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(54) Title: SIGNATURE OF CYCLING HYPOXIA AND USE THEREOF FOR THE PROGNOSIS OF CANCER

(57) Abstract: The present invention relates to a signature comprising at least 2 cycling hypoxia markers. The present invention also relates to a non-invasive method for the prognosis of cancer in a subject, wherein said method comprises assessing the expression of markers of a signature of the invention in a sample from said subject; and to a kit for implementing this non-invasive method.

SIGNATURE OF CYCLING HYPOXIA AND USE THEREOF FOR THE PROGNOSIS OF CANCER

FIELD OF INVENTION

The present invention relates to the field of cancer prognosis. More specifically, the present invention relates to a signature based on differential gene expression in conditions of cycling hypoxia, for the prognosis of cancer in a subject.

BACKGROUND OF INVENTION

Cancer is a general term referring to a broad group of diseases characterized by unregulated and uncontrolled cell growth and division. These diseases caused in 2007 about 8 million death worldwide, and are currently the second leading cause of death in developed countries. As prognostic and response to treatments are subject-dependent, there is a need for prognostic and/or predictive means, allowing estimating for each subject the progression of his/her disease and/or his/her response to a given treatment.

Several prognostic or predictive means are currently known in the prior art. Among them, some correspond to a signature, i.e. are based on specific gene expression of tumors or peritumoral tissues.

For example, the European patent application EP 1 754 795 describes a method for predicting relapse of breast cancer in bone by analyzing the expression of a group of 76 genes. This prognostic signature is known in the art as the Gene76 signature.

Moreover, the international patent application WO 02/103320 describes genetic markers whose expression is correlated with breast cancer. More specifically, this patent application describes a genetic signature comprising 70 genes, known as Gene70 or Mammaprint, for the diagnosis and the prognosis of breast cancer in a subject.

Furthermore, the international patent application WO2006/052862 describes a signature useful for predicting whether cancer patients are likely to have a beneficial response to treatment with chemotherapy. The specific signature disclosed by WO2006/052862 corresponds to the Oncotype DX signature developed for breast cancer patients.

Both Oncotype DX signature and Mammaprint signature are approved for clinical use.

However, the signatures of the prior art present the drawback to be designed for one type of cancer only. For example, the above cited signatures were developed for breast cancer. There is thus a need for a genetic signature that may be used for the prognosis of not only one cancer type, but of several cancers. Especially, there is a need for a signature that may be used for the prognosis of all tumors.

A common characteristic of tumors is cycling hypoxia. Cycling hypoxia corresponds to a temporal instability in oxygen transport, as a result of instabilities in microvessel red blood cell flux within tumors. Indeed, tumor angiogenesis and glycolytic metabolism are two responses of cancer cells to a deficit in oxygen. The building of new blood vessels to bring 0_2 and the uncoupling from mitochondrial oxidative phosphorylation to survive under low 0_2 are actually two complementary responses to hypoxia. These somehow opposite modes of adaptation account for local and temporal heterogeneities in tumor 0_2 distribution. The extent of cycling hypoxia may reflect tumor plasticity and thus may be a mark of the capacity of tumor cells to survive and proliferate in a hostile environment.

The inventors herein showed that cycling hypoxia has the potential to lead to common alterations in the expression of some transcripts. They thus developed a signature of cycling hypoxia of particular clinical relevance for the prognosis of cancers.

SUMMARY

The present invention thus relates to a signature comprising at least 2 cycling hypoxia markers. In one embodiment, the signature comprises at least 3, preferably at least 5, more preferably at least 10 cycling hypoxia markers. In one embodiment, said cycling

hypoxia markers are selected from the list of 1379 cycling hypoxia markers of Table 1, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 651 cycling hypoxia markers of Table 2, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 298 cycling hypoxia markers of Table 3, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 167 cycling hypoxia markers of Table 4, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 96 cycling hypoxia markers of Table 5, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 74 cycling hypoxia markers of Table 6, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 37 cycling hypoxia markers of Table 7, fragments, variants and equivalents thereof. In another embodiment, said cycling hypoxia markers are selected from the list of 10 cycling hypoxia markers of Table 8, fragments, variants and equivalents thereof. In another embodiment, said signature comprises the 10 cycling hypoxia markers of Table 8, variants, fragments and equivalents thereof.

The present invention also relates to a non-invasive method for the prognosis of cancer in a subject, or for predicting the response of a subject to a specific treatment, wherein said method comprises assessing the expression of markers of a signature as described hereinabove in a sample from said subject. Therefore, the present invention also relates to a non-invasive method for the prognosis of cancer in a subject, or for predicting the response of a subject to a specific treatment, wherein said method comprises assessing the expression of markers of a signature comprising at least 2 cycling hypoxia markers in a sample from said subject. In one embodiment, the signature comprises at least 3, preferably at least 5, more preferably at least 10 cycling hypoxia markers. In one embodiment, the cycling hypoxia markers are selected from the list of 1379 cycling hypoxia markers of Table 1, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 651 cycling hypoxia markers of Table 2, fragments, variants and equivalents thereof. In one

embodiment, the cycling hypoxia markers are selected from the list of 298 cycling hypoxia markers of Table 3, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 167 cycling hypoxia markers of Table 4, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 96 cycling hypoxia markers of Table 5, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 74 cycling hypoxia markers of Table 6, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 37 cycling hypoxia markers of Table 7, fragments, variants and equivalents thereof. In one embodiment, the cycling hypoxia markers are selected from the list of 10 cycling hypoxia markers of Table 8, fragments, variants and equivalents thereof. In one embodiment, the signature comprises the 10 cycling hypoxia markers of Table 8, variants, fragments and equivalents thereof.

In one embodiment, said method comprises mathematically combining the expression profile of markers in a score. In one embodiment, said sample is a biopsy sample or a bodily fluid sample of said subject. In one embodiment, the method of the invention further comprises comparing said expression with a reference expression profile.

The present invention further relates to a kit for determining the expression profile of a genetic signature as described hereinabove, or for implementing the non-invasive method as described hereinabove, wherein said kit comprises means for determining the expression of the cycling hypoxia markers of the signature of the invention. In one embodiment, said means for determining the expression of the markers of the signature is a microarray comprising probes specific for said cycling hypoxia markers. In another embodiment, said means for determining the expression of the cycling hypoxia markers are qPCR primers specific for said cycling hypoxia markers.

DEFINITIONS

In the present invention, the following terms have the following meanings:

- "**Prognosis**" refers to the likelihood of cancer-attributable death or cancer progression, including recurrence and metastatic spread of a neoplastic disease, during the natural history of the disease, or to the likelihood of a beneficial response to a specific treatment, wherein a beneficial response means an improvement in any measure of patient status including, but not limited to, overall survival, long-term survival (i.e. survival for at least 3, preferably at least 5, 8, or 10 years following diagnosis, surgery or other treatment), recurrence-free survival, and distant recurrence-free survival. Accordingly, a "**prognostic signature**" refers to a signature that may be used for the prognosis of a subject. In one embodiment, the term "prognostic signature" also includes "**predictive signature",** wherein said term refers to a signature that may be used for anticipating the response of a subject to a specific treatment.

- "**Normoxia**" refers to an oxygen tension condition corresponding to healthy tissues. In one embodiment, in conditions of in vitro cell culture, normoxia may refer to a condition with a concentration of $\mathbf{0}_2$ ranging from about 10 to about 21%, preferably from about 15 to about 21%, and more preferably of about 20-21% $\mathbf{0}_2$.

- "**Hypoxia**" refers to a condition wherein the oxygen tension is inferior to the oxygen tension of healthy tissues. In one embodiment, in conditions of in vitro cell culture, hypoxia may refer to a condition with at most 5% $\mathbf{0}_2$, preferably to a condition with about 1% $\mathbf{0}_2$.

- "**Cycling hypoxia**" (also known as "cyclic hypoxia") refers to a temporal instability in oxygen transport. Cycling hypoxia thus corresponds to alternating normoxia and hypoxia cycles.

- "**Signature**" refers to a group of markers (i.e. at least 2, preferably at least 3, more preferably at least 5, and even more preferably at least 10 markers) whose combined expression profile is indicative of a biological condition (such as, for example, cycling hypoxia), or of a particular prognosis or of a particular response of a subject to a treatment.

- A "**marker**" corresponds to a nucleotide sequence isolated from the genome, preferably to a gene in the genome, i.e. each marker is identifiable as all or a portion of a gene. A marker may thus correspond to an entire gene, or to an EST (wherein EST stands for Expressed Sequence Tag) derived from this gene.
- "**Expression**" refers interchangeably to expression of a marker, including the encoded polypeptide or protein. Expression of a marker may be determined, for example, by immunoassay using one or more antibody(ies) that bind(s) with the polypeptide. Alternatively, expression of a marker may be determined by measurement of mRNA levels, for example, by RT-PCR, RT-qPCR (wherein qPCR stands for quantitative PCR), or using a microarray, or using sequencing methods. In one embodiment, the term "expression" of a marker may also refer to modification of a protein or peptide, preferably to post-translational modification of a protein or peptide.
- "**Subject**" refers to an animal, preferably a mammal, more preferably a human. In one embodiment, the subject is a patient, i.e. a recipient of health care services. Preferably, the subject is a cancer patient, i.e. he/she was previously diagnosed with cancer.
- "**About**" preceding a figure means plus or less 10% of the value of said figure.

DETAILED DESCRIPTION

The present invention first relates to a signature of cycling hypoxia, wherein said signature comprises markers whose expression is different between a normoxic condition and a cycling hypoxia condition.

In one embodiment of the invention, the signature of the invention comprises at least 2 markers, preferably at least 3 markers, 4 markers, more preferably at least 5 markers, and even more preferably at least 10 markers.

The present invention thus also relates to a marker whose expression is different between a normoxic condition and a cycling hypoxia condition. A marker whose

expression is different between a normoxic condition and a cycling hypoxia condition will be hereinafter referred as a "cycling hypoxia marker".

Methods for determining cycling hypoxia markers are well-known from the skilled artisan, and include, without limitation, comparing the transcriptome (in an embodiment wherein expression relates to transcription of a marker) or proteome (in an embodiment wherein expression relates to translation of a marker) in a condition of normoxia and in a condition of cycling hypoxia. An example of such a method, based on the comparison of transcriptomes, is presented in the Examples.

Examples of post-translational modifications of a protein or peptide include, but are not limited to, phosphorylation, myristoylation, palmitoylation, isoprenylation, glypiation, lipoylation, **0-,** N- or S- acylation, alkylation, glycosylation, malonylation, hydroxylation, nucleotide addition, oxidation, sumoylation, ubiquitination, citrullination, deamidation, formation of disulfide bridges, proteolytic cleavage, racemization and the like. Examples of methods for assessing post-translational modifications of a protein or peptide include, but are not limited to, mass spectroscopy, immunoblotting, Eastern blotting, and the like.

In one embodiment of the invention, a marker is considered as differentially expressed in conditions of normoxia and cycling hypoxia if, according to a t-test, the p-value after FDR correction is lower than 0.05, preferably lower than 0.01.

In one embodiment, cycling hypoxia markers are selected from the list of the 1379 cycling hypoxia markers of **Table 1** below, as well as their variants, fragments or equivalents. Table 1 comprises cycling hypoxia markers identified in the conditions of the Example and presenting a p-value after FDR correction lower than 0.05.

Pathways refer to the KEGG pathway database (http://www.genome.jp/kegg/).

In the Table 1 below, and in Tables 2-8, probesets are indicated according to the nomenclature of "Human gene LOST".

GeneBank Accession Number	Name of the marker	Pathways	Probeset
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
NR_003287	RN28S1		7942875, 8059576, 7917645, 7942791 or 8151234
AF284753	UIMC1		7911343 or 8165703
NM_0 14248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NM_177987	TUBB8	04145, 04540, 05130	7911355
NM_170601	SIAE		7944867
NM_001012708	KRTAP5-3		7945652
NR_029710	MIR193A		8006321
NM_000981	RPL19	3010	8006845
NM_012217	TPSD1		7992191
NM_003792	EDF1		8165309
BC013044	DNAJA2	4141	7995379
NR_029824	MIR128-2		8078527
NM_004352	CBLN1		8001329
NM_001017	RPS13	3010	7946812
NM_00 1037 160	CYS1		8050232
NM_003731	SSNA1		8159609
NM_006160	NEUROD2		8014865
NM_001417	EIF4B	03013, 04150	7963575
NM_017854	TMEM160		8037853
NM_0 16057	COPZ1		7955896
NM_152568	NKX6-3		8150433
NM_016170	TLX2		8042896
NR_002715	RN7SL1		8040338
NM_016564	CEND1		7945536
AK302042	LOC440518		8027343
NM_0 14206	CllorflO		7948606
NR_033335	SNORA70G		7964830
NM_003094	SNRPE	3040	8160033 or 7908988
NM_0 12322	LSM5	03018, 03040	8138912
NM_145232	CTU1	4122	8038782
NR_029583	MIR197		7903717
NM_032231	FAM96A		7989611
NR_024583	POM121L8P		8071168
NM_007241	SNF8	4144	8016508
NM_000307	POU3F4		8168567
NM_0 13299	SAC3D1		7941122

NM_005608	PTPRCAP		7949792
NM_006327	TIMM23		7927548
NM_0 16424	LUC7L3		8016733
NM_144615	TMIGD2		8032782
NM_001 135086	PRSS41		7992716
NM_003512	HIST1H2AC	5322	8117372
NM_000863	HTR1B	4080	8127692
NM_145203	CSNK1A1L	04310, 04340	7971071
NR_000009	SNORD4B		8005957
NM_001080113	C14orfl84		7980859
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861 or 8180305
NM_031210	SLIRP		7975989
NM_023002	HAPLN4		8035646
NM_1 82532	TMEM61		7901687
NM_003538	HIST1H4A	5322	8117334
AK125166	LOC441268		8141166
NM_00 100 1521	UGP2	00040, 00052, 00500, 00520, 01100	8052624
NR_001445	RN7SK		8120249
NM_001551	IGBP1		8168087
NM_138417	KTI12		7916130
NM_031213	FAM108A1		8032371, 7904869, 7904948, 7924230 or 8074842
BC001181	FAM173A		7992043
NM_001031	RPS28	3010	8005471, 8025395 or 7942824
NM_004175	SNRPD3	03040, 05322	8071920
NM_00 1044370	MPPED1		8073623
BC005079	C2orf42		8052834
NM_003542	HIST1H4C	5322	8117368
BC033986	LOC440934		8048712
NM_00 1082575	RBFOX3		8018993
NM_0 17900	AURKAIP1		7911532 or 8039923
NM_001024598	HES3		7897280
NM_022061	MRPL17		7946267
NM_001029	RPS26	3010	8007797 or 8154363
NM_0 16060	MED31		8011968
NM_0 12394	PFDN2		7921786
NM_0 15965	NDUFA13	00190, 05010, 05012, 05016	8027205
NM_080603	ZSWIM1		8063074

NM_021104	RPL41	3010	7957530, 7965467, 7982129, 8105432, 8075691 or 8061364
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_032753	RAX2		8032601
NM_003684	MKNK1	04010, 04910	7915846
NM_003577	UTF1		7931553
NM_022363	LHX5		7966631
NM_00 1037495	DYNLL1	4962	7967067 or 7959164
NM_004609	TCF15		8064370
AK098732	TRAP1		7992954
NM_144999	LRRC45		8010719
NM_001018138	NME2	00230, 00240, 01100	8180388, 8180389, 8180387 or 8180386
NM_002528	NTHL1	3410	7998692
NM_006087	TUBB4	04145, 04540, 05130	8025051
NM_003493	HIST3H3	5322	7924884
NR_026800	KIAA0125		7977440
NM_015456	COBRA1		8159654
NM_006088	TUBB2C	04145, 04540, 05130	8165496
NM_002307	LGALS7		8036584 or 8028546
NM_181887	UBE2D3	04120, 04141	8180330, 8180335, 8180334, 8180331, 8180333, 8180329, 8180332 or 8102024
NM_001348	DAPK3	05200, 05219	8032718
NM_005319	HIST1H1C		8124397
NM_178536	LCN12		8159501
NR_003666	SPDYE7P		8133209
AK125308	LOCI 00129484		8137962
NM_020412	CHMP1B	4144	8020179
NM_003550	MAD1L1	04110, 04914	8137805
NM_032527	ZGPAT		8064156
NR_003051	RMRP		8161024
NR_029681	MIR 140		7997008
NM_006858	TMED1		8034101
NM_006312	NCOR2	4330	7959772
AK095987	FLJ38668		8054449
ENST00000427835	C20orf61		8065013
NM_001 144936	Cllorf95		7949015
NM_173547	TRIM65		8018502
NM_0 14370	SRPK3		8170753

NM_005574	LM02		7947450
NM_00 1007595	C2CD4B		7989473
NM_001168	BIRC5	05200, 05210	8018860
NM_021012	KCNJ12		8005726
NM_144589	COMTD1		7934544
NM_016589	TIMMDCl		8081867
NM_012315	KLK9		8038716
NM_006292	TSG101	4144	7947015
NM_033055	HIATI		7903294
NM_001 113201	NACA		7964262
NM_181838	UBE2D2	04120, 04141, 05131	8108435
NM_005973	PRCC		7906235
NM_005274	GNG5	4062	8174509
NM_006770	MARCO	4145	8044773
NM_0 14674	EDEM1	4141	8085116
NM_145657	GSX1		7968260
NM_002003	FCN1		8165011
NM_003001	SDHC	00020, 00190, 01100, 05010, 05012, 05016	8011212
NM_0 18942	HMX1		8104136
NM_006848	CCDC85B		7941457
NM_032338	LLPH		7956876
NM_0 15971	MRPS7		8009784
NM_020180	CELF4		8022952
NM_00 1080495	TNRC18		8137959
NM_006181	NTN3	4360	7992632
AK094921	LOC100131763		8049950
NM_198545	Clorfl87		7897737
NM_002066	GML		8148565
NM_031899	GORASP1		8086317
NM_0 12452	TNFRSF13B	04060, 04672, 05340	8013061
NM_138574	HDGFL1		8117172
NM_024816	RABEP2		8000616
NM_022097	CHP2	04010, 04020, 04114, 04210, 04310, 04360, 04370, 04650, 04660, 04662, 04720, 05010, 05014	7994123
NM_006801	KDELR1	5110	8038078
NM_004939	DDX1		8040386
NM_1 30784	SYCE1		7937247
NM_0 19082	DDX56		8139392
NM_00 10399 16	ZNF384		7953390
NM_0 16602	CCR10	04060, 04062, 04672	8015681

NR_024591	POM121L1P		8074714 or 8074867
NM_020064	BARHL1		8158912
NM_006356	ATP5H	00190, 01100, 05010, 05012, 05016	8018288
NM_0 12249	RHOQ	4910	8041808
NR_002951	SNORA2B		7962829
NR_004430	RNUl-1		7919269, 7919349, 7898375, 7898411, 7912800, 7912850, 7919576, 7973896 or 7978568
NM_00 1126128	PROK2		8088813
NM_0 16063	HDDC2		8129363
NM_005706	TSSC4		7937813
NR_002781	TSPY26P		8065603
NM_175064	SPDYE1		8140424, 8140454 or 8132531
NM_138350	THAP3		7897329
AY730278	CENPVL1		8167652 or 8172715
NM_002669	PLRG1	3040	8103289
NM_006476	ATP5L	00190, 01100	7944216
NM_031909	C1QTNF4		7947928
NM_032805	ZSCAN10		7998921
NM_001804	CDX1		8109226
NM_0 14976	PDCD11		7936096
AK097604	LOCI 00 130285		7998265
NM_003168	SUPT4H1		8016982
NM_016835	MAPT	04010, 05010	8016263
NM_001002	RPLP0	3010	8109750 or 7966996
NM_0 16305	SS18L2		8079074
NM_001033113	ENTPD8	00230, 00240	8165538
NM_003926	MBD3		8032275
NM_031280	MRPS15		7914940
NR_026676	RPS2P32		8131869
NM_145803	TRAF6	04010, 04120, 04144, 04380, 04620, 04621, 04622, 04722, 05140, 05142, 05145, 05160, 05200, 05222,	7947540
NM_000858	GUK1	00230, 01100	7910241
NM_139172	TMEM190		8031475
NM_0 18047	RBM22	3040	8115168
NM_1 82702	PRSS42		8086683

NM_003859	DPMI	00510, 01100	8067017
NM_003002	SDHD	00020, 00190, 01100, 05010, 05012, 05016,	7943853 or 7899016
NR_026716	KIR3DX1		8031200
NM_015719	COL5A3	04510, 04512, 04974, 05146	8033825
L20860	SEPT5-GP1BB		8071272
NM_101395	DYRK1A		8068551
NM_014419	DKKL1		8030292
NR_026557	PLK5		8024331
BC043386	C19orf68		8029996
NM_00 1080440	OTOL1		8083770
NM_144578	MAPK1IP1L		7974455
NM_012145	DTYMK	00240, 01100	8060286 or 8077262
NM_002804	PSMC3	3050	7947867
NM_00 1172743	RAI2		8171539
NM_0 16547	SDF4		7911422
NM_175741	C15orf55		7982516
NM_003910	BUD31	3040	8134589
NM_0 14342	MTCH2		7947934
NM_001013	RPS9	3010	8180398 or 8031152
NM_021646	ZNF500		7999196
AY341951	FAM138D		7960172
NM_005034	POLR2K	00230, 00240, 01100, 03020, 05016	8147654
NM_00 1005922	KRTAP5-1		7945645
NM_001 105669	TTC24		7906177
NM_006043	HS3ST2	534	7994052
NM_173641	EPHA10		7915078
NM_001010908	C1QL3		7932308
NM_00 1164094	COPS7A		7953395
NM_014582	OBP2A		8180231
NM_024319	Clorf35		7924842
NM_003375	VDAC2	04020, 05012, 05016	8042335 or 7928524
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NM_016512	SPAG11B		8144460
NM_0 12473	TXN2		8075778
NM_020143	PNOl		8052719
NM_018652	GOLGA6B		7984961, 7984662 or 7985221
NM_004911	PDIA4	04141, 05110	8143684
NM_007208	MRPL3		8090678
NM_005547	IVL		7905533
NM_00 1009994	RIPPLY2		8120937
NM_003505	FZD1	04310, 04916, 05200, 05217	8134117
NM_174889	NDUFAF2		8105499
NM_002506	NGF	04010, 04210, 04722	7918869
NM_022157	RRAGC		7915160
NR_004387	SCARNA10		7953383
NM_001864	COX7A1	00190, 04260, 05010, 05012, 05016	8036284
NM_004314	ART1		7937882

NM_001695	ATP6V1C1	00190, 01100, 04145, 04966, 05110, 05120, 05323	8147724
NM_023007	JMJD4		7924823
NM_002377	MAS1	04080, 04614	8123176
NM_00 1142648	SARI A	4141	7934122
NM_020971	SPTBN4		8028806
NM_004470	FKBP2		7940914
NM_002032	FTH1	860	8170360
NM_001017928	CCDC58		8089988
NM_001098169	BSX		7952321
NM_00 1145030	C3orf77		8079167
NM_006294	UQCRB	00190, 01100, 04260, 05010, 05012, 05016	8151909
NM_198492	CLEC4G		8033433
NM_138364	PRMT10		8103079
NM_006362	NXF1	03008, 03013, 03015	7948839
NM_00 1130963	TMEM194A		7964347
NM_144720	JAKMIP1		8099200
NM_031209	QTRT1		8025728
NM_0 15092	SMG1	3015	8000687
NM_0 14637	MTFR1		8146649
NM_003837	FBP2	00010, 00030, 00051, 01100, 04910	8162492
NM_00 1172129	HCK	04062, 04666	8061668
NR_003260	DNM1P46		7986426
NM_016013	NDUFAF1		7987642
NM_004831	MED26		8035187
NM_022728	NEUROD6		8138882
NM_153442	GPR26		7931199
NM_152864	NKAIN4		8067602
NM_002309	LIF	04060, 04630	8072314
NM_003951	SLC25A14		8169904
NM_033341	BIRC8		8039078
NM_018698	NXT2	03008, 03013, 03015	8169352
NM_198353	KCTD8		8100070
NM_00 1127258	HHIPL1		7976669
NR_027001	LOC388152		7991159 or 7991088
NM_0 13270	PRSS50		8086660

NM_00 1105572	PLA2G2C	00564, 00565, 00590, 00591, 00592, 01100, 04010, 04270, 04370, 04664, 04730, 04912, 04972, 04975, 05145	7913235
NM_0 14846	KIAA0196		8152782
NM_005205	COX6A2	00190, 01100, 04260, 05010, 05012, 05016	8001041
NM_1 30777	XAGE2		8167693 or 8172749
NR_024151	HSPA7		7906775
AY358690	EEF1D		8153457
NM_005800	USPL1		7968333
NM_016486	TMEM69		7901135
NM_020649	CBX8		8019010
NM_152516	COMMD1		8042207
NM_015933	CCDC72		7899346
NM_016125	RNFT1		8017162
NM_001485	GBX2		8059864
NM_032730	RTN4IP1		8128606
NM_00 1143938	ZNF534		8030939
NM_0 17622	C17orf59		8012397
AK313893	CCDC82		7951157
NM_013334	GMPPB	00051, 00520, 01100	8087461
NM_181788	H1FNT		7955112
NM_023039	ANKRA2		8112596
NM_172239	REX01L1	3008	8151609
NM_032834	ALG10	00510, 01100	7954777
NM_1 82546	VSTM2A		8132851
NM_015871	ZNF593		7899096
NR_002912	SNORA67		8004508
NM_002860	ALDH18A1	00330, 01100	7935230
NM_00 1166222	CARNS1		7941890
NM_022662	ANAPC1	04110, 04114, 04120, 04914	8054437 or 8043322
NM_025263	PRR3		8117922
NM_1 39062	CSNK1D	04340, 04540, 04710	8019463
NM_080864	RLN3		8026265
NR_002450	SNORD68		7997940
NM_003224	ARFRP1		8067727
NM_00 1145928	SAP 130		8055104
NM_006741	PPP1R1A	4720	7963826
NM_139174	ADAD2		7997569
NM_199193	BRE		8041031
NM_021190	PTBP2		7903188
NM_005634	SOX3		8175528
NM_021211	ZBED5		7946635
NM_0 15267	CUX2		7958726
NM_020755	SERINC1		8129317

NM_144632	TMEM182		8044094
NM_006036	PREPL		8051928
NM_015634	KIAA1279		7927955
NM_004450	ERH		7979864
NM_015676	C14orfl09		7976333
NM_0 14655	SLC25A44		7906128
NM_018641	CHST12	00532, 00920	8131135
NM_004793	LONP1		8033002
NM_1 39209	GRK7	04062, 04144, 04744	8083129
NM_001641	APEX1	3410	7973056
NM_178510	ANKK1		7943943
NM_1 82520	C22orfl5		8071745
NM_0 14675	CROCC		7898377
NM_001013632	TCTEX1D4		7915609
NM_00 1080469	FBX046		8037647
NR_026833	LOC400940		8040077
NM_006137	CD7	4640	8019478
NM_002987	CCL17	04060, 04062	7996034
NM_012112	TPX2		8061579
NM_015910	WDPCP		8052598
NM_00 1003938	HBM		7991758
NR_029857	MIR302B		8102406
NM_003198	TCEB3		7898881
NM_001690	ATP6V1A	00190, 01100, 04145, 04966, 05110, 05120, 05323	8081740
NM_005153	USP10		7997633
NR_029495	MIR23A		8034698
NM_00 1077621	VPS37D	4144	8133339
NM_00 1100600	MMD2		8137931
NR_027284	LOC441177		8123334
NM_032819	ZNF341		8061946
NM_017438	SETD4		8070215
NM_005744	ARIH1		7984641
NM_030571	NDFIP1		8108861
NM_0 14275	MGAT4B	00510, 01100	8116316
NR_002922	SNORA13		8107326
NR_024532	ALG2	00510, 01100	8162827
NM_016172	UBAC1		8165064
NM_001023560	ZNF187		8117667
AK125652	NIF3L1		8047370
NM_017638	MED 18		7899448
NM_032339	C17orf37		8014882
NM_152494	DCST1		7905862
NM_00 100 1973	ATP5C1	00190, 01100, 05010, 05012, 05016	7926084
NM_0 16237	ANAPC5	04110, 04114, 04120, 04914	7967149
NM_030578	B9D2		8037018

