SUPPLEMENTARY INFORMATION

Development of the prediction model

Before we applied the prognostic classification algorithms, gene expression data for the training and test sets were normalized by centralizing the gene expression level across the tissues. Gene symbols were used to match orthologous genes between humans and mice. To stratify HCC patients according to the mouse SOH gene expression signature, we used a classification algorithm based on Bayesian compound covariate predictor (BCCP), as described below.

To generate the probability of silence of the Hippo pathway in each patient with HCC, we used expression data in the mouse SOH signature (training set, **Fig. 1B**) to build a classifier based on the BCCP algorithm.[1] The paragraphs below describe the classifier development algorithms that were applied in the training and test sets.

Let t_j denote the t statistic for gene j for comparing class 1 (SOH) to class 2 (AH) in the training set.

$$t_j = \frac{\overline{x}_j^{(1)} - \overline{x}_j^{(2)}}{s_j\sqrt{1/n_1 + 1/n_2}} \qquad (1)$$

where $\overline{x}_j^{(m)}$ denotes the mean of log expression j for training samples in class m (m=1,2), s_j is an estimate of intra-class variance for gene j, and n_m is the number of cases in the training set in class m (m=1,2).

Let x_{ij} denote the log expression for gene j in sample i of the training set. For each sample of the training set, the compound covariate value is computed as follows:

$$C_i = \sum_{j\varepsilon Selected} t_j x_{ij} \qquad (2)$$

Let $\overline{C}^{(1)}$ denote the mean of the C_i values for samples in class 1 in the training set and let $\overline{C}^{(2)}$ denote the mean for samples in class 2 of the training set.

The compound covariate for sample y in the test set is defined by the following:

$$C = \sum_{j\varepsilon Selected} t_j y_j \qquad (3)$$

To classify a case not in the training set with log expression values Y = (y_1, y_2, …, y_p), the compound covariate value C is computed using expression (3). The probability that sample Y came from class 1 is estimated as

$$\Pr[Y \text{ in class } 1] = \frac{\phi(C;\overline{C}^{(1)},V)\pi_1}{\phi(C;\overline{C}^{(1)},V)\pi_1 + \phi(C;\overline{C}^{(2)},V)(1-\pi_1)} \qquad (4),$$

where $\phi(C;\overline{C}^{(1)},V)$ denotes the Gaussian density of a value C when the mean is $\overline{C}^{(1)}$ and the variance is V. π_1 denotes equal prior probability that the class is 1 (0.5).

In equation (4),

$$\bar{C}^{(1)} = \sum_{j\ in\ class\ 1} C_j,\ \bar{C}^{(2)} = \sum_{j\ in\ class\ 2} C_j$$

$$\text{Gaussian Density } \phi(C;\overline{C}^{(1)},V) = \frac{1}{\sqrt{2\pi V}}\exp(-\frac{(C-\bar{C}^{(1)})^2}{2V})$$

$$\mathrm{V} = \frac{\sum_{j\ in\ Class\ 1}(C_j-\overline{C}^{(1)})^2+\sum_{j\ in\ Class\ 2}(C_j-\overline{C}^{(2)})^2}{n1+n2-2}$$

The probability that the new sample Y is from class 2 is 1 minus the value given in (4). The class with the greater computed probability is predicted for the new sample. The Bayesian compound covariate method was developed by Wright et al.[2]

The trained BCCP was applied to gene expression data from the NCI cohort (test set 1) and a probability of SOH was generated for each patient. SOH probabilities ranged from 0.888 to 0.127 among all HCC patients in the NCI cohort and were significantly associated with overall survival (hazard ratio [HR], 10.6; 95% confidence interval [CI], 3.0 – 37.2; $P = 2.3 \times 10^{-4}$) and recurrence-free survival (HR, 9.8; 95% CI, 1.6 – 61.5; $P = 0.01$) as a continuous prediction value.

