Original article

A Global Risk Score (GRS) to simultaneously predict early and late tumor recurrence risk after resection of hepatocellular carcinoma

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Supplementary data

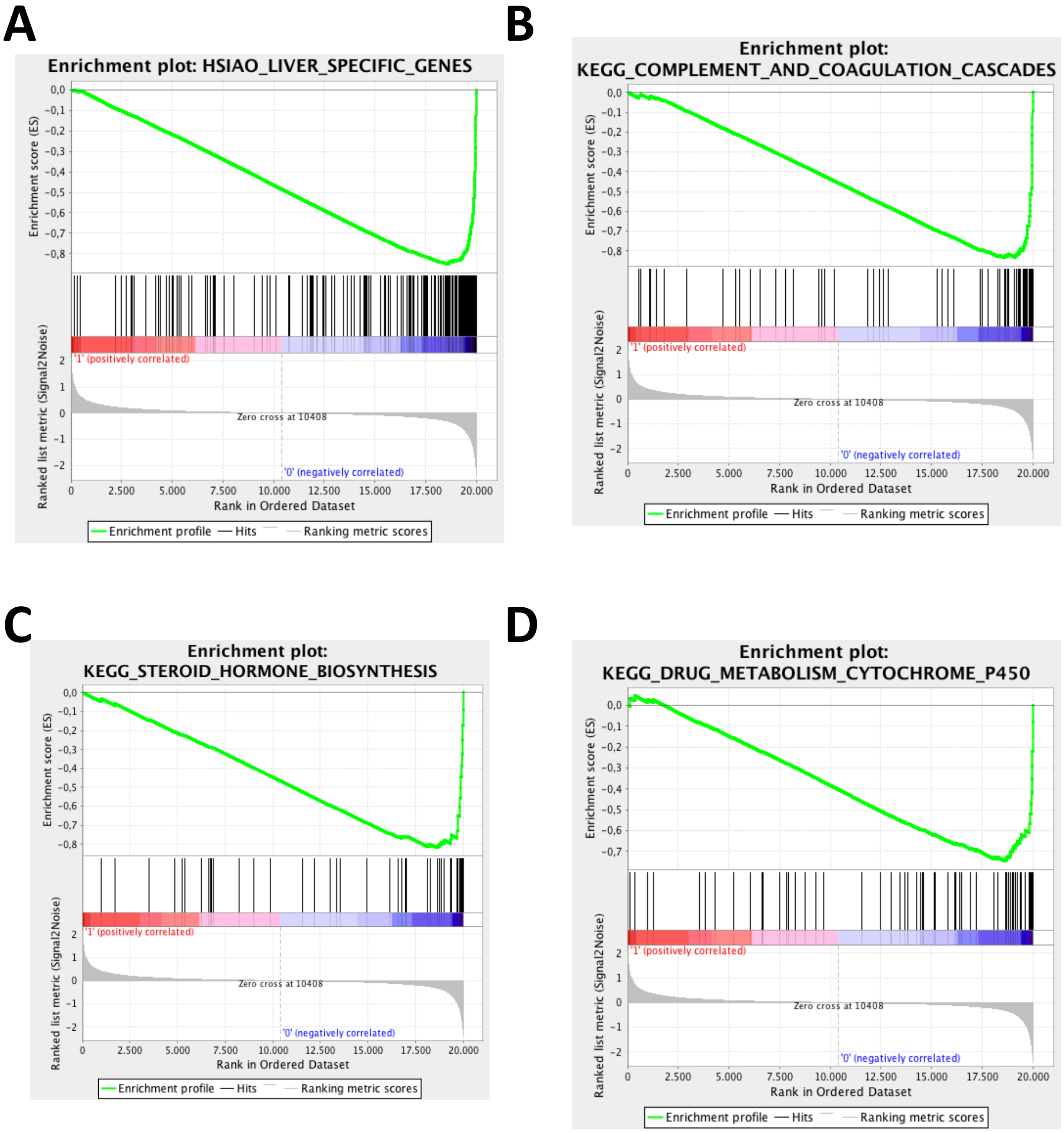
Suppl Fig. 1. **Selected top-ranked enrichment plots using Gene Set Enrichment Analysis of the differentially expressed genes between HepG2S1 and HepG2 cells.** A-D: Loss of hepatocyte specific markers and functions in HepG2S1 cells compared to HepG2. E-G: Enrichment of poor prognostic molecular subclasses of HCC in HepG2S1 cells (see also supplementary table 1).

Suppl Fig. 2. **Overlap between the Global Recurrence Score and the most relevant published signatures derived from the non-tumoral surrounding liver**: the hepatic injury signature of 233 genes (Kim et al. [14]) and the 186 gene signature (Hoshida et al. [13])

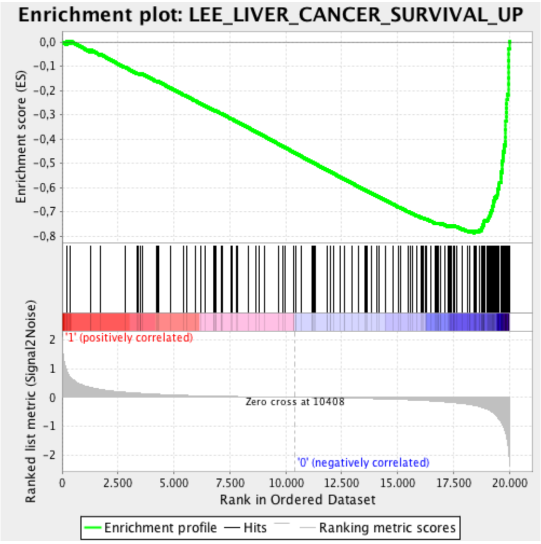
Supplementary table 1. Overview off all significant gene sets enriched by the Gene Set Enrichment Analysis using all gene sets in the MSig database.

Supplementary table 2. Uni- and multivariable Cox regression analysis on known clinical variables in the NCI data set. Global Risk Score groups: GRS I = low GRS in tumor and liver; GRS II = low GRS in tumor, high in liver; GRS III = high GRS in tumor, low in liver; GRS IV = high GRS in tumor and liver.

