0.4	205242_at	CXCL13	chemokine (C-X-C motif) ligand 13	10563
1.65E-03	0.0716	0.0019	0.4	214768_x_at	IGKC	immunoglobulin kappa constant	3514
5.56E-04	0.0479	0.0005	0.4	203915_at	CXCL9	chemokine (C-X-C motif) ligand 9	4283
2.06E-04	0.0327	0.0006	0.4	211637_x_at			
1.66E-03	0.0717	0.0021	0.4	214777_at			

1.57E-03	0.0701	0.0019	0.4	217148_x_at			
2.77E-04	0.0358	0.0006	0.4	214916_x_at			
3.35E-05	0.0173	< 1e-07	0.4	211633_x_at	IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	3500
2.82E-04	0.0358	0.0003	0.4	205267_at	POU2AF1	POU class 2 associating factor 1	5450
1.31E-03	0.0645	0.0018	0.4	216576_x_at			
1.22E-04	0.0277	0.0001	0.4	214973_x_at	IGHD	immunoglobulin heavy constant delta	3495
1.79E-04	0.0303	< 1e-07	0.4	217179_x_at			
2.22E-04	0.0332	0.0003	0.4	217281_x_at			
1.64E-03	0.0716	0.0011	0.4	216510_x_at			
2.50E-06	0.00587	< 1e-07	0.4	207238_s_at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
7.63E-03	0.142	0.008	0.4	205890_s_at			
9.88E-05	0.0245	< 1e-07	0.4	217235_x_at	IGLL5	immunoglobulin lambda-like polypeptide 5	1E+08
7.52E-03	0.141	0.0079	0.4	211644_x_at			
1.73E-05	0.0159	< 1e-07	0.4	207339_s_at	LTB	lymphotoxin beta (TNF superfamily, member 3)	4050
5.60E-04	0.0479	0.0007	0.4	216557_x_at			
3.98E-05	0.0173	0.0002	0.4	212588_at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
1.05E-04	0.0249	0.0001	0.4	211796_s_at			
5.16E-04	0.0464	0.0008	0.4	211650_x_at			
7.81E-05	0.0223	0.0002	0.5	204563_at	SELL	selectin L	6402
1.04E-03	0.058	0.0013	0.5	211643_x_at			
6.02E-03	0.127	0.0077	0.5	211645_x_at			
1.50E-05	0.0145	< 1e-07	0.5	215949_x_at			
8.04E-05	0.0223	0.0001	0.5	211640_x_at			
1.07E-03	0.0587	0.0011	0.5	205861_at	SPIB	Spi-B transcription factor (Spi-1/PU.1 related)	6689
8.17E-04	0.0537	0.0006	0.5	210915_x_at	TRBC1	T cell receptor beta constant 1	28639
1.10E-02	0.171	0.0109	0.5	211122_s_at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
1.51E-03	0.0688	0.0019	0.5	216207_x_at			
4.11E-04	0.0435	0.0002	0.5	219014_at	PLAC8	placenta-specific 8	51316

6.57E-03	0.133	0.007 7	0.5	216560_x_at	IGLC1	immunoglobulin lambda constant 1 (Mcg marker)	3537
2.74E-03	0.088	0.002 5	0.5	204439_at	IFI44L	interferon-induced protein 44-like	10964
3.00E-07	0.002 23	< 1e-07	0.5	211649_x_at			
3.16E-04	0.038 4	0.000 2	0.5	AFFX-HUMISGF3A/M97935_MA_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
3.65E-04	0.041 4	0.000 5	0.5	216541_x_at			
1.85E-03	0.075	0.002 2	0.5	217227_x_at	IGLV1-44	immunoglobulin lambda variable 1-44	28823
4.80E-03	0.115	0.006 7	0.5	216984_x_at			
1.41E-02	0.191	0.014 7	0.5	210029_at	IDO1	indoleamine 2,3-dioxygenase 1	3620
4.18E-04	0.043 5	0.000 3	0.5	211881_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
4.54E-04	0.043 6	0.000 8	0.5	205831_at	CD2	CD2 molecule	914
2.84E-04	0.035 8	0.000 3	0.5	206666_at	GZMK	granzyme K (granzyme 3; tryptase II)	3003
2.66E-04	0.035 3	0.000 3	0.5	211908_x_at	IGK@	immunoglobulin kappa locus	50802
1.30E-02	0.184	0.014 8	0.5	215176_x_at	IGKC	immunoglobulin kappa constant	3514
6.25E-03	0.129	0.005	0.5	206134_at	ADAMDEC1	ADAM-like, decysin 1	27299
1.28E-05	0.013	< 1e-07	0.5	209670_at	TRAC	T cell receptor alpha constant	28755
8.47E-03	0.15	0.009 8	0.5	217378_x_at			
1.68E-04	0.029 9	0.000 4	0.5	211868_x_at			
1.31E-02	0.184	0.014 2	0.5	210163_at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
1.88E-03	0.075 5	0.002 5	0.5	211798_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
2.66E-04	0.035 3	0.000 2	0.5	211641_x_at			
4.18E-03	0.107	0.003 4	0.5	204533_at	CXCL10	chemokine (C-X-C motif) ligand 10	3627
1.76E-03	0.073 7	0.001 7	0.5	214657_s_at			
3.66E-03	0.099 9	0.002 9	0.5	205569_at	LAMP3	lysosomal-associated membrane protein 3	27074
1.56E-02	0.2	0.017 1	0.5	216401_x_at			
1.93E-05	0.015 9	< 1e-07	0.5	204912_at	IL10RA	interleukin 10 receptor, alpha	3587
1.10E-04	0.025 8	< 1e-07	0.5	210538_s_at	BIRC3	baculoviral IAP repeat containing 3	330
6.40E-06	0.008 39	0.000 1	0.5	203471_s_at	PLEK	pleckstrin	5341
2.71E-03	0.087 6	0.003 3	0.5	217480_x_at			

6.37E-04	0.0493	0.0006	0.5	214453_s_at	IFI44	interferon-induced protein 44	10561
8.90E-04	0.0547	0.0007	0.5	AFFX-HUMISGF3A/M97935_MB_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
2.46E-03	0.0834	0.0028	0.5	212671_s_at			
7.63E-05	0.0223	0.0002	0.5	211639_x_at			
2.12E-04	0.0328	< 1e-07	0.5	205671_s_at	HLA-DOB	major histocompatibility complex, class II, DO beta	3112
3.29E-05	0.0173	< 1e-07	0.5	212314_at	SEL1L3	sel-1 suppressor of lin-12-like 3 (C. elegans)	23231
1.38E-03	0.066	0.0011	0.5	204891_s_at	LCK	lymphocyte-specific protein tyrosine kinase	3932
5.95E-05	0.0201	0.0001	0.5	204118_at	CD48	CD48 molecule	962
3.18E-04	0.0385	0.0004	0.5	203868_s_at	VCAM1	vascular cell adhesion molecule 1	7412
6.25E-04	0.0493	0.0009	0.5	217258_x_at	IGLV1-44	immunoglobulin lambda variable 1-44	28823
1.22E-03	0.0622	0.0014	0.5	213888_s_at	TRAF3IP3	TRAF3 interacting protein 3	80342
1.91E-03	0.0755	0.002	0.5	204279_at	PSMB9	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	5698
4.04E-03	0.105	0.0037	0.5	205159_at	CSF2RB	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	1439
2.62E-04	0.0353	0.0001	0.5	213193_x_at	TRBC1	T cell receptor beta constant 1	28639
8.93E-03	0.154	0.0087	0.5	204006_s_at			
3.28E-02	0.284	0.0353	0.5	209374_s_at	IGHM	immunoglobulin heavy constant mu	3507
8.66E-04	0.0543	0.0004	0.5	210972_x_at			
8.23E-04	0.0537	0.0006	0.5	213539_at	CD3D	CD3d molecule, delta (CD3-TCR complex)	915
9.90E-05	0.0245	< 1e-07	0.5	209671_x_at			
3.98E-04	0.0433	0.0006	0.6	217157_x_at			
2.57E-03	0.0851	0.0025	0.6	212311_at	SEL1L3	sel-1 suppressor of lin-12-like 3 (C. elegans)	23231
4.26E-02	0.321	0.0396	0.6	209116_x_at	HBB	hemoglobin, beta	3043
1.15E-03	0.0608	0.0008	0.6	206715_at	TFEC	transcription factor EC	22797
8.48E-03	0.15	0.0099	0.6	203639_s_at	FGFR2	fibroblast growth factor receptor 2	2263
2.87E-03	0.0895	0.0027	0.6	204834_at	FGL2	fibrinogen-like 2	10875
2.99E-02	0.273	0.0283	0.6	210072_at	CCL19	chemokine (C-C motif) ligand 19	6363
1.81E-	0.074	0.001	0.6	215049_	CD163	CD163 molecule	9332

03		8		x_at			
4.40E-03	0.109	0.0039	0.6	205488_at	GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	3001
5.45E-04	0.0478	0.0006	0.6	209606_at	CYTIP	cytohesin 1 interacting protein	9595
8.00E-06	0.0099	< 1e-07	0.6	212307_s_at	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	8473
1.46E-03	0.0676	0.0012	0.6	209823_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
2.10E-04	0.0328	< 1e-07	0.6	204890_s_at	LCK	lymphocyte-specific protein tyrosine kinase	3932
9.72E-04	0.0567	0.001	0.6	203922_s_at	CYBB	cytochrome b-245, beta polypeptide	1536
2.89E-04	0.0361	0.0005	0.6	216250_s_at	LPXN	leupaxin	9404
2.32E-03	0.0816	0.0018	0.6	209846_s_at	BTN3A2	butyrophilin, subfamily 3, member A2	11118
8.91E-05	0.0231	0.0001	0.6	202524_s_at	SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	9806
3.98E-04	0.0433	0.0004	0.6	213915_at	NKG7	natural killer cell group 7 sequence	4818
3.46E-03	0.0971	0.0028	0.6	205541_s_at	GSPT2	G1 to S phase transition 2	23708
2.70E-05	0.0167	< 1e-07	0.6	221978_at	HLA-F	major histocompatibility complex, class I, F	3134
9.54E-04	0.056	0.0003	0.6	204116_at	IL2RG	interleukin 2 receptor, gamma	3561
3.31E-05	0.0173	< 1e-07	0.6	221087_s_at	APOL3	apolipoprotein L, 3	80833
4.17E-04	0.0435	0.0002	0.6	202510_s_at	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	7127
6.02E-04	0.049	0.0004	0.6	210356_x_at	MS4A1	membrane-spanning 4-domains, subfamily A, member 1	931
1.44E-04	0.0299	0.0002	0.6	218805_at			
7.51E-04	0.0523	0.0005	0.6	221973_at			
5.02E-03	0.116	0.0035	0.6	209969_s_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
2.73E-02	0.263	0.0282	0.6	209924_at	CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	6362
3.89E-03	0.103	0.0033	0.6	208798_x_at	GOLGA8A	golgin A8 family, member A	23015
2.79E-02	0.266	0.0264	0.6	205681_at	BCL2A1	BCL2-related protein A1	597
1.65E-03	0.0716	0.0016	0.6	203645_s_at	CD163	CD163 molecule	9332
3.67E-03	0.0999	0.0037	0.6	205692_s_at	CD38	CD38 molecule	952
6.18E-03	0.129	0.0049	0.6	34210_at	CD52	CD52 molecule	1043
2.67E-05	0.0167	< 1e-07	0.6	203416_at	CD53	CD53 molecule	963

1.97E-03	0.076	0.0019	0.6	204057_at	IRF8	interferon regulatory iactor 8	3394
4.55E-04	0.0436	0,0003	0.6	222150_s_at	PION	pigeon homo log (Drosophila)	54103
5.98E-04	0.049	0,0006	0.6	210982_s_at	HLA-DRA	major histocompatibility complex. Class Π, DR alpha	3122
2.20E-03	0.0794	0.0023	0.6	200796_s_at	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	4170
3.21E-04	.0.0386	0.0005	0.6	202531_at	lRFi	interferon regulatory factor 1	3659
2.07E-04	0.0327	0.0002	0.6	38149_at	ARHGAP25	Rho GTPase activating: protein 25	9938
2.33E-04	0.034	<; 1e-07	0,6	204821_at	BTN3A3	feutyrophilin* subfamily 3, member A3	10384
8.49E-05	0.0223	0.0001	0.6	212950_at	USP34	uhiquitin ..specific peptidase 34	9736
1.05E-02,	0.167	0.01	0.6	202902_s_at	CTSS	eathepsin S	1520
7.52E-04	0.0523	0.0004	0,6	205049_s_at	CD79A	CD79a molecule. imrnunoglobulin-associated alpha	973
2.90E-06	0.00587	< 1c-07	0.6	207564_x_at	OGT	Q-linked N-acetylglueosamine (GlcNAc) transferase	8473
4.23!:-04	0.0435	0.001	0.6	212384_at			
1.35E-04	0.0291	0.0003	0.6	213160_at	DOCK2.	dedicator of cytokinesis 2:	1794
1.14E-03	0.0603	0,0013	0.6	221286_s_at	MZB1	marginal zone B and B1 cell-specific protein	51237
1.64E-04	0.0299	0.0001	0.6	205997_at	ADAM28	ADAM metallopeptidase domain 28	10863
5.11E-04	0.0463	0.0002	0.6	204192_at	CD37	CD37 molecule	951
1.46E-03	0.0676	0.0012	0.6	212827_at	IGHM	immunoglobulin heavy constant mu	3507
8.33E-05	0.0223	< le-07	0.6	207563_s_al	OGT	Q-linked N-acetylglucosamine (GlcNAc) transferase	8473
1.04E-04	0.0249	0.0002	0.6	214093_s_at	FUBP1	far upstream element (FUSE) binding protein 1	8880
1>59E-02	0,201	0.0168	0.6	208228_s_at	FGFR2	fibroblast growth Iactor receptor 2	2263
1.62E-04	0.0299	< 1e-07	0.6	205291_at	IL2RB	interleukin 2 receptor, beta	3560
4.74E-03	0.114	0.0062	0.6	214753_at	N4BP2L2	NEDD4 binding protein 2-like 2	10443
3.50E-04	0.0407	0.0003	0,6	206337_at	CCR7	chemokine (C-C motif) receptor 7	1236
5,11E-04	0.0463	0.0003	0.6	211991_s_at	HLA-DPA1	major hi sincompatibility complex, class II. DP alpha 1	3113
2.76E-03	0.0881	0.0014	0.6	204661_at	CD52	CD52 molecule	1043
6.S4E-04	0.0509	0.0007	0.6	203760_s_at	SLA	Src-like-adaptor	6503
2.95E-03	0.09:	0.0029	0,6	202988_s_at	RGS1	regulator of G-protein signaling 1	5996
2.751·.-	0.088	0.002	0,6	203381_	APOE	apolipoprotein E	348

03	1	5		s_at			
3.65E-02	0.3	0.0351	0.6	214023_x_at	TUBB2B	tubulin, beta 2B class IIb	347733
1.92E-05	0.0159	0.0001	0.6	212577_at	SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1	23347
4.68E-02	0.333	0.0425	0.6	217414_x_at			
3.00E-07	0.00223	< 1e-07	0.6	205298_s_at	BTN2A2	butyrophilin, subfamily 2, member A2	10385
2.51E-03	0.084	0.002	0.6	202953_at	C1QB	complement component 1, q subcomponent, B chain	713
4.09E-02	0.313	0.0404	0.6	215214_at			
7.67E-04	0.0525	0.0004	0.6	210425_x_at			
1.76E-04	0.0303	0.0001	0.6	209685_s_at	PRKCB	protein kinase C, beta	5579
6.04E-04	0.049	0.0006	0.6	202643_s_at	TNFAIP3	tumor necrosis factor, alpha-induced protein 3	7128
4.20E-06	0.00624	< 1e-07	0.6	212232_at	FNBP4	formin binding protein 4	23360
4.86E-02	0.337	0.0442	0.6	209458_x_at			
2.47E-04	0.0352	0.0002	0.6	209312_x_at			
4.92E-03	0.116	0.0047	0.6	201858_s_at	SRGN	serglycin	5552
3.21E-02	0.281	0.0292	0.6	216853_x_at			
2.09E-03	0.0782	0.0021	0.6	208894_at	HLA-DRA	major histocompatibility complex, class II, DR alpha	3122
1.44E-03	0.0676	0.0012	0.6	211902_x_at	YME1L1	YME1-like 1 (S. cerevisiae)	10730
3.15E-03	0.0927	0.0033	0.6	AFFX-HUMISGF3A/M97935_5_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
4.50E-03	0.11	0.0052	0.6	218232_at	C1QA	complement component 1, q subcomponent, A chain	712
9.04E-04	0.0547	0.0009	0.6	213502_x_at	GUSBP11	glucuronidase, beta pseudogene 11	91316
2.47E-02	0.249	0.0283	0.6	221728_x_at	XIST	X inactive specific transcript (non-protein coding)	7503
7.01E-04	0.0509	0.0006	0.6	221989_at			
7.23E-04	0.0515	0.0007	0.6	211656_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
5.81E-04	0.0487	0.0005	0.6	215193_x_at			
5.71E-04	0.0485	0.0009	0.6	203470_s_at	PLEK	pleckstrin	5341
5.58E-04	0.0479	0.0004	0.6	216542_x_at			
2.43E-03	0.083	0.0018	0.6	214617_at	PRF1	perforin 1 (pore forming protein)	5551
3.23E-03	0.0933	0.0028	0.6	217143_s_at	YME1L1	YME1-like 1 (S. cerevisiae)	10730

2.76E-03	0.0881	0.0033	0.6	20392¾_s_at	CYBB	cytochrome b-245, beta polypeptide	1536
1.91E-03	0.0755	0.0016	0,6	2!3703_at	IJMCO0342	long intergenie non-protein coding RNA 342	150759
2.9m-03	0,09	0,0021	0.6	209083_at	CORO1A	eoronin, actin binding protein, 1A	1I151
5.67E-05	0.02	0.0002	0.6	203932_at	HLA-DMB	major histommpati bility complex, class II, DM beta	3109
5.46E-03	0.121	0.0047	0.6	201718_s_at	EPB41L2	erythrocyte membrane protein hand 4.1-like 2	2037
3.f1E-02	0.277	0.0332	0.6	2!0164_at	GZMB	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)	3002
1.78E-04	0.0303	0,0004	0,6	204670_x_at			
5.68E-03	0.123	0.006	0.6	2H742_s_at	EVI2B	ecotropic viral integration site 2B	2124
1.62E-03	0.071	0.0022	0.6	221768_at			
3.55E-04	0.041	0.0001	0,6	201720_s_at	LAPTM5	lysosomal protein transmembrane 5	7805
1.80E-06	0.00573	< 1e-07	0.6	2!2036_&at	PNN	pinin, desmosome associated protein	5411
8.48E-05	0.0223	< 1e-07	0.6	204674_at	LRMP	lymphoid-restrieted membrane protein	4033
1.16E-03	0.0608	0.0011	*0.6*	213142_x_at	PION	pigeon homolog (Drosophila)	54103
5.741;-05	0.02	< 1e-07	0.6	205270_s_at	LCP2	lymphocyte cylosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	3937
5.88E-03	0.126	0.005	0.6	211654_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
3,00E-03	0.0909	0.0033	0.6	215946_x_at	IC.LE3P	iiiimuiiogiobulin lambda-like polypeptide 3, pseudogene	91353
1.OOE-03	0.0571	0.0008	0.6	209723_at	SERPINB9	serpin peptidase inhibitor, clade B (ovalbumin), member 9	5272
8..78E-04	0.0545	0,0007	0.6	205842_s_at	JAK2	Janus kinase 2	3717
4.43E-04	0.0435	0.0004	0.6	203236_s_at	LGALS9	lectin, galaetoside-binding, soluble, 9	3965
2.42E-03	0.083	0.002	0.6	2!7418_x_at	MS4A1	membrane-spanning 4-domains, subfamily A, member 1	931
1.14E-02	0.174	0.0105	0.6	202086_at	MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	4599
9.48E-03	0.159	0.0085	0.6	213875_x_at	C6orf62	chromosome 6 open reading frame 62	81688
5.771·-03	0.124	0.0047	0,6	203879_at	PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	5293
8.98E-04	0.0547	0.0003	0.6	204882_at	ARHGAP25	Rho GTPase activating protein 25	9938
6.21B-04	0.0493	0.0009	0.6	221427_s_at	CCNL2	evelin L2	81669
1.60E-	0.202	0.013	0.6	210663_	KYNU	kynureninase	8942

02		7		s_at			
9.08E-04	0.0547	0.0004	0.6	210116_at	SH2D1A	SH2 domain containing 1A	4068
4.28E-03	0.108	0.0041	0.6	216614_at			
1.30E-03	0.0644	0.0015	0.6	213326_at	VAMP1	vesicle-associated membrane protein 1 (synaptobrevin 1)	6843
1.78E-03	0.074	0.0016	0.6	221602_s_at	FAIM3	Fas apoptotic inhibitory molecule 3	9214
3.19E-03	0.0931	0.0029	0.6	38241_at	BTN3A3	butyrophilin, subfamily 3, member A3	10384
2.58E-03	0.0851	0.0021	0.6	205758_at	CD8A	CD8a molecule	925
4.94E-03	0.116	0.0048	0.6	213359_at	HNRNPD	heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa)	3184
1.04E-02	0.166	0.0093	0.6	204959_at	MNDA	myeloid cell nuclear differentiation antigen	4332
3.44E-03	0.0969	0.0034	0.6	206133_at	XAF1	XIAP associated factor 1	54739
4.31E-02	0.322	0.043	0.6	217388_s_at	KYNU	kynureninase	8942
1.20E-03	0.0616	0.0011	0.6	213293_s_at	TRIM22	tripartite motif containing 22	10346
6.36E-03	0.13	0.0067	0.6	208018_s_at	HCK	hemopoietic cell kinase	3055
7.89E-04	0.0528	0.0018	0.6	214132_at	ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	509
1.49E-02	0.196	0.0147	0.6	212998_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
1.13E-02	0.174	0.0111	0.6	219666_at	MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	64231
2.30E-06	0.00587	< 1e-07	0.6	202380_s_at	NKTR	natural killer-tumor recognition sequence	4820
1.05E-02	0.167	0.0102	0.6	219209_at	IFIH1	interferon induced with helicase C domain 1	64135
1.76E-02	0.212	0.0158	0.6	206641_at	TNFRSF17	tumor necrosis factor receptor superfamily, member 17	608
3.90E-03	0.103	0.0036	0.7	206978_at	CCR2	chemokine (C-C motif) receptor 2	729230
4.75E-05	0.0186	0.0001	0.7	204923_at	SASH3	SAM and SH3 domain containing 3	54440
1.94E-03	0.0755	0.0013	0.7	218543_s_at	PARP12	poly (ADP-ribose) polymerase family, member 12	64761
6.79E-05	0.0214	0.0002	0.7	213269_at	ZNF248	zinc finger protein 248	57209
8.26E-05	0.0223	0.0001	0.7	204234_s_at	ZNF195	zinc finger protein 195	7748
6.48E-04	0.0498	0.0005	0.7	203761_at	SLA	Src-like-adaptor	6503
6.59E-03	0.133	0.0047	0.7	201104_x_at			

1.92E-02	0.223	0.018	0.7	211090_s_at	PRPF4B	PRP4 pre-mRNA processing factor 4 homolog B (yeast)	8899
3.28E-03	0.0942	0.0022	0.7	213603_s_at	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	5880
2.15E-03	0.0786	0.0023	0.7	203382_s_at	APOE	apolipoprotein E	348
1.23E-02	0.18	0.0124	0.7	216920_s_at			
1.74E-02	0.212	0.0196	0.7	211996_s_at			
4.63E-03	0.112	0.0049	0.7	202803_s_at	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	3689
1.73E-04	0.0301	0.0001	0.7	212613_at	BTN3A2	butyrophilin, subfamily 3, member A2	11118
1.81E-03	0.074	0.0016	0.7	210279_at	GPR18	G protein-coupled receptor 18	2841
3.02E-04	0.0374	0.0006	0.7	221971_x_at			
1.40E-02	0.191	0.0148	0.7	211317_s_at	CFLAR	CASP8 and FADD-like apoptosis regulator	8837
2.51E-03	0.084	0.0016	0.7	203185_at	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	9770
1.58E-02	0.201	0.0169	0.7	214059_at	IFI44	interferon-induced protein 44	10561
6.57E-03	0.133	0.0067	0.7	208747_s_at	C1S	complement component 1, s subcomponent	716
7.43E-04	0.0523	0.0008	0.7	208885_at	LCP1	lymphocyte cytosolic protein 1 (L-plastin)	3936
1.12E-02	0.173	0.0099	0.7	216829_at			
1.57E-03	0.0701	0.001	0.7	210031_at	CD247	CD247 molecule	919
1.87E-02	0.22	0.0177	0.7	219505_at	CECR1	cat eye syndrome chromosome region, candidate 1	51816
2.67E-03	0.0869	0.0027	0.7	202957_at	HCLS1	hematopoietic cell-specific Lyn substrate 1	3059
1.67E-04	0.0299	0.0001	0.7	208306_x_at			
2.56E-04	0.0353	0.0004	0.7	221850_x_at			
5.66E-03	0.123	0.0054	0.7	212187_x_at	PTGDS	prostaglandin D2 synthase 21kDa (brain)	5730
3.30E-04	0.0394	0.0005	0.7	220046_s_at	CCNL1	cyclin L1	57018
7.28E-03	0.139	0.0073	0.7	222018_at	NACA	nascent polypeptide-associated complex alpha subunit	4666
1.32E-02	0.185	0.0133	0.7	214567_s_at			
2.61E-02	0.258	0.0261	0.7	213537_at	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	3113
2.18E-04	0.0328	0.0003	0.7	207734_at	LAX1	lymphocyte transmembrane adaptor 1	54900

1.65E-04	0.0299	0.0003	0.7	217610_at	SPDYE2	speedy homolog E2 (Xenopus laevis)	441273
4.96E-04	0.046	0.0001	0.7	206150_at	CD27	CD27 molecule	939

Table 16. Class comparison of the global gene expression profiles of high TN score ER- tumors to low TN score ER- tumors in the ROCK dataset (highlighted probe set indicates common in high TN score BLBC and ER- breast tumours).

Parametric p-value	FDR	Permutation p-value	Fold-change for high TN score vs. Low TN score	ProbeSet	Symbol	Name	EntrezID
< 1e-07	< 1e-07	< 1e-07	3.0	209803_s_at	PHLDA2	pleckstrin homology-like domain, family A, member 2	7262
2.72E-05	0.000683	0.0002	2.9	211657_at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
5.00E-07	0.000338	< 1e-07	2.8	203108_at	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
1.28E-04	0.00209	0.0001	2.7	204351_at	S100P	S100 calcium binding protein P	6286
2.00E-07	0.000168	< 1e-07	2.4	202489_s_at	FXYD3	FXYD domain containing ion transport regulator 3	5349
< 1e-07	< 1e-07	< 1e-07	2.3	201467_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
5.00E-07	0.000338	< 1e-07	2.2	210519_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
4.88E-04	0.00588	0.0005	2.1	203021_at	SLPI	secretory leukocyte peptidase inhibitor	6590
< 1e-07	< 1e-07	< 1e-07	2.1	219232_s_at	EGLN3	egl nine homolog 3 (C. elegans)	112399
1.96E-05	0.000531	< 1e-07	2.1	218309_at	CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	55450
5.00E-07	0.000338	< 1e-07	2.1	204144_at	QPRT	quinolinate phosphoribosyltransferase	23475
2.00E-07	0.000168	< 1e-07	2.1	201468_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
3.00E-07	0.000224	< 1e-07	2.0	205968_at	KCNS3	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	3790
< 1e-07	< 1e-07	< 1e-07	2.0	201286_at	SDC1	syndecan 1	6382
3.60E-06	0.000144	< 1e-07	2.0	203803_at	PCYOX1	prenylcysteine oxidase 1	51449
1.00E-05	0.000317	< 1e-07	2.0	200862_at	DHCR24	24-dehydrocholesterol reductase	1718
8.43E-	0.048	0.009	2.0	204268_	S100A2	S100 calcium binding	6273

03	1	9		at		protein A2	
< 1e-07	< 1e-07	< 1e-07	2.0	209146_at	MSMO1	methylsterol monooxygenase 1	6307
1.30E-06	0.0000677	< 1e-07	1.9	203058_s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
3.20E-05	0.000761	0.0001	1.9	203060_s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
3.84E-05	0.00087	< 1e-07	1.9	210652_s_at	TTC39A	tetratricopeptide repeat domain 39A	22996
6.51E-04	0.00727	0.0006	1.9	213693_s_at	MUC1	mucin 1, cell surface associated	4582
1.56E-04	0.00243	0.0002	1.9	212444_at	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
2.00E-07	0.0000168	< 1e-07	1.9	205709_s_at	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1	1040
< 1e-07	< 1e-07	< 1e-07	1.9	202068_s_at	LDLR	low density lipoprotein receptor	3949
< 1e-07	< 1e-07	< 1e-07	1.8	201849_at	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3	664
1.10E-06	0.0000599	< 1e-07	1.8	218273_s_at	PDP1	pyruvate dehyrogenase phosphatase catalytic subunit 1	54704
9.00E-07	0.0000513	< 1e-07	1.8	213577_at	SQLE	squalene epoxidase	6713
2.60E-06	0.000114	< 1e-07	1.8	36711_at	MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	23764
3.60E-03	0.0257	0.0025	1.8	207847_s_at	MUC1	mucin 1, cell surface associated	4582
6.90E-06	0.000234	< 1e-07	1.8	201596_x_at	KRT18	keratin 18	3875
3.11E-04	0.00416	0.0005	1.8	201951_at	ALCAM	activated leukocyte cell adhesion molecule	214
8.00E-07	0.0000477	< 1e-07	1.8	222258_s_at	SH3BP4	SH3-domain binding protein 4	23677
1.36E-02	0.0676	0.0127	1.8	203453_at	SCNN1A	sodium channel, non-voltage-gated 1 alpha subunit	6337
3.00E-07	0.0000224	< 1e-07	1.8	219496_at	SOWAHC	sosondowah ankyrin repeat domain family member C	65124
8.54E-05	0.00157	0.0001	1.8	218959_at	HOXC10	homeobox C10	3226
1.01E-05	0.000319	< 1e-07	1.8	203407_at	PPL	periplakin	5493
5.20E-05	0.0011	0.0001	1.8	219127_at	PRR15L	proline rich 15-like	79170
2.00E-07	0.0000168	< 1e-07	1.8	221042_s_at	CLMN	calmin (calponin-like, transmembrane)	79789
1.84E-02	0.083	0.0181	1.8	214079_at	DHRS2	dehydrogenase/reductase (SDR family) member 2	10202
1.00E-06	0.0000561	< 1e-07	1.8	209260_at	SFN	stratifin	2810
1.80E-02	0.0818	0.0183	1.8	218211_s_at	MLPH	melanophilin	79083
1.57E-03	0.0141	0.0021	1.8	221024_s_at	SLC2A10	solute carrier family 2 (facilitated glucose transporter), member 10	81031

2.40E-03	0.0193	0.0029	1.8	219580_s_at	TMC5	transmembrane channel-like 5	79838
1.90E-03	0.0162	0.0024	1.8	214580_x_at	KRT6C		
6.25E-05	0.00125	0.0001	1.7	219959_at	MOCOS	molybdenum cofactor sulfurase	55034
< 1e-07	< 1e-07	< 1e-07	1.7	202314_at	CYP51A1		
6.32E-03	0.0392	0.0074	1.7	219956_at	GALNT6	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6)	11226
1.60E-06	0.0000801	< 1e-07	1.7	213285_at	TMEM30B	transmembrane protein 30B	161291
1.45E-03	0.0133	0.0013	1.7	209875_s_at	SPP1	secreted phosphoprotein 1	6696
5.93E-05	0.00121	0.0002	1.7	210372_s_at	TPD52L1	tumor protein D52-like 1	7164
8.05E-05	0.00151	< 1e-07	1.7	209373_at	MALL	mal, T-cell differentiation protein-like	7851
1.70E-06	0.0000836	< 1e-07	1.7	219458_s_at	CUEDC1	CUE domain containing 1	404093
2.27E-02	0.0956	0.0217	1.7	207802_at	CRISP3	cysteine-rich secretory protein 3	10321
4.60E-06	0.000174	0.0001	1.7	202984_s_at	BAG5	BCL2-associated athanogene 5	9529
1.00E-07	9.52E-06	< 1e-07	1.7	202733_at	P4HA2	prolyl 4-hydroxylase, alpha polypeptide II	8974
< 1e-07	< 1e-07	< 1e-07	1.7	209945_s_at	GSK3B	glycogen synthase kinase 3 beta	2932
< 1e-07	< 1e-07	< 1e-07	1.7	202929_s_at	DDT	D-dopachrome tautomerase	1652
9.92E-05	0.00175	< 1e-07	1.7	210239_at	IRX5	iroquois homeobox 5	10265
< 1e-07	< 1e-07	< 1e-07	1.7	201926_s_at	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	1604
< 1e-07	< 1e-07	< 1e-07	1.7	202552_s_at	C14orf1	chromosome 14 open reading frame 1	11161
3.30E-06	0.000135	< 1e-07	1.6	203916_s_at	ARG2	arginase, type II	384
1.03E-02	0.0554	0.0089	1.6	204913_s_at	SOX11	SRY (sex determining region Y)-box 11	6664
8.35E-04	0.0087	0.0008	1.6	213397_x_at	RNASE4		
4.72E-04	0.00571	0.0007	1.6	205110_s_at	FGF13	fibroblast growth factor 13	2258
1.70E-02	0.0786	0.0166	1.6	209699_x_at	AKR1C2	aldo-keto reductase family 1, member C2	1646
5.32E-05	0.00112	< 1e-07	1.6	221577_x_at	GDF15	growth differentiation factor 15	9518
2.77E-02	0.109	0.0253	1.6	209800_at	KRT16	keratin 16	3868
8.59E-04	0.00887	0.0009	1.6	204595_s_at	STC1	stanniocalcin 1	6781
6.45E-04	0.00722	0.0005	1.6	204284_at	PPP1R3C	protein phosphatase 1, regulatory subunit 3C	5507

< 1e-07	< 1e-07	< le-07	1.6	203042_at	LAMP2	lysomai-associated membrane protein 2	3920
9.00E-07	o.0QO 0513	< le-07	1.6	219377_at	GAREM	GRB2 associated, regulator of MAPK1	64762
9.13E-04	0,009 26	0.000 9	1.6	204818_at	HSD17B 2	hydroxy steroid (17-betaj dehydrogenase 2	3294
< 1e-07	< ie-07	< 1e-07	1.6	204175_atIIIIII	ZNF593	zinc finger protein 593	51042
1.79E-03	0,015 5	0.002 7	1.6	203180_at	ALDH1 A3	aldehyde dehydrogenase 1 family, member A3	220
1.27E-04	0,002 09	0.000 2	1.6	:13506_at	F2RL1	coagulation factor II (thrombin) receptor-like 1	2150
8.05E-05	0,000 737	< le-07	1.6	222158_s_at	DESI2	desumoylating isopeptidase 2	51029
1.09E-04	0.001 88	< 1e-07	1.6	221589_s_at	ALDH6 A1	aldehyde dehydrogenase 6 family, member A1	4329
4.56E-04	0,005 55	0.000 8	1.5	220230_s_at	CYB5R2-	cytochrome *b*5 reductase 2	51700
2.20E-06	0,000 102	< 1e-07	1.5	32313 6_x_at	PARD3	par-3 partitioning defective 3 homolog (C. elegans)	56288
3.98E-04	0.005 02	0.000 6	1.5	206326_at	GRP	gastrin-releasing peptide	2922
1.17E-04	0.001 99	0.000 1	1.5	208110_s_at	AP3D1	adaptor-related protein complex 3, delta 1 subunit	8943
7.70E-04	0.008 19	0.000 5	1.5	220161_s_at	EPB41L 4B	erythrocyte membrane protein band 4.1 like 4B	54566
3.03*E*-02	0.1 16	().032 8	1.5	209160_at	AKR1C3	aldo-keto reductase family 1. member C3	8644
8.78E-03	0,049 5	0.008 9	1.5	201242_s_*a*	ATP1B 1	ATPase, Na+/K+ transporting, beta 1 polypentide	481
1.23E-02	0.062 8	0,012 4	1,5	203215_s_at	MY06	myosin VI	4646
7.09E-03	0.042 5	0.005 5	1.5	205594_at	ZNF652	zinc finger protein 652	22834
3.42E-05	0.000 804	< 1e-07	4.5	205916_at	S100A7	S100 calcium binding protein A7	6278
3.40E-05	0,000 802	0.000 2	3.0	203757_s_at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
1.56E-03	0.014 1	0.001 3	2.8	AFFX-HUMRGE/M10098_5_at	LINC00273	long intergenie non-protein coding RNA 273	649159
1.96E-03	0.0 16 6	0.001 7	2.7	AFFX-r2-Hs18SrRNA-5_at			
1.1 IE-04	0.001 91	< le-07	2.7	203535_at	S100A9	S100 calcium binding protein A9	6280
5.14E-03	0,033 7	0.004 8	2.6	206378_at	SCGB2A 2	secretoglobin, family 2A, member 2	4250
1.75E-04	0.002 65	0.000 3	2,6	217528_at	CLCA2	chloride channel accessory 2	9635
5.53E-05	0.001 15	< le-07	2.4	206166_s_at	CLCA2	chloride channel accessory 2	9635
3.78E-03	0.026 6	0.003 9	2.2	202917_s_at	S100A8	S100 calcium binding protein A8	6279

3.17E-04	0.00422	0.0004	2.2	206165_s_at	CLCA2	chloride channel accessory 2	9635
2.46E-04	0.00347	0.0001	2.2	2Q6164_at	CLCA2	chloride channel accessory 2	9635
1.15E-02	0.0598	0.0118	2.2	209173_at	AGE2	anterior gradient 2 homolog (Xenopus laevis)	10551
1.45E-03	0.0133	0.0011	2.1	214461_at	LBP	lipopolys,accharid e binding protein	3929
1.99E-03	0.0168	0.0019	2.1	220192_x_at	SPDEF	SAM pointed domain containing ets transcription factor	25803
4.50E-06	0,00017 1	< le-07	2.1	20656 1_s_at	AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	57016
5.91E-04	0.00679	0.0004	2.0	204942_s_a!	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	222
1.76E-03	0.0153	0.0014	2.0	214774_x_at	T0X3	TQX high mobility group box family member 3	27324
2.33E-05	0i)00:604	< le-07	2.0	202712_s_at			
< le-07	< le-07	< le-07	2.0	218145_at	TRIB3	tribbles homolog 3 (Drosophila)	57761
1.99E-03	0.0168	0.0018	2.0	217284_x_at	SERHL2	serine hydrolase-like 2	253190
1.58E-03	0.0142	0.0018	2.0	217276_x_at	SERHL2	serine hydrolase-like 2	253190
1.43E-03	0.0131	0.0012	2.0	216623_x_at	TQX3	TOX high mobility group box family member 3	27324
< le-07	< le-07	< le-07	2.0	214073_at	CTTN	cortactin	2017
1.11E-02	0.0586	0.0091	2.0	209309_at	AZGP1	aJpha-2-giycopiOtei n 1, zinc-binding	563
1.36E-03	0.0126	0.0014	1.9	205979_at	SCGB2A1	SeeretOglobin, family 2A, member 1	4246
2.08E-02	0.0898	0.02	1.9	214451_at	TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	7021
1.79E-02	0.0814	0.0182	1.9	206799_at	SCGB1D2	secreioglobin, family 1D, member 2	10647
3.40E-06	0.000138	< le-07	1.9	203967_at	CDC6	cell division cycle 6	990
2.84E-04	0.00388	0.0005	1.9	201650_at	KRT19	keratin 19	3880
1.00E-07	9.52E-06	< le-07	1.8	209605_at	TST	thiosulfate .sulfurtransferase (rhodanese)	7263:
8.02E-05	0.00151	< le-cs?	1.8	209016_s_at	KRT7	keratin 7	3855
2.491·;·04	0.0035	0.0002	1.8	219300_s_at	CNTNAP2	contactin associated protein-like 2	26047
3.36E-03	0.0244	0.0032	1.8	216836_s_at	ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblasioma derived oncogene homolog (avian)	2064
< le-07	< le-07	< le-07	1.8	211752_s_at	NDUFS7	NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase)	374291
3.49E-	0.025	0.002	1.8	210397_	DEFB1	defensin, beta 1	1672

03	1			at			
4.06E-05	0.000909	< 1e-07	1.8	209398_at	HIST1H1C	**histone** cluster 1, H1c	3006
7.29E-03	0.0433	0.0069	1.8	214243_s_at			
5.00E-07	0.0000338	< 1e-07	1.8	205774_at	FI2	coagulation factor XII (Hageman factor)	2161
5.83E-04	0,006:71	0.0007	1.8	208978_at	GRIP2	cysteine-rich protein 2	1397
5.68E-04	0.00659	0.0006	1.8	218677_at	S1Q0A14	S100 calcium binding protein A14	57402
7.30E-06	0.000244	< 1.e-07	1.8	2i4469_at			
1.00E-07	9.52E-06	< 1e-07	1.8	213508_at	SPTSSA	serine paknitoyltfanslerase, small subunit A	171546
3.08E-04	0,00414	0.0001	1.8	201291_s_at	TOP2A	topoisomerase (DNA) II alpha 170kDa	7153
< 1e-07	< 1e-07	< 1e-07	1.8	202993_at	ILVBL	ilvB (bacterial aeetolactate syntbase)-like	10994
7.30E-05	0.0014	< 1e-07	1.8	219962_at	ACE2	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	59272
3.70E-06	0.000146	< 1e-07	1.8	203968_s_ai	CDC6	cell division cycle 6	990
4.51E-05	0.000986	< 1e-07	1.8	222257_s_at	ACE2	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	59272
6.22E-05	0.00125	0.0001	1.8	205364_at	ACOX2	acyl-CoA oxidase 2, branched chain	8309
5.08E-04	0.00606	0.0005	1.8	219010_at	C1ori'106	chromosome 1 open reading frame 106	55765
4.00E-07	0.0000288	< 1e-07	1.8	209164_s_at	CYB561	cytochrome b-561	1534
3.00E-07	0.0000224	< 1e-07	1.8	218507_at	HILPDA	hypoxia inducible lipid droplet-associated	29923
6.59E-05	0.0013	< 1e-cs:'	1.7	201340_s_a.t	ENC1	ectoderma!-neur&t cortex 1 (with BTB domain)	8507
2.301·06	0.000104	< 1e-07	1.7	209714_s_at	GDKN3	cyclin-dependent kinase inhibitor 3	1033
2.55E-03	0.0201	0.0031	1.7	210387_at			
7.46E-04	0.008	0,0008	1,7	219410_at	TMEM45A	transmembrane protein 45A	55076
1.21E-03	0.0115	0.001	1.7	219630_at	PDZKIIP1	PDZKl interacting protein 1	10158
< 1e-07	< 1e-07	< 1e-07	1.7	204824_at	ENDOG	endonuelease G	2021
< 1e-07	< 1e-07	< 1e-07	1.7	218001_at	MRPS2	mitochondrial ribosomal protein S2	51116
6.00E-07	0.0000386	< 1e-07	1,7	204975_at	EMP2	epithelial membrane protein 2	2013
1.33E-03	0.0124	0.0011	1.7	205258_at	INHBB	inhibit!, beta B	3625
5.60E-06	0.000202	< 1e-07	1.7	205253_at	PBX1	pre-B-celi leukemia homeobox 1	5087
5.66E-03	0.0361	0.0052	1.7	202859_x_at	IL8	interleukin 8	3576
2.35E-04	0.00335	0,0003	1,7	209621_s_at	PDL1M3	**PDZ** and LIM doniain 3	27295

< 1e-07	< 1e-07	< 1e-07	1.7	215093_at	NSDHL	NAD(P) dependent steroid dehydrogenase-like	50814
4.72E-05	0.00102	0.0001	1.7	206110_at	HIST1H3H	histone cluster 1, H3h	8357
3.61E-03	0.0257	0.0036	1.7	211652_s_at	LBP	lipopolysaccharide binding protein	3929
6.62E-03	0.0404	0.007	1.7	206714_at	ALOX15B	arachidonate 15-lipoxygenase, type B	247
7.28E-03	0.0433	0.0068	1.7	215108_x_at	TOX3	TOX high mobility group box family member 3	27324
8.53E-04	0.00882	0.0012	1.7	205442_at	MFAP3L	microfibrillar-associated protein 3-like	9848
1.00E-07	9.52E-06	< 1e-07	1.7	201848_s_at	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3	664
< 1e-07	< 1e-07	< 1e-07	1.7	208817_at	COMT	catechol-O-methyltransferase	1312
3.45E-02	0.128	0.0335	1.7	220414_at	CALML5	calmodulin-like 5	51806
4.75E-05	0.00103	0.0001	1.7	209114_at	TSPAN1	tetraspanin 1	10103
1.60E-06	0.0000801	< 1e-07	1.7	219038_at	MORC4	MORC family CW-type zinc finger 4	79710
2.99E-05	0.000729	< 1e-07	1.7	203207_s_at	MTFR1	mitochondrial fission regulator 1	9650
2.84E-05	0.000708	< 1e-07	1.7	212325_at	LIMCH1	LIM and calponin homology domains 1	22998
1.07E-05	0.000333	< 1e-07	1.7	221563_at	DUSP10	dual specificity phosphatase 10	11221
< 1e-07	< 1e-07	< 1e-07	1.7	214264_s_at	EFCAB11	EF-hand calcium binding domain 11	90141
1.80E-06	0.000088	< 1e-07	1.7	202219_at	SLC6A8	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	6535
5.37E-04	0.00632	0.0003	1.7	209773_s_at	RRM2	ribonucleotide reductase M2	6241
9.38E-05	0.00168	0.0002	1.7	219288_at	C3orf14	chromosome 3 open reading frame 14	57415
8.20E-03	0.0471	0.0086	1.7	214598_at	CLDN8	claudin 8	9073
3.28E-04	0.00433	0.0004	1.7	208284_x_at			
3.63E-04	0.00468	0.0003	1.7	211417_x_at			
1.02E-03	0.0101	0.0009	1.6	208180_s_at			
7.10E-06	0.000239	< 1e-07	1.6	201287_s_at	SDC1	syndecan 1	6382
3.82E-02	0.137	0.0352	1.6	AFFX-HUMRGE/M10098_M_at			
8.00E-07	0.0000477	< 1e-07	1.6	218261_at	AP1M2	adaptor-related protein complex 1, mu 2 subunit	10053
1.38E-04	0.00222	< 1e-07	1.6	204678_s_at	KCNK1	potassium channel, subfamily K, member 1	3775
1.51E-05	0.000431	< 1e-07	1.6	204179_at	MB	myoglobin	4151
< 1e-	< 1e-	< 1e-	1.6	564_at	GNA11	guanine nucleotide binding	2767

07	07	07				protein (G protein), alpha 11 (Gq class)	
1.39E-02	0.0686	0.0137	1.6	219612_s_at	FGG	fibrinogen gamma chain	2266
1.25E-04	0.00207	0.0001	1.6	201846_s_at	RYBP	RING1 and YY1 binding protein	23429
3.79E-02	0.136	0.0349	1.6	AFFX-r2-Hs18SrRNA-M_x_at			
3.60E-06	0.000144	< 1e-07	1.6	202275_at	G6PD	glucose-6-phosphate dehydrogenase	2539
2.80E-06	0.00012	< 1e-07	1.6	213246_at	TMEM251	transmembrane protein 251	26175
1.50E-06	0.000076	< 1e-07	1.6	212460_at	SPTSSA	serine palmitoyltransferase, small subunit A	171546
1.00E-07	9.52E-06	< 1e-07	1.6	203189_s_at			
1.69E-04	0.00258	0.0002	1.6	208546_x_at	HIST1H2BH	histone cluster 1, H2bh	8345
1.99E-05	0.000537	< 1e-07	1.6	216607_s_at			
2.00E-07	0.0000168	< 1e-07	1.6	202528_at	GALE	UDP-galactose-4-epimerase	2582
< 1e-07	< 1e-07	< 1e-07	1.6	202587_s_at	AK1	adenylate kinase 1	203
2.81E-04	0.00384	0.0003	1.6	212328_at	LIMCH1	LIM and calponin homology domains 1	22998
2.36E-04	0.00335	0.0002	1.6	204679_at	KCNK1	potassium channel, subfamily K, member 1	3775
1.39E-05	0.000407	< 1e-07	1.6	208677_s_at	BSG	basigin (Ok blood group)	682
9.60E-06	0.000306	< 1e-07	1.6	209008_x_at	KRT8	keratin 8	3856
1.76E-03	0.0153	0.0017	1.6	202619_s_at	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	5352
6.73E-05	0.00132	< 1e-07	1.6	204017_at	KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	11015
1.90E-06	0.0000909	< 1e-07	1.6	202790_at	CLDN7	claudin 7	1366
2.08E-02	0.0898	0.0168	1.6	204914_s_at	SOX11	SRY (sex determining region Y)-box 11	6664
5.70E-04	0.0066	0.0007	1.6	202912_at	ADM	adrenomedullin	133
4.28E-03	0.0294	0.0039	1.6	201884_at	CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5	1048
3.57E-02	0.13	0.0347	1.6	211682_x_at	UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	54490
4.00E-07	0.0000288	< 1e-07	1.6	204867_at	GCHFR	GTP cyclohydrolase I feedback regulator	2644
< 1e-07	< 1e-07	< 1e-07	1.6	214463_x_at			
1.98E-02	0.0873	0.0226	1.6	209125_at	KRT6A	keratin 6A	3853

8.76E-05	0.0016	0.0001	1.6	208579_x_at			
2.39E-02	0.0992	0.0201	1.6	212531_at	LCN2	lipocalin 2	3934
1.07E-03	0.0105	0.0018	1.6	215779_s_at			
1.92E-04	0.00285	0.0002	1.6	214710_s_at	CCNB1	cyclin B1	891
3.95E-03	0.0275	0.0037	1.6	202870_s_at	CDC20	cell division cycle 20	991
9.86E-04	0.00985	0.0011	1.6	205158_at	RNASE4	ribonuclease, RNase A family, 4	6038
3.82E-05	0.000869	< 1e-07	1.6	208963_x_at			
5.04E-03	0.0332	0.0046	1.6	211110_s_at	AR	androgen receptor	367
1.11E-03	0.0108	0.0016	1.6	204952_at	LYPD3	LY6/PLAUR domain containing 3	27076
2.92E-04	0.00395	0.0001	1.6	205311_at	DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	1644
1.07E-03	0.0105	0.0015	1.6	209919_x_at			
3.10E-04	0.00415	0.0004	1.6	211423_s_at	SC5DL	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, S. cerevisiae)-like	6309
< 1e-07	< 1e-07	< 1e-07	1.6	209482_at	POP7	processing of precursor 7, ribonuclease P/MRP subunit (S. cerevisiae)	10248
4.53E-02	0.152	0.045	1.6	204623_at	TFF3	trefoil factor 3 (intestinal)	7033
4.92E-04	0.0059	0.0005	1.6	205066_s_at	ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1	5167
1.56E-05	0.000443	< 1e-07	1.6	212051_at	WIPF2	WAS/WASL interacting protein family, member 2	147179
6.79E-05	0.00133	< 1e-07	1.6	218260_at	DDA1	DET1 and DDB1 associated 1	79016
3.70E-06	0.000146	< 1e-07	1.6	200616_s_at	MLEC	malectin	9761
2.47E-03	0.0196	0.0031	1.6	201952_at	ALCAM	activated leukocyte cell adhesion molecule	214
1.00E-07	9.52E-06	< 1e-07	1.6	214212_x_at	FERMT2	fermitin family member 2	10979
1.20E-04	0.00203	< 1e-07	1.6	200832_s_at	SCD	stearoyl-CoA desaturase (delta-9-desaturase)	6319
1.90E-05	0.000519	0.0001	1.6	214088_s_at	FUT3	fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group)	2525
1.09E-03	0.0106	0.0012	1.6	212327_at	LIMCH1	LIM and calponin homology domains 1	22998
4.06E-04	0.0051	0.0001	1.6	203764_at	DLGAP5	discs, large (Drosophila) homolog-associated protein 5	9787
3.00E-07	0.0000224	< 1e-07	1.6	219819_s_at	MRPS28	mitochondrial ribosomal protein S28	28957
3.00E-	0.000	< 1e-	1.6	202201_	BLVRB	biliverdin reductase B	645

06	126	07		at		(flavin reductase (NADPH))	
1.50E-06	0.000076	< 1e-07	1.6	218451_at	CDCP1	CUB domain containing protein 1	64866
1.09E-04	0.00189	0.0002	1.6	201037_at	PFKP	phosphofructokinase, platelet	5214
< 1e-07	< 1e-07	< 1e-07	1.6	218189_s_at	NANS	N-acetylneuraminic acid synthase	54187
1.42E-02	0.0697	0.0141	1.6	205239_at			
1.88E-03	0.0161	0.0017	1.6	218888_s_at	NETO2	neuropilin (NRP) and tolloid (TLL)-like 2	81831
1.69E-04	0.00258	0.0001	1.6	215145_s_at	CNTNAP2	contactin associated protein-like 2	26047
< 1e-07	< 1e-07	< 1e-07	1.6	220688_s_at	MRTO4	mRNA turnover 4 homolog (S. cerevisiae)	51154
< 1e-07	< 1e-07	< 1e-07	1.6	202839_s_at	NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	4713
1.00E-07	9.52E-06	< 1e-07	1.6	31874_at	GAS2L1	growth arrest-specific 2 like 1	10634
1.03E-02	0.0552	0.0082	1.6	210761_s_at	GRB7	growth factor receptor-bound protein 7	2886
5.55E-04	0.00647	0.0006	1.6	217771_at	GOLM1	golgi membrane protein 1	51280
9.00E-07	0.0000513	< 1e-07	1.6	218493_at	SNRNP25	small nuclear ribonucleoprotein 25kDa (U11/U12)	79622
< 1e-07	< 1e-07	< 1e-07	1.6	218206_x_at	SCAND1	SCAN domain containing 1	51282
1.77E-04	0.00266	0.0002	1.5	203786_s_at	TPD52L1	tumor protein D52-like 1	7164
9.00E-05	0.00163	0.0002	1.5	204348_s_at			
< 1e-07	< 1e-07	< 1e-07	1.5	212540_at	CDC34	cell division cycle 34	997
6.20E-05	0.00125	< 1e-07	1.5	201702_s_at	PPP1R10	protein phosphatase 1, regulatory subunit 10	5514
3.53E-04	0.00458	0.0006	1.5	200632_s_at	NDRG1	N-myc downstream regulated 1	10397
< 1e-07	< 1e-07	< 1e-07	1.5	208336_s_at	TECR	trans-2,3-enoyl-CoA reductase	9524
< 1e-07	< 1e-07	< 1e-07	1.5	205141_at	ANG	angiogenin, ribonuclease, RNase A family, 5	283
9.00E-07	0.0000513	< 1e-07	1.5	212807_s_at	SORT1	sortilin 1	6272
2.39E-02	0.0994	0.0215	1.5	213711_at	KRT81	keratin 81	3887
2.91E-05	0.000717	< 1e-07	1.5	219929_s_at	ZFYVE21	zinc finger, FYVE domain containing 21	79038
1.58E-05	0.000447	< 1e-07	1.5	214004_s_at	VGLL4	vestigial like 4 (Drosophila)	9686
1.32E-04	0.00214	0.0002	1.5	217188_s_at	C14orf1	chromosome 14 open reading frame 1	11161
1.66E-05	0.000464	< 1e-07	1.5	211612_s_at	IL13RA1	interleukin 13 receptor, alpha 1	3597
9.06E-04	0.0092	0.001	1.5	209522_s_at	CRAT	carnitine O-acetyltransferase	1384
< 1e-	< 1e-	< 1e-	1.5	218188_s	TIMM13	translocase of inner	26517

07	07	07		_at		mitochondrial membrane 13 homolog (yeasty	
1.57E-04	0.00244	0.0002	1.5	212141_at	MCM4	minichiOmosome maintenance complex component 4	4173
8.24E-04	0.00862	0.0004	1.5	2l09l9_s_at	SRIXv Vi	steroid-5-alpha-reductase, alpha polypeptide 1 (3-6x0-5 alpha-steroid delta 4-deliydrogenase alpha 1)	6715
2.12E-04	0.0030S	0.0003	1.5	202890_at	MAP?	mierotiibde-assoeiated protein 7	9053
5.30E-06	0,000:196	< le-07	1.5	2 18049_s_at	MRPL13	mitoehondri al ribosomal protein L I3	28998
1.88E-03	0.0161	0.0013	1.5	217562_at	EAM5C	family with sequence similarity 5, member C	339479
1,15E-05	0.000349	< le-07	1.5	2l9390_at	FKBP14	FK506 binding protein 14, 22 kDa	55033
6.30E-06	0.00022	< 1e-07	1.5	202671_s_at	PDXK	pyridoxal (pyridexine , vitamin B6) kinase	8566
2.34E-03	0.019	0.0029	1.5.	205990_s__at	WNT5A	wingless-type MMTV integration site family, member 5A	7474
1.15E-02	0.06	0,0114	1.5	219529_at	CL1C3	chloride intracellular channel 3	9022
< 1e-07	< le-tr7	< le-07	1.5	218460_.at	NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	4702
1.91E-03	0.0163	0.0012	1,5	202095_s_at	BIRC5	baculoviral IAP repeat containing 5	332
8.76E-04	0.00898	0.0008	1.5	203397__s_at	GALNT3	UDP-N-acetyl-alpha-D-galactosaimne:polypept:ide N-aeetylgalactosaminyltransferase 3 (GalNAc-T3)	2591
1.71E-05	0.000475	< le-07	1.5	221734_at	PRRC1	proline-rich coiled-coil 1	133619
1.53E-03	0.013g	0.0011	1.5	218186_at	RAB25	RAB25, member RAS oncogene family	57111
l.OOE-07	9.52E-06	< le-07	1.5	203190_at			
1.19E-03	0.0114	0.0009	1.5	20494 l_s_at	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	222
< 1e-07	< 1e-er7	< le-07	1.5	209194_at	CETN2	centrin, EE-hand protein, 2.	1069
2.691·;·02	0.107	0.0262	1.5	206463_s_at	DHRS2	dehydrogenase/reductase (SDR family) member 2	10202
4.31E-04	0.00532	0.0003	1.5	21061.3_S_at	SYNGR1	synaptogyriii 1	9145
2.69E-02	0.107	0.026	1.5	AFFX-r2-Hs28SrRNA-3_at			
2.25E-03	0.0184	0.0014	1.5	208079_s_a.t	AURKA	aurora kinase A	6790
2.73E-02	0.108	0.0294	1.5	211653_x_at	AKR1C2	aldo-keto reductase family L member C2	1.646
1.30E-05	0.000387	< 1e-07	1.5	20374Q_at	MPHOSPH6	M-phase phosphoproiein 6	10200
8.66E-	0.001	0.000	1.5	213843_	SLC6A8	solute carrier family 6	65:35

05	59	1		x_at		(neurotransmitter transporter, creatine), member 8	
1.77E-03	0.0154	0.0013	1.5	219978_s_at	NUSAP1	nucleolar and spindle associated protein 1	51203
5.00E-07	0,0000338	< 1e-07	1.5	2032S2_at	GBE1	glucan (1,4-alpha-), branching enzyme 1	2632
2.39E-03	0.0192	0.0024	1.5	207469_s_at	PIR	pirin (iron-binding nuclear protein)	8544
4.08E-02	0,142	0.0447	1.5	201983_s_at	EGFR	epidermal growth factor receptor	1956
4.10E-06	0.000158	< 1e-07	1.5	21Q058_at	MAPK13	mitogen-activated protein kinase 13	5603
1.46E-02	0.071	0.0133	1.5	217014_s_at			
7.60E-06	0.000251	< 1e-07	1.5	208928_at	FOR	P450 (cytochrome) oxidoredijctase	5447
1.91E-02	0,0851	0.0204	1.5	205306_x_at	KMO	fcynurenine 3-moiraoxygenase (kynurenine 3-hydroxylase)	8564
2.26E-05	0.000592	< 1e-07	1.5	209806_at	HIST1H2BK	histone cluster 1, H2bk	85236
4.98E-03	0.033	0.0051	1.5	212458_at	SPRED2	sprouty-related, EVH1 domain containing 2	200734
3.04E-04	0.00409	0.0006	1,5	2182S0_x_at			
< 1e-07	< 1e-07	< 1e-07	1.5	40562__at	GNA11	guanine nucleotide binding protein (G protein), alpha 11 **(Gq** class)	2767
5,23E-04	0.00619	o.ooo2	1.5	209911_x_at	HIST1H2BD	histone cluster 1, H2bd	3017
1.29E-04	0.0021	< 1e-07	1.5	214472_at			
6,52E-04	0.00727	0,001	1,5	215780_s_at			
3.09E-03	0.023	0.0038	1.5	202975_s_at	RHGBTB3	Rho-related BTB: domain containing 3	22836
5.10E-06	0.00019	< 1e-07	1.5	219061_s_at	LAGE3	L antigen family, member 3	8270
1.24E-03	0.0117	0.001	1.5	210904_s_at	IL13RA1	interleukin 13 receptor, alpha 1	3597
1.70E-04	0.00259	0,0001	1,5	201791_s_at	DHCR7	7-dehydrocholesterol reductase	1717
1.00E-06	0.0000561	< 1e-07	1.5	218498_s_at	ERGIL	ERQ1-like (S. cerevisiae)	30001
1.38E-05	0.000406	< 1e-cs?	1.5	201925_s_at	CD55	**GD55** molecule, decay-accelerating factor for complement (Cromer blood group)	1604
3.43E-02	0.127	0.0344	1.5	203571_s_at	ADIRF	adipogenesis regulatory factor	10974
2.80E-04	0.00384	0.0005	1.5	205379_at	CBR3	carbonyl reductase 3	874
1.02E-04	0.00179	0.0001	1.5	216804_s_at	PDL1M5	PDZ and L1M domain 5	10611
8.32E-04	0.00868	0.0012	1.5	214290_s_at			
2.62E-03	0.020:5	0.003	1.5	202620_s_at	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase	5352

						2	
2.00E-07	0.0000168	< 1e-07	0.3	214768_x_at	IGKC	immunoglobulin kappa constant	3514
1.00E-07	9.52E-06	< 1e-07	0.3	211644_x_at			
< 1e-07	< 1e-07	< 1e-07	0.3	217148_x_at			
2.00E-07	0.0000168	< 1e-07	0.3	216491_x_at	IGHM	immunoglobulin heavy constant mu	3507
< 1e-07	< 1e-07	< 1e-07	0.3	205267_at	POU2AF1	POU class 2 associating factor 1	5450
< 1e-07	< 1e-07	< 1e-07	0.3	211637_x_at			
2.20E-06	0.000102	< 1e-07	0.3	214777_at			
1.10E-06	0.0000599	< 1e-07	0.3	211634_x_at			
2.00E-07	0.0000168	< 1e-07	0.3	209374_s_at	IGHM	immunoglobulin heavy constant mu	3507
< 1e-07	< 1e-07	< 1e-07	0.3	217179_x_at			
< 1e-07	< 1e-07	< 1e-07	0.4	216984_x_at			
3.00E-07	0.0000224	< 1e-07	0.4	216576_x_at			
9.00E-07	0.0000513	< 1e-07	0.4	217022_s_at			
< 1e-07	< 1e-07	< 1e-07	0.4	217235_x_at	IGLL5	immunoglobulin lambda-like polypeptide 5	1E+08
1.70E-06	0.0000836	< 1e-07	0.4	211635_x_at			
1.10E-06	0.0000599	< 1e-07	0.4	216401_x_at			
1.00E-07	9.52E-06	< 1e-07	0.4	217281_x_at			
2.70E-06	0.000116	< 1e-07	0.4	216510_x_at			
1.00E-07	9.52E-06	< 1e-07	0.4	211643_x_at			
1.20E-06	0.0000634	< 1e-07	0.4	215176_x_at	IGKC	immunoglobulin kappa constant	3514
1.00E-07	9.52E-06	< 1e-07	0.4	216557_x_at			
5.00E-07	0.0000338	< 1e-07	0.4	212592_at	IGJ	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	3512
9.00E-07	0.0000513	< 1e-07	0.4	214916_x_at			
1.74E-03	0.0152	0.0013	0.4	205044_at	GABRP	gamma-aminobutyric acid (GABA) A receptor, pi	2568
7.20E-06	0.000241	< 1e-07	0.4	211645_x_at			
< 1e-07	< 1e-07	< 1e-07	0.4	212588_at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
< 1e-07	< 1e-07	< 1e-07	0.4	210915_x_at	TRBC1	T cell receptor beta constant 1	28639

7.62E-05	0.00145	0.0005	0.4	203915_at	CXCL9	chemokine (C-X-C motif) ligand 9	4283
2.00E-07	0.0000168	< 1e-07	0.4	211650_x_at			
1.40E-06	0.0000717	< 1e-07	0.4	214973_x_at	IGHD	immunoglobulin heavy constant delta	3495
< 1e-07	< 1e-07	< 1e-07	0.4	207238_s_at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
6.00E-07	0.0000386	< 1e-07	0.4	217227_x_at	IGLV1-44	immunoglobulin lambda variable 1-44	28823
1.00E-07	9.52E-06	< 1e-07	0.4	211796_s_at			
< 1e-07	< 1e-07	< 1e-07	0.4	206666_at	GZMK	granzyme K (granzyme 3; tryptase II)	3003
5.05E-05	0.00107	0.0001	0.4	216560_x_at	IGLC1	immunoglobulin lambda constant 1 (Mcg marker)	3537
7.00E-07	0.0000425	< 1e-07	0.4	216207_x_at			
2.01E-04	0.00295	< 1e-07	0.4	205890_s_at			
2.92E-05	0.000717	< 1e-07	0.4	210072_at	CCL19	chemokine (C-C motif) ligand 19	6363
9.00E-06	0.000289	0.0001	0.4	217378_x_at			
1.90E-06	0.0000909	0.0001	0.4	209138_x_at			
< 1e-07	< 1e-07	< 1e-07	0.5	208798_x_at	GOLGA8A	golgin A8 family, member A	23015
3.10E-06	0.000129	0.0001	0.5	214677_x_at			
< 1e-07	< 1e-07	< 1e-07	0.5	211868_x_at			
4.00E-07	0.0000288	< 1e-07	0.5	205159_at	CSF2RB	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	1439
3.80E-06	0.000149	< 1e-07	0.5	211798_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
1.03E-04	0.00181	0.0001	0.5	211430_s_at			
2.70E-06	0.000116	< 1e-07	0.5	204891_s_at	LCK	lymphocyte-specific protein tyrosine kinase	3932
3.60E-06	0.000144	< 1e-07	0.5	217480_x_at			
1.88E-03	0.0161	0.0013	0.5	205242_at	CXCL13	chemokine (C-X-C motif) ligand 13	10563
3.00E-07	0.0000224	< 1e-07	0.5	205831_at	CD2	CD2 molecule	914
< 1e-07	< 1e-07	< 1e-07	0.5	204116_at	IL2RG	interleukin 2 receptor, gamma	3561
8.00E-07	0.0000477	< 1e-07	0.5	207339_s_at	LTB	lymphotoxin beta (TNF superfamily, member 3)	4050
6.00E-07	0.0000386	< 1e-07	0.5	212827_at	IGHM	immunoglobulin heavy constant mu	3507
8.31E-05	0.00155	0.0002	0.5	215214_at			
1.00E-07	9.52E-06	< 1e-07	0.5	215949_x_at			
7.93E-	0.001	0.000	0.5	204563_	SELL	selectin L	6402

05	49	1		at			
2.50E-06	0.000111	0.0001	0.5	214669_x_at	IGKC	immunoglobulin kappa constant	3514
1.07E-04	0.00186	< 1e-07	0.5	206134_at	ADAMDEC1	ADAM-like, decysin 1	27299
7.00E-07	0.0000425	< 1e-07	0.5	217258_x_at	IGLV1-44	immunoglobulin lambda variable 1-44	28823
3.94E-05	0.000888	< 1e-07	0.5	211633_x_at	IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	3500
< 1e-07	< 1e-07	< 1e-07	0.5	210425_x_at			
3.00E-07	0.0000224	< 1e-07	0.5	211639_x_at			
5.16E-05	0.00109	< 1e-07	0.5	209392_at	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	5168
3.00E-07	0.0000224	< 1e-07	0.5	213193_x_at	TRBC1	T cell receptor beta constant 1	28639
1.00E-07	9.52E-06	< 1e-07	0.5	212314_at	SEL1L3	sel-1 suppressor of lin-12-like 3 (C. elegans)	23231
4.40E-06	0.000168	0.0001	0.5	215379_x_at			
7.35E-03	0.0436	0.0059	0.5	203290_at	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	3117
2.70E-06	0.000116	0.0001	0.5	215121_x_at			
< 1e-07	< 1e-07	< 1e-07	0.5	213142_x_at	PION	pigeon homolog (Drosophila)	54103
1.00E-07	9.52E-06	< 1e-07	0.5	217157_x_at			
1.20E-05	0.000362	0.0001	0.5	211881_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
6.74E-03	0.0409	0.0057	0.5	213831_at			
< 1e-07	< 1e-07	< 1e-07	0.5	209670_at	TRAC	T cell receptor alpha constant	28755
5.37E-05	0.00112	0.0001	0.5	217767_at	C3	complement component 3	718
< 1e-07	< 1e-07	< 1e-07	0.5	213502_x_at	GUSBP11	glucuronidase, beta pseudogene 11	91316
< 1e-07	< 1e-07	< 1e-07	0.5	204912_at	IL10RA	interleukin 10 receptor, alpha	3587
< 1e-07	< 1e-07	< 1e-07	0.5	209685_s_at	PRKCB	protein kinase C, beta	5579
< 1e-07	< 1e-07	< 1e-07	0.5	222150_s_at	PION	pigeon homolog (Drosophila)	54103
< 1e-07	< 1e-07	< 1e-07	0.5	215946_x_at	IGLL3P	immunoglobulin lambda-like polypeptide 3, pseudogene	91353
5.00E-07	0.0000338	< 1e-07	0.5	206337_at	CCR7	chemokine (C-C motif) receptor 7	1236
7.40E-06	0.000246	< 1e-07	0.5	213888_s_at	TRAF3IP3	TRAF3 interacting protein 3	80342
1.00E-06	0.0000561	0.0001	0.5	214836_x_at			
2.00E-07	0.0000168	< 1e-07	0.5	204674_at	LRMP	lymphoid-restricted membrane protein	4033

6.80E-06	0.000232	0.0001	0.5	211908_x_at	IGK@	immunoglobulin kappa locus	50802
< 1e-07	< 1e-07	< 1e-07	0.5	211649_x_at			
8.14E-05	0.00152	0.0003	0.5	221728_x_at	XIST	X inactive specific transcript (non-protein coding)	7503
1.00E-07	9.52E-06	< 1e-07	0.5	203879_at	PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	5293
< 1e-07	< 1e-07	< 1e-07	0.5	38149_at	ARHGAP25	Rho GTPase activating protein 25	9938
6.00E-07	0.0000386	< 1e-07	0.5	205668_at	LY75	lymphocyte antigen 75	4065
2.00E-07	0.0000168	< 1e-07	0.5	204057_at	IRF8	interferon regulatory factor 8	3394
1.28E-02	0.0646	0.0134	0.5	220625_s_at	ELF5	E74-like factor 5 (ets domain transcription factor)	2001
6.20E-06	0.000217	0.0001	0.5	221671_x_at			
1.37E-04	0.0022	0.0004	0.5	214657_s_at			
5.00E-07	0.0000338	< 1e-07	0.5	204118_at	CD48	CD48 molecule	962
4.70E-06	0.000178	0.0001	0.5	221651_x_at			
6.00E-07	0.0000386	0.0001	0.5	205049_s_at	CD79A	CD79a molecule, immunoglobulin-associated alpha	973
1.90E-06	0.0000909	< 1e-07	0.5	211742_s_at	EVI2B	ecotropic viral integration site 2B	2124
3.74E-05	0.000856	< 1e-07	0.5	202746_at	ITM2A	integral membrane protein 2A	9452
4.44E-05	0.00098	< 1e-07	0.5	203868_s_at	VCAM1	vascular cell adhesion molecule 1	7412
3.66E-04	0.00471	0.0005	0.5	216853_x_at			
4.80E-04	0.00579	0.0007	0.5	205569_at	LAMP3	lysosomal-associated membrane protein 3	27074
3.51E-05	0.00082	< 1e-07	0.5	210356_x_at	MS4A1	membrane-spanning 4-domains, subfamily A, member 1	931
9.10E-06	0.000292	< 1e-07	0.5	211641_x_at			
5.23E-05	0.0011	< 1e-07	0.6	212311_at	SEL1L3	sel-1 suppressor of lin-12-like 3 (C. elegans)	23231
< 1e-07	< 1e-07	< 1e-07	0.6	221978_at	HLA-F	major histocompatibility complex, class I, F	3134
3.19E-05	0.000759	0.0001	0.6	208335_s_at	DARC	Duffy blood group, chemokine receptor	2532
< 1e-07	< 1e-07	< 1e-07	0.6	213160_at	DOCK2	dedicator of cytokinesis 2	1794
< 1e-07	< 1e-07	< 1e-07	0.6	202510_s_at	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	7127
2.59E-05	0.000657	< 1e-07	0.6	205861_at	SPIB	Spi-B transcription factor (Spi-1/PU.1 related)	6689
< 1e-07	< 1e-07	< 1e-07	0.6	213375_s_at	N4BP2L1	NEDD4 binding protein 2-like 1	90634
4.81E-	0.001	0.000	0.6	212671_s			

05	04	1		_at			
< 1e-07	< 1e-07	< 1e-07	0.6	211339_s_at	ITK	IL2-inducible T-cell kinase	3702
1.00E-07	9.52E-06	< 1e-07	0.6	203471_s_at	PLEK	pleckstrin	5341
< 1e-07	< 1e-07	< 1e-07	0.6	212232_at	FNBP4	formin binding protein 4	23360
9.41E-05	0.00169	< 1e-07	0.6	205488_at	GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	3001
0.00003	0.000731	< 1e-07	0.6	213539_at	CD3D	CD3d molecule, delta (CD3-TCR complex)	915
0.0000013	0.0000677	< 1e-07	0.6	211748_x_at	PTGDS	prostaglandin D2 synthase 21kDa (brain)	5730
0.0000164	0.000461	< 1e-07	0.6	204198_s_at	RUNX3	runt-related transcription factor 3	864
< 1e-07	< 1e-07	< 1e-07	0.6	214093_s_at	FUBP1	far upstream element (FUSE) binding protein 1	8880
0.0000045	0.000171	< 1e-07	0.6	209606_at	CYTIP	cytohesin 1 interacting protein	9595
< 1e-07	< 1e-07	< 1e-07	0.6	212980_at	USP34	ubiquitin specific peptidase 34	9736
0.0005974	0.00683	0.001	0.6	219014_at	PLAC8	placenta-specific 8	51316
0.0000165	0.000462	< 1e-07	0.6	210972_x_at			
0.0000847	0.00157	< 1e-07	0.6	210839_s_at	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	5168
0.0000634	0.00127	0.0001	0.6	211640_x_at			
0.0173219	0.0795	0.0166	0.6	209480_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0000024	0.000107	< 1e-07	0.6	219505_at	CECR1	cat eye syndrome chromosome region, candidate 1	51816
0.0000308	0.000742	< 1e-07	0.6	221601_s_at	FAIM3	Fas apoptotic inhibitory molecule 3	9214
0.0000007	0.00000425	< 1e-07	0.6	219812_at	PVRIG	poliovirus receptor related immunoglobulin domain containing	79037
0.000328	0.00433	0.0003	0.6	214453_s_at	IFI44	interferon-induced protein 44	10561
< 1e-07	< 1e-07	< 1e-07	0.6	203332_s_at	INPP5D	inositol polyphosphate-5-phosphatase, 145kDa	3635
0.0000143	0.000415	< 1e-07	0.6	204661_at	CD52	CD52 molecule	1043
0.0000513	0.00108	0.0004	0.6	214218_s_at	XIST	X inactive specific transcript (non-protein coding)	7503
0.0001076	0.00186	0.0002	0.6	34210_at	CD52	CD52 molecule	1043
< 1e-07	< 1e-07	< 1e-07	0.6	217317_s_at			
0.0000002	0.0000168	< 1e-07	0.6	210538_s_at	BIRC3	baculoviral IAP repeat containing 3	330
0.0000068	0.000232	< 1e-07	0.6	221602_s_at	FAIM3	Fas apoptotic inhibitory molecule 3	9214

0.0000 044	0.000 168	< 1e- 07	0.6	204S82_ at	ARHGA P25	Rho GTPase activating protein 25	9938
0.0000 062	0.000 217	< 1e- 07	0.6	204192_ at	CD37	CD37 molecule	951
< 1e- 07	< 1e- 07	< 1e- 07	0.6	205997_ at	ADAM2 8	ADAM metallopeptidase domain 28	10863
0.0000 037	0.000 146	< 1e- 07	0.6	209829,_ at	FAM65B	family with sequence similarity 65, member f	9750
0.0000 158	0,000: 447	< 1e- 07	0.6	219359_ at	ATH1	ATH1, acid trehaiase-like 1 (yeast)	80162
0.0000 136	0.000 401	0.000 1	0.6	212187_ x_at	PTGDS	prostaglandin D2 synthase 21kDa (brain)	5730
0.0000 114	0.000 347	< 1e- 07	0.6	204890_s _at	LCK	lynrphocyte-speeilic protein **tyrosine** kinase	3932
0.0000 01	0.000 0561	< 1e- 07	0.6	216542_ x_at			
0.0000 001	9.52E -06	< 1e- 07	0.6	219279_ at	DOCK10	dedicator **of cytoldnesis** 10	55619
0.0000 242	0.000 623	< 1e- 07	0.6	211:996_s _at:			
0.0000 059	0.000 211	< 1e- 07	0.6	209671 _ x_at			
0.0000 003	0.000 0224	< 1e- 07	0.6	2\8805_ at			
< 1e- 07	< ie- 07	< 1e- 07	0.6	218614_ at	KIAA 15 51	K1AA 1551	55196
0.0000 287	0.000 713	< 1e- 07	0.6	201236_s _at	BTG2	BTG family, member 2	7832
0.0000 033	0.000 135	< 1e- 07	0.6	213359_ at	HNRNP D	heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa)	3184
0.0000 002	0.000 0168	< 1e- 07	0,6	202957_ at	HGLS1	hematopoietic cell-specific Lyri substrate 1	3059
0.0000 01	0.000 0561	< 1e- 07	0.6	213603_s _at	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	5880
0.0297 372	0.115	0.027 6	0.6	202037_s _at	SFRP1	secreted frizzled-related protein 1	6422
0.0000 737	0.00 141	0.000 2	0.6	205692_s _at	CD38	CD38 molecule	952
0.001 1 094	0.010 8	0.000 8	0.6	209504_s _at	PLFKH B1	pleckstrin homology domain containing, family B (evectins) member 1	58473
< 1e- 07	< 1e- 07	< 1e- 07	0.6	218456_ at	CAPRIN 2	caprin family member 2	65981
0.0000 002	0.000 0168	< 1e- cs?	0.6	205291_ at	IL2RB	interleukin 2 receptor, beta	3560
0.0000 037	0.000 146	< 1e- 07	0.6	205821_ at			
< 1e- 07	< 1e- 07	< 1e- 07	0.6	203528_ at	SEMA4 D	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short. cytoplasmic domain. (semaphorin) 41)	10507
0.0000 019	0.000 0909	< 1e- 07	0.6	209723_ at	SERPIN B9	serpin peptidase inhibitor, clade B (ovalbumin).	5272

						member 9	
0.0001686	0.00258	< 1e-07	0.6	217418_x_at	MS4A1	membrane-spanning 4-domains, subfamily A, member 1	931
0.0000253	0.000646	0.0002	0.6	220954_s_at	PILRB	paired immunoglobin-like type 2 receptor beta	29990
0.0000013	0.0000677	< 1e-07	0.6	205758_at	CD8A	CD8a molecule	925
0.0001079	0.00187	0.0002	0.6	204834_at	FGL2	fibrinogen-like 2	10875
< 1e-07	< 1e-07	< 1e-07	0.6	209619_at	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	972
0.0000232	0.000603	0.0001	0.6	213915_at	NKG7	natural killer cell group 7 sequence	4818
0.0000023	0.000104	< 1e-07	0.6	210116_at	SH2D1A	SH2 domain containing 1A	4068
< 1e-07	< 1e-07	< 1e-07	0.6	215193_x_at			
0.000104	0.00182	< 1e-07	0.6	209083_at	CORO1A	coronin, actin binding protein, 1A	11151
0.0224506	0.0946	0.0201	0.6	209842_at	SOX10	SRY (sex determining region Y)-box 10	6663
0.0004459	0.00546	0.0006	0.6	205798_at	IL7R	interleukin 7 receptor	3575
0.0039118	0.0274	0.0032	0.6	208791_at	CLU	clusterin	1191
0.0013661	0.0126	0.0013	0.6	213674_x_at			
0.0000003	0.0000224	< 1e-07	0.6	202803_s_at	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	3689
0.0000048	0.00018	< 1e-07	0.6	35974_at	LRMP	lymphoid-restricted membrane protein	4033
< 1e-07	< 1e-07	< 1e-07	0.6	203416_at	CD53	CD53 molecule	963
0.0000038	0.000149	< 1e-07	0.6	203382_s_at	APOE	apolipoprotein E	348
0.0000005	0.0000338	< 1e-07	0.6	211991_s_at	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	3113
0.0000101	0.000319	< 1e-07	0.6	221768_at			
< 1e-07	< 1e-07	< 1e-07	0.6	220046_s_at	CCNL1	cyclin L1	57018
0.0000005	0.0000338	< 1e-07	0.6	208894_at	HLA-DRA	major histocompatibility complex, class II, DR alpha	3122
0.0000622	0.00125	< 1e-07	0.6	220330_s_at	SAMSN1	SAM domain, SH3 domain and nuclear localization signals 1	64092
< 1e-07	< 1e-07	< 1e-07	0.6	204670_x_at			
< 1e-07	< 1e-07	< 1e-07	0.6	209312_x_at			
< 1e-07	< 1e-07	< 1e-07	0.6	204923_at	SASH3	SAM and SH3 domain containing 3	54440
0.0000001	9.52E-06	< 1e-07	0.6	212307_s_at	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	8473

0.0000 007	0.000 0425	< 1e- 0?	0.6	202663_ at	WIPF1	WASAVASL interacting protein family, member 1	7456
< 1e- 07	< 1e- 07	< 1e- 07	0.6	221087_s _at	APOL3	apolipoprotein L, 3	80833
0.0000 056	0,000 202	< 1e- 07	0.6	213326_ at	VAMP1	vesicle-associated nietiibrafie protein 1 (synaptobreYin 1)	6843
< 1e- 07	< 1e- 07	< 1e- 07	0.6	20461 3_ at	PLCG2	phospholipase C, gamma 2 (phosphatidylinositdl-specifie)	5336
0.0000 003	0,000: 0224	< 1e- 07	0.6	210982_s _at	H11.A-DRA	major histocompatibility complex, class II, DR alpha	3122
0.0001 138	0.00! 94	0.000 4	0.6	204994_ at	MX2	myxovirus (influenza virus) resistance 2 (mouse)	4600
0.0059 061	0,037 4	0.005 8	0.6	203638_s _a!	FGFR2	fibroblast growth factor receptor 2	2263
< 1e- 07	< 1e- 07	< 1e- 07	0.6	209734_ at	NCKAP 1L	NGK-assoeiated protein 1-like	3071
0.0000 001	9.52E -06	< 1e- 07	0.6	207777_s _a.t	SP140	SP140 nuclear body protei n	11262
0.0000 025	0.000 111	< 1e- 07	0.6	203185_ at	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	9770
0.0000 149	0,000 43	< 1e- 07	0.6	204446_s _at	AL0X5	arachidonate 5-lipoxygenase	240
0,0000 204	o.ooo 548	0,000 1	0,6	216250_s _at	LPXN	leupaxin	9404
0.0000 47	0.001 02	< 1e- 07	0.6	202747_s _at	ITM2A	integral membrane protein 2A	9452
0.0000 678	o.ooi 33	< 1e- 07	0.6	2Ï 19Ï 9_s _at	CXCR4	chemoldne (C-X-C motif) receptor 4	7852
0.0000 778	0.001 47	< 1e- 07	0.6	21 1654_. _at	HLA-DQB1	major histocompatibility complex, class Π, DQ beta 1	3119
0.0001 269	0.002 09	0,000 2.	0,6	20554l_s _at	GSPT2	G1 to S phase transition 2	23708
0.0166 882	0.077 7	0.015 9	0.6	204259_ . at	MMP7	matrix metallopeptidase 7 (matrilysin, uterine)	4316
0.0003 392	0.004 45	0.000 4	0.6	209846_s _at	BTN3A2	butyrophilin, subfamily 3, member A2	11118
0.0000 007	0,000 0425	< 1e- 07	0.6	219191_s _at	B1N2	bridging integrator 2	5141 1
< 1e- 07	< 1e- 07	< 1e- 07	0.6	212176 _ at	PNISR	PNN-interacting serine/arginine-rich protein	25957
0.0000 15	0.000 43	< 1e- 07	0,6	204352 _ at	TRAF5	TNF receptor-associated factor 5	7188
0.0000 142	0.000 4 13	< 1e- 07	0.6	217143_S _a.t	YME-1L1	YMEl-like 1 (S. cerevisiae)	10730
0.0148 915	0.072	0.017 7	0.6	206157_ at	PTX3	pentraxin 3. long	5806
0.0008 368	0.008 72	0.000 9	0.6	216541_ x_at			
< 1e- 07	< 1e- 07	< 1e- 07	0.6	20S298_s _at	BTN2A2	butyrophilin, subfamily 2, member A2	10385
0.0000 003	0.000 0224	< 1e- 07	0.6	2 11(0)5_ at	LAT	linker for activation of T cells	27040
0.0000 522	0.001 1	< 1e- 07	0.6	206133 _. at	XAFl	XIAP associated factor I	54739
0.0000	0.001	0.000	0.6	20338 1_s	APOE	apolipoprotein E	348