NM_021970	LAMTOR3	4010	8101925
NM_002568	PABPC1	03013, 03015, 03018	8152079
NM_00 1164416	H2BFM	5322	8169080
NM_003353	UCN		8051061
NM_003477	PDHX	1100	7939329
NM_181806	AASDH		8100478
NM_00 108 1461	JMJD6		8018793
NM_153358	ZNF791		8026007
NM_006077	MICUl		7934255
NM_00 1005470	OR4B1	4740	7939865
NM_022101	CXorf56		8180338
NM_012318	LETM1		8098924
NM_0 18241	TMEM184C		8097704
NR_026961	LOC284837		8070708
NM_001008536	TCHHL1		7920135
NM_203348	MGC50722		8180347
NM_0 16091	EIF3L		8072946
NM_018129	PNPO	00750, 01100	8008064
NM_138277	C6orf25		8178074
NR_002950	SNORA2A		7962827
NR_033338	C17orf70		8019194
L23320	RFC1	03030, 03420, 03430	8165672
NM_152888	COL22A1		8153101
NR_026686	PDIK1L		7899087
NM_00 1004341	ETV3L		7921222
NM_014885	ANAPC10	04110, 04114, 04120, 04914	8103005
NM_025134	CHD9		8001402
NM_00 1130059	ATF7		7963698
NM_002484	NUBP1		7993185
NM_00 1024594	Clorf53		7908525
NM_005897	IPP		7915775
NM_032878	ALKBH6		8036242
NM_000144	FXN		8155699
NM_032802	SPPL2A		7988753
NM_001051	SSTR3	4080	8075906
NM_0 16293	BIN2		7963289
NM_147191	MMP21		7936928
NM_0 13239	PPP2R3B	3015	8176986 or 8171087
NM_001080483	TMEM8C		8164931
NM_002796	PSMB4	3050	7905395
NM_032663	USP30		7958439
NM_172140	IL29	04060, 04630	8028613
NM_014018	MRPS28		8151471
AK299337	FAM65C		8066985
NM_148961	OTOS		8060094
NM_00 1134875	C14orf80		7977418

NM_00 1003703	ATP5J	00190, 01100, 05010, 05012, 05016	8069633
NM_032048	EMILIN2		8019912
NM_1 83401	RNF14		8108847
NM_030943	AMN		7977033
NM_001827	CKS2		8156290
NR_003049	SNORD32B		8117746
NM_053284	WFIKKN1		7991927
NM_006830	UQCR11	00190, 01100, 04260, 05010, 05012, 05016	8032284
NM_0 16222	DDX41		8116096
NM_001326	CSTF3	3015	7947396
NM_003434	ZNF133		8061154
NM_0 18049	PLEKHJ1		8032455
NR_027686	LINC00176		8064242
NM_012183	FOXD3		7901913
BC071695	Cllorf71		7951781
NR_024209	RNF185		8075477
NM_000738	CHRM1	04020, 04080, 04810	7948912
NM_022465	IKZF4		7956105
NM_004420	DUSP8	4010	7945641
NM_004550	NDUFS2	00190, 01100, 05010, 05012, 05016	7906703
NM_018691	FAM114A2		8115375
NM_173680	ZNF775		8137228
NM_138414	CCDC101		7994362
NM_178554	KY		8090872
NM_178842	CERS3		7991546
NM_152414	BHLHE22		8146645
NM_005370	RAB8A	4972	8026520
NR_001543	TTTY14		8177217
NM_016585	THEG		8032023
NM_173575	STK32C		7937089
NM_004479	FUT7	00514, 00601, 01100	8165398
NM_078483	SLC36A1	4974	8109350
NM_016617	UFM1		7968670
NM_017838	NHP2	3008	8116168
NM_000947	PRIM2	00230, 00240, 01100, 03030	8120411
BC063891	Clorf201		7913787
NM_001010903	C6orf222		8125980
NM_002751	MAPK11	04010, 04370, 04380, 04620, 04621, 04622, 04660, 04664, 04670, 04722, 04912, 04914, 05014, 05120, 05131, 05140, 05142, 05145, 05160	8076978
NM_00 1002255	SUM04	3013	8122684
NM_198989	DLEU7		7971663
BC063653	LOC441239		8139828
NM_194328	RNF38		8161192
NM_007097	CLTB	04142, 04144, 05016, 05100	8115918
NM_152665	TCTEX1D1		7902158

NM_020679	MIF4GD		8018343
NM_014736	KIAA0101		7989647
NM_148886	SMCR7		8005435
NM_1 39286	CDC26	04110, 04114, 04120, 04914	8163481
NM_138771	CCDC126		8131871
NM_000252	MTM1		8170428
NM_020862	LRFN1		8036707
NM_173860	HOXC12		7955852
NM_001169	AQP8	4976	7994252
NM_194248	OTOF		8050942
NM_0 19070	DDX49		8027100
NR_027138	Cllorf36		7937868
NM_032539	SLITRK2		8170307
NM_016310	POLR3K	00230, 00240, 01100, 03020, 04623	7998129
NR_004388	SCARNA14		7989922
NM_032556	IL1F10		8044563
NM_016215	EGFL7		8159354
NM_0 14402	UQCRQ	00190, 01100, 04260, 05010, 05012, 05016	8107998
NM_016581	ECSIT	4010	8034286
NM_005632	SOLH		7991877
NM_152779	GLIPR1L1		7957245
NM_003807	TNFSF14	4060	8033248
NR_027241	LOC388796		8066247
NM_031941	USHBP1		8035254
NM_020967	NCOA5		8066668
NM_153477	UXT		8172358
NM_025029	MZT2B		8045142
NM_001887	CRYBB1		8075118
NR_027283	LOC440461		8009430
NM_005171	ATF1		7955425
NR_024075	EMR4P		8033332
NM_000409	GUCA1A	04740, 04744	8119515
NM_00 1080461	UNCX		8131087
NM_001031834	RAB40AL		8169006
NM_0 14669	NUP93	3013	7995843
NM_0 14647	KIAA0430		7999642
NM_001852	COL9A2	4974	7915297
NM_003544	HIST1H4B	5322	8124385
NM_00 1037 125	UNKL		7998466
NM_174937	TCERG1L		7937059
BC028365	C7orf62		8140852
NM_198317	KLHL17		7896779
NM_0 14044	UNC50		8043820
NM_001436	FBL	3008	8036777
NM_138568	EXOC3L2		8037513
NM_018011	ARGLU1		7972723
BC001912	FAM195A		7991932

NM_002688	SEPTIN5	5012	8071259
NM_001991	EZH1		8015685
NM_080651	MED30		8148022
NM_001099784	FBXL19		7994967
NM_030755	TMX1		7974303
NR_026925	LOC151174		8059985
NR_031565	MIR320C1		8020419
NM_030895	ZNF696		8148615
NR_027238	LOC654342		8053722
NR_026974	C8orf77		8148951
NM_012384	GMEB2		8067709
NM_138454	NXNL1		8035315
NR_003004	SCARNA22		8093576
NM_172251	MRPL54		8024708
NM_001005188	OR6X1	4740	7952373
NM_0 13245	VPS4A	4144	7996919
NM_0 12267	HSPBP1	4141	8039440
NM_002795	PSMB3	3050	8006812
NM_021066	HIST1H2AJ	5322	8124518
NM_001344	DAD1	00510, 01100, 04141	7977775
NM_003348	UBE2N	4120	7965471

Table 1

In one embodiment, a variant of a nucleotide sequence SEQ ID NO: X is a nucleotide sequence comprising at least 25 contiguous nucleotides, preferably of at least 50, 100, 150, 200 or at least 500 contiguous nucleotides of said nucleotide sequence SEQ ID NO: X.

In another embodiment, a variant of a nucleotide sequence SEQ ID NO: X is a nucleotide sequence comprising the nucleotide sequence SEQ ID NO: X and additional nucleic acids in 3' and/or 5' of SEQ ID NO: X, wherein the number of additional nucleic acids ranges from 1 to 500, preferably from 1 to 200, more preferably from 1 to 100 nucleotides.

In another embodiment, a variant of a nucleotide sequence SEQ ID NO: X is a nucleotide sequence that typically differs from said nucleotide sequence SEQ ID NO: X in one or more substitutions, deletions, additions and/or insertions. In one embodiment, said substitutions, deletions, additions and/or insertions may affect 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleic acids.

In another embodiment, a variant of a nucleotide sequence SEQ ID NO: X is a nucleotide sequence of at least 25, preferably of at least 50, 100, 150, 200, 300, 400, 500, 1000, 1500, 2000 or 3000 nucleotides having at least 75%, 80%, 90%, 95%, or at least 96%, 97%, 98%, 99% identity with the nucleotide sequence SEQ ID NO: X.

The term "identity" or "identical", when used in a relationship between the sequences of two or more polypeptides, refers to the degree of sequence relatedness between polypeptides, as determined by the number of matches between strings of two or more amino acid residues. "Identity" measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., "algorithms"). Identity of related polypeptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo et al., SIAM J. Applied Math. 48, 1073 (1988). Preferred methods for determining identity are designed to give the largest match between the sequences tested. Methods of determining identity are described in publicly available computer programs. Preferred computer program methods for determining identity between two sequences include the GCG program package, including GAP (Devereux et al., Nucl. Acid. Res. \2, 387 (1984); Genetics Computer Group, University of Wisconsin, Madison, Wis.), BLASTP, BLASTN, and FASTA (Altschul et al., J. Mol. Biol. 215, 403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul et al. NCB/NLM/NIH Bethesda, Md. 20894; Altschul et al., supra). The well-known Smith Waterman algorithm may also be used to determine identity.

In one embodiment of the invention, a fragment is a nucleotide sequence of at least 25 nucleotides, preferably of at least 50, 100, 150, 200 or at least 500 nucleotides. In one embodiment of the invention, a fragment of a sequence SEQ ID NO: X is a sequence of at least 25 contiguous nucleotides, preferably of at least 50, 100, 150, 200 or at least 500 contiguous nucleotides of SEQ ID NO: X.

In one embodiment, an equivalent of a nucleotide sequence SEQ ID NO: X, preferably of a gene having the sequence SEQ ID NO: X, is a nucleotide sequence, preferably a gene involved in the same pathway than the nucleotide sequence SEQ ID NO: X. A list of pathways and proteins involved in these pathways is available, for example, on the websites http://www.genome.jp/kegg/pathway.html or http://www.mybiosource.com/page.php?name=pathways.

In another embodiment, cycling hypoxia markers are selected from the list of the 651 cycling hypoxia markers of Table 2 below, as well as their variants, fragments or equivalents. Table 2 comprises cycling hypoxia markers identified in the conditions of the Example and presenting a p-value after FDR correction lower than 0.01.

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
NR_003287	RN28S1		7942875 or 8059576
AF284753	UIMC1		7911343 or 8165703
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NM_177987	TUBB8	04145, 04540, 05130	7911355
NM_170601	SIAE		7944867
NM_001012708	KRTAP5-3		7945652
NR_029710	MIR193A		8006321
NM_000981	RPL19	3010	8006845
NM_012217	TPSD1		7992191
NM_003792	EDF1		8165309
BC013044	DNAJA2	4141	7995379
NR_029824	MIR128-2		8078527

NM_004352	CBLN1		8001329
NM_001017	RPS13	3010	7946812
NM_00 1037 160	CYS1		8050232
NM_003731	SSNA1		8159609
NM_006160	NEUROD2		8014865
NM_001417	EIF4B	03013, 04150	7963575
NM_017854	TMEM160		8037853
NM_0 16057	COPZ1		7955896
NM_152568	NKX6-3		8150433
NM_016170	TLX2		8042896
NR_002715	RN7SL1		8040338
NM_016564	CEND1		7945536
AK302042	LOC440518		8027343
NM_0 14206	CllorflO		7948606
NR_033335	SNORA70G		7964830
NM_003094	SNRPE	3040	8160033 or 7908988
NM_0 12322	LSM5	03018, 03040	8138912
NM_145232	CTU1	4122	8038782
NR_029583	MIR 197		7903717
NM_032231	FAM96A		7989611
NR_024583	POM121L8P		8071168
NM_007241	SNF8	4144	8016508
NM_000307	POU3F4		8168567
NM_0 13299	SAC3D1		7941122
NM_005608	PTPRCAP		7949792
NM_006327	TIMM23		7927548
NM_0 16424	LUC7L3		8016733
NM_144615	TMIGD2		8032782
NM_001 135086	PRSS41		7992716
NM_003512	HIST1H2AC	5322	8117372
NM_000863	HTR1B	4080	8127692
NM_145203	CSNK1A1L	04310, 04340	7971071
NR_000009	SNORD4B		8005957
NM_001080113	C14orfl84		7980859
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861
NM_031210	SLIRP		7975989
NM_023002	HAPLN4		8035646
NM_1 82532	TMEM61		7901687
NM_003538	HIST1H4A	5322	8117334
AK125166	LOC441268		8141166
NM_00 100 1521	UGP2	00040, 00052, 00500, 00520, 01100	8052624
NR_001445	RN7SK		8120249
NM_001551	IGBP1		8168087
NM_138417	KTI12		7916130

NM_031213	FAM108A1		8032371, 7904869, 7904948, 7924230 or 8074842
BC001181	FAM173A		7992043
NM_001031	RPS28	3010	8005471, 8025395 or 7942824
NM_004175	SNRPD3	03040, 05322	8071920
NM_001044370	MPPED1		8073623
BC005079	C2orf42		8052834
NM_003542	HIST1H4C	5322	8117368
BC033986	LOC440934		8048712
NM_001082575	RBFOX3		8018993
NM_017900	AURKAIP1		7911532 or 8039923
NM_001024598	HES3		7897280
NM_022061	MRPL17		7946267
NM_001029	RPS26	3010	8007797
NM_016060	MED31		8011968
NM_012394	PFDN2		7921786
NM_015965	NDUFA13	00190, 05010, 05012, 05016	8027205
NM_080603	ZSWIM1		8063074
NM_021104	RPL41	3010	7957530, 7965467, 7982129, 8105432 or 8075691
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_032753	RAX2		8032601
NM_003684	MKNK1	04010, 04910	7915846
NM_003577	UTF1		7931553
NM_022363	LHX5		7966631
NM_001037495	DYNLL1	4962	7967067
NM_004609	TCF15		8064370
AK098732	TRAP1		7992954
NM_144999	LRRC45		8010719
NM_001018138	NME2	00230, 00240, 01100	8180388, 8180389, 8180387 or 8180386
NM_002528	NTHL1	3410	7998692
NM_006087	TUBB4	04145, 04540, 05130	8025051
NM_003493	HIST3H3	5322	7924884
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NM_024718	C9orf86		8159415
NM_145729	MRPL24		7921121

NM_030662	MAP2K2	04010, 04012, 04270, 04370, 04540, 04620, 04650, 04660, 04662, 04664, 04720, 04722, 04730, 04810, 04910, 04912, 04916, 05020, 05200, 05211, 05213, 05214, 05215, 05216, 05218, 05219, 05220, 05221, 05223	8032761
NM_058190	FAM207A		8180370
NM_001011	RPS7	3010	8005877
NM_014336	AIPL1		8011912
NM_178354	LCE1F		7905517
NM_005470	ABI1		7932616
NM_006357	UBE2E3	04120, 04141	8166124
NR_002182	NACAP1		8147693
NM_00 1109763	GSG1L		8000467
NM_001085365	MZT2A		8055287
NM_001080468	SYCN		8036699
NM_003365	UQCRC1	00190, 01100, 04260, 05010, 05012, 05016	8087100
NM_153207	AEBP2		7954279
NM_032477	MRPL41		8159687
NM_152911	PAOX	4146	7931582
NM_002488	NDUFA2	00190, 01100, 05010, 05012, 05016	8114618
NM_175895	C12orf61		7964642
NM_004558	NRTN		8024995
NM_198850	PHLDB3		8037315
NR_023343	RNU4ATAC		8044961
NM_004976	KCNC1		7938738
NM_012184	FOXD4L1		8044634
NM_054028	SLC35G5		8020162
NM_006985	NPIP		7999766
NM_138334	JOSD2		8038571
NM_014613	FAF2		8110169
NM_022466	IKZF5		7936826
NM_022731	NUCKS1		7909142
NM_138284	IL17D		7967969
NM_004851	NAPSA	4142	8038556
NM_031292	PUS7L		7962427
NM_017871	CPSF3L		7911486

NM_0 12476	VAX2		8042532
NM_032343	CHCHD6		8082305
NM_199287	CCDC137		8010629
BC043417	TMEM68		8146480
NR_029714	MIR320A		8149705
NM_207163	LMOD2		8135821
NM_024339	THOC6	3013	7992795
NM_032411	C2orf40		8044143
NM_0 16491	MRPL37		7901601
NM_003089	SNRNP70	3040	8030199
NM_014360	NKX2-8		7978686
NM_201589	MAFA	04930, 04950	8153409
AK289373	IGHG1		8001104
NM_005583	LYL1		8034608
NM_022375	OCLM		7908347
NM_00 10066 10	SIAH1	04115, 04120, 04310	8001306
NM_172229	KREMEN2		7992758
NM_021996	GBGT1	00603, 01100	8164833
NM_194249	DND1		8114625
NM_001 142864	PIEZOl		7997827
NM_178438	LCE5A		7905483
NM_001349	DARS	970	8055445
NM_176806	MOCS2	4122	8112020
NR_024355	BK250D10.8		8073546
NM_024768	CCDC48		8082465
AK093505	SPANXA2-OT1		8175537
NM_024754	PTCD2		8106107
AK 125905	LOC100129581		8050113
NM_175619	ZAR1		8094968
NM_001867	COX7C	00190, 01100, 04260, 05010, 05012, 05016	8106776
NM_031492	RBM4B		7949674
NM_153376	CCDC96		8099242
NM_002034	FUT5	00601, 01100	8033064
NM_181462	MRPL55		7924853
NM_0 12257	HBP1		8135392
NR_027780	HMGXB4		8072645
NM_004822	NTN1	4360	8004880
NM_178454	DRAM2		7918474
NM_015893	PRLH		8049509
NM_024313	NOLI 2		8072883
NM_006522	WNT6	04310, 04340, 04916, 05200, 05217	8048445
NM_017832	FAM206A		8157144
NM_006947	SRP72	3060	8095230
NM_021948	BCAN		7906205

NM_00 1164405	BHLHA9		8003633
NM_032830	CIRH1A	3008	7996891
NM_080680	COL11A2	04510, 04512, 04974, 05146	8125568
NM_002622	PFDN1		8114567
NM_002196	INSM1		8061303
NM_002370	MAGOH	03013, 03015, 03040	7916274
NR_024406	LOC732275		8003230
NM_201653	CHIA	520	7903945
AK296222	LOC728093		8112476
NM_004343	CALR	04141, 04145, 04612, 05142	8026106
NM_00 1003892	DUPD1		7934527
NR_026837	LOC283392		7964976
NM_006274	CCL19	04060, 04062	8160879
NM_0 14847	UBAP2L		7905700
NM_0 16396	CTDSPL2		7983335
NM_0 15944	AMDHD2	520	7992656
NM_144567	ANGEL2		7924190
NM_153270	KLHL34		8171786
NM_080622	ABHD16B		8064203
NM_022753	S100PBP		7899829
AK290103	LOC100287934		7909990
NR_000011	SNORA70		8170863
NM_003968	UBA3	4120	8088718
NM_033257	DGCR6L		8074565
NM_016468	COX 16		7979906
NM_030642	APOL5		8072721
NM_002565	P2RY4	4080	8173366
NM_014017	LAMTOR2		7906072
NM_006192	PAX1		8061357
NM_1 33450	ANKS3		7999177
NM_024302	MMP28		8014282
NM_016166	PIAS1	04120, 04630, 05160, 05200, 05222	7984453
NM_007037	ADAMTS8		7952752
NR_033192	CCDC59		7965200
NM_174895	PCP2		8033414
NM_003279	TNNC2	4020	8066590
NM_001 136262	ATXN7L3B		7957242
NM_004108	FCN2		8159211
NM_032829	C12orf34		7958577
NM_139136	KCNC2		7964987
NM_033113	ZNF628		8031489
NM_005687	FARSB	970	8059319
NM_000180	GUCY2D	00230, 04740, 04744	8004763

NM_024309	TNIP2		8099029
NM_014554	SENP1		7962760
NM_001013735	FOXB2		8155942
NM_174922	ADCK5		8148850
NM_032704	TUBA1C	04145, 04540, 05130	7955179
NM_020385	REX04		8164907
NR_029894	MIR148B		7955906
NM_001040425	U2AF1L4		8036143
NR_029945	MIR423		8006119
U63828	C20orfl81		8067754
NM_133636	HELQ		8101467
NM_001102614	SLC35G6		8004428
NM_004549	NDUFC2	00190, 01100, 05010, 05012, 05016	7950644
AY358101	DBF4B		8007673
NM_032842	TMEM209		8142912
NM_001862	COX5B	00190, 01100, 04260, 05010, 05012, 05016	8043718
NM_020535	KIR2DL5A	04612, 04650, 05332	8039884

Table 2

In another embodiment, cycling hypoxia markers are selected from the list of the 298 cycling hypoxia markers of Table 3 below, as well as their variants, fragments or equivalents. Table 3 comprises cycling hypoxia markers identified in the conditions of the Example and presenting an average FDR corrected p-value over 200 data resampling lower than 0.05.

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
AF284753	UIMC1		8165703, or 7911343
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NR_003287	RN28S1		7942875
NM_177987	TUBB8	04145, 04540, 05130	7911355
NM_170601	SIAE		7944867

NM_001012708	KRTAP5-3		7945652
NR_029710	MIR 193A		8006321
NM_000981	RPL19	3010	8006845
NM_003792	EDF1		8165309
NM_012217	TPSD1		7992191
NR_029824	MIR128-2		8078527
NM_003731	SSNA1		8159609
BC013044	DNAJA2	4141	7995379
NM_00 1037 160	CYS1		8050232
NM_004352	CBLN1		8001329
NM_006160	NEUROD2		8014865
NM_001017	RPS13	3010	7946812
NM_017854	TMEM160		8037853
NM_152568	NKX6-3		8150433
NM_001417	EIF4B	03013, 04150	7963575
NM_003094	SNRPE	3040	8160033
NR_002715	RN7SL1		8040338
NM_016170	TLX2		8042896
NM_000307	POU3F4		8168567
NM_0 16057	COPZ1		7955896
NM_0 12322	LSM5	03018, 03040	8138912
AK302042	LOC440518		8027343
NM_000863	HTR1B	4080	8127692
NM_003512	HIST1H2AC	5322	8117372
NM_001080113	C14orfl84		7980859
NR_024583	POM121L8P		8071168
NM_145232	CTU1	4122	8038782
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861
NM_007241	SNF8	4144	8016508
NM_016564	CEND1		7945536
NR_033335	SNORA70G		7964830
NM_144615	TMIGD2		8032782
NM_003538	HIST1H4A	5322	8117334
NM_0 16424	LUC7L3		8016733
NM_032231	FAM96A		7989611
NM_0 14206	CllorflO		7948606
NR_000009	SNORD4B		8005957
NM_001 135086	PRSS41		7992716
AK125166	LOC441268		8141166
NR_001445	RN7SK		8120249
NM_001551	IGBP1		8168087
NM_005608	PTPRCAP		7949792
NM_145203	CSNK1A1L	04310, 04340	7971071
NM_023002	HAPLN4		8035646
NM_003542	HIST1H4C	5322	8117368
NM_00 100 1521	UGP2	00040, 00052, 00500, 00520, 01100	8052624

NM_031210	SLIRP		7975989
NM_0 13299	SAC3D1		7941122
NM_00 1044370	MPPED1		8073623
NM_004175	SNRPD3	03040, 05322	8071920
NM_006327	TIMM23		7927548
NM_031213	FAM108A1		8032371
NM_001031	RPS28	3010	8025395, 8005471, or 7942824
BC033986	LOC440934		8048712
BC005079	C2orf42		8052834
BC001181	FAM173A		7992043
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_0 17900	AURKAIP1		8039923 or 7911532
NM_001018138	NME2	00230, 00240, 01100	8180388, 8180389, 8180387 or 8180386
NM_00 1082575	RBFOX3		8018993
NM_015456	COBRA1		8159654
NM_080603	ZSWIM1		8063074
NM_001029	RPS26	3010	8007797
NM_006088	TUBB2C	04145, 04540, 05130	8165496
NM_004609	TCF15		8064370
NM_181887	UBE2D3	04120, 04141	8180330, 8180335, 8180331, 8180334, 8180333, 8180329 or 8180332
NM_0 15965	NDUFA13	00190, 05010, 05012, 05016	8027205
NM_178536	LCN12		8159501
NM_032753	RAX2		8032601
NM_0 16060	MED31		8011968
NR_003666	SPDYE7P		8133209
AK125308	LOCI 00 129484		8137962
NR_003051	RMRP		8161024
NM_005319	HIST1H1C		8124397
NM_003550	MAD1L1	04110, 04914	8137805
ENST00000427835	C20orf61		8065013
NM_144999	LRRC45		8010719
NM_006087	TUBB4	04145, 04540, 05130	8025051
NR_029583	MIR 197		7903717
NM_002307	LGALS7		8036584 or 8028546
NM_0 14370	SRPK3		8170753
AK098732	TRAP1		7992954
NM_001348	DAPK3	05200, 05219	8032718

NM_022061	MRPL17		7946267
NM_002528	NTHL1	3410	7998692
NM_032527	ZGPAT		8064156
NM_006858	TMED1		8034101
NM_005274	GNG5	4062	8174509
NM_022363	LHX5		7966631
NM_00 1037495	DYNLL1	4962	7967067
NM_021104	RPL41	3010	7957530
AK095987	FLJ38668		8054449
NM_181838	UBE2D2	04120, 04141, 05131	8108435
NM_002003	FCN1		8165011
NM_016589	TIMMDCl		8081867
NM_020412	CHMP1B	4144	8020179
NR_026800	KIAA0125		7977440
NM_0 14674	EDEM1	4141	8085116
NM_138417	KTI12		7916130
NM_012315	KLK9		8038716
NR_029681	MIR 140		7997008
NM_173547	TRIM65		8018502
NM_003577	UTF1		7931553
NM_138574	HDGFL1		8117172
NM_0 18942	HMX1		8104136
NM_00 1080495	TNRC18		8137959
NM_002066	GML		8148565
NM_001168	BIRC5	05200, 05210	8018860
NM_020064	BARHL1		8158912
NM_021012	KCNJ12		8005726
NM_00 1007595	C2CD4B		7989473
NM_031899	GORASP1		8086317
NM_0 19082	DDX56		8139392
AY730278	CENPVL1		8172715 or 8167652
NM_175064	SPDYE1		8140424 or 8140454
NM_001033113	ENTPD8	00230, 00240	8165538
NM_006770	MARCO	4145	8044773
AK094921	LOC100131763		8049950
NM_00 1126128	PROK2		8088813
NM_0 16063	HDDC2		8129363
NM_1 82532	TMEM61		7901687
NR_024591	POM121L1P		8074714
NM_020180	CELF4		8022952
NM_0 12394	PFDN2		7921786
NM_006312	NCOR2	4330	7959772
NM_001804	CDX1		8109226
NR_026676	RPS2P32		8131869
NM_001002	RPLPO	3010	8109750
NR_002781	TSPY26P		8065603

NM_003001	SDHC	00020, 00190, 01100, 05010, 05012, 05016	8011212
NM_002669	PLRG1	3040	8103289
NM_006801	KDELR1	5110	8038078
NM_0 15971	MRPS7		8009784
NM_003684	MKNK1	04010, 04910	7915846
NM_0 18047	RBM22	3040	8115168
NM_0 12249	RHOQ	4910	8041808
NM_00 1172743	RAI2		8171539
NM_0 16305	SS18L2		8079074
NM_001 113201	NACA		7964262
NM_001 144936	Cllorf95		7949015
NM_0 12452	TNFRSF13B	04060, 04672, 05340	8013061
NM_004939	DDX1		8040386
NM_003493	HIST3H3	5322	7924884
NM_001013	RPS9	3010	8180398
NM_006356	ATP5H	00190, 01100, 05010, 05012, 05016	8018288
NM_145657	GSX1		7968260
NM_1 82702	PRSS42		8086683
NM_005574	LM02		7947450
NM_003926	MBD3		8032275
NM_024816	RABEP2		8000616
NM_003859	DPMI	00510, 01100	8067017
NM_022097	CHP2	04010, 04020, 04114, 04210, 04310, 04360, 04370, 04650, 04660, 04662, 04720, 05010, 05014	7994123
NM_014582	OBP2A		8180231
L20860	SEPT5-GP1BB		8071272
NM_0 16602	CCR10	04060, 04062, 04672	8015681
NM_006292	TSG101	4144	7947015
NM_003910	BUD31	3040	8134589
NM_005034	POLR2K	00230, 00240, 01100, 03020, 05016	8147654
NM_032338	LLPH		7956876
NM_003168	SUPT4H1		8016982
NM_006181	NTN3	4360	7992632
NM_012145	DTYMK	00240, 01100	8077262 or 8060286
NM_032805	ZSCAN10		7998921
NR_026716	KIR3DX1		8031200