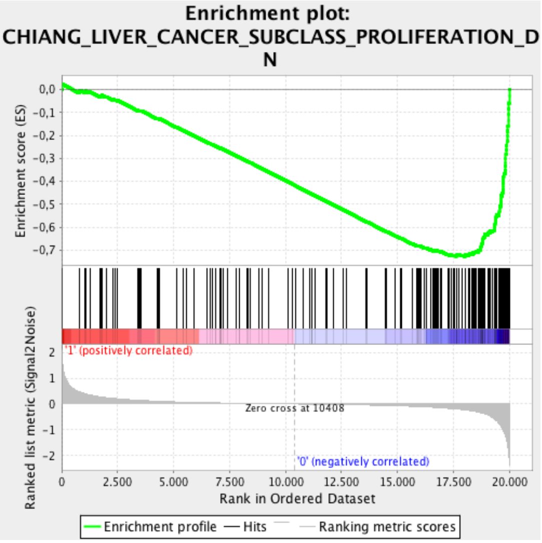
Supplementary figure 1


A
Enrichment plot: HSIAO_LIVER_SPECIFIC_GENES
Enrichment score (ES)
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
Ranked list metric (Signal2Noise)
'1' (positively correlated)
Zero cross at 10408
'0' (negatively correlated)
2
1
0
-1
-2
0
2.500
5.000
7.500
10.000
12.500
15.000
17.500
20.000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores
B
Enrichment plot: KEGG_COMPLEMENT_AND_COAGULATION_CASCADES
Enrichment score (ES)
Ranked list metric (Signal2Noise)
'1' (positively correlated)
Zero cross at 10408
'0' (negatively correlated)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores
C
Enrichment plot: KEGG_STEROID_HORMONE_BIOSYNTHESIS
Enrichment score (ES)
Ranked list metric (Signal2Noise)
'1' (positively correlated)
Zero cross at 10408
'0' (negatively correlated)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores
D
Enrichment plot: KEGG_DRUG_METABOLISM_CYTOCHROME_P450
Enrichment score (ES)
-0,7
Ranked list metric (Signal2Noise)
'1' (positively correlated)
Zero cross at 10408
'0' (negatively correlated)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

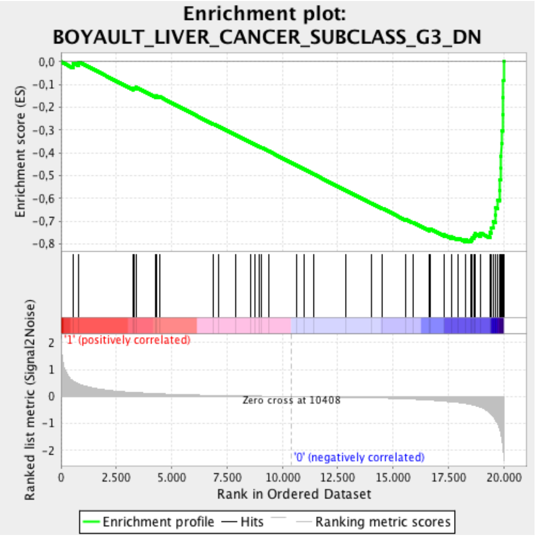
E


Enrichment plot: LEE_LIVER_CANCER_SURVIVAL_UP
Enrichment score (ES)
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
Ranked list metric (Signal2Noise)
'1' (positively correlated)
2
1
0
-1
-2
Zero cross at 10408
'0' (negatively correlated)
0
2.500
5.000
7.500
10.000
12.500
15.000
17.500
20.000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

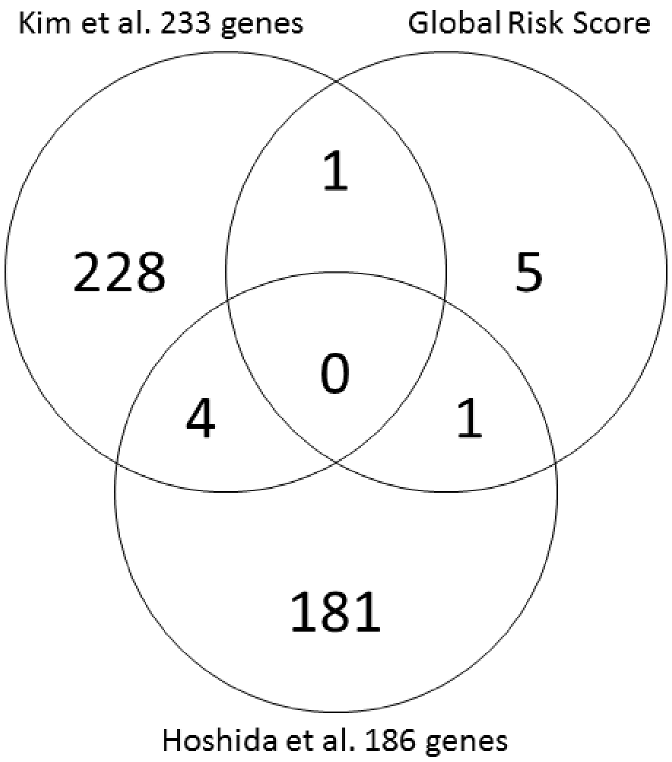
F


Enrichment plot:
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_DN
Enrichment score (ES)
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
Ranked list metric (Signal2Noise)
'1' (positively correlated)
2
1
0
-1
-2
Zero cross at 10408
'0' (negatively correlated)
0
2.500
5.000
7.500
10.000
12.500
15.000
17.500
20.000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

G


Enrichment plot:
BOYAULT_LIVER_CANCER_SUBCLASS_G3_DN
Enrichment score (ES)
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
-0,8
Ranked list metric (Signal2Noise)
'1' (positively correlated)
2
1
0
-1
-2
Zero cross at 10408
'0' (negatively correlated)
0
2.500
5.000
7.500
10.000
12.500
15.000
17.500
20.000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