795	5	2		_at			
0.009593	0.0527	0.0096	0.6	204439_at	IFI44L	interferon-induced protein 44-like	10964
< 1e-07	< 1e-07	< 1e-07	0.6	201137_s_at	HLA-DPB1	major histocompatibility complex, class II, DP beta 1	3115
0.0000012	0.0000634	< 1e-07	0.6	212179_at	PNISR	PNN-interacting serine/arginine-rich protein	25957
0.0000006	0.0000386	< 1e-07	0.6	213293_s_at	TRIM22	tripartite motif containing 22	10346
0.0005693	0.0066	0.0002	0.6	204655_at	CCL5	chemokine (C-C motif) ligand 5	6352
< 1e-07	< 1e-07	< 1e-07	0.6	203547_at	CD4	CD4 molecule	920
0.0120383	0.062	0.0126	0.6	210029_at	IDO1	indoleamine 2,3-dioxygenase 1	3620
0.0000011	0.0000599	< 1e-07	0.6	210346_s_at	CLK4	CDC-like kinase 4	57396
0.0000422	0.000939	< 1e-07	0.6	206978_at	CCR2	chemokine (C-C motif) receptor 2	729230
0.0000505	0.00107	< 1e-07	0.6	221969_at	PAX5	paired box 5	5079
0.0000239	0.000617	< 1e-07	0.6	205269_at	LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	3937
< 1e-07	< 1e-07	< 1e-07	0.6	213475_s_at	ITGAL	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	3683
0.0008431	0.00876	0.0007	0.6	208747_s_at	C1S	complement component 1, s subcomponent	716
0.0006505	0.00727	0.0004	0.6	213537_at	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	3113
0.0000027	0.000116	< 1e-07	0.6	207957_s_at	PRKCB	protein kinase C, beta	5579
0.0000007	0.0000425	< 1e-07	0.6	214016_s_at	SFPQ	splicing factor proline/glutamine-rich	6421
0.0000024	0.000107	< 1e-07	0.6	207563_s_at	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	8473
0.002433	0.0195	0.0028	0.6	205590_at	RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	10125
0.0000204	0.000548	< 1e-07	0.6	202531_at	IRF1	interferon regulatory factor 1	3659
0.0008485	0.00879	0.0005	0.6	203413_at	NELL2	NEL-like 2 (chicken)	4753
< 1e-07	< 1e-07	< 1e-07	0.6	221850_x_at			
0.0105274	0.0563	0.0094	0.6	212587_s_at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
0.0000003	0.0000224	< 1e-07	0.6	204294_at	AMT	aminomethyltransferase	275
0.0000167	0.000465	< 1e-07	0.6	221427_s_at	CCNL2	cyclin L2	81669
0.0000011	0.0000599	< 1e-07	0.6	205270_s_at	LCP2	lymphocyte cytosolic protein 2 (SH2 domain	3937

						containing leukocyte protein of 76kDa)	
0.0000059	0.000211	< 1e-07	0.6	202524_s_at	SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	9806
0.0000159	0.000448	< 1e-07	0.6	202643_s_at	TNFAIP3	tumor necrosis factor, alpha-induced protein 3	7128
0.0016349	0.0145	0.002	0.6	202902_s_at	CTSS	cathepsin S	1520
0.0002622	0.00364	0.0002	0.6	209403_at			
0.0000009	0.0000513	< 1e-07	0.6	203761_at	SLA	Src-like-adaptor	6503
0.0000729	0.0014	0.0001	0.6	216614_at			
0.0003988	0.00502	0.0006	0.6	205671_s_at	HLA-DOB	major histocompatibility complex, class II, DO beta	3112
0.0000012	0.0000634	< 1e-07	0.6	205213_at	ACAP1	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1	9744
0.0000001	9.52E-06	< 1e-07	0.6	221501_x_at			
0.0000038	0.000149	< 1e-07	0.6	212706_at			
0.0024604	0.0196	0.0021	0.6	1405_i_at	CCL5	chemokine (C-C motif) ligand 5	6352
0.0000022	0.000102	< 1e-07	0.6	202664_at	WIPF1	WAS/WASL interacting protein family, member 1	7456
0.0001581	0.00245	0.0005	0.6	221286_s_at	MZB1	marginal zone B and B1 cell-specific protein	51237
0.0012371	0.0117	0.0009	0.6	209763_at	CHRDL1	chordin-like 1	91851
0.0001288	0.0021	< 1e-07	0.6	221973_at			
0.0006328	0.00712	0.001	0.6	209823_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0000026	0.000114	< 1e-07	0.6	206118_at	STAT4	signal transducer and activator of transcription 4	6775
0.0016038	0.0143	0.0017	0.6	212998_x_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0000888	0.00162	0.0003	0.6	214617_at	PRF1	perforin 1 (pore forming protein)	5551
0.0250316	0.102	0.024	0.6	209687_at	CXCL12	chemokine (C-X-C motif) ligand 12	6387
0.0000106	0.000331	< 1e-07	0.6	221899_at	N4BP2L2	NEDD4 binding protein 2-like 2	10443
0.0000053	0.000196	< 1e-07	0.6	202644_s_at	TNFAIP3	tumor necrosis factor, alpha-induced protein 3	7128
0.000015	0.00043	< 1e-07	0.6	204821_at	BTN3A3	butyrophilin, subfamily 3, member A3	10384
< 1e-07	< 1e-07	< 1e-07	0.6	202380_s_at	NKTR	natural killer-tumor recognition sequence	4820
0.0002911	0.00394	0.0002	0.6	203922_s_at	CYBB	cytochrome b-245, beta polypeptide	1536
0.0000396	0.000891	0.0001	0.6	212847_at	FUBP1	far upstream element (FUSE) binding protein 1	8880
0.0027	0.021	0.002	0.6	AFFX-	STAT1	signal transducer and	6772

593	2	9		HUMISGF3A/M97935_MA_at		activator of transcription 1, 91kDa	
0.009096 5	0.0508	0.0103	0.6	219497_s_at	BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	53335
0.000322 7	0.00428	0.0001	0.6	210279_at	GPR18	G protein-coupled receptor 18	2841
0.005935 5	0.0375	0.0069	0.6	217430_x_at	COL1A1	collagen, type I, alpha 1	1277
0.000000 3	0.0000224	< 1e-07	0.6	204538_x_at	NPIP	nuclear pore complex interacting protein	9284
0.000003 5	0.000141	< 1e-07	0.6	208885_at	LCP1	lymphocyte cytosolic protein 1 (L-plastin)	3936
< 1e-07	< 1e-07	< 1e-07	0.6	210313_at	LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4	23547
0.000015 1	0.000431	< 1e-07	0.6	207651_at	GPR171	G protein-coupled receptor 171	29909
0.000000 2	0.0000168	< 1e-07	0.6	214870_x_at			
0.000193 2	0.00286	0.0001	0.6	209201_x_at	CXCR4	chemokine (C-X-C motif) receptor 4	7852
0.000000 7	0.0000425	< 1e-07	0.6	202813_at	TARBP1	TAR (HIV-1) RNA binding protein 1	6894
0.000013	0.000387	< 1e-07	0.6	206150_at	CD27	CD27 molecule	939
0.002619	0.0205	0.0024	0.6	215806_x_at			
0.029873 7	0.115	0.0289	0.6	212730_at	SYNM	synemin, intermediate filament protein	23336
0.000002 1	0.0000985	< 1e-07	0.7	213106_at	ATP8A1	ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	10396
0.000506 7	0.00604	0.0004	0.7	214059_at	IFI44	interferon-induced protein 44	10561
0.000005 7	0.000206	< 1e-07	0.7	219243_at	GIMAP4	GTPase, IMAP family member 4	55303
0.000005 6	0.000202	< 1e-07	0.7	212577_at	SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1	23347
0.000004 9	0.000184	< 1e-07	0.7	219471_at	KIAA0226L	KIAA0226-like	80183
0.012644 5	0.0641	0.012	0.7	201348_at	GPX3	glutathione peroxidase 3 (plasma)	2878
0.000002 3	0.000104	< 1e-07	0.7	204236_at	FLI1	Friend leukemia virus integration 1	2313
0.028463 8	0.111	0.0307	0.7	210163_at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
0.000144 3	0.00228	< 1e-07	0.7	204774_at	EVI2A	ecotropic viral integration site 2A	2123
0.006521 6	0.04	0.0063	0.7	221185_s_at	IQCG	IQ motif containing G	84223
0.014111 1	0.0694	0.0159	0.7	201069_at	MMP2	matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	4313

< 1e-07	< 1e-07	< 1e-0?	0.7	212454_x_at	HNRPDL	heterogeneous nuclear ribonucleoprotein D-like	9987
0.0194654	0.0862	0.0191	0.7	32121S_at	CCL18	ehemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	6362
0.(5029865	0.022:5	0.003	0.7	222162_s_at	ADAMIS1	ADAM metallopeptidase with wrombospondin type 1 motif. 1	9510
0.047.8513	0.158	0.0481	0.7	211122_s_at	CXCL11	ehemokine (C-X-C motif) lis and 1i	6373
0.0006993	0,00765	0.0007	0.7	201131_s_at	MBNL1	muscleblind-like splicing regulator 1	4154
< 1e-07	< 1e-07	< 1e-07	0.7	209827_s_at	IL16	interleukin 16	3603
0.00 17313	0.0152	0.0014	0.7	204205_at	APOBEC3G	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	60489
0.00082 5	0.00863	0.0008	0.7	2029;88_s_at	RGS1	regulator of G-protein signaling 1	5996
0.0000464	0.00101	0.0001	0.7	210031_at	CD247	CD247 molecule	919
0.0000146	0.000422	< 1e-07	0.7	2I4132_at	ATP5C1	ATP synthase, H+ transporting, mitochondrial Fi complex, gamma polypeptide 1	509
< 1e-07	< 1e-07	< 1e-07	0.7	202665_s_at	WIPF1	WAS/WASL interacting protein family, member 1	7456
0.0000006	0.0000386	< 1e-07	0.7	207564_x_at	OGT	O-linked N-aeetylglueosamine (GlcNAc) transferase	8473
0.0004522	0.00552	0.0001	0.7	209795_.at	CD69	CD69 molecule	969
0.0000422	0.000939	< 1e-07	0.7	203845_at	KAT2B	K(lysine) aeetyltransferase 2B	8850
0.0043937	0.0299	0.0049	0.7	AFFX-HUMISGF3A/M97935_MB_at	STAT1	signal transducer and activator of transcription 1, 9lkDa	6772
0.0002641	0.00366	0.0001	0.7	217478:_s_at	HLA-DMA	major histocompatibiliiy complex., class II, DM alpha	3108
0.0000105	0.000328	< 1e-07	0.7	209879_at	SELPLG	selectin P ligand	6404
0.0000917	0.00166	< 1e-07	0.7	20350S_at	TNFRSF1B	tumor necrosis factor receptor superfamily, member 1B	7133
0.0000461	0.001	< 1e-07	0.7	200953_s_at	CCND2	cyclin D2	894
0.0001309	0.00213	0.0002	0.7	207677_s_at	NCF4	neutrophil cytosolic factor 4, 40kDa	4689
0.0009618	0.00965	0.0009	0.7	206715_at	TFEC	transcription factor EC	22797
0.000 i349	0.00218	0.0002	0.7	212873_at	HMHA1	histocompatibility (minor). HA-1	23526
0.0000008	0.0000477	< 1e-07	0.7	203932_at	HLA-DMB	major histocompatibility complex, class II, DM beta	3109
0.0006183	0.007	0.0003	0.7	206082_at	HCP5	HLA complex P5 (non-protein coding)	10866

0.0001573	0.00244	0.0003	0.7	216834_at	RGS1	regulator of G-protein signaling 1	5996
0.0000022	0.000102	< 1e-07	0.7	206296_x_at	MAP4K1	mitogen-activated protein kinase kinase kinase kinase 1	11184
0.0000011	0.0000599	< 1e-07	0.7	64064_at			
0.0000005	0.0000338	< 1e-07	0.7	207734_at	LAX1	lymphocyte transmembrane adaptor 1	54900
0.0028821	0.0219	0.0027	0.7	222043_at	CLU	clusterin	1191
< 1e-07	< 1e-07	< 1e-07	0.7	208306_x_at			
0.0000927	0.00167	0.0002	0.7	201720_s_at	LAPTM5	lysosomal protein transmembrane 5	7805
0.0000022	0.000102	< 1e-07	0.7	204440_at	CD83	CD83 molecule	9308
0.0000006	0.0000386	< 1e-07	0.7	204562_at	IRF4	interferon regulatory factor 4	3662
0.0000175	0.000484	< 1e-07	0.7	221249_s_at	FAM117A	family with sequence similarity 117, member A	81558
0.0006184	0.007	0.0005	0.7	219689_at	SEMA3G	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3G	56920
0.0060147	0.0379	0.0059	0.7	220232_at	SCD5	stearoyl-CoA desaturase 5	79966
0.0000054	0.000198	< 1e-07	0.7	211038_s_at	CROCCP2	ciliary rootlet coiled-coil, rootletin pseudogene 2	84809
0.0197569	0.0871	0.0207	0.7	204533_at	CXCL10	chemokine (C-X-C motif) ligand 10	3627
0.0004576	0.00557	0.0007	0.7	204150_at	STAB1	stabilin 1	23166
0.0005043	0.00603	0.0005	0.7	208018_s_at	HCK	hemopoietic cell kinase	3055

Table 17. Class comparison of tbe global gene expression profiles of high iBCR score ER- and ER+ tumors to low iBCR score tumors post comparison to normal breast in the ROCK dataset

ProbeSet	Name	Accession	UGCluster	Symbol	ER- vs. Normal		ER+ vs. Normal		Cluster 2 vs. Cluster 1	
					Clust 1 ER-	Clust 2 ER-	Clust 1 ER+	Clust 2 ER+	ER-	ER+
204475_at	matrix metallopeptidase 1 (interstitial collagenase)	NM_002421	Hs.83169	MMP1	3.06	14.30	0.71	2.62	4.67	3.70
202917_s_at	S100 calcium binding protein A8	NM_002964	Hs.416073	S100A8	10.45	31.38	1.02	2.32	3.00	2.28
204351_at	S100 calcium binding protein P	NM_005980	Hs.2962	S100P	3.89	11.22	2.59	6.30	2.88	2.43
217388_s_at	kynureninase	D55639	Hs.470126	KYNU	0.69	1.81	0.27	0.54	2.64	2.01
204846_at	ceruloplasmin (ferroxidase)	NM_000096	Hs.558314	CP	1.69	4.34	0.61	0.95	2.56	1.57
202870_s_at	cell division cycle 20	NM_001255	Hs.524947	CDC20	5.82	14.57	0.89	4.71	2.50	5.30
209803_s_at	pleckstrin homology-like domain, family A, member 2	AF001294	Hs.154036	PHLDA2	0.66	1.65	0.57	1.17	2.50	2.06
209773_s_at	ribonucleotide reductase M2	BC001886	Hs.226390	RRM2	4.47	11.10	0.79	5.61	2.49	7.07
219010_at	chromosome 1 open reading frame 106	NM_018265	Hs.518997	C1orf106	1.61	3.88	0.45	0.92	2.41	2.04
204044_at	quinolinate phosphoribosyltransferase	NM_014298	Hs.513484	QPRT	1.04	2.45	0.73	1.31	2.34	1.80
208079_s_at	aurora kinase A	NM_003158	Hs.250822	AURKA	1.49	3.44	0.39	2.07	2.31	5.31
209942_x_at	melanoma antigen family A, 3	BC000340	Hs.417816	MAGEA3	1.53	3.52	0.87	1.33	2.29	1.54
209714_s_at	cyclin-dependent kinase inhibitor 3	AF213033	Hs.84113	CDKN3	3.47	7.84	1.15	4.75	2.26	4.12
220414_at	calmodulin-like 5	NM_017422	Hs.180142	CALML5	2.64	5.94	0.85	1.46	2.25	1.73
220615_s_at	fatty acyl CoA reductase 2	NM_018099	Hs.728955	FAR2	1.19	2.65	0.81	1.38	2.24	1.70
214612_x_at	melanoma antigen family A, 6	U10691	Hs.441113	MAGEA6	1.49	3.32	0.87	1.34	2.23	1.54
218009_s_at	protein regulator of cytokinesis 1	NM_003981	Hs.366401	PRC1	1.78	3.69	0.47	2.40	2.07	5.12
214710_s_at	cyclin B1	BE407516	Hs.23960	CCNB1	2.63	5.42	0.87	4.07	2.06	4.67
205347_		NM_021		TMS	1.9	3.8	0.3	0.7	1.9	1.8

s_at		992		BI5A	5	5	9	1	7	3
201890_at	ribonucleotide reductase M2	BE966236	Hs.226390	RRM2	2.10	4.13	0.60	2.77	1.97	4.66
204678_s_at	potassium channel, subfamily K, member 1	U90065	Hs.208544	KCNK1	2.15	4.23	1.85	2.87	1.96	1.55
202095_s_at	baculoviral IAP repeat containing 5	NM_001168	Hs.514527	BIRC5	3.22	6.27	0.82	4.10	1.95	4.99
219121_s_at	epithelial splicing regulatory protein 1	NM_017697	Hs.487471	ESRP1	4.47	8.69	2.47	6.70	1.94	2.71
203744_at	high mobility group box 3	NM_005342	Hs.19114	HMGB3	1.08	2.07	0.54	1.12	1.91	2.06
217755_at	hematological and neurological expressed 1	NM_016185	Hs.532803	HN1	5.36	10.05	2.98	7.25	1.87	2.43
202954_at	ubiquitin-conjugating enzyme E2C	NM_007019	Hs.93002	UBE2C	3.81	7.07	1.29	4.44	1.85	3.43
201291_s_at	topoisomerase (DNA) II alpha 170kDa	AU159942	Hs.156346	TOP2A	3.31	6.13	1.24	5.26	1.85	4.24
209875_s_at	secreted phosphoprotein 1	M83248	Hs.313	SPP1	5.04	9.30	3.31	5.61	1.84	1.70
204059_s_at	malic enzyme 1, NADP(+)-dependent, cytosolic	NM_002395	Hs.21160	ME1	1.94	3.56	0.77	1.39	1.84	1.82
210387_at		BC001131		HIST1H2BG	1.92	3.47	1.82	2.85	1.80	1.56
202671_s_at	pyridoxal (pyridoxine, vitamin B6) kinase	NM_003681	Hs.284491	PDXK	3.06	5.52	1.67	3.15	1.80	1.89
219978_s_at	nucleolar and spindle associated protein 1	NM_018454	Hs.615092	NUSAP1	4.06	7.27	1.50	4.51	1.79	3.01
203207_s_at	mitochondrial fission regulator 1	BF214329	Hs.584788	MTFR1	3.57	6.38	1.61	4.03	1.79	2.51
205943_at	tryptophan 2,3-dioxygenase	NM_005651	Hs.183671	TDO2	1.62	2.88	0.65	1.00	1.79	1.54
218355_at	kinesin family member 4A	NM_012310	Hs.648326	KIF4A	2.15	3.84	0.72	2.32	1.78	3.21
218039_at	nucleolar and spindle associated protein 1	NM_016359	Hs.615092	NUSAP1	2.02	3.58	0.86	2.67	1.77	3.10
202705_at	cyclin B2	NM_004701	Hs.194698	CCNB2	2.93	5.16	0.81	3.02	1.76	3.73
204641_at	NIMA-related kinase 2	NM_002497	Hs.153704	NEK2	2.99	5.26	1.20	4.38	1.76	3.66
203755_at	BUB1 mitotic checkpoint serine/threonine kinase B	NM_001211	Hs.513645	BUB1B	1.48	2.60	0.41	1.67	1.75	4.04
202338_at	thymidine kinase 1, soluble	NM_003258	Hs.515122	TK1	1.92	3.35	1.04	2.24	1.75	2.15
203764_	discs, large	NM_014	Hs.77695	DLG	2.6	4.6	0.8	2.2	1.7	2.8

at	(Drosophila) homolog-associated protein 5	750		APS	7	3	1	7	3	1
203554_x_at	pituitary tumor-transforming 1 enhancer of zeste	NM_004219	Hs.350966	PTTG1	3.65	6.30	1.03	4.12	1.73	3.99
203358_s_at	homolog 2 (Drosophila) thyroid hormone	NM_004456	Hs.444082	EZH2	1.05	1.79	0.34	0.88	1.71	2.62
204033_at	receptor interactor 13 centromere	NM_004237	Hs.436187	TRIP13	3.36	5.74	0.74	2.95	1.71	4.01
207828_s_at	protein F, 350/400kDa antigen identified	NM_005196	Hs.497741	CENPF	2.92	4.95	0.89	3.01	1.70	3.39
212022_s_at	by monoclonal antibody Ki-67	BF001806	Hs.689823	MKI67	2.50	4.23	1.02	2.08	1.69	2.03
215779_s_at		BE271470		HIST1H2BG	2.76	4.66	2.48	4.01	1.69	1.62
218883_s_at	MLF1 interacting protein	NM_024629	Hs.575032	MLF1IP	2.44	4.12	1.34	3.83	1.69	2.85
204170_s_at	CDC28 protein kinase regulatory subunit 2	NM_001827	Hs.83758	CKS2	2.48	4.18	1.07	3.12	1.69	2.93
201037_at	phosphofructokinase, platelet	NM_002627	Hs.26010	PFKP	1.56	2.63	0.57	0.88	1.69	1.54
201195_s_at	solute carrier family 7 (amino acid transporter light chain, L system), member 5	AB018009	Hs.513797	SLC7A5	2.12	3.51	0.34	1.15	1.66	3.35
205034_at	cyclin E2	NM_004702	Hs.521693	CCNE2	1.67	2.75	0.73	2.22	1.65	3.03
210559_s_at	cyclin-dependent kinase 1	D88357	Hs.732435	CDK1	6.88	11.35	2.05	8.63	1.65	4.21
217785_s_at	YKT6 v-SNARE homolog (S. cerevisiae)	NM_006555	Hs.520794	YKT6	2.37	3.90	1.76	2.82	1.64	1.60
200658_s_at	prohibitin	AL560017	Hs.514303	PHB	1.59	2.57	1.09	2.26	1.62	2.07
203126_at	inositol(myo)-1(or 4)-monophosphatase 2	NM_014214	Hs.743311	IMPA2	1.84	2.98	0.51	1.12	1.62	2.19
206102_at	GINS complex subunit 1 (Psf1 homolog)	NM_021067	Hs.658464	GINS1	2.12	3.44	0.78	2.52	1.62	3.25
221922_at	G-protein signaling modulator 2	AW195581	Hs.584901	GPSM2	1.04	1.67	0.53	0.92	1.60	1.76
221676_s_at	coronin, actin binding protein, 1C	BC002342	Hs.330384	CORO1C	1.57	2.51	0.79	1.40	1.59	1.77
219918_s_at	asp (abnormal spindle) homolog, microcephaly associated	NM_018123	Hs.121028	ASPM	5.76	9.16	1.33	5.56	1.59	4.18

	(Drosophila) epithelial cell transforming									
219787_s_at	sequence 2 oncogene	NM_018098	Hs.518299	ECT2	1.01	1.60	0.54	1.20	1.59	2.24
218260_at	DET1 and DDB1 associated 1	NM_024050	Hs.466154	DDA1	5.79	9.20	4.04	7.66	1.59	1.89
204580_at	matrix metallopeptidase 12 (macrophage elastase)	NM_002426	Hs.1695	MMP12	3.14	4.96	0.59	0.89	1.58	1.51
203967_at	cell division cycle 6	U77949	Hs.405958	CDC6	1.64	2.59	0.99	1.78	1.58	1.80
215145_s_at	contactin associated protein-like 2	AC005378	Hs.655684	CNTNAP2	1.17	1.85	1.41	2.33	1.58	1.66
204026_s_at	ZW10 interactor, kinetochore protein	NM_007057	Hs.591363	ZWINT	1.20	1.86	0.61	1.68	1.55	2.78
218728_s_at	cornichon homolog 4 (Drosophila)	NM_014184	Hs.445890	CNIH4	1.30	2.03	0.87	1.67	1.55	1.93
203968_s_at	cell division cycle 6	NM_001254	Hs.405958	CDC6	1.60	2.47	0.91	1.68	1.55	1.84
209642_at	BUB1 mitotic checkpoint serine/threonine kinase	AF043294	Hs.469649	BUB1	2.85	4.39	0.84	1.96	1.54	2.34
204092_s_at	aurora kinase A	NM_003600	Hs.250822	AURKA	1.43	2.20	0.68	1.56	1.53	2.29
215223_s_at		W46388		SOD2	1.76	2.69	0.42	0.70	1.53	1.66
201292_at	topoisomerase (DNA) II alpha 170kDa	AL561834	Hs.156346	TOP2A	5.12	7.83	2.04	7.48	1.53	3.66
214431_at	guanine monphosphate synthetase	NM_003875	Hs.591314	GMPS	0.99	1.51	0.53	0.91	1.52	1.72
203214_x_at	cyclin-dependent kinase 1	NM_001786	Hs.732435	CDK1	5.94	9.00	2.03	6.92	1.52	3.41
218585_s_at	denticleless E3 ubiquitin protein ligase homolog (Drosophila)	NM_016448	Hs.656473	DTL	2.62	3.95	1.32	3.82	1.51	2.90
208433_s_at	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	NM_017522	Hs.280387	LRP8	1.78	2.68	0.76	1.16	1.51	1.53
204162_at	NDC80 kinetochore complex component	NM_006101	Hs.414407	NDC80	2.43	3.66	0.81	1.92	1.50	2.38
205916_at	S100 calcium binding protein A7	NM_002963	Hs.112408	S100A7	2.34	13.17	1.67	2.28	5.64	1.36
203535_at	S100 calcium binding protein A9	NM_002965	Hs.112405	S100A9	6.16	19.24	1.52	2.25	3.12	1.48

205029_s_at	fatty acid binding protein 7, brain	NM_001446	Hs.26770	FABP7	2.73	7.91	0.67	0.65	2.89	0.97
205030_at	fatty acid binding protein 7, brain	NM_001446	Hs.26770	FABP7	0.77	1.94	0.13	0.12	2.51	0.94
204913_s_at	SRY (sex determining region Y)-box 11	AI360875	Hs.432638	SOX11	1.22	2.95	0.53	0.71	2.43	1.34
219410_at	transmembrane protein 45A	NM_018004	Hs.658956	TMEM45A	0.87	2.10	0.60	0.66	2.42	1.10
204914_s_at	SRY (sex determining region Y)-box 11	AW157202	Hs.432638	SOX11	2.19	5.08	0.64	0.95	2.32	1.47
210663_s_at	kynureninase	BC000879	Hs.470126	KYNU	1.28	2.80	0.65	0.95	2.18	1.45
204915_s_at	SRY (sex determining region Y)-box 11	AB028641	Hs.432638	SOX11	1.41	3.01	0.75	0.91	2.13	1.22
219529_at	chloride intracellular channel 3	NM_004669	Hs.64746	CLIC3	1.87	3.91	1.13	1.51	2.10	1.34
214461_at	lipopolysaccharide binding protein	NM_004139	Hs.154078	LBP	1.26	2.62	0.80	0.90	2.07	1.13
202912_at	adrenomedullin	NM_001124	Hs.441047	ADM	0.84	1.70	0.40	0.48	2.02	1.20
214370_at	S100 calcium binding protein A8	AW238654	Hs.416073	S100A8	2.66	5.24	1.42	1.50	1.97	1.05
211527_x_at	vascular endothelial growth factor A	M27281	Hs.73793	VEGFA	2.01	3.91	1.24	1.50	1.94	1.21
204679_at	potassium channel, subfamily K, member 1	NM_002245	Hs.208544	KCNK1	1.32	2.44	0.88	1.29	1.85	1.47
201848_s_at	BCL2/adenovirus E1B 19kDa interacting protein 3	U15174	Hs.144873	BNIP3	2.14	3.88	1.57	2.34	1.81	1.49
202859_x_at	interleukin 8	NM_000584	Hs.624	IL8	1.75	3.17	0.68	0.86	1.81	1.25
211110_s_at	androgen receptor	AF162704	Hs.76704	AR	0.92	1.65	5.33	3.87	1.80	0.73
208650_s_at	CD24 molecule	BG327863	Hs.644105	CD24	2.38	4.18	1.29	1.59	1.75	1.24
203397_s_at	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3 (GalNAc-T3)	BF063271	Hs.170986	GALNT3	0.95	1.65	0.52	0.63	1.74	1.20
209924_at	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	AB000221	Hs.143961	CCL18	2.28	3.96	0.69	0.98	1.74	1.42
207802_at	cysteine-rich secretory protein 3	NM_006061	Hs.404466	CRISP3	1.08	1.86	1.01	1.35	1.72	1.33

32128_at	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	Y13710	Hs.143961	CCL18	2.22	3.72	0.69	0.96	1.67	1.40
205311_at	dopa decarboxylase (aromatic L-amino acid decarboxylase)	NM_000790	Hs.359698	DDC	1.02	1.69	0.98	0.96	1.67	0.98
219962_at	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	NM_021804	Hs.178098	ACE2	1.03	1.72	0.87	0.91	1.67	1.04
211708_s_at	stearoyl-CoA desaturase (delta-9-desaturase)	BC005807	Hs.558396	SCD	1.69	2.76	1.37	2.02	1.63	1.47
211056_s_at	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	BC006373	Hs.552	SRD5A1	1.30	2.11	0.73	0.84	1.62	1.15
211162_x_at	stearoyl-CoA desaturase (delta-9-desaturase)	AF116616	Hs.558396	SCD	1.34	2.15	1.22	1.59	1.61	1.31
209772_s_at	CD24 molecule	X69397	Hs.644105	CD24	4.36	6.86	2.09	3.05	1.57	1.46
215729_s_at	vestigial like 1 (Drosophila)	BE542323	Hs.496843	VGLL1	2.33	3.63	0.36	0.43	1.56	1.18
209990_s_at	gamma-aminobutyric acid (GABA) B receptor, 2	AF056085	Hs.198612	GABBR2	1.64	2.50	0.84	0.89	1.53	1.07
212816_s_at	cystathionine-beta-synthase	BE613178	Hs.533013	CBS	2.11	3.21	0.89	1.25	1.52	1.41
216915_s_at	protein tyrosine phosphatase, non-receptor type 12	S69182	Hs.61812	PTPN12	3.33	5.06	2.88	3.49	1.52	1.21
216905_s_at	suppression of tumorigenicity 14 (colon carcinoma)	U20428	Hs.504315	ST14	1.35	2.02	0.95	1.16	1.50	1.22
219148_at	PDZ binding kinase	NM_018492	Hs.104741	PBK	2.86	3.50	0.91	3.49	1.22	3.82
203362_s_at	MAD2 mitotic arrest deficient-like 1 (yeast)	NM_002358	Hs.591697	MAD2L1	1.94	2.80	0.62	2.04	1.44	3.30
221521_s_at	GINS complex subunit 2 (Psf2 homolog)	BC003186	Hs.433180	GINS2	1.00	1.37	0.57	1.86	1.37	3.28
202503_s_at	KIAA0101	NM_014736	Hs.81892	KIAA0101	2.71	4.05	1.38	4.34	1.49	3.13
203213_at	cyclin-dependent kinase 1	AL524035	Hs.732435	CDK1	2.54	3.73	1.06	3.23	1.47	3.03
202779_s_at	ubiquitin-conjugating enzyme E2S	NM_014501	Hs.396393	UBE2S	9.42	13.46	3.83	11.41	1.43	2.98
202589_	thymidylate	NM_001	Hs.36976	TYMS	2.6	3.4	0.8	2.3	1.3	2.8

at	synthetase	071	2	S	0	0	1	2	1	7
204444_at	kinesin family member 11	NM_004523	Hs.8878	KIF11	1.6 8	2.3 0	0.6 8	1.9 5	1.3 7	2.8 6
218782_s_at	ATPase family, AAA domain containing 2	NM_014109	Hs.370834	ATAD2	4.2 1	4.6 9	1.4 0	3.9 1	1.1 1	2.7 9
218755_at	kinesin family member 20A	NM_005733	Hs.718626	KIF20A	2.8 3	4.0 9	0.9 2	2.4 3	1.4 5	2.6 6
222077_s_at	Rac GTPase activating protein 1	AU153848	Hs.505469	RACGAP1	1.7 8	2.4 4	0.8 5	2.2 0	1.3 7	2.5 8
208767_s_at	lysosomal protein transmembrane 4 beta	AW149681	Hs.492314	LAPTM4B	5.0 9	7.3 0	2.0 9	5.3 8	1.4 3	2.5 7
204533_at	chemokine (C-X-C motif) ligand 10	NM_001565	Hs.632586	CXCL10	7.3 4	10. 17	1.8 4	4.6 2	1.3 9	2.5 2
213797_at	radical S-adenosyl methionine domain containing 2	AI337069	Hs.175182	RSAD2	2.9 4	3.2 6	1.2 0	3.0 1	1.1 1	2.5 1
212009_s_at	stress-induced-phosphoprotein 1	AL553320	Hs.337295	STIP1	5.0 5	7.0 7	2.3 8	5.9 4	1.4 0	2.4 9
206364_at	kinesin family member 14	NM_014875	Hs.3104	KIF14	2.7 8	3.5 1	0.8 6	2.1 3	1.2 6	2.4 8
211762_s_at	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	BC005978	Hs.594238	KPNA2	2.8 1	4.0 8	1.2 6	3.1 3	1.4 6	2.4 8
206632_s_at	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	NM_004900	Hs.226307	APOBEC3B	2.4 2	3.5 5	0.6 5	1.6 2	1.4 7	2.4 8
207165_at	hyaluronan-mediated motility receptor (RHAMM)	NM_012485	Hs.740467	HMMR	1.8 1	2.2 4	0.7 9	1.8 6	1.2 4	2.3 6
211122_s_at	chemokine (C-X-C motif) ligand 11	AF002985	Hs.632592	CXCL11	4.1 7	4.9 5	0.9 8	2.2 8	1.1 9	2.3 3
201663_s_at	structural maintenance of chromosomes 4	NM_005496	Hs.589924	SMC4	6.4 4	7.0 2	2.0 9	4.8 0	1.0 9	2.2 9
218662_s_at	non-SMC condensin I complex, subunit G	NM_022346	Hs.446201	NCAPG	2.4 9	3.0 9	1.0 0	2.2 8	1.2 4	2.2 9
213226_at	cyclin A2	AI346350	Hs.589744	CCNA2	1.7 8	2.4 6	0.6 9	1.5 5	1.3 8	2.2 6
212141_at	minichromosome maintenance complex component 4	AA604621	Hs.460184	MCM4	3.1 8	4.3 4	1.2 9	2.8 9	1.3 7	2.2 4
210163_at	chemokine (C-X-C motif) ligand 11	AF030514	Hs.632592	CXCL11	3.0 5	4.1 5	0.7 7	1.7 3	1.3 6	2.2 3
213007_at	Fanconi anemia, complementation group I	W74442	Hs.513126	FANCI	1.4 5	1.8 4	0.7 2	1.6 0	1.2 7	2.2 3
214437_s_at	serine hydroxymethyltransferase 2 (mitochondrial)	NM_005412	Hs.741179	SHMT2	3.4 4	4.6 2	1.4 9	3.2 9	1.3 4	2.2 0

218049_s_at	mitochondrial ribosomal protein L13	NM_014078	Hs.333823	MRPL13	3.55	4.68	2.40	5.28	1.32	2.20
218663_at	non-SMC condensin I complex, subunit G	NM_022346	Hs.446201	NCAPG	2.61	3.21	1.04	2.27	1.23	2.19
201629_s_at	acid phosphatase 1, soluble	BE872974	Hs.558296	ACP1	4.41	6.28	2.32	5.06	1.42	2.18
213562_s_at	squalene epoxidase	BF979497	Hs.71465	SQLE	2.47	3.36	1.41	3.02	1.36	2.14
203418_at	cyclin A2	NM_001237	Hs.58974	CCNA2	2.98	4.25	0.95	2.03	1.42	2.14
218308_at	transforming, acidic coiled-coil containing protein 3	NM_006342	Hs.104019	TACC3	2.46	2.84	1.15	2.45	1.15	2.13
200607_s_at	RAD21 homolog (S. pombe)	BG289967	Hs.81848	RAD21	3.81	3.87	1.98	4.11	1.01	2.10
219494_at		NM_012415		RAD54B	2.19	2.52	1.06	2.21	1.15	2.09
201946_s_at	chaperonin containing TCP1, subunit 2 (beta)	AL545982	Hs.189772	CCT2	5.54	5.71	3.26	6.78	1.03	2.08
219000_s_at	defective in sister chromatid cohesion 1 homolog (S. cerevisiae)	NM_024094	Hs.315167	DSCC1	2.01	2.37	0.86	1.77	1.18	2.07
213008_at	Fanconi anemia, complementation group I	BG403615	Hs.513126	FANCI	1.97	2.44	1.03	2.13	1.24	2.06
201897_s_at	CDC28 protein kinase regulatory subunit 1B	NM_001826	Hs.374378	CKS1B	2.14	2.86	1.00	2.04	1.33	2.04
201123_s_at	eukaryotic translation initiation factor 5A	NM_001970	Hs.534314	EIF5A	8.04	10.77	3.81	7.54	1.34	1.98
209825_s_at		BC002906		UCK2	2.12	2.79	0.96	1.89	1.32	1.97
210983_s_at	minichromosome maintenance complex component 7	AF279900	Hs.438720	MCM7	5.44	6.19	1.90	3.69	1.14	1.94
216088_s_at	proteasome (prosome, macropain) subunit, alpha type, 7	AL078633	Hs.233952	PSMA7	3.85	5.55	2.67	5.18	1.44	1.94
203432_at	thymopoietin	AW272611	Hs.11355	TMPO	1.70	2.09	1.03	1.98	1.23	1.93
218349_s_at	zwilch kinetochore protein	NM_017975	Hs.213317	ZWILCH	2.88	3.56	1.67	3.22	1.24	1.93
219402_s_at	derlin 1	NM_024295	Hs.241576	DERL1	1.31	1.93	0.80	1.53	1.47	1.92
202736_s_at	LSM4 homolog, U6 small nuclear RNA associated	AA112507	Hs.515255	LSM4	14.79	17.02	9.31	17.67	1.15	1.90

	(S. cerevisiae)									
218549_s_at	regulator of microtubule dynamics 1	NM_016033	Hs.145386	RMND1	1.75	2.20	1.24	2.35	1.25	1.90
213599_at	Opa interacting protein 5	BE045993	Hs.661645	OIP5	1.74	2.28	0.86	1.63	1.31	1.90
209464_at	aurora kinase B	AB011446	Hs.442658	AURKB	3.11	3.72	1.07	2.01	1.19	1.88
218027_at	mitochondrial ribosomal protein L15	NM_014175	Hs.183491	MRPL15	1.96	2.38	1.07	2.01	1.22	1.88
213330_s_at	stress-induced-phosphoprotein 1	BE886580	Hs.337295	STIP1	9.60	12.32	5.70	10.67	1.28	1.87
218695_at	exosome component 4	NM_019037	Hs.632041	EXOSC4	1.51	1.81	0.94	1.75	1.20	1.86
220085_at	helicase, lymphoid-specific	NM_018063	Hs.655830	HELLS	1.55	1.82	0.90	1.65	1.17	1.84
203145_at	sperm associated antigen 5	NM_006461	Hs.514033	SPAG5	1.35	1.96	0.89	1.63	1.45	1.84
221539_at	eukaryotic translation initiation factor 4E binding protein 1	AB044548	Hs.411641	EIF4EBP1	3.57	4.57	1.82	3.32	1.28	1.83
204086_at	preferentially expressed antigen in melanoma	NM_006115	Hs.30743	PRAME	2.73	2.69	0.98	1.80	0.98	1.82
218057_x_at	ER membrane protein complex subunit 8	NM_006067	Hs.173162	EMC8	1.79	2.05	0.99	1.77	1.15	1.79
221677_s_at	downstream neighbor of SON	AF232674	Hs.436341	DONSON	1.98	2.82	0.94	1.68	1.42	1.79
200841_s_at	glutamyl-prolyl-tRNA synthetase	AI142677	Hs.497788	EPRS	2.64	3.32	1.65	2.95	1.26	1.79
221436_s_at	cell division cycle associated 3	NM_031299	Hs.524216	CDCA3	2.15	2.70	0.94	1.68	1.25	1.79
210691_s_at	calcyclin binding protein	AF275803	Hs.508524	CACYBP	2.71	3.51	1.79	3.19	1.29	1.79
201710_at	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	NM_002466	Hs.179718	MYBL2	2.55	3.46	1.17	2.09	1.36	1.79
202145_at	lymphocyte antigen 6 complex, locus E	NM_002346	Hs.521903	LY6E	3.24	2.77	1.45	2.57	0.85	1.77
211450_s_at	mutS homolog 6 (E. coli)	D89646	Hs.445052	MSH6	6.01	5.91	3.08	5.38	0.98	1.77
212563_at	block of proliferation 1	BG491842	Hs.645279	BOP1	2.51	2.80	1.08	1.91	1.11	1.77
202619_s_at	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	AI754404	Hs.477866	PLOD2	1.58	2.27	0.88	1.56	1.43	1.77
202697_at	nudix (nucleoside diphosphate linked moiety X)-type motif 21	NM_007006	Hs.528834	NUDT21	1.69	2.45	1.05	1.84	1.45	1.75
217294_s_at	enolase 1, (alpha)	U88968	Hs.517145	ENO1	39.74	45.04	13.17	23.05	1.13	1.75

209053_s_at	Wolf-Hirschhorn syndrome candidate 1	BE793789	Hs.113876	WHSC1	1.36	1.50	0.87	1.52	1.10	1.74
213520_at	RecQ protein-like 4	NM_004260	Hs.31442	RECQL4	1.44	1.63	0.93	1.61	1.13	1.74
217356_s_at	phosphoglycerate kinase 1	S81916	Hs.78771	PGK1	12.50	17.81	6.96	12.00	1.43	1.72
201930_at	minichromosome maintenance complex component 6	NM_005915	Hs.444118	MCM6	2.05	2.56	1.05	1.78	1.25	1.70
222037_at	minichromosome maintenance complex component 4	AI859865	Hs.460184	MCM4	1.86	2.22	0.97	1.64	1.19	1.70
200853_at	H2A histone family, member Z	NM_002106	Hs.119192	H2AFZ	2.04	2.72	1.41	2.40	1.33	1.70
204238_s_at	2'-deoxynucleoside 5'-phosphate N-hydrolase 1	NM_006443	Hs.109752	DNPH1	2.74	2.79	1.57	2.66	1.02	1.70
201821_s_at	translocase of inner mitochondrial membrane 17 homolog A (yeast)	BC004439	Hs.207160	TIMM17A	2.10	2.50	1.55	2.63	1.19	1.69
202483_s_at	RAN binding protein 1	NM_002882	Hs.247638	RANBP1	6.58	8.14	3.44	5.78	1.24	1.68
201202_at	proliferating cell nuclear antigen	NM_002592	Hs.147433	PCNA	1.96	2.26	1.29	2.16	1.15	1.68
202397_at		NM_005796		NUTF2	2.63	3.66	1.50	2.49	1.39	1.66
203189_s_at		NM_002496		NDUFS8	6.17	8.07	6.21	10.27	1.31	1.65
208744_x_at	heat shock 105kDa/110kDa protein 1	BG403660	Hs.743267	HSPH1	2.47	2.93	1.66	2.71	1.18	1.65
204203_at	CCAAT/enhancer binding protein (C/EBP), gamma	NM_001806	Hs.429666	CEBPG	2.96	4.12	1.43	2.33	1.39	1.64
203276_at	lamin B1	NM_005573	Hs.89497	LMNB1	1.75	2.14	1.12	1.84	1.22	1.64
208963_x_at		BG165833		FADS1	1.68	2.35	1.12	1.83	1.40	1.63
215942_s_at	G-2 and S-phase expressed 1	BF973178	Hs.386189	GTSE1	2.36	3.43	1.07	1.74	1.45	1.62
201267_s_at	proteasome (prosome, macropain) 26S subunit, ATPase, 3	AL545523	Hs.250758	PSMC3	4.16	4.98	2.76	4.37	1.20	1.58
203715_at	tubulin folding cofactor E	NM_003193	Hs.498143	TBCE	1.78	2.18	1.54	2.43	1.22	1.58
214845_s_at	calumenin	AF257659	Hs.743262	CALU	8.35	11.82	3.98	6.28	1.41	1.58
202533_s_at	dihydrofolate reductase	BC003584	Hs.592364	DHFR	1.58	1.77	1.09	1.68	1.12	1.54
201504_s_at	translin	AI435302	Hs.750663	TSN	2.27	2.88	1.68	2.57	1.26	1.53

1053_at	replication factor C (activator 1) 2, 40kDa	M87338	Hs.647062	RFC2	2.10	2.64	1.46	2.23	1.26	1.53
209653_at	karyopherin alpha 4 (importin alpha 3)	U93240	Hs.467866	KPNA4	2.57	3.48	1.25	1.89	1.35	1.51
212914_at	chromobox homolog 7	AV648364	Hs.356416	CBX7	0.39	0.26	0.65	0.38	0.67	0.58
203485_at	reticulon 1	NM_021136	Hs.368626	RTN1	0.15	0.10	0.42	0.23	0.66	0.55
205513_at	transcobalamin I (vitamin B12 binding protein, R binder family)	NM_001062	Hs.2012	TCN1	0.37	0.24	0.93	0.43	0.66	0.46
213451_x_at		BE044614		TNXB1	0.80	0.53	1.10	0.59	0.66	0.54
205933_at	SET binding protein 1	NM_015559	Hs.435458	SETBP1	0.44	0.29	1.02	0.45	0.66	0.44
202768_at	FBJ murine osteosarcoma viral oncogene homolog B	NM_006732	Hs.590958	FOSB	0.10	0.07	0.24	0.08	0.65	0.34
212560_at	sortilin-related receptor, L(DLR class) A repeats containing	AV728268	Hs.368592	SORL1	0.37	0.24	0.91	0.49	0.65	0.53
209869_at	adrenoceptor alpha 2A	AF284095	Hs.249159	ADRA2A	0.43	0.28	1.33	0.54	0.65	0.41
207961_x_at	myosin, heavy chain 11, smooth muscle	NM_022870	Hs.460109	MYH11	0.29	0.18	0.52	0.22	0.65	0.43
220177_s_at	transmembrane protease, serine 3	NM_024022	Hs.208600	TMPRSS3	0.84	0.54	1.46	0.64	0.65	0.44
209460_at	4-aminobutyrate aminotransferase	AF237813	Hs.336768	ABAT	0.21	0.14	1.64	1.04	0.65	0.64
208004_at	proline rich, lacrimal 1	NM_021225	Hs.661425	PRL1	0.33	0.21	0.41	0.23	0.64	0.56
201693_s_at	early growth response 1	AV733950	Hs.326035	EGR1	0.26	0.17	0.63	0.21	0.63	0.33
204863_s_at	interleukin 6 signal transducer (gp130, oncostatin M receptor)	BE856546	Hs.532082	IL6ST	0.18	0.11	0.86	0.52	0.63	0.60
213933_at	prostaglandin E receptor 3 (subtype EP3)	AW242315	Hs.445000	PTGER3	0.26	0.16	1.20	0.52	0.62	0.44
204663_at	malic enzyme 3, NADP(+)-dependent, mitochondrial	NM_006680	Hs.199743	ME3	0.34	0.21	0.63	0.36	0.62	0.58
209687_at	chemokine (C-X-C motif) ligand 12	U19495	Hs.522891	CXCL12	0.66	0.41	1.53	0.77	0.62	0.51
205357_s_at	angiotensin II receptor, type 1	NM_000685	Hs.477887	AGTR1	0.36	0.22	1.69	0.79	0.62	0.46
201497_x_at	myosin, heavy chain 11, smooth muscle	NM_022844	Hs.460109	MYH11	0.26	0.16	0.60	0.21	0.61	0.35
212774_at	zinc finger and BTB domain	AJ223321	Hs.699977	ZBTB18	0.79	0.48	1.52	0.64	0.61	0.42

	containing 18									
212713_at	microfibrillar-associated protein 4	R72286	Hs.296049	MFAP4	1.06	0.64	2.21	0.81	0.61	0.37
206115_at	early growth response 3	NM_004430	Hs.534313	EGR3	0.18	0.11	0.47	0.24	0.60	0.51
203697_at	frizzled-related protein	U91903	Hs.128453	FRZB	0.51	0.30	1.02	0.47	0.60	0.46
203892_at	WAP four-disulfide core domain 2	NM_006103	Hs.2719	WFDC2	0.80	0.48	2.11	0.97	0.60	0.46
202746_at	integral membrane protein 2A	AL021786	Hs.171094	ITM2A	0.70	0.42	0.91	0.44	0.60	0.48
219359_at	ATH1, acid trehalase-like 1 (yeast)	NM_025092	Hs.353181	ATHL1	0.57	0.33	0.97	0.59	0.58	0.61
212865_s_at	collagen, type XIV, alpha 1	BF449063	Hs.409662	COL14A1	0.72	0.41	3.11	0.75	0.57	0.24
209541_at	insulin-like growth factor 1 (somatomedin C)	AI972496	Hs.160562	IGF1	0.64	0.36	1.93	0.61	0.57	0.32
205913_at	perilipin 1	NM_002666	Hs.103253	PLIN1	1.09	0.62	2.11	0.96	0.56	0.45
219064_at	inter-alpha-trypsin inhibitor heavy chain family, member 5	NM_030569	Hs.498586	ITIH5	0.40	0.23	0.47	0.26	0.56	0.56
208335_s_at	Duffy blood group, chemokine receptor	NM_002036	Hs.153381	DARC	0.57	0.32	1.19	0.41	0.56	0.35
205898_at	chemokine (C-X3-C motif) receptor 1	U20350	Hs.789131	CX3CR1	0.42	0.24	1.40	0.30	0.56	0.28
209763_at	chordin-like 1	AL049176	Hs.496587	CHRDL1	0.76	0.42	1.10	0.40	0.56	0.45
219689_at	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3G	NM_020163	Hs.597293	SEMA3G	0.39	0.22	0.89	0.41	0.56	0.46
209540_at	insulin-like growth factor 1 (somatomedin C)	AU144912	Hs.160562	IGF1	0.61	0.33	1.47	0.47	0.55	0.32
43427_at	acetyl-CoA carboxylase beta	AI970898	Hs.234898	ACACB	0.12	0.06	0.30	0.15	0.54	0.50
204719_at	ATP-binding cassette, sub-family A (ABC1), member 8	NM_007168	Hs.58351	ABCA8	0.43	0.23	1.03	0.39	0.54	0.38
207414_s_at		NM_002570		PCSK6	0.62	0.33	2.13	1.23	0.53	0.57
217838_s_at	Enah/Vasp-like	NM_016337	Hs.125867	EVL	0.89	0.47	3.61	2.00	0.53	0.55
205979_at	secretoglobin, family 2A, member 1	NM_002407	Hs.97644	SCGB2A1	0.57	0.30	1.76	1.07	0.53	0.61
203980_at	fatty acid binding protein 4,	NM_001442	Hs.391561	FABP4	1.08	0.56	2.93	1.27	0.52	0.43

	adipocyte										
49452_at	acetyl-CoA carboxylase beta	AI05763 7	Hs.23489 8	ACACB	0.10	0.05	0.26	0.12	0.52	0.48
206378_at	secretoglobin, family 2A, member 2	NM_002411	Hs.46452	SCGB2A2	0.15	0.07	2.37	0.73	0.51	0.31
221139_s_at	cysteine sulfinic acid decarboxylase	NM_015989	Hs.27981 5	CSAD	0.42	0.21	0.93	0.54	0.51	0.58
219197_s_at	signal peptide, CUB domain, EGF-like 2	AI42424 3	Hs.52346 8	SCUBE2	0.27	0.13	7.96	2.44	0.50	0.31
204041_at	monoamine oxidase B	NM_000898	Hs.65447 3	MAOB	0.33	0.16	0.55	0.34	0.48	0.63
214053_at	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	AW7721 92	Hs.39072 9	ERBB4	0.10	0.05	0.95	0.37	0.48	0.39
205440_s_at	neuropeptide Y receptor Y1	NM_000909	Hs.51905 7	NPY1R	0.53	0.24	2.10	1.23	0.46	0.58
218002_s_at	chemokine (C-X-C motif) ligand 14	NM_004887	Hs.48344 4	CXCL14	0.52	0.23	2.84	1.17	0.45	0.41
213156_at		BG25152 1		MIRN568	0.24	0.11	0.51	0.18	0.45	0.35
204731_at	transforming growth factor, beta receptor III	NM_003243	Hs.48239 0	TGFBR3	0.22	0.09	0.37	0.15	0.40	0.40
206799_at	secretoglobin, family 1D, member 2	NM_006551	Hs.20409 6	SCGB1D2	0.16	0.06	1.62	0.51	0.37	0.31
221796_at	neurotrophic tyrosine kinase, receptor, type 2	AA7071 99	Hs.49431 2	NTRK2	0.28	0.10	0.53	0.15	0.36	0.28
203281_s_at	ubiquitin-like modifier activating enzyme 7	NM_003335	Hs.16695	UBA7	0.56	0.37	0.78	0.57	0.67	0.74
204029_at	cadherin, EGF LAG seven-pass G-type receptor 2	NM_001408	Hs.57652	CELSR2	0.62	0.41	1.57	1.24	0.66	0.79
205009_at	trefoil factor 1	NM_003225	Hs.16280 7	TFF1	0.28	0.18	10.876	7.31	0.65	0.68
204508_s_at	carbonic anhydrase XII	BC00101 2	Hs.21099 5	CA12	0.30	0.20	4.46	3.65	0.65	0.82
205862_at	growth regulation by estrogen in breast cancer 1	NM_014668	Hs.46773 3	GREB1	0.47	0.31	1.99	1.66	0.65	0.83
209341_s_at	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	AU1533 66	Hs.59766 4	IKBKB	0.30	0.20	0.71	0.50	0.65	0.71
205696_s_at	GDNF family receptor alpha 1	NM_005264	Hs.38834 7	GFRA1	0.79	0.51	3.52	4.51	0.64	1.28
203726_s_at	laminin, alpha 3	NM_000227	Hs.43636 7	LAMA3	0.23	0.14	0.38	0.28	0.62	0.72
206754_s_at		NM_000767		CYP2B6	0.35	0.21	3.99	3.19	0.61	0.80
218976_	DnaJ (Hsp40)	NM_021	Hs.26072	DNA	0.2	0.1	2.4	1.7	0.6	0.7

at	homolog, subfamily C, member 12 interleukin 6 signal transducer (gp130,	800	0	JC12	1	3	8	3	1	0
212195_at	oncostatin M receptor)	AL049265	Hs.532082	IL6ST	0.50	0.30	1.61	1.11	0.60	0.69
205509_at	carboxypeptidase B1 (tissue)	NM_001871	Hs.477891	CPB1	0.68	0.40	3.60	3.15	0.59	0.87
212196_at	interleukin 6 signal transducer (gp130, oncostatin M receptor)	AW242916	Hs.532082	IL6ST	1.01	0.59	3.16	2.35	0.59	0.74
220625_s_at	E74-like factor 5 (ets domain transcription factor)	AF115403	Hs.11713	ELF5	0.59	0.34	0.08	0.08	0.58	0.94
202376_at	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	NM_001085	Hs.534293	SERPINA3	0.91	0.53	2.91	2.08	0.58	0.72
209443_at	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5	J02639	Hs.159628	SERPINA5	0.48	0.26	1.62	2.12	0.56	1.31
205225_at	estrogen receptor 1	NM_000125	Hs.208124	ESR1	0.07	0.02	3.66	2.59	0.30	0.71
202018_s_at	lactotransferrin	NM_002343	Hs.529517	LTF	0.59	0.51	1.01	0.20	0.86	0.20
206509_at	prolactin-induced protein	NM_002652	Hs.99949	PIP	0.09	0.11	2.07	0.44	1.19	0.21
209189_at	FBJ murine osteosarcoma viral oncogene homolog	BC004490	Hs.731317	FOS	0.49	0.37	1.94	0.57	0.76	0.29
204014_at	dual specificity phosphatase 4	NM_001394	Hs.417962	DUSP4	0.09	0.09	0.76	0.26	0.97	0.35
218087_s_at	sorbin and SH3 domain containing 1	NM_015385	Hs.386219	SORBS1	0.32	0.22	0.85	0.29	0.68	0.35
219580_s_at	transmembrane channel-like 5	NM_024780	Hs.115838	TMC5	0.23	0.27	1.27	0.48	1.17	0.38
219304_s_at	platelet derived growth factor D	NM_025208	Hs.352298	PDGFD	0.22	0.16	0.72	0.28	0.71	0.39
219440_at	retinoic acid induced 2	NM_021785	Hs.446680	RAI2	0.36	0.25	1.50	0.60	0.68	0.40
203355_s_at	pleckstrin and Sec7 domain containing 3	NM_015310	Hs.434255	PSD3	0.17	0.16	0.74	0.30	0.94	0.41
217967_s_at	family with sequence similarity 129, member A	AF288391	Hs.518662	FAM129A	0.74	0.59	1.41	0.61	0.80	0.43
214218_	X inactive	AV6993	Hs.52990	XIST	0.3	0.2	0.6	0.3	0.6	0.4

s_at	specific transcript (non-protein coding)	47	1		1	1	9	0	8	4
202962_at	kinesin family member 13B	NM_015254	Hs.444767	KIF13B	0.21	0.17	0.78	0.34	0.82	0.44
204607_at	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)	NM_005518	Hs.59889	HMGCS2	0.36	0.41	1.29	0.58	1.11	0.45
221728_x_at	X inactive specific transcript (non-protein coding)	AA628440	Hs.529901	XIST	0.30	0.20	0.66	0.29	0.67	0.45
218353_at	regulator of G-protein signaling 5	NM_025226	Hs.24950	RGS5	0.36	0.26	1.34	0.60	0.72	0.45
213110_s_at	collagen, type IV, alpha 5	AW052179	Hs.369089	COL4A5	0.20	0.16	0.87	0.40	0.81	0.45
201694_s_at	early growth response 1	NM_001964	Hs.326035	EGR1	0.18	0.14	0.34	0.16	0.74	0.47
203240_at	Fc fragment of IgG binding protein	NM_003890	Hs.111732	FCGBP	0.39	0.32	0.63	0.29	0.83	0.47
203130_s_at	kinesin family member 5C	NM_004522	Hs.435557	KIF5C	0.34	0.27	1.39	0.66	0.79	0.48
209706_at	NK3 homeobox 1	AF247704	Hs.559993	NKX3-1	0.59	0.41	1.25	0.60	0.69	0.48
212419_at	zinc finger, CCHC domain containing 24	AA131324	Hs.523080	ZCCHC24	0.35	0.27	1.03	0.50	0.77	0.49
200795_at	SPARC-like 1 (hevin)	NM_004684	Hs.628861	SPARCL1	0.41	0.33	1.21	0.60	0.80	0.49
205883_at	zinc finger and BTB domain containing 16	NM_006006	Hs.591945	ZBTB16	0.43	0.42	0.75	0.37	0.98	0.49
221748_s_at	tensin 1	AL046979	Hs.471381	TNS1	0.27	0.17	0.46	0.23	0.79	0.50
201041_s_at	dual specificity phosphatase 1	NM_004417	Hs.171695	DUSP1	0.33	0.30	0.75	0.38	0.93	0.50
205776_at	flavin containing monooxygenase 5	NM_001461	Hs.642706	FMO5	0.22	0.29	0.70	0.36	1.29	0.52
204072_s_at	furry homolog (Drosophila)	NM_023037	Hs.507669	FRY	0.15	0.13	0.56	0.29	0.89	0.52
1598_g_at	growth arrest-specific 6	L13720	Hs.646346	GAS6	0.75	0.55	1.25	0.65	0.73	0.53
214657_s_at		AU134977		NEAT1	0.21	0.16	0.39	0.20	0.74	0.53
204418_x_at	glutathione S-transferase mu 2 (muscle)	NM_000848	Hs.279837	GSTM2	0.41	0.39	0.95	0.53	0.95	0.56
210365_at		D43967		RUNX1	0.18	0.16	0.31	0.18	0.89	0.56
218552_at	enoyl CoA hydratase domain containing 2	NM_018281	Hs.476319	ECHDC2	0.46	0.39	0.84	0.47	0.85	0.57
202992_at	complement component 7	NM_000587	Hs.780651	C7	0.77	0.59	1.15	0.65	0.77	0.57
205794_s_at	neuro-oncological ventral antigen 1	NM_002515	Hs.315881	NOVA1	0.24	0.16	0.66	0.39	0.68	0.57
204622_	nuclear receptor	NM_006	Hs.56334	NR4	0.1	0.1	0.4	0.2	0.9	0.5

x_at	subfamily 4, group A, member 2	186	4	A2	6	4	3	5	0	7
216248_s_at	nuclear receptor subfamily 4, group A, member 2	S77154	Hs.563344	NR4A2	0.18	0.19	0.56	0.33	1.02	0.58
205380_at	PDZ domain containing 1	NM_002614	Hs.444751	PDZK1	0.19	0.15	0.82	0.48	0.78	0.58
212741_at	monoamine oxidase A	AA923354	Hs.183109	MAOA	0.44	0.34	1.02	0.60	0.76	0.59
201983_s_at	epidermal growth factor receptor	AW157070	Hs.488293	EGFR	0.72	0.92	0.31	0.19	1.27	0.60
205157_s_at		NM_000422		KRT17	1.29	0.99	0.46	0.27	0.77	0.60
212095_s_at	microtubule associated tumor suppressor 1	BE552421	Hs.7946	MTUS1	0.29	0.31	0.71	0.43	1.07	0.60
204294_at	aminomethyltransferase	NM_000481	Hs.102	AMT	0.16	0.11	0.20	0.12	0.68	0.60
216333_x_at		M25813		TNXA	0.82	0.59	1.05	0.64	0.72	0.61
211986_at	AHNAK nucleoprotein	BG287862	Hs.502756	AHNAK	0.42	0.35	1.00	0.62	0.84	0.62
206143_at	solute carrier family 26, member 3	NM_000111	Hs.1650	SLC26A3	0.42	0.45	0.52	0.32	1.08	0.62
206093_x_at		NM_007116		TNXB2	0.82	0.59	1.01	0.63	0.72	0.62
203710_at	inositol 1,4,5-trisphosphate receptor, type 1	NM_002222	Hs.567295	ITPR1	0.28	0.20	0.90	0.56	0.72	0.62
211596_s_at	leucine-rich repeats and immunoglobulin-like domains 1	AB050468	Hs.518055	LRIG1	0.28	0.24	0.97	0.61	0.86	0.63
212448_at	neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	AB007899	Hs.185677	NEDD4L	0.27	0.19	0.59	0.37	0.71	0.63
216264_s_at	laminin, beta 2 (laminin S)	X79683	Hs.439726	LAMB2	0.24	0.21	0.72	0.46	0.88	0.64
202723_s_at	forkhead box O1	AW117498	Hs.370666	FOXO1	0.55	0.45	0.63	0.40	0.82	0.64
204823_at	neuron navigator 3	NM_014903	Hs.655301	NAV3	0.39	0.30	0.67	0.42	0.76	0.64
203510_at	met proto-oncogene (hepatocyte growth factor receptor)	BG170541	Hs.132966	MET	0.47	0.55	0.26	0.17	1.16	0.66
213298_at	nuclear factor I/C (CCAAT-binding transcription factor)	X12492	Hs.170131	NFIC	0.54	0.47	0.88	0.58	0.86	0.66

Table 18. Upregulated targets of the downregulated hsa-mir-568 in high iBCR score ER-/ER+ tumors.

Fold-change ↑	ProbeSet	Symbol	Name	EntrezID	Accession	UGCluster
3,0	220085..at	HELLS	helicase, lymphoid-speeifie	3070	NM_018063	Hs.655830
2.5	201291_s_at	TOP2A	topoisomerase (DNA) Π alpha 170kDa	7153	AU159942	Hs. 156346
2.4	203213..at	CDK1	cyelin-dependent kinase 1	983	AL524035	Ms,732435
2.3	212009._s_at	STIP1	slress-induced-phosphoprotein 1	10963	AL553320	Hs,337295
1.7	203755._at	BUB1B	BUBI mitotic checkpoint serine/threonine kinase B	701	NMJ 3012 11	Hs.513645
1.6	205282..at	LRP8	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	7804	NMJ 3046 31	Ms.280387
1.6	202697._at	NUDT21	nudix (nucleoside diphosphate linked moiety XVtype motif 21	11051	NM_007006	Hs,528834
1.5	209053_s_at	WHSC1	Wolf-Hirsehhorn syndrome: candidate 1	7468	BE793789	Hs.l 13876
1.9	202134_s_at	WWTR1	WW domain containing transcription regulator 1	25937	NM_015472	Hs.594912
1.9	213906,_at	MYBL1	v-myb myeloblastosis viral oncogene homolog (avian)-Hke 1	4603	AW592266	Hs.445898
1.8	206348_s_at	PDK3	pyruvate dehydrogenase kinase, isozyme 3	5165	NM_005391	Hs.296031
1.8	219927_at	FCFl	FCFl small subunit (SSU) processome component homolog (S. eerevisiae)	51077	NML015962	Hs.579828
1.8	209757._s_at	MYCN	v-myc myelocytomatoas viral related oncogene. neuroblastoma derived (avian)	4613	BC002712	Hs,25960
1.8	217562_at	FAM5C	family with sequence similarity 5, member C	339479	BF589529	Hs.65765
1.7	219875_s_at	DESI2	desumoylating isopeptidase 2	51029	NM_016076	Hs.498317
1.7	215305_at	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide	5156	1179306	Hs.74615
1.7	219434_at	TREM1	triggering receptor expressed on myeloid cells 1	54210	NM_018643	Hs.283022
1.7	217834_s_at	SYNCRIP	synaptotagmin binding. cytoplasmic RNA interacting protein	10492	NM_006372	Hs.571177
1.6	205646._s_at	PAX6	paired box 6	5080	NM_000280	Hs.270303
1.6	205796..at	TCP11L1	l-complex 11, testis-speciiic-like 1	55346	NM_018393	Hs.655341
1.6	222269,..at	APOOL	apolipoprotein O-like	139322	W87634	Hs.512181
1.6	219311_at	CEP76	centrosomal protein 76kDa	79959	NMJ)24899	Hs.2.36940
1.6	214708_at	SNTB1	syntrophin, beta 1	6641	BG484314	Hs.46701

			(dysto phin-associated protein A 1, 59kDa, basic component 1)			
1.6	210073..at	ST8SI A1	ST8 atpha-N-acetyl-neuraminide alpha-2,8-sialyitransferase 1	6489	L32867	Ms,408614
1.6	205490._x_at	GJB3	gap junction protein, beta 3, 31kDa	2707	BF060667	Ms,522561
1.6	219944..at	CL1P4	CAP-GLY domain containing linker protein family, member 4	79745	NML0246 92	Ms, 122927
1.6	206357..at	OPA3	optic atropiiy 3 (atitosomal recessive, with chorea-and spastic paraplegia)	80207	NMJ)251 36	Ms,466945
1.6	219262..at	SLJV39 H2	Suppressor of variegation 3-9 homolog 2 (Drosophila)	79723	NM_0246 70	Hs.554883
1.5	201602_s_at	PPPIR I2A	protein phosphatase- 1, regulatory suhunit 12A	4659	BE 737620	Hs.49582
1.5	21.6008,_s_at	AR1H2	ariadne homolog 2 (Drosophila)	10425	AV694434	Hs.633601
1.5	200671._s_.at	SPTBN I	spectrin, beta, non-erytltroeytic 1	6711	N92501	Hs.503178
1.5	210041_s_.at	PGM3	phosphogiucomutase 3	5238	BC001258	Hs.661665
1,5	206376_at	SLC6A 15	solute carrier. family 6 (neutral amino acid transporter), member 15	551 17	NM_0180 37	Hs.44424

Bolded genes upresulated in high iBCR score ER-/ER+ vs. normal breast

5

EXAMPLE 3

The iBCR test described herein was developed from **a meta-analysis of** gene expression profiles of breast cancer. This test is based on the expression of 43 genes which are prognostic as a signature in breast cancer irrespective of subtype. This test was also found to be prognostic in lung adenocarcinoma. Patients with high iBCR score have much poorer overall survival than patients with low iBCR score.

In the **-current** study, The Cancer Genome Atlas (TCGA) datasets for several cancer types were investigated for three **purposes.** First, to determine the differences at .the protein level between high iBCR score breast cancer cases to low iBCR score breast cancer cases. This comparison was also carried out for lung adenocarcinoma. Secondly, to determine whether deregulated proteins/phosphoproteins between high and low iBCR score tumours are prognostic. Finally, the prognostic value of the iBCR mRNA signature and associated protein signature are prognostic in other cancer types profiled by the TCGA.

As shown in Figure 48A&B, comparison of the reverse phase protein array (RPPA) data between ER+ breast cancer cases with high iBCR score and low iBCR score identified several deregulated proteins and phosphoproteins between these two patient subgroups. Similar analysis in ER- breast cancer cases with high iBCR score compared to those with low iBCR score also identified deregulated proteins and phosphoproteins between these two patient subgroups (Fig.48C&D). These significantly deregulated proteins and **phosphoproteins** were then tested for association with overall survival. The upregulation of 9 and down regulation **of** 8 proteins/phosphoproteins were highly prognostic in breast cancer (Fig.49A). Importantly, the integration of the iBCR mRNA and protein signatures is the most significant indicator of overall survival of breast cancer patients irrespective of subtypes and in comparison to all known ciinicopathological indicators (Fig.49B).

Similar analysis in the lung adenocarcinoma TCGA dataset identified proteins/phosphoproteins based on the iBCR mRNA signature which are prognostic as a protein signature (Fig.50A-C), The integration of the iBCR mRNA/protein signatures were highly prognostic and outperformed the standard ciinicopathological indicators in lung adenocarcinoma (Fig.50D&E).

Table 19 summarises the 43 genes at the mRNA level and 23 proteins/phosphoproteins in the iBCR test. The components which were prognostic

in breast cancer (Fig.48 & Fig.49) and lung adenocarcinoma (Fig.50) are labelled in Table 19. Next, the association of the mRNA and protein/phosphoprotein levels of the genes in Table J9 with overall survival was tested in other cancer types. The deregulation of mRNA and protein levels of the iBCR test components that associate with overall survival is summarised in Table 19. For each cancer type, the marked components were used as a signature and the stratification of overall survival of kidney renal clear cell carcinoma (KIRC), skin cutaneous melanoma (SKCM), uterine corpus endometrioid carcinoma (UCEC), ovarian adenocarcinoma (OVAC), head and neck squamous cell carcinoma (HNSC), colon/rectal adenocarcinoma (COREAD), lower grade glioma (LGG), baldder urothelial carcinoma (BLCA). lung squamous cell carcinoma (LUSC^ kidney renal papillary cell carcinoma (KIRP), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), liver hepatocellular carcinoma (LIHC) and pancreatic ductal adenocarcinoma (PDAC).is shown Figures 51 to 54.

In conclusion, the iBCR test including the mRNA and protein components (Table **1.9)** is a highly prognostic test in all cancers tests. **This** test identifies aggressive human cancers and is enriched for protein-protein interactions (Figure 55) as well as biological functions related to the hallmarks of cancer (Table 20).

Table 19: The iBCR test components in differenl t cancers from T tCGA dattasets

iBCR test component	BRCA	LUAD	KIRC	SKCM	UCEC	OVCA	HNSC	COREAD	LGG	BLCA	LUSC	AAC	KIRP	PDAC	LIHC	CESC
mRNA																
GNB2L1	+	+			+	+	+			-	+	+	+		+	
EIF3K	+		+	+	+	+		+		-		+		+		-
TXN	+	+				+	+	+	+	-		+			+	-
ADORA2B	+		+	+		+	+			+		+	+	+		
KCNG1	+	+	+		+	+	+			+		+	+			
BCAP31	+	+	+	-	+				+	-		+				-
GSK3B	+	+		+	+	+					-		+	+		
EXOSC7	+		+	+	+					-				+	+	-
FOXM1	+	+	+	+	+							+	+	+		
CD55	+		+				+	+		-			+	+		
ZNF593	+	+	+		+		+				+	+				
EXO1	+	+		+	+							+	+	+		
KIF2C	+	+	+	+	+							+	+			
STAU1	+					+			+	+			+	+		+
MAP2K5	+				+	+				+	-	+				
TTK	+	+	+		+							+	+			
MELK	+	+	+		+							+	+			
CENPA	+	+	+	+								+	+			
TPX2	+	+	+	+								+	+			
NDUFC1	+						+	+		-	-					
CA9	+	+											+		+	+
CAMSA	+			+						+	-			+		

P1																
GRHPR	+	+			+					-		+				
HCFC1R1	+	+				+	+	+								
CEP55	+	+	+									+	+			
MCM10	+	+		+								+	+			
PML	+		+		+			+	+							
CENPN	+	+	+									+				
CARHSP1	+	+	+						+							
CETN3	+									-				+		
ABHD5	+			+							-					
BTN2A2	-	-		-		-	-	-	+	-				-		
SMPDL3B	-			-				-		-	+		-	-		
MTMR7	-	-		-			-					-		-	-	
ME1	-			-				-			-			-		+
BCL2	-		-									-	-	-		
ZNRD1-AS1	-	-				-										-
MAPT	-	-	-									-				
ERC2	-									-				-		
BTG2	-	-		-												
MYB	-				-							-				
STC2	-											-				
IGH@	-															

Protein											
DVL3	+	+	+		+			+	+	+	+
PAI-1		+	+	+		+	+	+	+		+
VEGFR2	+					+	-		+	+	+
INPP4B	+				+		+	+			+
EIF4EBP 1	+		+	+	+			+			
EGFR	+			+			+	+			+
Ku80		+		+					+	+	
HER3	+		-				+	+			
SMAD1	+						+		+	+	
GATA3		+					+				+
ITGA2		+					+				
AKT1		+								+	
NFKB1	+								+		
HER2	+										
ASNS	-			-	+	-	-	-		-	-
MAPK9	-		-	-	-	-		-			
ESR1		-	-	-	-	-			-		
YWHAE	-				-	-		-	-		
RAD50	-		-					-			
PGR	-					-			-		
COL6A1	-						+				
PEA15	-							-			
RPS6	-										

+ denotes the association of overexpression with poorer survival (also shaded as red).

- denotes the association of underexpression with poorer survival (also shaded in green)

Table 20: Enrichment of biological functions related to the hallmarks of cancer in the iBCR test

ID	TERM	# GENES	P-VALUE	P-VALUE FDR	P-VALUE BONFERRONI
GO:0009719	response to endogenous stimulus	22	9.17E-11	1.13E-06	1.13E-06
GO:1901700	response to oxygen-containing compound	18	9.10E-08	2.90E-04	1.13E-03
GO:0032268	regulation of cellular protein metabolic process	20	1.58E-07	2.90E-04	1.96E-03
GO:0035556	intracellular signal transduction	20	1.66E-07	2.90E-04	2.05E-03
GO:0010243	response to organonitrogen compound	14	1.80E-07	2.90E-04	2.22E-03
GO:0010033	response to organic substance	24	1.82E-07	2.90E-04	2.25E-03
GO:0000278	mitotic cell cycle	14	1.83E-07	2.90E-04	2.27E-03
GO:0051049	regulation of transport	18	1.87E-07	2.90E-04	2.32E-03
GO:0031401	positive regulation of protein modification process	15	2.68E-07	3.41E-04	3.32E-03
GO:0022402	cell cycle process	16	2.86E-07	3.41E-04	3.54E-03
GO:0044093	positive regulation of molecular function	18	3.47E-07	3.41E-04	4.30E-03
GO:0051051	negative regulation of transport	10	3.75E-07	3.41E-04	4.64E-03
GO:0042493	response to drug	11	3.76E-07	3.41E-04	4.66E-03
GO:0007049	cell cycle	18	3.85E-07	3.41E-04	4.77E-03
GO:0009612	response to mechanical stimulus	8	4.36E-07	3.60E-04	5.40E-03
GO:0001934	positive regulation of protein phosphorylation	13	5.76E-07	4.13E-04	7.13E-03
GO:0008283	cell proliferation	13	6.10E-07	4.13E-04	7.55E-03
GO:0009967	positive regulation of signal transduction	16	6.12E-07	4.13E-04	7.57E-03
GO:0051130	positive regulation of cellular component organization	13	6.34E-07	4.13E-04	7.85E-03
GO:0022603	regulation of anatomical structure morphogenesis	13	8.87E-07	5.49E-04	1.10E-02
GO:0072507	divalent inorganic cation homeostasis	9	9.96E-07	5.70E-04	1.23E-02
GO:0023056	positive regulation of signaling	16	1.12E-06	5.70E-04	1.38E-02
GO:0032270	positive regulation of cellular protein metabolic process	15	1.13E-06	5.70E-04	1.40E-02

GO:0048732	gland development	9	1.13E-06	5.70E-04	1.40E-02
GO:0010647	positive regulation of cell communication	16	1.18E-06	5.70E-04	1.46E-02
GO:0051246	regulation of protein metabolic process	20	1.20E-06	5.70E-04	1.48E-02
GO:0051128	regulation of cellular component organization	19	1.51E-06	6.91E-04	1.87E-02
GO:0071310	cellular response to organic substance	19	1.89E-06	8.34E-04	2.34E-02
GO:0042327	positive regulation of phosphorylation	13	2.51E-06	1.07E-03	3.10E-02
GO:1901698	response to nitrogen compound	13	2.90E-06	1.18E-03	3.59E-02
GO:0009725	response to hormone	13	2.95E-06	1.18E-03	3.65E-02
GO:0048584	positive regulation of response to stimulus	18	3.30E-06	1.24E-03	4.08E-02
GO:0042127	regulation of cell proliferation	17	3.36E-06	1.24E-03	4.16E-02
GO:0070887	cellular response to chemical stimulus	21	3.40E-06	1.24E-03	4.21E-02
GO:0010608	posttranscriptional regulation of gene expression	10	3.65E-06	1.29E-03	4.52E-02
GO:0043085	positive regulation of catalytic activity	15	3.78E-06	1.30E-03	4.68E-02

EXAMPLE 4

The study by Westin *et al. (Lancet Oncol,* 2014, vol 15(1)) perfomied gene expression profiling on 18 folLicular lymphoma patients before receiving pidilizumab in combination with rituximab. **The** expression of the genes in the iBCR signature was investigated for **association** with progression free survival (PES) in these patients. Twelve genes showed a strong association with PFS (Figure 56A) (all the genes that associated with survival belonged to the TN component of the iBCR test). As shown in Figure 56B, a score calculated based on the iBCR signature was highly predictive of patient survival after pidilizumab + rituximab immunotherapy. The study also profiled eight of the patients 15 days post treatment. The expression of the genes in the signature was compared in these patients before and after treatment. Apart from a tend towards an inversion of the expression profile in general which was most obvious for the one patient who survived (Figure 56C —patient number 9), one gene *(ADORA2B)* was significantly different in tumours after treatment compared to that before treatment (Figure 56D). This gene could be used to confirm response after selection of patients based on the iBCR test.

The data presented here indicate the iBCR test can be a companion diagnostic for certain immunotherapy which is not surprising since the **TN** component includes several immune related genes in addition to genes involved in redox reactions and kinases.

EXAMPLE 5

A meta-analysis was performed in **Oncomine™** using breast cancer datasets irrespective of subtypes or gene expression array platforms used. **The** global gene expression profiles of breast tumors that led to metastatic or death event within 5 years were compared to those that did not and the top overexpressed (OE) and underexpressed genes (UE) in these comparisons were selected. The commonly deregulated genes **in the** primary tumors that led to metastatic and death events (depending on the annotation of each dataset) were then interrogated using the online tool KM-Plotter™ (n>4000 patients with some overlap with the datasets in Oncomine™). Genes which associated with relapse-free survival of breast cancer patients were selected.

The 860 genes identified from this analysis were then subjected to network analysis using the Ingenuity Pathway Analysis (IPA®) software to identify functional networks within this gene list (see Table 21), Figure 57 shows the eleven functional networks that contain the 860 genes identified from the meta-analysis where the function of each network is specified and the interactions amongst these networks are depicted with the connecting lines. Genes whose overexpression is associated with poorer survival are marked in red and those whose underexpression is associated with poorer survival are marked in green, Larger circles mark genes with highest association with patient survival in any given network.

These 860 genes identified from the meta-analysis were then filtered for genes with the highest association with patient survival in each of the eleven functional networks, From this, the selected 133 genes (listed in Table 22) from the eleven functional networks are shown in Figure 58 (panel A) where the function of each network is displayed. Based on these networks, the 133 genes were classified to six functional metagenes (listed in Table 22) which include: Metabolism, Signalling, Development and Growth, Chromosome segregation/Replication, Immune response and Protein synthesis/Modification metagenes. The association of each of these metagenes with relapse-free survival of breast cancer patients in the KM Plotter dataset is shown in panel B of Figure 58, Each of these metagenes were scored by calculating the ratio of the expression level (sum or average) of the overexpressed genes in the metagene to the expression level (sum or average) of the underexpressed genes in the metagene. The green lines (with better survival) denote lower score (ratio of the overexpressed to the underexpressed genes) of the metagene whereas the red line (with worse survival) denote high score (ratio of the overexpressed genes to the underexpressed genes).

Table 21. 860 genes associated with relapse-free survival of breast cancer patients*

Carbohydrate/Lipid Metabolism		Cell Signaling	Cellular Development		
ARHGEF3	**ATP6V0A1**	AGBL2	ABCA8	KIF5C	ZNF211
ASAH1	**ATP6V1C1**	ARFRP1	APBB2	LRIG1	**AP3B1**
ASB1	**COX4I1**	ARNT2	ART4	MADD	**DYNC1LI2**
ATP2A2	**DHRS7**	CCR1	ATHL1	MAPT	**ESRP1**
BRD8	**EPCAM**	DST	BCL2	MIER2	**GMPS**
BTG2	**HN1**	EEF1A1	BEND5	MIS18A	**GPI**
BTN2A2	**IDH3A**	LUZP1	CABYR	MR1	**HCCS**
C1QB	**IDH3G**	MYBPC1	CASP10	N4BP1	**HCFC1R1**
CERS6	**LAMTOR2**	PIP	CHPT1	NEDD4L	**KCNG1**
CYP2C9	**LAMTOR3**	S1PR1	CYBRD1	OGN	**NAPG**
ELOVL2	**MATR3**	SNED1	ERC2	PRKCB	**NDRG1**
ELOVL5	**NPR3**	TAZ	FHL5	PROL1	**NDUFB6**
ERBB4	**NRIP1**	TP63	GAB1	RERE	**NDUFS6**
FLNB	**PFKP**	**ADORA2B**	GDNF	SETBP1	**NME1**
HIF3A	**RAP2A**	**CMC4**	GLRB	SGCD	**OIP5**
KIR2DL4	**SLC16A3**	**DDX39A**	GOLGB1	SGSM2	**PGAM1**
LRP2	**TK1**	**GAPDH**	GOSR1	SLC45A2	**PIR**
LRP8	**VDAC1**	**GSK3B**	GPR12	SOD2	**PRRG1**
ME1	RAPGEF6	**HIF1A**	HLA-B	SPAG8	**RTCA**
NCOA1	RBM38	**HSPA14**	ITM2A	SPG20	**S100A11**
NR1H3	SEC14L2	**LAMA4**	KIAA0247	SSPN	**SMS**
PBXIP1	SRSF5	**MAP2K5**	KIAA0430	SSX2	**TARS**
PIK3IP1	STARD13		STX18	XBP1	**TRAK2**
PSEN2			TRAK1	ZC3H14	
			TRAPPC10	ZMYM5	

Cellular Growth			Chromosome segregation	
ASF1B	SLC11A1	BCAP31	AFF1	**AURKB**
BBS1	SMARCA2	**BYSL**	ATP1A2	**BUB1**
CCL13	SNX1	**CCNA2**	CDC14A	BUB1B
CCND2	SORL1	CCNE2	CDC27	BUB3
CDKN2A	SPDEF	CDC25A	CSPG4	**C20orf24**
DI8AS3	STAT5B	CDC45	FOXK2	CCNB1
DIXDCI	TAOK3	CDC6	MAGI1	CCNB2
DOCK1	TGQLN2	CDCA3	MLLT10	**CDC20**
DOK1	THPO	CDGA8	MTUSI	CDK1
EPOR	TIMELESS	CHEK1	NUP62	**CENPE**
FLT3	TNN	**DERL1**	NXF1	CENPF
FOSB	TNXB	DHFR	PKMYT1	CKS1B
GGA2	TYR03	E2F8	RAPGEF2	CKS2
HAVCR1	ULK2	ECT2	SLC25A12	**FOXM1**
IL1RAPL1	VPS39	**GINS3**	SLC8A1	KIF2C
IL6ST	PIM1	**RAD51**	**KIF4A**	**NUP93**
JAK2	PGLD1	**RRM2**	**MAD2L1**	**NUSAP1**
LEPR	**PLK4**	**SKP2**	**MXI1**	**NUTF2**
LIG1	**PSMD10**	**UBE2C**	**NCAPG**	PLK1
LZTFL1	**MCM6**	**ULBP2**	**NDC80**	**PRC1**
MTF1	**MELK**	**WDHD1**	**NUP155**	**PTTG1**
PCM1	**MMP1**	**IL1RAP**	**TPX2**	**SPC25**
PIK3R4	**MYBL2**	**MCM10**	**TTK**	**TACC3**
POU6F1	**ORC6**	MCM2	**ZWINT**	
NF1	**PDAP1**	**MCM4**		

DNA Replication/ Recombination		immune system				
ALDH3A2	ADRM1	ABCA1	DTX3	SARM1	**PBK**	ACOT7
ATAD5	**BIRC5**	AHSG	DYNC2H1	SIRT3	PFDN5	ANP32E
ATF5	**CARHSP1**	ANK3	EFCAB6	SMPDL3B	**PSMA2**	APOBEC3B
BLM	CENPA	APOBEC3A	EFNB3	*SUN*	RNASE4	CAST
BRD4	CENPI	BATF	ERAP1	TTC28	RNF141	**CCT5**
BRF2	CENPN	BECN1	EVI	WFDC2	S100A9	CCT6A
BTN3A2	CENPU	BUD31	FBX041	ZMYM6	SHMT2	CCT7
CLASP2	DL6AP5	C2	FBXW4	ZNF516	SLC7A5	CD36
FANCA	ERCC6L	C3	FCGBP	IGHG3	SOX11	**CD55**
FBLN1	**EXO1**	CAGNA1D	FCGR1A	IGHM	**TBPL1**	**CDK8**
KIF18B	FANCI	CAROIO	FCGRIB	IGK	**TCP1**	CHD1
NPR2	**H2AFX**	CD163	FOS	IGKC	TOPORS	**CXCL8**
PLXNA3	H2AFZ	CD1A	FRZB	IGSF9B	**TREM1**	DHCR7
PSMD2	**IMPDH2**	CD1B	GAS7	il6	**TXN**	**DSCC1**
STC2	**MAPRE1**	CD1C	GCH1	KCNMA1	**TXNRD1**	ELF3
TCF3	W1SH6	CD22	GLi3	K!F13B	WNT5A	**GEMIN4**
TCF7L1	**PML**	CD68	GPRASP1	KL	**GM2A**	
TCF7L2	POMP	CD80	GREB1	LAD1	GPSM2	
TXNIP	P5MB4	CDK5R1	1GH	LAT	**GSPTI**	
RYBP	PSMB5	CFB	IGHG1	LFNG	**HMGB3**	
TOP2A	PSMB7	CHL1	NBPF10	MED12	HMMR	
UBE2A	**PSMD14**	C1ITA	NUMA1	MSG	HNRNPAB	
UBE2B	PSMD3	CR1	PDE6B	MX2	**HPSE**	
PSMD7		CRP	PGR	MCCC2	**HRASLS**	
		CST3	PHLDA2	MRPL12	IDH2	
		CXCL14	PPY	**NAE1**	**K!AAOIOI**	
		CXCR4	RLN2	**NXN**	LGALS1	

Metabolic Disease					
					NMEI-
AASS	ENOSF1	MMRN2	SESN1	**CALM1**	**NME2**
ABCC8	FAM105A	MPP2	SFI1	**CAMSAP1**	**PARPBP**
ACAP2	FAM117A	MY019	SLC35A2	**CETN3**	**PGK1**
ACSF2	FAM12QA	N4BP2L1	SLC6A5	CFAP20	**PLCH1**
AHCYL1	FAM129A	NBEA	SLC01A2	CMG2	**RAB22A**
ALDH1A2	FAM49B	NCAPD3	SPATA6	**CNOT8**	SFXN1
ANKHD1-EIF4EBP3	FAM86B1	NDUFAF5	TBRG4	COGS	**SHMTI**
ANKRD11	FCER1A	NFATC1	TCTN1	**COQ9**	SMC4
APOM	GCC2	NOP2	TLDC1	**COR01C**	SNRPAI
ARL3	GLTSCR2	NSUN5	TLE4	DKC1	**STIL**
BIN3	GTPBP2	OSBPL1A	TMC6	DONSON	SUGCT
BSDC1	HAUS5	PADI1	TSKS	**EMC8**	TMEM208
BTD	HDC	PDK3	TSR1	ENY2	TPD52L2
BTN2A1	HOOK2	PHFg	TTC12	**FKBP3**	**TRIP13**
BTN3A3	HOXA4	PIEZO1	VAMP1	**GGH**	**WOR41**
C12orf49	HPN	PPIL2	VAMP2	**GLT8D1**	YIPF3
CALR	HS3ST1	PPP3R1	WDR19	**GRHPR**	2NF593
CAMK2B	HTNI	PSD4	ZCCHC24	GTSE1	
CAMK4	HYI	PUM1	ZFP36L2	**HELLS**	
CASC1	INADL	RAB30	ZMYND10	**HJURP**	
CCDC176	ITM2C	RAB6B	ZNF22	**KCMF1**	
CCDC25	ITPR1	RAI2	ZNF506	**KDM5A**	
CDIE	IVD	RAL6APA1	ZNF778	KIF14	
CNTRL	KIAA0930	RAPGEF3	ZSCAN32	**MRPL18**	
CPSF7	XIAA1549L	RCAN1	ZZEFI	MRPL9	
CROCC	LAP3	RPS6KA6	**ACOT13**	**MRPS17**	
CTDSPL	ME3	SERHL2	B9D2	**NFATC3**	

Nucleic Acid Metabolism			Post-Translational Modification	
ABAT	RECQL5	HEATR3	ABCB1	RTN1
AHNAK	RUNX1	KIF18A	ACAN	TENCI
ALPK1	SCUBE2	KIF23	AMN	TGFB3
BCAT2	SF3B1	KPNA2	CQL4A6	TGFBR3
BMP8A	SF3B2	PAPOLA	CSF1	ADAMS
BTRC	SLC27A2	RAD51AP1	DDX11	ADM
CACNA1G	SLC6A2	RFC4	FGFRI	CALB2
CALCQCQI	SMARCC2	**RPN1**	FGFR2	**CTSV**
CBX7	SNRNP70	SEC61G	GSTMI	**DBNDD1**
COL14A1	SRSF7	5F3B3	GUSB	FAM96B
DCLRE1C	SSX3	SMAD5	IGF1	IGF1R
ESRI	SYMPK	**SMYD2**	LRRN3	**KIF11**
FBX04	SYNC	SPAG5	MAP3K12	KIF20A
FMQ5	TMC5	**SRPK1**	MSTI	LAPTM4B
GART	USP19	**SUB1**	MYB	**MMP15**
H6PD	USP4	TAF11	NTRK2	RAB2A
JADE2	WSB1	**TAF2**	RBM5	SERPIMHI
KLRG1	ACTR3	TCEBI	RLN1	TCEB2
KMT2A	AQP9	**USP10**		
MAFG	ARPC4	VPS28		
MAPRE2	ATAD2	WWTR1		
iVIYOF	AURKA	XPOT		
NOVA1	CA9			
NSMCE4A	CDK7			
POLE2	CEP55			
PTGDS	**CFDP1**			
PTGER3	**DSN1**			

Protein Synthesis/Modification					Multiple networks	
ACAAI	MTMR3	RPS28	**EIF6**	**SLC25A5**	ABHD14A	RP54XP2
ACKR1	MTMR7	RPS4X	**EPRS**	**SLC52A2**	Clorf21	RPS4XP3
AGSL6	**MXD4**	RPS6	**ETFA**	**SPiNI**	C3orfl8	SLC35D2
ADRA2A	MYQZ3	SAMD4A	**EXOSC4**	**SQLE**	C4A	SLG38A7
AGTR2	**MVT 1**	sIRPA	**EXOSG7**	**STAU1**	CCDC30	SPATA6L
AUISIIP	NMES	SLC16A5	**GNB2L1**	**SYNCR!P**	CFAP69	SSX7
C2CD2	**NMT1**	SLC4A7	**GPR56**	**TKT**	CLUL1	TNXA
CCDC170	NPY1R	SLC7A6	**6TPBP4**	**TMEM194A**	FCGR3B	TPSAB1
CELSR2	NPY5R	SORBS1	**ILF2**	**TUBAIB**	GUSBPll	TPSB2
CHAD	QSGEPLI	SQSTM1	**KARS**	**UBE2V1**	IGHD	UGT1A8
CREBL2	P2RY4	SRPK3	**LAMA3**	**YWHAZ**	IGHJ3	WDR78
C5DE1	P2RY6	THEMiS2	**LRPPRC**		IGHV3-20	ZNF710
CX3CR1	PAPPA	TTLLI	**NDUFC1**		IGHV3-23	ZNRD1-ASI
CYR61	PDCD2	ZNF395	**NELFE**		IGLJ3	**BOLA2**
DDX3X	PDCD4	**ABHD5**	**NOP56**		KIAAG040	**MRPL23**
DHTKDI	PER3	**ADRBK2**	**QARS**		KIR2DL1	
EGOT	PNPLA4	**AIMP1**	**RACGAP1**		KIR2DL3	
E1F1	PTCD3	**ALG3**	**RAD21**		LINC01260	
EIV1L2	**PTPN.1**	**BRIX1**	**RAD23B**		LOC389906	
EPHX2	PTPRO	**CDKN3**	**RC3H2**		LRRC48	
FAM 134A	PTPRT	**CHAF1A**	**RPL14**		NBPF8	
FRS3	PURA	**EIF3A**	**RPL15**		NSUN7	
ICA 1	RAMP2	**EIF3B**	**RPL29**		PGAP2	
LAMA2	RGS5	**EIF3K**	**RPS9**		PGPEP1	
LPAR2	RHBDD3	**EIF4B**	**RPSA**		RBMY1J	
LZTS1	RPLiO	**EIF4E**	**SFPQ**		RBMY2MP	
MAOA	RPL22	**EIF4G1**	**SHCBP1**		RGPD6	

Genes whose overexpression is associated with poorer survival are in bold and those whose underexpression is associated with poorer survival are underlined

Table 22. 133 genes associated with relapse-free survival of breast cancer patients.

