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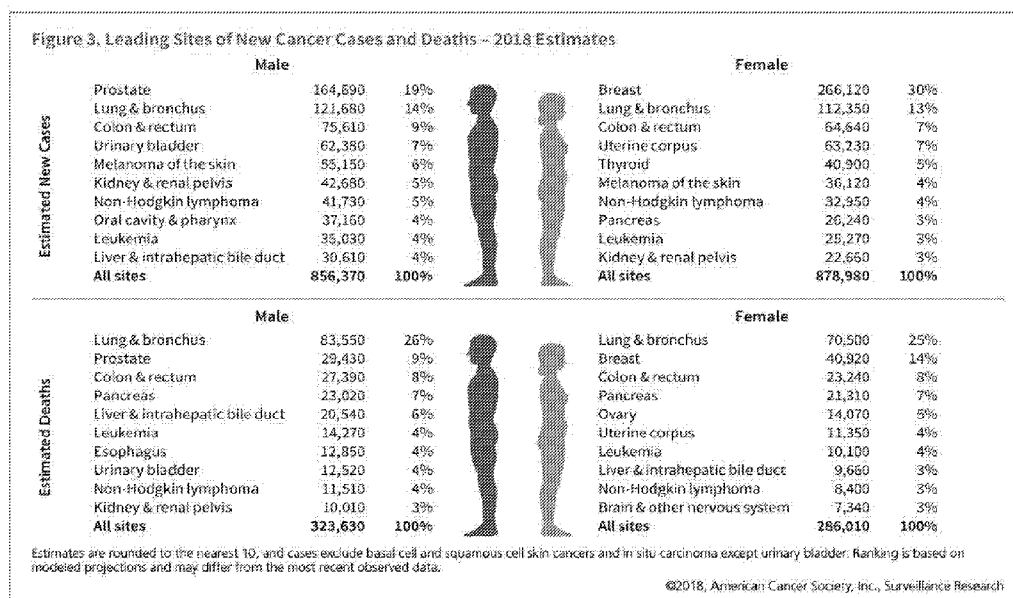
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(54) Title: METHODS FOR TARGETED TREATMENT AND PREDICTION OF PATIENT SURVIVAL IN CANCER

FIGURE 1



(57) Abstract: Provided herein are methods of assessing, detecting, monitoring the presence, or monitoring progression of cancer in a subject, or assessing or predicting prognosis or survival of a subject having cancer. Also provided are methods of treating cancer based on an increase in the expression of one or more top master regulators of a cancer.

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METHODS FOR TARGETED TREATMENT AND PREDICTION OF PATIENT SURVIVAL IN CANCER

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0001] This invention was made with government support under K08 CA160824 awarded by NIH/NCI. The government has certain rights in the invention.

BACKGROUND

[0002] In 2018, the American Cancer Society estimated that there were 856,370 new cases of cancer in men and 878,980 new cases of cancer in women. Additionally, there were an estimated 323,630 cancer deaths in men and 286,010 cancer deaths in women. The leading sites of new cancer in men were prostate (19%), lung and bronchus (14%), and colon and rectum (9%). The leading sites of new cancer in women were breast (30%), lung and bronchus (13%), and colon and rectum (7%).

[0003] There remains a need to understand and treat cancer and to identify new targets for cancer therapeutics.

SUMMARY

[0004] Provided are methods of assessing, detecting, monitoring the presence, or monitoring progression of cancer in a subject, or assessing or predicting prognosis or survival of a subject having cancer. The methods comprise measuring the expression level of at least one master regulator in a sample from the subject and comparing the expression level with the expression level of a corresponding master regulator gene in a healthy reference sample. An increase in the expression level of the at least one master regulator in the subject relative to the expression level of the corresponding master regulator in a healthy reference sample indicates the possible presence of cancer in the subject, an increase or risk of increase in cancer progression in the subject, a possible increased risk of developing cancer in the subject, a poor prognosis, or reduced predicted survival time for the subject.

[0005] Described herein are methods of treating cancer based on an increase in the expression of one or more top master regulators (also termed “master of death” or “master regulator or poor prognosis”). In some embodiments, an increase in the expression level of a top master regulator is a statistically significant increase in expression. In some embodiments, an increase in the expression level of a top master regulator is an increase of at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, or at least 50%. In some embodiments, an

increase in the expression level of a top master regulator is an increase of at least 1.5×, at least 2×, at least 2.5×, at least 3×, at least 4× or at least 5×.

[0006] An increase in the expression of one or more top master regulators of a cancer in a subject is indicative of poor prognosis for the subject. The described methods can be used to diagnosis cancer in a subject. The described methods can be used diagnose poor prognosis in a subject having cancer. The described methods can be used to guide or suggest treatments or changes in treatment of cancer. The described methods can be used to diagnose or provide guidance for treatment or changes in treatment of an individual subject. The described methods can be used to diagnose or provide guidance for treatment or changes in treatment of an individual subject based on the expression profile of one or more top master regulators. In some embodiments, the subject is a human patient.

[0007] The master regulators can be grouped according to cancer type or according to certain cellular processes. In some embodiments, elevated expression of one or more of the top regulators of death associated with any of the cancers of Tables 2 and 3 is indicative of poor prognosis for the that cancer. In some embodiments, elevated expression of one or more of the top regulators of death associated with the cellular processes of as in FIG. 17 is indicative of poor prognosis. In some embodiments, an indication of poor prognosis indicates the subject having the cancer should be treated more aggressively. In some embodiments, an indication of poor prognosis indicates the subject should be treated with one or more therapeutics known to have effectiveness in treating cancers having with a similar master regulator expression profile, *i.e.*, having increase expression of one or more of the same top master regulators.

[0008] We have observed expression of the top master regulators is several different cancers is predictive of poor prognosis. Classes or types of cancer that effect similar cells or tissues or appear similar morphologically or histologically may be different with respect to gene expression. Similarly, cancers that have certain detectable genomic mutations may not express the mutant gene(s). For this reason, treatment cancer based expression of master regulators can better predict treatment effectiveness and prognosis. Further, such analyses can be performed on samples from individual subjects, allowing for improved diagnosis and treatment base on the expression of master regulators in the individual subject. The described methods also provide for correlation of treatment of the cancer with the master regulator expression profile of the cancer in the individual.

[0009] In some embodiments, the methods are used to assess whether a subject has a poor survival prognosis for cancer comprising: analyzing the expression level of at least one master regulator in a sample from the subject, wherein an increase in the expression level of the at

least one master regulator relative to the expression level of the corresponding master regulator in a healthy reference sample, is indicative that the subject has a poor survival prognosis for the cancer. In some embodiments, the master regulator is a gene as in Tables 2 and 3.

[0010] In some embodiments, one or more cancer therapies is administered to a subject identified as having a poor prognosis or reduced predicted survival time.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Having thus described the invention in general terms, reference will now be made to the accompanying drawings, which are not necessarily drawn to scale.

[0012] FIG. 1 illustrates leading sites of new cancer cases and deaths – 2018 estimates.

[0013] FIG. 2 illustrates the top master regulators of poor prognosis in lung adenocarcinoma.

[0014] FIG. 3 illustrates the top master regulators of poor prognosis in lung squamous cell carcinoma.

[0015] FIG. 4 illustrates the top master regulators of poor prognosis in breast invasive carcinoma.

[0016] FIG. 5 illustrates the top master regulators of poor prognosis in prostate adenocarcinoma.

[0017] FIG. 6 illustrates the top master regulators of poor prognosis in colon and rectum adenocarcinoma.

[0018] FIG. 7 illustrates the top master regulators of poor prognosis in pancreatic adenocarcinoma.

[0019] FIG. 8 illustrates the top master regulators of poor prognosis in liver hepatocellular carcinoma.

[0020] FIG. 9 illustrates the top master regulators of poor prognosis in acute myeloid leukemia.

[0021] FIG. 10 illustrates the top master regulators of poor prognosis in ovarian serous cystadenocarcinoma.

[0022] FIG. 11 illustrates the top master regulators of poor prognosis in glioblastoma multiforme.

[0023] FIG. 12 illustrates the top master regulator of poor prognosis for each cancer subtype.

[0024] FIG. 13A illustrates the frequency of master regulators of poor prognosis.

[0025] FIG. 13B illustrates the most frequent master regulators of poor prognosis.

- [0026] FIG. 14 illustrates 4 cancer groups by master regulators of poor prognosis.
- [0027] FIG. 15 illustrates heatmap of common master regulators of poor prognosis. nScore values of Masters of death that present in at least two cancer subtypes.
- [0028] FIG. 16 illustrates frequency of pathways of poor prognosis in different cancer subtypes.
- [0029] FIG. 17 illustrates the master regulators in selected pathways of poor prognosis.
- [0030] FIG. 18A-B illustrate the effect of knockdown of VDR expression on MYD88, CLCF1, LIF, and OSMR in GBM cell lines. The indicated GBM cells were transfected with empty vector (EV; left bar in each gene) or short hairpin VDR (shVDR; right bar for each gene). shVDR inhibits expression of VDR
- [0031] FIG. 18C illustrates the effect of knockdown of VDR expression on MYD88, CLCF1, LIF, and OSMR in a GBM cell line. The indicated GBM cells were transfected with empty vector (EV; left bar in each gene) or short hairpin VDR (shVDR; right bar for each gene). shVDR inhibits expression of VDR.
- [0032] FIG. 19A-B illustrate the effect of knockdown of VDR expression on various genes in GBM cell lines. The indicated GBM cells were transfected with empty vector (EV; left bar in each gene) or short hairpin VDR (shVDR; right bar in each gene). shVDR inhibits expression of VDR.
- [0033] FIG. 19C-D illustrate the effect of knockdown of VDR expression on various genes in GBM cell lines. The indicated GBM cells were transfected with empty vector (EV; left bar in each gene) or short hairpin VDR (shVDR; right bar in each gene). shVDR inhibits expression of VDR.
- [0034] FIG. 20 illustrates genes in the VDR network.
- [0035] FIG. 21A illustrates correlation of MYBL2 expression with survival in renal and liver cancer patients.
- [0036] FIG. 21B illustrates correlation of FOXM1 expression with survival in renal and pancreatic cancer patients.
- [0037] FIG. 21C illustrates correlation of PTTG1 expression with survival in renal and liver cancer patients.

DEFINITIONS

[0038] The terms “nucleic acid” and “polynucleotide,” used interchangeably herein, refer to polymeric forms of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, or analogs or modified versions thereof. They include single-, double-,

and multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, and polymers comprising purine bases, pyrimidine bases, or other natural, chemically modified, biochemically modified, non-natural, or derivatized nucleotide bases.

[0039] The term “in vitro” refers to artificial environments and to processes or reactions that occur within an artificial environment (e.g., a test tube).

[0040] The term “in vivo” refers to natural environments (e.g., a cell or organism or body) and to processes or reactions that occur within a natural environment.

[0041] Expression of master regulator genes in cancer drive bad cancer behavior or poor prognosis of the cancer. Poor prognosis can include, but is not limited to, poor response to typical cancer treatment, aggressive cancer growth, increased metastasis, and/or reduced survival time. Identification of poor prognosis in a subject can be used to diagnose and/or prescribe treatment. Such treatment can include, but is not limited to, master regulator-specific treatment and/or more aggressive treatment. Master regulator-specific treatment includes treatments, including adjuvants, known to be effective in treating similar cancers in other subjects expressing the same master regulator gene(s). As an example, subjects having increased expression of VDR or VDR-related genes may be given vitamin D.

[0042] A “sample” comprises any tissue or material isolated from a subject, such as a patient. The sample may contain cellular and/or non-cellular material from the subject, and may contain any biological material suitable for detecting a desired biomarker, such a DNA or RNA. The sample can be isolated from any suitable biological tissue or fluid such as, but not limited to, a tissue or blood. A sample may be treated physically, chemically, and/or mechanically to disrupt tissue or cell structure, thus releasing intracellular components into a solution which may further contain enzymes, buffers, salts, detergents and the like, which are used to prepare the sample for analysis.

[0043] The “epithelial-mesenchymal transition” (EMT) is a process by which epithelial cells lose gene expression patterns and behaviors characteristic of epithelial cells, including adhesion and apical-basal polarity, and begin to look and behave like, and express genes typical of, mesenchymal cells, gaining migratory and invasive properties. EMT has also been shown to occur in the initiation of metastasis in cancer progression.

[0044] Compositions or methods “comprising” or “including” one or more recited elements may include other elements not specifically recited. For example, a composition that “comprises” or “includes” a protein may contain the protein alone or in combination with other ingredients.

[0045] Designation of a range of values includes all integers within or defining the range, and all subranges defined by integers within the range.

[0046] Unless otherwise apparent from the context, the term “about” encompasses values within a standard margin of error of measurement (e.g., SEM) of a stated value or variations $\pm$ 0.5%, 1%, 5%, or 10% from a specified value.

[0047] The singular forms of the articles “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “an antigen” or “at least one antigen” can include a plurality of antigens, including mixtures thereof.

Statistically significant means $p \leq 0.05$.

DETAILED DESCRIPTION

[0048] Various embodiments of the inventions now will be described more fully hereinafter, in which some, but not all embodiments of the inventions are shown. Indeed, these inventions may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. The term “or” is used herein in both the alternative and conjunctive sense, unless otherwise indicated. The terms “illustrative” and “exemplary” are used to be examples with no indication of quality level.

[0049] Described are detailed reference gene networks for major types of cancers based on genome-wide expression profiles in the Cancer Genome Atlas, using the GeneRep algorithm. Reference gene networks provide a foundational framework on which to understand the mechanism of cancer development on a global scale and to identify master regulators and therapeutic development. Master regulators are genes at the top of a gene network that can alter the expression of downstream genes in a network. The described networks contain the largest number of connections with the highest statistical confidence.

[0050] Using nScore algorithms applied to survival time, we have identified master regulators of poor prognosis in a number of different cancers. Poor prognosis refers to reduced predicted survival time. These will be critical in understanding the global properties of cancer cells across multiple major cancers in humans and serve as a foundation for diagnostic and therapeutic development.

[0051] Described are methods assessing, detecting, monitoring the presence, or monitoring progression of cancer in a subject, or assessing or predicting prognosis or survival of a subject having cancer. The methods comprise

- a) obtaining or having obtained a sample from a subject

b) measuring or having measured the expression level of at least one master regulator in the sample; and

c) comparing the expression level with the expression level of a corresponding master regulator gene in a healthy reference sample;

wherein an increase in the expression level of the at least one master regulator in the subject relative to the expression level of the corresponding master regulator in the healthy reference sample indicates the possible presence of cancer in the subject, an increase or risk of increase in cancer progression in the subject, an increased risk of developing cancer in the subject, a poor prognosis, or decreased predicted survival time for the subject. The methods can be used to suggest treatments or changes in treatment of the subject.

[0052] In some embodiments, the methods are used to assess whether a subject has a decreased predicted survival time for cancer comprising: measuring the expression level of at least one master regulator in a sample from the subject, wherein an increase in the expression level of the at least one master regulator relative to the expression level of the corresponding master regulator in a healthy reference sample, is indicative that the subject has a poor survival prognosis for the cancer. In some embodiments, the master regulator is a gene as in Tables 2 and 3.

[0053] In some embodiments, measuring expression levels of one or more of the master regulators of Tables 2 and 3 can be used to monitor cancer growth in a subject.

[0054] In some embodiments, expression levels of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 master regulators in a subject sample are measured and compared with the expression level of the corresponding master regulators in a healthy reference (control) sample.

[0055] In some embodiments, master regulators are selected based on the cancer type. The top 20 master regulators for several cancer types are shown in Tables 2 and 3.

[0056] In some embodiments, master regulators are selected based of the occurrence of the master regulator in several cancer types. Master regulators that have increase expression in several cancer types may be selected from the group consisting of: MYBL2, MYBL2, PTTG1, FOXM1, E2F7, CDK1, UHRF1, TRIP13, TRIM29, HDAC7, ARNTL2, AEBP1, or ACTL6A.

[0057] In some embodiments, master regulators can be grouped based on their association with certain cellular processes, such as, but not limited to, cell cycle, epigenetic/chromosome remodeling, Epithelial Mesenchymal Transitions (EMT), immune/development, angiogenesis, immune response, and inflammatory response. Detection of increased expression of one or more of the master regulators in any of the groups of FIG. 17 is indicative of poor prognosis.

Detection of increased expression of one or more of the master regulators in any of the groups of FIG. 17 indicates treatment with one or more therapeutics known to have effectiveness in treating cancers having with a similar master regulator expression profile is recommended.

[0058] Methods of determining gene expression in a sample can be performed using methods known in the art. Such methods included, but are not limited to, nucleotide amplification assays (including but not limited to PCR, RT-PCR, serial analysis of gene expression, and differential display), RNA sequencing, microarray technologies, proteomics, HPLC, Western electrophoresis.

[0059] Monitoring cancer growth can be used to direct treatment of the cancer, wherein an increase in expression of one or more master regulators indicates poor prognosis or decreased predicted survival time. In some embodiments, one or more cancer therapies is administered to a subject identified as having a poor prognosis or decreased predicted survival time.

TREATMENT

[0060] In some embodiments, we describe methods of treating cancer comprising inhibiting one or more master regulators. Inhibiting one or more master regulators can comprise using or administering one or more master regulator antagonists or inhibitors. A master regulator can be inhibited at the gene level, such as by using or administering RNA interference agents or antisense oligonucleotides to inhibit expression of the gene. The master regulators can be inhibited at the protein level, such as by using or administering an immunotherapy composition that binds to the master regulator protein and inhibits activity of the protein or by using or administering a small molecule drug known to inhibit activity of the master regulator protein. In some embodiments, we described methods of treating cancer comprising using or administering an immunotherapy composition against a master regulator protein or a combination of master regulator proteins. An immunotherapy composition can comprise one or more antibodies having affinity for one or more master regulators. An antibody can be, but is not limited to, an immunoglobulin, an immunoglobulin fragment having affinity for the master regulator, a chimeric antibody, a bispecific antibody, an antibody conjugate, or the like.

[0061] In some embodiments, an immunotherapy composition comprises a peptide formulation derived from a master regulator of poor prognosis. The peptide can be an immunogenic fragment of a master regulator protein. The peptide can be combined with an immune stimulating adjuvant. The immunotherapy composition can be administered locally (*e.g.*, subcutaneously) or systemically (*e.g.*, intravenously) with or without the presence of adjuvant. The immunotherapy composition can be used to stimulate the immune system to

develop an immune reaction specifically against the master regulator of poor prognosis. Development of an immune reaction can eliminate or aid in eliminating cancer cells expressing the master regulator of poor prognosis.

[0062] In some embodiments, we describe methods of treating cancer comprising using or administering one or more small molecule drugs to inhibit activity of a master regulator protein or a combination of master regulator proteins. Small molecule drugs include, but are not limited to those in Table A.

Table A. Master regulators and known therapies directed at the master regulator.

Master regulators (Cancers)	Inhibitors, drugs, or hormones that can block or mitigate abnormal signals emanating from these master regulators
VDR (GBM, glioma, AML)	Vitamin D: In GBM cells with high VDR expression, which has abnormal signaling leading to higher Sox2 expression and driving cancer stem cell growth. Treating cells with vitamin D reduces this abnormal signal from VDR, leading to lower Sox2, while VDR expression is relatively unaffected.
CDK1 (lung adenocarcinoma)	CDK1/2 inhibitors, e.g. Flavopiridol
HDAC7 (Lung squamous cell carcinoma, colon & rectal adenocarcinoma, GBM, AML)	HDAC inhibitors, e.g. vorinostat, romidepsin, belinostat, panobinostat, entinostat, valproic acid
YAP1 (Pancreatic adenocarcinoma)	Yap1 inhibitors: Vereporfin, CA3, or drugs that targeting downstream or in the pathways of YAP1, e.g., Trametinib, dasatinib, metformin
HDAC2 (hepatocellular carcinoma)	HDAC inhibitors, e.g. vorinostat, romidepsin, belinostat, panobinostat, entinostat, valproic acid
SMAD7 (Lung squamous cell carcinoma)	Mongersen or the TGFbeta pathway inhibitors, e.g. galunisertib, AVID200

[0063] In some embodiments, we describe methods of treating cancer comprising using or administering one or more antisense oligonucleotides or RNA interference agents to knock down expression of a master regulator gene or a combination of master regulator genes. An antisense oligonucleotide is a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding region or segment of a target nucleic acid. An RNA interference agent is an oligonucleotide that mediates the targeted cleavage of an RNA transcript in a sequence specific manner via an RNA-induced silencing complex (RISC) pathway.