NM_016835	MAPT	04010, 05010	8016263
NM_00 1080440	OTOL1		8083770
NM_198180	QRFP		8164630
NM_139172	TMEM190		8031475
NM_101395	DYRK1A		8068551
NM_003537	HIST1H3B	5322	8124388
BC043386	C19orf68		8029996
NM_144589	COMTD1		7934544
NM_005922	MAP3K4	04010, 04912	8130624
NM_0 18462	BRK1	4810	8085287
AK097604	LOCI 00 130285		7998265
NM_015719	COL5A3	04510, 04512, 04974, 05146	8033825
NR_002951	SNORA2B		7962829
NM_00 10399 16	ZNF384		7953390
AF304442	C21orfll8		8068046
NR_026557	PLK5		8024331
NM_000377	WAS	04062, 04520, 04666, 04810, 05100, 05130, 05131	8167334
NM_006848	CCDC85B		7941457
NR_001555	GOLGA2P2Y		8177413 or 8176910
NM_001003684	UQCR10	00190, 01100, 04260, 05010, 05012, 05016	8072274
NM_174923	CCDC107		8155073
NM_014419	DKKL1		8030292
NM_025072	PTGES2	00590, 01100	8164362
NM_00 1164447	FAM90A10		8144448
AK 125575	ZNF425		8143708
NM_006808	SEC61B	03060, 04141, 04145, 05110	8156838
NM_007255	B4GALT7	00532, 00534, 01100	8110399
NM_00 1164440	ANKRD33B		8104499
NM_021646	ZNF500		7999196
NM_031909	C1QTNF4		7947928
NM_002297	LCN1		8159255
NM_001013653	LRRC26		8165453
NM_014171	CRIPT		8041813
NM_003375	VDAC2	04020, 05012, 05016	8042335
NM_003513	HIST1H2AB	5322	8124391
NM_001024678	LRRC24		8153868
NR_024593	POM121L10P		8075024
NR_026713	FAM182A		8065527
NM_00 1144954	C5orf47		8110068
NM_00 1099435	SPDYE5		8133654

NM_175741	C15orf55		7982516
NM_020199	C5orfl5		8114138
NM_000183	HADHB	00062, 00071, 00280, 01100	8040639
NM_014860	SUPT7L		8051204
NM_016568	RXFP3		8104781
NM_0 14976	PDCD11		7936096
NR_002576	SNORA21		8014755
NM_144578	MAPK1IP1L		7974455
NM_006476	ATP5L	00190, 01100	7944216
NM_1 30784	SYCE1		7937247
NM_006043	HS3ST2	534	7994052
NR_002144	LOC407835		8136065
NM_001800	CDKN2D	4110	8034075
NM_005007	NFKBIL1		8179249, 8177967 or 8118127
NM_003278	CLEC3B		8079305
NM_002494	NDUFC1	00190, 01100, 05010, 05012, 05016	8102839
NM_006855	KDELR3	5110	8073015
BC004943	MGC10814		8035551
NM_019107	C19orfl0		8032863
NM_145803	TRAF6	04010, 04120, 04144, 04380, 04620, 04621, 04622, 04722, 05140, 05142, 05145, 05160, 05200, 05222	7947540
NR_003013	SCARNA16		8010137
NM_014170	GTPBP8		8081676
NM_016438	HIGD1B		8007701
NM_016199	LSM7	03018, 03040	8032480
NM_004637	RAB7A	04144, 04145, 05146	8082431
NM_015679	TRUB2		8164428
NM_138983	OLIG1		8068235
NM_005706	TSSC4		7937813
NM_003002	SDHD	00020, 00190, 01100, 05010, 05012, 05016	7943853
NM_0 16734	PAX5		8161211
NM_001 164456	FAM90A13		8149204
NM_0 14064	METTL11A		8158544
NM_006686	ACTL7B		8163019
NM_001258	CDK3		8010021
NM_030811	MRPS26		8060599
NM_1 33261	GIPC3		8024676
AF067420	IGHA1		7995263

NM_002764	PRPS1	00030, 00230, 01100	8169240
NM_152898	FERD3L		8138450
NM_0 15276	USP22		8013486
NM_144727	CRYGN		8143949
NM_001037984	SLC38A10		8019149
NM_002804	PSMC3	3050	7947867
NM_0 18250	INTS9		8150014
NM_033644	FBXW11	04114, 04120, 04310, 04340, 04710, 05131	8115765
NM_021570	BARX1		8162472
NM_007374	SIX6		7974793
NR_003502	ZNRF2P1		8132209
AY341951	FAM138D		7960172
NM_004640	DDX39B	03013, 03015, 03040	8178476 or 8179750
BC104424	FAHD2B		8043682
NM_000383	AIRE	04120, 05340	8069037
NM_001 164453	FAM90A20		8144388
NM_004855	PIGB	00563, 01100	7983811
NM_00 1145250	SP9		8056825
NM_178138	LHX3		8165083
NM_152914	C17orfl03		8013509
NM_173660	DOK7		8093807
NM_006299	ZNF193		8117655
NM_1 82498	ZNF428		8037355
NM_148172	PEMT	00564, 01100	8013120
AB016902	HGC6.3		8130824
NM_002949	MRPL12		8010664
NR_002911	SNORA71A		8066258
NM_005091	PGLYRP1		8037742
AK291454	UBE2K	4120	8099918
NM_016312	WBP11	3040	7961489
NM_004435	ENDOG	4210	8158418
NM_173514	SLC38A9		8112121
NM_0 14342	MTCH2		7947934
NM_152778	MFSD8	4142	8102730
NR_004430	RNUl-1		7919349 or 7919269
NM_00 1135580	C19orf71		8024655
NM_014581	OBP2B		8180358
NM_000479	AMH	04060, 04350	8024429
NM_00 1164094	COPS7A		7953395
NM_001001410	C16orf42		7998449
NM_00 1005922	KRTAP5-1		7945645
NM_003013	SFRP2	4310	8103254
NM_052945	TNFRSF13C	04060, 04672, 05340	8076387

NM_000290	PGAM2	00010, 01100	8139276
NM_001100418	C19orf60		8027032
NM_002714	PPP1R10		8179664 or 8178358
NM_015568	PPP1R16B		8062557
NM_020070	IGLL1	5340	8074909
NM_012188	FOXI1		8109901

Table 3

In another embodiment, cycling hypoxia markers are selected from the list of the 167 cycling hypoxia markers of Table 4 below, as well as their variants, fragments or equivalents. Table 4 comprises cycling hypoxia markers identified in the conditions of the Example and presenting an average FDR corrected p-value over **200** data resampling lower than **0.01.**

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
AF284753	UIMC1		8165703 or 7911343
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NR_003287	RN28S1		7942875
NM_177987	TUBB8	04145, 04540, 05130	7911355
NM_170601	SIAE		7944867
NM_001012708	KRTAP5-3		7945652
NR_029710	MIR193A		8006321
NM_000981	RPL19	3010	8006845
NM_003792	EDF1		8165309
NM_012217	TPSD1		7992191
NR_029824	MIR128-2		8078527
NM_003731	SSNA1		8159609
BC013044	DNAJA2	4141	7995379
NM_001037160	CYS1		8050232
NM_004352	CBLN1		8001329
NM_006160	NEUROD2		8014865
NM_001017	RPS13	3010	7946812
NM_017854	TMEM160		8037853
NM_152568	NKX6-3		8150433
NM_001417	EIF4B	03013, 04150	7963575

NM_003094	SNRPE	3040	8160033
NR_002715	RN7SL1		8040338
NM_016170	TLX2		8042896
NM_000307	POU3F4		8168567
NM_0 16057	COPZ1		7955896
NM_0 12322	LSM5	03018, 03040	8138912
AK302042	LOC440518		8027343
NM_000863	HTR1B	4080	8127692
NM_003512	HIST1H2AC	5322	8117372
NM_001080113	C14orfl84		7980859
NR_024583	POM121L8P		8071168
NM_145232	CTU1	4122	8038782
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861
NM_007241	SNF8	4144	8016508
NM_016564	CEND1		7945536
NR_033335	SNORA70G		7964830
NM_144615	TMIGD2		8032782
NM_003538	HIST1H4A	5322	8117334
NM_0 16424	LUC7L3		8016733
NM_032231	FAM96A		7989611
NM_0 14206	CllorflO		7948606
NR_000009	SNORD4B		8005957
NM_001 135086	PRSS41		7992716
AK125166	LOC441268		8141166
NR_001445	RN7SK		8120249
NM_001551	IGBP1		8168087
NM_005608	PTPRCAP		7949792
NM_145203	CSNK1A1L	04310, 04340	7971071
NM_023002	HAPLN4		8035646
NM_003542	HIST 1H4C	5322	8117368
NM_00 100 1521	UGP2	00040, 00052, 00500, 00520, 01100	8052624
NM_031210	SLIRP		7975989
NM_0 13299	SAC3D1		7941122
NM_00 1044370	MPPED1		8073623
NM_004175	SNRPD3	03040, 05322	8071920
NM_006327	TIMM23		7927548
NM_031213	FAM108A1		8032371
NM_001031	RPS28	3010	8025395, 8005471 or 7942824
BC033986	LOC440934		8048712
BC005079	C2orf42		8052834
BC001181	FAM173A		7992043
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_0 17900	AURKAIP1		8039923, 7911532

NM_001018138	NME2	00230, 00240, 01100	8180388, 8180389, 8180387 or 8180386
NM_00 1082575	RBFOX3		8018993
NM_015456	COBRA 1		8159654
NM_080603	ZSWIM1		8063074
NM_001029	RPS26	3010	8007797
NM_006088	TUBB2C	04145, 04540, 05130	8165496
NM_004609	TCF15		8064370
NM_181887	UBE2D3	04120, 04141	8180330, 8180335, 8180331, 8180334, 8180333, 8180329 or 8180332
NM_0 15965	NDUFA13	00190, 05010, 05012, 05016	8027205
NM_178536	LCN12		8159501
NM_032753	RAX2		8032601
NM_0 16060	MED31		8011968
NR_003666	SPDYE7P		8133209
AK125308	LOCI 00 129484		8137962
NR_003051	RMRP		8161024
NM_005319	HIST1H1C		8124397
NM_003550	MAD1L1	04110, 04914	8137805
ENST00000427835	C20orf61		8065013
NM_144999	LRRC45		8010719
NM_006087	TUBB4	04145, 04540, 05130	8025051
NR_029583	MIR197		7903717
NM_002307	LGALS7		8036584 or 8028546
NM_0 14370	SRPK3		8170753
AK098732	TRAP1		7992954
NM_001348	DAPK3	05200, 05219,	8032718
NM_022061	MRPL17		7946267
NM_002528	NTHL1	3410	7998692
NM_032527	ZGPAT		8064156
NM_006858	TMED1		8034101
NM_005274	GNG5	4062	8174509
NM_022363	LHX5		7966631
NM_00 1037495	DYNLL1	4962	7967067
NM_021104	RPL41	3010	7957530
AK095987	FLJ38668		8054449
NM_181838	UBE2D2	04120, 04141, 05131	8108435
NM_002003	FCN1		8165011
NM_016589	TIMMDCl		8081867
NM_020412	CHMP1B	4144	8020179
NR_026800	KIAA0125		7977440
NM_0 14674	EDEM1	4141	8085116

NM_138417	KTI12		7916130
NM_012315	KLK9		8038716
NR_029681	MIR140		7997008
NM_173547	TRIM65		8018502
NM_003577	UTF1		7931553
NM_138574	HDGFL1		8117172
NM_0 18942	HMX1		8104136
NM_00 1080495	TNRC18		8137959
NM_002066	GML		8148565
NM_001168	BIRC5	05200, 05210	8018860
NM_020064	BARHL1		8158912
NM_021012	KCNJ12		8005726
NM_00 1007595	C2CD4B		7989473
NM_031899	GORASP1		8086317
NM_0 19082	DDX56		8139392
AY730278	CENPVL1		8172715 or 8167652
NM_175064	SPDYE1		8140424
NM_001033113	ENTPD8	00230, 00240,	8165538
NM_006770	MARCO	4145	8044773
AK094921	LOC100131763		8049950
NM_00 1126128	PROK2		8088813
NM_0 16063	HDDC2		8129363
NM_1 82532	TMEM61		7901687
NR_024591	POM121L1P		8074714
NM_020180	CELF4		8022952
NM_0 12394	PFDN2		7921786
NM_006312	NCOR2	4330	7959772
NM_001804	CDX1		8109226
NR_026676	RPS2P32		8131869
NM_001002	RPLPO	3010	8109750
NR_002781	TSPY26P		8065603
NM_003001	SDHC	00020, 00190, 01100, 05010, 05012, 05016,	8011212
NM_002669	PLRG1	3040	8103289
NM_006801	KDELR1	5110	8038078
NM_0 15971	MRPS7		8009784
NM_003684	MKNK1	04010, 04910	7915846
NM_0 18047	RBM22	3040	8115168
NM_0 12249	RHOQ	4910	8041808
NM_00 1172743	RAI2		8171539
NM_0 16305	SS18L2		8079074
NM_001 113201	NACA		7964262
NM_001 144936	Cllorf95		7949015
NM_0 12452	TNFRSF13B	04060, 04672, 05340	8013061
NM_004939	DDX1		8040386
NM_003493	HIST3H3	5322	7924884

NM_001013	RPS9	3010	8180398
NM_006356	ATP5H	00190, 01100, 05010, 05012, 05016	8018288
NM_145657	GSX1		7968260
NM_1 82702	PRSS42		8086683
NM_005574	LM02		7947450
NM_003926	MBD3		8032275
NM_024816	RABEP2		8000616
NM_003859	DPMI	00510, 01100	8067017
NM_022097	CHP2	04010, 04020, 04114, 04210, 04310, 04360, 04370, 04650, 04660, 04662, 04720, 05010, 05014	7994123
NM_014582	OBP2A		8180231
L20860	SEPT5-GP1BB		8071272
NM_0 16602	CCR10	04060, 04062, 04672	8015681
NM_006292	TSG101	4144	7947015
NM_003910	BUD31	3040	8134589
NM_005034	POLR2K	00230, 00240, 01100, 03020, 05016	8147654

Table 4

In another embodiment, cycling hypoxia markers are selected from the list of the cycling hypoxia markers of Table 5 below, as well as their variants, fragments or equivalents. Table 5 comprises cycling hypoxia markers identified in the conditions of the Example and which are the 100 probe sets with the lowest FDR corrected p-values average over 200 data resampling, corresponding to 96 annoted genes. **Table 5** thus comprises 96 cycling hypoxia markers.

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NM_001168	BIRC5	05200, 05210	8018860
NM_032527	ZGPAT		8064156
NM_0 12322	LSM5	03018, 03040	8138912
NM_0 12394	PFDN2		7921786
NM_002003	FCN1		8165011
NM_001 113201	NACA		7964262
NM_005608	PTPRCAP		7949792
NM_006858	TMED1		8034101

NM_001551	IGBP1		8168087
NM_001417	EIF4B	03013, 04150	7963575
NM_005319	HIST1H1C		8124397
NM_031210	SLIRP		7975989
NM_000863	HTR1B	4080	8127692
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_0 13299	SAC3D1		7941122
NM_002528	NTHL1	3410	7998692
NM_00 1044370	MPPED1		8073623
NM_006160	NEUROD2		8014865
NM_021012	KCNJ12		8005726
NM_022363	LHX5		7966631
NM_017854	TMEM160		8037853
NM_0 18942	HMX1		8104136
NM_0 14206	CllorflO		7948606
NM_006770	MARCO	4145	8044773
NM_006292	TSG101	4144	7947015
NM_003577	UTF1		7931553
NM_032338	LLPH		7956876
NM_003512	HIST1H2AC	5322	8117372
NM_004352	CBLN1		8001329
NM_0 15965	NDUFA13	00190, 05010, 05012, 05016	8027205
NM_016170	TLX2		8042896
NM_0 17900	AURKAIP1		7911532 or 8039923
BC001181	FAM173A		7992043
NM_080603	ZSWIM1		8063074
NM_012217	TPSD1		7992191
NM_181838	UBE2D2	04120, 04141, 05131	8108435
NM_003792	EDF1		8165309
NM_022061	MRPL17		7946267
NM_016564	CEND1		7945536
NM_003731	SSNA1		8159609
NM_001031	RPS28	3010	8005471, 8025395 or 7942824
NM_0 14370	SRPK3		8170753
NM_001348	DAPK3	05200, 05219,	8032718
NM_00 1037495	DYNLL1	4962	7967067
NM_015456	COBRA1		8159654
NM_003001	SDHC	00020, 00190, 01100, 05010, 05012, 05016	8011212
NM_0 16060	MED31		8011968
NR_026800	KIAA0125		7977440
NM_007241	SNF8	4144	8016508
NM_000307	POU3F4		8168567

NM_031899	GORASP1		8086317
BC005079	C2orf42		8052834
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NM_003684	MKNK1	04010, 04910	7915846
NM_004175	SNRPD3	03040, 05322	8071920
NM_031213	FAM108A1		8032371
NM_003493	HIST3H3	5322	7924884
NM_000981	RPL19	3010	8006845
NM_001017	RPS13	3010	7946812
NM_001144936	Cllorf95		7949015
NM_015971	MRPS7		8009784
NM_005274	GNG5	4062	8174509
NM_005973	PRCC		7906235
NM_020412	CHMP1B	4144	8020179
NM_005574	LM02		7947450
NM_004609	TCF15		8064370
NM_016057	COPZ1		7955896
NM_003550	MAD1L1	04110, 04914	8137805
NM_003538	HIST1H4A	5322	8117334
NM_003542	HIST1H4C	5322	8117368
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
NM_152568	NKX6-3		8150433
NR_024583	POM121L8P		8071168
NM_032231	FAM96A		7989611
NM_001080113	C14orfl84		7980859
NM_144615	TMIGD2		8032782
NM_032479	MRPL36		8110861
NM_182532	TMEM61		7901687
NM_138417	KTI12		7916130
BC033986	LOC440934		8048712
NM_001082575	RBFOX3		8018993
NM_032753	RAX2		8032601
NM_144999	LRRC45		8010719
NM_002307	LGALS7		8036584 or 8028546
NR_003666	SPDYE7P		8133209
NM_178536	LCN12		8159501
ENST00000427835	C20orf61		8065013
NM_173547	TRIM65		8018502
NM_033055	HIATI		7903294
NM_001007595	C2CD4B		7989473
AK095987	FLJ38668		8054449
NM_016589	TIMMDCl		8081867
NM_144589	COMTD1		7934544

NM_145657	GSX1	7968260
NM_020180	CELF4	8022952

Table 5

In another embodiment, cycling hypoxia markers are selected from the list of the 74 cycling hypoxia markers of Table 6 below, as well as their variants, fragments or equivalents. Table 6 comprises cycling hypoxia markers identified in the conditions of the Example and presenting an average FDR corrected p-value over **200** data resampling lower than **0.001.**

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
AF284753	UIMC1		8165703 or 7911343
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NR_003287	RN28S1		7942875
NM_177987	TUBB8	04145, 04540 05130	7911355
NM_170601	SIAE		7944867
NM_001012708	KRTAP5-3		7945652
NR_029710	MIR193A		8006321
NM_000981	RPL19	3010	8006845
NM_003792	EDF1		8165309
NM_012217	TPSD1		7992191
NR_029824	MIR128-2		8078527
NM_003731	SSNA1		8159609
BC013044	DNAJA2	4141	7995379
NM_001037160	CYS1		8050232
NM_004352	CBLN1		8001329
NM_006160	NEUROD2		8014865
NM_001017	RPS13	3010	7946812
NM_017854	TMEM160		8037853
NM_152568	NKX6-3		8150433
NM_001417	EIF4B	03013, 04150	7963575
NM_003094	SNRPE	3040	8160033
NR_002715	RN7SL1		8040338
NM_016170	TLX2		8042896
NM_000307	POU3F4		8168567
NM_016057	COPZ1		7955896

NM_0 12322	LSM5	03018, 03040	8138912
AK302042	LOC440518		8027343
NM_000863	HTR1B	4080	8127692
NM_003512	HIST1H2AC	5322	8117372
NM_001080113	C14orfl84		7980859
NR_024583	POM121L8P		8071168
NM_145232	CTU1	4122	8038782
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861
NM_007241	SNF8	4144	8016508
NM_016564	CEND1		7945536
NR_033335	SNORA70G		7964830
NM_144615	TMIGD2		8032782
NM_003538	HIST1H4A	5322	8117334
NM_0 16424	LUC7L3		8016733
NM_032231	FAM96A		7989611
NM_0 14206	CllorflO		7948606
NR_000009	SNORD4B		8005957
NM_001 135086	PRSS41		7992716
AK125166	LOC441268		8141166
NR_001445	RN7SK		8120249
NM_001551	IGBP1		8168087
NM_005608	PTPRCAP		7949792
NM_145203	CSNK1A1L	04310, 04340	7971071
NM_023002	HAPLN4		8035646
NM_003542	HIST1H4C	5322	8117368
NM_00 100 1521	UGP2	00040, 00052, 00500, 00520, 01100	8052624
NM_031210	SLIRP		7975989
NM_0 13299	SAC3D1		7941122
NM_00 1044370	MPPED1		8073623
NM_004175	SNRPD3	03040, 05322	8071920
NM_006327	TIMM23		7927548
NM_031213	FAM108A1		8032371
NM_001031	RPS28	3010	8025395 or 8005471
BC033986	LOC440934		8048712
BC005079	C2orf42		8052834
BC001181	FAM173A		7992043
NM_000847	GSTA3	00480, 00980, 00982	8127087
NM_0 17900	AURKAIP1		8039923
NM_001018138	NME2	00230, 00240, 01100	8180388 or 8180389
NM_00 1082575	RBFOX3		8018993
NM_015456	COBRA1		8159654
NM_080603	ZSWIM1		8063074
NM_001029	RPS26	3010	8007797

NM_006088	TUBB2C	04145, 04540, 05130	8165496
NM_004609	TCF15		8064370
NM_181887	UBE2D3	04120 04141	8180330, 8180335, 8180331, 8180334 or 8180333

Table 6

In another embodiment, cycling hypoxia markers are selected from the list of the **37** cycling hypoxia markers of Table **7** below, as well as their variants, fragments or equivalents. Table **7** comprises cycling hypoxia markers identified in the conditions of the Example and presenting an average FDR corrected p-value over **200** data resampling lower than **0.0001.**

GeneBank Accession Number	**Name of the marker**	**Pathways**	**Probeset**
NR_002312	RPPH1		7977507
BC018448	MALAT1		7949410
AF284753	UIMC1		8165703 or 7911343
NM_014248	RBX1	03420, 04110, 04114, 04120, 04141, 04310, 04350, 04710, 05200, 05211	8073334
NR_003287	RN28S1		7942875
NM_177987	TUBB8	04145, 04540, 05130	7911355
NM_170601	SIAE		7944867
NM_001012708	KRTAP5-3		7945652
NR_029710	MIR193A		8006321
NM_000981	RPL19	3010	8006845
NM_003792	EDF1		8165309
NM_012217	TPSD1		7992191
NR_029824	MIR128-2		8078527
NM_003731	SSNA1		8159609
BC013044	DNAJA2	4141	7995379
NM_001037160	CYS1		8050232
NM_004352	CBLN1		8001329
NM_006160	NEUROD2		8014865
NM_001017	RPS13	3010	7946812
NM_017854	TMEM160		8037853
NM_152568	NKX6-3		8150433
NM_001417	EIF4B	03013, 04150	7963575
NM_003094	SNRPE	3040	8160033
NR_002715	RN7SL1		8040338

NM_016170	TLX2		8042896
NM_000307	POU3F4		8168567
NM_016057	COPZ1		7955896
NM_012322	LSM5	03018, 03040	8138912
AK302042	LOC440518		8027343
NM_000863	HTR1B	4080	8127692
NM_003512	HIST1H2AC	5322	8117372
NM_001080113	C14orfl84		7980859
NR_024583	POM121L8P		8071168
NM_145232	CTU1	4122	8038782
AK123383	LOC642648		8076747
NM_032479	MRPL36		8110861
NM_007241	SNF8	4144	8016508

Table 7

In one embodiment, cycling hypoxia markers are selected from the list of the cycling hypoxia markers of Table 8 below, as well as their variants, fragments or equivalents.

GeneBank Accession Number	Name of the marker	Pathways	Probeset
NM_001168	BIRC5	05200, 05210	8018860
NM_032527	ZGPAT		8064156
NM_012322	LSM5	03018, 03040	8138912
NM_012394	PFDN2		7921786
NM_002003	FCN1		8165011
NM_001 113201	NACA		7964262
NM_005608	PTPRCAP		7949792
NM_006858	TMED1		8034101
NM_001551	IGBP1		8168087
NM_001417	EIF4B	03013, 04150	7963575

Table 8

In one embodiment of the invention, the signature of the invention comprises or consists of at least 2, preferably at least 3, more preferably at least 5, and even more preferably at least 10 cycling hypoxia markers.

In one embodiment of the invention, the signature of the invention comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9 or 10 cycling hypoxia markers.

In one embodiment of the invention, the signature of the invention comprises at least 10 markers selected from the list of Table 1, preferably from the list of Table 2, more preferably from the list of Table 3, even more preferably from the list of Table 4, still

even more preferably from the list of Table 5, still even more preferably from the list of Table 6, still even more preferably from the list of Table 7, and still even more preferably from the list of Table 8.

In one embodiment of the invention, the signature of the invention comprises or consists of 8, 9 or 10 markers selected from the list of Table 1, preferably from the list of Table 2, more preferably from the list of Table 3, even more preferably from the list of Table 4, still even more preferably from the list of Table 5, still even more preferably from the list of Table 6, still even more preferably from the list of Table 7, and still even more preferably from the list of Table 8.

In one embodiment of the invention, the signature of the invention comprises at least 3 markers. In one embodiment of the invention, the signature of the invention comprises one, two or three of BIRC5, IGBP1 and EIF4B. In one embodiment of the invention, the signature of the invention comprises at least the three markers BIRC5, IGBP1 and EIF4B. In one embodiment of the invention, the signature of the invention consists in the three markers BIRC5, IGBP1 and EIF4B.

In one embodiment, the signature of the invention comprises or consists of 1, 2 or 3 markers selected from the list of Table 8, preferably BIRC5, IGBP1 and/or EIF4B, and 5, 6, 7, 8, or 9 markers selected from the list of Table 1, preferably from the list of Table 2, more preferably from the list of Table 3, even more preferably from the list of Table 4, still even more preferably from the list of Table 5, still even more preferably from the list of Table 6, still even more preferably from the list of Table 7, and still even more preferably from the list of Table 8.

In one embodiment, the signature of the invention comprises or consists of 1 marker selected from the list of Table 8, and 1, 2, 3, 4, 5, 6, 7, 8, or 9 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 2 markers selected from the list of Table 8, and 1, 2, 3, 4, 5, 6, 7, or 8 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 3 markers selected from the list of Table 8, and 1, 2, 3, 4, 5, 6, or 7 markers selected from the list of Table 5. In another embodiment, the

signature of the invention comprises or consists of 4 markers selected from the list of Table 8, and 1, 2, 3, 4, 5, or 6 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 5 markers selected from the list of Table 8, and 1, 2, 3, 4, or 5 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 6 markers selected from the list of Table 8, and 1, 2, 3, or 4 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 7 markers selected from the list of Table 8, and 1, 2, or 3 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 8 markers selected from the list of Table 8, and 1, or 2 markers selected from the list of Table 5. In another embodiment, the signature of the invention comprises or consists of 9 markers selected from the list of Table 8, and 1 marker selected from the list of Table 5.

In one embodiment, the signature of the invention comprises or consists of the 8 markers BIRC5, LM02, NTHL1, RPS13, SNF8, LSM5, NACA and RPS28.

In another embodiment, the signature of the invention comprises or consists of the 9 markers BIRC5, C14orfl56, LSM5, DYNLL1, SNF8, RPS28, RPS13, NACA and CHMP1B.