ID	SEQ ID NO:	Network	Metagene
BRD8	1	Carbohydrate/Lipid Metabolism	Metabolism
BTG2	2	Carbohydrate/Lipid Metabolism	
BTN2A2	3	Carbohydrate/Lipid Metabolism	
KIR2DL4	4	Carbohydrate/Lipid Metabolism	
ME1	5	Carbohydrate/Lipid Metabolism	
PIK3IP1	6	Carbohydrate/Lipid Metabolism	
SEC14L2	7	Carbohydrate/Lipid Metabolism	
PSEN2	8	Carbohydrate/Lipid Metabolism	
FLNB	9	Carbohydrate/Lipid Metabolism	
AGSF2	10	Metabolic Disease	
APOM	11	Metabolic Disease	
B1N3	12	Metabolic Disease	
CALR	13	Metabolic Disease	
CAMK4	14	Metabolic Disease	
GLTSCR2	15	Metabolic Disease	
ITM2C	18	Metabolic Disease	
NOP2	17	Metabolic Disease	
NSUN5	18	Metabolic Disease	
ZMYND10	19	Metabolic Disease	
ABAT	20	Nucleic Acid Metabolism	
BCAT2	21	Nucleic Acid Metabolism	
SCUBE2	22	Nucleic Acid Metabolism	
SF3B1	23	Nucleic Acid Metabolism	
RUNX1	24	Nucleic Acid Metabolism	
ZNRD1-AS1	25	Nucleic Acid Metabolism	
ATP6V1C1	26	Carbohydrate/Lipid Metabolism	
RAP2A	27	Carbohydrate/Lipid Metabolism	
CALM1	28	Metabolic Disease	
CAMSAP1	29	Metabolic Disease	
GETN3	30	Metabolic Disease	
COG8	31	Metabolic Disease	
GRHPR	32	Metabolic Disease	
HELLS	33	Metabolic Disease	
KDM5A	34	Metabolic Disease	
PGK1	35	Metabolic Disease	
PLGHi	36	Metabolic Disease	
ZNF593	37	Metabolic Disease	
CA9	38	Nucleic Acid Metabolism	

CEP55	39	Nucleic Acid Metabolism	
CFDP1	40	Nucleic Acid Metabolism	
RFC4	41	Nucleic Acid Metabolism	
TAF2	42	Nucleic Acid Metabolism	
VPS28	43	Nucleic Acid Metabolism	
SF3B3	44	Nucleic Acid Metabolism	
LRRC48	45	Cell Signaling	Signalling
ARNT2	46	Cell Signaling	
MYBPC1	47	Cell Signaling	
ADORA2B	48	Cell Signaling	
GSK3B	49	Cell Signaling	
LAMA4	50	Cell Signaling	
MAP2K5	51	Cell Signaling	
BCL2	52	Cellular Development	Development&Growth
CHPT1	53	Cellular Development	
ERC2	54	Cellular Development	
ITM2A	55	Cellular Development	
LRIG1	56	Cellular Development	
MAPT	57	Cellular Development	
PRKCB	58	Cellular Development	
RERE	59	Cellular Development	
ABHD14A	60	Cellular Development	
FLT3	61	Cellular Growth	
SLC11A1	62	Cellular Growth	
TNN	63	Cellular Growth	
GPI	64	Cellular Development	
HCFC1R1	65	Cellular Development	
KCNG1	66	Cellular Development	
PIR	67	Cellular Development	
BCAP31	68	Cellular Growth	
MCM10	69	Cellular Growth	
MELK	70	Cellular Growth	
ULBP2	71	Cellular Growth	
BRD4	72	DNA Replication/Recombination	Chromosome segregation/Replication
STC2	73	DNA Replication/Recombination	
FOXM1	74	Chromosome segregation	
KIF2C	75	Chromosome segregation	
NUP155	76	Chromosome segregation	
TPX2	77	Chromosome segregation	
TTK	78	Chromosome segregation	
CARHSP1	79	DNA Replication/Recombination	

CENPA	80	DNA Repiication/Recomb ination	
CENPN	81	DNA Repiication/Recomb ination	
EX01	82	DNA Repiication/Recomb ination	
MAPRE1	83	DNA Repiication/Recomb ination	
PML	84	DNA Repiication/Recomb ination	
APOBEC3A	85	Immune system	Immune response
BATF	86	Immune system	
CD1A	87	Immune system	
CD1B	88	Immune system	
CD1G	89	Immune system	
CD1E	90	Immune system	
CFB	91	Immune system	
CXGR4	92	Immune system	
EVL	93	Immune system	
FBXW4	94	Immune system	
HLA-B	95	Immune system	
IGH	96	Immune system	
KIR2DL3	97	Immune system	
SMPDL3B	98	Immune system	
ACOT7	99	Immune system	
CD36	100	Immune system	
CD55	101	Immune system	
GEMIN4	102	Immune system	
NAE1	103	Immune system	
SHMT2	104	Immune system	
TCP1	105	Immune system	
TXN	106	Immune system	
TXNRD1	107	Immune system	
ABCB1	108	Post-Tran slational Modification	Protein synthesis/Modification
MVS	109	Post-Tran slational Modification	
RLN1	110	Post-Tran slational Modification	
ACAA1	111	Protein Synthes is/Mod ification	
CHAD	112	Protein Synthes is/Mod ification	
MTMR7	113	Protein Synthes is/Mod ification	
PDCD4	114	Protein Synthes is/Mod ification	
RPL10	115	Protein Synthes is/Mod ification	
RPS28	116	Protein Synthes is/Mod ification	
RPS4X	117	Protein Synthes is/Mod ification	
RPS6	118	Protein Synthes is/Mod ification	
SORBS1	119	Protein Synthes is/Mod ification	
SRPK3	120	Protein Synthes is/Mod ification	

RPL22	121	Protein Synthesis/Modification
RPS4XP3	122	Protein Synthesis/Modification
ADM	123	Post-Translational Modification
ABHD5	124	Protein Synthesis/Modification
GHAF1A	125	Protein Synthesis/Modification
E1F3K	126	Protein Synthesis/Modification
E1F4B	127	Protein Synthesis/Modification
EXOSC7	128	Protein Synthesis/Modification
GNB2L1	129	Protein Synthesis/Modification
LAMAS	130	Protein Synthesis/Modification
NDUFC1	131	Protein Synthesis/Modification
STAU1	132	Protein Synthesis/Modification
SYNCRIP	133	Protein Synthesis/Modification

Genes whose overexpression is associated with poorer survival are in bold and those whose underexpression is associated with poorer survival are underlined

EXAMPLE 6

The preceding example identified 133 genes, assoeiated with 12 oncogenic functions, the expression of which is strongly associated with cancer aggressiveness and clinical outcome (Table 22). The expression of genes from this list was investigated for association with **survival in:** (i) follicular lymphoma patients before receiving pidilizumab in combination with rituximab (Westin et al. *Lancet Oncol,* 2014, vol 15(1)) (ii) colorectal cancer patients treated with cetuximab (GSE5851); (iii) triple negative breast cancer patients treated with **cetuximab** and cisplatin (GSE23428); (iv) lung cancer patients treated with erlotinib (GSE33072); and (v) lung cancer patients treated with sorafenib (GSE33072). This analysis identified new sets of genes, with partial overlap to the iJBCR signature, the expression of which was highly associated with survival in the different treatment groups (Table 23). Scores for each patient group, which were calculated based on these gene signatures were shown to be highly predictive of survival in these patient groups (pidilizumab + rituximab: Figure 56E; all other treatments Figure 59).

Table 23. iBCR gene signatures associated with survival in patients receiving anticancer therapy.

Follicular Lymphoma (pidilizumab + rituximab)	Lung Cancer (erlotinib)	Lung Cancer (sorafenib)	Colorectal cancer (cetuximab)	Triple negative breast cancer (cetuximab)
APOBEC3A	**CD1C**	**NOP2**	**ARNT2**	**SF3B3**
BCL2	**CD1E**	**CALR**	**NDUFC1**	**CETN3**
BTN2A2	**CD1B**	**MAPRE1**	**BCL2**	**SYNCRIP**
CAMK4	**KDM5A**	**KCNG1**	**ABHD14A**	**TAF2**
FBXW4	**BATF**	**PGK1**	**EVL**	**CENPN**
PSEN2	**EVL**	**SRPK3**	**ULBP2**	**ATP6V1C1**
MYB	**PRKCB**	**RERE**	**BIN3**	**CD55**
ADORA2B	**HCFC1R1**	**ADM**	MAPRE1	**ADORA2B**
CD36	**CARHSP1**	**LAMA3**	BRD4	RPL22
KCNG1	**CHAD**	**KIR2DL4**	STAU1	ABAT
LAMA3	**KIR2DL4**	**ULBP2**	TAF2	BTN2A2
MAP2K5	**ABHD5**	**LAMA4**	GSK3B	CD1B
NAE1	**ABHD14A**	**CA9**	PDCD4	ITM2A
PGK1	**ACAA1**	**BCAP31**	KCNG1	BCL2
STAU1	**SRPK3**	SCUBE2	*ZNRD1-AS1*	CXCR4
CFDP1	**CFB**	CHPT1	EIF4B	ARNT2
SF3B3	NAE1	CD1C	HELLS	
	GSK3B	BTG2		
	TAF2	ADORA2B		
		BCL2		

Genes whose underexpression is associated with a response to treatment are in bold and those whose overexpression is associated with a response to treatment **are underlined.**

SEQUENCE LISTING

The sequences set forth in SEQ ID NOs: 1-133 below correspond sequentially to the 133 genes provided in Table 22.

>SEQ ID NO: 1
MATGTGKHRLLSTGPTEPWSIRERLGLASSVMRSGDQNWVSVSRAIKPFAEPGRPPDWFSQKHCASQY
SELLETTETPKRKRGEKGEVVETVEDVIVRKLTAERVEELKKVIKETQERYRRLKRDAELIQAGHMDS
RLDELCNDIATRRRLEBEEAJSVKRKATDAAYQARQ AVKTPPRRLPTVMVRSPIDSASPGGDYPLGDLT
PTTMEEATSGVNESEMAVASGHLNSTGVLLEVGGVLPMIHGGEIQQTPNTVAASPAASGAPTLSRLLE
AGPTQFTTPLASFTTVASEPPVKLVPPPVESVSQATIVMMPALPAPSSAPAVSTTESVAPVSQPDNCY
PMEAVGDPHTVTVSMDSSEISMI INSIKEECFRS GVAE APVGSKAPSIDGKEELDLAEKMDIAVSYTG
EELDFETVGDIIAIIEDKVDDHPEVLDVAAVEAALSFCEENDDPQSLPGPWEHPIQQERDKPVPLPAP
EMTVKQERLDFEETENKGIHELVDIREPSAEIKVEPAEPEPVISGAEIVAGVVPATSMEPPELRSQDL
DEELGSTAAGEIVEADVAIGKGDETPLTNVKTEASPESMLSPSHGSNPIEDPLEAETQHKFEMSDSLK
EESGTIFGSQIKDAPGEDEEECGVSEAASLEEPREEDQGEGYLSEMDNEPPVSESDDGFBIHNATLQS
HTLADSTPSSPASSQFSVCSEDQEAIQAQKIWRRAIML VWRAAAN HRYANVFLQPVTDDI AFGYHSIV
QRPMDLSTIKKNIENGLIRSTAEFQRDIMLMFQNAVMYNSSDHDVYHMAVEMQRDVLEQIQQFLATQL
IMQTSESGISARSLRGRDSTRKQDASER:DS\?PMGSPAFLLSLFMGHEWVWLDSEQDHPNDSELSNDCR
SLFSSWDSSLDLDVGNWRETEDPEAEELEE SSPEREPSELLVGDGGSEESQEAARKASHQK 1LLHFLSE
VAYLMEPLCISSMESSEGeCPPSGTRQEGREIKASEGERELCRETEELSARGDPFVAEKPLGENGKPE
VASAPSV1CTVQGL.LTESEEGEAQQE SKGEDQGEVYV SEMEDQPP SGECDDAFNIKETPLVDTLFSHA
TSSKLTDLSQDDPVQDHLLFKIKTLLPVWKMIASHREFSSPFLKPVSERQAPGYKDVVKRPMDLTSLKRN
LSKGRIRTMAQFLRDLMLMFQNA\MYNDSDHHVYHMAV¼MRQEVLEQIQVLNIWLDRRRGSSSLEGEP
AMPVpDGRPVF

>SEQ ID NO: 2
MSHGKGIDMLPEIAAAVGFLSSLLRTRGCV?SEQRLKVFSGALQ:EALTEHYKHHWFPEKPSRGSGYRCI
RINHRMDPIISRVASQIGLSQPQLHQLLPSELTLWVDPYEVSYRIGEDGSICVLYEEAPLAASCGLLI'
CKNQVLLGRSSPSKNYVMAVSS

>SEQ ID NO: 3
MEPAAALHFSLPASLLLLLLLLLLLSLCALVSAQFTVVGPANPILAMVGENTTLRCHLSPEKNAEDMEV
RWFRSQFSPAVFVYKGGRERTEEQMEEYRGRITFVSKDINRGSVALVIHNVTAQENGIYRCYFQEGRS
YDEAILRLVVAGLGSKPLIEIKAQEDGSIWLECISGGWYPEPLTVWRDPYGEVVPALKEVSIADADGL
FMVTTAVIIRDKYVRSAVSCSYNNTLLGQEKETVIFIPESFMPSASPWMVALAVILTASPWMVSMTVIL
AVFIIFMAVSICCIRKLQREKKILSGEKKVEQEEKFIAQQLQEELRWRRTFLHAADVVLDPDTAHPEL
FLSEDRRSVRRGPYRQRVPDNPERFDSQPCVLGWESFASGKHYWEVEVENVMVWTVGVCRHSVERKGE
VLLrPQNGFWTLEMFGNQYRALSSPERILPLKESLCRVGVFLDYEAGDVSFYHMRDRSHIYICPRSAF
TVPVRPFFRLGSDDSPIFICPALIGASGVMVPEEGLRLHRVGTHQSL

>SEQ ID NO: 4
MSMSPTVIILACLGFFLDQSVWAHVGGQDKPFCSAWPSAVVPQGGHVTLRCHYRRGFNIFTLYKKDGV
PVPELYNRIFWNSFLISPVraAimGTYRCi \GFHPHSFTEWSIAPSi^lVIMVTGLYEKPSLTARPGPTV
RAGENVTLSCSSQSSFDIYHLSREGEAHELRLPAVPSINGTFQAD FPLGPATHGETYRCFGSFHGSPY
EWSDPSDPLPVSVTGNPSSSWP8PTEPSFKTGIAR.HLHAVIRYSVAIIL FTILPFFLLHRWCSKKKDA
.WMNQEPAGHRTVNREDSDEQDPQEVTYA QLDHCIFTQRKITGPSQRSKRPSTDTSVCIELPNAEPRA
LSPAHEHHSQALMG SSRETIALSQ TQLA 5SNVPAAGI

>SEQ ID NO: 5
MEPEAFRRRHXHQRGYLLTRNPHLNKDLAF TLEERQQLNIHGLLPPSFNSQEIQVLRVVKNFEHLNSD
FDRYLLLMDLQDRNEKLFYRVLTSDIEKFMPIVYTPTVGLACQQYSLVFRKPRGLFITIHDRGHIASV
LIlAWEEDVIRAIVVTDGERILGLGDLGCNGMGIPVGRLAtrYTACGGMNPQECLPVILDVG TENEELLK
DPLYIGLRQRRVRGSFYDDFLDEFMEAySSKYGMNCLIQFEDFAN^ AFRLLNKYRNQYCTFNDDIQG
TASVAVAGLLAALRITRMKLSDQTILFQGAGEAALGIAHLIVI^LEKEGLPKEKAIRRIWLVDSRGLI
VKGRASLTQEKEKFAHEHEEMKNLEAIVQEIRPTALIGVAAIGGAFSEQILKDMAAFNERPIIFALSN
PTSKAECS.AEQCYRI TEGRAIFASGSPFDPVTLPNGQTLYPGQGNNSYVFPG VALGVVACGLRQITDN
IFLTTAEVIAQQVSDKHLEEGRLYPPLNTIRDVSLKIAEKIVKDAYQEKTATVYPEPQNKEAFVRSQM
YSTDYDQILPDCYSWPEEVQRI QTKVDQ

>SEQ ID NO: 6
MLLAWVQAFLVX3NMLLAEAYGSGGCFWDNGHLYREDQTSPAPGLRCLNWLDAQSGLASAPVSGAGNHS
YGB¾PDEDPRGPWCYVSGEAGVPEKBPCEDLRCPETTSQALPaFTIEI.QEA SEGPGADEVQVFAPANA
IPARSEAAAVQPVIGISQRVRMNSKEKKDLGTLGYVLGITMMVIIIAIGAGIILGYS YKRGKDLKEQH
DQKVCEEEMQRITLPLSAETNPTCEIVDEKTVVVHTSQTPVDPQEGTTPLMGQAGTPSA

>SEQ ID NO: 7
MSGRVGDLSPRQKEALAKFRENVQDVLPALP NPDDYFLLRWLRARSFDLQKSEAMLRKHVEFRKQKDI
DNIISWQPPEXIQQYLSGGMCGYDLDGCPVWYDIIGPLDAKGLLFSASKQDLLRTKMRECELLLQECA
HQTTKLGRKVETITIIYDCEGLGLKHLWKPAVEAYGEFLCMFEENYPETLKRLFVVKAPKLFPVAYNL
TKPFLSEDTRKKIMVLGANWKEVLLKRISPDQVPVEYGGTMTDPDGNPKCKSKINYGGDIPRKYYVRD
QVKQQYEHaVQISRGSSHQVEYEILFPGGVLRWQFMSDGADVGFGIFLKIKMGERQRAGEMIEVLPNQ:
RYNSHLVPEDGTLTCSDPGIYVLRFDNTYSFIHAKKVNFTVEVLLPDKABEEKMKQLGAGTPK

>SEQ ID NO:8
ML**TFMAS**DSEEEVCDERISLMSAESP TPRSCQEGRQGPE DGENTAQWRSQENEEDGEEDP DRYVC3**GV**
PGRPPGLEEELTLKYGAKHVIMLFVPVTLCMIVWATIKSVRFYTEKNGQLIYIPFTEDTPSVGQRLL
NSVLNTLIMISVIVVMIIFLVVLYKYRCYKFTHGWLIMSSLMLLFLFT^ IYLGEVLKTYNVAMDYPTL
LLTVWNFGAVGMVCIH¾ GPLVL(2QAYLIMISALMALVFIKYLPEWSAWVILGAISVYDLVAVLCPKG
PLRMLVETŠQERNEPIFPALIYSSAIMVWTVGMAKLDPSSQGALQLPYDPEMEED.S;YDSFGEPS;YPEVF
EPPLTGYPGE ELEEEEERGVKL GLGDFIFYSVLVGKAAATGSGDWNITLACFVAILIGLCLTLLLLAV
FKKALPALPISITFGLIFYFSTDNLVRPFMDTLASHQLYI

>SEQ ID NO: 9
MPVTEKDLXf DAPWKKIQQNTFTRWCNEHLKCVNKRIGNLQTDLSDGLRLTALLEVLSQKRMYRKYHQ
RPTFRJ3MQLENVSVALEFLDRESIKLVSIDSKAIVDGNLKLILGLVWTLILHYSISMFVWEDEGDDDA
KKQTPKQRLLGWIQNKIPYLPITNFNQNWQDGKALGALVDSCAPGLCPDWESWDPQKPVDNAREAMQQ
ADDWLGVPQVITPEEIIHPD¾DEHSVMTYLSQFPKAKLKPGAPLKPKLNPKKARAYGRGIEPTGNMVK
QPAKFTVBTISAGQGDWVFVEDPEGNKEE AQVTPDSDKNKTYSVEYLPKVTGLHKVTVLFAGQHISK
SPFEVSVDKAQGDASKyTARGPGLEAVGNI^ NKPTYFDIYTAGAGVGDIGVEVEDPQGKNTVELLVED
KGNQVYRCVYKPMGPGPHVVKIFFAGDTIPKSPFVVQVGEACNPNACRASGRGLQPKGVRIRETTDFK
VDTKAAGSGELGyrMKGPKGLEELVKQKDFLDGvYAFEYYPSTPGRYSIAITWGGHHIPKSPFEVQVG
PEAGMQWRAWGPGLHGGIVGRSADFVVESIGSEVGSLGFA IEGPSQAKIEYNDQNDGSCDVKYWPKE
PGEYAVH IMCDDEDIKDSPYMAF IHPATGGYNPDLVRAYGPGL EKSGCIVNNLAEFTVDPKDAGKAPL
RIFAQDGEGQRIDIQMRNRMDGTYACSYTPVKAIKH^ IAVVWGGVNIPHSPYRVNIGQGSHPQKVKVF
GPGVERSGLKAJSEPIHFTVDCTEAGEGDVS?GIRCDAR:VLSEDEED VDFDIIHNANDTFTVKYVPPAA
GRYTIKVLFASQETPASPFRVKVDPSHDASKVKAEGPGLSKAGVENGKPrHFTVYTKGAGKAPLNVQF
NSPLPGDAVKDLDIIDNYDYSHTVKYTPTQQGNMQVLVTYGGDPIPKSPFTVGVAAPLDLSKIKLNGL
ENRVEVGKDQEFTVDTRGAGGQGKLDVTILSPSRKVVPCLVTPVTGRENSTAKFIPREEGLYAVDVIY
DGHPVPGSPYTVEASLPPDPSKVKAHGPGLEGGLvGKPAEFTIDTKGAGTGGLGLTVEGPCEAKIECS
DNGDGTCSVSYLPTKPGEYFVNILFEEVHTPGSPFKA DIEMPFDPSKVVASGPGLEHGKVGEAGLLSV
DCSEAGPGALGLEAVSDSGTKAEVSIQNNKDGTYAVTYVPLTAGMYTLTMKYGGELVPHFPARVKVEP
AVDTSRIKVFGPGIEGKDVFREATIDFTVDSRPLTQVGGDHIP¾ HIANPSGASTECFVTDNADGTYQV
EYTPFEKGLHWEVIYDDVPIPNSPFKVZWTEGCQPSRvQAQGPGLKEATTNKPNVFTV VTRGAGIGG
LGITVEGPSESKINCRDNKDGSCSAEYIPFAPGDYDVNITYGGAHIPGSPFRVPVKDVVDPSKVKIAG
PGLGSGVRARVL<2SFTVDSSKAGLAPLEVR\?LGPRGLVEPVNWDNGDGTHTVIYTPSQEGPYMVSVK
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RAIVH DNKDGTYAVTYIPDKTGRYMIGVTYGGDDIPLSPYRIRATQ.TGDASKCLAT.GPGIASTVKTGE
EvGFVVDAKIAGKGKVTCTVLTPDGTEAEADVIENEDGTYDIFYTAAKPGTYVIYVRFGGVDIPNSPF
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GKIATPEIVDTKDGTVIVRYAPTEVGLHEMHIKYMGSHIPESPLQFYVNYPNSGSVSAYGPGLVYGVA
NKIATFTIVTEDAGEGGLDLAIEGPS.KAEIS.CIDNKDGT CTVTYLPTLPGDY SI.LVKYNDKHIPGSPF
TAKITDDSRRC SQVKLGSAADFLLDISETDLSSLTASIKAPSGRDEPCLLKRLPNNHIGISFIPREVG
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GPSKVDIQTEDLEDGTCKVSYFPTVPGVYIVSTKFADEHVPGSPFTVKISGEGRVKESITRTSRAPSV
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TGSPFQFTVGPLGEGGAHKVRAGGPGLERGEAGVPAEFSIWTREAGAGGLSIAVEGPSKAEITFDDHK
NGSCGVSYIAQEPGNYEVSIKFNDEHIPESPYLVPVIAPSDDARRLTVMSLQESGLKVNQPASFAIRL
NGAKGKIDAKVHSPSGAVEECHVSELEPDKYAVRFIPHENGVHTII/VKFNGSHVVGSPFKVRVGEPGQ
AGNPALVSAYGTGLEGGTTGIQSEFFINTTRAGPGTLSVTIEGPSKVKMDCQETPEGY KVMYTPMAPG

NYL/I SVKYGGPNHIVGSPFKAKVTGQRLVSPGSANETSSILVESVTRSSTETCYSAIPKASSDASKVT
SKGAGLSKAFVGQESSFLVDOSKAGSNMLLIGVHGPTTPCEEVSMKHVGNQQYNVTYVVKERGDYVLA
VKWGEEHIPGSPFHVTVP

>SEQ ID NO:1Q
MAVYVGMLRL GRLCAGSSGVLGARAAL SRSWQE.ARLQGVRF LSSREVDRMVS TPIGGLSYVQGC TKKH
LNSKTVGQCLETTAQRVPEREALVVLHEDVRLTFAQLKEEVDKAASGLLSIGLCKGDRLGMWGPNSYA
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LKSQRLP DLTTVISVDAPLPGTLLLDEWAAGS TRQHLDQLQYNQQF LSCHDPINI QFTSGTTGSPKG
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ALEAISRERGTFLYGTPTMFVDILNQPDFSSYDISTMCGGVIAGSPAPPELIRAIINKINMKDLVVAY
GTTENSPVTFAHFPEDTVEQKAESVGRIRPHTEARTJ4MMEAG TLAKLNTPGELCIRGYCVMLGYWGEP
QKTEEAVDQDKWYWTGDVSTMNEQGFGKIVSRSKDMIIRQGENIYPAELEDFFHTHPKVQEVOVVGVK
DDRMGEElCACTRLKDGEETTVEEIKAFCKGKISHFKIPKYIVFVINYPLTISGKIQKFKLREQMERH
LNL

>SEQ ID NOi11
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>SEQ ID NO:12
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RLQAKVEKYEEKEKTGPVLAKLHQAREELRPVREDFEAKNRQLLEEMPRFYGSRLDYFQPSFESLIRA
QVVY YSEMHKIFGDL3HQLDQPGHSDEQRERENEAK1.SERRAL SIVADD

>SEQ ID NO:13
MLLSVPLLLGLLGI-AVAEPAVYFKEQFLDGDGWTS RWIESKHKSDFGKFVLSSGKFYGDEEKDKGLQT
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CGPGTKKVHVIFNYKGKNVLINKDIRCKDDEFTHLYTLIVRPDNTYEVKIDNSQVESGSLEDDWDFLP
PKKIKDPDASKPEDWDERAKIDDPTDSKPEDWDKPEHIPDPDAKKPEDWDEE^GEWEPPVIQNPEYK
GEWKPRQITOPDYKGTOIJBPEIDNPEYSPPPSIYAYDNFGVLGJ-DLWQVKSGTIFDNFLITNDEAYAE
EFGNETWGVTKAAEKQMKDKQDEEQRLKEEEEDKKRKEEEEAEDKEDDEDKDEDEEDEEDKEEDEEED
VPGQAKDEL

>SEQ ID NO: 14
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SERDAADAyKQILEAVAYLHENGIVHRDLKPENLLYATPAPDAPLKIADFGLSKIVEHQVLMKTVCGT
PGYCAPET LRGCAYGPE VDMWSVGIITYILLCGFEPFYDERGDQFMFRRI LNCEYYF ISPWWDEVSLN
AKDLVRKLIVLDPKKRLTTFQALQHPWVTGKAANFVHMDTAQKKLQEFNARRKLKAAVKAVVASSRLG
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>SEQ ID NO: 15
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HQVPNAKKLRRKEQLWEKLAKQGELPREVRRAQARLLNPSATRAKPGPQDTVEIPFYDLW¾SDNPLDR:
PLyGQ:DEFFLEQTRKKGvKRPARM TKPSQAPAVEVAPAGASYNPSFEDHQTLLSAAHEVELQRQKEA
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QRRREKAVHRLRVQQAALRAARLRHQELFRLRGIKAQVALRLAELARRQRRRQARREAEADKPRRLGR
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QL

>SEQ ID NO: 16
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GGGDPADIIHDFQRGLTAYHDISLDKCYVIEI^TTIVLPPRNFWEL LMNVKRGTYLPQTYIIQEEMVV
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>SEQ ID NO:17
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EADGGLQINVDEEEFVLPPAGEMEQDAQAPDLQRVHKRIQDIVGILRDFGAQREEGRSRSEYLNRLKK
DLAIYYS-YGDFLLGKLMDLFPLSELVEFLE¾NEVPRPVTLRTNTLKTRRRD,LAQ,¾LINRGVNLDPLGK
WSKTGLVVYDSSVPIGATPEYLAGHYMLQGASSMLPVMALAPQERERI LDMCCAPGGKTSYMAQLMKN
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DFGQEGFTRFRERRFHPSLRSTRRFYP HTHNMDGFFIAKFKKFSNSIPQSQTGNSETATPTNVDLPQV
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>SEQ ID NO:1B
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AGHLILQDRASCLPAMLLDPPPGSHVIDACAAPGNKT SHLAALLKNQGKIFAFDLDAKRLASMATLLA
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ALCHALTFPSLQRLVYSTCSLCQEENEDVVRDALQQNPGAFRLAPALPAWPHRGLSTFPGAEHGlRAS
PETTL SSGFFVAVI ERVEVPR

>SEQ ID NO:19
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LVDYCHRKLTLLVAQSGCGGPPEGEGSQDSNPMQELQKQAELMEFEIALKALSVLRYITDCVDSLSLS
TLSRML STHNLPCLLVELLEHSPWSRREGGKLQQFEGSRWHIVAPSEQQKLSKLDGQVWIALYNLLLS
PEAQARYCLTSFAKGRLLKLRA FLTDTLLDQLPNLAHLQSFLAHLTLTETQPPKKDLVLEQIPEIWER
LERENRGKWQA IAKHQLQHVF SPSEQDLRIQARRWAETYRLDVLEAVAPERPRCAYCSAEASKRCSRC
QNEWYeCRECQVKHWEKHGKTCVLAAQGDRAK

>SEQ ID NO;20
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CPDYSILSFMGAFHGRTMGCLATIHSKAIHKIDIPSFDWPIAPFPRLKYPLEEFVKENQQEEARCLEE
VEDLlVKYRKKKKTVAGIIVEPIQSEGGDNHASDDFFRI¾LRDIARKHGCAFLVDEVQIGGGCTGKFWA
HEHWGLDDPADVMTFSKKMMT6GFFHKEEFRPNAPYRIFNTWLGDPSKNLLLAEVINIIKREDLLNNA
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>SEQ ID NO;21
MAAAALGQIWARKLISVp»LLCGPRRYASSSFKAADIQLEMIQKPHKKPGPGEPLVFGKTFTDHMLMV
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PSFDKLBLLECIRRLIEVDKDWVPBAAGTSLYVRPVLIGNBPSLGVSQPTRALLFVILCPVGAYFPGG
SVTPVSLLADPAFIRAWGGVGNYKLGGNYGPTVLVQQEALKRGCEOVLWLYGPDHQLTEVGTMNIFV
YWTHEDGVLEWTPPLNGVILPGVVRQS LLDMAQTWGEFRVVERTITMKQLLRALEEGRVREVFGSGT
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>SEQ ID NO:22
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GGCQHTCVNVMGSYECCCKEGFFLSDNQHTCIHRSEEGLSCMNKDHGCSHICKEAPRGSVACECRPGF
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GDKR¥KRRLLMETCAVNNGGCDRTCKDISTGYHCSCPVGFTLQLDGKTCKDIDECQTRM GGCDHFCKN
IVGSFDCGCKKGFKLLTDEKSCQDVDECSLDRTCDHSCINHPGTFACACNRGYILYGFTHCGDINECS
INNGGCQQVCVNTVGSYECQCHPGYKLHWNKKDEVEVKGLLPTSVSPRVSLHCGKSGGGDGCFLRCHS
GIHLSSDVTTIRTSVTFKLNEGKCSLKNAELFPEGLRPALPEKHSSVKESFRYVNLTCSSGKQVPGAP
GRPSTPKEKFITVEFELETNQKM?TASCDLS:CIVKRTEKRLRKAIRTLRKA\N IREQFHLQLSGMNLDV
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GALKTPEAWNMSECGGLCQPGEYSADGFAPCHLCALGTFQPEAGRTSCFPCGGGLATKHQGATSFQDC
EIRvQCSPGHFYNXIIHRCIRCPVGiYQPEFGK¾^ CVSCPGNTTTDFDGSTNITQCKNRRCGGELGDF
TGYIESPNYPGNYPSNTECTWTINPPPKRRILIVVPEIFLPIEDDCGDYLVMRKTSSSNSVTTYETCQ
TYERPIAFTSRSKKLWIQFKSNEGNSARGFQVPYVTYDEDYQELIEDIVRDGRLYASENHQEILKDKK
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>SEQ ID NO: 23
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ADGGKXFIJFKMNARIYM¾ MREQHLTKEEREIRQQLAEKAKAGELKVVNGAAASQPPSKRKRRWDQTA
DQTPGATPRKLSS¾DQAFRPGHTPSLRWDETPGRAKGSETPGATPGSKIWDPTPSHTPAGAATPGRGD
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TPASQMGGSTPVLTPGKTPIGTPAMNMATPTPGHIMSMTPEQLQAWRWEREIDERNRPLSDEELDAMF
PEGYKVLPPPAGYVPIRTPARKLTATPTPLGGMTGFHMQTEBRXMKSVNBQPSGNLPFLK PDDIQYFD
KLLVDVDEST.LSPEEQKERKI>IKLLLKI,KNGTPPMRKAALRQITDKAREFGAGPLFNQ:ILPLLMSPTL
EDQERHLLVKVIDRILYKLDDLVRPYVHKIL¥VIEPLLIDEDYYARVEGREIISSLAKAAGLATMIST
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PHLRSLVEIIEHGLVDEQQRVRTISALAIAALAEAATPYGIESFDSVLKPLWKGIRQHRGKGLAAFLK:
AIGYLIPLMDAEYANYYTREVMLILIREFSSPDEEMKKIVLKWKQCCGID GVEANYIKTEILPPFFK
HFWQHRMALDRRNYRQLVDTTVELANKVGAAEIISRIVDDLKDEAEQYRKMVMETIEKIMGNLGAADI
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OLISRTAVVMRTCQEEKLMGHLGVVLYEYLGEEYPEVLGSILGALRAIVNVIGMHKMTPPIRDLLPRL
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GPHDVL ATLLN.NL.KVQERQNRVCXXVAIAIVAEICSPFTVLP ALMNE YRVPELNVQNGVLKSLSFLFE
YIGEMGKDYIYAVTPLIEDALMDRDLVHRQTASAVVQHMSLGVYGFGGEDSLNHLLNYVWPNVFETSP
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NIYIRYELDYIL

>SEQ ID NO:24
MRIPVDASTSRRFTPRSIALSPGKMSEALPLGAPDAGAALAGKLRSGDRSM^EVLADHP GELVRTDSP
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VGRSGRGKSFILIITVFINPPQVAIYHRAIKXTVDGPREPRRHRQKLDDQIKPGS.LSFSERLSELEQL
RRTAMRV SPHHPAPTPNPRA SLNHSTAFNPQPQSQMQDTRQIQP SPPWSYDQSYQYLGLSIASP SVHPA
TPISPGRASGMTTLSAELSSRLST.APDLTAFSDPRQFPA LPSISDPRMHYPGAFTYSPTPVTSGIGIG
MSSMGSATRYHTYLPPPYPGSSQAQGGPFQASSPSYHLYYGASAGSYQFSMVGGERSPPRILPPCTNA
STGSALLNP SLPNQSDVVEAEG SHSN SPTNMAP SARLE EAVWRP Y

>SEQ ID NO: 25
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FQPCSRSRIKVSILMDKSQNGEKWIIVKPYQRKFLAMPPFLRSQIGKIRD

>SEQ ID NO; 26
MTEFWLISAPGEKTCQQTWEKLHAATSKNNNLAVTSKFNIPDLKVGTLDVLVGLSDELAKLDAFVEGV
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KSRASAYNNLKGNLQNLERKNAGSLLXRSLAEIVKKDDFVLDSEYLVTLLVVVPKLNHNDWIKQYETL
AEMVVPRSSNVLSEDQDSyLCNVILFRKAVDDFRHKARENKFIVRDFQYNEEEMKADREEMNRLSIDK
KKQFGPLVRWLKVNFSEAFIAWIHVRALRVFVESVLRYGLPVNFQAMLLQPNKKXLKKLREVLHELYK
HLDS SAAAI IDAPMD IPGLNLSQQEYYPYVYYKIDCNLLEFK

>SEQ ID NO: 27
MREYKWVLGSGGVGKSALXVQFVIGXFIERyDPIIEDFyRKEIEVDSSPSVLEILDIAGXEQFASMR
DLYIKNGQGFILVYSLVNQQSFQDIKPMRDQIIRVKRYEKVPVILVGNKVDLESEREVSSSEGRALAE
EWCCPFMETSAKSKTMVDELF&EIVRQMNY&AQPDKDPPCCSACNIQ

>SEQ ID NO: 28
RADQLIEEQIAEEKEAFSLFDKDGDGXIXXKELGXVMRSLGQNPXEAELQDMINEVDADGNGXIDFPE
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VNYEEFVQMMTAK.

>SEQ ID NO: 29

MVDASGRAAAEGWRKMEAPPDGAAPLyPLDRYDAARAKIAANLQWICAKAYGRDNIPEDLRDPFYVDQ
YEQF¾IKPPVIRLLL.S:SELYCRVCSLILK^ DQVAALQGHQSVIQALSRKGIYVMESDDTPVTESDLSR
APIKMSAHMAMVDALMMAYTVEMISIEKVVASVKRFSTFSASKELPYDLEDAMVFWINKVNLKMREIT
EKEVKLKQQLLESPAHQKVRYRRERLSARQSPYFPLLEDLMR DGSDGAALLAVIHYYCPEQMKLDDIC
LKEVT SMADSLYNIRLLREFSNEYLNKCFYLTLEDMLYAPLVLKPNV¾ VFIAELFWWFENVKPDFVQP
RDVQELKDAKTVLHQKSSRPPVPrSNATKE-S-FLGSPAAGTLAELQPPVQLEAEGCHRHYLHPEEPEYL
GKGTAAFSPSHPLLP LRQKQQKSIQGEDIPDQRHRSNSLTRVDGQPRGAAIAWPEKKTRPASQPTPFA
LHHAAS CEVDPSSGDSISLARS.I:SKDSLASNI:VNLTPQNQPHPTAIKSHGKSLLSNVSIEDEEEELVA
IVRADVVPQQADPEFPRASPRALGLTANARSPQGQLDTSESKPDSFFLEPLMPAVLKPAKEKQVITKE
DERGEGRPRSIVSRRPSEGPQPLVRRKMTGSRDLNRTFTPIPCSEFPMGIDPTETGPLSVETAGEVCG
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FAERKI:QRLNSC:ETKS:ST.SSSQKTTPDASESCPAPLTTWRQKREQSPSQEGKB'F ¾SLLASELVQLHMQ:
LEEKRRAIEAQKKKMEALSARQRLKLGKAAFLHVVKKGKAEAAPPLRPEHFAKEYSQHNGEDCGDAVS
KTEDFLVKEEQREELLHEPQPVDKES-LAFAQQHKAKDPVALHELERNKVISAALLEDTVGEWDVNEC.
DLSIEKLNETISTLQQAILKISQQQEQLLMKSPTVPVPGSKNNSQDHKVKAPVHFVEPLSPTGVAGHR
KAPRLGQGRNSRSGRPAELKVPKDRPQGSSRSKTPTPSVETLPHLRPFPASSHPRTPTDPGLDSALEP
SGDPHSKCLFDS YRLHDESNQRTLTLSSSKDANILSEQMSLKEVLDASVKEVGSSSSDVSGKESVPVE
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KQQRKAEEARVRKQQLEAEVELKRPEARRKAEEDRVRK^ EEKARRELIKQEYLRRKQQQILEEQGLGK
PKSKPKKPRPKSVHREESGSDSGTKCSSTPDNLSRTQSGSSLSLASAAT-TEPESVHSGGTPSQRVESH
EALPILSRNPSRSTDRDWETASAASSLASWAEYTGPKLFKEPSSKSNKPIIHNAISHCCLAGKVMEPH
KNJSILEELEKCDANHYIILFRDAGCQFR&LYCYYPDTEEIYKLTGTGPKNITKKMIDKLYKYSSDRKQ
FNLIPAK**IMS**VSVDALTIHNHLWQFKRPAVPKKAQ**IR**K

>SEQ ID NO: 30
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ILKDYDREAIGKXXFEPFNEVVTPWILERPPHEEILKAFKLFPPDDSGKI SLRNLRRVARELGENMSD:
EELRAMIEEF DKDGDGEINQEEF**I**AIMTGDI

>SEQ **I**D NO: **31**
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AEERAQLLQeTRDLAFANYKTFIRGAECTERIHRLFGDVEASLGRLLDRLPSFQQaCRNFVKEAEEIS
SNRRMNSLTLNRHTEILEILEIPQLMPXCVPNSYYEEALELAAYVRRLERKYSSIPVIQGIVNEVRQS
MQLMLSQLIQQLRTNI-QLPACLRVIGYLRRMDVFTEAELRVKFLQARDAWLRS ILTAIPNDDPYFHIT
KTIEA**S**RVHLFDII**T**Q**Y**R**&**IFSDEDPLLPPAMG**E**H**T**V**N**ESAIFHGWVL**Q**K**V****SQ**F½ VLE**T**DLYR**G**I**G**G
HLDSLLGQCMYFGLSFSRVGADFRGQPAPVFQRVAISIFQKAIQEIVEKFQEEMNSYMLISAPAILGX
SNMPAAVPAIQPGTLQPPMVLLDFPPLACFLNNILVAFNDLRLCCPvALAQDVTGALEDALAKVTKII
LAFH RAKE AAF SSGEQELFVQF CXVF LED LVPYLNRCLQVLFP PAQXAQTLGIPPTQLSKYGNLGHVN
IGAIQEPLAFILPKREX LFXL.DDQALGPE LTAPAPEPPAEEPRLEPAGPACPEGGRAE TQAEPP S**VGP**

>SEQ ID NO: 32
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IAAGANLKVISXMSVGIPHLALDEXKKRGIRVGYTPDVLTDTTAELAVSLLLTTCRRLPEAIEEVKNG
GWISWKPLWLCGYGLXQSXVGIlGLGRIGQAI.¾RRLKPFGVQRFirYXGRQPRPEEAAFFQAEFVSXPE
LAAQSDFIVVACSLXPAIEGLCNKDFFQKMKETAVFINISRGDVVNQDDLYQALASGKIAAAGLDVTS
PEPLPINHFLLXLKMCVILPHIGSAIHRIRMXMSLLAANNLLAGLRGEPMPSELKL

>SEQ ID NO: 33
MPAERPAGSGGSEAPAMVEQLDTAyITFAMLEEEEQLEAAGLERERKMLEKARMSWDRESTEIRYRRL
QHLLEKSNIYSKFLLTKMEQQQLEEQKKEKLERKKESLKVKKGKNSIDASEEKPVMRKKRGREDESY
NISEVHSKEEILSVAKKNKRENEPENSSSINLCV^ DLQKNKDSNSIIKDRLSETVRQNTKFFFDPVRK
CNGSPVPFQQPKHFTGGVMRWYQVEGMEWDRMLWENGINGILADEMGLGKXVQCIATIALMIQRGVPG
PFL¥CGPLSTLPN¾MAEEKRFTPIIIPTMlY'HGXQEERQKLVRNIYKRKGTLQIHPVVITSFEIAMRDR
NALQHCYWKYLIVDEGHRIKNMKCRLIRELKRFNADNKLLLTGTPLQNNLSELWSLLNFLLPDVFDDL
KSFESWFD**I**TSLSEXAEDIIAKERE QNVLHMLHQ**I**LXPFLLRRL KSDVALEVPPEREVVVYAPLSKKQ
EXFYXAXVNRIIANMFGSSEKEIIELSPIGRPKRRXRKSINYSKIDDFPNELEKLISQIQPEVDRERA
WEVNIPVESEVNLKLQNIMMLLRKeeNHPYLIEYPIDPVXQEFKIDEELVXNSGKFLILDRMLPELK
KRGHKVLLFSQMTSMLDILMDYCHLRDFNFSRLDGSMSYSEREKNMHSFNTDPEVFIFLVSTRAGGLG
INLTAADTVIIYDSDWNPQSDLQAQDRCHRIGQTKPVVVYRLVTANTIDQKIVERAAAKRKLEKLIIH

KNHFKGGQS GLNL SKNFL DFKE LME LLK 3RD YERE IKG SREKVI SDKDLE LLLDR SDLI DQMNAS GPI
KEKMG IFKI EN SEDSSPEC LF

>SEQ ID NQ;34
MAGVGPGGYAAEFVPPPECPVFEPSWEEFTDPLSF'IGRIRPIAEKTGICKIRPPKDWQPPFACEVKSF
RFTPRVQPLNELEAMTRVRLDFLDQLAKFWELQGSTLKIPVVERKILDLYALSKIVASKGGFEMVTKE
KKWSKVGSRLGYLPGEGTGSLLKSHYERILYPYELFQSGvSLMGVQMPNLDLKEKVEPEVLSTDTQTS
PEPGTRMNILPKRTRRVKXeSESGD^SRNTELKKbQrFGAGPKVVGLAMGTKDKEDEVXRREKVTNRS
DAFNMQMRQRKGTLSVNFVDLYVCMFCGRGNNEDKLLLCDGCDDSYHTFCLIPPLPDVFKGDWRCPKC
VAEECSKPREAFGFEQAVRE YTLQSFGEMADNFKSDYFNMP VHMVPTELVEKEFWRLVS SIEEDVIVE
YGADiS:SKDFGSGFPVKDGRRKILPEEEEYALSGWM LNNMPVLEQSVLAHINVDISGMKVPWLYVGMC
FSSPCWHTEDHWSYSINYLHWGEPKiWYGVPSHAAEQLEEVMRELAPELFESQPDLLHQLVTIMNPNV
LMEHGV7PVYRTNQCAGEFVVTFPRAYHSGFNQGYNFAEAVNFCTADWLPIGRQCVNHYRRLRRHCVFS
HEELIFKMAADPECLDVGLAAMVCKELXLMIEEEIRLRESVVQMGVLMSEEEVFELVPDDERQCSACR
TXCFLSALTCSCNPERLVCLYHPXDLCPCPMQKKCLRYRYPLEDLPSLLYGVKVRAQSYDTWVSRVTE
ALSANFNHKKDLIELRVMLEDAEDRiYPENDLFRKLRDAVKEAETCASVAQLLLSKKQKHRQSPDSGR
XRIKLIVEELKAFyQQLFSLPCv ISQA RQVKNLLDDVEEFHERAQEAMMDETPDSSKLQMLIDMGSSL
¾¾ LPELPRLKQEL QQARWLDEVRL XLSDPQQVILDVMKKLIDSGVGL APHHAVEKAMAELQELLXVS
ERWEEKAKVCLQARPRH SVASLES IVNEAKN IPAFL PNVLSLKEAL QKAREWXAKVE AI QSG SNYAYL
EQLESI ,SAKGRPIPVRLEALPQ VESQVAAARAWRERTGRTFLKKNSSHTLLQVLSPRTDIGVYGSGKN
RRKKVKELIEKEKE KDLDLEPLSDLEEGLEEXRDXAMVVAVFKEREQKEIEAMHSLRAANLAKMTMVD
RIEEVOTCICRKXASGFMLQCELCKDWFHNSCVPLPKSaSQKKGSSWQAKEVKFLCPLCMRSRRPRLE
XILSLLVSLQKLPVRLPEGEALQCLXERAMSWQDRARQALAXDELSSALAliLSVLSQRMVEQAAREKX
EKIISAELQKAAANPr)LQGHLPSFQQSAFNPa ?VSSVS5nSPRQXMDYDDEEXDSDEDI RETYGYDMKDT
ASVKSSSSLEPNLFCDEEXPIKSEEWXHi^fXA^SFCAEHAYSSAS KSCSQGSSIPRKQPRKSPLVPR
SLEPFVLEL SPGAKAQLEELMMVGBLLEVS LDEXQ.HIWRILQAIHPPSEDRFLHI MBDD SMEEKPLKV
KGKDSSEKKRKRKLEKVEQLFGEGKQKSKELKKMDKPRKKKLKLGADKSKELNKLAKKLAKEEERKKK
KEKAAAAKVELVKESXEKKREKKVLDIPSKYDWSGAEESDDENAVCAAQNCQRPCKDKyDWyQCDGGC
DEWFHQVCVGVSPEMAENEDYICIN CAKKQGPVSP GPAPPP SF IMSYKLFME DLKEXS

>SEQ ID NO: 35
MSLSNKLTLDKLDVKGKRVVMRVDFNVPMKNNQIINNQRI KAAVP SIKFC LDNGAKSWLMSHLGRPD
GVPMPDKYSLEPVAVELKSLLGKDVLFLKDC^VGPEVEKACAiiPAAGSVILLENLRFHVEEEGKGKDAS
GNKVKAEPAKIEAFRA-SLSKLGDVYVNDAFGXAHRAHSSM VGVNLPQKAGGFLMKKELNYFAKALESP
ERPF LAILGGAKVA.DKIQLINNMLDKVNEMI IGGGMAF XFLKVLNNME IGISLFDEEGAK IVKDLMSK
AEKNGVKIILPVDFVTADKFDENAKTGQATYASGTPAGWGLDCGPESSKKYAEAVTRAKQIVWNGPV
GVFEWEAFARGXKALMDEWKAXSRGCIIIIGGGDXAICCARWXEDKVSHVSIGGGASLELLEGRVL
PGVDALSNI

>SEQ ID NO: 36
MADLEVYKNLSPEKVERGMSVMQSGXQMIKLKRGXKGLVRLFYLDEHRXRLRWRP SRKSEKAKILIDS
lYKVXEGRQSEIFHRQAEGNFDPSCCFXIYHGNHMESLDLIISNPEEARIWIXGLKYLMAGISDEDS.L
SKRQRTHDQWVKQTFEEADKNGDGLLNIEEIHQLMHKLNVNLPRRKVRQMFQEADTDENQGTLTFEEF
CVFYKMMSLRRDLYLLLLSYSDKKDHLTVEELAQFLKVEQKMNNVTTDYCLDIIKKFEVSEENKVKNV
LGIEGFTMFMRSPACDIFNPLHHEVYQDMDQFLCNYYIASSHNTYLTGDQLLSQS KVDMYARVLQEGC.
RCVEVDCWDGPDGEPVVHHGYTLTSKILFRDVVETINKHAFVKNEFPVILSIENHCSIQQQRKIAQYL
KGIFGDKLDLSS VDIGECKQLPS.PQSLKGKILVKGKKLPYHLGDDAEEGEVSDEDSADE lEDECEFKL
HYSNGTTEHQVE SFIRKKLESLLKESQIRDKEDPDSFTVRALLKAXHEGLNAHLKQSPDVKESGKKSH
GRSLMTNFGKHKK.TTKSRSKSYSTDDEEDTQQSTGKEGGQLYRLGR¾RKTMKLCRELSDLV VYTNSVA
AQDIVDDGTTGNVLSFSETRAHQXVQQKSEQFMIYNQKQLTRIYPSAYRIDSSNFNPLPYWNAGCQLV7
ALNYQSEGRtMQLNRAKFKANGNCGYVLKPQQMCKGTFNPFSGDPLPANPKKQLILKVISGQQLPKPP
DSMFGDRGEIIDPFVEVEIIGLPVDGGKDQTRVVDDNGFNPVWEETLTFTVHMPEJALVRFLVWDHDP
IGRDFVGQRTVTFSSLVPGYRHVYLEGLTEASIFVHITINEIYGKWSPLILNPSYTILHFLGATKNRQ
LQGLKGLFNKNPRHSSSENNSHYVRKRSIGDRILRRXASAPAKGRKKSKMGFQEMVEIKDSVSEATRD
QDGVLRRXXRS LQARPVSMPVDRNLLGALSLPVSETAKDIEGKENSLAEDKDGRRKGKAS IKDPHFLN
FNKKLSSSSSALLHKDTSQGDTIVSTAHMSVTGEQLGMSS.PRGGRTTSNATSNCQENPCPSKS LSPKQ
HLAPDPVVNPTQDLHGVKIKEKGNPEDFVEGKSILSGSVLSHSNLEIKNLEGNRGKGRAATSFSLSDV
SMLCSDTPDLHSXAILQESV ISHLIDNVXLXNENEPGSSISALIGQFDEINNQALXVVSHLHNXSVMS
GHCPLPSLGLKMPIKHGFCKGKSKSSFLCSSPELIALSSSETTKHAXNXVYETXCTPlSKXKPDDDLS
SKAKTAALESNLPGSPNTSRGWLPKSPTKGEDWETLKSCSPASSPDLTLEDVIADPTLCFNSGESSLV
EIDGESENLSLTTCEYRREGTSQIASPLKLKYNQGVVEHFQRGLRNGYCKETLRPSVPEIFNNIQDVK

TQSISYLAYQGAGFVHNHFSDSDAKMFQTCVPQQSSAQDMHVPVPKQLAHLPLPALKLPSPCKSKSLG
DLTSEDIACNFESKYQCISKSFVTTGIRDKKGVTVKTKSLEPIDALTEQLRKLVSFDQEDNCQVLYSK
QDANQLPRALVRKLSSRSQSRVRNIASRAKEKQEANKQKVPNP SNGAGVVLRNKP SAPTPAVNRHSTG
SYIAGYLKNXKGGGLEGRGIPEGACTALHYO^ VDQFCSDNSVLQTEPSSDDKPEIYFLLRL

>SEQ ID NG:37
MGRSRRTGAHRAHSLARQMKAKRRRPD1.DE IHRELRPQGSARPQPDPNAEFDPDLPGGGLiiR CLACAR
YFIDSINLKTHFRSKDHKKRLKQLSYEPYSQEEAERAAGMGSYVPPRRLAVPIEVSTEVPEMDIST

>SEQ ID NO: 38
MAPLCPSPWLPLLIPAPAPGLTVQLLLSLLLLVPVHPQRLPRMQEDSPLGGGSSGEDDPLGEEDLPSE
EDSPREEDPPGEEDLPGEEDLPGEEDLPEVKPICSEEEGSLKL EDLPTVEAPGDPQEPQNNAHRDKEGD
D;Q;SHWRYGGDPPWPRVSPACAGRF;QSPVDIRPQLAAFGPALRPLELLGFQLPPLPELRLRNNGHS VQL.
TLPPGLEMALGPGREYRALQLHLHMGAAGRPGSEHTVEGHRFPAEIHVVHLSTAFARVDEALGRPGGL
AVLAA FLEEGPEENSAYEQLLSRLEEIAEEGSETQVPGLDISALLPSDFSRYFQ¥EGSLTTPPCAQGV
XWTVFNQTVMLSAKQLHTLSDTLWGPGDSRLQLNFRATQPLNGRVIEASFPAGVDSSPRAAEPVQLNS
CLAAGDILAIV'FGLLFAVTSFAFI V'QMRROHRRGIKGGVSYRPAEVAETGA

>SEQ ID MO:39
MSSRSTKDLIKSKWGSKPSNSKSETTLEKLKGEIAHLKTSVDEITSGKGKLTDKERHRLLEKIRVLEA
EKEKNAYQLTEKDE¼ IQRLRDQLKARYSTTTLLEQLEETTREGERREQVLKALSEEKDVLKQQLAAAT
SP¾IAELESKTNTLRI-SQTVAPNCFNSSINNIHEMEIQLKDALEKNQQWLVYDQQRE\'YVKGLLAKIFE
XEKKTETAAHSLPQQTKKPESEGYLQEEKQKCYNDLLASAKKDLEVERQTITQLSFELSEFRRKYEET
QKEVHNLNQLLYSQRRADVQHLEDDRHKTEKIQKLREENDXARGKLEEEKKRSEELLSQVQFLYXSXL
KQQEEQXRVALLEQQMQACILDFENEKLDRQHVQHQLHVILKELRKARNQITQLESLKQLHEFAXXEP
LVXFQGEXENREKVAASPKSPXAALNESLVEGPKCNIQYPAXEHRDLLVHVEYCSK

>SEQ ID NO:40
MEEFDSEDFSX SEEDEDYVPSGGEYSEDDVNELVKEDEVDGEEQTQKTQGKKRKAQ SIPARKRRQGG L
SLEEEEEEDANSESEGSSSEEEDDAAEQEKGIGSEDARKKKEDELWASFLNDVGPKSKVPPSXQVKKG
EETEEXSSSKLLVKAEELEKPKETEKVKIXKVFDFAGEEVRVTKEVDATSKEAKSFFKQNEKEKPQAN
VPSALPSLPAGSGLKRSSGHSSLLGKIGAKKQKM.SXLEKSKLDWESFKEEEGIGEELAIHNRGKEGYI
ERKAF LDRVDHRQF EIERDLRL 8KMKP

>SEQ ID NO:41
MQAFLKGXSISXKPPLTKDRGVAASAGSSGENKIKAKPVPWVEKYRPKCVDEVAFQEEVVAVLKKSLEG
ADLPNLLFYGPPGIGKXSTILAAARELFGPELFRLRVLELNASDERGIQVVREKVKNFAQLIVSGSRS
DGKPCPPFKIVILDEADSMXSAAQAALRRXMEKESKXXRFCLieNYvSRIIEPLXSReSKERFKPLSD:
KIQQQRLLDIAKKENVKlSnE5IAYLVK¾S:EGDLRKAIXELQSAXRLXGGKEIXEKVlXDlAGVlPAE
KIDGVFAACQSGSFDKLEAVVKDLIDEGHAAXQLVNQLHDWVENNLSDKO KSIITEKLAEVDKCLAD
GADEHLQLI SLCAIVMQQLSQNC

>SEQ ID NO; 42
MPLTGVEPARMNRKKGDKGFESPRPYKLTHQVVCINNINFQRKSVVGFVELTIFPTVANLNRIKLNSK
QCRIYRVRINDIEAAFI¾NDPTLEVCHSE5KQRNLNYFSNAYAAAVSAVDPDAGNGELCIKVPSELWK
HVDELKVLRIHINFSLDQPKGGLHFWPSVF^ MAERGAHVFSCGYQNSTRFWFPCVDSYSELCTWKL
EFT YDAAMVAVS NGDL VEIVYTHDMRKKX FHYML TIPTAASN ISLAIGPFEILVDPYMHEVIHFCLPQ:
LLPLLKHXISYLHEVFEFYEEILXCRYPYSCFKXVFIDEAYVEVAAYASMSIFSXNLLHSAMIIDEXP
LIRRCLAQSLAQQFFGCFISRMSWSDEWVLKGISGYIYGLWMKKTFGVNEYRHWIKEELDKIVAYELK
IGGVLLHPIFGGGKEKDNPASHXHFSIKHPHTLSWEYYSMFQCKAHLVMRLIENRISMEFMLQVFNKL
LSLASTASSQKFQSHMWSQMLVSISGFLK.S1SNVS GKDIQPLIKQWVDQSGVVKF YGSF AFNRKRNVL
ELEIKQDYTSPGTQKYVGPLIWTVQELDGSFNHTLQIEENSLKHDIPGHSKSRRNKKKKIPLMNGEEV
DMDLSAMDADSPLLWIRIDPDMSVLRKVEFEQADFMWQYQLRYERDVVAQQESILALEKFPTPASRLA
LTDILEQEQCFYRVRMSACFCLAKIANSMVSXWXGPPAMKSLFTRMFCCKSCPNIVKXNNFMSFQSYF
LQKXMPVAMALLRDVHNLCPKEVLTFILDLIKYNDNRKNKFSDNYYRAEMIDALANSVXPAVSWTOE V
RXLDN LNPDVRLILEEITRFLNMEKLLPSY'RETTIXVSCLRAIRVIQKNGHVPSDPALFKSYAEYGHFV
DIRIAALEAWDYIKVDRSYEELQWLLNMIQNDPVPYVRHKILNMLXKNPPFXKNMESPLCNEALVDQ:
LWKLMNSGXSHDWRLRCGAVDLYFXLFGLSRPSCLPLPELGLVLNLKEKKAVLNPXIIPESVAGNQEA
ANNP SSHPQLVGF QNPFS SSQDEEE IDMDXVHD SQ.AF ISHK LNMLERP SIPGLSKYRPASSRSAL IPQ
HSAGCDSXPIXKPQWSLELAMiGXGKEQAPLEMSMHPAASAPLSVFXKESXASKHSDHHH HHHHEHKK
KKKKHKHKHKHKHKHD SKEKDKEPFTFSSPASGRS IRSPS LSD

>SEQ ID NO: 43
MFHGIFATPGIG¾PG¾ PELYEEVKLYKNARELEKYDNMAELFAVVKTMQALEKAYIKDCVSPSEYTA
AGSRLLVQYKAAFRQVQGSEISSIDEFCRKFRLDCPLAMERIKEDRP ITIKDDKGNLNPCIADVVSLF
ITVMDKLRLEIRAMDEIQPD^ ELMETMHRMSHLPPDFEGRQTVSQWLQTLSGMSASDELDDSQVRQM
LFDLESAYNAFNRFLHA

>SEQ ID NO: 44
MELYNLTLQRATGISFAIHGNFSGXKQQEIVVSRGKILELLRPDPNTGKVHTLLTVEVFGVIRSLMAF
RLTGGTKDYIVVGSDSGRIVILEYQPSKNMFEKIHQETFGKSGCRRIVPGQFLAVDPKGRWViiISAIE
KQKLVYILNRDAAARLTISSPLEAHKANTLVYHVVGVDVGFENPMFACLEMDYEEADNDPTGEAAANT
QQILTFYELDLGLNHVWKYSEPLEEHGNFLITVPGGSDGPSGVLICSENYITY^ FGDQPDIRCPIP
RRRNDLDDPERGMIFVCSATHKTKSMFFELAQTEQGDIFKITLETDEDMVTEIRLKYFDTVPVAAAMC
VLKTGFLFV¾ SEFGNHYLYQIAHLGDDDEEPEFSSAMPLEEGDTFFFQPRPLKNLVLVDELDSLSPIL
FCQIADLANEDTPQ LYVACGRGFRSSLRVLRHGLEVSEMAVSELPGNPNAVWTVRRHIEDEFD¾YIIV
SFVNATLVLSIGETVEEVTDSGFLGTTPTLSCSLLGDDALVQVYPDGIRHIRADKRVNEWKTPGKKTI
VKCAVNQRQVVIALTGGEIAYFEMDPSGQLNEYTERKEMSADVVCMSLANVPPGEQRSRFLAVGLVDN
TVRIISLOPSDCLQPL SMQALPAQPE SLCIVEMGGTEKQDELGERGSIGF LYDNIGLQNGVLLRTVL
PVTGDLSDTRTRYLGSRP VKLFRVRMQGQEAVLAMSSRSWLSYSYQSRFHLTPLSYETLEFASGFASE
QCPEGIVAISTNTLRILALEKLGAVFNQVAFPLQYTPRKFVIHPESNNLIIIETDHNAYTEATKAQRK
QQMAEEMVEAAGEDERELAAEMAAAFLNENLPESIFGAPKAGNGQWASVIRVMNPIQGNTLDLVQLEQ
NEAAFSVAVCRFSNTGEDWYVLVGVAKDLILNPRSVAGGFVYTYKLVNNGEKLEFLHKTPVEEVPAAI
APFQGRVLIGVGKLLRVYDLGKKKLLRKCENKHIANYISGIQTIGHRVIVSDVQESFIWVRYKRNENQ
LIIFADDTYPRWVTTASLLDYDTVAGADKFGNICVVRLPPNTNDEVDEDPTGNKALWDRGLLNGASQK
AEVIMNYHVGETVLSLGKTTLIPGGSESLVYTTLSGGIGILVPFTSHEDHDFFQHVEMHLRSEHPPLC
GRDHLSFRSYYFPVKNVIDGDLCEQFNSMEPNKQKNVSEELDRTPPEVSKKLEDIRTRYAF

>SEQ ID NO: 45
MNQPCNSMEPRVMDDDMLKLAVGDQGPQEEAGQLAKQEGILFKDVLSLQLDFRNILRIDNLWQFENLR
KLQLDNNIIEKIEGLENIAHLVWLDLSFNNIETIEGLDTLW LEDLSLFNNRISKIDSLDAXVKLQVL
SLGNNRIDNt-IMNIIYLRRFKCLRTLSLSRNPISEAEDYI^lFICAYLPDLMYLDYRRrDDHTKKLAEAK
HQYSIDELKHQENLMQAQLEDEQAQREELEKHKIAFVEHLNGSFLFDSMYAEDSEGNNLSYLPGVGEL
LETYKDKFVIJGVNIFEYGLKQQEKR KTELDTFSECVREAIQENQEQGKRKIAKFEEKHLSSLSAIRE
ELELPNIEKMT I,ECSADISELF DAM TLEMQLVEQLEETINMFERNIVDMVGLFIENVQSLMAQCRDL
ENHHHEKLLEISISTLEKIVEGDLDEDLPNDIRALF**VDKDTIV**NAVG¾SHDIHlLKIDNREDELVTRI
NSWCTRLIDRIHKDEiMRNRKRVKEINQYIDHMQSELDNLECGDILD

>SEQ ID NO: 46
MATPAAVNPPEMASDIPGSVTLPVAPMAATGQVRMAGAMPARGGKRRSGMDFDDEDGEGPSKFSRENH
SEIERRRRNKMTQYITELSDMVPTCSALARKPDKLTILRMAVSHMKSMRGTGNKSTDGAYKPSFLTEQ
ELKHLILEAADGFLFVVAAETGRVIYVSDSVTPVLNQPQSEWFGSTLYEQVHPDDVEKLREQLCTSEN
SMTGRILDLKTGTVKKEGQQSSMRMCMGSRRSFICRMRCGNAPLDHLPLNRITTMRKRFRNGLGPVKE
GEAQYAVVHCTGYIKAWPPAGMTIPEEDADVGQGSKYCLVAIGRLQVTSSPVCMDMNGMSVPTEFLSR
HNSDGIIXFVDPRCJSVIGYQPQDLLGKDXLEFCHPEPQSHLRESFQQVVKLKGQVLSVMYRFRTKNR
EWMLIRT3SFTF0NPYSDEIEYIICrNTNVKQLQQQQAELEVHQRDGLSSYDLSQVPVPNLPAGVHEA
GKSVBKADAIFS^.ERDPRFAEMFAGISASEKKt^MSSASAAG-TQQIYS QGSPFPSGHSGKAFSS SVVHV
PGVNDIQSSSSTGQNMSQISRQLNQSQVA¾TG SRP PFPGQQ IP SQS SKIQSSPFGIGTSHTYPADPSS
YSPLSSPATSSPSGNAYSSLANRIPGFAESGQSSGQFQGRPSEVWSQWQSQHHGQQSGEQHSHQQPGQ
TEVFQ DMLPMP GDP TQGTGNY.NIEDFADL GMFPPF SE

>SEQ ID NO: 47
MPEPTKKEENEYPAPAPPPEEPSKEKEAGTTPAEIDWTLVETPPGEE QAKQNANSQLSILFIEKPQGGT
VKVGEDITFIAKVKAEDLLRKPIIKWFKGKWMDLASKAGKHLQLKETFERHSRVYTFEMQIIKAKDNF
AGNYRCEVTYKDKFDSCSFDLEVHESTGTTPNIDIRSAFKRSGEGQEDAGELDFSGLLKRREVKQQEE
EPQVDVWELLKNAKPSEYEKIAFQYGITDLRGMLKRLKRMRREEKKSAAFAKILDPAYQVDKGGRVRF
VVELADPKLEVKWYKNGQEIRPSTKYIFEHKGCQRILFINNCQMTDDSEYYVTAGDEKCSTELFVREP
PIMVTKQLEDTTAYCGERVELECEVSEDDANVKWFKNGEEIIPGPKSRYRIRVEGKKHILIIEGATKA
DAAEYSVMTTGGQSSAKLSVDLKPLKILTPLTDQTVNLGKEICLKCEISENIPGKWTKNGLPVQESDR
LKVVHKGRIHKLVIANALTEDEGDYVFAPDAYNVTLPAKVHVIDPPKIILDGLDADNTVTVIAGNKLR
LEIPISGEPPPKAM'JSRGDKAIMEGSGRIRT^ SYPDSSTLVIDIAERDDSGVYHINLKNEAGEAHASI
KVKVVDFPDPPVAPT VT:EVGDD WCIMNWEPPAYDGGSPILGYFIERKKKQSSRWMRLNFDLCKETTFE

PKKMIEGVAYEVRIFAVNAIGISKPSMPSRPFVPLAVTSPPTLLTVDSVTDTTVIMRWRPPDHIGAAG
LDGYVLEYCFEGSTSAXQSDENGEAAYDLPAEDWI^ /ANKDLIDKTKFTITGLPTDAKIFVRVKAVNAA
GASEPKYYSQPILyKEIIEPPKIRIP RHLKQTYIRRVGEAVNLVIPFQGKPRPELTWKKDGAEIDKNQ
INIRNSETDTIIFIRKAERS HSGKYDLQVKVDKFVETASIDIQIIERPGPPQIVKIEDVWGEKVALT W
TPPKDDGNAAIT.GS? TIQKADKKSMESETVIEHYHRTSATITELVIGNEYYFRVFSENMCGLSEDATMT
KESAVIARDGKIYKNPVYEDFDFSEAi?MFTQPLVNTYAIAGYNATLNCSVRGNPKPKITWMKNKVAIV
DDPRYRMFSNQGVCTLEIRKPSPYDGGTYCCKAWDLGTVEIECKLEVKVIAQ.

>SEQ ID MO: 48
MLLETQDALYVALELVIAALSVAGNVLVCAAVGTANTLQTPTNYFLVSLAAADVAVGLFAIPFAITIS
LGFGTDFYGGLFlACFVLyLTCiS.SlFSLLAVAVD RYLAICVPLRYKSLVTGTRARGVIAVLWVLAFGI
GI^PFLGWNSKDSATNNCTEP WDGTTNESCCLVKCLFENVVPMSYMVYFNFFGCVLPPLLIMLVIYIK
IFLVACRGLQRTELMDHSRTTLQREIHAAKSLAMIVGIFALCWLPVHAVNCVTLFQPAQGKNKPKWAM
NMAILLSHANSVVNPIVYAYRNRDFRYXFHKIISRYLLCQAD¾ SGNGQAGVQPALGVGL

>SEQ ID NO:49
MSGRPRITSFAESCKP¾QQPSAFGSMKVSRDKDGSKVTTVVAIPGQGPDRPQEVSYTDTKVIGNGSFG
VyYQAKLCDSGELVAIKKVLQDmFKNRELQIMRKLDHCNIVRERYFFYSSGEKKDEVYDNLVLDYVP
ETVYRVARHYSRAKQTLPVIYyKLYMYQLFRSLAYIHSFGICHRDIKPQNLLLDPDTAVLK LCDFGSA
KQLVRGEPNVSYICSRYYRAPELIF GATDYTSSIDVWSAGCVLAELLLGQPIFPGDSGVDQLVEIIKV
LGTPTREQIREMNPNYTEFKFPQIKAHPW^ KVFRPRTPPEAIALCSRLLEYTPTARLTPLEACAHSFF
DELRDPIWKLPNGRDIPALENFTTQELSSNPPLAIILIPPHARIQAAASTPTNATAASDANTGDRGQ T
NNAASASASNSX

>SEQ ID NO: 50
1ALSSAWRSVLPIWLLWSAACSRAASGDDN2FPFDIEGSSAVGRQDPPETSEPRVALGRLPPAAEKCN
AGFFHTLSGECVP€DCNGNSNECLDGSGYC\?HCQRNTIGEHCEKCLDGYIGDSIRGAPQFCQPCPCPL
PHLANFAESCYRKNGAVRCICNENYAGPNCERCAPGYYGNPLLIGSTCKKCDCSGNSDPNLIFEDCDE
VTGQCRNCLRWTTGFKCERCAPGYYGDARIAKNCAVCNCGGGP-CDSVTGECLEEGFEPPTGMDCPTIS
CDKGVW)LTDALRU^SIEEGKSG^LSVSSGAAA^RHVNEINATIYi.LKTKLSEREN©YALRKIOIN
NAENTMKSLLSDVEELVEKENQASRKGQLVQKESMDTINHASQLVEQAHDMRDKIQEINNKMLYYGEE
HELSPI<EISEKLVLAQKMLEEIRSRvQPFFTQREL\^EEADEAYELLi]QAESWQRLHNEIRTLFPVVLE
QLDDYNAKLSDLQEALDQALNyy rRDAEDMMRATAARQRDHEKQ QERVREQMEVVNMSLSTSADSLTTP
RLTLSELDDIIKNASGIYAEIDGAKSEtQVKLSNLSNLSHDIVQEAIDHAQDLQQEANELSRKLHSSD
BNGLVQKSLDASNVYENIVNYVSEANETAEFALNTTDRIXDAVSGIDTQITYHKDESENLINQARELQ
AKAESSSDEAVADT SRRVGGALARKSALKIRLSDAVKQLQAAERGDAQQRLGQSRLITEEANRTTMEV
QQATAPMANNLTNWSQNLQHFDSSAYNTAVNSARDAVRNLTEVVPQLLDQLRTVEQKRPASNVSASIQ
RIRELIAQTRSVASKIQVSMMFDGQSAVEyHSRISMDDLKAFTSLSLYMKPPyKRPELTETADQFILY
LGSKNiiKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSSWPAYFSIVKIERVGKHGKVFLTVPSL
SSIAEEKFIKKGEFSGDDSLLDLDPEDTVFYVGS VPSNFKLPTSLNLPGFVGCLELATLNNDVISLYN
PKHIYNMDPSTSVPCARDKLAFTQSRAASYFFDG3GYAVVRDITRRGKFG0\TTRFDIEyRTPADNGLI
LLM¥NGSMFFRLEMRNGYLHVFYDFGFSGGPVHLEDTLKKAQINDAKYHEISIIYHNDKKMILVVDRR
HVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAiiLPLDINFRGCMKGFQFSKKDFNLLEQTETLGVG
YGCPEDSLISRRAYFNGQSFIASIQKISFFDGFEGGFNFRTLQPNGLLFYYASGSDVFSISLDNGTVI
MDVKGIKVQSVDKQYNDGLSHFVISSVSPTRYELIVDKSRVGSKNPTKGKIEQTQASEKKFYFGGSPI
SAQYANFTGCISNAYFXRVDRDVEVEDFQRYTEKVHTSLYECPIESSPLFLLHKKGKNLSKPKASQiiK
KGGKSKDAPSWDPVALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQEF EHLKGDFGAKSQFS
IRLRTRSSHGMIFYVSDQEENDFMTLFLAHGRLWMFNyGHKKLKIRSQEKYNDGLWHDyiFTRERSS
GRLyIDGLRyLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCLSNLQLNGASITSAS
OTFSVTPCFEGPMETGTYFSTEGGYVVLDESFNIGLKFEIAFEV^^ RSSSGTLVHGHSVNGEYLNVHM
KNGQVIyKVNNG IRDFS TSVTP KQSLGDGRWHRITVIRDSNVVQLDVDSEVNHVVGPLNPKPTDHREP
VFVGGVPESLLTPRLAP SKPFTGCIRHFVI DGHPV SFSKAAL VSGAVSINSGPAA

:>SEQ ID NO: 51
MLWlALGPFPAMENQyLyIRIKIPNSGAyDWTyHSGPQILFRDVLDVIGQVLPEATTTAFEYEDEDGD
RITVRSDEEMKAMLSY YYSTVMEQQVNGQLIEPLQIFPRACKPPGERNIHGLKVNTRAGPSQHSSPAV
SDSLPSNSLKKSSAELKKr^ NGQMNEQDIRYRDTLGHGNGGTVYKAYHVPSGKILAVKVILLDITLE
LQKQIMoELEILYKCDSSYIIGFYGAFFyENRISICTEFMDGGSLDvYRKMPEHyLGRIAyAyyKGLT
YLWSLKILHRDVKPSNMLVNTRGQVKLCDFGVSTQLVNSIAKTYVGTNAYMAPERISGEQYGIHSDVW
SLGISFMELALGRFPYPQIQKNQGSLMPLQLLQCIVDEDSPVLPVGEFSEPFVHFITQCMRKQPKERP
APEELMGHPFIVQFNDGNAAVySMWVGRALEERRSQQGPP

>SEQ ID NO: 52
MAHAGRI GYDNREIVMK.YIHYKL SQRGYEWDAGDVGAAP PGAAPAPGIFSS QPGHIPHPAASRDP VAR
TSPLGTPAAPGAAAGPALSPWPWHLILRQAGDDFSRRYRRD FAEMSSQLHLTPFTARGRFATVVEE
LFRDGVNWGRIVAFFEFGGVMCVESVNREMSPLVDNIALWMTEYLNRHLHTWIQDNGGWDAFVELYGP
SMRPLF DFS-WL SLKTLLSLALVGACI ILGAYLGHK

>SEQ ID NO: 53
MAAGAGAGSAPRWLBALSEPLSAAQLRRLEEHRYSAAGVSLLEPPLQLYWTWLLQW IPLWMAPNSITL
LGLA^NVVTTWLISYCPTATEEAPYWTYLLCALGLFIYQSLDAIDGKQ ARRTNSCSPLGELFDHGCD
SLSTVFMAVGASIAARLGTY PDWFFFCSFIGMFVFYCAHWQTYV SGMLRFGKVDVTEIQIALVIVFVL
SAFGGATMWDYTIPITEIKLKILPVLGFLGGVIFSCSNW HVILHGGVGKNGSTIFGTSVLSPGLHIG
LIIILAIMIYKKSAIDVFEEBPCLYILMFGCY FAKVSQKLVVAHMTKSELYLQDTVFLGPGLLFLDQY
FNNFIDEYVVLWMAIVISSFDMVIYFSALCLQISRHLHLNIFKTACHQAPEQVQVLSSKSHQNNMD

>SEQ ID NG;54
MYGSARTIXNLEGSPSRSPRLPRSPRLGHRRTSSGGGGGTGKXLSMENIQSLNAAYATSGPMYLSDHE
G¥ASXIYPKGXMXLGRAXNRAVYGGRVIAMGSSPHIASAGLSHXDVLSYXDQHGGLXGSSHHHHHQVP
SMLRQVRDSXMLDL QAQLKELQREN DLLRKELDIKDSKLGSSMNSIKXFWSPELKKERVL RKEEAARM
SVLKEQMRV SHEENQHLQLXIQALQDELRTQRDLNHLLQQESGNRGAEHFTIELTEENFRRLQAEHDR
QAKELFLLRKTLEEMELRIETQKQTLNARDESIKKLLEMLQSKGLPSKSLEDDNERTRRMAEAESQVS
HLEVILDQKEKENIHLREELHRRS:QLQPEPAKXKALQXVIEMKDXKIASLERNIRDLEDEIQMLKANG.
VLNXEDREEEIKQIEVYKSHSKFMKXKIDQLKQELSKKESELLALQIKLEXLSNQNSDCKQHXEVLKE
SLIAKEQRAJVILQXEVDALRLRLEEKE^^ LNKKTKQLQDLTEEKGTLAGEIRDMKDMLEVKERKINVL
QKKIENLQEQLRDKDKQLTNLKDRVKSLQTDSSNTDTALATLEE&LSEKERI IERLKEQRERDDRERL
EEIESFRKENKDLKEKVNALQAELTEKESSLIDLKEHASSLASAGLKRDSKLKSLEIAIEQKKEECSK
LEAQLKKAHNIEDDSRMNPEFADQIKQLDKEASYYRDECGKAQAEVDRLLEILKEVENEKNDKDKKIA
ELESLTLRHMKDQNKKVANLKHNQQLEKKKNAQLLEEVRRREDSMADNSQHLQIEELMNALEKTRQEL
DATKARLASTQQSLAEKEAHLANLRIERRKQLEEILEMKQEALLAAISEKDANIALLELSASKKKKTQ
EEVMALKREKDRLVHQLKQQTQNRMKLMADNYDDDHHHYHHHHHHHHHRSPGRSQHSNHRPSPDQDDE
EGIWA

>SEQ ID NO; 55
MYKIAFNXPXAVQKEEARQDVEALLSRXVRTQIL XGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI
VGGACIYKYFMPKSXIYRGEMCFFDSEDPANSLRGGEPNFLPVXEBADIREDDNIAIIDVPVPSFSDS
DPAAIIBDFEKGMISYLDLLLGNCYLMPLNXSIVMPPINLVELFGKLASGRYLPQTYVVREDLVAVEE
IRDVSNLGIFIYQLCNNRKS FRLr<RRDLLLGFNKRAIDKCWKIRHFPNEFIVEIKICQE

>SEQ ID NO: 56
MARPVRGGL GAPRRS PCLLLLWLLLLRLEPVTAAAGPRAPCAAACXCAGDSLDCGGRGLAALP GDLPS
WTRSLNLSYNKLSEIDPAGFEDLPNLQEVYLNNNELTAVPSLGAASSHVVSLFLQHNKIRSVEGSQLK
AYLSLE^LDLSLNNIXEVRNXCFPHGPPIKELNLAGNRIGXLELGAFDGLSRSLLILRLSKNRIXQLP
VRAFKLPRLXQLDLNRNRIRLIEGLTFQGLNSLEVLKLQRNNISKLXDGAi'WGLSKMHVLHLEYNSLV
EVNSGSLYGLTALHQLHLSNNSIARIHRKGWSFCQKLHELVLSFNNLTRLDEESLAELSSLSVLRLSH
NSISHIAEGAFKGLRSLRVLD LDHNEISGTIEDTSGAFSGLDSLSKLTLFGNKIKSVAKRAF SGLEGL
EHLNLGGNAIRSVQFDAF VKMKNLKELHISSDSFLCDCQLKWLPPWLIGRMLQAFVTATCAHPESLKG
QSIFSypPESFVCDDFLKPQIIIQPEIIMAMVGKDIRFICSAASSS.SSP¾^ FAWKKDNEVLTNADMEN
FVHVHAQDGEVMEYXXILHLRQVXFGHEGRYQCVIXNHFGSXYSHKARLIVNVLPSFIKXPHDIXIRX
IXMSRLEC AATGBPNPQ IAWQKDGG XDFPAARERRMB VMPDODVFF ITDVKIDDAGVY SCXAQN SAGS
ISANAILXVLEXPSLWPLEDR\A.¾vGEXVALQCKAXGNPPiRIXWFKGDRPLSLXERIiIiLXPDNQLL
VvQNVVAEDAGRYICEMSNXLGXERAHSQL SyLPAAGCRKDGXXVGIFXIAVVSSIVLTSLVWVCIIY
QXRKKSEEYSVXNXDEIVvPPDypSYLSSQGILSDRQEXWRXEGGPQANGHIESNGyGPRDASHFPE
PDTHSVACRQPKLCAGSAYHKEPWKA&EKAEGTPGPHKMEHGGRVVCSDCNTEVDCYSRGQAFHPQPV
SRDSAQPS.APNGPEPGGSDQEHSPHHQCSRXAAGSCPECQGSL YPSNHDRMLTAVKKKPMASLDGKGD
SSWILARLYHPDSXELQPASSLXSGSPERAEAQYLLVSNGHLPKACDASPESXPLXGQLPGKQRVPLL
LAPKS

>SEQ ID NO: 57
MAEPRQEFEyMEDBAGlYGLGDRKDQGGYlMHQD QEGDTDAGLKESPLQTPTEDGSEEPGSETSDAKS
IPXAEDyXAPLyDEGAPGKQAAAQPHXEIPEGXIAEEAGIGDXPSLEDEAAGHyXQEPESGKVyQEGF
LREPGPPGLSHOLMSGMPGAPLLPEGPREAXRQPSGXGPEDXEGGRHAPi,LLKHQLLGDLHQEGPPLK

GAGGKERPGSKEEVDEDRDVDESSPQDSPPSKASPAQDGRPPQTAAREATSIPGFPAEGAIPLPVDFL
SKVSTEIPASEPDGPSV¾ RAKGQDAPLEFTFHVEITPNVQKEQAHSEEHLGRAAFPGAPGEGPEARGP
SLGEDTKEADLPEPSEKQPAAAPRGKPVSRVPQLKARMVSKSKDGTGSDDKKAKTSTRSSAKTLKNRP
CLSPKHPTPGSSDPLIQPBSPA^CPEPPSSPKYVSSVISRTGSSGAKEMKLKGADGKTKIAIPRGAAP
PGQKGQANATRIPAKTPPAI?KTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVA
VVRTPPKSPSSAKSRLQTAPVI?MPDLKNVKSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKD
NIKHVPGGGSVQIVYKPVDLSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHV
PGGGHKKIETHKLTFRENAKAKTDHGAEIVYKSPVYSGDXSPRHLSNVSSTGGLDMX/DSPQLATLADE
VSASLAKQGL