[0064] In some embodiments, we describe methods of treating cancer comprising using or administering a combination of one or more master regulator antagonists or inhibitors.

[0065] In some embodiments, treating a cancer of any of the cancer types in Tables 2 and 3 comprises administering one or more inhibitors of at least one master regulator identified as a top 20 master regulator for the cancer type as indicated in Tables 2 and 3.

EXAMPLES

Example 1: Identifying Masters Regulators of Poor Prognosis using GeneRep algorithm

[0066] We analyzed the cancers in Table 1 based on genome-wide expression profiles in the Cancer Genome Atlas, using the GeneRep algorithm. A method of determining the master regulators of a particular cancer is GeneRep/nSCORE described in WO-2018/069891 which is incorporated by reference in its entirety.

Table 1.

Study Abbreviation	Cancer Type
LAML	Acute Myeloid Leukemia
ACC	Adrenocortical carcinoma
BLCA	Bladder Urothelial Carcinoma
LGG	Brain Lower Grade Glioma
BRCA	Breast invasive carcinoma
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangiocarcinoma
LCML	Chronic Myelogenous Leukemia
COAD	Colon adenocarcinoma
CNTL	Controls

ESCA	Esophageal carcinoma
FPPP	FFPE Pilot Phase II
GBM	Glioblastoma multiforme
HNSC	Head and Neck squamous cell carcinoma
KICH	Kidney Chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
MESO	Mesothelioma
MISC	Miscellaneous
OV	Ovarian serous cystadenocarcinoma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
SARC	Sarcoma
SKCM	Skin Cutaneous Melanoma
STAD	Stomach adenocarcinoma
TGCT	Testicular Germ Cell Tumors
THYM	Thymoma
THCA	Thyroid carcinoma
UCS	Uterine Carcinosarcoma
UCEC	Uterine Corpus Endometrial Carcinoma
UVM	Uveal Melanoma

[0067] Results from our study are described in Tables 2 and 3 below and FIGs. 2-15.

Table 2. Top 20 master regulator genes (masters of death), labeled 1-20, for various cancer types. Cancer types corresponding to the indicated abbreviations are listed in Table 1.

gene	Cancer type														
	acc	blca	brca	cesc	coadread	esca	gbm	hnsc	kirc	kirp	laml	lgg	lihc	luad	lusc
MYBL2	15								7	3			2		
FOXMI	2								16	4				3	

CDK1	10								2			12	10	
PTTG1								8	1			4		
E2F7									9		9		11	
UHRF1	17								17					
TRIP13	9								16			1		
AEBP1				2		4								
HDAC7				16		3				6				17
ACTL6A							19					14		
ARNTL2											16		1	
TRIM29													8	
HMGA2	11						3							
TCF3	7							15						
LOXL2			1										2	
MEIS3				6										
TGFB111				10										
HIC1				19										7
SPI1					16									16
FOSL1						6	9						9	
MMP14						2							5	
VDR						1				2	13			
MAFK						12							4	13
SLC2A4RG						10					17			
NPM1							18		18			11		
CCNE1								4	5					
CDK2									19		4			
HTATIP2										4	19			
NFE2L3											10			
PLSCR1											15		14	
KDM1A												18		
FOXD1	12													
EZH2	5													
PLK4	16												16	
DNMT1	3													
ETV4	4					13								
PCGF6	20				12									
PPRC1	14													
ATF6		7												
HEYL		14												
OTX1		18									14			
SSRP1		11										15		
BNC1		20												
ZNF521		10		15										
ZNF532		19								18				
REST			12								20			
KLF17				9										
LIF				4										
NCOR2				17										5
SALL2				8										
HAND2					12									
LZTS1					18	8								
TCF7L1					7									
TSHZ3					9									
ZNF512B					20									
MAFB					8									

DEK						5				14				
SNAI2						8							13	
TDG						2							18	
BASP1						6			20					
ZNF280C						19				10				
TSHZ2							17							
LMX1B								15						
SMARCD3								17						
RAD9A									14					
DBF4										20				
RBMS1										11				
TRIM32											20			
MEOX2												7		
SP100												3		
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ZEB1					3										
MECP2					14										
HLX					1										
MEIS1					5										
ZNF154					13										
ZNF676					11										
HEY1						4									
YAF2						10									
HSF2						20									
TAF9B						7									
MAF						1									
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DMTF1						3									
HSA_MIR_30E						9									
HSA_MIR_3653						18									
MICAL2							15								
RELB							19								
C9ORF64							16								
EVC2							14								
CD300E							18								
PLEKHN1							11								
BCL3							9								
BHLHE40							5								
EPS8L2							20								
LRRFIP1							7								
DDN								5							
FHL2								8							
NFE2L1								4							
ZFP42								10							
POLR2C								16							
HOXA1								6							
MSX2								12							
PCGF2								20							
SMYD1								7							

CCND1							1							
E2F4							14							
LHX1							11							
MLXIPL							13							
PERINEURAL _ INVASION							2							
DLX4								10						
ETV6								6						
LBX2								19						
STAT2								1						
ZGLP1								18						
KAT2A								2						
IFI16								11						
RUNX1								12						
RBCK1								17						
ZNF335								13						
IRF3								9						
TAF10								5						
TFAP2E								3						
ZNF488									15					
AATF									12					
PRRX1									7					
AHCTF1									13					
FOXD2									6					
ELF4									8					
HOXA10										14				
SREBF1										8				
HOXA6										16				
PLA2G4A										11				
BATF										15				
NFKB2										9				
TCF15										17				
LPIN1										19				
STAT6										7				
CC2D1A										10				
DAXX										3				
ETS2										5				
HOXA7										12				
PPP1R13L										13				
TFEB										1				
NR2E1											6			
OTP											18			
PHTF1											5			
TGIF1											1			
ZNF217											2			
DMRTA2											8			
TEAD3											11			
MYCBP											12			
E2F6												19		
HMGA1												8		
PITX2												7		
SMARCD1												5		
YBX1												10		
ZNF207												17		

ENO1													9		
FUBP1													13		
MAFG													16		
NPAS2														15	
SMAD3														19	
BCL9L														17	
HOXA13														20	
LDB2															19
ELANE															4
SKI															18
NACC2															8
TCF21															1
RARA															11
SMAD7															3
CALCOCO1															6
PBX4															12
SOX18															20
HNF1B															15
ATOH8															2
CSRNPI															14

Table 3. Top 20 master regulator genes (masters of death), labeled 1-20, for various cancer types. Cancer types corresponding to the indicated abbreviations are listed in Table 1. n_top and top_frequency are described below.

gene	Cancer type													n_top	top_frequency
	meso	ov	paad	pcpg	prad	sarc	skcm	stad	tgct	thca	thym	ucec	uvm		
MYBL2	2											5		6	0.21
FOXM1							5							5	0.18
CDK1	8													5	0.18
PTTG1	11											15		5	0.18
E2F7	20		16											5	0.18
UHRF1	5		17											4	0.14
TRIP13	3													4	0.14
AEBP1								4				11		4	0.14
HDAC7														4	0.14
ACTL6A			2			17								4	0.14
ARNTL2	4		5											4	0.14
TRIM29			4				1				13			4	0.14
HMGA2						18								3	0.11
TCF3						9								3	0.11
LOXL2	1													3	0.11
MEIS3	9							16						3	0.11
TGFB111	6							1						3	0.11
HIC1								3						3	0.11
SPI1								11						3	0.11
FOSL1														3	0.11

MMP14								17					3	0.11
VDR													3	0.11
MAFK													3	0.11
SLC2A4RG											13		3	0.11
NPM1													3	0.11
CCNE1											8		3	0.11
CDK2						2							3	0.11
HTATIP2												2	3	0.11
NFE2L3			10							14			3	0.11
PLSCR1										17			3	0.11
KDM1A		13				1							3	0.11
GRHL2			1				19				15		3	0.11
FOXD1												14	2	0.07
EZH2	18												2	0.07
PLK4													2	0.07
DNMT1	19												2	0.07
ETV4													2	0.07
PCGF6													2	0.07
PPRC1						20							2	0.07
ATF6				14									2	0.07
HEYL								17					2	0.07
OTX1													2	0.07
SSRP1													2	0.07
BNC1		14											2	0.07
ZNF521													2	0.07
ZNF532													2	0.07
REST													2	0.07
KLF17								13					2	0.07
LIF												12	2	0.07
NCOR2													2	0.07
SALL2							15						2	0.07
HAND2							7						2	0.07
LZTS1													2	0.07
TCF7L1		15											2	0.07
TSHZ3							2						2	0.07
ZNF512B									11				2	0.07
MAFB							6						2	0.07
DEK													2	0.07
SNAI2													2	0.07
TDG													2	0.07
BASP1													2	0.07
ZNF280C													2	0.07
TSHZ2									4				2	0.07
LMX1B									3				2	0.07
SMARCD3							18						2	0.07
RAD9A											16		2	0.07
DBF4					5								2	0.07
RBMS1			13										2	0.07
TRIM32							8						2	0.07
MEOX2								20					2	0.07
SP100			12										2	0.07
HDAC2						10							2	0.07
RAN						13							2	0.07
SOX11						6							2	0.07

ZNF697					8								2	0.07
SNAI1									5				2	0.07
PKNOX2							12						2	0.07
E2F1	14										4		2	0.07
E2F8	13		11										2	0.07
EHF				13						16			2	0.07
NOC2L					12						9		2	0.07
ZBTB9					11	16							2	0.07
POU3F1						13		18					2	0.07
FOSL2						18				9			2	0.07
FLI1							13					6	2	0.07
HOXA11													1	0.04
ZIC2													1	0.04
PITX1													1	0.04
PSMC3IP													1	0.04
HOXC11													1	0.04
SNAPC4													1	0.04
PRMT5													1	0.04
RCOR1													1	0.04
TEAD4													1	0.04
WWTR1													1	0.04
BARX2													1	0.04
CALU													1	0.04
CD109													1	0.04
NFIC													1	0.04
SOX7													1	0.04
TCF4													1	0.04
ZHX3													1	0.04
PDE3A													1	0.04
CCNT1													1	0.04
CLOCK													1	0.04
KIAA0754													1	0.04
NCOA2													1	0.04
TAF13													1	0.04
AFF4													1	0.04
MED13													1	0.04
MED23													1	0.04
MTDH													1	0.04
PGK1													1	0.04
SMAD5													1	0.04
STON1_GTF2A 1L													1	0.04
XRCC4													1	0.04
YWHAB													1	0.04
ZFH3													1	0.04
ZNF623													1	0.04
ATF2													1	0.04
ITGB1													1	0.04
PDIA6													1	0.04
TUBB3													1	0.04
ELK3													1	0.04
FNDC3B													1	0.04
ITGA5													1	0.04
KIRREL													1	0.04

SPRY4															1	0.04
FNDC3A															1	0.04
HSP90AB1															1	0.04
KLF7															1	0.04
PEAR1															1	0.04
ZNF281															1	0.04
GLI3															1	0.04
GLIS2															1	0.04
ZEB1															1	0.04
MECP2															1	0.04
HLX															1	0.04
MEIS1															1	0.04
ZNF154															1	0.04
ZNF676															1	0.04
HEY1															1	0.04
YAF2															1	0.04
HSF2															1	0.04
TAF9B															1	0.04
MAF															1	0.04
TP63															1	0.04
AEBP2															1	0.04
DMTF1															1	0.04
HSA_MIR_30E															1	0.04
HSA_MIR_365 3															1	0.04
MICAL2															1	0.04
RELB															1	0.04
C9ORF64															1	0.04
EVC2															1	0.04
CD300E															1	0.04
PLEKHN1															1	0.04
BCL3															1	0.04
BHLHE40															1	0.04
EPS8L2															1	0.04
LRRFIP1															1	0.04
DDN															1	0.04
FHL2															1	0.04
NFE2L1															1	0.04
ZFP42															1	0.04
POLR2C															1	0.04
HOXA1															1	0.04
MSX2															1	0.04
PCGF2															1	0.04
SMYD1															1	0.04
CCND1															1	0.04
E2F4															1	0.04
LHX1															1	0.04
MLXIPL															1	0.04
PERINEURAL_ INVASION															1	0.04
DLX4															1	0.04
ETV6															1	0.04
LBX2															1	0.04
STAT2															1	0.04

ZGLP1															1	0.04
KAT2A															1	0.04
IFI16															1	0.04
RUNX1															1	0.04
RBCK1															1	0.04
ZNF335															1	0.04
IRF3															1	0.04
TAF10															1	0.04
TFAP2E															1	0.04
ZNF488															1	0.04
AATF															1	0.04
PRRX1															1	0.04
AHCTF1															1	0.04
FOXD2															1	0.04
ELF4															1	0.04
HOXA10															1	0.04
SREBF1															1	0.04
HOXA6															1	0.04
PLA2G4A															1	0.04
BATF															1	0.04
NFKB2															1	0.04
TCF15															1	0.04
LPIN1															1	0.04
STAT6															1	0.04
CC2D1A															1	0.04
DAXX															1	0.04
ETS2															1	0.04
HOXA7															1	0.04
PPP1R13L															1	0.04
TFEB															1	0.04
NR2E1															1	0.04
OTP															1	0.04
PHTF1															1	0.04
TGIF1															1	0.04
ZNF217															1	0.04
DMRTA2															1	0.04
TEAD3															1	0.04
MYCBP															1	0.04
E2F6															1	0.04
HMGA1															1	0.04
PITX2															1	0.04
SMARCD1															1	0.04
YBX1															1	0.04
ZNF207															1	0.04
ENO1															1	0.04
FUBP1															1	0.04
MAFG															1	0.04
NPAS2															1	0.04
SMAD3															1	0.04
BCL9L															1	0.04
HOXA13															1	0.04
LDB2															1	0.04
ELANE															1	0.04
SKI															1	0.04

NACC2															1	0.04
TCF21															1	0.04
RARA															1	0.04
SMAD7															1	0.04
CALCOCO1															1	0.04
PBX4															1	0.04
SOX18															1	0.04
HNF1B															1	0.04
ATOH8															1	0.04
CSRNP1															1	0.04
BRCA1	10														1	0.04
BRIP1	15														1	0.04
DNMT3B	7														1	0.04
MYBL1	12														1	0.04
BEND6	16														1	0.04
NRG1	17														1	0.04
ZNF90		16													1	0.04
HCG22		9													1	0.04
ARID1B		19													1	0.04
TEX261		7													1	0.04
SLC1A6		8													1	0.04
SOCS5		6													1	0.04
ZNF781		12													1	0.04
HTR3C		5													1	0.04
PAX3		17													1	0.04
STAC2		4													1	0.04
BUD31		20													1	0.04
NFKBIB		1													1	0.04
CDSN		10													1	0.04
HIF3A		18													1	0.04
PER1		3													1	0.04
PFDN5		11													1	0.04
SNORD15A		2													1	0.04
KLF5			6												1	0.04
POU2F3			18												1	0.04
PTPN14			20												1	0.04
YAP1			3												1	0.04
MSLN			15												1	0.04
KLF3			14												1	0.04
AHR			8												1	0.04
ZFP36L1			7												1	0.04
NMI			9												1	0.04
YY1			19												1	0.04
BRCA2				2											1	0.04
CASC5				18											1	0.04
COPA				8											1	0.04
LHX4				3											1	0.04
RFX5				6											1	0.04
ZBTB37				4											1	0.04
BLZF1				5											1	0.04
C11ORF42				1											1	0.04
IRF6				7											1	0.04
TAF2				20											1	0.04
ZNF157				15											1	0.04

ZNF195				12										1	0.04
S100A5				10										1	0.04
TTY14				9										1	0.04
TSG101				19										1	0.04
PAX5				17										1	0.04
TFAP2B				11										1	0.04
PATE2				16										1	0.04
CIZ1					18									1	0.04
NUP62					6									1	0.04
POLE3					4									1	0.04
POP1					17									1	0.04
RAB14					16									1	0.04
TIAL1					14									1	0.04
KIAA0319					8									1	0.04
QTRTD1					12									1	0.04
ZNF57					10									1	0.04
MBD1					1									1	0.04
U2AF2					2									1	0.04
GAS2					3									1	0.04
KCNC3					13									1	0.04
NCBP2					11									1	0.04
DDX27					20									1	0.04
SLC12A5					19									1	0.04
GGA3					9									1	0.04
SRC					15									1	0.04
ZNF274					7									1	0.04
GMEB1						7								1	0.04
MEX3A						14								1	0.04
SERBP1						15								1	0.04
TARDBP						2								1	0.04
LHX8						5								1	0.04
MYBBP1A						16								1	0.04
MAGED1						19								1	0.04
C1QBP						20								1	0.04
HES6							9							1	0.04
MED15							14							1	0.04
OVOL1							7							1	0.04
PA2G4							15							1	0.04
GATAD2A							10							1	0.04
SOX15							17							1	0.04
TFAP2A							6							1	0.04
ZNF750							11							1	0.04
SLC38A8							12							1	0.04
OVOL2							4							1	0.04
ERG								10						1	0.04
PTGER3								19						1	0.04
RUNX1T1								8						1	0.04
ZFPM2								5						1	0.04
FOXC2									12					1	0.04
FOXD3									9					1	0.04
HOXD11									4					1	0.04
LIMS3									11					1	0.04
TREX2									10					1	0.04
ZSCAN10									6					1	0.04

HSA_MIR_483									2					1	0.04
IGF2									3					1	0.04
SOX2									19					1	0.04
TNFRSF1A									16					1	0.04
TFE3									20					1	0.04
ZFP57									7					1	0.04
CDX4									14					1	0.04
DPPA2									15					1	0.04
LOC100287704									8					1	0.04
ZNF679									5					1	0.04
ANTXR1										19				1	0.04
DCAF17										10				1	0.04
SIX2										12				1	0.04
UCHL5										16				1	0.04
PIAS2										1				1	0.04
SMAD1										13				1	0.04
ZFH4										18				1	0.04
PEG3										8				1	0.04
SMAD9										9				1	0.04
GZF1										6				1	0.04
ZFP41										17				1	0.04
SIX4										15				1	0.04
MED13L										20				1	0.04
NR0B2										14				1	0.04
PPARGC1A										2				1	0.04
PRDM12										7				1	0.04
ZNF462											20			1	0.04
FXN											6			1	0.04
JUN											19			1	0.04
HDAC9											5			1	0.04
PBX3											3			1	0.04
LPIN3											1			1	0.04
ZNF80											7			1	0.04
EOMES											10			1	0.04
BATF2											11			1	0.04
CIITA											18			1	0.04
PRDM1											8			1	0.04
ZBTB7B											2			1	0.04
ZNF768											12			1	0.04
SPIC											4			1	0.04
FOXP4												19		1	0.04
MED8												12		1	0.04
TRIB3												7		1	0.04
DDX41												1		1	0.04
HGS												3		1	0.04
DRAP1												20		1	0.04
CCDC137												2		1	0.04
GMEB2												18		1	0.04
RFX2												17		1	0.04
THRB												6		1	0.04
DMAP1												14		1	0.04
RBPJL												10		1	0.04
GLI2													5	1	0.04

TSC22D1														13	1	0.04
GATA6														3	1	0.04
GLIS3														8	1	0.04
FOXF1														18	1	0.04
NR5A2														1	1	0.04
BATF3														7	1	0.04
IRF1														10	1	0.04
SNCAIP														16	1	0.04
CITED1														4	1	0.04
CEBPG														19	1	0.04
IRF5														15	1	0.04
BCL11B														11	1	0.04
XBP1														17	1	0.04
ZNF576														20	1	0.04
SAP30														9	1	0.04

[0068] n_top is the number of cancer subtypes out of 28 cancer subtypes for which the indicated gene is considered a top master regulator of poor prognosis, *i.e.*, top 20 highest rank for this tumor. top_frequency is the percentage of n_top/total number of cancer subtypes (28). A high n_top and top_frequency indicates that this gene is a master regulator of poor prognosis across many cancer subtypes which is an indication that this gene plays an important role in patient deaths.

[0069] Many modifications and other embodiments of the inventions set forth herein will come to mind to one skilled in the art to which the inventions pertain having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the inventions are not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

Example 2: Cancer diagnosis

[0070] Analysis of master regulator genes can be used in the diagnosis of cancer. Diagnosis can be used to detect cancer, monitor cancer, detect risk of developing cancer, or analyze prognosis in a patient known to have cancer.

