

TITLEDETERMINING CANCER AGGRESSIVENESS, PROGNOSIS AND
RESPONSIVENESS TO TREATMENTFIELD

5 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
10 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
15 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 chemotherapy³,
20 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 outcomes⁴⁻⁸. Several gene signatures have been developed to predict outcome or response to treatment
25 including: MammaPrint⁹, OncotypeDx^{10,11}, Theros¹²⁻¹⁵. 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
30 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.

5 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
10 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
20 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
25 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
5 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
10 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
15 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
20 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
25 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
30 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;
 5 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.

10 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*, *FOXMI*, *KIF2C*, *NUP155*, *TPX2*, *TTK*, *CENPA*, *CENPN*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*,
 15 *TCPI*, *TXNRD1*, *ADM*, *CHAF1A* and *SYNCRIP*. Preferably, the genes are selected from the group consisting of: *MELK*, *MCM10*, *CENPA*, *EXO1*, *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*,
 20 *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*.

25 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*, *KCNIG1*, *BCAP31*, *ULBP2*, *CARHSP1*, *PML*, *CD36*, *CD55*, *GEMIN4*,
 30 *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*, *RLN1*, *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 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*, *RLN1*, *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 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*, *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*, *RLN1*, *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 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*, *NDUFC1*, *PML*, *STAU1*, *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
5 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,
10 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
15 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
20 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,
25 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
30 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
5 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
10 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
15 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
20 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
25 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
30 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*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*, *TCPI1*, *TXNRD1*, *ADM*, *CHAF1A* and *SYNCRIP*. Preferably, the genes are selected from the group consisting of: *MELK*, *MCM10*, *CENPA*, *EXO1*, *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*.

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, RLN1, MTMR7, SORBS1 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
5 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
10 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
15 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*, in one or a plurality of cancer cells, tissues or organs of the mammal, wherein an altered or modulated
20 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*,
25 *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.

30 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*, *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 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*, *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 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
- 5
- (v) the comparison of the expression level of the overexpressed genes and an expression level of the underexpressed genes, wherein the genes
- 10
- 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.
- 15
- 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.

- 20
- 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
- 25
- 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.

- 30
- 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, 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
5 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,
10 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
15 (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 (MEK1/2) inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitor, an insulin-like growth factor 1 receptor
20 (IGF1R) inhibitor, a phospholipase C- γ (PLC γ) 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 (HDAC) 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
25 (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
30 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 of *APOBEC3A*, *BTN2A2*, *BCL2*, *CAMK4*,
5 *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
10 immunotherapeutic agent.

Suitably, the immunotherapeutic agent is an immune checkpoint inhibitor. Preferably, the immune checkpoint inhibitor is or comprises an anti-PD1 antibody or an anti-PDL1 antibody.

In an eighteenth aspect is provided a method of predicting the responsiveness
15 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
20 expression level of one or a plurality of underexpressed genes selected from the group consisting of *CD1C*, *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*, *ATP6VIC1*, *CD55* and *ADORA2B* in one or a plurality of cancer cells, tissues or
25 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
30 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

5 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

10 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 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 immunotherapeutic agent, EGFR

15 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,

20 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

25 comparing an expression level of one or a plurality of overexpressed 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

30 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
5 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.

10 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*, *NDUFC1*, *CAMSAP1*, *CETN3*, *EIF3K*, *STAU1*, *EXOSC7*, *COG8*, *CFDP1* and/or *KCNG1* with a test agent; and

(ii) determining whether the test agent, at least partly, reduces, eliminates,
15 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
20 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.

25 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*, *NDUFC1*, *CAMSAP1*, *CETN3*, *EIF3K*, *STAU1*, *EXOSC7*, *COG8*, *CFDP1*, *KCNG1* and any combination thereof.

Suitably, the method of the aforementioned aspects further includes the step of
30 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, EXO1, 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) GSE2990¹⁵, (B) GSE3494⁶⁵, (C) GSE2034⁶⁶ and (D) GSE25066⁵³. 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 *** $p < 0.001$ 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 CellTiter[®] 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 or 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 adenocarcinoma 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 adenocarcinoma (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 adenocarcinoma 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 adenocarcinoma (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 OncoPrint™ 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 OncomineTM). 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 clinicopathological indicators in TNBC, 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 - log10[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=1106, 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 ER⁺HER2⁻

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 ER⁻HER2⁻ 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 overcome 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)** ER⁻HER2⁻ 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⁺ N0 patients with high iBCR score have poor RFS compared low iBCR score counterparts. **(B)** RFS of all ER⁺ patients and N0 and N1 subsets stratified by the Agro and iBCR scores. **(C)** DMFS survival of all ER⁺ and N0 and N1 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, 2011); from Rody et al. (Breast Cancer Res, 2011) (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 IC₅₀ 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 IC₅₀ 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 *t*-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 $-\log_{10}IC_{50}$) 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 *t*-test.

- 5 **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
- 10 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
- 15 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
- 20 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
- 25 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
- 30 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

5 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
10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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
25 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
30 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 further 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
5 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
10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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
25 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
30 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.

5 Non-limiting examples of genes are set forth herein, particularly in Tables 4, 21 and 22, which include Accession Numbers referencing the nucleotide 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,
10 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, methylcytosine, methylinosine, methyladenosine and/or thiouridine, although without limitation thereto.

15 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
20 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-limiting example is an amplification product or a primer or probe. In particular embodiments, a nucleic acid fragment may
25 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)
30 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 SequenaseTM. A “*template*” nucleic acid is a nucleic acid subjected to nucleic acid amplification.

5 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
10 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.

15 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
20 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
25 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
30 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, colorectal cancer, glioblastoma, lower grade glioma, head & neck cancer, kidney
5 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
10 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
15 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
20 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
25 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.
30 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 naturally 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 that 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-
5 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
10 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
15 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,
20 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 TissueMicroArrayTM (TMA), MSD MultiArraysTM and multiwell ELISA, although without limitation thereto.

25 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
30 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 *ATP6VIC1*, *RAP2A*, *CALM1*, *COG8*, *HELLS*, *KDM5A*, *PGK1*, *PLCH1*, *CEP55*, *RFC4*, *TAF2*, *SF3B3*, *GPI*, *PIR*, *MCM10*, *MELK*, *FOXMI*, *KIF2C*, *NUP155*, *TPX2*, *TTK*, *CENPA*, *CENPN*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*, *TCPI*, *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*, *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* 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 *ATP6VIC1*, *RAP2A*, *CALM1*, *COG8*, *HELLS*, *KDM5A*, *PGK1*, *PLCH1*, *CEP55*, *RFC4*, *TAF2*, *SF3B3*, *GPI*, *PIR*, *MCM10*, *MELK*, *FOXMI*, *KIF2C*, *NUP155*, *TPX2*, *TTK*, *CENPA*, *CENPN*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*,
5 *TCPI*, *TXNRD1*, *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*, *EXO1*, *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*,
10 *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*, although without limitation thereto. In one preferred embodiment, the estrogen receptor signalling genes are selected
15 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*,
20 *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*,
25 *APOBEC3A*, *CD1A*, *CD1B*, *CD1C*, *CXCR4*, *HLA-B*, *IGH*, *KIR2DL3*, *SMPDL3B*, *MYB*, *RLN1*, *MTMR7*, *SORBS1* 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
30 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*.

5 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
10 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
15 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
20 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
25 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,
30 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*, *RLN1*, *MTMR7*, *SORBS1* 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*, *CAMSAP1*, *CARHSP1*, *CD55*, *CETN3*, *EIF3K*, *EXOSC7*, *GNB2L1*, *GRHPR*, *GSK3B*, *HCFC1R1*, *KCNIG1*, *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 *CAMSAP1*, *CETN3*, *GRHPR*, *ZNF593*, *CA9*, *CFDP1*, *VPS28*, *ADORA2B*, *GSK3B*, *LAMA4*, *MAP2K5*, *HCFC1R1*, *KCNIG1*, *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*, *RLN1*, *MTMR7*, *SORBS1* 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*, *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
 5 *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, NFKB1, HER2,
 10 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
 15 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
 20 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
 25 or more phosphoproteins selected from the group consisting of pEIF4EBP1^{S65}, pEIF4EBP1^{T37}, pEIF4EBP1^{T46} and pEIF4EBP1^{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, AKT1 is or comprises one or more
 30 phosphoproteins selected from the group consisting of pAKT1^{S473} and pAKT1^{T308}. In one embodiment, NFKB1 is or comprises pNFKB1^{S536}. In one embodiment, HER2 is or comprises pHER2^{Y1248}. In one embodiment, ESR1 is or comprises pESR1^{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, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3 to derive a fourth integrated score; or

- 5 (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
- 10 (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.
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- 20

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

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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.

5 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
10 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
15 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
20 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
25 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
30 a gene or protein may be deemed to be "*altered*" or "*modulated*" when the expression level is higher/increased or lower/decreased 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.

5 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
10 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
15 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
20 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
25 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
30 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-
5 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
10 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,
15 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
20 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
25 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.

30 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 diaminobenzidine (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-1-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*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*, *TCPI1*, *TXNRD1*, *ADM*, *CHAF1A* and *SYNCRIP*. In one preferred embodiment, the chromosomal instability genes are selected from the group consisting of *MELK*, *MCM10*, *CENPA*, *EXO1*, *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. 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, RLN1, MTMR7, SORBS1 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, 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 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*, *KCNIG1*, *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*, *RLN1*, *MTMR7*, *SORBS1* 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*, *KCNIG1*, *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*, *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 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, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLN1, MTMR7, SORBS1 and SRPK3 to derive a fourth integrated score; or

- 5 (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
- 10 (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,
- 15
- 20

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.

- 25 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, 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,

30

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
5 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
10 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.
15 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
20 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
25 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
30 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 others⁷³⁻⁷⁶ 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*, *KCNIG1*, *BCAP31*, *ULBP2*, *CARHSP1*, *PML*, *CD36*, *CD55*, *GEMIN4*, *TXN*, *ABHD5*, *EIF3K*, *EIF4B*, *EXOSC7*, *GNB2L1*, *LAMA3*, *NDUFC1* and *STAU1*) 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*, *RLN1*, *MTMR7*, *SORBS1* 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*, *AKT1*, *NFKB1*, *HER2*, *ASNS* and *COL6A1*) when compared to one or more of the underexpressed proteins (*i.e.*, *VEGFR2*, *HER3*, *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), PF0429113, 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 MEK1/2 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/apelalisib, copanlisib, GSK-2636771,

pictilisib, AMG-319, AZD-8186), an IGF1R inhibitor (*e.g.*, BMS-754807, dalotuzumab, ganitumab, linsitinib), a PLC γ inhibitor (*e.g.*, U73122), a JNK inhibitor (*e.g.*, SP600125), a PAK1 inhibitor (*e.g.*, IPA3), a SYK inhibitor (*e.g.*, BAY613606), a HDAC inhibitor (*e.g.*, Vorinostat), an FGFR inhibitor (*e.g.*, Dovitinib), a XIAP
5 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-1161909) 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 21 gene signature, when compared to
10 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
15 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
20 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
25 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, PLC γ , 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
30 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,

NFKB1 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
5 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*, *FOXMI*, *ZNF593*, *EXO1*, *KIF2C*, *TTK*, *MELK*, *CENPA*, *TPX2*, *CA9*, *GRHPR*, *HCFC1R1*, *CEP55*, *MCM10*, *CENPN* and *CARHSP1*, and the one or more underexpressed genes are selected from
10 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 AKT1, 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
15 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*, *FOXMI*, *CD55*, *ZNF593*, *KIF2C*, *TTK*, *MELK*, *CENPA*, *TPX2*, *CEP55*, *PML*, *CENPN* and *CARHSP1*, and the one or more underexpressed genes are selected from the group
20 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.

25 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*, *FOXMI*, *EXO1*, *KIF2C*, *CENPA*, *TPX2*, *CAMSAP1*, *MCM10* and *ABHD5* and the one or more
30 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 ESR1.

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

5 (i) the one or more overexpressed genes are selected from the group consisting of *GNB2L1*, *EIF3K*, *KCNG1*, *BCAP31*, *GSK3B*, *EXOSC7*, *FOXMI*, *ZNF593*, *EXO1*, *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
10 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:

15 (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
20 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:

25 (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
30 consisting of PAI-1, INPP4B, EGFR, HER3, SMAD1, 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*, *NDUFC1*, *HCFC1R1*, and *PML*, and the one or more underexpressed genes are selected from the group consisting of *BTN2A2*, *SMPDL3B*, and *ME1*; and/or

5 (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
10 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*, *STAUI*, *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
15 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
20 consisting of *ADORA2B*, *KCNIG1*, *STAUI*, *MAP2K5*, and *CAMSAPI*, and the one or more underexpressed genes are selected from the group consisting of *GNB2L1*, *EIF3K*, *TXN*, *BCAP31*, *EXOSC7*, *CD55*, *NDUFC1*, *GRHPR*, *CETN3*, *BTN2A2*, *SMPDL3B*, and *ERC2*; and/or

(ii) the one or more overexpressed proteins are selected from the group
25 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
30 consisting of *GNB2L1*, *ZNF593*, and *SMPDL3B*, and the one or more underexpressed genes are selected from the group consisting of *GSK3B*, *MAP2K5*, *NDUFC1*, *CAMSAPI*, *ABHD5*, and *ME1*; 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
5 is adrenocortical carcinoma, and wherein:

the one or more overexpressed genes are selected from the group consisting of *GNB2L1*, *EIF3K*, *TXN*, *ADORA2B*, *KCNG1*, *BCAP31*, *FOXMI*, *ZNF593*, *EXO1*, *KIF2C*, *MAP2K5*, *TTK*, *MELK*, *CENPA*, *TPX2*, *GRHPR*, *CEP55*, *MCM10*, and *CENPN*, and the one or more underexpressed genes are selected from the group
10 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*, *FOXMI*, *CD55*, *EXO1*, *KIF2C*, *STAU1*,
15 *TTK*, *MELK*, *CENPA*, *TPX2*, *CA9*, *CEP55*, and *MCM10*, 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:

20 the one or more overexpressed genes are selected from the group consisting of *EIF3K*, *ADORA2B*, *GSK3B*, *EXOSC7*, *FOXMI*, *CD55*, *EXO1*, *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
25 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
30 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 of *EIF3K*, *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*, *KCNIG1*, *LAMA3*, *MAP2K5*, *NAE1*, *PGK1*, *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*, *KCNIG1*, *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*, *KCNIG1*, *LAMA3*, *MAP2K5*, *NAE1*, *PGK1*, *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-PD1 or anti-PDL1 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, pembrolizumab, 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-PD1 antibody (*e.g.*, pidilizumab, nivolumab, lambrolkizumab, pembrolizumab), an anti-PDL1 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, 4-1BB (CD137), 4-1BBL (CD137L), PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, TIM3, B7H3, B7H4, VISTA, KIR, 2B4, CD160 and CGEN-15049. Illustrative immune checkpoint inhibitors include tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-H1; MEDI4736), MK-3475 (PD-1 blocker), nivolumab (anti-PD1 antibody), pidilizumab (CT-011; anti-PD1 antibody), BY55 monoclonal antibody, AMP224 (anti-PDL1 antibody), BMS-936559 (anti-PDL1 antibody), MPLDL3280A (anti-PDL1 antibody), MSB0010718C (anti-PDL1 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 of *NAE1*, *GSK3B*, *TAF2*, *MAPRE1*, *BRD4*, *STAU1*, *TAF2*, *PDCD4*, *KCNG1*, *ZNRD1-AS1*, *EIF4B*, *HELLS*, *RPL22*, *ABAT*, *BTN2A2*, *CD1B*, *ITM2A*, *BCL2*, *CXCR4*, and *ARNT2* and an expression level of one or more underexpressed genes selected from the group consisting of *CD1C*, *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*, *ATP6VIC1*, *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.

5 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*, *CD1B*, *KDM5A*, *BATF*, *EVL*, *PRKCB*, *HCFC1R1*, *CARHSP1*, *CHAD*, *KIR2DL4*, *ABHD5*, *ABHD14A*, *ACAA1*, *SRPK3*, and *CFB*.

10 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*.

15 In one embodiment, the one or more overexpressed genes are selected from the group consisting of *RPL22*, *ABAT*, *BTN2A2*, *CD1B*, *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*, *ATP6VIC1*, *CD55* and *ADORA2B*.

20 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
25 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
30 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
5 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
10 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.

15 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*, *COG8*, *CFDP1* and/or *KCNG1* with a test agent; and

(ii) determining whether the test agent, at least partly, reduces, eliminates,
20 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*, *COG8*, *CFDP1* and *KCNG1* and any combination thereof,

25 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
30 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 Köhler & 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.

- 5 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.
- 10 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.

- 15 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
- 20 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.

- 25 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*,
30 *EXOSC7*, *COG8*, *CFDP1*, *KCNIG1* 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*, *NDUFC1*, *CAMSAP1*, *CETN3*, *EIF3K*, *STAU1*, *EXOSC7*, *COG8*, *CFDPI* and/or *KCNG1* may then be administered to patients who are suffering from
5 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.

10 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*, *CFDPI*, *KCNG1* and any combination thereof.

All computer programs, algorithms, patent and scientific literature referred to
15 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.

20

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

25

Materials and Methods

Meta-analysis of global gene expression in TNBC

We performed a meta-analysis of global gene expression data in the OncomineTM database¹⁹ (Compendia Bioscience, MI) using a primary filter for breast
30 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 datasets⁴⁹⁻⁵⁶; (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).

- 5 The union of these three deregulated gene lists resulted in a gene list of deregulated genes in aggressive breast cancers (Figure 9). The METABRIC dataset²¹ was used as the validation set for further analysis. The normalized z-score expression data of the METABRIC dataset was extracted from OncomineTM and imported into BRB-ArrayTools⁶⁴ (V4.2, Biometric Research Branch, NCI, Maryland, USA) with built in
- 10 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
- 15 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
- 20 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
- 25 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 aggressiveness score tumors. The METABRIC dataset and four publically available datasets were used to validate the 8-genes score. The four datasets (GSE25066⁵³, GSE3494⁶⁵, GSE2990¹⁵, GSE2034⁶⁶)
- 30 were analyzed as described previously⁶⁷.

Cell culture and drug treatments

Breast cancer cell lines were obtained from ATCCTM (VA, USA) and cultured as per ATCCTM 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-MPS1 mouse monoclonal antibody [N1] ab11108 (Abcam, 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-Alexa₄₈₈ 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).

5

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™ database¹⁹ (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 $< 1 \times 10^{-5}$ from a Student's *t*-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 *t*-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 *t*-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) dataset²¹ 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).

30

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 classification²². As shown in Figure 1A, ER⁻/HER2⁻ (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 ER⁻/HER2⁻ (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 classification⁸ and the ten integrative clustering (intClust) subtypes defined by combined clustering of gene expression and copy number data subtypes²¹ (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 1B). Among ER⁺ tumors we found that high aggressiveness score predicted poor survival in both Grade 2 (Figure 1B) 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*, *EXO1*, *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 ERLN⁻ and ERLN⁺ 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 MammaPrint⁹, OncotypeDx^{10,11}, proliferation/cell cycle^{16,20} and CIN²⁰ signatures. Moreover, our aggressiveness scores outperformed the CIN4 classifier²³ 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)-plotter²⁴ (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*, *EXO1*, *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/AURKB²⁷ and have been trialed pre-clinically and clinically²⁸. 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).

5 ***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).

10 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.

15 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 mitosis²⁹. 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
20 (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).
25 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
30 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
5 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
10 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
15 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*, *FOXMI* 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
20 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
25 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
30 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, colorectal cancer, glioblastoma, lower grade glioma, head & neck cancer, kidney cancer, liver cancer, lung adenocarcinoma, acute myeloid leukaemia, pancreatic cancer and lung squamous cell carcinoma.

Discussion

This meta-analysis of gene expression in the OncomineTM database identified a list of 206 genes 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 tumors¹⁶. 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 aneuploidy³¹. 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 cancers²⁰. More recently, a minimal gene set that captures the CIN signature, CIN4 (*AURKA*, *FOXMI*, *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 classifier is the stratification of Grade 2 tumors into good and poor prognosis groups²³. 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 classifier 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 previously¹⁶. 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 score²³.

Chromosome missegregation and aneuploidy enhance genetic recombination and defective DNA damage repair³⁴ to drive a “mutator phenotype” required for oncogenesis³⁵. 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 TNBC³⁸ 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 cancer⁴¹, MELK/FOXMI in glioblastoma^{42,43}, MELK⁴⁴ and MAD2⁴⁵ in breast cancer and SKP2 in several
5 cancers⁴⁶. 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
10 quiescent aneuploid cells as a mechanism for therapy resistance³⁹. 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
15 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
20 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
25 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
30 (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 TTK⁶⁷⁻⁷⁰) or by other drugs that target the aneuploidy state (such as PLK1^{71,72} or others⁷³⁻⁷⁶).

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)	<0.0001	1.5188 (1.3227 - 1.7440)	<0.0001
8 genes score (high, low)	1.5853 (1.2883 - 1.8103)	<0.0001	1.4760 (1.2198 - 1.6344)	<0.0001
Lymph node (+, -)	1.8594 (1.6289 - 2.1224)	<0.0001	1.6807 (1.4610 - 1.9334)	<0.0001
Tumor size (T1, T2, T3)	1.4354 (1.2813 - 1.6080)	<0.0001	1.3666 (1.1642 - 1.6041)	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)	<0.0001	ns	ns
Ki67 (+, -)	1.4184 (1.2399 - 1.6226)	<0.0001	ns	ns
MammaPrint (high, low)	1.3320 (1.1669 - 1.5204)	<0.0001	ns	ns
CIN4 (high, low)	1.5310 (1.3413 - 1.7476)	<0.0001	ns	ns
CIN75 (high, low)	1.5004 (1.3132 - 1.7143)	<0.0001	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%)	p<1.0E-6
High	237 (11%)	831 (39%)	
Immunohistochemical subtypes			
ER negative	71 (4%)	369 (19%)	p<1.0E-6
ER positive	827 (42%)	681 (35%)	p<1.0E-6
PR negative	306 (15%)	637 (32%)	
PR positive	617 (31%)	432 (22%)	p<1.0E-6
HER2 negative	802 (40%)	744 (37%)	
HER2 positive	118 (6%)	323 (16%)	p<1.0E-6
non-TNBC	885 (45%)	840 (43%)	p<1.0E-6
Triple negative (TNBC)	29 (1%)	221 (11%)	
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	167 (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 (48%)	331 (40%)	p<1.0E-6
Mutant	14 (2%)	85 (10%)	

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 %)	0.0265
Lobular	43(76.8 %)	10 (17.9 %)	3 (5.4 %)	
Mixed ducto-lobular	31(88.6 %)	4 (11.4 %)	0 (0.0 %)	
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 %)	<0.0001
2	162(77.5 %)	41 (19.6 %)	6 (2.9 %)	
3	73(47.7 %)	50 (32.7 %)	30 (19.6 %)	
Mitotic score				
1	193(79.8 %)	44(18.2 %)	5 (2.1 %)	<0.0001
2	33(61.1 %)	18 (33.3 %)	3 (5.6 %)	
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 %)	ns
2	52(69.3 %)	20 (26.7 %)	3 (4.0 %)	
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 %)	ns
2-5 cm	104(66.2 %)	38 (24.2 %)	15 (9.6 %)	
>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 %)	0.0007
Mild	115(63.9 %)	47 (26.1 %)	18 (10.0 %)	
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 %)	0.0003
Pushing (<50%)	11(36.7 %)	11 (36.7 %)	8 (26.7 %)	
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 %)	<0.0001
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 %)	
TN (basal-like)	23(41.8 %)	20 (36.4 %)	12 (21.8 %)	
TN (non-basal)	10(71.4 %)	1 (7.1 %)	3 (21.4 %)	

TMA 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[®] Prism. 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 (<i>Xenopus laevis</i>)	HGNC:24167	7p21.1
AHNAK	AHNAK nucleoprotein	HGNC:347	11q12-q13
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	HGNC:403	17p11.2
ANLN	anillin, actin binding protein	HGNC:14082	7p15-p14
APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	HGNC:17352	22q13.1-q13.2
AQP9	aquaporin 9	HGNC:643	15q
ATP6V1C2	ATPase, H ⁺ transporting, lysosomal 42kDa, V1 subunit C2	HGNC:18264	2p25.1
AUNIP	aurora kinase A and ninein interacting protein	HGNC:28363	1p36.11
AURKA	aurora kinase A	HGNC:11393	20q13
AURKB	aurora kinase B	HGNC:11390	17p13.1
AZGP1	alpha-2-glycoprotein 1, zinc-binding	HGNC:910	7q22.1
BBS1	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	HGNC:23516	10q24.33
C18orf56	chromosome 18 open reading frame 56	HGNC:29553	18p11.32
C1orf106	chromosome 1 open reading frame 106	HGNC:25599	1q32.1
C1orf21	chromosome 1 open reading frame 21	HGNC:15494	1q25
C7orf63	chromosome 7 open reading frame 63	HGNC:26107	7q21.13
CA9	carbonic anhydrase IX	HGNC:1383	9p13.3
CARD10	caspase recruitment domain family, member 10	HGNC:16422	22q13.1
CASC1	cancer susceptibility candidate 1	HGNC:29599	12p12.1
CCDC170	coiled-coil domain containing 170	HGNC:21177	6q25.1
CCDC176	coiled-coil domain containing 176	HGNC:19855	14q24.3
CCNA2	cyclin A2	HGNC:1578	4q27
CCNB2	cyclin B2	HGNC:1580	15q21.3
CCNE1	cyclin E1	HGNC:1589	19q12
CCNG2	cyclin G2	HGNC:1593	4q21.22
CD163	CD163 molecule	HGNC:1631	12p13
CDC20	cell division cycle 20	HGNC:1723	1p34.1
CDC25A	cell division cycle 25A	HGNC:1725	3p21
CDC25B	cell division cycle 25B	HGNC:1726	20p13
CDC45	cell division cycle 45	HGNC:1739	22q11.21

CDCA3	cell division cycle associated 3	HGNC:14624	12p13.31
CDCA5	cell division cycle associated 5	HGNC:14626	11q13.1
CDCA7	cell division cycle associated 7	HGNC:14628	2q31.1
CDCA8	cell division cycle associated 8	HGNC:14629	1p34.3
CDK1	cyclin-dependent kinase 1	HGNC:1722	10q21.2
CDKN2A	cyclin-dependent kinase inhibitor 2A	HGNC:1787	9p21
CENPA	centromere protein A	HGNC:1851	2p23.3
CENPE	centromere protein E, 312kDa	HGNC:1856	4q24-q25
CENPN	centromere protein N	HGNC:30873	16q23.2
CENPW	centromere protein W	HGNC:21488	6q22.32
CEP55	centrosomal protein 55kDa	HGNC:1161	10q24.1
CHEK1	checkpoint kinase 1	HGNC:1925	11q24.2
CIRBP	cold inducible RNA binding protein	HGNC:1982	19p13.3
CKAP2L	cytoskeleton associated protein 2-like	HGNC:26877	2q13
CKS1B	CDC28 protein kinase regulatory subunit 1B	HGNC:19083	1q21.2
CKS2	CDC28 protein kinase regulatory subunit 2	HGNC:2000	9q22
CLIC6	chloride intracellular channel 6	HGNC:2065	21q22.12
CMC2	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
CST3	cystatin C	HGNC:2475	20p11.2
CSTB	cystatin B (stefin B)	HGNC:2482	21q22.3
CTSV	cathepsin V	HGNC:2538	9q22.33
CYB5D1	cytochrome b5 domain containing 1	HGNC:26516	17p13.1
CYBRD1	cytochrome b reductase 1	HGNC:20797	2q31
DACH1	dachshund homolog 1 (Drosophila)	HGNC:2663	13q22
DAPK1	death-associated protein kinase 1	HGNC:2674	9q34.1
DEPDC1	DEP domain containing 1	HGNC:22949	1p31.2
DKC1	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
ECI2	enoyl-CoA delta isomerase 2	HGNC:14601	6p24.3
ELOVL5	ELOVL fatty acid elongase 5	HGNC:21308	6p21.1-p12.1
ESR1	estrogen receptor 1	HGNC:3467	6q24-q27
EXO1	exonuclease 1	HGNC:3511	1q42-q43
FAM198B	family with sequence similarity 198, member B	HGNC:25312	4q32.1
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
FOXM1	forkhead box M1	HGNC:3818	12p13

FPR3	formyl peptide receptor 3	HGNC:3828	19q13.3-q13.4
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	HGNC:4141	12p13.31
GFRA1	GNDF family receptor alpha 1	HGNC:4243	10q25-q26
GGH	gamma-glutamyl hydrolase (conjugase, folylpoly gammaglutamyl hydrolase)	HGNC:4248	8q12.3
GLI3	GLI family zinc finger 3	HGNC:4319	7p13
GLYATL2	glycine-N-acyltransferase-like 2	HGNC:24178	11q12.1
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	HGNC:28956	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:21535	10p15-p14
GTSE1	G-2 and S-phase expressed 1	HGNC:13698	22q13.2-q13.3
HJURP	Holliday junction recognition protein	HGNC:25444	2q37.1
HRASLS	HRAS-like suppressor	HGNC:14922	3q29
HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4	HGNC:5213	5q2
HSD17B8	hydroxysteroid (17-beta) dehydrogenase 8	HGNC:3554	6p21.3
IGFBP2	insulin-like growth factor binding protein 2, 36kDa	HGNC:5471	2q33-q34
IGFBP4	insulin-like growth factor binding protein 4	HGNC:5473	17q12-q21.1
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:6248	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	1q32.1
KIF20A	kinesin family member 20A	HGNC:9787	5q31
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
KRT6A	keratin 6A	HGNC:6443	12q13.13
LAD1	ladinin 1	HGNC:6472	1q25.1-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
LOC100286909	-	-	-
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	MAD2 mitotic arrest deficient-like 1 (yeast)	HGNC:6763	4q27
MAPT	microtubule-associated protein tau	HGNC:6893	17q21
MCM10	minichromosome maintenance complex component 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:7867	12p13
NOSTRIN	nitric oxide synthase trafficker	HGNC:20203	2q31.1
NOVA1	neuro-oncological ventral antigen 1	HGNC:7886	14q12
NRIP1	nuclear receptor interacting protein 1	HGNC:8001	21q11.2
NUP205	nucleoporin 205kDa	HGNC:18658	7q31.32
NUP93	nucleoporin 93kDa	HGNC:28958	16q13
NUSAP1	nucleolar and spindle associated protein 1	HGNC:18538	15q14
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	8p11.21
PLCH1	phospholipase C, eta 1	HGNC:29185	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
PSMB2	proteasome (prosome, macropain) subunit, beta type, 2	HGNC:9539	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
RAD51API	RAD51 associated protein 1	HGNC:16956	12p13.2-p13.1
RBM38	RNA binding motif protein 38	HGNC:15818	20q13.31
REERG	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
SH3BGR1	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 (<i>Xenopus laevis</i>)	HGNC:1249	20q11.2
TRIP13	thyroid hormone receptor interactor 13	HGNC:12307	5p15
TROAP	trophinin associated protein	HGNC:12327	12q13.12

TTK	TTK protein kinase	HGNC:12401	6q13-q21
TUBA4A	tubulin, alpha 4a	HGNC:12407	2q36.1
UBE2C	ubiquitin-conjugating enzyme E2C	HGNC:15937	20q13.12
USB1	U6 snRNA biogenesis 1	HGNC:25792	16q13
VGLL1	vestigial like 1 (Drosophila)	HGNC:20985	Xq26.3
XBPI	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 metagene							High vs. Low score
	Symbol	UniqueID	Correlation coefficient	Parametric p-value	FDR	Permutation p-value	Fold-change
ER Metagene	<i>MAPT</i>	<i>ILMN_2310814</i>	0.755	< 1e-07	< 1e-07	< 1e-07	-4.55
	<i>MYB</i>	<i>ILMN_1711894</i>	0.718	< 1e-07	< 1e-07	< 1e-07	-3.33
	<i>BCL2</i>	<i>ILMN_2246956</i>	0.682	< 1e-07	< 1e-07	< 1e-07	-2.86
	<i>STC2</i>	<i>ILMN_1691884</i>	0.65	< 1e-07	< 1e-07	< 1e-07	-4.55
	<i>BTG2</i>	<i>ILMN_1770085</i>	0.544	< 1e-07	< 1e-07	< 1e-07	-2.38
	<i>CLIC6</i>	<i>ILMN_1699665</i>	0.403	< 1e-07	< 1e-07	< 1e-07	-3.45
	<i>ESR1</i>	<i>ILMN_1678535</i>	0.842	< 1e-07	< 1e-07	< 1e-07	-12.99
	<i>FOXA1</i>	<i>ILMN_1766650</i>	0.78	< 1e-07	< 1e-07	< 1e-07	-5.56
	<i>XBP1</i>	<i>ILMN_1809433</i>	0.741	< 1e-07	< 1e-07	< 1e-07	-2.56
	<i>TFF3</i>	<i>ILMN_1811387</i>	0.73	< 1e-07	< 1e-07	< 1e-07	-10.75
	<i>DACH1</i>	<i>ILMN_1755741</i>	0.684	< 1e-07	< 1e-07	< 1e-07	-3.85
	<i>TFF1</i>	<i>ILMN_1722489</i>	0.645	< 1e-07	< 1e-07	< 1e-07	-10.00
	<i>PTPRT</i>	<i>ILMN_1698885</i>	0.637	< 1e-07	< 1e-07	< 1e-07	-2.63
	<i>PLAT</i>	<i>ILMN_1738742</i>	0.557	< 1e-07	< 1e-07	< 1e-07	-2.38
	<i>GSTM3</i>	<i>ILMN_1736184</i>	0.5	< 1e-07	< 1e-07	< 1e-07	-2.00
	<i>RPS23</i>	<i>ILMN_1772459</i>	0.467	< 1e-07	< 1e-07	< 1e-07	-2.00
	<i>GSTM1</i>	<i>ILMN_2391861</i>	0.384	< 1e-07	< 1e-07	< 1e-07	-2.00
	<i>ITPR1</i>	<i>ILMN_1789505</i>	0.546	< 1e-07	< 1e-07	< 1e-07	-1.85
	<i>SKP1</i>	<i>ILMN_1711766</i>	0.689	< 1e-07	< 1e-07	< 1e-07	-1.75
	<i>IGFBP2</i>	<i>ILMN_1725193</i>	0.38	< 1e-07	< 1e-07	< 1e-07	-1.72
	<i>GLI3</i>	<i>ILMN_1771962</i>	0.486	< 1e-07	< 1e-07	< 1e-07	-1.61
	<i>AHNAK</i>	<i>ILMN_1714567</i>	0.551	< 1e-07	< 1e-07	< 1e-07	-1.59
	<i>NRIP1</i>	<i>ILMN_1718629</i>	0.548	< 1e-07	< 1e-07	< 1e-07	-1.59
	<i>TAT</i>	<i>ILMN_1791678</i>	0.304	< 1e-07	< 1e-07	< 1e-07	-1.56
	<i>PDCD4</i>	<i>ILMN_1768004</i>	0.44	< 1e-07	< 1e-07	< 1e-07	-1.54
CIN Metagene	<i>MELK</i>	<i>ILMN_1731184</i>	0.9	< 1e-07	< 1e-07	< 1e-07	2.29
	<i>MCM10</i>	<i>ILMN_2413898</i>	0.868	< 1e-07	< 1e-07	< 1e-07	2.22
	<i>CENPA</i>	<i>ILMN_1801257</i>	0.909	< 1e-07	< 1e-07	< 1e-07	2.2
	<i>EXO1</i>	<i>ILMN_1673721</i>	0.885	< 1e-07	< 1e-07	< 1e-07	2.15
	<i>TTK</i>	<i>ILMN_1788166</i>	0.837	< 1e-07	< 1e-07	< 1e-07	2.15
	<i>KIF2C</i>	<i>ILMN_1685916</i>	0.888	< 1e-07	< 1e-07	< 1e-07	2.13
	<i>CENPN</i>	<i>ILMN_1720526</i>	0.814	< 1e-07	< 1e-07	< 1e-07	2.04
	<i>CEP55</i>	<i>ILMN_1747016</i>	0.891	< 1e-07	< 1e-07	< 1e-07	2.03
	<i>FOXM1</i>	<i>ILMN_2344971</i>	0.869	< 1e-07	< 1e-07	< 1e-07	2.01
	<i>TPX2</i>	<i>ILMN_1796949</i>	0.88	< 1e-07	< 1e-07	< 1e-07	2.01
	<i>AURKB</i>	<i>ILMN_1684217</i>	0.884	< 1e-07	< 1e-07	< 1e-07	2.25
	<i>AURKA</i>	<i>ILMN_1680955</i>	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
HBURP	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	Sum159P T	Hs578T
5.00E-07	1.47E-06	< 1e-07	1.1123470 52	1.567			
0.0008816	1.28E-03	8.00E-04	1.0917030 57	1.258			
< 1e-07	< 1e-07	< 1e-07	1.2091898 43	1.043			
2.86E-05	5.55E-05	< 1e-07	1.0741138 56	1.938			
2.45E-05	4.95E-05	< 1e-07	1.1547344 11	1.03			
< 1e-07	< 1e-07	< 1e-07	1.1111111 11	2.214			