>SEQ ID NO: 58
fclADPAAGPPPSEGEE.STvRFARKGALP,QKNV?HEVKNHKF TARFFKQPTFC¾HCTDFIWGFGKQGFQCQ
VCGFVVHKRCHEFVXFS,GPGADKGPASDDPRSKHKFKIHTY3SPTFCDHCGS LLYGLIHQGMKCDTCM
MNVHKRCVMNVPSLCGIDHTERRGRIYIQAHIDRDVLIVLVRDAKNLVPMDPNGLSDPYVKLKLIPDP
KSESKQKTKTIKCSLNPEWNETFRFQLKESDKDRRLSVEIWDWDLTSRNDFMG&LSFGISELQKASVD
GWFKLLSQEEGEYFNVPVPPEGSEAMEELRQKFERAKISQGTC^ PEEKTTNTVSKFDNNGNRDRMKLT
DFNFIMVLGKGSFGKVMLSERKGTDELYAVKILKKDVVIQDDDVECTMVEKRVXALPGKPPF LTQLHS
CFQXMDRLYFVMEyVNGGDLMYHIQQVGRFKEPHAVFYAAEIAIGLFFLQSKGIIYRDLKLDNVMLDS
EGHIKIADFGMCKENIWDGVTTKXFCGTPDYIAPEIIAYQPYGKSVDWWAFGVLLYEMLAGQAPFEGE
DEDELFQSIMEHNVAYPKSMSKEAVAXCKGLMXKHPGKRLGCGPEGERDIKEHAFFRYIDWEKLERKE
IQPPYKPKARDKRDTSNFDKEFTRQPVELTPTDKLFIMNLDQNEFAGFSYTNPEFVINV

>SEQ ID NO: 59
MIADKDf^KDKEKDRDRDRDREREKERDKARESENSRPRRSCTLEGGAKNYAESDHS EDEDNDNNSATA
EESTKKNKKKPPKKKSRYERTDTGEITSYITEDDVVYRPGDCVYIESRRPNTPYFICSIQDFKLVHNS
QA€CRSPTPALCDPPACSLPVASQPPQHL£3EAGRGPVG6KRDHLLMTiVKWYYRQSEVPDSV"YQHLVQP
RHNEWDSGRFiLVIXDPVIKNRELFISDYVDTYHAAALRGKCNISHFSDIFAAREFKARVDSFFYILGY
NPETRRLNSXQGEIRVGPSHQAKLPDLQPFPSPDGDXVXQHEELVWMPGVNDCDLLMYLRAARSMAAF
AGMCDGGSXEDGGVAASRDDXXLNALNXLHESGYDAGKALQRLVKKPVP KLIEKCWTEDEVKRFVKGL
RQYGKNFFRIRKELLPNKEXGELITFYYYWKKTPEAASSRAHRRHRRQAVFRRIKTRTIASTPVNTPSR
PPSSEFLDLSSASEDDFDSED SEQEIKGYACRHCFTTTSKDWHHGGRENILLCTDCRIHFKKYGELPP
IEKPVDPPPFMFI\PYKEEDDGLSGKHSMRXRRSRGSMSXLRSGRKJ<QPASPDGRXSPINEDIRSSGRN.
SPSAASTSSNDSKAETVKKSAKKVKEEASSPLKSNKRQREKVASDTEEADRTSSKKTKTQEISRPNSP
SEGEGESSD¾RSVI^DEG.SSDP-KDIDQDNRST:SP SIPSPQDNESDSDSSAQQQMLQAQPPALQAPTGVT
P.APSSAPPGXPQLPXPGPXPSAXAVPPQGSPXASQAPNQPQAPXAPVPHXHIQQAPAIHPQRPPSPHP
PPHPSPHPPLQPLTGSAGQPSAPSHAQPPLH GQGPPGP-HS.LQAGPLLQHPGPPQPFGLPPQAS QGQAP
LGTSPftftAYPHXSLQLPASQ;SALQSQ:QPPREQPLPPAPLAMFHIKPPPXIPIPQLPAPQAHKHPPHLS
GPSPFSMNANLPPPPALKPLSSiLSXHHPPSAHPPPLQLMPQSQPLPSSPAQPPGLXQSQNLPPPPASK
PFTGLHQVAPQPPFAQHPFVPGGPPPITPPTCPSTSTPPAGPGTSAQPPCSGaAASGGSI&GGSSCPL
PTVQIKEEAIDDAEEPESPPPPPRSPSPEPTVVDTPSHASQSARFYKHIDRGYNSCARTDLYFMPLAG
SKLAKKREEAIEKAKREAEQKAREERERERERERERERERERAERAAKA8SSAHEGRLSDPQLSG
PGHMRPSFE PPPTTlAAVPPYIGPDXPALRTLSEYARPHVMSPTNRNHPFYMPLNPXDPLLAYHMPGL
YNVDPTIRERFLRERERIRERERIRERERLRERMKPGFEVKPPELDPLHPAANPMEHFARHSALTIPPTAG
PHPFASFHPGLNPLERERLALAGPQLRPEMSYPDRLAAERIHAERMASLTSDPLARLQMFNVTPHHHQ
HSHIHSHLHLHQQPPLHQGSAGPVHPLVDPLTAGPFILARFPYPPGTLPNPLLGQPPHEHEMLRFLPVFG
TPYPRDLPGAIPPPMSAA HQLQAMHAQSAELQRLAMEQQWLHGHPHMHGGHLPSQEDYYSRLKKEGDK
QL

>SEQ ID NO: 60
MVGALCGCWPRLGGARPLJPLGPXVVQXSMSRS.QVALLGLSILLMLLLYVGLPGPPEQTSOLWGDPNV
TVLAGLTPGNSPIFYREVLPLNQAHRVEVVLLHGKAFNSHTWEQLGTLQLLSQRGYRAVALELPGFGN
SAPSKEASXEAGRAALLERALRDLEVQNAVLVSPSLSGHYALPFLMRGHHQLHGFVPIAPXSXQNYIQ
EQFWAVKIPTLILyGELDHILARESLRQLRHLPNHSVV¾LRNAGHACYLHKPQDFHLVLLAFLDHLP

>SEQ ID NO: 61
MPALARDGGQLPLLVVFSAMIFGXITNQDLPVIKCVLINHKNNDSSVGKSSSYPMVSESPEDLGCALR
PQSSGIVYEAAAVEVDVSASIXLQVLVDAPGNISCLWyFKHSSLNCQPHFDLQIRGVVSMVILKMXEX
QAGEYLLFIQSEAXNYXILFXVSlRNTLLYXLRRPYERKMENQDALvCISESVPEPIVEWVLCDSQGE
SCKEESPAVVKKEEKVLHELFGTDIRCCARNELGRECTRLFTIDLNQTPQTTLPQLFLKVGEPLWIRC
KAVHVNHGFGLTWELENKALEEGNYFEMSTYSTNRTMIRILFAEVSSVARNDTGYYTCSSSKHPSQSA
LVTIVEKGFINATNSSEDYETDQYEEFCFSVRFKAYPQIRCTWTFSRKSFPGEQKGIDNGYSISKFCN

HKHQPGEYIFH¾ENDD¾QFTKMFTLNIRRKPQVLAEASASQASCFSDGYPLPSWIWKKCSDKSPNCTE
EITEGVWNRKANRKVFGQWVSSSTLNM.SEAIKGF LVKC CAYN SLGTSGETIXILN SPGP FPFIQDNIS F
YAXIGVCLLFIYVLXLLICHKYKKQFRYE.SQL^^^ IVQVTGSSDNEYFYVDFREYEYDLKWEFFRENLEF
GKVLGSGAFGKVMNAIAYGI SKTGVSIQVA^KMLKEKADSSEREALMSELKMMIQX,GSHENIVNLLGA
CT.LSGPI YLIFEYCCYGDLLNYLRSKREKFHRTWT EIFKEHNFSFYPTFQSHPNSSMPGSREVQIHPD
SDQISGLHGNSFHSEDEIEYENQKRLEEEEDLNVLTFEDLLCFAYQVAKGMEFLEFKSCVHRDLAARN
VLVT.HGKVVKIC:DFGLA¾:DIMSDSNYVVRGNARLEVKMAPESLFEGIYTI:KSDWSYGILLWEXFSL
G'vTSPYPGIPyDANFyKLIQNGFKMDQPFYA TEEIYIIMQSCWAFDSRKRPSFPNLTSFLGCQLADAEE
AMYQNVDGRV SECPHTYQNRRP FSREMDL GLLSPQAQVEDS

>SEQ ID NO: 62
MTGDRGPQRLSGSSYGSISSPTSPTSPGPQQ APPRETYLSEKIPIPDTKPGTFSLRKLWAFTGPGFLM
SIAFLDPGNIESDLQAGAVAGFKLLW LLWATVLGLLCQRLAARLGVVTGKDLGEVCHLYYPKVPRTV
LWLIIELAIYGSDMQEYIGXAIAFNLLSAGRIPLWGGVLIIIVDXFFFLFLDNYGLRKLEAFFGLLII
II^LTFGYEYVVARPEQGALLRGLFLPSCPGCGHPELLQAVGTVGAIIMPHNIYLHSALVKSREIDRA
RRADIREANMYFLIEATIALSVSFIINIFVMAVFGQAFYQKTNQAAFNICANSSLHDYAKIFPMNNAT
VAVDIYQGGVILGCLFGPAALYIWAIGLLAAGQSSTMTGTYAGQFVMEGFLRLRWSRFARVLLTRSCA
ILPXyLyAVFRDLRDLSGLNDLLN ¾ QSLLLPFAVLPILTFTSMPTLMQEFANGLLNKVVTSSIMVLV
CAINLYFVVSYLPSLPHPAYFGLAALLAAAYLGLSTYLVWTCCLAHGATFLAHSSHHHFLYGLLEEDQ
KGEXSG

>SEQ ID NO: 63
MSLQEMFRFPMGLLiGSVLLV¾ SAPAXLEPPGCSNKEQQVTVSHTYKIDVF?KSALVQVDADPQPLSDD
GASLLALGEAREEQNI XFRHNIRDQXPQKDCELAGSVQDLLARVKKLEEEMVEMKEQCSAQRCCQGVT
DLSRHC.SGHGXFSLFiXCSCKCEEGREGPACERLACPGACSGHGRCVDGRCLCHEPYVGADCGYPACPE
NCSGHGECVRG\'X¾CHEDFM8EDCSEKRCPGDC:SGHGFC^ TGECYCEEGFTGLDCAQVVTPQGLQLLK
NIEDSLLVSWEPSSQVDHYLLSYYFLGKELSGKQIQVPKEQHSYEILGLLPGTKYIVXLRNVKNEVSS
SPQHLLAXXDLAVLGXAWyTDEXENSLDVEwENPSTEyDYYKLRYGPMXGQEVAEVXVPKSSDPKSRY
DITGLHPGTEYKIXVVPHRGEDEGKPILLNGRTEIDSPXNWTDRV TEDTATVSWDPVQAVIDKYVVR
YTSADGDTKEMAVHKDESSTVLTGLKPGEAYKVYVWAERGNQGSKKADTN ALTEIDSPANLVTDRVTE
NTATISWDPV^ATIDKYVVRYTSADDQETREVL^^ KEQSSTVLTGLRPGVEYTVHVWAQKGDRESKKA
DTNAPXDIOSPKNLVXDRVXENMATVSWDPVQAAIDKYWRYISAGGETREyPVGK EQSSTVLTGLRP
GMEYMVHVWAQKGDQESKKADXKAQIDID^ PQNLVTDRVTENMATVSWDPVRATIDRYVVRYTSAKDG
EXREypyGKEQSSTyLXGLRPGyEYXyHWAQKGAQESK KADTKAQTDIDSPQNLVTDWVTENTATVS
WDPVQATIDRYVVHYTSANGETREVPVGKEQSSTVLTGLRPGMEYTVHVWAQKGNQESKKADTKAQTE
IDGPKNLVIDWVIENMAIVSWDpyQAIIDKYMVRYISADGEIREV^ VGKEHSSTVLTGLRPGMEYMVH
yWAQKGAQESKKADTKAQTEXDPPRNLRPSAyTQSGGILXWIPPSAQIHGYILIYQFPDGTyKEMQLG
REDQRFALQGLEQGAXYPySLyAFKGGRRSRNVSTTLSXyGARFPHPSDCSaVQQNSNAASGLYXXYL
HGDASRPLQVYCDMETDGGG¾IVFQRRNTGQLDFFKRWRSYV¾GFGDPMKEFWLGLDKLHNLTTGTPA
RYFVRVDLQXANE SAYAIYDFFQVASSKERYKX TVGKYRGTAGDALTYHNGWKFTTFDRDNDIALSNC
ALTHHGGW YKNCHXANPNGRYGEXKHSEGVNWEPWKGHEFSIPYyELKIRPHGYSREPVLGRKKRTL
RGRXRXF

>SEQ ID NO: 64
MAALIRDPQFQKLQQWYREHRSELNLRRLFDANKDRFNHFSLI^ LNTNHGHILVDYSKNLVTEDVMRML
VDLAKSRGVEAARERMFNGEKINYIEGRAyLHVALRNRSNXPIIA'DGK^^ VMPEVNKVLDKMKSFCQRV
RSGDWKGYIGKXIIDyiNIGIGGSDLGPLMyiEALKPYSSGGPRyWYVSNIDGIHIAKXLAQLNPESS
LFIIASKTFTTQEXITNAEXAKEWFLQAAKDPSAVAKHFV ALSTNIXKVKEFG IDPQNMF EFWDWVGG
RYSLWSAIGLSIALHVGF DNFE QLLSGAH WMDQ HFRXTP LEKNAPVL LALLGIWYINC.FGCEX HAML P
YDQY LHRFAAYFQQGDMESNGKYITKSGXRVDHQTGPIVWGEPGTNGQHAFYQLIHQGTKMIPCDFLI
PVQTQHP I^KGLHHKILLANFLAQTEALMRGKSXEEAR^ELQAAGKBPEDLERLLPHKVFEGNRPTNS
iyFXKLXPFMLGALyAMYEHKIFVQGXIWDINSFDQWGyELGKQLAimiEPELDGSAQVXSHDASING.
LXNFIKQQREARVQ

>SEQ ID NO: 65
MILQQPLQRGPQGGA QRLPRAALG VTWGLDAS;SPLRGAVPM STKRRLEEE QEPLRKQF LSEENMATHF
SQLSLHNDHPYC-SPPMIFSPALPPLRSPCSELLLWRYPGSLIPEALRLLRLGDIPSPPYPAIPAGDIM
EL

>SEQ ID NO: 66

MTLLPGDNSDYDYSALSCTSDASFHPAFLPQRQAIKGAFYRRAQRLRPQDEPRQGCQPEDRRRRIIIN
VGGIKYSLPWTTLDEFPLTRLGQLKACTNFDDILNVCDDYDVTCNEFFFDRNPGAFGTILTFLRAGKL
RLLREMCAiSFQEELLYWGIAEDHLDGCCKRRYLQKIEEFAEMy^ REEEDDALDSEGRDSEGPAEGEG
RLGRCYRRJRDMVERFHSGLPGKVFACLSVLFVTyTAVNLSVSTLPSLREEEEQGHCSQMCHNVFIVE
SVCVGWFSLEFLLRLIQiPSKFfFLRSPLTLIDLVAILPYYITLLVDGAAAGRRKPGAGNSYLDKVGL
VLRVLRALRILYVM¾R-LARHSL.GLQTL¾LTARRCTREFG.LLLLFLCVA.IALFAPLLYVIE-NEMA.DSPEF
TSIPACYWWAVITMTTVGYGDMVPRSTPGQVVALSSILSGILLMAFPVTSIFHTFSRSYLELKQEQER
VMFRRAQFLTKTKSQLSy8QDSDILFGS.ASSDTRDNN

>SEQ ID NO: 67
MS8SKKVTLSVLSEEQSEGVGARVRRSIGEPELKNLDPFLLFDEFKGGRP GGFP DHPHRGFE TVSYLL
EGGSMAHEDFCGHTGKMNiPGDLQWMiAGRGILHAEMPCSEEPAHGLQLWVNLRSSEKMVEPQYQELKS
EEIPKPSKDGyTVAVISGEALGIKSKWIRTPTLYLDFKLDPGAKHSQPIPKGWTSFIYTISGDVYIG
PDLmQQKIEPHHTAyLGEGDSVQVENKDPKRSHFVLIAGEPLREPVIQHGPFVMNTNEEISQA ILDFR
NAKNGFERAKT WKSKIGN

>SEQ ID NO: 68
MSLQWIAVATFLYAEWVVLLLGIPFIS:PKRWQKIFKSRLV ELLVSYGNTFFVVLIVILVLLVIDAVR
EIRKYDDyTEKVNLQNNPGAMEEFHMKLFRAQRNLYIAGFSLLLSFLLRRLVTLISQQATLLASNEAF
KKQAESASEAAKKYMEENDQLKKGAAVDGGKLDVGNAEVKLEEENRSLKADL QKLKDELASTKQKLEK
AENQVLAMRKQSEGLTKFYDRLLEEHAKLQAAVDGPMDKKEE

>SEQ ID NO: 69
MDEEEDNLSLLTALLEENESALDCNgEENNFLTRENGEPDAFpELFDADGDGESyTEEADDGETGETR
DEKENLATLFGDMEDLIDEEEVPASQSXBNPA ?LPAPAPRREK^ EELQEELRNLQEQMKALQEQLKVT
TIKQTA£3PAT!.LQKSPVEKSPRPPLKERRVQRIQESTCFSAELDVPALPRTKRVARTPI5ASPPDPKSSS
SRMI SAPSQPLQTIS RNKP SGITRGQ.IVGIPGSSGETIQPI CVEAF SGLRL RRP RVS STEMNKKMT GR
KLIRLSQIKEKMAREKLEEIDSVIFGVILKKVTPQSVNSGKTFSIWKLNDLRDLIQCVSLFLFGEVHK
ALWKTEQGTVVGILNIANPMKPKDGSEEVCLSIDHPQKVLIMGEALDLGTCKAKKKNGEPCTQTVNLRD
CEYCQYH¥QAQYKKLSAKRADLQSTFSGGRIPKKFARRGTS:LKERLCQDGFYYGGV SSASYAASIAAA
VAPKKKIQTTLSNIVM¾ GTNLIIQETRQKLGIPQKSL8CSEEFKELMDLPTCGARNLKQHLAKATASG
IMGSPKPAIKSISASALLKQQKQRMLEMRRRKSEEIQKRFLQSSSEVESPAVPSS:SRQPPAQPPRIGS
EFPRLEGAPATMTPKLGRGyLEGDDVLFYDESPPPRPKLSALAEAKKLAAITKLRAKGQVLTKTNPNS
IKKKQKDPQDILEVKERVEKNTMFSSQAEDELEPARKKRREQLAYLESEEFQKILKAKSKHTGILKEA
FAIiMQERYFEPLVKKEQMEEKMRNIREVKCRVVTCKTCAYTHFKLLETCVSEQHEYHWHDGVKRFFKC
PCGNRSISLDRLPNRHCSNCGLYKWERDGMLKEKTGPKIGGE TLLPRGEE HAKF LNSLK

>SEQ ID NO: 70
MKDYDELLKYYELHETIGTGGFAKV¾ LACHILTGEMVAIKlMDKNJILGSDLPRIKTEIEALKNLRHQH
ICQLYHVLEIANKIF>WLEYepGGELFDYIISQDRLSEEETRvVFRQIVSAVAYVHS QGYAHRDLKPE
NLLFDEYHKLKLIDFGLCAKPKGNKDYHLQTCCGSLAYAAPELIQGKSYLGSEADVWSMGILLYVLMC
GFLPFDDDNVMALYKKIMRGKYDVPKWLSPaSILLLQQMLQVDPKKRISMKNLLNHPWIMQDYNYpyE
WQSKNPFJHLDDCVTELSVHHRNNRQTMEDLISLWQYDFLIATYLLLLAKKARGKPVRLRLSSFSCG
QASATPFTDIKSNNWSLEDVTASDKNIYVAGLIDYDWCEDDLSIGAATPRTSQFTKYWTESNGVESKSL
TPALCRTPMIKLKNKENVYTPKSAVKNEEYFMFPEPKTPyNKNQHKREIL TTPNRYTTPSKARNQCLK
ETPIKIPVNSTGTDHLMrGVISPERRCRSvELDLNQA HMEETPKRKGAKVFGSLERGLDKVITVLTRS
KRKGSARDGPRRLKLHYNVTTrRLWFDQLLbJEIMSILPKKHVDFVQKGYTLKCQTQSDFGKVTMQFE
LEVCQLQKPDVVG IRRQRL KGD AWVYKRL VEDILSS.CKV

>SEQ ID NO: 71
MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRW CAVQGQVDEKTFLHYDCGN
KTVTPVSPLGKKLSVTTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLTLQARMSCEQKAEGHSS
GSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAMSFHYFSMGDCIGWLEDFLMGMDiT
LEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPeFILPGI

>SEQ ID NO: 72
MSAESGPGIRLRNLPVMGDGLETSQMSTIQAQAQPQPANAASTNPPPPETSNPNKPKRQTNQLQYLLR
WLKTLWKHQFAWPFQQPVDAVKLNLPDYYKIIKTPMDMGTIKKRLENNYY¾NAQECIQDFNIMFINC
YIYNKPGDDIVLtfeEALEKLFLQKINBLPTEETEIMIVQAKGRGRGRKETGTAKPGYS TVPNTTQAST
PPQTQTPi2PNPPPVQATPHPFPAVTPDLIVQTpyMIVVPPQPLQTPPPVPPQPQPPPAPAPQ PVQSHP
PIIAATPQPVKTKKGVKRK ADTTTPTTIDPI.HEPPSLPPEPKTTKLGQRRES SRPVKPPKKDVPDSQQ

HPAPEKS SKVSEQLKCGSGILKEMFAKKHAAYAWPFYKPVDVEALGLHDYCDIIKHPMDMSTIKSKLE
AREYRDAQEFGADVRLMFSNC¾ YNPPDHEVVAMARKLQDVFEMRFAKMPDEPEEPVVAVSSPAVPPP
TKVVAPP SSSDSSSDSSSDSDSSTDDSEEERAQRLAELQEQLKAVHEQLAALSQPQQNKPKKKEKDKK
EKKKEKHKRKEEVEENKKSKAKEPPPKKTKKNNSSNSNVSKKEPAPMKSKPPPTYESEEEDKCKPMSY
EEKRQLSLDINKLPGEKLGRVVHIIQSREPSLKNSNPDEIEIDFETLKPSTLRELERYVTSCLRKKRK
PQAEKVDVIAGSSKMKGFSSSESESSSESSSSDSEDSETEMAPKSKKKGHPGREQKKHHHHHHQQMQQ
APAPVPQQPFPPPPQQPFPPPPPQQQQQPPPPPPPPSMPQQAAPAMKSSPPPFIATQVPVLEPQLPGSV
FDPLGHFTQPxlaHLPQPELPPHLPQPPEaSTPPHLNQHAVVSPPALHNALPQQPSRPSHRAAALPPKP
ARPPAVSPALTQTPLLPQPPMAQPPQVLLEDEEPPAPPLTSMQMQLYLQQLQKVQPPTPLLPSVKVQS
QPPPPLFPPPHPSVQQQI¾ QPPPPPPPQPQPPPQQQHQPPPRPVHLQPMQFSTHIQQPPPPQGQQPP
HPPPGQOPPPPQPAKPQ QVIQHHHSPRHHKSDPYSTGHLREAPSPLMIHSPQMSQFQSLTHQSPPQQN
VQPKKQELRAASVVQPQPLVVVKEEKIHSPIIRSEPFSPSLRPEPPKHPESIKAPVHLPQRPEMKPVD
VGRPVIRPPEGNAPPPGAPDRDKQKG^ PKTPVAPKKDLKIKNMGSWASLVQKHPTTPSSTAKSSSDSF
EQFRRAARFKEEREKALKAQAEHAEKEKERLRgEPimSREDE DALEQARRAHEEARRRQEQQQQQRQE
QQQQQQQQAAAVAAAATPQAQSS¾PQSMLDQQRELARKREQERRRREAMAATIDMNFQSDLLSIFEEN
LF

>SEQ ID NO: 73
ITCAERLGQFMTLALVLAT FDPARGTDATNFFEGP QDRSSQQKGRLSLQNTAEIQHCLVNAGDVGCGVF
ECFENNSCEIRGLHGICHTFLHNAGKFDAQGKSFIKDALKCKAHALRHRFGCISRKCPAIREMVSQLQ
RECYLKHDLCAAAQENIRVIVEMIHFKDLLLHEPYVDLVNLLLTCGEEVKEAITHSVQVQCEQNWG3SL
CSILSFCTSAIQKPPTAPPERQPQVDRTKLSRAHHGEAGHHLPEPSSRETGRGAKGERGSKSHPNAHA
RGRVGGLGAQGPSGSSEWEDEQSEYSDIRR

>SEQ ID NO: 74
MKTSPRRPLILKRFYRLPLPVQN¾PSETSEEEPKRSPAQQESNQAEASKEVAESNSCKFPAGIKIINHP
TMPNTQVVAIPNNANIHSIITALTAKGKESGSSGPNKFILISCGGAPTQPPGLRPQTQTSYDAKRTEV
TLETLGPKPAARDVNLPRPPGALCEQKRETCADGEAAGCTINWSLSNIQWLRKMSSDGLGSRSIKQEM
EEKFENCHLEQRQVKVEEPSRPSASWQNSVSERPPYSYMAMIQFAINSTERKRMTLKDIYTWIEDHFPY
FKHIAKPGWKNSIRHNLSLHDMFVRETSANGKVSFWTIHPSANRYLTLDQVFKPLDPGSPQLPEHLES
QQKRPNPEXRRNMTIKTELPLGARRKMKPLLPRVSSYLVPIQFPVNQSLVLQPSVKVPLPLAASLMSS
ELARHSKRVRIAPKVLLAEEGIAPLSSAGPGKEEKLLFGEGFSPLLPVQTIKEEEIQPGEEMPHLARP
IKVESPPLEEWPSPAPSFKEESSHSWEDSSQSPXPRPKKSYSGLRSPXRCVSEMXVIQHRERRERSRS
RRKQHLLPPGVDEPELLFSEGPST8RWAAELPFPADSSDPASQLSYSQEVGGPFKTPIKETLPISSTP
SKSV'LPRTPESWRLTPPAKVGGLDFSPVQTSQGASDPLPDPLGLMDLS.TTPLQSAPPLESPQRLLSSE
PLDDI,ISVPFGNSSPSDIDVPKP G3PEP QVSGLAANRS LTEGLVLDTMNDSLSKILLDISFPGLDEDP L
GPDNINWSQFIPE LQ

>SEQ ID NO: 75
MAMDSSLQARLFPGLAIKIQRSNGLIH3ANVRTVNLEKSCVSVEWAEGGATKGKEIDFDDVAAINPEL
LQLLPLHPKDNLPLQENVTIQKQKRRSVNSKIPAPKESLRSRSTRMSTVSELRITAQENDMEVELPAA
ANSRKQF SVPPAPTRPSCPAVAE IPLRMVSEEMEEQVH.SIRGSSSANPVNS VRRKSC LVKEVEKMKNK
REEKKAQNSEMRMKRAQEYDSSFPNWEFARMIKEFRATLECHPLTMTDPIEEHRICVCVRKRPLIKQE
LARKEIDVI SlPSKCLLLVHEPKLKVDITPGLENQAFGFDFAFDETASNEVVYRFTARPLVQTIFEGG
KATCFAYGQTGSGKTHTMGGDLSGKAQNASKGIYAMASRDVFLLKNQPCYRKLGLEVYVTFFEIYNGK
LFDI,LNKKAKLRVLEDGKQQVQVVGLQEHLVNSADDVIKMIDMGSACRTS GQTFANSNSSRSHACFQI
ILRAKGRMHGKFSL\.¾LAGNERGADTSSADRQTRMEGAEINKSLLALKECIRALGQNKAHTPFRESKL
TQVLRDSFIGEN SRTCMI ATI SPGISSCEY TLNTLRYADRVKE L3PHSGPSGEQ LIQMETEEME ACSN
GALIPGNLSKEEEELSSQMSSFNEAMTQIRELEEKAMEELKEIIQQGPDWLELSEMTEQPDYDLETFV
NKAESALAQQAKHFSALRDVIKALRLAMQLEEQASRQISSKKRPQ

>SEQ ID NO: 76
TPPSSLLGSAMPASXSAAALQEALENAGRLXDRQLQEDRMYPDLSELLMVSAPNISPTVSGMSDMDYPLQ
GPGLLSVPNLPEISSIRRVPIPPELVEQFGHMQCNCMMGVFPPISRAWLTIDSDIFMWNYEDGGDLAY
FDGIISEIILAVGLVKPKAGIFQPHVRHILLVLATPVDIVILGLSYANILQTGSGVLNDSLSGGMQLLPDP
LYSLPIDNXYLLIIXSXDNGRIFLAGKQ CLYEVAYQAEAGWFSQRCRKINHSKSSLSFLVPSLLQFX
FSEDDPILQIAIDNSRNrLYTRSEKGVTQVYDLGQDGQGMSRVASVSQNAIVSAAGNIARTIDRSVFK
PIVQIAVIENSESLDCQLLAVTHAGVRLYFSTCPFRQPXARPMTLTLVHVRLPPGFSASSTVEKPSKV
HRALYSKGLLLMAASENEDNDILWCVNHDTFPFOKPMHETQMrAGVDGHSWALSA IDELKVDKIITPL
NKDHIPITDSPVVVQQHMLPPKKFVLLSAQQGSLMFHKLRPVDQX,RHLLVSNVGGDGEEIERFFKLHQE
DOACATCLILACSTAACDREVSAWATRAFFRYGGEAQimFPTTLPPPSNVGPILGSPVYSSSPVPSGS

PYPNP SFLGTP SHGIQPPAMSTPVCALGNPATQAINMSCVXGPEI VYSGKHNGlCIYFSRaMGNIWPA
SLVVERIFKSlGNREIIAIESSVPCQLLESVLQEL^ LQEFLDRNSQFAGGPLGNPNTTAKVQQRLIGF
MRPENGNPQQMQQELQRKFHEAQLSEKISLQAIQQLVRKSYQALALWKLLCEHQFTIIVAELQKELQE
QLKITTFKDLVIRDKELTGALIASLINCYIRDNAAVDGISLHLQDICPLLYSTDDAICSKANELLQRS
RQVQNKTEKERMLRESLKEYQKISNQVDLSNVCAQYRQVRFYEGVVELSLTAAEKKDPQGLGLHFYKH
GEPEEDIVGLQAFQERLNSYKCITDTLQELVNQSKAAPQSPSVPKKPGPPVLSSDPNMLSNEEAGHHF
EQMLKLSQRSKDELFSIALYNWLIQVDLADKLLQVASPFLEPHLVRMAKVDQNRVRYMDLLWRYYEKN
RSFSNAARVLSRLADMHSIEISL3QRLEYIARA ILSAKSSXA ISSIAADGEF LHELEEKMEVARIQLQ
IQEILQRQYSHHSSYQPAVSQLPSELMPIIK^ YGEFADPFKLAECKLAIIHCAGYSDPILVQTLWQDI
IEKELSPSVTLSSSPRMHALSLKIVLLGKTYAGTPRFFPLDFIVQFLEQQVCTLNWDVGFVIQTMNEI
GWLPRLLEVYPQLFKSRPPFWNRMK^ ,HLLDCIHVLLIRYVENPSQVLNCERRRFTNLCLDAVCGY
LVELQSMSS¾VAVQA ITGNFKSLQAKLERLH.

>SEQ ID NO:7?
MSQyKSSYSYDAPSDFINFSSLDDEGDTQNIDSWFEEK¾NLENKLLGKNGTGGLFQGKTPLRKANLQQ
AIVTPLKPVDNTYYKEAEKENLVEQSIPSNACSSŁEVEAAISRKTPAQPQRRSLRLSAQKDLEQKEKH
HVKMKAKRCATPVIIDEI.LPSKKMKVSNNKKKPEEEGSAHQDTAEKNA3SPEKAKGRHTVPCMPPAKQ
KFLKSTEEQELEKSMKMQQEVVEMRKKNEEFKKLALAGIGQPVKKSVSQVTKSVPFHFRTPERIKQHP
KNQEEYKEVNFXSELRKHP38PARVIKGCIIVKP FNLSQGKKRTFDETVSTYVPLAQQVEDFHKRTPN
RYHLRSKKDDINLLPSKSSVTKICRDPQTPVLQTKHRARAVTCKSTAELEAEELEKLQQYKFKARELD
PRILEGGPIlPKKPPVKPPTEPIGFPLEIEKRIQERESKKKTEPEHFEFHSRPCPTKILEDyVGVPEK
KVLPIIVPKSPAFALKHRIR>iPTKEPEEEPEPVVI^ AQPVPHYGVPFKPQIPEARTVEICPFSFDSRD
KERQLQKEKKIKELQKGEVPKFKALPLPHFDTINLPEKiVKNVTQIEPFCLETIRRGALKAQIWKHQL
EEELRQQKEAACFKARPNTVI SQEPFVPKKEKKSVAFGLSGSLVQEPFQLATEKRAKERQELEKRMAE
VEAQKAQQLEEARLQEEEQKKEELARL RRE LVHKANPIRKYGGLEIK3SDQ.PLXVPVSPKFSIRFHC

>SEQ IP NO:78
MESEPLSGRELXIPSIMNKVRPIKNKFKNEPLTPELSLNKISAPTTPNSGTVNQIMMMANNPEPWLSL
LLKLEKNSVPLSDALLNKLIGRYSQAIEALPPDKYGQNESFARIQ-VRFAELKAIQEPDDARDYFQMAR:
ANGKKFAFVHISFAQFELSQGNVIKKSKQLLQKAyERGAVPLEMLEIALRNLNLQKKQLLSEEEKKNLS
ASTVLTAQESFSGSLGHLQNR¾NSCPSRGQTTKARFLYGENMPPQDAEIGYRNSLRQTNKTKQSCPFG
RVPVNLLL3SPDCPVKTPDSVVP CFMKRQ TSRSEC RPLW PGSKPSGNDSCE L.RMLKSVQNSHFKEPLV
SDEKSSELIITDSIXLKNKTESSLLAKLEETKEYQEPEVPESNQKQWQSKRKSECINQNPAASSNHWQ
IPELARKVNIEQKH TTFEQPVFSVS.KQSPPISX3KWFPPKSICKTPSSNJILPDYMSGFRTP VVKNPFP
PACQLSTPYGQPACFQQQQHQILATPLQNLQVLASSSANECISVKGRIYSFLKQIGSGGSSKVFQVLN
EKKQIYSIKYVNILEEADNQTLDSYRNEIAYLNKLQQHSDKIIRLYDYEITDQYIYMVMECGNIDLNSW
LKKKKSIDPWERKSYWKNMLEAVHTIHQHGIVHSDLKPANFLIVDGMLKLIDFGIANQMQPDTTSVV¾
PSQVGIVNYMPPEA.IK.PMS SSRENGKS KSKISPKS PVW.SLGC ILYYMTYGKTPFQQI INQISKLHAII
DPNHEIEFPDIPEKDLQDVLKCCLKRDPKQRISIPELLAHPYVQIQTHPVNQMAKGTTEEMKYVLGQL
VGLN SPSSILKAAKTLYE HYSGGESHN33SS.KTFERKRGKK

>SEQ IP NO:79
HSSEPPPPPQPPTaQftSVGLLOXPRSRERSPSPLRGNWPSPLPTRRTRIFSATVRASQGPVYKGVCK
CFCRSKGHGFITF&DGGPDIFLHISDVEGEYVIVEGDEVTYKMCSIPPKNEKLQfVBW ITHL¾PGXK
HEIW8GHVISS

>SEQ IP NO: 8O
MGPRRRSRKPEAPRRRSPSPXPXPGPSRRGPSLGASSHOHSRRRQGWLKEIRKLOKSIHLLIRKLPFS
RLAREICVKFTRGVPFNWQAQALLALQEAAEAFLVHLFEPAYLLXLH AGRVTLFPKDVQLARRIRGLE
EGLG

>SEQ IP NO:81
MDETVAEFIKRTILKIPMNELTTILKAWDFLSENQLQTVNFRQRKESVVQHLIHLCEEKRASISDAAL
LDIIYMQFHQHQKVWEVFQMSKGPGEDVDLFDMKQFKNSFKKILQRALKNVTVSFRETEENAVWIRIA
WGTQYTKPNQYKPTYVVYYSQTPYAFTSSSMLRRNTPLLGQALTIASKHHQIVKMDLRSRYLDSLKAI
VFKQYNQTFETHNSTTPLQERSLGLDIl^SRriHENIVEKERVQRIT-QETFGDYPQPQJ-EFAQYKLE
TKFKSGLNGS ILAEREEP LRCLIEFSSPHLLEALKSLAPAGIAPAP LSPLLXCIPNERMN YFKIRPK

>SEQ IP NO: 82
MGIQGLLQFIKEASFPIHVRKYKGQVVAVPXYCWLHKGAIACAEKLAKGEPTPRYVGFCMKFVNMLLS
HGIKPILVFPGC XLPSKKEVERSRRE RRQANLLKGKQLL.REGKVSEAREC FTRSIN1THAMAHKVI KA

ARSQGVDCLVAPYEADAQLAYLNKAGIVQAIITEDSDLLAFGCKKVILKMDQFGNGLEIDQARLGMCR
QLGDVFTEEKFRYMCXL¾ CDYLSSLRGIGLAKACKVLRLANNPDIVKVIKKIGHYLKMNITVPEDYI
NGFIRANNTFLYQLVFDPIKRKLIPLNAYEDDVDPETLSYAGQYVDDSIALQIALGNKDINTFEQIDD
YNPDTAMPAHSRSHSWDDKTGQKSANVSSIWHRNYSPRPESGIVSDAPQLKENPSTVGVERVISTKGL
NLPRKSSI VKRPRSAELSEDDLLSQYSLSFTKKTKKNSSEGNKSLSFSEVFVPDLVNGPTNKKSVSTP
PRTRNKFATFLQRKNEESGAVVVT GTRSRFFCSSDSTDC¥SNKVSIQPLDETAVTDKENNLHESEYGD
QEGKRLVDTDVARNSSDDIPINNHlPGDHIPDKATVFTDEESYSFESSKFTRTISPPTLGTLRSCFSWS
GGLGDFSRTPSPSPBTALQQFRRKSDSPTSLPENNMSDVSQLKSEESSDDESHPLREEACSSQSQESG
EFSLQSSNASKLSQCSSKDSDSEE gDCNIKLLDSQSDQTSKLRL SHFSKKD TPLRNKVP GLYKS SSAD
SLSiTKTKPLGPARASGLSKKPASIQKRKHHNAENKPGLQIKLNELWKNFGFKKDSEKLPPCKKPLSP
VRDNIQL.TPEAEED IFNKPECGRVQRAIF©

>SEQ I0 NO:83
MAVNVY STSVTSDNLSRHDHLAWINESLQLNLIKIEQLCSGAAYCQFMDMLFPG SIALKKVKFQAKLE
HEYIQNFKILQAGFKRMGVDKIIPVDKLVKGKFQDNFEFVQWFKKFFDANYDGKDYDPVAARQGQETA
VAPSLVAPALNKPKKPLTSSSAAPQRPISTQRTAAAPKAGPGVVRKNPGVGNGDDEAAELMQQVNVLK
LTVEDLEKERDFYFGKLRNI.ELICQENEGEWDPVL/QRIVDILYATDEGFVIPDEGGP.Q EEQEEY

>SEQ ID MO:84
MEPAPARS PRP QQDPARPQEPTMPPP EXP SEGRQP SP SP SP TE RAP A SEEE FQFLRC QQCQAEAKGPK
LLPCLHTLCSGCLF^SGMQCPICQAPWPLGADTPALDNWFESL QRRLSVYRQIVDAQAVCTRCKESA
DFWCFECEQLLCAKCFEAHQWFLKHEARPLAELPNQSVREFLDGTRKTNNIFCSNPNHRTPTLTSIYC
RGCSKPLCCSC¾LLDSSHSELKCDISAEIQQRQEELDAMTQALQEQDSAFGAVHAQMHAAV¾ QLGRAR
AETEELI RERVRQWAHVRAQERELLE,AVDARYQRDYEEMASRLGRLDAV LQRIRTGSALVQRMKCYA
SDQEVLDMHGFLRQALCRLRQEEPQSLQAAVRTDGFDEFKVRL/QDLSSCITQGKDAAVSKKA SPEAAS
TPRDPIDVDLPEEAERVKAQVQALGLAEAQPMAVVQSVPGAHPVPVYAFSIKGPSYGEDVSNTTXAQK
RKC SQIQCPRKVIKME SEEGKEARL ARSSPEQPRP STSKAVSPPHL DGPP SPRSPVIGSEVFLPNSNH
VAS GAGEAEE RVVVISSSEDS DAENSSSREL DDSSSESS DLQ.LEGPSTLRVLDE NLADPQAEDRPLVF
FDLKlDNETQ;ElSQLAAWRESKER¾VlQPEAFFSiY SKAVSLEVGLQHFLSFLSSMRRPILACYKLW
GPGLPNFFRALEDTNRLWEFQEAISGFLAALPLIRERVPGASSFKLKSXAQ TYLARNMSERSAMAAVL
AMRriLCRLLEA'SPGPi2LAQHVYPFSSLQCFASLQPLVQAA\'%PRAEARLLALHNV\SFMELLSAHRRDR
QGGLKKYSRyLSLGTTTLPPAQPAFNLQALGTYFEGLLEGP ALARAEGVSTPLAGRGLAERASQQS

>SEQ ID NO: 85
MEA SPASG PRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYG
RHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFS¾GCAGEVRAFLQENTWVRLRIFAARIYDYDPLY
KEALQMLRDAGAQySIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGN

>SEQ ID NO: 86
MPHSSDSSDSSFSRS PPPGKQDSSDDVRRVQRREKNRIAAQKS RQRQIQKADTL HLESEDLEEQNAAL
RKEIKQLTEELKYFTSVLNSHEPLCSVLAA STPSPPEVVYSAHAFHQPHVSSPRFQP

>SEQ ID NO; 87
MLFLLLPLLAVLPGDGNApGLKEPLSFHVTWIASFYNHSWKQNLVSGWLSDLQTHTWDSNSSTIVFLC
PWSR^FSNEEWKELEXLFRIRTIRSFE^IRRYJffiELQFEYPFEIQVTGGCELIISGKVSGSFLQLAyQ
GSDFVSFQNNSWLPYPVAGNMAKHFCKVL^ IQHENDITHNLLSDTCPRFILGLLDAGKAHLQRQVKP
EAWLSHGPSPGPGHLQLVCHVSGFYPKPVW^MWMRGEQEQQGIQRGDILPSADGTWYLRATLEVAAGE
AADLSCRVKHSSLEGQDIVLYWEHHSSVGFIILAVIVPLLLLIGLALWFRKRCFC

>SEQ ID NO: 88
MLLLPFGJLLAVLFPGGNSEHAFQGPISFHVIQTSSFTNS^ AQTQGSGWLDDLQIHGWDSDSGTAIFL
KPWSKGNFSDKEVAELEEIFRVYIFGFAREVQDFAGDFQMKYPFEIQGIAGGELHSGGAIVSFLRGAL
GGLDF LSVKNAS CVPSPEGGSRAQKF GAL IIQYQGIMETVRILLYETCPRYLLGVLNAGKADL QR.QVK
PEAWLSSGPSPGPGRLQLVCHVSGFYPKPVWVMWMRGEQEQQGTQLGDILPNANWIWYLRATLDVADG
EAAGL SCRVKH SSLEGQD I1LYWRNPTSIGSIVLAIIVPSLLLLLCLALWYMRRRS YQNIP

>SEQ ID NO: 89
MLFLQFLLLALLLPGGDNADASQEHVSFHVIQIFSFVNQSWARGQGSGWLDELQIHGWDSESGrilFL
HlWSK.GNFSNEELSDLELLFR^YLFGLTREjQDHA&QDYSKY'PFEyQVKAGCE LHSGKSPEGFFQ\¾F
NGLDLLSFQNTTWVPSPGCGSLAQSVGHLLNHQYEGVTETVYNLIRSTCPRFLLGLLDAGKMYVHRQV

RPEAWLSSRPSLGSGQLLLVCHASGFYPKPVWVTWMRNEQEQLGTKHGDILPNADGTWYLQVILEVAS
EEPAGLSCRVM SSLGGQDIILYWGHHFSMNWIALVVIVPLVILIVLVLWFKKHCSYQDIL

>SEQ ID NO: 90
MLLLFLLFEGLCCPGENTAAPQftLQSYHLAAEEQLSFRMLQTSSFANHSWAHSEGS.GWLGDLQTHGWD
TVLGTIRFLKPWSHGNFSKQELKNLQSLFQLYFHSFIQIVQASAGQFQLEYPFEIQILAGCRMNAPQI
FLNMAYOGSDF.LSFQGISWEPSPGAGIRAQNICKVLNRYLDIKEILQSLLGHTCPRFLAGLMEAGESE
LKRKVKPEAWLSCGPSPGPGRLQLVCHVSGFYPKPVWVMWMRGEQEQRGTQRGDVLPNADEIWYLRAT
LDVAAGEAAGLSCRVKKSSLGGHDLIIHWGGYSIFLILICLTVIVTLVILVVVDSRLKKQSSNKNILS
PHTPSPVTLMGANTQDTKNSRHQFCLAQ VSWIKNRVLKKWKTRLNQLW

>SEQ ID NO: 91
MGSNLSPeLCLMPFILGLLSGCVTITPWSLARPQGSCSLEGVEIKGGSFRLLQEGQALEYVGPSGFYP
YPVQTRTCRSTGSWSILKTQDQKTVRKAECRAIHCPRPHDFENGEYWPRSPYYNVSDEISFHCYDGYT
LRGSANRTCQVNGRWSGQTAICDNGAQYCSWPGTPIGTRKVGSQYRLEDSVTYBC&RGLTLRGSQRRT
CQEGGSWSGTEPSC.QDSFMYD IPQEVAEAF LSSLTETIEGVDAEDG.HGPGE QQKRKIVLDPSGSMNIY
LVLDGSDSTGASNFTGAKKCLVNLIEKVASYGVKPRYGLVTYATYPKIWVKVSEADSSNADWVTKQLN
EINYEDHKLKSGTNTKKALQAVYSmSWPDDVPPEGWNRTRHyilLMTDGLHNMGGDPITVIDEIRDL
LYIGKDRKNFREDYLDVYVFGVGPL VNQVNINALASKKDNEQHVFKyKDMENLEDVF YQMIDESQSLS
LCGMVWE.HRKGTDYHKQPWQA.KIS VIRPSKGHESCMGAVVSEYFVLTAAHCFTVDDKEHSIKVSVGGE
KRDLETEWLFHPNYNIMGKKEAGIPEFYDYDVALIKLKKiKLKYGQTIRPICI ,PCTEGTTRALRLPPT
TTCQQQI<EELLPAQDIKALFVSEEEKKLTRKEVYIKNGDKKG.SG.ERDA/jYAPGYDKVK.DISEWTPRF
LCTGGVSPYADPNICRGDSGGPLIVHKRSRFIQVGVISWGVVDVCKNQERQKQVPAHAilDFHTNLFQV
LPWLKEKLQDEDLGFL

>SEQ ID NO: 92
MEGISIYTSDNYTEEMGSGDYDSMKEPCFREENANFNKIFLPTIYSIIFLTGIVGNGLVILVMGYQKK
LRSMTDKYRLHL SVADLLFVITLPFWAVDAVANWYFGNFLCKAVHVIYTVNLYSSVLILAF ISLDRYL
AIVHAT.NSQRPRKLLAEKVVYVGVWI PALLITIPDFIFANVSE ADDRY ICDRFYPNDLWVVVFQFQHl
MVGLILPGIVILJCYC1IISKiSHSKGHQKRKAL KTTVILILAFFACWLP YYIGTsIOSFILLE 11KQ
GCEFENTVHKWISTTEALAFFHCCLNPILYAFLGAKFKTSAQHALTS:VSRGSSLKILSKGKRGGHS.SV
STESESSSFHSS

>SEQ ID NO: 93
MSEQSICQAl^SVlrn7YDDTSKKWVPIKPGQQGFSRINIYHNTASNTFRVVGVKLQDQQVVINYSTVKG
LKYNQATPTFHQWRDAi^QVYGLNFASKEEATTFSNAMLFALNIMNSQEGGPSSQRQVQNGPSPDEMDI
QRRQVMEQHQQQRQESLERRTSATGPILPPGHPSSAASAPVSCSGPPPPPPPPVPPPPTGATPPPPPP
LPAGGAQGSSHDESSMSGLAAAIAGAKLRRVQRPEDASGGSSPSGTSKSDANRASSGGGGGGLMEEMN
KLLAKRRKAASQSDKPAEKKEDESQMEDPSTSPSPGTSAASQPPNSSEAGRKPWERSNSVEKPVSSIL
SRTP3VAKSPEAK.SPLQSQPHSRMKPAGSW DMALDAFDLDRMKQEILEEVVRELHKVKEEIIDAIRQ
ELSGISTT

>SEQ ID NO: 94
WAAAAGEEEEEEEAARE .SAARPAAGPALWRLPEELLLLICSYLDMRA.LGRLAQVCRWLRRFTSCDLLW
RRIARASLNSGFTRLGTDLMTSVPVKERVKvSQNWRLGRCREGILLKWRCSQMPWMQLEDDSLYTSQA
NFTLAYQFRPDGASLNRRPLGVFAGHDEDVCHFVLANSHIVSAGGDGKIGIHKIHSTFTVKYSAHEQE
VNCVDCKGGIIVSGSRDRIAKVWPLASGRLGQCLHTIQTEDRVWSIAISFLLSSFVTGTACCGHFSPL
RIWDLNSGQLMTHLGSDFPPGAGVLDVMYE SPFTLLSCGYDTYVRYWDLRTSVRKCVMEWEEPHDSTL
YCLQTDGNHLLATGS SYYGVVRLWDRRQRACLHAFPLTSTPLSSPVYCLRLTTKHLYAALSYNLHVLD
FQNP

>SEQ ID NO: 95
MLVMAPRTVLLLLSAALALTETWAGSHSMRyFYTSVSRPGRGEPRFISVGYVDDT^ FVRFDSDAASPR
EEPRAPWIEQ .EGPEYWDRNTQI.YKAQAQTDRESLRNLRGYYNQSEAGS;HTLQSNIYGCDVGPDGRLLRG
HDQYAYDGKDYIALNEDLRSWTAADTAAQITQRKWEAAREAEQRRAY'LEGECVFWLRRYLENGKDKLE
RADPPKTHVTHHPTSDHEA-TLRCWALGFYPAEITLTWQRDGEDQTQDTELVETRPAGDRTFQKWAAVV
WSGEEQRYTCHVQHEGLPKPLTLRWEPSSQSTVPIVGIVAGLAVLAVVVIGAVVAAVMCRRKSSGGK
GGSYSQAACSDSAQGSDVSLTA

>SEQ ID NO: 96

MKHLWFFLLL¾ APRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSISGYYWSWIRQPAGKGLEWIG
RIYISGSXNYNPSLKSRVIMSVDXSK^^ QFSLKLSSVTAADTAVYYCARGRFTYFDYWGQGTLVTVSSA
S.TKGPSVFPLAPSSKSXSGGTAALGCLyRDYFPEPyX VSWNSGALTSQVHXFPAVLQ SSGLY SLSSVV
XVFSSSDGXQIY ICNVNHKPSNIKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVnGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTXSKAKGQPREPQVY'TLPPSRDELTKNQVSLTCLVKSFYPSDIAVEWESNGQPENN
YKXTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHyXTQKSLSLSPGK

>SEQ ID MO: 97
MSLMVVSMVCVGFFLLQGAWPHEGVHRKPSLLAHPGPLVKSEETVILQCWSDVRFQHFLLHREGKFKD
TLHLIGEHHDGVSKANFSIGPMMQDLAGTYRCYGSVTHSPYQLSAPSDPLDIVITGLYEKPSLSAQPG
PIVLAGESVILSCSSRSSYDMYHLSREGEAHERRFSAGPKVNGTFQADFPLGPATHGGTYRCFGSFRD
aPYEWSNSSDPLXVS¥X.GNPSNaWPSPXEPSSEXGNPRHLHVLIGISVVIILFILLLFFLLHRWCGNK
KNAyyMDQEPAGNRXWREDBDEQDPQEVIYAQ LNHCVFTQRKITRPSQRPKTPPTDIIVYTELPNAE
P

>SEQ ID NO: 98
MRLLAWLIFLAKWGGARAEPGKFWHIADLHLDPDYKVgKDPFQVCPSAGSQPVPDAGPWGDYLGDSPW
ALINSSXYAMKEIEPEPDFILWXGDDTPHyFDEKLGEAAVLEIVERLXKLIREvFPDXKy YAALGNHD
FHPKNQFPAGSNNIYNQIAELWKPWLSNESIALFKKGAFYCEKLPGPSGAGRIVVLNTNLYYTSNALT
ADMADPGQQFQWLEDVLTDASKAGDMyYIVGHVPPGFFEKIQNKAWFREGFNEKYL KVVRKHHRVIAG
QFFGHHHIDSFRMLyDDAGyX°ISAMFIXPGVIPWKTTLPGVVNGANNPAIRVFEYDRATLSLKDMVTY
FHMLSQANAQGXPR^ELEYQLXEAYGypDASAHSMHTVLDRIAGDQSXLQRYYVYW SVSYSAGVCDEA
CSMQHVCAMRQYDXDAY XXCLYASGXTPVPQLFLLLMALLGL CXLVL

>SEQ ID NO: 99
MKXLARALRLCEFGRQASSRRLyAGQGCyGPRRGCCApyQyyGPRADLPPCGACIXGRIMRPDDANVA
GNyHGGXIXKMIEEAGAIISXRHCNSQHGERCyAALARvERIDFLSPMCXGEVAHySAEIXYXSKRSV
E¾ VNyMSENILXGAKKLTNKAXLWYVFLSLKNVDKVLEVPPVVYSKQEQEEEGRKRYEAQKLERMET
KWRNGDxyQPVLNPEPNXVSYSQSSLIHLyGPSDCXLHGFXmGGVXMKLMDFA'AG IVAARHCKTNIVT
ASVDAINFHDKIRKGCVITISGRMTFTS« SMEIEVLVDADPVVDSSQKRYRAASAFFTYVSLSQEGR
SXPvPQLypEXEDERKRFEEGKGRYLQMKAKRQGHAEPQP

>3EQ ID NO: 100.
MGGDRNCGLXAGAVXGAVIAVFGGXLMPVSDLLIQKTIKKQVVLEEGTIAFKNWVKTGTEVYRQFWTF
DyQNPOEyiMNSSNXQVKQRGPYXYRyRFIAKENVXQDAEDNXVSFLQPNGAIFEPSLSVGTEADNFT
yLNLAyAAASHIYQWQFVQMILNSLXNKSKSSMFQVRILRELLWGYRDPFLSLVPYPVXXXyGLFYPY
NNXADGyYKyFNGKDNISKVAIIDXYKGKRNLSYWESRCDMINGXDAASFPPFVEKSQyLQFFSSDIC
RSI YAVFESDVNLKGl PyYRFVLPSKAFASPVENP DNYCFCTEKIISKNCTSYGVLDISKCKEGRPVY
ISLPHFLYASPDySEPIDGLNPNEEEHRIYLDIEPIXGFTLQFAKRLQVNLLVKPSEKIQVLKNLKRN
YIVPILWLNETGXIGDE KANMFRS QVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKXXK

>SEQ ID NO;101
WXVARPSVPAALPLLGELPRLLLLYLLCLPAWGpCGLPPDVPNAQPALEGRTSFPEDTVIXYKCEES
FVKIPGEKDSV'ICLKGSQWSDIEEFCNRSCEVPTRLNSASLKQPYITQNYFPVGTVVEYECRPGYRRE
PSLSPKLTCLQNLKWSTAVEFCJ^KSCPNPGEIKNGQIOVPGGILFGATISFSCNTGYKLFGSTSSFC.
LXSGSSyQWSDPLPECREIYCPAPFQXDNGIIQGERDHYGYRQSVIYACNKGFIMIGEHSIYCiyNND
EGEWSGPPPEeRGKoLXSKypPXyQKPXXyNyPIXEySPXSQKXXIKXXIPNAQAXRSXPVSRXXKHF
HEXXFNKGSGXXSGXXRLLSGHXCFXLXGLLGXLVXMGLLX

>SEQ ID NO: 102
MDLGPLIsUCEEMIILBGGFXLAEQLFHPKALAELXKSDWERVGRPIVEALREISSAAAHSQPFAWKKK
ALIIIW¾KVLQPHPVTPSDTETKWQE1LFFSVGNMIPTINHTILFELLKSLEASGbFIQLLMALPTTI
CHAELERFLEH¥TVDTSAEDVAFFLDVWWE¾KHKGHPQDPLLSQFSAMAHKYLPALDEFPHPPKRLR
SDPDACPTi^LLAMLLRGLTOI-QSRILGPGRKCCALANLADMLTVT-ALTEDDPQEVSATVYLDKLATV
ISVWNSDTQNPYHQQALAEKVKEAERDVSLTS.LAKLPSETIFVGCEFLHHLLREWGEELQAVLRSSQG
ISYDSYRLCDSLXSFSQNAXLYLNRXSLSKEDRQWSELAECVRDFLRKXSXVLKNRALEDIXASIAM
AyiQQKMDRHMEVCYIFASEKKWAFSDEWvACLGSNRALFRQPDLVLRLLEXVIDySXADRAIPESQI
RQVIHLILECYAD LSLPGKNKVLAGILRSWGRKGLSEKLLAYVEGFQEDLNTTFNQLTQSASEQGLAK
AVASVARLVIVHPEVTVKKMCSLAVVNLGTHKFLAQILTAFPALRFVEEQGPNSSATFMVSCLKETVW
MKFBTPKEEKQFLELLNCLHSPVKPQGIPVAALLEPDEVLKEFVLPFLRLDVEEVDLSLRIFIQ TLEA

NAQREEYWLQTCs PFPL LPSLCQLLDRF SKYWQLFKEKRC LSLDRKDLAIHILEL.LCEIVSANAE TFS
PDVWIKSLSWLHRKLEQLDWTVGLRLKSFFEGHFKCEVPATLFEICKLSEDEWTSQAHPGYGAGTGLL
AWMECCCVSSGISERMLSLLVVDVGNPEEVRLFSKGFLVALVQVMPWCSPQEWQRLHQLTRRLLEKQL
LHVPYSLEYIQFVPLLNLKPFAQELQLSVLFLRTFQFLCSHSCRDWLPLEGWNHVVKLLCGSLTRLLD
SVRAIQAAGPWVQGPEQDLTQEALFVYTQVFCHALHIMAMLHPEVCEPLYVLALETLTCYETLSKTNP
SVSSLLQRAHE QRFLKs IAEG IGPEE RRQTL LQKMS SF

>SEQ ID NO: 103
MAQLGKLLKEQKYDRQLRLWGDHGQEALESABVC LINATATGTEILKNLVLPGIGSFTIIDGNQVSGE
DAGNNFF LQR SSIGKNRAEAAMEFLQELN SDVSGSFVEESPENLLDNDPSFFCRFTVVVATQLPESTS
LRL ADV LWNSQ:I PLL IGRT YGLVGYHR ITIKE HPV IESHPDNALEDLRLDKFFPE.LREHEQSYDLDHM
EKKDH SHTPWIVIIAKYLAQWYSETNGRIPKTYKEKEDFRDLIRQGTLKNENGAPEDEENFEEAIKNV
NTMLNT TQIPSSIE DIFNDDRCXNITKQTPSFWILARALHEFYAKEGQSN .LPVRGTIPDMIADSGKXI
KLQNVYRERAKKDAAAVGNHVAKLLQS IGQAPE SISEKE LRL LCSNSAFLRVVRCRS LAEEYGLDTIN
KBEIISSMa PDNEIVLYLMLRAVI5KPHKQO^RYPGVSNYQVEEDIQKLKSCLTGFLi^YGLS^?KD
DYVHEFCRYG^EPHTIA^FLGGAAAQEVIKIITKQFVIFNNTYI-Y-SGM-SQTSATFQL

>SEQ ID NO: 104
MLYFSLFWAARPLQRCGQLVRM¾IRAQHSNAAQTQTGEANRGWTGQESLSDSDPEMWELLQREKDRQC
RGLELIASENF CSRAALE ALG SCI NNKY SE GYPGKR YYGGAE VVDE IELL G QRRALEAFDLDPAQWGV
W QPYSGSPANLAIVYTALIIQPHDRIMGLDLPDGGHLTHG¾ SDVKRXSATSIFFESMPYKLNPKTGLI
DYNQLAL TARLFRPRL1IAGTSAYARLI DYARMRE VCDEVKAHLLADMAHISGLVAAKVIPSPFKHAD
IVTTTTHKTLRGARSGLIFYRKGVKAyDPKTGREIPYT FEDRINFAVFPSLQGGPHNHAIAAVAVALK
QAGTPMFREYSLQVLKNARAMADA-LLE,RGY 'S7uvsGGTDKHLVLVDLRPKGLDGARAERVLELVSITAN
KNXCPG DRSAIIPGGLRLGAPALXSRQFREDDFRRVVDFIDEGVNIGLEVKSKIAKLQDFKSFLLKDS
ETSQRLANLRQRVE QFARAFPHP GFDE H

>SEQ ID NO: 105
MEGPLSVFGDRSTGETIRSQNVDXAAASIANIVKSSLGPVGLDKMLVDDIGDVTITNDGATILKLLEVE
HPAAKVLCELADLQDKEVGDGTTSWI IAAELLKNADELVKQKIHPTSVISGYRLACKEAVRYINENL
IVNTDELGRDGLINAAKTSMSSKIIGINGDFFANW VDAVLAIKYTDIRGQPRYPVNSVNILKAHGRS
QMESMLISGYALNCVVGSQGMPKRIVNAKIACLDFSLQKTKMKLGVQVVITDPEKLDQIRQRESDITK
ERIQKIL&TGANVILTXGGJDDMCLKYFVEAGAtiAVRRVLKRDLKRIAKASGATILST!LANLEGEETF
EAAMLGQAEE VVQERIGDDEL ILIKNTKARTSASIILRGANDFMCDEMERS LHDA.LCVVKRVLESKSV
VPGGGAVEAAL SIYLENYAT5MG3RE QLAlAEFARS LLVIPNTLAVNAAQDSTDLVAKLRAFHNEAQV
NPERKWLKWIGLDLSNGKPRDNRQAGVFEPTIVICvKSLKFATEAA ,ITILRlDDLrKLHPESKD DKHGS
YEDAVHSGALND

>SEQ ID ND:106
iVKQIESKTAFQEALDAAGDKLVVVDFSATWCGPCRMTKPFFHSLSEKYSNVIFLEVDVDDCQDVASE
CEVRCMPTFQFFKKGQKVGEFSGANKEKLEATINELV

>SEQ ID NO; 107
MGGAEGKAVAAAAPTELQTKGKKGDGRRRS AKDHHPGKTLPEMPAGFT STATADSRALLQAYIDGHSV
VIFSRSTCTRCTEVRRLFKSLCVPYFVLELDQTEDGRALEGTLSELAAETDLPWFVKQRKIGGHGPT
LI¾ YQEGRLQKXLKMNGPEDLPK3YDYBLIIIGGGSGGLAAAKEAAQYGKKVMVLDFVTPTPLGTRWG
LGGTC VNVGCIPRKLMHQAA LLGQALQDSRNYGWIWEE TVKHDWDRMIEAVQ.NHIGSLNWGYRVALRE
KKVVYENAYGQFIGPHRIRATNSKGKERIYSAERFLIATGERPRYLGIPGDKEYCISSDDLFSLPYCP
GKTLVVGASYVALECAGFLAGIGLDVTVMVRSlLLRGFDQDMANKIGEHMEEHGIKFIRQFVPIKVEQ
IEAGXPGRLRVVAQ STNSEEXIEGEYNXVMLAIGRDACXRKIGLEXVGVKINEKXGKIPVXDEE QINV
PYIYAlGDILEDKVELTPVAIQAGRLLAQRLYAGSTVKCDYENVPTTVFTPLEYGACGLSEEKAVEKF
GEENIEVYHSYFWPLEWTIPSRDNNKGYAKIICNTKDmR\^/GFHVLGPNAGEVTQGFAAALKCGLTK
KQLDSTiGIHPVeAEVFTTLSVTRRSGASILQAGCUG

>SEQ ID NO: 108
MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLYMVVGTLAAIIHGAGLPLM
MLVFGEMTDIFANAGNLEDLMSTD TNRSDINDTGFFMNLEEDMTRYAYYYSGIGAGVLVAAYIQVSFW
CLAAGRQiaKIRKQFFHAIMRQEIGWFDVHDVGELNTRLTDDVSRINEGlGDRIGMFFQSMATFFTGF
lVGFTRGiWKLTLVlLAI:SPVLGLS:AAVWAKTL3SFTDKEL LAYAKAGAVAEEVLAAIRTVIAFGGQKK
ELERYNKNLEEAKRIGIKKAI XANISIGAA FLLIYASYALAFWYGXXLVLSGEYSIGQVLXVFFSVLI
GAFSVGQAS PSIEAFANARGAAYE IFKIIDNKPSIDSYSKSGHRPDNIKGNLEFRNVHFSYPSRKEVR

ILKGLNLKVQSGQTVALVGNSGCGKSTTVQLMQRLYDPTEGMVSVDGQDIRTINVRFLREIIGVVSQE
PVLEATTIAENIRYGRENVTMDE IEKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIARA.
LvRNPKILLLBEAT SALDTESEAWQmL0KARKGRTTIVrAHRLSTVRNADVIAGFDDGVIVEKGiJH
DELMKEKG IYFKLVTMQTAGNEVELENAADESKSEIDALEMSSNDSRSSLIRKRSTRRSVRGSQAQDR
KLSTKEALDBSIPPVSFWRIMKLNLTEWPYFVVGVFC¾1INGGLQPAFAIIFSKIIGVFTRIDDPETK
RQNSNLFSLLFLALGIISFITFFLQGFTFGKAGEILTKRLRYMVFRSMLRQDVSWFDDPKNTTGALTT
RLANDAAQVKGAIG&RLAVITQNXANLGTGIIISFTYGWQLTLLLLAIVPIIAIAGVVEMKMLSGQAL
KDKKELEGSGKIATEAIENFRTVVSLTQEQKFEHMYAQSLQVPYRNSLRKAHrFGITFSFTQAMMYFS
YAGC FRF GAY LVAHKLMSFEDFL LVF SAVVFGAMAVGQvs> SFAPDYAKAKISAAHI IMIIEKTPLIDS
YSTEGLMPNTLEGNVTFGEVVFNYPTRPDTPVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYD
FLAGKyLLDGKEIKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEIVRAAKEANIHA
FIFSLPNKySTKyGDKGrQLSGGQKQRIAIA RALVRQPHILLLDEATSALDTESEKVVQEALDKAREG
RICIVIAHRLSTIQNADLIVyFQNGRyKEHGTHQQLLAQKGIYFSMVSVQAGTKRQ

>SEQ ID NOilQ9
MARRPRHSIYSSDE DDEDFEHG DHDYDGLLPKSGKRHLGKTRWTREE DEKLKKLVEQNGTDDWKVIAN
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HLNPEVKKTSWIEEEDRIIYQAHKRLGNRWAEIAKLLPGRTDNAIKNHWNSTMRRKVEQEGYLQESSK
ASQPAVATSFQKNSHLMGFAQAPPTAQLPATGQPTVNNDYSYY¾ISEAQNVSSHVPYPVALHVNIVNV
PQPAAAAIQRHYHDEDPEKEKRIKELE LLLMSTENELKGQQVLPTQNHTCSYPGWHSTTIADHTRPHG
DSAW SCLGEHHSTPSLPADPGSLPEESASPARCMIVHQGTILDNVKNLLEFAETLQFIDSFLNTSSN
HENSDLEMPSLTSTPLIGHKLTVTTPFBRDQT\¾ IQKENTVFRTPAIKRSILESSPRTPTPFKHALAA
QEIKYGPWiLPQIPSKLVEDLQDVIKQESDESGIVAEFQENGPPLLKKIKQEVESPIDKSGNFFCSH
HWEGDSLNTQLFTQTSPVADAPNILTSSVLJ¾APASEDEDNVLKAFTVPK NRSLASPLQPCSSTWEPAS
CGKMEEQMTSSSQARKYVNAFSARILVM

>SEQ ID NO: 110
MPRLFLFHLLEFCLLLNQFSRAVAAKWKDDVIKLCGRELVRAQIAICGMSTSiSKRSLSQEDAPQTPRP
VAEIVPSFINKDTE TIIIMLEFIANLPPELKAAL SERQPSLPEiQQYVPALKDSNLSFEEFKKLIRNR:
QSEAADSNPSELKY LGLDTHSQKKRRP YVAL.FEKCCLIGCTKRS LAKYC

>SEQ ID NO: 111
MQRLQVVLGHLRGPADSGWMPQASPGLSGAPQASAADV'V'/VHGRRTAICRAGRGGFKDTTPPELLS.AV
MTAVXKDVNLRPEQLGDICVGNVLQPGAGAIMARIAQFLSDIPETVPLSTVNRQC&SGLQAVASIAGG.
IRNGSYDXGMACGVESMSLADRGNPGNITSRLMEKEKARDCLIPMGITSENVAERFGISREKQDTFAL
ASQQKAARAQSKGCFQAEIVI?VTTTVHDDKGTKRSITVTQDEGIRPSTTMEGLAKLKPAFKKDGSTTA
GNSSQVSDGAAAILXARRSKAEELGLPILGVLRSYAVVGVPPDIMGIGPAYAIPVALQKAGLTVSDVD
IFEINEAFASQAAYCVEKLRLPPEKyNPLGGAVALGHPlGCIGARQVITLLNELKRRGKRAYGVVSMC
IGTGMGAAAVFEYPGN

>SEQ ID NO: 112
MVRPMLLLSLGLLAGLLPALAACPQNGHCHSDLQHVICDKVGLQKIPKVSEKIKLLNLQRNNFPVLAA
NSFRAMPNLVSLHLQHCQIREVAAGAFRGLKQLIYLYLSHNDIRVLRAGAFDDLTELTYLYLDHNKVT
ELPRGLLSPLVNLFILQLNNNKIRELRAGAEQGAKDLRWLYLSENALSSLQPGALDDVENLAKFHVDR
NQLSSYPSAAL SKLRVVEELKLSHNPLKSIP DNAF QSFGRYLETLWLDNTNLEKFSDGAF LGVTX LKH
VHLENNRLNQLPSNFPFDSLETLALTNNPWKCTCQLRGLRRWLEAKASRPDATCASPAKFKGQHIRDT
DAFRSCKFPTKRSKKAGRH

>SEQ ID NO: 113
MEiIRTPKVENVRLVDRVSPKISAALGTLYIXATHVIFVENSPDPRKETWILHSQISTIEKQATTATGC
PLLIRCKNFQI IQLX IPQERDCHDVYISLIRLARPVKYEEIaY'CFSFNPMLDKEEREQGW\'LIDLSEEY
TRMGLPNHY.WQLSDVNRDYRVCDS:YPIELYVPKSATA HII\¾SSKFRSRRRFPVLSyYYKDMHASIGR
SSQPLSGFSARCLEDEQMLQAIRKANPGSDFVYyVDTRPKLNAMANRAAGKGYENEDIYSNIKFQFIG
IENIHV¾RNSLQKHLEyCELKSPSMSDFLWGLENSGWLRHIKAIMDAGIFIAKAVSEEGASVLVHCSD
GW RTAQVGSVASLLLDPHYRTLKGFIVLIEKDWISFGHKFNHRyGNLDGDPKEISPVIDQFIECVWQ
LMEQFPCAFEFNERFL IHIQHHIYSCQFGNFLCNSQKERRELK IQERTYSLWAHLWKNRADYLNPLFR
ADHSQIQGTLHLPXXPCNFMYKFWSGMYW FEKGMQPRQSVTDYLMAVKEETQQLEEELEALEERLEK
IQKyQLNCTKVKSKQSEPSKHSGFSTSDNSIANIPQDYSGNMKSFPSRSPSaGDEDSALILTQDNLKS
SDPDLS ANSDQESGVEDLSCRSPSGGEHAP SEDSGKDRDSDEAVFLTA

>SEQ ID NO: 114

MDVENEQILNVNPADPDNLSDSLFSGDEENAGTEEIKNEINGNWISASSINEARINAKAKRRLRKNSS
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DVKPPNYPPPQENGVYETVVLPLPERAFEKTLTPIIQEYFEHGDTNEVAEMLRDLNLGEMKSGVPVLA
VSLALEGKASHREMTSKLLSDLCGTVMSTTDVEKSFDKLLKDLPELALDTPRAPQLVGQFIARAVGDG
ILCNTYIDSYKGTVDCYQARAALDKATW LSMSKGGKRKDSVWGSGGGQQSVNHLVKEIDMLLKEYLL
SGDISEAEHCLKELEVPHFHHELVYEAIIMVLESTGESTFKMILDLLKSLWKSSTITVDQMKRGYERI
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>SEQ ID MO:115
MGRRPARCYRYCKNKPYPKSREC RGVP DARIRIFDLGRKKAKVDEFP LCGHMVSDEYEQLSSEALEAA
RICANKYMW SCGKDGFHIRVRLHPFHVIRINKMLSCAGADRLQTGMRGAFGKPQGTVARVHIGQVIM
SIRviRLONKEHVIEALRRARFKFPGRQRIH^ SKKWGFTKFNADEFEDMVAEKRLIPDGCGVKYIPNRG
PLPRWRALHS

>SEQ ID NO;116
MDTSRVQPIKLARVTEVLGRTGSQGQCTQVRVEFMDDTSRSI IRNVKGPVREGDVLTLLESEREARRL
R

>SEQ ID NO:XX7
MARSPRRHLKR¥AAPRHWMLPRLTGVFAPRPSTGPHKLRECLPLIIFLRNRLKYALTGDEVKKICMQR
PIKID GKVRTDITYP¾GFMDVISIDKTGENFa IYDTKSRFAVHRITPEEAKYKLCKVRKIFVGTKGI
PHLVTHDARIIRYPDPLIK^mDTIQIDLETGKIIDFII<FDTGNLCMVTGGANLGRIGVITNRERHPGS
FDVVHVKDANGNSFATRLSNIFVIGKGNRPWISLPRGKG IRLTIAEERDKRLAAKQSSG

>SEQ ID MO:118
MKLNISFPATGCQKLIEVDDERKLRTFYEKRMATEVAiADALGEEWKGYVVRI**SG**G**NDKQ**G**FP**MKQ**6V**L
T¾GR\^i.LLSKGHSCYRPRRIGEr<KRKSVRGCIVDAxNLSVLNLVIVKKGEKDIPGLIDTTVPRRLGPK
RASRIRKLFMLgKEDDVRQYVVRKPLNKEGKKPRTKAPKIQRLVTPRVLQHKRRRIALKKQRIKKMKE
EAAE YARL LAKRMRE AREKRQE QIAKRRRL SSLRAS T SRS ESS OR

>:SEQ ID NO: 119
MSSECDGQSKAVMNQLAPGSNGQDKATADPLRARSISAVKI IPVKXVKN¾SGLVLFTDMDLTKICTGJ
GAVTLRAS SSYRE IPS SSPASPQE TRQHE SKPGLEPEP SSADE WRLSSSADANGNAQPSSLAAKG YRS
VHPNLPSDKSQDATSSSAAQPEVIVVPLYLWTDRGQ EGTARPPTPLGPLGCVPTIPATASAASPLTF
PILDDFIPPHLQRWPHHSQPARASGSFAPISQTPPSFSPPPPLVPPAPEDLRRVSEPDLTGAVSSTDS
SPLLNEVSSSLIGTDSQAFPSVSKPSSAYPSTTIVNPTIVLLQHNREQQRRLSSLSDPVS ERRVGE Q**D**
SAPIQEKPTSPGKAIERRAJCDD^ RVVKSTQDLSDVSMDEVGIPLRNIERSKDWYKTMFKQIHKLNRD
IPEENPYFPTYKFPELPEIQQTSEEDNPYTPTYQFPASTPSPKSEDDDSDLYSPRYSFSEDTKSPLSV
PR:SKSEMSYIDGEKWKRSATLPLPARSSSI^<SSSERNDWEPPDK KVDTRKYRAEPKSIYEYQPGKSS
VLINERMSRDISPEEIDLKNEPWYKFFSELEFGKPPPRRIWPYT^ DCSILPREDRKTNLDKDLSLCQ
TELEADLEKMETLNKAPSANVPQSSAISPTPEISSETPGYiYSSNFHAVKRESDGAPGDLTSLENERQ
IYKSVLEGGDIPLQGLSGLKRPSSSASTKDSESPRHFIPADYLESIEEFIRRRHDDKEKLLADQRRLK
REQEEADJAARRHTGVIPTHHQFITNERFGDLLNIDDTAKRKSGSEMRPARAKFDFKAQILKELPLQK
GDIVYIYKQIDQNWYEGEHHGRVGIFPRTYIELLPPAEKAQPKKLTPVQVLEYGEAIAKFNFNGDTQV
EMSFRKGERITLLRQVDENWYEGRIPGTSRQGiFPITYVDVIKRPLVKNPVDYMDLPFSSSPSRSATA
SPQFSSHSKLITPAPSSLPHSRiALSPEMHAVTSEWXSLTVGVPGRRSL&LTPPLPPLPEASIYNTDH
LALSPRASPSL SLSLPHLSWSDRPIPRSVASP LALP SPHKTYSLAPTSQA SLHMNGDGGVH TPSSGIH
QDSFLQLPLGSSDSVISQLSDAFSSQSKRQPWREESGQYERKAERGAGERGPGGPKISKKSCLKPSDV
VRCL STEQRLSDLNTPEESRPGKPLGSAFPGSEAEQTERHRGGE QAGRKAARRGGS QQPQAQQRRVTP
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>SEQ ID NO;120:
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DPKRETXVQLIDDFRISG¥NeVHVCIWLEVLGHQLLKWIIKSNYQ©LPVPCVKSIVRQVLH©LDYLHT
KCKIIHTDIKPENILLCVGPZYlRRLAAEATEWQQAGAPPPSRSIVSTAPQEVLQTGKLSKNKRKI¾lR
RKRKQOKRLLESRLRPLQRLEAMEAATQAEDSGLRLPGGSGSTSSSGCHPGGARAGPSPASS.SPAPGG
GRSLSAGSQTSGF SGSLFSPASCSILSGSSNQRETGGLLSPSTPFGASNLLVNPLEPQNADKIKIKIA
DLGNACW\HKHFTEDlQTRQYRAVEVLIGAEYGPPADIWSTAeMAFELATGDYLFEPH6GEDYSRDED
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>SEQ ID NO: 121
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TCCCCACAATTTGAGAGAGTGTCTCCCCCTCATCATTTCCTAAGGAAC AGACTTAAGTATGTCCTCA
CTGGAAATGAAGTAAAGAAGAT.TTGCATGCAGCGGTTCATTAAGATCAATGGCAAGG TCCGTACTGAT
ATAACCTACTCTGCTGGATTCATGGATGTCAACAGCATTGAGAAGTCGGGAGAGAATTTC CGTCTGAT
CTATGACACGAAGGGTCGCTTTGCTGT.ACATCGTATTACACCTGAGGAGGCCAA

>8EQ ID NO: 123
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RPC)DMKG:ASRSPEDSSPDAARIRVKRYRQSMNNFQ GLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA
PRSKISPQGYGRRRRRSLPEAGPGRTLVSSKPQAHGAPAPPSGSAPHFL

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MAAEEEEVDSADTGERSGWLTGWLPIWCPTS ISHLKEAEEKMLRCVPCTYKKEPVRI SNGNRIWTLKF
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EWRGALGLDKMILLGHNLGGFLAAAYSLKYPSRVNHLILVEPWGFPERPDLADQDRPIPVWIRALGAA
LTPFNPLAGLRIAGPFGLSLVQRLRPDFKRKYSSIFEDDTVTEYI¾HCNVQXPSGETAFKNMTIPYGW
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VREICDTvD

>SEQ ID NO: 12.5
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RSCPELTSGPRMCPRKEQDSWSEAGGILFRGKVPMVVTXIDILA\¾PPQIKSLPATPQGK NMTPESEVL
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LGA.S

>SEQ ID NO: 126
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ILL**KA**LTNL**P**H**TDFT**L**CKCM**I**DQ**A**H**QEE**RP**I**R**QI**LYLGDLL**ETCH**FQ**AF**W**QA**L**DE**NMDLL**E**G**ITGFED**
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DRSILP TAPRAAREPNIDRSRLPKSPPYIAFLGNLPYDVTEESIREFFRGLNISAVRLPREPSNPERL
KGFGiAEFEDI-DSLLSALSLNEESLGNRRIRVDVADQAQDKDRDDRSFGRDRNRDaDKTDTD-WRARPA
TDgFDDYPPRRSDDSFGPKYRDRYDSDRYRDGYRpGYRDGPRRDidDRYGGRDRYDDRGS.RDYDRGY.DS
RIGSGRRAFGSGYRRDDDYRiaGGDRYEDRYD.RRDDRSWS SRDPYSRDDYRRDDRGPPQRPKLNLKPRS
TPKEDDSS ASTSQSTRAAS IFGGARP VDTAARERE VEERLQKEQEKLQRGLDEP KLERRPRERHPSSR
SEETQERERSRTGSESSQTGTSTTSSRNARRRESEKSLENETLNKEEDCHSPTSKPPRPDQPLKVMPA
PPPKENAWVKRSSNP^ 'ARSQSSDTEQQSPTSGGGKVAPAQPSEEGPGRKDENKVDGMNAPKGQTGNSS
RGPGDGGNRDHWKESDRKDGKHDQDSRSAPEPKKPEENPASKFSSASKYAALSVDGEDENJEGEDYAE

>SEQ ID NO: 128

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VDVXXLECGGNLFDAISIAVKAALFNTRIPRVRVLEDEEGSKDIELSDDPYDCIRLSVENVPCIVTLC
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>SEQ ID NG:129
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VCK¾TVQDESHSE«VSCW FSPNSSNP IIV SCGWDKLVKVWNLAiNCKLKTNHIGHTGYLNTVTVSPDG
SLCASGGKDGQAMLWDLNEGKHLYTLDGGDIINALCFSPNRYWLCAATGPSIKIWDLEGKIIVDELKQ
EVISTSS KAEPPQCTSLAWSAD.GQTLEAGY TDNLVRVWQVTIGTR

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QYNRVNLXLDLGQLFHVAY ILIKFANSPRPDLWVLERSVDFGSTYSPWQYFAHSKVDCLKEFGREANM
AVXRDDDVLE¥XEYSRIVPLENGE¥WS,LTMGRPGARNFXFSHXLREFXKAXNIRLRFLRXNXLLGILL
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XPSSEDPV? GDIKGCDCNLEGVLPEIGDAHGRCLCRPGVEGPRCDICRSGFYSFPICQACWCSALGSY
QT^CSSVXGQCEERPGVXGQRCDRCL.SGAYDFPHCQGSS.SACDPAGTI NSNLGYCQCKLHVEGPTCSR
CKLLYWNLDKENPSGCSECKCHKAGTVSGTGECRQGDGDCHCKSHVGGDSCDTCEDGYFALEKSNYFG
CQGCQCDIGGALSSMCSGPSGVCQCREHVVGKVCQRPENNYYFPDLHHMKYEIEDGSTPNGRDLRFGF
DPLAFPEFSWRGYAQMTSVQNDVRITLNVGKSSGSLFRVILRYVNPGTEAVSGHITIYPSWGAAQSKE
IIFLPSKEPAFVTVPGNGFADPFSITPGIWVACIKAEGVLLDYLVLLPRDYYEASVLQLPVTEPCAYA
GPPQENCLLYQHLPVTRFPCTLACEARHFLLDGEPRPVAVRQPTPAHPVMVDLSGREVELHLRLRIPQ
VGHYVVVVEYSTEAAQLFVVDVNVKSSGSVLAGQVNIYSCNYSVLCRSAVIDHMSRIAMYELLADADI
QLKGHMARFLLHQVCIIPIEEFSAEYVRPQVHCIASYGRFVNQSATCVSLAHETPPTALILDVLSGRP
FPHLPQQSSPSVDVLPGVTLKAPQNQVTLRGRVPHLGRYVFVIHFYQAAHPTFPAQVSVDGGWPRAGS
FHASFCPHVLGCRDQVIAEGQIEFDISEPEVAATVKVPEGKSLVLVRVLVVPAENYDYQILHKKSMDK
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GIGVNCQHNIAGEHGERCQEGYYGNAVHGSCRACPCPHTNSFATGCVVNGGDVRCSCKAGYTGTQCER
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>SEQ ID MO: 132
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ARESGPPHMKNFVTKVSVGEFVGEGEGKSKKISKKNAAIAVLEELKKLPPLPAVERVKPRIKKKTKPI
VKPQXSPEYGQGINPi SRLAQIQQAKKEKEFE YTLLTERGLPRRREFVMQyKVGNHTAEGTGrNKKVA
KRNA AENMLE ILGFKV P Q¾QPTKPA LKSEEKTP IKKPGDGRKVTFFEP GSGDENGTSNKEDEFRMPYL
SHQpLPAGILPMVPEVAQAVGVSQGftHTKDFTP-^PNPAKATVTAMIARELLYG.GTSPTAETILKNMI
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AA LNILKLLSE LDQQSTEHPRT GNGPHSVCGEC

>SF,Q ID NO: 133
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YAFVTFCTKEAAQEAVKLYNNHEIRSGKHIGVCISVANNRLFVGSIPKSKTKEQIL.EE FSKVTEGLTD
VILYHQPDDKKKNRGFCFLEYEDHKTAAQARRRLMSGKVKVWGNVGTVEWADPIEDPDPEVMAKVKVL
FVRNLANTVTEE I.LEKAF SQFGKLERVKKLKDYAFIHFDERDGAVKAMEEMNGKDLEGENIEIVFAKP
PDQI<RKERKAQRQAAKNQMYDDY YYYGPPHMPPPTRGRGRGGRGGYGYPPDYYGYEDYYDYYGYDYHN
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FYQDTFGQQWK

CLAIMS

1. A method of detenmning the aggressiveness of a cancer in a mammal, said method including the step of **comparing** an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a **plurality** of metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an **Immune** System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein **Synthesis/Modification** metagene and a Multiple Networks metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes Indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

2. A method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the **mammal,** wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Carbohydrate/Lipid **Metabolism** metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, **a** Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple

Networks metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or eorrelates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis,

3. The method of Claim 1 or Claim 2, wherein the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one of the metagenes or are selected from a plurality of the metagenes.

4. The method of any one of the preceding claims, wherein the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene comprise one or a plurality of genes listed in Table 21.

5. A method of determining the aggressiveness of a Cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modification metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

6. A method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of rnetagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an immune Response metagene and a Protein .Synthesis/Modification metagene, wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis.

7. The method of Claim 5 or Claim 6, wherein the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one of the rnetagenes or are selected from a plurality of the rnetagenes.

8. The method of any one of Claims 5 to 7, wherein the Metabolism metagene. the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein **Synthesis/Modification** metagene comprise one or more genes listed in Table 22.

9. The method of any one of Claims 5 to 8, wherein the one or plurality of overexpressed genes and the one or plurality of underexpressed genes are from one or a plurality of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an **Immune** System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein **Synthesis/Modification** metagene and a Multiple Networks metagene.

10. The method of any one of the preceding claims, wherein the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes includes comparing an average expression level of the one or plurality of overexpressed genes and/or an average expression level of the one or plurality of underexpressed genes.

11. The method of Claim 10, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes and the average expression level of the plurality of underexpressed genes.

12. The method of any one of Claims 1-9, wherein the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes includes comparing the sum of expression levels of the one or plurality of overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes.

13. The method of Claim 12, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes and the sum of expression levels of the one or plurality of underexpressed genes.

14. A method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

15. A method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes associated with chromosomal instability compared to the one or plurality of underexpressed genes associated with estrogen receptor signalling indicates or correlates with a more favourable cancer prognosis.

16. The method of Claim 15, wherein the cancer prognosis includes determining responsiveness to anti-cancer therapies targeting aneuploid tumours.

17. The method of Claim 15, wherein the cancer prognosis includes determining responsiveness to anti-cancer therapies targeting chromosomal instability.