In another embodiment, the signature of the invention comprises or consists of the 9 markers BIRC5, EIF4B, C14orfl56, LSM5, DYNLL1, SNF8, RPS28, RPS13 and NACA.

In a preferred embodiment, the signature of the invention comprises or consists of 10 markers selected from the list of Table 8, their variants, fragments and equivalents. More preferably, the signature comprises or consists of the 10 markers of Table 8, i.e. BIRC5, ZGPAT, LSM5, PFDN2, FCN1, NACA, PTPRCAP, TMED1, IGBP1 and EIF4B.

In one embodiment, the signature of the invention comprises or consists of the 9 markers LM02, NTHL1, RPS13, SNF8, RPS28, MRPL17, TSG101, DYNLL1 and MKNK1.

In another embodiment, the signature of the invention comprises or consists of the markers EIF4B, LM02, NTHL1, RPS13, SNF8, RPS28, MRPL17, TSG101, DYNLL1 and MKNK1.

In another embodiment, the signature of the invention comprises or consists of the markers BIRC5, EIF4B, LM02, NTHL1, RPS13, SNF8, RPS28, MRPL17, TSG101 and DYNLL1.

In one embodiment, the signature of the invention does not consist of markers selected from the group consisting of PTPRCAP, HIST1H1C, CllorflO, HIST1H2AC, SSNA1, RPS28, RBX1, RPS13, MAD1L1, HIST1H4A and HIST1H4C.

The present invention also relates to a signature as hereinabove described, for the prognosis of cancer in a subject, wherein the signature of the invention is a signature of cycling hypoxia, i.e. comprises markers whose expression is different between a normoxic condition and a cycling hypoxia condition.

The present invention further relates to a non-invasive method for the prognosis of cancer in a subject, wherein said method comprises assessing the expression of markers in a sample of said subject, whose expressions are different between a normoxic condition and a cycling hypoxia condition. In one embodiment, the markers whose expressions are different between a normoxic condition and a cycling hypoxia condition together form a signature according to the invention.

In one embodiment of the invention, the method of the invention is for determining a personalized course of treatment of the subject. Indeed, according to the prognosis obtained, a personalized treatment may be administered to the subject.

In one embodiment of the invention, the expression of at least 2, preferably of at least 3, more preferably of at least 5, and even more preferably of at least 10 markers is assessed.

The present invention also relates to a signature as hereinabove described, wherein said signature is a predictive signature and is a signature of cycling hypoxia, i.e. comprises markers whose expression is different between a normoxic condition and a cycling hypoxia condition.

The present invention further relates to a non-invasive method for predicting or anticipating the response of a subject, preferably of a patient, to a specific treatment, wherein said method comprises assessing the expression of markers in a sample of said subject, whose expressions are different between a normoxic condition and a cycling hypoxia condition. In one embodiment, the markers whose expressions are different between a normoxic condition and a cycling hypoxia condition together form a predictive signature according to the invention.

In one embodiment of the invention, the method of the invention is for determining a personalized course of treatment of the subject. Indeed, according to the result obtained with the predictive signature, a personalized treatment may be administered to the subject.

In one embodiment of the invention, the expression of at least 2, preferably of at least 3, more preferably of at least 5, and even more preferably of at least 10 markers is assessed.

In one embodiment, the subject is diagnosed with cancer. In another embodiment, the subject is at risk of cancer. Examples of risks include, but are not limited to, familial history of cancer, genetic predisposition to cancer, environmental risks such as, for example, exposure to carcinogenic chemicals or other types of carcinogenic agents, diet, clinical factors such as, for example, hormonal deregulation or presence of another cancer-inducing disease, and the like.

In one embodiment, the subject is a cancer patient. In one embodiment, the subject is a patient with precancerous lesions or adenoma.

According to this embodiment, the signature or the non-invasive method may be for predicting overall survival of the subject, wherein the overall survival refers to the survival at 2 years, preferably at 3, 5, 8 years, more preferably at 10 years.

Still according to this embodiment, the signature or the non-invasive method may be for identifying patients who could benefit from a specific treatment, such as, for example, a chemotherapeutic treatment.

Still according to this embodiment, the signature or the non-invasive method may be for assessing the likelihood of a beneficial response of the patient to a specific anti-cancer treatment. The signature or the non-invasive method of the invention may also be for predicting the resistance of a patient to a specific anti-cancer treatment.

Still according to this embodiment, the signature or the non-invasive method of the invention may be for classifying a patient as a good prognosis or poor prognosis patient, wherein a good prognosis means that a patient is expected to have no distant metastases of a tumor within 2, preferably 3, 5, 8 or 10 years, and a poor prognosis means that a patient is expected to have distant metastases of a tumor within 2, preferably 3, 5, 8 or 10 years.

In another embodiment, signature or the non-invasive method of the invention may be for classifying a patient as a progression-free survival (PFS) patient, wherein progression-free survival means that the cancer does not get worse.

In a first embodiment, the subject previously received an anticancer treatment. In another embodiment, the subject did not receive any anticancer treatment. Examples of treatment include, but are not limited to, surgery for removing the tumor, chemotherapy and/or radiotherapy.

In one embodiment, the subject was previously treated for a cancer.

In one embodiment, the subject is considered as substantially healthy as regard to this cancer, i.e. the treatment is considered to have been successful.

According to this embodiment, the signature or the non-invasive method may be for assessing the likelihood of distal recurrence of the cancer. In one embodiment, distal recurrence refers to recurrence within 2 years, preferably within 3, 5, 8 years, more preferably within 10 years. In one embodiment, the term "recurrence" may refer to the reappearance of cancer (preferably of a tumor) either within the same organ or elsewhere in the body.

According to this embodiment, the signature or the non-invasive method may be for predicting overall survival of the subject, wherein the overall survival refers to the survival at 2 years, preferably at 3, 5, 8 years, more preferably at 10 years.

In one embodiment of the invention, the cancer is a neoplasm, i.e. a cancer characterized by the presence of at least one malignant tumor.

Examples of cancers include, but are not limited to, breast cancer, prostate cancer, lung cancer, colon cancer, cervix cancer, prostate cancer, brain cancer, liver cancer, kidney cancer and connective tissue cancer.

In one embodiment, the cancer may originate in the bladder, blood, bone, bone marrow, brain, breast, cervic area, colon, connective tissue, esophagus, eye and periocular tissues including subconjunctival tissues, duodenum, small intestine, large intestine, rectum, anus, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, pancreas, prostate, skin, stomach, testis, tongue, or uterus.

Examples of cancer include, but are not limited to, fibrosarcoma, carcinoma, adenocarcinoma, lymphoma, blastoma, hepatoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, such as, for example, pancreatic carcinoma, glioblastoma, cervical cancer, ovarian

cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, such as, for example, colon adenocarcinoma (including a colon adenocarcinoma grade II), colorectal cancer, such as, for example, colorectal carcinoma, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, such as, for example, prostate adenocarcinoma, vulval cancer, thyroid cancer, osteosarcoma, neuroblastoma, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; Burkitt's lymphoma; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

Other examples of cancers include, but are not limited to, adenocarcinoma, such as, for example, breast adenocarcinoma, prostate adenocarcinoma, liver adenocarcinoma or colorectal adenocarcinoma; ductal carcinoma, such as, for example, breast ductal carcinoma; carcinoma such as, for example, colorectal carcinoma, kidney carcinoma or squamous cell carcinoma (such as, for example, squamous cell carcinoma of the cervix); glioblastoma; hepatocellular carcinoma; hepatoma; or fibrosarcoma.

In one embodiment of the invention, the cancer is breast cancer, and the patient may be classified in different subgroups determined on the basis of clinicopathologic criteria. In one embodiment, the breast cancer patient is node negative or node positive. In another embodiment, the breast cancer patient is ER+ or ER-, wherein ER stands for estrogens receptor. In another embodiment, the breast cancer patient is HER2+ or HER2-, wherein HER2 stands for Human Epidermal Growth Factor Receptor-2. In one embodiment, the breast cancer patient is ER+/HER2-, ER-/HER2- or HER2+. In another embodiment, the breast cancer patient is ER+/HER2- node negative. In another embodiment, the

breast cancer patient is ER+/HER2- node negative and did not receive any anticancer treatment.

In another embodiment of the invention, the cancer is colorectal cancer and the patient may be classified in different subgroups determined on the basis of clinicopathologic criteria, according to the American Joint Committee on Cancer (AJCC). In one embodiment, the colorectal cancer is a submucosa and muscularis propria tumor (stage I or 1). In another embodiment, the colorectal cancer is a tumor invading through the muscularis propria (stage II or 2). In another embodiment, the colorectal cancer is node positive (stage III or 3). In another embodiment, the colorectal cancer is associated with distant metastases (stage IV or 4).

In one embodiment of the invention, the non-invasive method of the invention for the prognosis of cancer in a subject comprises determining the expression profile of markers of a signature of the invention in a sample of said subject.

According to a preferred embodiment, the sample was previously taken from the subject, i.e. the method of the invention does not comprise a step of recovering a sample from the subject. Consequently, according to this embodiment, the method of the invention is a non-invasive method.

In one embodiment of the invention, the sample is a biopsy sample or a fine-needle aspirate. In one embodiment, the biopsy or the fine-needle aspiration is a biopsy or a fine-needle aspiration of the mass of cells suspected to be a tumor. In another embodiment, when a tumor has already been identified, the biopsy or the fine-needle aspiration is a biopsy or a fine-needle aspiration of this tumor.

In another embodiment of the invention, the sample is a sample of a bodily fluid. Examples of bodily fluids include, but are not limited to, blood, plasma, serum, lymph, ascetic fluid, cystic fluid, urine, bile, nipple exudate, synovial fluid, bronchoalveolar lavage fluid, sputum, amniotic fluid, peritoneal fluid, cerebrospinal fluid, pleural fluid, pericardial fluid, semen, saliva, sweat and alveolar macrophages.

In one embodiment of the invention, the non-invasive method of the invention comprises a step of comparing the expression profile of the markers of the signature of the invention measured in the sample of the subject with a reference expression profile, measured in a reference sample.

A reference expression profile can be relative to an expression profile derived from population studies, including without limitation, such subjects having similar age range, subjects in the same or similar ethnic group, similar cancer history and the like.

In one embodiment, the reference expression profile is constructed using algorithms and other methods of statistical and structural classification.

In one embodiment of the invention, the reference expression profile is derived from the measurement of the expression profile of markers of a signature of the invention in a control sample derived from one or more substantially healthy subjects. As used herein, a "substantially healthy subject" has not been previously diagnosed or identified as having or suffering from cancer.

In one embodiment of the invention, the reference expression profile is derived from the measurement of the expression profile of markers of a signature of the invention in a reference sample derived from a healthy tissue or sample of the same subject, whereas the expression profile to be compared was measured in a sample taken from a suspect mass of cells (i.e. from the suspected tumor) within the body of the subject.

In one embodiment of the invention, the reference expression profile is derived from the previous measurement of the expression profile of markers of a signature of the invention in a reference sample derived from the same subject, such as, for example, the expression profile measured one month before, preferably six months before, more preferably one year before or more.

In another embodiment of the invention, the reference expression profile is derived from the measurement of the expression profile of markers of a signature of the invention in a reference population. In one embodiment, the reference sample is thus derived from a reference population.

In one embodiment, the reference population comprises substantially healthy subjects, preferably at least 50, more preferably at least 100, more preferably at least 200 and even more preferably at least 500 substantially healthy subjects.

In another embodiment, the reference population comprises subjects diagnosed with cancer, preferably at least 100, more preferably at least 250, more preferably at least 500 subjects diagnosed with cancer.

In another embodiment of the invention, the reference expression profile is derived from the measurement of the expression profile in a reference sample derived from one or more subjects who are diagnosed or identified as having or suffering from cancer.

In one embodiment, the reference expression profile corresponds to the mean expression profile of the markers of the signature of the invention measured in the reference population.

In one embodiment of the invention, the reference expression profile corresponds to the median expression profile of the markers of the genetic signature of the invention measured in the reference population.

In one embodiment of the invention, the expression of the cycling hypoxia markers corresponds to the transcription level (i.e. expression of the RNA), or to the translation level (i.e. expression of the protein) of the marker.

In one embodiment of the invention, the expression of the cycling hypoxia markers is assessed at the protein level. Methods for determining a protein level in a sample are well-known in the art. Examples of such methods include, but are not limited to, immunohistochemistry, Multiplex methods (Luminex), western blot, enzyme-linked immunosorbent assay (ELISA), sandwich ELISA, fluorescent-linked immunosorbent assay (FLISA), enzyme immunoassay (EIA), radioimmunoassay (RIA) and the like.

In another embodiment of the invention, the expression of the cycling hypoxia markers is assessed at the RNA level. Methods for assessing the transcription level of a marker are well known in the prior art. Examples of such methods include, but are not limited to, RT-PCR, RT-qPCR, Northern Blot, hybridization techniques such as, for example,

use of microarrays, and combination thereof including but not limited to, hybridization of amplicons obtained by RT-PCR, sequencing such as, for example, next-generation DNA sequencing (NGS) or RNA-seq (also known as "Whole Transcriptome Shotgun Sequencing") and the like.

In one embodiment, the non-invasive method comprises the steps of:

- extracting total RNA from the sample from the subject,
- retro-transcribing these total RNA, thereby obtaining total cDNA,
- specifically amplifying by PCR, preferably by qPCR, the cDNA corresponding to the cycling hypoxia markers of the signature of the invention, thereby determining the expression profile of the markers of the signature, and
- comparing said expression profile with a reference expression profile determined in a reference sample.

In one embodiment, the expression profile of markers of the signature of the invention is measured using a polynucleotide microarray, so that the expression profiles of each of the markers of the signature of the invention are simultaneously measured.

In one embodiment, the non-invasive method comprises the steps of:

- extracting total RNA from the sample from the subject, retro-transcribing these total RNA, thereby obtaining total cDNA from the sample, and labeling said total cDNA,
- extracting total RNA from the reference sample, retro-transcribing these total RNA, thereby obtaining total cDNA from the reference sample, and labeling said total cDNA with a different label that the one used for the total cDNA of the sample from the subject,
- applying the total cDNA from the sample from the subject, and the total cDNA from the reference sample, on a microarray, and
- identifying markers which are differentially expressed between the sample from the subject and the reference sample, based on differential hybridization profile.

In one embodiment, the non-invasive method comprises the steps of:

- in a first step, extracting total RNA from the reference sample, retro-transcribing these total RNA, thereby obtaining total cDNA from the reference sample, and labeling said total cDNA,
- applying the total cDNA from the reference sample on a microarray, thereby obtaining a reference hybridization profile,
- in a second, preferably subsequent step, extracting total RNA from the sample from the subject, retro-transcribing these total RNA, thereby obtaining total cDNA from the sample, and labeling said total cDNA,
- applying the total cDNA from the sample from the subject on another microarray, thereby obtaining a sample hybridization profile, and
- identifying markers which are differentially expressed between the sample from the subject and the reference sample, based on the differences of both hybridization profiles.

In one embodiment of the invention, the labeling of total cDNA is performed using fluorochromes, such as, for example, Cy3 and Cy5.

In one embodiment, the non-invasive method comprises the steps of:

- extracting total RNA from the sample from the subject, retro-transcribing these total RNA, thereby obtaining total cDNA from the sample, and sequencing the total cDNA from the sample from the subject,
- extracting total RNA from the reference sample, retro-transcribing these total RNA, thereby obtaining total cDNA from the reference sample, and sequencing the total cDNA from the reference sample, and
- comparing the results of the cDNA sequencing and identifying markers which are differentially expressed between the sample from the subject and the reference sample.

In another embodiment, the non-invasive method comprises the steps of:

- extracting total RNA from the sample from the subject, and sequencing the total RNA, preferably the total mRNA, from the sample from the subject,
- extracting total RNA from the reference sample, and sequencing the total RNA, preferably the total mRNA from the reference sample, and

- comparing the results of the RNA, preferably mRNA, sequencing and identifying markers which are differentially expressed between the sample from the subject and the reference sample.

In one embodiment of the invention, a marker of the invention is considered as differentially expressed in the sample from the subject as compared to a reference sample if both expression levels differ by a factor of at least 1.1, preferably at least 1.5, more preferably at least 2 and even more preferably at least 5.

In one embodiment of the invention, the post-translational modifications of a marker of the invention corresponds to a modification selected from the list comprising or consisting of phosphorylation, myristoylation, palmitoylation, isoprenylation, glypiation, lipoylation, 0-, N- or S- acylation, alkylation, glycosylation, malonylation, hydroxylation, nucleotide addition, oxidation, sumoylation, ubiquitination, citrullination, deamidation, formation of disulfide bridges, proteolytic cleavage, racemization and the like.

Examples of methods for assessing post-translational modifications of a protein or peptide are well-known from the skilled artisan and include, but are not limited to, mass spectroscopy, methods using antibodies directed against the post-translational modification including, but not limited to, immunoblotting, immunoprecipitation, bead-based multiplexing, Eastern blotting, and the like.

The present invention also relates to a kit for measuring the expression profile of markers of the signature of the invention, and/or for implementing the non-invasive method of the invention. In one embodiment, the kit comprises means for determining the expression of the cycling hypoxia markers of the signature of the invention.

In one embodiment of the invention, the expression profile is measured at the protein level, and the kit of the invention comprises means for total protein extraction, as well as antibodies for detecting the cycling hypoxia markers of the invention.

The present invention also relates to a kit for determining the post-translational modification profile of markers of the signature of the invention, and/or for

implementing the non-invasive method of the invention. In one embodiment, the kit comprises means for determining the post-translational modification of the cycling hypoxia markers of the genetic signature of the invention.

In another embodiment, the expression profile is measured at the RNA level, and the kit of the invention comprises means for total RNA extraction, means for reverse transcription of total RNA, and means for quantifying the expression of RNA corresponding to the cycling hypoxia markers of the invention.

In one embodiment, the means for determining the expression of the cycling hypoxia markers are PCR primers, preferably qPCR primers, specific for said cycling hypoxia markers. In one embodiment, said means for determining the expression of the cycling hypoxia markers are probes to detect qPCR amplicons obtained with qPCR primers as hereinabove described.

In one embodiment, said means for quantifying the expression of RNA corresponding to the cycling hypoxia markers of the invention is PCR, preferably qPCR.

Examples of set of primers and probes that may be used for quantifying the expression of the cycling hypoxia markers of Table 8 are shown in the Table 9 below:

The TaqMan gene expression assay references can be found on http://www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/PCR/real-time-pcr/real-time-pcr-assays/taqman-gene-expression/single-tube-taqman-gene-expression-analysis.html.

GeneBank Accession Number	**Name of the marker**	**TaqMan gene expression assay references (primer/probe set)**
NM_001168	BIRC5	**Hs04194392_sl**
NM_032527	ZGPAT	**Hs00738790_ml**
NM_012322	LSM5	**Hs01123609_gl**
NM_012394	PFDN2	**Hs00276171_ml**
NM_002003	FCN1	**Hs00157572_ml**
NM_001 113201	NACA	**Hs01903640_uH**
NM_005608	PTPRCAP	**Hs02519237_sl or Hs00174778_ml**

NM_006858	TMED1	**Hs00183648_ml or Hs00970159_gl**
NM_001551	IGBP1	**Hs00426831_mH**
NM_001417	EIF4B	**Hs01903212_gH or Hs00251278_sl**

Table 9

In one embodiment of the invention, set of primers and probe that are used for quantifying the expression of the cycling hypoxia marker BIRC5 are the following sequences : AGGGCTGAAGTCTGGCGTAA (forward primer, SEQ ID NO:l), AACAATCCACCCTGCAGCTCTA (reverse primer, SEQ ID NO:2) and ATGATGGATTTGATTCGC (probe, SEQ ID NO:3).

In one embodiment of the invention, set of primers and probe that are used for quantifying the expression of the cycling hypoxia marker NACA are the following sequences : CCACCCCTAAATCTGCTGGAA (forward primer, SEQ ID NO:4), TCCAGACCCCTTGTTGTTCTTC (reverse primer, SEQ ID NO:5) and CCCTGTCCCAACCC (probe, SEQ ID NO:6).

In one embodiment of the invention, set of primers and probe that are used for quantifying the expression of the cycling hypoxia marker IGBP1 are the following sequences : GTCCGCGCTCGCCTAAT (forward primer, SEQ ID NO:7), GAGAGAGGAACCCGGAAGATCT (reverse primer, SEQ ID NO:8) and CTTTATCAAGGTTGCCTTTG (probe, SEQ ID NO:9).

In one embodiment of the invention, the kit of the invention also comprises primers for amplifying reference genes. Reference genes are genes expressed at a constant level among different tissues and/or conditions. Examples of reference genes include, but are not limited to, β-actin, genes encoding ribosomal proteins and the like.

In one embodiment of the invention, the kit of the invention comprises means for total RNA extraction, means for reverse transcription of total RNA, and reagents for carrying out a quantitative PCR as hereinabove described (such as, for example, primers, buffers,

enzyme, and the like). In one embodiment, the kit of the invention also comprises a reference sample.

In one embodiment of the invention, the kit of the invention comprises DNA probes, which may be hybridized to the qPCR amplicons to detect said cycling hypoxia marker.

In one embodiment, the means for determining the expression of the markers of the signature is a microarray comprising probes specific for said cycling hypoxia markers.

In one embodiment, said means for quantifying the expression of RNA corresponding to the cycling hypoxia markers of the invention is a microarray. The present invention thus also relates to microarrays for measuring the RNA expression profile of markers of the signature of the invention, and/or for implementing the non-invasive method of the invention.

In one embodiment of the invention, the microarray of the invention comprises DNA probes, which may be hybridized to the retro-transcribed RNA corresponding to the cycling hypoxia markers of the invention.

In one embodiment of the invention, the microarray of the invention comprises probes specific of at least 3, 5, 10, 15, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 750, 1000, or at least 1350 cycling hypoxia markers of the invention, and up to the 1379 cycling hypoxia markers of Table 1.

In one embodiment of the invention, the microarray of the invention comprises probes specific of the 1379 markers of Table 1, and/or of the 651 markers of Table 2, and/or of the 298 markers of Table 3, and/or of the 167 markers of Table 4, and/or of the 96 markers of Table 5, and/or of the 74 markers of Table 6, and/or of the 37 markers of Table 7, and/or of the 10 markers of Table 8.

Examples of probes specific of the cycling hypoxia markers of the invention include, but are not limited to those corresponding to the probesets shown in the columns "probeset" of Tables 1 to 8, wherein numbers correspond to Affymetrix references. The oligonucleotide sequence corresponding to the Affymetrix references may be easily found on the product support page of Affymetrix

(https://www.affymetrix.com/user/login.jsp?toURL=/analysis/netaffx/xmlquery_ex.affx?netaffx=wtgene_transcript) by selecting Human Gene 1.X ST.

In one embodiment of the invention, the microarray comprises probes specific of the 96 markers of Table 5.

In one embodiment of the invention, the microarray comprises probes specific of the 10 markers of Table 8.

In one embodiment, the microarray of the invention also comprises probes for reference genes. Reference genes are genes expressed at a constant level among different tissues and/or conditions. Examples of reference genes include, but are not limited to, β-actin, genes encoding ribosomal proteins and the like.

In one embodiment, the microarray of the invention also comprises probes for quality control genes. Quality control genes expression allows verifying the quality of the microarray and/or of the cDNA applied on the microarray.

In one embodiment of the invention, the kit of the invention comprises means for total RNA extraction, means for reverse transcription of total RNA, and a microarray of the invention as well as buffers and materials for use thereof. In one embodiment, the kit of the invention also comprises a reference sample.

In one embodiment, the means for determining the expression of the markers of the signature is sequencing means, allowing sequencing total RNA, preferably mRNA, or total cDNA of the sample from the subject, preferably using high-throughput sequencing technologies, more preferably using the RNA-Seq technology.

Examples of means for total sequencing of cDNA of a sample include, but are not limited to, poly(T) oligos, poly(T) magnetic beads, probes for removing ribosomal RNA, reverse transcriptase, emulsion PCR buffers and reagents, bridge amplification buffers and reagents, ligase and the like.

In another embodiment of the invention, the non-invasive method of the invention also comprises a step of measuring clinical data. Examples of clinical data which may be

relevant for the prognosis of cancer in a subject and/or for predicting the response of a subject, preferably of a patient, to a specific treatment include, but are not limited to, gender, age, size of the tumor, tumor histological grade, lymph node status, presence of a treatment, presence of metastases, specific expression profiles (such as, for example, expression status for estrogen receptor or for HER2 receptor), Nottingham grading system (NGS), Nottingham Prognostic Index (NPI), and the like.

In one embodiment of the invention, the non-invasive method of the invention comprises a step of combining the expression profiles of the markers of the signature of the invention and optionally of the value of clinical data as hereinabove described in a score.

In one embodiment, said combination is a mathematical combination in a mathematical function. Preferably, said mathematical function is a weighted sum. In one embodiment, the weighted sum is adjusted on the reference sample.

In one embodiment, the method of the invention comprises comparing the score obtained with a threshold value. In one embodiment, the threshold value corresponds to the score obtained in a reference population or in a reference sample. In another embodiment, the weighted sum is adjusted on the reference sample such that the threshold value is equal to 0.

In one embodiment, the score of the invention is a prognostic score, and may be used for the prognosis of cancer in the subject. In another embodiment, the score of the invention is a predictive score, and may be used for predicting the response of a subject, preferably of a patient, to a specific treatment.

The present invention thus also relates to a non-invasive method for the prognosis of cancer in a subject, or for predicting the response of a subject to a specific treatment, wherein said method comprises:

- assessing the expression profiles of markers of a signature comprising at least 2 cycling hypoxia markers in a sample from said subject, and
- mathematically combining the measured expression profiles in a score.

The present invention presents the following advantages:

(i) As cycling hypoxia is a hallmark of a vast majority of tumors, the signature of the invention allows the prognosis of all tumor types, and of all neoplasms;

(ii) The prognosis method of the invention, based on the identification of the signature of the invention, is easy and rapid to implement, as the inventors showed that a signature of the invention, comprising as few as about 10 markers, allows an efficient prognosis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a heatmap depicting transcripts from a signature of the invention (CycHyp) either underexpressed (green) or overexpressed (red) (centered to median values). Each column corresponds to a specific Human Gene 1.0 ST probeset; each line represents a specific cell line either maintained under normoxia (black label) or exposed to cycling hypoxia (red label); cell under normoxia and cycling hypoxia are perfectly separated in two distinct clusters, except for one cycling hypoxia sample in the normoxia cluster.

Figure 2 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer, as determined by using a signature of the invention (CycHyp). (A): All patients; (B): ER+/HER2- patients; (C): node-negative ER+/HER-2 patients; and (D): node-negative, untreated patients (DFS Mantel-Cox comparison).

Figure 3 is a comparison of the prognostic potential of the CycHyp signature vs. Gene 70 (Mammaprint), Gene 76 and Oncotype Dx signatures to discriminate patients with progressing disease versus disease-free at 5-years. (A) Balance Classification Rate (BCR), i.e. the arithmetic average between specificity and sensitivity (also depicted) determined on the validation sets only (to avoid an optimistic bias if computed on the training set) [see text for p-values] and Concordance Index (CI) between high and low risk patients, [$p<0.05$ vs. Oncotype DX, $p=0.07$ vs. Gene70 and $p=0.063$ vs. Gene76]. (B.) Kaplan-Meier survival curves of node-negative, untreated ER+/HER2- patients, as determined by using the indicated signature (DFS Mantel-Cox comparison); hazard

ratio (HR) for the prediction in high risk vs. low risk groups are presented with their associated confidence interval and p-values.

Figure 4 is a combination of Kaplan-Meier survival curves of node-negative, untreated ER+/HER2- patients stratified by using a signature of the invention (CycHyp) to detect (A) false-positive patients among those identified at high risk based on the NPI nomenclature and (B) false-negative patients among those identified at low risk based on the NPI nomenclature (DFS Mantel-Cox comparison).

Figure 5 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a signature of the invention (CycHyp) or the NPI nomenclature (DFS Mantel-Cox comparison). (A): all patients; (B): ER+/HER2- patients; (C): node-negative ER+/HER2- patients; (D): node-negative, untreated ER+/HER2- patients.

Figure 6 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature (see Table 14) of the invention.

Figure 7 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature selected from those shown in Table 11 without any overlap with the probes reported in Table 14. Note that the probesets for BIRC5 and NACA are different in Table 14 and Table 15.

Figure 8 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature selected from those shown in Table 11 with a single one (BIRC5) overlapping with those reported in Table 14. Note that the probesets for NACA are different in Table 14 and Table 16.