			-		
< 1e-07	< 1e-07	< 1e-07	1.2077294 69	1.076	
			-		
6.00E-07	1.62E-06	< 1e-07	1.1337868 48	1.358	
			-		
2.43E-05	4.95E-05	< 1e-07	1.2048192 77	0.736	
			-		
5.66E-05	9.98E-05	< 1e-07	1.0964912 28	1.625	
			-		
5.50E-06	1.21E-05	< 1e-07	1.2422360 25	0.723	
< 1e-07	< 1e-07	< 1e-07	1.274	0.799	91 ± 3% (n=3)
7.00E-07	1.84E-06	< 1e-07	1.221	0.791	46 ± 4 (n=5)
1.00E-07	3.46E-07	< 1e-07	1.253	0.762	92 ± 3 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.267	0.767	98 ± 6% (n=3)
4.00E-07	1.25E-06	< 1e-07	1.222	0.799	68 ± 8 (n=6)
< 1e-07	< 1e-07	< 1e-07	1.271	0.756	83 ± 2 (n=3)
					155 ± 17% (n=3)
					100 ± 1 (n=3)
					52 ± 2 (n=3)
					51 ± 1% (n=3)
					34 ± 6 (n=6)
					19 ± 1 (n=3)
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)
1.00E-07	3.46E-07	< 1e-07	1.247	0.744	37 ± 1 (n=6)
< 1e-07	< 1e-07	< 1e-07	1.326	0.782	57 ± 1 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.256	0.836	66 ± 1% (n=3)
< 1e-07	< 1e-07	< 1e-07	1.273	0.873	72 ± 2 (n=5)
3.30E-06	7.81E-06	< 1e-07	1.182	0.878	62 ± 2 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.246	0.882	57 ± 7% (n=3)
< 1e-07	< 1e-07	< 1e-07	1.259	0.958	64 ± 1 (n=3)
5.00E-07	1.47E-06	< 1e-07	1.184	0.965	24 ± 3 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.232	0.966	100 ± 26% (n=3)
< 1e-07	< 1e-07	< 1e-07	1.271	0.998	79 ± 3 (n=6)
< 1e-07	< 1e-07	< 1e-07	1.184	1.194	100 ± 1 (n=3)
< 1e-07	< 1e-07	< 1e-07	1.208	1.239	98 ± 5% (n=3)
3.29E-05	6.06E-05	< 1e-07	1.109	1.299	101 ± 1 (n=6)
< 1e-07	< 1e-07	< 1e-07	1.279	0.726	110 ± 1 (n=3)
					91 ± 4% (n=3)
					76 ± 2 (n=6)
					83 ± 3 (n=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-05	< 1e-07	1.133	1.029			

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 - 2.89)	<1.00E-16	2.16 (1.90 - 2.47)	<1.00E-16
	Quartile	3.03 (2.43 - 3.78)	<1.00E-16	2.46 (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 (2.39 - 3.67)	<1.00E-16	2.64 (2.16 - 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	2.76 (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 (2.31 - 3.87)	4.30E-13	2.53 (2.00 - 3.19)	1.00E-13
LN+	Median	2.20 (1.57 - 3.08)	2.40E-06	1.88 (1.40 - 2.53)	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-13	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)	3.20E-12
	Tertile	3.53 (2.48 - 5.04)	8.70E-14	2.92 (2.18 - 3.90)	3.70E-14
ER+	Median	3.43 (2.49 - 4.74)	1.30E-13	2.63 (2.00 - 3.45)	4.20E-13
	Quartile	3.41 (2.31 - 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 - 9.28)	1.40E-07	2.80 (2.00 - 3.93)	4.20E-10
	Quartile	4.86 (2.82 - 9.37)	2.70E-10	4.46 (2.61 - 7.60)	1.30E-09
	Tertile	3.98 (2.61 - 6.07)	4.20E-12	3.76 (2.46 - 5.74)	4.50E-11
LN+	Median	2.12 (1.19 - 3.80)	9.40E-03	2.16 (1.28 - 3.62)	3.00E-03
	Quartile	2.97 (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 - 5.68)	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 – 0.61)	<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)	1.20E-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)	2.20E-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 (0.42 – 0.84)	3.00E-03	0.70 (0.50 – 0.98)	3.50E-02
	Tertile	0.57 (0.41 – 0.78)	4.00E-04	0.68 (0.50 – 0.91)	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)	3.00E-04	0.57 (0.42 – 0.78)	3.00E-04
LN-	Median	0.74 (0.54 – 1.00)	4.60E-02	0.74 (0.54 – 1.00)	4.60E-02
	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 R-M-planner

Table 8: details of antibodies and immunohistochemistry 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) <i>Regarding estimating % of cells stained, we disregarded mitotic cells to assess mitosis-independent expression of TTK</i>

*Antigen retrieval in 0.01M 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		1.59	10CIN		2.2	AJCC stage N	0	1.73 (1.5 - 1.99)
2ER signature	0.0002	(1.25 - 2.04)	2ER signature	0	(1.73 - 2.79)	10CIN		1.35
						2ER signature	0.0075	(1.08 - 1.69)

EXAMPLE 2**Materials and Methods*****Meta-analysis of global gene expression in TNBC***

5 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
10 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
15 two differential analyses.

Deriving the 28-signature (the TN signature)

The online tool KM-Plotter [38] which collates gene expression data from Affymetrix platform for more than 4000 breast cancer patients were used for developing the 28-gene signature. From the deregulated genes in primary tumors
20 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
25 survival (OS) in either ER⁺ or BLBC subtypes were short selected. The 96 genes that were significant in this filtering were then sorted for their level of significance as well as the prevalence of significance across the different survival outcomes (RFS, 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
30 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 cancer 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-ArrayTools [65] (V4.2, Biometric 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=1106 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 $\div$ 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 (pCR) 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], GSE22226 [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 GSE17705 [51]. These datasets using the Affymetrix 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 dataset 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 TCGA dataset (Illumina RNA-Seq platform) and the ISPY-1 trial dataset (GSE22226 [41, 46], Agilent platform), illustrating the platform-independence of the iBCR score which is driven by the platform independence of the 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 (mRNA Cancer Cell Line Profiles GSE10843), Pfizer (Pfizer Molecular Profile Data for Cell Line GSE34211) and Broad Institute/Novartis (Cancer Cell Line Encyclopedia [CCLE] 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 determined 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, Ostend, Belgium).

Results

Meta-analysis of gene expression profile in Oncomine™

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 *t*-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 *t*-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 ER⁻ breast cancer subtypes

- 5 The 166 deregulated genes in primary breast tumors that associated with poor outcome discovered from the OncomineTM 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
- 10 significance across the different disease outcomes (RFS, 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
- 15 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
- 20 of TNBC (Figure 21A), BLBC (Figure 21B) and ER⁻ (Figure 21C) patients and outperformed all standard clinicopathological 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
- 25 published signatures that are prognostic in ER⁻, TNBC or BLBC subtypes [30-35] (Figure 32).

- While the discovery of the signature in OncomineTM included datasets using the Affymetrix, Illumina and Agilent platforms, the training and validation above was limited to the Affymetrix platform. Thus, we validated the TN score in The Cancer
- 30 Genome Atlas (TCGA) dataset [39] which used the Illumina 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 ER⁻ 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 (GSE18728), 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 systemically untreated and treated patients separately. As summarized in Table 11 (Figure 34 for survival curves), the TN signature was prognostic in either systemically untreated or treated ER- and BLBC subtypes.

Therapeutic targets based on the TN signature

5 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*, *CAMSAP1*, *CETN3*, *EIF3K*, *STAU1*, *EXOSC7* and *KCNGL1*. 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
10 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
15 molecularly 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
20 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
25 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
30 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 (Tanespimycin [17-AAG]) and EGFR (Erlotinib or Lapatinib) (Figure 35). In a similar method, we also analyzed a second large study, Garnett et al. [49], which tested 130 drugs against more than 600 cancer cell lines. As shown in Figure 24, cell 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-119) inhibition.

Integration of the TN score and the aggressiveness score

We have recently published the aggressiveness gene signature/score (Agro score) [36] from a meta-analysis in OncomineTM 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/MPS1, 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 immunohistochemistry (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 survival 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 ER-/HER2- patients were less likely to achieve pCR (Figure 27), which could explain the poorer survival 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 ER-/HER2-). 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-/HER2- 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), FEC/TX (GSE42822) and FAC/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 ER⁺/HER2⁻ breast cancer, low iBCR score patients may be spared from additional treatments particularly if they achieve pCR after chemotherapy. On the 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 upregulated 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 35).

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 the 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 (N0) 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 MammaPrint[®] and more recently the PAM50 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 N0 and N1 subsets. For the iBCR score, as shown in Figure 29A, this score was prognostic in ER⁺ N0 patients who were not treated with tamoxifen indicating that high iBCR ER⁺ N0 patients should be treated with tamoxifen. When ER⁺ N0 or N1 patients are treated with tamoxifen, the iBCR score can still identify patients who have poor RFS (Figure 29B) and DMFS (Figure 29C). Thus, ER⁺ N0 or N1 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 N1, 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 after the standard treatments. Similar to the analysis performed for the TN signature above, we took two approaches 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 upregulated in high iBCR score ER⁺ vs. normal breast and low iBCR ER⁺ and 95 genes were specifically upregulated in high iBCR score ER⁻ vs. normal breast and low iBCR ER⁻. As shown in Table 13, 49 genes were uniquely upregulated in high iBCR score ER⁻ tumors compared to low score iBCR score ER⁻ tumors and normal

breast tissue. Similar comparison 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 comparison 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 micro-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 ER⁺ 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 IGF1R (BMS-536924) as also observed in the TN score results. Additionally, high iBCR score cell lines were more sensitive to inhibition of PI3K (GDC0941), mTOR (JW-7-25-1), XIAP (Embelin) and PLK1 (BI-2536) which also matched results from Agro score results (Figure 30). The Agro score also identified sensitivity to inhibition of RSK (CMK), 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 (BAY613606), 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 log₁₀ of IC₅₀ (IC₅₀ is the dose required to kill 50% of the cells). Sensitivity was presented as the -log₁₀[IC₅₀]. 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 or 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 (LY2228820), PLC γ (U73122), JNK (SP600125), PAK1 (IPA3), MEK (AS703026 and AZD6244), ERK5 (XMD 8-92 and BIX02188), HSP90 (17-AAG, PF0429113 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 OncomineTM database has previously identified a signature, the Aggressiveness signature (Agro 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
5 (exclusive of mitotic cells) 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
10 standard clinicopathological 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
15 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
20 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
25 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
30 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
5 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
10 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
15 signatures and the iBCR test in clinical trials and pre-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 (N0) breast cancer patients treated with endocrine therapy whether patients
20 with high risk according to these tests are recommended for adjuvant chemotherapy. Our signatures and the iBCR test outperformed these tests in a direct comparison in ER⁺ N0 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
25 capability. Importantly, our signatures and the iBCR test was also prognostic in the subgroup with unmet need, ER⁺ lymph node positive breast cancer (ER⁺ N1). 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
30 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 vivo*, 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 PLK1 and HSP90 inhibition (Figure 30) 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 HSP90 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/iBCR 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 OncomineTM 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
5 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 Oncomine™

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
↑CAMSA P1	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, subcomplex 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-value	HR	CI 95%	p-value
ER-	RFS	2.02	1.25 – 3.26	3.20E-03	2.59	1.84 – 3.60	1.70E-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	1.94 – 4.28	4.50E-08
	DMFS	5.54	1.66 – 18.48	1.70E-03	3.14	1.38 – 7.19	4.20E-03
	OS	2.42	0.79 – 7.47	0.11	4.89	1.65 – 14.46	1.50E-03

5 The 28-gene signature was used as described in Figure 2 in the online tool KM-plotter but restricting the analysis on ER- or BLBC 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.

10 **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 (63.9%)	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 GSE20194), FEC/TX (GSE42822) and FAC/TX (GSE23988)

15

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	MLF11P	
CALML5	LRP8		CACYBP	GIN52	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	NDUF8	SPAG5			CDC20	NEK2	ZW1NT
CLIC3	MMP12	VEGFA	CDCA3	HMMR	NUDT21	SQLE			CDC6	NUSAP1	
CORO1C	PFKP	VGLL1	CEBPG	HSPH1	NUTF2	STIP1			CDK1	PDXK	
CP	PHLD A2		CKS1B	KIAA0101	OIP5	TACC3			CDKN3	PHB	
CRISP3	PTPN12		CXCL10	KIF11	PBK	TBCE			CENPF	PRC1	
DDC	QPRT		CXCL11	KIF14	PCNA	TIMM17A			CKS2	PITG1	
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	
GMP8	SRD5A1		EIF5A	LY6E	RAD21	ZWILCH			GIN51	TRIP13	
GPSM2	ST14		EMC8	MAD2L1	RAD54B				HIST1H2BG	UBE2C	

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

Gene Name	Affy Probe ID	Basal-like breast cancer					
		RFS		DMFS		OS	
		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
MEI	211204_at	0.65	2.30E-03	0.38	2.10E-03	0.66	2.00E-01
BRF3	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
ASPB	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
AIM1L	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
KCNQ1	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
PMIL	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
DYNC1L2	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		Avg P	Count of Sig. p val
HR	P	HR	P	HR	P		
0.45	6.50E-13	0.44	1.10E-04	0.55	1.10E-01	1.85E-02	5
0.59	2.40E-06	0.51	8.50E-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	4.10E-02	0.88	6.00E-01	1.42E-01	4
0.58	4.30E-05	0.45	2.20E-04	0.36	8.40E-06	7.72E-04	6
0.58	3.50E-06	0.65	3.50E-02	0.68	9.60E-02	2.36E-02	5
0.65	1.40E-04	0.59	1.20E-02	0.73	2.10E-01	5.11E-02	4
0.67	4.40E-04	0.67	7.10E-02	0.82	4.20E-01	8.74E-02	4
0.58	1.70E-06	0.58	8.70E-03	0.6	2.30E-02	6.88E-03	6
0.57	4.70E-07	0.66	4.20E-02	0.74	2.00E-01	5.82E-02	4
0.53	1.50E-08	0.42	1.00E-05	0.58	1.40E-02	1.13E-01	5
0.62	3.20E-05	0.69	6.80E-02	0.68	8.40E-02	2.88E-02	4
0.67	3.00E-04	0.74	1.40E-01	0.79	3.00E-01	8.32E-02	4
0.65	1.00E-04	0.6	1.40E-02	0.64	4.90E-02	1.85E-02	6
0.55	5.40E-08	0.67	5.10E-02	0.64	5.10E-02	3.68E-02	5
0.6	6.60E-06	0.64	3.20E-02	0.82	4.20E-01	1.44E-01	4
0.62	5.90E-05	0.64	5.60E-02	0.69	1.50E-01	7.14E-02	4
0.73	7.30E-03	0.58	1.10E-02	0.79	3.20E-01	1.15E-01	4
0.67	3.20E-03	0.69	7.70E-02	0.69	1.10E-01	4.90E-02	4
0.64	9.50E-05	0.58	6.70E-03	0.54	6.50E-03	4.32E-02	4
0.63	1.80E-04	0.67	1.00E-01	0.93	7.80E-01	2.05E-01	3
1.01	9.50E-01	0.56	4.90E-03	0.63	4.40E-02	3.12E-01	3
0.82	1.00E-01	0.79	2.50E-01	0.86	5.20E-01	1.51E-01	3
0.64	5.10E-05	0.81	3.00E-01	1.05	8.50E-01	2.67E-01	3
0.75	1.40E-02	0.81	3.00E-01	0.74	1.90E-01	9.92E-02	3
0.76	1.40E-02	0.76	1.90E-01	1.08	7.40E-01	2.46E-01	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-01	2.37E-01	3
0.71	2.20E-03	0.77	2.00E-01	0.88	5.80E-01	1.62E-01	3
0.65	1.60E-04	0.74	1.40E-01	1.02	9.40E-01	3.14E-01	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

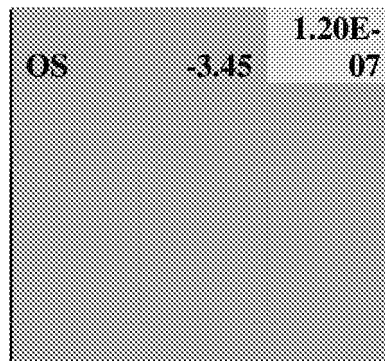
RFS	-2.38	3.30E-15
DMFS	-2.08	2.40E-04
OS	-2.13	7.10E-04

Using top 4 genes from first module and top 3 genes from the second module

BLBC			BTN2A2
RFS	-2.86	1.10E-16	IGHA1
DMFS	-5.00	7.80E-10	MTMR7
OS	-4.76	1.50E-08	ME1
ER negative			NCRNA00171
RFS	-2.50	1.00E-16	SMPDL3B
DMFS	-3.13	2.40E-08	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

[illegible]

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-acetyltransferase 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	PHLD A2	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	0.040	1.8	209800 at	KRT16	keratin 16	3868
1.13E-03	0.060	0.000	1.8	201951 at	ALCAM	activated leukocyte cell adhesion molecule	214
5.40E-04	0.047	0.000	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	0.075	0.001	1.8	203060 s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
2.71E-02	0.261	0.028	1.8	218211 s_at	MLPH	melanophilin	79083
4.52E-03	0.111	0.004	1.8	201242 s_at	ATP1B1	ATPase, Na+/K+-transporting, beta 1 polypeptide	481
1.19E-03	0.061	0.000	1.8	220230 s_at	CYB5R2	cytochrome b5 reductase 2	51700
2.38E-03	0.082	0.002	1.8	218959 at	HOXC10	homeobox C10	3226
5.29E-03	0.12	0.003	1.8	219959 at	MOCO S	molybdenum cofactor sulfurase	55034
2.58E-03	0.085	0.002	1.8	219580 s_at	TMC5	transmembrane channel-like 5	79838
1.98E-03	0.076	0.001	1.8	204595 s_at	STC1	stanniocalcin 1	6781
3.06E-03	0.091	0.002	1.8	200862 at	DHCR24	24-dehydrocholesterol reductase	1718
3.44E-02	0.291	0.033	1.7	211657 at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
8.94E-03	0.154	0.007	1.7	210652 s_at	TTC39A	tetratricopeptide repeat domain 39A	22996
2.16E-03	0.078	0.002	1.7	201467 s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
2.45E-02	0.248	0.021	1.7	209699 x_at	AKR1C2	aldo-keto reductase family 1, member C2	1646
1.02E-02	0.165	0.011	1.7	203215 s_at	MYO6	myosin VI	4646
8.95E-04	0.054	0.000	1.7	204284 at	PPP1R3C	protein phosphatase 1, regulatory subunit 3C	5507
4.66E-02	0.332	0.045	1.7	203453 at	SCNN1A	sodium channel, non-voltage-gated 1 alpha subunit	6337
4.38E-04	0.043	0.000	1.7	206326 at	GRP	gastrin-releasing peptide	2922
2.35E-03	0.082	0.002	1.7	219127 at	PRR15L	proline rich 15-like	79170
3.86E-02	0.306	0.034	1.7	214580 x_at	KRT6C		
1.94E-03	0.075	0.001	1.7	203058 s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
8.03E-03	0.146	0.006	1.7	209373 at	MALL	mal, T-cell differentiation protein-like	7851
5.88E-04	0.048	0.000	1.7	213285 at	TMEM30B	transmembrane protein 30B	161291
8.97E-03	0.154	0.009	1.7	205110 s_at	FGF13	fibroblast growth factor 13	2258

4.44E-04	0.0435	0.0005	1.7	<u>221042</u> s_at	CLMN	calmin (calponin-like, transmembrane)	79789
1.44E-02	0.193	0.0151	1.7	<u>214079</u> at	DHRS2	dehydrogenase/reductase (SDR family) member 2	10202
3.70E-02	0.302	0.0377	1.7	<u>204913</u> s_at	SOX11	SRX (sex determining region Y)-box 11	6664
9.09E-04	0.0547	0.0014	1.6	<u>209260</u> at	SFN	stratifin	2810
5.49E-03	0.121	0.0057	1.6	<u>203946</u> s_at	ARG2	arginase, type II	384
1.01E-03	0.0571	0.0012	1.6	<u>221589</u> s_at	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	4329
8.30E-04	0.0537	0.0005	1.6	<u>222258</u> s_at	SH3BP4	SH3-domain binding protein 4	23677
8.16E-03	0.147	0.0083	1.6	<u>205968</u> at	KCNS3	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	3790
8.44E-03	0.15	0.0094	1.6	<u>203180</u> at	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	220
2.13E-03	0.0786	0.003	1.6	<u>201596</u> x_at	KRT18	keratin 18	3875
1.60E-03	0.0707	0.0022	1.6	<u>219232</u> s_at	EGLN3	egl nine homolog 3 (C. elegans)	112399
4.28E-04	0.0435	0.0003	1.6	<u>208710</u> s_at	AP3D1	adaptor-related protein complex 3, delta 1 subunit	8943
9.84E-04	0.0569	0.0009	1.6	<u>218273</u> s_at	PDP1	pyruvate dehydrogenase phosphatase catalytic subunit 1	54704
1.83E-04	0.0306	0.0003	1.6	<u>209945</u> s_at	GSK3B	glycogen synthase kinase 3 beta	2932
3.77E-03	0.101	0.0046	1.6	<u>203407</u> at	PPL	periplakin	5493
3.03E-02	0.275	0.0263	1.6	<u>207802</u> at	CRISP3	cysteine-rich secretory protein 3	10321
1.65E-02	0.205	0.0179	1.6	<u>205594</u> at	ZNF652	zinc finger protein 652	22834
1.72E-02	0.21	0.0165	1.6	<u>210372</u> s_at	TPD52L1	tumor protein D52-like 1	7164
2.32E-02	0.242	0.0222	1.6	<u>203803</u> at	PCYOX1	prenylcysteine oxidase 1	51449
2.10E-02	0.233	0.0239	1.6	<u>209875</u> s_at	SPP1	secreted phosphoprotein 1	6696
6.66E-03	0.133	0.0077	1.6	<u>213577</u> at	SQLE	squalene epoxidase	6713
2.54E-05	0.0167	< 1e-07	1.6	<u>201926</u> s_at	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	1604
7.46E-03	0.141	0.0065	1.6	<u>213397</u> x_at	RNAS E4		
2.15E-03	0.0786	0.0025	1.6	<u>219468</u> s_at	CUEDC1	CUE domain containing 1	404093
3.26E-03	0.094	0.0034	1.6	<u>36711</u> at	MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	23764
3.75E-03	0.101	0.0039	1.6	<u>205709</u> s_at	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 1	1040
1.72E-	0.21	0.016	1.6	<u>220161</u> s_at	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	SOWA HC	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	EMPI	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	UBR1-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	SERP1NB3	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	OSBP10	oxysterol binding protein-like 10	114884
2.98E-02	0.273	0.0313	1.5	209488_s_at	RBPM5	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	SERPIN A5	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	0.0077	0.5	216560_x_at	IGLC1	immunoglobulin lambda constant 1 (Mcg marker)	3537
2.74E-03	0.088	0.0025	0.5	204439_at	IFI44L	interferon-induced protein 44-like	10964
3.00E-07	0.00223	< 1e-07	0.5	211649_x_at			
3.16E-04	0.0384	0.0002	0.5	AFFX-HUMIS GF3A/M 97935_MA_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
3.65E-04	0.0414	0.0005	0.5	216541_x_at			
1.85E-03	0.075	0.0022	0.5	217227_x_at	IGLV1-44	immunoglobulin lambda variable 1-44	28823
4.80E-03	0.115	0.0067	0.5	216984_x_at			
1.41E-02	0.191	0.0147	0.5	210029_at	IDO1	indoleamine 2,3-dioxygenase 1	3620
4.18E-04	0.0435	0.0003	0.5	211881_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
4.54E-04	0.0436	0.0008	0.5	205831_at	CD2	CD2 molecule	914
2.84E-04	0.0358	0.0003	0.5	206666_at	GZMK	granzyme K (granzyme 3; tryptase II)	3003
2.66E-04	0.0353	0.0003	0.5	211908_x_at	IGK@	immunoglobulin kappa locus	50802
1.30E-02	0.184	0.0148	0.5	215176_x_at	IGKC	immunoglobulin kappa constant	3514
6.25E-03	0.129	0.005	0.5	206134_at	ADAM DEC1	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	0.0098	0.5	217378_x_at			
1.68E-04	0.0299	0.0004	0.5	211868_x_at			
1.31E-02	0.184	0.0142	0.5	210163_at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
1.88E-03	0.0755	0.0025	0.5	211798_x_at	IGLJ3	immunoglobulin lambda joining 3	28831
2.66E-04	0.0353	0.0002	0.5	211641_x_at			
4.18E-03	0.107	0.0034	0.5	204533_at	CXCL10	chemokine (C-X-C motif) ligand 10	3627
1.76E-03	0.0737	0.0017	0.5	214657_s_at			
3.66E-03	0.0999	0.0029	0.5	205569_at	LAMP3	lysosomal-associated membrane protein 3	27074
1.56E-02	0.2	0.0171	0.5	216401_x_at			
1.93E-05	0.0159	< 1e-07	0.5	204912_at	IL10RA	interleukin 10 receptor, alpha	3587
1.10E-04	0.0258	< 1e-07	0.5	210538_s_at	BIRC3	baculoviral IAP repeat containing 3	330
6.40E-06	0.00839	0.0001	0.5	203471_s_at	PLEK	pleckstrin	5341
2.71E-03	0.0876	0.0033	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-HUMIS GF3A/M 97935_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 I 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 factor 8	3394
4.55E-04	0.0436	0.0003	0.6	222150_s_at	PION	pigeon homolog (Drosophila)	54103
5.98E-04	0.049	0.0006	0.6	210982_s_at	HLA-DRA	major histocompatibility complex, class II, 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	IRF1	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	butyrophilin, subfamily 3, member A3	10384
8.49E-05	0.0223	0.0001	0.6	212980_at	USP34	ubiquitin specific peptidase 34	9736
1.05E-02	0.167	0.01	0.6	202902_s_at	CTSS	cathepsin S	1520
7.52E-04	0.0523	0.0004	0.6	205049_s_at	CD79A	CD79a molecule, immunoglobulin-associated alpha	973
2.90E-06	0.00587	< 1e-07	0.6	207564_x_at	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase	8473
4.23E-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	< 1e-07	0.6	207563_s_at	OGT	O-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 factor 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 histocompatibility complex, class II, DP alpha 1	3113
2.76E-03	0.0881	0.0014	0.6	204661_at	CD52	CD52 molecule	1043
6.84E-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
2.75E-	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	PRKC B	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	YME1 L1	YME1-like 1 (S. cerevisiae)	10730
3.15E-03	0.0927	0.0033	0.6	AFFX-HUMIS GF3A/M 97935_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	GUSB P11	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	YME1 L1	YME1-like 1 (S. cerevisiae)	10730

2.76E-03	0.0881	0.0033	0.6	203923_s_at	CYBB	cytochrome b-245, beta polypeptide	1536
1.91E-03	0.0755	0.0016	0.6	213703_at	LINC00342	long intergenic non-protein coding RNA 342	150759
2.96E-03	0.09	0.0021	0.6	209083_at	CORO1A	coronin, actin binding protein, 1A	11151
5.67E-05	0.02	0.0002	0.6	203932_at	HLA-DMB	major histocompatibility complex, class II, DM beta	3109
5.46E-03	0.121	0.0047	0.6	201718_s_at	EPB41L2	erythrocyte membrane protein band 4.1-like 2	2037
3.11E-02	0.277	0.0332	0.6	210164_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	211742_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	LAPT M5	lysosomal protein transmembrane 5	7805
1.80E-06	0.00573	< 1e-07	0.6	212036_s_at	PNN	pinin, desmosome associated protein	5411
8.48E-05	0.0223	< 1e-07	0.6	204674_at	LRMP	lymphoid-restricted membrane protein	4033
1.16E-03	0.0608	0.0011	0.6	213142_x_at	PION	pigeon homolog (Drosophila)	54103
5.74E-05	0.02	< 1e-07	0.6	205270_s_at	LCP2	lymphocyte cytosolic 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	IGLL3 P	immunoglobulin lambda-like polypeptide 3, pseudogene	91353
1.00E-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, galactoside-binding, soluble, 9	3965
2.42E-03	0.083	0.002	0.6	217418_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
5.77E-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
6.21E-04	0.0493	0.0009	0.6	221427_s_at	CCNL2	cyclin 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).