Supplementary figure 2



Gene Signatures	# genes	Genes
Global Risk Score AND Kim et al. 233 genes	1	F11
Hoshida et al. 186 genes AND Kim et al. 233 genes	4	IER3 SERPINB8 TSC22D2 DUSP5
Global Risk Score AND Hoshida et al. 186 genes	1	GCKR
Kim et al. 233 genes	228	EMP1 B3GNT5 RGS2 ZNF295 LOC151438 LOC387763 CDC37L1 SERPINE1 VCAN ZFP62 TGIF1 FOSL2 NUFIP2 CDK6 ZNF84 CEBPD PPP1R15A LOC254128 C14orf43 TM4SF1 H3F3A JUND ZFP36 NHSL1 C2orf68 ZC3H12A PRKAB2 NIP7 RTP3 TIA1 LOC653506 SOD2 PTPN1 WWC1 C14orf139 JMJD3 MREG IRF1 LDLR CDKN1A PRUNE MPHOSPH9 SLC2A14 KLF2 KLF15 SGK1 SDC4 GIMAP8 TBC1D13 SPSB1 PLK2 HSPA1B LOC729082 FAM168A USP36 TSC22D1 KIAA1949 NAMPT ERCC4 MAP1LC3B RPL37A NOLC1 CCNL1 DUSP6 TGFB3 C9orf21 SERTAD1 C5AR1 SNIP1 TNFRSF1A PTPRJ C6orf130 GPR183 ADM CCL20 EPHA2 ADAMTS1 JMJD6 TJP2 MXD1 IDH1 PLK3 CBX1 ATF3 GLIPR2 ITPKC YRDC PTPRF ADO STK17A BCL3 ZBTB44 SERPINB9 RIPK4 FAM46C RP5-1022P6.2 EIF4A1 BAG3 TNKS C13orf15 RSC1A1 CCL4 FAM82A1 ARL5B DCUN1D1 FLJ36031 PURA F11R RLIM PLEKHO2 SERPINB1 FAM46A ZNF226 ALB C16orf70 JUNB PIM3 TIPARP IL15RA PNRC1 MDM1 KIAA0146 SRGN CSNK1D SLC2A3 ZKSCAN1 MAP3K14 SLC40A1 AKAP12 MAFK RALGDS LRRC37A2 FCN1 NCOA7 BCL6 ELF3 C14orf132 G0S2 TRAF4 EHD4 SLC20A1 AGPAT3 GRAMD4 MAP1LC3B2 CDC42EP1 CASP4 B4GALT5 CYP4A11 ICAM1 MYC THBS1 JUN PELI1 DHODH SOCS3 MAPRE1 JOSD1 PHLDA1 ETS2 PLAUR MAP2K3 RND1 ARID5B ARL4C CMTM4 ZNF573 NCRNA00087 TNFRSF12A GNA13 C5orf54 MAFF ZNF658 SGMS2 TNFAIP3 C5orf53 UBE4B CCRN4L MCL1 CBR4 KRT18 RASD1 TNFRSF10D FOSL1 SOCS1 BHLHE40 TMEM49 LOC100130097 PGPEP1 SPRY2 C7orf40 ZNF260 IL1RL1 CCDC93 NXT1 DDX21 NOP58 BTG3 PHLDA2 LOC400657 RIPK2 CREM TEF C15orf40 ZNF410 HIF1AN WEE1 NR2F2 WTAP ARHGEF5 C14orf101 GADD45B C1orf25 ZFP36L2 AXUD1 IL1RN ODC1 S100A10 COQ10B MYADM PIM1 MS4A6A ZBTB43 PPRC1 SENP5 BIRC3 FPR1 FAM60A KLHDC10
Global Risk Score	5	OXCT1 COL4A2 LRRC16A ATP11C PCSK6
Hoshida et al. 186 genes	181	HMGCR FSHB TM7SF2 ERCC5 SDHC CCL21 NCAPH LPP SLC37A4 PLG ART1 ACOT2 ZNF185 ATP6AP2 COL4A1 RNASE1 CXCR4 CCDC6 POLRMT NOL7 IGF1 SERPINB2 NENF CTNND2 ADD3 ANXA1 SFRS2 MMP7 TRIO PFKFB1 PON3 RBM34 PTPN18 AKAP13 HMG20B C5 EGF ANKRD46 HAAO DAB2 TRAF6 RFC2 ATP5D SLC7A1 PLCG2 LIPC CUTL2 EIF2B1 CPOX TTR PCYT2 IMPA1 RPS6KA5 ITGA9 CHSY1 FAM129A INSM1 DAD1 CPN1 RAD52 SLIT3 CHERP SP100 ACSM3 GSTM1 TAF1C COL6A3 LOXL2 HRASLS3 ANXA3 PPP1R1A TNK2 CYP2B6 ADRA2B ASAHL SC5DL PCK1 MGC29506 GHR C8B CCL19 C4BPB GCGR WIPF1 ADH6 USP14 MSH6 EMP2 IGFBP6 PSMB3 CREB1 TGFB1I1 TDO2 GJB1 SH3GL2 BRP44 IQGAP1 TXN2 ADH5 EMD DDR1 GBA PMM1 PODXL NFKB2 GPX2 BCL2 XPA PKLR AKR1D1 GRM5 CYB5A PRKG2 ARF4 AKR1A1 IFI30 AP1B1 PROS1 SREBF2 EDG4 NARS2 DOCK4 CPA3 CCT8 ELOVL2 F9 NTS PLCB3 AEBP1 PIGK FMO1 FBN1 DLGAP4 CALCR HMGCL AR SLC4A4 CTBS SCG5 HSPE1 KCNJ3 EPM2AIP1 ATP4B AOX1 ALAS1 TMEM97 SELENBP1 EPHA4 ALDH9A1 VPS41 BAIAP2 GGCX WDR23 AARS TCF4 SNX10 ATP2C1 HABP2 PTPN2 DST COL16A1 SLC12A2 ABLIM1 HDAC9 CD48 SSFA2 NOS2A ZBTB17 C9 ZER1 TEAD4 GRK4 PSMB9 ICK RRM1 TIMM8A KRT7 ACTR2 SUCLG1 RLF FILIP1L

Supplementary table 1. Overview off all significant gene sets enriched by the Gene Set Enrichment Analysis using all gene sets in the MSig database.

NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val	RANK AT MAX	LEADING EDGE
HSIAO_LIVER_SPECIFIC_GENES	240	-0,85035366	-2,838637	0	0	0	1377	tags=53%, list=7%, signal=56%
GNF2_HPX	133	-0,8692438	-2,7082028	0	0	0	1420	tags=62%, list=7%, signal=66%
GNF2_HPN	131	-0,85049784	-2,647056	0	0	0	1420	tags=58%, list=7%, signal=62%
GNF2_LCAT	122	-0,85488456	-2,642469	0	0	0	1420	tags=60%, list=7%, signal=64%
GNF2_GSTM1	107	-0,85367393	-2,613708	0	0	0	1498	tags=60%, list=7%, signal=64%
GNF2_TST	102	-0,847545	-2,5667343	0	0	0	1420	tags=58%, list=7%, signal=62%
CAR_HPX	73	-0,88122684	-2,5552695	0	0	0	687	tags=55%, list=3%, signal=57%
LEE_LIVER_CANCER_SURVIVAL_UP	176	-0,78775233	-2,553504	0	0	0	1566	tags=43%, list=8%, signal=46%
OHGUCHI_LIVER_HNF4A_TARGETS_DN	145	-0,7831885	-2,4633949	0	0	0	1420	tags=43%, list=7%, signal=46%
MODULE_24	442	-0,6853321	-2,4168966	0	0	0	2080	tags=38%, list=10%, signal=41%
CAIRO_LIVER_DEVELOPMENT_DN	222	-0,72469515	-2,4024942	0	0	0	1399	tags=37%, list=7%, signal=39%
GNF2_CEBPA	64	-0,84795237	-2,3736157	0	0	0	1402	tags=53%, list=7%, signal=57%
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_DN	174	-0,7281584	-2,3703747	0	0	0	1994	tags=45%, list=10%, signal=49%
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	68	-0,83506405	-2,3547575	0	0	0	1377	tags=51%, list=7%, signal=55%
WOO_LIVER_CANCER_RECURRENCE_DN	79	-0,8104265	-2,3431206	0	0	0	1691	tags=54%, list=8%, signal=59%
CAR_IGFBP1	57	-0,8416861	-2,335342	0	0	0	1372	tags=56%, list=7%, signal=60%
KEGG_RETINOL_METABOLISM	56	-0,8152509	-2,2632332	0	0	0	1346	tags=32%, list=7%, signal=34%
SERVITJA_ISLET_HNF1A_TARGETS_DN	105	-0,7348611	-2,2517767	0	0	0	1399	tags=35%, list=7%, signal=38%
GNF2_CYP2B6	49	-0,8281264	-2,2435067	0	0	0	1174	tags=45%, list=6%, signal=48%
SERVITJA_LIVER_HNF1A_TARGETS_DN	154	-0,7126978	-2,2403612	0	0	0	1526	tags=37%, list=8%, signal=40%
V$HNF1_Q6	239	-0,6717297	-2,2364502	0	0	0	1202	tags=24%, list=6%, signal=26%
HOSHIDA_LIVER_CANCER_SUBCLASS_S3	263	-0,65341055	-2,2108023	0	0	0	1816	tags=36%, list=9%, signal=39%
SU_LIVER	55	-0,80610263	-2,2042704	0	0	0	1372	tags=40%, list=7%, signal=43%
REACTOME_FORMATION_OF_FIBRIN_CLOT_CLOTTING_CASCADE	32	-0,87470883	-2,199526	0	0	0	719	tags=44%, list=4%, signal=45%
KEGG_STEROID_HORMONE_BIOSYNTHESIS	47	-0,820295	-2,1754558	0	0	0	1346	tags=40%, list=7%, signal=43%
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	64	-0,74764746	-2,1468518	0	0	0	1346	tags=34%, list=7%, signal=37%
REACTOME_PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS	69	-0,7481085	-2,137083	0	0	0	1472	tags=30%, list=7%, signal=33%
REACTOME_BIOLOGICAL_OXIDATIONS	129	-0,6843673	-2,134809	0	0	0	1784	tags=33%, list=9%, signal=36%
CHR4Q13	49	-0,7957459	-2,1317494	0	0	0	1381	tags=22%, list=7%, signal=24%
BOYAULT_LIVER_CANCER_SUBCLASS_G3_DN	51	-0,7929626	-2,1311717	0	0	0	1498	tags=41%, list=7%, signal=44%
CHIANG_LIVER_CANCER_SUBCLASS_CTNNB1_UP	168	-0,6603729	-2,1146398	0	0	0	1691	tags=38%, list=8%, signal=41%
MODULE_172	94	-0,7087767	-2,11412	0	0	0	1375	tags=38%, list=7%, signal=41%
LEE_LIVER_CANCER_ACOX1_DN	63	-0,74582374	-2,1113396	0	0	0	2020	tags=49%, list=10%, signal=55%
SUMI_HNF4A_TARGETS	31	-0,8465868	-2,100197	0	2,50E-05	0,001	761	tags=55%, list=4%, signal=57%
REACTOME_LIPOPROTEIN_METABOLISM	28	-0,85197884	-2,0970247	0	2,43E-05	0,001	383	tags=39%, list=2%, signal=40%
COULOUARN_TEMPORAL_TGFB1_SIGNATURE_DN	134	-0,6638792	-2,0861661	0	2,36E-05	0,001	2482	tags=42%, list=12%, signal=47%
MODULE_209	87	-0,6989485	-2,0854492	0	2,30E-05	0,001	1375	tags=39%, list=7%, signal=42%
MODULE_40	81	-0,70752865	-2,0816782	0	2,24E-05	0,001	2116	tags=36%, list=11%, signal=40%
REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT	27	-0,85083514	-2,069728	0	4,39E-05	0,002	1473	tags=41%, list=7%, signal=44%
LEE_LIVER_CANCER_CIPROFIBRATE_DN	64	-0,7315983	-2,0508535	0	8,56E-05	0,004	1526	tags=38%, list=8%, signal=40%
LUCAS_HNF4A_TARGETS_UP	58	-0,73900163	-2,049681	0	8,36E-05	0,004	1368	tags=40%, list=7%, signal=42%
ACEVEDO_LIVER_TUMOR_VS_NORMAL_ADJACENT_TISSUE_DN	263	-0,6109878	-2,0446548	0	8,16E-05	0,004	3132	tags=40%, list=16%, signal=46%
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	62	-0,7392671	-2,042973	0	7,97E-05	0,004	1346	tags=34%, list=7%, signal=36%
BLOOD_COAGULATION	42	-0,7778204	-2,0412366	0	7,79E-05	0,004	2081	tags=40%, list=10%, signal=45%