Figure 9 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature selected from those shown in

Table 11 with two probesets (BIRC5 and EIF4B) overlapping with those reported in Table 14. Note that the probesets for NACA are different in Table 14 and Table 17.

Figure 10 is a graph representing the power of discrimination in high vs. low risk groups (expressed as the logarithm of the p-values of the logrank) of the ContHyp (left) and CycHyp (right) signatures (see black dots) versus 1,000 randomly generated signatures of breast cancer patients (gray shapes depicting their distribution).

Figure 11 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature (see Table 18') selected from those shown in Table 11 without any overlap with the probes reported in Table 14.

Figure 12 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature selected from those shown in Table 18 with a single one (EIF4B) overlapping with those reported in Table 14.

Figure 13 is a combination of Kaplan-Meier survival curves of patients with primary breast cancer stratified at low or high risk according to a 10-probesets signature of the invention. This is an example of a 10-probesets signature selected from those shown in Table 18 with two probesets (EIF4B and BIRC5) overlapping with those reported in Table 14.

Figure 14 is combination of Kaplan-Meier survival curves of node-negative, untreated ER+/HER2- patients stratified at low or high risk according to the ContHyp signature (DFS Mantel-Cox comparison).

Figure 15 is a graph representing the power of discrimination in high vs. low risk groups (expressed as the logarithm of the p-values of the logrank) of the CycHyp signatures (see black dots) versus 1,000 randomly generated signatures of colorectal cancer patients (gray shapes depicting their distribution).

Figure 16 is a combination of Kaplan-Meier survival curves of stage II colorectal

cancer patients stratified at low or high risk according to the CycHyp signature.

Figure 17 is a combination of Kaplan-Meier survival curve of patients with primary breast cancer stratified at low or high risk according to a 3-probesets signature (see Table 21) of the invention.

EXAMPLES

The present invention is further illustrated by the following examples.

Example 1: CycHyp signature on breast cancer patients

PATIENTS AND METHODS

Tumor cells

Twenty tumor cells (see Table 10 for details) were submitted to cycling hypoxia (CycHyp), i.e. 24 cycles of 30 min incubation under normoxia and 30 min incubation under hypoxic (1% 0_2) conditions to reproduce the frequency of tumor hypoxic fluctuations, as previously reported (Dewhirst, Radiat Res 172:653-665, 2009).

Table 10. List of Human Tumor Cells used for Microarray Analysis.

Cell line	Organ	Disease
MCF-7	Breast	Adenocarcinoma
MDA-MB-231	Breast	Adenocarcinoma
T47D	Breast	Ductal carcinoma
A549	Lung	Carcinoma
Widr	Colon	Colorectal adenocarcinoma
$HCT1_{16}$ WTP53	Colon	Colorectal carcinoma
$HCT116^{-/-P53}$	Colon	Colorectal carcinoma
HT29	Colon	Colorectal adenocarcinoma
Colo-205	Colon	Colorectal adenocarcinoma
LoVo	Colon	Colorectal adenocarcinoma
HCT15	Colon	Colorectal adenocarcinoma
SiHa	Cervix	Squamous cell carcinoma
PC3	Prostate	Adenocarcinoma
U373	Brain	Glioblastoma
HepG2	Liver	Hepatocellular carcinoma
Hep3B	Liver	Hepatocellular carcinoma
PLC/PRF/5	Liver	Hepatoma

SK-HEP-1	Liver	Adenocarcinoma
A498	Kidney	Carcinoma
HT1080	Connective tissue	Fibrosarcoma

Identification of the signature

mRNA extracts from each tumor cell cultured under both the above conditions (normoxia and cycling hypoxia) were analysed by hybridization on Human Gene 1.0 ST Affymetrix microarrays (GEO access number: GSE42416). The extent of the resulting tumor cell datasets (20 samples in each of the three conditions) led us to resort on a resampling mechanism to increase the robustness of the signatures to be identified. For every resampling experiment, a subset of 90 % of the samples was chosen uniformly at random without replacement. Differentially expressed probesets were assessed on each subset according to a t-test and the corresponding p-values were reported. The 100 probesets with the lowest p-values, averaged over 200 resamplings, formed the CycHyp signature. All such expression differences were highly significant ($p < 10^{-4}$) after Benjamini-Hochberg FDR correction for the multiplicity of the test (Benjamini et al, J R Stat Soc 57:289-300, 1995). The 100 HGU1.0 ST probesets forming the CycHyp signature corresponded to 94 unique Entrez GenelD in the NCBI database, out of which 69 genes were available on the HGU133a platform (i.e., the technology used in most clinical studies considered here). Those 69 genes were represented by 87 HGU133a probesets. The few datasets collected on HGU133plus2 were reduced to the probesets also present on HGU133a, thus with an identical CycHyp signature of 87 probesets.

Patient data sets

All breast cancer expression data were summarized with MAS5 and represented in log2 scale (except for GSE6532 already summarized with RMA). Breast cancer subtypes (ER+/HER2-, ER-/HER2- and HER2+) were identified with the genefu R package (Haibe-Kains et al, Genome Biol 11:R18, 2010). Disease-free survival at 5 years was used as the survival endpoint. The data from all patients were censored at 10 years to have comparable follow-up times across clinical studies (Haibe-Kains et al, Bioinformatics 24:2200-2208, 2008).

Prognostic models of the clinical outcome

The VDX dataset (GSE2034 and GSE5327 from the GEO database) was considered as a reference because of its large number of node-negative untreated patients (Wang et al, Lancet 365:671-679, 2005). This dataset formed the training set used to estimate a prognostic model of the clinical outcome. A risk score for each patient was computed from a penalized Cox proportional hazards model implemented in the Penalized R package (Goeman, Biom J 52:70-84, 2010). Prediction into a high risk vs. low risk group resulted from a predefined threshold value on this risk score. The decision threshold was chosen on the training set to maximize the specificity and sensitivity of the discrimination between patients with progressing disease versus disease-free patients at 5 years. Following the methodology described by Haibe-Kains et al. (Haibe-Kains et al, Bioinformatics 24:2200-2208, 2008), all other datasets were used as validations to assess the prognostic performances on independent samples. Performance metrics included the balanced classification rate (BCR), i.e. the arithmetic average between specificity and sensitivity (determined on the validation sets only to avoid an optimistic bias if computed on the training set), the concordance index (CI) (Harrell et al, Stat Med 15:361-387, 1996) and the hazard ratio (HR) (Cox, J R Stat Soc 34:187-220, 1972) for the prediction in high risk vs. low risk groups, with their associated confidence interval and p-values. Prognostic performances of a penalized Cox model defined on the CycHyp signature were also compared with well-established prognosis models for breast cancer, namely Gene 70 (Mammaprint) (van't Veer et al, Nature 415:530-536, 2002), Gene 76 (Wang et al, Lancet 365:671-679, 2005) and Oncotype DX (Paik et al, N Engl J Med 351:2817-2826, 2004) signatures. Those existing signatures were associated to specific prognostic models implemented in the genefu R package (Haibe-Kains et al, Genome Biol 11:R18, 2010).

RESULTS

Identification of the CycHyp signature

Tumor cells were submitted to cycling hypoxia for 24 hours or maintained under normoxic conditions for the same period of time. Corresponding mRNA samples were

analysed by hybridization using Human Gene 1.0 ST Affymetrix microarrays. Gene expression profiles of each cell type under normoxia vs. cycling hypoxia were produced to identify the most differentially expressed probesets.

The CycHyp signature was determined as the top 100 probesets with the lowest average pvalues over 200 resamplings, corresponding to 96 markers. These probesets are shown in the Table 11 below.

	Probeset	**GenBank Accession Number**	**Name of the marker**
1	8018860	NM_001168	BIRC5
2	8064156	NM_032527	ZGPAT
3	8138912	NM_0 12322	LSM5
4	7921786	NM_0 12394	PFDN2
5	8165011	NM_002003	FCN1
6	7964262	NM_001 113201	NACA
7	7949792	NM_005608	PTPRCAP
8	8034101	NM_006858	TMED1
9	8168087	NM_001551	IGBP1
10	7963575	NM_001417	EIF4B
11	8124397	NM_005319	HIST1H1C
12	7975989	NM_031210	SLIRP
13	8127692	NM_000863	HTR1B
14	8127087	NM_000847	GSTA3
15	7941122	NM_0 13299	SAC3D1
16	7998692	NM_002528	NTHL1
17	8073623	NM_00 1044370	MPPED1
18	8014865	NM_006160	NEUROD2
19	8005726	NM_021012	KCNJ12
20	7966631	NM_022363	LHX5
21	8037853	NM_017854	TMEM160
22	8104136	NM_0 18942	HMX1
23	7948606	NM_0 14206	CllorflO
24	8044773	NM_006770	MARCO
25	7947015	NM_006292	TSG101
26	7931553	NM_003577	UTF1
27	7956876	NM_032338	LLPH
28	8117372	NM_003512	HIST1H2AC
29	8001329	NM_004352	CBLN1
30	8027205	NM_0 15965	NDUFA13
31	8042896	NM_016170	TLX2
32	7911532	NM_0 17900	AURKAIP1
33	8039923	NM_0 17900	AURKAIP1
34	7992043	BC001181	FAM173A
35	8063074	NM_080603	ZSWIM1

36	7992191	NM_012217	TPSD1
37	8108435	NM_181838	UBE2D2
38	8165309	NM_003792	EDF1
39	7946267	NM_022061	MRPL17
40	7945536	NM_016564	CEND1
41	8159609	NM_003731	SSNA1
42	8005471	NM_001031	RPS28
43	8025395	NM_001031	RPS28
44	7942824	NM_001031	RPS28
45	8170753	NM_0 14370	SRPK3
46	8032718	NM_001348	DAPK3
47	7967067	NM_00 1037495	DYNLL1
48	8159654	NM_015456	COBRA1
49	8011212	NM_003001	SDHC
50	8011968	NM_0 16060	MED31
51	7977440	NR_026800	KIAA0125
52	8016508	NM_007241	SNF8
53	8168567	NM_000307	POU3F4
54	8086317	NM_031899	GORASP1
55	8052834	BC005079	C2orf42
56	8073334	NM_0 14248	RBX1
57	7915846	NM_003684	MKNK1
58	8071920	NM_004175	SNRPD3
59	8032371	NM_031213	FAM108A1
60	7924884	NM_003493	HIST3H3
61	8006845	NM_000981	RPL19
62	7946812	NM_001017	RPS13
63	7949015	NM_001 144936	Cllorf95
64	8009784	NM_0 15971	MRPS7
65	8174509	NM_005274	GNG5
66	7906235	NM_005973	PRCC
67	8020179	NM_020412	CHMP1B
68	7947450	NM_005574	LM02
69	8064370	NM_004609	TCF15
70	7955896	NM_0 16057	COPZ1
71	8137805	NM_003550	MAD1L1
72	8117334	NM_003538	HIST1H4A
73	8117368	NM_003542	HIST1H4C
74	7977507	NR_002312	RPPH1
75	7949410	BC018448	MALAT1
76	8150433	NM_152568	NKX6-3
77	8071168	NR_024583	POM121L8P
78	7989611	NM_032231	FAM96A
79	7980859	NM_001080113	
80	8032782	NM_144615	TMIGD2
81	8110861	NM_032479	MRPL36
82	7901687	NM_1 82532	TMEM61
83	7916130	NM_138417	KTI12
84	8048712	BC033986	LOC440934

85	8018993	NM_001082575	RBFOX3
86	8032601	NM_032753	RAX2
87	8010719	NM_144999	LRRC45
88	8036584	NM_002307	LGALS7
89	8133209	NR_003666	SPDYE7P
90	8159501	NM_178536	LCN12
91	8028546	NM_002307	LGALS7
92	8065013	ENST00000427835	
93	8018502	NM_173547	TRIM65
94	7903294	NM_033055	HIATI
95	7989473	NM_001007595	C2CD4B
96	8054449	AK095987	FLJ38668
97	8081867	NM_016589	TIMMDCl
98	7934544	NM_144589	COMTD1
99	7968260	NM_145657	GSX1
100	8022952	NM_020180	CELF4

Table 11

The heatmap (Figure 1) made with the 100 probe sets of the CycHyp signature confirmed its excellent potential of discrimination between cycling hypoxia and normoxia.

The CycHyp signature predicts clinical outcome in breast cancer patients

To evaluate the prognostic value of the CycHyp signature, we focused on breast cancer because of the very large amounts of well-annotated clinical data sets available and a clearly identified need to discriminate between patients at low and high risks among subgroups determined on the basis of clinicopathologic criteria (Reis-Filho et al, Lancet 378:1812-1823, 2011; Prat et al, Nat Rev Clin Oncol 9:48-57, 2011). Publicly available GEO data sets allowed us to collect information on the survival of 2,150 patients with primary breast cancer (see clinical features in Table 12).

Table 12: Breast Cancer Patient Demographics and Characteristics

	All patients n = 2150		ER+/HER2- n=1452		ER+/HER2- Node neg. n=899		ER+/HER2- Node neg. Untreated n=590	
	No	%	**No**	%	**No**	%	**No**	%
Age								
<50	**649**	*30*	**388**	*27*	**218**	*24*	**190**	*32*
>50	**945**	*44*	**649**	*45*	**367**	*41*	**237**	*40*
NA	**556**	*26*	**415**	*28*	**314**	*35*	**163**	*28*
Tumor size								
≤2cm	**742**	*35*	**537**	*37*	**474**	*53*	**424**	*72*
>2cm	**473**	*22*	**326**	*22*	**210**	*23*	**158**	*28*
NA	**935**	*43*	**589**	*41*	**215**	*24*	**8**	*1*
Grade								
0-1	**224**	*10*	**200**	*14*	**148**	*17*	**104**	*18*
2	**605**	*28*	**485**	*33*	**346**	*38*	**270**	*46*
3	**487**	*23*	**206**	*14*	**162**	*18*	**137**	*23*
NA	**834**	*39*	**561**	*39*	**243**	*27*	**79**	*13*
Node status								
Negative	**1329**	*62*	**899**	*62*	**899**	*100*	**590**	*100*
Positive	**821**	*38*	**553**	*38*	**0**	*0*	**0**	*0*
Estrogen receptor								
Negative	**443**	*21*	**0**	*0*	**0**	*0*	**0**	*0*
Positive	**1607**	*75*	**1452**	*100*	**899**	*100*	**590**	*100*
NA	**100**	*4*	**0**	*0*	**0**	*0*	**0**	*0*
HER2 status								
Negative	**1835**	*85*	**1452**	*100*	**899**	*100*	**590**	*100*
Positive	**315**	*15*	**0**	*0*	**0**	*0*	**0**	*0*
Treatment								
None	**901**	*42*	**590**	*41*	**590**	*66*	**590**	*100*
Chemotherapy	**691**	*32*	**410**	*28*	**73**	*8*	**0**	*0*
Hormonotherapy	**558**	*26*	**452**	*31*	**236**	*26*	**0**	*0*

In order to exploit these data sets, we first transferred the Gene LOST technology in the HGU133 platform. The 100 HGUl.O ST probesets forming the CycHyp signature correspond to 94 unique Entrez GenelD in the NCBI database (Table 11), out of which 69 genes were available on the HGU133a platform. Those 69 genes are represented by

87 HGU133a probesets. The few datasets collected on HGU133plus2 were reduced to the probesets also present on HGU133a.

We then used the VDX dataset (GSE2034 and GSE5327) as a reference because of its large number of node negative untreated patients (Wang et al, Lancet 365:671-679, 2005). This training dataset was used to estimate a prognostic Cox proportional hazard model built on the CycHyp signature. The other datasets were used according to the methodology described by Haibe-Kains and colleagues (Haibe-Kains et al, Bioinformatics 24:2200-2208, 2008), to assess the prognostic performance of the CycHyp signature on independent samples. We first chose to evaluate our signature independently of the receptor status of the tumors. The prognostic potential of the CycHyp signature to discriminate between patients at low or high risk was confirmed with a HR=1.97 and a p-value = $1.8.\ 10^{-12}$ (Figure 2A). We then focused on the ER+ HER2- population which is known to be heterogeneous and thus difficult to treat (Reis-Filho et al, Lancet 378:1812-1823, 2011; Prat et al, Nat Rev Clin Oncol 9:48-57, 2011). The discriminating capacity of the CycHyp signature remained strikingly high in the ER+ HER2- patient populations (HR = 2.34, p-value = $9.\ 10^{-12}$, Figure 2B). Finally, among this subpopulation of patients, we considered those with a node negative status (Figure 2C) and among the latter, those who did not receive any treatment (Figure 2D). Hazard ratios rose to 3.32 and 5.51 in these conditions (p-values = $5.61.\ 10^{-10}$ and $8.15.\ 10^{-11}$, respectively), further supporting the discriminating potential of the CycHyp signature. In particular, the data presented in Figure 2D allowed to exclude any confounding influence of the potential benefit arising from the treatment administered to these patients and thus clearly identified a population of patients who remained inadequately untreated.

The CycHyp signature provides significant additional prognostic information to available multigene assays

To evaluate the performance of the CycHyp signature, we compared it with other well-established prognostic multigene assays for breast cancer, namely Gene70 or Mammaprint (van't Veer et al, Nature 415:530-536, 2002), Gene76 (Wang et al, Lancet

365:671-679, 2005) and Oncotype Dx (Paik et al, N Engl J Med 351:2817-2826, 2004). Using the same set of ER+/HER2- node negative patients as used in Figure 2D, we could determine the low vs. high risk patient stratification according to these signatures. The Balanced Classification Rate (BCR) represents the average between sensitivity and specificity to discriminate between patients with progressing disease vs. disease-free at 5 years. The BCR was significantly higher for the CycHyp signature than the three other multigene assays (Figure 3A) (p-values = 1.3e-4, 1.4e-21 and 6e-10 vs. Gene70, Gene76 and Oncotype DX, respectively). The sensitivity and the specificity of CycHyp were actually both above 70% while for each of the three other signatures, the specificity parameter was below 45% (Figure 3A). The concordance index, which is the probability of a high risk patient to relapse before a low risk patient, was also higher with the CycHyp signature (Figure 3A). The superior prognostic potential of the CycHyp signature could also be captured from the comparison of the Kaplan Meier curves obtained with the Gene 70, Gene76 and Oncotype DX signatures (HR in the 2-3 range) and that derived from the CycHyp signature (compare Figure 3B with Figure 2D).

The CycHyp signature in association with NPI offers a powerful prognostic tool

We then aimed to determine whether the CycHyp signature could improve the Nottingham Prognostic Index (NPI) for better predicting the survival of operable breast cancers.

The NPI algorithm combines nodal status, tumour size and histological grade and allows modeling a continuum of clinical aggressiveness with 3 subsets of patients divided into good, moderate, and poor prognostic groups with 15-year survival (Rakha et al, Breas Cancer Res 12:207, 2010; Galea et al, Breast Cancer Res Treat 22:207-219, 1992; Balslev et al, Breast Cancer Res Treat 32:281-290, 1994). Since few patients were assigned a poor index, we merged here the moderate and poor indices into a high risk group to facilitate the comparison with the CycHyp signature. We found that by integrating the CycHyp signature, an important proportion of patients could be reclassified to another risk group (Figure 4). 52.9% of patients classified at high risk using the NPI algorithm were "false positive" since identified at low risk when using

the CycHyp signature and actually exhibited a profile of survival closer to the low risk NPI patient (Figure 4A). Inversely, using the CycHyp signature, we also identified in the patients at low risk based on the NPI criteria, 23.4% of patients with a risk profile closer to the patients with a negative outcome (Figure 4B).

This increased discriminating potential remained highly relevant when considering all patients (Figure 5A) or patients with a ER+ HER2- status (Figure 5B). Three subgroups of patients could be clearly identified: patients identified at low and high risks with both the CycHyp signature or the NPI criteria (Low-Low or High-High), and patients at intermediary risk, i.e. at low risk with NPI but high risk according to CycHyp signature (Low-High or false negative) or inversely (High-Low or false positive) (Figures 5A and 5B). Among the ER+ HER2- patients with a node negative status (Figure 5C), although a similar profiling of three subpopulations of patients could be proposed up to 5 years based on the combination of CycHyp signature and NPI, the gene signature was more efficient to predict survival on the longer term. Two subgroups of patients with either poor or good outcomes could actually be discriminated on the basis of the CycHyp signature (see L-L/H-L vs. L-H/H-H curves in Figure 5C). Finally, when only considering untreated patients within the ER+ HER2- node negative patients (Figure 5D), four subgroups of patients were observed. Interestingly, within the subgroups of patients classified at intermediary risk, those at low risk based on the NPI but at high risk following the CycHyp (see L-H curve in Figure 5D) had actually a worse outcome than those classified at high risk based on the NPI but at low risk according to the CycHyp signature (see red curve in Figure 5D).

Numerical values obtained for patients and used for drafting figures 5A-D are shown in the Table 13 below, wherein indicated p-values were derived from Mantel-Cox, log-rank tests.

		L-L		H-L		L-H	
		HR	p	HR	p	HR	p
All patients	H-L	2.33	3.73e-07				
	L-H	2.96	2.20e-04	1.22	0.392		
	H-H	3.86	1.49e-17	1.69	3.04e-07	1.39	0.135
ER+ HER2- (N+/N-)	H-L	2.72	3.45e-06				
	L-H	3.35	5.67e-04	1.17	0.569		
	H-H	5.32	7.28e-17	1.97	3.63e-07	1.70	0.034
ER+ HER2- (N-)	H-L	2.11	1.89e-02				
	L-H	4.41	9.83e-05	2.03	2.82e-02		
	H-H	5.61	4.38e-10	2.72	9.12e-06	1.37	0.265
ER+ HER2- (N-) untreated	H-L	3.93	5.42e-03				
	L-H	7.81	l.lle-04	1.88	1.43e-01		
	H-H	14.34	9.17e-13	3.63	2.48e-05	1.98	0.044

Table 13

Using the same protocol, the prognostic values of other signatures of the invention, comprising 10 probesets out of the 87 HGU133a probesets (themselves covering 69 genes of the CycHyp signature that are available on the HGU133a platform), were assessed.

The first 10-probesets signature comprises the following markers:

	Probeset (HGU 1.0 ST)	Probeset (HGU133a)	GenBank Accession Number	Name of the marker
1	8018860	202095_s_at	NM_001168	BIRC5
2	8064156	221848_at	NM_032527	ZGPAT
3	8138912	202903_at	NM_012322	LSM5
4	7921786	218336_at	NM_012394	PFDN2
5	8165011	205237_at	NM_002003	FCN1
6	7964262	200735_x_at	NM_001113201	NACA
7	7949792	204960_at	NM_005608	PTPRCAP
8	8034101	203679_at	NM_006858	TMED1
9	8168087	202105_at	NM_001551	IGBP1
10	7963575	211938_at	NM_001417	EIF4B

Table 14

Probesets according to the HGU 1.0 ST platform and to the HGU133a platform are indicated.

The prognostic efficiency of this signature is illustrated by the results of Figure 6.

The second 10-probesets signature comprises the following markers:

	Probeset (HGU133a)	GenBank Accession Number	Name of the marker
1	202094_at	AA648913	BIRC5
2	210334_x_at	AB028869	BIRC5
3	204249_s_at	NM_005574	LM02
4	209731_at	U79718	NTHL1
5	200018_at	NM_001017	RPS13
6	218391_at	NM_007241	SNF8
7	202904_s_at	NM_012322	LSM5
8	208635_x_at	BF976260	NACA
9	211747_s_at	BC005938	LSM5
10	208904_s_at	BC000354	RPS28

Table 15

The prognostic efficiency of this signature is illustrated by the results of Figure 7.

The third 10-probesets signature comprises the following markers:

	Probeset (HGU133a)	GenBank Accession Number	Name of the marker
1	202095_s_at	NM_001168	BIRC5
2	221434_s_at	NM_031210	C14orfl56
3	202904_s_at	NM_012322	LSM5
4	33 211747_s_at	BC005938	LSM5
5	200703_at	NM_003746	DYNLL1
6	218391_at	NM_007241	SNF8
7	208903_at	BF431363	RPS28
8	200018_at	NM_001017	RPS13
9	208635_x_at	BF976260	NACA
10	218177_at	AA293502	CHMP1B

Table 16

The prognostic efficiency of this signature is illustrated by the results of Figure 8.

The fourth 10-probesets signature comprises the following markers:

	Probeset (HGU133a)	GenBank Accession Number	Name of the marker
1	202095_s_at	NM_001168	BIRC5
2	211938_at	BF247371	EIF4B
3	221434_s_at	NM_031210	C14orfl56
4	202904_s_at	NM_012322	LSM5
5	33 211747_s_at	BC005938	LSM5
6	200703_at	NM_003746	DYNLL1
7	218391_at	NM_007241	SNF8
8	208903_at	BF431363	RPS28
9	200018_at	NM_001017	RPS13
10	208635_x_at	BF976260	NACA

Table 17

The prognostic efficiency of this signature is illustrated by the results of Figure 9.

Taken together, these data demonstrate that the signatures of the present invention, which are derived from the transcriptomic adaptation of tumor cells to cycling hypoxia is prognostic of cancer.

To confirm the specificity of these results, random gene signatures were tested for their prognostic capacity (negative control). These random signatures were constituted of 10 genes randomly selected amongst the totality of the genome. To have a significant value, 1000 such random signatures were used according the same methodology than

with the CycHyp signature. The logrank test (or Mantel-Haenszel test; Balsev et al, Breast Cancer Res Treat, 1994) is commonly used to assess whether there is a significant survival difference between risk groups. The discrimination between risk groups was significantly higher ($P < 0.001$) with the CycHyp signature as compared to each of the random signatures, therefore validating the prognostic potential of the CycHyp signature (right panel, Figure 10).

Example 2: Alternative lists of 10 genes

METHODS

To assess the prognosis value of an alternative list of 10 genes representative of Cycling Hypoxia, we compared the CycHyp signature with alternative lists of 10 probesets (Table 18) out of the 87 HGU133a probesets (themselves covering 69 genes of the CycHyp signature that are available on the HGU133a platform but without overlap with the CycHyp signature of 10 genes shown in Table 8. Using the same set of ER+/HER2- node negative patients as used in Figure 2D, we could determine the low vs. high risk patient stratification according to these signatures.

	Probeset (HGU133a)	**GenBank Accession number**	**Name of the marker**
1	204249_s_at	NM_005574	LM02
2	209731_at	U79718	NTHL1
3	200018_at	NM_001017	RPS13
4	218391_at	NM_007241	SNF8
5	208904_s_at	BC000354	RPS28
6	222216_s_at	AK026857	MRPL17
7	201758_at	NM_006292	TSG101
8	200703_at	NM_003746	DYNLL1
9	209467_s_at	BC002755	MKNK1
10	208903_at	BF431363	RPS28

Table 18

RESULTS

The prognostic efficiency of one of these alternative signatures is illustrated by the results of Figure 11. Such a model may have a good prognosis performance with a hazard ratio of 2.78 for that particular alternative list, but is significantly lesser than the CycHyp model (HR = 5.51, see Figure 2D).

Another 10-probesets signature wherein one probeset of Table 18 is replaced by one probeset of Table 14 comprises the following markers:

	Probeset (HGU133a)	**GenBank Accession number**	**Name of the marker**
1	211938_at	BF247371	EIF4B
2	204249_s_at	NM_005574	LM02
3	209731_at	U79718	NTHL1
4	200018_at	NM_001017	RPS13
5	218391_at	NM_007241	SNF8
6	208904_s_at	BC000354	RPS28
7	222216_s_at	AK026857	MRPL17
8	201758_at	NM_006292	TSG101
9	200703_at	NM_003746	DYNLL1
10	209467_s_at	BC002755	MKNK1

Table 19

The prognostic efficiency of this signature is illustrated by the results of Figure 12.

Another 10-probesets signature where two probesets of Table 18 are replaced by two probesets of Table 14 comprises the following markers:

	Probeset (HGU133a)	GenBank Accession number	Name of the marker
1	202095_s_at	NM_001168	BIRC5
2	211938_at	BF247371	EIF4B
3	204249_s_at	NM_005574	LM02
4	209731_at	U79718	NTHL1
5	200018_at	NM_001017	RPS13
6	218391_at	NM_007241	SNF8
7	208904_s_at	BC000354	RPS28
8	222216_s_at	AK026857	MRPL17
9	201758_at	NM_006292	TSG101
10	200703_at	NM_003746	DYNLL1

Table 20

The prognostic efficiency of this signature is illustrated by the results of Figure 13.

Equivalent results were obtained with the other alternative lists tested. These results thus demonstrated that any combination of 10 genes of Table 5 or Table 11 has a high prognosis performance.