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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_s_at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
5.00E-07	0.0000338	< 1e-07	2.8	203108_s_at	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
1.28E-04	0.00209	0.0001	2.7	204351_s_at	S100P	S100 calcium binding protein P	6286
2.00E-07	0.0000168	< 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	0.0000338	< 1e-07	2.2	210519_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
4.88E-04	0.000588	0.0005	2.1	203021_s_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_s_at	CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	55450
5.00E-07	0.0000338	< 1e-07	2.1	204044_s_at	QPRT	quinolinate phosphoribosyltransferase	23475
2.00E-07	0.0000168	< 1e-07	2.1	201468_s_at	NQO1	NAD(P)H dehydrogenase, quinone 1	1728
3.00E-07	0.0000224	< 1e-07	2.0	205968_s_at	KCNS3	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	3790
< 1e-07	< 1e-07	< 1e-07	2.0	201286_s_at	SDC1	syndecan 1	6382
3.60E-06	0.000144	< 1e-07	2.0	203803_s_at	PCYOX1	prenylcysteine oxidase 1	51449
1.00E-05	0.000317	< 1e-07	2.0	200862_s_at	DHCR24	24-dehydrocholesterol reductase	1718
8.43E-07	0.048	0.009	2.0	204268_s_at	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	0.000 0677	< 1e-07	1.9	203058_s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
3.20E-05	0.000 761	0.000 1	1.9	203060_s_at	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	9060
3.84E-05	0.000 87	< 1e-07	1.9	210652_s_at	TTC39A	tetratricopeptide repeat domain 39A	22996
6.51E-04	0.007 27	0.000 6	1.9	213693_s_at	MUC1	mucin 1, cell surface associated	4582
1.56E-04	0.002 43	0.000 2	1.9	212444_at	GPRC5A	G protein-coupled receptor, family C, group 5, member A	9052
2.00E-07	0.000 0168	< 1e-07	1.9	205709_s_at	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 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	0.000 0599	< 1e-07	1.8	218273_s_at	PDP1	pyruvate dehydrogenase phosphatase catalytic subunit 1	54704
9.00E-07	0.000 0513	< 1e-07	1.8	213577_at	SQLE	squalene epoxidase	6713
2.60E-06	0.000 114	< 1e-07	1.8	36711_at	MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	23764
3.60E-03	0.025 7	0.002 5	1.8	207847_s_at	MUC1	mucin 1, cell surface associated	4582
6.90E-06	0.000 234	< 1e-07	1.8	201596_x_at	KRT18	keratin 18	3875
3.11E-04	0.004 16	0.000 5	1.8	201951_at	ALCAM	activated leukocyte cell adhesion molecule	214
8.00E-07	0.000 0477	< 1e-07	1.8	222258_s_at	SH3BP4	SH3-domain binding protein 4	23677
1.36E-02	0.067 6	0.012 7	1.8	203453_at	SCNN1A	sodium channel, non-voltage-gated 1 alpha subunit	6337
3.00E-07	0.000 0224	< 1e-07	1.8	219496_at	SOWAH C	sosondowah ankyrin repeat domain family member C	65124
8.54E-05	0.001 57	0.000 1	1.8	218959_at	HOXC10	homeobox C10	3226
1.01E-05	0.000 319	< 1e-07	1.8	203407_at	PPL	periplakin	5493
5.20E-05	0.001 1	0.000 1	1.8	219127_at	PRR15L	proline rich 15-like	79170
2.00E-07	0.000 0168	< 1e-07	1.8	221042_s_at	CLMN	calmin (calponin-like, transmembrane)	79789
1.84E-02	0.083 1	0.018 1	1.8	214079_at	DHRS2	dehydrogenase/reductase (SDR family) member 2	10202
1.00E-06	0.000 0561	< 1e-07	1.8	209260_at	SFN	stratifin	2810
1.80E-02	0.081 8	0.018 3	1.8	218211_s_at	MLPH	melanophilin	79083
1.57E-03	0.014 1	0.002 1	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-acetylglactosaminyltransferase 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	219468_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	202562_s_at	C14orf1	chromosome 14 open reading frame 1	11161
3.30E-06	0.000135	< 1e-07	1.6	203946_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	< 1e-07	1.6	203042_at	LAMP2	lysosomal-associated membrane protein 2	3920
9.00E-07	0.0000513	< 1e-07	1.6	219377_at	GAREM	GRB2 associated, regulator of MAPK1	64762
9.13E-04	0.00926	0.0009	1.6	204818_at	HSD17B2	hydroxysteroid (17-beta) dehydrogenase 2	3294
< 1e-07	< 1e-07	< 1e-07	1.6	204175_at	ZNF593	zinc finger protein 593	51042
1.79E-03	0.0155	0.0027	1.6	203180_at	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	220
1.27E-04	0.00209	0.0002	1.6	213506_at	F2RL1	coagulation factor II (thrombin) receptor-like 1	2150
3.05E-05	0.000737	< 1e-07	1.6	222158_s_at	DESI2	desumoylating isopeptidase 2	51029
1.09E-04	0.00188	< 1e-07	1.6	221589_s_at	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	4329
4.56E-04	0.00555	0.0008	1.5	220230_s_at	CYB5R2	cytochrome b5 reductase 2	51700
2.20E-06	0.000102	< 1e-07	1.5	221526_s_at	PARD3	par-3 partitioning defective 3 homolog (C. elegans)	56288
3.98E-04	0.00502	0.0006	1.5	206326_at	GRP	gastrin-releasing peptide	2922
1.17E-04	0.00199	0.0001	1.5	208710_s_at	AP3D1	adaptor-related protein complex 3, delta 1 subunit	8943
7.70E-04	0.00819	0.0005	1.5	220161_s_at	EPB41L4B	erythrocyte membrane protein band 4.1 like 4B	54566
3.03E-02	0.116	0.0328	1.5	209160_at	AKR1C3	aldo-keto reductase family 1, member C3	8644
8.78E-03	0.0495	0.0089	1.5	201242_s_at	ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	481
1.23E-02	0.0628	0.0124	1.5	203215_s_at	MYO6	myosin VI	4646
7.09E-03	0.0425	0.0055	1.5	205594_at	ZNF652	zinc finger protein 652	22834
3.42E-05	0.000804	< 1e-07	4.5	205916_at	S100A7	S100 calcium binding protein A7	6278
3.40E-05	0.000802	0.0002	3.0	203757_s_at	CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	4680
1.56E-03	0.0141	0.0013	2.8	AFFX-HUMRG E/M1009 8_5_at	LINC00273	long intergenic non-protein coding RNA 273	649159
1.96E-03	0.0166	0.0017	2.7	AFFX-r2-Hs18SrR NA-5_at			
1.11E-04	0.00191	< 1e-07	2.7	203535_at	S100A9	S100 calcium binding protein A9	6280
5.14E-03	0.0337	0.0048	2.6	206378_at	SCGB2A2	secretoglobin, family 2A, member 2	4250
1.75E-04	0.00265	0.0003	2.6	217528_at	CLCA2	chloride channel accessory 2	9635
5.53E-05	0.00115	< 1e-07	2.4	206166_s_at	CLCA2	chloride channel accessory 2	9635
3.78E-03	0.0266	0.0039	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	206164_at	CLCA2	chloride channel accessory 2	9635
1.15E-02	0.0598	0.0118	2.2	209173_at	AGR2	anterior gradient 2 homolog (Xenopus laevis)	10551
1.45E-03	0.0133	0.0011	2.1	214461_at	LBP	lipopolysaccharide 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	0.000171	< 1e-07	2.1	206561_s_at	AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	57016
5.91E-04	0.00679	0.0004	2.0	204942_s_at	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	222
1.76E-03	0.0153	0.0014	2.0	214774_x_at	TOX3	TOX high mobility group box family member 3	27324
2.33E-05	0.000604	< 1e-07	2.0	202712_s_at			
< 1e-07	< 1e-07	< 1e-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	TOX3	TOX high mobility group box family member 3	27324
< 1e-07	< 1e-07	< 1e-07	2.0	214073_at	CTTN	cortactin	2017
1.11E-02	0.0586	0.0091	2.0	209309_at	AZGP1	alpha-2-glycoprotein 1, zinc-binding	563
1.36E-03	0.0126	0.0014	1.9	205979_at	SCGB2A1	secretoglobin, 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	secretoglobin, family 1D, member 2	10647
3.40E-06	0.000138	< 1e-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	< 1e-07	1.8	209605_at	TST	thiosulfate sulfurtransferase (rhodanese)	7263
8.02E-05	0.00151	< 1e-07	1.8	209016_s_at	KRT7	keratin 7	3855
2.49E-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/glioblastoma derived oncogene homolog (avian)	2064
< 1e-07	< 1e-07	< 1e-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	F12	coagulation factor XII (Hageman factor)	2161
5.83E-04	0.00671	0.0007	1.8	208978_at	CRIP2	cysteine-rich protein 2	1397
5.68E-04	0.00659	0.0006	1.8	218677_at	S100A14	S100 calcium binding protein A14	57402
7.30E-06	0.000244	< 1e-07	1.8	214469_at			
1.00E-07	9.52E-06	< 1e-07	1.8	213508_at	SPTSSA	serine palmitoyltransferase, 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 acetolactate synthase)-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_at	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	C1orf106	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-07	1.7	201340_s_at	ENC1	ectodermal-neural cortex 1 (with BTB domain)	8507
2.30E-06	0.000104	< 1e-07	1.7	209714_s_at	CDKN3	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	PDZK1P1	PDZK1 interacting protein 1	10158
< 1e-07	< 1e-07	< 1e-07	1.7	204824_at	ENDOG	endonuclease 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	inhibin, beta B	3625
5.60E-06	0.000202	< 1e-07	1.7	205253_at	PBX1	pre-B-cell 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	PDLIM3	PDZ and LIM domain 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-HUMRG E/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-07	< 1e-07	< 1e-07	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	KDEL3	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 1 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	0.000 076	< 1e-07	1.6	218451_at	CDCP1	CUB domain containing protein 1	64866
1.09E-04	0.001 89	0.000 2	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	0.069 7	0.014 1	1.6	205239_at			
1.88E-03	0.016 1	0.001 7	1.6	218888_s_at	NETO2	neuropilin (NRP) and tolloid (TLL)-like 2	81831
1.69E-04	0.002 58	0.000 1	1.6	215145_s_at	CNTNA P2	contactin associated protein-like 2	26047
< 1e-07	< 1e-07	< 1e-07	1.6	220688_s_at	MRT04	mRNA turnover 4 homolog (S. cerevisiae)	51154
< 1e-07	< 1e-07	< 1e-07	1.6	202839_s_at	NDUFB 7	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	0.055 2	0.008 2	1.6	210761_s_at	GRB7	growth factor receptor-bound protein 7	2886
5.55E-04	0.006 47	0.000 6	1.6	217771_at	GOLM1	golgi membrane protein 1	51280
9.00E-07	0.000 0513	< 1e-07	1.6	218493_at	SNRNP2 5	small nuclear ribonucleoprotein 25kDa (U11/U12)	79622
< 1e-07	< 1e-07	< 1e-07	1.6	218206_x_at	SCAND 1	SCAN domain containing 1	51282
1.77E-04	0.002 66	0.000 2	1.5	203786_s_at	TPD52L 1	tumor protein D52-like 1	7164
9.00E-05	0.001 63	0.000 2	1.5	204348_s_at			
< 1e-07	< 1e-07	< 1e-07	1.5	212540_at	CDC34	cell division cycle 34	997
6.20E-05	0.001 25	< 1e-07	1.5	201702_s_at	PPP1R10	protein phosphatase 1, regulatory subunit 10	5514
3.53E-04	0.004 58	0.000 6	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	0.000 0513	< 1e-07	1.5	212807_s_at	SORT1	sortilin 1	6272
2.39E-02	0.099 4	0.021 5	1.5	213711_at	KRT81	keratin 81	3887
2.91E-05	0.000 717	< 1e-07	1.5	219929_s_at	ZFYVE2 1	zinc finger, FYVE domain containing 21	79038
1.58E-05	0.000 447	< 1e-07	1.5	214004_s_at	VGLL4	vestigial like 4 (Drosophila)	9686
1.32E-04	0.002 14	0.000 2	1.5	217188_s_at	C14orf1	chromosome 14 open reading frame 1	11161
1.66E-05	0.000 464	< 1e-07	1.5	211612_s_at	IL13RA1	interleukin 13 receptor, alpha 1	3597
9.06E-04	0.009 2	0.001	1.5	209522_s_at	CRAT	carnitine O-acetyltransferase	1384
< 1e-07	< 1e-07	< 1e-07	1.5	218188_s	TIMM13	translocase of inner	26517

07	07	07		_at		mitochondrial membrane 13 homolog (yeast)	
1.57E-04	0.00244	0.0002	1.5	212141_at	MCM4	minichromosome maintenance complex component 4	4173
8.24E-04	0.00862	0.0004	1.5	210959_s_at	SRD5A1	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo- 5 alpha-steroid delta 4- dehydrogenase alpha 1)	6715
2.12E-04	0.00308	0.0003	1.5	202890_at	MAP7	microtubule-associated protein 7	9053
5.30E-06	0.000196	< 1e-07	1.5	218049_s_at	MRPL13	mitochondrial ribosomal protein L13	28998
1.88E-03	0.0161	0.0013	1.5	217562_at	FAM5C	family with sequence similarity 5, member C	339479
1.15E-05	0.000349	< 1e-07	1.5	219390_at	FKBP14	FK506 binding protein 14, 22 kDa	55033
6.30E-06	0.00022	< 1e-07	1.5	202671_s_at	PDXK	pyridoxal (pyridoxine, 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	CLIC3	chloride intracellular channel 3	9022
< 1e-07	< 1e-07	< 1e-07	1.5	218160_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- galactosamine:polypeptide N- acetylgalactosaminyltransfe rase 3 (GalNAc-T3)	2591
1.71E-05	0.000475	< 1e-07	1.5	221734_at	PRRC1	proline-rich coiled-coil 1	133619
1.53E-03	0.0139	0.0011	1.5	218186_at	RAB25	RAB25, member RAS oncogene family	57111
1.00E-07	9.52E-06	< 1e-07	1.5	203190_at			
1.19E-03	0.0114	0.0009	1.5	204941_s_at	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	222
< 1e-07	< 1e-07	< 1e-07	1.5	209194_at	CETN2	centrin, EF-hand protein, 2	1069
2.69E-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	210613_s_at	SYNGR1	synaptogyrin 1	9145
2.69E-02	0.107	0.026	1.5	AFFX-r2-Hs28SrR-NA-3_at			
2.25E-03	0.0184	0.0014	1.5	208079_s_at	AURKA	aurora kinase A	6790
2.73E-02	0.108	0.0294	1.5	211653_x_at	AKR1C2	aldo-keto reductase family 1, member C2	1646
1.30E-05	0.000387	< 1e-07	1.5	203740_at	MPHOSPH6	M-phase phosphoprotein 6	10200
8.66E-	0.001	0.000	1.5	213843_	SLC6A8	solute carrier family 6	6535

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	203282_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	210058_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	POR	P450 (cytochrome) oxidoreductase	5447
1.91E-02	0.0851	0.0204	1.5	205306_x_at	KMO	kynurenine 3-monooxygenase (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	218280_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	0.0002	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	RHOBTB3	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	ERO1L	ERO1-like (<i>S. cerevisiae</i>)	30001
1.38E-05	0.000406	< 1e-07	1.5	201925_s_at	CD55	CD55 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	PDLIM5	PDZ and LIM domain 5	10611
8.32E-04	0.00868	0.0012	1.5	214290_s_at			
2.62E-03	0.0205	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	ADAMD EC1	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	GUSBP1 1	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	ARHGA P25	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	0.000683	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	0.0000425	< 1e-07	0.6	219812_at	PVRIG	poliovirus receptor related immunoglobulin domain containing	79037
0.0000328	0.000433	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
0.0000076	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	204882_ 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 metalloproteinase domain 28	10863
0.0000 037	0.000 146	< 1e- 07	0.6	209829_ at	FAM65B	family with sequence similarity 65, member B	9750
0.0000 158	0.000 447	< 1e- 07	0.6	219359_ at	ATHL1	ATH1, acid trehalase-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	lymphocyte-specific 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 cytokinesis 10	55619
0.0000 242	0.000 623	< 1e- 07	0.6	211996_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	218805_ at			
< 1e- 07	< 1e- 07	< 1e- 07	0.6	218614_ at	KIAA15 51	KIAA1551	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	HCLS1	hematopoietic cell-specific Lyn 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	SERP1	secreted frizzled-related protein 1	6422
0.0000 737	0.001 41	0.000 2	0.6	205692_s _at	CD38	CD38 molecule	952
0.0011 094	0.010 8	0.000 8	0.6	209504_s _at	PLEKH 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- 07	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) 4D	10507
0.0000 019	0.000 0909	< 1e- 07	0.6	209723_ at	SERPIN B9	serpin peptidase inhibitor, clade B (ovalbumin),	5272

						member 9	
0.0001 686	0.002 58	< 1e- 07	0.6	217418_ x_at	MS4A1	membrane-spanning 4- domains, subfamily A, member 1	931
0.0000 253	0.000 646	0.000 2	0.6	220954_ _at	PILRB	paired immunoglobulin-like type 2 receptor beta	29990
0.0000 013	0.000 0677	< 1e- 07	0.6	205758_ at	CD8A	CD8a molecule	925
0.0001 079	0.001 87	0.000 2	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
0.0000 232	0.000 603	0.000 1	0.6	213915_ at	NKG7	natural killer cell group 7 sequence	4818
0.0000 023	0.000 104	< 1e- 07	0.6	210116_ at	SH2D1A	SH2 domain containing 1A	4068
< 1e- 07	< 1e- 07	< 1e- 07	0.6	215193_ x_at			
0.0001 04	0.001 82	< 1e- 07	0.6	209083_ at	CORO1 A	coronin, actin binding protein, 1A	11151
0.0224 506	0.094 6	0.020 1	0.6	209842_ at	SOX10	SRY (sex determining region Y)-box 10	6663
0.0004 459	0.005 46	0.000 6	0.6	205798_ at	IL7R	interleukin 7 receptor	3575
0.0039 118	0.027 4	0.003 2	0.6	208791_ at	CLU	clusterin	1191
0.0013 661	0.012 6	0.001 3	0.6	213674_ x_at			
0.0000 003	0.000 0224	< 1e- 07	0.6	202803_ _at	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	3689
0.0000 048	0.000 18	< 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
0.0000 038	0.000 149	< 1e- 07	0.6	203382_ _at	APOE	apolipoprotein E	348
0.0000 005	0.000 0338	< 1e- 07	0.6	211991_ _at	HLA- DPA1	major histocompatibility complex, class II, DP alpha 1	3113
0.0000 101	0.000 319	< 1e- 07	0.6	221768_ at			
< 1e- 07	< 1e- 07	< 1e- 07	0.6	220046_ _at	CCNL1	cyclin L1	57018
0.0000 005	0.000 0338	< 1e- 07	0.6	208894_ at	HLA- DRA	major histocompatibility complex, class II, DR alpha	3122
0.0000 622	0.001 25	< 1e- 07	0.6	220330_ _at	SAMSN 1	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
0.0000 001	9.52E -06	< 1e- 07	0.6	212307_ _at	OGT	O-linked N- acetylglucosamine (GlcNAc) transferase	8473

0.0000 007	0.000 0425	< 1e- 07	0.6	202663_ at	WIPF1	WAS/WASL 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 membrane protein 1 (synaptobrevin 1)	6843
< 1e- 07	< 1e- 07	< 1e- 07	0.6	204613_ at	PLCG2	phospholipase C, gamma 2 (phosphatidylinositol- specific)	5336
0.0000 003	0.000 0224	< 1e- 07	0.6	210982_s _at	HLA- DRA	major histocompatibility complex, class II, DR alpha	3122
0.0001 138	0.001 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 _at	FGFR2	fibroblast growth factor receptor 2	2263
< 1e- 07	< 1e- 07	< 1e- 07	0.6	209734_ at	NCKAP 1L	NCK-associated protein 1- like	3071
0.0000 001	9.52E -06	< 1e- 07	0.6	207777_s _at	SP140	SP140 nuclear body protein	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	ALOX5	arachidonate 5- lipoxygenase	240
0.0000 204	0.000 548	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	0.001 33	< 1e- 07	0.6	211919_s _at	CXCR4	chemokine (C-X-C motif) receptor 4	7852
0.0000 778	0.001 47	< 1e- 07	0.6	211654_ x_at	HLA- DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0001 269	0.002 09	0.000 2	0.6	205541_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 metalloproteinase 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	BIN2	bridging integrator 2	51411
< 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	0.000 413	< 1e- 07	0.6	217143_s _at	YME1L1	YME1-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	205298_s _at	BTN2A2	butyrophilin, subfamily 2, member A2	10385
0.0000 003	0.000 0224	< 1e- 07	0.6	211005_ at	LAT	linker for activation of T cells	27040
0.0000 522	0.001 1	< 1e- 07	0.6	206133_ at	XAF1	XIAP associated factor 1	54739
0.0000	0.001	0.000	0.6	203381_s	APOE	apolipoprotein E	348

795	5	2		_at			
0.0095 93	0.052 7	0.009 6	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
0.0000 012	0.000 0634	< 1e- 07	0.6	212179_ at	PNISR	PNN-interacting serine/arginine-rich protein	25957
0.0000 006	0.000 0386	< 1e- 07	0.6	213293_s _at	TRIM22	tripartite motif containing 22	10346
0.0005 693	0.006 6	0.000 2	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
0.0120 383	0.062	0.012 6	0.6	210029_ at	IDO1	indoleamine 2,3- dioxygenase 1	3620
0.0000 011	0.000 0599	< 1e- 07	0.6	210346_s _at	CLK4	CDC-like kinase 4	57396
0.0000 422	0.000 939	< 1e- 07	0.6	206978_ at	CCR2	chemokine (C-C motif) receptor 2	729230
0.0000 505	0.001 07	< 1e- 07	0.6	221969_ at	PAX5	paired box 5	5079
0.0000 239	0.000 617	< 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
0.0008 431	0.008 76	0.000 7	0.6	208747_s _at	C1S	complement component 1, s subcomponent	716
0.0006 505	0.007 27	0.000 4	0.6	213537_ at	HLA- DPA1	major histocompatibility complex, class II, DP alpha 1	3113
0.0000 027	0.000 116	< 1e- 07	0.6	207957_s _at	PRKCB	protein kinase C, beta	5579
0.0000 007	0.000 0425	< 1e- 07	0.6	214016_s _at	SFPQ	splicing factor proline/glutamine-rich	6421
0.0000 024	0.000 107	< 1e- 07	0.6	207563_s _at	OGT	O-linked N- acetylglucosamine (GlcNAc) transferase	8473
0.0024 33	0.019 5	0.002 8	0.6	205590_ at	RASGR P1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	10125
0.0000 204	0.000 548	< 1e- 07	0.6	202531_ at	IRF1	interferon regulatory factor 1	3659
0.0008 485	0.008 79	0.000 5	0.6	203413_ at	NELL2	NEL-like 2 (chicken)	4753
< 1e- 07	< 1e- 07	< 1e- 07	0.6	221850_ x_at			
0.0105 274	0.056 3	0.009 4	0.6	212587_s _at	PTPRC	protein tyrosine phosphatase, receptor type, C	5788
0.0000 003	0.000 0224	< 1e- 07	0.6	204294_ at	AMT	aminomethyltransferase	275
0.0000 167	0.000 465	< 1e- 07	0.6	221427_s _at	CCNL2	cyclin L2	81669
0.0000 011	0.000 0599	< 1e- 07	0.6	205270_s _at	LCP2	lymphocyte cytosolic protein 2 (SH2 domain	3937

						containing leukocyte protein of 76kDa)	
0.0000 059	0.000 211	< 1e- 07	0.6	202524_s _at	SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2	9806
0.0000 159	0.000 448	< 1e- 07	0.6	202643_s _at	TNFAIP 3	tumor necrosis factor, alpha-induced protein 3	7128
0.0016 349	0.014 5	0.002	0.6	202902_s _at	CTSS	cathepsin S	1520
0.0002 622	0.003 64	0.000 2	0.6	209403_ at			
0.0000 009	0.000 0513	< 1e- 07	0.6	203761_ at	SLA	Src-like-adaptor	6503
0.0000 729	0.001 4	0.000 1	0.6	216614_ at			
0.0003 988	0.005 02	0.000 6	0.6	205671_s _at	HLA- DOB	major histocompatibility complex, class II, DO beta	3112
0.0000 012	0.000 0634	< 1e- 07	0.6	205213_ at	ACAP1	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1	9744
0.0000 001	9.52E -06	< 1e- 07	0.6	221501_ x_at			
0.0000 038	0.000 149	< 1e- 07	0.6	212706_ at			
0.0024 604	0.019 6	0.002 1	0.6	1405_i_a t	CCL5	chemokine (C-C motif) ligand 5	6352
0.0000 022	0.000 102	< 1e- 07	0.6	202664_ at	WIPF1	WAS/WASL interacting protein family, member 1	7456
0.0001 581	0.002 45	0.000 5	0.6	221286_s _at	MZB1	marginal zone B and B1 cell-specific protein	51237
0.0012 371	0.011 7	0.000 9	0.6	209763_ at	CHRD1 1	chordin-like 1	91851
0.0001 288	0.002 1	< 1e- 07	0.6	221973_ at			
0.0006 328	0.007 12	0.001	0.6	209823_ x_at	HLA- DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0000 026	0.000 114	< 1e- 07	0.6	206118_ at	STAT4	signal transducer and activator of transcription 4	6775
0.0016 038	0.014 3	0.001 7	0.6	212998_ x_at	HLA- DQB1	major histocompatibility complex, class II, DQ beta 1	3119
0.0000 888	0.001 62	0.000 3	0.6	214617_ at	PRF1	perforin 1 (pore forming protein)	5551
0.0250 316	0.102	0.024	0.6	209687_ at	CXCL12	chemokine (C-X-C motif) ligand 12	6387
0.0000 106	0.000 331	< 1e- 07	0.6	221899_ at	N4BP2L 2	NEDD4 binding protein 2-like 2	10443
0.0000 053	0.000 196	< 1e- 07	0.6	202644_s _at	TNFAIP 3	tumor necrosis factor, alpha-induced protein 3	7128
0.0000 15	0.000 43	< 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
0.0002 911	0.003 94	0.000 2	0.6	203922_s _at	CYBB	cytochrome b-245, beta polypeptide	1536
0.0000 396	0.000 891	0.000 1	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		HUMIS GF3A/M 97935_M A_at		activator of transcription 1, 91kDa	
0.0090 965	0.050 8	0.010 3	0.6	219497_s _at	BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	53335
0.0003 227	0.004 28	0.000 1	0.6	210279_ at	GPR18	G protein-coupled receptor 18	2841
0.0059 355	0.037 5	0.006 9	0.6	217430_ x_at	COL1A1	collagen, type I, alpha 1	1277
0.0000 003	0.000 0224	< 1e- 07	0.6	204538_ x_at	NPIP	nuclear pore complex interacting protein	9284
0.0000 035	0.000 141	< 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
0.0000 151	0.000 431	< 1e- 07	0.6	207651_ at	GPR171	G protein-coupled receptor 171	29909
0.0000 002	0.000 0168	< 1e- 07	0.6	214870_ x_at			
0.0001 932	0.002 86	0.000 1	0.6	209201_ x_at	CXCR4	chemokine (C-X-C motif) receptor 4	7852
0.0000 007	0.000 0425	< 1e- 07	0.6	202813_ at	TARBP1	TAR (HIV-1) RNA binding protein 1	6894
0.0000 13	0.000 387	< 1e- 07	0.6	206150_ at	CD27	CD27 molecule	939
0.0026 19	0.020 5	0.002 4	0.6	215806_ x_at			
0.0298 737	0.115	0.028 9	0.6	212730_ at	SYNM	synemin, intermediate filament protein	23336
0.0000 021	0.000 0985	< 1e- 07	0.7	213106_ at	ATP8A1	ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	10396
0.0005 067	0.006 04	0.000 4	0.7	214059_ at	IFI44	interferon-induced protein 44	10561
0.0000 057	0.000 206	< 1e- 07	0.7	219243_ at	GIMAP4	GTPase, IMAP family member 4	55303
0.0000 056	0.000 202	< 1e- 07	0.7	212577_ at	SMCHD 1	structural maintenance of chromosomes flexible hinge domain containing 1	23347
0.0000 049	0.000 184	< 1e- 07	0.7	219471_ at	KIAA02 26L	KIAA0226-like	80183
0.0126 445	0.064 1	0.012	0.7	201348_ at	GPX3	glutathione peroxidase 3 (plasma)	2878
0.0000 023	0.000 104	< 1e- 07	0.7	204236_ at	FLI1	Friend leukemia virus integration 1	2313
0.0284 638	0.111	0.030 7	0.7	210163_ at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
0.0001 443	0.002 28	< 1e- 07	0.7	204774_ at	EVI2A	ecotropic viral integration site 2A	2123
0.0065 216	0.04	0.006 3	0.7	221185_s _at	IQCG	IQ motif containing G	84223
0.0141 111	0.069 4	0.015 9	0.7	201069_ at	MMP2	matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	4313

< 1e-07	< 1e-07	< 1e-07	0.7	212454_x_at	HNRPD L	heterogeneous nuclear ribonucleoprotein D-like	9987
0.0194654	0.0862	0.0191	0.7	32128_at	CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	6362
0.0029865	0.0225	0.003	0.7	222162_s_at	ADAMT S1	ADAM metalloproteinase with thrombospondin type 1 motif, 1	9510
0.0478513	0.158	0.0481	0.7	211122_s_at	CXCL11	chemokine (C-X-C motif) ligand 11	6373
0.0006993	0.00765	0.0007	0.7	201151_s_at	MBNL1	muscleblind-like splicing regulator 1	4154
< 1e-07	< 1e-07	< 1e-07	0.7	209827_s_at	IL16	interleukin 16	3603
0.0017313	0.0152	0.0014	0.7	204205_at	APOBE C3G	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	60489
0.000825	0.00863	0.0008	0.7	202988_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	214132_at	ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 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-acetylglucosamine (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) acetyltransferase 2B	8850
0.0043937	0.0299	0.0049	0.7	AFFX-HUMIS GF3A/M 97935_M B_at	STAT1	signal transducer and activator of transcription 1, 91kDa	6772
0.0002641	0.00366	0.0001	0.7	217478_s_at	HLA-DMA	major histocompatibility 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	203508_at	TNFRSF 1B	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
0.0001349	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

0.0001 573	0.002 44	0.000 3	0.7	216834_ at	RGS1	regulator of G-protein signaling 1	5996
0.0000 022	0.000 102	< 1e- 07	0.7	206296_ x_at	MAP4K 1	mitogen-activated protein kinase kinase kinase 1	11184
0.0000 011	0.000 0599	< 1e- 07	0.7	64064_ at			
0.0000 005	0.000 0338	< 1e- 07	0.7	207734_ at	LAX1	lymphocyte transmembrane adaptor 1	54900
0.0028 821	0.021 9	0.002 7	0.7	222043_ at	CLU	clusterin	1191
< 1e- 07	< 1e- 07	< 1e- 07	0.7	208306_ x_at			
0.0000 927	0.001 67	0.000 2	0.7	201720_ s_at	LAPTM 5	lysosomal protein transmembrane 5	7805
0.0000 022	0.000 102	< 1e- 07	0.7	204440_ at	CD83	CD83 molecule	9308
0.0000 006	0.000 0386	< 1e- 07	0.7	204562_ at	IRF4	interferon regulatory factor 4	3662
0.0000 175	0.000 484	< 1e- 07	0.7	221249_ s_at	FAM117 A	family with sequence similarity 117, member A	81558
0.0006 184	0.007	0.000 5	0.7	219689_ at	SEMA3 G	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3G	56920
0.0060 147	0.037 9	0.005 9	0.7	220232_ at	SCD5	stearoyl-CoA desaturase 5	79966
0.0000 054	0.000 198	< 1e- 07	0.7	211038_ s_at	CROCC P2	ciliary rootlet coiled-coil, rootletin pseudogene 2	84809
0.0197 569	0.087 1	0.020 7	0.7	204533_ at	CXCL10	chemokine (C-X-C motif) ligand 10	3627
0.0004 576	0.005 57	0.000 7	0.7	204150_ at	STAB1	stabilin 1	23166
0.0005 043	0.006 03	0.000 5	0.7	208018_ s_at	HCK	hemopoietic cell kinase	3055

Table 17. Class comparison of the 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	Clust 2	Clust 1	Clust 2	E R-	E R+
	matrix metalloproteinase 1 (interstitial collagenase)	NM_002421	Hs.83169	MMPI	3.0	14.6	0.7	2.6	4.6	3.7
204475_at	S100 calcium binding protein A8	NM_002964	Hs.41607	S100A8	10.45	31.38	1.0	2.3	3.0	2.2
202917_s_at	S100 calcium binding protein P	NM_005980	Hs.2962	S100P	3.8	11.9	2.5	6.3	2.8	2.4
204351_at	kynureninase	D55639	Hs.47012	KYN	0.6	1.8	0.2	0.5	2.6	2.0
217388_s_at	ceruloplasmin (ferroxidase)	NM_000096	Hs.55831	CER	0.6	4.3	0.6	0.9	2.5	1.5
204846_at	cell division cycle 20	NM_001255	Hs.52494	CDC20	5.8	14.2	0.8	4.7	2.5	5.3
202870_s_at	pleckstrin homology-like domain, family A, member 2	AF001294	Hs.15403	PHLDA2	0.6	1.6	0.5	1.1	2.5	2.0
209803_s_at	ribonucleotide reductase M2	BC001886	Hs.22639	RRM2	4.4	11.7	0.7	5.6	2.4	7.0
209773_s_at	chromosome 1 open reading frame 106	NM_018265	Hs.51899	C1orf106	1.6	3.8	0.4	0.9	2.4	2.0
219010_at	quinolinate phosphoribosyltransferase	NM_014298	Hs.51348	QPR	1.0	2.4	0.7	1.3	2.3	1.8
204044_at	aurora kinase A	NM_003158	Hs.25082	AURKA	1.4	3.4	0.3	2.0	2.3	5.3
208079_s_at	melanoma antigen family A, 3	BC000340	Hs.41781	MAG3	1.5	3.5	0.8	1.3	2.2	1.5
209942_x_at	cyclin-dependent kinase inhibitor 3	AF213033	Hs.84113	CDKN3	3.4	7.8	1.1	4.7	2.2	4.1
209714_s_at	calmodulin-like 5	NM_017422	Hs.18014	CALML5	2.6	5.9	0.8	1.4	2.2	1.7
220414_at	fatty acyl CoA reductase 2	NM_018099	Hs.72895	FAR2	1.1	2.6	0.8	1.3	2.2	1.7
220615_s_at	melanoma antigen family A, 6	U10691	Hs.44111	MAG6	1.4	3.3	0.8	1.3	2.2	1.5
214612_x_at	protein regulator of cytokinesis 1	NM_003981	Hs.36640	PRCK1	1.7	3.6	0.4	2.4	2.0	5.1
218009_s_at	cyclin B1	BE407516	Hs.23960	CCNB1	2.6	5.4	0.8	4.0	2.0	4.6
214710_s_at		NM_021		TMS	1.9	3.8	0.3	0.7	1.9	1.8

s_at		992		B15A	5	5	9	1	7	3
201890_ at	ribonucleotide reductase M2 potassium channel,	BE96623 6	Hs.22639 0	RRM 2	2.1 0	4.1 3	0.6 0	2.7 7	1.9 7	4.6 6
204678_ s_at	subfamily K, member 1	U90065	Hs.20854 4	KCN K1	2.1 5	4.2 3	1.8 5	2.8 7	1.9 6	1.5 5
202095_ s_at	baculoviral IAP repeat containing 5	NM_001 168	Hs.51452 7	BIR C5	3.2 2	6.2 7	0.8 2	4.1 0	1.9 5	4.9 9
219121_ s_at	epithelial splicing regulatory protein 1	NM_017 697	Hs.48747 1	ESR P1	4.4 7	8.6 9	2.4 7	6.7 0	1.9 4	2.7 1
203744_ at	high mobility group box 3	NM_005 342	Hs.19114	HM GB3	1.0 8	2.0 7	0.5 4	1.1 2	1.9 1	2.0 6
217755_ at	hematological and neurological expressed 1	NM_016 185	Hs.53280 3	HNI	5.3 6	10. 05	2.9 8	7.2 5	1.8 7	2.4 3
202954_ at	ubiquitin- conjugating enzyme E2C	NM_007 019	Hs.93002	UBE 2C	3.8 1	7.0 7	1.2 9	4.4 4	1.8 5	3.4 3
201291_ s_at	topoisomerase (DNA) II alpha 170kDa	AU1599 42	Hs.15634 6	TOP 2A	3.3 1	6.1 3	1.2 4	5.2 6	1.8 5	4.2 4
209875_ s_at	secreted phosphoprotein 1	M83248	Hs.313	SPP1	5.0 4	9.3 0	3.3 1	5.6 1	1.8 4	1.7 0
204059_ s_at	malic enzyme 1, NADP(+)- dependent, cytosolic	NM_002 395	Hs.21160	ME1 HIST IH2B G	1.9 4	3.5 6	0.7 7	1.3 9	1.8 4	1.8 2
210387_ at	pyridoxal (pyridoxine, vitamin B6)	BC00113 1			1.9 2	3.4 7	1.8 2	2.8 5	1.8 0	1.5 6
202671_ s_at	kinase nucleolar and	NM_003 681	Hs.28449 1	PDX K	3.0 6	5.5 2	1.6 7	3.1 5	1.8 0	1.8 9
219978_ s_at	spindle associated protein 1	NM_018 454	Hs.61509 2	NUS AP1	4.0 6	7.2 7	1.5 0	4.5 1	1.7 9	3.0 1
203207_ s_at	mitochondrial fission regulator 1	BF21432 9	Hs.58478 8	MTF R1	3.5 7	6.3 8	1.6 1	4.0 3	1.7 9	2.5 1
205943_ at	tryptophan 2,3- dioxygenase	NM_005 651	Hs.18367 1	TDO 2	1.6 2	2.8 8	0.6 5	1.0 0	1.7 9	1.5 4
218355_ at	kinesin family member 4A	NM_012 310	Hs.64832 6	KIF4 A	2.1 5	3.8 4	0.7 2	2.3 2	1.7 8	3.2 1
218039_ at	nucleolar and spindle associated protein 1	NM_016 359	Hs.61509 2	NUS AP1	2.0 2	3.5 8	0.8 6	2.6 7	1.7 7	3.1 0
202705_ at	cyclin B2	NM_004 701	Hs.19469 8	CCN B2	2.9 3	5.1 6	0.8 1	3.0 2	1.7 6	3.7 3
204641_ at	NIMA-related kinase 2	NM_002 497	Hs.15370 4	NEK 2	2.9 9	5.2 6	1.2 0	4.3 8	1.7 6	3.6 6
203755_ at	BUB1 mitotic checkpoint serine/threonine kinase B	NM_001 211	Hs.51364 5	BUB IB	1.4 8	2.6 0	0.4 1	1.6 7	1.7 5	4.0 4
202338_ at	thymidine kinase 1, soluble	NM_003 258	Hs.51512 2	TK1	1.9 2	3.3 5	1.0 4	2.2 4	1.7 5	2.1 5
203764_ at	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		AP5	7	3	1	7	3	1
203554_ x_at	pituitary tumor- transforming 1 enhancer of zeste	NM_004 219	Hs.35096 6	PTT G1	3.6 5	6.3 0	1.0 3	4.1 2	1.7 3	3.9 9
203358_ s_at	homolog 2 (Drosophila) thyroid hormone	NM_004 456	Hs.44408 2	EZH 2	1.0 5	1.7 9	0.3 4	0.8 8	1.7 1	2.6 2
204033_ at	receptor interactor 13 centromere	NM_004 237	Hs.43618 7	TRIP 13	3.3 6	5.7 4	0.7 4	2.9 5	1.7 1	4.0 1
207828_ s_at	protein F, 350/400kDa antigen identified	NM_005 196	Hs.49774 1	CEN PF	2.9 2	4.9 5	0.8 9	3.0 1	1.7 0	3.3 9
212022_ s_at	by monoclonal antibody Ki-67	BF00180 6	Hs.68982 3	MKI 67	2.5 0	4.2 3	1.0 2	2.0 8	1.6 9	2.0 3
215779_ s_at		BE27147 0		HIST H2B G	2.7 6	4.6 6	2.4 8	4.0 1	1.6 9	1.6 2
218883_ s_at	MLF1 interacting protein CDC28 protein	NM_024 629	Hs.57503 2	MLF 1IP	2.4 4	4.1 2	1.3 4	3.8 3	1.6 9	2.8 5
204170_ s_at	kinase regulatory subunit 2	NM_001 827	Hs.83758	CKS 2	2.4 8	4.1 8	1.0 7	3.1 2	1.6 9	2.9 3
201037_ at	phosphofructokin ase, platelet solute carrier family 7 (amino acid transporter light chain, L system), member 5	NM_002 627	Hs.26010	PFK P	1.5 6	2.6 3	0.5 7	0.8 8	1.6 9	1.5 4
201195_ s_at		AB01800 9	Hs.51379 7	SLC7 A5	2.1 2	3.5 1	0.3 4	1.1 5	1.6 6	3.3 5
205034_ at	cyclin E2	NM_004 702	Hs.52169 3	CCN E2	1.6 7	2.7 5	0.7 3	2.2 2	1.6 5	3.0 3
210559_ s_at	cyclin-dependent kinase 1 YKT6 v-SNARE	D88357 5	Hs.73243 5	CDK 1	6.8 8	11. 35	2.0 5	8.6 3	1.6 5	4.2 1
217785_ s_at	homolog (S. cerevisiae)	NM_006 555	Hs.52079 4	YKT 6	2.3 7	3.9 0	1.7 6	2.8 2	1.6 4	1.6 0
200658_ s_at	prohibitin inositol(myo)- 1(or 4)- monophosphatase	AL56001 7	Hs.51430 3	PHB	1.5 9	2.5 7	1.0 9	2.2 6	1.6 2	2.0 7
203126_ at		NM_014 214	Hs.74331 1	IMP A2	1.8 4	2.9 8	0.5 1	1.1 2	1.6 2	2.1 9
206102_ at	GINS complex subunit 1 (Psf1 homolog) G-protein	NM_021 067	Hs.65846 4	GINS 1	2.1 2	3.4 4	0.7 8	2.5 2	1.6 2	3.2 5
221922_ at	signaling modulator 2 coronin, actin	AW1955 81	Hs.58490 1	GPS M2	1.0 4	1.6 7	0.5 3	0.9 2	1.6 0	1.7 6
221676_ s_at	binding protein, IC asp (abnormal spindle) homolog, microcephaly associated	BC00234 2	Hs.33038 4	COR OIC	1.5 7	2.5 1	0.7 9	1.4 0	1.5 9	1.7 7
219918_ s_at		NM_018 123	Hs.12102 8	ASP M	5.7 6	9.1 6	1.3 3	5.5 6	1.5 9	4.1 8