[0071] A sample is collected from a patient having cancer, suspected of having cancer, or suspected of being at risk of developing cancer and expression of at least one gene of a master regulator in the sample is measured. The expression of one or more master regulator genes in the patient sample is then compared with expression the same master regulator genes in a corresponding healthy reference sample. Increased expression in the patient sample relative to

the healthy reference sample is an indicator of the possible presence of cancer, risk of developing cancer, or of poor prognosis.

[0072] An increase in the expression of one or more of MYBL2, PTTG1, FOXM1, E2F7, CDK1, UHRF1, TRIP13, TRIM29, HDAC7, ARNTL2, AEBP1, or ACTL6A relative to the healthy reference sample indicates the possible presence of cancer, risk of developing cancer, or poor prognosis in a patient with cancer.

[0073] An increase in the expression of one or more of ARNTL2, LOXL2, FOXM1, MAFK, MMP14, TRIM29, FOSL1, CDK1, E2F7, ZNF697, SNAI2, PLSCR1, NPAS2, PLK4, BCL9L, TDG, SMAD3, HOXA13, MYBL2, or BRIP1 relative to the healthy reference sample indicates the possible presence of lung adenocarcinoma, risk of developing lung adenocarcinoma, or poor prognosis in a patient known to have lung adenocarcinoma.

[0074] An increase in the expression of one or more of TCF21, ATOH8, SMAD7, ELANE, NCOR2, CALCOCO1, HIC1, NACC2, PKNX2, SNAI1, RARA, PBX4, MAFK, CSRP1, HNF1B, SPI1, HDAC7, SKI LDB2, or SOX18 relative to the healthy reference sample indicates the possible presence of lung squamous cell carcinoma, risk of developing lung squamous cell carcinoma, or poor prognosis in a patient known to have lung squamous cell carcinoma.

[0075] An increase in the expression of one or more of CLOCK, AFF4, PGK1, STON1_GTF2A1L, MTDH, MED13, NCOA2, YWHAB, TAF13, REST, ZNF623, ZFH3, PDE3A, KIAA0754, MED23, SMAD5, XRCC4, CCNT1, ADAMTS12, or ZNF699 relative to the healthy reference sample indicates the possible presence of breast invasive carcinoma, risk of developing breast invasive carcinoma, or poor prognosis in a patient known to have breast invasive carcinoma.

[0076] An increase in the expression of one or more of MBD1, U2AF2, GAS2, POLE3, DBF4, NUP62, ZNF274, KIAA0319, GGA3, ZNF57, NCBP2, QTRTD1, KCNC3, TIAL1, SRC, RAB14, POP1, CIZ1, SLC12A5, or DDX27 relative to the healthy reference sample indicates the possible presence of prostate adenocarcinoma, risk of developing prostate adenocarcinoma, or poor prognosis in a patient known to have prostate adenocarcinoma.

[0077] An increase in the expression of one or more of HLX, AEBP1, ZEB1, GLI3, MEIS1, MEIS3, TCF7L1, MAFB, TSHZ3, TGFB1I1, ZNF676, HAND2, ZNF154, MECP2, ZNF521, HDAC7, GLIS2, LZTS1, HIC1, or ZNF512B relative to the healthy reference sample indicates the possible presence of colon and/or rectum adenocarcinoma, risk of developing colon and/or rectum adenocarcinoma, or poor prognosis in a patient known to have colon and/or rectum adenocarcinoma.

[0078] An increase in the expression of one or more of GRHL2, ACTL6A, YAP1, TRIM29, ARNTL2, KLF5, ZFP36L1, AHR, NMI, NFE2L3, E2F8, SP100, RBMS1, KLF3, MSLN, E2F7, UHRF1, POU2F3, YY1, or PTPN14 relative to the healthy reference sample indicates the possible presence of pancreatic adenocarcinoma, risk of developing pancreatic adenocarcinoma, or poor prognosis in a patient known to have pancreatic adenocarcinoma.

[0079] An increase in the expression of one or more of TRIP13, MYBL2, HDAC2, PTTG1, SMARCD1, RAN, PITX2, HMGA1, ENO1, YBX1, NPM1, CDK1, FUBP1, ACTL6A, SSRP1, MAFG, ZNF207, KDM1A, E2F6, or SOX11 relative to the healthy reference sample indicates the possible presence of liver hepatocellular carcinoma, risk of developing liver hepatocellular carcinoma, or poor prognosis in a patient known to have liver hepatocellular carcinoma.

[0080] An increase in the expression of one or more of TFEB, VDR, DAXX, HTATIP2, ETS2, HDAC7, STAT6, SREBF1, NFKB2, CC2D1A, PLA2G4A, HOXA7, PPP1R13L, HOXA10, BATF, HOXA6, TCF15, ZNF532, LPIN1, or TRIM32 relative to the healthy reference sample indicates the possible presence of acute myeloid leukemia, risk of developing acute myeloid leukemia, or poor prognosis in a patient known to have acute myeloid leukemia.

[0081] An increase in the expression of one or more of NFKBIB, SNORD15A, PER1, STAC2, HTR3C, SOCS5, TEX261, SLC1A6, HCG22, CDSN, PFDN5, ZNF781, KDM1A, BNC1, TCF7L1, ZNF90, PAX3, HIF3A, ARID1B, or BUD31 relative to the healthy reference sample indicates the possible presence of ovarian serous cystadenocarcinoma, risk of developing ovarian serous cystadenocarcinoma, or poor prognosis in a patient known to have ovarian serous cystadenocarcinoma.

[0082] An increase in the expression of one or more of VDR, MMP14, HDAC7, AEBP1, BHLHE40, FOSL1, LRRFIP1, LZTS1, BCL3, SLC2A4RG, PLEKHN1, MAFK, ETV4, EVC2, MICAL2, C9ORF64, TSHZ2, CD300E, RELB, or EPS8L2 relative to the healthy reference sample indicates the possible presence of glioblastoma multiforme, risk of developing glioblastoma multiforme, or poor prognosis in a patient known to have glioblastoma multiforme.

[0083] Similarly, an increase in the expression of one or more of the genes labeled 1-20 in any one of the columns in Tables 2 and 3 relative to expression of the same gene(s) in the healthy reference sample indicates the possible presence, risk, or poor prognosis for the cancer type listed at the top of the corresponding column.

[0084] In some embodiments, a statistically significant increase in expression of at least one master regulator indicates a poor prognosis, reduced response to standard treatment or a predicted decrease in survival time.

[0085] In some embodiments, a statistically significant increase in expression of at least two master regulators indicates a poor prognosis, reduced response to standard treatment or a predicted reduced survival time.

[0086] In some embodiments, a statistically significant increase in expression of at least three master regulators indicates a poor prognosis, reduced response to standard treatment or a predicted reduced survival time.

Example 3: Predicting patient survival

[0087] Calculating Risk Scores: Risk scores are calculated by comparing the expression level of one or more master regulator genes involved in certain pathways in a test sample with the expression levels of the same genes in a healthy reference sample. Increased expression in the test sample relative to the healthy reference sample is an indicator of increased risk. A positive risk score indicates increased expression of one or more master regulator genes in a pathway of A, B, C, or D (below) of FIG. 17 in a test sample from a subject relative to expression of the same gene(s) in a healthy reference sample.

[0088] A) Cell cycle risk score is determined by obtaining a risk score for one or more master regulators selected from the group consisting of: CDK2, CCNE1, FOXM1, UHRF1, CDK1, PTTG1, MYBL2, and TRIP13.

[0089] B) Epigenetic/chromosome remodeling risk score is determined by obtaining a risk score for one or more master regulators selected from the group consisting of: RAN, ACTL6A, NPM1, HDAC2, SOX11, KDM1A, NOC2L, ZBTB9, ZNF697, TRIM32, PPRC1, POU3F1, BNC1, ATF6, OTX1, SSRP1, ETV4, EZH2, DNMT1, PLK4, E2F8, E2F1, DBF4, RAD9A, ZNF280C, DEK, PCGF6, and TDG.

[0090] C) Epithelial Mesenchymal Transitions (EMT) risk score is determined by obtaining a risk score for one or more master regulators selected from the group consisting of: SNAI2, E2F7, ARNTL2, LOXL2, HMGA4, MMP14, FOSL1, LIF, FOXD1, LMX1B, TSHZ2, ZNF512B, SNAI1, MEOX2, C2A4RG, MAFK, NCOR2, ZNF532, HADC7, VDR, HTATIP2, NFE2L3, SP100, REST, PLSCR1, FOSL2, TRIM29, and GRHL2.

[0091] D) Immune/development risk score is determined by obtaining a risk score for one or more master regulators selected from the group consisting of: EHF, RBMS1, FLI1, MAFB,

SPI1, BASP1, SMARCD3, HAND2, TCFL1, TSHZ3, ZNF521, HEYL, PKNOX2, HIC1, SALL2, KLF17, MEIS3, TGFB1I1, LZTS1, and AEBP1.

[0092] Prognosis and/or prediction of patient survival can be analyzed across multiple cancer type by analyzing expression of master regulators in various pathways, including epithelial mesenchymal transition (EMT), cell cycle, angiogenesis, immune response, and inflammatory response.

[0093] A sample is collected from a patient having cancer, suspected of having cancer, or at risk of developing cancer and expression of at least one gene of a master regulator in the sample is measured. The expression of the master regulator gene in the patient sample is then compared with expression of the master regulator gene in a corresponding healthy reference sample. Increased expression of the master regulator in the patient sample relative to the healthy reference sample is an indicator of poor prognosis or reduced predicted survival time.

[0094] In some embodiments, master regulator gene is in the hallmark epithelial mesenchymal transition pathway, reactome cell cycle pathway, angiogenesis pathway, immune response pathway, or inflammatory response pathway.

[0095] Master regulator genes in the EMT hallmark pathway can be selected from the group consisting of: ZNF469, PRRX1, AEBP1, MEIS3, SNAI1, MMP14, ADAMTS12, ITGA5, TGFB1I1, and CREB3L1.

[0096] Master regulator genes in the reactome cell cycle pathway can be selected from the group consisting of: MYBL2, CDK1, TRIP13, EZH2, FOXM1, UHRF1, PTTG1, E2F7, BRCA1, and E2F8.

[0097] Master regulator genes in the angiogenesis pathway can be selected from the group consisting of: HEYL, LZTS1, COL4A1, ERG, SOX18, LDB2, GJC1, HLX, SOX17, and PDE3A.

[0098] Master regulator genes in the immune response pathway can be selected from the group consisting of: SPI1, IRF1, GATA3, IL2RB, BCL3, FOXP3, ACAP1, GBP1, CXCL13, and WWTR1.

[0099] Master regulator genes in the inflammatory response pathway can be selected from the group consisting of: SPI1, MS4A4A, CIITA, MAFB, VDR, BCL3, LILRB2, IRF5, WWTR1, and CALU.

Example 5: Master of Death gene VDR

[00100] VDR is ranked 1st in Glioblastoma multiforme (GBM) and surprisingly 2nd in Acute Myeloid Leukemia (AML, termed LAML in Tables 1 and 2). AML is a very phenotypically

distinct cancer from GBM. Further, these two very different cancers share three common master of death genes: VDR, HDAC7 and NFKB2/RELB (Table 4). The identification of common masters of death indicate these two cancers are more similar molecularly than previous physiological and/or morphological data would suggest.

Table 4. Masters of Death in Glioblastoma multiforme Acute Myeloid Leukemia.

Master of death	Glioblastoma multiforme	Master of death	Acute Myeloid Leukemia
VDR	1	TFEB	1
MMP14	2	VDR	2
HDAC7	3	DAXX	3
AEBP1	4	HTATIP2	4
BHLHE40	5	ETS2	5
FOSL1	6	HDAC7	6
LRRFIP1	7	STAT6	7
LZTS1	8	SREBF1	8
BCL3	9	NFKB2	9
SLC2A4RG	10	CC2D1A	10
PLEKHN1	11	PLA2G4A	11
MAFK	12	HOXA7	12
ETV4	13	PPP1R13L	13
EVC2	14	HOXA10	14
MICAL2	15	BATF	15
C9ORF64	16	HOXA6	16
TSHZ2	17	TCF15	17
CD300E	18	ZNF532	18
RELB	19	LPIN1	19
EPS8L2	20	TRIM32	20

[00101] VDR-dependent regulation of immune activation (i.e. innate immune) is well characterized. However, a role for VDR in regulating cancer stem cell factors (e.g., SOX2, BHLHE40, SNAI2) was not previously recognized. Many of top 50 genes downstream and connected with VDR are immune related due to VDR's role in innate immunity. Without wishing to be bound by theory, is it possible the regulation of immune activation could be the mechanism of how VDR regulates poor prognosis and survival, i.e. by regulating cancer stem cells, which are the cells that can propagate cancers, are resistant to therapy, and a major cause of tumor recurrence and poor prognosis.

Gene Networks

[00102] Gene network analysis using GeneRep/nSCORE indicates the VDR is networked with BHLHE40, BCL3, NFKB2, RELB, LRRFIP1, HES6, among others (Table 5 and FIG. 20).

[00103] Gene network analysis using GeneRep/nSCORE indicates that BHLHE40, TCF12, BCL3, SOX2, and RELP are networked with genes up-regulated in response to low oxygen levels (hypoxia); genes defining the EMT, as in wound healing, fibrosis and metastasis; genes up-regulated through activation of mTORC1 complex; heparin binding; and response to hypoxia.

[00104] Gene network analysis using GeneRep/nSCORE indicates that VDR, ZFP1, MYO1C, NFKB2, and ARID3A are networked with GTPase activity, RNA polymerase II core promoter proximal region sequence-specific DNA binding; membrane raft; pathways of cancer, and multicellular organism development.

[00105] Gene network analysis using GeneRep/nSCORE indicates that SNAI2, CYGB, ZIC3, SEMA3F, and LAMB1 are networked with angiogenesis; extracellular matrix organization; proteinaceous extracellular matrix; positive regulation of cell proliferation; and focal adhesion.

[00106] Gene network analysis using GeneRep/nSCORE indicates that VDR1, BHLHE40, TCF12, BCL3, and SOX2 are networked with genes involved in immune system; inflammatory response; neutrophil degranulation; immune response; and innate immune response.

Table 5. GBM Network of top VDR connected genes.

CLCF1	23529	Interleukin-6 family signaling
		Cytokine Signaling in Immune system
MYCBPAP	84073	May play a role in spermatogenesis
STEAP3	55240	DNA Damage Response
		Direct p53 effectors
ADAMTSL4	54507	O-glycosylation of TSR domain-containing proteins
		O-linked glycosylation
ITGA5	3678	Developmental Biology
		Shigellosis
CTSZ	1522	Lysosome
		Innate Immune System
NRP1	8829	Developmental Biology
		Apoptotic Pathways in Synovial Fibroblasts
NFKB2	4791	TNFR1 Pathway
		Interleukin-1 processing
ZDHC5	25921	
MSN	4478	RhoA signaling pathway

		Diseases associated with MSN include Immunodeficiency 50 and Verrucous carcinoma
TCIRG1	10312	Insulin receptor recycling
		Lysosome
P4HA2	8974	Collagen chain trimerization
		Metabolism
BCL3	602	Apoptosis-related network due to altered Notch3 in ovarian cancer
		NF-KappaB Family Pathway
RELB	5971	TNFR1 Pathway
		CD209 (DC-SIGN) signaling
PLXND1	23129	Semaphorin interactions
SGMS2	166929	Metabolism and Sphingolipid metabolism
RUNX1	861	Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds
		Transcriptional misregulation in cancer
ELK3	2004	ID signaling pathway
		ERK Signaling
LIF	3976	PEDF Induced Signaling
		PAK Pathway
		Diseases associated with LIF include Leukemia and Ectopic Pregnancy
NFKBIZ	64332	Transcriptional misregulation in cancer
		NF-kappaB Signaling
HES6	55502	Notch signaling pathway (KEGG
		Notch-mediated HES/HEY network

[00107] We show that VDR knockdown is correlated with downregulation of two key downstream immune factors, LIF and OSMR, in three GBM cell lines examined. These data confirm that VDR is linked to immune regulation (FIGs. 18A-B).

[00108] In four independent human GBM cell lines, VDR was shown to be required for the expression of Sox2 (FIGs. 19A-B). In U87 cells, we had to increase the input RNA from 10 to 50 ng in order to detect Sox2 and showed that the correlation between VDR and Sox2 also held true in this cell. Other cancer stem cell factors, BHLHE40, SNAI2 and ZFP1 are also regulated by VDR in three out of the four cell lines. This finding confirms the connection between VDR and cancer stem cell factors, especially Sox2, which was not previously known.

Example 6: Role of VDR and Sox2 in GBM prognosis

[00109] Analysis of whether VDR knockdown impairs GSC viability and whether Sox2 expression can rescue VDR knockdown effect is performed to examine the role of the VDR and Sox2 link in GBM stem cells formation and survival.

[00110] The influence of vitamin D is also examined for its role the link between VDR (vitamin D receptor) and GBM prognosis. Addition of vitamin D is used to determine if vitamin D will direct VDR to a beneficial pro-immune function of liganded VDR. Removal of vitamin

D is used to determine if vitamin D deficiency leads to harmful pro-tumor unliganded VDR signal.

[00111] We show that the identified masters of death regulate critical pathways that have been shown to be critical for aggressive phenotypes and treatment resistance in cancers.

[00112] Further we show that the masters of death are shared among cancers of a similar cellular origin or type, that cancers can be classified into distinct groups based on their master of death profiles even if the cancers are not traditionally thought of as phenotypically similar, and that targeting these shared common masters of death have a potential to impact efficacy in multiple cancers.

[00113] The validation of the above masters of death in distinct cancer types, demonstrates that predictive quality of the method of identifying target genes for diagnosis and/or treatment of cancer.

Example 7: Master of Death genes MYBL2, FOXM1, and PTTG1

[00114] MYBL2, FOXM1, and PTTG1 are shared and correlated with poor survival in more than multiple cancer types. We have shown that MYBL2 is a master regulator in renal and liver cancer; FOXM1 is a master regulator in renal and pancreatic cancer, and PTTG1 is a master regulator in renal and liver cancer. For each of these genes, high expression correlated with decreased survival probability (FIG. 21A-C). The identification of common master regulators indicates these cancers are more similar molecularly than previous physiological and/or morphological data would suggest.

Example 8: Treating cancer

[00115] The cancers listed in Tables 2 and 3 can be treated by administering immunotherapy compositions, small molecules, RNA interference agents, antisense oligonucleotides, or combinations thereof that target one or more of the master regulators associated with the cancer.

WHAT IS CLAIMED IS:

1. A method for detecting poor prognosis in a subject with cancer comprising measuring the expression of MYBL2 in a sample from the subject with cancer and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis.

2. A method for detecting poor prognosis in a subject with cancer comprising measuring the expression of one or more of MYBL2, PTTG1, FOXM1, E2F7, and CDK1 in a sample from the subject with cancer and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis.

3. A method for detecting poor prognosis in a subject with cancer comprising measuring the expression of one or more of UHRF1, TRIP13, TRIM29, HDAC7, ARNTL2, AEBP1, or ACTL6A in a sample from the subject with cancer and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis.