REACTOME_CYTOCHROME_P450_ARRANGED_BY_SUBSTRATE_TYPE	50	-0,7589615	-2,0384402	0	9,52E-05	0,005	1472	tags=32%, list=7%, signal=34%
CAVARD_LIVER_CANCER_MALIGNANT_VS_BENIGN	30	-0,8342905	-2,0329576	0	9,31E-05	0,005	429	tags=40%, list=2%, signal=41%
HALLMARK_COAGULATION	138	-0,6461675	-2,0317268	0	9,12E-05	0,005	1633	tags=40%, list=8%, signal=43%
CHIANG_LIVER_CANCER_SUBCLASS_INTERFERON_DN	50	-0,7488816	-2,0315318	0	8,93E-05	0,005	1138	tags=44%, list=6%, signal=47%
COAGULATION	43	-0,7723051	-2,0241187	0	1,40E-04	0,008	1498	tags=35%, list=7%, signal=38%
ZHAN_MULTIPLE_MYELOMA_DN	41	-0,78584445	-2,0234628	0	1,37E-04	0,008	1423	tags=27%, list=7%, signal=29%
MODULE_109	37	-0,7932153	-2,021432	0	1,34E-04	0,008	799	tags=38%, list=4%, signal=39%
EXTRACELLULAR_SPACE	238	-0,6089458	-2,020942	0	1,48E-04	0,009	1468	tags=20%, list=7%, signal=22%
LEE_LIVER_CANCER_DENA_DN	73	-0,69706917	-2,0152638	0	1,45E-04	0,009	1363	tags=34%, list=7%, signal=37%
KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG	23	-0,8681525	-2,0148342	0	1,42E-04	0,009	1473	tags=52%, list=7%, signal=56%
CHIANG_LIVER_CANCER_SUBCLASS_UNANNOTATED_UP	79	-0,68702763	-2,0122488	0	1,40E-04	0,009	2493	tags=33%, list=12%, signal=37%
CHRYQ11	24	-0,8622386	-2,0116878	0	1,37E-04	0,009	900	tags=25%, list=4%, signal=26%
STEROID_METABOLIC_PROCESS	71	-0,7035984	-2,006378	0	1,35E-04	0,009	1896	tags=37%, list=9%, signal=40%
SERINE_HYDROLASE_ACTIVITY	45	-0,74967754	-2,0057976	0	1,33E-04	0,009	1727	tags=31%, list=9%, signal=34%
REACTOME_PLATELET_AGGREGATION_PLUG_FORMATION	36	-0,7812874	-1,9960127	0	1,45E-04	0,01	581	tags=19%, list=3%, signal=20%
HEMOSTASIS	47	-0,7538902	-1,983364	0	2,00E-04	0,014	2197	tags=38%, list=11%, signal=43%
BIOCARTA_INTRINSIC_PATHWAY	23	-0,83486015	-1,9826647	0	1,96E-04	0,014	284	tags=48%, list=1%, signal=48%
LEE_LIVER_CANCER_MYC_TGFA_DN	64	-0,7110937	-1,9777722	0	2,62E-04	0,019	1424	tags=38%, list=7%, signal=40%
SERINE_TYPE_PEPTIDASE_ACTIVITY	44	-0,749839	-1,9701627	0	2,85E-04	0,021	1727	tags=32%, list=9%, signal=35%
YAMASHITA_LIVER_CANCER_STEM_CELL_DN	76	-0,6837091	-1,9698523	0	2,81E-04	0,021	1802	tags=50%, list=9%, signal=55%
MODULE_280	44	-0,74700236	-1,9672607	0	2,90E-04	0,022	1288	tags=27%, list=6%, signal=29%
IIZUKA_LIVER_CANCER_PROGRESSION_G2_G3_UP	27	-0,80951446	-1,9616258	0	3,49E-04	0,027	1527	tags=44%, list=8%, signal=48%
ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_DN	49	-0,71906453	-1,9585825	0	4,08E-04	0,032	1529	tags=33%, list=8%, signal=35%
CAHOY_ASTROCYTIC	99	-0,6530977	-1,958336	0	4,15E-04	0,033	1194	tags=22%, list=6%, signal=24%
ESC_J1_UP_LATE.V1_UP	176	-0,6087403	-1,9563848	0	4,34E-04	0,035	1446	tags=32%, list=7%, signal=35%
MODULE_93	179	-0,61053425	-1,9561827	0	4,27E-04	0,035	1476	tags=21%, list=7%, signal=22%
CHR14Q11	132	-0,62754583	-1,9557534	0	4,34E-04	0,036	3787	tags=43%, list=19%, signal=53%
ESC_V6.5_UP_LATE.V1_UP	171	-0,6002555	-1,9555494	0	4,27E-04	0,036	754	tags=22%, list=4%, signal=22%
MODULE_235	81	-0,66868013	-1,9504397	0	4,80E-04	0,041	2288	tags=38%, list=11%, signal=43%
MODULE_107	77	-0,6676715	-1,9480317	0	5,19E-04	0,045	1348	tags=36%, list=7%, signal=39%
EXOPEPTIDASE_ACTIVITY	31	-0,7869064	-1,9471925	0	5,35E-04	0,047	1616	tags=29%, list=8%, signal=32%
KONDO_PROSTATE_CANCER_WITH_H3K27ME3	192	-0,59839565	-1,9471629	0	5,28E-04	0,047	1316	tags=11%, list=7%, signal=12%
DUTERTRE_ESTRADIOL_RESPONSE_24HR_UP	315	0,6917961	2,486304	0	0	0	2372	tags=60%, list=12%, signal=67%
ROSTY_CERVICAL_CANCER_PROLIFERATION_CLUSTER	139	0,7624695	2,4852664	0	0	0	2724	tags=70%, list=14%, signal=80%
GSE15750_DAY6_VS_DAY10_TRAF6KO_EFF_CD8_TCELL_UP	191	0,7232829	2,473114	0	0	0	2819	tags=61%, list=14%, signal=71%
GNF2_CCNA2	67	0,8343797	2,4730728	0	0	0	2369	tags=79%, list=12%, signal=89%
SOTIRIOU_BREAST_CANCER_GRADE_1_VS_3_UP	147	0,7584709	2,4729047	0	0	0	2935	tags=64%, list=15%, signal=74%
CHANG_CYCLING_GENES	141	0,73290133	2,4378781	0	0	0	2636	tags=62%, list=13%, signal=71%
GSE15750_DAY6_VS_DAY10_EFF_CD8_TCELL_UP	193	0,70652604	2,4132524	0	0	0	2280	tags=54%, list=11%, signal=61%
KONG_E2F3_TARGETS	95	0,7787713	2,4023178	0	0	0	2461	tags=65%, list=12%, signal=74%
GNF2_RRM1	87	0,7796591	2,3969138	0	0	0	2233	tags=59%, list=11%, signal=66%
GNF2_PCNA	67	0,81516105	2,387705	0	0	0	2369	tags=75%, list=12%, signal=84%
PYEON_CANCER_HEAD_AND_NECK_VS_CERVICAL_UP	173	0,7009693	2,3736532	0	0	0	2778	tags=54%, list=14%, signal=62%
HALLMARK_E2F_TARGETS	191	0,69841295	2,3475907	0	0	0	3721	tags=64%, list=19%, signal=78%
ZHANG_TLX_TARGETS_UP	84	0,75309104	2,3388782	0	0	0	2291	tags=70%, list=11%, signal=79%
GNF2_SMC4L1	82	0,7701622	2,3347073	0	0	0	3069	tags=65%, list=15%, signal=76%
GNF2_CENPF	61	0,8072771	2,3295014	0	0	0	3069	tags=80%, list=15%, signal=95%