	(Drosophila)										
	epithelial cell										
	transforming										
219787_	sequence 2	NM_018	Hs.51829	ECT	1.0	1.6	0.5	1.2	1.5	2.2	
s_at	oncogene	098	9	2	1	0	4	0	9	4	
218260_	DET1 and DDB1	NM_024	Hs.46615	DDA	5.7	9.2	4.0	7.6	1.5	1.8	
at	associated 1	050	4	1	9	0	4	6	9	9	
	matrix										
	metallopeptidase										
204580_	12 (macrophage	NM_002		MM	3.1	4.9	0.5	0.8	1.5	1.5	
at	elastase)	426	Hs.1695	PI2	4	6	9	9	8	1	
203967_	cell division cycle		Hs.40595	CDC	1.6	2.5	0.9	1.7	1.5	1.8	
at	6	U77949	8	6	4	9	9	8	8	0	
	contactin			CNT							
215145_	associated	AC00537	Hs.65568	NAP	1.1	1.8	1.4	2.3	1.5	1.6	
s_at	protein-like 2	8	4	2	7	5	1	3	8	6	
	ZW10 interactor,										
204026_	kinetochore	NM_007	Hs.59136	ZWI	1.2	1.8	0.6	1.6	1.5	2.7	
s_at	protein	057	3	NT	0	6	1	8	5	8	
	cornichon										
218728_	homolog 4	NM_014	Hs.44589	CNI	1.3	2.0	0.8	1.6	1.5	1.9	
s_at	(Drosophila)	184	0	H4	0	3	7	7	5	3	
203968_	cell division cycle	NM_001	Hs.40595	CDC	1.6	2.4	0.9	1.6	1.5	1.8	
s_at	6	254	8	6	0	7	1	8	5	4	
	BUB1 mitotic										
	checkpoint										
209642_	serine/threonine	AF04329	Hs.46964	BUB	2.8	4.3	0.8	1.9	1.5	2.3	
at	kinase	4	9	1	5	9	4	6	4	4	
204092_		NM_003	Hs.25082	AUR	1.4	2.2	0.6	1.5	1.5	2.2	
s_at	aurora kinase A	600	2	KA	3	0	8	6	3	9	
215223_				SOD	1.7	2.6	0.4	0.7	1.5	1.6	
s_at		W46388		2	6	9	2	0	3	6	
	topoisomerase										
201292_	(DNA) II alpha	AL56183	Hs.15634	TOP	5.1	7.8	2.0	7.4	1.5	3.6	
at	170kDa	4	6	2A	2	3	4	8	3	6	
	guanine										
214431_	monophosphate	NM_003	Hs.59131	GMP	0.9	1.5	0.5	0.9	1.5	1.7	
at	synthetase	875	4	S	9	1	3	1	2	2	
203214_	cyclin-dependent	NM_001	Hs.73243	CDK	5.9	9.0	2.0	6.9	1.5	3.4	
x_at	kinase 1	786	5	1	4	0	3	2	2	1	
	denticleless E3										
	ubiquitin protein										
218585_	ligase homolog	NM_016	Hs.65647		2.6	3.9	1.3	3.8	1.5	2.9	
s_at	(Drosophila)	448	3	DTL	2	5	2	2	1	0	
	low density										
	lipoprotein										
	receptor-related										
	protein 8,										
208433_	apolipoprotein e	NM_017	Hs.28038	LRP	1.7	2.6	0.7	1.1	1.5	1.5	
s_at	receptor	522	7	8	8	8	6	6	1	3	
	NDC80										
	kinetochore										
204162_	complex	NM_006	Hs.41440	NDC	2.4	3.6	0.8	1.9	1.5	2.3	
at	component	101	7	80	3	6	1	2	0	8	
	S100 calcium										
205916_	binding protein	NM_002	Hs.11240	S100	2.3	13.	1.6	2.2	5.6	1.3	
at	A7	963	8	A7	4	17	7	8	4	6	
	S100 calcium										
203535_	binding protein	NM_002	Hs.11240	S100	6.1	19.	1.5	2.2	3.1	1.4	
at	A9	965	5	A9	6	24	2	5	2	8	

205029_	fatty acid binding	NM_001		FAB	2.7	7.9	0.6	0.6	2.8	0.9
s_at	protein 7, brain	446	Hs.26770	P7	3	1	7	5	9	7
205030_	fatty acid binding	NM_001		FAB	0.7	1.9	0.1	0.1	2.5	0.9
at	protein 7, brain	446	Hs.26770	P7	7	4	3	2	1	4
	SRY (sex									
204913_	determining	AI36087	Hs.43263	SOX	1.2	2.9	0.5	0.7	2.4	1.3
s_at	region Y)-box 11	5	8	H	2	5	3	1	3	4
				TME						
219410_	transmembrane	NM_018	Hs.65895	M45	0.8	2.1	0.6	0.6	2.4	1.1
at	protein 45A	004	6	A	7	0	0	6	2	0
	SRY (sex									
204914_	determining	AW1572	Hs.43263	SOX	2.1	5.0	0.6	0.9	2.3	1.4
s_at	region Y)-box 11	02	8	H	9	8	4	5	2	7
210663_		BC00087	Hs.47012	KYN	1.2	2.8	0.6	0.9	2.1	1.4
s_at	kynureninase	9	6	U	8	0	5	5	8	5
	SRY (sex									
204915_	determining	AB02864	Hs.43263	SOX	1.4	3.0	0.7	0.9	2.1	1.2
s_at	region Y)-box 11	1	8	H	1	1	5	1	3	2
	chloride									
219529_	intracellular	NM_004		CL1	1.8	3.9	1.1	1.5	2.1	1.3
at	channel 3	669	Hs.64746	C3	7	1	3	1	0	4
214461_	lipopolysaccharid	NM_004	Hs.15407		1.2	2.6	0.8	0.9	2.0	1.1
at	e binding protein	139	8	LBP	6	2	0	0	7	3
202912_		NM_001	Hs.44104		0.8	1.7	0.4	0.4	2.0	1.2
at	adrenomedullin	124	7	ADM	4	0	0	8	2	0
	S100 calcium									
214370_	binding protein	AW2386	Hs.41607	S100	2.6	5.2	1.4	1.5	1.9	1.0
at	A8	54	3	A8	6	4	2	0	7	5
	vascular									
211527_	endothelial			VEG	2.0	3.9	1.2	1.5	1.9	1.2
x_at	growth factor A	M27281	Hs.73793	FA	1	1	4	0	4	1
	potassium									
	channel,									
204679_	subfamily K,	NM_002	Hs.20854	KCN	1.3	2.4	0.8	1.2	1.8	1.4
at	member 1	245	4	K1	2	4	8	9	5	7
	BCL2/adenovirus									
	E1B 19kDa									
201848_	interacting protein		Hs.14487	BNIP	2.1	3.8	1.5	2.3	1.8	1.4
s_at	3	U15174	3	3	4	8	7	4	1	9
202859_		NM_000			1.7	3.1	0.6	0.8	1.8	1.2
x_at	interleukin 8	584	Hs.624	IL8	5	7	8	6	1	5
211110_		AF16270			0.9	1.6	5.3	3.8	1.8	0.7
s_at	androgen receptor	4	Hs.76704	AR	2	5	3	7	0	3
208650_		BG32786	Hs.64410		2.3	4.1	1.2	1.5	1.7	1.2
s_at	CD24 molecule	3	5	CD24	8	8	9	9	5	4
	UDP-N-acetyl-									
	alpha-D-									
	galactosamine:pol									
	ypeptide N-									
	acetylgalactosami									
203397_	nyltransferase 3	BF06327	Hs.17098	GAL	0.9	1.6	0.5	0.6	1.7	1.2
s_at	(GalNAc-T3)	1	6	NT3	5	5	2	3	4	0
	chemokine (C-C									
	motif) ligand 18									
	(pulmonary and									
209924_	activation-	AB00022	Hs.14396	CCL	2.2	3.9	0.6	0.9	1.7	1.4
at	regulated)	1	1	18	8	6	9	8	4	2
	cysteine-rich									
207802_	secretory protein	NM_006	Hs.40446	CRIS	1.0	1.8	1.0	1.3	1.7	1.3
at	3	061	6	P3	8	6	1	5	2	3

32128_at	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated) dopa decarboxylase (aromatic L-amino acid decarboxylase)	Y13710	Hs.143961	CCL18	2.2 2	3.7 2	0.6 9	0.9 6	1.6 7	1.4 0
205311_at	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	NM_000790	Hs.359698	DDC	1.0 2	1.6 9	0.9 8	0.9 6	1.6 7	0.9 8
219962_at	stearoyl-CoA desaturase (delta-9-desaturase)	NM_021804	Hs.178098	ACE2	1.0 3	1.7 2	0.8 7	0.9 1	1.6 7	1.0 4
211708_s_at	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	BC005807	Hs.558396	SCD	1.6 9	2.7 6	1.3 7	2.0 2	1.6 3	1.4 7
211056_s_at	stearoyl-CoA desaturase (delta-9-desaturase)	BC006373	Hs.552	SRD5A1	1.3 0	2.1 1	0.7 3	0.8 4	1.6 2	1.1 5
211162_x_at	CD24 molecule	AF116616	Hs.558396	SCD	1.3 4	2.1 5	1.2 2	1.5 9	1.6 1	1.3 1
209772_s_at	vestigial like 1 (Drosophila)	X69397	Hs.644105	CD24	4.3 6	6.8 6	2.0 9	3.0 5	1.5 7	1.4 6
215729_s_at	gamma-aminobutyric acid (GABA) B receptor, 2	BE542323	Hs.496843	VGLL1	2.3 3	3.6 3	0.3 6	0.4 3	1.5 6	1.1 8
209990_s_at	cystathionine-beta-synthase	AF056085	Hs.198612	GABBR2	1.6 4	2.5 0	0.8 4	0.8 9	1.5 3	1.0 7
212816_s_at	protein tyrosine phosphatase, non-receptor type 12	BE613178	Hs.533013	CBS	2.1 1	3.2 1	0.8 9	1.2 5	1.5 2	1.4 1
216915_s_at	suppression of tumorigenicity 14 (colon carcinoma)	S69182	Hs.61812	PTPNI2	3.3 3	5.0 6	2.8 8	3.4 9	1.5 2	1.2 1
216905_s_at	PDZ binding kinase	U20428	Hs.504315	STI4	1.3 5	2.0 2	0.9 5	1.1 6	1.5 0	1.2 2
219148_at	MAD2 mitotic arrest deficient-like 1 (yeast)	NM_018492	Hs.104741	PBK	2.8 6	3.5 0	0.9 1	3.4 9	1.2 2	3.8 2
203362_s_at	GIN5 complex subunit 2 (Psf2 homolog)	NM_002358	Hs.591697	MAD2L1	1.9 4	2.8 0	0.6 2	2.0 4	1.4 4	3.3 0
221521_s_at	KIAA0101	BC003186	Hs.433180	GIN52	1.0 0	1.3 7	0.5 7	1.8 6	1.3 7	3.2 8
202503_s_at	cyclin-dependent kinase 1	NM_014736	Hs.81892	KIAA0101	2.7 1	4.0 5	1.3 8	4.3 4	1.4 9	3.1 3
203213_at	ubiquitin-conjugating enzyme E2S	AL524035	Hs.732435	CDK1	2.5 4	3.7 3	1.0 6	3.2 3	1.4 7	3.0 3
202779_s_at	thymidylate	NM_014501	Hs.396393	UBE2S	9.4 2	13. 46	3.8 3	11. 41	1.4 3	2.9 8
202589_s_at		NM_001	Hs.36976	TVM	2.6	3.4	0.8	2.3	1.3	2.8

at	synthetase	071	2	S	0	0	1	2	1	7
204444_	kinesin family	NM_004		KIF1	1.6	2.3	0.6	1.9	1.3	2.8
at	member 11	523	Hs.8878	I	8	0	8	5	7	6
218782_	ATPase family,	NM_014	Hs.37083	ATA	4.2	4.6	1.4	3.9	1.1	2.7
s_at	containing 2	109	4	D2	1	9	0	1	1	9
218755_	kinesin family	NM_005	Hs.71862	KIF2	2.8	4.0	0.9	2.4	1.4	2.6
at	member 20A	733	6	0A	3	9	2	3	5	6
222077_	Rac GTPase	AU1538	Hs.50546	RAC						
s_at	activating protein	48	9	GAP	1.7	2.4	0.8	2.2	1.3	2.5
	1			I	8	4	5	0	7	8
208767_	lysosomal protein	AW1496	Hs.49231	LAP						
s_at	transmembrane 4	81	4	TM4	5.0	7.3	2.0	5.3	1.4	2.5
204533_	beta	NM_001	Hs.63258	B	9	0	9	8	3	7
at	chemokine (C-X-	565	6	CXC	7.3	10.	1.8	4.6	1.3	2.5
	C motif) ligand 10			L10	4	17	4	2	9	2
213797_	radical S-adenosyl	AI33706		RSA	2.9	3.2	1.2	3.0	1.1	2.5
at	methionine	9	Hs.17518	D2	4	6	0	1	1	1
212009_	domain	AL55332	Hs.33729	STIP	5.0	7.0	2.3	5.9	1.4	2.4
s_at	containing 2	0	5	I	5	7	8	4	0	9
206364_	stress-induced-	NM_014		KIF1	2.7	3.5	0.8	2.1	1.2	2.4
at	phosphoprotein 1	875	Hs.3104	4	8	1	6	3	6	8
211762_	kinesin family	BC00597	Hs.59423	KPN	2.8	4.0	1.2	3.1	1.4	2.4
s_at	member 14	8	8	A2	1	8	6	3	6	8
	karyopherin alpha									
	2 (RAG cohort 1,									
	importin alpha 1)									
	apolipoprotein B									
	mRNA editing									
	enzyme, catalytic			APO						
206632_	polypeptide-like	NM_004	Hs.22630	BEC	2.4	3.5	0.6	1.6	1.4	2.4
s_at	3B	900	7	3B	2	5	5	2	7	8
	hyaluronan-									
	mediated motility									
207165_	receptor	NM_012	Hs.74046	HM	1.8	2.2	0.7	1.8	1.2	2.3
at	(RHAMM)	485	7	MR	1	4	9	6	4	6
211122_	chemokine (C-X-	AF00298	Hs.63259	CXC	4.1	4.9	0.9	2.2	1.1	2.3
s_at	C motif) ligand 11	5	2	L11	7	5	8	8	9	3
201663_	structural	NM_005		SMC	6.4	7.0	2.0	4.8	1.0	2.2
s_at	maintenance of	496	Hs.58992	4	4	2	9	0	9	9
	chromosomes 4									
	non-SMC									
	condensin I									
218662_	complex, subunit	NM_022	Hs.44620	NCA	2.4	3.0	1.0	2.2	1.2	2.2
s_at	G	346	1	PG	9	9	0	8	4	9
213226_		AI34635		CCN	1.7	2.4	0.6	1.5	1.3	2.2
at	cyclin A2	0	Hs.58974	A2	8	6	9	5	8	6
	minichromosome									
	maintenance									
212141_	complex	AA6046	Hs.46018	MC	3.1	4.3	1.2	2.8	1.3	2.2
at	component 4	21	4	M4	8	4	9	9	7	4
210163_	chemokine (C-X-	AF03051	Hs.63259	CXC	3.0	4.1	0.7	1.7	1.3	2.2
at	C motif) ligand 11	4	2	L11	5	5	7	3	6	3
213007_	Fanconi anemia,		Hs.51312	FAN	1.4	1.8	0.7	1.6	1.2	2.2
at	complementation	W74442	6	CI	5	4	2	0	7	3
	group I									
	serine									
214437_	hydroxymethyltra	NM_005	Hs.74117	SHM	3.4	4.6	1.4	3.2	1.3	2.2
s_at	nsferase 2	412	9	T2	4	2	9	9	4	0
	(mitochondrial)									

218049_ s_at	mitochondrial ribosomal protein L13	NM_014 078	Hs.33382 3	MRP L13	3.5 5	4.6 8	2.4 0	5.2 8	1.3 2	2.2 0
218663_ at	non-SMC condensin I complex, subunit G	NM_022 346	Hs.44620 1	NCA PG	2.6 1	3.2 1	1.0 4	2.2 7	1.2 3	2.1 9
201629_ s_at	acid phosphatase 1, soluble	BE87297 4	Hs.55829 6	ACP I	4.4 1	6.2 8	2.3 2	5.0 6	1.4 2	2.1 8
213562_ s_at	squalene epoxidase	BF97949 7	Hs.71465	SQL E	2.4 7	3.3 6	1.4 1	3.0 2	1.3 6	2.1 4
203418_ at	cyclin A2	NM_001 237	Hs.58974	CCN A2	2.9 8	4.2 5	0.9 5	2.0 3	1.4 2	2.1 4
218308_ at	transforming, acidic coiled-coil containing protein 3	NM_006 342	Hs.10401 9	TAC C3	2.4 6	2.8 4	1.1 5	2.4 5	1.1 5	2.1 3
200607_ s_at	RAD21 homolog (S. pombe)	BG28996 7	Hs.81848	RAD 21	3.8 1	3.8 7	1.9 8	4.1 6	1.0 1	2.1 0
219494_ at		NM_012 415		RAD 54B	2.1 9	2.5 2	1.0 6	2.2 1	1.1 5	2.0 9
201946_ s_at	chaperonin containing TCP1, subunit 2 (beta) defective in sister chromatid cohesion 1	AL54598 2	Hs.18977 2	CCT 2	5.5 4	5.7 1	3.2 6	6.7 8	1.0 3	2.0 8
219000_ s_at	homolog (S. cerevisiae)	NM_024 094	Hs.31516 7	DSC C1	2.0 1	2.3 7	0.8 6	1.7 7	1.1 8	2.0 7
213008_ at	Fanconi anemia, complementation group I	BG40361 5	Hs.51312 6	FAN CI	1.9 7	2.4 4	1.0 3	2.1 3	1.2 4	2.0 6
201897_ s_at	CDC28 protein kinase regulatory subunit 1B	NM_001 826	Hs.37437 8	CKS 1B	2.1 4	2.8 6	1.0 0	2.0 4	1.3 3	2.0 4
201123_ s_at	eukaryotic translation initiation factor 5A	NM_001 970	Hs.53431 4	EIF5 A	8.0 4	10. 77	3.8 1	7.5 4	1.3 4	1.9 8
209825_ s_at		BC00290 6		UCK 2	2.1 2	2.7 9	0.9 6	1.8 9	1.3 2	1.9 7
210983_ s_at	minichromosome maintenance complex component 7	AF27990 0	Hs.43872 0	MC M7	5.4 4	6.1 9	1.9 0	3.6 9	1.1 4	1.9 4
216088_ s_at	proteasome (prosome, macropain)	AL07863 3	Hs.23395 2	PSM A7	3.8 5	5.5 5	2.6 7	5.1 8	1.4 4	1.9 4
203432_ at	subunit, alpha type, 7	AW2726 11	Hs.11355	TMP O	1.7 0	2.0 9	1.0 3	1.9 8	1.2 3	1.9 3
218349_ s_at	thymopoietin zwilch	NM_017 975	Hs.21331	ZWI LCH	2.8 8	3.5 6	1.6 7	3.2 2	1.2 4	1.9 3
219402_ s_at	kinetochore protein	NM_024 295	Hs.24157 6	DER L1	1.3 1	1.9 3	0.8 0	1.5 3	1.4 7	1.9 2
202736_ s_at	derlin 1 LSM4 homolog, U6 small nuclear RNA associated	AA1125 07	Hs.51525 5	LSM 4	14. 79	17. 02	9.3 1	17. 67	1.1 5	1.9 0

	(<i>S. cerevisiae</i>)									
218549_	regulator of	NM_016	Hs.14538	RMD	1.7	2.2	1.2	2.3	1.2	1.9
s_at	microtubule	033	6	NI	5	0	4	5	5	0
213599_	dynamics 1	BE04599	Hs.66164		1.7	2.2	0.8	1.6	1.3	1.9
at	Opa interacting	3	5	OIP5	4	8	6	3	1	0
209464_	protein 5	AB01144	Hs.44265	AUR	3.1	3.7	1.0	2.0	1.1	1.8
at	aurora kinase B	6	8	KB	1	2	7	1	9	8
	mitochondrial									
218027_	ribosomal protein	NM_014		MRP	1.9	2.3	1.0	2.0	1.2	1.8
at	L15	175	Hs.18349	L15	6	8	7	1	2	8
213330_	stress-induced-	BE88658	Hs.33729	STIP	9.6	12	5.7	10	1.2	1.8
s_at	phosphoprotein 1	0	5	I	0	32	0	67	8	7
218695_	exosome	NM_019	Hs.63204	EXO	1.5	1.8	0.9	1.7	1.2	1.8
at	component 4	037	1	SC4	1	1	4	5	0	6
220085_	helicase,	NM_018	Hs.65583	HEL	1.5	1.8	0.9	1.6	1.1	1.8
at	lymphoid-specific	063	0	LS	5	2	0	5	7	4
203145_	sperm associated	NM_006	Hs.51403	SPA	1.3	1.9	0.8	1.6	1.4	1.8
at	antigen 5	461	3	G5	5	6	9	3	5	4
	eukaryotic									
	translation									
	initiation factor									
221539_	4E binding	AB04454	Hs.41164	EIF4	3.5	4.5	1.8	3.3	1.2	1.8
at	protein 1	8	1	EBP1	7	7	2	2	8	3
	preferentially									
204086_	expressed antigen	NM_006		PRA	2.7	2.6	0.9	1.8	0.9	1.8
at	in melanoma	115	Hs.30743	ME	3	9	8	0	8	2
	ER membrane									
218057_	protein complex	NM_006	Hs.17316	EMC	1.7	2.0	0.9	1.7	1.1	1.7
x_at	subunit 8	067	2	8	9	5	9	7	5	9
221677_	downstream	AF23267	Hs.43634	DON	1.9	2.8	0.9	1.6	1.4	1.7
s_at	neighbor of SON	4	1	SON	8	2	4	8	2	9
200841_	glutamyl-prolyl-	AI14267	Hs.49778	EPR	2.6	3.3	1.6	2.9	1.2	1.7
s_at	tRNA synthetase	7	8	S	4	2	5	5	6	9
221436_	cell division cycle	NM_031	Hs.52421	CDC	2.1	2.7	0.9	1.6	1.2	1.7
s_at	associated 3	299	6	A3	5	0	4	8	5	9
210691_	calcyclin binding	AF27580	Hs.50852	CAC	2.7	3.5	1.7	3.1	1.2	1.7
s_at	protein	3	4	YBP	1	1	9	9	9	9
	v-myb									
	myeloblastosis									
	viral oncogene									
201710_	homolog (avian)-	NM_002	Hs.17971	MYB	2.5	3.4	1.1	2.0	1.3	1.7
at	like 2	466	8	L2	5	6	7	9	6	9
	lymphocyte									
202145_	antigen 6	NM_002	Hs.52190	LY6	3.2	2.7	1.4	2.5	0.8	1.7
at	complex, locus E	346	3	E	4	7	5	7	5	7
211450_	mutS homolog 6		Hs.44505	MSH	6.0	5.9	3.0	5.3	0.9	1.7
s_at	(<i>E. coli</i>)	D89646	2	6	1	1	4	8	8	7
212563_	block of	BG49184	Hs.64527	BOP	2.5	2.8	1.0	1.9	1.1	1.7
at	proliferation 1	2	9	I	1	0	8	1	1	7
	procollagen-									
	lysine, 2-									
202619_	oxoglutarate 5-	AI75440	Hs.47786	PLO	1.5	2.2	0.8	1.5	1.4	1.7
s_at	dioxygenase 2	4	6	D2	8	7	8	6	3	7
	nudix (nucleoside									
	diphosphate									
202697_	linked moiety X)-	NM_007	Hs.52883	NUD	1.6	2.4	1.0	1.8	1.4	1.7
at	type motif 21	006	4	T21	9	5	5	4	5	5
217294_			Hs.51714	ENO	39	45	13	23	1.1	1.7
s_at	enolase I, (alpha)	U88968	5	I	74	04	17	05	3	5

209053_s_at	Wolf-Hirschhorn syndrome candidate 1	BE793789	Hs.113876	WHS C1	1.3	1.5	0.8	1.5	1.1	1.7
213520_at	RecQ protein-like 4	NM_004260	Hs.31442	REC QL4	1.4	1.6	0.9	1.6	1.1	1.7
217356_s_at	phosphoglycerate kinase I	S81916	Hs.78771	PGK I	12.50	17.81	6.9	12.00	1.4	1.7
201930_at	minichromosome maintenance complex component 6	NM_005915	Hs.444118	MC M6	2.0	2.5	1.0	1.7	1.2	1.7
222037_at	minichromosome maintenance complex component 4	AI859865	Hs.460184	MC M4	1.8	2.2	0.9	1.6	1.1	1.7
200853_at	H2A histone family, member Z 2'	NM_002106	Hs.119192	H2A FZ	2.0	2.7	1.4	2.4	1.3	1.7
204238_s_at	deoxynucleoside 5'-phosphate N-hydrolase I	NM_006443	Hs.109752	DNP HI	2.7	2.7	1.5	2.6	1.0	1.7
201821_s_at	translocase of inner mitochondrial membrane 17 homolog A (yeast)	BC004439	Hs.20716	TIM MI7 A	2.1	2.5	1.5	2.6	1.1	1.6
202483_s_at	RAN binding protein 1	NM_002882	Hs.24763	RAN BP1	6.5	8.1	3.4	5.7	1.2	1.6
201202_at	proliferating cell nuclear antigen	NM_002592	Hs.147433	PCN A	1.9	2.2	1.2	2.1	1.1	1.6
202397_at		NM_005796		NUT F2	2.6	3.6	1.5	2.4	1.3	1.6
203189_s_at		NM_002496		NDU PS8	6.1	8.0	6.2	10.27	1.3	1.6
208744_x_at	heat shock 105kDa/110kDa protein I	BG403660	Hs.743267	HSP HI	2.4	2.9	1.6	2.7	1.1	1.6
204203_at	CCAAT/enhancer binding protein (C/EBP), gamma	NM_001806	Hs.429666	CEB PG	2.9	4.1	1.4	2.3	1.3	1.6
203276_at	lamin B I	NM_005573	Hs.89497	LMN BI	1.7	2.1	1.1	1.8	1.2	1.6
208963_x_at		BG165833		FAD SI	1.6	2.3	1.1	1.8	1.4	1.6
215942_s_at	G-2 and S-phase expressed I proteasome (prosome, macropain) 26S subunit, ATPase, 3	BF973178	Hs.386189	GTS EI	2.3	3.4	1.0	1.7	1.4	1.6
201267_s_at		AL545523	Hs.250758	PSM C3	4.1	4.9	2.7	4.3	1.2	1.5
203715_at	tubulin folding cofactor E	NM_003193	Hs.498143	TBC E	1.7	2.1	1.5	2.4	1.2	1.5
214845_s_at	calumenin	AF257659	Hs.743262	CAL U	8.3	11.82	3.9	6.2	1.4	1.5
202533_s_at	dihydrofolate reductase	BC003584	Hs.592364	DHF R	1.5	1.7	1.0	1.6	1.1	1.5
201504_s_at		AI435302	Hs.75066	TSN	2.2	2.8	1.6	2.5	1.2	1.5

1053_at	replication factor C (activator 1) 2, 40kDa	M87338	Hs.64706 2	RFC 2	2.1 0	2.6 4	1.4 6	2.2 3	1.2 6	1.5 3
209653_at	karyopherin alpha 4 (importin alpha 3)	U93240	Hs.46786 6	KPN A4	2.5 7	3.4 8	1.2 5	1.8 9	1.3 5	1.5 1
212914_at	chromobox homolog 7	AV6483 64	Hs.35641 6	CBX 7	0.3 9	0.2 6	0.6 5	0.3 8	0.6 7	0.5 8
203485_at	reticulon 1 transcobalamin I (vitamin B12 binding protein, R binder family)	NM_021 136	Hs.36862 6	RTN 1	0.1 5	0.1 0	0.4 2	0.2 3	0.6 6	0.5 5
205513_at	SET binding protein 1	NM_001 062	Hs.2012	TCN 1	0.3 7	0.2 4	0.9 3	0.4 3	0.6 6	0.4 6
213451_x_at	FBJ murine osteosarcoma viral oncogene homolog B	BE04461 4	Hs.43545 8	TNX B1	0.8 0	0.5 3	1.1 0	0.5 9	0.6 6	0.5 4
205933_at	sortilin-related receptor, L(DLR class) A repeats containing	NM_015 559	Hs.59095 8	SETB P1	0.4 4	0.2 9	1.0 2	0.4 5	0.6 6	0.4 4
202768_at	myosin, heavy chain 11, smooth muscle	NM_006 732	Hs.36859 2	FOS B	0.1 0	0.0 7	0.2 4	0.0 8	0.6 5	0.3 4
212560_at	transmembrane protease, serine 3	AV7282 68	Hs.24915 9	SOR L1	0.3 7	0.2 4	0.9 1	0.4 9	0.6 5	0.5 3
209869_at	4-aminobutyrate aminotransferase	AF28409 5	Hs.66142 5	ADR A2A	0.4 3	0.2 8	1.3 3	0.5 4	0.6 5	0.4 1
207961_x_at	proline rich, lacrimal 1	NM_022 870	Hs.32603 5	MYH 11	0.2 9	0.1 8	0.5 2	0.2 2	0.6 5	0.4 3
220177_s_at	early growth response 1	NM_024 022	Hs.53208 2	TMP RSS3	0.8 4	0.5 4	1.4 6	0.6 4	0.6 5	0.4 4
209460_at	interleukin 6 signal transducer (gp130, oncostatin M receptor)	AF23781 3	Hs.44500 0	ABA T	0.2 1	0.1 4	1.6 4	1.0 4	0.6 5	0.6 4
208004_at	prostaglandin E receptor 3 (subtype EP3)	NM_021 225	Hs.19974 3	PRO L1	0.3 3	0.2 1	0.4 1	0.2 3	0.6 4	0.5 6
201693_s_at	malic enzyme 3, NADP(+)-dependent, mitochondrial	AV7339 50	Hs.52289 1	EGR 1	0.2 6	0.1 7	0.6 3	0.2 1	0.6 3	0.3 3
204863_s_at	chemokine (C-X-C motif) ligand 12	BE85654 6	Hs.47788 7	IL6S T	0.1 8	0.1 1	0.8 6	0.5 2	0.6 3	0.6 0
213933_at	angiotensin II receptor, type 1	AW2423 15	Hs.69997 1	PTG ER3	0.2 6	0.1 6	1.2 0	0.5 2	0.6 2	0.4 4
204663_at	myosin, heavy chain 11, smooth muscle	NM_006 680	Hs.52289 1	ME3 L12	0.3 4	0.2 1	0.6 3	0.3 6	0.6 2	0.5 8
209687_at	zinc finger and BTB domain	U19495	Hs.52289 1	CXC L12	0.6 6	0.4 1	1.5 3	0.7 7	0.6 2	0.5 1
205357_s_at		NM_000 685	Hs.47788 7	AGT R1	0.3 6	0.2 2	1.6 9	0.7 9	0.6 2	0.4 6
201497_x_at		NM_022 844	Hs.46010 9	MYH 11	0.2 6	0.1 6	0.6 0	0.2 1	0.6 1	0.3 5
212774_at		AJ22332 1	Hs.69997 1	ZBT B18	0.7 9	0.4 8	1.5 2	0.6 4	0.6 1	0.4 2