4. A method for detecting poor prognosis in a subject with lung adenocarcinoma comprising measuring the expression of ARNTL2 in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

5. The method of claim 4, further comprising measuring the expression of at least one of LOXL2, FOXM1, MAFK, MMP14, TRIM29, FOSL1, CDK1, E2F7, ZNF697, SNAI2, PLSCR1, NPAS2, PLK4, BCL9L, TDG, SMAD3, HOXA13, MYBL2, or BRIP1 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

6. A method for detecting poor prognosis in a subject with lung squamous cell carcinoma comprising measuring the expression of TCF21 in a sample from

the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

7. The method of claim 6, further comprising measuring the expression of at least one of ATOH8, SMAD7, ELANE, NCOR2, CALCOCO1, HIC1, NACC2, PKNOX2, SNAI1, RARA, PBX4, MAFK, CSRNP1, HNF1B, SPI1, HDAC7, SKI LDB2, or SOX18 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

8. A method for detecting poor prognosis in a subject with breast invasive carcinoma comprising measuring the expression of CLOCK in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

9. The method of claim 8, further comprising measuring the expression of at least one of AFF4, PGK1, STON1_GTF2A1L, MTDH, MED13, NCOA2, YWHAB, TAF13, REST, ZNF623, ZFH3, PDE3A, KIAA0754, MED23, SMAD5, XRCC4, CCNT1, ADAMTS12, or ZNF699 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

10. A method for detecting poor prognosis in a subject with prostate adenocarcinoma comprising measuring the expression of MBD1 in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

11. The method of claim 10, further comprising measuring the expression of at least one of U2AF2, GAS2, POLE3, DBF4, NUP62, ZNF274, KIAA0319, GGA3, ZNF57, NCBP2, QTRTD1, KCNC3, TIAL1, SRC, RAB14, POP1, CIZ1, SLC12A5, or DDX27 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

12. A method for detecting poor prognosis in a subject with colon and/or rectum adenocarcinoma comprising measuring the expression of HLX in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

13. The method of claim 10, further comprising measuring the expression of at least one of AEBP1, ZEB1, GLI3, MEIS1, MEIS3, TCF7L1, MAFB, TSHZ3, TGFB1I1, ZNF676, HAND2, ZNF154, MECP2, ZNF521, HDAC7, GLIS2, LZTS1, HIC1, or ZNF512B in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

14. A method for detecting poor prognosis in a subject with pancreatic adenocarcinoma comprising measuring the expression of GRHL2 in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

15. The method of claim 14, further comprising measuring the expression of at least one of ACTL6A, YAP1, TRIM29, ARNTL2, KLF5, ZFP36L1, AHR, NMI, NFE2L3, E2F8, SP100, RBMS1, KLF3, MSLN, E2F7, UHRF1, POU2F3, YY1, or PTPN14 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

16. A method for detecting poor prognosis in a subject with liver hepatocellular carcinoma comprising measuring the expression of TRIP13 in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

17. The method of claim 16, further comprising measuring the expression of at least one of MYBL2, HDAC2, PTTG1, SMARCD1, RAN, PITX2, HMGA1, ENO1, YBX1, NPM1, CDK1, FUBP1, ACTL6A, SSRP1, MAFG, ZNF207, KDM1A, E2F6, or SOX11 in the sample from the subject and comparing the expression with a healthy reference

sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

18. A method for detecting poor prognosis in a subject with acute myeloid leukemia comprising measuring the expression of TFEB in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

19. The method of claim 18, further comprising measuring the expression of at least one of VDR, DAXX, HTATIP2, ETS2, HDAC7, STAT6, SREBF1, NFKB2, CC2D1A, PLA2G4A, HOXA7, PPP1R13L, HOXA10, BATF, HOXA6, TCF15, ZNF532, LPIN1, or TRIM32 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

20. A method for detecting poor prognosis in a subject with ovarian serous cystadenocarcinoma comprising measuring the expression of NFKBIB in a sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

21. The method of claim 20, further comprising measuring the expression of at least one of SNORD15A, PER1, STAC2, HTR3C, SOCS5, TEX261, SLC1A6, HCG22, CDSN, PFDN5, ZNF781, KDM1A, BNC1, TCF7L1, ZNF90, PAX3, HIF3A, ARID1B, or BUD31 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

22. A method for detecting poor prognosis in a subject with glioblastoma multiforme comprising measuring the expression of VDR in a sample from the subject and comparing the expression with a reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

23. The method of claim 22, further comprising measuring the expression of at least one of MMP14, HDAC7, AEBP1, BHLHE40, FOSL1, LRRFIP1, LZTS1, BCL3, SLC2A4RG, PLEKHN1, MAFK, ETV4, EVC2, MICAL2, C9ORF64, TSHZ2, CD300E, RELB, or EPS8L2 in the sample from the subject and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject relative to the healthy reference sample is an indicator of poor prognosis.

24. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one of 409 genes for master regulators of poor prognosis which are selected from the group consisting of: MYBL2, FOXM1, CDK1, PTTG1, E2F7, UHRF1, TRIP13, AEBP1, HDAC7, ACTL6A, ARNTL2, TRIM29, HMGA2, TCF3, LOXL2, MEIS3, TGFB1I1, HIC1, SPI1, FOSL1, MMP14, VDR, MAFK, SLC2A4RG, NPM1, CCNE1, CDK2, HTATIP2, NFE2L3, PLSCR1, KDM1A, GRHL2, FOXD1, EZH2, PLK4, DNMT1, ETV4, PCGF6, PPRC1, ATF6, HEYL, OTX1, SSRP1, BNC1, ZNF521, ZNF532, REST, KLF17, LIF, NCOR2, SALL2, HAND2, LZTS1, TCF7L1, TSHZ3, ZNF512B, MAFB, DEK, SNAI2, TDG, BASP1, ZNF280C, TSHZ2, LMX1B, SMARCD3, RAD9A, DBF4, RBMS1, TRIM32, MEOX2, SP100, HDAC2, RAN, SOX11, ZNF697, SNAI1, PKNOX2, E2F1, E2F8, EHF, NOC2L, ZBTB9, POU3F1, FOSL2, FLI1, HOXA11, ZIC2, PITX1, PSMC3IP, HOXC11, SNAPC4, PRMT5, RCOR1, TEAD4, WWTR1, BARX2, CALU, CD109, NFIC, SOX7, TCF4, ZHX3, PDE3A, CCNT1, CLOCK, KIAA0754, NCOA2, TAF13, AFF4, MED13, MED23, MTDH, PGK1, SMAD5, STON1_GTF2A1L, XRCC4, YWHAB, ZFHX3, ZNF623, ATF2, ITGB1, PDIA6, TUBB3, ELK3, FNDC3B, ITGA5, KIRREL, SPRY4, FNDC3A, HSP90AB1, KLF7, PEAR1, ZNF281, GLI3, GLIS2, ZEB1, MECP2, HLX, MEIS1, ZNF154, ZNF676, HEY1, YAF2, HSF2, TAF9B, MAF, TP63, AEBP2, DMTF1, HSA_MIR_30E, HSA_MIR_3653, MICAL2, RELB, C9ORF64, EVC2, CD300E, PLEKHN1, BCL3, BHLHE40, EPS8L2, LRRFIP1, DDN, FHL2, NFE2L1, ZFP42, POLR2C, HOXA1, MSX2, PCGF2, SMYD1, CCND1, E2F4, LHX1, MLXIPL, PERINEURAL_INVASION, DLX4, ETV6, LBX2, STAT2, ZGLP1, KAT2A, IFI16, RUNX1, RBCK1, ZNF335, IRF3, TAF10, TFAP2E, ZNF488, AATF, PRRX1, AHCTF1, FOXD2, ELF4, HOXA10, SREBF1, HOXA6, PLA2G4A, BATF, NFKB2, TCF15, LPIN1, STAT6, CC2D1A, DAXX, ETS2, HOXA7, PPP1R13L, TFEB, NR2E1, OTP, PHTF1, TGIF1, ZNF217, DMRTA2, TEAD3, MYCBP, E2F6, HMGA1, PITX2, SMARCD1, YBX1, ZNF207, ENO1, FUBP1, MAFG, NPAS2, SMAD3, BCL9L, HOXA13, LDB2, ELANE, SKI, NACC2, TCF21, RARA, SMAD7,

CALCOCO1, PBX4, SOX18, HNF1B, ATOH8, CSRN1, BRCA1, BRIP1, DNMT3B, MYBL1, BEND6, NRG1, ZNF90, HCG22, ARID1B, TEX261, SLC1A6, SOCS5, ZNF781, HTR3C, PAX3, STAC2, BUD31, NFKBIB, CDSN, HIF3A, PER1, PFDN5, SNORD15A, KLF5, POU2F3, PTPN14, YAP1, MSLN, KLF3, AHR, ZFP36L1, NMI, YY1, BRCA2, CASC5, COPA, LHX4, RFX5, ZBTB37, BLZF1, C11ORF42, IRF6, TAF2, ZNF157, ZNF195, S100A5, TTTY14, TSG101, PAX5, TFAP2B, PATE2, CIZ1, NUP62, POLE3, POP1, RAB14, TIAL1, KIAA0319, QTRTD1, ZNF57, MBD1, U2AF2, GAS2, KCNC3, NCBP2, DDX27, SLC12A5, GGA3, SRC, ZNF274, GMEB1, MEX3A, SERBP1, TARDBP, LHX8, MYBBP1A, MAGED1, C1QBP, HES6, MED15, OVOL1, PA2G4, GATAD2A, SOX15, TFAP2A, ZNF750, SLC38A8, OVOL2, ERG, PTGER3, RUNX1T1, ZFPM2, FOXC2, FOXD3, HOXD11, LIMS3, TREX2, ZSCAN10, HSA_MIR_483, IGF2, SOX2, TNFRSF1A, TFE3, ZFP57, CDX4, DPPA2, LOC100287704, ZNF679, ANTXR1, DCAF17, SIX2, UCHL5, PIAS2, SMAD1, ZFH4, PEG3, SMAD9, GZF1, ZFP41, SIX4, MED13L, NR0B2, PPARGC1A, PRDM12, ZNF462, FXN, JUN, HDAC9, PBX3, LPIN3, ZNF80, EOMES, BATF2, CIITA, PRDM1, ZBTB7B, ZNF768, SPIC, FOXN4, MED8, TRIB3, DDX41, HGS, DRAP1, CCDC137, GMEB2, RFX2, THRB, DMAP1, RBPJL, GLI2, TSC22D1, GATA6, GLIS3, FOXF1, NR5A2, BATF3, IRF1, SNCAIP, CITED1, CEBPG, IRF5, BCL11B, XBP1, ZNF576, and SAP30 and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

25. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one of 85 genes for master regulators of poor prognosis which are selected from the group consisting of: MYBL2, FOXM1, CDK1, PTTG1, E2F7, UHRF1, TRIP13, AEBP1, HDAC7, ACTL6A, ARNTL2, TRIM29, HMGA2, TCF3, LOXL2, MEIS3, TGFB1I1, HIC1, SPI1, FOSL1, MMP14, VDR, MAFK, SLC2A4RG, NPM1, CCNE1, CDK2, HTATIP2, NFE2L3, PLSCR1, KDM1A, GRHL2, FOXD1, EZH2, PLK4, DNMT1, ETV4, PCGF6, PPRC1, ATF6, HEYL, OTX1, SSRP1, BNC1, ZNF521, ZNF532, REST, KLF17, LIF, NCOR2, SALL2, HAND2, LZTS1, TCF7L1, TSHZ3, ZNF512B, MAFB, DEK, SNAI2, TDG, BASP1, ZNF280C, TSHZ2, LMX1B, SMARCD3, RAD9A, DBF4, RBMS1, TRIM32, MEOX2, SP100, HDAC2, RAN, SOX11, ZNF697, SNAI1, PKNOX2, E2F1, E2F8, EHF, NOC2L, ZBTB9, POU3F1, FOSL2, and FLI1 and comparing the expression with a healthy reference sample,

wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

26. The method of claim 25, further comprising calculating cell cycle, epigenetic/chromosome remodeling, Epithelial Mesenchymal Transitions (EMT), immune/development risk scores.

27. The method of claim 26, wherein calculating the cell cycle risk score comprises measuring the expression of at least one of CDK2, CCNE1, FOXM1, UHRF1, CDK1, PTTG1, MYBL2, or TRIP13.

28. The method of claim 26, wherein calculating the epigenetic risk score comprises measuring the expression of at least one of RAN, ACTL6A, NPM1, HDAC2, SOX11, KDM1A, NOC2L, ZBTB9, ZNF697, TRIM32, PPRC1, POU3F1, BNC1, ATF6, OTX1, SSRP1, ETV4, EZH2, DNMT1, PLK4, E2F8, E2F1, DBF4, RAD9A, ZNF280C, DEK, PCGF6, or TDG.

29. The method of claim 26, wherein calculating the EMT risk score comprises measuring the expression of at least one of SNAI2, E2F7, ARNTL2, LOXL2, HMGA4, MMP14, FOSL1, LIF, FOXD1, LMX1B, TSHZ2, ZNF512B, SNAI1, MEOX2, C2A4RG, MAFK, NCOR2, ZNF532, HADC7, VDR, HTATIP2, NFE2L3, SP100, REST, PLSCR1, FOSL2, TRIM29, or GRHL2.

30. The method of claim 26, wherein calculating the immune/developmental risk score comprises measuring the expression of at least one of EHF, RBMS1, FLI1, MAFB, SPI1, BASP1, SMARCD3, HAND2, TCFL1, TSHZ3, ZNF521, HEYL, PKNOX2, HIC1, SALL2, KLF17, MEIS3, TGFB1I1, LZTS1, or AEBP1.

31. A method for treating a subject with cancer comprising administering an immunotherapy composition or small molecule that targets a master regulator of poor prognosis.

32. The method of claim 31, wherein the immunotherapy composition comprises a peptide formulation derived from a master regulator of poor prognosis or a nanoparticle or dendritic cell containing peptides derived from a master regulator of poor prognosis.

33. The method of claim 31, wherein the immunotherapy composition comprises a nanoparticle or dendritic cells containing RNA which codes for a master regulator of poor prognosis.

34. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: MYBL2, FOXM1, CDK1, PTTG1, E2F7, UHRF1, TRIP13, AEBP1, HDAC7, ACTL6A, ARNTL2, TRIM29, HMGA2, TCF3, LOXL2, MEIS3, TGFB1I1, HIC1, SPI1, FOSL1, MMP14, VDR, MAFK, SLC2A4RG, NPM1, CCNE1, CDK2, HTATIP2, NFE2L3, PLSCR1, KDM1A, GRHL2, FOXD1, EZH2, PLK4, DNMT1, ETV4, PCGF6, PPRC1, ATF6, HEYL, OTX1, SSRP1, BNC1, ZNF521, ZNF532, REST, KLF17, LIF, NCOR2, SALL2, HAND2, LZTS1, TCF7L1, TSHZ3, ZNF512B, MAFB, DEK, SNAI2, TDG, BASP1, ZNF280C, TSHZ2, LMX1B, SMARCD3, RAD9A, DBF4, RBMS1, TRIM32, MEOX2, SP100, HDAC2, RAN, SOX11, ZNF697, SNAI1, PKNOX2, E2F1, E2F8, EHF, NOC2L, ZBTB9, POU3F1, FOSL2, FLI1, HOXA11, ZIC2, PITX1, PSMC3IP, HOXC11, SNAPC4, PRMT5, RCOR1, TEAD4, WWTR1, BARX2, CALU, CD109, NFIC, SOX7, TCF4, ZHX3, PDE3A, CCNT1, CLOCK, KIAA0754, NCOA2, TAF13, AFF4, MED13, MED23, MTDH, PGK1, SMAD5, STON1_GTF2A1L, XRCC4, YWHAB, ZFHX3, ZNF623, ATF2, ITGB1, PDIA6, TUBB3, ELK3, FNDC3B, ITGA5, KIRREL, SPRY4, FNDC3A, HSP90AB1, KLF7, PEAR1, ZNF281, GLI3, GLIS2, ZEB1, MECP2, HLX, MEIS1, ZNF154, ZNF676, HEY1, YAF2, HSF2, TAF9B, MAF, TP63, AEBP2, DMTF1, HSA_MIR_30E, HSA_MIR_3653, MICAL2, RELB, C9ORF64, EVC2, CD300E, PLEKHN1, BCL3, BHLHE40, EPS8L2, LRRFIP1, DDN, FHL2, NFE2L1, ZFP42, POLR2C, HOXA1, MSX2, PCGF2, SMYD1, CCND1, E2F4, LHX1, MLXIPL, PERINEURAL_INVASION, DLX4, ETV6, LBX2, STAT2, ZGLP1, KAT2A, IFI16, RUNX1, RBCK1, ZNF335, IRF3, TAF10, TFAP2E, ZNF488, AATF, PRRX1, AHCTF1, FOXD2, ELF4, HOXA10, SREBF1, HOXA6, PLA2G4A, BATF, NFKB2, TCF15, LPIN1, STAT6, CC2D1A, DAXX, ETS2, HOXA7, PPP1R13L, TFEB, NR2E1, OTP, PHTF1, TGIF1, ZNF217, DMRTA2, TEAD3, MYCBP, E2F6, HMGA1, PITX2, SMARCD1, YBX1, ZNF207, ENO1, FUBP1, MAFG, NPAS2, SMAD3, BCL9L, HOXA13, LDB2, ELANE, SKI, NACC2, TCF21, RARA, SMAD7, CALCOCO1, PBX4, SOX18, HNF1B, ATOH8, CSRNP1, BRCA1, BRIP1, DNMT3B, MYBL1, BEND6, NRG1, ZNF90, HCG22, ARID1B, TEX261, SLC1A6, SOCS5, ZNF781, HTR3C, PAX3, STAC2, BUD31, NFKBIB, CDSN, HIF3A, PER1, PFDN5, SNORD15A, KLF5, POU2F3, PTPN14, YAP1, MSLN, KLF3, AHR, ZFP36L1, NMI, YY1, BRCA2, CASC5, COPA, LHX4, RFX5,

ZBTB37, BLZF1, C11ORF42, IRF6, TAF2, ZNF157, ZNF195, S100A5, TTTY14, TSG101, PAX5, TFAP2B, PATE2, CIZ1, NUP62, POLE3, POP1, RAB14, TIAL1, KIAA0319, QTRTD1, ZNF57, MBD1, U2AF2, GAS2, KCNC3, NCBP2, DDX27, SLC12A5, GGA3, SRC, ZNF274, GMEB1, MEX3A, SERBP1, TARDBP, LHX8, MYBBP1A, MAGED1, C1QBP, HES6, MED15, OVOL1, PA2G4, GATAD2A, SOX15, TFAP2A, ZNF750, SLC38A8, OVOL2, ERG, PTGER3, RUNX1T1, ZFPM2, FOXC2, FOXD3, HOXD11, LIMS3, TREX2, ZSCAN10, HSA_MIR_483, IGF2, SOX2, TNFRSF1A, TFE3, ZFP57, CDX4, DPPA2, LOC100287704, ZNF679, ANTXR1, DCAF17, SIX2, UCHL5, PIAS2, SMAD1, ZFHx4, PEG3, SMAD9, GZF1, ZFP41, SIX4, MED13L, NR0B2, PPARGC1A, PRDM12, ZNF462, FXN, JUN, HDAC9, PBX3, LPIN3, ZNF80, EOMES, BATF2, CIITA, PRDM1, ZBTB7B, ZNF768, SPIC, FOXN4, MED8, TRIB3, DDX41, HGS, DRAP1, CCDC137, GMEB2, RFX2, THRB, DMAP1, RBPJL, GLI2, TSC22D1, GATA6, GLIS3, FOXF1, NR5A2, BATF3, IRF1, SNCAIP, CITED1, CEBPG, IRF5, BCL11B, XBP1, ZNF576, and SAP30.

35. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: CDK2, CCNE1, FOXM1, UHRF1, CDK1, PTTG1, MYBL2, and TRIP13.

36. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: RAN, ACTL6A, NPM1, HDAC2, SOX11, KDM1A, NOC2L, ZBTB9, ZNF697, TRIM32, PPRC1, POU3F1, BNC1, ATF6, OTX1, SSRP1, ETV4, EZH2, DNMT1, PLK4, E2F8, E2F1, DBF4, RAD9A, ZNF280C, DEK, PCGF6, and TDG.

37. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: SNAI2, E2F7, ARNTL2, LOXL2, HMGA4, MMP14, FOSL1, LIF, FOXD1, LMX1B, TSHZ2, ZNF512B, SNAI1, MEOX2, C2A4RG, MAFK, NCOR2, ZNF532, HADC7, VDR, HTATIP2, NFE2L3, SP100, REST, PLSCR1, FOSL2, TRIM29, and GRHL2.

38. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: EHF, RBMS1, FLI1, MAFB, SPI1, BASP1, SMARCD3, HAND2, TCFL1, TSHZ3, ZNF521, HEYL, PKNOX2, HIC1, SALL2, KLF17, MEIS3, TGFB1I1, LZTS1, and AEBP1.

39. The method of any one of claims 31-33, wherein the master regulator of poor prognosis is selected from the group consisting of: MYBL2, PTTG1, FOXM1, E2F7, CDK1, UHRF1, TRIP13, TRIM29, HDAC7, ARNTL2, AEBP1, or ACTL6A.