Example 3: Comparison of the signature of cyclic hypoxia of the invention (CycHyp) with a signature of continuous hypoxia (ContHyp)

METHODS

Using the same protocol as for the identification of the CycHyp signature, we determined a ContHyp signature which corresponds to continuous hypoxia conditions, i.e. 24 h continuous exposure to 1% 0_2.

RESULTS

A heatmap made with the 100 probe sets of the CycHyp signature shown its important potential of discrimination between cycling hypoxia and continuous hypoxia (data not shown).

We then used the Gene Set Enrichment Analysis described by Subramanian et al. (Proc Natl Acad Sci U S A, 2005) which is a method for identifying differentially expressed genes that share some characteristic. The analysis indicated that when considering

differentially expressed probesets (after FDR correction), only 2 gene sets were significantly enriched in the CycHyp signature whereas 52 gene sets were enriched in the ContHyp signature, including 17 directly related to hypoxia.

Also, when using the MSigDB molecular signature database referring to hypoxia or HIF (www.broadinstitute.org), we found only 13 hypoxia gene sets sharing, on average, 1.4 gene with CycHyp whereas 44 hypoxia gene sets showed overlap with ContHyp with an average of 6.6 common genes.

To further validate the prognosis significance of the CycHyp signature compared to the ContHyp signature, we performed a comparison with random gene signatures according to the methodology described by Venet et al. (PLoS Comput Biol, 201 1) and Beck et al. (PLoS Comput Biol, 2013). Figure 10 shows the distribution of the p-values (logrank test in log 10) for 1000 randomly generated signatures together with the p-values of the CycHyp and ContHyp signatures. The discrimination between risk groups was significantly higher ($P < 0.001$) with the CycHyp signature as compared to each of the random signatures whereas the ContHyp signature (left panel) was not significantly better (vs. random ones; P=0.141).

Using the same methodology, we examined the prognostic capacity of the ContHyp signature (discriminating between normoxia and continuous hypoxia). The performance of the ContHyp signature was satisfactory on the ER+ HER2- untreated population (HR = 2.58, p-value = 1.46e-4, see Figure 14) but was significantly lower (p-value = 3.61e-8) than the CycHyp signature.

Taken together, these data confirm the significantly high value of the CycHyp signature of the present invention, and confirm the prognostic advantage of a signature based on cyclic hypoxia compared to a signature based on continuous hypoxia.

Example 4: CycHyp signature on colorectal cancer patients

PATIENTS AND METHODS

To validate the use of the CycHyp signature on colorectal cancer, we used 2 public microarray data sets: GSE39582 (566 patients) and GSE17536 (177 patients).

The GSE39582 dataset was used as the training set used to estimate a prognostic model of the clinical outcome. This training dataset was used to estimate a prognostic Cox or equal weights linear (EWL) regression models built on the CycHyp signature. The GSE17536 dataset was then used according to the methodology described for breast cancer samples to assess the prognostic performance of the CycHyp signature on independent samples.

RESULTS

As for breast cancer, we first compared the CycHyp signature with randomly selected genes on the colon data sets. Each random signature has the same size as the CycHyp signature. We generated 1,000 such random signatures and use the same methodology to estimate a prognosis model from the GSE39582 dataset. We then assess the performance of those prognosis models on the independent validation sets of 177 patients (GSE17536).

Figure 15 represents in gray the distribution of those prognosis models built from random signatures on the stage 2 patients. The discrimination between high and low risk groups is assessed according to a logrank test and its associated p-value (reported in loglO scale). The logrank p-values of the CycHyp signature is represented with black dots on the same plot. The CycHyp signature is significantly better than random signature on the stage 2 patients (p-value 0:027).

To evaluate the discriminating capacity of the CycHyp signature, we chose to focus on the stage II colorectal cancer population which is known to be heterogeneous and thus difficult to treat. The prognostic efficiency of the CycHyp signature is illustrated by the

results of Figure 16. The discriminating capacity of the CycHyp signature was strikingly high in this patient population (HR = 5.35, p-value = 0.03) when compared with the whole colorectal cancer patient population (HR=2.52, p-value =0.017) (not shown).

These results demonstrate that the CycHyp signature of the invention also has high prognosis performance for colorectal cancer.

Example 5: Prognostic performance of a signature consisting of BIRC5, IGBP1 and EIF4B

METHODS

The prognostic values of another signature of the invention, comprising 3 probesets, was assessed. Using the same set of ER+/HER2- node negative patients as used in Figure 2D, we could determine the low vs. high risk patient stratification according to these signatures.

The 3-probesets signature comprises the following markers:

	Probeset (HGU133a)	GenBank Accession number	Name of the marker
1	202095_s_at	NM_001168	BIRC5
2	202105_at	NM_001551	IGBP1
3	211938_at	BF247371	EIF4B

Table 21

RESULTS

The prognostic efficiency of this signature is illustrated by the results of Figure 17. Such a model has a good prognosis performance with a hazard ratio of 5.09 that is almost as good as the CycHyp model (HR = 5.51, see Figure 2D).

CLAIMS

1. A non-invasive method for the prognosis of cancer in a subject, or for predicting the response of a subject to a specific treatment, wherein said method comprises assessing the expression of markers of a signature comprising at least 2 cycling hypoxia markers in a sample from said subject.

2. The non-invasive method according to claim **1,** wherein said signature comprises at least 3, preferably at least 5, more preferably at least 10 cycling hypoxia markers.

3. The non-invasive method according to claim **1** or claim **2,** wherein said cycling hypoxia markers are selected from the list of 1379 cycling hypoxia markers of Table 1, fragments, variants and equivalents thereof.

4. The non-invasive method according to anyone of claims **1** to **3,** wherein said cycling hypoxia markers are selected from the list of 651 cycling hypoxia markers of Table 2, fragments, variants and equivalents thereof.

5. The non-invasive method according to anyone of claims **1** to **4,** wherein said cycling hypoxia markers are selected from the list of 298 cycling hypoxia markers of Table 3, fragments, variants and equivalents thereof.

6. The non-invasive method according to anyone of claims **1** to **5,** wherein said cycling hypoxia markers are selected from the list of 167 cycling hypoxia markers of Table 4, fragments, variants and equivalents thereof.

7. The non-invasive method according to anyone of claims **1** to **6,** wherein said cycling hypoxia markers are selected from the list of 96 cycling hypoxia markers of Table 5, fragments, variants and equivalents thereof.

8. The non-invasive method according to anyone of claims **1** to **7,** wherein said cycling hypoxia markers are selected from the list of 74 cycling hypoxia markers of Table 6, fragments, variants and equivalents thereof.

9. The non-invasive method according to anyone of claims **1** to **8,** wherein said cycling hypoxia markers are selected from the list of 37 cycling hypoxia markers of Table 7, fragments, variants and equivalents thereof.

10. The non-invasive method according to anyone of claims **1** to **9,** wherein said cycling hypoxia markers are selected from the list of 10 cycling hypoxia markers of Table 8, fragments, variants and equivalents thereof.

11. The non-invasive method according to anyone of claims **1** to **10,** wherein said signature comprises the 10 cycling hypoxia markers of Table 8, variants, fragments and equivalents thereof.

12. The non-invasive method according to anyone of claims **1** to **11,** wherein said method comprises mathematically combining the expression profile of markers in a score.

13. The non-invasive method according to anyone of claims **1** to **12,** wherein said sample is a biopsy sample or a bodily fluid sample of said subject.

14. The non-invasive method according to anyone of claims **1** to **13,** further comprising comparing said expression with a reference expression profile.

15. A kit for implementing the non-invasive method according to anyone of claims **1** to **14,** wherein said kit comprises means for determining the expression of the cycling hypoxia markers of the signature.

16. The kit according to claim **15,** wherein said means for determining the expression of the markers of the signature is a microarray comprising probes specific for said cycling hypoxia markers.

17. The kit according to claim **15,** wherein said means for determining the expression of the cycling hypoxia markers are qPCR primers specific for said cycling hypoxia markers.

18. The kit according to claim **15,** wherein said means for determining the expression of the cycling hypoxia markers are probes to detect qPCR amplicons obtained with qPCR primers according to claim **17.**

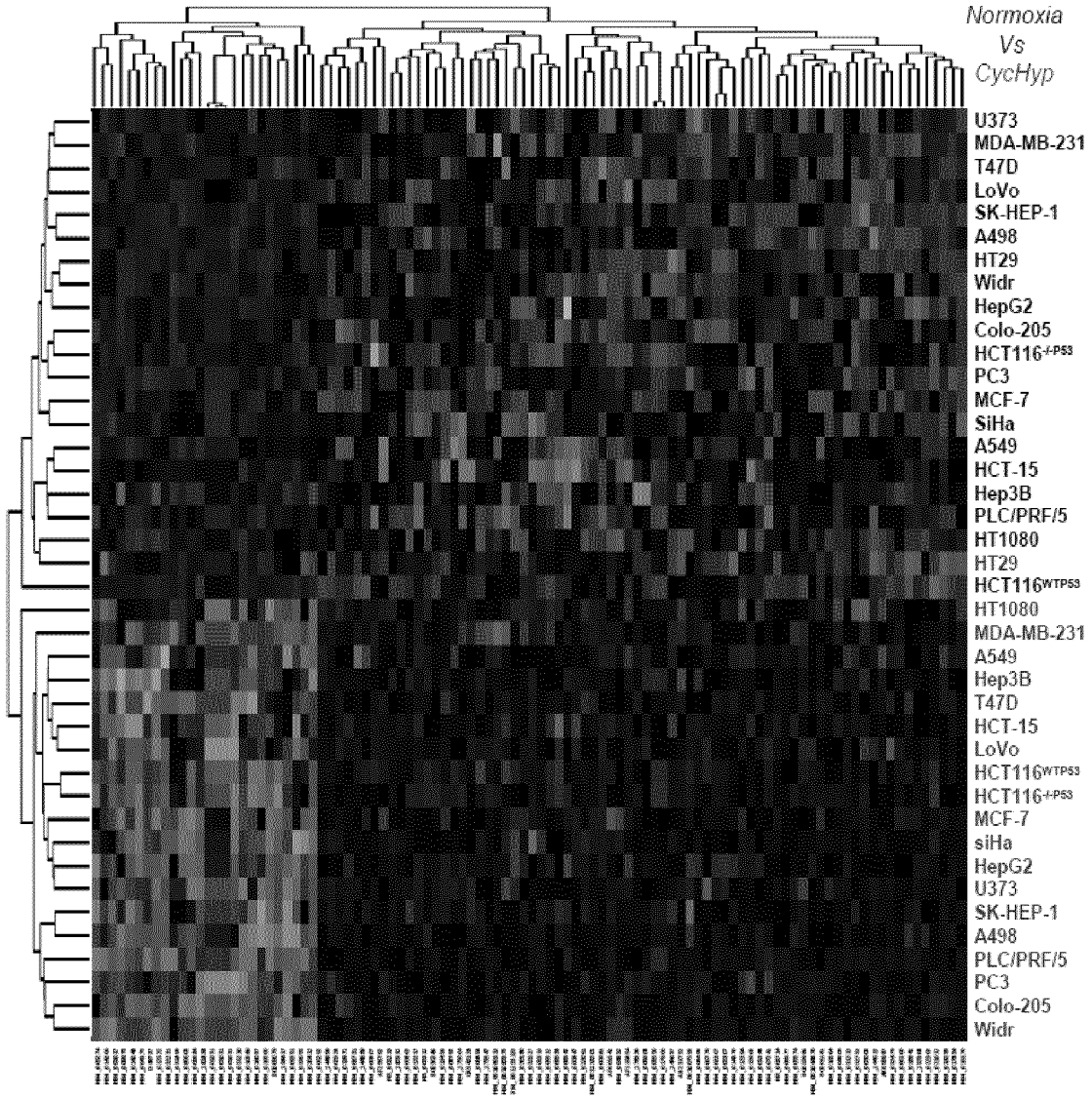
Normoxia
Vs
CycHyp
U373
MDA-MB-231
T47D
LoVo
SK-HEP-1
A498
HT29
Widr
HepG2
Colo-205
HCT116-/-P53
PC3
MCF-7
SiHa
A549
HCT-15
Hep3B
PLC/PRF/5
HT1080
HT29
HCT116WTP53
HT1080
MDA-MB-231
A549
Hep3B
T47D
HCT-15
LoVo
HCT116WTP53
HCT116-/-P53
MCF-7
siHa
HepG2
U373
SK-HEP-1
A498
PLC/PRF/5
PC3
Colo-205
Widr

FIG. 1

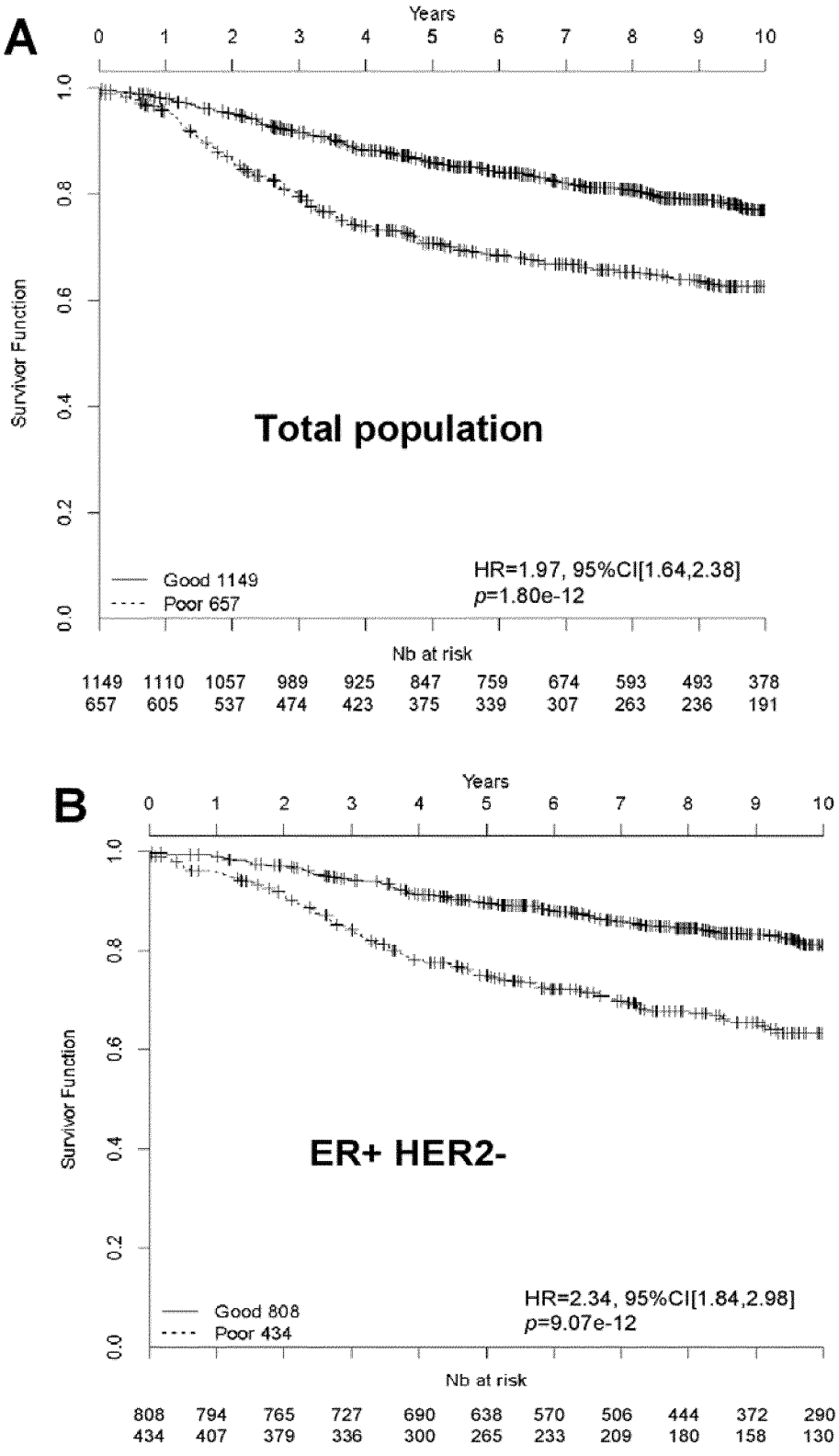
A
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0.0 0.2 0.4 0.6 0.8 1.0
Total population
Good 1149
Poor 657
HR=1.97, 95%CI[1.64,2.38]
p=1.80e-12
Nb at risk
1149 1110 1057 989 925 847 759 674 593 493 378
657 605 537 474 423 375 339 307 263 236 191
B
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0.0 0.2 0.4 0.6 0.8 1.0
ER+ HER2-
Good 808
Poor 434
HR=2.34, 95%CI[1.84,2.98]
p=9.07e-12
Nb at risk
808 794 765 727 690 638 570 506 444 372 290
434 407 379 336 300 265 233 209 180 158 130

FIG. 2A-B

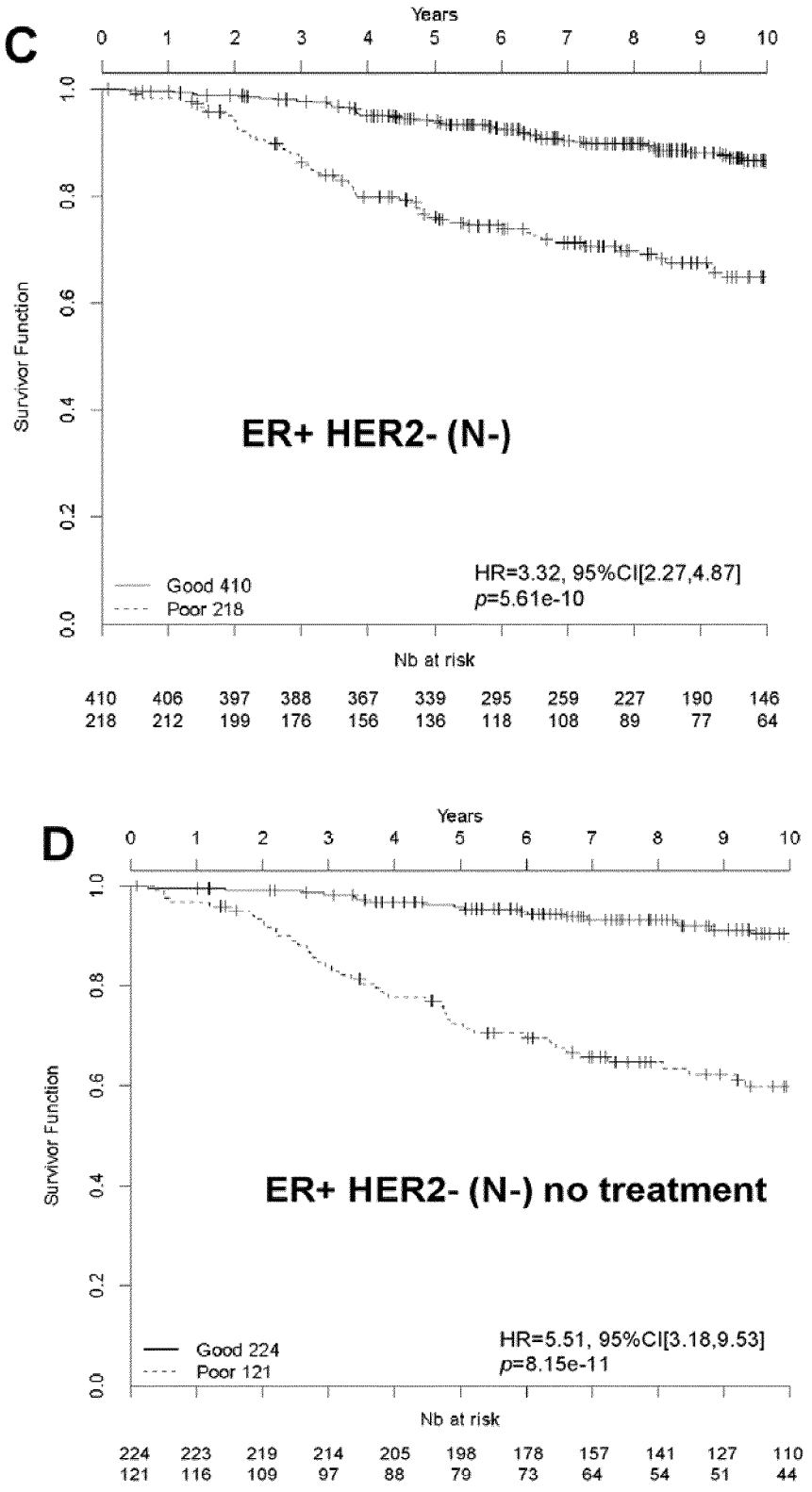
C
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0.0 0.2 0.4 0.6 0.8 1.0
ER+ HER2- (N-)
Good 410
Poor 218
HR=3.32, 95%CI[2.27,4.87]
p=5.61e-10
Nb at risk
410 406 397 388 367 339 295 259 227 190 146
218 212 199 176 156 136 118 108 89 77 64
D
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0.0 0.2 0.4 0.6 0.8 1.0
ER+ HER2- (N-) no treatment
Good 224
Poor 121
HR=5.51, 95%CI[3.18,9.53]
p=8.15e-11
Nb at risk
224 223 219 214 205 198 178 157 141 127 110
121 116 109 97 88 79 73 64 54 51 44

FIG. 2C-D

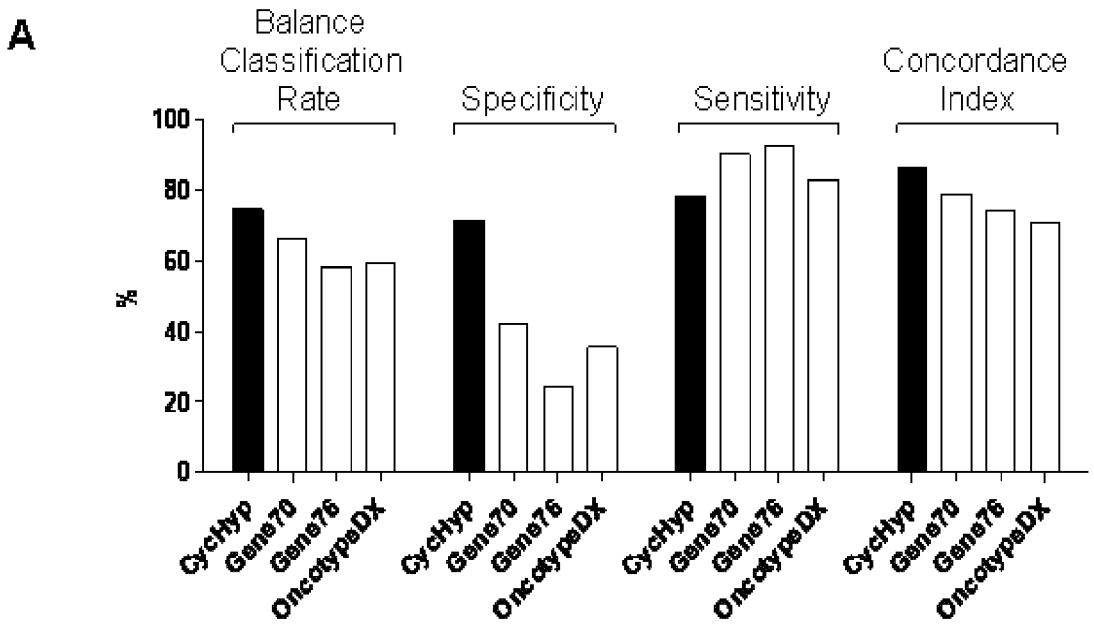
A
Balance Classification Rate
Specificity
Sensitivity
Concordance Index
100
80
60
40
20
0
%
CycHyp
Gene70
Gene76
OncotypeDX

FIG. 3A

B

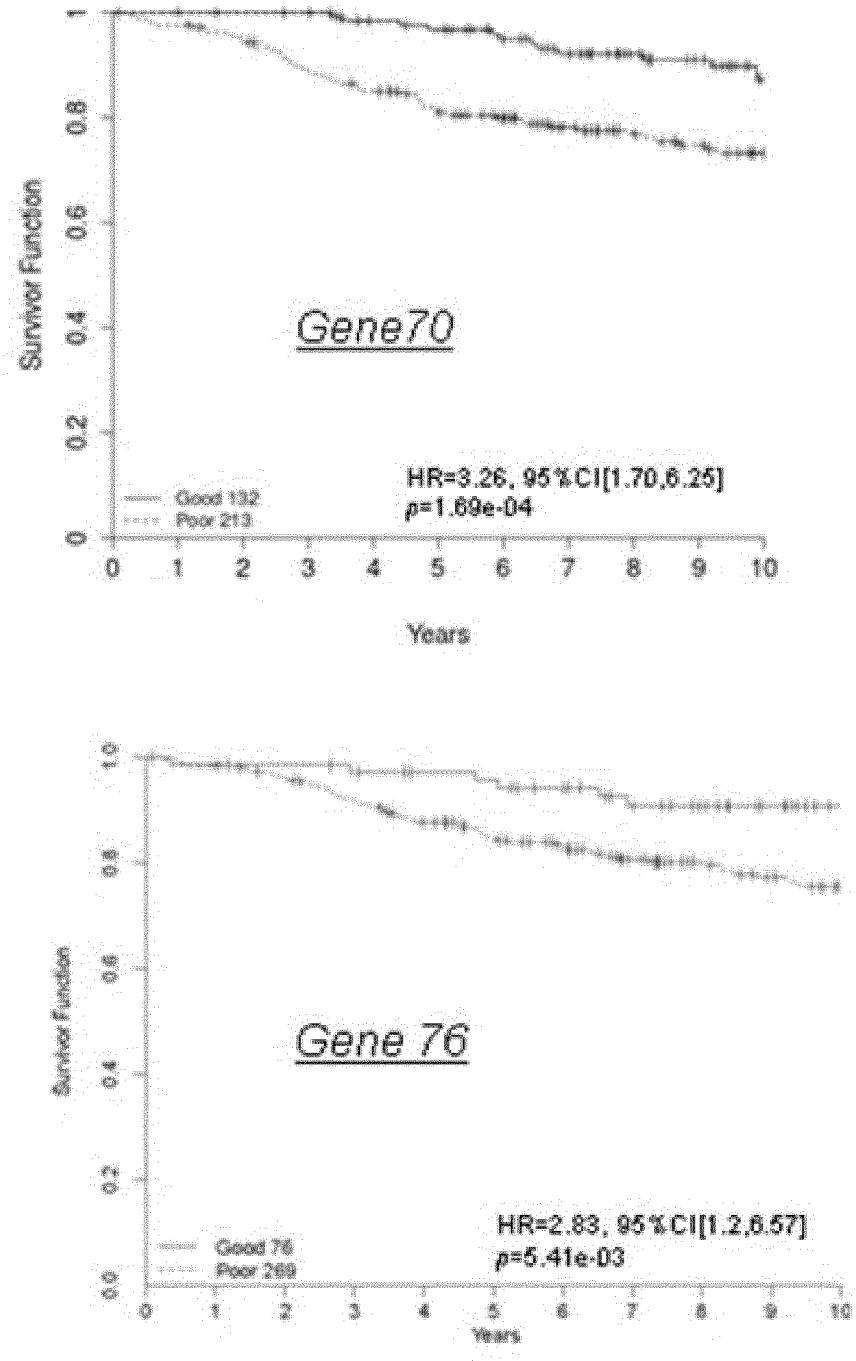
Survivor Function
0
0.2
0.4
0.6
0.8
1
Gene70
Good 132
Poor 213
HR=3.26, 95%CI[1.70,6.25]
p=1.69e-04
0
1
2
3
4
5
6
7
8
9
10
Years
Survivor Function
0.0
0.2
0.4
0.6
0.8
1.0
Gene 76
Good 76
Poor 269
HR=2.83, 95%CI[1.2,6.57]
p=5.41e-03
0
1
2
3
4
5
6
7
8
9
10
Years