We next carried out receiver operating characteristic (ROC) plotting to identify an optimal threshold of SOH probability that would best discriminate high-risk patients from low-risk patients for 3-year recurrence using data from the NCI cohort. According to the Youden indices,[3] the optimal threshold value was 0.65. An ROC analysis was performed using the pROC package in R.[4]

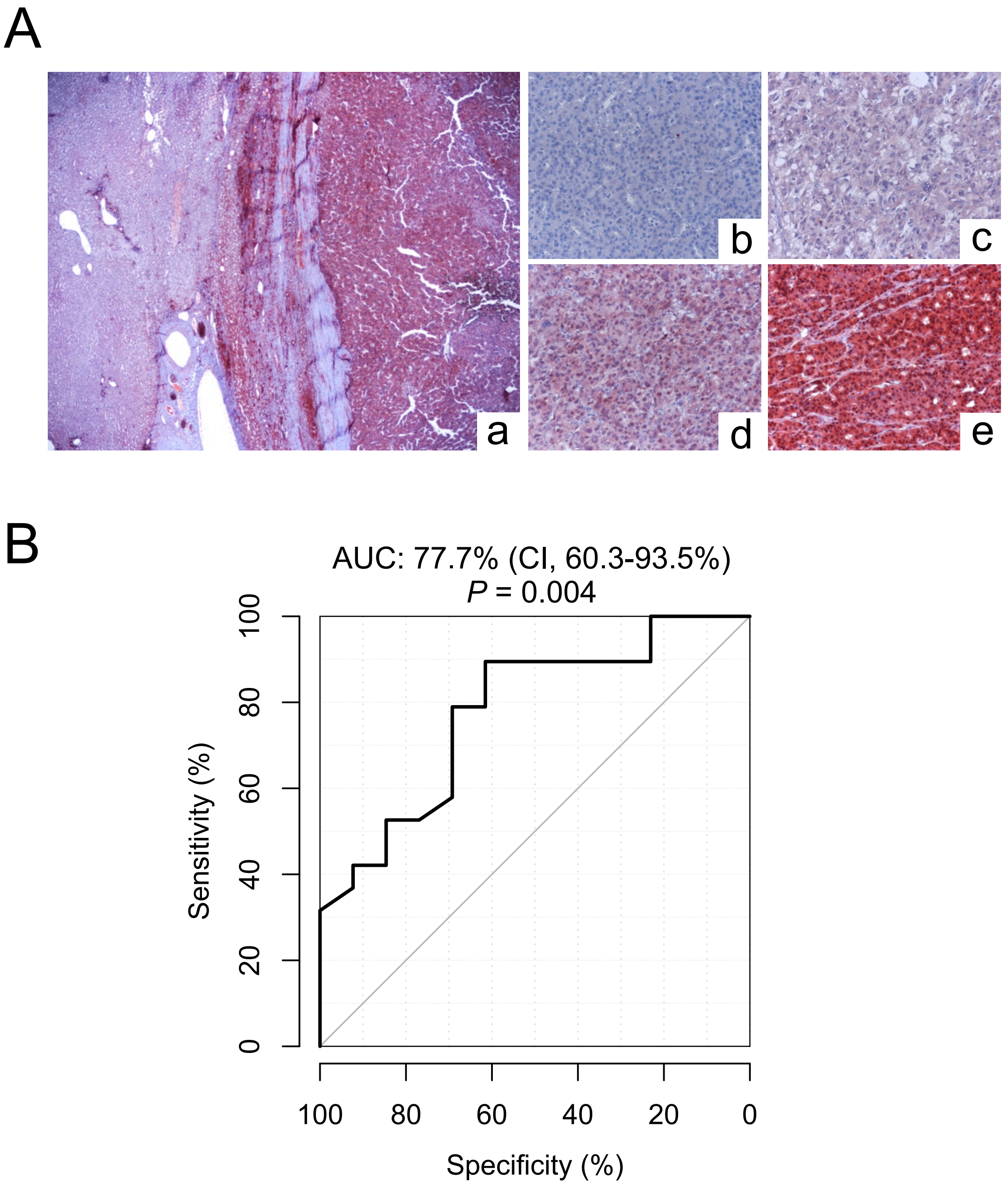
Reference List

1. Radmacher MD, McShane LM, Simon R. A paradigm for class prediction using gene expression profiles. J Comput Biol 2002;9:505-511.