40. The method of any one of claims 31-33, wherein cancer is a cancer type selected from Tables 2 and 3 and the master regulator of poor prognosis is selected from a gene in Tables 2 and 3 and identified as being one of the top 20 master regulators of the cancer type.

41. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis in the hallmark of epithelial mesenchymal transition pathway selected from the group consisting of: ZNF469, PRRX1, AEBP1, MEIS3, SNAI1, MMP14, ADAMTS12, ITGA5, TGFB1I1, and CREB3L1 and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

42. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis in the reactome cell cycle pathway selected from the group consisting of: MYBL2, CDK1, TRIP13, EZH2, FOXM1, UHRF1, PTTG1, E2F7, BRCA1, and E2F8 and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

43. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis in the angiogenesis pathway selected from the group consisting of: HEYL, LZTS1, COL4A1, ERG, SOX18, LDB2, GJC1, HLX, SOX17, and PDE3A and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

44. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis in the immune response pathway selected from the

group consisting of: SPI1, IRF1, GATA3, IL2RB, BCL3, FOXP3, ACAP1, GBP1, CXCL13, and WWTR1 and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

45. A method for predicting patient survival in multiple cancer types comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis in the inflammatory response pathway selected from the group consisting of: SPI1, MS4A4A, CIITA, MAFB, VDR, BCL3, LILRB2, IRF5, WWTR1, and CALU and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

46. The method for predicting patient survival comprising measuring in a sample from a cancer patient the expression of at least one gene of a master regulator of poor prognosis and comparing the expression with a healthy reference sample, wherein the cancer is a cancer type as in Tables 2 and 3 and the at least one gene of a master regulator of poor prognosis is selected from a gene in Tables 2 and 3 and identified as being one of the top 20 master regulators of the cancer type, wherein increased expression of the at least one gene of a master regulator of poor prognosis in the sample from the patient relative to the healthy reference sample is an indicator of reduced predicted survival time.

47. A method for treating cancer in a subject with cancer comprising:

- (a) obtaining or having obtained a sample from the subject;
- (b) measuring or having measured the expression level in the sample of one or more master regulator genes selected from the groups consisting of VDR, CDK1, HDAC7, YAP1, HDAC2, and SMAD7;
- (c) comparing the expression level of the one or more master regulators in the sample with the expression level of the one or more master regulators a healthy reference sample, wherein
 - (i) if VDR expression level is increased in the sample from the subject cancer relative to the healthy reference sample and the subject has GBM, glioma, or AML, administering vitamin D to the subject,

(ii) if CDK1 expression level is increased in the sample from the subject with cancer relative to the healthy reference sample and the subject has lung adenocarcinoma, administering a CDK1/2 inhibitor to the subject,

(iii) if HDAC7 expression level is increased in the sample from the subject with cancer relative to the healthy reference sample and the subject has lung squamous cell carcinoma, colon and/or rectal adenocarcinoma, GBM, or AML, administering an HDAC inhibitor to the subject,

(iv) if YAP1 expression level is increased in the sample from the subject with cancer relative to the healthy reference sample and the subject has pancreatic adenocarcinoma, administering a Yap1 inhibitor to the subject,

(v) if HDAC2 expression level is increased in the sample from the subject with cancer relative to the healthy reference sample and the subject has hepatocellular carcinoma, administering an HDAC inhibitor to the subject, and/or

(vi) if SMAD7 expression level is increased in the sample from the subject with cancer relative to the healthy reference sample and the subject has lung squamous cell carcinoma, administering mongersen and/or a TGFbeta pathway inhibitor to the subject.

48. The method of claim 47, wherein the CDK1/2 inhibitor is flavopiridol; the HDAC inhibitor is vorinostat, romidepsin, belinostat, panobinostat, entinostat, or valproic acid; the Yap1 inhibitor is vereporfin, CA3, trametinib, dasatinib, or metformin; and the TGFbeta pathway inhibitors is galunisertib or AVID200.

Figure 1

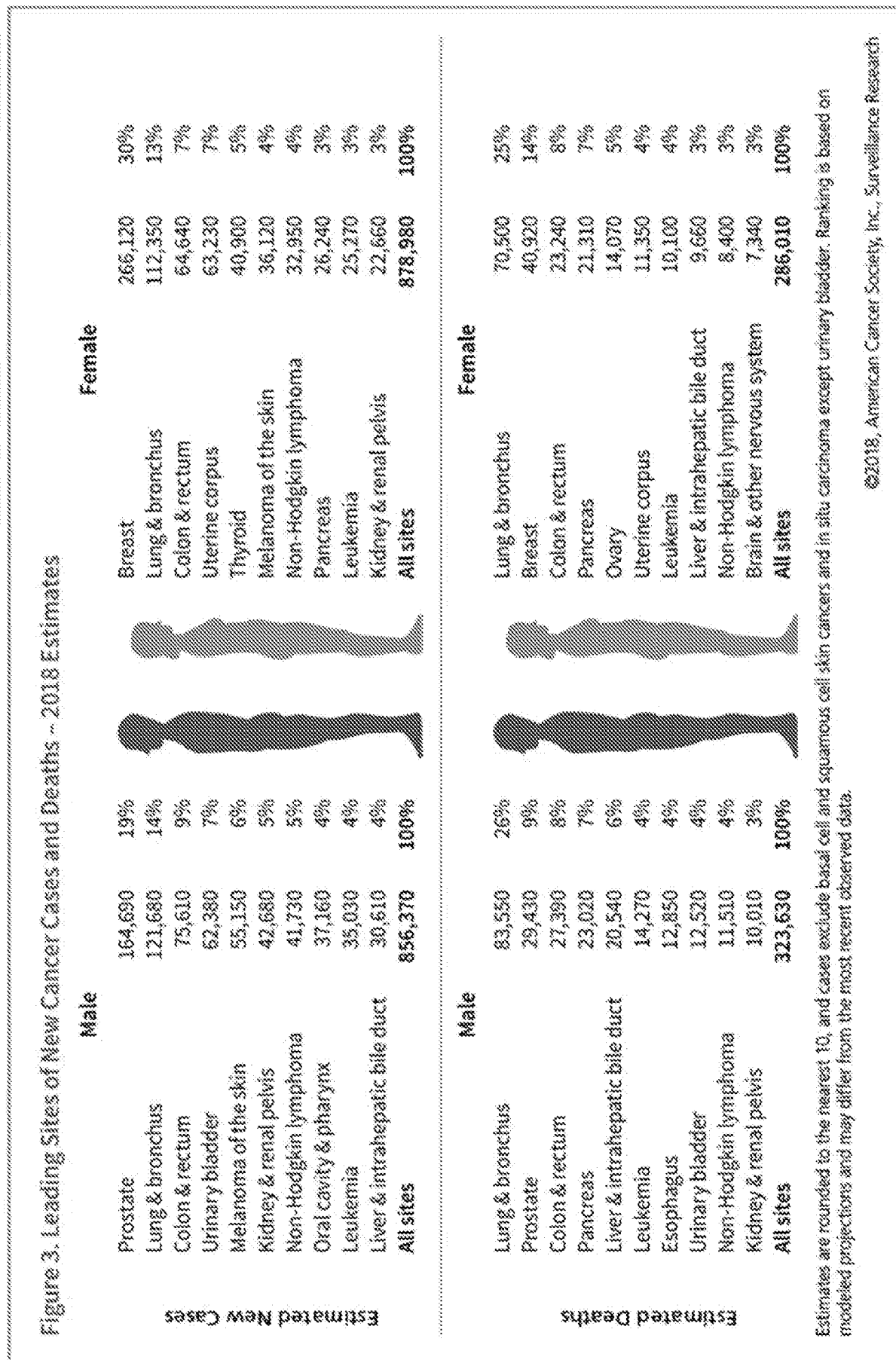


FIGURE 2
Lung Adenocarcinoma

- 1.11 FOXM, CDK1, E2F7, PLK4, TDG
Genes involved in cell cycle.
Genes involved in cell cycle, mitotic.
Genes encoding cell cycle related targets of E2F transcription factors.
Cell division
Genes involved in G2/M checkpoint, as in progression through cell division cycle.
- 1.2 ARNTL2, LOXL2, MMP14, FOSL1, PLSCR1
Genes involved in metabolism of lipids and lipoproteins.
Genes involved in transmembrane transport of small molecules.
Apical plasma membrane.
Genes defining early response to estrogen.
Genes defining late response to estrogen.
- 1.9 MAFK, DDX54, TRIM28, MED15, TFAM
Nuclear speck.
Protein serine/threonine kinase activity.
Protein phosphorylation.
Intracellular protein transport.
Endosome.
- 1.3 BCL9L, SKIL, FUBP3, ZBTB38
Mitochondrial inner membrane.
Genes involved in metabolism of proteins.
Genes involved in metabolism of RNA.
Genes involved in metabolism of mRNA.
Structural constituent of ribosome.

Master of death	rank
ARNTL2	1
LOXL2	2
FOXM1	3
MAFK	4
MMP14	5
TRIM29	6
FOSL1	7
CDK1	8
E2F7	9
ZNF697	10
SNAI2	11
PLSCR1	12
NPAS2	13
PLK4	14
BCL9L	15
TDG	16
SMAD3	17
HOXA13	18
MYBL2	19
BRIP1	20

FIGURE 3
Lung squamous cell carcinoma

- 1.2 TCF21, ATOH8, SMAD7, HIC1, PKNOX2
Cell adhesion
Proteinaceous extracellular matrix
Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis.
Proteolysis
Extracellular matrix organization
- 1.7 MAFK, HDAC7, CC2D1B, CEBPB, BCL9L
Genes involved in cell cycle
Genes involved in cell cycle, mitotic
Genes encoding cell cycle related targets of E2F transcription factors.
Genes involved in the G2/M checkpoint, as in progression through the cell division cycle.
Genes involved in DNA Replication
- 1.9 NCOR2, NACC2, SKI, MLXIP, KLF7
Mitochondrial inner membrane
Genes involved in metabolism of proteins
Genes involved in metabolism of RNA
Structural constituent of ribosome
Genes involved in metabolism of mRNA
- 1.6 SPI1, AKNA, ZNF331, IRF7, CCDC69
Genes involved in immune system
Immune response
Inflammatory response
Innate immune response
Genes up-regulated in response to IFNG (GeneID-3458)

Master of death	rank
TCF21	1
ATOH8	2
SMAD7	3
ELANE	4
NCOR2	5
CALCOCO1	6
HIC1	7
NACC2	8
PKNOX2	9
SNAI1	10
RARA	11
PBX4	12
MAFK	13
CSRNP1	14
HNF1B	15
SPI1	16
HDAC7	17
SKI	18
LDB2	19
SOX18	20

FIGURE 4
Breast Invasive Cancer

- 1.2 MTDH, YWHAB, TAF13, ZNF623, GTF2H3,
Protein phosphorylation
Nuclear speck
mRNA splicing, via spliceosome
Chromatin binding
Ubiquitin protein ligase binding
- 1.1 PTGES3, HDAC2, ZNF710
Genes involved in cell cycle, mitotic
Genes encoding cell cycle related targets of E2F transcription factors
Cell division
Genes involved in the G2/M checkpoint, as in progression through the cell division cycle
Genes involved in DNA Replication
- 1.6 ZFHX3, SMAD5, XRCC4, YIPF5, RNF4
Genes defining early response to estrogen.
Genes defining late response to estrogen.
Cilium assembly
Cilium
Transmembrane transport
- 1.4 CLOCK, AFF4, MED13, NCOA2 REST
Mitochondrial inner membrane
Genes involved in metabolism of RNA
Structural constituent of ribosome
rRNA processing
Genes involved in metabolism of mRNA

Master of death	rank
CLOCK	1
AFF4	2
PGK1	3
STON1_GTF2A1L	4
MTDH	5
MED13	6
NCOA2	7
YWHAB	8
TAF13	9
REST	10
ZNF623	11
ZFHX3	12
PDE3A	13
KIAA0754	14
MED23	15
SMAD5	16
XRCC4	17
CCNT1	18
ADAMTS12	19
ZNF699	20

FIGURE 5
Prostate adenocarcinoma

Master of death	rank
MBD1	1
U2AF2	2
GAS2	3
POLE3	4
DBF4	5
NUP62	6
ZNF274	7
KIAA0319	8
GGA3	9
ZNF57	10
NCBP2	11
QTRTD1	12
KCNC3	13
TIAL1	14
SRC	15
RAB14	16
POP1	17
CIZ1	18
SLC12A5	19
DDX27	20

- 1.9 MBD1, U2AF2, NUP62, ZNF274, GGA3
Genes involved in generic transcription pathway
Nucleic acid binding
RNA processing
Exocytosis
Regulation of vesicle fusion
- 1.5 POLE3, DBF4, NCBP2, QTRTD1, TIAL1
GTPase activity
Genes up-regulated through activation of mTORC1 complex.
mRNA splicing, via spliceosome
Protein folding
Genes up-regulated during adipocyte differentiation (adipogenesis).
- 1.4 RAB14, ADNP, ZNF791, ZNF28
Regulation of transcription from RNA polymerase II
Transcription of coactivator activity
Genes involved in Class I MHC mediated antigen
Protein polyubiquitination
Huntington's disease

FIGURE 6
Colon & Rectum adenocarcinoma

1.6 HLX, AEBP1, ZEB1, GLI3, MEIS1
Cell adhesion
Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis.
Proteinaceous extracellular matrix
Cell junction
Extracellular matrix organization

1.8 SPI1, STAT2, POU2F2, ZNF438, NFATC1
Genes involved in immune system
Inflammatory response
Immune response
Innate immune response
Genes up-regulated in response to IFNG (GeneID=3458)

Master of death	rank
HLX	1
AEBP1	2
ZEB1	3
GLI3	4
MEIS1	5
MEIS3	6
TCF7L1	7
MAFB	8
TSHZ3	9
TGFB111	10
ZNF676	11
HAND2	12
ZNF154	13
MECP2	14
ZNF521	15
HDAC7	16
GLIS2	17
LZTS1	18
HIC1	19
ZNF512B	20

FIGURE 7
Pancreatic adenocarcinoma

Master of death	rank
GRHL2	1
ACTL6A	2
YAP1	3
TRIM29	4
ARNTL2	5
KLF5	6
ZFP36L1	7
AHR	8
NMI	9
NFE2L3	10
E2F8	11
SP100	12
RBMS1	13
KLF3	14
MSLN	15
E2F7	16
UHRF1	17
POU2F3	18
YY1	19
PTPN14	20

FIGURE 8
Liver hepatocellular carcinoma

1.7 TRIP13, MYBL2, PTTG1, ENO1, YBX1	Master of death	rank
Genes involved in cell cycle	TRIP13	1
Genes involved in cell cycle, mitotic	MYBL2	2
Genes encoding cell cycle related targets of E2F transcription factors.	HDAC2	3
Cell division	PTTG1	4
Genes involved in the G2/M checkpoint, as in progression through the cell division cycle.	SMARCD1	5
	RAN	6
1.2 HDAC2, SMARCD1, HMGA1, ZNF207, E2F6	PITX2	7
Genes involved in metabolism of lipids and lipoproteins	HMGA1	8
Mitochondrial matrix	ENO1	9
Genes encoding proteins involved in processing of drugs and other xenobiotics.	YBX1	10
Genes involved in transmembrane transport of small molecules	NPM1	11
Genes involved in metabolism of amino acids and derivatives	CDK1	12
	FUBP1	13
1.5 RAN, NPM1, PSMD14, NCL, GTPBP4	ACTL6A	14
Genes involved in metabolism of proteins	SSRP1	15
A subgroup of genes regulated by MYC – version 1 (v1).	MAFG	16
Cadherin binding	ZNF207	17
Genes up-regulated through activation of mTORC1 complex.	KDM1A	18
Protein phosphorylation	E2F6	19
	SOX11	20

FIGURE 9
Acute Myeloid Leukemia

- 1.1 TFEB, VDR, STAT6, NFKB2, RIPK3
Neutrophil degranulation
Genes involved in immune system
Inflammatory response
Innate immune response
Genes regulated by NF-κB in response to TNF (GeneID=7124)
- 1.4 HTATIP2, ETS2, HDAC7, SREBF1, PLA2G4A
Genes involved in hemostasis
Focal adhesion
Cytoskeleton
Genes involved in developmental biology
Positive regulation of cell proliferation
- 1.7 CC2D1A, BATF, SREBF2, CREB2, MTA2
Genes involved in generic transcription pathway
Genes involved in adaptive immune system
Protein phosphorylation
Ubiquitin-protein transferase activity
Protein serine/threonine kinase activity

Master of death	rank
TFEB	1
VDR	2
DAXX	3
HTATIP2	4
ETS2	5
HDAC7	6
STAT6	7
SREBF1	8
NFKB2	9
CC2D1A	10
PLA2G4A	11
HOXA7	12
PPP1R13L	13
HOXA10	14
BATF	15
HOXA6	16
TCF15	17
ZNF532	18
LPIN1	19
TRIM32	20

FIGURE 10
Ovarian serous cystadenocarcinoma

1.16 KLF12, ARHGAP33, NFATC4, ZNF483, AATF	Master of death	rank
Regulation of intracellular pH	NFKB1B	1
Voltage-gated calcium channel activity	SNORD15A	2
Sulfate transmembrane transporter activity	PER1	3
Sulfate transmembrane transport	STAC2	4
Spliceosomal tri-snRNP complex assembly	HTR3C	5
	SOC5	6
1.18 SOCS5, CDSN, ZNF781, KDM1A, TCF7L1	TEX261	7
Genes involved in transmembrane transport of small molecules	SLC1A6	8
Apical plasma membrane	HCG22	9
Genes defining early response to estrogen	CDSN	10
Postsynaptic density	PFDN5	11
Genes defining late response to estrogen.	ZNF781	12
	KDM1A	13
1.20 PER1, BNC1, KLF14, AEBP1, FGF2	BNC1	14
Cell adhesion	TCF7L1	15
Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis	ZNF90	16
Proteinaceous reticulum lumen	PAX3	17
Extracellular matrix	HIF3A	18
	ARID1B	19
	BUD31	20

FIGURE 11
Glioblastome multiforme

Master of death	rank
VDR	1
MMP14	2
HDAC7	3
AEBP1	4
BHLHE40	5
FOSL1	6
LRRFIP1	7
LZTS1	8
BCL3	9
SLC2A4RG	10
PLEKHN1	11
MAFK	12
ETV4	13
EVC2	14
MICAL2	15
C9ORF64	16
TSHZ2	17
CD300E	18
RELB	19
EPS8L2	20

- 1.2 VDR, BHLHE40, BCL3, TSHZ2, RELB
Genes involved in immune system
Inflammatory response
Neutrophil degranulation
Immune response
Innate immune response
- 1.3 MMP14, HDAC7, AEBP1, FOSL1, LRRFIP1
GTP binding
Protein kinase binding
Genes up-regulated in response to IFNG [GeneID=3458].
Cytoskeleton
- 1.4 MICAL2, ATXN7L3, ACTR3C, TSPAN2, ANK1
Cell junction
Genes involved in signaling by GPCR
Genes involved in neuronal system
Genes involved in GPCR downstream signaling
chemical synaptic transmission

FIGURE 12

Top Master of Death for each cancer subtype

Study Abbreviation	Study Name	Master of Death
ACC	Adrenocortical carcinoma	ZIC2
BLCA	Bladder Urothelial Carcinoma	RCOR1
BRCA	Breast invasive carcinoma	CLOCK
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	LOXL2
COADREAD	Colon Rectum adenocarcinoma	HLX
ESCA	Esophageal carcinoma	MAF
GBM	Glioblastoma multiforme	VDR
HNSC	Head and Neck squamous cell carcinoma	CCND1
KIRC	Kidney renal clear cell carcinoma	STAT2
KIRP	Kidney renal papillary cell carcinoma	PTTG1
LAML	Acute Myeloid Leukemia	TFEB
LGG	Brain Lower Grade Glioma	TGIF1
LIHC	Liver hepatocellular carcinoma	TRIP13
LUAD	Lung adenocarcinoma	ARNTL2
LUSC	Lung squamous cell carcinoma	TCF21
MESO	Mesothelioma	LOXL2
OV	Ovarian serous cystadenocarcinoma	NFKBIB
PAAD	Pancreatic adenocarcinoma	GRHL2
PCPG	Pheochromocytoma and Paraganglioma	C11ORF42
PRAD	Prostate adenocarcinoma	MBD1
SARC	Sarcoma	KDM1A
SKCM	Skin Cutaneous Melanoma	TRIM29
STAD	Stomach adenocarcinoma	TGFB1I1
TGCT	Testicular Germ Cell Tumors	HSA_MIR_483
THCA	Thyroid carcinoma	PIAS2
THYM	Thymoma	LPIN3
UCEC	Uterine Corpus Endometrial Carcinoma	DDX41
UVM	Uveal Melanoma	NR5A2