GNF2_CDC2	61	0,8098275	2,326205	0	0	0	3069	tags=80%, list=15%, signal=95%
KOBAYASHI_EGFR_SIGNALING_24HR_DN	242	0,6662867	2,3255022	0	0	0	2691	tags=55%, list=13%, signal=63%
GNF2_CCNB2	56	0,81472474	2,324234	0	0	0	1866	tags=71%, list=9%, signal=79%
GNF2_CDC20	55	0,8162621	2,323976	0	0	0	3069	tags=82%, list=15%, signal=96%
GNF2_RFC4	59	0,79451287	2,318092	0	0	0	2233	tags=66%, list=11%, signal=74%
GRAHAM_NORMAL_QUIESCENT_VS_NORMAL_DIVIDING_DN	85	0,7422044	2,3104448	0	0	0	2691	tags=65%, list=13%, signal=74%
GNF2_FEN1	55	0,8140996	2,3052032	0	0	0	2233	tags=67%, list=11%, signal=76%
ZHAN_MULTIPLE_MYELOMA_PR_UP	44	0,84615934	2,3031518	0	0	0	1832	tags=68%, list=9%, signal=75%
PUJANA_XPRSS_INT_NETWORK	160	0,6877427	2,303086	0	0	0	3524	tags=59%, list=18%, signal=71%
GNF2_MCM4	53	0,81696784	2,303046	0	0	0	3069	tags=81%, list=15%, signal=96%
GNF2_HMMR	46	0,8257336	2,2922444	0	0	0	1866	tags=74%, list=9%, signal=81%
RUIZ_TNC_TARGETS_DN	137	0,6928864	2,2920208	0	0	0	2352	tags=47%, list=12%, signal=53%
BASAKI_YBX1_TARGETS_UP	277	0,6465856	2,2773166	0	0	0	2935	tags=49%, list=15%, signal=57%
REACTOME_CELL_CYCLE	381	0,6210166	2,2740698	0	0	0	3641	tags=50%, list=18%, signal=60%
REACTOME_DNA_REPLICATION	181	0,6636968	2,273592	0	0	0	3513	tags=53%, list=18%, signal=64%
PUJANA_BRCA_CENTERED_NETWORK	114	0,7125453	2,269872	0	0	0	3085	tags=56%, list=15%, signal=66%
ZHANG_TLX_TARGETS_60HR_DN	264	0,63686436	2,2615795	0	0	0	3062	tags=56%, list=15%, signal=66%
WHITFIELD_CELL_CYCLE_G1_S	133	0,69366056	2,2563674	0	0	0	3113	tags=56%, list=16%, signal=65%
GNF2_CKS2	49	0,7977298	2,256035	0	0	0	1832	tags=63%, list=9%, signal=69%
GNF2_TTK	38	0,8472715	2,2529984	0	0	0	3069	tags=95%, list=15%, signal=112%
REACTOME_CHROMOSOME_MAINTENANCE	112	0,7040509	2,2377305	0	0	0	3622	tags=65%, list=18%, signal=79%
MISSIAGLIA_REGULATED_BY_METHYLATION_DN	114	0,70240897	2,2310767	0	0	0	3387	tags=59%, list=17%, signal=70%
REACTOME_MITOTIC_PROMETAPHASE	86	0,71806604	2,225502	0	0	0	3513	tags=59%, list=18%, signal=72%
MODULE_54	257	0,6255082	2,2214375	0	0	0	2738	tags=51%, list=14%, signal=58%
GNF2_BUB1B	49	0,8119712	2,2190492	0	0	0	2372	tags=71%, list=12%, signal=81%
LEE_EARLY_T_LYMPHOCYTE_UP	98	0,7064498	2,218211	0	0	0	2071	tags=55%, list=10%, signal=61%
CROONQUIST_NRAS_SIGNALING_DN	71	0,75077355	2,2180734	0	0	0	4178	tags=82%, list=21%, signal=103%
WHITFIELD_CELL_CYCLE_S	148	0,6649231	2,2106705	0	0	0	2769	tags=53%, list=14%, signal=61%
ZHOU_CELL_CYCLE_GENES_IN_IR_RESPONSE_24HR	124	0,69303405	2,2103035	0	0	0	3150	tags=63%, list=16%, signal=74%
PUJANA_BRCA2_PCC_NETWORK	407	0,6062187	2,2088754	0	0	0	3524	tags=47%, list=18%, signal=56%
KANG_DOXORUBICIN_RESISTANCE_UP	53	0,7819401	2,199376	0	0	0	2691	tags=72%, list=13%, signal=83%
GRAHAM_CML_DIVIDING_VS_NORMAL_QUIESCENT_UP	176	0,6514625	2,1920369	0	0	0	2691	tags=48%, list=13%, signal=55%
KAUFFMANN_MELANOMA_RELAPSE_UP	57	0,75921124	2,1906793	0	0	0	3797	tags=79%, list=19%, signal=97%
GNF2_RRM2	39	0,8228133	2,190278	0	0	0	2164	tags=74%, list=11%, signal=83%
REACTOME_CELL_CYCLE_MITOTIC	296	0,61743397	2,1869044	0	0	0	3641	tags=49%, list=18%, signal=59%
MORI_LARGE_PRE_BII_LYMPHOCYTE_UP	84	0,71142	2,1827993	0	0	0	3217	tags=56%, list=16%, signal=66%
FERREIRA_EWINGS_SARCOMA_UNSTABLE_VS_STABLE_UP	163	0,65204215	2,181116	0	0	0	3049	tags=48%, list=15%, signal=56%
ZHOU_CELL_CYCLE_GENES_IN_IR_RESPONSE_6HR	83	0,71642536	2,1734047	0	0	0	2637	tags=69%, list=13%, signal=79%
ISHIDA_E2F_TARGETS	52	0,7806304	2,1705883	0	0	0	2233	tags=63%, list=11%, signal=71%
HALLMARK_G2M_CHECKPOINT	191	0,6343775	2,1685627	0	0	0	3541	tags=52%, list=18%, signal=63%
MODULE_125	41	0,7872572	2,1635118	0	0	0	3622	tags=85%, list=18%, signal=104%
GNF2_ESPL1	35	0,8339714	2,1610467	0	0	0	3069	tags=89%, list=15%, signal=104%
CROONQUIST_IL6_DEPRIVATION_DN	96	0,6898783	2,1596212	0	0	0	3622	tags=73%, list=18%, signal=89%
WINNEPENNINCKX_MELANOMA_METASTASIS_UP	157	0,6464272	2,1594985	0	0	0	2268	tags=45%, list=11%, signal=51%
REACTOME_MITOTIC_M_M_G1_PHASES	161	0,6497497	2,158652	0	0	0	3513	tags=52%, list=18%, signal=62%
GNF2_CENPE	40	0,8077438	2,1583965	0	0	0	3069	tags=80%, list=15%, signal=94%
MODULE_158	40	0,7912699	2,1479478	0	0	0	3309	tags=80%, list=17%, signal=96%
GNF2_RFC3	40	0,80318165	2,1413867	0	0	0	2214	tags=65%, list=11%, signal=73%