18. The method of any one of Claims 15 to 17, wherein the Cancer prognosis includes determining responsiveness to one or more anti-cancer therapies that comprise targeting TTK, PLK1 and/or one or more Aurora Kinases.

19. The method of any one of Claims 14 to 18, wherein the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling includes comparing an average expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or an average expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

20, The method of Claim 19, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes associated with chromosomal instability and the average expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

21. The method of any one of Claims 14-18, wherein the step of comparing an expression level of one or a plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling includes comparing the sum of expression levels of the one or plurality of overexpressed genes associated with chromosomal instability and/or the sum of expression levels of the one or plurality of underexpressed genes associated with estrogen receptor signalling,

22. The method of Claim 21, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes associated with chromosomal instability and the sum of expression levels of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

23. The method of Claim 20 or Claim 22, wherein the ratio provides an aggressiveness score which is indicative of, or correlates with, cancer aggressiveness and a less favourable prognosis.

24. The method of any preceding claim, wherein the genes associated with chromosomal instability are of a CIN metagene.

25. The method of Claim 24, wherein the CIN metagene comprises a plurality of genes listed in Table 4.

26. The method of Claim 25, wherein the genes are selected from the group consisting of: ***ATP6V1CI,*** *RAP2A, CALMl, COGS, HELLS,* ***KDM5A,*** *PGKl, PLCHl, CEP55, RFC4, TAF2, SF3B3, GPI, FIR, MCMI0, MELK, FOXMl, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOL MAPREl, ACOT7, NAE1, SHMT2, TCP1, TXNRDl, AIM, CHAFIA and SYNCRIP.*

27. The method of Claim 26, wherein the genes are selected from the group consisting of: *MELK, MCM10, CENPA, EXOL TTK* and *KIF2C.*

28. The method of any one of Claims 14 to 27, wherein the genes associated with estrogen receptor signalling are of an ER metagene.

29. The method of Claim 28, wherein the genes are selected from the group consisting of: *BTG2, PIK3IPL SEC14L2, FLNB, ACSF2, APOM, BINS, GLTSCR2, ZMYNDH), ABAT, BCAT2. SCUBE2, RUNXI, LRRC48, MYBPCI, BCL2, CHPTl, IIM2A, LRIGI, MAPZ PRKCB, RERE, ABHDI4A,* ***FLT3****, TNN, STC2, BATE, CD1E, CFB,* ***EVL,*** *FBXW4, ABCBI,*

ACAAl, CHAD, PDCD4, RPLIO, RPS2S, RPS4X, RPS6, SORBSL RPL22 and RPS4XP3.

30. The **method** of Claim 29, wherein the genes are selected from the group consisting of: *MAPT* and *MYB*.

31. The method of any one of Claims 14 to 30, further including the step of comparing an expression level of one or a plurality of other overexpressed genes selected from the group consisting of *CAMSAPI, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFCIRl, KCNGI, BCAP31, ULBP2, CARHSPL PML, CD36,* (7)55, *GEMIN4, TXN, ABHD5, E1F3K, EIF4B, EXOSC7, GNB2LL LAMA3, NDUFCl* and *STAUl,* and/or an expression level of one or a plurality of other underexpressed genes selected from the group consisting of *BRDS, BTN2A2. KIR2DL4. ME1, PSEN2, CALR, CAMK4, YTM2C, NOP2, NSUN5, SF3B1, ZNRDl-ASl, ARNT2, ERC2, SLCllAl, BRD4, APOBEC3A, CD IA, CD IB, CDIC, CXCR4, HLA-B, IGff, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBS1 and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein; a higher relative expression level of the one or plurality of other overexpressed genes compared to the one or plurality of other underexpressed genes indicates or correlates with higher aggressiveness of the cancer **and/or** a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of other overexpressed genes compared to the one or plurality of other underexpressed genes indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

32. The method of Claim 31, wherein the one or plurality of other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP3L, CA9, CAMSAPI, CARHSPL CD55, CETN3, E1F3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFCIRL KCNGL MAP2K5, NDUFCl, PML, STAU1, TXN* and *ZNF593* and/or the one or plurality of other underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDIJB* and *ZNRDl-ASl* .

33. The method of Claim 31 or Claim 32, wherein the step of comparing the expression level of the one or plurality of other overexpressed genes and/or the expression level of the one or plurality of other underexpressed genes

includes comparing an average expression level of the one or plurality of other overexpressed genes and/or an average expression level of the one or plurality of other underexpressed genes,

34. The method of Claim 33, which includes calculating a ratio of the average expression level of the other overexpressed genes and the average expression level of the other underexpressed genes,

35. The method of Claim 31 or Claim 32, wherein the step of comparing an expression level of the one or plurality of other overexpressed genes and/or an expression level of the one or plurality of other underexpressed genes includes comparing the sum of expression levels of the one or plurality **of** other overexpressed genes and/or the sum of expression levels of the one or plurality of other underexpressed genes,

36. The method of Claim 35, which includes calculating a ratio of the sum of expression levels **of** the one or plurality of other overexpressed genes and the sum of expression levels of the one or plurality of other underexpressed genes.

37. The method of any one of Claims 31 to 36, wherein the comparison of the expression level of the overexpressed genes associated with **chromosomal** instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling is integrated with the comparison of the expression level of the other overexpressed genes and/or the expression level of the other underexpressed genes **to** derive a first integrated score.

38. A method of determining the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level **of** one or a plurality of overexpressed genes selected from the group consisting of *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFCIRL KCNG1, BCAP31 ULBP2, CARHSP1, PML, CD36, CDS5, GEMIN4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFCl* and *STAUL* and/or an expression level **of** one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. MEL PSEN2, CALR, CAMK4, [TM2C, NOP2, NSUN5, SF3B1, ZNRDI-ASL ARNT2, ERC2, SECUAl, BRD4, APOBEC3A, CD1A, CDIB, CDIC, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBS! and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative

expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level.

39. A method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *CAMSAPl, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFCIRI, KCNGL BCAP3L ULBP2, CARHSPl, PML, CD36, CD55, GEMIN4, TXN, ABHD5, EIF3K, FJF4B, EXOSC7, GNB2LI, 1AMA3, NDUFCl* and *STAUI,* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2, KJR2DL4 ME1, PSEN2, CALR, CAMK4, ITM2C, NOP2, NSUN5, SF3BL ZNRDl-ASI, ARNT2, ERC2, SLCl lAl BRD4, APOBEC3A, CDIA, CDIB, CD1C, CXCR4,* HIΛ -B, *IGH, KIR2DL3, SMPDL3B, MYB, RLNl, MTMR7, SORBS! and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal wherein: a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

40. The method of Claim 38 or Claim 39, wherein the one or plurality of overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAPl, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GKHPR, GSK3B, HCFCIRL KCNGJ, MAP2K5, NDUFCL PML, STAUI , TXN* and *ZNF593* and/or the one or plurality of underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1*.

41. The method of any one of Claims 38 to 40, wherein the step of comparing the expression level of the one or plurality of overexpressed genes and/or the expression level of the one or plurality of underexpressed genes includes comparing an average expression level of the one or plurality of overexpressed genes and/or an average expression level of the one or plurality of underexpressed genes,

42. The method of Claim 41, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes and the average expression level of the one or plurality of underexpressed genes.

43. The method of any one of Claims 38 to Claim 40, wherein the step of comparing an expression level of the one or plurality of overexpressed genes and/or an expression level of the one or plurality of underexpressed genes includes comparing the sum of expression levels of the one or plurality of overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes.

44. The method of Claim 43, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes and the sum of expression levels of the one or plurality of underexpressed genes.

45. The method of any one of Claims 1 to 44, further including the step of comparing an expression level of a one or a plurality of overexpressed proteins, and/or an expression level of one or a plurality of underexpressed proteins, in one or a plurality of cancer cells, tissues or organs of the mammal to thereby derive an integrated score.

46. The method of Claim 38, wherein the one or plurality of overexpressed proteins are selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, SMADl, GATA3, ITGA2, AKT1, NFKB1, HER2, ASMS and COL6A1, and/or the one or plurality of underexpressed proteins are selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESRL YWHAE, RAD50, PGR, COL6A1, PEA 15 and RPS6, wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with higher aggressiveness of the cancer and/or a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or

plurality of underexpressed proteins indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

47. The method of Claim 45 or Claim 46, wherein the step of comparing the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins includes comparing an average expression level of the one or plurality of overexpressed proteins and/or an average expression level of the one or plurality of underexpressed proteins.

48. The method of Claim 47, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed proteins and the average expression level of the one or plurality of underexpressed proteins.

49. The method of Claim 45 or Claim 46, wherein the step of comparing an expression level of the one or plurality of overexpressed proteins and/or an expression level of the one or plurality of underexpressed proteins includes comparing the sum of expression levels of the one or plurality of overexpressed proteins and/or the sum of expression levels of the one or plurality of underexpressed proteins.

50. The method of Claim 49, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed proteins and the sum of expression levels of the one or plurality of underexpressed proteins,

51. The method of any one of Claims 45 to 50, wherein the comparison of the expression level of the one or plurality of overexpressed proteins and the expression level of the one or plurality of underexpressed proteins is integrated with;

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(iii) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAPL CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNGl, BCAP3I, ULBP2, CARHSPI, PML,*

*CD36, **CD55,** GEMJN4, TXN, **ABHD5,** EIF3K, **EIF4B,** EXOSC7, GNB2L1, LAMAS, NDUFC1* and ***STAU1*** and/of **the** expression level of the underexpressed genes selected from the group consisting of *BRD8, BTN2A2. KIR2DL4. ME1, PSEN2, **CALR,** CAMK4, ITM2Q NOP2, **NSUN5,** SF3B1, ZNRD1-AS1,* ARN12, ***ERC2,*** *SLC11A1, BRD4, AP0BEC3A, GDIA, CD1B, CD1C, CXCR4, HLA^B, IGH, KIR2DL3, SMPDL3B, MYB, RUN1, MTMR7, SORBS! and SRPK3* to derive a fourth integrated **score;** or

(iv) the **comparison** of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene^, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene, to derive a fifth integrated score; or

(v) the comparison of **the** expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregatioii/Replication metagene, the Immune Response metagene and/or the Protein **Synthesis/Modification** metagene, to derive a **sixth** integrated score.

52, The method of Claim **51,** wherein the first, second, third, fourth, fifth and/or sixth integrated scores are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation.

53, A method of **determining** the aggressiveness of a cancer in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3. PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku8**0,** HER3, SMAD1, GATA3, 1TGA2, AKT1, NFKB1, HER2. ASNS and COL6AL

and/or an expression level of one or a plurality of underexpressed proteins **selected** from the group consisting of VEOFR2, HER3, ASNS, MAPK9, ESRl, YWHAE, RAD50, PGR, CGL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with higher aggressiveness of the cancer; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with lower aggressiveness of the cancer compared to a mammal having a higher expression level,

54. A method of determining a cancer prognosis for a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, 1NPP4B, EIF4EBPJ, EGFR, Ku80, HER3, SMADl, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESRl, YWHAE, RAD50, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with a more favourable cancer prognosis compared to a mammal having a higher expression level.

55. The method of Claim 53 or Claim 54, wherein the step of comparing the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins includes comparing an average expression level of the one or plurality of overexpressed proteins and/or an average expression level of the one or plurality of underexpressed proteins.

56. The method of Claim 55, which includes **calculating** a ratio of the average expression level of the one or plurality of overexpressed proteins and the average expression level of the one or plurality of underexpressed proteins,

57. The method of Claim 53 or Claim 54, wherein the step of comparing an expression level of the one or plurality of overexpressed proteins and/or an expression level of the one or plurality **of** underexpressed proteins includes comparing the sum of expression levels of the one or plurality of overexpressed proteins and/or the sum of expression levels of the one or plurality of underexpressed proteins.

58. The method of Claim 57, which includes calculating a ratio of the sum of expression levels of the overexpressed proteins and the sum of expression levels of the underexpressed proteins.

59. A method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of determining an expression level of one or plurality of genes associated with chromosomal instability in one or a plurality of non-mitotic cells of the mammal, wherein a higher expression level indicates or **correlates** with relatively increased responsiveness of the cancer to the anti-cancer treatment.

60. The method of Claim 59, wherein the one or plurality of genes associated with chromosomal instability are targeted by the anti-cancer treatment.

61. The method of Claim 59 or Claim 60, wherein the one or plurality of genes associated with chromosomal instability are listed in Table 4 and/or include one or more genes associated with aneuploidy.

62. The method of Claim 61, wherein the one or plurality of genes associated with chromosomal instability and/or aneuploidy are selected from the group consisting of: *TTK, CEP55, FOXMl, SKIP2, PLKl* **and/or** Aurora kinases.

63. The method of any one of Claims 59 to **62,** wherein the anti-cancer treatment is a treatment targeted to aneuploid tumours.

64. The method of any one of Claims 59 to 63, wherein the anti-cancer treatment is a treatment targeted to chromosomal instability.

65. A method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a

plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular Growth metagene, a Chromosome Segregation metagene, a DNA Replication/Recombination metagene, an Immune System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene, wherein an altered or modulated relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

66. The method of Claim 65, wherein the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one metagene or are selected from a plurality of metagenes.

67. The metliod of Claim 65 or Claim 66, wherein the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein Synthesis/Modification metagene and/or the Multiple Networks metagene comprise one or more genes listed in Table 21.

68. A metliod of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes and/or an expression level of one or a plurality of underexpressed genes in one or a plurality of cancer cells, tissues or organs of the mammal, wherein the overexpressed genes and the underexpressed genes are from one or a plurality of metagenes selected from the group consisting of a Metabolism metagene, a Signalling metagene, a Development and Growth metagene, a Chromosome Segregation/Replication metagene, an Immune Response metagene and a Protein Synthesis/Modificatioii metagene, wherein an altered or modulated

relative expression level of the overexpressed genes compared to the underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment,

69. The method of Claim 68, wherein the one or plurality of overexpressed genes and/or the one or plurality of underexpressed genes are selected from one metagene or are selected from a plurality of metagenes,

70. The method of Claim 68 or Claim 69, wherein the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene comprise one or more genes listed in Table 22.

71. The method of any one of Claims 68 to 70, wherein the one or plurality of overexpressed genes and the one or plurality of underexpressed genes are from one or a plurality of **of** a Carbohydrate/Lipid Metabolism metagene, a Cell Signalling metagene, a Cellular Development metagene, a Cellular **Growth** metagene, a **Chromosome** Segregation metagene, a DNA Replication/Recombination metagene, an **Immune** System metagene, a Metabolic Disease metagene, a Nucleic Acid Metabolism metagene, a Post-Translational Modification metagene, a Protein Synthesis/Modification metagene and a Multiple Networks metagene.

72. The method of any one of Claims 65 to 71, wherein the step of comparing an expression level of the one or plurality of overexpressed genes and/or an expression level of the one or plurality of underexpressed genes includes comparing an average expression level of the plurality **of** overexpressed genes and/or an average expression level of the plurality **of** underexpressed genes.

73. The method of Claim 72, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes and the average expression level of the one or plurality of underexpressed genes.

74. The method of any one of Claims 65 to 71, wherein the step of comparing an expression level of the one or plurality of overexpressed genes and/or an expression level of the one or plurality of underexpressed genes includes comparing the sum of expression levels of the one or plurality of

overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes.

75. The method of Claim 74, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes and the sum of expression levels of the one or plurality of underexpressed genes.

76. A method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of a one or plurality of overexpressed genes associated with chromosomal instability and/or an expression level of one or a plurality of underexpressed genes associated with estrogen receptor signalling in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the overexpressed genes associated with chromosomal instability compared to the underexpressed genes associated with estrogen receptor signalling indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti¬cancer treatment,

77. The metliod of Claim 76, wherein the genes associated with chromosomal instability are of a CIN metagene.

78. The method of Claim 77, wherein the CIN metagene comprises a plurality of genes listed in Table 4.

79. The metliod of Claim 78, wherein the genes are selected from the group consisting of: *ATP6VIC1, RAP2A, CALMI, COG8, HELLS, KDM5A, PGKl, PLCH1, CEP55, RFC4, TAF2, SF3B3, GPL PIR, MCMIO, MELK, **FOXMl**, KIF2C, NUP155, TPX2, TTK, CENPA, CENPN, EXOl, MAPREl, ACOT7, NAEl, SHMT2, TCP I, TXNRDl, ADM, CHAF!A and SYNCRIP.*

80. The method of Claim 79, wherein the genes are selected from the group consisting of: *MELK, MCM10, CENPA, EXOL TTK* and *K1F2C.*

81. The method of any one or Claims 76 to 80, wherein the genes associated with estrogen receptor signalling are of an ER metagene.

82. The metliod of Claim 81, wherein the genes are selected from the group consisting of: *BTG2, P1K3IPI, SEC14L2, FLNB, ACSF2, APOM, BIN3, GLTSCR2, ZMYNDIO, ABAT, BCAT2, SCUBE2, RUNXI, LRRC48, MYBPCL BCL2, CHPTL TTM2A, LRIG1, MAPT, PRKCB, RERE ABHD14A, FLT3, TNN, STC2, BATE, CDTE, CFB, EVL, FBXW4, ABCBl,*

ACAAl CHAD, PDCD4, RPLIO, RPS2S, RPS4X, RPS6, SORBS1, RPL22 and RPS4XP3.

83. The method of Claim 82, wherein the genes are selected from the group consisting of: *MAPT* and *MYB*.

84. The method of any one of Claims 76 to 83, wherein the step of comparing an expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or an expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling includes comparing an average expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or an average expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

85. The method of Claim 84, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes associated with chromosomal instability and the average expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling,

86. The method of any one of Claims 76 to 83, wherein the step of comparing an expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or an expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling includes comparing the sum of expression levels of the one or plurality of overexpressed genes associated with chromosomal instability and/or the sum of expression levels of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

87. The metliod of Claim 86, which includes calculating a ratio of **the** sum of expression levels of the one or plurality of overexpressed genes associated with chromosomal instability and the sum of expression levels of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

88. The method of any one or Claims 76 to 87, further including the step of comparing an expression level of one or a plurality of other overexpressed genes selected from the group consisting of *CAMSAPI, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2KS, HCFC1R1, KCNG1, BCAP31, IJLBP2, CARHSPi, PML, CD36, CD55,*

GEMIN4, TIN, ABHD5, EJF3K, EIF4B, EXOSC7, GNB2L1, LAMA3, NDUFCl and *STAUl,* and/or an expression **level** of one or a plurality of **.other** underexpressed genes selected from the group consisting of *BRD8, BTN2A2. K1R2DL4. MEl, PSEN2, CALR, CAMK4, TTM2C,* NOP*2, NSUN5, SF3B1, ZNRD1-AS1, ARNT2, ERC2, SLC11A1, BRD4, APOBEC3A, CD4A, CD1B, CDIC CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS! and SRPK3* in one or a plurality of cancer ceils, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of other overexpressed genes compared to the one or plurality of other underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti¬cancer treatment.

89- The method of Claim 88, wherein the one or plurality of other overexpressed genes are selected from the group consisting of *ABHD5, ADORA2B, BCAP31,* CAP, *CAMSAPL CARHSPl,* **(7)**5.5, *CETN3, E1F3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFCIRI, KCNG1, MAP2K5, NDUFCl, PML, STAUl, TXN* and *ZNF593* and/or the one or plurality of **other** underexpressed genes are selected from the group consisting of *BTN2A2, ERC2, IGH, MEL MTMR7, SMPDL3B* and *ZNRD1-AS1*.

90. The method of Claim 88 or Claim 89, wherein the comparison of the expression level of the one or plurality **of** other overexpressed genes and/or the expression level of the one or plurality of other underexpressed genes is integrated with the comparison of the expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or the expression level of the one or **plurality** of underexpressed genes associated with estrogen receptor signalling to derive a first integrated score, which is indicative of, or correlates with, responsiveness of the cancer to the anti-Cancer treatment.

91. The method of Claim 90, wherein the first integrated score is derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation,

92, The method of Claim 91, wherein the first integrated score is derived by exponentiation, wherein the comparison of the expression level of one or a plurality of other overexpressed genes and/or the expression level of one or a

plurality of other underexpressed genes is raised to the power of the comparison of the expression level of the one or plurality of overexpressed genes associated with chromosomal instability and/or the expression level of the one or plurality of underexpressed genes associated with estrogen receptor signalling.

93. The method of any one of Claims 88 to 92, wherein the step of comparing an expression level of the one or plurality of other overexpressed genes and/or an expression level of the one or plurality of other underexpressed genes includes comparing an average expression level of the one or plurality of other overexpressed genes and/or an average expression level of the one or plurality of other underexpressed genes,

94. The method of Claim 93, which includes calculating a ratio of the average expression level of the one or plurality of other overexpressed genes and the average expression level of the one or plurality of other underexpressed genes.

95. The method of any one of Claims 88 to 92, wherein the step of comparing an expression level of the one or plurality of other overexpressed genes and/or an expression level of the one or plurality of other underexpressed genes includes comparing the sum of expression levels of the one or plurality of other overexpressed genes and/or the sum of expression levels of the one or plurality of other underexpressed genes,

96. The method of Claim 95, which includes calculating a ratio of the sum of expression levels of the one or plurality of other overexpressed genes and the sum of expression levels of the one or plurality of other underexpressed genes.

97. A metliod of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of *CAMSAPl, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFCIR!, KCNG1, BCAP31, ULBP2, CARHSPl, PML, CD36, CD55, GEM1N4, TXN, ABHD5, EIF3K, EIF4B, EXOSC7, GNB2LI, IAMA3, NDUFC1* and *STAU1*, and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *BRD8, BTN2A2, KIR2DL4. MEL, PSEN2, CALR, CAMK4, JTM2C, NOP2, NSUN5, SF3B1, ZNRD!-ASl, ARNT2, ERC2,*

SLCliAl, BRD4, APOBEC3A, CDLA, CDIB, CDIC, CXCR4, ***HLA-B,*** *IGB, KIR2BL3, SMPDL3B, MYB,* ***RLN1,*** *MTMR7, SQRBS1 and SRPK3,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the anti-cancer treatment.

98. The method of Claim 97, wherein the one or plurality of overexpressed genes are selected from the group consisting oi *ABHD5, ADORA2B, BCAP3L CA9, CAMSAPI, CARHSP!, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFCIRI, KCNGl, MAP2K5, NDUFC1, PML, STAUl, TXN* and *ZNF593* and/or the one or plurality of underexpressed genes are selected from the group consisting of *BTN2A2, ERC2,* ***IGH,*** *MEL MTMR7, SMPDL3B* and *ZNRDl-ASJ.*

99. The method of Claim 97 or Claim 98, wherein the step of comparing the expression level of the one or plurality of overexpressed genes and/or the expression level of the one or plurality of underexpressed genes includes comparing an average expression level of the one or plurality of overexpressed genes and/Or an average expression level of the one or plurality of underexpressed genes.

100. The method of Claim 99, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed genes and the average expression level of the one or plurality of underexpressed genes.

101. The method of Claim 97 or Claim 98, wherein the step of comparing an expression level of the one or plurality of overexpressed genes and/or an expression level of the one or a plurality of underexpressed genes includes comparing the sum of expression levels of the one or plurality of overexpressed genes and/or the sum of expression levels of the one or plurality of underexpressed genes.

102. The method of Claim 101, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed genes and the sum of expression levels of the one or plurality of underexpressed genes.

103. The method of any one of Claims 65 to 103, further including the step of comparing an expression level of a one or plurality of overexpressed

proteins, and/or an expression level of one or a plurality of underexpressed proteins, in one or a plurality of cancer cells, tissues or organs of the mammal to thereby derive an integrated score.

104. The method of Claim 103, wherein the one or plurality of overexpressed proteins are selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, **HER3,** SMADl, GATA3, ITGA2, AKT1, NFKB 1, HER2, ASNS and CGL6AI, and/or the one or plurality of underexpressed proteins are selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD5Q, PGR, COL6A1, PEALS and RPS6, wherein: a higher relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with higher aggressiveness of the cancer arid/or a less favourable cancer prognosis; and/or a lower relative expression level of the one or plurality of overexpressed proteins compared to the one or plurality of underexpressed proteins indicates or correlates with lower aggressiveness of the cancer and/or a more favourable cancer prognosis compared to a mammal having a higher expression level.

105. The method of Claim 103 or Claim 104, wherein the step of comparing the expression level of the one or plurality of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins includes comparing an average expression level of the one or plurality of overexpressed proteins and/or an average expression level of the one or plurality of underexpressed proteins.

106. The method of Claim 105, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed proteins and the average expression level of the one or plurality of underexpressed proteins.

107. The method of Claim 103 or Claim 104, wherein the step of comparing an expression level of the one or plurality of overexpressed proteins and/or an expression level of the one or plurality of underexpressed proteins includes comparing the sum of expression levels of the one or plurality of overexpressed proteins and/or the sum of expression levels of the one or a plurality of underexpressed proteins.

108. The method of Claim 107, which includes calculating a ratio of the sum of expression levels of the one or plurality of averexpressed proteins and the sum of expression levels of the one or plurality of underexpxessed proteins,

109. The method of any one of Claims 103 to 108, wherein the comparison of the expression level of the one or plurality of overexpressed proteins and the expression level of the one or plurality of underexpressed proteins is integrated with:

(i) the comparison of the expression level of the overexpressed genes associated with chromosomal instability and/or the expression level of the underexpressed genes associated with estrogen receptor signalling to derive a second integrated score; or

(ii) the first integrated score to derive a third integrated score; or

(i) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP!, CETN3, GRHPR, ZNF593, CA9, CFDPl, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFCIR1, KCNG1, BCAP31* ***ULBP2,*** *CARHSPL PML, CD36, CD55, GEMIN4, TXN, ABHD5,* ***EIF3K,*** *EIF4B, EXOSC7, GNB2L1,* ***LAMAS;*** *NDUFCl* and *STAU1* **and/or** the expression level of the underexpressed genes selected from the group consisting **of** *BRD8, BTN2A2, KJR2DL4. MET, PSEN2,* ***CALM,*** *CAMK4, LTM2C,* N'OP*2, NSUN5, SF3BI, ZNRDl-ASF ARNT2, ERC2, SLCllAl, BRD4, APOBEC3A, CD!A,* ***CD IB, CD1C,*** *CXCR4,* ***HlA-B, IGH,*** *KIR2DL3,* ***SMPDLSB, MYB,*** *RLNl, MTMR7, SORBS! and SRPK3* to derive a fourth integrated score; or

(ii) the comparison of the expression level of **the** overexpressed genes **and/or** an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Carbohydrate/Lipid Metabolism metagene, the Cell Signalling metagene, the Cellular Development metagene, the Cellular Growth metagene, the Chromosome Segregation metagene, the DNA Replication/Recombination metagene, the Immune System metagene, the Metabolic Disease metagene, the Nucleic Acid Metabolism metagene, the Post-Translational Modification metagene, the Protein

Synthesis/Modification metagene and/or the Multiple Networks metagene., to derive a fifth integrated score; or

(iii) the comparison of **the-** expression level of the overexpressed genes **and/or** an expression level of the underexpressed genes, wherein the genes are from one or a plurality of the Metabolism metagene, the Signalling metagene, the Development and Growth metagene, the Chromosome Segregation/Replication metagene, the Immune Response metagene and/or the Protein Synthesis/Modification metagene, to derive a sixth integrated score.

110. The method of Claim 109, wherein the first, second, third, fourth, f fth and/or sixth integrated scores are derived, at least in part, by addition, subtraction, multiplication, division and/or exponentiation,

111. A method of predicting the responsiveness of a cancer to an anti-cancer treatment in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed proteins selected from the group consisting of DVL3, PAI-1, VEGFR2, INPP4B, EIF4EBP1, EGFR, Ku80, HER3, **SMAD1,** GATA3, ITGA2, AKT1, **NFKB1,** HER2, ASMS and COL6A1, and/or an expression level of one or a plurality of underexpressed proteins selected from the group consisting of VEGFR2, HER3, **ASNS,** MAPK9, ESR1, **YWHAE,** RAD5Q, PGR, COL6A1, PEA15 and RPS6, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed proteins **compared** to the one or plurality of underexpressed proteins indicates or correlates with relatively increased **or** decreased responsiveness of the cancer to the anti-cancer treatment.

112. The method of Claim 111, wherein the step of comparing the expression level of the one or **plurality** of overexpressed proteins and/or the expression level of the one or plurality of underexpressed proteins includes comparing an average expression level of the one or plurality of overexpressed proteins and/or an average expression level of **the** one or plurality of underexpressed proteins.

113. The method of Claim 112, which includes calculating a ratio of the average expression level of the one or plurality of overexpressed proteins and

the average expression level of the one or plurality of underexpressed proteins.

114. The method of Claim 111, wherein the step of comparing an expression level of the one or plurality of overexpressed proteins and/or an expression level of the one or plurality of underexpressed proteins includes comparing the sum of expression levels of the one or plurality of overexpressed proteins and/or the sum of expression levels of the one or plurality of underexpressed proteins,

115. The method of Claim 114, which includes calculating a ratio of the sum of expression levels of the one or plurality of overexpressed proteins and the sum of expression levels of the one or plurality of underexpressed proteins,

116. The method of any one of Claims 59 to 115, wherein the anti-cancer treatment is selected from the group consisting of a endocrine therapy, chemotherapy, immunotherapy and a moleculaiiy targeted therapy.

117. The method of Claim 116, wherein the treatment comprises administration of an agent selected from the group consisting of an ALK inhibitor, a BCR-ABL inhibitor, a HSP90 inhibitor, an EGFR inhibitor, a PARP inhibitor, retinoic acid, a Bcl2 inhibitor, a gluconeogenesis inhibitor, a p38 MAPK inhibitor, a MEK1/2 inhibitor, a mTOR inhibitor, a P13K inhibitor, an IGF1R inhibitor, a PLCy inhibitor, a JNK inhibitor, a PAK1 inhibitor, a SYK inhibitor, a HDAC inhibitor, an FGFR inhibitor, a XIAP inhibitor, a PLK1 inhibitor, an ERK5 inhibitor, a TTK inhibitor, an Aurora Kinase Inhibitor and/or any combination thereof.

118. The method of Claim 116, wherein immunotherapy is or comprises an immune checkpoint inhibitor,

119. The method of Claim 118, wherein the immune checkpoint inhibitor is or comprises an anti-PD1 antibody or an anti-PDL1 antibody.

120. A method of predicting the responsiveness of a cancer to an immunotherapeutic agent in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting *of ADORA2B, CD36, CETN3, KCNG1, LAMAS, MAP2K5, MAE1, PGK1, STAU1, CFDP1, SF3B3* and *TXN*, and/or an expression level of one or a plurality of underexpressed genes selected

from the group consisting of *APOBEC3A*, ***BCL2,*** *BTN2A2,* ***CAMSAPI,*** *CAMK4, CARHSPl, FBXW4, GSK3B, HCFCIRL* ***MYB,*** *PSEN2* and *ZNF593,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the inmiunotherapeutic agent.

121. The method of Claim 120, wherein a higher relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or correlates with a relatively increased responsiveness of the cancer to the immunotherapeutie agent; and/or a lower relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of underexpressed genes indicates or **correlates** with a relatively decreased responsiveness of the cancer to the immunotherapeutie agent.

122. The method of Claim 120 or Claim J21, wherein the immunotherapeutie agent is an immune checkpoint inhibitor.

123. The method of Claim 122, wherein the immune checkpoint inhibitor is or comprises an anti-PDl antibody or an anti-PDLl antibody.

124. A method of predicting the responsiveness of a cancer to an epidermal growth factor receptor (EGFR) inhibitor in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of ***NAE1,*** *GSK3B, TAF2, MAPREL* ***BRIM,*** *STAUL TAF2,* ***PDCD4,*** *KCNGL ZNRDI-AS1, EIF4B, HELLS, RPL22, ABAT, BTN2A2, CD1B, ITM2A, BCL2, CXCR4,* and *ARNT2* and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *CDIC,* ***CD****IE, CDIB, KDM5A, BATF, EVE PRKCB, HCFCIRL CARHSPL CHAD, KIR2DL4. ABHD5,* ***ABHD14A,*** *ACAAL SRPK3, CFB, ARNT2, NDUFCL BCL2, EVE ULBP2, BIN3, SF3B3, CETN3, SYNCRIP, TAF2, CENPN, ATP6VICI, CD55* and *ADORA2B,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to the one or plurality of

underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the irnraunotherapeutic agent.

125. A method of predicting the responsiveness of a cancer to a multikinase inhibitor in a mammal, said method including the step of comparing an expression level of one or a plurality of overexpressed genes selected from the group consisting of ***SCUBE,*** *CHPTL CDCl,* ***BTG2.,*** *ADORA2B* and *BCL2*, and/or an expression level of one or a plurality of underexpressed genes selected from the group consisting of *NOP2, CALR, MAPRE1, KCNGl, PGKl, SRPK3, RERE, ADM, LAMAS. KIR2DIA, ULBP2, LAMA4, CA9,* and *BCAP31,* in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated relative expression level of the one or plurality of overexpressed genes compared to tire one or plurality of underexpressed genes indicates or correlates with relatively increased or decreased responsiveness of the cancer to the multikinase inhibitor.

126. The method of any preceding claim, which includes the further step of treating cancer in the mammal.

127. A method for identifying an agent for use in the treatment of cancer including the steps of:

(i) contacting a protein product of ***GRHPR, NDUFCl,*** *CAMSAPI, CETN3, EIF3K, STAU1, EXOSC7, COG8, CFDPl* and/or *KCNGJ* with a test agent; and

(ii) determining whether the test agent, at least partly, reduces, eliminates, suppresses or inhibits the expression and/or an activity of the protein product.

128. The method of Claim 127, wherein **the** agent possesses or displays little or no significant off-target and/or nonspecific effects.

129. The method of Claim 127 or Claim 128, wherein the agent is an antibody or a small organic molecule.

130. A method of treating a cancer in a mammal, including the step of administering to tire mammal a therapeutically effective amount of the agent identified by the method of any one of Claims 127 to 129.

131. The method of any preceding claim wherein the mammal is a human.

132. The method of any preceding claim wherein the cancer includes breast cancer, lung cancer, ovarian cancer, cervical cancer, uterine cancer,

prostate caneer, cancer of the brain and nervous system, head and neck cancer, colon cancer, colorectal cancer, gastric cancer, liver cancer, kidney cancer, bladder cancer, melanoma, lymphoid cancers, myelomonocytic cancers, pancreatic cancer, pituitary cancer, adrenal cancer or musculoskeletal cancer.

133. The method of Claim 132, wherein breast cancer includes aggressive breast cancers and cancer subtypes such as triple negative breast cancer, grade *2* breast cancer, grade 3 breast cancer, lymph node positive (LNT) breast cancer. HER2 positive ($HER2^+$) breast cancer and ER positive (ER^+) breast cancer.

134. An agent identified by the method of any one of Claims 127 to 129 for use in the treatment of cancer.

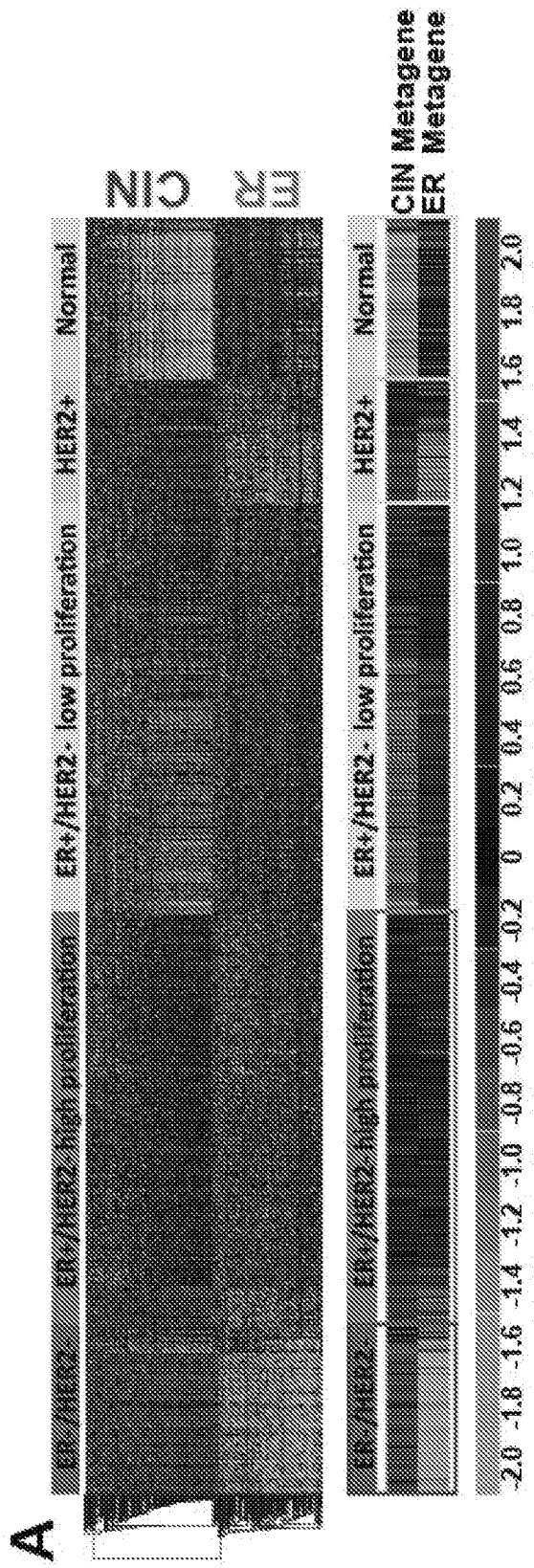
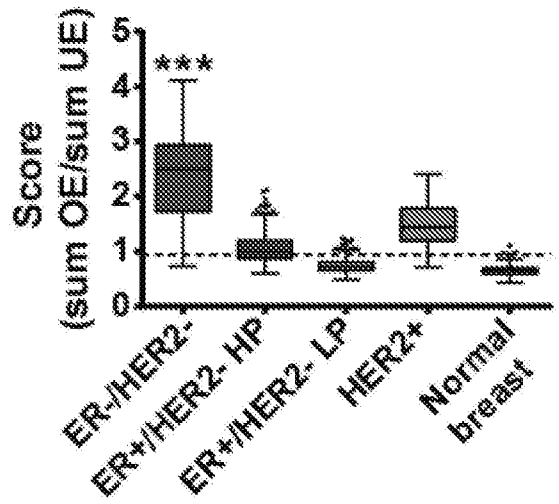

A
CIN
ER
ER-/HER2-
ER+/HER2- high proliferation
ER+/HER2- low proliferation
HER2+
Normal
CIN Metagene
ER Metagene
-2.0 -1.8 -1.6 -1.4 -1.2 -1.0 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

FIG. 1


Score
(sum OE/sum UE)
0
1
2
3
4
5
***
ER-/HER2-
ER+/HER2- HP
ER+/HER2- LP
HER2+
Normal breast

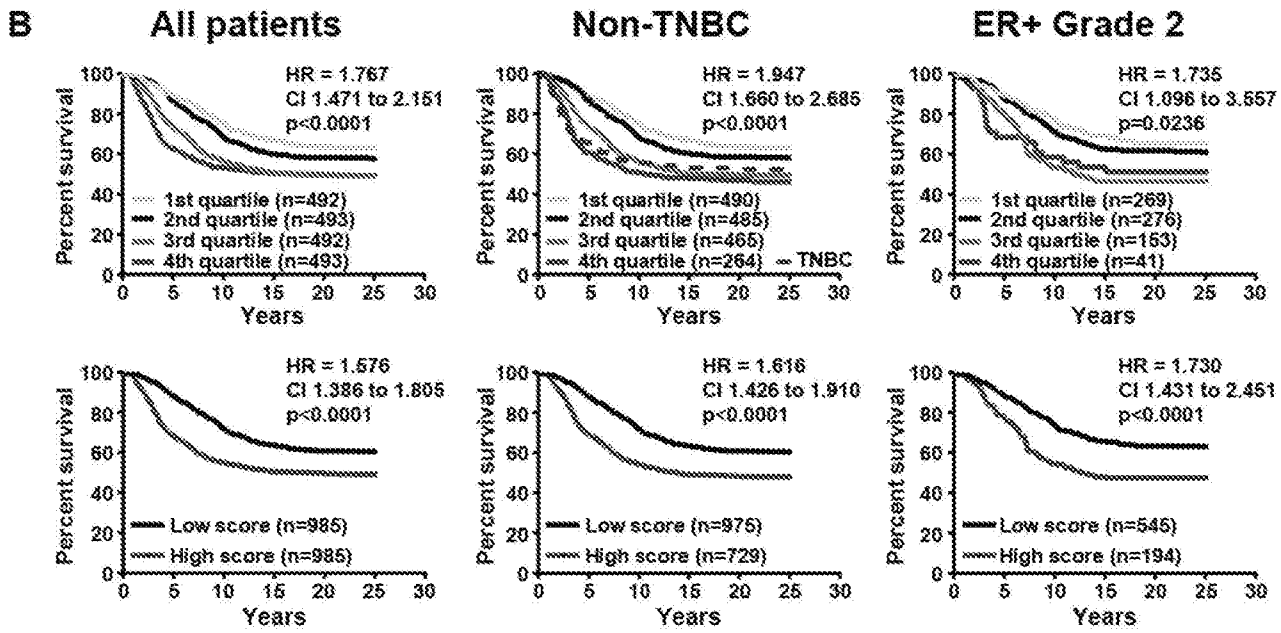

B
All patients
Non-TNBC
ER+ Grade 2
Percent survival
Years
HR = 1.767
CI 1.471 to 2.151
p<0.0001
1st quartile (n=492)
2nd quartile (n=493)
3rd quartile (n=492)
4th quartile (n=493)
HR = 1.947
CI 1.660 to 2.685
p<0.0001
1st quartile (n=490)
2nd quartile (n=485)
3rd quartile (n=465)
4th quartile (n=264) – TNBC
HR = 1.735
CI 1.096 to 3.557
p=0.0236
1st quartile (n=269)
2nd quartile (n=276)
3rd quartile (n=153)
4th quartile (n=41)
HR = 1.576
CI 1.386 to 1.805
p<0.0001
Low score (n=985)
High score (n=985)
HR = 1.616
CI 1.426 to 1.910
p<0.0001
Low score (n=976)
High score (n=729)
HR = 1.730
CI 1.431 to 2.451
p<0.0001
Low score (n=545)
High score (n=194)

FIG. 1 cont'd

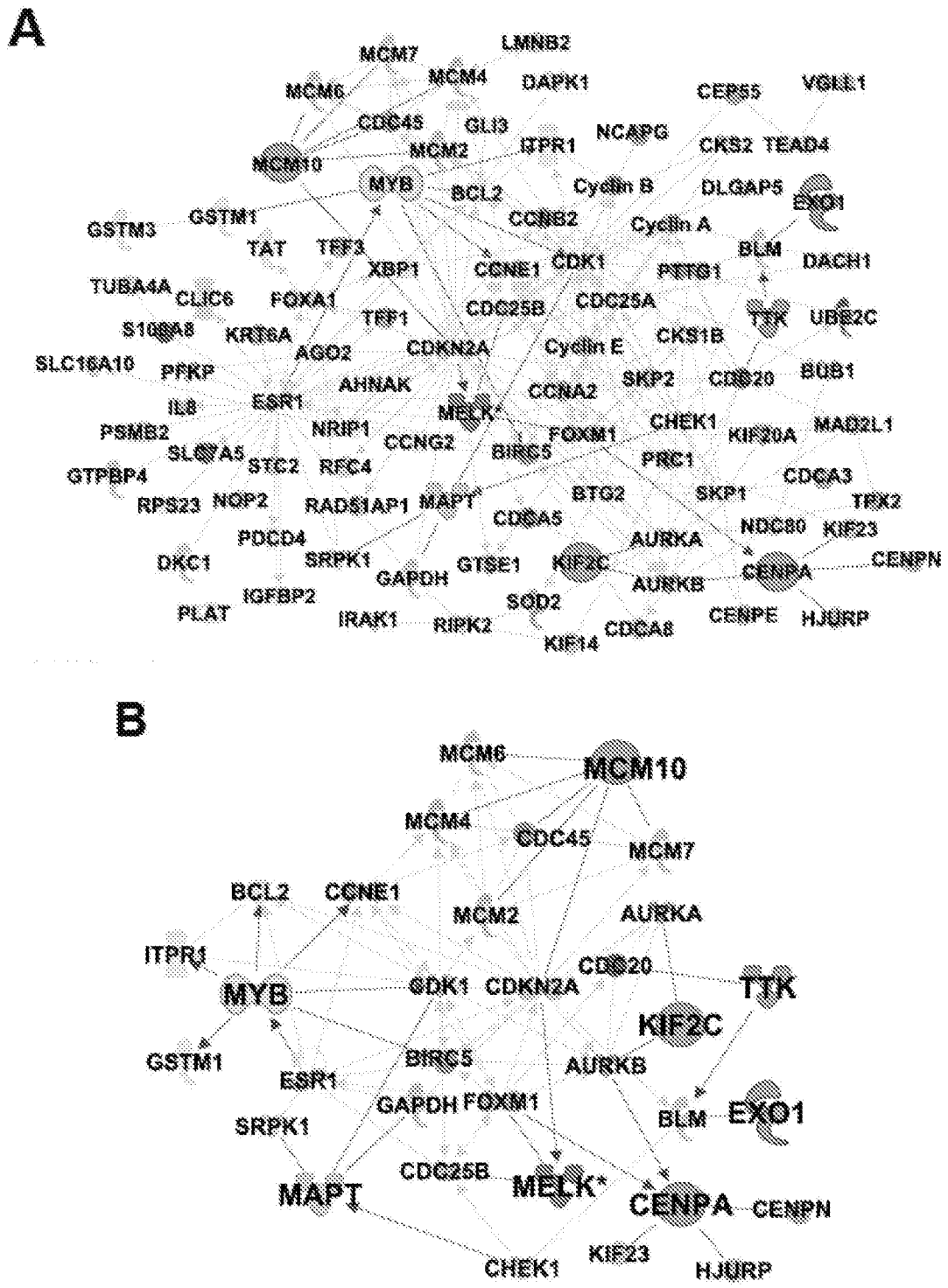

A
MCM7
LMNB2
MCM6
MCM4
DAPK1
CEP55
VGLL1
CDC45
GLI3
NCAPG
MCM10
MCM2
ITPR1
CKS2
TEAD4
MYB
BCL2
Cyclin B
DLGAP5
EXO1
GSTM3
GSTM1
CCNB2
Cyclin A
TAT
TFF3
BLM
DACH1
XBP1
CCNE1
CDK1
PTTG1
TUBA4A
CLIC6
FOXA1
CDC25B
CDC25A
TTK
UBE2C
S100A8
KRT6A
TFF1
AGR2
CDKN2A
Cyclin E
CKS1B
SLC16A10
PFKP
AHNAK
SKP2
CDC20
BUB1
IL8
ESR1
CCNA2
MELK*
PSMB2
NRIP1
CCNG2
FOXM1
CHEK1
KIF20A
MAD2L1
SLC7A5
STC2
RFC4
BIRC5
PRC1
GTPBP4
CDCA3
RPS23
NOP2
RAD51AP1
MAPT
BTG2
SKP1
TFDP2
CDCA5
PDCD4
AURKA
NDC80
KIF23
DKC1
SRPK1
GTSE1
KIF2C
CENPA
CENPN
GAPDH
AURKB
IGFBP2
SOD2
PLAT
IRAK1
RIPK2
CENPE
HJURP
CDCA8
KIF14
B
MCM6
MCM10
MCM4
CDC45
MCM7
BCL2
CCNE1
MCM2
AURKA
ITPR1
CDC20
MYB
CDK1
CDKN2A
TTK
KIF2C
GSTM1
BIRC5
AURKB
ESR1
GAPDH
FOXM1
EXO1
BLM
SRPK1
CDC25B
MAPT
MELK*
CENPA
CENPN
CHEK1
KIF23
HJURP

FIG. 2

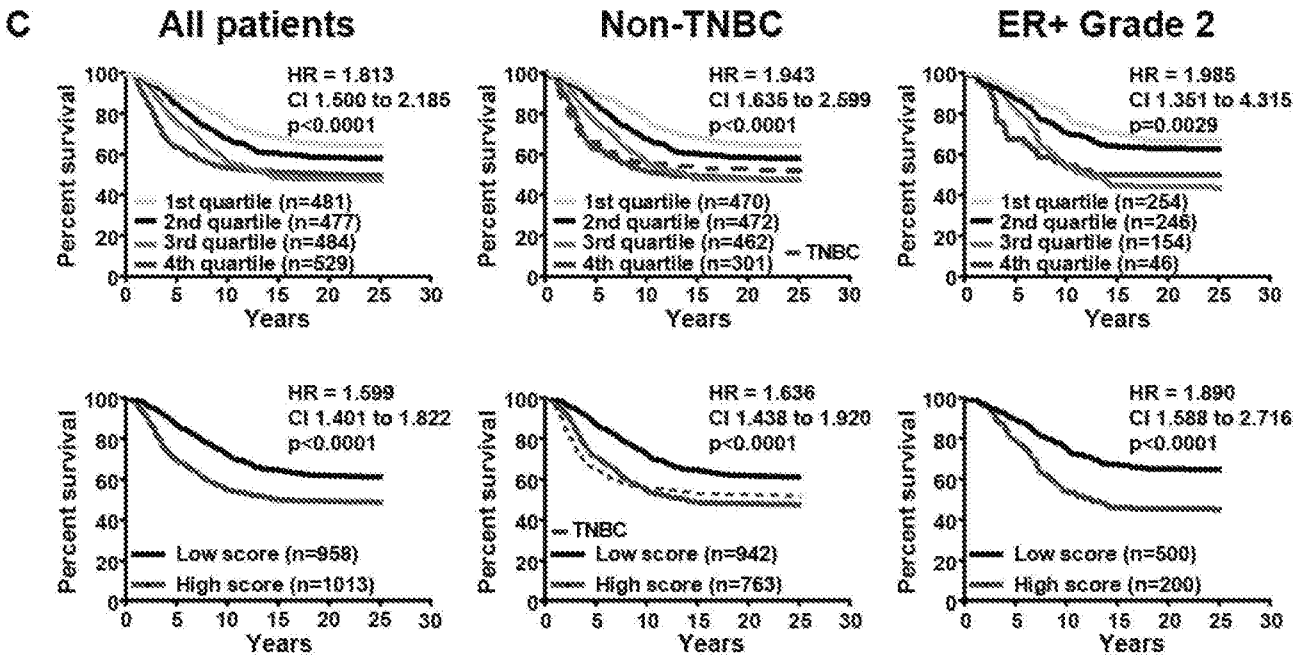

C
All patients
Non-TNBC
ER+ Grade 2
HR = 1.813
CI 1.500 to 2.185
p<0.0001
1st quartile (n=481)
2nd quartile (n=477)
3rd quartile (n=484)
4th quartile (n=529)
HR = 1.943
CI 1.635 to 2.599
p<0.0001
1st quartile (n=470)
2nd quartile (n=472)
3rd quartile (n=462)
4th quartile (n=301)
TNBC
HR = 1.985
CI 1.351 to 4.315
p=0.0029
1st quartile (n=254)
2nd quartile (n=248)
3rd quartile (n=154)
4th quartile (n=46)
HR = 1.599
CI 1.401 to 1.822
p<0.0001
Low score (n=958)
High score (n=1013)
HR = 1.636
CI 1.438 to 1.920
p<0.0001
TNBC
Low score (n=942)
High score (n=763)
HR = 1.890
CI 1.588 to 2.716
p<0.0001
Low score (n=500)
High score (n=200)
Percent survival
Years

FIG. 2 cont'd

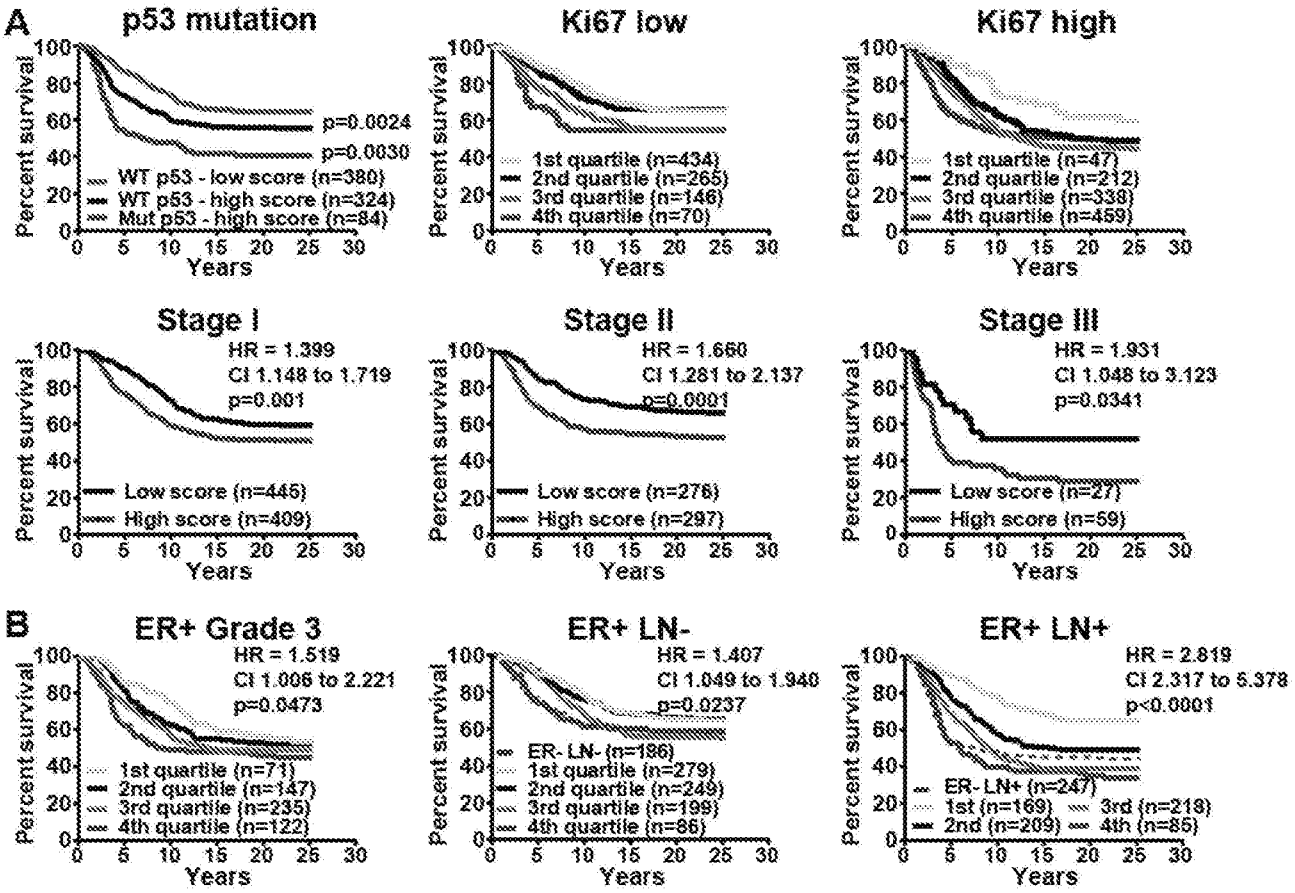
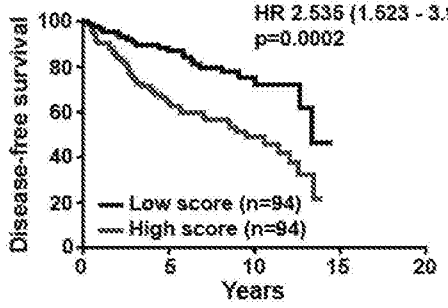

A
p53 mutation
Percent survival
Years
p=0.0024
p=0.0030
WT p53 - low score (n=380)
WT p53 - high score (n=324)
Mut p53 - high score (n=84)
Ki67 low
1st quartile (n=434)
2nd quartile (n=265)
3rd quartile (n=146)
4th quartile (n=70)
Ki67 high
1st quartile (n=47)
2nd quartile (n=212)
3rd quartile (n=338)
4th quartile (n=459)
Stage I
HR = 1.399
CI 1.148 to 1.719
p=0.001
Low score (n=445)
High score (n=409)
Stage II
HR = 1.660
CI 1.281 to 2.137
p=0.0001
Low score (n=276)
High score (n=297)
Stage III
HR = 1.931
CI 1.048 to 3.123
p=0.0341
Low score (n=27)
High score (n=59)
B
ER+ Grade 3
HR = 1.519
CI 1.006 to 2.221
p=0.0473
1st quartile (n=71)
2nd quartile (n=147)
3rd quartile (n=235)
4th quartile (n=122)
ER+ LN-
HR = 1.407
CI 1.049 to 1.940
p=0.0237
ER- LN- (n=186)
1st quartile (n=279)
2nd quartile (n=249)
3rd quartile (n=199)
4th quartile (n=86)
ER+ LN+
HR = 2.819
CI 2.317 to 5.378
p<0.0001
ER- LN+ (n=247)
1st (n=169)
2nd (n=209)
3rd (n=218)
4th (n=85)

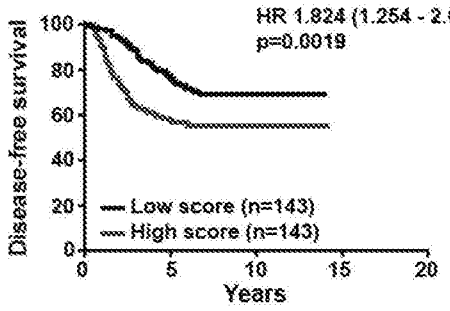
FIG. 3

A



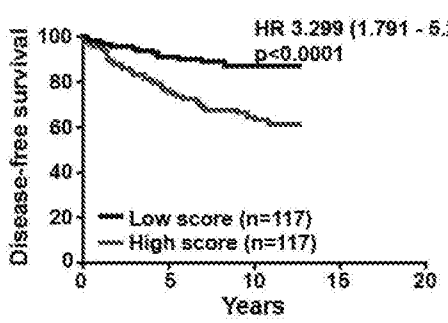
Covariate	HR (95% CI)	P-value
8 genes Score (high, low)	2.6267 (1.3695 - 5.0378)	0.0038
Lymph node (+, -)	0.9409 (0.4327 - 2.0459)	0.8785
Grade (1, 2, 3)	1.0276 (0.7178 - 1.4713)	0.8826
ER (+,-)	0.9833 (0.5223 - 1.8512)	0.9587

C



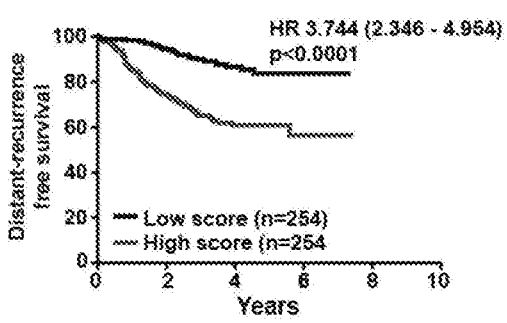
Covariate	HR (95% CI)	P-value
8 genes Score (high, low)	2.2123 (1.4438 - 3.3910)	0.0003
ER (+,-)	1.5586 (0.9634 - 2.5214)	0.072

B



Covariate	HR (95% CI)	P-value
8 genes Score (high, low)	2.1445 (1.0906 - 4.2176)	0.015
Lymph node (+, -)	2.8619 (1.5138 - 5.0751)	0.0003
ER (+,-)	0.5962 (0.2470 - 1.4394)	0.2526
Grade (1, 2, 3)	1.2947 (0.8032 - 2.0869)	0.2914
p53 (mut, WT)	1.2607 (0.6670 - 2.3825)	0.478

D



Covariate	HR (95% CI)	P-value
8 genes Score (high, low)	3.4442 (1.5914 - 7.4540)	0.0018
Lymph node (+, -)	5.4825 (1.7112 - 16.753)	0.0044
Tumor size (1, 2, 3)	1.6679 (1.0037 - 2.7718)	0.0495
ER (+,-)	1.6261 (0.7056 - 3.7473)	0.2561
Grade (1, 2, 3)	0.8233 (0.4696 - 1.4435)	0.4996
PR (+,-)	1.2716 (0.5866 - 2.7561)	0.5448

FIG. 4

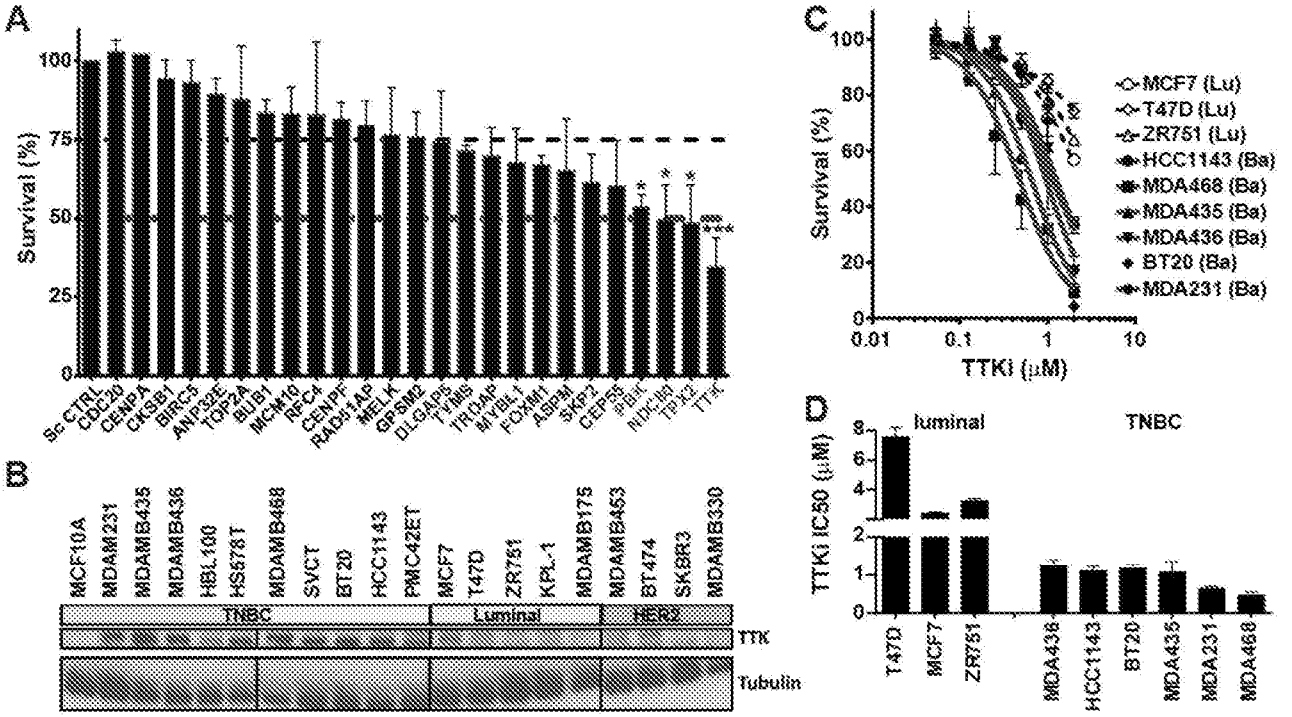

A
Survival (%)
Sc CTRL
CDC20
CENPA
CKS81
BIRC5
ANP32E
TOP2A
BUB1
MCM10
RFC4
CENPF
RAD51AP
MELK
GPSM2
DLGAP5
TYMS
TROAP
MYBL1
FOXM1
ASPM
SKP2
CEP55
PBK
NUCKS1
TPX2
TTK
B
MCF10A
MDAMB231
MDAMB435
MDAMB436
HBL100
HS578T
MDAMB468
SVCT
BT20
HCC1143
PMC42ET
MCF7
T47D
ZR751
KPL-1
MDAMB175
MDAMB453
BT474
SKBR3
MDAMB330
TNBC
Luminal
HER2
TTK
Tubulin
C
Survival (%)
TTKi (μM)
MCF7 (Lu)
T47D (Lu)
ZR751 (Lu)
HCC1143 (Ba)
MDA468 (Ba)
MDA435 (Ba)
MDA436 (Ba)
BT20 (Ba)
MDA231 (Ba)
D
luminal
TNBC
TTKi IC50 (μM)
T47D
MCF7
ZR751
MDA436
HCC1143
BT20
MDA435
MDA231
MDA468

FIG. 5

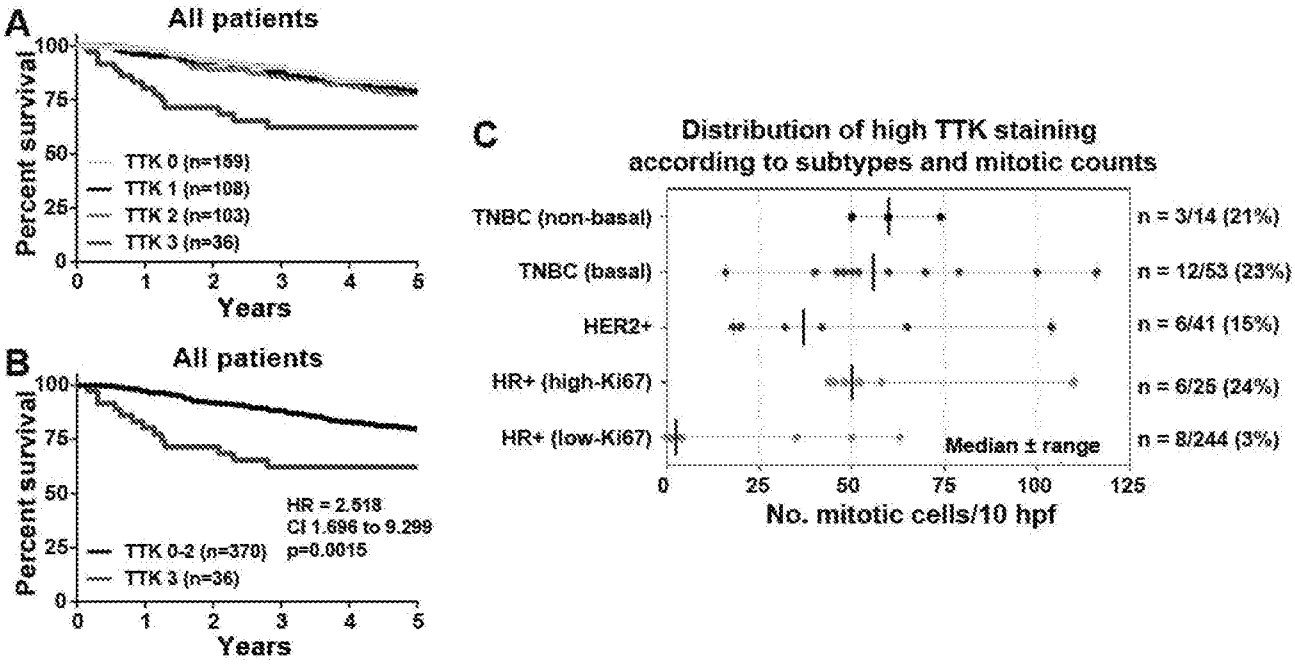

A
All patients
Percent survival
TTK 0 (n=159)
TTK 1 (n=108)
TTK 2 (n=103)
TTK 3 (n=36)
Years
B
All patients
Percent survival
HR = 2.518
CI 1.696 to 9.299
p=8.0015
TTK 0-2 (n=370)
TTK 3 (n=36)
Years
C
Distribution of high TTK staining
according to subtypes and mitotic counts
TNBC (non-basal)
TNBC (basal)
HER2+
HR+ (high-Ki67)
HR+ (low-Ki67)
n = 3/14 (21%)
n = 12/53 (23%)
n = 6/41 (15%)
n = 6/25 (24%)
n = 8/244 (3%)
Median ± range
No. mitotic cells/10 hpf

FIG. 6

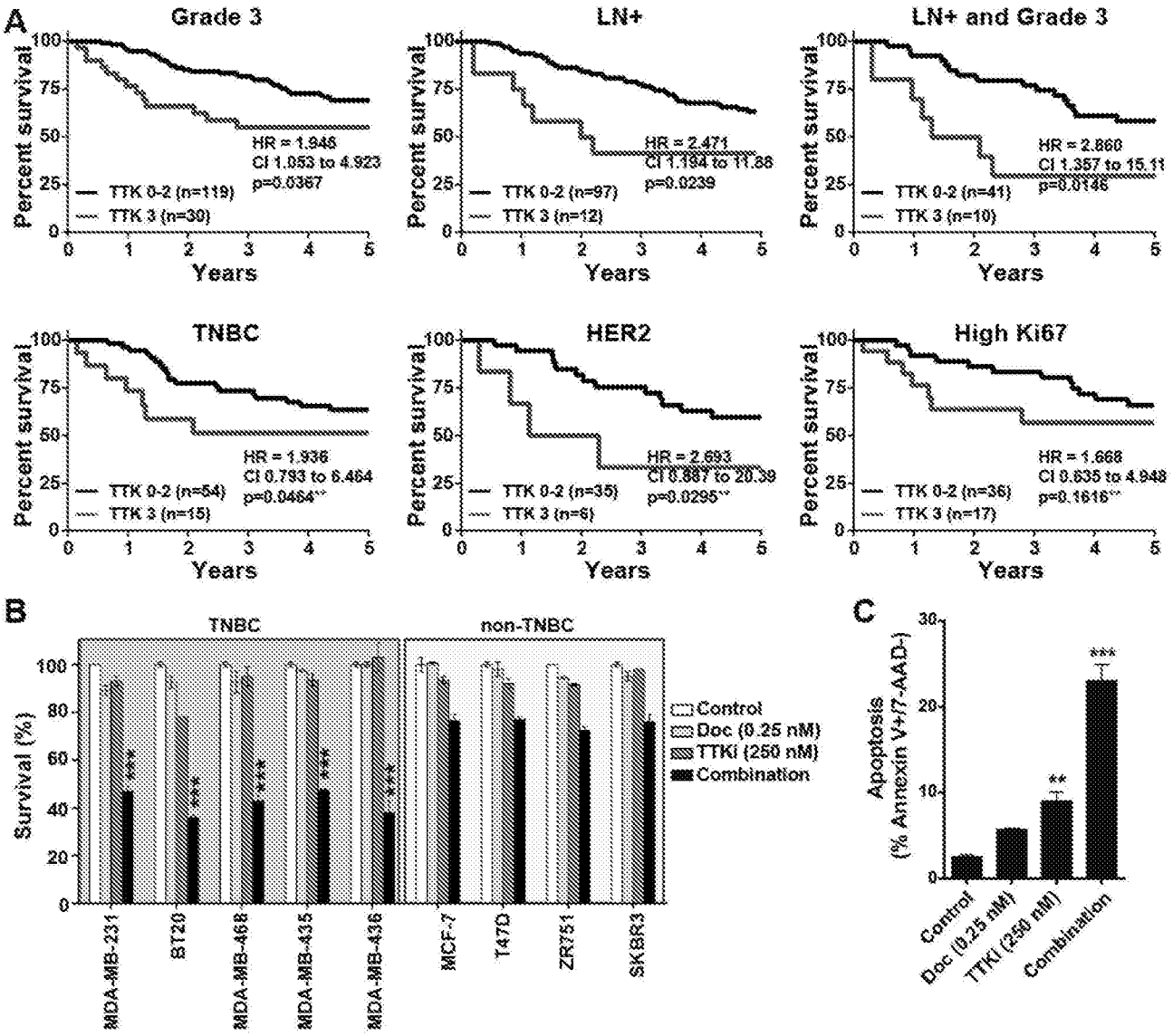

A
Grade 3
Percent survival
Years
HR = 1.946
CI 1.053 to 4.923
p=0.0367
TTK 0-2 (n=119)
TTK 3 (n=30)
LN+
HR = 2.471
CI 1.194 to 11.88
p=0.0239
TTK 0-2 (n=97)
TTK 3 (n=12)
LN+ and Grade 3
HR = 2.860
CI 1.357 to 15.11
p=0.0146
TTK 0-2 (n=41)
TTK 3 (n=10)
TNBC
HR = 1.936
CI 0.793 to 6.464
p=0.0464**
TTK 0-2 (n=54)
TTK 3 (n=15)
HER2
HR = 2.693
CI 0.887 to 20.39
p=0.0295**
TTK 0-2 (n=35)
TTK 3 (n=6)
High Ki67
HR = 1.668
CI 0.635 to 4.948
p=0.1616**
TTK 0-2 (n=36)
TTK 3 (n=17)
B
TNBC
non-TNBC
Survival (%)
Control
Doc (0.25 nM)
TTKi (250 nM)
Combination
MDA-MB-231
BT20
MDA-MB-468
MDA-MB-435
MDA-MB-436
MCF-7
T47D
ZR751
SKBR3
C
Apoptosis
(% Annexin V+/7-AAD-)
Control
Doc (0.25 nM)
TTKi (250 nM)
Combination

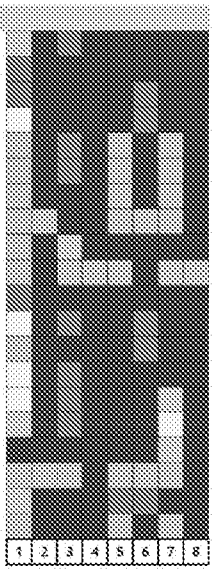
FIG. 7

A

Comparison of All Genes Across 8 Analyses

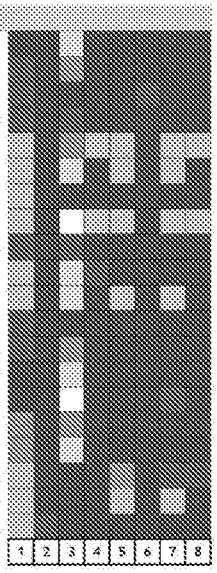
Overexpression

Median Rank	p-Value	Gene
6.0	3.11E-12	GSTP1
11.0	1.74E-10	BCL11A
15.0	1.08E-10	FOXC1
15.5	1.35E-8	GABRP
20.0	1.45E-28	CDCA7
21.0	7.62E-10	B3GNT5
23.0	1.98E-27	PM20D2
26.0	1.74E-9	ROPN1B
29.0	2.40E-7	PISAT1
34.5	2.48E-8	RPL32P16
37.5	2.61E-9	FAM171A1
41.5	4.58E-9	DSC2
45.0	6.40E-7	ROPN1
47.5	2.39E-9	PRKX
54.0	4.25E-9	PRKD3
57.0	3.67E-9	YBX1
59.0	4.08E-9	LBR
59.0	6.61E-9	MSL3L2
64.5	1.71E-8	UGT8
65.0	4.91E-8	MTHFD1L



Underexpression

Median Rank	p-Value	Gene
3.5	2.39E-20	ESR1
4.5	4.58E-17	NAT1
11.5	1.45E-14	FOXA1
12.5	5.14E-15	TBC1D9
13.0	5.29E-16	CAPN8
14.0	1.45E-44	AGR3
14.0	5.01E-14	MLPH
19.0	1.99E-15	FLJ45983
20.5	2.04E-13	GATA3
24.0	5.93E-42	C6orf211
24.0	1.71E-14	FSIP1
24.5	1.70E-11	AGR2
26.0	1.90E-17	CA12
26.5	2.54E-12	ANXA9
28.5	2.70E-5	CYP2B6
29.0	2.14E-10	ABAT
29.0	5.77E-10	SLC39A6
40.0	1.85E-9	PGAP3
43.0	2.50E-9	PRR15
45.0	9.59E-13	MAGED2



Legend

1. Breast Carcinoma - ERBB2/ER/PR Negative
Bild Breast, Nature, 2006
2. Ductal Breast Carcinoma - ERBB2/ER/PR Negative
Bittner Breast, Not Published, 2005
3. Ductal Breast Carcinoma - ERBB2/ER/PR Negative
Bonnefoi Breast, Lancet Oncol, 2007
4. Invasive Breast Carcinoma - ERBB2/ER/PR Negative
Gluck Breast, Breast Cancer Res Treat, 2011
5. Invasive Breast Carcinoma - ERBB2/ER/PR Negative
Hatzis Breast, JAMA, 2011
6. Breast Carcinoma - ERBB2/ER/PR Negative
Kao Breast, BMC Cancer, 2011
7. Invasive Ductal Breast Carcinoma - ERBB2/ER/PR Negative
Tabchy Breast, Clin Cancer Res, 2010
8. Invasive Ductal Breast Carcinoma - ERBB2/ER/PR Negative
TCGA Breast, No Associated Paper, 2011

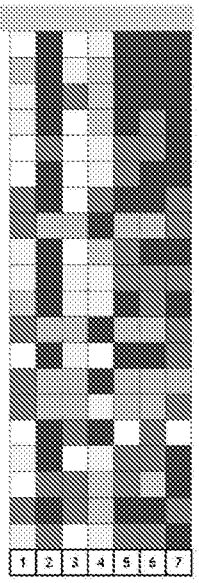
The rank for a gene is the median rank for that gene across each of the analyses.
The p-Value for a gene is its p-Value for the median-ranked analysis

FIG. 8

B **Comparison of All Genes Across 7 Analyses**

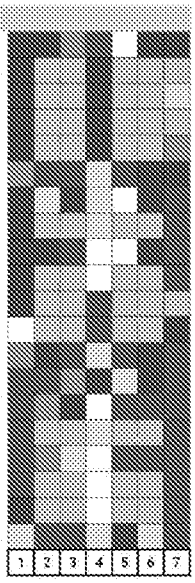
Overexpression

Median Rank	p-Value	Gene
38.0	8.23E-5	NUSAP1
124.0	5.13E-4	CENPA
124.0	0.002	BUB1
147.0	0.003	PRC1
159.0	0.003	FOXM1
161.0	6.57E-4	NEK2
174.0	7.34E-5	KIF23
177.0	7.63E-5	DHTF8
215.0	0.001	RAD51
223.0	1.41E-4	CDK1
254.0	0.005	CCNB2
260.0	2.26E-4	DNAJB11
273.0	2.60E-4	DLGAP5
276.5	0.006	UNC13D
279.0	0.005	PRELID1
287.0	0.006	GLP1R
293.0	0.006	MAD2L1
304.0	0.002	LRP8
304.0	0.005	MCM10
304.0	0.007	BUB1B



Underexpression

Median Rank	p-Value	Gene
79.0	0.003	GLTSCR2
102.0	0.001	MTMR9L
139.0	0.002	CCDC30
147.5	0.002	C14orf167
155.0	0.002	ABCA3
189.0	3.35E-6	CIRBP
210.0	2.95E-4	BTF3
225.0	3.50E-4	STON2
227.0	3.55E-4	NPY1R
228.0	3.59E-4	LOC283788
256.0	0.005	C1QTNF9
260.0	0.005	CDRT4
264.0	4.76E-4	PDCD4
265.0	4.78E-4	RPL13A
266.0	0.005	ABAT
272.0	0.005	ZBTB38
316.0	0.014	CREBL2
330.0	8.45E-4	TRIM35
331.0	8.45E-4	HNRNPA1L2
344.0	9.03E-4	EVL



Legend

1. Breast Carcinoma - Metastatic Event at 5 Years
Bos Breast, Nature, 2009

2. Invasive Ductal Breast Carcinoma - Metastatic Event at 5 Years
Desmedt Breast, Clin Cancer Res, 2007

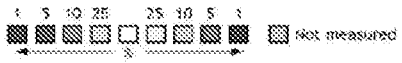
3. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Hatzis Breast, JAMA, 2011

4. Breast Carcinoma - Metastatic Event at 5 Years
Kao Breast, BMC Cancer, 2011

5. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Schmidt Breast, Cancer Res, 2008

6. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Symmans Breast, J Clin Oncol, 2010

7. Breast Carcinoma - Metastatic Event at 5 Years
vandeVijver Breast, N Engl J Med, 2002



The rank for a gene is the median rank for that gene across each of the analyses.
The p-Value for a gene is its p-Value for the median-ranked analysis.

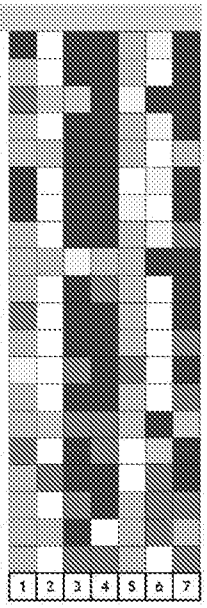
FIG. 8 cont'd

C

Comparison of All Genes Across 7 Analyses

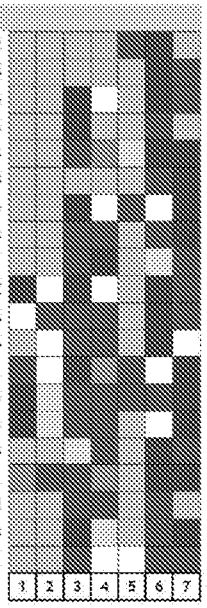
Overexpression

Median Rank	p-Value	Gene
109.5	1.48E-4	CCNB2
110.0	1.61E-4	KIF20A
126.0	0.005	PGK1
135.0	2.23E-4	RACGAP1
136.0	1.47E-4	CDCA5
146.0	2.45E-4	CCNB1
168.0	2.96E-4	FOXM1
171.0	2.96E-5	DEPDC1
171.0	0.003	PGAM5
184.0	2.36E-4	HJURP
187.0	0.004	CDC20
231.0	5.72E-5	MCM10
241.0	0.015	BUB1
242.0	6.04E-5	GTSE1
256.0	4.38E-4	ARFGAP1
257.0	0.010	BIRC5
266.0	0.008	CENPN
273.0	0.005	C16orf61
312.0	0.005	JMY
317.0	1.39E-4	KIF4A



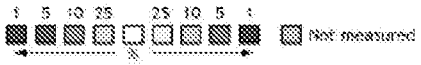
Underexpression

Median Rank	p-Value	Gene
100.0	0.003	CBLN2
121.5	2.00E-4	DCDC5
181.5	2.78E-5	FGD3
195.0	0.002	TMEM26
214.0	6.88E-4	ZNF385B
230.0	0.003	RPL26
248.0	0.019	RERG
249.0	0.002	CCDC74B
255.0	8.65E-4	C5orf41
256.0	3.76E-4	SEC14L2
261.5	0.009	FAM105A
270.0	0.002	BEND5
271.0	0.011	NAT1
271.0	0.021	PTGER3
276.0	0.001	ERBB4
277.5	0.002	KIAA2026
280.0	0.009	MEIS3P1
290.0	0.002	PAPLN
307.5	0.004	SUSD3
311.0	0.001	ADHFE1



Legend

1. Breast Carcinoma - Dead at 5 Years
Bild Breast, Nature, 2006
2. Invasive Ductal Breast Carcinoma - Dead at 5 Years
Desmedt Breast, Clin Cancer Res, 2007
3. Breast Carcinoma - Dead at 5 Years
Kao Breast, BMC Cancer, 2011
4. Breast Carcinoma - Dead at 5 Years
Pawitan Breast, Breast Cancer Res, 2005
5. Ductal Breast Carcinoma - Dead at 5 Years
Sorlie Breast 2, Proc Natl Acad Sci U S A, 2003
6. Invasive Ductal Breast Carcinoma - Dead at 5 Years
TCGA Breast, No Associated Paper, 2011
7. Breast Carcinoma - Dead at 5 Years
vandeVijver Breast, N Engl J Med, 2002



The rank for a gene is the median rank for that gene across each of the analyses.
The p-Value for a gene is its p-Value for the median-ranked analysis.