2. Wright G, Tan B, Rosenwald A et al. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 2003;100:9991-9996.

3. YOUDEN WJ. Index for rating diagnostic tests. Cancer 1950;3:32-35.

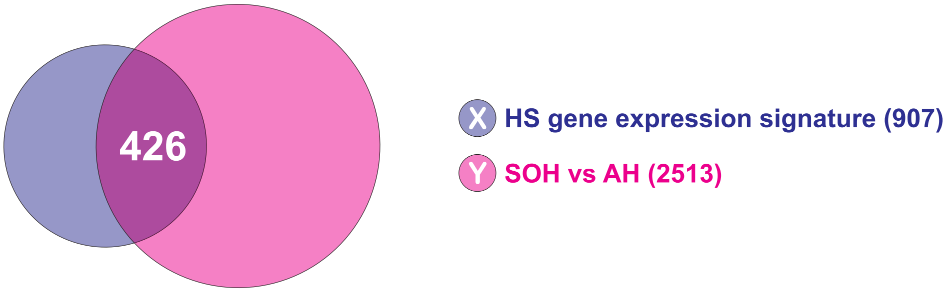
4. Robin X, Turck N, Hainard A et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011;12:77. doi: 10.1186/1471-2105-12-77.:77-12.



Supplementary Figure 1. Significant concordance between silence of Hippo signature and YAP1 expression in human hepatocellular carcinoma (HCC).

(A) Immunohistochemical staining of YAP1 in human HCC tissues from the Korean patient cohort. a, On low-power view, the expression of YAP1 was higher in tumors (right) than in adjacent non-tumoral hepatocytes (left). b-e, Variable expression of YAP1 in HCC: b) negative, c) weak expression, d) intermediate expression, and e) strong expression. Original magnification: a,x20, b-e, x200.

(B) The significance of concordance between YAP1 expression and SOH probability in human HCC from the Korean cohort was estimated using the area under the curve (AUC) from the receiver operating characteristics analysis after immunohistochemically 1staining HCC tissues with anti-YAP1 antibody (1 for positive and 0 for negative staining). CI: confidence interval.



Supporting Figure 2 Venn diagram of gene lists from two different gene expression signatures

The blue circle (gene list X) represents genes from the previously identified HS signature from the NCI cohort. The magenta circle (gene list Y) represents genes differentially expressed between silence of Hippo (SOH) subtype and active Hippo (AH) subtype in the NCI cohort (*P* < 0.001, 2513 gene features). Of 907 genes in the HS signature, 426 genes (47%) were present in the gene list specific to SOH subtype in the NCI cohort.

Supplementary Table 1. Genes in the SOH signature.