WU_APOPTOSIS_BY_CDKN1A_VIA_TP53	52	0,7583867	2,1376994	0	0	0	2369	tags=62%, list=12%, signal=70%
ZHANG_TLX_TARGETS_36HR_DN	174	0,641358	2,136574	0	0	0	3540	tags=60%, list=18%, signal=72%
BENPORATH_PROLIFERATION	143	0,6429572	2,1312232	0	0	0	3858	tags=62%, list=19%, signal=77%
FRASOR_RESPONSE_TO_SERM_OR_FULVESTRANT_DN	49	0,74729747	2,1178951	0	1,77E-05	0,001	3055	tags=67%, list=15%, signal=79%
REN_BOUND_BY_E2F	59	0,74397874	2,1166155	0	3,53E-05	0,002	3614	tags=76%, list=18%, signal=93%
STEIN_ESRRA_TARGETS_RESPONSIVE_TO_ESTROGEN_DN	41	0,8044296	2,1160629	0	3,48E-05	0,002	2636	tags=66%, list=13%, signal=76%
GSE24634_TEFF_VS_TCONV_DAY7_IN_CULTURE_UP	195	0,6226167	2,1159556	0	3,43E-05	0,002	3519	tags=52%, list=18%, signal=62%
SHEDDEN_LUNG_CANCER_POOR_SURVIVAL_A6	444	0,57340264	2,1145852	0	3,38E-05	0,002	3541	tags=45%, list=18%, signal=54%
GNF2_CKS1B	37	0,79219073	2,110269	0	3,33E-05	0,002	2935	tags=68%, list=15%, signal=79%
GSE36476_CTRL_VS_TSST_ACT_72H_MEMORY_CD4_TCELL_YOUNG_DN	194	0,6181239	2,108073	0	3,29E-05	0,002	3541	tags=55%, list=18%, signal=66%
GNF2_SMC2L1	32	0,8284759	2,1075385	0	3,24E-05	0,002	3069	tags=91%, list=15%, signal=107%
REACTOME_TELOMERE_MAINTENANCE	72	0,7083104	2,099143	0	3,20E-05	0,002	3932	tags=72%, list=20%, signal=90%
KAUFFMANN_DNA_REPAIR_GENES	220	0,6057437	2,0972955	0	3,16E-05	0,002	3649	tags=47%, list=18%, signal=57%
FARMER_BREAST_CANCER_CLUSTER_2	33	0,81017816	2,0920348	0	3,12E-05	0,002	2578	tags=79%, list=13%, signal=90%
RHODES_UNDIFFERENTIATED_CANCER	67	0,7105781	2,0903919	0	3,08E-05	0,002	3309	tags=55%, list=17%, signal=66%
NADERI_BREAST_CANCER_PROGNOSIS_UP	50	0,73980063	2,0871153	0	3,04E-05	0,002	2459	tags=54%, list=12%, signal=61%
GSE30962_PRIMARY_VS_SECONDARY_ACUTE_LCMV_INF_CD8_TCELL_UP	196	0,60984117	2,0870917	0	3,00E-05	0,002	2844	tags=49%, list=14%, signal=57%
SONG_TARGETS_OF_IE86_CMV_PROTEIN	58	0,7233464	2,0735993	0	5,93E-05	0,004	3111	tags=66%, list=16%, signal=77%
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	23	0,8531888	2,072939	0	5,85E-05	0,004	2258	tags=91%, list=11%, signal=103%
GNF2_H2AFX	30	0,80945647	2,0722835	0	5,78E-05	0,004	3069	tags=77%, list=15%, signal=90%
PUJANA_BREAST_CANCER_WITH_BRCA1_MUTATED_UP	52	0,7309945	2,0722783	0	5,71E-05	0,004	3051	tags=71%, list=15%, signal=84%
GNF2_BUB1	26	0,85009503	2,061894	0	7,04E-05	0,005	2691	tags=88%, list=13%, signal=102%
CHICAS_RB1_TARGETS_GROWING	235	0,60011584	2,059875	0	6,96E-05	0,005	2224	tags=46%, list=11%, signal=51%
EGUCHI_CELL_CYCLE_RB1_TARGETS	23	0,85704434	2,0551212	0	6,88E-05	0,005	2233	tags=87%, list=11%, signal=98%
MORI_IMMATURE_B_LYMPHOCYTE_DN	87	0,67707175	2,055107	0	6,80E-05	0,005	3069	tags=55%, list=15%, signal=65%
GREENBAUM_E2A_TARGETS_UP	33	0,7877247	2,0507402	0	6,73E-05	0,005	1866	tags=55%, list=9%, signal=60%
GNF2_MCM5	58	0,70801383	2,048269	0	6,65E-05	0,005	3663	tags=57%, list=18%, signal=69%
REACTOME_DEPOSITION_OF_NEW_CENPA_CONTAINING_NUCLEOSOMES_AT_THE_CENTROMERE	57	0,7211916	2,0440392	0	6,58E-05	0,005	3932	tags=77%, list=20%, signal=96%
VERNELL_RETINOBLASTOMA_PATHWAY_UP	69	0,6806404	2,041346	0	6,51E-05	0,005	3663	tags=70%, list=18%, signal=85%
CHR18Q21	77	0,67318034	2,0339878	0	8,96E-05	0,007	3247	tags=47%, list=16%, signal=56%
YU_MYC_TARGETS_UP	41	0,753539	2,0308	0	8,87E-05	0,007	3721	tags=68%, list=19%, signal=84%
MARKEY_RB1_ACUTE_LOF_DN	219	0,5816713	2,0270572	0	8,77E-05	0,007	3387	tags=46%, list=17%, signal=55%
KAUFFMANN_DNA_REPLICATION_GENES	135	0,6182577	2,026068	0	8,68E-05	0,007	3797	tags=49%, list=19%, signal=60%
WHITFIELD_CELL_CYCLE_G2	170	0,59635717	2,0223694	0	9,82E-05	0,008	3129	tags=44%, list=16%, signal=51%
REACTOME_DNA_STRAND_ELONGATION	29	0,8104022	2,019993	0	9,72E-05	0,008	3622	tags=93%, list=18%, signal=114%
GNF2_MKI67	27	0,81130487	2,0196621	0	9,62E-05	0,008	1581	tags=70%, list=8%, signal=76%
MOLENAAR_TARGETS_OF_CCND1_AND_CDK4_DN	56	0,69964415	2,013272	0	9,52E-05	0,008	2669	tags=71%, list=13%, signal=82%
MODULE_403	44	0,74029666	2,0128918	0	9,43E-05	0,008	3503	tags=73%, list=18%, signal=88%
TANG_SENESCENCE_TP53_TARGETS_DN	55	0,7100634	2,0124357	0	9,33E-05	0,008	3145	tags=71%, list=16%, signal=84%
CHR5P13	46	0,7222294	2,0092008	0	1,61E-04	0,014	1936	tags=48%, list=10%, signal=53%
WHITFIELD_CELL_CYCLE_LITERATURE	42	0,7411932	2,005866	0	1,60E-04	0,014	3069	tags=60%, list=15%, signal=70%
NAKAYAMA_SOFT_TISSUE_TUMORS_PCA2_UP	86	0,6490785	2,005475	0	1,58E-04	0,014	2809	tags=51%, list=14%, signal=59%
TOYOTA_TARGETS_OF_MIR34B_AND_MIR34C	418	0,5446545	2,004331	0	1,57E-04	0,014	3721	tags=42%, list=19%, signal=51%
FUJII_YBX1_TARGETS_DN	199	0,5893885	2,0021698	0	1,55E-04	0,014	2687	tags=46%, list=13%, signal=52%
GSE36476_CTRL_VS_TSST_ACT_40H_MEMORY_CD4_TCELL_YOUNG_DN	195	0,5895264	1,9974505	0	1,65E-04	0,015	3309	tags=48%, list=17%, signal=57%
REACTOME_G2_M_CHECKPOINTS	33	0,7891561	1,9925712	0	1,74E-04	0,016	3541	tags=88%, list=18%, signal=107%
VECCHI_GASTRIC_CANCER_EARLY_UP	404	0,5451752	1,99179	0	1,73E-04	0,016	2459	tags=36%, list=12%, signal=40%
REICHERT_MITOSIS_LIN9_TARGETS	27	0,8055816	1,9865597	0	1,93E-04	0,018	1656	tags=63%, list=8%, signal=69%