Figure 13A-B
Most of masters of death are cancer subtype unique

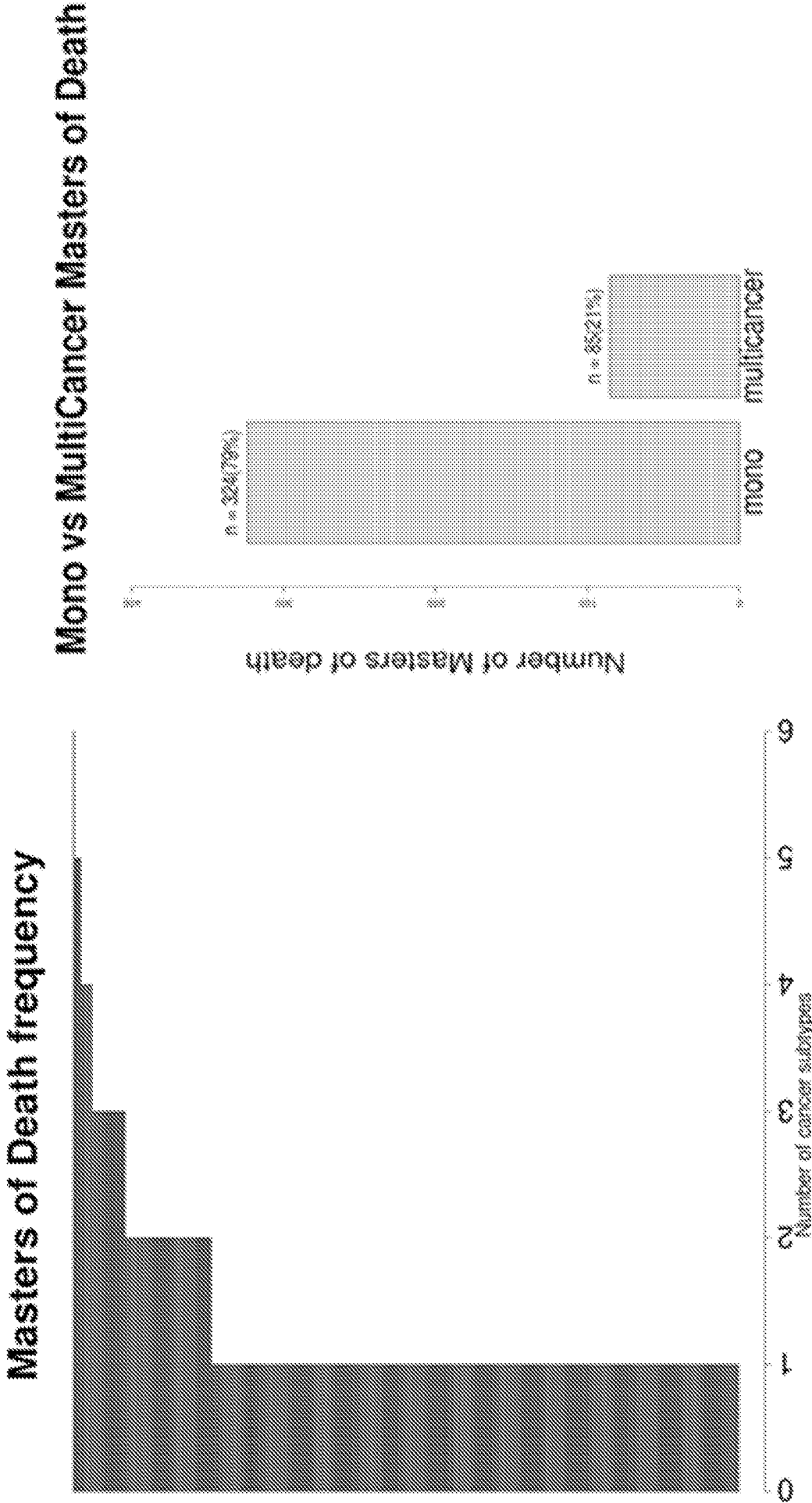


Figure 13B
Most Frequent Masters of Death

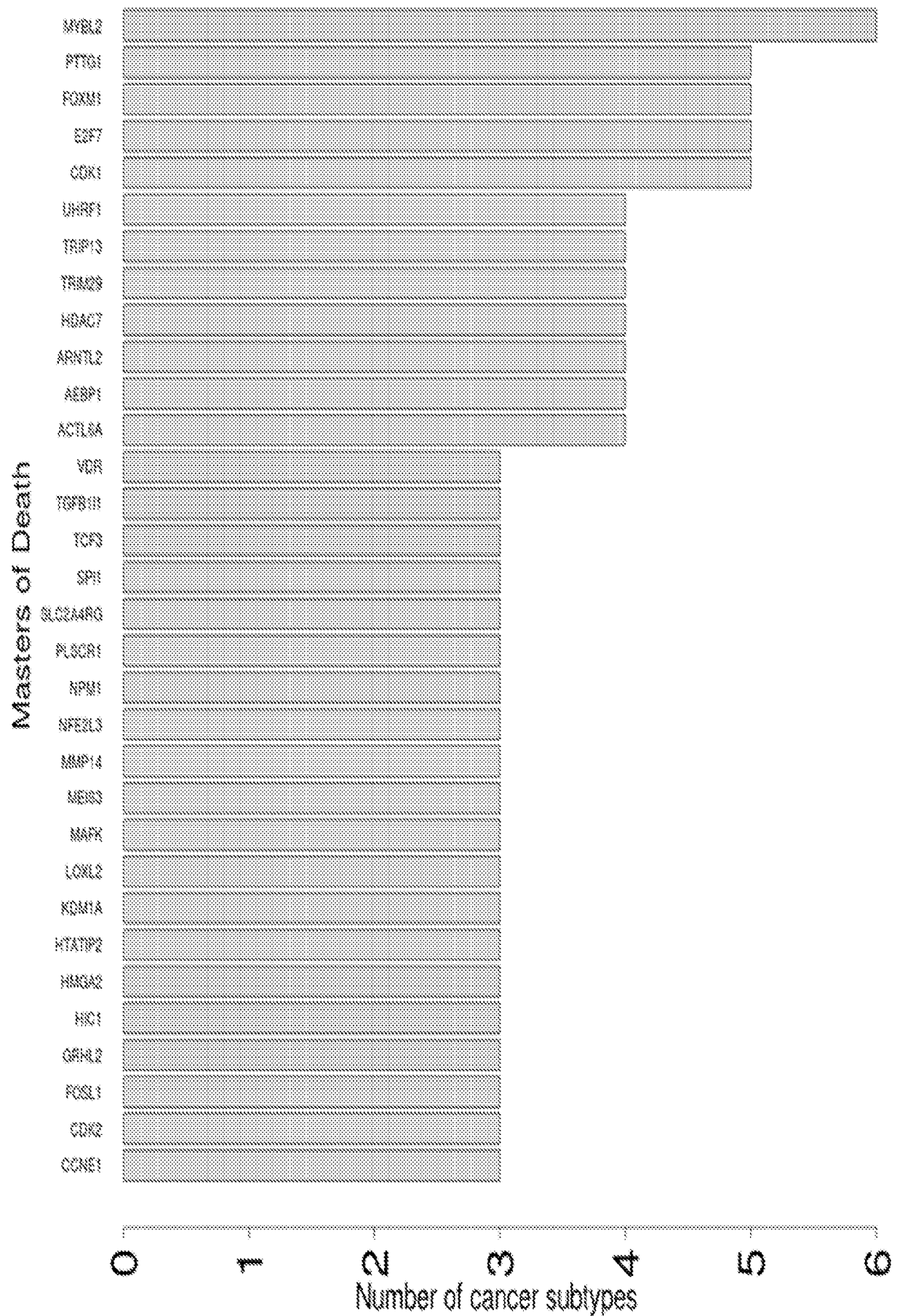


Figure 14

4 cancer groups by masters of death; Masters of death nScore Values in cancer subtypes heatmap

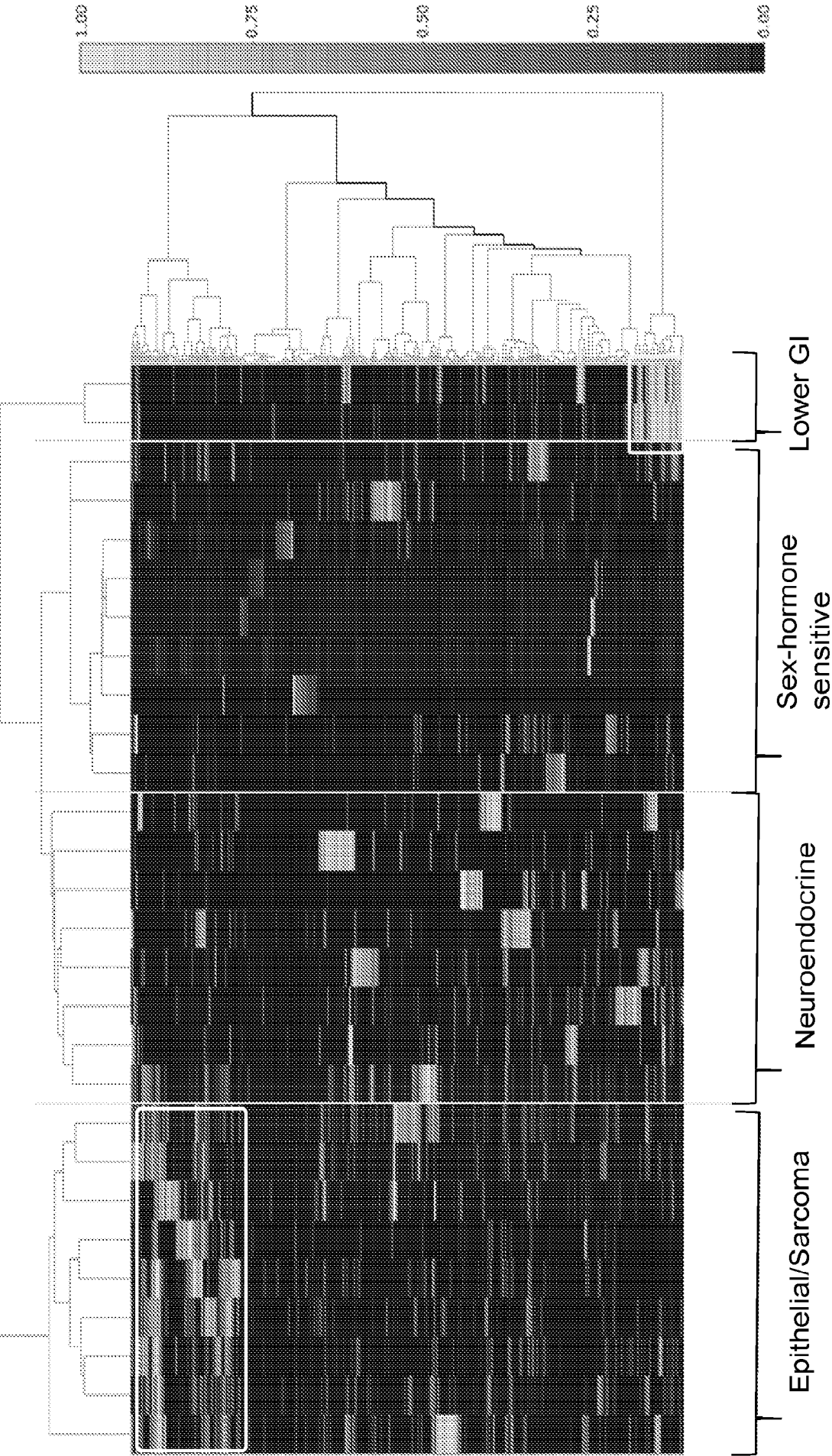


Figure 15

Common Masters of death heatmap; Masters of death nScore Values in cancer subtypes heatmap;
Heatmap of nScore values of Masters of death that present in at least two cancer subtypes

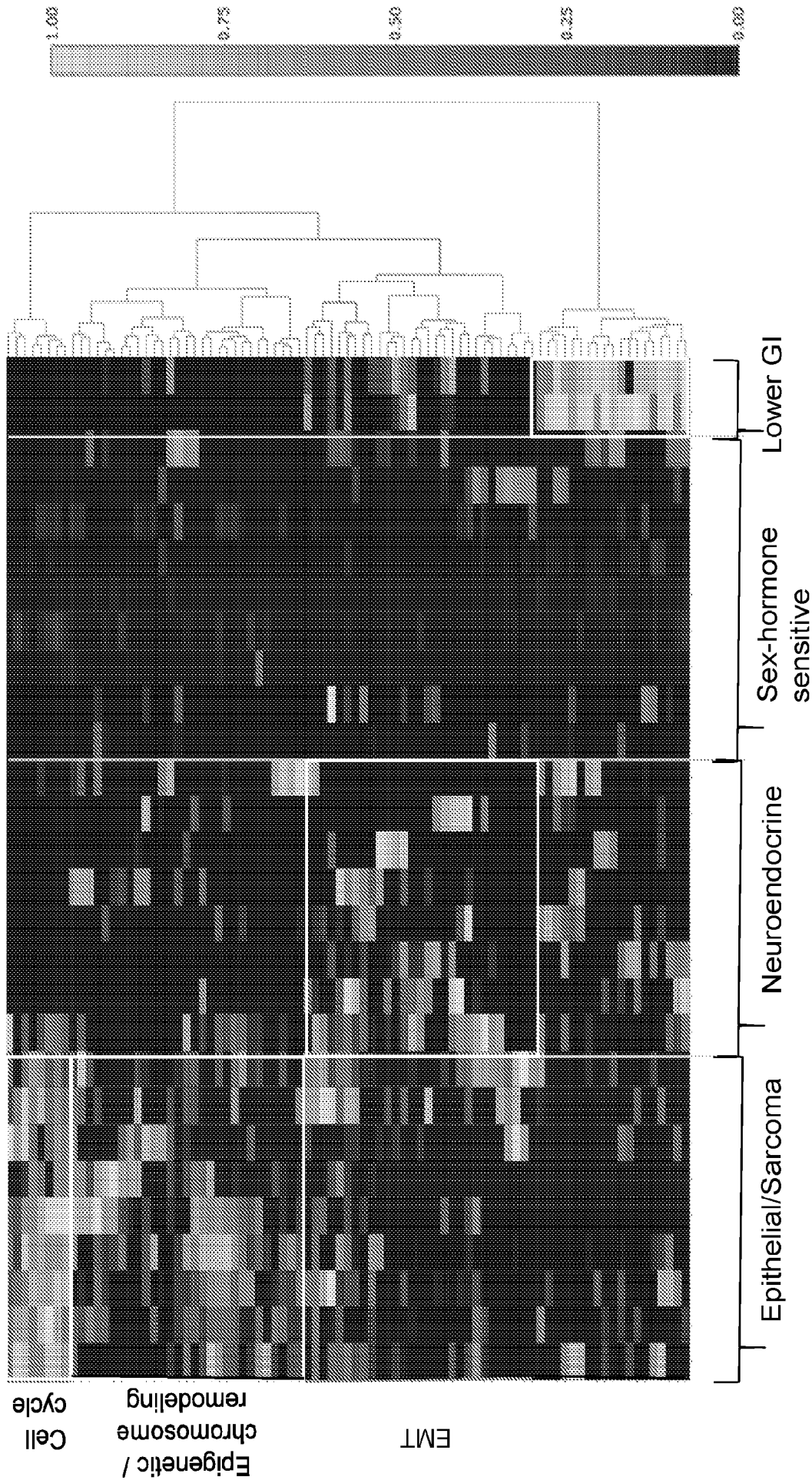


Figure 16
Pathways of Poor Prognosis

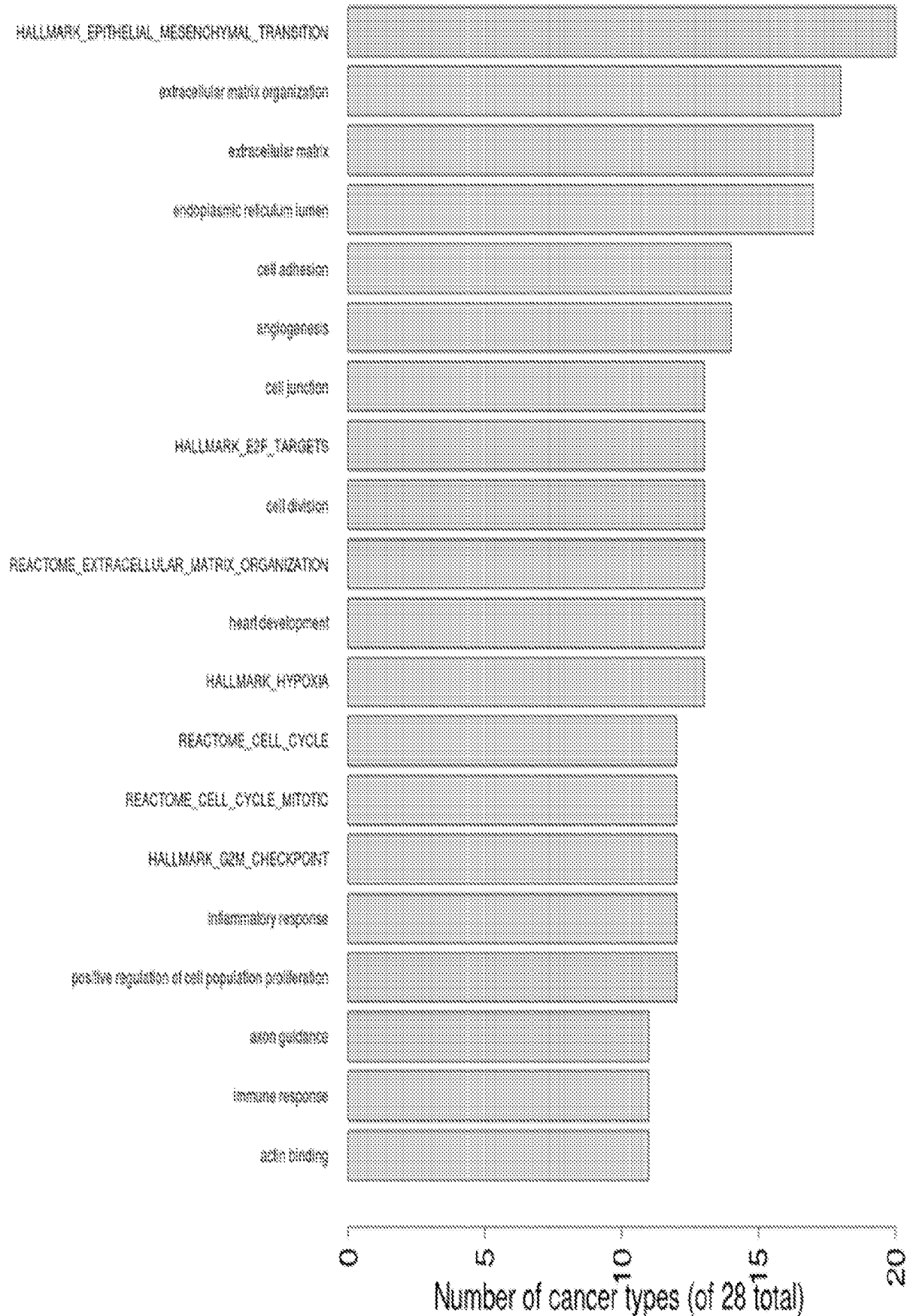
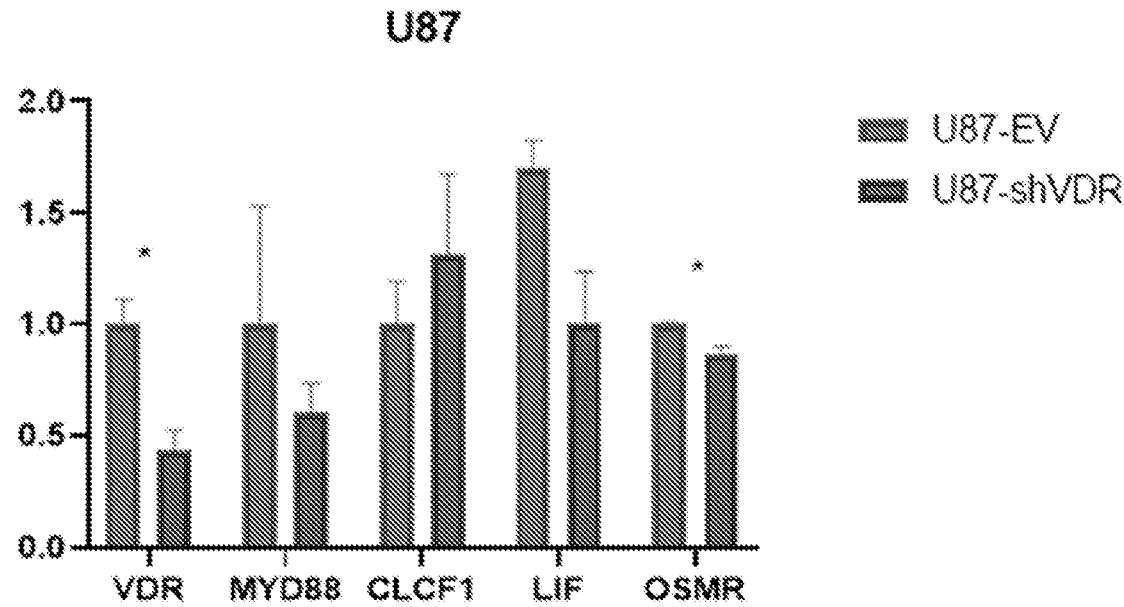


FIGURE 17

Gene	no. of cancer types (of 28 total)	Gene	no. of cancer types (of 28 total)
Hallmark Epithelial Mesenchymal Transition		Immune Response	
ZNF469	8	SPI1	4
PRRX1	8	IRF1	3
AEBP1	7	GATA3	2
MEIS3	5	IL2RB	2
SNAI1	5	BCL3	2
MMP14	4	FOXP3	2
ADAMTS12	3	ACAP1	2
ITGA5	3	GBP1	2
TGFB1I1	3	CXCL13	2
CREB3L1	3	WWTR1	1
Reactome Cell Cycle		Inflammatory response	
MYBL2	12	SPI1	5
CDK1	10	MS4A4A	3
TRIP13	9	CIITA	3
EZH2	7	MAFB	3
FOXM1	6	VDR	2
UHRF1	6	BCL3	2
PTTG1	5	LILRB2	2
E2F2	3	IRF5	2
BRCA1	3	WWTR1	1
E2F8	2	CALU	1
Angiogenesis			
HEYL	6		
LZTS1	4		
COL4A1	4		
ERG	4		
SOX18	4		
LDB2	3		
GJC1	3		
HLX	3		
SOX17	3		
PDE3A	2		

FIGURE 18A-B

A.