Probe ID	Symbol	ENTREZ_ID	T value
ILMN_1212836	Ptprc	19264	2.765
ILMN_1213708	4732462B05Rik		-0.988
ILMN_1213958	Sec23a	20334	-2.799
ILMN_1214118	Plekha2	83436	3.511
ILMN_1214498	Cyp2d22	56448	-5.185
ILMN_1214838	Hsd3b2	15493	-4.724
ILMN_1214918	LOC546015	546015	4.227
ILMN_1215124	Klhl13	67455	4.777
ILMN_1215212	Rhob	11852	4.395
ILMN_1215305	Kat2b	18519	-3.056
ILMN_1215791	Alox5ap		0.922
ILMN_1215807	Glipr1	73690	4.099
ILMN_1216409	1500012F01Rik	68949	4.135
ILMN_1216764	Ier3	15937	5.91
ILMN_1216880	Emr1	13733	0.807
ILMN_1217180	Ifitm1	68713	-0.088
ILMN_1217280	4930528F23Rik	75178	-3.528
ILMN_1217389	Pkib	18768	1.358
ILMN_1217849	Laptm5	16792	2.564
ILMN_1218592	Tes	21753	5.254
ILMN_1218681	Cp		3.166
ILMN_1218799	Emb	13723	2.119
ILMN_1219016	Wwtr1	97064	5.265
ILMN_1219298	Art4	109978	-1.141
ILMN_1219583	Capn2	12334	-1.062
ILMN_1219820	1200002N14Rik	71712	2.558
ILMN_1219904	Tspan33	232670	-3.093
ILMN_1220121	Kif23		4.716
ILMN_1220261	Tspan8	216350	3.752
ILMN_1220939	Epb4.1l4a		3.152
ILMN_1220974	B3galnt2	97884	-3.186
ILMN_1221102	Arl5a	75423	-2.991
ILMN_1221157	Krt8	16691	5.37
ILMN_1221290	LOC636952	636952	4.148
ILMN_1221817	Cd74	16149	4.227
ILMN_1222246	Adfp	11520	-3.438
ILMN_1222269	1810011H11Rik	69069	1.708
ILMN_1222500	LOC100047162	1E+08	0.952
ILMN_1222860	Gm5150	381484	-0.964
ILMN_1223041	Abi3		1.164

ILMN_1223257	Ccl4	20303	4.102
ILMN_1223285	Hspa2	15512	3.52
ILMN_1223317	Lgals3	16854	3.699
ILMN_1223552	Fbn1		3.048
ILMN_1223949	Cldn4	12740	1.588
ILMN_1223999	LOC381222		-5.605
ILMN_1224635	Fkbp11	66120	5.185
ILMN_1224719	LOC665032	665032	3.416
ILMN_1224754	Ckb	12709	0.841
ILMN_1224768	Ehd4	98878	5.427
ILMN_1224855	Samd9l	209086	2.918
ILMN_1225535	Ganab	14376	-3.987
ILMN_1225985	Serpina7	331535	1.62
ILMN_1226455	Ftcd	14317	-5.603
ILMN_1226525	H2-Ab1	14961	3.986
ILMN_1226829	Cd93	17064	4.42
ILMN_1226978	Pex5		-3.956
ILMN_1227111	LOC240549		-3.749
ILMN_1227573	Irf7	54123	-0.296
ILMN_1227831	Trfr2	50765	-4.738
ILMN_1227875	Fkbp7	14231	1.542
ILMN_1227907	Gmfg	63986	0.457
ILMN_1228213	Ifi30	65972	1.35
ILMN_1228474	Ctsj	26898	-0.422
ILMN_1228535	Pmp22	18858	-0.558
ILMN_1228948	Ugt1a1	394436	-5.064
ILMN_1229082	Klhl21	242785	-2.891
ILMN_1229577	Sstr2		5.309
ILMN_1229667	Slc43a1	72401	-4.58
ILMN_1230032	EG384596	384596	3.475
ILMN_1230119	Gcap27		4.688
ILMN_1230318	Cbs		-5.191
ILMN_1230788	Tle1	21885	-2.716
ILMN_1231012	Lcp2	16822	1.233
ILMN_1231513	Tacstd2	56753	1.276
ILMN_1231814	Ccl5	20304	2.145
ILMN_1231896	Ssbp4		3.182
ILMN_1232495	LOC100044177		3.101
ILMN_1232537	Arl4c	320982	3
ILMN_1232601	Cyb561	13056	2.751
ILMN_1232716	Cyp1b1	13078	1.534
ILMN_1232884	Sphk1	20698	2.681
ILMN_1232948	Pnp		-0.111