FIG. 8 cont'd

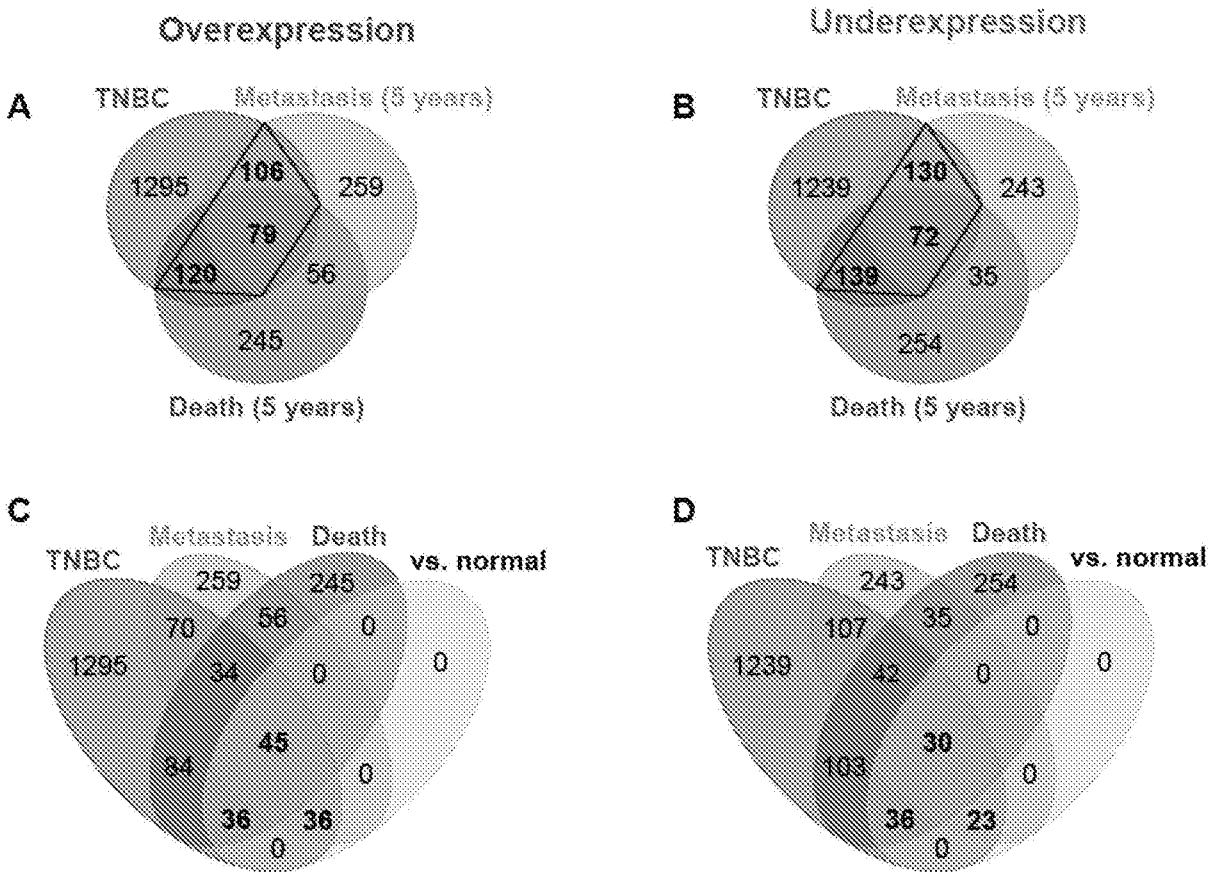

Overexpression
A
TNBC
Metastasis (5 years)
1295
106
259
79
120
56
245
Death (5 years)
Underexpression
B
TNBC
Metastasis (5 years)
1239
130
243
72
139
35
254
Death (5 years)
C
TNBC
Metastasis
Death
vs. normal
259
245
70
56
0
1295
34
0
0
45
84
0
36
36
0
D
TNBC
Metastasis
Death
vs. normal
243
254
107
35
0
1239
42
0
0
30
103
0
36
23
0

FIG. 9

Gene lists	total	Gene
206 genelist AND CIN attractor	45	AURKB FAM83D TPX2 CENPE EXO1 CDCA3 ANLN KIF2C BIRC5 KIF20A MCM10 STIL UBE2C FOXM1 CCNB2 PRC1 CDK1 CENPA CHEK1 MELK CENPW CEP55 CDC20 CENPN NDC80 CCNA2 TTK GTSE1 CDC45 BUB1 NCAPG TRIP13 PTTG1 CDCA5 AURKA FAM64A NUSAP1 KIF14 MAD2L1 DLGAP5 KIF23 DEPDC1 HJURP RAD51AP1 CDCA8
206 genelist AND lymphocyte specific attractor	2	CD163 FPR3
206 genelist AND estrogen receptor attractor	19	CCDC170 FAM214A AGR3 SCUBE2 DACH1 GFRA1 FOXA1 ESR1 DNAJC12 MLPH TBC1D9 TFF1 IL6ST TFF3 *MAPT* XBP1 DNALI1 *MYB* SLC39A6
206 genelist Unique (cell cycle enriched based on gene set enrichment analysis, GSEA)	140	PTGER3 KIF13B KCNMA1 SH3BGRL C1orf106 BTG2 CKS1B STK32B BYSL PFKP CKAP2L KCNG1 IRAK1 GGH SYTL4 TUBA4A ATP6V1C2 RAB27B GPSM2 CMYA5 SOD2 AQP3 NOSTRIN BLM AGO2 SRPK1 PSMB2 OGN NFIA PLCH1 IL8 ELOVL5 PIP CDC25B GSTM1 CYB5D1 MCM6 FAM198B CASC1 CIRBP CSTB LMNB2 CPEB2 RPS23 NOVA1 CA9 RPP40 PNPLA7 NUP93 PDCD4 SLC7A5 HSD17B8 PLAT ALDH3A2 RERG TAT SOX11 SKP1 CARD10 NUP205 GTPBP4 CMC2 MEIS3P1 CCNE1 IGFBP2 STC2 IMPA2 MCM7 GDPR SRD5A1 CCDC176 GDCA7 YEATS2 LRP8 BCL2 SKP2 IGFBP4 SLC40A1 LRIG1 PTPRT AZGP1 KCTD3 GAPDH HSD17B4 AUNIP DKC1 LAD1 NOP2 CDKN2A GLI3 LOC100286909 CYBRD1 CTSV MST1 RFC4 PHYHD1 S100A8 NRIP1 CCNG2 BBS1 MTHFD1L LFNG CST3 KRT6A GPD1L USB1 TMEM26 DAPK1 KIF5C RABEP1 MCM2 LAPTM4B HRASLS MCM4 RNASE4 CLIC6 APOBEC3B C18orf56 TROAP NME5 ECI2 GSTM3 C10orf32 SLC2A1 RIPK2 ADIRF C1orf21 SLC16A10 AHNAK CKS2 VGLL1 MX2 TEAD4 PNP RBM38 GLYATL2 C7orf63 LYPD6 AFF3 CDC25A

FIG. 10

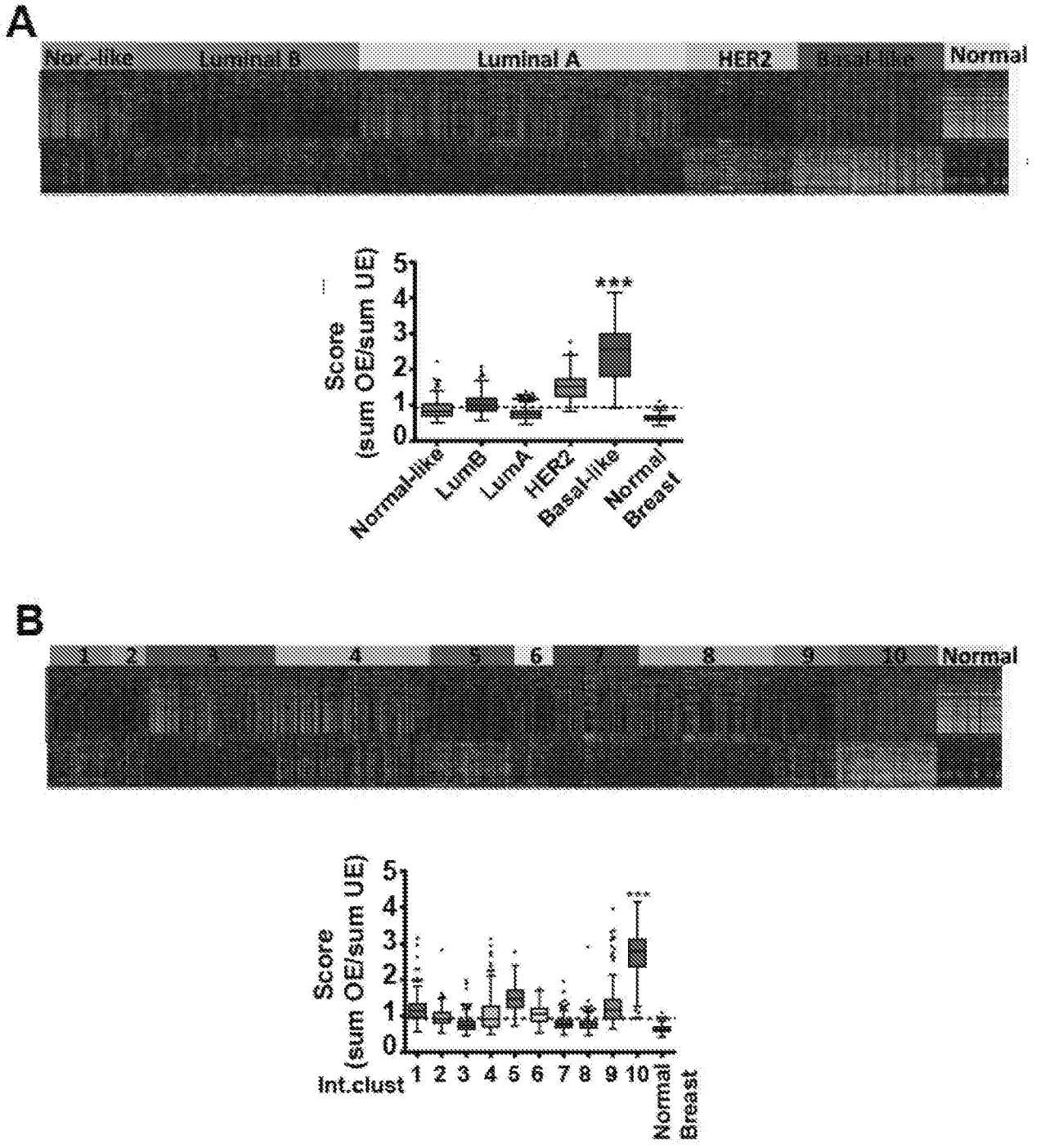

A
Nor.-like
Luminal B
Luminal A
HER2
Basal-like
Normal
Score (sum OE/sum UE)
***
Normal-like
LumB
LumA
HER2
Basal-like
Normal Breast
B
1
2
3
4
5
6
7
8
9
10
Normal
Score (sum OE/sum UE)
Int.clust
Normal Breast
ER+ Grade 3
HR = 1.576
CI 1.069 to 2.137
p=0.0196
1st quartile (n=73)
2nd quartile (n=154)
3rd quartile (n=279)
4th quartile (n=217)
Years
ER+ Grade 3
HR = 1.294
CI 1.027 to 1.575
0.0276
Low score (n=227)
High score (n=496)
Percent survival
Years
PAM50 - high score
n.s.
Normal-like (n=71)
basal-like (n=328)
Her2 (n=226)
LumA (n=79)
LumB (n=279)
Percent survival
Years

FIG. 11

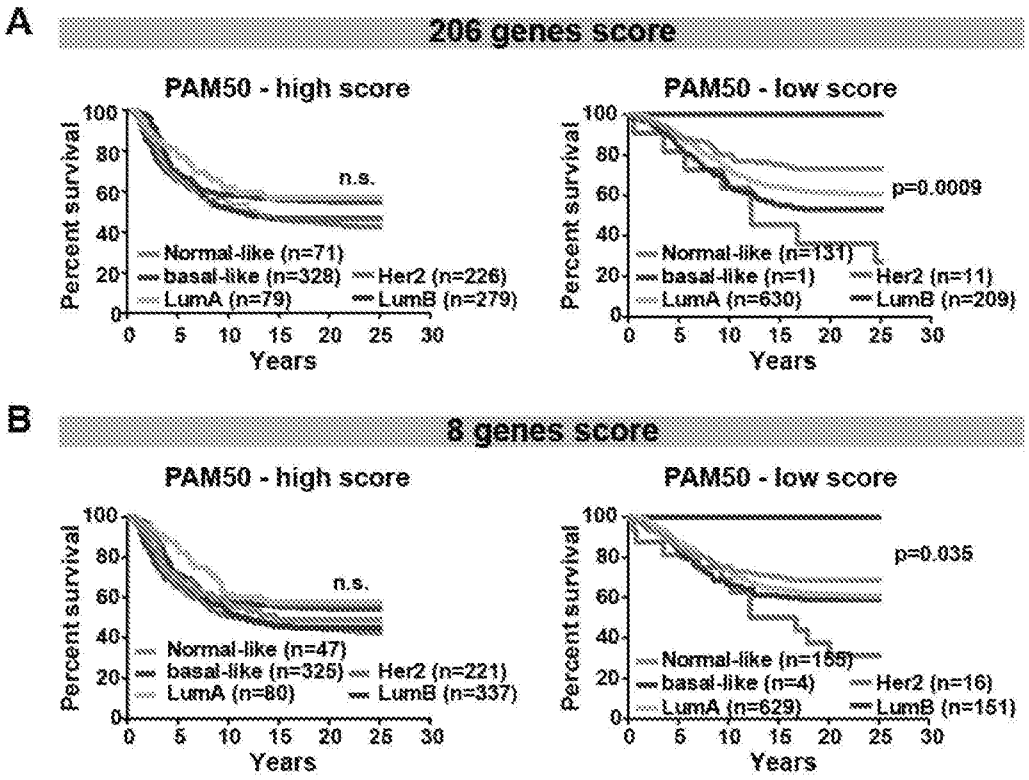

A
206 genes score
PAM50 - high score
Percent survival
Years
n.s.
Normal-like (n=71)
basal-like (n=328)
Her2 (n=226)
LumA (n=79)
LumB (n=279)
PAM50 - low score
p=0.0009
Normal-like (n=131)
basal-like (n=1)
Her2 (n=11)
LumA (n=630)
LumB (n=209)
B
8 genes score
PAM50 - high score
n.s.
Normal-like (n=47)
basal-like (n=325)
Her2 (n=221)
LumA (n=80)
LumB (n=337)
PAM50 - low score
p=0.035
Normal-like (n=155)
basal-like (n=4)
Her2 (n=16)
LumA (n=629)
LumB (n=151)

FIG. 12

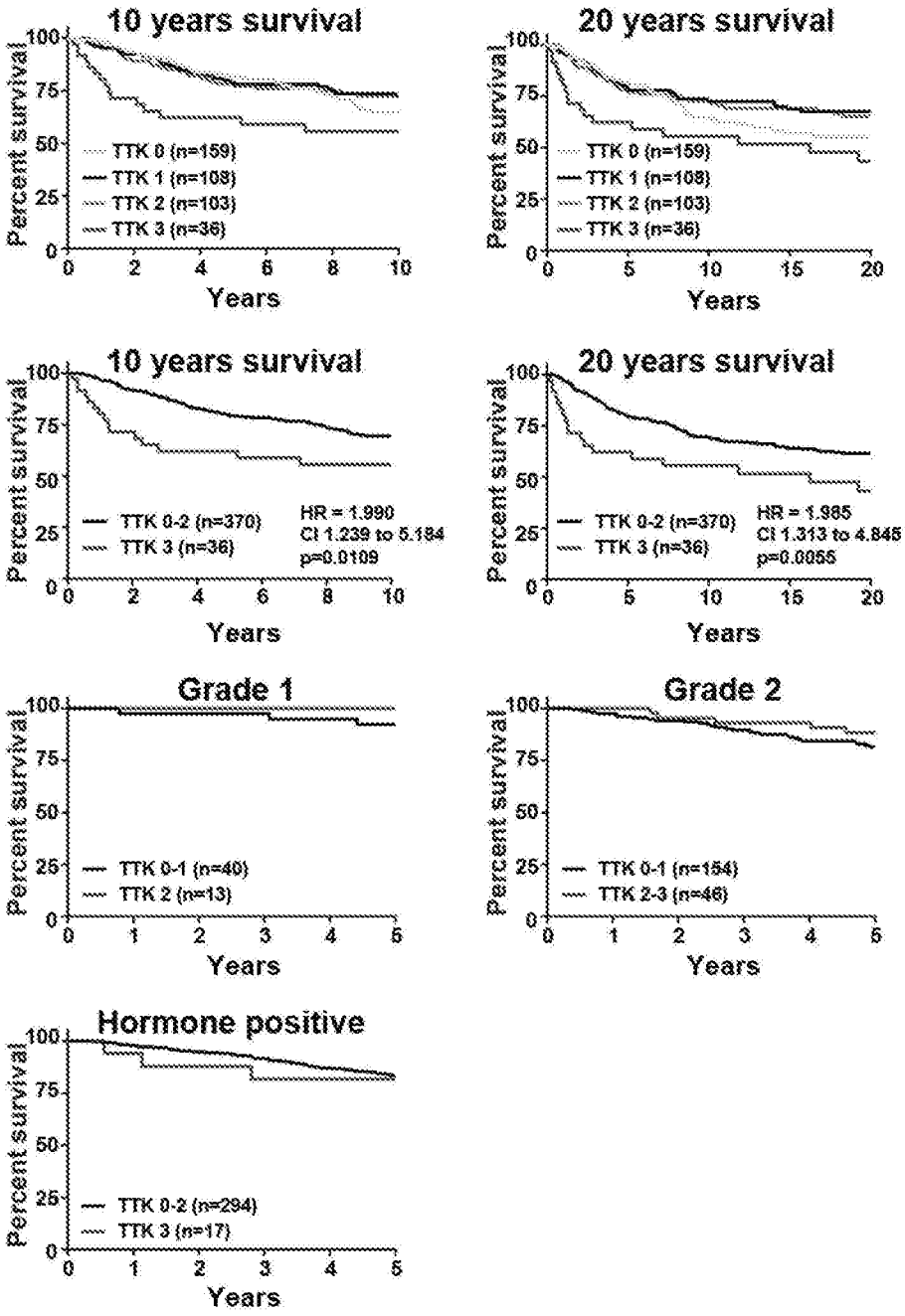

10 years survival
Percent survival
Years
TTK 0 (n=159)
TTK 1 (n=108)
TTK 2 (n=103)
TTK 3 (n=36)
20 years survival
Percent survival
Years
TTK 0 (n=159)
TTK 1 (n=108)
TTK 2 (n=103)
TTK 3 (n=36)
10 years survival
Percent survival
Years
TTK 0-2 (n=370)
TTK 3 (n=36)
HR = 1.990
CI 1.239 to 5.184
p=0.0109
20 years survival
Percent survival
Years
TTK 0-2 (n=370)
TTK 3 (n=36)
HR = 1.985
CI 1.313 to 4.845
p=0.0055
Grade 1
Percent survival
Years
TTK 0-1 (n=40)
TTK 2 (n=13)
Grade 2
Percent survival
Years
TTK 0-1 (n=154)
TTK 2-3 (n=46)
Hormone positive
Percent survival
Years
TTK 0-2 (n=294)
TTK 3 (n=17)

FIG. 13

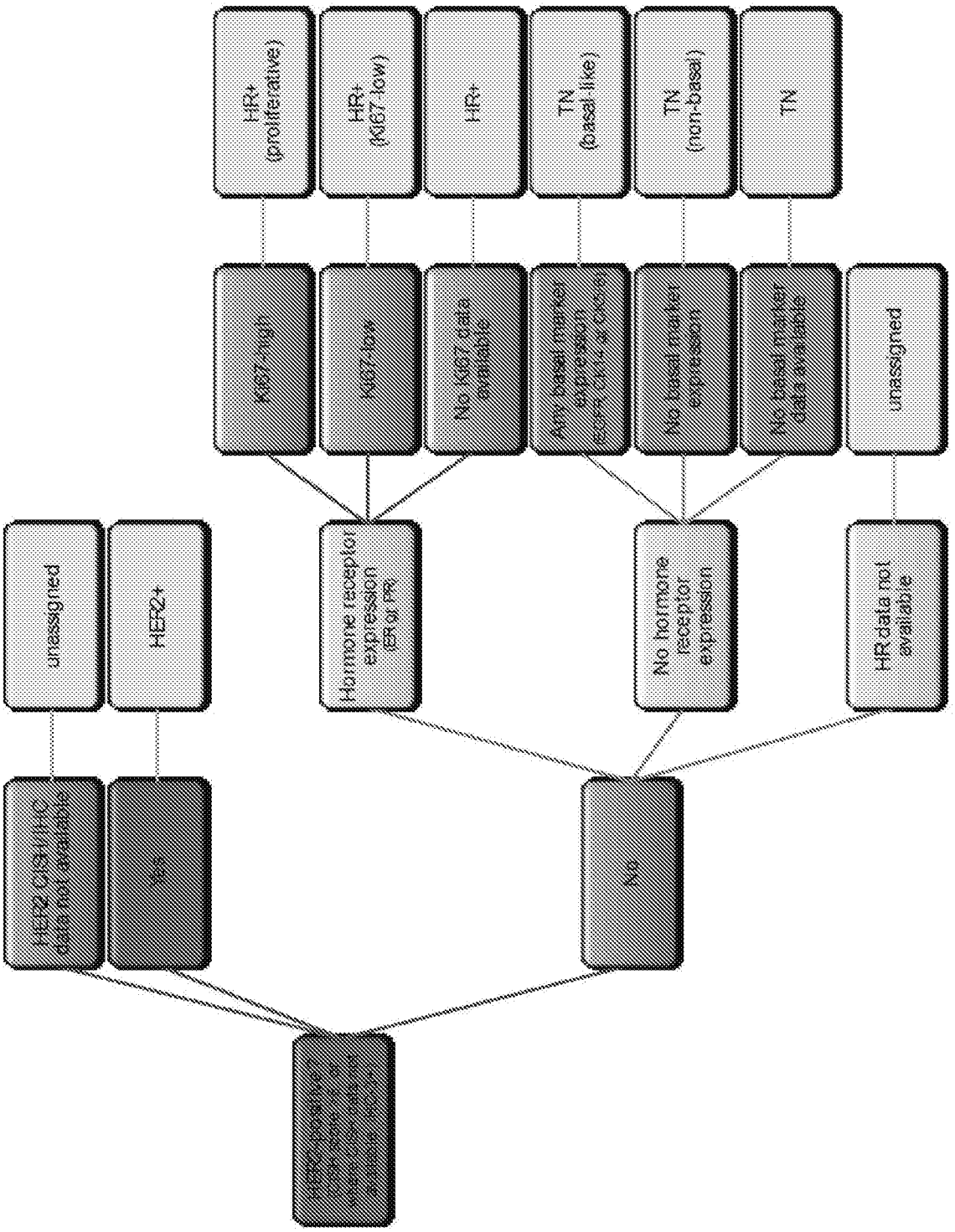

HR+ (proliferative)
HR+ (Ki67-low)
HR+
TN (basal like)
TN (non-basal)
TN
Ki67 -high
Ki67-low
No Ki67 data available
Any basal marker expression
No basal marker expression
No basal marker data available
unassigned
unassigned
HER2+
Hormone receptor expression (ER or PR
No hormone receptor expression
HR data not available
HER2 IHC/ISH data not available
HER2
No

FIG. 14

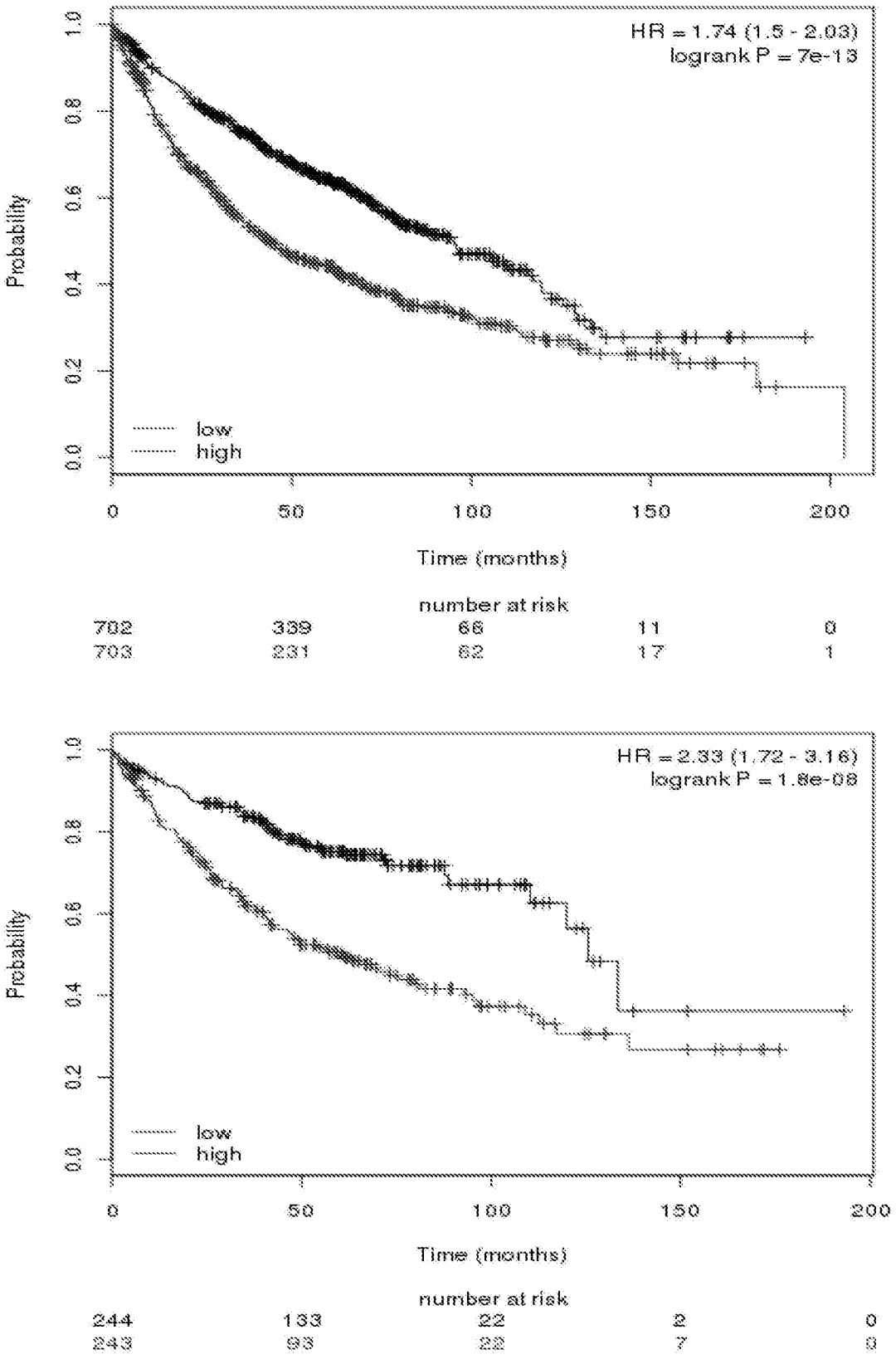

HR = 1.74 (1.5 - 2.03)
logrank P = 7e-13
Probability
1.0
0.8
0.6
0.4
0.2
0.0
low
high
0
50
100
150
200
Time (months)
number at risk
702 339 66 11 0
703 231 62 17 1
HR = 2.33 (1.72 - 3.16)
logrank P = 1.8e-08
Probability
1.0
0.8
0.6
0.4
0.2
0.0
low
high
0
50
100
150
200
Time (months)
number at risk
244 133 22 2 0
243 93 22 7 0

FIG. 15

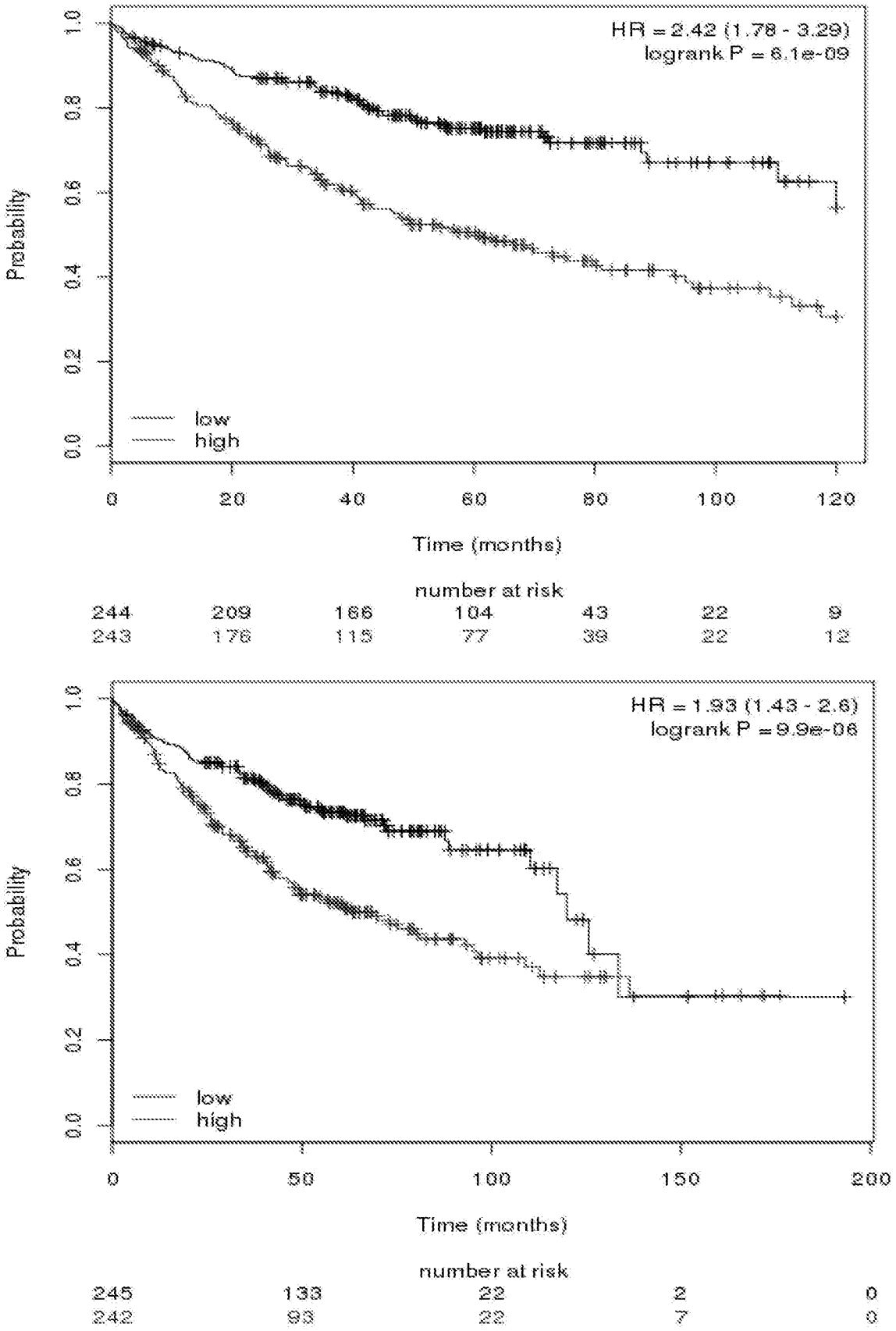

HR = 2.42 (1.78 - 3.29)
logrank P = 6.1e-09
Probability
1.0
0.8
0.6
0.4
0.2
0.0
low
high
0
20
40
60
80
100
120
Time (months)
number at risk
244 209 166 104 43 22 9
243 176 115 77 39 22 12
HR = 1.93 (1.43 - 2.6)
logrank P = 9.9e-06
Probability
1.0
0.8
0.6
0.4
0.2
0.0
low
high
0
50
100
150
200
Time (months)
number at risk
245 133 22 2 0
242 93 22 7 0

FIG. 15 cont'd

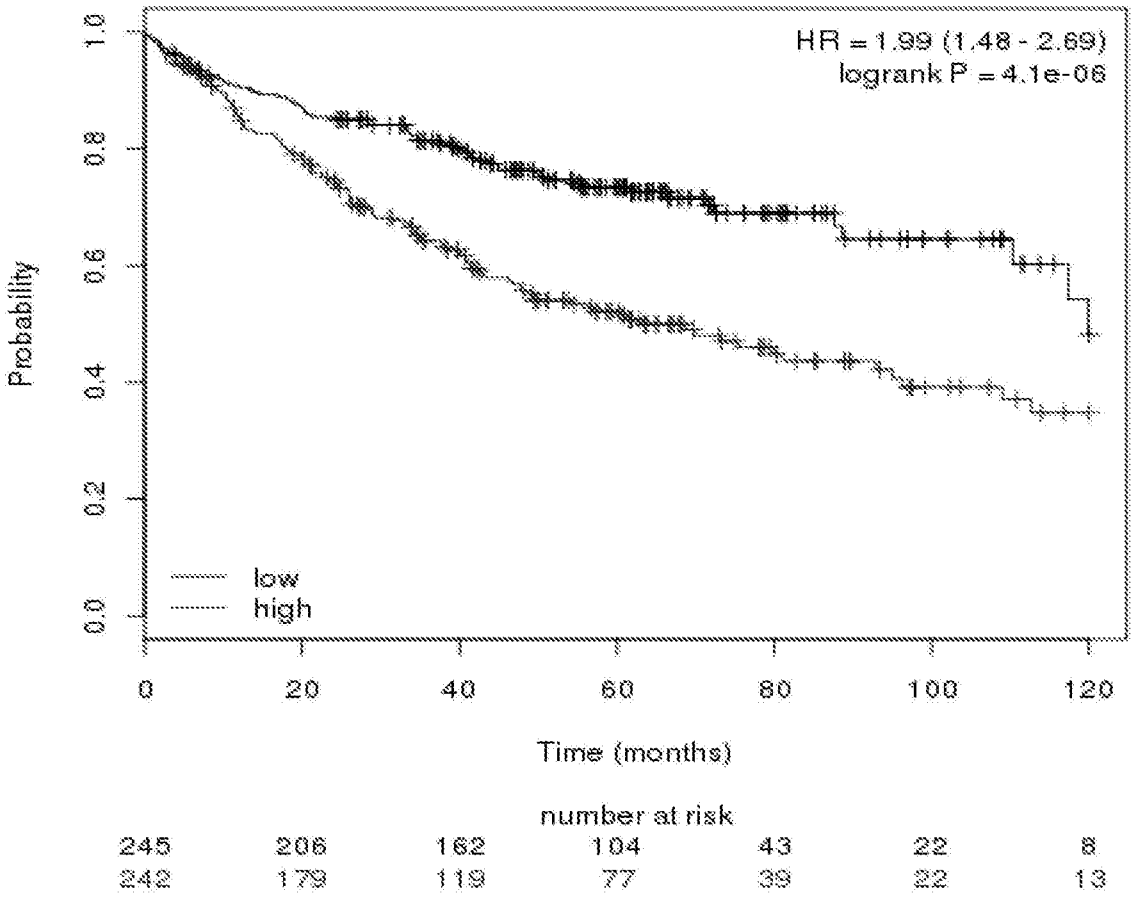

HR = 1.99 (1.48 - 2.69)
logrank P = 4.1e-06
Probability
1.0
0.8
0.6
0.4
0.2
0.0
low
high
0
20
40
60
80
100
120
Time (months)
number at risk
245 206 162 104 43 22 8
242 179 119 77 39 22 13

FIG. 15 cont'd

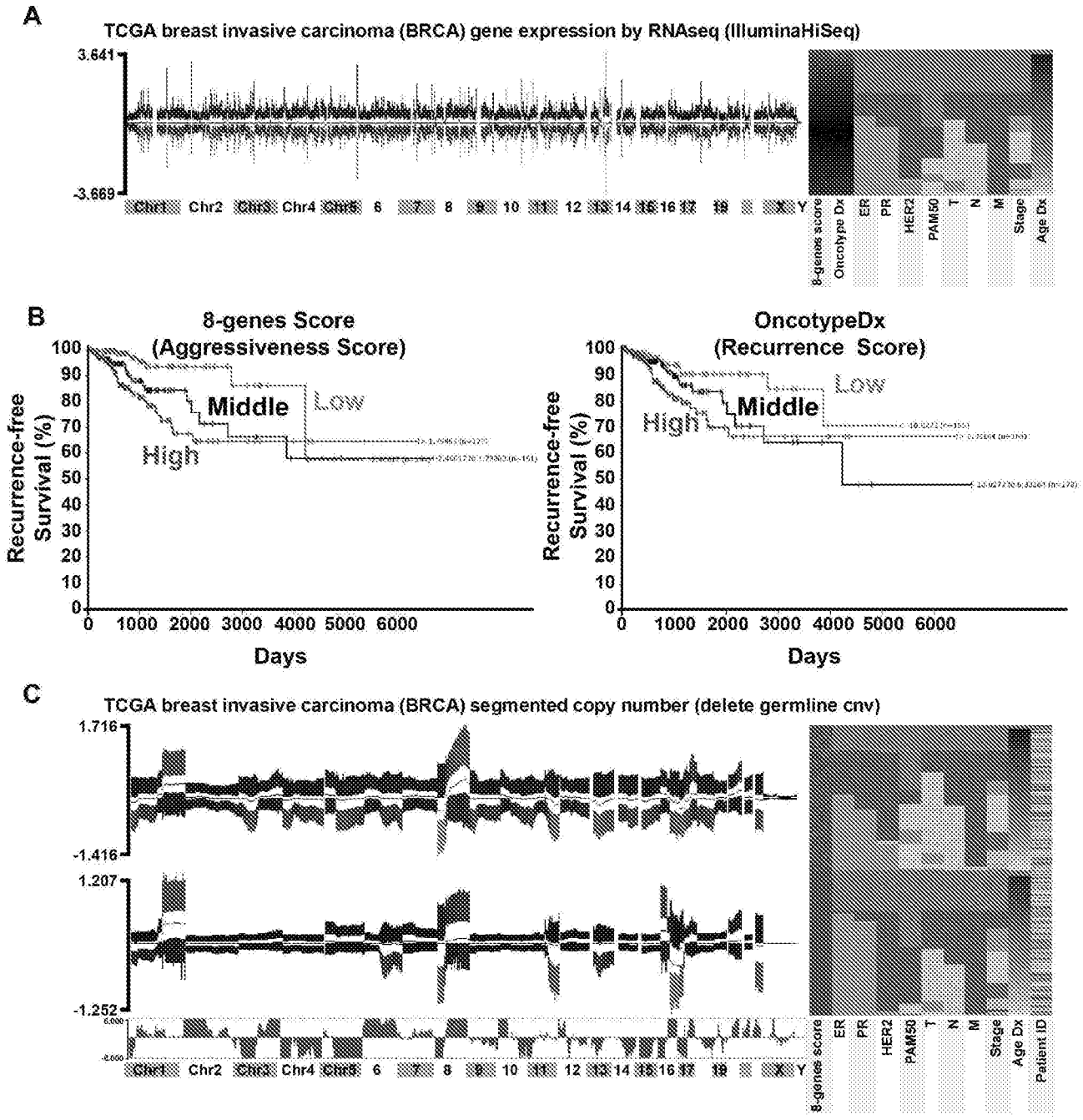

A
TCGA breast invasive carcinoma (BRCA) gene expression by RNAseq (IlluminaHiSeq)
3.641
-3.669
Chr1 Chr2 Chr3 Chr4 Chr5 6 7 8 9 10 11 12 13 14 15 16 17 19 X Y
8-genes score
Oncotype Dx
ER
PR
HER2
PAM50
T
N
M
Stage
Age Dx
B
8-genes Score
(Aggressiveness Score)
Recurrence-free Survival (%)
Middle
Low
High
Days
OncotypeDx
(Recurrence Score)
Recurrence-free Survival (%)
Low
Middle
High
Days
C
TCGA breast invasive carcinoma (BRCA) segmented copy number (delete germline cnv)
1.716
-1.416
1.207
-1.252
Chr1 Chr2 Chr3 Chr4 Chr5 6 7 8 9 10 11 12 13 14 15 16 17 19 X Y
8-genes score
ER
PR
HER2
PAM50
T
N
M
Stage
Age Dx
Patient ID

FIG. 16

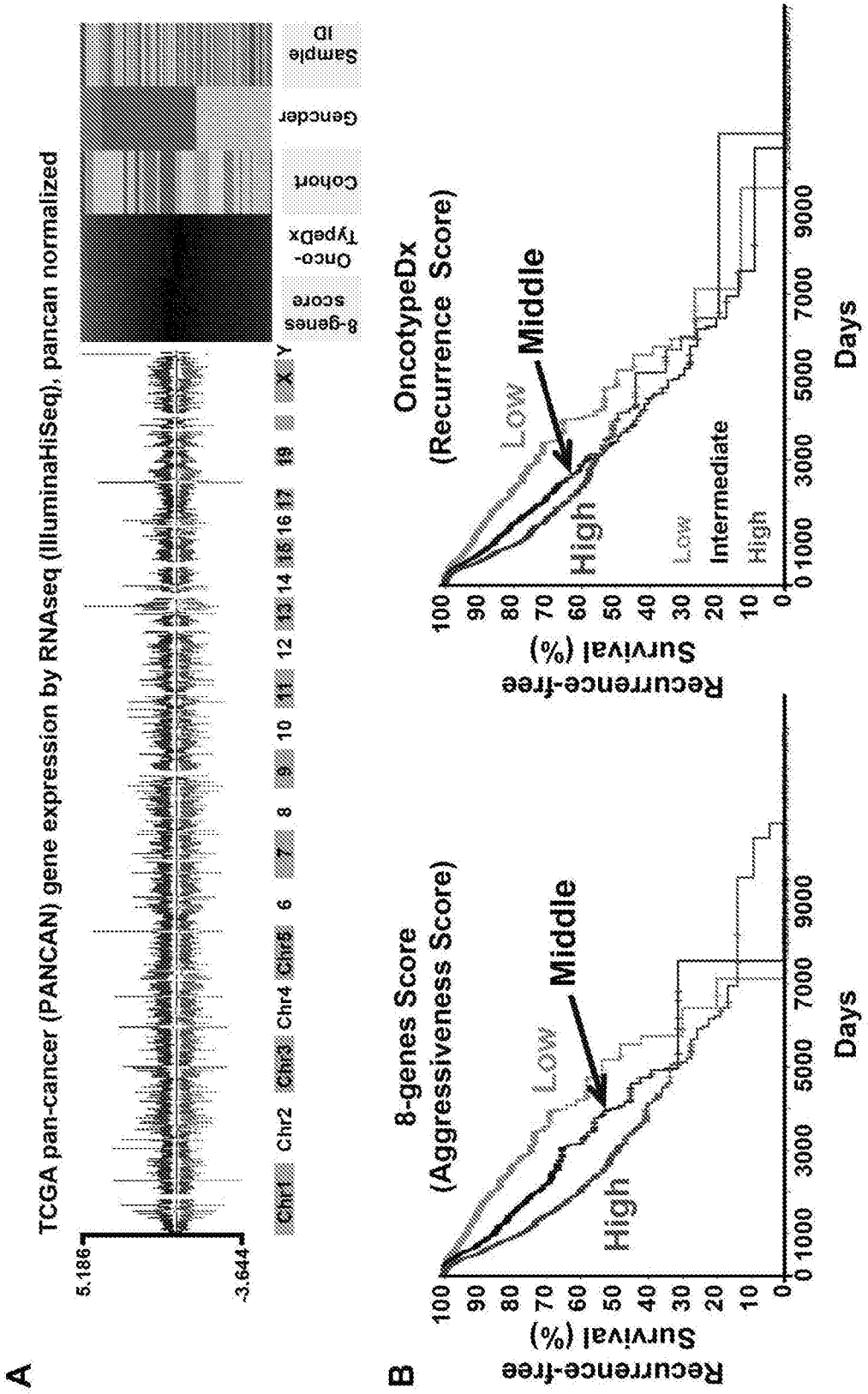

A
TCGA pan-cancer (PANCAN) gene expression by RNAseq (IlluminaHiSeq), pancan normalized
5.186
-3.644
8-genes score
Onco-TypeDx
Cohort
Gencder
Sample ID
Chr1 Chr2 Chr3 Chr4 Chr5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 X Y
B
Recurrence-free Survival (%)
8-genes Score (Aggressiveness Score)
Low
Middle
High
Days
Recurrence-free Survival (%)
OncotypeDx (Recurrence Score)
Low
Middle
High
Low
Intermediate
High
Days

FIG. 17

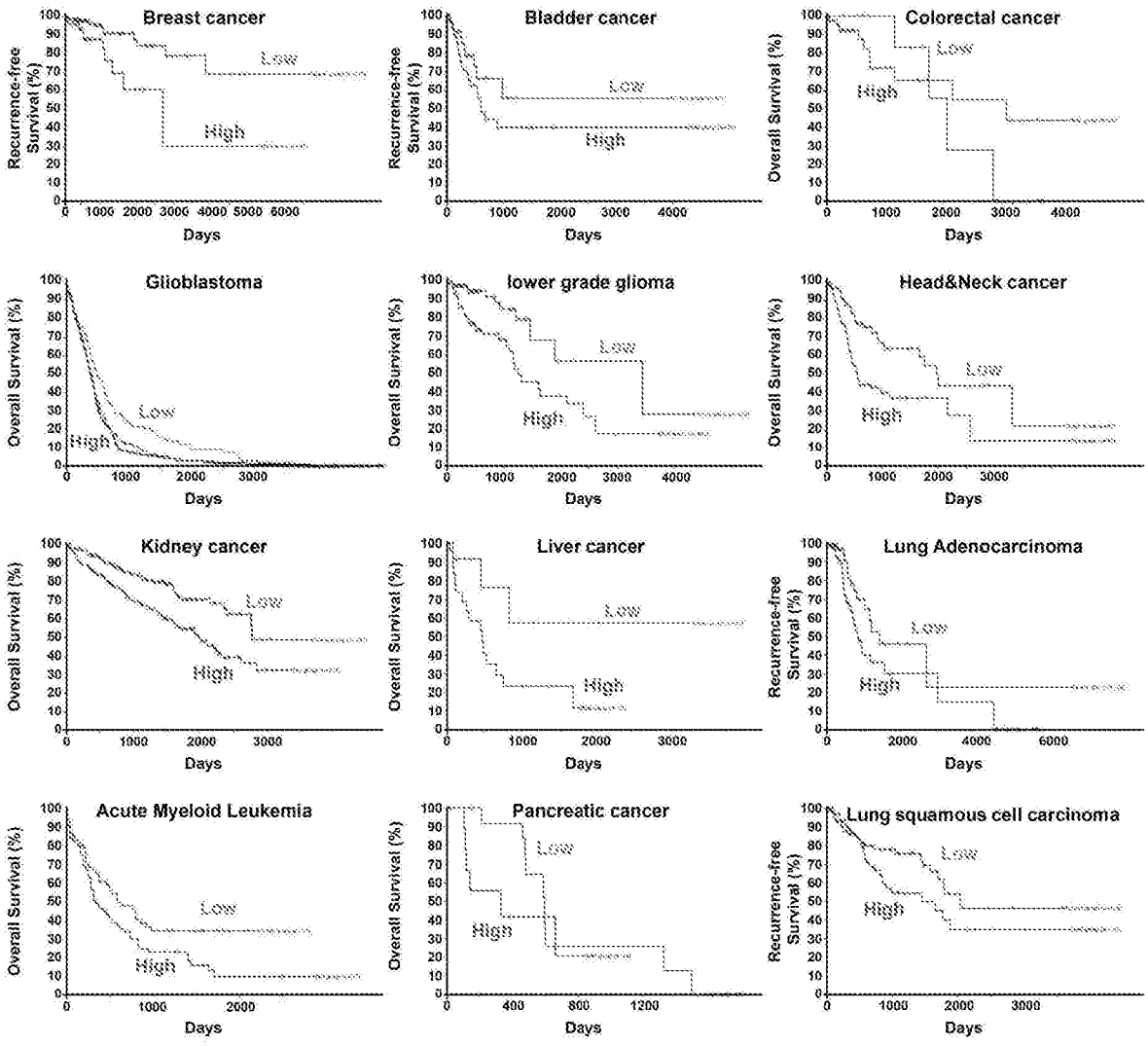

Breast cancer
Recurrence-free Survival (%)
Low
High
Days
Bladder cancer
Recurrence-free Survival (%)
Low
High
Days
Colorectal cancer
Overall Survival (%)
Low
High
Days
Glioblastoma
Overall Survival (%)
Low
High
Days
lower grade glioma
Overall Survival (%)
Low
High
Days
Head&Neck cancer
Overall Survival (%)
Low
High
Days
Kidney cancer
Overall Survival (%)
Low
High
Days
Liver cancer
Overall Survival (%)
Low
High
Days
Lung Adenocarcinoma
Recurrence-free Survival (%)
Low
High
Days
Acute Myeloid Leukemia
Overall Survival (%)
Low
High
Days
Pancreatic cancer
Overall Survival (%)
Low
High
Days
Lung squamous cell carcinoma
Recurrence-free Survival (%)
Low
High
Days

FIG. 18

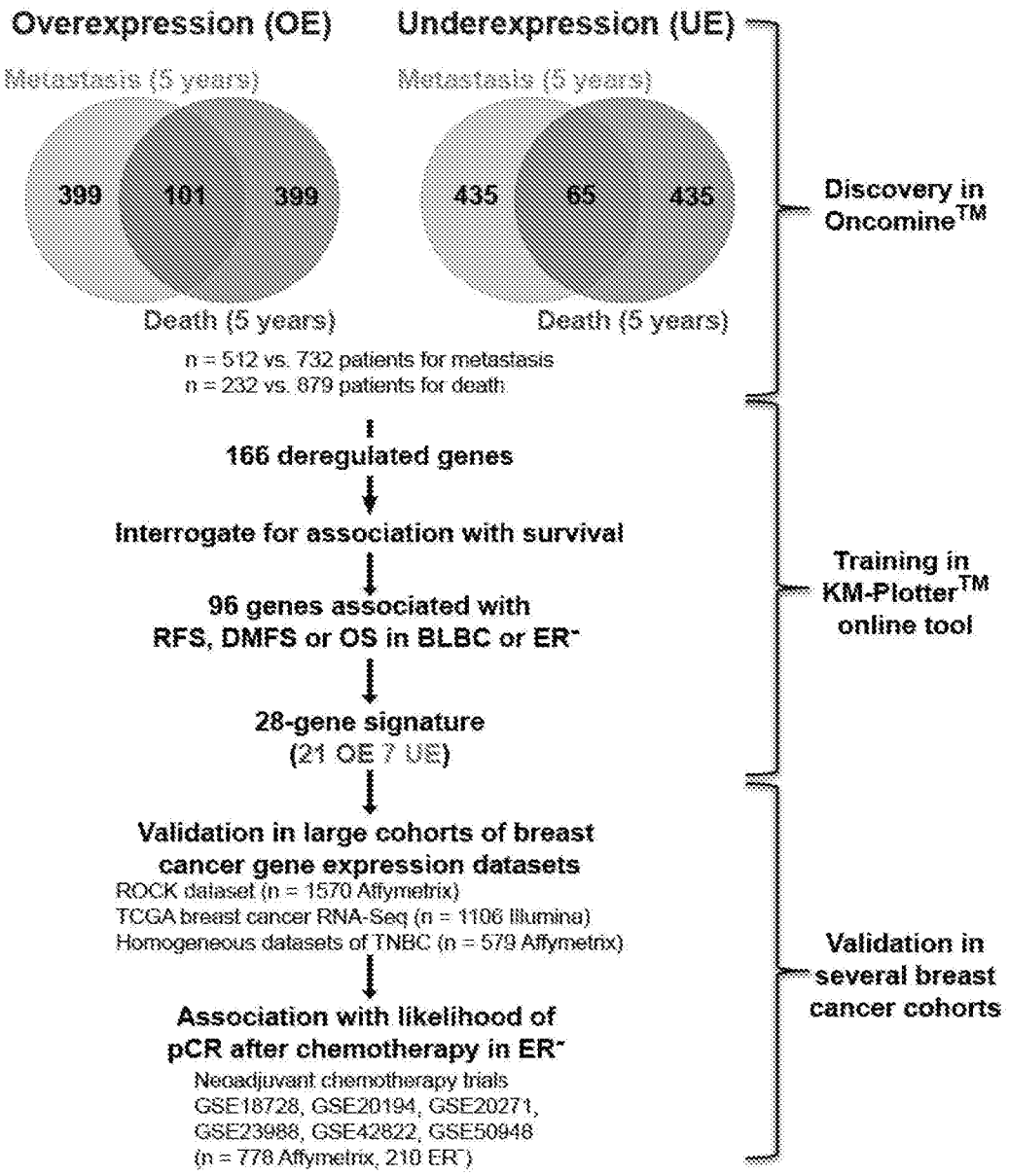

Overexpression (OE)
Underexpression (UE)
Metastasis (5 years)
Metastasis (5 years)
399
101
399
435
65
435
Death (5 years)
Death (5 years)
n = 512 vs. 732 patients for metastasis
n = 232 vs. 879 patients for death
166 deregulated genes
Interrogate for association with survival
96 genes associated with RFS, DMFS or OS in BLBC or ER-
28-gene signature (21 OE 7 UE)
Validation in large cohorts of breast cancer gene expression datasets
ROCK dataset (n = 1570 Affymetrix)
TCGA breast cancer RNA-Seq (n = 1106 Illumina)
Homogeneous datasets of TNBC (n = 579 Affymetrix)
Association with likelihood of pCR after chemotherapy in ER-
Neoadjuvant chemotherapy trials
GSE18728, GSE20194, GSE20271, GSE23988, GSE42822, GSE50948
(n = 778 Affymetrix, 210 ER-)
Discovery in Oncomine™
Training in KM-Plotter™ online tool
Validation in several breast cancer cohorts

FIG. 19

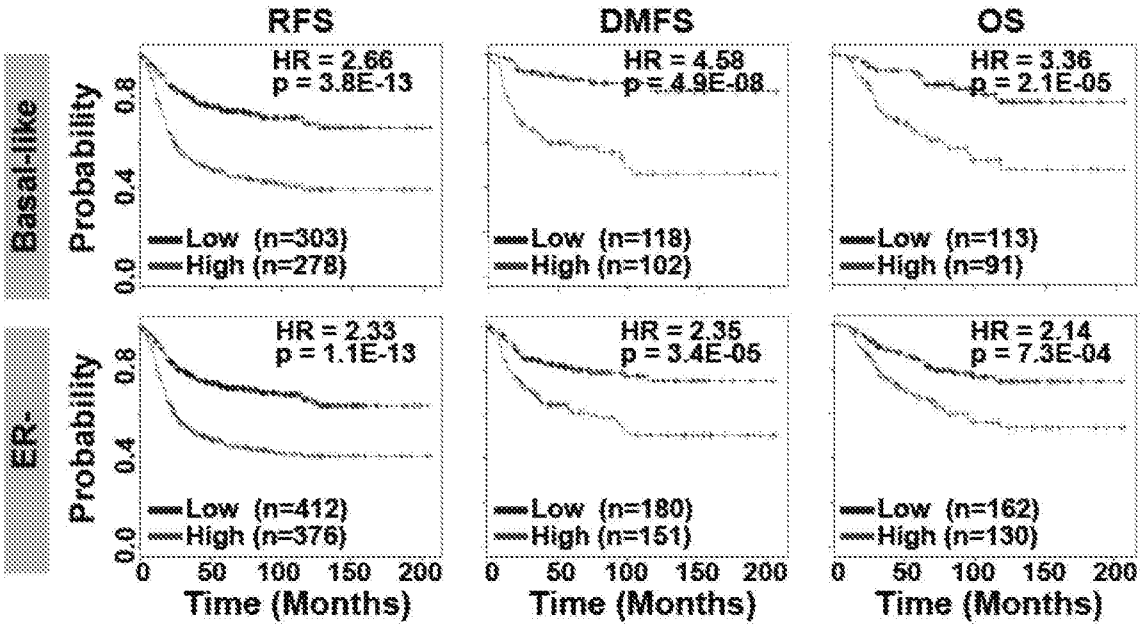
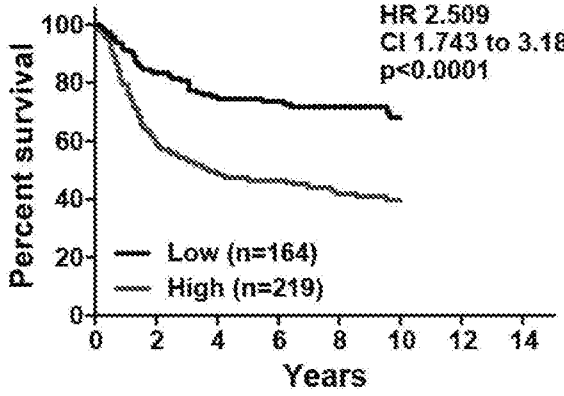

RFS
DMFS
OS
Basal-like
ER-
Probability
0.0
0.4
0.8
HR = 2.66
p = 3.8E-13
Low (n=303)
High (n=278)
HR = 4.58
p = 4.9E-08
Low (n=118)
High (n=102)
HR = 3.36
p = 2.1E-05
Low (n=113)
High (n=91)
HR = 2.33
p = 1.1E-13
Low (n=412)
High (n=376)
HR = 2.35
p = 3.4E-05
Low (n=180)
High (n=151)
HR = 2.14
p = 7.3E-04
Low (n=162)
High (n=130)
0
50
100
150
200
Time (Months)

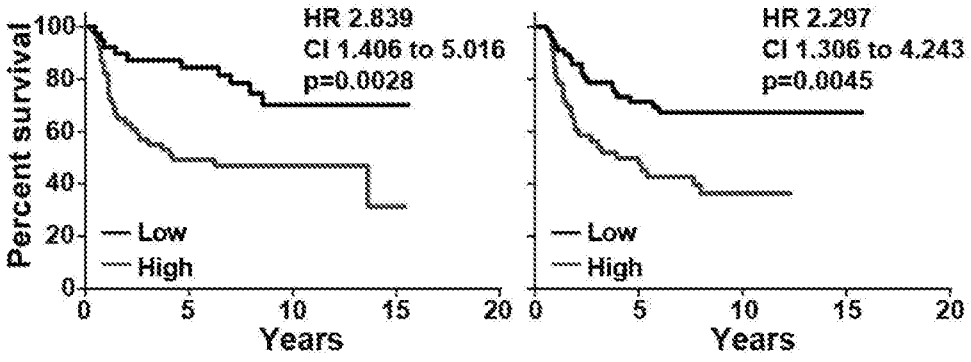
FIG. 20

A



	Univariate Cox-proportional hazards model			Multivariate Cox-proportional hazards model		
	HR	95 % CI	p-value	HR	95 % CI	p-value
TN score (high vs. low)	**2.5172**	1.7819-3.5361	**<0.0001**	**2.2892**	1.5217-3.4438	**0.0001**
Tumor size (T1, T2, T3)	**0.7097**	0.4893-1.0292	0.0720	**0.8148**	0.5522-1.2023	0.3046
Grade (G1, G2, G3)	**1.3036**	0.9102-1.8670	0.1501	**1.1794**	0.8023-1.7338	0.4052
Age (<50, >50)	**0.9009**	0.6572-1.2349	0.5186	**0.9908**	0.6965-1.4095	0.9592
Nodal status (N0, N1)	**1.0922**	0.6949-1.7165	0.7037	**1.4758**	0.6935-3.1406	0.3150
Adj. chemo (Yes, No)	1.0564	0.7320-1.5247	0.7705	1.1582	0.7464-1.7974	0.5145

B

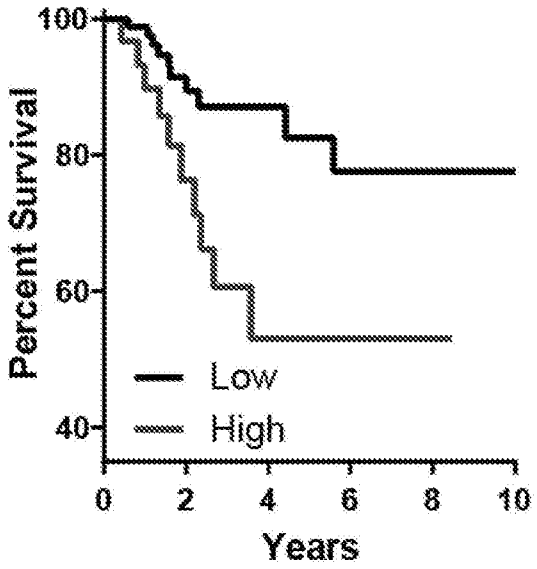


	RFS Multivariate Cox-proportional hazards model			DMFS Multivariate Cox-proportional hazards model		
	HR	95 % CI	p-value	HR	95 % CI	p-value
TN score (high vs. low)	**3.0343**	1.3703-6.7194	**0.0065**	**2.7139**	1.1723-6.2829	**0.0204**
Tumor size (T1, T2, T3)	**3.3223**	0.4135-26.694	0.2612	**2.8371**	0.4681-31.452	0.2126
Grade (G1, G2, G3)	**1.2288**	0.3377-4.4713	0.7557	**1.8560**	0.5153-6.6855	0.3467
Age (<50, >50)	**1.0481**	0.4964-2.2129	0.9024	**0.9172**	0.4225-1.9911	0.8279
Nodal status (N0, N1)	**2.5022**	0.4817-12.997	0.2777	**0.9240**	0.1052-8.1176	0.9435
ER status (ER+, ER-)	**0.5828**	0.1753-1.9374	0.3808	**0.6780**	0.1986-2.3141	0.5370

C

	RFS Multivariate Cox-proportional hazards model			DMFS Multivariate Cox-proportional hazards model		
	HR	95 % CI	p-value	HR	95 % CI	p-value
TN score (high vs. low)	**2.0323**	1.2211-3.3822	**0.0066**	**2.2830**	1.1859-4.3953	**0.0140**
Tumor size (T1, T2, T3)	**1.1703**	0.2562-5.3460	0.8400	**0.7795**	0.0908-6.6911	0.8213
Grade (G1, G2, G3)	**0.7299**	0.0983-5.4204	0.7505	**1.3221**	0.1718-10.177	0.7896
Age (<50, >50)	**1.0969**	0.6835-1.7604	0.7030	**0.9745**	0.5558-1.7087	0.9286
Nodal status (N0, N1)	**1.5488**	0.5542-4.3274	0.4066	**1.6229**	0.5052-5.2136	0.4185

FIG. 21



	Univariate Cox-proportional hazards model			Multivariate Cox-proportional hazards model		
	HR	95 % CI	p-value	HR	95 % CI	p-value
TN score (high vs. low)	2.9993	1.2533-7.1778	0.0141	3.3316	1.2323-9.0069	0.0183
Stage (I, II, III)	3.4112	1.2738-9.1355	0.0151	3.2814	0.8902-12.095	0.0757
Nodal status (N0, N1)	3.4618	1.2525-9.5680	0.0172	0.9415	0.2092-4.2375	0.9377
HER2 (Neg, Pos)	0.3487	0.0456-2.6680	0.3127			
Age (<50, >50)	1.2375	0.4502-3.4018	0.6812			
Tumor size (T2/3 vs T1)	1.0393	0.2916-3.7046	0.9528			

FIG. 22

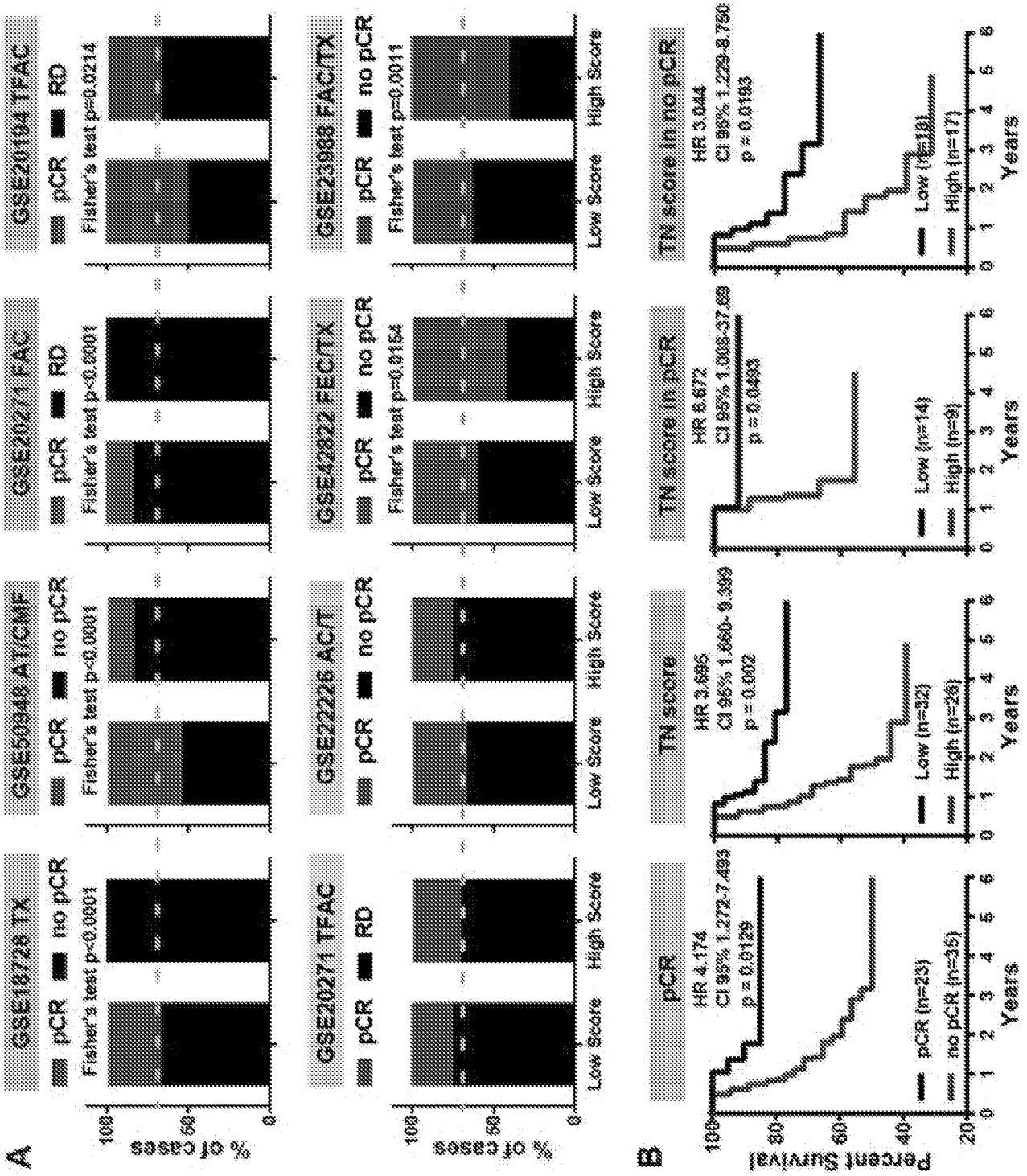

A
GSE18728 TX
GSE50948 AT/CMF
GSE20271 FAC
GSE20194 TFAC
GSE20271 TFAC
GSE22226 ACT
GSE42822 FEC/TX
GSE23988 FAC/TX
pCR
no pCR
RD
Fisher's test p<0.0001
Fisher's test p<0.0001
Fisher's test p<0.0001
Fisher's test p=0.0214
Fisher's test p=0.0154
Fisher's test p=0.0011
% of cases
Low Score
High Score
B
pCR
TN score
TN score in pCR
TN score in no pCR
HR 4.174
CI 95% 1.272-7.493
p = 0.0129
HR 3.695
CI 95% 1.660- 8.399
p = 0.002
HR 6.672
CI 95% 1.008-37.69
p = 0.0493
HR 3.044
CI 95% 1.229-8.760
p = 0.0193
pCR (n=23)
no pCR (n=36)
Low (n=32)
High (n=26)
Low (n=14)
High (n=9)
Low (n=18)
High (n=17)
Percent Survival
Years

FIG. 23

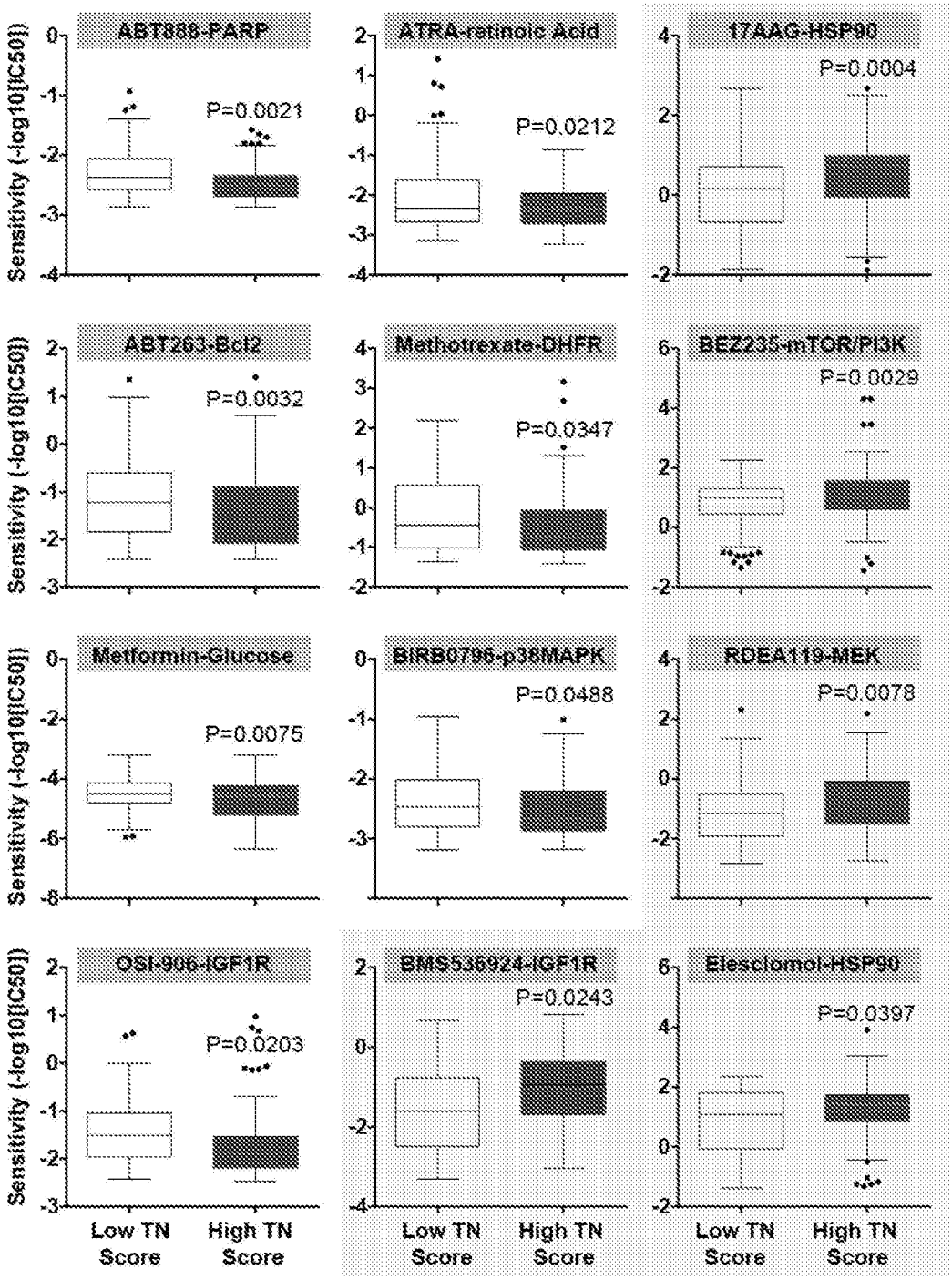

ABT888-PARP
P=0.0021
ATRA-retinoic Acid
P=0.0212
17AAG-HSP90
P=0.0004
ABT263-Bcl2
P=0.0032
Methotrexate-DHFR
P=0.0347
BEZ235-mTOR/PI3K
P=0.0029
Metformin-Glucose
P=0.0075
BIRB0796-p38MAPK
P=0.0488
RDEA119-MEK
P=0.0078
OSI-906-IGF1R
P=0.0203
BMS536924-IGF1R
P=0.0243
Elesclomol-HSP90
P=0.0397
Sensitivity (-log10[IC50])
Low TN Score
High TN Score

FIG. 24

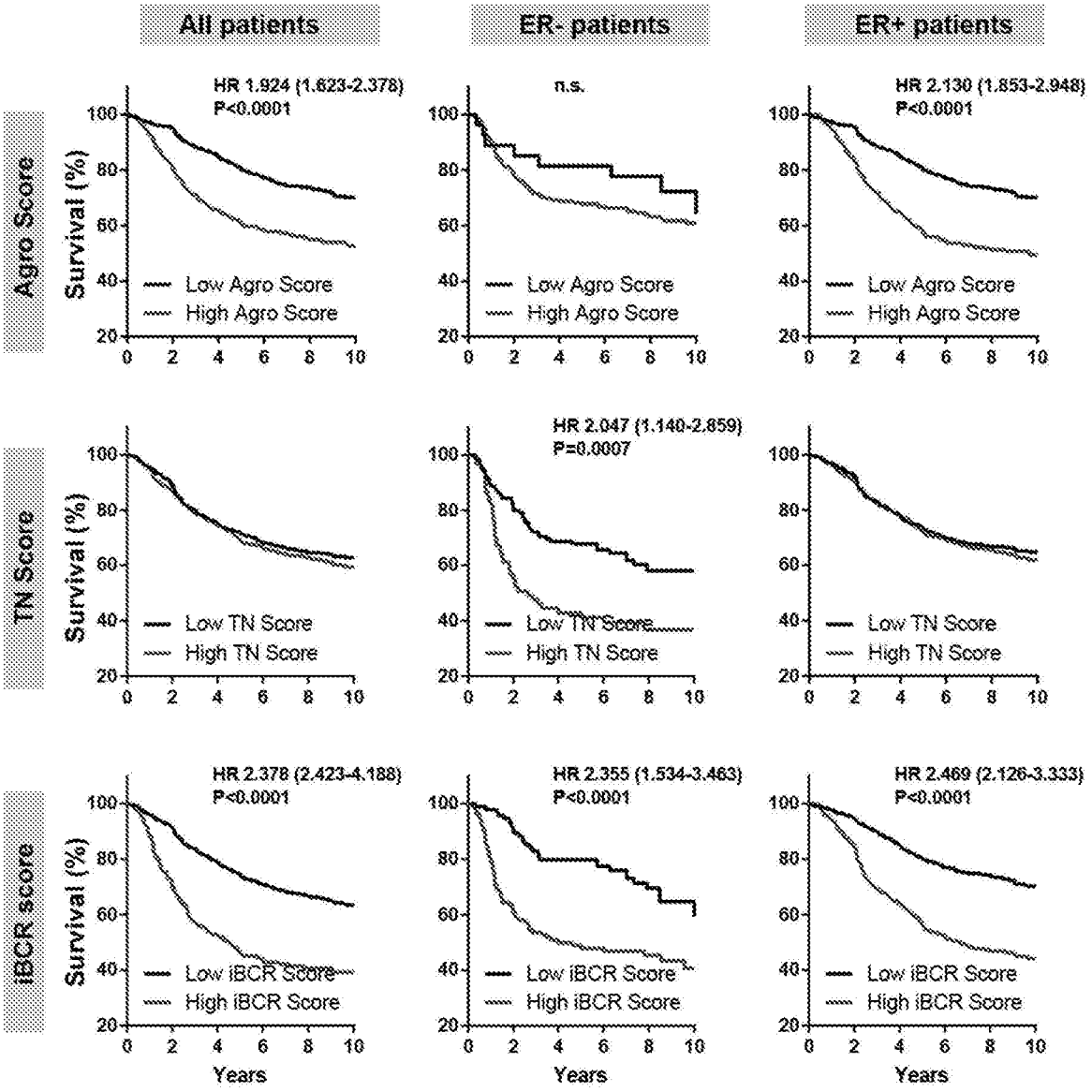

All patients
ER- patients
ER+ patients
Agro Score
TN Score
iBCR score
Survival (%)
HR 1.924 (1.623-2.378)
P<0.0001
n.s.
HR 2.130 (1.853-2.948)
P<0.0001
HR 2.047 (1.140-2.859)
P=0.0007
HR 2.378 (2.423-4.188)
P<0.0001
HR 2.355 (1.534-3.463)
P<0.0001
HR 2.469 (2.126-3.333)
P<0.0001
Low Agro Score
High Agro Score
Low TN Score
High TN Score
Low iBCR Score
High iBCR Score
Years

FIG. 25

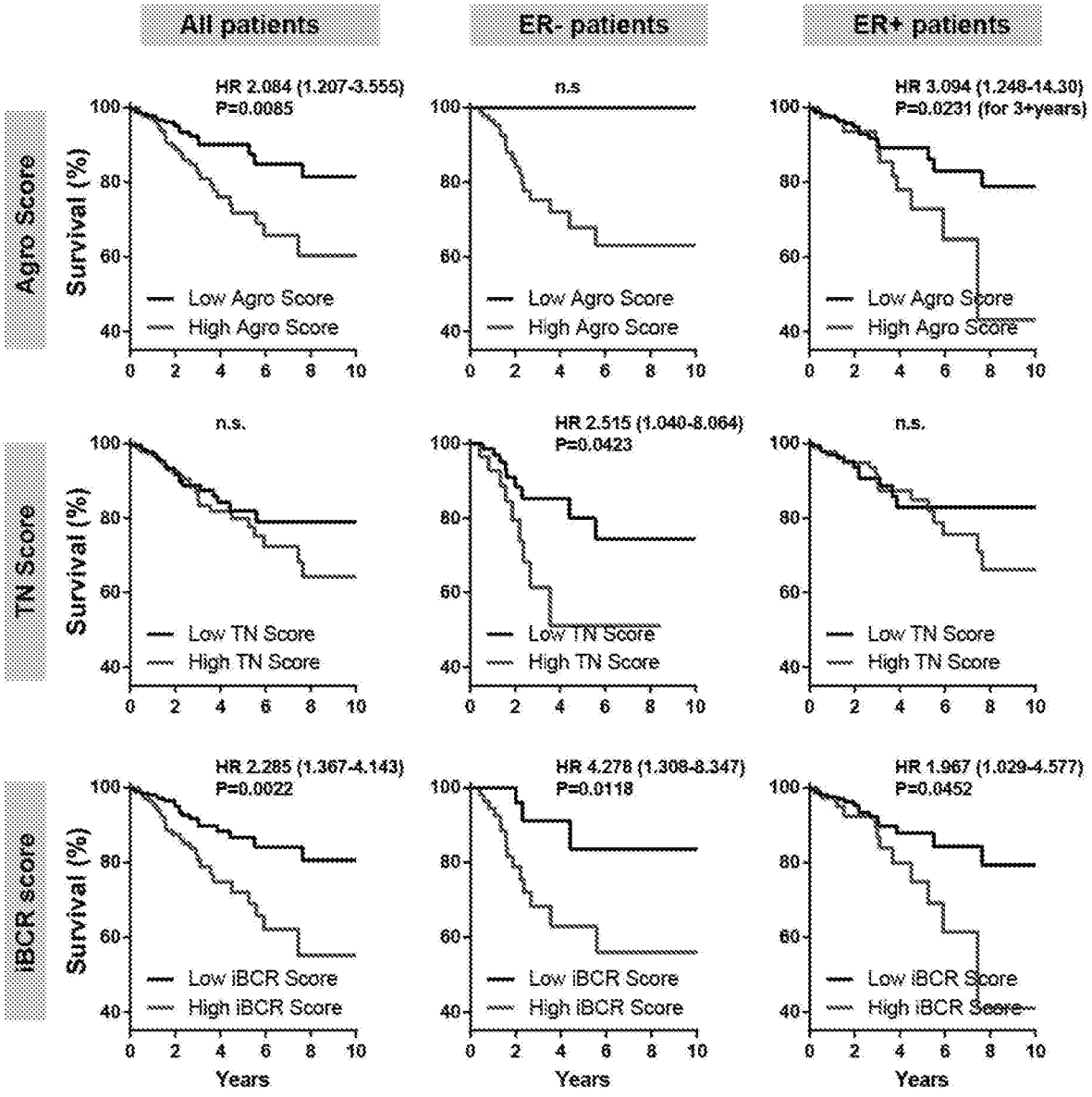

All patients
ER- patients
ER+ patients
Agro Score
TN Score
iBCR score
Survival (%)
HR 2.084 (1.207-3.555)
P=0.0085
n.s
HR 3.094 (1.248-14.30)
P=0.0231 (for 3+years)
Low Agro Score
High Agro Score
n.s.
HR 2.515 (1.040-8.064)
P=0.0423
Low TN Score
High TN Score
HR 2.285 (1.367-4.143)
P=0.0022
HR 4.278 (1.308-8.347)
P=0.0118
HR 1.967 (1.029-4.577)
P=0.0452
Low iBCR Score
High iBCR Score
Years

FIG. 26

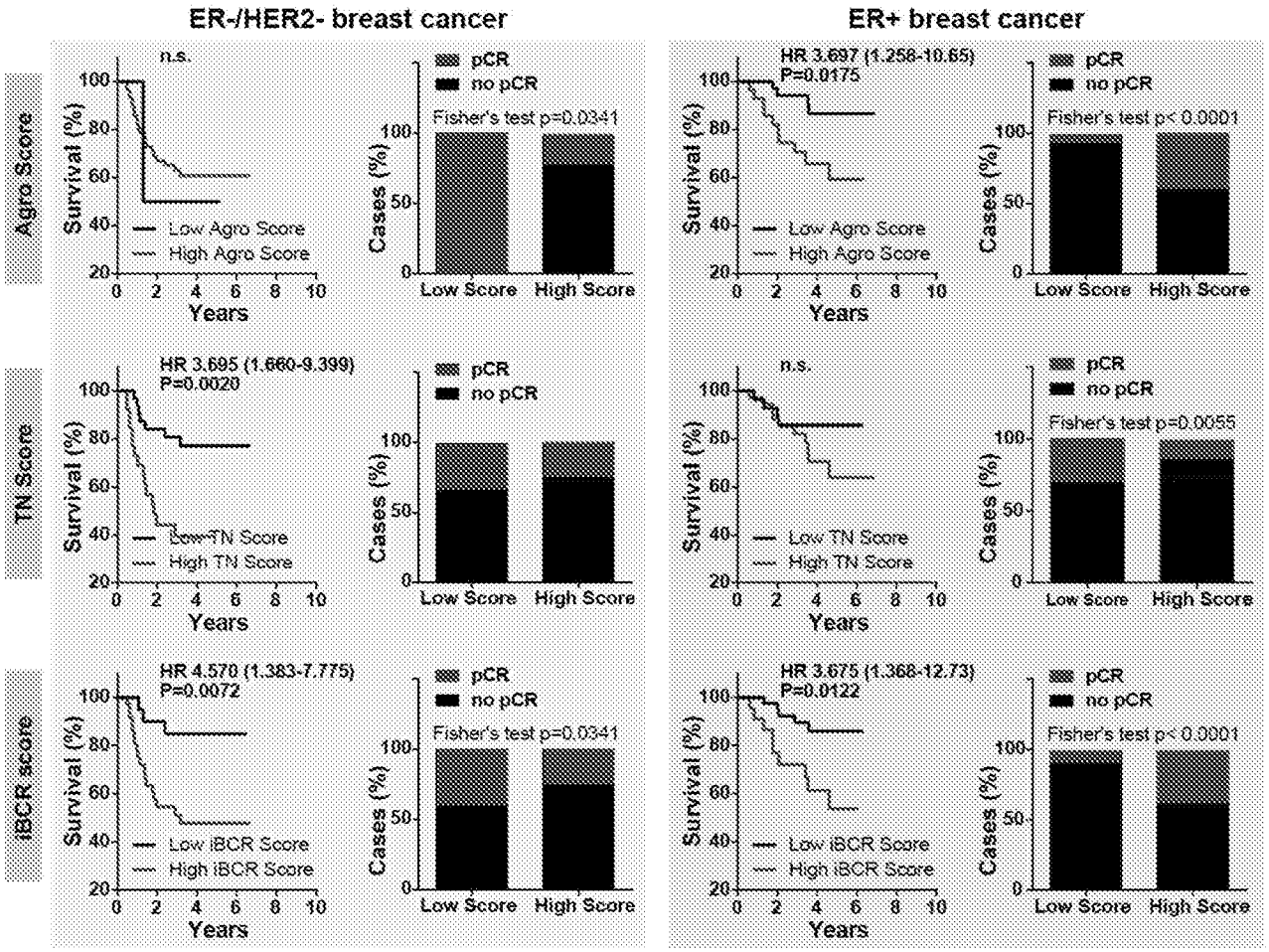

ER-/HER2- breast cancer
ER+ breast cancer
Agro Score
TN Score
iBCR score
n.s.
HR 3.697 (1.258-10.65)
P=0.0175
HR 3.695 (1.660-9.399)
P=0.0020
HR 4.570 (1.383-7.775)
P=0.0072
HR 3.675 (1.368-12.73)
P=0.0122
Survival (%)
Years
Low Agro Score
High Agro Score
Low TN Score
High TN Score
Low iBCR Score
High iBCR Score
pCR
no pCR
Cases (%)
Fisher's test p=0.0341
Fisher's test p< 0.0001
Fisher's test p=0.0055
Low Score
High Score

FIG. 27

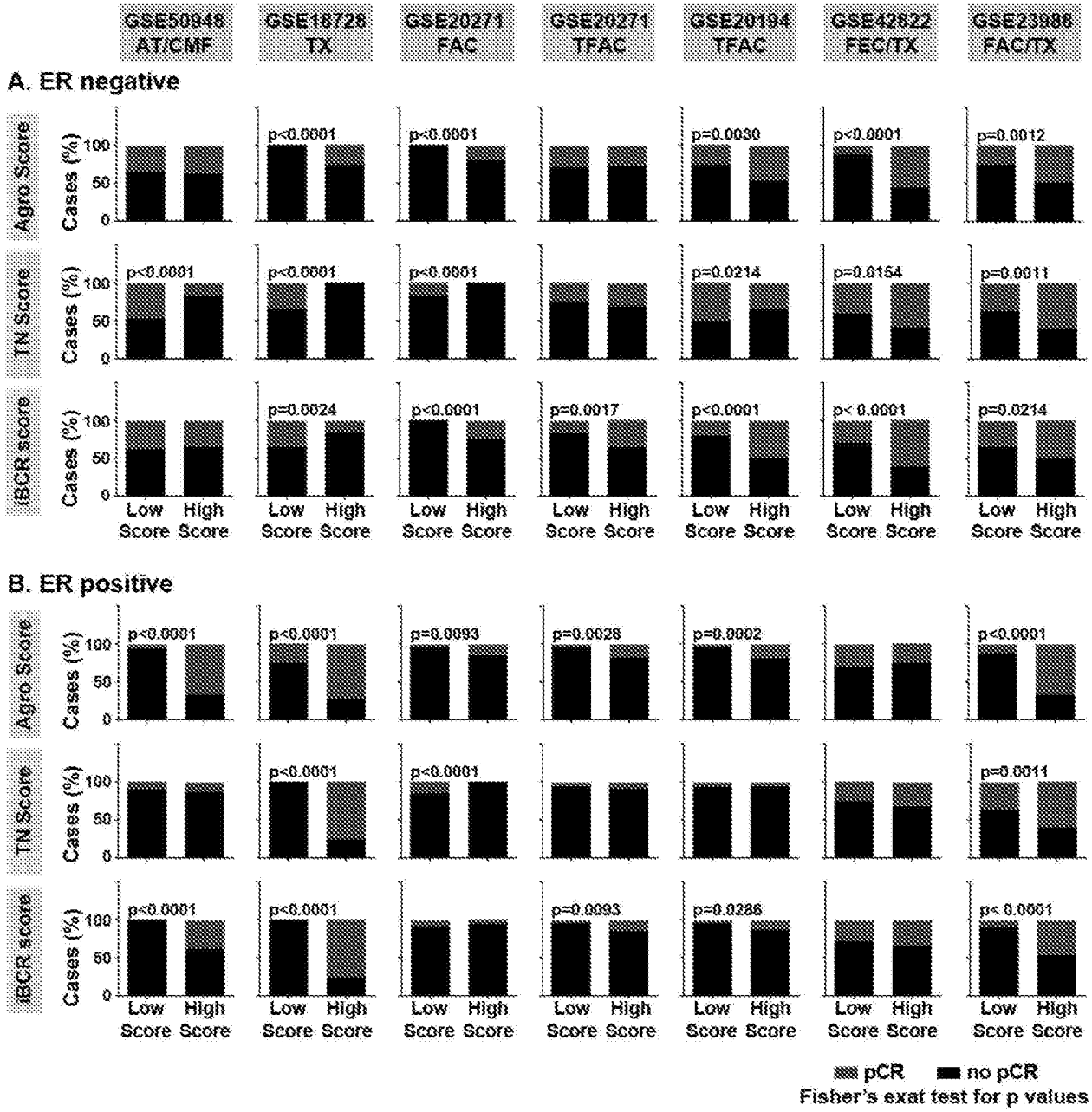

GSE50948 AT/CMF
GSE18728 TX
GSE20271 FAC
GSE20271 TFAC
GSE20194 TFAC
GSE42822 FEC/TX
GSE23988 FAC/TX
A. ER negative
Agro Score
TN Score
iBCR score
Cases (%)
100
50
0
p<0.0001
p=0.0030
p<0.0001
p=0.0012
p<0.0001
p<0.0001
p=0.0214
p=0.0154
p=0.0011
p<0.0001
p=0.0024
p<0.0001
p=0.0017
p<0.0001
p< 0.0001
p=0.0214
Low Score
High Score
B. ER positive
p<0.0001
p=0.0093
p=0.0028
p=0.0002
p<0.0001
p=0.0011
p<0.0001
p=0.0093
p=0.0286
p< 0.0001
pCR
no pCR
Fisher's exat test for p values

FIG. 28

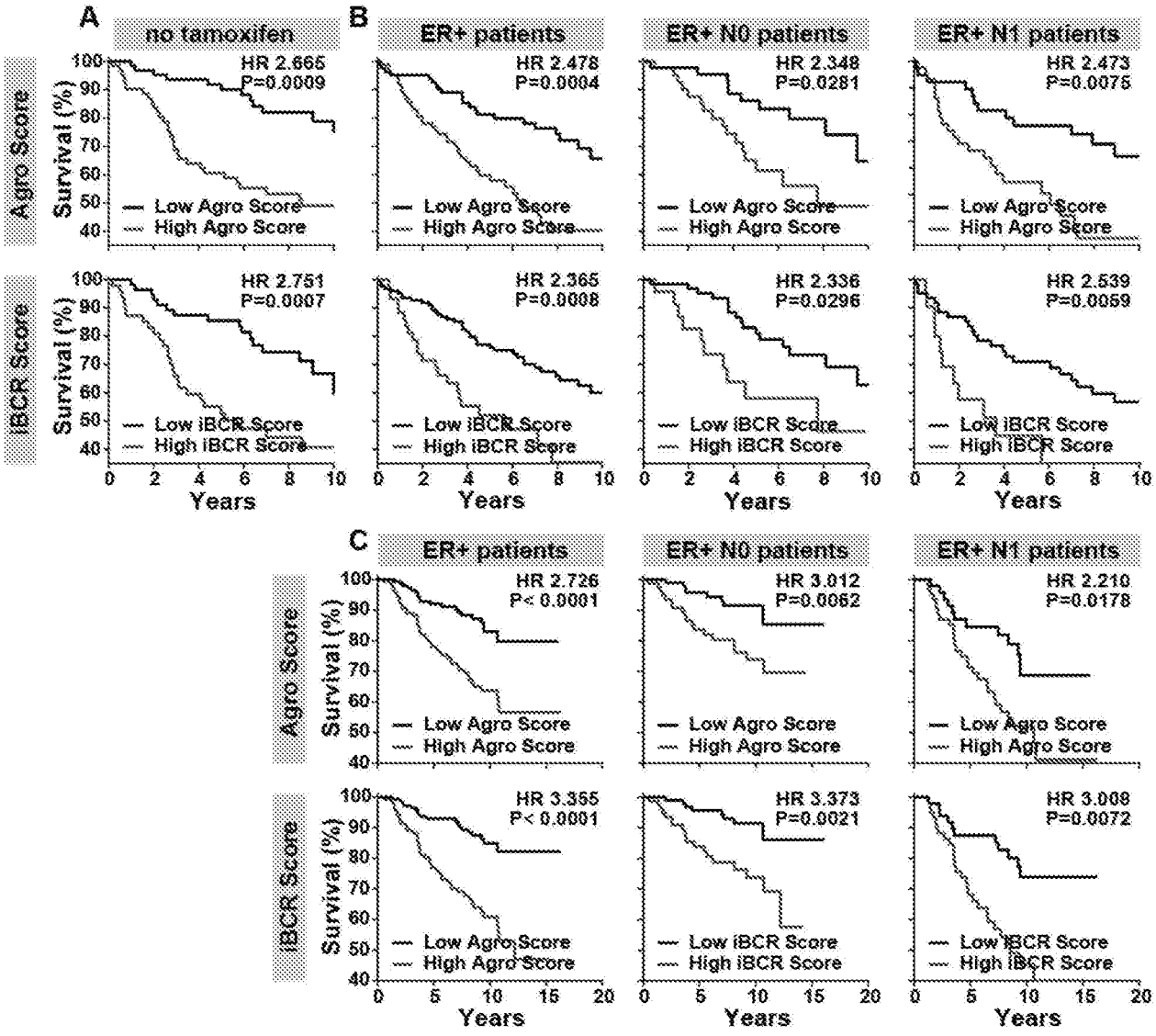

A
no tamoxifen
B
ER+ patients
ER+ N0 patients
ER+ N1 patients
C
ER+ patients
ER+ N0 patients
ER+ N1 patients
Agro Score
IBCR Score
Survival (%)
Years
HR 2.665
P=0.0009
HR 2.478
P=0.0004
HR 2.348
P=0.0281
HR 2.473
P=0.0075
HR 2.751
P=0.0007
HR 2.365
P=0.0008
HR 2.336
P=0.0296
HR 2.539
P=0.0059
HR 2.726
P< 0.0001
HR 3.012
P=0.0062
HR 2.210
P=0.0178
HR 3.355
P< 0.0001
HR 3.373
P=0.0021
HR 3.008
P=0.0072
Low Agro Score
High Agro Score
Low iBCR Score
High iBCR Score