	containing 18									
	microfibrillar-									
212713_	associated protein		Hs.29604	MFA	1.0	0.6	2.2	0.8	0.6	0.3
at	4	R72286	9	P4	6	4	1	1	1	7
206115_	early growth	NM_004	Hs.53431	EGR	0.1	0.1	0.4	0.2	0.6	0.5
at	response 3	430	3	3	8	1	7	4	0	1
203697_	frizzled-related		Hs.12845	FRZ	0.5	0.3	1.0	0.4	0.6	0.4
at	protein	U91903	3	B	1	0	2	7	0	6
	WAP four-									
203892_	disulfide core	NM_006		WFD	0.8	0.4	2.1	0.9	0.6	0.4
at	domain 2	103	Hs.2719	C2	0	8	1	7	0	6
	integral									
202746_	membrane protein	AL02178		ITM2	0.7	0.4	0.9	0.4	0.6	0.4
at	2A	6	Hs.17109	A	0	2	1	4	0	8
	ATH1, acid									
219359_	trehalase-like 1	NM_025	Hs.35318	ATH	0.5	0.3	0.9	0.5	0.5	0.6
at	(yeast)	092	1	L1	7	3	7	9	8	1
212865_	collagen, type	BF44906	Hs.40966	COL	0.7	0.4	3.1	0.7	0.5	0.2
s_at	XIV, alpha 1	3	2	14A1	2	1	1	5	7	4
	insulin-like									
209541_	growth factor 1	AI97249	Hs.16056		0.6	0.3	1.9	0.6	0.5	0.3
at	(somatomedin C)	6	2	IGF1	4	6	3	1	7	2
205913_		NM_002	Hs.10325	PLIN	1.0	0.6	2.1	0.9	0.5	0.4
at	perilipin 1	666	3	1	9	2	1	6	6	5
	inter-alpha-									
	trypsin inhibitor									
219064_	heavy chain	NM_030	Hs.49858	ITIH	0.4	0.2	0.4	0.2	0.5	0.5
at	family, member 5	569	6	5	0	3	7	6	6	6
	Duffy blood									
208335_	group, chemokine	NM_002	Hs.15338	DAR	0.5	0.3	1.1	0.4	0.5	0.3
s_at	receptor	036	1	C	7	2	9	1	6	5
	chemokine (C-									
205898_	X3-C motif)			CX3	0.4	0.2	1.4	0.3	0.5	0.2
at	receptor 1	U20350	Hs.78913	CR1	2	4	0	9	6	8
209763_		AL04917	Hs.49658	CHR	0.7	0.4	1.1	0.4	0.5	0.4
at	chordin-like 1	6	7	DL1	6	2	0	9	6	5
	sema domain,									
	immunoglobulin									
	domain (Ig), short									
	basic domain,									
219689_	secreted,	NM_020		SEM	0.3	0.2	0.8	0.4	0.5	0.4
at	(semaphorin) 3G	163	Hs.59729	A3G	9	2	9	1	6	6
	insulin-like									
209540_	growth factor 1	AU1449	Hs.16056		0.6	0.3	1.4	0.4	0.5	0.3
at	(somatomedin C)	12	2	IGF1	1	3	7	7	5	2
43427_a	acetyl-CoA	AI97089	Hs.23489	ACA	0.1	0.0	0.3	0.1	0.5	0.5
t	carboxylase beta	8	8	CB	2	6	0	5	4	0
	ATP-binding									
	cassette, sub-									
204719_	family A (ABC1),	NM_007		ABC	0.4	0.2	1.0	0.3	0.5	0.3
at	member 8	168	Hs.58351	A8	3	3	3	9	4	8
207414_		NM_002		PCS	0.6	0.3	2.1	1.2	0.5	0.5
s_at		570		K6	2	3	3	1	3	7
217838_		NM_016	Hs.12586		0.8	0.4	3.6	2.0	0.5	0.5
s_at	Enah/Vasp-like	337	7	EVL	9	7	1	0	3	5
	secretoglobin,									
205979_	family 2A,	NM_002		SCG	0.5	0.3	1.7	1.0	0.5	0.6
at	member 1	407	Hs.97644	B2A1	7	0	6	7	3	1
203980_	fatty acid binding	NM_001	Hs.39156	FAB	1.0	0.5	2.9	1.2	0.5	0.4
at	protein 4,	442	1	P4	8	6	3	7	2	3

	adipocyte										
49452_a	acetyl-CoA	AI05763	Hs.23489	ACA	0.1	0.0	0.2	0.1	0.5	0.4	
t	carboxylase beta	7	8	CB	0	5	6	2	2	8	
	secretoglobulin,										
206378_	family 2A,	NM_002		SCG	0.1	0.0	2.3	0.7	0.5	0.3	
at	member 2	411	Hs.46452	B2A2	5	7	7	3	1	1	
	cysteine sulfinic										
221139_	acid	NM_015	Hs.27981	CSA	0.4	0.2	0.9	0.5	0.5	0.5	
s_at	decarboxylase	989	5	D	2	1	3	4	1	8	
	signal peptide,										
219197_	CUB domain,	AI42424	Hs.52346	SCU	0.2	0.1	7.9	2.4	0.5	0.3	
s_at	EGF-like 2	3	8	BE2	7	3	6	4	0	1	
204041_	monoamine	NM_000	Hs.65447	MAO	0.3	0.1	0.5	0.3	0.4	0.6	
at	oxidase B	898	3	B	3	6	5	4	8	3	
	v-erb-a										
	erythroblastic										
	leukemia viral										
214053_	oncogene	AW7721	Hs.39072	ERB	0.1	0.0	0.9	0.3	0.4	0.3	
at	homolog 4 (avian)	92	9	B4	0	5	5	7	8	9	
205440_	neuropeptide Y	NM_000	Hs.51905	NPY	0.5	0.2	2.1	1.2	0.4	0.5	
s_at	receptor Y1	909	7	1R	3	4	0	3	6	8	
218002_	chemokine (C-X-	NM_004	Hs.48344	CXC	0.5	0.2	2.8	1.1	0.4	0.4	
s_at	C motif) ligand 14	887	4	L14	2	3	4	7	5	1	
213156_		BG25152		MIR	0.2	0.1	0.5	0.1	0.4	0.3	
at		1		N568	4	1	1	8	4	5	
	transforming										
204731_	growth factor,	NM_003	Hs.48239	TGF	0.2	0.0	0.3	0.1	0.4	0.4	
at	beta receptor III	243	0	BR3	2	9	7	5	0	0	
	secretoglobulin,										
206799_	family ID,	NM_006	Hs.20409	SCG	0.1	0.0	1.6	0.5	0.3	0.3	
at	member 2	551	6	B1D2	6	6	2	1	7	1	
	neurotrophic										
221796_	tyrosine kinase,	AA7071	Hs.49431	NTR	0.2	0.1	0.5	0.1	0.3	0.2	
at	receptor, type 2	99	2	K2	8	0	3	5	6	8	
	ubiquitin-like										
	modifier										
203281_	activating enzyme	NM_003		UBA	0.5	0.3	0.7	0.5	0.6	0.7	
s_at	7	335	Hs.16695	7	6	7	8	7	7	4	
	cadherin, EGF										
204029_	LAG seven-pass	NM_001		CELS	0.6	0.4	1.5	1.2	0.6	0.7	
at	G-type receptor 2	408	Hs.57652	R2	2	1	7	4	6	9	
205009_		NM_003	Hs.16280		0.2	0.1	10.	7.3	0.6	0.6	
at	trefoil factor 1	225	7	TFF1	8	8	76	1	5	8	
204508_	carbonic	BC00101	Hs.21099		0.3	0.2	4.4	3.6	0.6	0.8	
s_at	anhydrase XII	2	5	CA12	0	0	6	5	5	2	
	growth regulation										
205862_	by estrogen in	NM_014	Hs.46773	GRE	0.4	0.3	1.9	1.6	0.6	0.8	
at	breast cancer 1	668	3	B1	7	1	9	6	5	3	
	inhibitor of kappa										
	light polypeptide										
	gene enhancer in										
209341_	B-cells, kinase	AU1533	Hs.59766	IKBK	0.3	0.2	0.7	0.5	0.6	0.7	
s_at	beta	66	4	B	0	0	1	0	5	1	
205696_	GDNF family	NM_005	Hs.38834	GFR	0.7	0.5	3.5	4.5	0.6	1.2	
s_at	receptor alpha 1	264	7	A1	9	1	2	1	4	8	
203726_		NM_000	Hs.43636	LAM	0.2	0.1	0.3	0.2	0.6	0.7	
s_at	laminin, alpha 3	227	7	A3	3	4	8	8	2	2	
206754_		NM_000		CYP2	0.3	0.2	3.9	3.1	0.6	0.8	
s_at		767		B6	5	1	9	9	1	0	
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)	AL04926 5	Hs.53208 2	IL6S T	0.5 0	0.3 0	1.6 1	1.1 1	0.6 0	0.6 9
205509_ at	carboxypeptidase B1 (tissue) interleukin 6 signal transducer (gp130,	NM_001 871	Hs.47789 1	CPB1	0.6 8	0.4 0	3.6 0	3.1 5	0.5 9	0.8 7
212196_ at	oncostatin M receptor) E74-like factor 5 (ets domain	AW2429 16	Hs.53208 2	IL6S T	1.0 1	0.5 9	3.1 6	2.3 5	0.5 9	0.7 4
220625_ s_at	transcription factor) serpin peptidase inhibitor, clade A (alpha-1 antiproteinase,	AF11540 3	Hs.11713	ELF5	0.5 9	0.3 4	0.0 8	0.0 8	0.5 8	0.9 4
202376_ at	antitrypsin), member 3 serpin peptidase inhibitor, clade A (alpha-1 antiproteinase,	NM_001 085	Hs.53429 3	SERP INA3	0.9 1	0.5 3	2.9 1	2.0 8	0.5 8	0.7 2
209443_ at	antitrypsin), member 5	J02639	Hs.15962 8	SERP INA5	0.4 8	0.2 6	1.6 2	2.1 2	0.5 6	1.3 1
205225_ at	estrogen receptor 1	NM_000 125	Hs.20812 4	ESR1	0.0 7	0.0 2	3.6 6	2.5 9	0.3 0	0.7 1
202018_ s_at	lactotransferrin	NM_002 343	Hs.52951 7	LTF	0.5 9	0.5 1	1.0 1	0.2 0	0.8 6	0.2 0
206509_ at	prolactin-induced protein FBJ murine osteosarcoma	NM_002 652	Hs.99949	PIP	0.0 9	0.1 1	2.0 7	0.4 4	1.1 9	0.2 1
209189_ at	viral oncogene homolog	BC00449 0	Hs.73131 7	FOS	0.4 9	0.3 7	1.9 4	0.5 7	0.7 6	0.2 9
204014_ at	dual specificity phosphatase 4 sorbin and SH3 domain	NM_001 394	Hs.41796 2	DUS P4	0.0 9	0.0 9	0.7 6	0.2 6	0.9 7	0.3 5
218087_ s_at	containing 1	NM_015 385	Hs.38621	SOR BS1	0.3 2	0.2 2	0.8 5	0.2 9	0.6 8	0.3 5
219580_ s_at	transmembrane channel-like 5	NM_024 780	Hs.11583 8	TMC 5	0.2 3	0.2 7	1.2 7	0.4 8	1.1 7	0.3 8
219304_ s_at	platelet derived growth factor D	NM_025 208	Hs.35229 8	PDG FD	0.2 2	0.1 6	0.7 2	0.2 8	0.7 1	0.3 9
219440_ at	retinoic acid induced 2 pleckstrin and	NM_021 785	Hs.44668 0	RAI2	0.3 6	0.2 5	1.5 0	0.6 0	0.6 8	0.4 0
203355_ s_at	Sec7 domain containing 3 family with sequence	NM_015 310	Hs.43425 5	PSD3	0.1 7	0.1 6	0.7 4	0.3 0	0.9 4	0.4 1
217967_ s_at	similarity 129, member A	AF28839 1	Hs.51866 2	FAM 129A	0.7 4	0.5 9	1.4 1	0.6 1	0.8 0	0.4 3
214218_ at	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	0.80	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.55999	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.62886	SPA1	0.41	0.33	1.21	0.66	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	0.22	0.11	0.40	0.22	0.70	0.50
201041_s_at	dual specificity phosphatase 1	NM_004417	Hs.171695	DUSP1	0.33	0.30	0.75	0.38	0.93	0.51
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	0.11	0.11	0.50	0.22	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	0.22	0.11	0.30	0.22	0.70	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	0.11	0.11	0.30	0.11	0.89	0.56
218552_at	enoyl CoA hydratase domain containing 2	NM_018281	Hs.476319	ECHDC2	0.40	0.33	0.84	0.47	0.85	0.57
202992_at	complement component 7	NM_000587	Hs.78065	C7	0.77	0.59	1.15	0.65	0.77	0.57
205794_s_at	neuro-oncological ventral antigen 1	NM_002515	Hs.31588	NOV1	0.22	0.11	0.60	0.30	0.60	0.57
204622_at	nuclear receptor	NM_006	Hs.56334	NR4	0.11	0.11	0.40	0.22	0.90	0.57

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.56334	NR4	0.1	0.1	0.5	0.3	1.0	0.5
205380_ at	PDZ domain containing 1	NM_002	Hs.44475	PDZ	0.1	0.1	0.8	0.4	0.7	0.5
212741_ at	monoamine oxidase A	AA9233	Hs.18310	MAO	0.4	0.3	1.0	0.6	0.7	0.5
201983_ s_at	epidermal growth factor receptor	AW1570	Hs.48829	EGF	0.7	0.9	0.3	0.1	1.2	0.6
205157_ s_at		70	3	R	2	2	1	9	7	0
		NM_000		KRT	1.2	0.9	0.4	0.2	0.7	0.6
		422		17	9	9	6	7	7	0
212095_ s_at	microtubule associated tumor suppressor 1	BE55242	Hs.7946	MTU	0.2	0.3	0.7	0.4	1.0	0.6
204294_ at	aminomethyltrans ferase	1		S1	9	1	1	3	7	0
216333_ x_at		NM_000			0.1	0.1	0.2	0.1	0.6	0.6
211986_ at		481	Hs.102	AMT	6	1	0	2	8	0
		M25813		TNX	0.8	0.5	1.0	0.6	0.7	0.6
		BG28786	Hs.50275	A	2	9	5	4	2	1
	AHNAK nucleoprotein	2	6	AHN	0.4	0.3	1.0	0.6	0.8	0.6
				AK	2	5	0	2	4	2
206143_ at	solute carrier family 26, member 3	NM_000		SLC2	0.4	0.4	0.5	0.3	1.0	0.6
206093_ x_at		111	Hs.1650	6A3	2	5	2	2	8	2
		NM_007		TNX	0.8	0.5	1.0	0.6	0.7	0.6
		116		B2	2	9	1	3	2	2
203710_ at	inositol 1,4,5- trisphosphate receptor, type 1	NM_002	Hs.56729	ITPR	0.2	0.2	0.9	0.5	0.7	0.6
	leucine-rich repeats and	222	5	1	8	0	0	6	2	2
211596_ s_at	immunoglobulin- like domains 1	AB05046	Hs.51805	LRIG	0.2	0.2	0.9	0.6	0.8	0.6
	neural precursor cell expressed, developmentally down-regulated 4-	8	5	1	8	4	7	1	6	3
212448_ at	like, E3 ubiquitin protein ligase	AB00789	Hs.18567	NED	0.2	0.1	0.5	0.3	0.7	0.6
216264_ s_at	laminin, beta 2 (laminin S)	9	7	D4L	7	9	9	7	1	3
202723_ s_at		Hs.43972		LAM	0.2	0.2	0.7	0.4	0.8	0.6
204823_ at		X79683	6	B2	4	1	2	6	8	4
		AW1174	Hs.37066	FOX	0.5	0.4	0.6	0.4	0.8	0.6
	forkhead box O1	98	6	O1	5	5	3	0	2	4
	neuron navigator	NM_014	Hs.65530	NAV	0.3	0.3	0.6	0.4	0.7	0.6
		903	1	3	9	0	7	2	6	4
	met proto- oncogene (hepatocyte growth factor receptor)	BG17054	Hs.13296		0.4	0.5	0.2	0.1	1.1	0.6
213298_ at	nuclear factor I/C (CCAAT-binding transcription factor)	1	6	MET	7	5	6	7	6	6
			Hs.17013		0.5	0.4	0.8	0.5	0.8	0.6
		X12492	1	NFIC	4	7	8	8	6	6

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-specific	3070	NM_018063	Hs.655830
2.5	201291_s_at	TOP2A	topoisomerase (DNA) II alpha 170kDa	7153	AU159942	Hs.156346
2.4	203213_at	CDK1	cyclin-dependent kinase 1	983	AL524035	Hs.732435
2.3	212009_s_at	STIP1	stress-induced-phosphoprotein 1	10963	AL553320	Hs.337295
1.7	203755_at	BUB1B	BUB1 mitotic checkpoint serine/threonine kinase B	701	NM_001211	Hs.513645
1.6	205282_at	LRP8	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor nudix (nucleoside diphosphate linked moiety X)-type motif 21	7804	NM_004631	Hs.280387
1.6	202697_at	NUDT21	diphosphate linked moiety X)-type motif 21	11051	NM_007006	Hs.528834
1.5	209053_s_at	WHSC1	Wolf-Hirschhorn syndrome candidate 1	7468	BE793789	Hs.113876
1.9	202134_s_at	WWT1	WW domain containing transcription regulator 1	25937	NM_015472	Hs.594912
1.9	213906_at	MYBL1	v-myb myeloblastosis viral oncogene homolog (avian)-like 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	FCF1	FCF1 small subunit (SSU) processome component homolog (S. cerevisiae)	51077	NM_015962	Hs.579828
1.8	209757_s_at	MYCN	v-myc myelocytomatosis 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	DES12	desumoylating isopeptidase 2	51029	NM_016076	Hs.498317
1.7	215305_at	PDGFR	platelet-derived growth factor receptor, alpha polypeptide	5156	H79306	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	TCP11L	t-complex 11, testis-specific-like 1	55346	NM_018393	Hs.655341
1.6	222269_at	APOO	apolipoprotein O-like	139322	W87634	Hs.512181
1.6	219311_at	CEP76	centrosomal protein 76kDa	79959	NM_024899	Hs.236940
1.6	214708_at	SNTB1	syntrophin, beta 1	6641	BG484314	Hs.46701

			(dystrophin-associated protein A1, 59kDa, basic component 1)			
1.6	210073_at	ST8SI	ST8 alpha-N-acetyl-neuraminide alpha-2,8-	6489	L32867	Hs.408614
	205490_x_at	A1	sialyltransferase 1			
1.6		GJB3	gap junction protein, beta 3, 31kDa	2707	BF060667	Hs.522561
			CAP-GLY domain containing linker protein family, member 4		NM_0246	
1.6	219944_at	CLIP4	optic atrophy 3 (autosomal recessive, with chorea and spastic paraplegia)	79745	92	Hs.122927
			suppressor of variegation		NM_0251	
1.6	206357_at	OPA3	3-9 homolog 2	80207	36	Hs.466945
		SUV39	(Drosophila)		NM_0246	
1.6	219262_at	H2	protein phosphatase 1,	79723	70	Hs.554883
	201602_s_at	PPP1R	regulatory subunit 12A			
1.5		12A	ariadne homolog 2	4659	BE737620	Hs.49582
	216008_s_at	ARIH2	(Drosophila)			
1.5		SPTBN	spectrin, beta, non-erythrocytic 1	10425	AV694434	Hs.633601
	200671_s_at	1		6711	N92501	Hs.503178
	210041_s_at	PGM3	phosphoglucomutase 3	5238	BC001258	Hs.661665
			solute carrier family 6 (neutral amino acid transporter), member 15		NM_0180	
1.5	206376_at	SLC6A15		55117	57	Hs.44424

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

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 clinicopathological 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 clinicopathological 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 19 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), bladder 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.

15 In conclusion, the iBCR test including the mRNA and protein components (Table 19) 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 different cancers from TCGA datasets

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	+	+			+					-	
HCFC1R 1	+	+				+	+	+			
CEP55	+	+	+								
MCM10	+	+		+							
PML	+		+		+			+	+		
CENPN	+	+	+								
CARHSP 1	+	+	+						+		
CETN3	+									-	
ABHD5	+			+							-
BTN2A2	-	-		-		-	-	-	+	-	
SMPDL3 B	-			-				-		-	+
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

GO 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:0048 732	gland development	9	1.13E- 06	5.70E- 04	1.40E-02
GO:0010 647	positive regulation of cell communication	16	1.18E- 06	5.70E- 04	1.46E-02
GO:0051 246	regulation of protein metabolic process	20	1.20E- 06	5.70E- 04	1.48E-02
GO:0051 128	regulation of cellular component organization	19	1.51E- 06	6.91E- 04	1.87E-02
GO:0071 310	cellular response to organic substance	19	1.89E- 06	8.34E- 04	2.34E-02
GO:0042 327	positive regulation of phosphorylation	13	2.51E- 06	1.07E- 03	3.10E-02
GO:1901 698	response to nitrogen compound	13	2.90E- 06	1.18E- 03	3.59E-02
GO:0009 725	response to hormone	13	2.95E- 06	1.18E- 03	3.65E-02
GO:0048 584	positive regulation of response to stimulus	18	3.30E- 06	1.24E- 03	4.08E-02
GO:0042 127	regulation of cell proliferation	17	3.36E- 06	1.24E- 03	4.16E-02
GO:0070 887	cellular response to chemical stimulus	21	3.40E- 06	1.24E- 03	4.21E-02
GO:0010 608	posttranscriptional regulation of gene expression	10	3.65E- 06	1.29E- 03	4.52E-02
GO:0043 085	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)) performed 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 (PFS) 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 trend 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 OncomineTM 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-PlotterTM (n>4000 patients with some overlap with the datasets in OncomineTM). 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		
<u>ARHGEF3</u>	<u>ATP6V0A1</u>	<u>AGBL2</u>	<u>ABCA8</u>	<u>KIF5C</u>	<u>ZNF211</u>
<u>ASAH1</u>	<u>ATP6V1C1</u>	<u>ARFRP1</u>	<u>APBB2</u>	<u>LRIG1</u>	<u>AP3B1</u>
<u>ASB1</u>	<u>COX4I1</u>	<u>ARNT2</u>	<u>ART4</u>	<u>MADD</u>	<u>DYNC1LI2</u>
<u>ATP2A2</u>	<u>DHRS7</u>	<u>CCR1</u>	<u>ATHL1</u>	<u>MAPT</u>	<u>ESRP1</u>
<u>BRD8</u>	<u>EPCAM</u>	<u>DST</u>	<u>BCL2</u>	<u>MIER2</u>	<u>GMPS</u>
<u>BTG2</u>	<u>HN1</u>	<u>EEF1A1</u>	<u>BEND5</u>	<u>MIS18A</u>	<u>GPI</u>
<u>BTN2A2</u>	<u>IDH3A</u>	<u>LUZP1</u>	<u>CABYR</u>	<u>MR1</u>	<u>HCCS</u>
<u>C1QB</u>	<u>IDH3G</u>	<u>MYBPC1</u>	<u>CASP10</u>	<u>N4BP1</u>	<u>HCFC1R1</u>
<u>CERS6</u>	<u>LAMTOR2</u>	<u>PIP</u>	<u>CHPT1</u>	<u>NEDD4L</u>	<u>KCNG1</u>
<u>CYP2C9</u>	<u>LAMTOR3</u>	<u>S1PR1</u>	<u>CYBRD1</u>	<u>OGN</u>	<u>NAPG</u>
<u>ELOVL2</u>	<u>MATR3</u>	<u>SNED1</u>	<u>ERC2</u>	<u>PRKCB</u>	<u>NDRG1</u>
<u>ELOVL5</u>	<u>NPR3</u>	<u>TAZ</u>	<u>FHL5</u>	<u>PROL1</u>	<u>NDUFB6</u>
<u>ERBB4</u>	<u>NRIP1</u>	<u>TP63</u>	<u>GAB1</u>	<u>RERE</u>	<u>NDUFS6</u>
<u>FLNB</u>	<u>PFKP</u>	<u>ADORA2B</u>	<u>GDNF</u>	<u>SETBP1</u>	<u>NME1</u>
<u>HIF3A</u>	<u>RAP2A</u>	<u>CMC4</u>	<u>GLRB</u>	<u>SGCD</u>	<u>OIP5</u>
<u>KIR2DL4</u>	<u>SLC16A3</u>	<u>DDX39A</u>	<u>GOLGB1</u>	<u>SGSM2</u>	<u>PGAM1</u>
<u>LRP2</u>	<u>TK1</u>	<u>GAPDH</u>	<u>GOSR1</u>	<u>SLC45A2</u>	<u>PIR</u>
<u>LRP8</u>	<u>VDAC1</u>	<u>GSK3B</u>	<u>GPR12</u>	<u>SOD2</u>	<u>PRRG1</u>
<u>ME1</u>	<u>RAPGEF6</u>	<u>HIF1A</u>	<u>HLA-B</u>	<u>SPAG8</u>	<u>RTCA</u>
<u>NCOA1</u>	<u>RBM38</u>	<u>HSPA14</u>	<u>ITM2A</u>	<u>SPG20</u>	<u>S100A11</u>
<u>NR1H3</u>	<u>SEC14L2</u>	<u>LAMA4</u>	<u>KIAA0247</u>	<u>SSPN</u>	<u>SMS</u>
<u>PBXIP1</u>	<u>SRSF5</u>	<u>MAP2K5</u>	<u>KIAA0430</u>	<u>SSX2</u>	<u>TARS</u>
<u>PIK3IP1</u>	<u>STARD13</u>		<u>STX18</u>	<u>XBP1</u>	<u>TRAK2</u>
<u>PSEN2</u>			<u>TRAK1</u>	<u>ZC3H14</u>	
			<u>TRAPPC10</u>	<u>ZMYM5</u>	

Cellular Growth			Chromosome segregation	
<u>ASF1B</u>	<u>SLC11A1</u>	<u>BCAP31</u>	<u>AFF1</u>	<u>AURKB</u>
<u>BBS1</u>	<u>SMARCA2</u>	<u>BYSL</u>	<u>ATP1A2</u>	<u>BUB1</u>
<u>CCL13</u>	<u>SNX1</u>	<u>CCNA2</u>	<u>CDC14A</u>	<u>BUB1B</u>
<u>CCND2</u>	<u>SORL1</u>	<u>CCNE2</u>	<u>CDC27</u>	<u>BUB3</u>
<u>CDKN2A</u>	<u>SPDEF</u>	<u>CDC25A</u>	<u>CSPG4</u>	<u>C20orf24</u>
<u>DIRAS3</u>	<u>STAT5B</u>	<u>CDC45</u>	<u>FO XK2</u>	<u>CCNB1</u>
<u>DIXDC1</u>	<u>TAOK3</u>	<u>CDC6</u>	<u>MAGI1</u>	<u>CCNB2</u>
<u>DOCK1</u>	<u>TGOLN2</u>	<u>CDCA3</u>	<u>MLLT10</u>	<u>CDC20</u>
<u>DOK1</u>	<u>THPO</u>	<u>CDCA8</u>	<u>MTUS1</u>	<u>CDK1</u>
<u>EPOR</u>	<u>TIMELESS</u>	<u>CHEK1</u>	<u>NUP62</u>	<u>CENPE</u>
<u>FLT3</u>	<u>TNN</u>	<u>DERL1</u>	<u>NXF1</u>	<u>CENPF</u>
<u>FOSB</u>	<u>TNXB</u>	<u>DHFR</u>	<u>PKMYT1</u>	<u>CKS1B</u>
<u>GGA2</u>	<u>TYRO3</u>	<u>E2F8</u>	<u>RAPGEF2</u>	<u>CKS2</u>
<u>HAVCR1</u>	<u>ULK2</u>	<u>ECT2</u>	<u>SLC25A12</u>	<u>FOXM1</u>
<u>IL1RAPL1</u>	<u>VPS39</u>	<u>GIN53</u>	<u>SLC8A1</u>	<u>KIF2C</u>
<u>IL6ST</u>	<u>PIM1</u>	<u>RAD51</u>	<u>KIF4A</u>	<u>NUP93</u>
<u>JAK2</u>	<u>POLD1</u>	<u>RRM2</u>	<u>MAD2L1</u>	<u>NUSAP1</u>
<u>LEPR</u>	<u>PLK4</u>	<u>SKP2</u>	<u>MXI1</u>	<u>NUTF2</u>
<u>LIG1</u>	<u>PSMD10</u>	<u>UBE2C</u>	<u>NCAPG</u>	<u>PLK1</u>
<u>LZTFL1</u>	<u>MCM6</u>	<u>ULBP2</u>	<u>NDC80</u>	<u>PRC1</u>
<u>MTF1</u>	<u>MELK</u>	<u>WDHD1</u>	<u>NUP155</u>	<u>PTTG1</u>
<u>PCM1</u>	<u>MMP1</u>	<u>IL1RAP</u>	<u>TPX2</u>	<u>SPC25</u>
<u>PIK3R4</u>	<u>MYBL2</u>	<u>MCM10</u>	<u>TTK</u>	<u>TACC3</u>
<u>POU6F1</u>	<u>ORC6</u>	<u>MCM2</u>	<u>ZWINT</u>	
<u>NF1</u>	<u>PDAP1</u>	<u>MCM4</u>		

DNA Replication/ Recombination		Immune system				
<u>ALDH3A2</u>	ADRM1	<u>ABCA1</u>	<u>DTX3</u>	<u>SARM1</u>	PBK	ACOT7
<u>ATAD5</u>	BIRC5	<u>AHSG</u>	<u>DYNC2H1</u>	<u>SIRT3</u>	PFDN5	ANP32E
<u>ATF5</u>	CARHSP1	<u>ANK3</u>	<u>EFCAB6</u>	<u>SMPDL3B</u>	PSMA2	APOBEC3B
<u>BLM</u>	CENPA	<u>APOBEC3A</u>	<u>EFNB3</u>	<u>SNN</u>	RNASE4	CAST
<u>BRD4</u>	CENPI	<u>BATF</u>	<u>ERAP1</u>	<u>TTC28</u>	RNF141	CCT5
<u>BRF2</u>	CENPN	<u>BECN1</u>	<u>EVL</u>	<u>WFDC2</u>	S100A9	CCT6A
<u>BTN3A2</u>	CENPU	<u>BUD31</u>	<u>FBXO41</u>	<u>ZMYM6</u>	SHMT2	CCT7
<u>CLASP2</u>	DLGAP5	<u>C2</u>	<u>FBXW4</u>	<u>ZNF516</u>	SLC7A5	CD36
<u>FANCA</u>	ERCC6L	<u>C3</u>	<u>FCGBP</u>	<u>IGHG3</u>	SOX11	CD55
<u>FBLN1</u>	EXO1	<u>CACNA1D</u>	<u>FCGR1A</u>	<u>IGHM</u>	TBPL1	CDK8
<u>KIF18B</u>	FANCI	<u>CARD10</u>	<u>FCGR1B</u>	<u>IGK</u>	TCP1	CHD1
<u>NPR2</u>	H2AFX	<u>CD163</u>	<u>FOS</u>	<u>IGKC</u>	TOPORS	CXCL8
<u>PLXNA3</u>	H2AFZ	<u>CD1A</u>	<u>FRZB</u>	<u>IGSF9B</u>	TREM1	DHCR7
<u>PSMD2</u>	IMPDH2	<u>CD1B</u>	<u>GA57</u>	<u>IL16</u>	TXN	DSCC1
<u>STC2</u>	MAPRE1	<u>CD1C</u>	<u>GCH1</u>	<u>KCNMA1</u>	TXNRD1	ELF3
<u>TCF3</u>	MSH6	<u>CD22</u>	<u>GLI3</u>	<u>KIF13B</u>	WNT5A	GEMIN4
<u>TCF7L1</u>	PML	<u>CD68</u>	<u>GPRASP1</u>	<u>KL</u>	GM2A	
<u>TCF7L2</u>	POMP	<u>CD80</u>	<u>GREB1</u>	<u>LAD1</u>	GPSM2	
<u>TXNIP</u>	PSMB4	<u>CDK5R1</u>	<u>IGH</u>	<u>LAT</u>	GSPT1	
RYBP	PSMB5	<u>CFB</u>	<u>IGHG1</u>	<u>LFNG</u>	HMGB3	
TOP2A	PSMB7	<u>CHL1</u>	<u>NBPF10</u>	<u>MED12</u>	HMMR	
UBE2A	PSMD14	<u>CIITA</u>	<u>NUMA1</u>	<u>MOG</u>	HNRNPAB	
UBE2B	PSMD3	<u>CR1</u>	<u>PDE6B</u>	<u>MX2</u>	HPSE	
PSMD7		<u>CRP</u>	<u>PGR</u>	MCCC2	HRASLS	
		<u>CST3</u>	<u>PHLDA2</u>	MRPL12	IDH2	
		<u>CXCL14</u>	<u>PPY</u>	NAE1	KIAA0101	
		<u>CXCR4</u>	<u>RLN2</u>	NXN	LGALS1	

Metabolic Disease

<u>AASS</u>	<u>ENOSF1</u>	<u>MMRN2</u>	<u>SESN1</u>	<u>CALM1</u>	NME1- NME2
<u>ABCC8</u>	<u>FAM105A</u>	<u>MPP2</u>	<u>SFI1</u>	<u>CAMSAP1</u>	PARPBP
<u>ACAP2</u>	<u>FAM117A</u>	<u>MYO19</u>	<u>SLC35A2</u>	<u>CETN3</u>	PGK1
<u>ACSF2</u>	<u>FAM120A</u>	<u>N4BP2L1</u>	<u>SLC6A5</u>	<u>CFAP20</u>	PLCH1
<u>AHCYL1</u>	<u>FAM129A</u>	<u>NBEA</u>	<u>SLCO1A2</u>	<u>CMC2</u>	RAB22A
<u>ALDH1A2</u>	<u>FAM49B</u>	<u>NCAPD3</u>	<u>SPATA6</u>	<u>CNOT8</u>	SFXN1
<u>ANKHD1-</u>					
<u>EIF4EBP3</u>	<u>FAM86B1</u>	<u>NDUFAF5</u>	<u>TBRG4</u>	<u>COG8</u>	SHMT1
<u>ANKRD11</u>	<u>FCER1A</u>	<u>NFATC1</u>	<u>TCTN1</u>	<u>COQ9</u>	SMC4
<u>APOM</u>	<u>GCC2</u>	<u>NOP2</u>	<u>TLDC1</u>	<u>CORO1C</u>	SNRPA1
<u>ARL3</u>	<u>GLTSCR2</u>	<u>NSUN5</u>	<u>TLE4</u>	<u>DKC1</u>	STIL
<u>BIN3</u>	<u>GTPBP2</u>	<u>OSBPL1A</u>	<u>TMC6</u>	<u>DONSON</u>	SUGCT
<u>BSDC1</u>	<u>HAUS5</u>	<u>PADI1</u>	<u>TSKS</u>	<u>EMC8</u>	TMEM208
<u>BTD</u>	<u>HDC</u>	<u>PDK3</u>	<u>TSR1</u>	<u>ENY2</u>	TPD52L2
<u>BTN2A1</u>	<u>HOOK2</u>	<u>PHF8</u>	<u>TTC12</u>	<u>FKBP3</u>	TRIP13
<u>BTN3A3</u>	<u>HOXA4</u>	<u>PIEZO1</u>	<u>VAMP1</u>	<u>GGH</u>	WDR41
<u>C12orf49</u>	<u>HPN</u>	<u>PPIL2</u>	<u>VAMP2</u>	<u>GLT8D1</u>	YIPF3
<u>CALR</u>	<u>HS3ST1</u>	<u>PPP3R1</u>	<u>WDR19</u>	<u>GRHPR</u>	ZNF593
<u>CAMK2B</u>	<u>HTN1</u>	<u>PSD4</u>	<u>ZCCHC24</u>	<u>GTSE1</u>	
<u>CAMK4</u>	<u>HYI</u>	<u>PUM1</u>	<u>ZFP36L2</u>	<u>HELLS</u>	
<u>CASC1</u>	<u>INADL</u>	<u>RAB30</u>	<u>ZMYND10</u>	<u>HJURP</u>	
<u>CCDC176</u>	<u>ITM2C</u>	<u>RAB6B</u>	<u>ZNF22</u>	<u>KCMF1</u>	
<u>CCDC25</u>	<u>ITPR1</u>	<u>RAI2</u>	<u>ZNF506</u>	<u>KDM5A</u>	
<u>CD1E</u>	<u>IVD</u>	<u>RALGAPA1</u>	<u>ZNF778</u>	<u>KIF14</u>	
<u>CNTRL</u>	<u>KIAA0930</u>	<u>RAPGEF3</u>	<u>ZSCAN32</u>	<u>MRPL18</u>	
<u>CPSF7</u>	<u>KIAA1549L</u>	<u>RCAN1</u>	<u>ZZEF1</u>	<u>MRPL9</u>	
<u>CROCC</u>	<u>LAP3</u>	<u>RP56KA6</u>	<u>ACOT13</u>	<u>MRPS17</u>	
<u>CTDSPL</u>	<u>ME3</u>	<u>SERHL2</u>	<u>B9D2</u>	<u>NFATC3</u>	