FIG. 3B

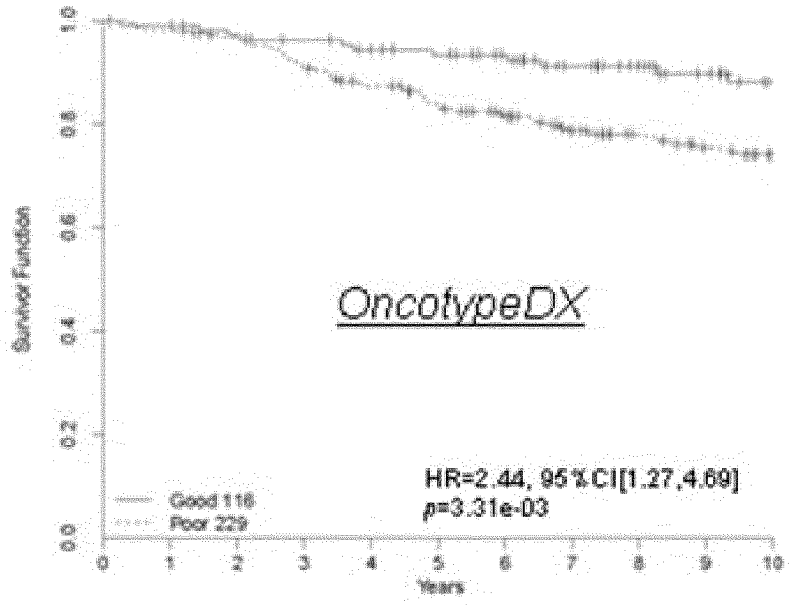
Survivor Function
0.0
0.2
0.4
0.6
0.8
1.0
OncotypeDX
HR=2.44, 95%CI[1.27,4.69]
p=3.31e-03
Good 116
Poor 229
0
1
2
3
4
5
6
7
8
9
10
Years

FIG. 3B (suite)

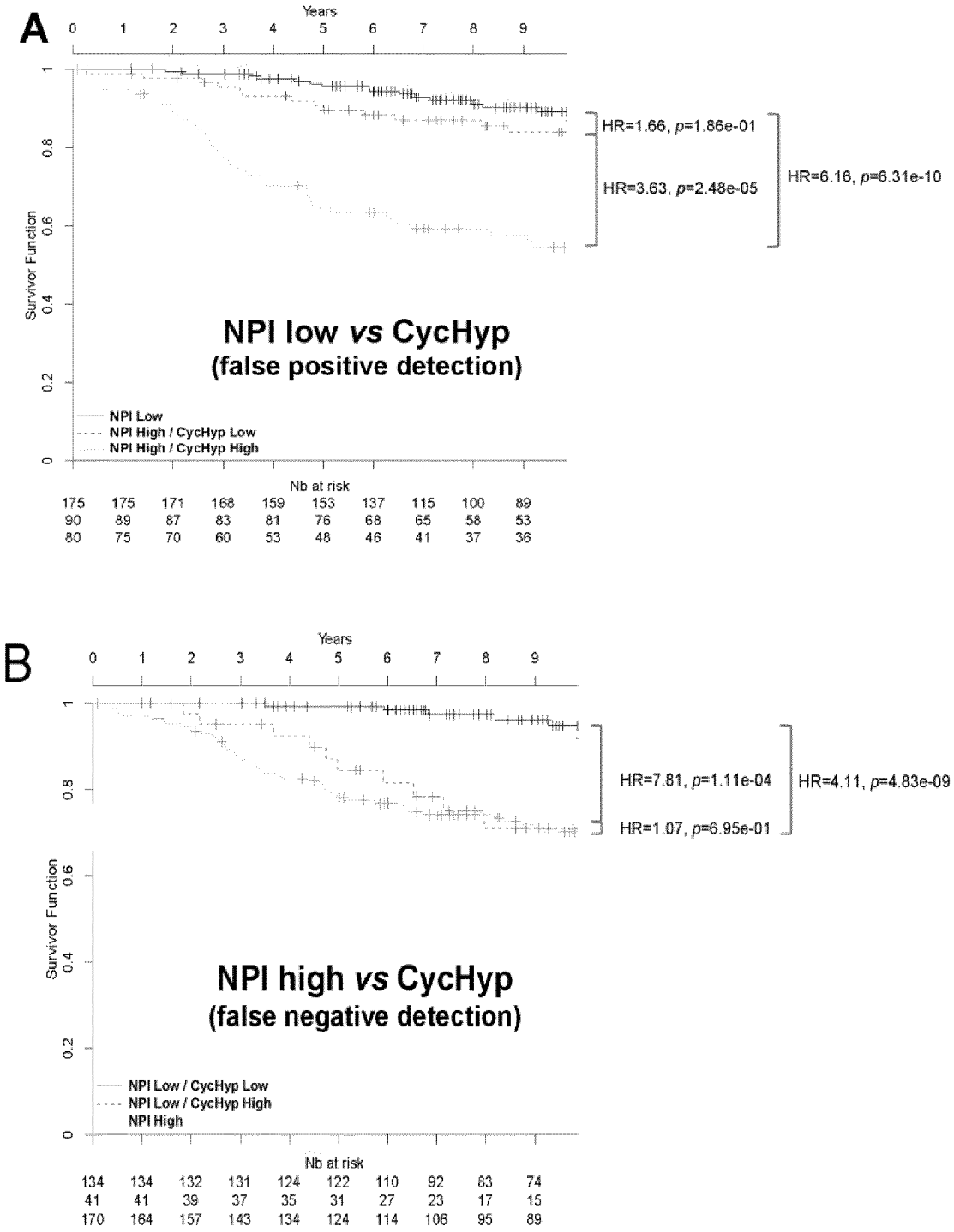
A
Years
0 1 2 3 4 5 6 7 8 9
Survivor Function
0 0.2 0.4 0.6 0.8 1
HR=1.66, p=1.86e-01
HR=3.63, p=2.48e-05
HR=6.16, p=6.31e-10
NPI low vs CycHyp
(false positive detection)
NPI Low
NPI High / CycHyp Low
NPI High / CycHyp High
Nb at risk
175 175 171 168 159 153 137 115 100 89
90 89 87 83 81 76 68 65 58 53
80 75 70 60 53 48 46 41 37 36
B
Years
0 1 2 3 4 5 6 7 8 9
Survivor Function
0 0.2 0.4 0.6 0.8 1
HR=7.81, p=1.11e-04
HR=1.07, p=6.95e-01
HR=4.11, p=4.83e-09
NPI high vs CycHyp
(false negative detection)
NPI Low / CycHyp Low
NPI Low / CycHyp High
NPI High
Nb at risk
134 134 132 131 124 122 110 92 83 74
41 41 39 37 35 31 27 23 17 15
170 164 157 143 134 124 114 106 95 89

FIG. 4

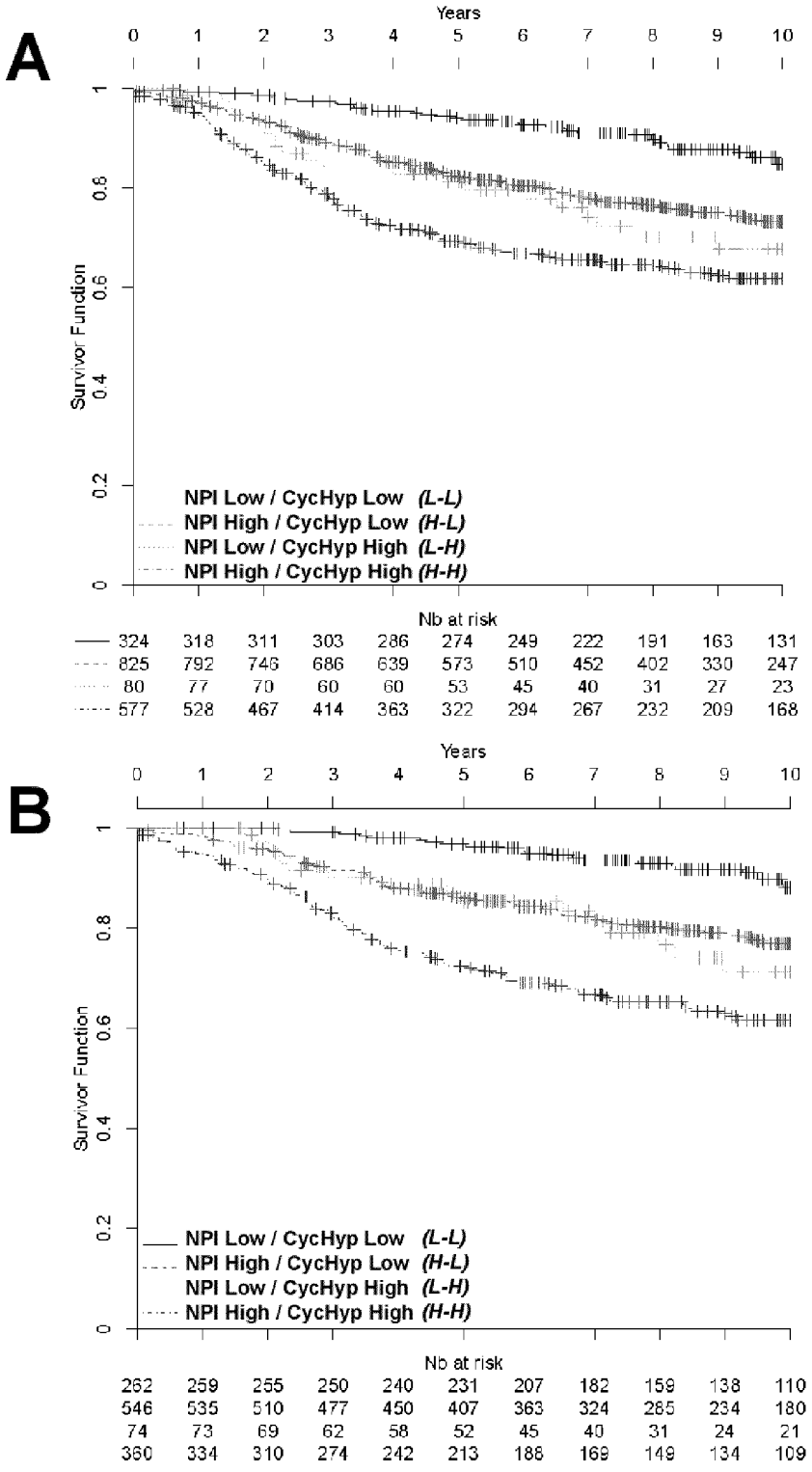
A
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0 0.2 0.4 0.6 0.8 1
NPI Low / CycHyp Low (L-L)
NPI High / CycHyp Low (H-L)
NPI Low / CycHyp High (L-H)
NPI High / CycHyp High (H-H)
Nb at risk
324 318 311 303 286 274 249 222 191 163 131
825 792 746 686 639 573 510 452 402 330 247
80 77 70 60 60 53 45 40 31 27 23
577 528 467 414 363 322 294 267 232 209 168
B
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0 0.2 0.4 0.6 0.8 1
NPI Low / CycHyp Low (L-L)
NPI High / CycHyp Low (H-L)
NPI Low / CycHyp High (L-H)
NPI High / CycHyp High (H-H)
Nb at risk
262 259 255 250 240 231 207 182 159 138 110
546 535 510 477 450 407 363 324 285 234 180
74 73 69 62 58 52 45 40 31 24 21
360 334 310 274 242 213 188 169 149 134 109

FIG. 5A-B

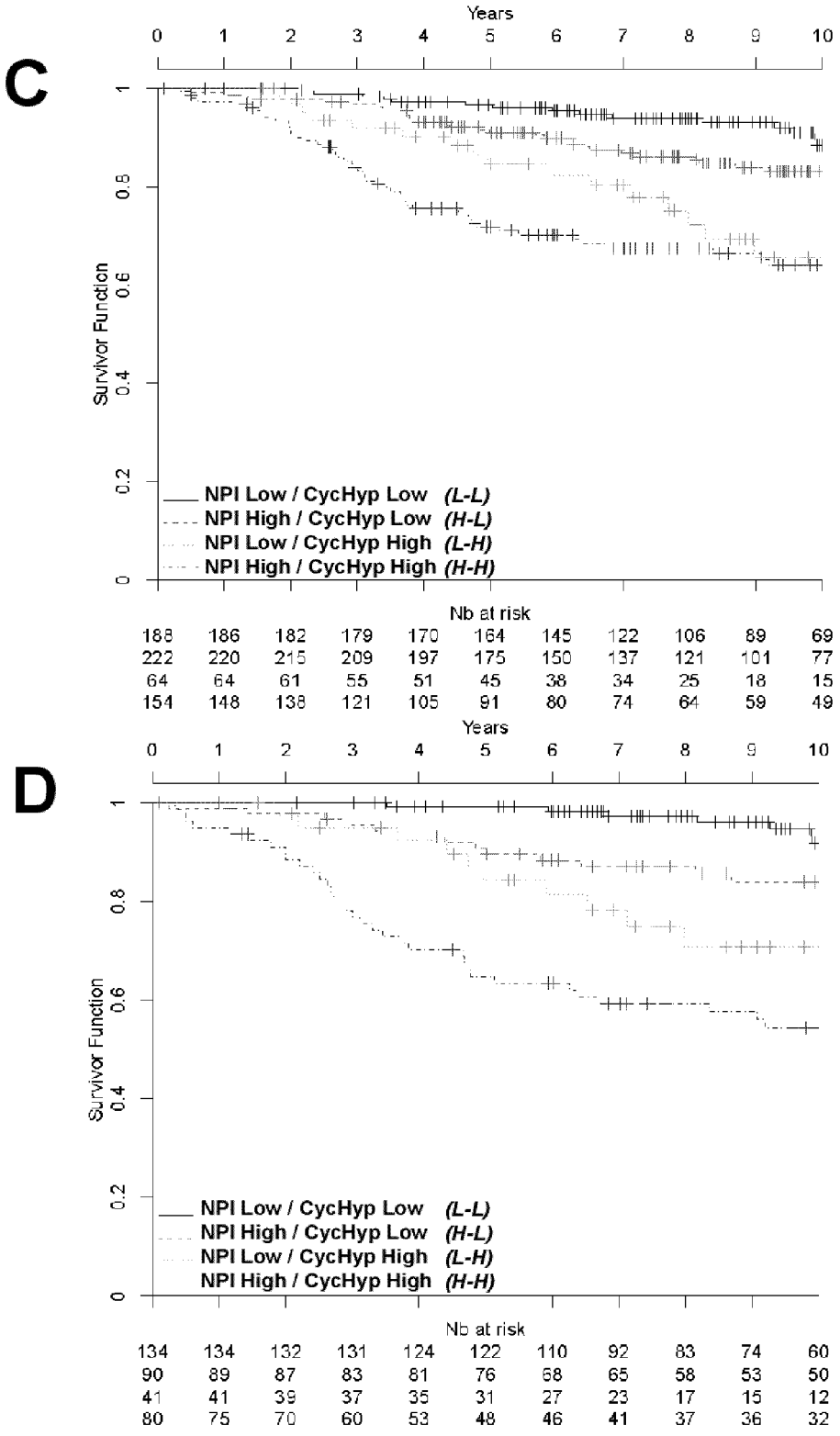
C
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0 0.2 0.4 0.6 0.8 1
NPI Low / CycHyp Low (L-L)
NPI High / CycHyp Low (H-L)
NPI Low / CycHyp High (L-H)
NPI High / CycHyp High (H-H)
Nb at risk
188 186 182 179 170 164 145 122 106 89 69
222 220 215 209 197 175 150 137 121 101 77
64 64 61 55 51 45 38 34 25 18 15
154 148 138 121 105 91 80 74 64 59 49
D
Years
0 1 2 3 4 5 6 7 8 9 10
Survivor Function
0 0.2 0.4 0.6 0.8 1
NPI Low / CycHyp Low (L-L)
NPI High / CycHyp Low (H-L)
NPI Low / CycHyp High (L-H)
NPI High / CycHyp High (H-H)
Nb at risk
134 134 132 131 124 122 110 92 83 74 60
90 89 87 83 81 76 68 65 58 53 50
41 41 39 37 35 31 27 23 17 15 12
80 75 70 60 53 48 46 41 37 36 32

FIG. 5C-D

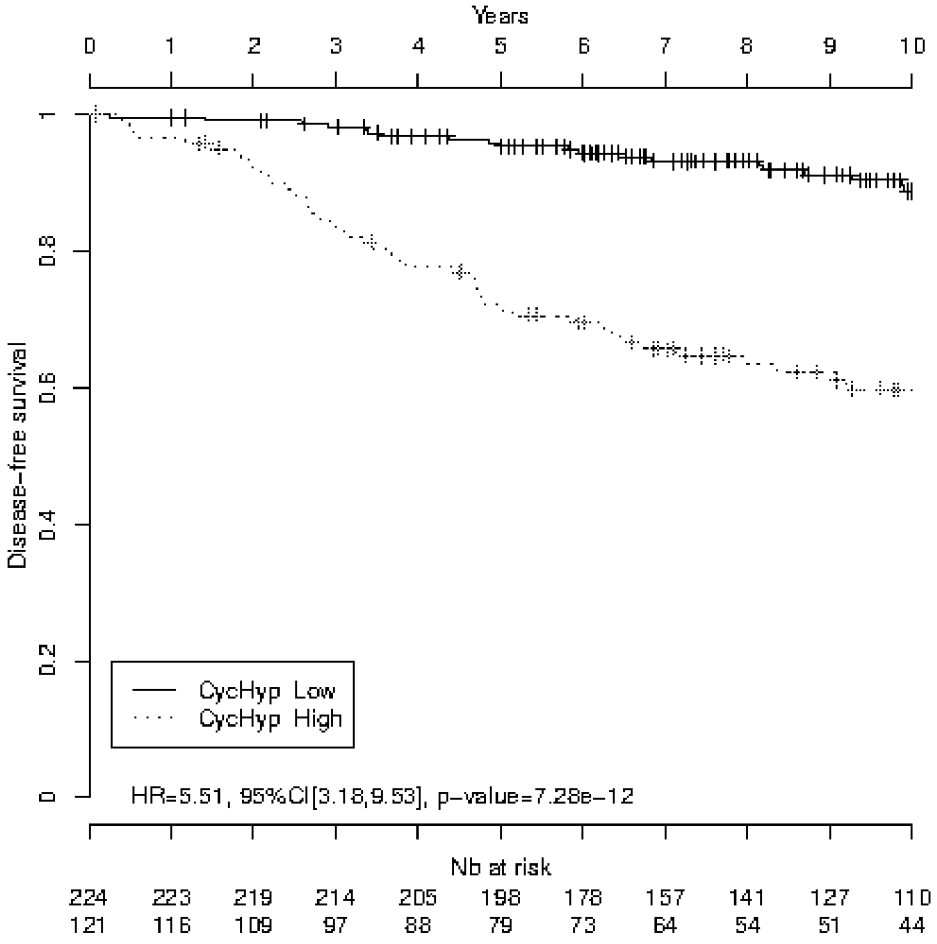
Years
0 1 2 3 4 5 6 7 8 9 10
Disease-free survival
0 0.2 0.4 0.6 0.8 1
CycHyp Low
CycHyp High
HR=5.51, 95%CI[3.18,9.53], p-value=7.28e-12
Nb at risk
224 223 219 214 205 198 178 157 141 127 110
121 116 109 97 88 79 73 64 54 51 44

FIG. 6

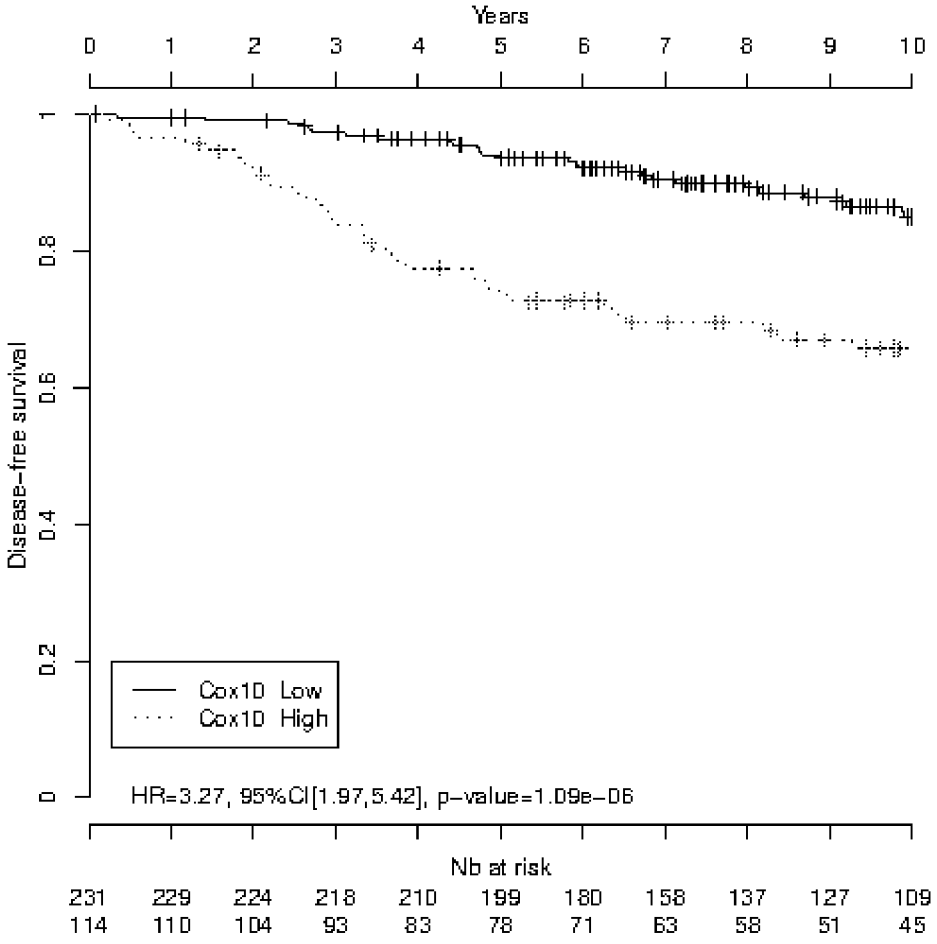
Years
0
1
2
3
4
5
6
7
8
9
10
Disease−free survival
0
0.2
0.4
0.6
0.8
1
Cox1D Low
Cox1D High
HR=3.27, 95%CI[1.97,5.42], p−value=1.09e−06
Nb at risk
231 229 224 218 210 199 180 158 137 127 109
114 110 104 93 83 78 71 63 58 51 45

FIG. 7

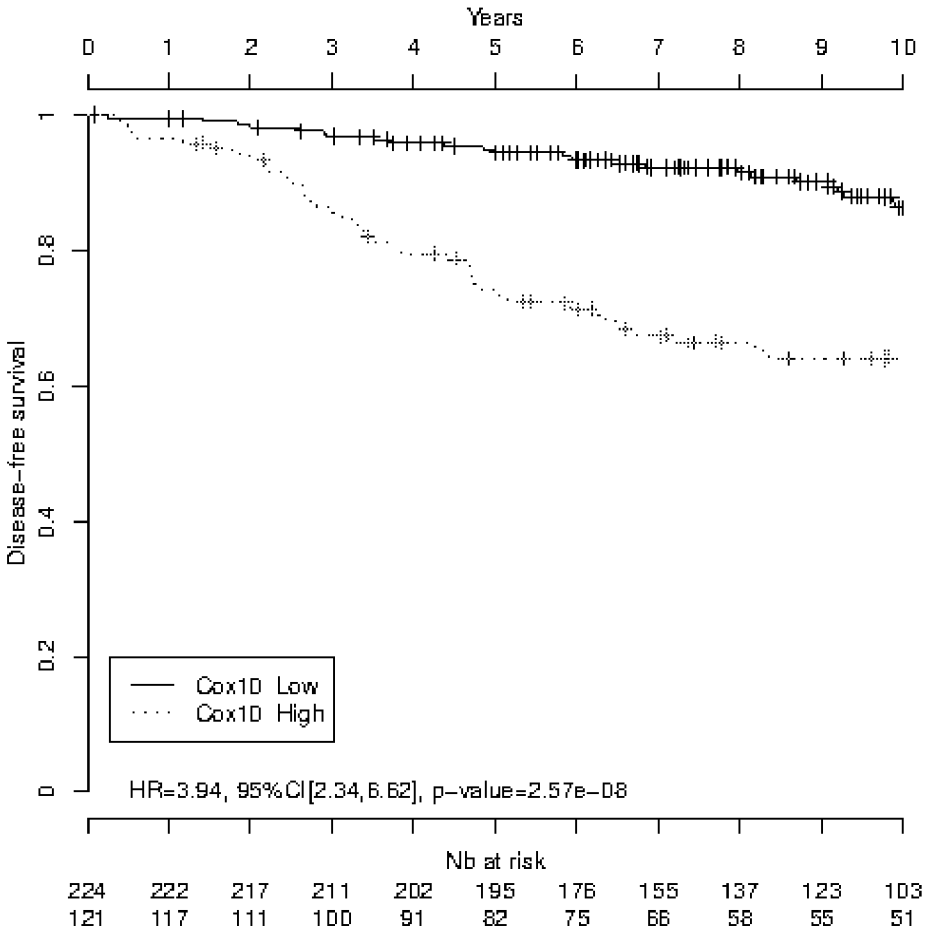
Years
0 1 2 3 4 5 6 7 8 9 10
Disease−free survival
0 0.2 0.4 0.6 0.8 1
Cox10 Low
Cox10 High
HR=3.94, 95%CI[2.34,6.62], p−value=2.57e−08
Nb at risk
224 222 217 211 202 195 176 155 137 123 103
121 117 111 100 91 82 75 66 58 55 51

FIG. 8

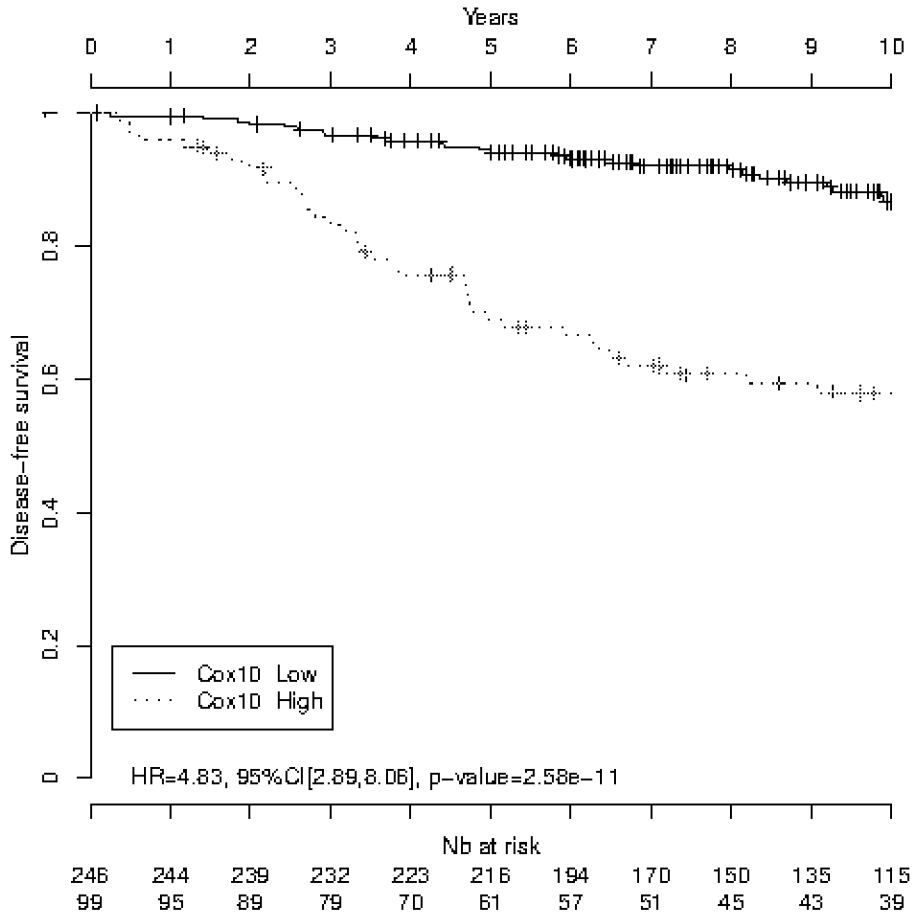
Years
0 1 2 3 4 5 6 7 8 9 10
Disease−free survival
0 0.2 0.4 0.6 0.8 1
Cox10 Low
Cox10 High
HR=4.83, 95%CI[2.89,8.06], p−value=2.58e−11
Nb at risk
246 244 239 232 223 216 194 170 150 135 115
99 95 89 79 70 61 57 51 45 43 39