SARRIO_EPITHELIAL_MESENCHYMAL_TRANSITION_UP	168	0,59520465	1,9843497	0	1,91E-04	0,018	2218	tags=45%, list=11%, signal=50%
CHR11Q22	50	0,70816123	1,9808456	0	2,21E-04	0,021	3595	tags=44%, list=18%, signal=54%
GNF2_HAT1	47	0,71651393	1,9805115	0	2,19E-04	0,021	2461	tags=45%, list=12%, signal=51%
CHARAFE_BREAST_CANCER_LUMINAL_VS_MESENCHYMAL_DN	448	0,5390391	1,9801952	0	2,28E-04	0,022	2253	tags=32%, list=11%, signal=35%
MODULE_320	19	0,85668194	1,9769638	0	2,56E-04	0,025	1981	tags=74%, list=10%, signal=82%
REACTOME_EXTENSION_OF_TELOMERES	27	0,78860384	1,9761571	0	2,54E-04	0,025	3622	tags=78%, list=18%, signal=95%
REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	28	0,7844834	1,9758263	0	2,52E-04	0,025	3797	tags=89%, list=19%, signal=110%
DNA_REPLICATION	93	0,639767	1,9749557	0	2,50E-04	0,025	2372	tags=39%, list=12%, signal=44%
MORF_BUB1	50	0,71406925	1,9700975	0	2,77E-04	0,028	3644	tags=58%, list=18%, signal=71%
KEGG_DNA_REPLICATION	36	0,7329825	1,968363	0	2,95E-04	0,03	3309	tags=75%, list=17%, signal=90%
KEGG_CELL_CYCLE	115	0,60934556	1,9654233	0	3,02E-04	0,031	4388	tags=58%, list=22%, signal=74%
HORIUCHI_WTAP_TARGETS_DN	298	0,5454231	1,9630828	0	3,19E-04	0,033	3245	tags=42%, list=16%, signal=49%
AMUNDSON_GAMMA_RADIATION_RESPONSE	39	0,7352462	1,9558483	0	3,92E-04	0,041	2935	tags=64%, list=15%, signal=75%
REACTOME_DNA_REPAIR	104	0,62272805	1,9549669	0	3,89E-04	0,041	3472	tags=47%, list=17%, signal=57%
HOFFMANN_LARGE_TO_SMALL_PRE_BII_LYMPHOCYTE_UP	156	0,59020585	1,9480788	0	4,05E-04	0,043	2291	tags=42%, list=11%, signal=47%

Supplementary table 2. Uni- and multivariable Cox regression analysis on known clinical variables in the NCI data set. Global Risk Score groups: GRS I = low GRS in tumor and liver; GRS II = low GRS in tumor, high in liver; GRS III = high GRS in tumor, low in liver; GRS IV = high GRS in tumor and liver**.**

	Disease free survival								Overall survival							
	Univariate cox regression				Multivariate cox regression				Univariate cox regression				Multivariate cox regression			
	p-value	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Gender (female vs male)	**,017**	,436	,221	,860	,083	,544	,273	1,082	,110	,533	,246	1,153				
Age	,968	1,000	,984	1,016					,254	,989	,970	1,008				
Hepatitis B status (AVR vs no AVR)	,257	1,263	,843	1,893					,318	1,281	,788	2,081				
ALT (> 50 IU/l vs < 50 IU/l)	,082	1,363	,961	1,933					,627	1,110	,729	1,690				
Size largest nodule (> 5 cm vs < 5 cm)	,067	1,398	,977	2,001					**,003**	1,870	1,229	2,844	,715	,900	,513	1,580
Multinodular (no vs yes)	,072	,682	,450	1,034					**,010**	,542	,341	,861	,145	1,785	,819	3,888
Cirrhosis (yes vs no)	,183	1,678	,783	3,596					**,039**	4,365	1,074	17,736	,060	3,941	,945	16,434
BCLC	**,000**				**,000**				**,000**				**,000**			
BCLC (A vs 0)	,092	2,043	,889	4,695	,045	2,381	1,021	5,552	,059	3,923	,952	16,162	,035	4,648	1,113	19,403
BCLC (B vs 0)	,002	4,506	1,751	11,594	,002	4,564	1,749	11,915	,002	10,186	2,289	45,325	,002	14,850	2,597	84,908
BCLC (C vs 0)	,000	6,930	2,782	17,264	,000	6,744	2,640	17,224	,000	18,429	4,272	79,492	,000	23,956	4,850	118,331
aFP (> 300 ng/ml vs < 300 ng/ml)	,089	1,354	,955	1,920					,006	1,807	1,185	2,756	,410	1,228	,754	2,001
Global Risk Score group	**,001**				**,007**				**,001**				**,024**			
GRS II vs I	,009	2,050	1,196	3,514	,002	2,458	1,380	4,377	,036	2,011	1,045	3,871	,025	2,315	1,112	4,820
GRS III vs I	,102	1,533	,919	2,556	,033	1,810	1,048	3,127	,263	1,436	,762	2,706	,086	1,848	,916	3,730
GRS IV vs I	,000	2,647	1,612	4,344	,002	2,372	1,378	4,083	,000	3,072	1,697	5,559	,003	2,870	1,446	5,696