ILMN_1232995	1810023F06Rik	217845	3.745
ILMN_1233175	LOC632667	632667	5.319
ILMN_1233334	Fpgs	14287	-3.462
ILMN_1233455	Olfml3	99543	2.187
ILMN_1234223	Pld4	104759	0.479
ILMN_1234773	Anxa13	69787	0.261
ILMN_1234824	Ccdc80	67896	0.725
ILMN_1235196	Atp10d	231287	5.038
ILMN_1235635	Slco3a1	108116	4.54
ILMN_1235932	Pdgfra	18595	-0.925
ILMN_1236010	scl0003799.1_2		5.315
ILMN_1236354	E130302P19Rik		-4.235
ILMN_1236757	Oxct1	67041	3.826
ILMN_1236758	Wfdc2	67701	3.545
ILMN_1237033	LOC384710	384710	5.001
ILMN_1237186	Spint1	20732	4.373
ILMN_1237886	Enc1	13803	4.748
ILMN_1238592	Pigh	110417	4.94
ILMN_1238597	Omd	27047	1.721
ILMN_1238603	Pcolce2	76477	-1.402
ILMN_1238838	LOC100045005	1E+08	4.258
ILMN_1238874	LOC100047759	1E+08	3.663
ILMN_1239102	H2-Eb1	14969	4.034
ILMN_1239196	1700088E04Rik	27660	3.824
ILMN_1239397	LOC100047934		1.371
ILMN_1239872	LOC665792	665792	-1.101
ILMN_1240471	Retsat	67442	-3.305
ILMN_1240624	1700011H14Rik	67082	3.137
ILMN_1240864	Tyki		2.133
ILMN_1241171	Anxa3	11745	3.635
ILMN_1241695	Ms4a6d	68774	3.185
ILMN_1242999	Avpr1a	54140	-1.207
ILMN_1243212	Sparc	20692	3.567
ILMN_1243433	LOC100048037		4.186
ILMN_1243507	Spsb4	211949	-0.702
ILMN_1243616	Cdkn3	72391	5.611
ILMN_1243900	LOC626152	626152	5.403
ILMN_1244169	Sftpd	20390	4.442
ILMN_1244291	Gja1	14609	2.088
ILMN_1244536	Hnrpa1		4.485
ILMN_1244977	H2-DMb1	14999	3.282
ILMN_1245307	Fbln2	14115	2.721
ILMN_1245693	A530020H22Rik		-2.429

ILMN_1245994	Flna	192176	4.612
ILMN_1246056	Gngt2	14710	-0.107
ILMN_1246558	Atad4	217138	4.552
ILMN_1246573	Calml4		5.758
ILMN_1246609	Rasgrp1	19419	0.423
ILMN_1246821	E130203B14Rik	320736	1.689
ILMN_1246861	Ctss	13040	2.626
ILMN_1247127	B930075F07		-2.928
ILMN_1247348	Ghr		-2.309
ILMN_1247377	Mpeg1	17476	4.091
ILMN_1247422	Ces1b	382044	-5.964
ILMN_1247592	Casp1	12362	5.709
ILMN_1247704	Hmgn3	94353	2.096
ILMN_1248099	Col16a1	107581	3.538
ILMN_1248132	Stmn1		5.361
ILMN_1248415	Tgoln1	22134	-5.16
ILMN_1248959	Tinag	26944	4.384
ILMN_1249021	Bcl2	12043	4.036
ILMN_1249220	Col6a3	12835	1.868
ILMN_1249246	LOC384022		-5.724
ILMN_1249366	LOC100046608		3.055
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ILMN_1249498	Plek	56193	3.115
ILMN_1249578	Sorl1	20660	4.016
ILMN_1249666	Ppap2c	50784	5.651
ILMN_1249945	9930004G02Rik		-2.42
ILMN_1250260	Il10rb	16155	3.973
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ILMN_1251669	Evi2a	14017	1.961
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ILMN_1251837	Slco1b2	28253	-3.841
ILMN_1252076	Lyz2	17105	1.833
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ILMN_1252831	2310014H01Rik	76448	2.716
ILMN_1253233	Dsg1c		3.302
ILMN_1253563	Cyp2d13	68444	-4.903
ILMN_1253741	Pcolce	18542	4.392
ILMN_1253808	Oas1g	23960	2.129
ILMN_1253813	Nckap1l	105855	1.842