FIG. 9

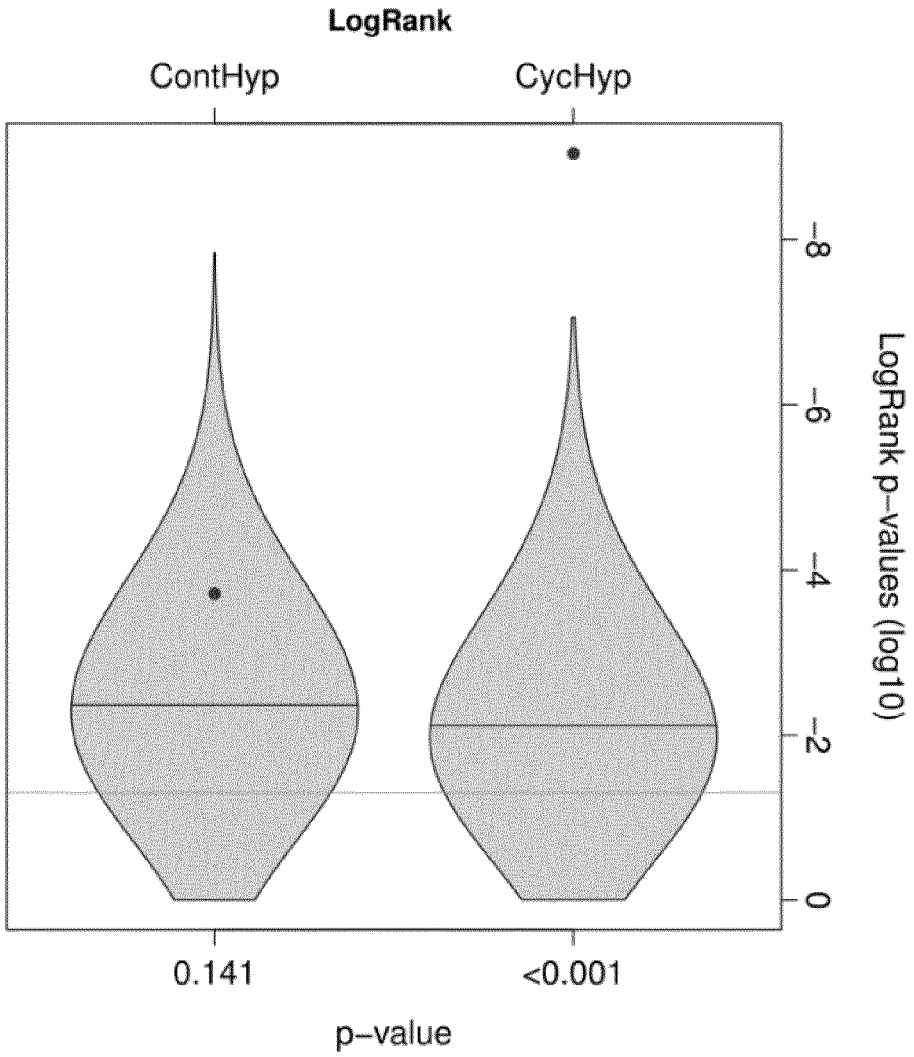
LogRank
ContHyp
CycHyp
0.141
<0.001
p−value
LogRank p−values (log10)
0
−2
−4
−6
−8

FIG. 10

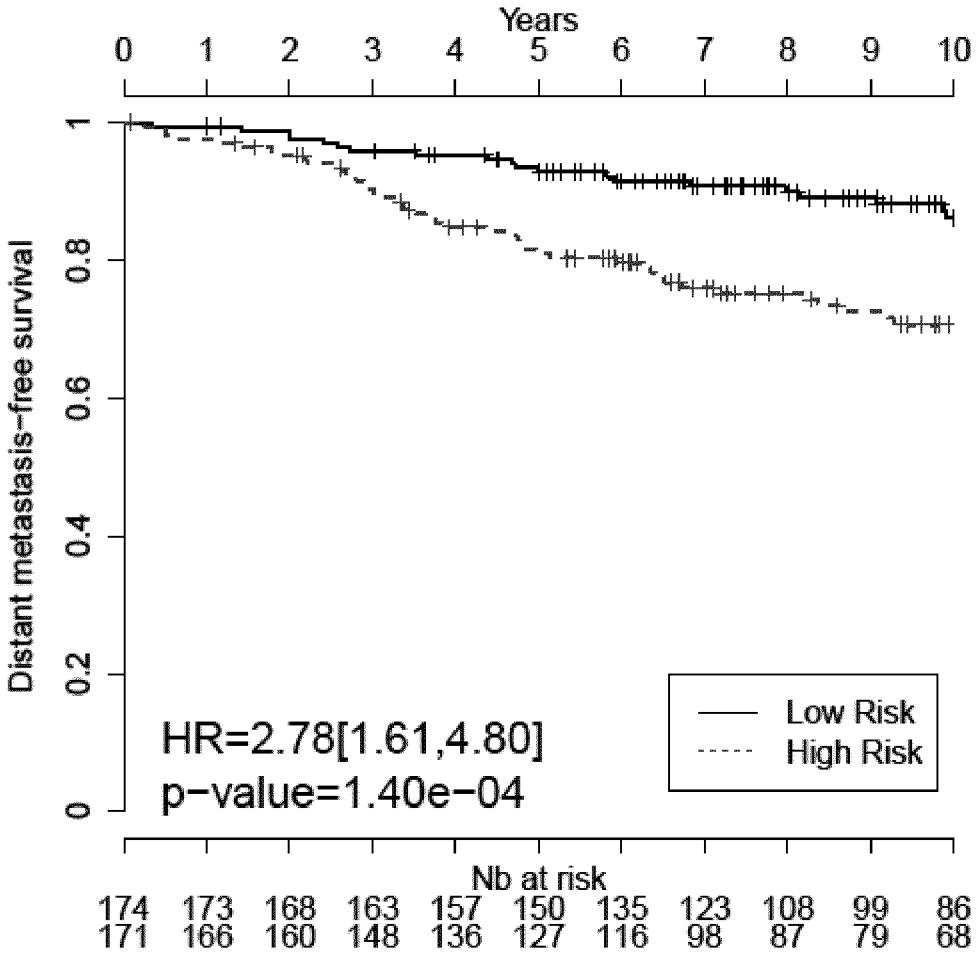
Years
0 1 2 3 4 5 6 7 8 9 10
Distant metastasis−free survival
0 0.2 0.4 0.6 0.8 1
HR=2.78[1.61,4.80]
p−value=1.40e−04
Low Risk
High Risk
Nb at risk
174 173 168 163 157 150 135 123 108 99 86
171 166 160 148 136 127 116 98 87 79 68

FIG. 11

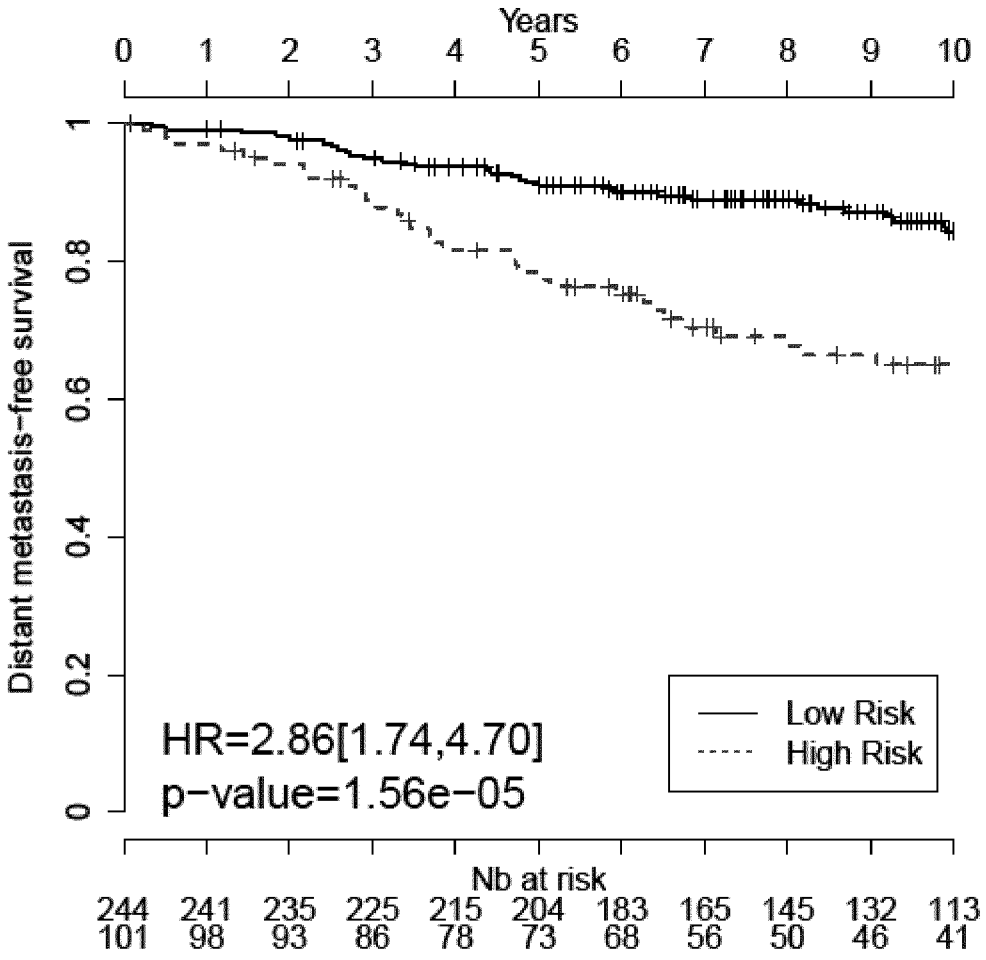
Years
0 1 2 3 4 5 6 7 8 9 10
Distant metastasis−free survival
0 0.2 0.4 0.6 0.8 1
HR=2.86[1.74,4.70]
p−value=1.56e−05
Low Risk
High Risk
Nb at risk
244 241 235 225 215 204 183 165 145 132 113
101 98 93 86 78 73 68 56 50 46 41

FIG. 12

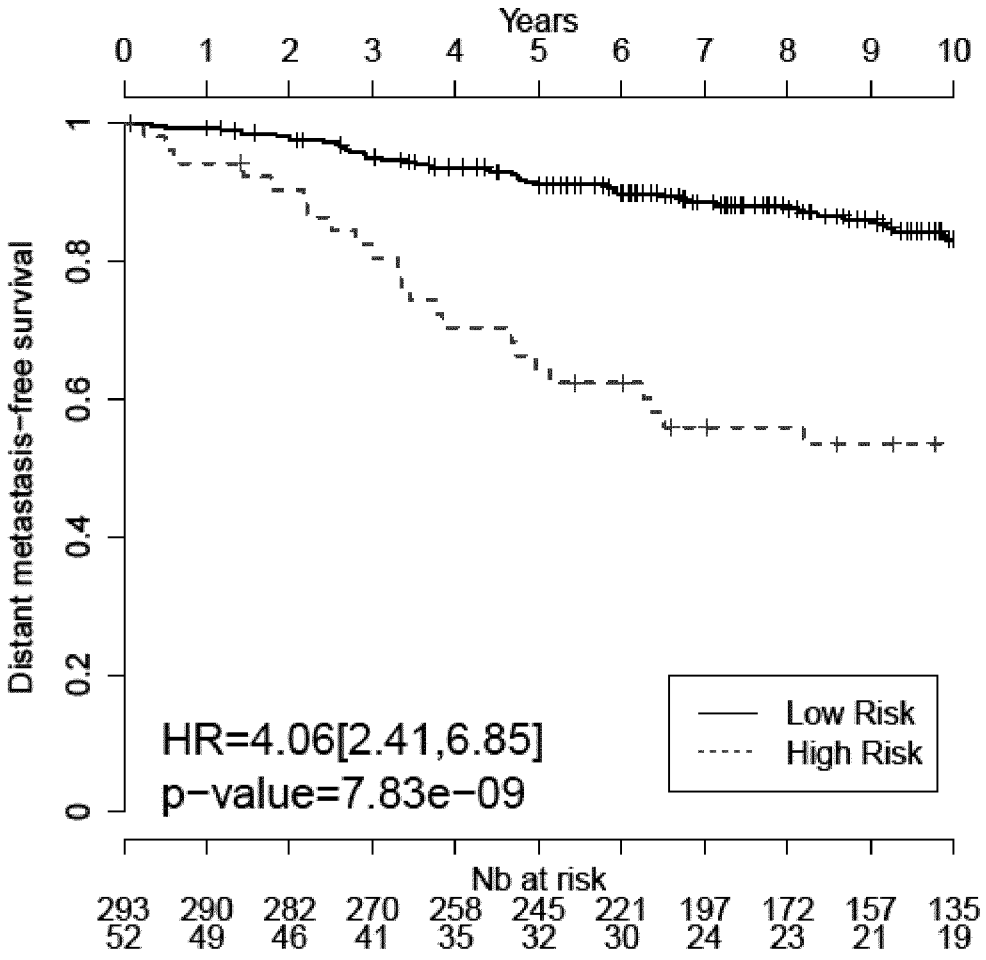
Years
0 1 2 3 4 5 6 7 8 9 10
Distant metastasis−free survival
0 0.2 0.4 0.6 0.8 1
HR=4.06[2.41,6.85]
p−value=7.83e−09
Low Risk
High Risk
Nb at risk
293 290 282 270 258 245 221 197 172 157 135
52 49 46 41 35 32 30 24 23 21 19

FIG. 13

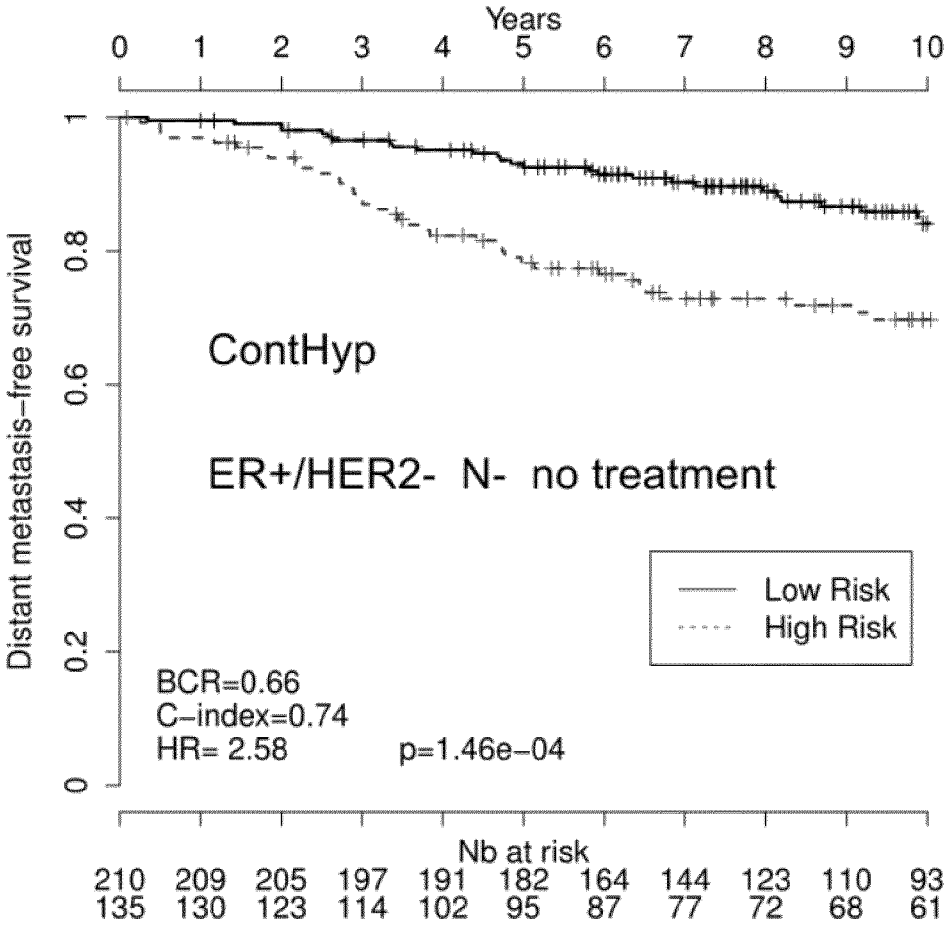
Years
0 1 2 3 4 5 6 7 8 9 10
Distant metastasis−free survival
0 0.2 0.4 0.6 0.8 1
ContHyp
ER+/HER2- N- no treatment
Low Risk
High Risk
BCR=0.66
C−index=0.74
HR= 2.58
p=1.46e−04
Nb at risk
210 209 205 197 191 182 164 144 123 110 93
135 130 123 114 102 95 87 77 72 68 61

FIG. 14

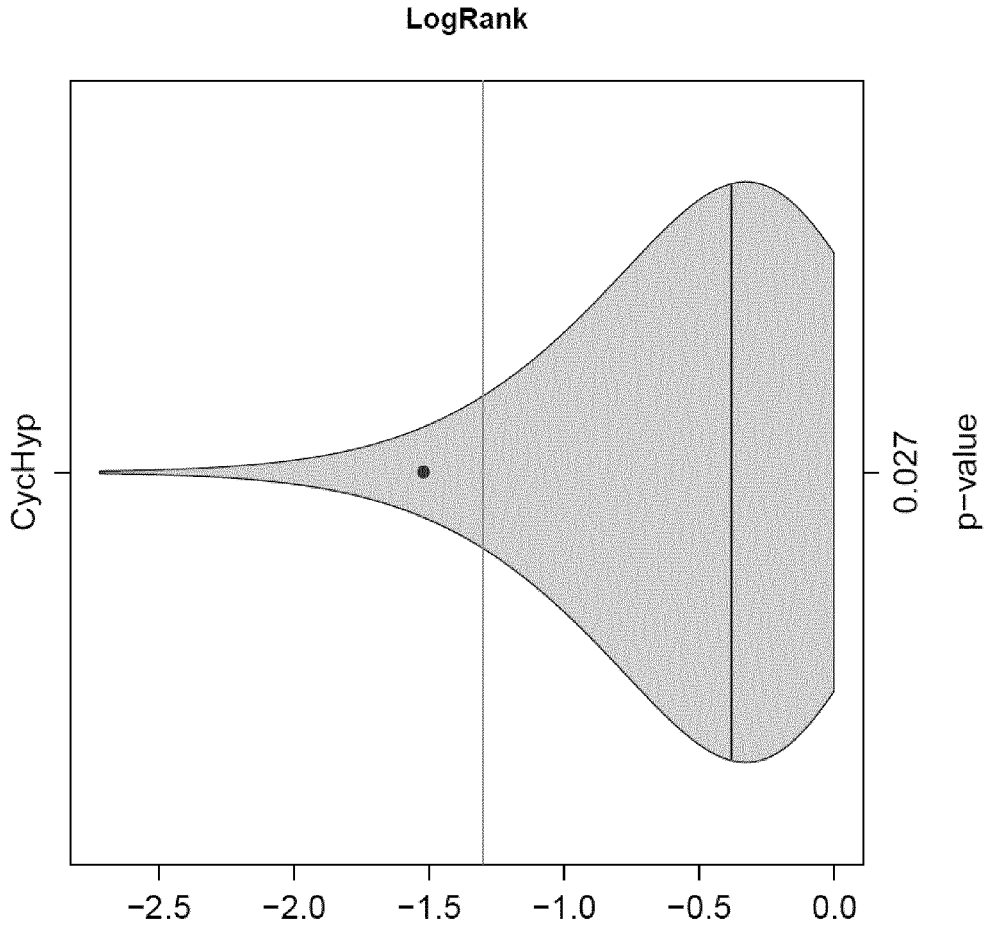

FIG. 15

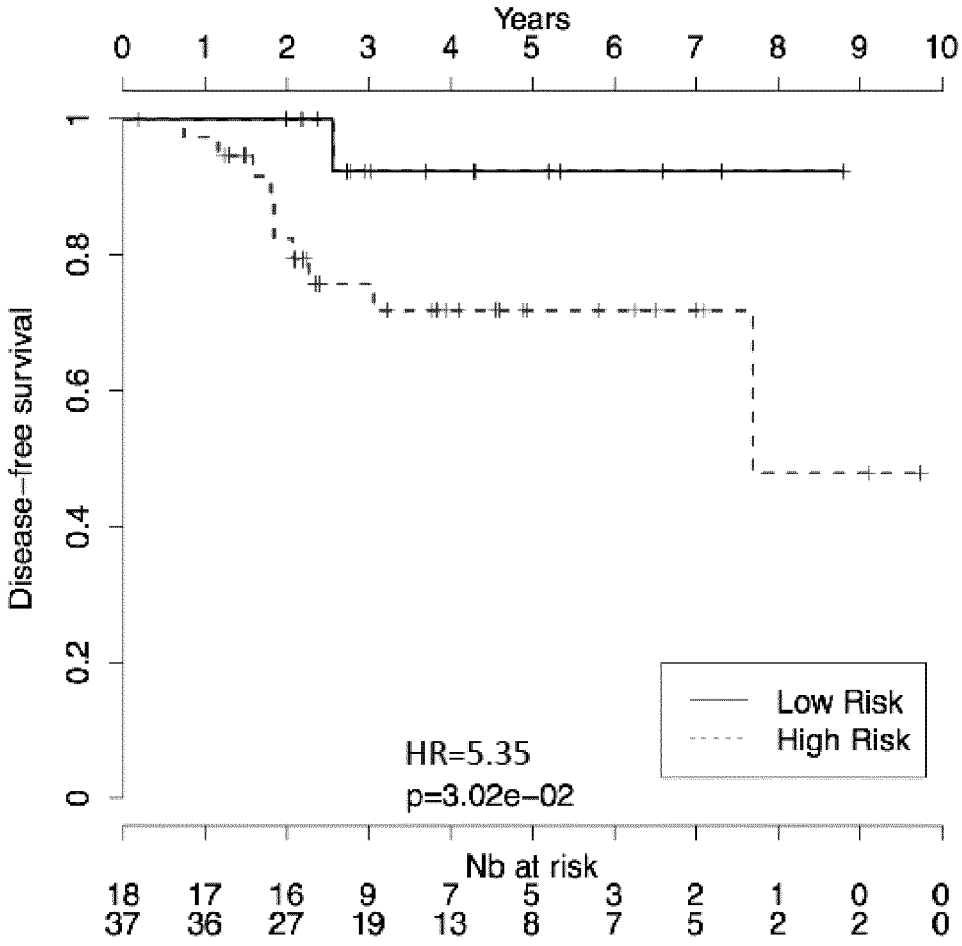
Years
0 1 2 3 4 5 6 7 8 9 10
Disease−free survival
0 0.2 0.4 0.6 0.8 1
Low Risk
High Risk
HR=5.35
p=3.02e−02
Nb at risk
18 17 16 9 7 5 3 2 1 0 0
37 36 27 19 13 8 7 5 2 2 0

FIG. 16

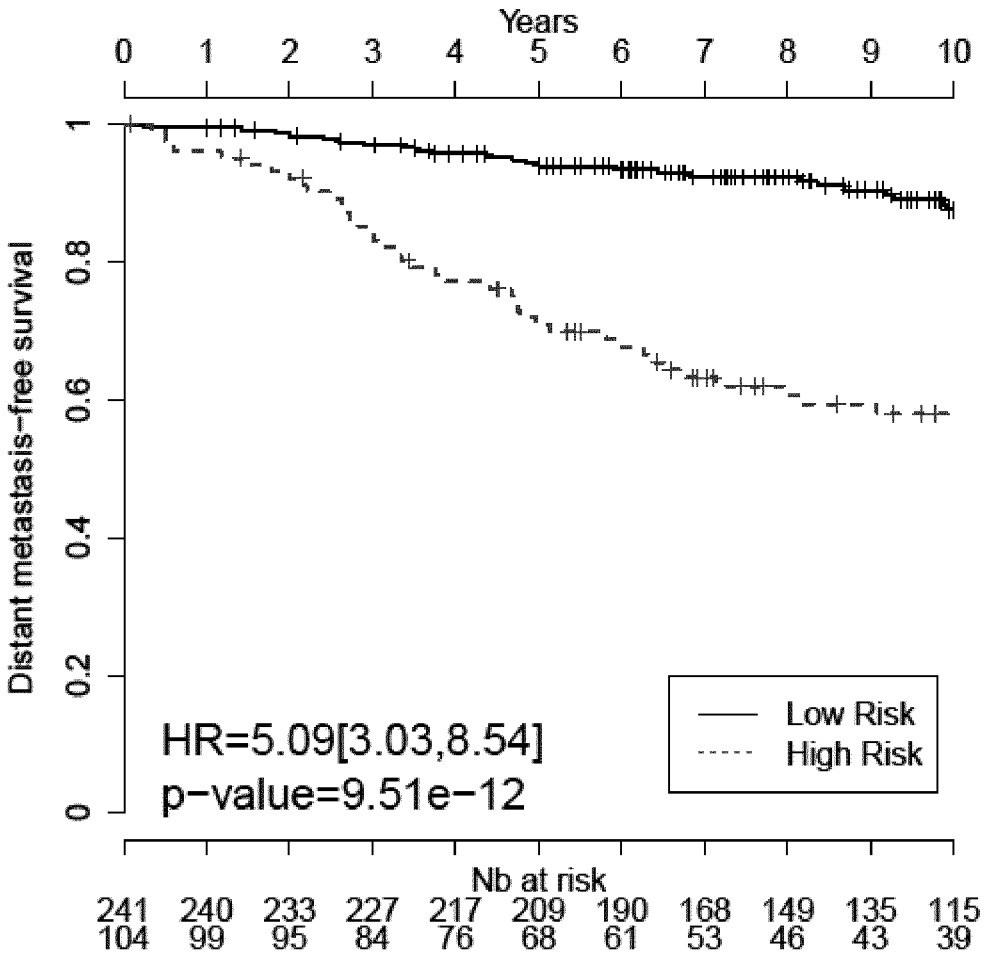
Years
0 1 2 3 4 5 6 7 8 9 10
Distant metastasis−free survival
0 0.2 0.4 0.6 0.8 1
HR=5.09[3.03,8.54]
p−value=9.51e−12
Low Risk
High Risk
Nb at risk
241 240 233 227 217 209 190 168 149 135 115
104 99 95 84 76 68 61 53 46 43 39

FIG. 17

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/066643

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, Sequence Search , EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/076895 A1 (CANCER REC TECH LTD [GB] ; WEST CATHARINE [GB] ; MILLER CRISPIN [GB] ; HA) 30 June 2011 (2011-06-30) claims 13, 18-29	1-10, 12-18
X	WO 2008/137089 A2 (SIEMENS MEDICAL SOLUTIONS [US] ; SEIGNEURIC RENAUD G [NL] ; STARMANS MAU) 13 November 2008 (2008-11-13) claims 1, 7, 12; example 1	1-10, 12-18

-/- .

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2014	29/10/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Santagati , Fabio

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"A GeneChip Gene 1.0 ST Array System A simple and affordable solution for advanced gene-level expression profiling" , , 1 January 2007 (2007-01-01) , XP055091929 , Retrieved from the Internet: URL: http://media.affymetrix.com/support/technical/datasheets/gene_1_0_st_datasheet.pdf [retrieved on 2013-12-05] the whole document	15, 16, 18
A	WO 2011/120984 A1 (SIVIDON DIAGNOSTICS GMBH [DE] ; DARTMANN MAREIKE [DE] ; FEDERINKE SABIN) 6 October 2011 (2011-10-06) claim 1	1-14
A	STUART C WINTER ET AL: "Relation of a hypoxia metagene derived from head and neck cancer to prognosis of multiple cancers" , CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 67, no. 7, 1 April 2007 (2007-04-01) , pages 3441-3449 , XP002628709 , ISSN: 0008-5472 , DOI: 10.1158/0008-5472.CAN-06-3322 the whole document	1-14
A	CHI JEN-TSAN ET AL: "Gene expression programs in response to hypoxia: Cell type specificity and prognostic significance in human cancers" , PLOS MEDICINE, PUBLIC LIBRARY OF SCIENCE, US, vol. 3, no. 3, 1 March 2006 (2006-03-01) , pages 395-409 , XP002503394, ISSN: 1549-1676, DOI: 10.1371/JOURNAL.PMED.0030047 the whole document	1-14
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	F M BUFFA ET AL: "Large meta-analysis of multiple cancers reveals a common, compact and highly prognostic hypoxia metagene", BRITISH JOURNAL OF CANCER, vol. 102, no. 2, 19 January 2010 (2010-01-19), pages 428-435, XP055091619, ISSN: 0007-0920, DOI: 10.1038/sj.bjc.6605450 the whole document ----	1-14

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Information on patent family members

International application No
PCT/EP2014/066643

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		CN 102971435 A	13-03-2013
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		US 2013065786 A1	14-03-2013
		WO 2011120984 A1	06-10-2011