Nucleic Acid Metabolism			Post-Translational Modification	
<u>ABAT</u>	<u>RECQL5</u>	<u>HEATR3</u>	<u>ABCB1</u>	<u>RTN1</u>
<u>AHNAK</u>	<u>RUNX1</u>	<u>KIF18A</u>	<u>ACAN</u>	<u>TENC1</u>
<u>ALPK1</u>	<u>SCUBE2</u>	<u>KIF23</u>	<u>AMN</u>	<u>TGFB3</u>
<u>BCAT2</u>	<u>SF3B1</u>	<u>KPNA2</u>	<u>COL4A6</u>	<u>TGFBR3</u>
<u>BMP8A</u>	<u>SF3B2</u>	<u>PAPOLA</u>	<u>CSF1</u>	<u>ADAM9</u>
<u>BTRC</u>	<u>SLC27A2</u>	<u>RAD51AP1</u>	<u>DDX11</u>	<u>ADM</u>
<u>CACNA1G</u>	<u>SLC6A2</u>	<u>RFC4</u>	<u>FGFR1</u>	<u>CALB2</u>
<u>CALCOCO1</u>	<u>SMARCC2</u>	<u>RPN1</u>	<u>FGFR2</u>	<u>CTSV</u>
<u>CBX7</u>	<u>SNRNP70</u>	<u>SEC61G</u>	<u>GSTM1</u>	<u>DBNDD1</u>
<u>COL14A1</u>	<u>SRSF7</u>	<u>SF3B3</u>	<u>GUSB</u>	<u>FAM96B</u>
<u>DCLRE1C</u>	<u>SSX3</u>	<u>SMAD5</u>	<u>IGF1</u>	<u>IGF1R</u>
<u>ESR1</u>	<u>SYMPK</u>	<u>SMYD2</u>	<u>LRRN3</u>	<u>KIF11</u>
<u>FBXO4</u>	<u>SYNC</u>	<u>SPAG5</u>	<u>MAP3K12</u>	<u>KIF20A</u>
<u>FMO5</u>	<u>TMC5</u>	<u>SRPK1</u>	<u>MST1</u>	<u>LAPTM4B</u>
<u>GART</u>	<u>USP19</u>	<u>SUB1</u>	<u>MYB</u>	<u>MMP15</u>
<u>H6PD</u>	<u>USP4</u>	<u>TAF11</u>	<u>NTRK2</u>	<u>RAB2A</u>
<u>JADE2</u>	<u>WSB1</u>	<u>TAF2</u>	<u>RBM5</u>	<u>SERPINH1</u>
<u>KLRG1</u>	<u>ACTR3</u>	<u>TCEB1</u>	<u>RLN1</u>	<u>TCEB2</u>
<u>KMT2A</u>	<u>AQP9</u>	<u>USP10</u>		
<u>MAFG</u>	<u>ARPC4</u>	<u>VPS28</u>		
<u>MAPRE2</u>	<u>ATAD2</u>	<u>WWTR1</u>		
<u>MYOF</u>	<u>AURKA</u>	<u>XPOT</u>		
<u>NOVA1</u>	<u>CA9</u>			
<u>NSMCE4A</u>	<u>CDK7</u>			
<u>POLE2</u>	<u>CEP55</u>			
<u>PTGDS</u>	<u>CFDP1</u>			
<u>PTGER3</u>	<u>DSN1</u>			

Protein Synthesis/Modification					Multiple networks	
<u>ACAA1</u>	<u>MTMR3</u>	<u>RPS28</u>	<u>EIF6</u>	<u>SLC25A5</u>	<u>ABHD14A</u>	<u>RPS4XP2</u>
<u>ACKR1</u>	<u>MTMR7</u>	<u>RPS4X</u>	<u>EPRS</u>	<u>SLC52A2</u>	<u>C1orf21</u>	<u>RPS4XP3</u>
<u>ACSL6</u>	<u>MXD4</u>	<u>RPS6</u>	<u>ETFA</u>	<u>SPIN1</u>	<u>C3orf18</u>	<u>SLC35D2</u>
<u>ADRA2A</u>	<u>MYOZ3</u>	<u>SAMD4A</u>	<u>EXOSC4</u>	<u>SQLE</u>	<u>C4A</u>	<u>SLC38A7</u>
<u>AGTR2</u>	<u>MYT1</u>	<u>SIRPA</u>	<u>EXOSC7</u>	<u>STAU1</u>	<u>CCDC30</u>	<u>SPATA6L</u>
<u>AUNIP</u>	<u>NME5</u>	<u>SLC16A5</u>	<u>GNB2L1</u>	<u>SYNCRIP</u>	<u>CFAP69</u>	<u>SSX7</u>
<u>C2CD2</u>	<u>NMT1</u>	<u>SLC4A7</u>	<u>GPR56</u>	<u>TKT</u>	<u>CLUL1</u>	<u>TNXA</u>
<u>CCDC170</u>	<u>NPY1R</u>	<u>SLC7A6</u>	<u>GTPBP4</u>	<u>TMEM194A</u>	<u>FCGR3B</u>	<u>TPSAB1</u>
<u>CELSR2</u>	<u>NPY5R</u>	<u>SORBS1</u>	<u>ILF2</u>	<u>TUBA1B</u>	<u>GUSBP11</u>	<u>TPSB2</u>
<u>CHAD</u>	<u>OSGEPL1</u>	<u>SQSTM1</u>	<u>KARS</u>	<u>UBE2V1</u>	<u>IGHD</u>	<u>UGT1A8</u>
<u>CREBL2</u>	<u>P2RY4</u>	<u>SRPK3</u>	<u>LAMA3</u>	<u>YWHAZ</u>	<u>IGHJ3</u>	<u>WDR78</u>
<u>CSDE1</u>	<u>P2RY6</u>	<u>THEMIS2</u>	<u>LRPPRC</u>		<u>IGHV3-20</u>	<u>ZNF710</u>
						<u>ZNRD1-</u>
<u>CX3CR1</u>	<u>PAPPA</u>	<u>TTLL1</u>	<u>NDUFC1</u>		<u>IGHV3-23</u>	<u>AS1</u>
<u>CYR61</u>	<u>PDCD2</u>	<u>ZNF395</u>	<u>NELFE</u>		<u>IGLJ3</u>	<u>BOLA2</u>
<u>DDX3X</u>	<u>PDCD4</u>	<u>ABHD5</u>	<u>NOP56</u>		<u>KIAA0040</u>	<u>MRPL23</u>
<u>DHTKD1</u>	<u>PER3</u>	<u>ADRBK2</u>	<u>QARS</u>		<u>KIR2DL1</u>	
<u>EGOT</u>	<u>PNPLA4</u>	<u>AIMP1</u>	<u>RACGAP1</u>		<u>KIR2DL3</u>	
<u>EIF1</u>	<u>PTCD3</u>	<u>ALG3</u>	<u>RAD21</u>		<u>LINC01260</u>	
<u>EML2</u>	<u>PTPN1</u>	<u>BRIX1</u>	<u>RAD23B</u>		<u>LOC389906</u>	
<u>EPHX2</u>	<u>PTPRO</u>	<u>CDKN3</u>	<u>RC3H2</u>		<u>LRRC48</u>	
<u>FAM134A</u>	<u>PTPRT</u>	<u>CHAF1A</u>	<u>RPL14</u>		<u>NBPF8</u>	
<u>FRS3</u>	<u>PURA</u>	<u>EIF3A</u>	<u>RPL15</u>		<u>NSUN7</u>	
<u>ICA1</u>	<u>RAMP2</u>	<u>EIF3B</u>	<u>RPL29</u>		<u>PGAP2</u>	
<u>LAMA2</u>	<u>RG55</u>	<u>EIF3K</u>	<u>RPS9</u>		<u>PGPEP1</u>	
<u>LPAR2</u>	<u>RHBDD3</u>	<u>EIF4B</u>	<u>RPSA</u>		<u>RBMV1J</u>	
<u>LZTS1</u>	<u>RPL10</u>	<u>EIF4E</u>	<u>SFPQ</u>		<u>RBMV2MP</u>	
<u>MAOA</u>	<u>RPL22</u>	<u>EIF4G1</u>	<u>SHCBP1</u>		<u>RGPD6</u>	

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
<u>BRD8</u>	1	Carbohydrate/Lipid Metabolism	Metabolism
<u>BTG2</u>	2	Carbohydrate/Lipid Metabolism	
<u>BTN2A2</u>	3	Carbohydrate/Lipid Metabolism	
<u>KIR2DL4</u>	4	Carbohydrate/Lipid Metabolism	
<u>ME1</u>	5	Carbohydrate/Lipid Metabolism	
<u>PIK3IP1</u>	6	Carbohydrate/Lipid Metabolism	
<u>SEC14L2</u>	7	Carbohydrate/Lipid Metabolism	
<u>PSEN2</u>	8	Carbohydrate/Lipid Metabolism	
<u>FLNB</u>	9	Carbohydrate/Lipid Metabolism	
<u>ACSF2</u>	10	Metabolic Disease	
<u>APOM</u>	11	Metabolic Disease	
<u>BIN3</u>	12	Metabolic Disease	
<u>CALR</u>	13	Metabolic Disease	
<u>CAMK4</u>	14	Metabolic Disease	
<u>GLTSCR2</u>	15	Metabolic Disease	
<u>ITM2C</u>	16	Metabolic Disease	
<u>NOP2</u>	17	Metabolic Disease	
<u>NSUN5</u>	18	Metabolic Disease	
<u>ZMYND10</u>	19	Metabolic Disease	
<u>ABAT</u>	20	Nucleic Acid Metabolism	
<u>BCAT2</u>	21	Nucleic Acid Metabolism	
<u>SCUBE2</u>	22	Nucleic Acid Metabolism	
<u>SF3B1</u>	23	Nucleic Acid Metabolism	
<u>RUNX1</u>	24	Nucleic Acid Metabolism	
<u>ZNRD1-AS1</u>	25	Nucleic Acid Metabolism	
ATP6V1C1	26	Carbohydrate/Lipid Metabolism	
RAP2A	27	Carbohydrate/Lipid Metabolism	
CALM1	28	Metabolic Disease	
CAMSAP1	29	Metabolic Disease	
CETN3	30	Metabolic Disease	
COG8	31	Metabolic Disease	
GRHPR	32	Metabolic Disease	
HELLS	33	Metabolic Disease	
KDM5A	34	Metabolic Disease	
PGK1	35	Metabolic Disease	
PLCH1	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
	73	DNA Replication/Recombination	
STC2		Chromosome segregation	
FOXN1	74	Chromosome segregation	
KIF2C	75	Chromosome segregation	
NUP155	76	Chromosome segregation	
TPX2	77	Chromosome segregation	
TTK	78	Chromosome segregation	
	79	DNA Replication/Recombination	
CARHSP1		Replication/Recombination	

CENPA	80	DNA Replication/Recombination	
CENPN	81	DNA Replication/Recombination	
EXO1	82	DNA Replication/Recombination	
MAPRE1	83	DNA Replication/Recombination	
PML	84	DNA Replication/Recombination	
APOBEC3A	85	Immune system	
BATF	86	Immune system	Immune response
CD1A	87	Immune system	
CD1B	88	Immune system	
CD1C	89	Immune system	
CD1E	90	Immune system	
CFB	91	Immune system	
CXCR4	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-Translational Modification	Protein synthesis/Modification
MYB	109	Post-Translational Modification	
RLN1	110	Post-Translational Modification	
ACAA1	111	Protein Synthesis/Modification	
CHAD	112	Protein Synthesis/Modification	
MTMR7	113	Protein Synthesis/Modification	
PDCD4	114	Protein Synthesis/Modification	
RPL10	115	Protein Synthesis/Modification	
RPS28	116	Protein Synthesis/Modification	
RPS4X	117	Protein Synthesis/Modification	
RPS6	118	Protein Synthesis/Modification	
SORBS1	119	Protein Synthesis/Modification	
SRPK3	120	Protein Synthesis/Modification	

<u>RPL22</u>	121	Protein Synthesis/Modification	
<u>RPS4XP3</u>	122	Protein Synthesis/Modification	
ADM	123	Post-Translational Modification	
ABHD5	124	Protein Synthesis/Modification	
CHAF1A	125	Protein Synthesis/Modification	
EIF3K	126	Protein Synthesis/Modification	
EIF4B	127	Protein Synthesis/Modification	
EXOSC7	128	Protein Synthesis/Modification	
GNB2L1	129	Protein Synthesis/Modification	
LAMA3	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, associated 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
5 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);
10 (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 iBCR 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:
15 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.

5

SEQUENCE LISTING

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

- 5 >SEQ ID NO:1
MATGTGKHKLLSTGPTEPWSIREKLCLASSVMRSGDQNWVSVSRAIKPFAEPGRFPDWFSSQKHCASQY
SELLETTETPKRKRGEKGEVETVEDVIVRKLTAERVEELKKVIKETQERYRRLKRDAELIQAGHMDS
RLDELNDIATKKKLEEEAEVKKRATDAAYQARQAVKTPPRRLPTVMVRSPIDSAASPGGDYPLGDLT
10 PTTMEEATSGVNESEMAVASGHLNSTGVLLLEVGGVLPMIHGGEIQQTPNTVAASPAASGAPTLSRLLE
AGPTQFTTTPLASFTTVASEPPVKLVPPPVESVSQATIVMMFALPAPSSAPAVSTTESVAPVSQPDNCV
PMEAVGDPHTVTVSMDSSSEISMIINSIKEECFRSGVAAEPVGSKAPSIDGKEELDIAEKMDIAVSYTG
EELDFETVGDIIAIIEDKVDDHPEVLDVAAVEAALSFCENDDPQSLPGPWEHPIQQRERDKPVLPAF
EMTVKQERLDFEETENKGIHELVDIREPSAEIKVEPAEPEPVISGAEIVAGVVPATSMPEPPELRSQDL
DEELGSTAAGEIVEADVAIGKGETPLTNVKTASPESSMLSPSHGSPNIEDPLEAETQHKFEMSDSLK
15 EESGTIFGSQIKDAPGEDEEDGVSEAAASLEEPKEEDQEGEYLSEMDNEPPVSESDDGFSIHNATLQS
HTLADSIPSSPASSQFSVCSEDQEAIIQAQKIWKKAIMLVWRAAANHRANVFLQPVTDIAPGYHSIV
QRPMDLSTIKKNIENGLIRSTAEFQORDIMLFQNAVMYNSSDHDVYHMAVEMQORDVLEQIQFLATQL
IMQTSSESGISAKSLRGRDSTRKQDASEKDSVPMGSPAFLLSLFMGHEWVWLDSEQDHPNDSLSNDCR
SLFSSWDSSLDLDVGNWRETDPEAELEEESSPEREPSELIVGDGGSEESQEAARKASHQNLHFLSE
20 VAYLMEPLCISSNESSEGCCPPSGTRQEGREIKASEGERELCRETEELSAKGDPLVAEKPLGENGKPE
VASAPSVICTVQGLLSESEGEAQQESKGEDQGEVYVSEMEDQPPSGECDDAFNIKETPLVDTLFSHA
TSSKLTDLSDDDPVQDHLFLFKKTLFPVWKMIASHRESSPFLKPVSERQAPGYKDVVKRPMDLTSLKRN
LSKGRIRTMQFLRDLMLMFQNAVMYNDSDDHVYHMAVEMRQEVLEQIQVLNIWLDKRRGSSSLEGEF
ANPVDDGKPVF
- 25 >SEQ ID NO:2
MSHGKGTDMLEPIAAAVGFLSSLLRTRGCVSEQRLKVFSGALQEALTEHYKHHWFPEKPSKSGSGYRCI
RINHKKMDFIISRVASQIGLSQFQLHQLLPSELTLWVDPYEVSYRIGEDGSICVLYEEAPLAASCGLLT
CKNQVLLGRSSPSKNYVMAVSS
- 30 >SEQ ID NO:3
MEFAAALHFSLPASLLLLLLLLLLLLSLCALVSAQFTVVG PANPILAMVGENTTLRCHLSPEKNAEDMEV
RWFRSQFSPAVFVYKGGREERTEEQMEEYRGRITFVSKDINRGVALVIHNVTAGENGIYRCYFQEGRS
YDEAILRLVAVAGLSKPLIEIKAQEDGSIWLECISGGWYPEPLTVWRDPYGEVVPALKEVSIADADGL
35 FMVTTAVIIRDKYVRNVSCSVNNTLLGQEKETVIFIPESFMPSPASPWMVALAVILTASPWMVMSMTVIL
AVFIIEMAVSICCIKKLQREKKILSGEKKVQEKEKIAQQLEELRWRRTFLHAADVLDPDTAHPEL
FLSEDRRSVRRGPYRQRPDPNPERFDSQPCVLGWSFASGKHYYEVEVENVMVWTVGVCRHSVERKGE
VLLIPQNGFWTLEMFGNQYRALSSPERILPLKESLCRVGVFLDYEAGDVSYNMRDRSHIYTCPRSAF
40 TVPVRPFERLGSDDSPIFICPALTGASGMVPEEGLKLHRVGT HQSL
- >SEQ ID NO:4
MSMSFTVILACLGFFLDQSVWAHVGGQDKPFCSAWPSAVVPQGGHVTLRCHYRRGFNIETLYKKDGV
PVPELYNRIFWNSFLISPVTPAHAGTYRCRGFHPHSPTESWAPSANPLVIMVTGLYEKPSLTARPGPTV
RAGENVTLSQSSQSSFDIYHLSREGEAHELRLPAVPSINGTFQADFP LPATHGETYRCFGSFGSPY
45 EWSDPDPLPVSVTGNPSSSWPSPTEPSEKTIARHLHAVIRYSVAIILFTILPFFLLHRWCSKKKDA
AVMNQEPAGHRTVNREDSDEQDPQEVTYAQLDHCIFTQRKITGPSQRSKRPSDTDSVCIELPNAEPRA
LSPAHEHHSQALMGSSRETTALSQTQLASSNVPAAGI
- >SEQ ID NO:5
50 MEPEAPRRRHTRQGYLLTRNPHLNKDIAFTLEERQQLNHGLLPPSFNSQEIQLRVVKNFEHLNSD
FDRYLLMLDQDRNEKLFYRVLTSDIEKFMPITYPTVGLACQQYSLVFRKPRGLFITIHDRGHIASV
LNAWPEVDVIAIVVTDGERILGLDGLCGNGMGIPVGKALALYTACGGMNPQECLPVILDVGTENEELLK
DPLYIGLRQRRVRGSEYDDFLDEFMEAVSSKYGMNCLIQFEDFANVNAFRLNKNYRNQYCTFNDDIQG
TASVAVAGLLAALRITKNKLSQDTILFQGAGEAALGIAHLIVMALEKEGLPKKAIKKIWLVDSEKGLI
55 VKGRASLTQEKKEKFAHEHEEMKNLEAIVQEIKP TALIGVAAIGGAFSEQILKDMAAFNERPIIFALSN
PTSKAECSAEQCYKITKGRAIFASGSPFDPVTLFNGQTLYPGQGNNSYVFPGVAGLVVACGLRQITDN
IFLTAEVIAQQVSDKHLEEGRLYPPLNTIRDVSLKIAEKIVKDAYQEKATATVYPEPQNKEAFVRSQM
YSTDYDQILPDCYSWPPEEVQKIQTQKVDQ

>SEQ ID NO:6

MLLAWVQAFILVSNMLLAEAYGSGGCFWDNGHLYREDQTSAPAGLRCLNWLDAQSGLASAPVSGAGNHS
YCRNPDEDPGRGPWCYVSGEAGVPEKRPCEDLRCPETTSQALPAFTTEIQEASEGPGADEVQVFAPANA
5 LPARSEAAAVQPVIGISQVRMNSKEKKDLGTLGYVLGITMMVIIIAIGAGIILGYSYKRGKDLKEQH
DQKVCEREMQRITLPLSAFTNPTCEIVDEKTVVHTSQTTPVDPQEGTTPLMGQAGTPGA

>SEQ ID NO:7

MSGRVGDLSFRQKEALAKFRENVDVLPALPNPDDYFLLRWLRARSFDLQKSEAMLRKHVEFRKQKDI
10 DNIISWQPPEVIQQYLSGGMCGYDLGCPVWYDIIGPLDAKGLLFSASKQDLLRTKMRECELLQCECA
HQTTKLGRKQVETITIIYDCEGLGLKHLWKPAVEAYGEFLCMFEENYPETLKRFLVVKAPKLPVAYNL
IKPFLSEDTRKKIMVLGANWKEVLLKHI SPDQVPVEYGGTMDPDGPNPKCKSKINYGGDI PRKYYVRD
QVKQQYEHVSQISRGSSHQVEYELFFPGCVLRWQFMSDGDVGFGLFKTKMGERQRAGEMTEVLPNQ
15 RYNHSLVPEDGTLTCSDFGIYVLRFDNTYSFIHAKKVNFTEVLLPDKASEEKMQLGAGTPK

>SEQ ID NO:8

MLTFMASDSEEEVCDERTSLMSAESPTPRSCQEGRQGPEDGENTAQWRSQENEEDEGEDPDRYVCSGV
PGRPPGLEEEELTKYGAKHVIMLFVPVTLCMIVVATIKSVRFYTEKNGQLIYTPFTEDTPSVGQRLL
NSVLNTLIMISVIVVMTIFLVVLYKYRCYKFTHGWLIMSSLMLEFLFTYIYLGEVLKTYNVAMDYPTL
20 LLTVWNFGAVGMVCIHWKGPLVLQQAYLIMISALMALVFIKYLPEWSAWVILGAISVYDLVAVLCPKG
PLRMLVETAQERNEPIFPALITYSSAMVWTVGMAKLDFSSQALQLPYDPEMEEDSYDSFGEPSYPEVE
EPPLTGYPGEELEEEEEERGVKLGGLGDFIFYSVLVGKAAATGSGDWNTTLACFVAILIGLCLTLLLLAV
FKKALPALPISITFGLIFYFSTDNLVRPFMDTLASHQLYI

25 >SEQ ID NO:9

MPVTEKDLAEDAPWKKIQQNTFTRWCNEHLKCVNKRIGNLQTDLSDGLRLIALLEVLSSQKRMRYKHYQ
RPTFRQQLLENVSVALEFLDRESIKLVSIDSKAIVDGNLKLILGLVWTLILHYSISMFWEDEGDDDA
KKQTPKQRLGWIQNKIPYLPITNFNQNWQDGKALGALVDSCAPGLCPDWESWDPQKFPVDNAREAMQ
ADDWLGVPPQVITPEEIIHPDVDEHSVMTYLSQFPKAKLKPAGPLKPKLNPKKARAYGRGIEPTGNMVK
30 QPAKFTVDTISAGQGDMVVFVEDPEGNKEEAQVTPDSKDKNTYSVEYLPKVTGLHKVTVLFAGQHISK
SPFEVSVDKAQGDASKVTAKGPGLEAVGNIAKPTYFDIYTAGAGVGDIGVEVEDPQKNTVELLVED
KGNQVYRCVYKPMQPGPHVVKIFFAGDTIPKSPFVVQVGEACNPNACRASGRGLQPKGVRIRETDFK
VDTKAAGSGELGVTMKGPKGLEELVKQKDFLDGVYAFEYYPSTPGRYSLAITWGGHHIPKSPFEVQVG
PEAGMQKVRAGWPGPLHGGIVGRSADFVVESIGSEVGSGLGFAIEGPSQAKIEYNDQNDGSCDVKYWPKE
35 PGEYAVHIMCDDEDIKDSPYMAFIHPATGGYNPDLVRAYGPGLEKSGCIVNNLAEFTVDPKDAGKAPL
KIFAQDGEGQRIDIQMKNRMDGTIACSYTPVKAIKHTIAVWGGVNIPIHSPYRVNIGQGSHPQVKVVF
GPGVERSGLKANEPHTFTVDCTEAGEGDVSVGIKCDARVLSDEEDVDFDI IHNANDTFTVKYVFPAA
GRYTIIKVLFAEQEIPASFPRVKVDP SHDASKVKAEGPGLSKAGVENGKPTHTFTVYTKGAGKAPLNVQF
NSPLPGDAVKDLDIIDNYDYSHTVKYTPTQCGNMQVLVTYGGDPIPKSPFTVGVAAPLDLSKIKLNGL
40 ENRVEVGKDQEFVTVDTRGAGGQGLDVTILSPSRKVVPCLVTPVTGRENSTAKFIPREEGLYAVDVTY
DGHVPVPGSPYTVEASLPDPFSKVKAHGPGLEGLVGKPAEFTIDTKGAGTGGLGLTVEGPCAEKIECS
DNGDGTCSVSYLFTKPGEFVNILFEEVHIPGSPFKADIEMPFDP SKVVASGPGLEHGKVGEAGLLSV
DCSEAGPGALGLEAVSDSGTKAEVSIQNNKDGTYAVTYVPLTAGMYTLTMKYGGELVPHFPARVKVEP
AVDTSRIKVFPGGIEGKDVFREATTDFTVDSRPLTQVGGDHIAHIANPSGASTECFVTDNADGTQV
45 EYTPFEKGLHVVEVTYDDVPIPNSPFKVAVTEGCQPSRVQAQGPGLKEAFTNKPNTFTVTRGAGIGG
LGITVEGPGSESKINCRDNKDGSCSAEYIPFAPGDYDVNITYGGAHIPGSPFRVPVKDVDP SKVKIAG
PGLGSGVRARVLQSF TVDSSKAGLAPLEVRLGPRGLVEPVNVVDNGDGTHTVITYPSQEGPYMVSVK
YADEEIPRSPFKVKVLPTYDASKVTASGPGGLSSYGVPA SLPVDF AIDARDAGEGLLAVQITDQEGKPK
RAIVHDNKDGTYAVTYIPDKTGRYMIGVTYGGDDIPLSPYRIRATQTDGASKCLATGPGIASTVKTGE
50 EVGFVVDAKTAGKGKVTCTVLTDPDTEAEADVIEDGTYDIFYTAAKPGTYVIYVREGGVDIPNSPF
TVMATDGEVTAVEEAPVNACPPGFRPWVTEEAYVPVSDMNGLGFKPFDLVIPFAVRKGEITGEVHMPS
GKTATPEIVDNKDGTVTVRYAPTEVGLHEMHIKYMGSHPESPLQFYVNYPNSSGVSAYGPGLVYGVA
NKTATFTIIVTEDAGEGLDLAIEGPSKAEISCIDNKDGTCTVTYLPTLPDYSILVKYNDKHIPGSFE
TAKITDSSRRCSQVKLGSAADFLLDISETDLSSLTASIKAPSGRDEPCLLKRLPNNHIGISFIPREVG
55 EHLVSIKKNNGNHVANSPPV SIMVVQSEIGDARRAKVYGRGLSEGRTFEMSDFI VDTRDAGYGGISLAVE
GPSKVDIQTEDLEDGTCKVSYFPTVPGVYIVSTKFADEHVPGPSFTVKISGEGRVKESITRTSRAPSV
ATVGSICDLNLKIPEINSSDMSAHVTSPPSGRVTEAEI VPMGKNSHCVRFPQEMGVHTSVSKYRGQHV
TGSPFQFTVGPGLGEGGAHKVRAGGPGLERGEAGVPAEFSIWTREAGAGGLSIAVEGPSKAEITFDDHK
NGSCGVSYYIAQEPGNYEVS IKFNDEHIPESPYLVPIAPSDDARRLTVMSLQESGLKVNQPASFAIRL
60 NGAKGKIDAKVHSPSGAVEECHVSELEPDKYAVRFIPHENGVHTIDVKFNNGSHVVGSPFKVRVGEPEGQ
AGNFALVSAYGTGLEGGTTGIQSEFFINTTRAGPGTLSVTIEGPSKVKMDCQETPEGYKVMYTPMAPG

NYLISVKYGGPNHIVGSPFKAKVTGQRLVSPGSANETSSILVESVTRSSSTETCYSAIPKASSDASKVT
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5 >SEQ ID NO:10

MAVYVGMRLRLCAGSSGVLGARAALSRSWQEARLQGVRFSSREVDMMVSTPIGGLSYVQGCTKKH
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LKSQRLPDLTTVISVDAFLPGTLLLDDEVVAAGSTRQHLDDQLQYNQQFLSCHDPINIQFTSGTTGSPKG
10 ATLSHYNIVNNSNILGERLKLHEKTPEQLRMILPNPLYHCLGSVAGTMMCLMYGATLILASPIFNGKK
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GTTENSPVTFFAHFPEDTVEQKAESVGRIMPHTEARIMNMEAGTLAKLNTPGELCIRGYCVMLGYWGEP
QKTEEAVDQDKWYWTGDVATMNEOGFCIKVGRSKDMIIRGGENIYPAELEDFFHTHPKVQEVQVVGVK
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15 LNL

>SEQ ID NO:11

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20 TGQGYQRFLLYNRSPHPPEKCVEEFKSLTSCLDKAFLLTPRNQEACELSN

>SEQ ID NO:12

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25 RLQAKVEKYEKEKTGPFVLAKLHQAREELRPVREDFEAKNRQLLEEMPRFYGSRLDYFQPSFESLIRA
QVVYYSEMHKTFGDLSHQLDQPGHSDEQRENEREAKLSELRAISIVADD

>SEQ ID NO:13

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30 SQDARFYALSASFEPFSNKGQTLVVQFTVKHEQNIDCGGGYVKLFPSNLDQTDHMGDSEYNIMFGPDI
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35 VPGQAKDEL

>SEQ ID NO:14

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40 SERDAADAVKQILEAVAYLHENGIVHRDLKPNLLYATPAPDAPLKIADFGLSKIVEHQVLMKTVCGT
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AKDLVRKLIVLDFPKRLTTFQALQHPWVTGKAANFVHMDTAQKKLQEFNARRKLKAAYKAVVASSRLG
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>SEQ ID NO:15

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50 PLVGQDEFFLEQTKKKGVKRPARLHTKPSQAPAVEVAPAGASYNPSFEDHQTLLSAAHEVELQRQKEA
EKLERQLALPATEQAATQESTFQELCEGLLEESDGEGEPEGQGEPEAGDAEVCPTPARLATTEKKTEQ
QRRREKAVHRLRVQQAALRAARLRHQELFRLRGIKAQVALRLAELARRQRRRQARREAEADKPRRLGR
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QL
55

>SEQ ID NO:16

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GGGDFADIIHDFQRGLTAYHDISLDKCYVIELNTTIVLPPRNFWELLMNVKRGTYLPQTYIIQEEMVV
60 TEHVSDKEALGSFIYHLCNGKDTYRLRRRATRRRINKRGAKNCNAIRHFENTFVETLICGVV

- >SEQ ID NO:17
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 5 EADGGLQINVDEEPFVLPFAGEMEQAQAPDLQRVHKRIQDIVGILRDFGAQREEGRSRSEYLNRLKK
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 10 DFGQEGFTRFRERRFHPSLRSTRRFYPHTHNMDFGFFIAKFKKFSNSIPQSQGTGNSETATPTNVDLPQV
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- 15 >SEQ ID NO:18
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- >SEQ ID NO:19
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 30 LERENRGKWQAI AKHQLQHVFSFSEQDLRLQARRWAET YRLDVLEAVAPERPRCAYCSAEASKRCSRC
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- >SEQ ID NO:20
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 40 AHAGKALLTGLLDLQARYPQFISRVRGRGTFC SFDTPDDSI RNKLIL IARNKGVVLGGCGDKSIRFRP
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- >SEQ ID NO:21
 45 MAAAALGQIWARKLLSVFWLLCGPERRYASSSFKAADLQLEMTQKPHKKPGPGEPLVFGKTFDTHMLMV
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 YWTHEDGVLELVTPPLNGVILPGVVRQSL LDMAQTWGEFRVVERTIIMKQLLRALEEGRVREVFSGT
 50 ACQVCPVHRILYKDRNLHIPTMENGPELILRFQKELKETIQYGIRAHWEMFPV
- >SEQ ID NO:22
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 GGCQHTCVNVMGSYECCCKEGFFLSDNQHTCIHRSEGLSCMNKD HGC SHICKEAPRGSVACECRPGF
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 60 GRPSTPKEMFITVEFELETNQKEVTASCDLSCIVKRTEKRLRKAIRTLRKAHVHREQFHLQLSGMNL DV
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 5 LIKALFDVLAHPQNYFKYTAQESREMFPRSFIRLLRSKVSRLRPYK

>SEQ ID NO:23

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 10 ADGGKTPDPKMNARTYMDVMREQHLTKEEREIRQQLAEKAKAGELKVVNGAAASQPPSKRKRWDQTA
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 15 KLLVDVDESTLSPEEQKERKIMKLLLIKNGTTPMRKAALRQITDKAREFGAGPLFNQILPLLMSPIL
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 20 HEWQHRLMALDRRNYRQLVDTTVELANKVGAAEIIISRIVDDLKDEAEQYRKMVMETIEKIMGNLGAADI
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 TPILKNRHEKVQENCIDLVGRIADRGAEYVSAREWMRICFELLELLKAHKKAIRRATVNTFGYIAKAI
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 25 YIGEMGKDYIYAVTPLLEDALMDRDLVHRQTASAVVQHMSLGVYGFCEDSLNNLLNYVWPNVFETSP
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>SEQ ID NO:24

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 35 MSAMGSATRYHTYLPPPYPGSSQAQGGPFQASSPSYHLYYGASAGSYQFSMVGGERSPPRILPPCTNA
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>SEQ ID NO:25

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 40 AQRRKQVNEREQMQTKDHQERMIRGRELAEQRLKERILRRSQSLLTYEKHERVKEIKEFERVIAYLL
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>SEQ ID NO:26

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 AEMVYPRSSNVLSQDSYLCNVTLFRKAVDDFRHKARENKFIVRDFQYNEEEMKADKEEMNRLSTDK
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>SEQ ID NO:27

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 55

>SEQ ID NO:28

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 60

>SEQ ID NO:29

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 10 IVRADVVFPQADPEFFPRASPRALGLTANARSPQGLDTSSESKPDSFFLEPLMPAVLKPAAKQVITKE
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 >SEQ ID NO:30
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 30 >SEQ ID NO:31
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 40 LAFHRAEEAAAFSSGEQELFVQFCTVFLLEDLVPLYNRCLQVLFPPAQIAQTILGIPPTQLSKYGNLGHVN
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 45 GWTSWKPLWLCCGYGLTQSTVGIIGLGRIGQAIARRLKPFQVQRFYLTGRQPRPEEAAEFQAEFVSTPE
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 >SEQ ID NO:33
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 60 INLTAADTVIYDSWDNPQSDLQAQDRCHRIGQTKPVVYRLVTANTIDQKIVERAAAKRKLEKLIH