ILMN_1253838	Pawr	114774	3.64
ILMN_1254721	EG13909	13909	-5.868
ILMN_1254878	Eif4e3	66892	3.193
ILMN_1255871	Loxl1	16949	1.79
ILMN_1256142	Marcks	17118	3.56
ILMN_1256257	LOC100038882	1E+08	1.281
ILMN_1256423	Ranbp3l	223332	0.606
ILMN_1256725	Acads	11409	-3.788
ILMN_1256817	Slpi	20568	5.041
ILMN_1257209	Wipf1	215280	1.724
ILMN_1257574	Esm1	71690	5.821
ILMN_1257575	Cst3	13010	3.387
ILMN_1257771	LOC638301	638301	1.183
ILMN_1258028	Gal3st1	53897	4.73
ILMN_1258283	Ltb	16994	3.843
ILMN_1258578	Ahnak	66395	4.134
ILMN_1258629	Col3a1	12825	2.807
ILMN_1258916	Atp13a3	224088	-2.959
ILMN_1259035	Wbscr14		-2.79
ILMN_1259388	Col6a1	12833	1.772
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ILMN_1259470	Tmem176b	65963	3.52
ILMN_1259754	Rnf4	19822	-2.534
ILMN_1259919	6332401O19Rik	319832	3.936
ILMN_1260378	Csrp1	13007	2.428
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ILMN_2419998	Soat1	20652	0.957
ILMN_2423730	A930008A22Rik		5.396
ILMN_2424268	Wtip	101543	3.871
ILMN_2426853	Ubd	24108	4.772
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ILMN_2467596	Dusp16	70686	3.108
ILMN_2476733	1200016E24Rik		2.701
ILMN_2479370	Tm4sf4	229302	2.955
ILMN_2483771	C920027I18Rik		3.644
ILMN_2483948	Specc1	432572	4.906
ILMN_2484274	0610010E21Rik	68332	1.714
ILMN_2484932	C030002B11Rik		1.65
ILMN_2485340	9530018I07Rik		2.923

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ILMN_2495446	0610037M15Rik		0.027
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ILMN_2503188	Ppl	19041	5.03
ILMN_2503553	Col8a1	12837	5.779
ILMN_2505185	LOC672274	672274	5.082
ILMN_2505841	Igsf4a		2.934
ILMN_2511953	Tnfaip8	106869	1.959
ILMN_2514377	Cxadr		2.889
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ILMN_2588759	Aph1a	226548	-3.53
ILMN_2588995	Rab8b	235442	3.886
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ILMN_2592881	Jam2	67374	-0.264
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ILMN_2596611	Clic1		3.38
ILMN_2596961	D430028G21Rik	228607	-5.069
ILMN_2598103	Emp2	13731	5.552
ILMN_2601072	Dab1	13131	4.986
ILMN_2601515	Bpnt1		-4.29
ILMN_2602858	Prickle3	54630	5.151
ILMN_2603568	Obrgrp		2.711
ILMN_2606162	Pdlim4	30794	2.985
ILMN_2609323	Lst1		1.252
ILMN_2609998	Fxyd6	59095	3.745
ILMN_2611180	Ccdc3		2.613
ILMN_2611755	Serpinb6b	20708	5.787