FIG. 29

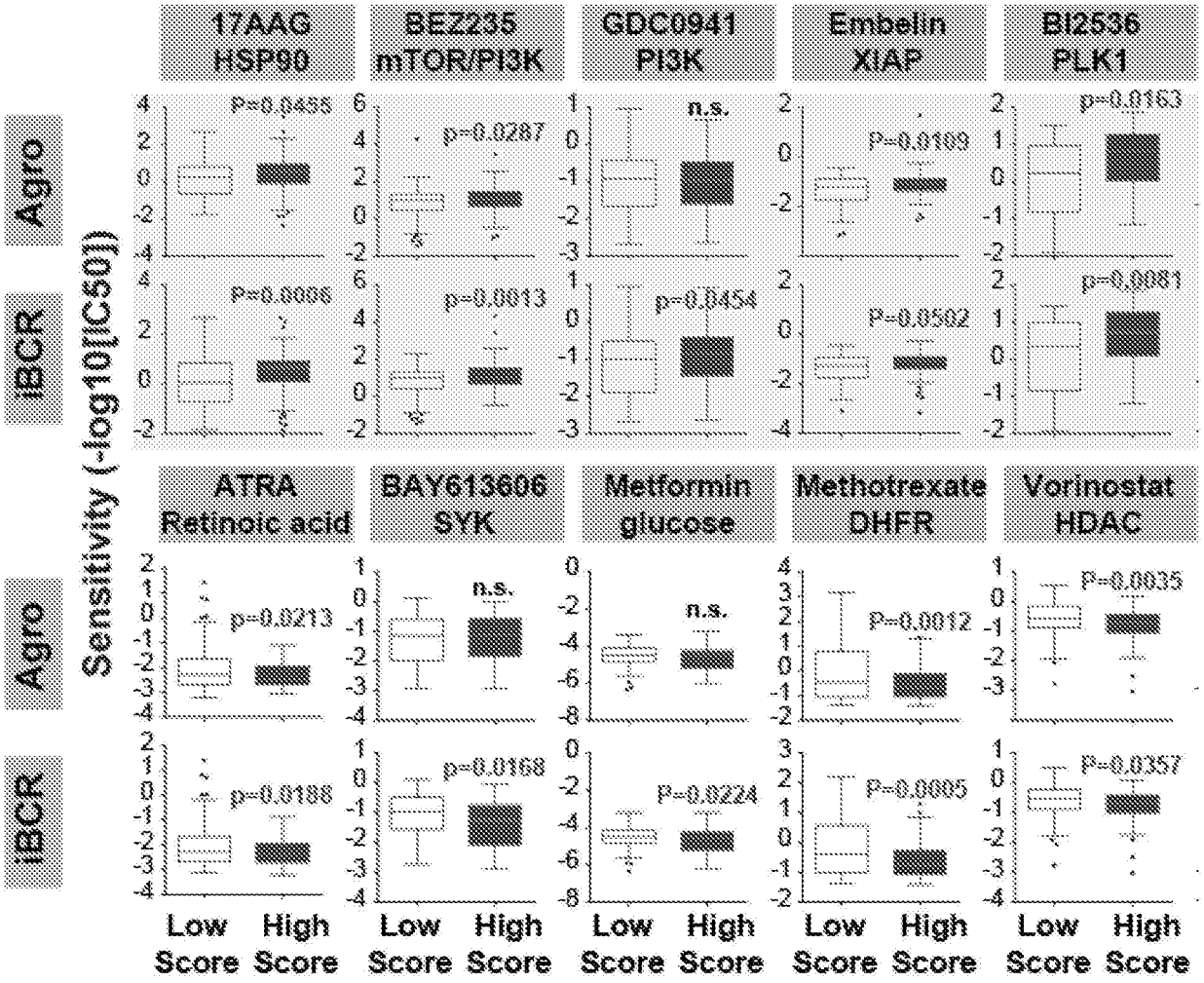

17AAG
HSP90
BEZ235
mTOR/PI3K
GDC0941
PI3K
Embelin
XIAP
BI2536
PLK1
Agro
iBCR
P=0.0455
p=0.0287
n.s.
P=0.0109
p=0.0163
P=0.0006
p=0.0013
p=0.0454
P=0.0502
p=0.0081
ATRA
Retinoic acid
BAY613606
SYK
Metformin
glucose
Methotrexate
DHFR
Vorinostat
HDAC
p=0.0213
n.s.
n.s.
P=0.0012
P=0.0035
p=0.0188
p=0.0168
P=0.0224
P=0.0005
P=0.0357
Sensitivity (-log10[IC50])
Low Score
High Score

FIG. 30

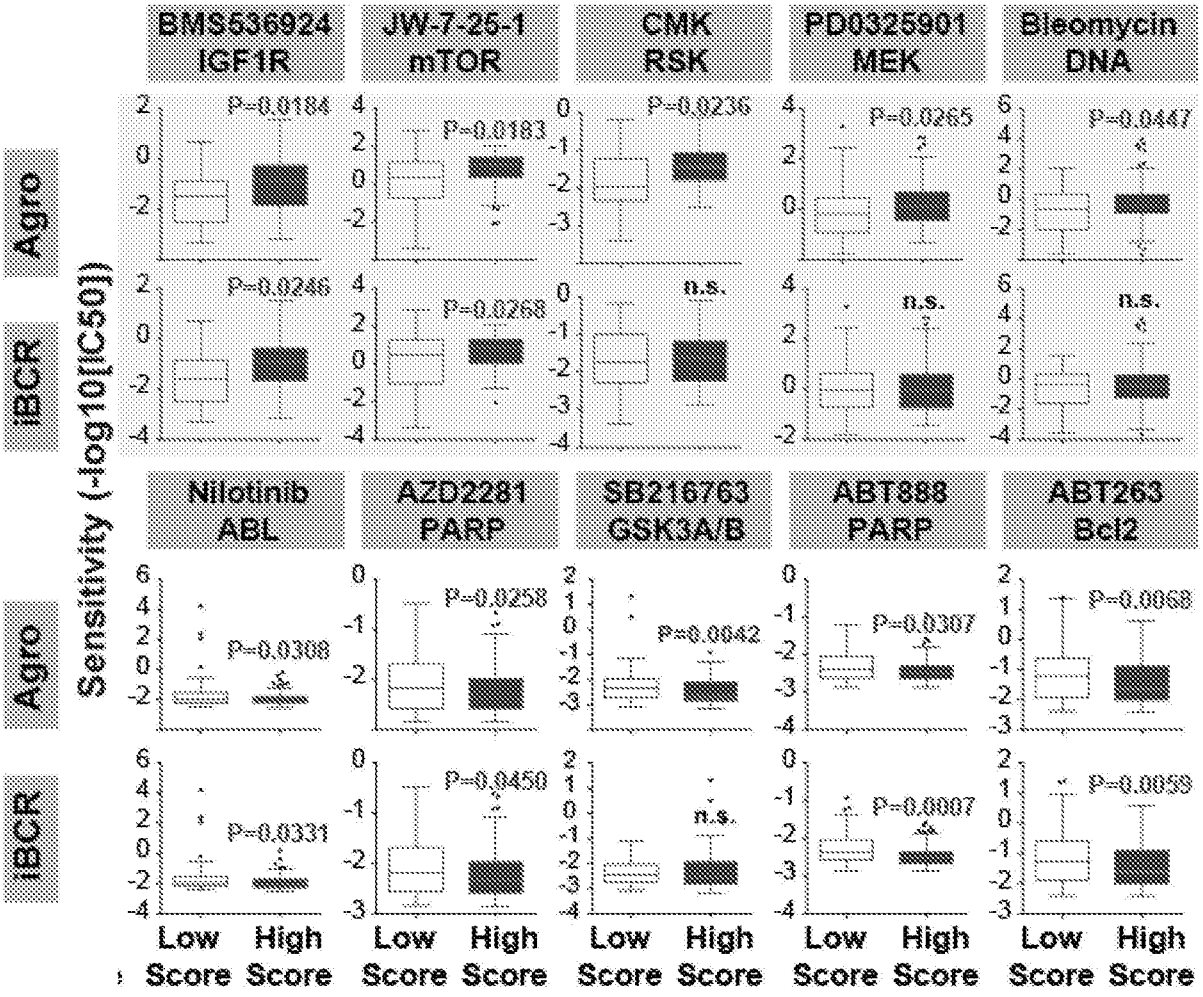
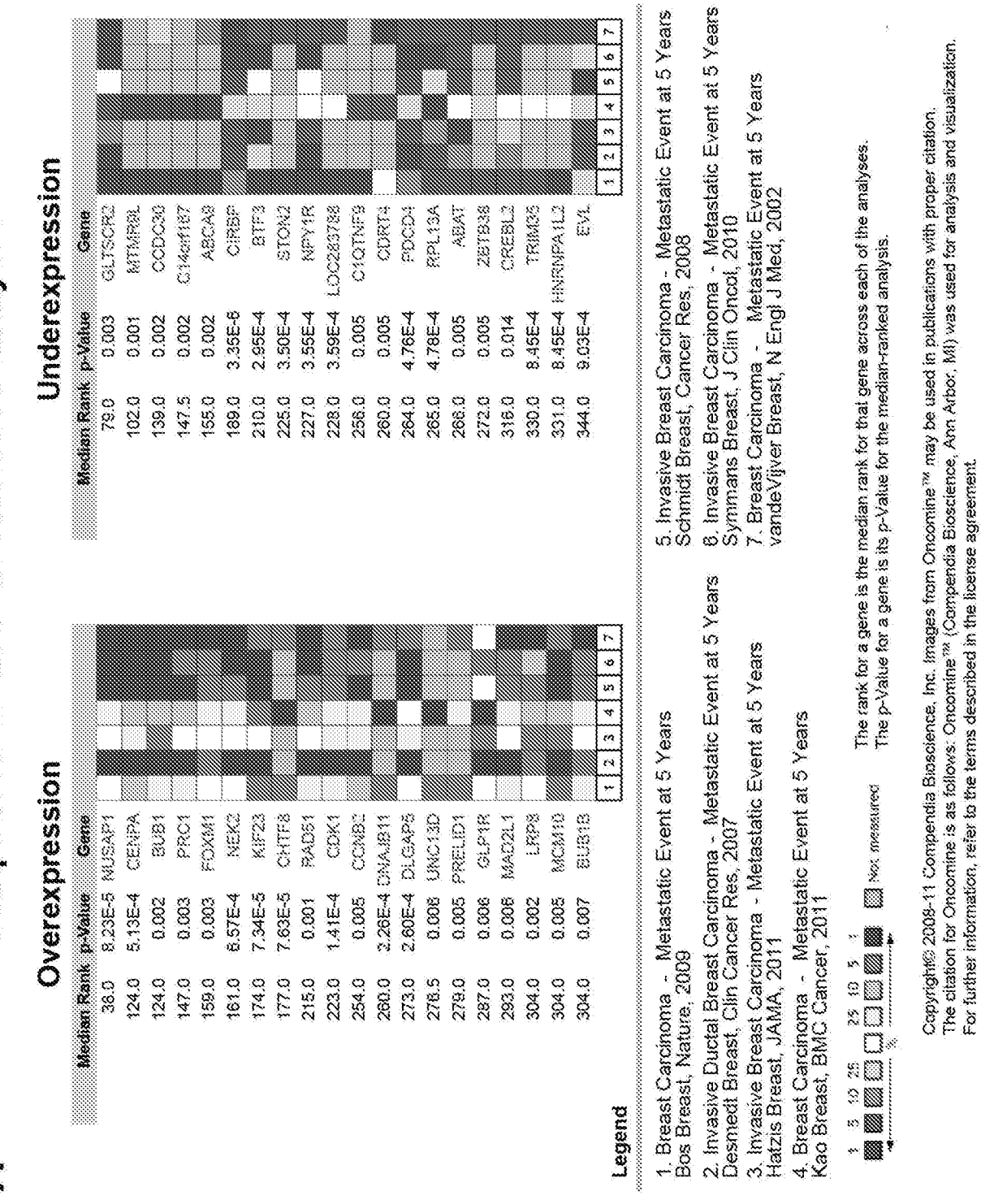

BMS536924
IGF1R
JW-7-25-1
mTOR
CMK
RSK
PD0325901
MEK
Bleomycin
DNA
Nilotinib
ABL
AZD2281
PARP
SB216763
GSK3A/B
ABT888
PARP
ABT263
Bcl2
Agro
iBCR
Agro
iBCR
Sensitivity (-log10[IC50])
P=0.0184
P=0.0183
P=0.0236
P=0.0265
P=0.0447
P=0.0246
P=0.0268
n.s.
n.s.
n.s.
P=0.0308
P=0.0258
P=0.0042
P=0.0307
P=0.0068
P=0.0331
P=0.0450
n.s.
P=0.0007
P=0.0058
Low Score
High Score

FIG. 30 cont'd


A
Comparison of All Genes Across 7 Analyses
Overexpression
Median Rank
p-Value
Gene
36.0 8.23E-5 NUSAP1
124.0 5.13E-4 CENPA
124.0 0.002 BUB1
147.0 0.003 PRC1
159.0 0.003 FOXM1
161.0 6.57E-4 NEK2
174.0 7.34E-5 KIF23
177.0 7.63E-5 CHTF8
215.0 0.001 RAD51
223.0 1.41E-4 CDK1
254.0 0.005 CCNB1
260.0 2.26E-4 DNAJB11
273.0 2.60E-4 DLGAP5
276.5 0.008 UNC13D
279.0 0.005 PRELID1
287.0 0.006 GLP1R
293.0 0.006 MAD2L1
304.0 0.002 LRP8
304.0 0.005 MCM10
304.0 0.007 BUB1B
1 2 3 4 5 6 7
Underexpression
Median Rank
p-Value
Gene
79.0 0.003 GLTSCR2
102.0 0.001 MTMR6L
139.0 0.002 CCDC30
147.5 0.002 C14orf167
155.0 0.002 ABCA8
189.0 3.35E-6 CIRBP
210.0 2.95E-4 BTF3
225.0 3.50E-4 STON2
227.0 3.55E-4 NPY1R
228.0 3.59E-4 LOC283788
256.0 0.005 C1QTNF3
260.0 0.005 CDRT4
264.0 4.76E-4 PDCD4
265.0 4.78E-4 RPL13A
266.0 0.005 ABAT
272.0 0.005 ZBTB38
316.0 0.014 CREBL2
330.0 8.45E-4 TRIM35
331.0 8.45E-4 HNRNPA1L2
344.0 9.03E-4 EVL
1 2 3 4 5 6 7
Legend
1. Breast Carcinoma - Metastatic Event at 5 Years
Bos Breast, Nature, 2009
2. Invasive Ductal Breast Carcinoma - Metastatic Event at 5 Years
Desmedt Breast, Clin Cancer Res, 2007
3. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Hatzis Breast, JAMA, 2011
4. Breast Carcinoma - Metastatic Event at 5 Years
Kao Breast, BMC Cancer, 2011
5. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Schmidt Breast, Cancer Res, 2008
8. Invasive Breast Carcinoma - Metastatic Event at 5 Years
Symmans Breast, J Clin Oncol, 2010
7. Breast Carcinoma - Metastatic Event at 5 Years
vandeVijver Breast, N Engl J Med, 2002
1 5 10 25 25 10 5 1
%
Not measured
The rank for a gene is the median rank for that gene across each of the analyses.
The p-Value for a gene is its p-Value for the median-ranked analysis.
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The citation for Oncomine is as follows: Oncomine™ (Compendia Bioscience, Ann Arbor, MI) was used for analysis and visualization.
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FIG. 31

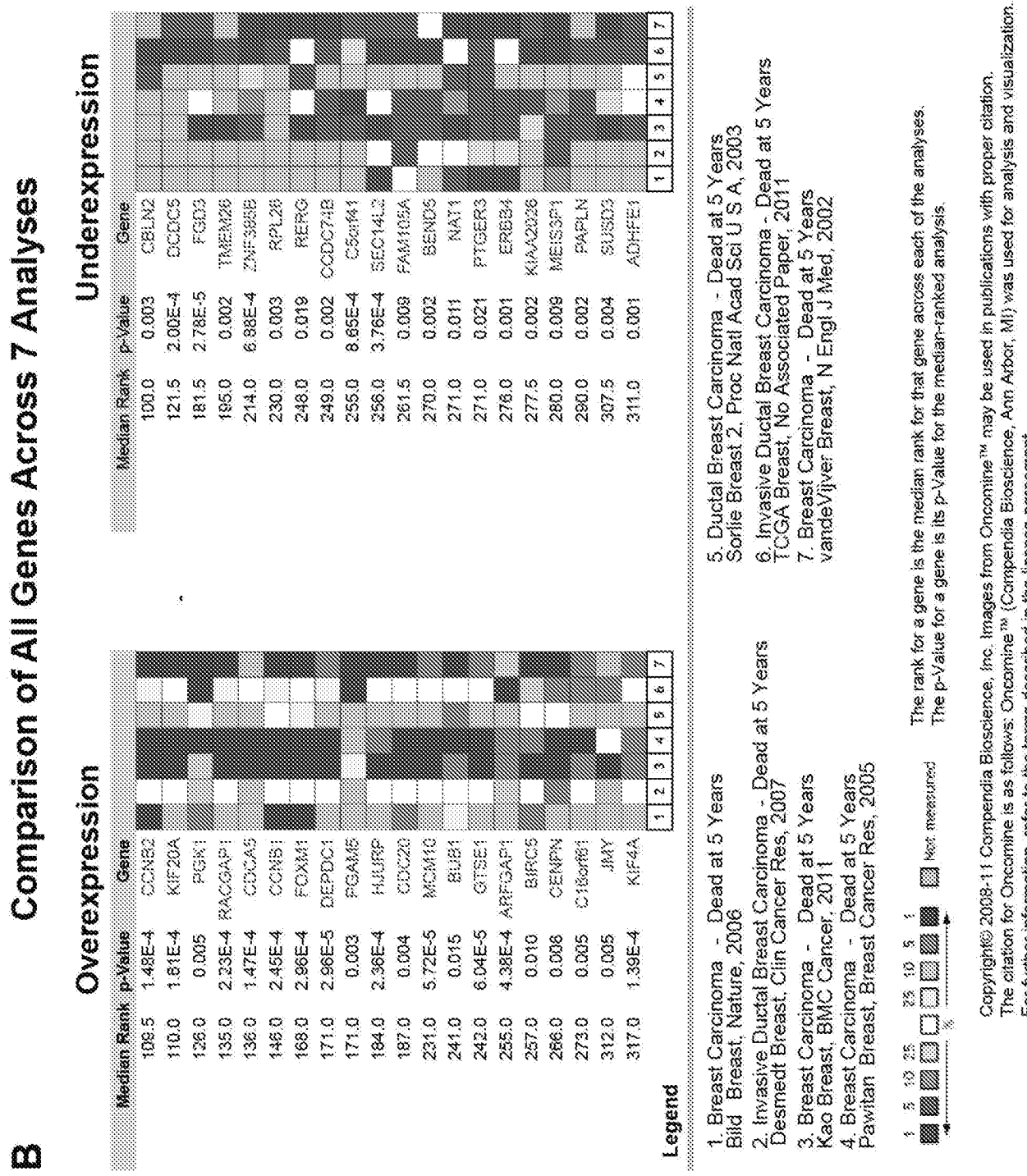

B
Comparison of All Genes Across 7 Analyses
Overexpression
Median Rank
p-Value
Gene
109.5 1.48E-4 CCNB2
110.0 1.81E-4 KIF20A
126.0 0.005 PGK1
135.0 2.23E-4 RACGAP1
136.0 1.47E-4 CDCA5
146.0 2.45E-4 CCNB1
168.0 2.96E-4 FOXM1
171.0 2.96E-5 DEPDC1
171.0 0.003 PGAM5
184.0 2.36E-4 HJURP
187.0 0.004 CDC20
231.0 5.72E-5 MCM10
241.0 0.015 BUB1
242.0 6.04E-5 GTSE1
255.0 4.38E-4 ARFGAP1
257.0 0.010 BIRC5
266.0 0.008 CENPN
273.0 0.005 C18orf61
312.0 0.005 JMY
317.0 1.39E-4 KIF4A
1 2 3 4 5 6 7
Underexpression
Median Rank
p-Value
Gene
100.0 0.003 CBLN2
121.5 2.00E-4 DCDC5
181.5 2.78E-5 FGD3
195.0 0.002 TMEM26
214.0 6.88E-4 ZNF385B
230.0 0.003 RPL26
248.0 0.019 RERG
249.0 0.002 CCDC74B
255.0 8.65E-4 C5orf41
356.0 3.76E-4 SEC14L2
261.5 0.009 FAM105A
270.0 0.002 BEND5
271.0 0.011 NAT1
271.0 0.021 PTGER3
276.0 0.001 ERBB4
277.5 0.002 KIAA2026
280.0 0.009 MEIS3P1
290.0 0.002 PAPLN
307.5 0.004 SUSD3
311.0 0.001 ADHFE1
1 2 3 4 5 6 7
Legend
1. Breast Carcinoma - Dead at 5 Years
Bild Breast, Nature, 2006
2. Invasive Ductal Breast Carcinoma - Dead at 5 Years
Desmedt Breast, Clin Cancer Res, 2007
3. Breast Carcinoma - Dead at 5 Years
Kao Breast, BMC Cancer, 2011
4. Breast Carcinoma - Dead at 5 Years
Pawitan Breast, Breast Cancer Res, 2005
5. Ductal Breast Carcinoma - Dead at 5 Years
Sorlie Breast 2, Proc Natl Acad Sci U S A, 2003
6. Invasive Ductal Breast Carcinoma - Dead at 5 Years
TCGA Breast, No Associated Paper, 2011
7. Breast Carcinoma - Dead at 5 Years
vandeVijver Breast, N Engl J Med, 2002
1 5 10 25 25 10 5 1
Not measured
The rank for a gene is the median rank for that gene across each of the analyses.
The p-Value for a gene is its p-Value for the median-ranked analysis.
Copyright© 2008-11 Compendia Bioscience, Inc. Images from Oncomine™ may be used in publications with proper citation.
The citation for Oncomine is as follows: Oncomine™ (Compendia Bioscience, Ann Arbor, MI) was used for analysis and visualization.
For further information, refer to the terms described in the license agreement.

FIG. 31 cont'd

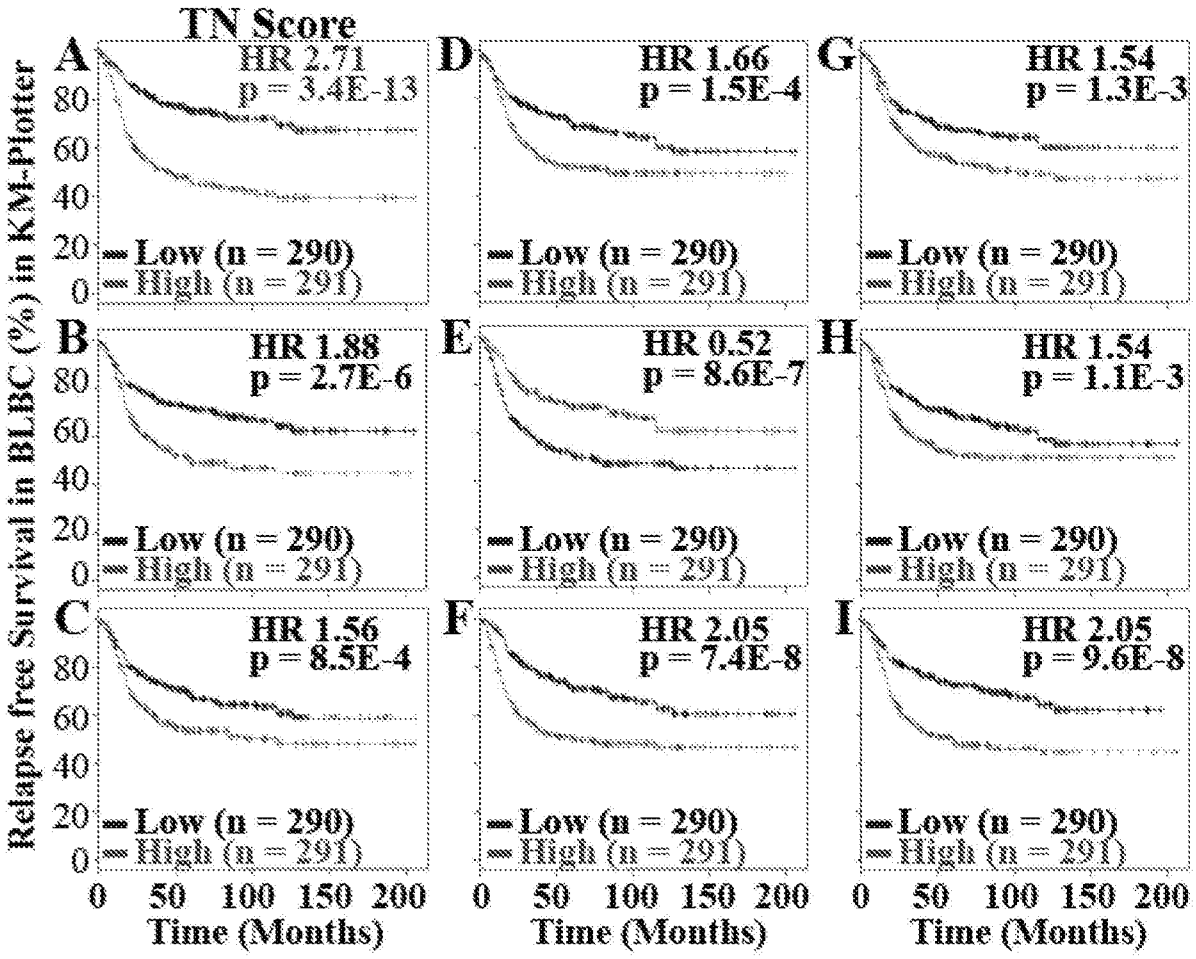

TN Score
A
HR 2.71
p = 3.4E-13
D
HR 1.66
p = 1.5E-4
G
HR 1.54
p = 1.3E-3
B
HR 1.88
p = 2.7E-6
E
HR 0.52
p = 8.6E-7
H
HR 1.54
p = 1.1E-3
C
HR 1.56
p = 8.5E-4
F
HR 2.05
p = 7.4E-8
I
HR 2.05
p = 9.6E-8
Low (n = 290)
High (n = 291)
Relapse free Survival in BLBC (%) in KM-Plotter
0
20
40
60
80
0 50 100 150 200
Time (Months)

FIG. 32

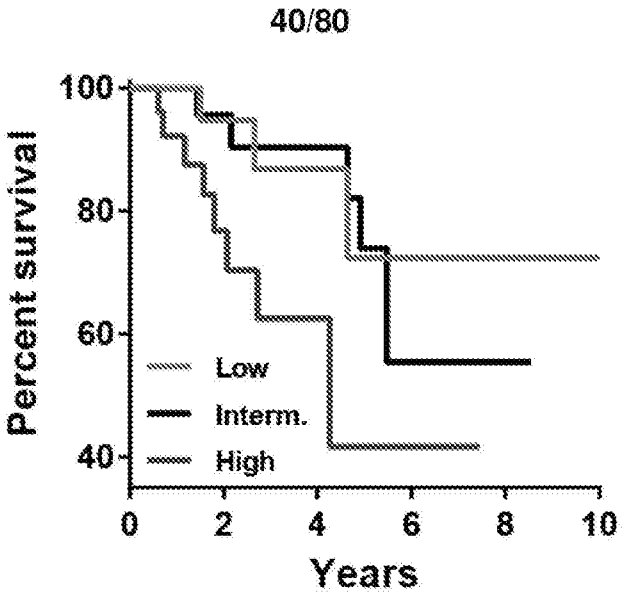

40/80
100
80
60
40
Percent survival
Low
Interm.
High
0
2
4
6
8
10
Years

FIG. 33

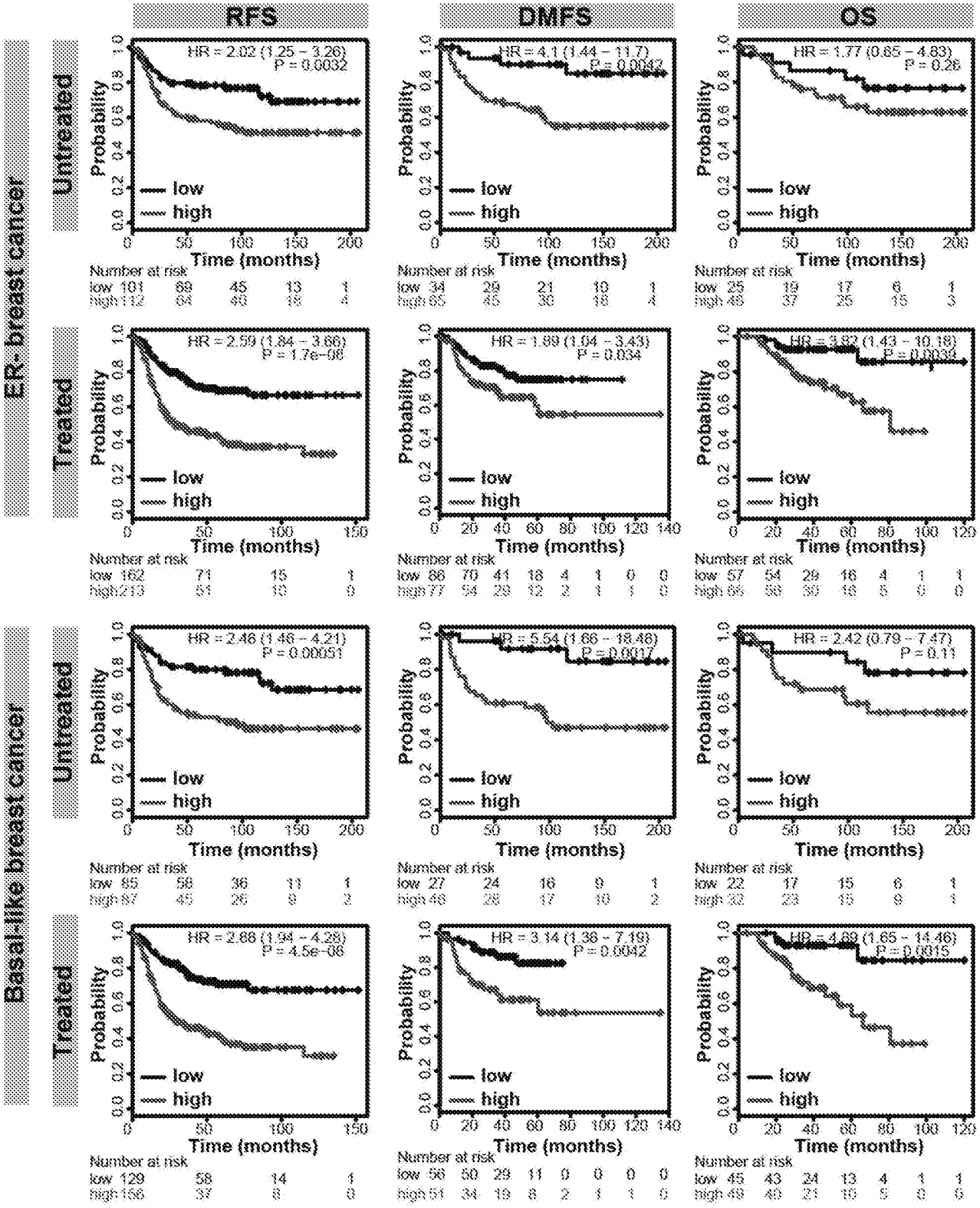

RFS
DMFS
OS
ER- breast cancer
Basal-like breast cancer
Untreated
Treated
Probability
Time (months)
low
high
HR = 2.02 (1.25 – 3.26)
P = 0.0032
HR = 4.1 (1.44 – 11.7)
P = 0.0042
HR = 1.77 (0.65 – 4.83)
P = 0.26
HR = 2.59 (1.84 – 3.66)
P = 1.7e−08
HR = 1.89 (1.04 – 3.43)
P = 0.034
HR = 3.92 (1.43 – 10.18)
P = 0.0039
HR = 2.46 (1.46 – 4.21)
P = 0.00051
HR = 5.54 (1.66 – 18.48)
P = 0.0017
HR = 2.42 (0.79 – 7.47)
P = 0.11
HR = 2.88 (1.94 – 4.28)
P = 4.5e−08
HR = 3.14 (1.38 – 7.19)
P = 0.0042
HR = 4.69 (1.65 – 14.46)
P = 0.0015
Number at risk
low 101 69 45 13 1
high 112 64 40 18 4
low 34 29 21 10 1
high 65 45 30 18 4
low 25 19 17 6 1
high 46 37 25 15 3
low 162 71 15 1
high 213 81 10 0
low 86 70 41 18 4 1 0 0
high 77 54 29 12 2 1 1 0
low 57 54 29 16 4 1 1
high 65 56 30 16 5 0 0
low 85 58 36 11 1
high 87 45 26 9 2
low 27 24 16 9 1
high 46 28 17 10 2
low 22 17 15 6 1
high 32 23 15 9 1
low 129 58 14 1
high 156 37 8 0
low 56 50 29 11 0 0 0 0
high 51 34 19 8 2 1 1 0
low 45 43 24 13 4 1 1
high 49 40 21 10 5 0 0

FIG. 34

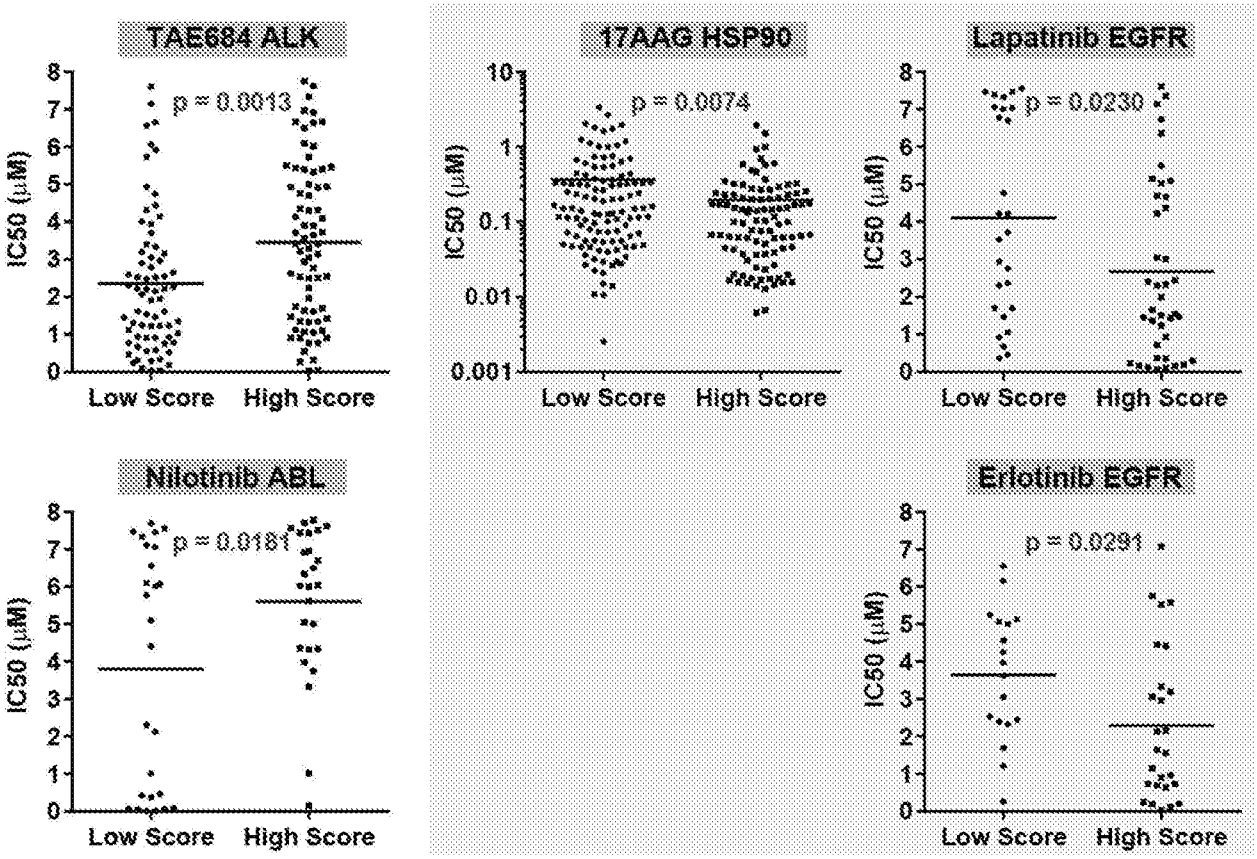

TAE684 ALK
p = 0.0013
IC50 (μM)
Low Score
High Score
17AAG HSP90
p = 0.0074
IC50 (μM)
Low Score
High Score
Lapatinib EGFR
p = 0.0230
IC50 (μM)
Low Score
High Score
Nilotinib ABL
p = 0.0181
IC50 (μM)
Low Score
High Score
Erlotinib EGFR
p = 0.0291
IC50 (μM)
Low Score
High Score

FIG. 35

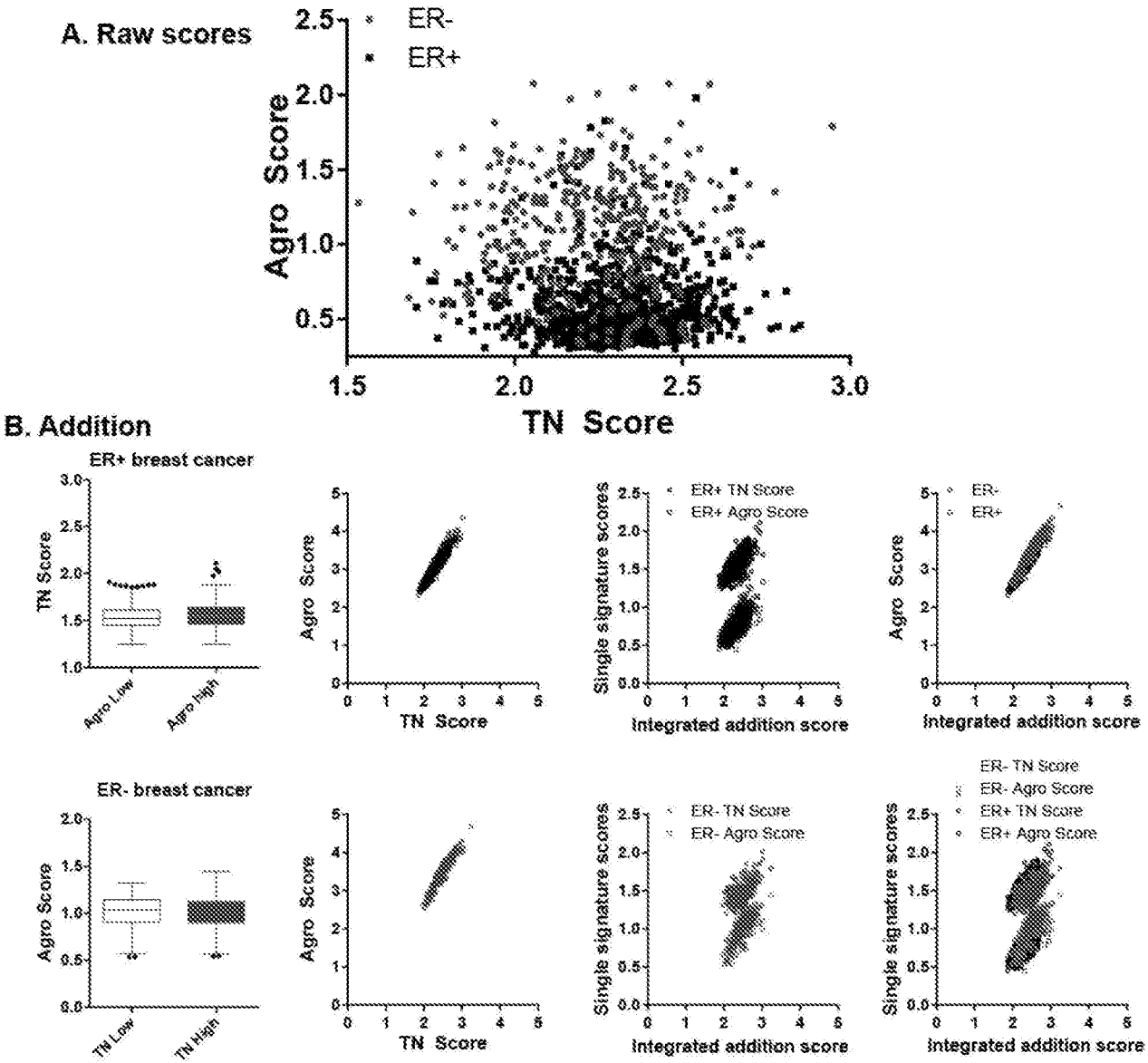

A. Raw scores
ER-
ER+
Agro Score
TN Score
B. Addition
ER+ breast cancer
TN Score
Agro Low
Agro High
Agro Score
TN Score
Single signature scores
ER+ TN Score
ER+ Agro Score
Integrated addition score
ER-
ER+
Agro Score
Integrated addition score
ER- breast cancer
Agro Score
TN Low
TN High
Agro Score
TN Score
Single signature scores
ER- TN Score
ER- Agro Score
Integrated addition score
ER- TN Score
ER- Agro Score
ER+ TN Score
ER+ Agro Score
Single signature scores
Integrated addition score

FIG. 36

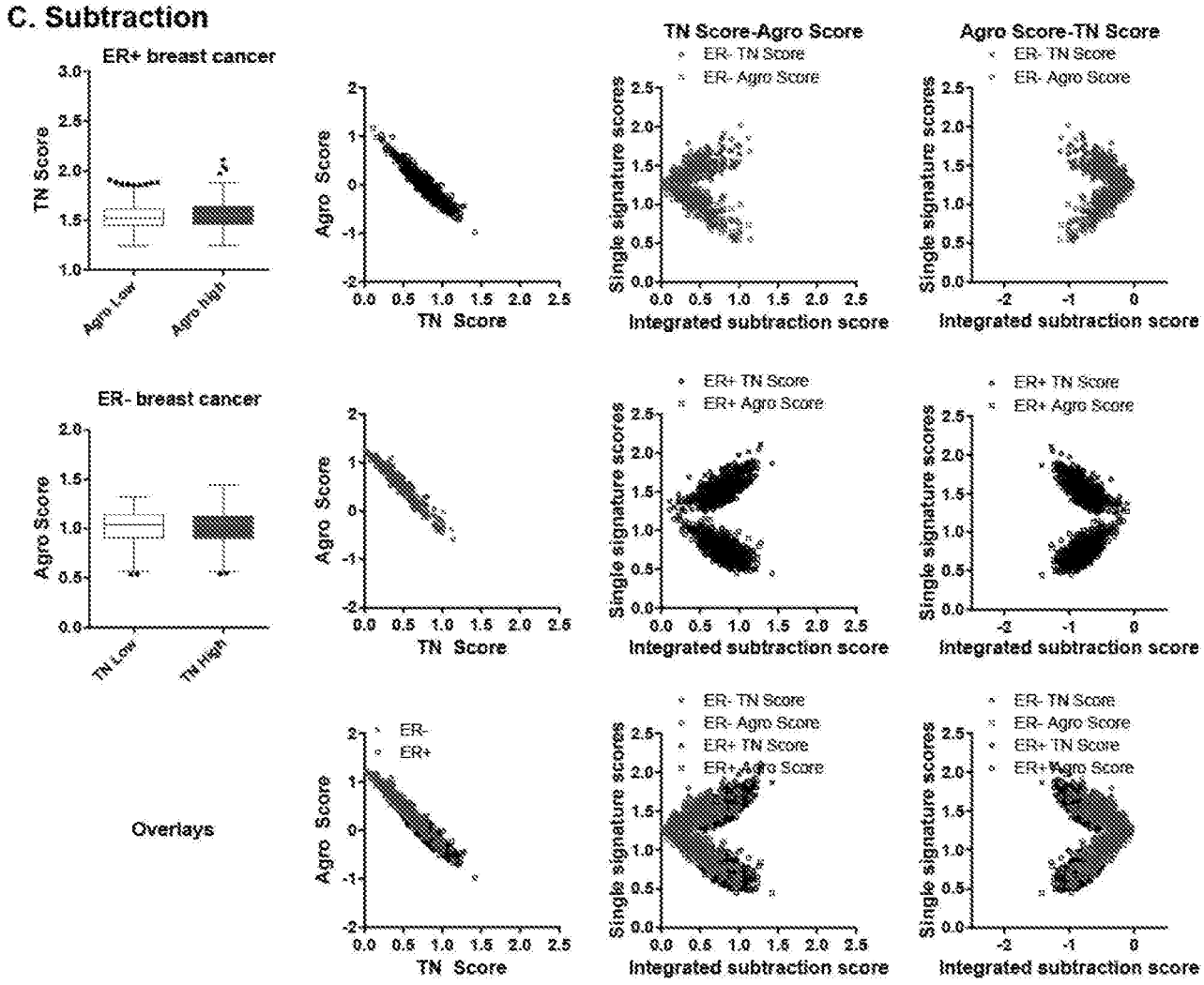

C. Subtraction
ER+ breast cancer
TN Score
Agro Low
Agro High
Agro Score
TN Score
TN Score-Agro Score
ER- TN Score
ER- Agro Score
Single signature scores
Integrated subtraction score
Agro Score-TN Score
ER- TN Score
ER- Agro Score
Single signature scores
Integrated subtraction score
ER- breast cancer
Agro Score
TN Low
TN High
Agro Score
TN Score
ER+ TN Score
ER+ Agro Score
Single signature scores
Integrated subtraction score
ER+ TN Score
ER+ Agro Score
Single signature scores
Integrated subtraction score
Overlays
ER-
ER+
Agro Score
TN Score
ER- TN Score
ER- Agro Score
ER+ TN Score
ER+ Agro Score
Single signature scores
Integrated subtraction score
ER- TN Score
ER- Agro Score
ER+ TN Score
ER+ Agro Score
Single signature scores
Integrated subtraction score

FIG. 36 cont'd

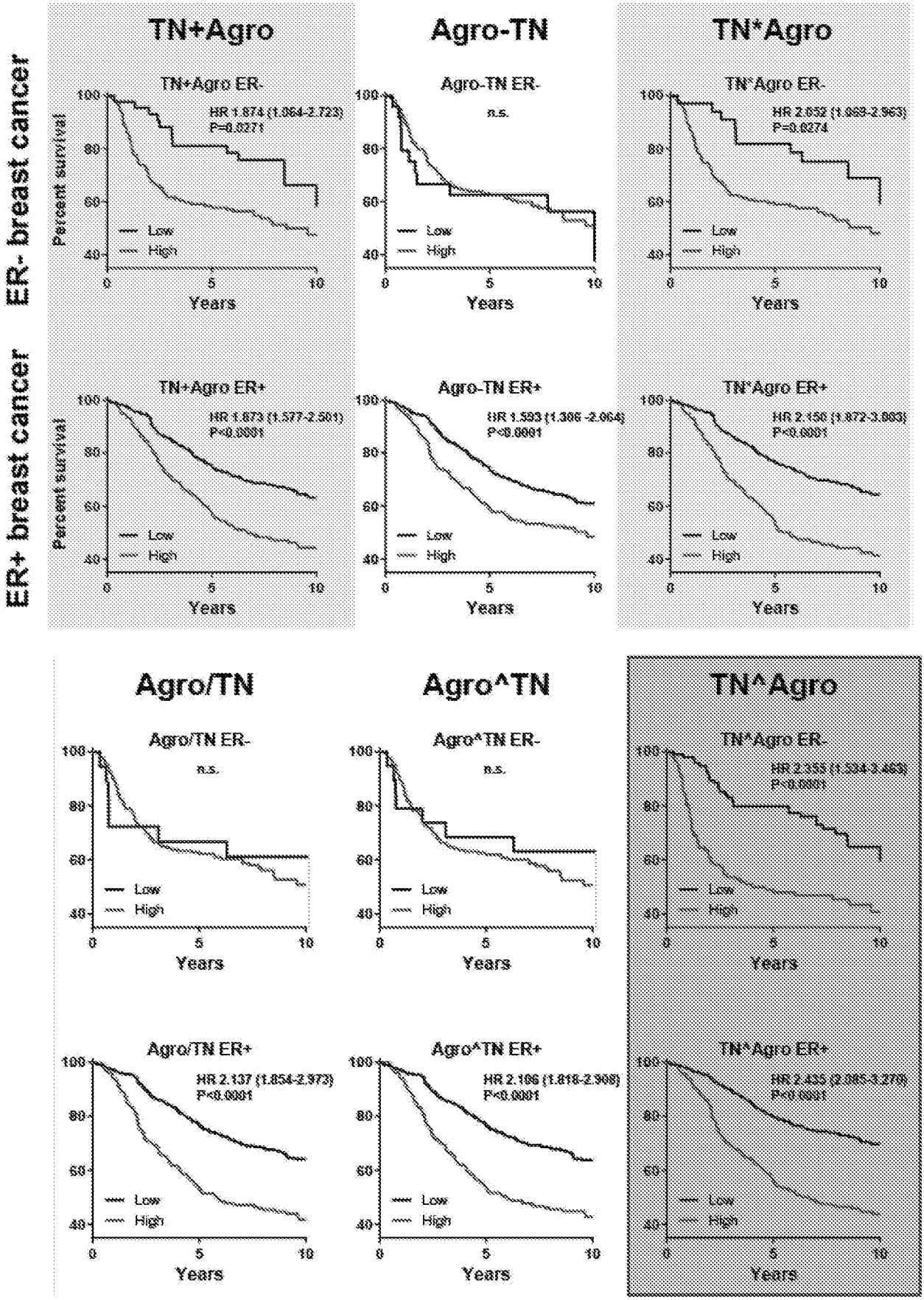

ER- breast cancer
ER+ breast cancer
TN+Agro
Agro-TN
TN*Agro
Agro/TN
Agro^TN
TN^Agro
TN+Agro ER-
HR 1.874 (1.064-2.723)
P=0.0271
Agro-TN ER-
n.s.
TN*Agro ER-
HR 2.852 (1.868-2.963)
P=0.0274
TN+Agro ER+
HR 1.873 (1.577-2.501)
P<0.0001
Agro-TN ER+
HR 1.593 (1.386 -2.064)
P<0.0001
TN*Agro ER+
HR 2.150 (1.872-3.883)
P<0.0001
Agro/TN ER-
n.s.
Agro^TN ER-
n.s.
TN^Agro ER-
HR 2.353 (1.524-3.463)
P<0.0001
Agro/TN ER+
HR 2.137 (1.854-2.973)
P<0.0001
Agro^TN ER+
HR 2.106 (1.818-2.908)
P<0.0001
TN^Agro ER+
HR 2.435 (2.085-3.270)
P<0.0001
Percent survival
Years
Low
High

FIG. 37

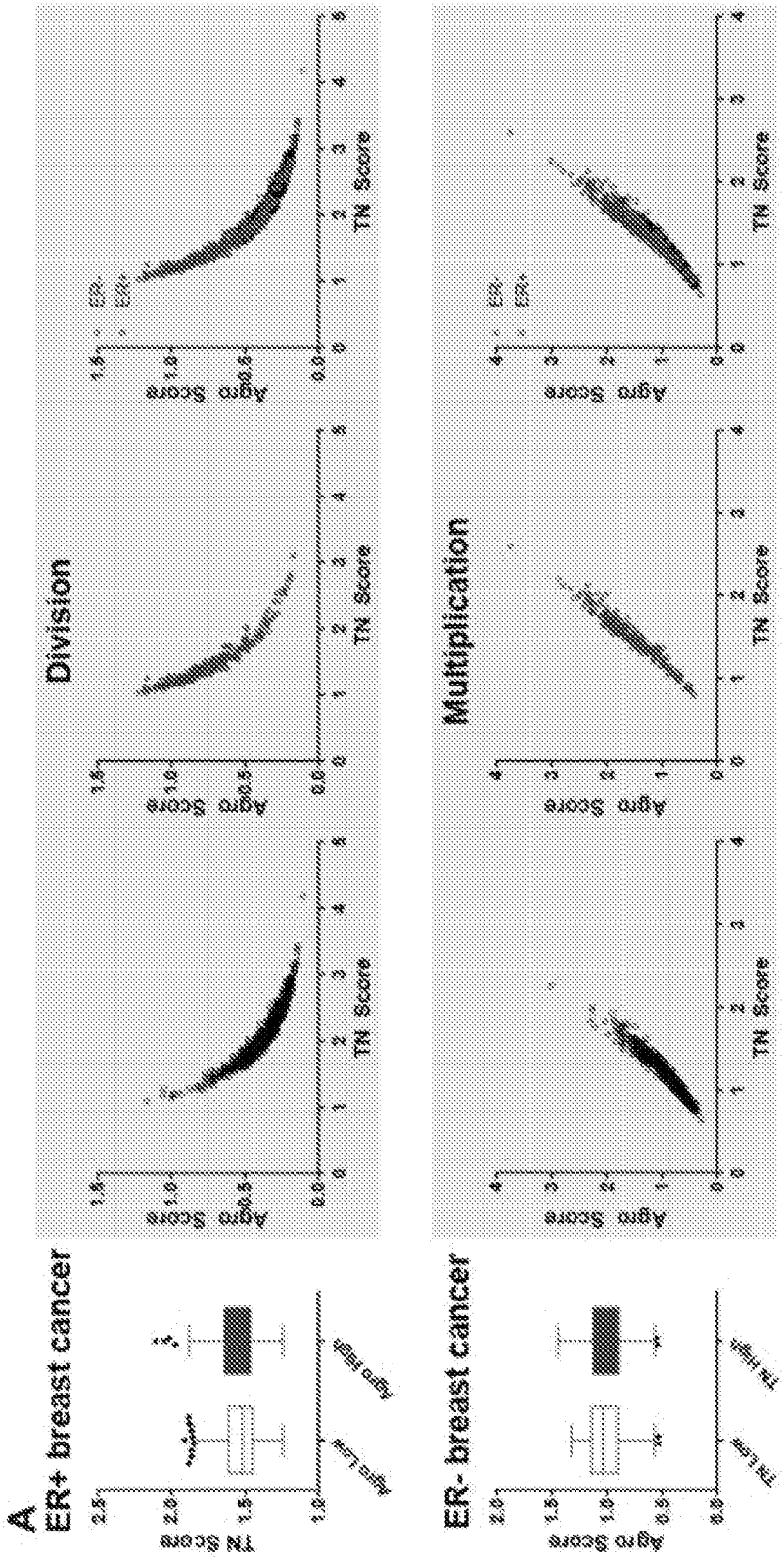

A
ER+ breast cancer
ER- breast cancer
TN Score
Agro Score
High Agro
Low Agro
High TN
Low TN
Division
Multiplication
ER-
ER+
Agro Score
TN Score

FIG. 38

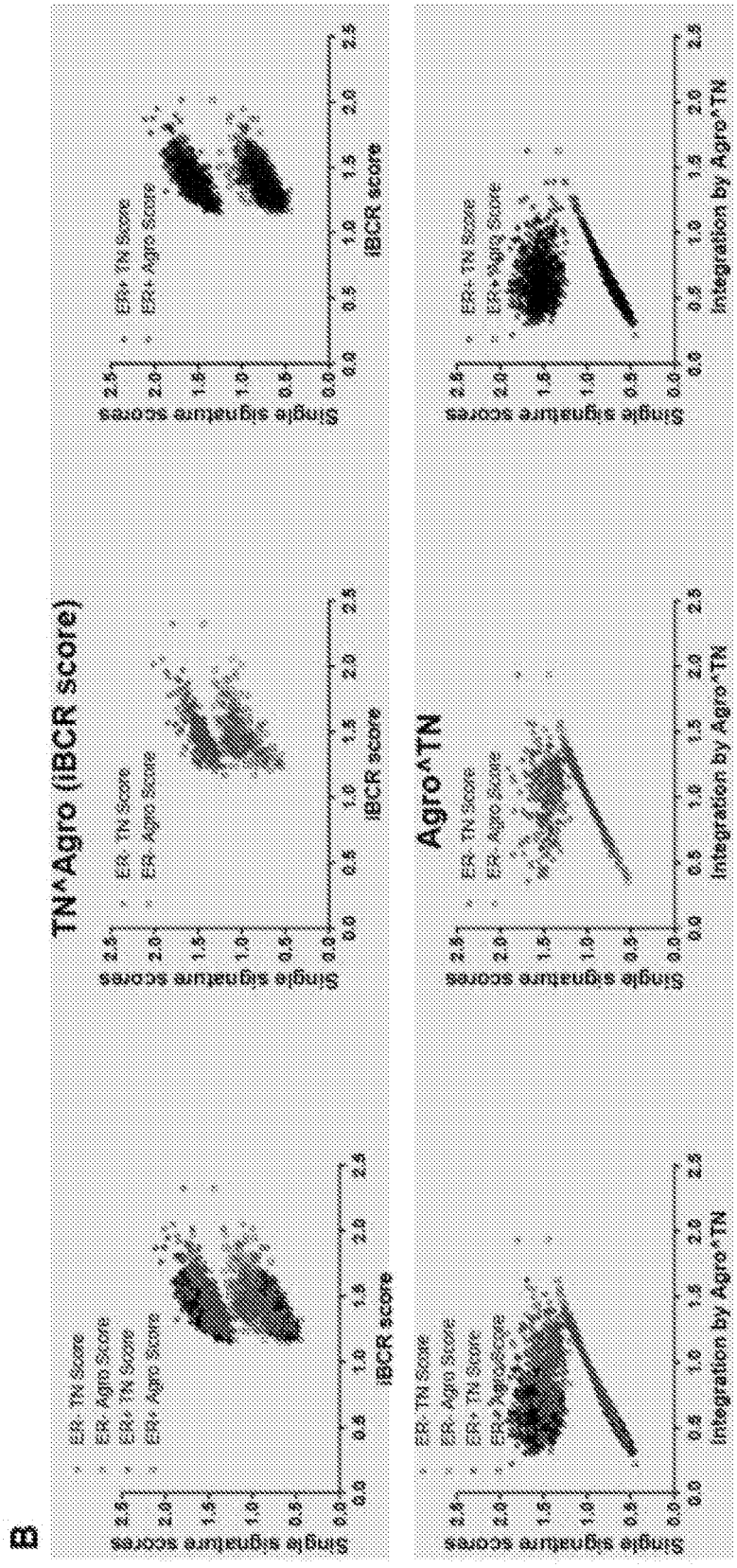

B
TN^Agro (iBCR score)
Agro^TN
ER- TN Score
ER- Agro Score
ER+ TN Score
ER+ Agro Score
Single signature scores
iBCR score
Integration by Agro^TN

FIG. 38 cont'd

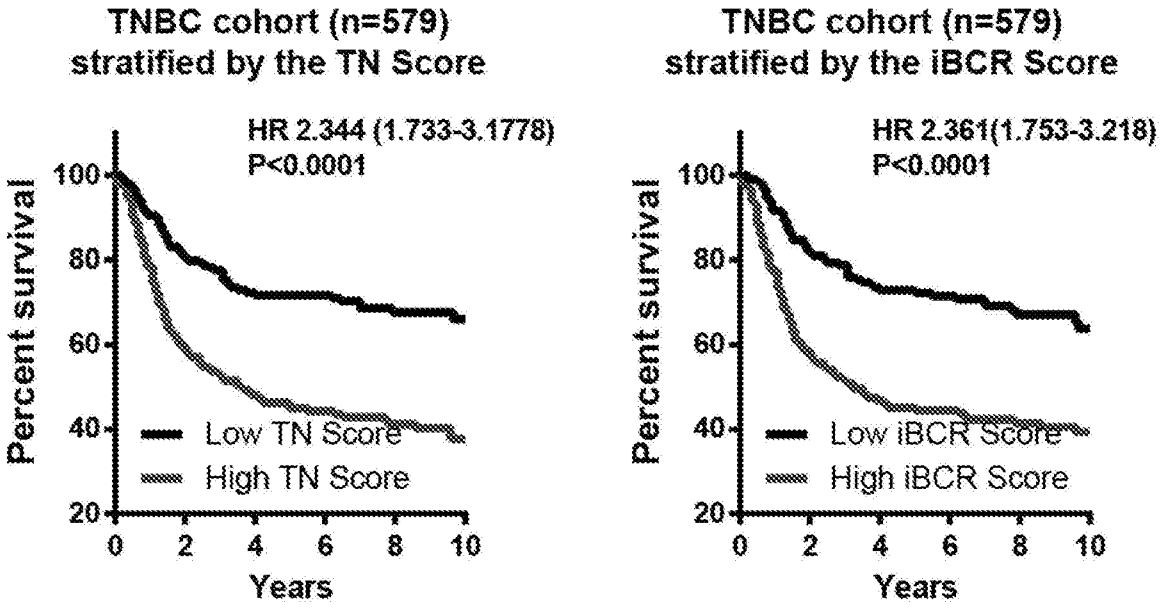

TNBC cohort (n=579)
stratified by the TN Score
HR 2.344 (1.733-3.1778)
P<0.0001
Percent survival
100
80
60
40
20
0
2
4
6
8
10
Years
Low TN Score
High TN Score
TNBC cohort (n=579)
stratified by the iBCR Score
HR 2.361(1.753-3.218)
P<0.0001
Percent survival
100
80
60
40
20
0
2
4
6
8
10
Years
Low iBCR Score
High iBCR Score

FIG. 39

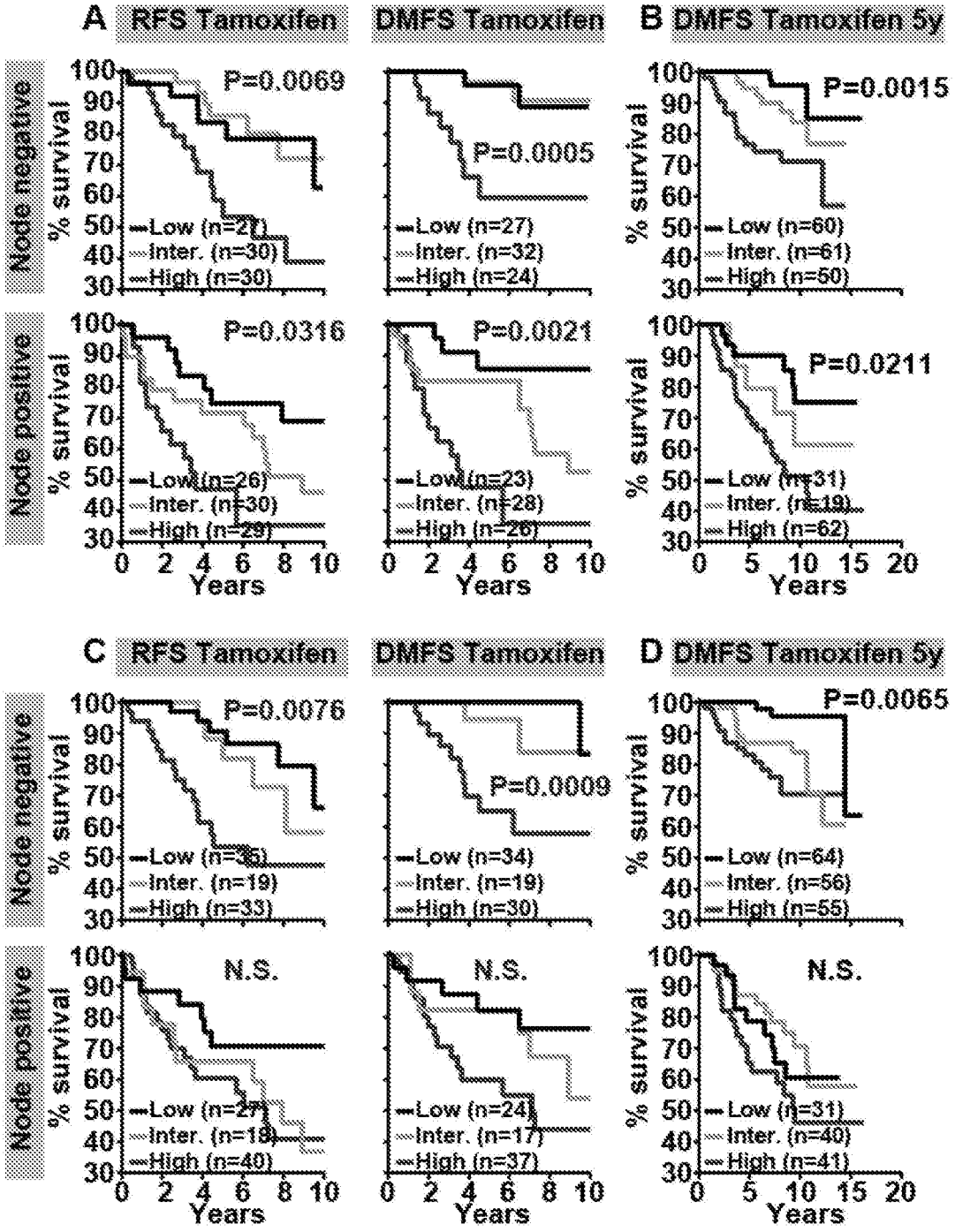

A RFS Tamoxifen
DMFS Tamoxifen
B DMFS Tamoxifen 5y
Node negative
Node positive
% survival
P=0.0069
P=0.0005
P=0.0015
P=0.0316
P=0.0021
P=0.0211
Low (n=27)
Inter. (n=30)
High (n=30)
Low (n=27)
Inter. (n=32)
High (n=24)
Low (n=60)
Inter. (n=61)
High (n=50)
Low (n=26)
Inter. (n=30)
High (n=29)
Low (n=23)
Inter. (n=28)
High (n=26)
Low (n=31)
Inter. (n=19)
High (n=62)
Years
C RFS Tamoxifen
DMFS Tamoxifen
D DMFS Tamoxifen 5y
P=0.0076
P=0.0009
P=0.0065
N.S.
N.S.
N.S.
Low (n=35)
Inter. (n=19)
High (n=33)
Low (n=34)
Inter. (n=19)
High (n=30)
Low (n=64)
Inter. (n=56)
High (n=55)
Low (n=27)
Inter. (n=19)
High (n=40)
Low (n=24)
Inter. (n=17)
High (n=37)
Low (n=31)
Inter. (n=40)
High (n=41)

FIG. 40

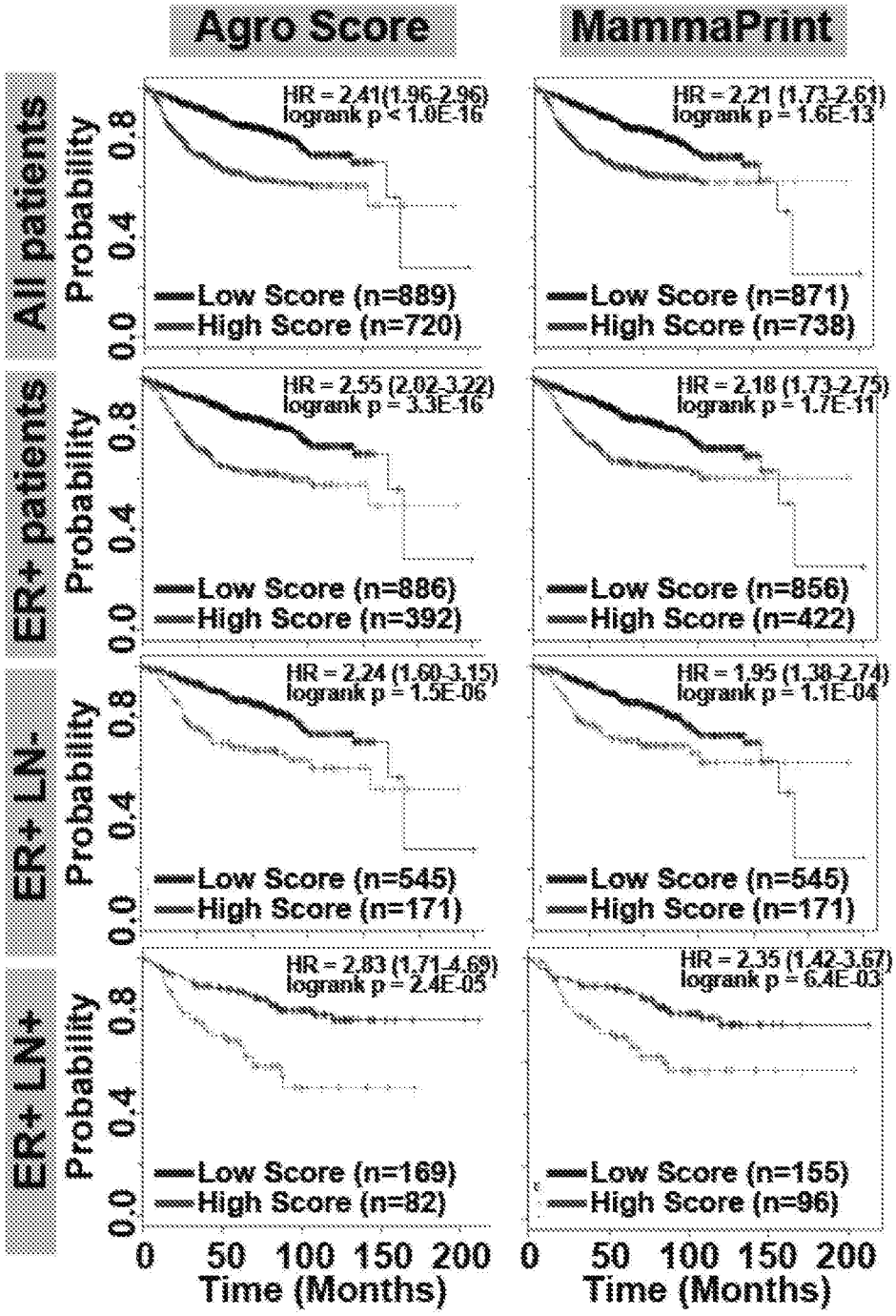

Agro Score
MammaPrint
All patients
ER+ patients
ER+ LN-
ER+ LN+
Probability
HR = 2.41(1.96-2.96)
logrank p < 1.0E-16
Low Score (n=889)
High Score (n=720)
HR = 2.21 (1.73-2.81)
logrank p = 1.6E-13
Low Score (n=871)
High Score (n=738)
HR = 2.55 (2.02-3.22)
logrank p = 3.3E-16
Low Score (n=886)
High Score (n=392)
HR = 2.18 (1.73-2.75)
logrank p = 1.7E-11
Low Score (n=856)
High Score (n=422)
HR = 2.24 (1.60-3.15)
logrank p = 1.5E-06
Low Score (n=545)
High Score (n=171)
HR = 1.95 (1.38-2.74)
logrank p = 1.1E-04
Low Score (n=545)
High Score (n=171)
HR = 2.83 (1.71-4.69)
logrank p = 2.4E-05
Low Score (n=169)
High Score (n=82)
HR = 2.35 (1.42-3.67)
logrank p = 6.4E-03
Low Score (n=155)
High Score (n=96)
0.0
0.4
0.8
0
50
100
150
200
Time (Months)

FIG. 41

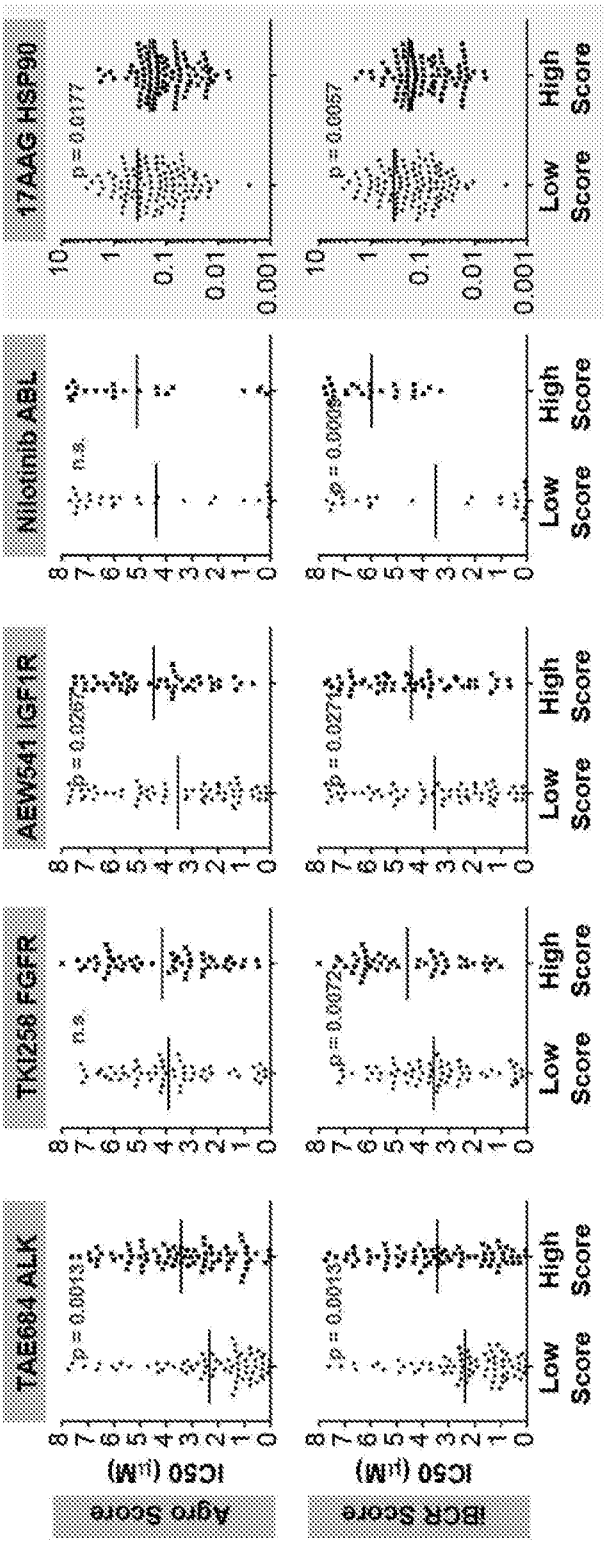

17AAG HSP90
Nilotinib ABL
AEW541 IGF1R
TKI258 FGFR
TAE684 ALK
p = 0.0177
p = 0.0057
p = 0.0287
p = 0.0272
p = 0.0072
p = 0.0013
n.s.
n.s.
10
1
0.1
0.01
0.001
Low Score
High Score
IC50 (μM)
Agro Score
IBCR Score

FIG. 42

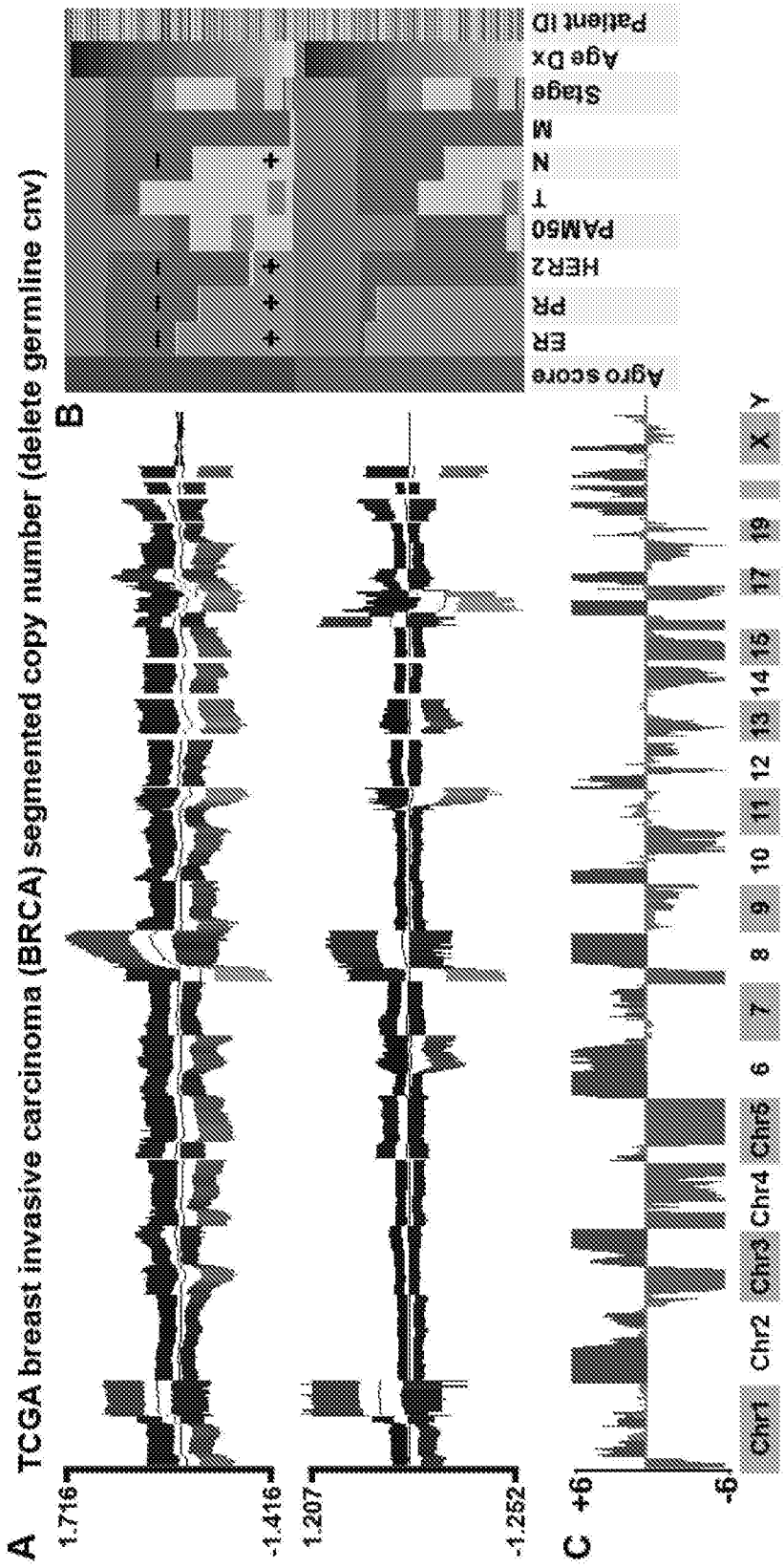

A
TCGA breast invasive carcinoma (BRCA) segmented copy number (delete germline cnv)
1.716
-1.416
1.207
-1.252
B
Agro score
ER
PR
HER2
PAM50
T
N
M
Stage
Age Dx
Patient ID
C
+6
-6
Chr1
Chr2
Chr3
Chr4
Chr5
6
7
8
9
10
11
12
13
14
15
17
19
X
Y

FIG. 43

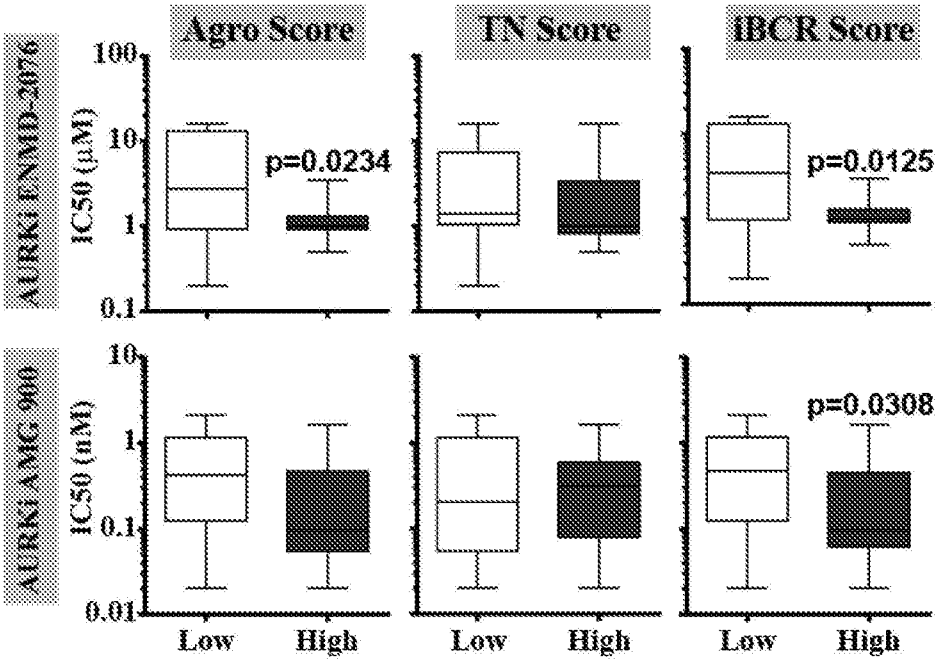

Agro Score
TN Score
IBCR Score
AURKi ENMD-2076
IC50 (μM)
100
10
1
0.1
p=0.0234
p=0.0125
AURKi AMG 900
IC50 (nM)
10
1
0.1
0.01
p=0.0308
Low
High
Low
High
Low
High

FIG. 44

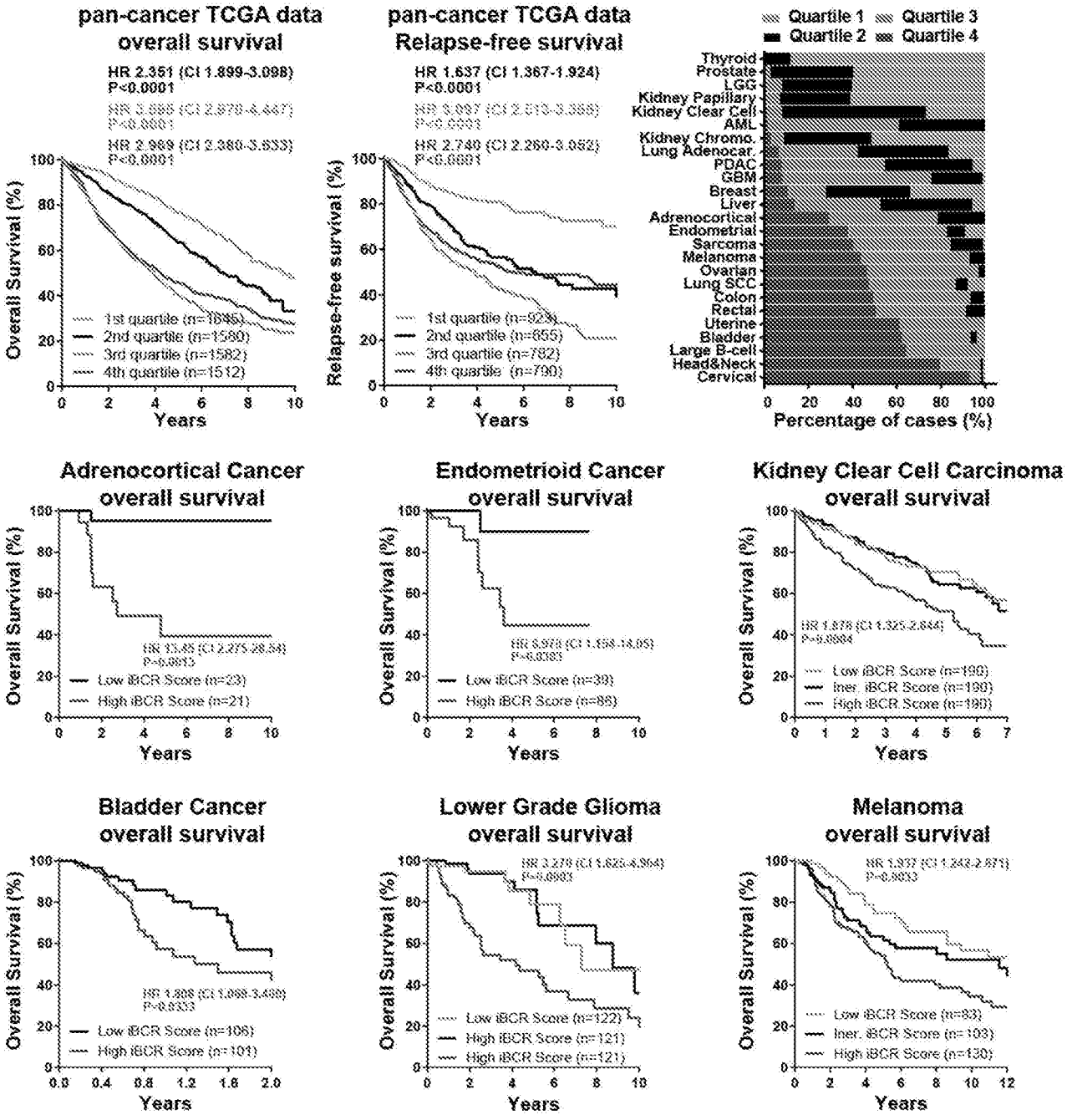
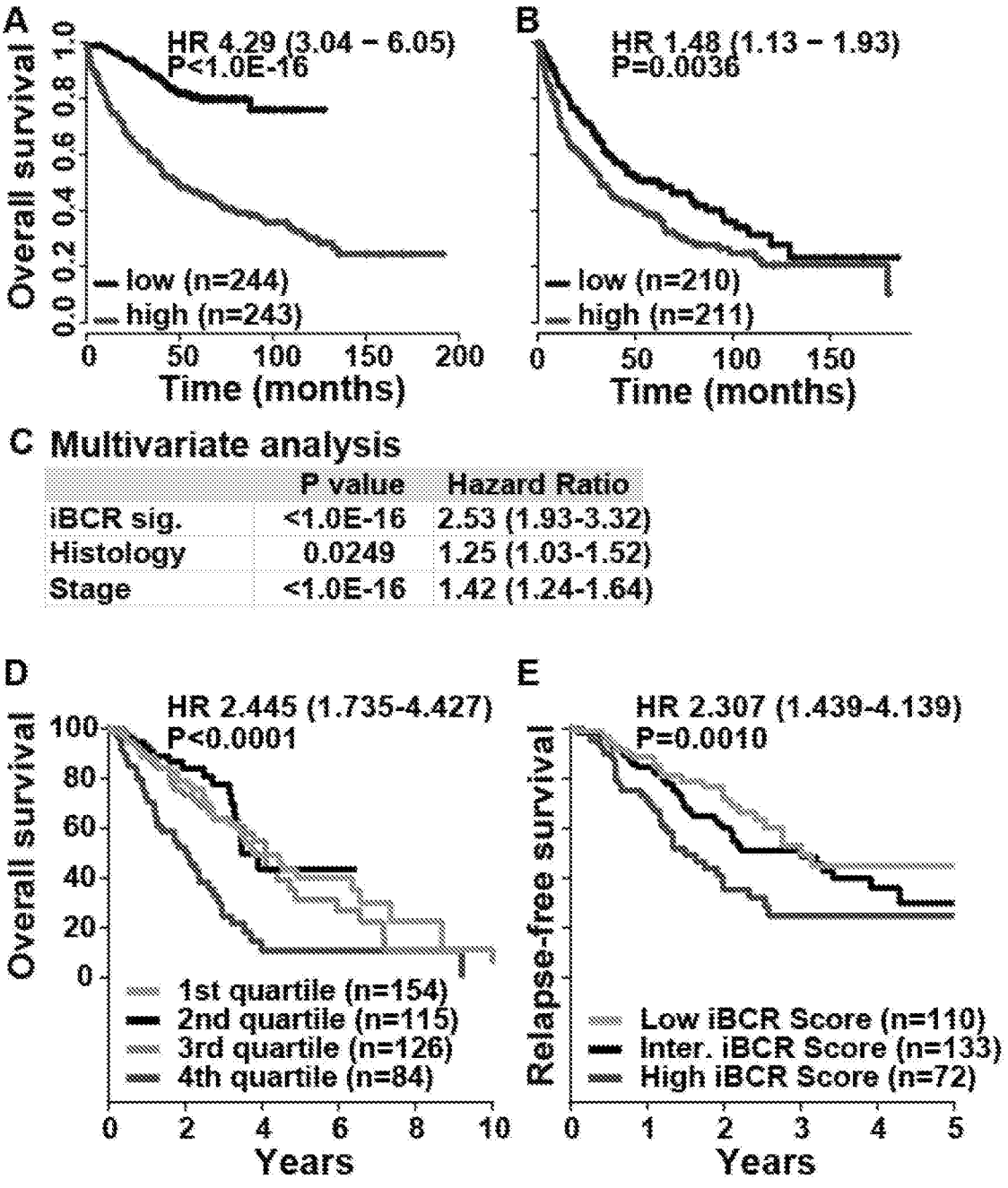

pan-cancer TCGA data
overall survival
HR 2.351 (CI 1.899-3.098)
P<0.0001
HR 3.585 (CI 2.879-4.447)
P<0.0001
HR 2.989 (CI 2.380-3.633)
P<0.0001
Overall Survival (%)
1st quartile (n=1545)
2nd quartile (n=1580)
3rd quartile (n=1582)
4th quartile (n=1512)
Years
pan-cancer TCGA data
Relapse-free survival
HR 1.637 (CI 1.367-1.924)
P<0.0001
HR 3.097 (CI 2.513-3.368)
P<0.0001
HR 2.740 (CI 2.260-3.052)
P<0.0001
Relapse-free survival (%)
1st quartile (n=923)
2nd quartile (n=855)
3rd quartile (n=782)
4th quartile (n=790)
Years
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Thyroid
Prostate
LGG
Kidney Papillary
Kidney Clear Cell
AML
Kidney Chromo.
Lung Adenocar.
PDAC
GBM
Breast
Liver
Adrenocortical
Endometrial
Sarcoma
Melanoma
Ovarian
Lung SCC
Colon
Rectal
Uterine
Bladder
Large B-cell
Head&Neck
Cervical
Percentage of cases (%)
Adrenocortical Cancer
overall survival
Overall Survival (%)
HR 13.45 (CI 2.275-28.84)
P<0.0013
Low iBCR Score (n=23)
High iBCR Score (n=21)
Years
Endometrioid Cancer
overall survival
Overall Survival (%)
HR 5.978 (CI 1.158-14.05)
P<0.0183
Low iBCR Score (n=39)
High iBCR Score (n=88)
Years
Kidney Clear Cell Carcinoma
overall survival
Overall Survival (%)
HR 1.878 (CI 1.325-2.644)
P<0.0004
Low iBCR Score (n=190)
Iner. iBCR Score (n=190)
High iBCR Score (n=190)
Years
Bladder Cancer
overall survival
Overall Survival (%)
HR 1.808 (CI 1.068-3.488)
P=0.0333
Low iBCR Score (n=106)
High iBCR Score (n=101)
Years
Lower Grade Glioma
overall survival
Overall Survival (%)
HR 3.278 (CI 1.823-4.964)
P<0.0001
Low iBCR Score (n=122)
High iBCR Score (n=121)
High iBCR Score (n=121)
Years
Melanoma
overall survival
Overall Survival (%)
HR 1.937 (CI 1.242-2.871)
P=0.0033
Low iBCR Score (n=83)
Iner. iBCR Score (n=103)
High iBCR Score (n=130)
Years