B.

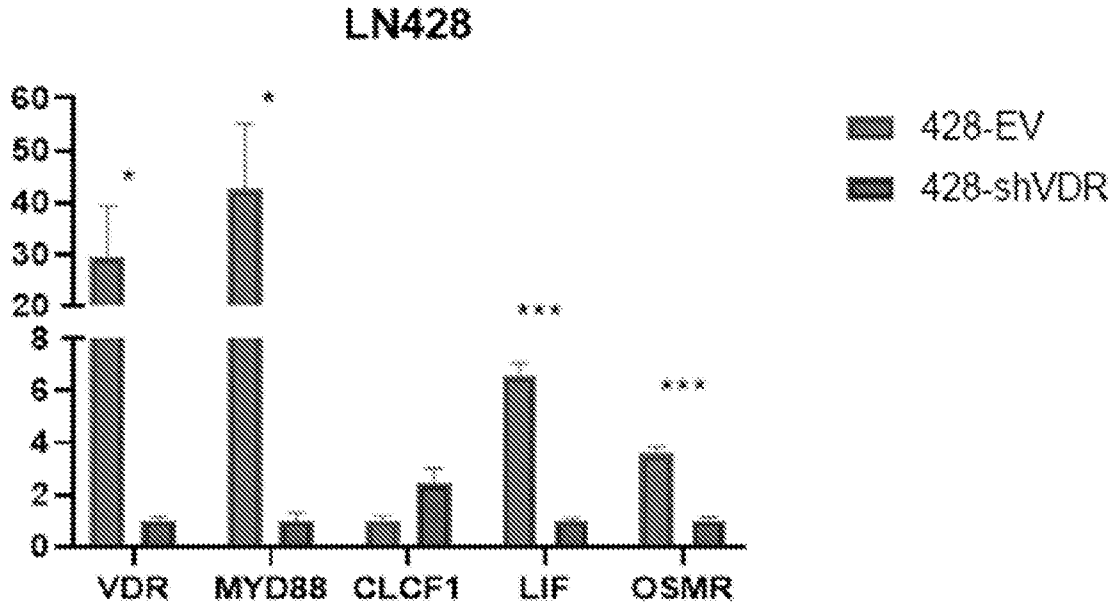


FIGURE 18C

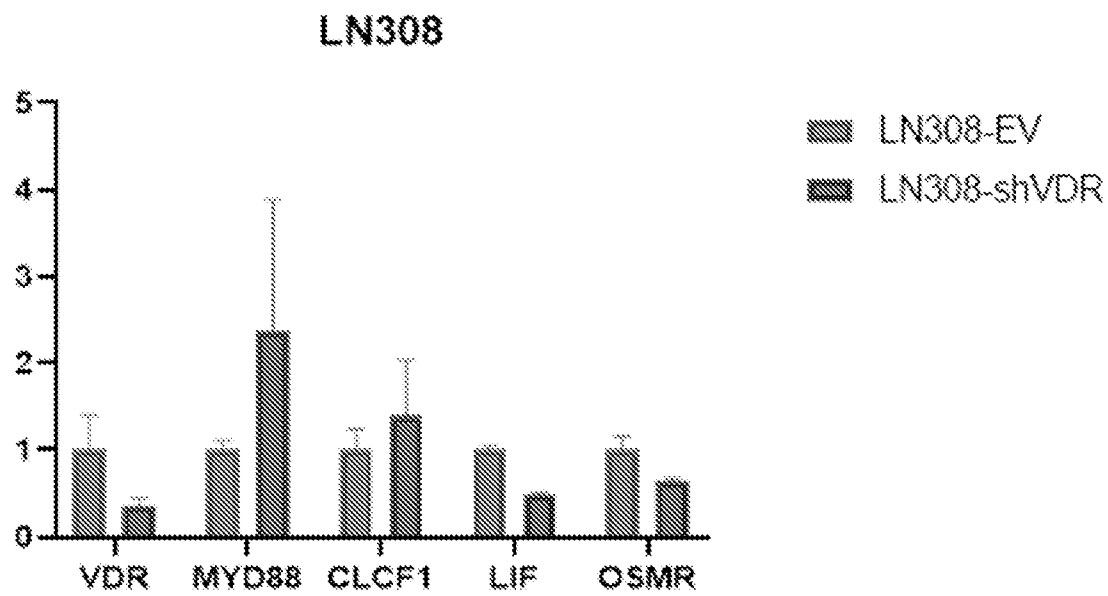


Figure 19A-B

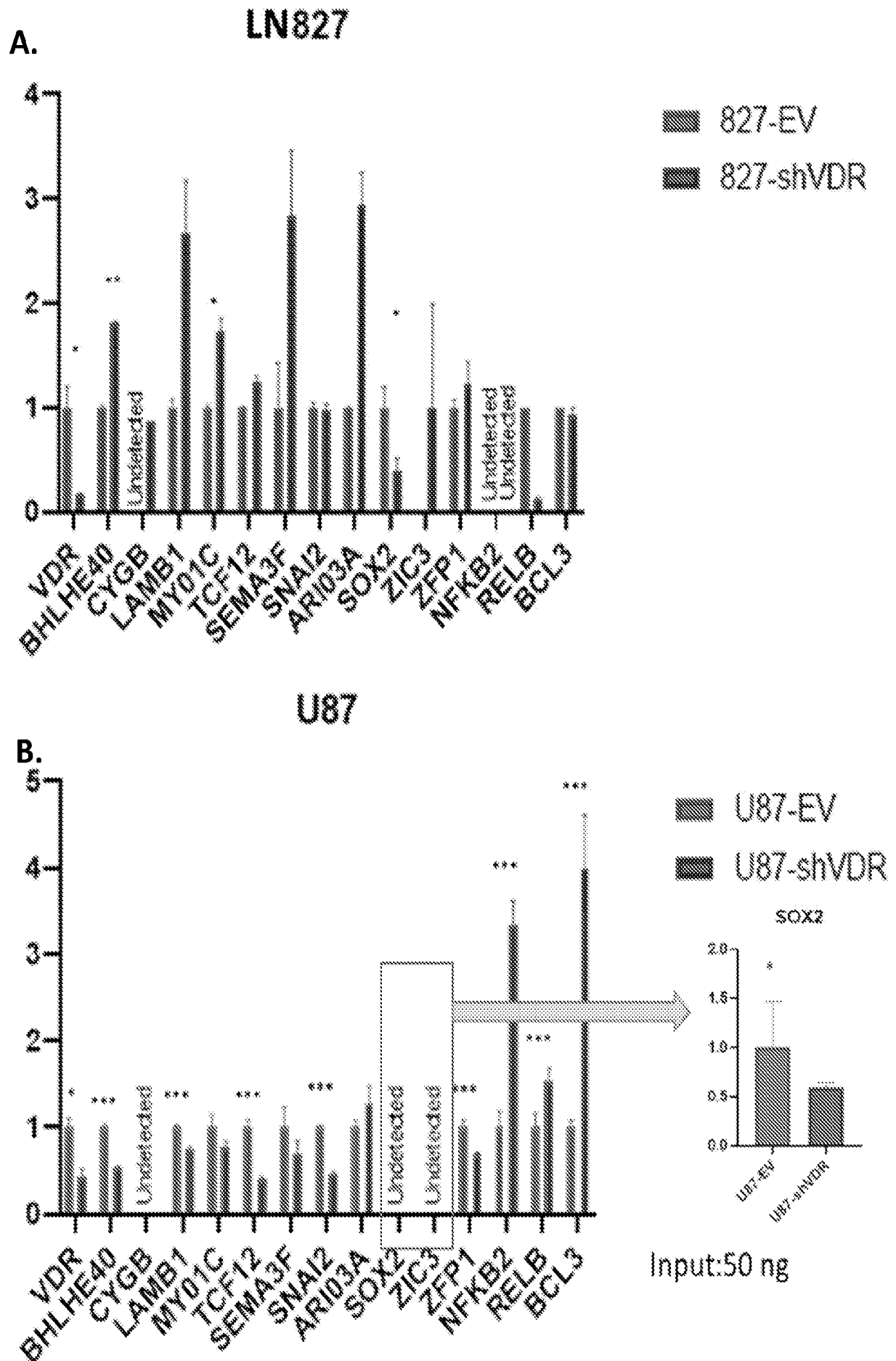


Figure 19C-D

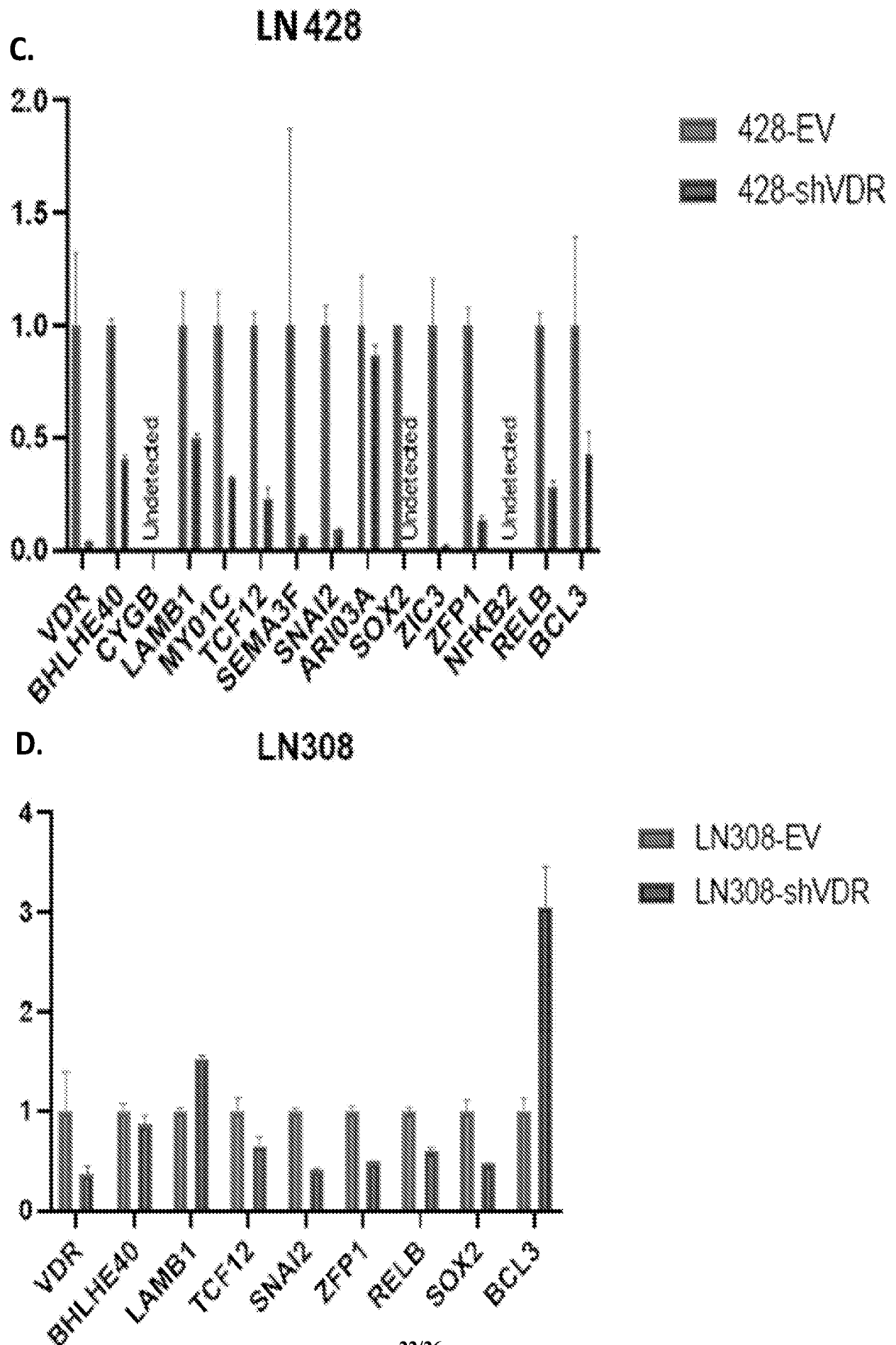


Figure 20

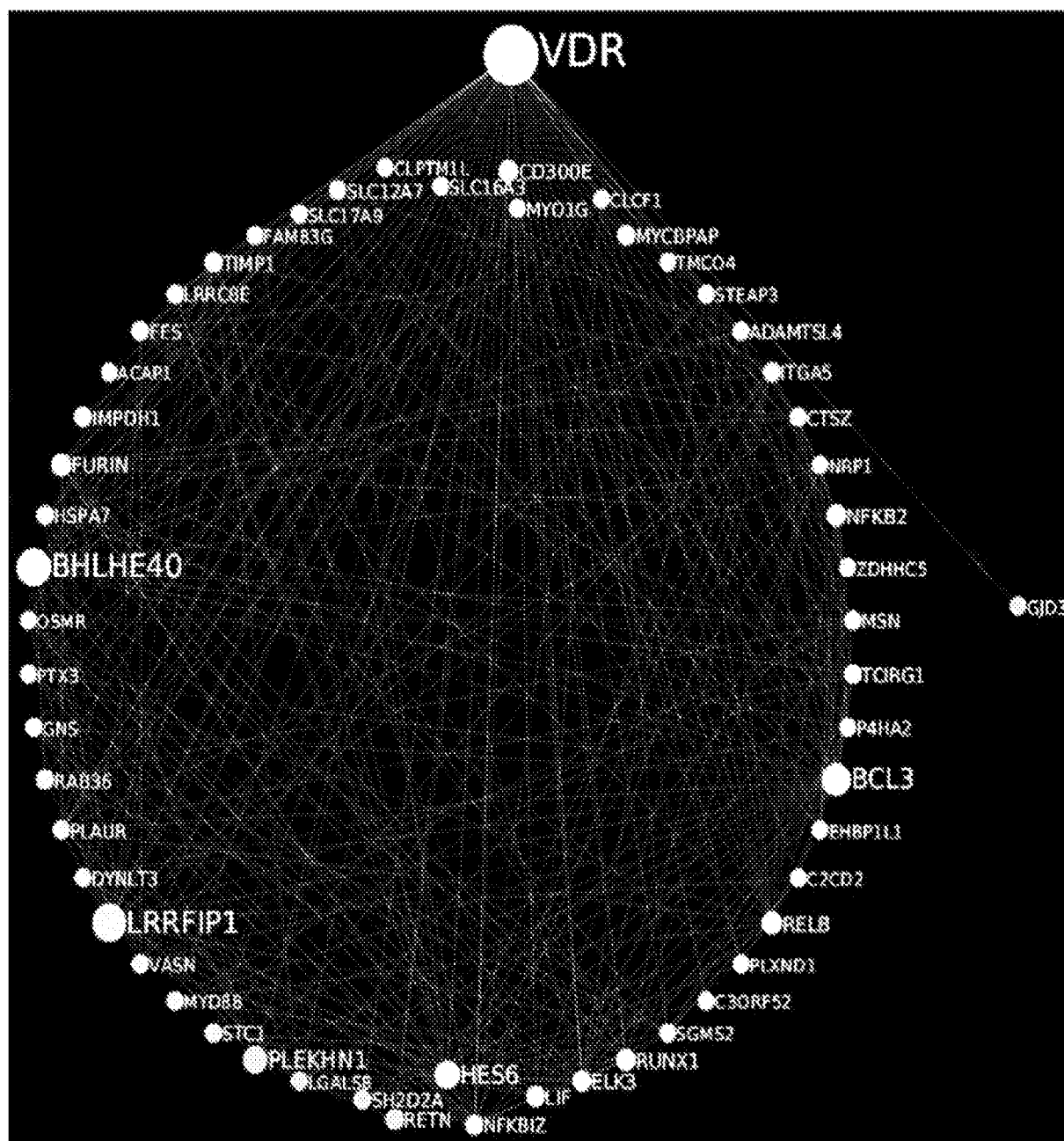


FIGURE 21A

MYBL2

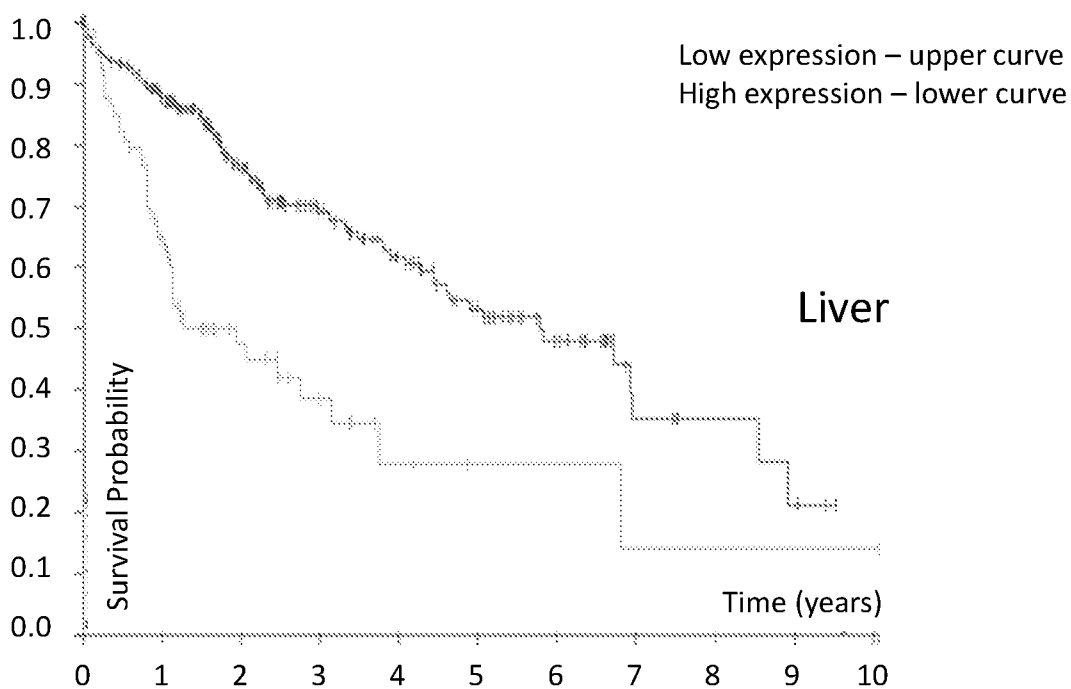
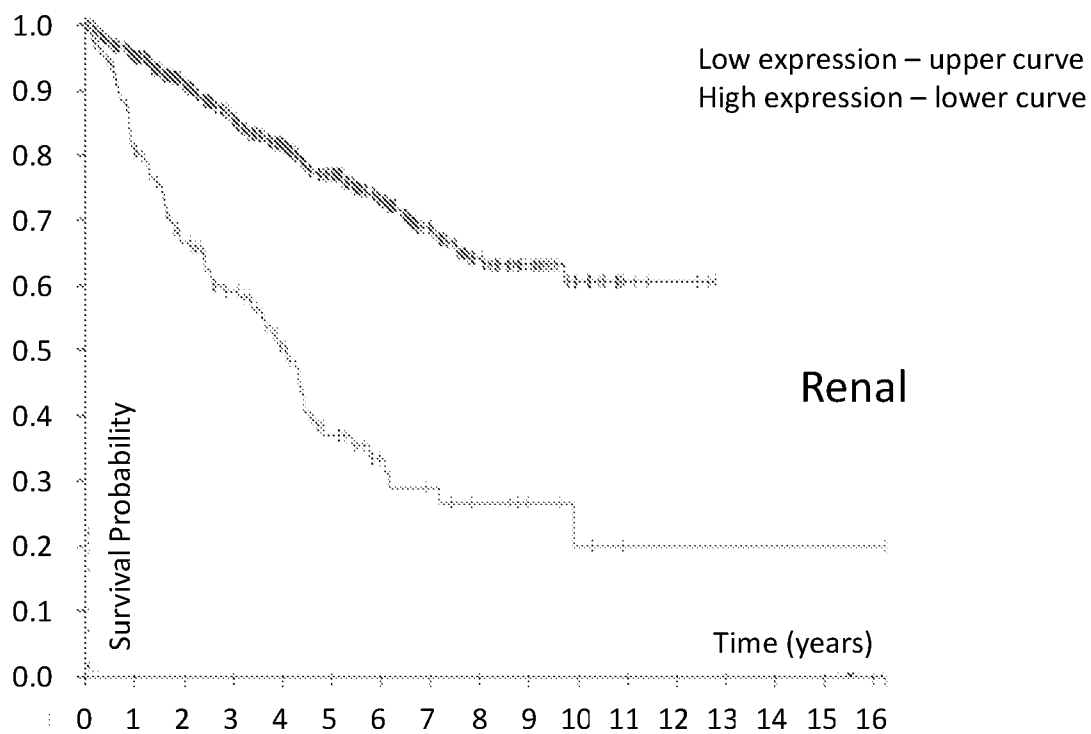


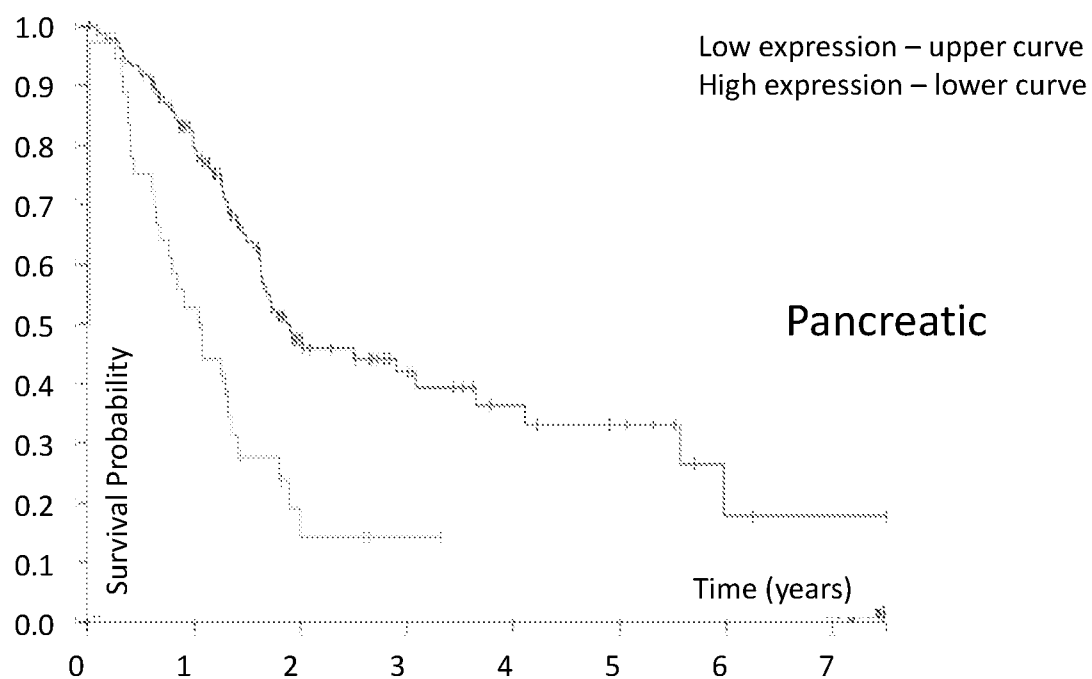
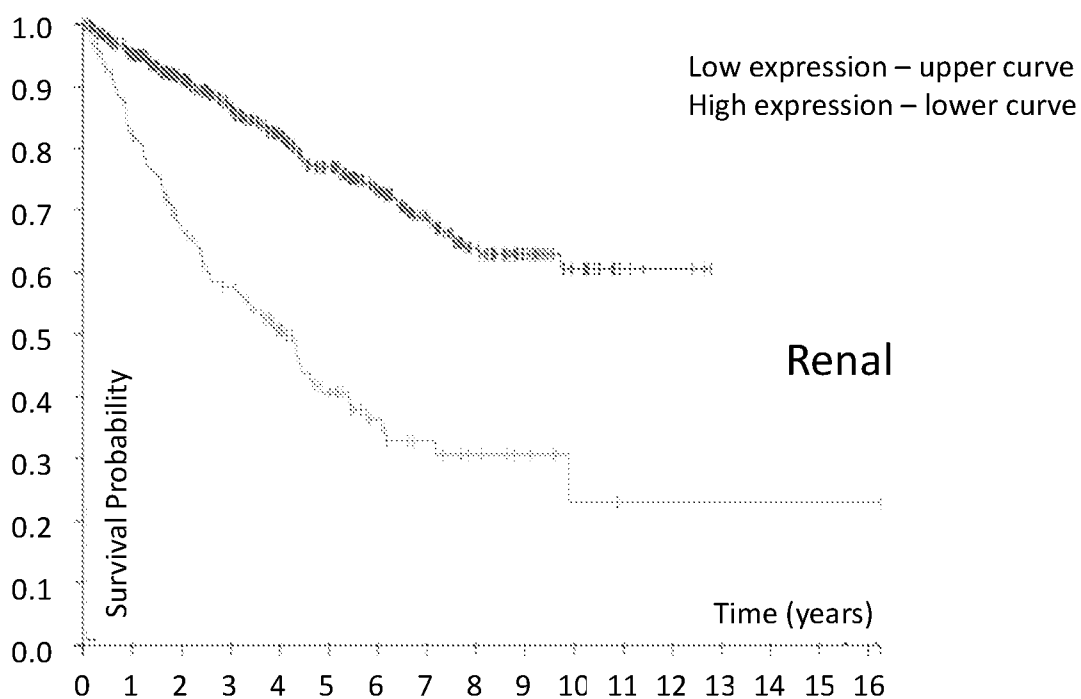
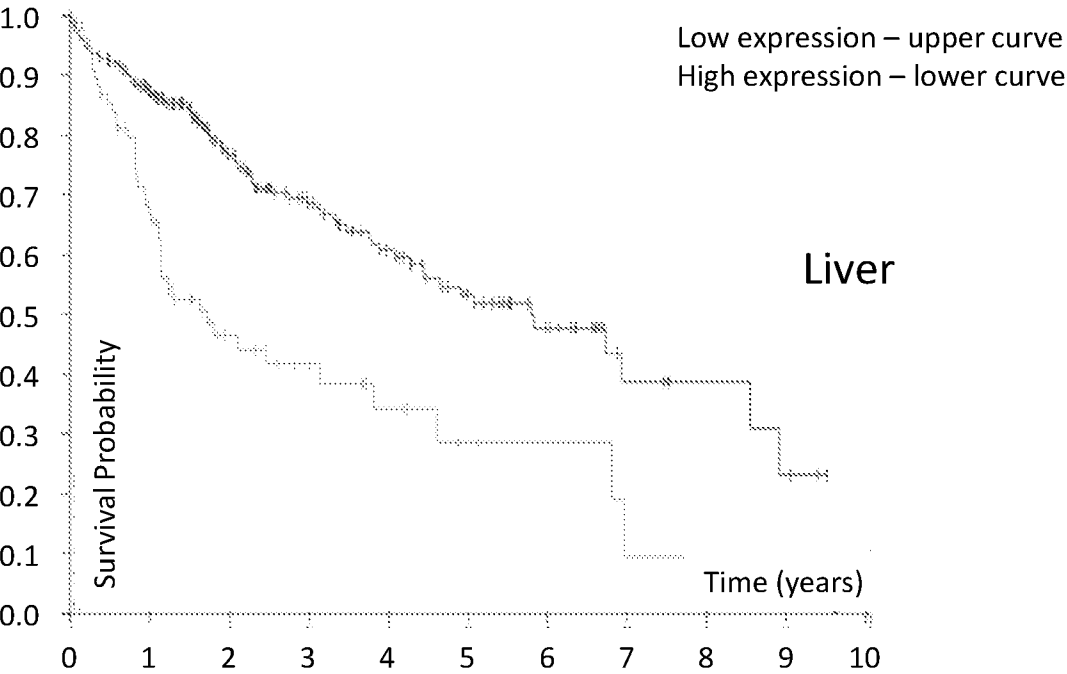
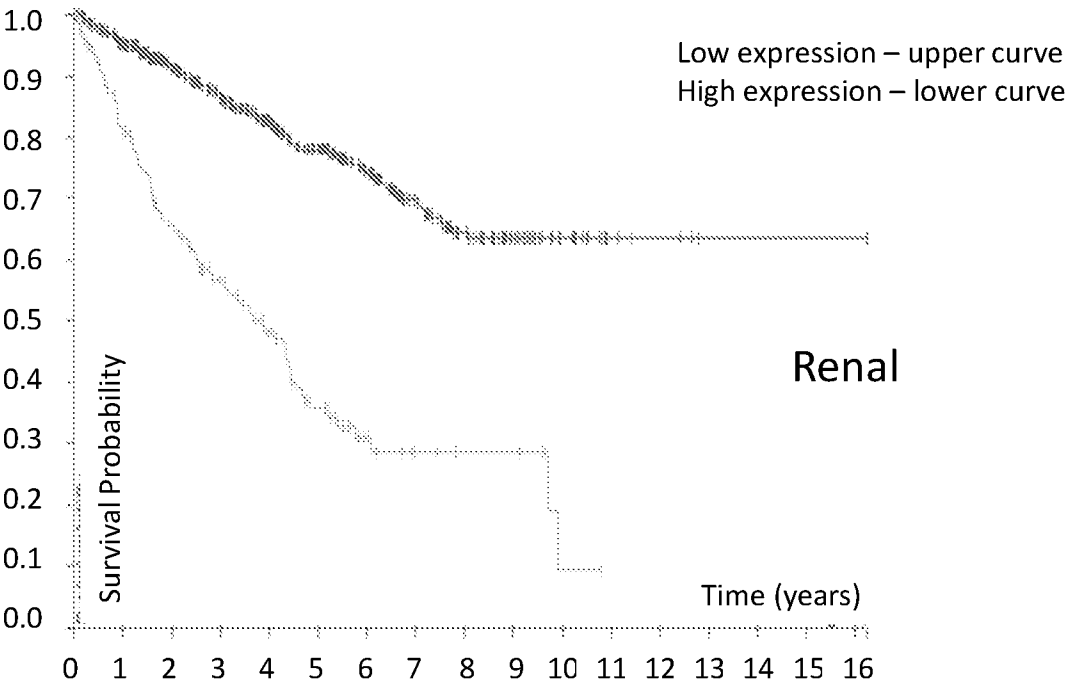
FIGURE 21B**FOXM1**

FIGURE 21C

PTTG1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/17073

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12Q 1/6886; G01N 33/574; C07K 14/47 (2020.01)

CPC - C12Q 1/6886; G01N 33/5748, 33/57438, 33/57442; C07K 14/4702

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 9,605,319 B2 (STONE et al.) 28 March 2017; column 3, lines 5-28; column 6, lines 3-20; column 11, lines 5-8; column 22, lines 6-22; column 22, lines 33-63	1-2, 24-27, 42
X	CALVISI, DF et al. Activation of v-Myb Avian Myeloblastosis Viral Oncogene Homolog-Like2 (MYBL2)-LIN9 Complex Contributes to Human Hepatocarcinogenesis and Identifies a Subset of Hepatocellular Carcinoma with Mutant p53. HEPATOLOGY. April 2011. Vol. 53, No. 4, pp. 1226-1236; abstract; page 1227; second column, third paragraph; page 1229; first column, first paragraph; figure 1A. DOI: 10.1002/hep.24174	1-2, 46
X	REN, F et al. MYBL2 is an independent prognostic marker that has tumor-promoting functions in colorectal cancer. American Journal of Cancer Research. 15 March 2015. Vol. 5, No. 4, pp. 1542-1552. abstract	1-2
P, X	SUN, S et al. Upregulation of MYBL2 independently predicts a poorer prognosis in patients with clear cell renal cell carcinoma. ONCOLOGY LETTERS. 17 February 2020. Vol. 19, pp. 2765-2772; entire document. DOI: 10.3892/ol.2020.11408	1-2, 46

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

19 May 2020 (19.05.2020)

Date of mailing of the international search report

09 JUN 2020

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/17073

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Groups I+, Claims 1, 2, 24-27, 42, 46; MYBL2 (master regulator gene)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/17073

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-30, 41-46 and MYBL2 (master regulator gene) are directed toward methods for detecting poor prognosis and predicting patient survival.

The methods will be searched to the extent they encompass a gene encompassing MYBL2 (first exemplary master regulator gene). Applicant is invited to elect additional master regulator gene(s) to be searched. Additional master regulator gene(s) sequences will be searched upon the payment of additional fees. It is believed that claims 1, 2 (in-part), 24-27 (each in-part), 42 (in-part), and 46 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass MYBL2 (master regulator gene). Applicants must specify the searchable claims that encompass any additionally elected master regulator gene(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be PTTG1 (master regulator gene).

Groups II+, Claims 31-40, 47, 48 and an immunotherapy composition targeted to MYBL2 (treatment) are directed toward methods for treating a subject with cancer.

The methods can be searched to the extent they encompass an immunotherapy composition targeted to MYBL2 (first exemplary treatment). Applicant is invited to elect additional treatment(s) with specified target(s) for each to be searched. Additional treatment(s) for specified target(s) can be searched upon the payment of additional fees. It is believed that claims 31-35 (each in-part) encompass this first named invention of Groups II+ and thus these claims can be searched with payment of a fee for the search of Groups II+, to the extent that they encompass an immunotherapy composition (treatment). Applicants must specify the searchable claims that encompass any additionally elected treatment(s) and/or specified target(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups II+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups II+ to be searched/examined. An exemplary election would be a small molecule that targets MYBL2 (treatment).

[It should be noted that, should applicant elect to pay for a search of Groups II+, any additional master regulator genes which are elected for search, and for which an additional invention search payment has been made, would be searched in both Groups I+ and II+ with the payment of a single additional invention election for each additional master regulator gene.]

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include detecting poor prognosis, not present in any of Groups II+; the special technical features of Groups II+ include an immunotherapy composition, not present in any of Groups I+.

Groups I+ and II+ share the technical features including: cancer associated with one or more master regulator genes selected from the group consisting of: VDR, HDAC7, YAP1, HDAC2, and SMAD7.

However, these shared technical features are previously disclosed by US 2011/0097423 A1 to Beauchamp et al. (hereinafter 'Beauchamp').