ILMN_2612738	Coq5	52064	-4.226
ILMN_2614313	Lin7a	108030	-4.4
ILMN_2614380	Map3k1	26401	4.622
ILMN_2615468	Fgfr1op2	67529	0.806
ILMN_2618176	Socs3	12702	4.018
ILMN_2618634	Spna2		4.732
ILMN_2619107	Lgals1		5.055
ILMN_2619620	C1qb	12260	1.231
ILMN_2620053	Als2	74018	-3.718
ILMN_2622671	Acsl1	14081	-4.529
ILMN_2623280	Osmr	18414	4.271
ILMN_2625351	Sh3bgrl3	73723	4.23
ILMN_2625940	Neurl		5.743
ILMN_2626294	Pam	18484	1.982
ILMN_2627041	Cx3cl1	20312	5.414
ILMN_2627557	Tbc1d19	67249	5.152
ILMN_2628594	Mttp	17777	-4.842
ILMN_2629112	Asah3l	230379	-2.443
ILMN_2630047	Car3	12350	-3.851
ILMN_2630946	Aprt		4.614
ILMN_2631161	Fcgr4	246256	-0.535
ILMN_2633096	Gstm6	14867	-0.124
ILMN_2634603	LOC56628	56628	0.251
ILMN_2635272	Igh-VJ558	16061	1.914
ILMN_2635813	Nudt12	67993	-3.56
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ILMN_2636424	Itgbl1	223272	2.594
ILMN_2637792	Cryz	12972	-3.014
ILMN_2639036	Hspd1	15510	-3.487
ILMN_2642913	Emp1	13730	3.584
ILMN_2642922	Mtmr11	194126	3.485
ILMN_2643092	Rps9	76846	5.048
ILMN_2644350	Thy1	21838	4.731
ILMN_2645662	Tmem86a	67893	2.058
ILMN_2645973	Tff3	21786	3.843
ILMN_2648409	Cmtm7	102545	3.061
ILMN_2648445	Slc27a2	26458	-3.824
ILMN_2650115	Adamtsl2	77794	-0.423
ILMN_2651076	Scotin	66940	2.828
ILMN_2651715	Axl	26362	1.467
ILMN_2653132	Clec7a	56644	3.682
ILMN_2653166	Gpx8	69590	1.897
ILMN_2654186	Nedd9	18003	5.244

ILMN_2654495	Iqgap1		3.663
ILMN_2654554	Fgl2	14190	1.417
ILMN_2654754	Gp38		2.409
ILMN_2656422	BC028528	229600	1.971
ILMN_2657478	Cd53	12508	1.878
ILMN_2657685	Aass	30956	-5.074
ILMN_2658130	Hkdc1	216019	1.131
ILMN_2658501	Ifitm3	66141	0.81
ILMN_2658804	Rras	20130	4.807
ILMN_2658815	Tmem98	103743	2.964
ILMN_2659426	Cxcl14		2.742
ILMN_2659824	Ppp1r14a	68458	0.88
ILMN_2659997	Acaa1b	235674	-3.436
ILMN_2660263	Bcl2a1b	12045	3.341
ILMN_2660551	Lat	16797	3.22
ILMN_2660555	Bcl2a1d		3.38
ILMN_2660862	Sepn1	74777	3.783
ILMN_2661576	Bicc1	83675	5.269
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ILMN_2663249	Slamf9	98365	4.587
ILMN_2663585	Jdp2	81703	3.632
ILMN_2665008	Rab31	106572	2.426
ILMN_2665307	Pilra	231805	-0.481
ILMN_2665629	Ldhd	52815	-5.361
ILMN_2666018	Mgp	17313	2.548
ILMN_2667091	Ppp1r3c	53412	-5.686
ILMN_2669289	Htra4	330723	-2.121
ILMN_2670038	Cdh16	12556	0.65
ILMN_2671195	St8sia4	20452	4.442
ILMN_2671923	Ly86	17084	2.452
ILMN_2673369	Irf8	15900	1.711
ILMN_2673668	LOC624662	624662	5.292
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ILMN_2674483	Gpx2	14776	5.606
ILMN_2675669	Cd72	12517	1.868
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ILMN_2684600	Nalp6		-3.094
ILMN_2685234	Hsd17b11	114664	-3.196