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>SEQ ID NO:34

5 MAGVGPGGYAAEFVPPPECPVFEPSSWEEFTDPLSFIGRIRPLAECTGICKIRPPKDWQPPFACEVKSF
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10 DAFNMQMKQRKGTLSVNFVDLYVCMFCGRGNNEKLLLCDGCDSDSYHTFCLIPPLPDVEKGDWRCPKC
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FSSFCWHIEDHWSYSINYLHWGEPKTWYGVPSHAAEQLEEVMLRELAPELFESQPDLLHQLVTIMNPNV
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15 TTCELSALTCSNPERLVCLYHPTDLCPCPMQKKCLRYRPLEDLPSLLYGKVRASQSYDTWVSRVTE
ALSANFNHKKDLIELRVMLEDAEDRKYPENDLFRKLRLDAVKEAETCASVAQLLLSKKQKHRQSPDSGR
TRTKLTVEELKAFVQQLFSLPCVISQARQVKNLDDVEEFHERAQEAMMDETDPSSKLQMLIDMGSSL
YVELPELPRLKQELQARWLDEVRLTSLDPQQVTLDVMKKLIDSGVGLAPHHAVEKAMAELQELLTVS
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20 EQLESLSAKGRPIPVRLALPQVESQVAAARAWRETRTGRFLKKNSSHTLLQVLSRPTDIGVYSGKN
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TILSLLVSLQKLPVRLPEGEALQCLTERAMSWQDRARQALATDELSSALAKLSVLSQRMVEQAAREKT
EKIISAELOKAAANPDLQGHLPSSFQQSFAFNRVSSVSSSPRQTMDDDEETDSDDEDIRETYGYDMKDT
25 ASVKSSSSLEPNLFCDEETPIKSEEVVTHMWTAPSFCAEHAYSSASKSCSQGSSTPRKQPRKSPLVPR
SLEPPVLELSPGAKAQLEELMMVGDLLEVSIDETQHIWRILQATHPPSEDRLHIMEDDSMEEKPLKV
KGKDSSEKKRKRKLEKVEQLFGEGKQKSKELKKMDKPRKKKLKLGADKSKELNKLAKKLAKKEERKKK
KEKAAAQKVELVKESTEKKREKKVLDIPSKYDWSGAEESDDENAVCAAQNCQRPCKDKVDWVQCDGGC
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>SEQ ID NO:35

30 MSLSNKLTLDKLDVKGKRVVMRVDFNVPMKNNQITNNQRIKAAVPSIKFCLDNGAKSVVLMSHLGRPD
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GNKVKAEPKIEAFRASLSKLGDVYVNDAFGTAAHRAHSSMVGVLNLPQKAGGFLMKKELNYFAKALESP
35 ERPFLLAILGGAKVADKIQLINNMLDKVNMIIIGGGMAFTFLKVLNNMEIGTSLFDEEGAKIVKDLMSK
AEKNGVKITLPVDFVTADKFEDENAKTGQATVASGIPAGWMGLDCGPESKKYAEAVTRAKQIVWNGPV
GVFEWEAFARGTKALMDEVVKATSRGCITIIIGGGDTATCCAKWNTEDKVSHVSTGGGASLELLEGKVL
PGVDALSNI

>SEQ ID NO:36

40 MADLEVYKNLSPEKVERCMSVMQSGTQMIKLKRGTKGLVRLFYLDHRTLRWRPSRKSEKAKILIDS
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AKRQRTDQWVKQTFEEADKNGDGLNIEIHLQMLHKLNVNLP RRKVRQMFQEADTDENQGLTTFEEF
CVFYKMMSLRRDLYL LLLSYSDKKDHLTVEELAQLKVEQKMNNVT TDYCLDIKKFEVSEENKVKNV
45 LGIEGFTNFMRSACDIFNPLHHEVYQDMDQPLCNYYIASSHNTYLTGDQLLSQSKVDMYARVLQEGC
KCEVDCWDGPDGEPVVHHGYTLTSLKILFRDVVETINKHAFVKNEFPVILSIENHCSIQQQRKIAQYL
KGIFGDKLDLSSVDTGECKQLPSPQSLKGLKLVKGKLPYHLGDDAEEGEVSDSDSADEIEDECKFKL
HYSNGTTEHQVESFIRKKLESLLKESQIRDKEDPDSFTVRALLKATHEGLNAHLKQSPDVKESGKKSH
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50 AQDIVDDGTTGNVLSFSETRAHQVQVKSEQFMIYNQKQLTRIYP SAYRIDSSNFPNLPYWNAGCQLV
ALNYQSEGRMMQLNRAKFKANGNCGYVLKPQMQCKGTFPNPSGDP LANPKQLILKVISGQQLPKPF
DSMFGDRGEIIDFFVEVEIIGLPVDCCKDQTRVDDNGFNVPWEETLTFTVHMFEIALVRLVWDHDP
IGRDFVGQRTVTFSSLVPGYRHVYLEGLTEASIFVHITINEIY GKWSPLILNPSYTIHLHLGATKNRQ
LQGLKGLFNKNPRHSSSENNSHYVRKRSIGDRILRRASAPAKGRKKSKMGFQEMVEIKDSVSEATRD
55 QDGVLRRTTRSLQARPVSMVDRNLLGALS LPVSETAKDIEGKENS LAEDKDGRKKGKASIKDPHFLN
FNKKLSSSSSALLHKDTSQGDITVSTAHSVTGEQLGMSSPRGGRTTSNATSNQCENPCPSKSLSPKQ
HLAPDPVVNFTQDLHG VKIKEKGNPEDFVEGKSILSGSVLSHSNLEIKNLEGNRGKGRAATSFSLSDV
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60 SKAKTAALESNLPGSPNTSRGWLPKSPTKGEDWETLKSCSPASSPDLTLEDVIADPTLCFNSGESSLV
EIDGSEENLSLTTC EYRREGTSQLASPLKLYNQGVVEHFQRLRNGYCKETLRPSVPEIFNNIQDVK

- TQSI SYLAYQGAGFVHNHFS DSDAKMFQTCVPQQSSAQDMHVPVPKQLAHLPLPALKLPSPCKSKSLG
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SYIAGYLKNTKGGGLEGRGIPEGACTALHYGHVDQFCSDNSVLQTEPSSDDKPEIYFLLRL
- 5 >SEQ ID NO:37
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- 10 >SEQ ID NO:38
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15 AVLAAFL EEGPEENSAYEQLLSRLEEIAEEGSETQVPGLDISALLPSDFSRYFQYEGSLTTPPCAQGV
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- >SEQ ID NO:39
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LEKKTETAHSLPQQTKKPESEGYLQEEKQKCYNDLLASAKKDLEVERQTITQLSFELSEFRKYEET
QKEVHNLNQLLYSQRRADVQHLEDDRHKTEKIQKLREENDIARGKLEEEKKRSEELLSQVQFLYTSL
25 KQEEQTRVALLEQQMQACTLDFENEKLD RQH VQHQLHVILKELRKARNQITQLES LKQLHEFAITEP
LVTFQGETENREKVAASPKSPTAALNESLVECPKCNIQYPATEHRDLLVHVEYCSK
- >SEQ ID NO:40
30 MEEFDSDEFSTSEEDDYVPSGGEYSEDDVNELVKEDEV DGEETQKTQGGKRRKAQSI PARKRRQGG
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- 35 >SEQ ID NO:41
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DGKPCPPFKIVILDEADSM TSAAQAALRRTMEKESKTTRFCLICNYVSRIIEPLT SRC SKFRFKPLSD
KIQQQRLLDIAKKENVKISDEGIAYLVKVSEGD LRKAITFLQSATRLTGGKEITEKVITDIAGVIPAE
40 KIDGVFAACQSGSFDKLEAVVKDLIDEGHAATQLVNQLHDVVNNLSDKQKSIITEKLA EVDKCLAD
GADEHLQLISLCATVMQQLSQNC
- >SEQ ID NO:42
45 MPLTGVEPARMNRKKGDKGFESPRPYKLTHQVVCINNINFORKSVVGFVELTIFPTVANLNRIKLNSK
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HVDLKV LKIHINFSLDQPKGGLHFVVP SVEGSM AERGAHVFS CGYQNSTRFWFPVDSYSELCTWKL
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50 TGGVLLHPIFGGGKEKDNFASHLHFSIKHPHTLSWEYYSMFQCKAHLVMRLIENRISMEFMLQVFNKL
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ELEIKQDYTSPGTQKYVGPLKVTVQELDGSFNHTLQIEENSLKHDIPCHSKSRNRKKKKIPLMNGEEV
DMDLSAMDADSPLLWIRIDPDMSVLRKVEFEQADFMWQYQLRYERDVVAQQESILALEKFPTPASRLA
LTDILEQEQC FYRVRMSACFCLAKIANS MVSTWTGPPAMKSLFTRMFCCCK3CPNIVKTNNFMSFQSYF
55 LQKTMFVAMALLRDVHNLCPKEVLTFLDLIKYNDNRKNKFS DNYRAEMIDALANSVTPAVSVNNEV
RTLDNLNEDVRLILEEITREFLNMEKLLPSYRHTITVSCLRAIRVLQKNGHVPSDPALFKSYAEYGHFV
DIRIAALEAVVDYTKVDRSYEELQWLLNMIQNDPVPYVRHKILNMLTKNPPFTKNMESPLCNEALVDQ
LWKLMNSGTSHDWRLRCGAVDLYFTLFGLSRPSCLPLPELGLVLNLKEKKA VLNPTTIIPESVAGNQEA
ANNPSSH PQLVGFQNPFFSSSQDEEIDMDTVHDSQAFISHHLNMLERPSTPGLSKYR PASSRSALIPQ
60 HSAGCDSTPTTKPQWSLELARKGTGKEQAPLEMSMHPAASAPLSVFTKESTAKHSDHHHHHHHEHKK
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>SEQ ID NO:43

MFHGIFATPGIGAFGNKPELYEEVKLYKNAREREKYDNMAELFAVVKTMQALEKAYIKDCVSPSEYTA
ACSRLLVQYKAAFRQVQGSSEISSIDEFCRKRFLDCPLAMERIKEDRPITIKDDKGNLNRCIADVVSLEF
5 ITVMDKLRLEIRAMDEIQPDLRELME TMHRMSHLPPDFEGRQTVSQWLQTLSGMSASDELDDSSQVRQM
LFDLESAYNAFNRLHA

>SEQ ID NO:44

MFLYNLTQRATGISFAIHGNFSGTKQQEIVVSRGKILELLRPDPNTGKVHTLLTVEVEFGVIRSLMAF
10 RLTTGGTKDYIVVGS DSGRIVILEYQPSKNMFEKIHQETFGKSGCRRIVPGQFLAVDPKGRAVMISAIE
KQKLVIYILNRDAAARLTISSPLEAHKANTLVYHVVGVDVGFENPMFACLEMDYEEADNDPTGEAAANT
QQTLTFYELDLGLNHVVRKYSEPLEEHGNFLITVPGGSDGPSGLICSENYITYKNFGDQPDIRCP
RRNDLDDPERGMIFVCSATHKTKSMFFFFLAQTEQGLDIFKITLETDEDMVTEIRLKYFDTVFVAAAMC
15 VLKTGFLFVASEFGNHLYQIAHLGDDDEEPEFSSAMPLEEGDTFFFQPRPLKNLVLDLSDLSPL
FCQIADLANEDTPQLYVACGRGPRSSRLVLRHGLEVSEMAVSELPGNPNNAVWTVRRHLEDEFDAYIIV
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VKCAVNQRQVVIALTGGELVYFEMDP SGQLNEYTERKEMSADVCM SLANVPPGEQR SRFLAVGLVDN
TVRIISLDP SDCLOPLSMQALPAQPESLCIVEMGGTEKQDELGERGSIGFLYLNIGLQNGVLLRTVLD
20 PVTGDLSDTRTRYLGSRPVKLFVRMQQGEAVLAMSSRSWLSYSYQSRFHLTPLSYETLEFASGFASE
QCPEGIVAISTNTLRILALEKLGAVFNQVAFPLQYTPRKFIHPESNNLII IETDHNAYTEATKAQRK
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NEAAFSVAVCRFSNTGEDWYVLVGVAKDLILNPRS VAGGFVYTYKLVNNGEKLFLHKTPEVEVPAAI
APFQGRVLIGVGKLLRVYDLGKKLLRK CENKHIANYISGIQTIGHRVIVSDVQESFIWVRYKRNEQ
25 LIIFADDTYPRWVTASLLDYDTVAGADKFGNICVVRLLPNTNDEVEDDEPTGNKALWDRGLLNGASQK
AEVIMNYHVGETVLSLQKTTLIPGGSES LVTTLSSGGIGILVPFTSHEDHDFQHVEMHLRSEHPFLC
GRDHL SFRSYYFPVKNVIDGDLCEQFNSMEPNKQKNVSEELDRTPPEVSKKLEDIRTRYAF

>SEQ ID NO:45

MNQPCNSMEPRVMDDDMLKLA VGDQGPQEEAGQLAQEGILFKDVL SLQLDFRNILRIDNLWQFENLR
30 KLQLDNNIIIEKIEGLENLAHLVWLDLSFNNIETIEGLDTLVNLEDLSLFNNRISKIDSLDALVKLQVL
SLGNNRIDNMMNIIYLRBFKCLRTL SLSRNPTSEAEDYKMFICAYLPDLMYLDYRRIDDHTEKLA
HQYSIDELKHQENLMQAQLEDEQAQREBLEKHKTAFVEHLNGSFLFDSMYAEDSEGNNLSYLPVG
LETYKDKFVVICVNI FEYGLKQQEKRKTELDTFSECVREAIQENQE QGKRKI AKFEKHLSSLSAIRE
ELELPNIEKMILECSADISELFDALMTLEMQLVEQLEETINMFERNIVDMVGLFIENVQSLMAQCRDL
35 ENHHHEKLL ETSISTLEKIVEGDLDEDLPNDLRALFVDKDTIVNAV GASHDIHLLKIDNREDELVTRI
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>SEQ ID NO:46

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40 SEIERRRRNKMTQYITELSDMVPTCSALARKPKDLTILRMVSHMKS MRGTGNKSTDGAYKPSFLTEQ
ELKHLILEAADGFLFVVAETGRVIVVSDSVTPVLNQPQSEWFGSTLYEQVHPDDVEKLRQLCTSEN
SMTGRILD LKTGTVKKEGQQSSMRMCMGSRRSFICRMRCGNAPLDHLPLNRITMRKRFRNGLGPVKE
GEAQYAVVHCTGYIKAWPPAGMTIPEEDADVGGSKYCLVAIGRLQVTS SPVCM DMNGMSVPTFLSR
HNSDGIITFVDP RCISVIGYQPQDLLGKDILEFCHPEDQSHLRESFQQVVKLKGQVLSVMYRFR TKNR
45 EWMLIRTSSFTFQNPYSDEIEYI ICTNTNVKQLQQQQAELEVHQ RDGLSSYDLSQVPVNLPA GVHEA
GKSVEKADAIFSQERDPRFAEMFAGISASEKKMSSASAAGTQQIYSQGSPFSGHSGKAFSSSVVHV
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YSPLSSPATSSPSGNAYSSLANRTPGFAESGQSSGQFQGRPSEVWSQWQSQH HGQSSGEQHSHQQPGQ
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>SEQ ID NO:47

MPEPTKKEENEVPAPAPPPPEEPSKEKEAGTTPAKDWTLVETPPGEEQAKQNANSQLSILFIEKPQGGT
VKVGEDITFIAKVAEDLLRKPTIKWFKGK WMDLASKAGKHLQLKETFERHSRVYTFEMQIIKAKDNF
AGNYRCEVITYKDKFDSCSFDLEVHESGTTPNIDIRSAFKRS GEGQEDAGELDFSGLLKRREVKQEE
55 EPQVDVWELLKNAKPSEYEKIAFYQGITDLRGLMLKRLKMRREEKKSAFAKILDPAYQVDKGGVRVF
VVELADEKLEVWKYKNGQEIRPSTKYIFEHKG CQRLLFINNCQMTDDSEYYVTAGDEK CSTELFVREP
FIMVTKQLEDTTAYCGERVELECEVSEDDANVWFKNGEEIIPGPKSRYRIRVEGKKHILIEGATKA
DAAEYSVMTTGGQSSAKLSVDLKLPLKILTP LDTQTVNLGKEICLKCEISENIPGKWTKNGLPVQESDR
LKVVHKGRIHKLVIANALTEDEGDYVFAPDAYNVTLPAKVHVIDPPKIILDGLDADNTVTVIAGNKLR
60 LEIPISGEPPPKAMWSRGDKAIMEGSGRIRTESY PDSSTLVIDIAERDDSGVYHINLKNEAGEAHASI
KVKVVDFFDPFPVAPTVEVGDDWCIMNWEPPAYDGGSPILGYFIERKKKQSSRWMLNFDLCKETTFE

- PKKMIEGVAYEVRIFAVNAIGISKPSMPSRPFVPLAVTSPPTLLTVDSVTDTTVTMRWRFPDHIGAAG
LDGYVLEYCFEGSTSAKQSDENGEAAAYDLPAEDWIVANKDLIDKTKFTITGLPTDAKIFVRVKAVNAA
GASEPKYYSQPILVKELIEFPKIRIPRHLKQTYIRRVGEAVNLVIFPQKPRPELTWKKDGAIEDKNQ
INIRNSETDTIIFIRKAERSHSGKYDLQVKVDKFVETASIDIQIIDRPGPPQIVKIEDVWGENVALTW
5 TTPKDDGNAAITGYTIQKADKKSMEWFTVIEHYHRTSATITELVIGNEYFRVFSENMCGLSSEDATMT
KESAVIARDGKIYKNPVYEDFDFSEAPMFTQPLVNTYAIAGYNATLNCSSVRGNPKPKITWMKNKVAIV
DDPRYRMFSNQGVCLEIRKPSPYDGGTYCCKAVNDLGTVEIECKLEVKVIAQ
- >SEQ ID NO:48
- 10 MLLETQDALYVALELVIAALS VAGNVLVCAAVGTANTLQTPTNYFLVSLAAADVAVGLFAIPFAITIS
LGFCCTDFYGCFLACFVLVLTQSSIFSLAVAVDRYLAICVPLRYKSLVTGTRARGVIAVLWVLAFIGI
GLTFELGWNSKDSATNNCTEPWDGTTNESCCLVKCLFENNVPMSYMVFYFNGFCVLPPLLIMLVIIYIK
IFLVACRQLQRTLEMDHSRTTLQREIHAAKSLAMIVGIFALCWLPVHAVNCVTLFQPAQGNKPKWAM
NMAILLSHANSVVPNIIVYAYRNRDFRYTFHKIISRYLLCQADVKSNGGQAGVQPALGVGL
- 15 >SEQ ID NO:49
- MSGRPRTTTSAESC KPVQQPSAFGSMKVS RDKDGS KVTTVVATPGQGPDRPQEVSYTDTKVIGNGSFG
VVYQAKLCDSGELVAIKKVLQDKRFKNRELQIMRKL DHCNIVRLRYFFYS SGEKKDEVYLNVLVDYVP
ETVYRVARHYSRAKQTLFVIYVKLYMYQLFRSLAYIHSFGICHARDIKPQNLLDPDTAVLKLCDFGSA
20 KQLVRGEPNVSYICSRYYRAPELIFGATDYTSSIDVWSAGCVLAELLLGQPIFPGDSGVDQLVEIIKV
LGTPTREQIREMNPNYTEFKFPQIKAPWTKVFRPRTPEAIALCSRLLEYTPTARLTPLEACAHSEF
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NNAASASASNST
- 25 >SEQ ID NO:50
- MALSSAWRSVLPLWLLWSAACSRASGDDNAFFFDIEGSSAVGRQDPPETSEPRVALGRLPAAEKCNC
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PHLANFAESC YRKN GAVRCICNENYAGPNCERCAPGYGNPLLIGSTCKKCDCSGNSDPNLFEDCDE
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30 CDKCVWDLTDALRLAALSIEEGKSGVLSVSSGAAHRHVNEINATIYLLKTKLSERENQYALRKIQIN
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HELSPKEISEKLVLAQKMLEEIRSRQPFPTQRELVDDEADEAYELLSQAESWQRLHNETRTLFPVVLE
QLDDYNAKLSDLQEA LDQALNYVRDAEDMNRATAARQRDHEKQQERVREQMEVNM SLSSTADS LTTTP
RLTLSELDDI IKNASGIYAEIDGAKSELQVKLSNL SNLSHDLVQEAIDHAQDLQQEANELSRKLHSSD
35 MNGLVQKALDASN VYENIVNYVSEANETA EFALNTTDRIYDAVSGIDTQIIYHKDESENLLNQARELQ
AKAESSSDEAVADTSRRVGGALARKSALKTRLSDAVKQLQAAERGDAQRLGQSRLITEANRTTMEV
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RIRELIAQTRSVASKIQVSMFDDGQSAVEVHSRTSMDLKAFTSLSLYMKPPVKRPELTETADQFILIY
LGSKNAKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSSWPAYFSIVKIERVVGKHKGVFLTVP SL
40 SSTAEKFIKKGEFSGDDSLDLDLPEDTVFYVGGVPSNFKLPTSLNLPGEFVGCELATLNNDVISLYN
FKHIYNMDPSTSVPCARDKLAFTQSRAAS YFFDGS GYAVVRDITRRGKFGQVTRFDIEVRTPADNGLI
LLMVNGSMFFRLEMRNGYLHVFDYDFGSGGPVHLEDTLKKAQINDAKYHEISIIYHNDKMMILVDDR
HVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMKGFQFQKKDFNLLEQTETLGVG
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45 MDVKGKIKVQSVDKQYNDGLSHFVIVSSVSPTRYELIVDKSRVGSKNPTKGKIEQTQASEKKFYFGGSP
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50 QTFSVTPCFEGPMETGYTFSTEGGYVVLDESFNIGLKFEIAFEVRPRSSSGTLVHGHSVNGEYLVNVM
KNGQVIVKVNNGIRDFSTSVTPKQSLCDGRWHRITVIRDSNVVQLDQDSEVNHVVGPLNPKPIDHREP
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- >SEQ ID NO:51
- 55 MLWLALGFPFAMENQVLVIRIKIPNSGAVDWTVHSGPQLLFRDVLVDVIGQVLPEATTTAFEYEDDGD
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LQKQIMSELEILYKCDSSYIIGFYGAFFVENRISICTEFMDGGS LDVYRKMPHEVLGRIAVAVVKGLT
YLWSLKILHRDVKPSNMLVNTRGQVKLCDFGVSTQLVNSIAKTYVGTNAYMAPEKISGEQYGIHSDVW
60 SLGISFMELALGRFPYPQIQKNQGS LMPLQLLQCIVDEDSPLVLPVGEFSEFEVHFITQCMRKQPKERF
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>SEQ ID NO:52

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5 LFRDGVNWGRIVAFFEFGGVMCVESVNREMSPLVDNIALWMTEYLNRLHHTWIQDNGGWDAFVELYGP
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>SEQ ID NO:53

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15 FNNFIDEYVVLWMMAMVISSFDMMVIYFSALCLQISRHLHLNIFKTACHQAPEQVQVLSSKSHQNNMD

>SEQ ID NO:54

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20 SVLKEQMKVSHREENQHLQTLTQALQDELRTQRLNHLQEQESGNRGAEHFTIELTEENFRRLQAEHDR
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25 QKKIENLQEQRLDKDKQLTNLKDVRKSLQTDSSNTDTALATLEEALSEKERIERLKEQREDDRERL
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>SEQ ID NO:55

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35 VGGACIYKYFMPKSTIYRGEMCFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDVPVPSFSDS
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>SEQ ID NO:56

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45 NSISHIAEGAFKGLRSLRVLDLDHNEISGTIEDTSGAFSGLDLSKLTLFGNLIKSVAKRAFSGLEGL
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>SEQ ID NO:57

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- HKHQPGGEYIFHAENDDAQFTKMFNLNIRRKQVLAEEASASQASCFSDGYPLPSWTWKKCSDKSPNCTE
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 5 CTLSGPIYILIFEYCCYGDLLNLYLSKREKFHRTWTEIFKEHNFsfyPTFQSHPNSSMPGSRVQIHPD
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- 10 >SEQ ID NO:62
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 20 KGETSG
- >SEQ ID NO:63
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 40 RYEVVRDLQTANESAYAIYDFFQVASSKERYKLTGKYRGTAGDALTYHNGWKFTTFDRDNDIALSNC
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- >SEQ ID NO:64
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- 55 >SEQ ID NO:65
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- 10 >SEQ ID NO:67
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15 NAKNGFERAKTWKSKIGN
- >SEQ ID NO:68
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20 KKQAESASEAAKKYMEENDQLKKGA AVDGGKLDVGN AEVKLEENRSLKADLQKLKDELASTKQKLEK
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- >SEQ ID NO:69
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- 50 >SEQ ID NO:71
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- >SEQ ID NO:72
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- >SEQ ID NO:73
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- >SEQ ID NO:74
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- >SEQ ID NO:75
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50 NKAESALAAQAKHFSALRDVIKALRLAMQLEE QASRQISSKKRPQ
- >SEQ ID NO:76
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55 FDGLSETILAVGLVKPKAGIFQPHVRHLLVLATPVDIVILGLSYANLQTGSGVLNDSL SGGMQLLPDP
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 5 RQVQNKTEKERMLRESLKEYQKISNQVDLSNVCAQYRQVRFYEGVVELSLTAAEKKDQGLGLHFYKH
 GEPEEDIVGLQAFQERLNSYKCIDDTLQELVNQSKAAPQSPSPVKKPGPPVLSSDPNMLSNEEAGHHF
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 RSFSNAARVLSRLADMHSTEISLQQRLEYIARAILSAKSSSTAISSIAADGEFLHELEEKMEVARIQLO
 IQETLQROYSHSSVQDAVSQDSELMEDITKLYGEFADPFKLAECKLAIHCAGYSDFILVQTLWQDI
 10 IEKELSDSVTLSSSDRMHALSLKIVLLGKIYAGTPREFFPLDFIVQFLEQQVCTLNWDVGEVIQTMNEI
 GVPFLPRLLEVYDQLFKSRDPFWNRMKKPLHLLDCHVLLIRYVENPSQVLNCCERRFTNLCLDAVCGY
 LVELQSMSSSVAVQAITGNFKSLQAKLERLH

>SEQ ID NO:77

15 MSQVKSSYSYDAPSDFINFSSLDDEGDTQNIIDSWFEEKANLENKLLGKNGTGGLFQGKTPLRKANLQQ
 AIVTPLKVPDNTYYKEAEKENLVEQSIPSNACSSLEVEAAISRKTPAQPPRRSLRLSAQKDLEQKEKH
 HVKMKAKRCATPVIIDEILPSKKMKVSNKKKPEEEGSAHQDTAEKNASSPEKAKGRHTVPCMPPAKQ
 KFLKSTEEQELEKSMKMQQEVVEMRKKNEEFKLLALAGIGQPVKKSVSQVTKSVDFHFRTERIKQHP
 KNQEEYKEVNFTSELRKHPSSPARVTKGCTIVKPFNLQSGKKRTFDETSTYVPLAQQVEDFHKRTFN
 20 RYHLRSKKDDINLLPSKSSVTIKICRDPQTPVLQTKHRAVTCSTAELEAELEKLQYKFKARELD
 PRILEGGPILPKKPPVKPPTPIGFDLETEKRIQERESKKKTEDEHFEFHSRCPCTKILEDVVGVPK
 KVLPIITVPKSPAFALKNRIRMPTKEDEEEDPEVVIKAQPVPHYGVFFKPQIPEARTVEICPFSFDSRD
 KERQLQKEKKIKELQKGEVPKFKALPLPHFDITNLPEKKVKNVTQIEPFCLETDRRGALKAQTWKHQL
 EEELRQQKEAACFKARPNTVISQEPFVPKKEKKSVAEGLSGSLVQEPFQLATEKRAKERQELEKMAE
 25 VEAQKAQQLEEARLQEEEQKKEELARLRRELHVKANPIRKYQGLEIKSSDQPLTVPVSPKFSTRFHC

>SEQ ID NO:78

MESEDLSGRELTIDSIMNKVRDIKNKFKNEDLTDELSLNKISADTTDNSGTVNQIMMANNPEDWLSL
 LLKLEKNSVPLSDALLNKLIGRYSQAIEALPPDKYQNESFARIQVRFAELKAIQEPDDARDYFQMAR
 30 ANCKKFAFVHISFAQFELSQGNVKKSKQLLQKAVERGAVPLEMLEIALRNLNLQKKQLLSEEEKNLS
 ASTVLTAQESFSGSLGHLQNRNNSCDSRGQTTKARFLYGENMPPQDAEIGYRNSLRQTNKTKQSCFP
 RVFVNLLNSPDCDVKTDDSVVPCFMKRQTSRSECRDLVVPKSGKPSGNDSCELRNLSVQNSHFKEPLV
 SDEKSSSELIITDSITLKNKTESSLLAKLEETKEYQEPEVPESNQKQWQSKRKSECINQNPAASSNHQ
 IPELARKVNTEQKHTTFEQPVFSVSKQSPPISTSKWFDPKSICKTPSSNTLDDYMSCFRTPVVKNDP
 35 PACQLSTPYGQFACFQQQHQILATPLQNLQVLASSANECISVKGRIYSILKQIGSGGSSKVFQVLN
 EKKQIYAIKYVNLEADNQTLDYSYRNEIAYLNKLQQHSDKIIRLYDYEITDQYIYMVMCEGNIDLSW
 LKKKKSIDPWERKSYWKNMLEAVHTIHQHGIVHSDLKPANFLIVDGMKLKIDFGIANQMOPDITSVVK
 DSQVGTVNYMPPEAIKDMSSSRENGKSKSKISPKSDVWSLGCILYMTYKTPFQOIINQISKLHAI
 DPNHEIEFPDIPEKDLQDVLKCCCLKRDPKQKISIPELLAHFYVQIQTHPVNQMAKGTTEEMKYVLGQL
 40 VGLNSPNSILKAAKTLYEYSGGESHSN3SSSKTFEKKRGKK

>SEQ ID NO:79

MSSEPPPPPPQPPTHQASVGLLDTPRSRERSPSPLRGNVVPSPPLPTRRTRTFSATVRASQGPVYKGVCK
 CFCSRSGHGFITPADGGPDIFLHISDVEGEYVPVEGDEVYKMCISPPKNEKLQAVEVITHLAPGK
 45 HETWSGHVISS

>SEQ ID NO:80

MGPRRRSRKPEAPRRRSPSPPTPTPGPSRRGFSLGASSHQHSRRRQGWLKEIRKLQKSTHLLIRKLFFS
 RLAREICVKFTRGVDFNWQAQALLALQEAEEAFVHLFEDAYLLTLHAGRVTLFPKDVQLARRIRGLE
 50 EGLG

>SEQ ID NO:81

MDETVAEFIKRTILKIPMNETTILKAWDFLSENQLQTVNFRQRKESVQHLIHLCEEKRASISDAAL
 LDIIYMQFHQHQKQVWEVFMQSKGPGEDVDLFDMDKQFNKSKKILQRAKKNVTVSFRETEENAVWIRIA
 55 WGTQYTKPNQYKPTYVVVYSQTPYAFTSSMLRRNTPLLGQALTIASKHHQIVKMDLRSRYLDSLKAI
 VFKQYNQTFETHNSTTLPQERSLGLDINMDSRIIHENIVEKERVQRITQETFGDYFPQPLEFAQYKLE
 TKFKSGLNGSILAEREEPLRCLIKFSSPHLLEALKSLAPAGIADAPLSPLLTICIPNKRMMNYFKIRDK

>SEQ ID NO:82

60 MGIQGLLQFIKEASEPIHVRKYKGQVAVDITYCWLHKGAIACAELAKGEPTDRYVGFCKMFVNMLLS
 HGIKPILVFDGCTLPSSKKEVERSRRERRQANLLKGKQLLREGKVSEARECFTRSINITHAMAHKVIKA

ARSQGVDCILVAPYEADAQLAYLNKAGIVQAIITEDSDLLAFGCKKVILKMDQFGNGLEIDQARLGMCR
 QLGDFVTEEEKFRYMCILSGCDYLSLRLGIGLAKACKVLRRLANNPDIVKVIKKIGHYLMKNITVPEDYI
 NGFIRANNTFLYQLVFDPIKRKLIPLNAYEDDVPETLSYAGQYVDDSIALQIALGNKDINTFEQIDD
 YNPDITAMPASHRSKSHSWDDKTCQKSANVSSIWHRNYSPRPESGTVSDAPQLKENFSTVGVERVISTKGL
 5 NLPRKSSIIVKRPRSAELSEDDLLSQYSLSFTHKTKKNSSEGNKSLSFSEVFVPDLVNGPTNKKSVSTP
 PRTRNKFATFLQRKNEESGAVVVPGTRSRFFCSDSTDCVSNKVSIIQPLDETAVTDKENNLHESEYGD
 QEGKRLVDITDVARNSSDDIPNNHIFGDHIPDKATVFTDEESYSFESSKFTRTISPPTLGLTRSCFSWS
 GGLGDFSRTFSPSPSTALQQFRKSDSPTSLPENNMSDVSQKSEESSDDESHPLREEACSSQSQESG
 EFSLQSSNASKLSQCSSKSDSEESDCNIKLLDSQSDQTSKLRLSHFSSKDTPLRNKVPGLYKSSSAD
 10 SLSTTKIKPLGPARASGLSKKPASIQKRKHNAENKPGQLIKLNLWKNFGFKKDSEKLFPCKKPLSP
 VRDNIQLTPEAEEDIFNKPECCGRVQRAIFQ

>SEQ ID NO:83

MAVNVYSTSVTSDNLSRHDMLAWINESLQLNLTKIEQLCSGAAYCQFMDMLFPGSIALKKVKFQAKLE
 15 HEYTQNFKILQAGFKRMGVDKIIPVDKLVKGGFQDNFEFVQWFKKFFDANYDGKDYDPVAARQGQETA
 VAPSLVAPALNKKPKPLTSSSAAPQRPISQRTAAAPKAGPGVVRKNPGVGNDDDEAAELMQQVNVLK
 LTVEDLEKERDFYFGKLRNIELICQENEGENDPVLQRIVDILYATDEGFVIPDEGGPQEEQEEY

>SEQ ID NO:84

MEPAPARSPRPQQDPARPQEPTMPPPETPSEGRQPSPPSPSPTERAPASEEEFQFLRCQQCQAEAKCPK
 20 LLPCLHTLCSCGLEASGMQCPICQAPWPLGADTPALDNVFFESLQRRLSVYRQIVDAQAVCTRCKESA
 DFWCFECEQLLCAKCFEAHQWFLKHEARPLAELRNQSVREFLDGTRKTNNIFCSNPNHRTPTLTISIYC
 RGCSKPLCCSCALLDSSHSELKCDISAEIIQQRQEELDAMTQALQEQDSAFGAVHAQMHAAGVQLGRAR
 AETEELIRERVRQVVAHVRAQERELLEAVDARYQRDYEMASRLGRDLAVLQIRITGSALVQRMKCYA
 25 SDQEVLDMMHGLRQALCRLRQEEFQSLQAAVRTDGFDEFKVRQLDLSSCITQGKDAVSKKASPEAAS
 TPRDPIDVDLPEEAERVKAQVQALGLAEAQPMVAVQSVPGAHVPVYAFSIIKGPSYGEDVSNITTAQK
 RKCSQTQCFRKVIKMESEEGKEARLARSSPEQPRPSTSKAVSPPHLDGPPSPRSPVIGSEVFLPNSNH
 VASGAGEAEERVVVISSSESDAENSSSRELDSSSESSDLQLEGPSTLRVLNADLPQAEADRPLVF
 FDLKIDNETQKISQLAAVNRESKFRVVIQPEAFFSIYSKAVSLEVGLQHFLSFLSSMRPILACYKLW
 30 GPGLNFNFRALEDINRLWEFQEAISGFLAALPLIRERVPGASSFKLKNLAQTYLARNMSERSAMAVAL
 AMRDLCKRLLEVSPGPQLAQHVYFPSSSLQCFASLQPLVQAAVLPRAEARLLALHNVSFMELLSAHRDR
 QGGLKKYSRYLSLQTTTLPPAQPAFNLQALGTYFEGLLGEPALARAEGVSTPLAGRGLAERASQQS