FIG. 45



C Multivariate analysis

	P value	Hazard Ratio
iBCR sig.	<1.0E-16	2.53 (1.93-3.32)
Histology	0.0249	1.25 (1.03-1.52)
Stage	<1.0E-16	1.42 (1.24-1.64)

FIG. 46

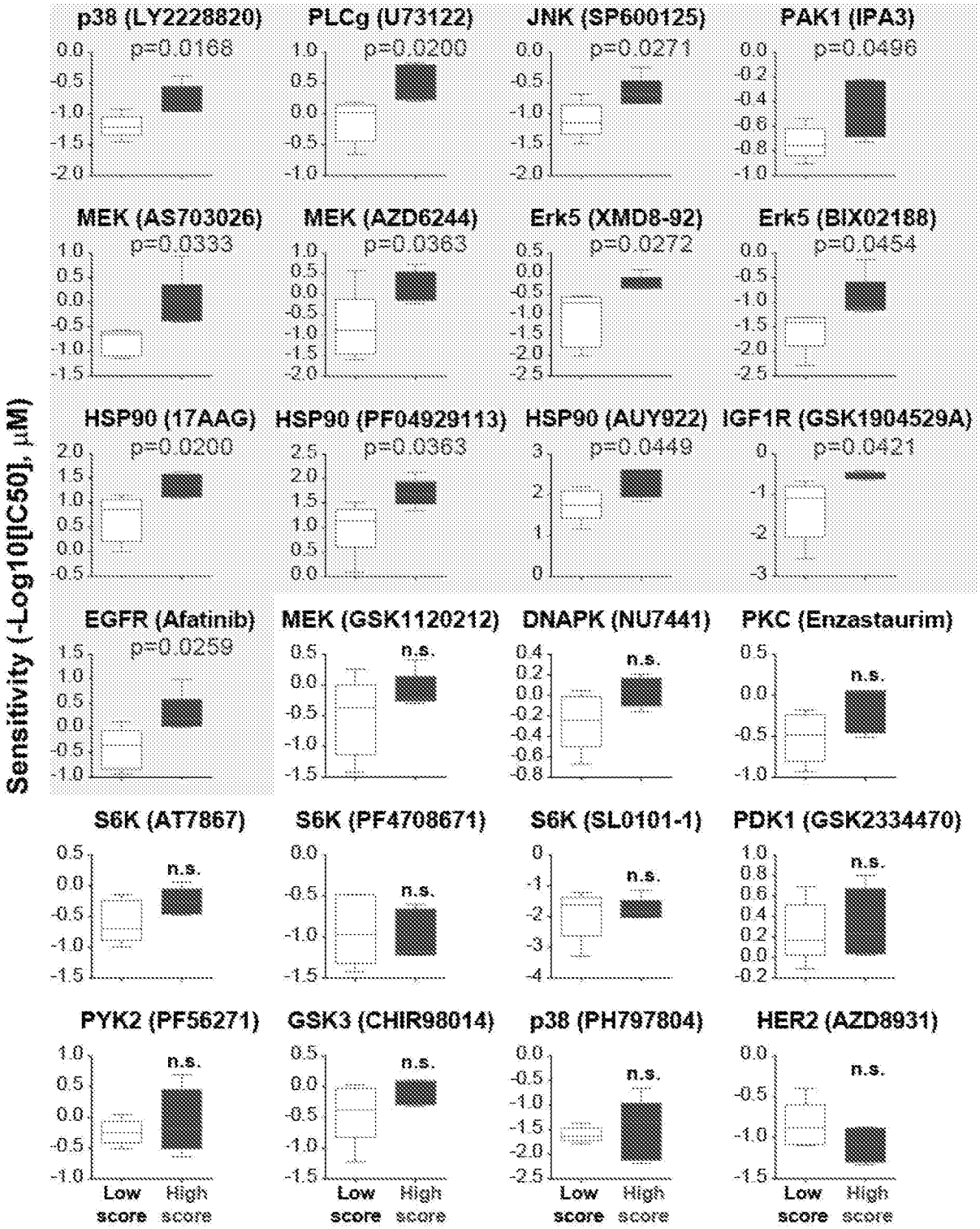

Sensitivity (-Log10[IC50], μM)
p38 (LY2228820)
p=0.0166
PLCg (U73122)
p=0.0200
JNK (SP600125)
p=0.0271
PAK1 (IPA3)
p=0.0496
MEK (AS703026)
p=0.0333
MEK (AZD6244)
p=0.0363
Erk5 (XMD8-92)
p=0.0272
Erk5 (BIX02188)
p=0.0454
HSP90 (17AAG)
p=0.0200
HSP90 (PF04929113)
p=0.0363
HSP90 (AUY922)
p=0.0449
IGF1R (GSK1904529A)
p=0.0421
EGFR (Afatinib)
p=0.0259
MEK (GSK1120212)
DNAPK (NU7441)
PKC (Enzastaurim)
S6K (AT7867)
S6K (PF4708671)
S6K (SL0101-1)
PDK1 (GSK2334470)
PYK2 (PF56271)
GSK3 (CHIR98014)
p38 (PH797804)
HER2 (AZD8931)
n.s.
Low score
High score

FIG. 47

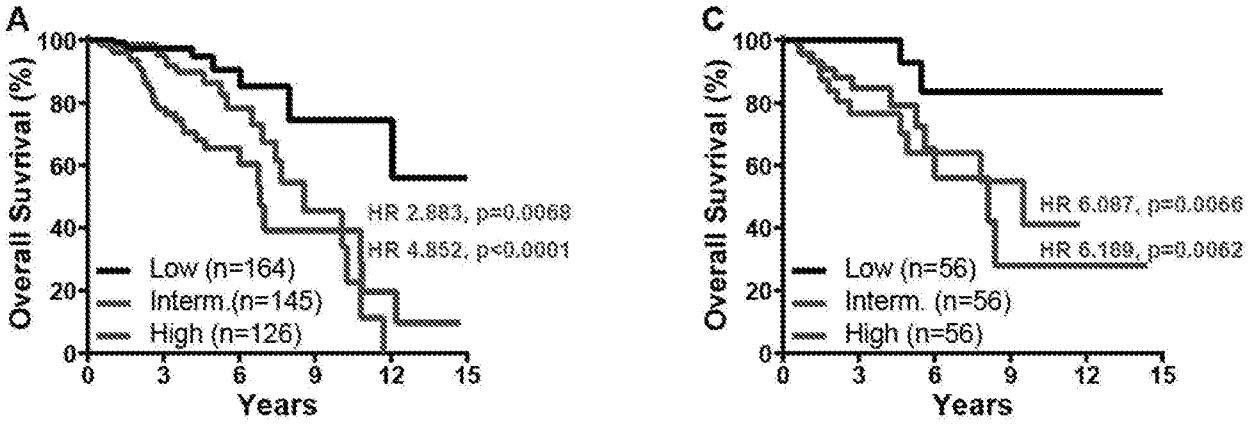

A
Overall Suvrival (%)
100
80
60
40
20
0
0
3
6
9
12
15
Years
HR 2.883, p=0.0069
HR 4.852, p<0.0001
Low (n=164)
Interm.(n=145)
High (n=126)
C
Overall Suvrival (%)
HR 6.087, p=0.0066
HR 6.189, p=0.0062
Low (n=56)
Interm. (n=56)
High (n=56)
Years

FIG. 48

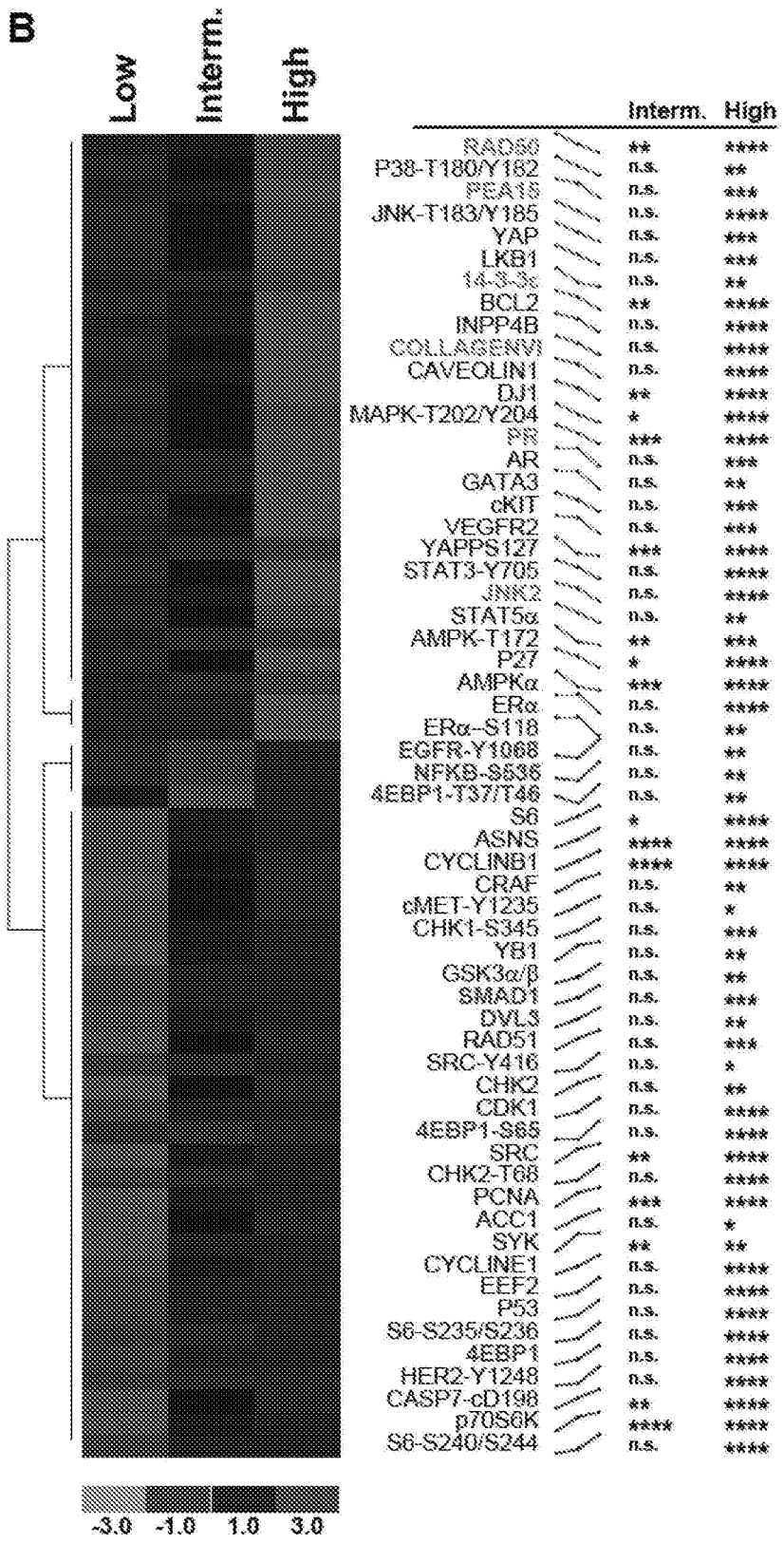

B
Low
Interm.
High
Interm.
High
RAD50 ** ****
P38-T180/Y182 n.s. **
PEA15 n.s. ***
JNK-T183/Y185 n.s. ****
YAP n.s. ***
LKB1 n.s. ***
14-3-3ε n.s. **
BCL2 ** ****
INPP4B n.s. ****
COLLAGENVI n.s. ****
CAVEOLIN1 n.s. ****
DJ1 ** ****
MAPK-T202/Y204 * ****
PR *** ****
AR n.s. ***
GATA3 n.s. **
cKIT n.s. ***
VEGFR2 n.s. ***
YAPPS127 *** ****
STAT3-Y705 n.s. ****
JNK2 n.s. ****
STAT5α n.s. **
AMPK-T172 ** ***
P27 * ****
AMPKα *** ****
ERα n.s. ****
ERα--S118 n.s. **
EGFR-Y1068 n.s. **
NFKB-S536 n.s. **
4EBP1-T37/T46 n.s. **
S6 * ****
ASNS **** ****
CYCLINB1 **** ****
CRAF n.s. **
cMET-Y1235 n.s. *
CHK1-S345 n.s. ***
YB1 n.s. **
GSK3α/β n.s. **
SMAD1 n.s. ***
DVL3 n.s. **
RAD51 n.s. ***
SRC-Y416 n.s. *
CHK2 n.s. **
CDK1 n.s. ****
4EBP1-S65 n.s. ****
SRC ** ****
CHK2-T68 n.s. ****
PCNA *** ****
ACC1 n.s. *
SYK ** **
CYCLINE1 n.s. ****
EEF2 n.s. ****
P53 n.s. ****
S6-S235/S236 n.s. ****
4EBP1 n.s. ****
HER2-Y1248 n.s. ****
CASP7-cD198 ** ****
p70S6K **** ****
S6-S240/S244 n.s. ****
-3.0 -1.0 1.0 3.0

FIG. 48 cont'd

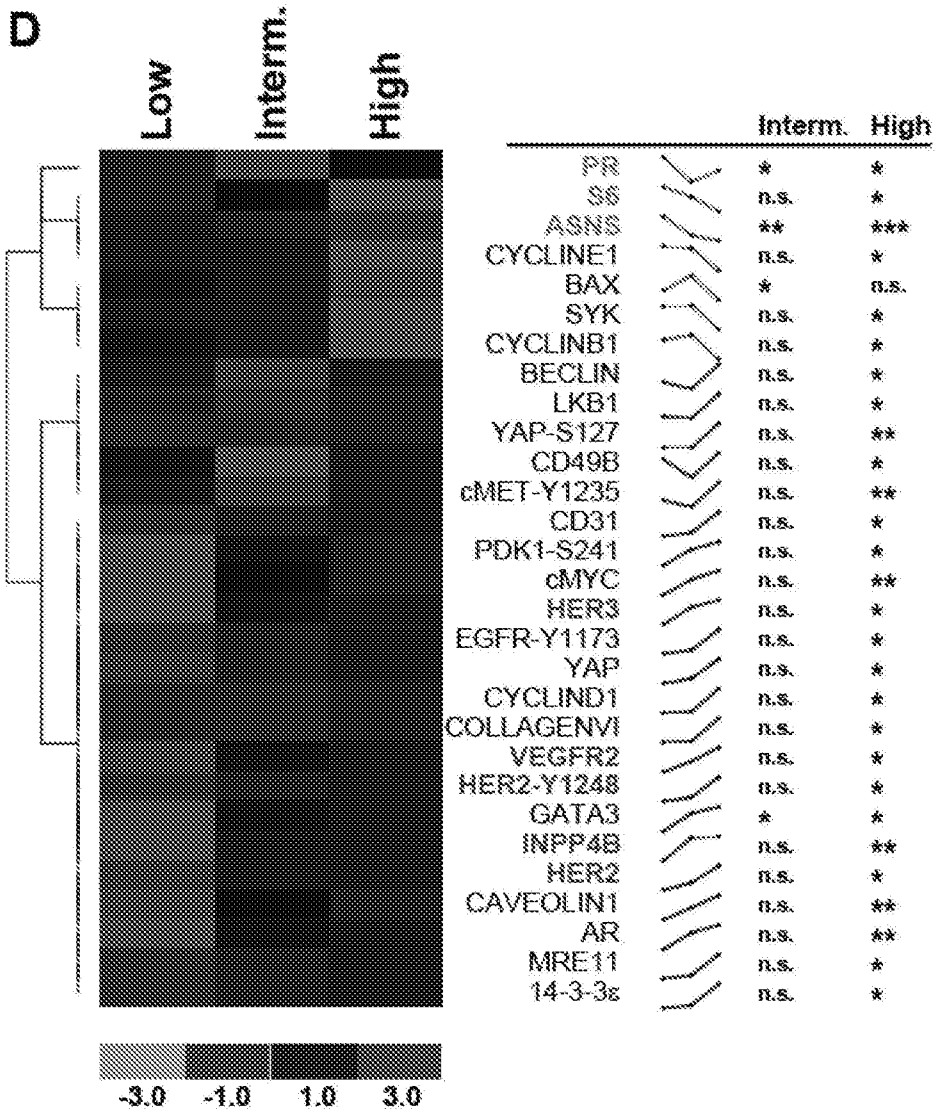

D
Low
Interm.
High
Interm.
High
PR * *
S6 n.s. *
ASNS ** ***
CYCLINE1 n.s. *
BAX * n.s.
SYK n.s. *
CYCLINB1 n.s. *
BECLIN n.s. *
LKB1 n.s. *
YAP-S127 n.s. **
CD49B n.s. *
cMET-Y1235 n.s. **
CD31 n.s. *
PDK1-S241 n.s. *
cMYC n.s. **
HER3 n.s. *
EGFR-Y1173 n.s. *
YAP n.s. *
CYCLIND1 n.s. *
COLLAGENVI n.s. *
VEGFR2 n.s. *
HER2-Y1248 n.s. *
GATA3 * *
INPP4B n.s. **
HER2 n.s. *
CAVEOLIN1 n.s. **
AR n.s. **
MRE11 n.s. *
14-3-3ε n.s. *
-3.0 -1.0 1.0 3.0

FIG. 48 cont'd

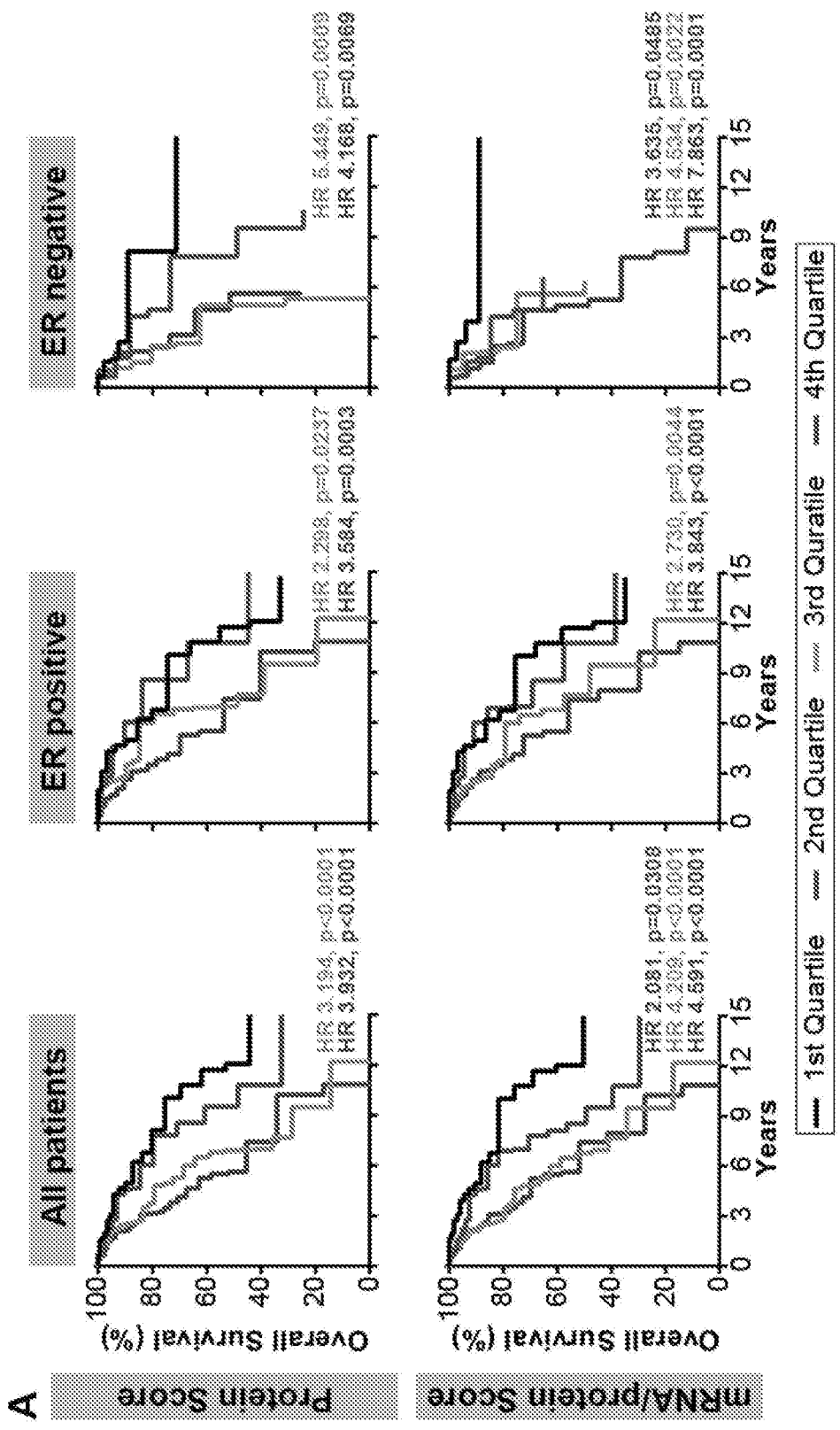

A
Protein Score
mRNA/protein Score
All patients
ER positive
ER negative
Overall Survival (%)
Years
HR 3.194, p<0.0001
HR 3.932, p<0.0001
HR 2.228, p=0.0237
HR 3.584, p=0.0003
HR 5.449, p=0.0000
HR 4.168, p=0.0069
HR 2.081, p=0.0308
HR 4.208, p<0.0001
HR 4.591, p<0.0001
HR 2.730, p=0.0044
HR 3.843, p<0.0001
HR 3.635, p=0.0485
HR 4.634, p=0.0022
HR 7.863, p=0.0001
1st Quartile
2nd Quartile
3rd Quartile
4th Quartile

FIG. 49

B

Parameter	Univariant Cox-proportional hazard model			Multivariant Cox-proportional hazard model		
	HR	95% CI	P	HR	95% CI	P
Combined iBCR mRNA/Protein Score (Q1, Q2, Q3, Q4)	1.75	1.45 - 2.12	<0.0001	3.46	1.51 - 7.92	0.0035
Stage (I, IIA, IIB, IIIA, IIIB, IIIC)	1.49	1.15 - 1.92	0.0023	3.81	1.30 - 11.17	0.0153
Tumor size (T1, T2, T3)	1.12	0.81 - 1.55	0.5094	3.88	0.72 - 20.53	0.1157
HER2 (pos vs. neg)	1.82	1.01 - 3.28	0.0466	6.24	0.43 - 9.34	0.1816
Radiotherapy (yes vs. no)	0.38	0.19 - 0.76	0.0063	0.27	0.04 - 1.98	0.1991
PAM50 subtypes	1.08	0.87 - 1.34	0.5048	0.69	0.36 - 1.34	0.2804
Lymph node (pos vs. neg)	2.14	1.35 - 3.39	0.0012	3.32	0.33 - 3.38	0.3127
ER (pos vs. neg)	0.76	0.48 - 1.21	0.2493	0.40	0.22 - 7.49	0.5439
Age at Dx (<50 vs. >50)	0.60	0.37 - 0.95	0.0295	0.28	0.04 - 2.32	0.5775
Surgery (lump, mastec, mod. rad. mastec., Other)	1.28	1.04 - 1.58	0.0191	0.75	0.27 - 2.12	0.5901
Molecular therapy (no vs. yes)	6.17	2.63 - 14.43	<0.0001	1.62	0.17 - 15.91	0.6805
Histology (ILC vs. IDC)	0.53	0.23 - 1.22	0.1399	0.54	0.27 - 10.69	0.6847
PR (pos vs. neg)	0.76	0.49 - 1.16	0.2035	0.72	0.414 - 1.25	0.8219
Menopause (post vs. pre)	2.04	1.03 - 4.05	0.0419	1.15	0.15 - 8.65	0.9483

FIG. 49 cont'd

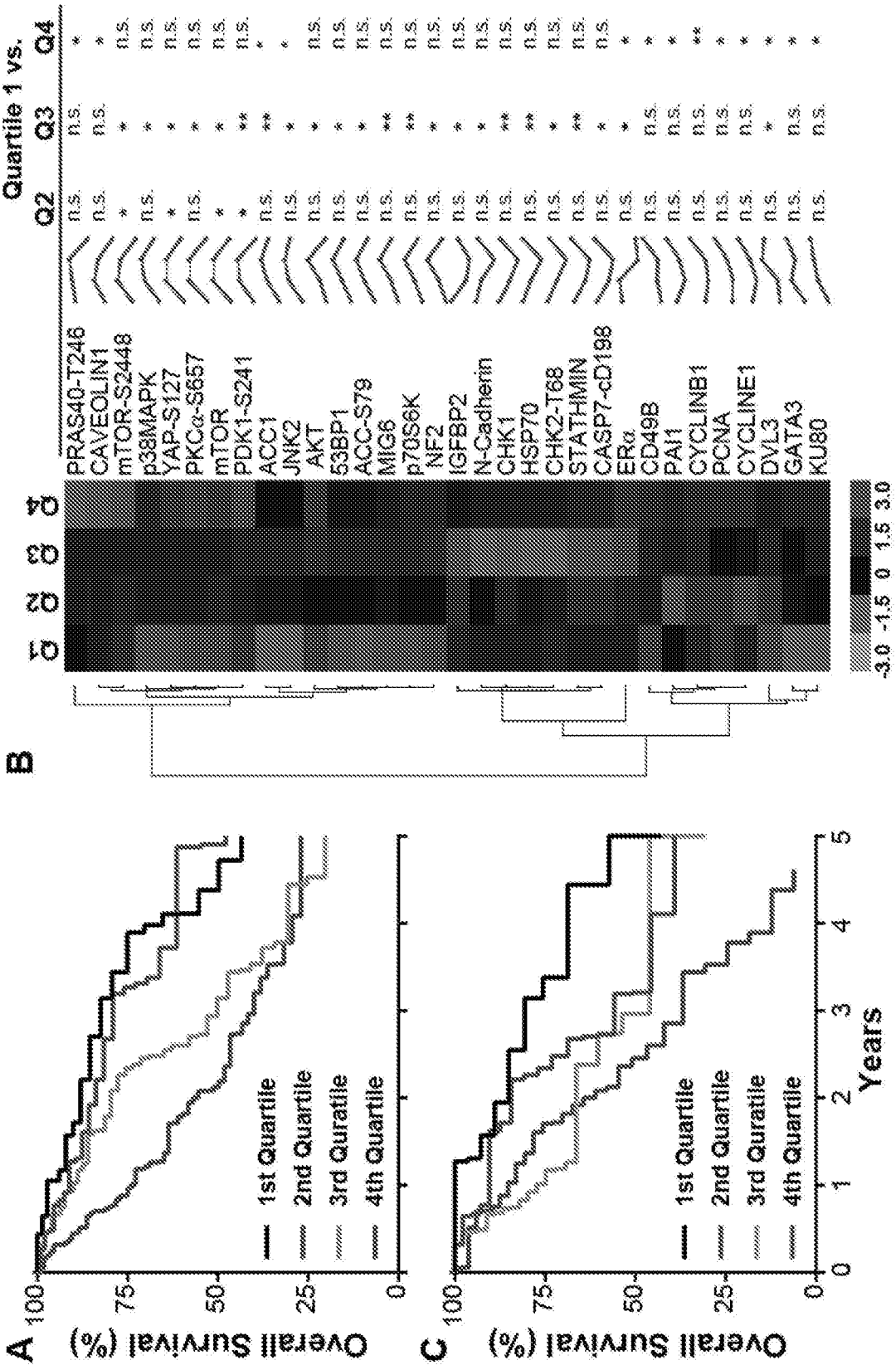

A
Overall Survival (%)
100
75
50
25
0
1st Quartile
2nd Quartile
3rd Quratile
4th Quartile
0
1
2
3
4
5
Years
B
Quartile 1 vs.
Q2
Q3
Q4
PRAS40-T246
CAVEOLIN1
mTOR-S2448
p38MAPK
YAP-S127
PKCα-S657
mTOR
PDK1-S241
ACC1
JNK2
AKT
53BP1
ACC-S79
MIG6
p70S6K
NF2
IGFBP2
N-Cadherin
CHK1
HSP70
CHK2-T68
STATHMIN
CASP7-cD198
ERα
CD49B
PAI1
CYCLINB1
PCNA
CYCLINE1
DVL3
GATA3
KU80
Q1
Q2
Q3
Q4
-3.0 -1.5 0 1.5 3.0
C
Overall Survival (%)
100
75
50
25
0
1st Quartile
2nd Quartile
3rd Quratile
4th Quartile
0
1
2
3
4
5
Years

FIG. 50

E

Covariate	HR	95% CI	P
Combined IBCR mRNA/Protein (Q1-Q4)	2.08	1.24 - 3.50	0.0056
Age (<60, 60-70, >70)	2.25	1.14 - 4.43	0.0198
Nodal status (N1 vs. N0)	1.73	1.40 - 2.10	0.0254
Tumor size (T1, T2, T3, T4)	1.63	0.83 - 3.19	0.1533
Residual tumor (yes vs. no)	3.70	0.46 - 30.06	0.2229
EGFR (mut vs. WT)	2.43	0.46 - 12.87	0.2935
Stage (Stage I, II, III)	0.58	0.11 - 3.03	0.5197
Targeted therapy (yes vs. no)	1.96	0.25 - 14.29	0.5218
Gender (F or M)	1.32	0.35 - 4.96	0.6797
KRAS (mut vs. WT)	1.33	0.25 - 7.01	0.7403
PIK3CA (mut vs. WT)	0.79	0.09 - 7.07	0.8321
ERBB4 (mut vs. WT)	0.84	0.11 - 6.72	0.8714
mRNA Subtype (Bronchioid, Magnoid, Squamoid)	0.98	0.54 - 1.78	0.9520

D

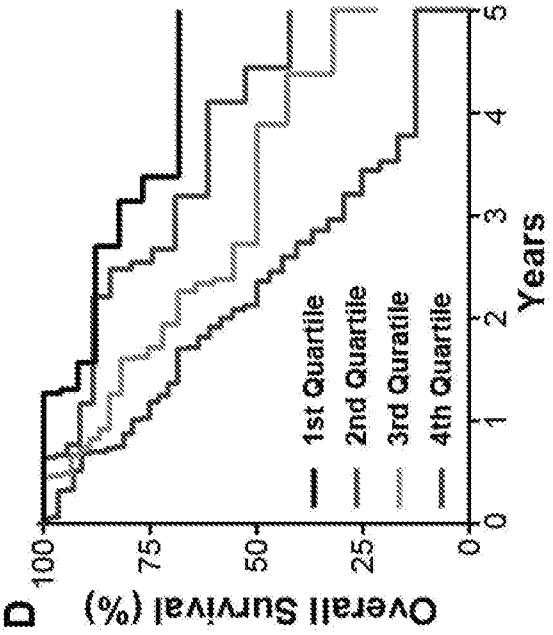


FIG. 50 cont'd

Kidney renal clear cell carcinoma (KIRC)

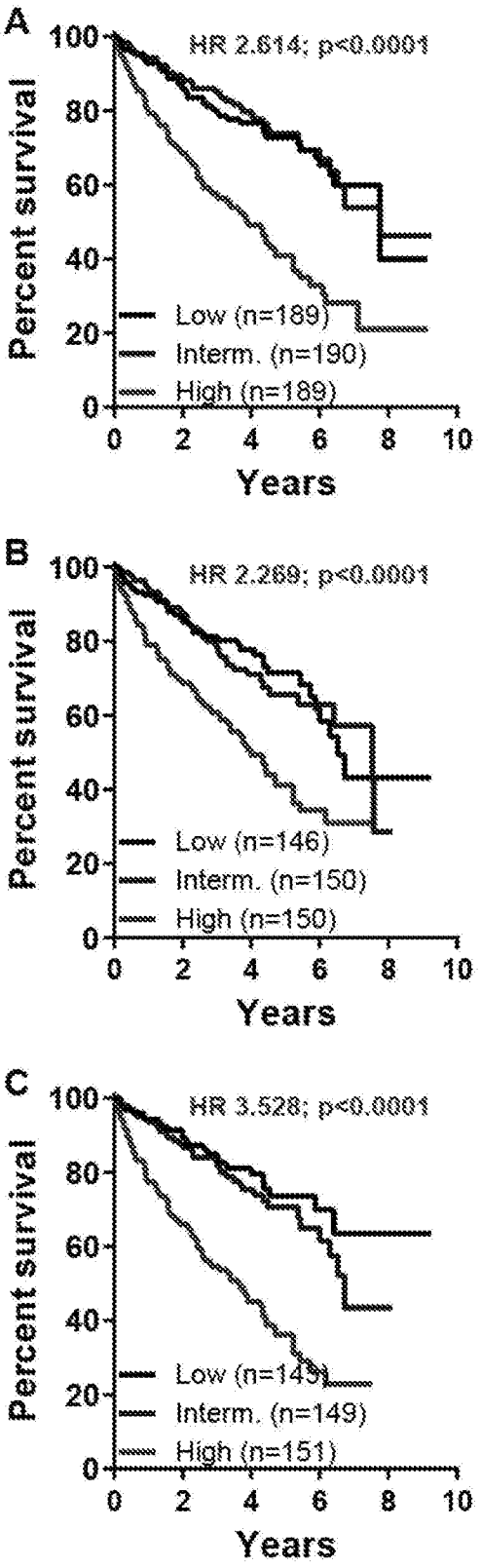


FIG. 51

Skin cutaneous melanoma (SKCM)

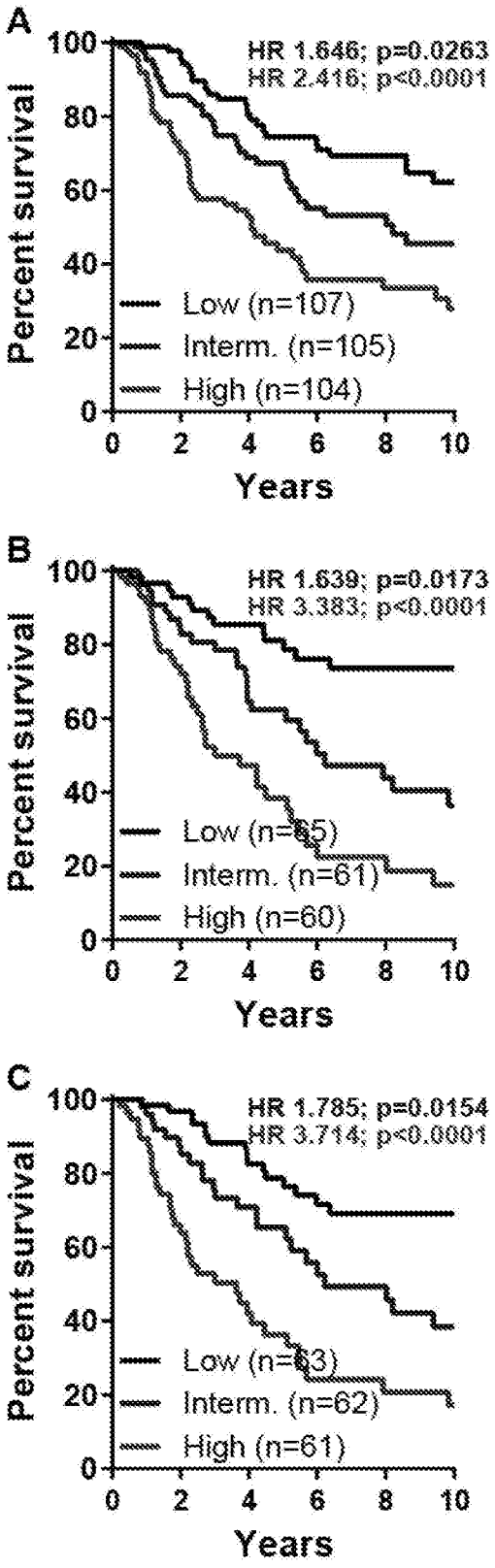


FIG. 51 cont'd

Uterine corpus endometrioid carcinoma (UCEC)

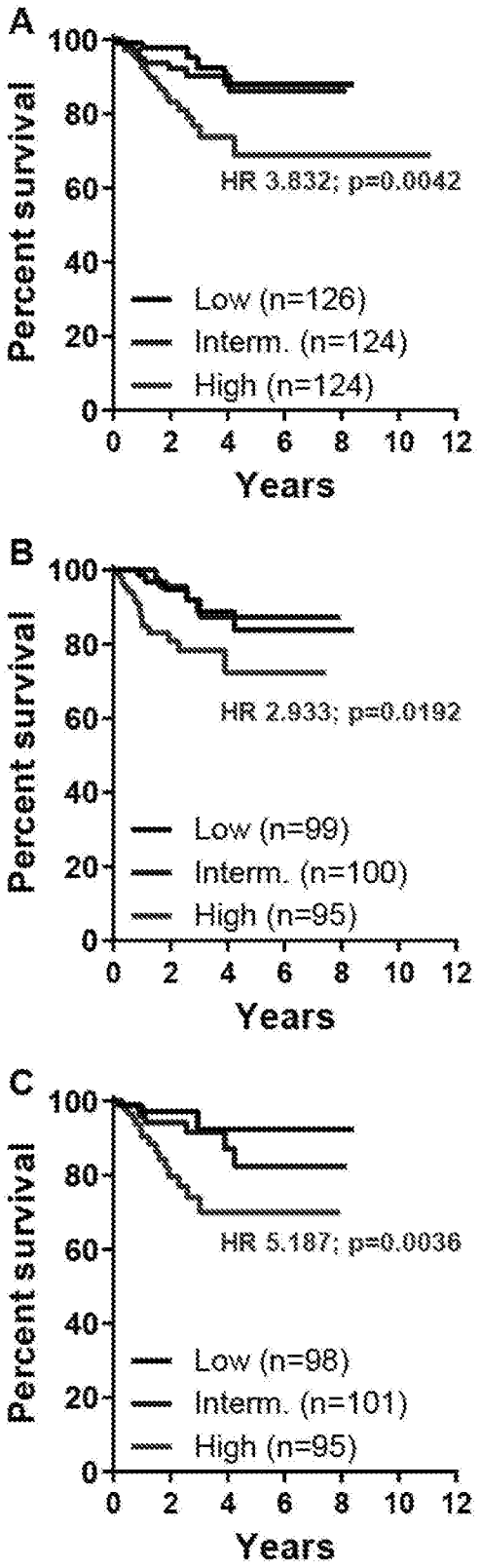


FIG. 51 cont'd

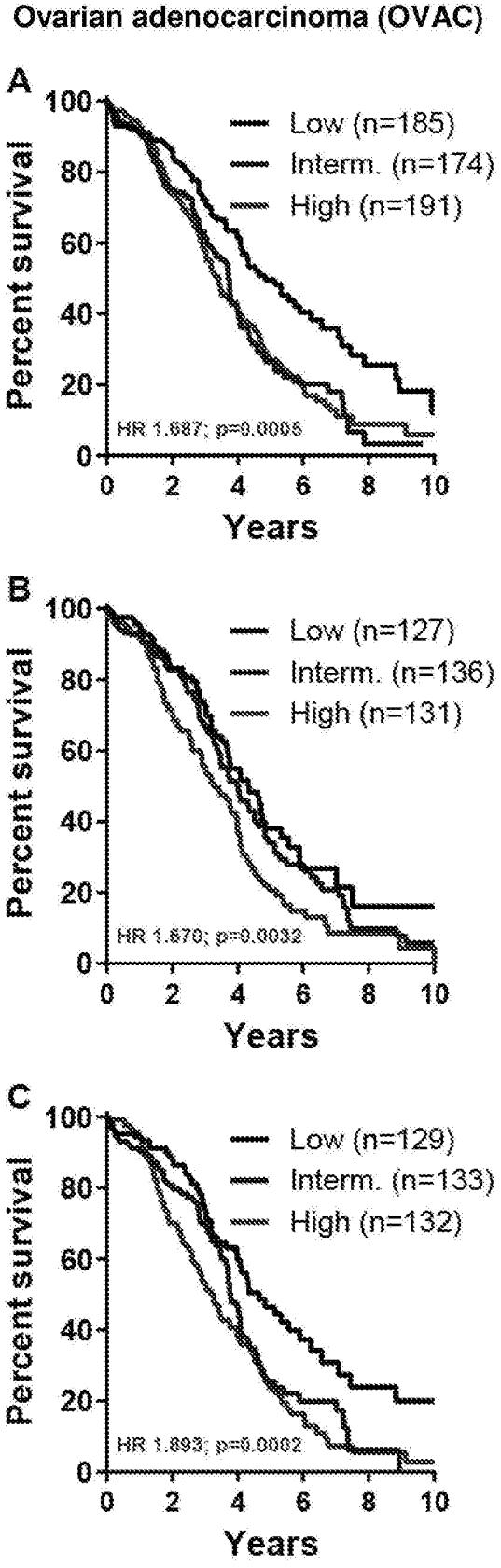

Ovarian adenocarcinoma (OVAC)
A
Percent survival
100
80
60
40
20
0
Low (n=185)
Interm. (n=174)
High (n=191)
HR 1.687; p=0.0005
0
2
4
6
8
10
Years
B
Percent survival
Low (n=127)
Interm. (n=136)
High (n=131)
HR 1.870; p=0.0032
Years
C
Percent survival
Low (n=129)
Interm. (n=133)
High (n=132)
HR 1.893; p=0.0002
Years

FIG. 52

Head & Neck squamous cell carcinoma (HNSC)

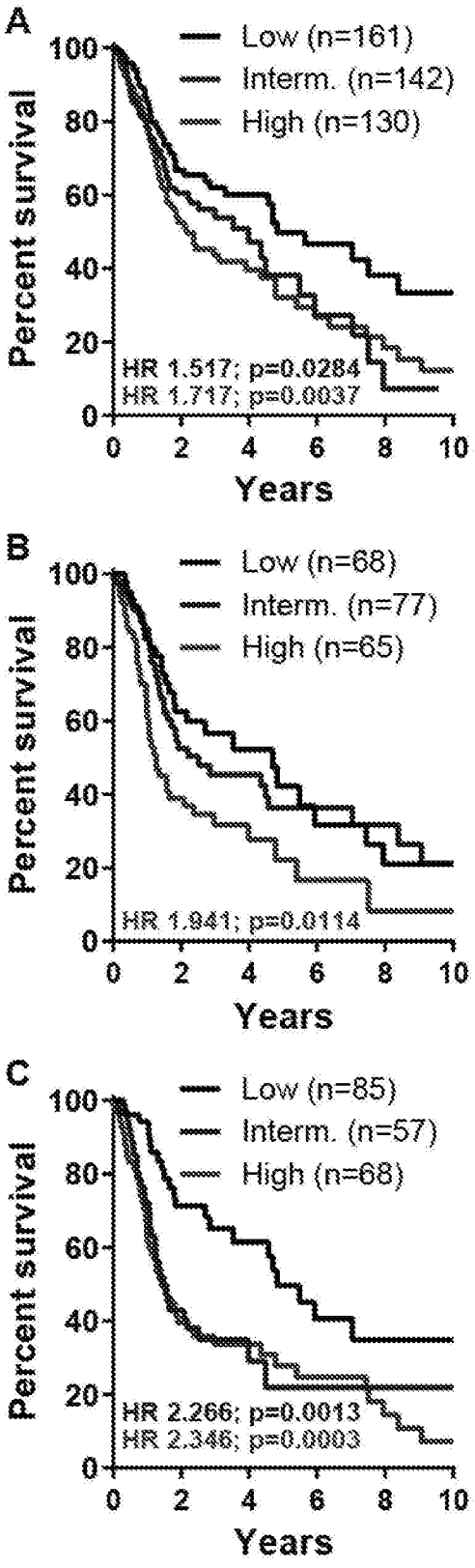


FIG. 52 cont'd

Colon/Rectal Adenocarcinoma (COREAD)

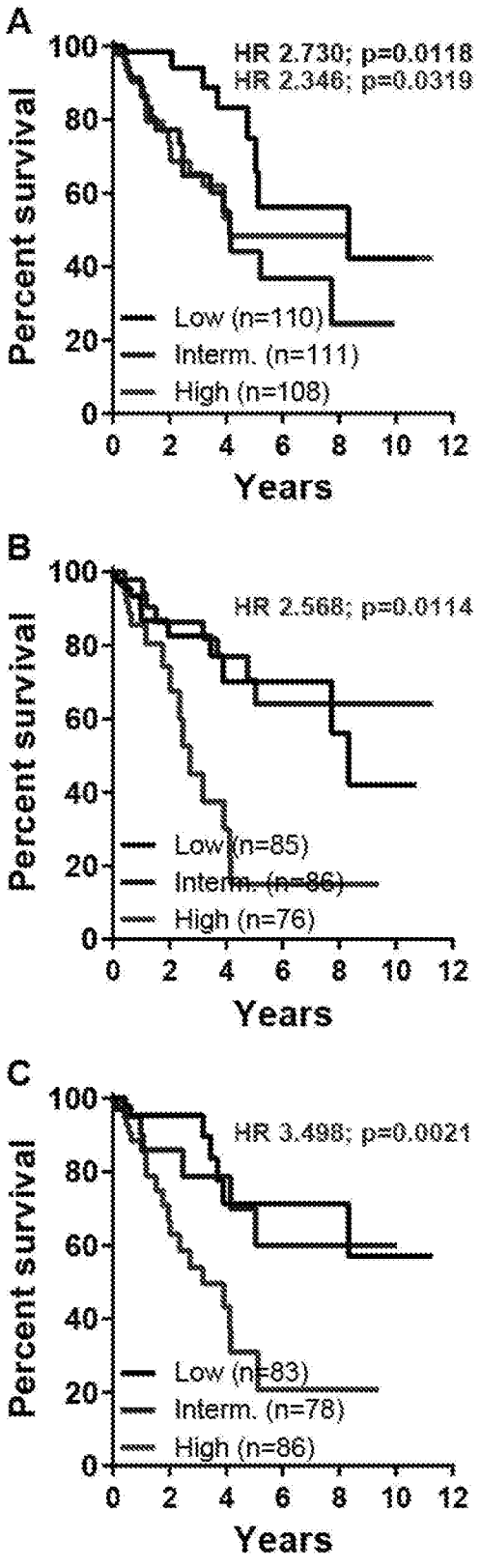


FIG. 52 cont'd

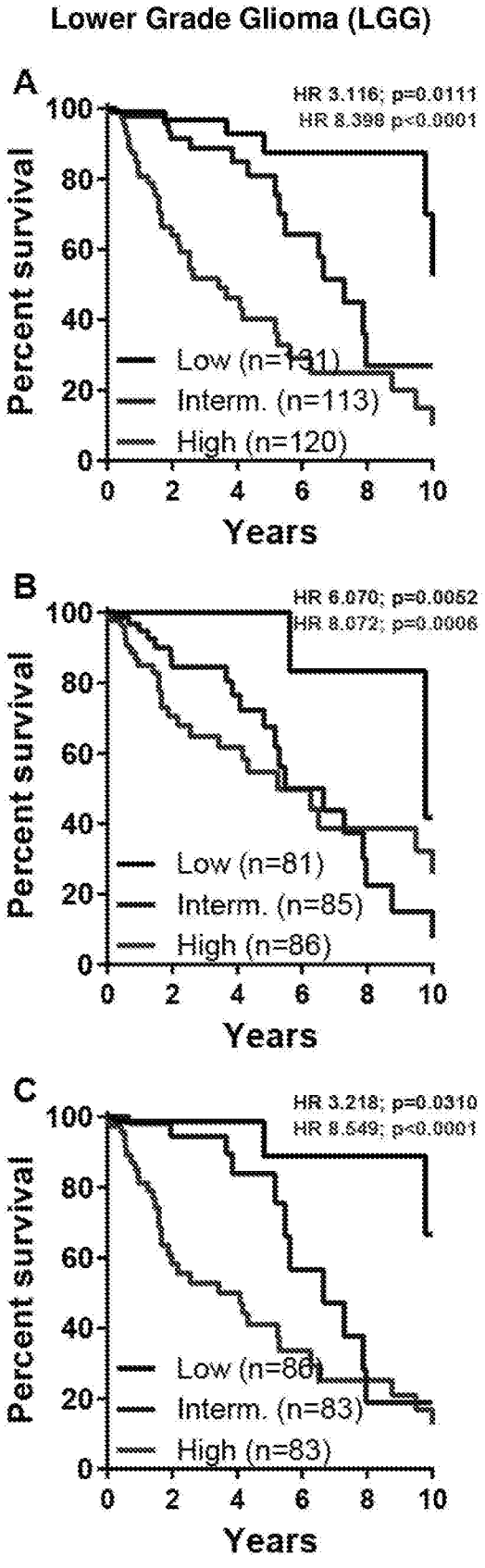

Lower Grade Glioma (LGG)
A
HR 3.116; p=0.0111
HR 8.398 p<0.0001
Percent survival
Low (n=131)
Interm. (n=113)
High (n=120)
Years
B
HR 6.070; p=0.0052
HR 8.072; p=0.0006
Percent survival
Low (n=81)
Interm. (n=85)
High (n=86)
Years
C
HR 3.218; p=0.0310
HR 8.549; p<0.0001
Percent survival
Low (n=86)
Interm. (n=83)
High (n=83)
Years

FIG. 53

Bladder urothelial carcinoma (BLCA)

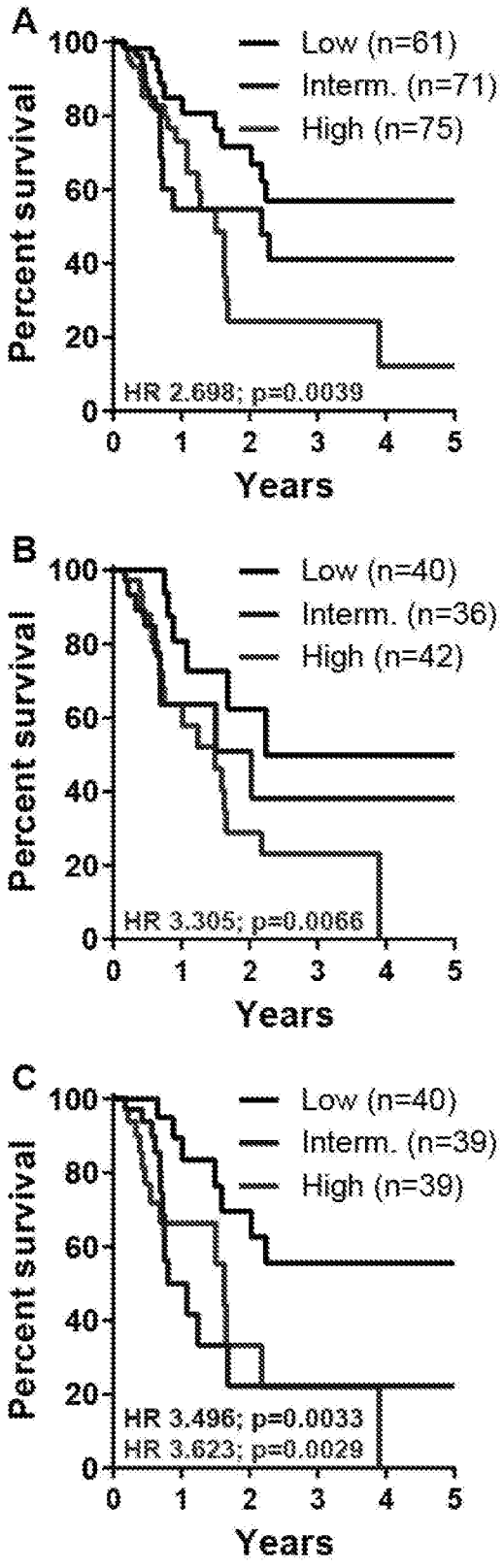


FIG. 53 cont'd

Lung squamous cell carcinoma (LUSC)

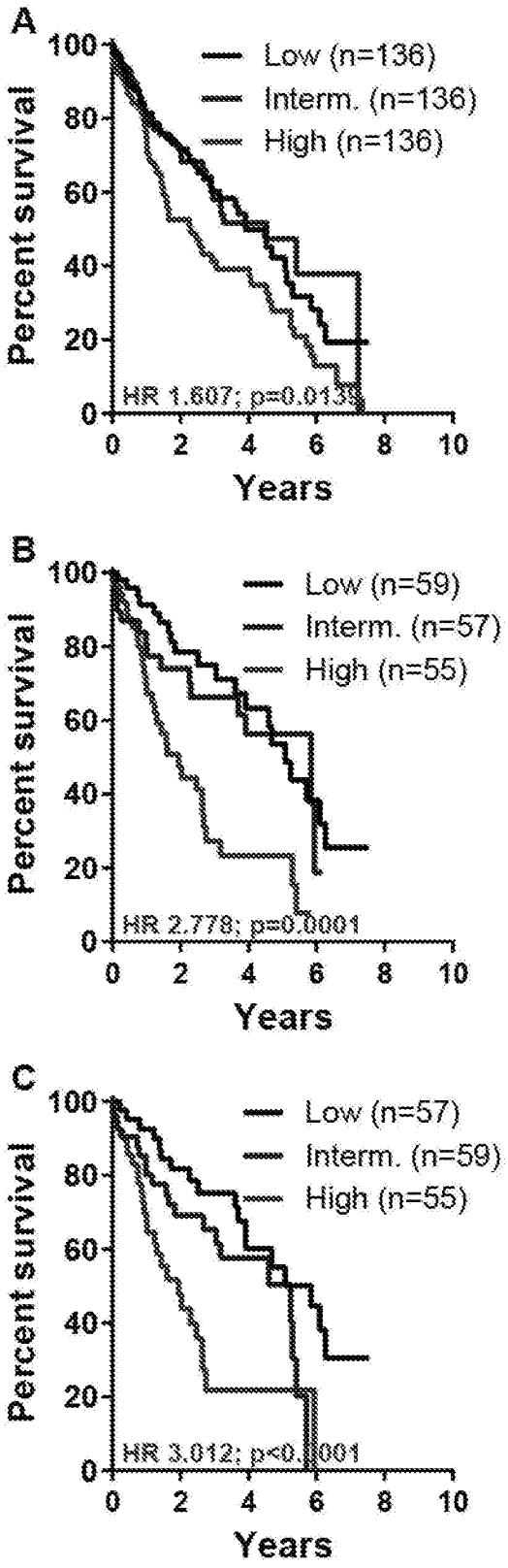


FIG. 53 cont'd

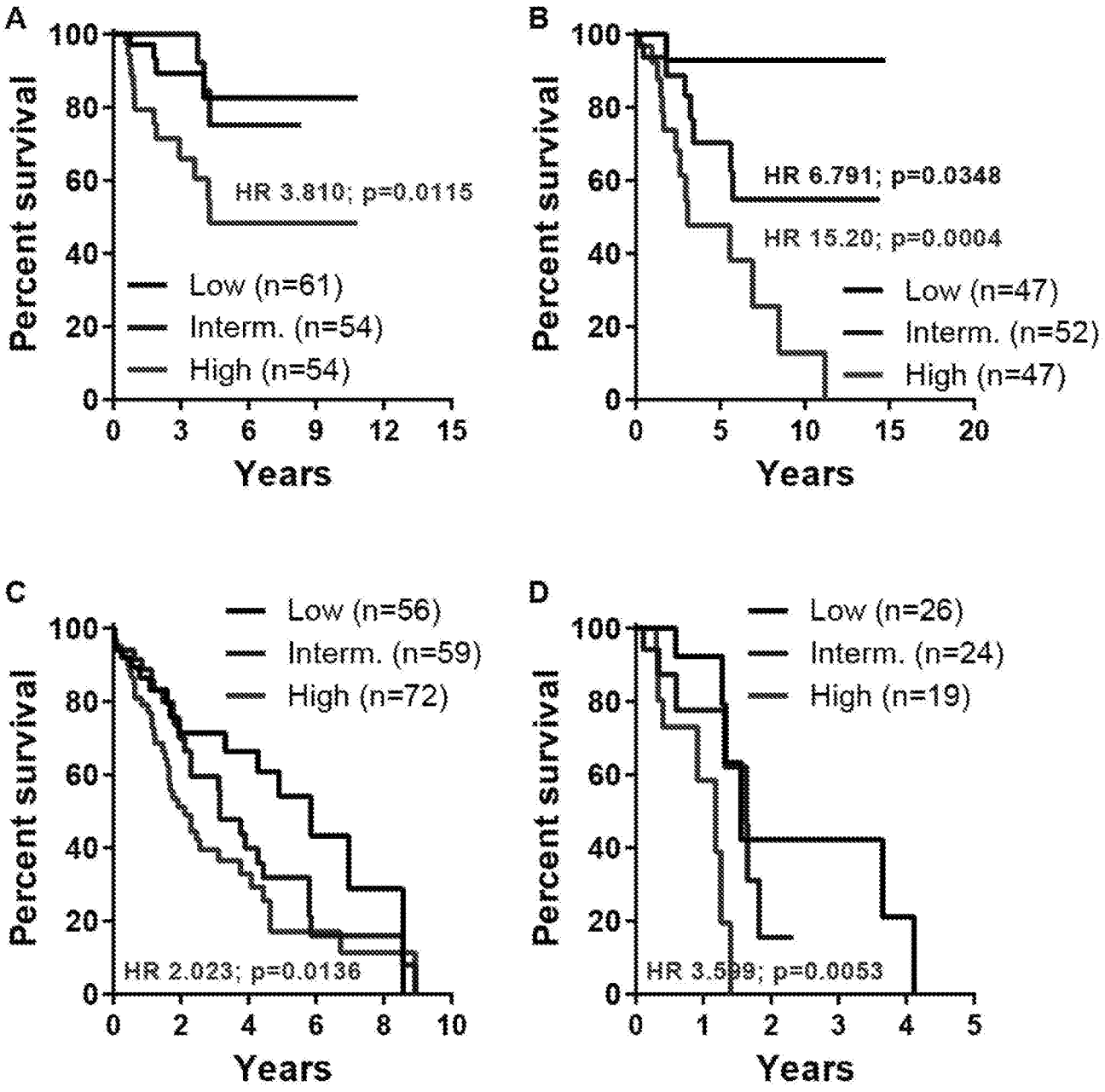

A
Percent survival
100
80
60
40
20
0
0 3 6 9 12 15
Years
HR 3.810; p=0.0115
Low (n=61)
Interm. (n=54)
High (n=54)
B
Percent survival
100
80
60
40
20
0
0 5 10 15 20
Years
HR 6.791; p=0.0348
HR 15.20; p=0.0004
Low (n=47)
Interm. (n=52)
High (n=47)
C
Percent survival
100
80
60
40
20
0
0 2 4 6 8 10
Years
HR 2.023; p=0.0136
Low (n=56)
Interm. (n=59)
High (n=72)
D
Percent survival
100
80
60
40
20
0
0 1 2 3 4 5
Years
HR 3.599; p=0.0053
Low (n=26)
Interm. (n=24)
High (n=19)

FIG. 54

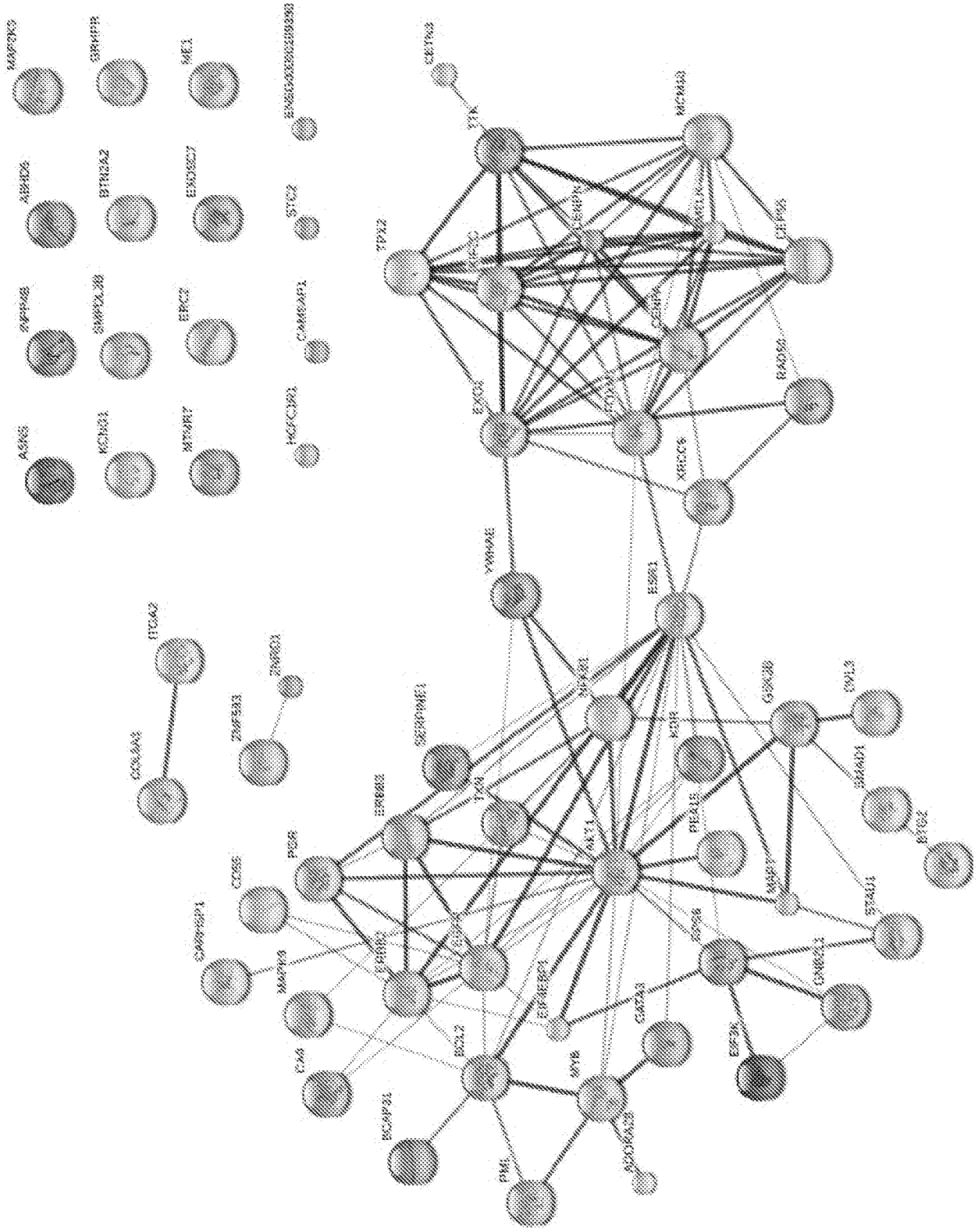


FIG. 55

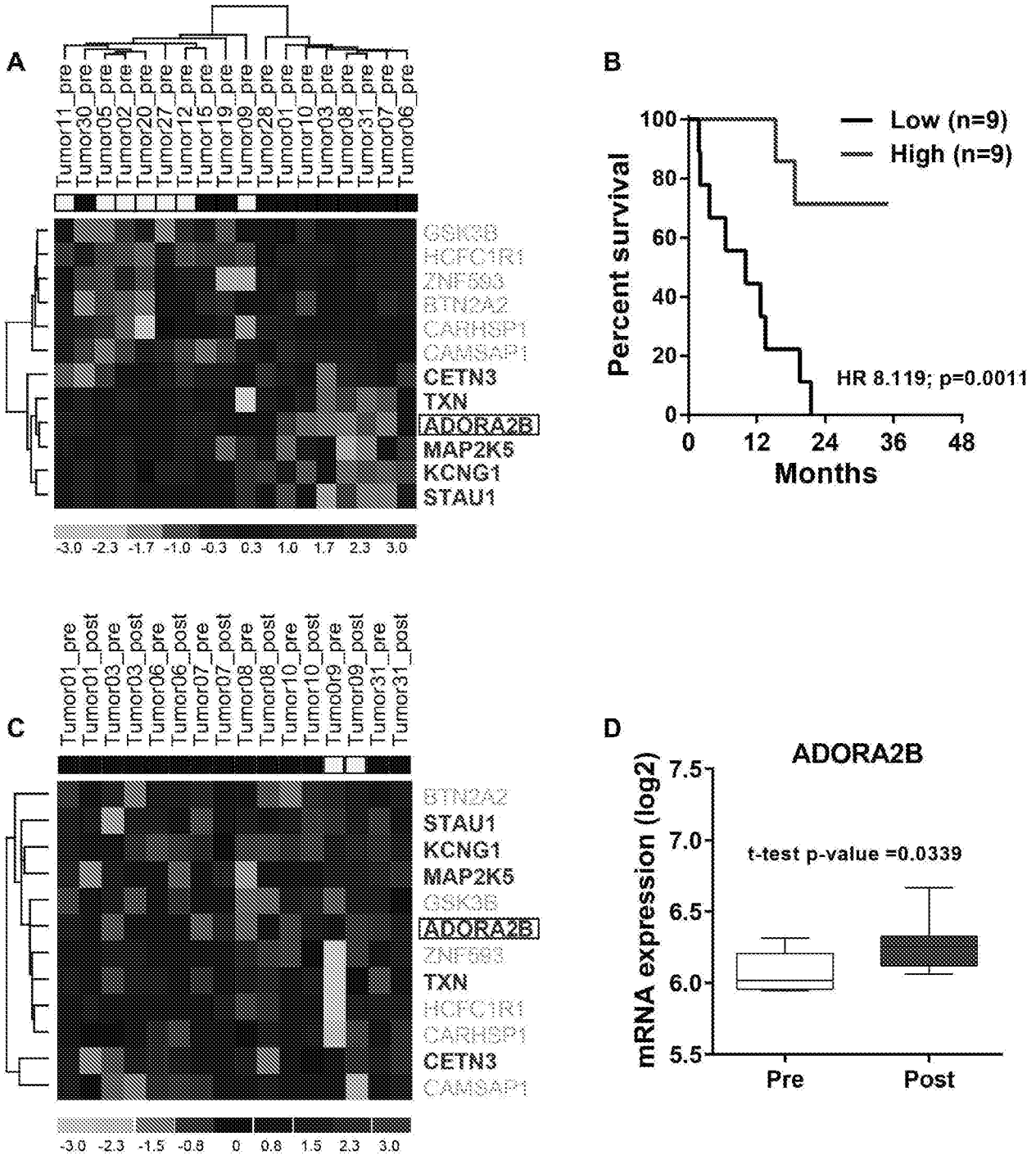

A
Tumor11_pre
Tumor30_pre
Tumor05_pre
Tumor02_pre
Tumor20_pre
Tumor27_pre
Tumor12_pre
Tumor15_pre
Tumor19_pre
Tumor09_pre
Tumor28_pre
Tumor01_pre
Tumor10_pre
Tumor03_pre
Tumor08_pre
Tumor31_pre
Tumor07_pre
Tumor06_pre
GSK3B
HCFC1R1
ZNF593
BTN2A2
CARHSP1
CAMSAP1
CETN3
TXN
ADORA2B
MAP2K5
KCNG1
STAU1
-3.0 -2.3 -1.7 -1.0 -0.3 0.3 1.0 1.7 2.3 3.0
B
Low (n=9)
High (n=9)
Percent survival
100
80
60
40
20
0
HR 8.119; p=0.0011
0 12 24 36 48
Months
C
Tumor01_pre
Tumor01_post
Tumor03_pre
Tumor03_post
Tumor06_pre
Tumor06_post
Tumor07_pre
Tumor07_post
Tumor08_pre
Tumor08_post
Tumor10_pre
Tumor10_post
Tumor09_pre
Tumor09_post
Tumor31_pre
Tumor31_post
BTN2A2
STAU1
KCNG1
MAP2K5
GSK3B
ADORA2B
ZNF593
TXN
HCFC1R1
CARHSP1
CETN3
CAMSAP1
-3.0 -2.3 -1.5 -0.8 0 0.8 1.5 2.3 3.0
D
ADORA2B
mRNA expression (log2)
7.5
7.0
6.5
6.0
5.5
t-test p-value =0.0339
Pre
Post

FIG. 56

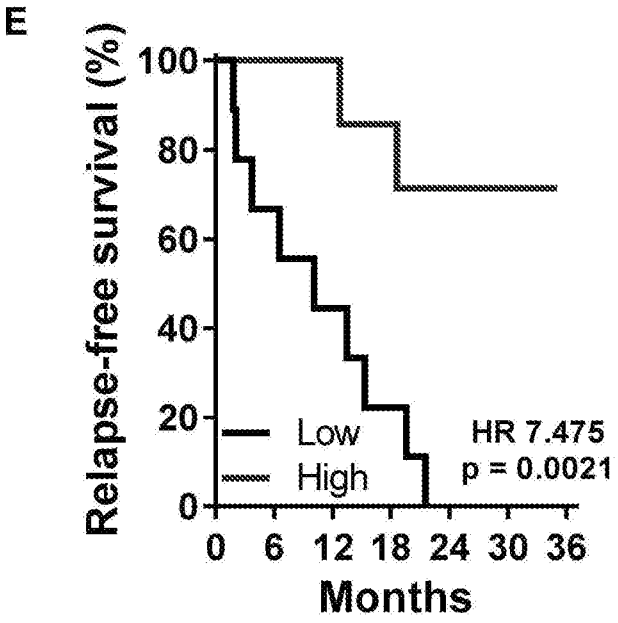

E
Relapse-free survival (%)
100
80
60
40
20
0
Low
High
HR 7.475
p = 0.0021
0 6 12 18 24 30 36
Months

FIG. 56 cont'd

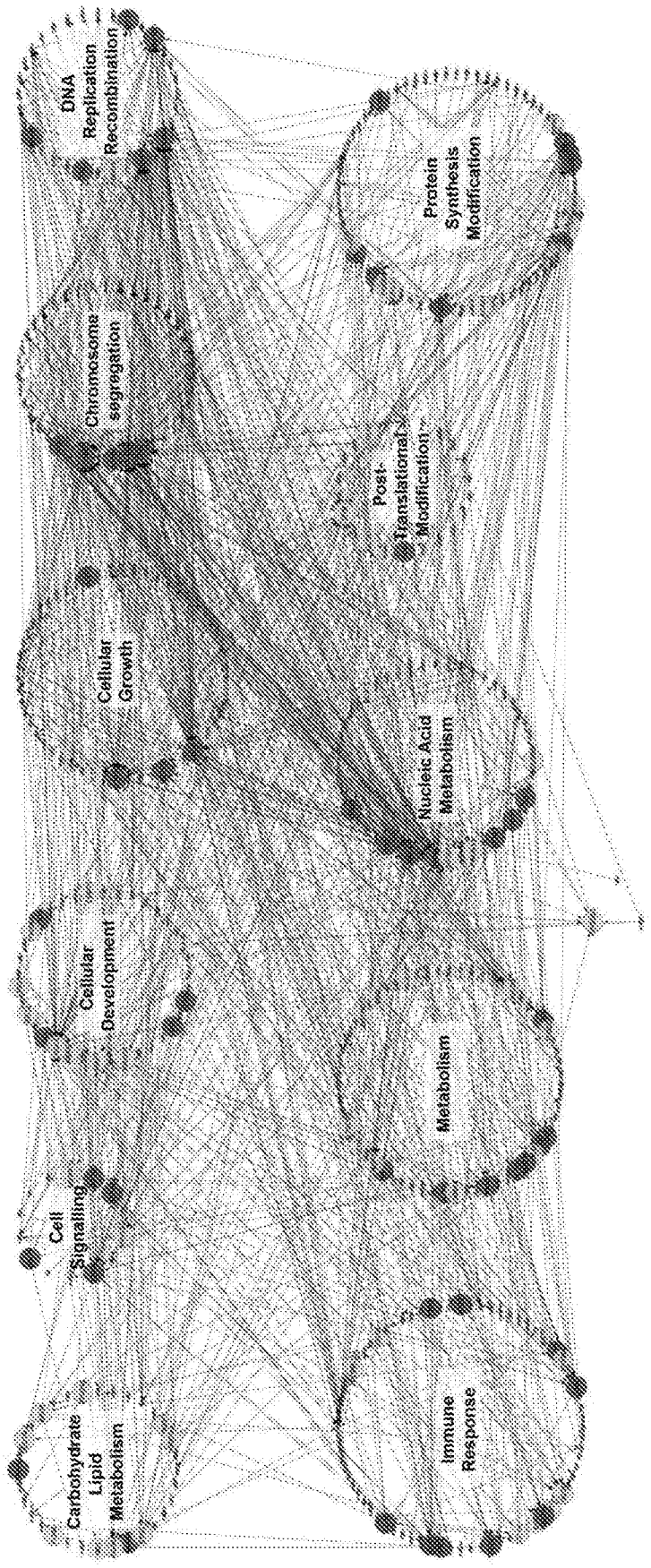

DNA Replication Recombination
Protein Synthesis Modification
Chromosome segregation
Post-Translational Modification
Cellular Growth
Nucleic Acid Metabolism
Cellular Development
Metabolism
Cell Signalling
Immune Response
Carbohydrate Lipid Metabolism

FIG. 57

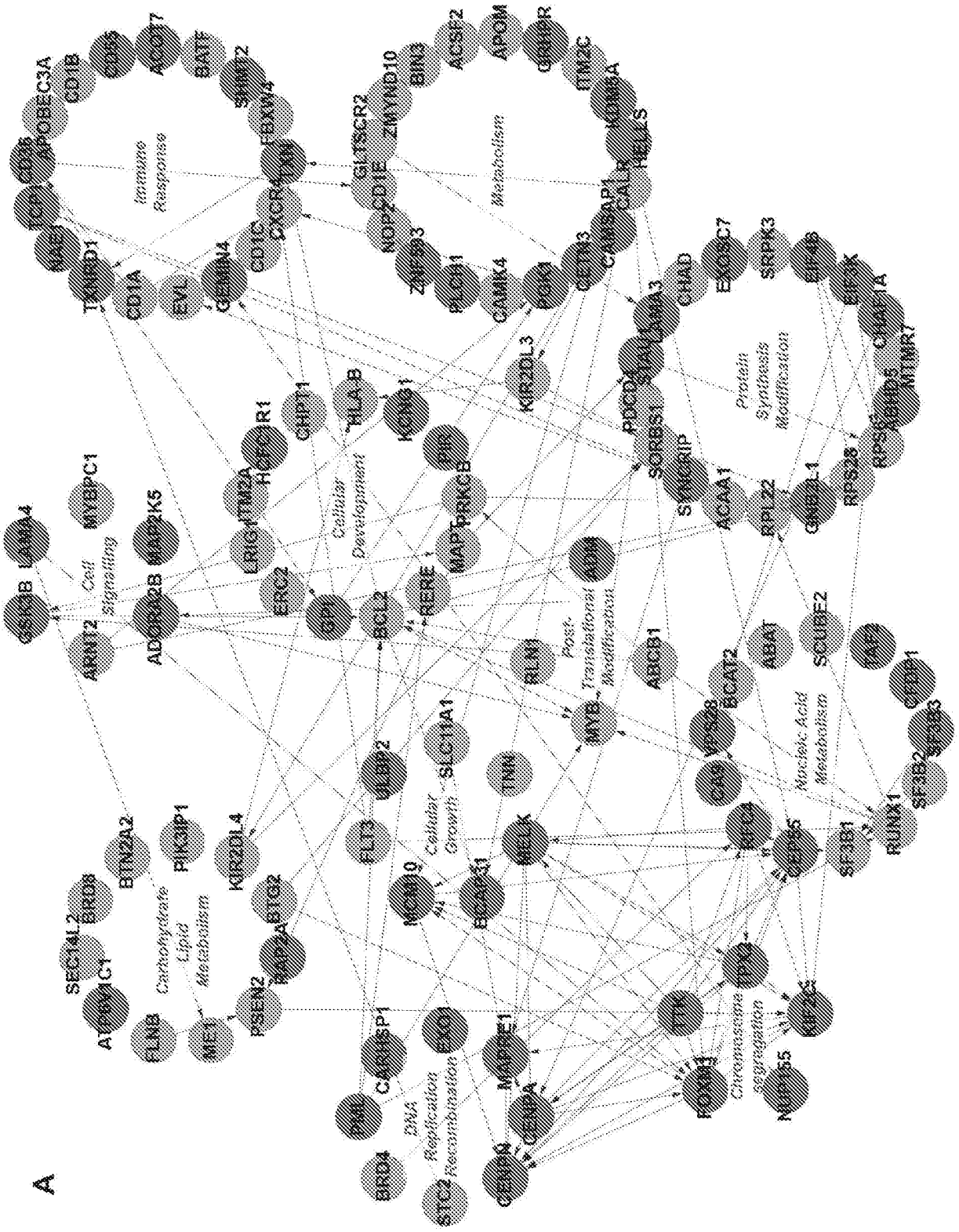

A
Immune Response
Metabolism
Protein Synthesis Modification
Cellular Development
Cell Signalling
Post-Translational Modification
Cellular Growth
Carbohydrate Lipid Metabolism
Nucleic Acid Metabolism
DNA Replication Recombination
Chromosome segregation

FIG. 58

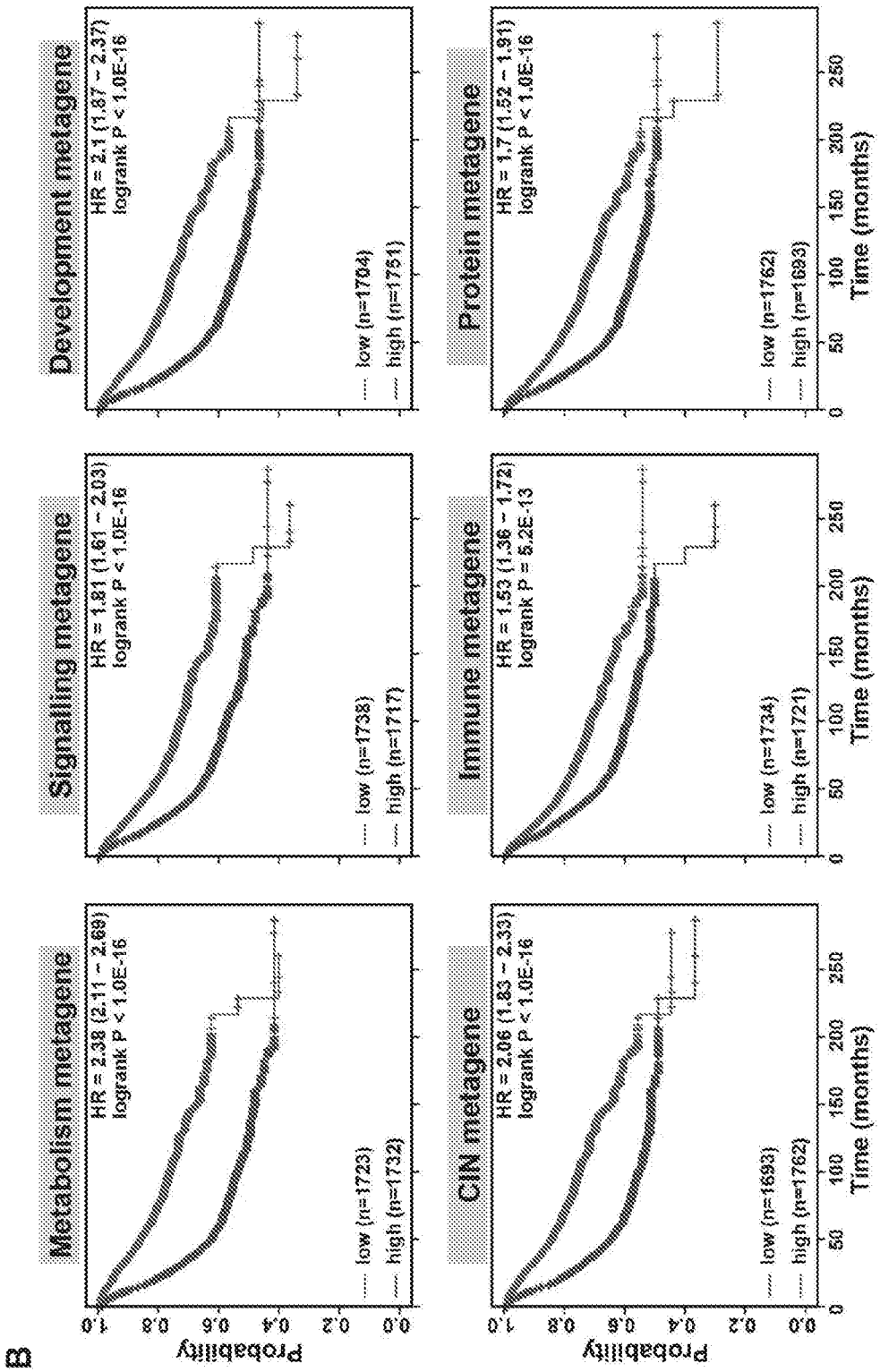

B
Metabolism metagene
HR = 2.38 (2.11 – 2.69)
logrank P < 1.0E-16
low (n=1723)
high (n=1732)
Signaling metagene
HR = 1.81 (1.61 – 2.03)
logrank P < 1.0E-16
low (n=1738)
high (n=1717)
Development metagene
HR = 2.1 (1.87 – 2.37)
logrank P < 1.0E-16
low (n=1704)
high (n=1751)
CIN metagene
HR = 2.06 (1.83 – 2.33)
logrank P < 1.0E-16
low (n=1693)
high (n=1762)
Immune metagene
HR = 1.53 (1.36 – 1.72)
logrank P = 5.2E-13
low (n=1734)
high (n=1721)
Protein metagene
HR = 1.7 (1.52 – 1.91)
logrank P < 1.0E-16
low (n=1762)
high (n=1693)
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
250
Time (months)

FIG. 58 cont'd

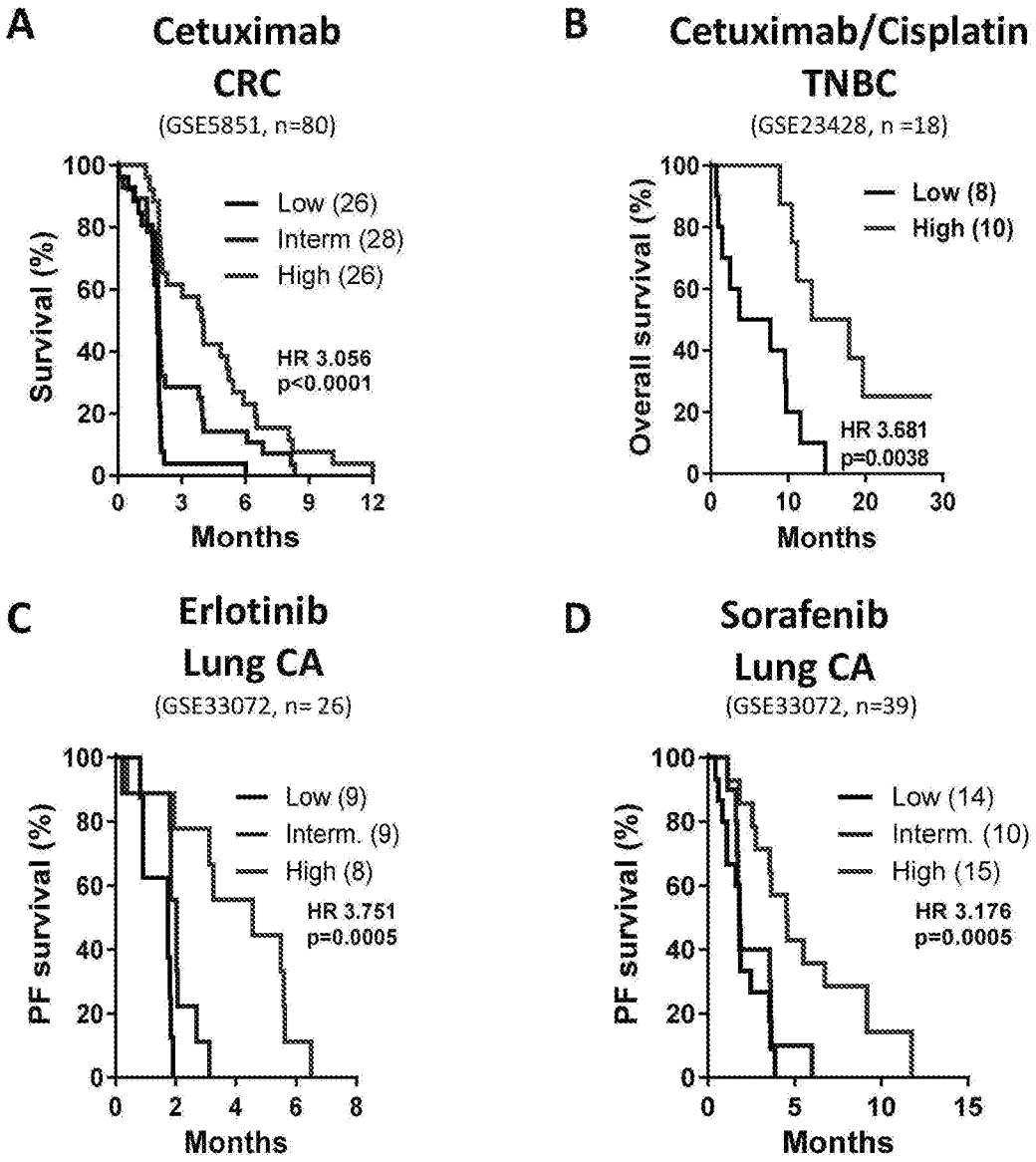

A
Cetuximab
CRC
(GSE5851, n=80)
Survival (%)
Low (26)
Interm (28)
High (26)
HR 3.056
p<0.0001
Months
B
Cetuximab/Cisplatin
TNBC
(GSE23428, n =18)
Overall survival (%)
Low (8)
High (10)
HR 3.681
p=0.0038
Months
C
Erlotinib
Lung CA
(GSE33072, n= 26)
PF survival (%)
Low (9)
Interm. (9)
High (8)
HR 3.751
p=0.0005
Months
D
Sorafenib
Lung CA
(GSE33072, n=39)
PF survival (%)
Low (14)
Interm. (10)
High (15)
HR 3.176
p=0.0005
Months

FIG. 59