Beauchamp discloses cancer associated with one or more master regulator genes, including VDR (a method of predicting prognosis comprising assessing expression of genes in a colorectal cancer sample, wherein increased expression of at least 2-fold of VDR, as compared to expression in non-cancer cells indicates a poor prognosis (cancer associated with one or more master regulator genes, including VDR); paragraph [0009]).

No technical features are shared between the master regulator genes and/or cancer types of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a method for detecting poor prognosis, and predicting patient survival in a subject with cancer comprising measuring the expression of one or more genes in a sample from the subject with cancer and comparing the expression with a healthy reference sample, wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis.

However, these shared technical features are previously disclosed by Beauchamp, as above.

Beauchamp discloses a method for detecting poor prognosis (a method for predicting (detecting) poor prognosis; paragraph [0009]), and predicting patient survival (and predicting patient survival; paragraphs [0009], [0011]) in a subject with cancer (in a subject from whom a cancer sample has been obtained (in a subject with cancer); paragraph [0009]) comprising measuring the expression of one or more genes in a sample from the subject with cancer (comprising measuring the expression of one or more genes in a sample from the subject with cancer; paragraph [0009]) and comparing the expression with a healthy reference sample (comparing the expression with a non-cancerous (healthy) reference sample; paragraph [0009]), wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis (wherein increased expression in the sample from the subject with cancer relative to the healthy reference sample is an indicator of poor prognosis; paragraph [0009]).

No technical features are shared between the master regulator genes and/or treatments of Groups II+ and, accordingly, these groups lack unity a priori.

Continued Within the Next Supplemental Box

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/17073

-Continued from Box No. III Observations where unity of invention is lacking-

Groups II+ share the technical features including: a method for treating a subject with cancer comprising administering an immunotherapy composition or small molecule that targets a master regulator of poor prognosis; and a method for treating cancer in a subject with cancer comprising: (a) obtaining or having obtained a sample from the subject; (b) measuring or having measured the expression level in the sample of one or more master regulator genes; (c) comparing the expression level of the one or more master regulators in the sample with the expression level of the one or more master regulators a healthy reference sample, wherein (i) if the master regulator gene expression level is increased in the sample from the subject cancer relative to the healthy reference sample and the subject has cancer, administering a treatment to the subject.

However, these shared technical features are previously disclosed by Beauchamp, as above.

Beauchamp discloses a method for treating a subject with cancer (a method for treating a subject with cancer; paragraph [0168]) comprising administering an immunotherapy composition (comprising administering an immunotherapy composition; paragraph [0171]); and a method for treating cancer in a subject with cancer (a method for treating cancer in a subject with cancer; paragraph [0168]) comprising: (a) obtaining or having obtained a sample from the subject (obtaining or having obtained a sample from the subject; paragraph [0009]); (b) measuring or having measured the expression level in the sample of one or more master regulator genes (measuring or having measured the expression level in the sample of one or more prognosis-determining (master regulator) genes; paragraph [0009]); (c) comparing the expression level of the one or more master regulators in the sample with the expression level of the one or more master regulators a healthy reference sample (comparing the expression level of the one or more prognosis-determining genes (master regulators) in the sample with the expression level of the one or more prognosis-determining genes (master regulators) a healthy reference sample; paragraph [0009]), wherein (i) if the master regulator gene expression level is increased in the sample from the subject cancer relative to the healthy reference sample (if the prognosis-determining (master regulator) gene expression level is increased in the sample from the subject cancer relative to the healthy reference sample; paragraph [0009]) and the subject has cancer (and the subject has cancer; paragraphs [0009], [0168]), administering a treatment to the subject (administering a treatment to the subject; paragraphs [0168], [0171]).

Since none of the special technical features of the Groups I+ and II+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Beauchamp reference, unity of invention is lacking.