>SEQ ID NO:85

MEASPASGPRHMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYG
 35 RHAELRFLDLVPSLQLDPAQIYRVTFEISWSPCFSWGCAGEVRAFLQENTHVRRLIFAARIYDYDPLY
 KEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCCPFQPWDGLDEHSQALSGLRLAILQNQGN

>SEQ ID NO:86

MPHSSDSSDFSRSPPPGKQDSSDDVRRVQRREKNRIAAQKSRQRQTQKADTLHLESEDLEKQNAAL
 40 RKEIKQLTEELKYFTSVLNSHEPLCSVLAASTPSPPEVVYSAHAFHQPHVSSPRFQP

>SEQ ID NO:87

MLFLLPLLAVALPFGDNADGLKEPLSFHVTWIASFYNHWSKQNLVSGWLSDLQTHTWDSNSSTIVFLC
 45 PWSRGNFSSNEEWKELETFRIRTISSFEIGIRRYAHELQFEYPFEIQVTGGCELHSGKVSFGLQLAYQ
 GSDVFSFQNNSWLPYPVAGNMAKHFKVLNQNQHENDITHNLSDTCPRFILGLLDAGKAHLQRQVKP
 EAWLSHGFSFGPGLQLVCHVSGFYPKPVWVMWMRGEQEQQGTQRGDILPSADGTWYLRATLEVAAGE
 AADLSCRVKHSSLEGQDIVLYWEHHSSVGFII LAVIVPLLLIGLALWFRKRFC

>SEQ ID NO:88

MLLLFFQQLLAVLFPGGNSEHAFQGPSTSFHVIQTSSETNSTWAQTQGGSGWLDLQIHGWDSDSGTAIFL
 50 KPWSKGNFSDKEVAELEEIFRVYIFGFAREVQDFAGDFQMKYPFEIQGIAGCELHSGGAIVSFLRGAL
 GGLDFLSVKNASCVPSPPEGGSRAQKFCALIIQYQGITMETVRILLYETCPRYLLGVNLNAGKADLQRQVK
 PEAWLSSGFSFGPGLQLVCHVSGFYPKPVWVMWMRGEQEQQGTQGLDILPNANWTWYLRATLDVADG
 55 EAAGLSCRVKHSSLEGQDIILYWRNPTSIGSIVLAIIVPSLLLLLCLALWYMRRRSYQNI

>SEQ ID NO:89

MLFLQFLLALLLPGGDNADASQEHVSFHVIIQIFSFVNQSWARGQGGSGWLDLQTHGWDSESGTIIIFL
 60 HNWSKGNFSSNEELSDLELLFRFYLFGLTREIQDHASQDYSKYPPFEVQVKAGCELHSGKSPEGFFQVAF
 NGLDLSFQNTTWVSPGCGSLAQSVCHLLNHQYEGVTETVYNLIRSTCPRELLGLLDAGKMYVHRQV

RPEAWLSSSRPSLGSGQLLLVCHASGFYPKPVVWTWMRNEQEQLGTHGDILPNADGTWYLQVILEVAS
EEPAGLSRVRHSSSLGGQDIILYWGHHFSMNWIALVIVPLVILIVLVLFKKHCSYQDIL

>SEQ ID NO:90

5 MLLLFLFFLEGLCCPGENTAAPQALQSYHLAAEEQLSFRMLQTSFANHSWAHSEGGSGWLGDQLQTHGWD
TVLGTIRFLKFWSHGNFSKQELKNLQSLFQLYFHSFIQIVQASAGQFQLEYPFQILAGCRMNAPQI
FLNMAYQGSDFLSFQGISWEPSFGAGIRAOQNICKVLNRYLDIKEILQSLLGHTCPRFLAGLMEAGESE
LKRKVKPEAWLSCGSPSPGPGRLQLVCHVSGFYPKPVVWMMRGEQEQRGTQRGDVLPNADETWYLRAT
10 LDVAAGEAAGLSRVRHSSSLGGHDLIIHWGGYSIFLILICLTIVITLVILVVDVSRLLKKQSSNKNILS
PHTPSPVFLMGANTQDTKNSRHQFCLAQVSWIKNRVLKKWKTRLNQLW

>SEQ ID NO:91

15 MGSNLSFQLCLMPFIFLGLLSGGVTTTPWSLARPPQSGSCSLEGVEIKGGSFRLLQEGQALEYVCPSGFYF
YPVQTRTCRSTGWSWTLKTQDQKTVRKAECRAIHCPRPDHFENGEYWPSPYYNVSDIEISFHCYDGYT
LRGSANRTCQVNGRWSGQTAICDNGAGYCSNPGIPIGTRKVGSGYRLEDSTVYHCSRGLTLRGSQRRT
CQEGGSWSGTEPSCQDSFMYDTPQEVAAEFLSSLTETIEGVDAEDGHGPGEQQRKIVLDPSGSMNIY
LVLDSGSDSIGASNFTGAKKCLVNLIKVASYGKPRYGLVYATYPKIWKVSEADSSNADWVTQKLN
EINYEDHKLKSGTNTKKALQAVYSMMSPDDVPPEGWNRTRHVIILMTDGLHNMGGDPITVIDEIRD
20 LYIGKDRKNPREDYLDVYVFGVGLVNVQVINALASKKDNEQHVFVKVMDENLEDVYQIMIDESQSLS
LCGMVWEHRKGTDYHKQPWQAKISVIRPSKGHESCMGAVVSEYFVLTAACHCTVDDKEHSIKVSVGGE
KRDLEIEVVLFFHPNYNINGKKEAGIPEFYDYDVALIKLKNKLYGQTIRPICLPCTEGTTRALRLPPT
TTCQQQKEELLPAQDIKALFVSEEEKLTRKEVYIKNGDKKSGCERDAQYAPGYDKVKDISEVVT
LCTGGVSPYADPNTCRGDSGGPLIVHKRSRFIQGVVISWGVVDVCKNQKQKQVPAHARDFHINLFQV
25 LPWLKEKLQDEDLGFL

>SEQ ID NO:92

MEGISIYTSDNYTEEMSGSDYDSMKEPCFREANANFNKIFLFTIYSIIFLTGIVGNGLVILVMGYQKK
LRSMTDKYRLHLSVADLLFVITLPPFWAVDAVANWYFGNLFCKAVHVIYTVNLVYSSVLILAFISLDRYL
AIVHATNSQRPRKLLAEKVYVGVWIPALLITIPDFIFANVSEADDRYICDRFYPNDLWVVVFQFQHI
30 MVGLILPGIVILSCYCIILSKLSHSGKHQKRKALKTTVILILAFFACWLPYYIGISIDSFILLEIKQ
GCEFENTVHKWISITEALAFFHCCLNPIFYAFLGAKFKTSAQHALTSVSRGSSSLKILSKGKRGGHSSV
STESSESSSFHSS

>SEQ ID NO:93

35 MSEQSICQARASVMVYDDTSKKWVPIKPGQQGFSRINIYHNTASNTFRVVGVLQDQQVINYISIVKG
LKYNQATPTFHWQWRDARQVYGLNFASKEEATTFSNAMLFALNIMNSQEGGPSSQRQVQNGSPDEMEDI
QRRQVMEQHQQQRQESLERRTSATGFILPPGHPSSAASAPVSCSGPPPPPPPPVPPPTGATPPPPPP
LPAGGAQGGSSHDESSMSGLAATAAGAKLRRVQRPEDASGGSSPSGTSKSDANRASSGGGGGGLMEEMN
KLLAKRRKAASQSDKPAEKKEDESQMEDPSTSPSPGTRAASQPPNSSEAGRKPWERSNSVEKPVSSIL
40 SRTPSVAKSPEAKSPLQSQPHSRMKPAGSVNDMALDAFDLDRMKQEILEEVVRELHKVKEEITIDAIRQ
ELSGISTT

>SEQ ID NO:94

45 MAAAAGEEEEEEEAARESAARPAAGPALWRLPEELLLILCSYLDMRALGRLAQVCRWLRRFTSCDLLW
RRIARASLNSGFTRLGTDLMTSVPVKERVKVSQNWRLGRCREGILLKWRCSQMPWMQLEDDSLYISQA
NFIAYQFRPDGASLNRRLPLGVFAGHDEDEVCHFVLANSIHVSAGGDGKIGIHKIHSFTVVKYSAHEQE
VNCVDCKGGIIVSGSRDRTAKVWPLASGRLGQCLHTIQTEDRVWSIAISPLLSSFVTGTACCGHFSPL
RIWDLNNGQLMTHLGSDFPPGAGVLDVMEYSPFTLLSCGYDTYVRYWDLRTSVRKCVMWEWEPHDSTL
50 YCLQTDGNHLLATGSSYYGVVRLWDRRQRACLHAFPLTSTPLSSPVYCLRLTTKHLYAALSYNLHVLD
EQNF

>SEQ ID NO:95

55 MLVMAFRTVLLLLSAALALTETWAGSHSMRYFYTSVSRPGRGEPRFISVGYVDDTQFVRFDSDAASPR
EEPAPWIEQEGPEYWRNTQIYKAQAQTDRESLRNLRGYYNQSEAGSHTLQSMYGCVDGPDGRLLRG
HDQYAYDGDYIALNEDLRSWTAADTAAQITQRKWEAAREAEQRRAYLEGECEVWLRRLYLENGKDKLE
RADPPKTHVTHHPISDHEATLRCWALGEYPAEITLTWQRDGEDQTQDTELVEPTRPAGDRTFQKWAADV
VPSGEEQRYTCHVQHEGLPKPLTLRWEPPSSQSTVPIVGIVAGLAVLAVVVIGAVVAVMCRKSSGGK
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60 >SEQ ID NO:96

- MKHLWFFLLLVAAAPRWVLSQVQLQESGPGLVKPSSETLSLTCTVSGGSIISGYIWSWIRQPAKGLEWIG
RIYTSGSTNYNPSLKSRTVMSVDTSKNQFSLKLSSVTAADTAVYYCARGRFTYFDYWGQGTLTVTSSA
STKGFSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
5 TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCTCPCPAPELLGGPSVFLFPPKPKDITLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAIKTPREEQYNSTYRVVSVLTVTLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
- >SEQ ID NO:97
- 10 MSLMVVSMVCGVFFLLQGAWPHEGVHRKPSLLAHPGPLVKSEETVILQCWSDVRFQHFLLHREGKFKD
TLHLIGEHHDGVSKANFSIGPMQDLAQTIRCYGSVTHSPYQLSAPSDPLDIVITGLYEKPSLSAQPG
PTVLAGESVTLSCSSRSSYDMYHLSREGEAHERRFSAQPKVNGTFQADFPGLPATHGGTYRCFGSFRD
SPYEWSNSSDPLLVSVTGNPSNSWSPTEPSSSETGNPRHLHLVIGTSVVIILFILLFFLLHRWCCNK
15 KNAVMDQEPAGNRTVNREDSDEQDPQEVTYAQLNHCVFTRQKITRFSQRPKTPFTDIIVYTELPNAE
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- >SEQ ID NO:98
- 20 MRLLAWLIFLANWGGARAEPGKFWHIADLHLDPDYKVS KDPPQVCP SAGSQPVDPAGPWGDYLCDSFW
ALINSSIIYAMKEIEPEPDFILWTGDDTPHPVDEKLGEAAVLEIVERLTKLIREVFPDTKVYAALGNHD
FHPKNQFPAGSNNIYNQIAELWKPWLSNESIALFKKGAFYCEKLPGPSGAGRIIVLNTNLYYTSNALT
ADMADGQQFQWLEDVLTDAASKAGDMVYIVGHVPPGFEKTKQKAWFREGFNEKYLKVVRKHHRVIAQ
QFFGHHHTDSFRMLYDDAGVPISAMFITPGVTPWKTTLPGVVNGANNPAIRVFEYDRATLSLKDMVTY
FMNLSQANAQGTFRWELEYQLTEAYGVPDASAHSMHTVLDRIAGDQSTLQRYVYNSVSYISAGVCDEA
25 CSMQHVCAMRQVDIDAYTTCLYASGTTVPVQLPLLLMALLGLCTLVL
- >SEQ ID NO:99
- 30 MKLLARALRLCEFGRRQASSRRLVAGQGCVGPRRGCCAPVQVVGPRADLPFCGACITGRIMRPDDANVA
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KWRNGDIVQPVNLNPEPNTVSYSSQSSLIHLVGPSDCTLHGFGVHGGVTMKLMDEVAGIVAARHCKTNIIVT
ASVDAINFHDKIRKGCVITISGRMTFTSNKSMIEVLVDADPVDSSQKRYRAASAFFTYVSLSQEGR
SLPVPQLVPETEDEKKRFEEGKGRYLQMKAKRQGHAEFPQ
- >SEQ ID NO:100
- 35 MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKTGTVEYRQFWIF
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VLNLAVAAASHIYQNFVQMILNSLINKSKSSMFQVRTLRELLWGYRDPFLSLVPYPVTTTTVGLFYFY
NNTADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWEHSCDMINGTDAASFPFVEKSSQVLQFFSSDIC
RSIYAVFESDVNLKGIPVYRFVLP SKAFASPVENPDNYCFCTEKIISKNCSTSYGVLDISKCKEGRPVY
40 ISLPHFLYASPDVSEPIDGLNPNEEEHRTYLDIEPITGFTLQFAKRLQVNLVLPSEKIQVLKNLKRN
YIVFILWLNETGTIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKTIK
- >SEQ ID NO:101
- 45 MTVARPSVPAALPLLGLPRLLLLVLCLPAVWGDGCLPPDVFNAPALEGRTSFPEDTVITYKCEES
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LISGSSVQWSDPLPECREIYCPAPPQIDNGIIQGERDHYGYRQSVTYACNKGFTMIGEHSIYCTVNND
EGEWSGPPPECRGKSLTSKVPPTVQKPTTVNVPTTEVSPTSQKTTTKTTPNAQATRSTPVSRTTKHF
50 HETTPNKGSGTTS GTTRLLSGHTCFTLTGLLGLTVMGLLT
- >SEQ ID NO:102
- 55 MDLGPLNICEEMTILHGGFLLAEQLFHPKALAE LTKSDWERVGRPIVEALREISSAAAHSQFFAWKKK
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SDPDACPTMPLLAMLLRGLTQIQSKILGPGRKCCALANLADMLTVFALTEDDPQEV SATVYLDKLATV
ISVWNSDTQNPYHQALAEKVKEAERDVSLTSLAKLPSETIFVGCEFLHLLREWGEELQAVLRSSQG
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AVIQQKMDRHEVCYIFASEKKWAFSDEWVACLGSNRALFRQPDVLRLLETVIDVSTADRAIPESQI
RQVIHLILECYADLSLPGKNKVLGILRSWGRKGLSEKLLAYVEGFQEDLNTTFNQLTQSASEQGLAK
60 AVASVARLVIVHPEVTVKMKCSLAVVNLGTHKFLAQILTAFFPALRFVEEQGNSSATFMVSCCLKETVW
MKFSTPKEEKQFLELLNCLMSPVKPQGIPVAALLEPDEV LKEFVLPFLRLDVEEVDLSLRIFIQTLEA

- NACREEYWLQTCSPFFLLFSLCQLLDRF\$KYWQLPKEKRCLSLDRKDLAIHILELLCEIVSANAETFS
PDVWIKSLSWLHRKLEQLDWTVGLRLKSFFEGHFKEVPATLFEICKLSEDEWTSQAHPGYGAGTGILL
AWMECCCVSSGISERMLSLLVVDVGNPEEVRLFSKGFLVALVQVMFWCSPQEWQRLHQLTRRLLEKQL
LHVPYSLEYIQFVPLLNLPFAQELQLSVLFLRTFQFLCSHSCRDWLPLEGWNHVVKLLCGSLTRLLD
5 SVRAIQAAAGFWVQGPEQDLTQEALFVYTQVFECHALHIMAMLHPEVCEPLYVLALETTLTCYETLSKTNP
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- >SEQ ID NO:103
MAQLGKLLKEQKYDRQLRLWGDHGQEALES\$AHVCLINATATGTEILKNLVLPGIGSFTIIDGNQVS\$E
10 DAGNFFFLQRSSIGKNRAEAAMEFLQELNSDVSG\$FVEESPENLLDNDP\$FFCRFTVVVATQLPESTS
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KLQNVYREKAKKDAAAVGNHVAKLLQ\$SIGQAPESISEKELKLLCSNSAFLRVRCRSLAE\$EYGLDTIN
15 KDEIIS\$MDNPDNEIVLYLMLRAVDRFHKQ\$GRYPGVSNYQVEEDIGKLSCLT\$GFLQ\$EYGLSVMVKD
DYVHEFCRYGAAEPHTIAAFLGGAA\$QEVIKIITKQFVIFNNTYIYSGMSQTSATFQL
- >SEQ ID NO:104
MLYFSLFWAARPLQRCGQLVRMAIRAQHSNAAQTQTGEANRGWTGQESLSDSDPEMWELLQREKDRQC
20 RGLELIASENFC\$SRAALEALG\$CLNNKYSEGYP\$GKRYYGGA\$EVVDEIELLCQRRALEAFDLDPAQWGV
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- >SEQ ID NO:105
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- >SEQ ID NO:106
40 MVKQIESKTA\$FQEALDAAGDKLVVVD\$F\$SATWCGPCKMIKPF\$FHSLS\$EKYSNVIFLEVDVDDCQDVASE
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- >SEQ ID NO:107
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50 IEAGTPGR\$LRVVAQ\$STNSEEII\$EGEYNTVMLAIGRDACTRKIGLET\$VGVKINEKTGKIPVTDEEQTNV
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- >SEQ ID NO:108
55 MDLEGDRNGGAKKKNFFKLN\$NKSEKDKKEKKPTVSV\$F\$SMFRYSNWLDKLYMVVGTLAAI\$IHGAGLPLM
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60 ELERYNKNLEEAKRIGIKKAITANISIGAA\$FLLIYAS\$YALAFWYGTTLVLSGEYSIGQVLT\$VFFSVLI
GAF\$SVGQASPSIEAFANARGAA\$YEIFKIIDNKPSIDSY\$SKSGHKPDNIKGNLEFRNVH\$F\$SYPSRKEVK

- ILKGLNLKVQSGQTVALVGNSSCGKSTTVQLMQRLYDPTGEMVSVDDGQDIRTINVRFLREIIGVVSQE
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 5 KLSTKEALDESIPPVSFWRIMKLNLTWPYFVVGVFCALINGGLQPAFAIIFSKIIGVFTRIDDPETK
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 10 YSTEGLMPNTLEGNVTFGEVVFNYPTRPDIPVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYD
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- 15 >SEQ ID NO:109
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 25 CGKMEEQMTSSSQARKYVNAFSARTLVM
- >SEQ ID NO:110
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 30 QSEAADSNPSELKYLGLDTHSQKRRFPYVALFEKCCCLIGCTKRSLAKYC
- >SEQ ID NO:111
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 35 IRNGSYDIGMACGVESMSLADRGNGNITSRLMEKEKARDCLIPMGITSENVAERFGISREKQDTFAL
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- >SEQ ID NO:112
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 45 NQLSSYPSAALSKLRVVEELKLSHNPLKSIPDNAFQSFGRYLETLWLDNTNLEKFSQGAFLGVTTLKH
 VHLENNRLNLQPSNFPFDSLETALTNPNWKCTCQLRGLRRWLEAKASRPDATCASPAPKFGQHIRD
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- >SEQ ID NO:113
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 55 GWDRTAQVCSVASLLLDPHYRTLKGFMVLEKDWISFGHKFNHRYGNLDGDPKEISPVIDQFIECVWQ
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 60
- >SEQ ID NO:114

- MDVENEQILNVNPPADPDNLSDSLFSGDEENAGTEEEKNEINGNWIASSINEARINAKAKRRLRKNSS
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5 ILCNTYIDSYKGTVDVQARAALDKATVLLSMSKGGKRKDSVWGSQGGGQSVNHLVKEIDMLLKEYLL
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- >SEQ ID NO:115
- 10 MGRRPARCYRYCKNKPYPKSRFCRGVPAKIRIFDLGRKKAKVDEFFLCGHMVSDEYEQLSSEALEAA
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SIRTKLQNKHEHVIEALRRAKFKFPGRQKIHTSKKWGFTKFNADDEFEDMVAEKRLIPDGCQVKYIPNRG
PLDKWRALHS
- >SEQ ID NO:116
- 15 MDTSRVQFIKLARVTKVLGRTGSQGCCTQVRVEFMDDTSRSIIRNVKGPVREGDVLTLLESEREARRL
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- >SEQ ID NO:117
- 20 MARGPKKHLKRVAAPKHWMLDKLTGVFAPRPSTGPHKLRECLPLIIFLRNRLKYALTGDEVKKICMQR
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FDVVHVKDANGNSFATRLSNIFVIGKGNKPWISLPRGKGIRLTIAEERDKRLAAKQSSG
- >SEQ ID NO:118
- 25 MKLNISFFPATGCQKLIIEVDDEKRLRTFYEKRMATEVAADALGEEWKGYVVRISGGNDKQGFPMKQGV
THGRVRLLLSKGHSCYRPRRTGERKRKSVRGCIVDANLSVLNLVIVKKGEKDIPLGTDITVPRRLGPK
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EAAEYAKLLAKRMKEAKEKQEQIAKRRLSSSLRASTSKSESSQK
- >SEQ ID NO:119
- 30 MSSECDGGSKAVMNGLAPGSNGQDKATADPLRARSISAVKIIPVKTIVKNASGLVLPTDMDLTKICTGK
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35 PTLDDFIPPHLQRPWPHHSQPARASGSFAPISQTPPSFSPPPPLVPPAPEDLRRVSEPDLTGAVSSTDS
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40 VLTNEKMSRDISPEEIDLKNEPWyKFFSELEFGKPPPKIWDYTPGDCSILPREDRKTNLDDKDLSCQ
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45 EMSFRKGERITLLRQVDENWYEGRIPTSRQGIFPITYVDVIKRLVKNPVDYMDLPFSSSPRSATA
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50 DRSQTSQDLFSYQALYSYIPQNDDELELRDGDIVDMEKDDGWFGVTSRRTKQFGTFPGNYVKPLYL
- >SEQ ID NO:120
- MSASTGGGGDSGGSGSSSSSSQASCGPESSGSELALATPVPQMLQGLLGSDDDEEQEDPKDYCKGGYHP
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55 DPKRETIVQLIDDFRISGVNGVHVCMVLEVLGHQLLKWIIKSNYQGLPVPCVKSIVRQVLHGLDYLHT
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60 HIAHIVELLGDIPPAFALSGRYSREFFNRRGELRHINLKHGGLYEVLMKEYEWPLEQATQFSAFLLE
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- >SEQ ID NO:121
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- 5 >SEQ ID NO:122
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10 CTGGAAATGAAGTAAAGAAGATTGCGATGCAGCGGTTTCTTAAGATCAATGGCAAGGTCCGTACTGAT
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CTATGACACCAAGGTCGCTTTGCTGTACATCGTATTACACCTGAGGAGGCCAA
- >SEQ ID NO:123
15 MKLVSVVALMYLGLSLAFLGADTARLDVASEFRKKWNKWLRSRGKRELRMSSSYPTGLADVKAGPAQTLI
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- >SEQ ID NO:124
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25 VKEICDITVD
- >SEQ ID NO:125
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30 NSEASPSREAINQREDTGDQOGLLKAIQNDKLAFFGETLS DIPCKTEEEG VGCGGAGRRGDSQECSP
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35 MVLAPRRRTAFHPDLCSQLDQLLQQQS GFESFLKDLKGRQPLRSGPTHVSTRNADIFNSDVVIVERGK
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LSHSEGGDDDDMGEDDEDDGFFVPHGYLSEDEGVTEECADPENHKVRQKLKAKEWDEFLAKGRFRV
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GSKV IIREFQEHCRGLLSNHTGSPRSPSTTYLHTPTP SEDAAIPSKSRLKRLISENSVYEKRPDFRM
40 CWYVHPQVLQSFQQEHLFPVPCQWSYVTSVPSAPKEDSGSV PSTGPSQGTPI SLKRKSAGSMCITQFMK
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- >SEQ ID NO:126
45 MAMFEQMRANVGKLLK GIDRYNPENLATLERYVETQAKENAYDLEANLAVLKLYQFNPAFFQTITVTAQ
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- 50 >SEQ ID NO:127
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55 RIGSGRRAFSGGYRDDD YRGGDYEDRYDRRDRSWSRDDYSRDDYRRDRGFPQRPKLN LKFRS
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60 >SEQ ID NO:128

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 5 VVHKEESLGPKRQKVGF LG

>SEQ ID NO:129

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 10 VCKYTVQDESHSEWVSCVRFSPNSSNP IIVSCGWKLVKVNLANCKLKNHIGHTGYLNTVTVSPDG
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>SEQ ID NO:130

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 15 ISKAQRDPTVTRYYYSIKDISIGGQVCNCHGAEVONINNPEKLFRCCEQHHTCGETCDRCCTGYNQR
 RWRPAWEQSHECEACNCHGHASNCYDDEVERQQASLNTQGIYAGGGVCINCQHNNTAGVNCEQCAKQ
 20 YYRPGYGVDPADPGCIPCSCDPEHADGCEQSSGRCHCKPNFHGDNCEKCAIGYINFPECLRIPIFPVS
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 25 CQGCQCDIGGALSSMCSGPGVCQCREHVVGKVCQRPENNYFPDLHHMKYEIEDGSTPNGRDLRFGF
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 30 QLKGHMARFLLHQVCIPIIEEFSAEYVRPQVHCIAASYGRFVNQSATCVSLAHETPPTALILDVLSGRF
 FPHLPQOSSPSVDVLPGLVTLKAPQNQVTLGRVPHLGRYVFIHFYQAAHPTFFAQVSDGGWPRAGS
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 35 RGTIEAMFECDRDSGQCRCKPRIITGRQCDRCASGFYRFECEVPCNCRDGTGEPVCDPPTGACLCKE
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 40 GICVNCQHNTAGEHCERCQEGYYGNAVHGSRCRACPCPHTNSFATGCVVNGGDVRCSCKAGYTGTQ CER
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 GEQLRLVKSQQLGLSASAGLLEQMRHMETQAKDLRNQLLNYSASINHGSKIEGLERELTDLNQEFET
 LQEKAAQVNSRKAQTLNNNVNRATQSAKELDVKIKNVIRNVHILLKQISGTDGEGNNVPSGDF SREWAE
 45 AQORMMRELRNRNFGKHLREAEADKRESQLLNRIKRTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRA
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5 >SEQ ID NO:131

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>SEQ ID NO:132

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20 >SEQ ID NO:133

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VTTGQRKYGGPPFDSVYSGQQPSVGTEIFVGKIPRDLFEDELVPLFEKAGPIWDLRLMMDPLTGLNRG
YAFVTCTKEAAQEAVKLYNNHEIRSGKHIGVCISVANNRLFVGSIPKSKTKEQILEEFSKVTEGLTD
25 VILYHQPDDDKKKNRGFCFLEYEDHKTAQAARRRLMSGKVKVWGNVGTVEWADPIEDPDPEVMAKVVL
FVRNLANTVTEEILEKAFSQFGKLERVKKLKDYAFIHFDERDGAVKAMEEMNGKDLEGENIEIVFAKP
PDQKRKERKAQRQAANKQMYDDYYYYGPPHMPPTRGRGRGGRGGYGYPPDYGYEDYYGYDYHN
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QRGRGVRGARGGRGNVGGKRAKADGYNQPD SKRRQTNNQNWGSQPIAQQPLQGGDHSNGYGYKSENQE
30 FYQDTEFGQQWK

CLAIMS

1. 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.
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 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.

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 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.
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 metagenes or are selected from a plurality of the metagenes.
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
 5 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
 10 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
 15 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.
- 20 26. The method of Claim 25, wherein the genes are selected from the group consisting of: *ATP6VIC1*, *RAP2A*, *CALM1*, *COG8*, *HELLS*, *KDM5A*, *PGK1*, *PLCH1*, *CEP55*, *RFC4*, *TAF2*, *SF3B3*, *GPI*, *PIR*, *MCM10*, *MELK*, *FOXMI*, *KIF2C*, *NUP155*, *TPX2*, *TTK*, *CENPA*, *CENPN*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*, *TCPI1*, *TXNRD1*, *ADM*, *CHAF1A* and *SYNCRIP*.
- 25 27. The method of Claim 26, wherein the genes are selected from the group consisting of: *MELK*, *MCM10*, *CENPA*, *EXO1*, *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
 30 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.

30. The method of Claim 29, wherein the genes are selected from the group consisting of: *MAPT* and *MYB*.

5 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 *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55,*
 10 *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,*
 15 *CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNI, 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
 20 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.

25 32. The method of Claim 31, wherein 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* and/or the one or plurality of other underexpressed
 30 genes are selected from the group consisting of *BTN2A2, ERC2, IGH, ME1, MTMR7, SMPDL3B* and *ZNRD1-AS1*.

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*, *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*, *RLN1*, *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 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 *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*, *RLN1*, *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 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*, *CAMSAP1*, *CARHSP1*, *CD55*, *CETN3*, *EIF3K*, *EXOSC7*, *GNB2L1*, *GRHPR*, *GSK3B*, *HCFC1R1*, *KCNG1*, *MAP2K5*, *NDUFC1*, *PML*, *STAU1*, *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, SMAD1, GATA3, ITGA2, AKT1, NFKB1, HER2, ASNS and COL6A1, and/or the one or plurality of underexpressed proteins are selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR, COL6A1, PEA15 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.

- 5 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.
- 10 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.
- 15 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.
- 20 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.
- 25 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
 - 30 (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 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.
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, 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.

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, 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.

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*, *FOXMI*, *SKIP2*, *PLK1* 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 method 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 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.

5 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.

10 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.

15 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.

20 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.

30 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 method 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 method of Claim 78, wherein the genes are selected from the group consisting of: *ATP6VIC1*, *RAP2A*, *CALM1*, *COG8*, *HELLS*, *KDM5A*, *PGK1*, *PLCH1*, *CEP55*, *RFC4*, *TAF2*, *SF3B3*, *GPI*, *PIR*, *MCM10*, *MELK*, *FOXMI*, *KIF2C*, *NUP155*, *TPX2*, *TTK*, *CENPA*, *CENPN*, *EXO1*, *MAPRE1*, *ACOT7*, *NAE1*, *SHMT2*, *TCPI*, *TXNRD1*, *ADM*, *CHAF1A* and *SYNCRIP*.

80. The method of Claim 79, wherein the genes are selected from the group consisting of: *MELK*, *MCM10*, *CENPA*, *EXO1*, *TTK* and *KIF2C*.

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 method of Claim 81, wherein the genes are selected from the group consisting of: *BTG2*, *PIK3IP1*, *SEC14L2*, *FLNB*, *ACSF2*, *APOM*, *BIN3*, *GLTSCR2*, *ZMYND10*, *ABAT*, *BCAT2*, *SCUBE2*, *RUNX1*, *LRRRC48*, *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.

83. The method of Claim 82, wherein the genes are selected from the group consisting of: *MAPT* and *MYB*.

5 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
10 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
15 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
20 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
25 associated with estrogen receptor signalling.

87. The method 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.

30 88. The method of any one of 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 *CAMSAP1, CETN3, GRHPR, ZNF593, CA9, CFDP1, VPS28, ADORA2B, GSK3B, LAMA4, MAP2K5, HCFC1R1, KCNG1, BCAP31, ULBP2, CARHSP1, PML, CD36, CD55,*

5 *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*,
 10 *SF3B1*, *ZNRD1-AS1*, *ARNT2*, *ERC2*, *SLC11A1*, *BRD4*, *APOBEC3A*, *CD1A*,
CD1B, *CD1C*, *CXCR4*, *HLA-B*, *IGH*, *KIR2DL3*, *SMPDL3B*, *MYB*, *RLN1*,
MTMR7, *SORBS1* 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
 10 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*,
 15 *CA9*, *CAMSAP1*, *CARHSP1*, *CD55*, *CETN3*, *EIF3K*, *EXOSC7*, *GNB2L1*,
GRHPR, *GSK3B*, *HCFC1R1*, *KCNG1*, *MAP2K5*, *NDUFC1*, *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, *SMPDL3B* and *ZNRD1-AS1*.

20 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
 25 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
 30 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.

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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.

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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.

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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.

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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.

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97. 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*, *KCNGL1*, *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*, *MEI*, *PSEN2*, *CALR*, *CAMK4*, *ITM2C*, *NOP2*, *NSUN5*, *SF3B1*, *ZNRD1-AS1*, *ARNT2*, *ERC2*,

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SLC11A1, BRD4, APOBEC3A, CD1A, CD1B, CD1C, CXCR4, HLA-B, IGH, KIR2DL3, SMPDL3B, MYB, RLNI, MTMR7, SORBS1 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 of *ABHD5, ADORA2B, BCAP31, CA9, CAMSAP1, CARHSP1, CD55, CETN3, EIF3K, EXOSC7, GNB2L1, GRHPR, GSK3B, HCFC1R1, KCNG1, MAP2K5, NDUFC1, PML, STAU1, 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*.

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
5 overexpressed proteins are 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 the one or plurality of underexpressed proteins are selected from the group consisting of VEGFR2, HER3, ASNS, MAPK9, ESR1, YWHAE, RAD50, PGR,
10 COL6A1, PEA15 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
15 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
20 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.

25 106. 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
30 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 overexpressed proteins and the sum of expression levels of the one or plurality of underexpressed proteins.

5 109. 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:

- 10 (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
- 15 (i) the comparison of the expression level of the overexpressed genes selected from the group consisting of *CAMSAP1*, *CETN3*, *GRHPR*, *ZNF593*, *CA9*, *CFDPI*, *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
 - 20 derive a fourth integrated score; or
 - 25 (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
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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, fifth 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, 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.

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 molecularly 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 Bel2 inhibitor, a gluconeogenesis inhibitor, a p38 MAPK inhibitor, a MEK1/2 inhibitor, a mTOR inhibitor, a PI3K inhibitor, an IGF1R inhibitor, a PLC γ 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*, *LAMA3*, *MAP2K5*, *NAE1*, *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*, *CAMSAP1*, *CAMK4*, *CARHSP1*, *FBXW4*, *GSK3B*, *HCFC1R1*, *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 immunotherapeutic 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 immunotherapeutic 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 immunotherapeutic agent.

122. The method of Claim 120 or Claim 121, wherein the immunotherapeutic agent is an immune checkpoint inhibitor.

123. The method of Claim 122, wherein the immune checkpoint inhibitor is or comprises an anti-PD1 antibody or an anti-PDL1 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*, *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 of *CD1C*, *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 immunotherapeutic 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*, *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.

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*, *NDUFC1*, *CAMSAP1*, *CETN3*, *EIF3K*, *STAU1*, *EXOSC7*, *COG8*, *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.

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 the 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 cancer, 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.

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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 (LN⁺) breast cancer, HER2 positive (HER2⁺) breast cancer and ER positive (ER⁺) breast cancer.

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134. An agent identified by the method of any one of Claims 127 to 129 for use in the treatment of cancer.