ILMN_2685565	Tymp	72962	-5.213
ILMN_2686327	Gas6	14456	4.1
ILMN_2686393	Gna12	14673	-3.618
ILMN_2686700	Abca8a	217258	-5.309
ILMN_2686975	Fam129b	227737	4.758
ILMN_2687403	Fcgr3	14131	1.212
ILMN_2687586	Cxcl16	66102	3.959
ILMN_2689785	Cd68	12514	0.794
ILMN_2690603	Spp1	20750	3.973
ILMN_2692615	Tgm2	21817	5.088
ILMN_2692986	2810410P22Rik		-2.496
ILMN_2693403	Ela1	109901	-2.01
ILMN_2695008	Ncoa4		-4.425
ILMN_2695819	Ddit4l	73284	1.494
ILMN_2696199	Prosc		-3.473
ILMN_2696232	Nme5	75533	3.642
ILMN_2696491	Phf11	219131	0.839
ILMN_2699222	LOC669053	669053	0.849
ILMN_2699531	Rgs10	67865	4.475
ILMN_2699880	Abca9	217262	-4.932
ILMN_2700715	Cstb	13014	4.861
ILMN_2702703	Shmt2	108037	-4.522
ILMN_2704562	LOC100047628		1.168
ILMN_2704822	Acaa2		-4.022
ILMN_2705460	Ntrk2	18212	1.781
ILMN_2705777	Gstm5	14866	4.535
ILMN_2705848	Decr2		-4.707
ILMN_2706268	Scara3	219151	1.128
ILMN_2708477	Spink3		4.289
ILMN_2708928	Bdh1	71911	-2.546
ILMN_2710185	Mylc2b	67938	3.784
ILMN_2710819	Csf1r	12978	1.338
ILMN_2710905	S100a8	20201	1.774
ILMN_2711163	Ctsk	13038	3.346
ILMN_2711267	Krt18	16668	5.885
ILMN_2712075	Lcn2	16819	3.609
ILMN_2712120	S100a6	20200	5.528
ILMN_2712578	Rbm47	245945	-3.238
ILMN_2713055	Psca	72373	5.428
ILMN_2713969	B9d1	27078	5.686
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ILMN_2714796	Coro1a	12721	3.056
ILMN_2715270	Slc5a1	20537	5.118

ILMN_2715840	C1qc	12262	0.473
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ILMN_2718217	Tubb6	67951	5.577
ILMN_2720047	AW124722		-4.208
ILMN_2722732	Srgn	19073	2.11
ILMN_2722784	Cd3g	12502	2.36
ILMN_2722893	LOC637227	637227	0.909
ILMN_2722996	Sirpa	19261	3.958
ILMN_2723369	Npal2	223473	2.214
ILMN_2724294	Gpx7	67305	5.625
ILMN_2725414	Cd9		3.26
ILMN_2725927	Serpina3g	20715	-0.58
ILMN_2726055	Shmt1		-5.394
ILMN_2727116	Sox4	20677	5.063
ILMN_2727251	Slc4a9	240215	1.209
ILMN_2728379	Ivd	56357	-4.587
ILMN_2728796	C1rl	232371	-5.932
ILMN_2729458	Idh1	15926	-4.473
ILMN_2730100	Cib3	234421	2.457
ILMN_2730797	Slc25a10	27376	-3.904
ILMN_2731020	Sult5a1	57429	-3.922
ILMN_2731454	Evl	14026	1.416
ILMN_2731550	Brp17		-5.14
ILMN_2731760	Myo1f	17916	2.456
ILMN_2731949	Klf6	23849	4.744
ILMN_2732848	Tagln2	21346	4.647
ILMN_2733356	Endod1	71946	4.452
ILMN_2734340	Stx11	74732	2.375
ILMN_2734683	Fstl1	14314	2.645
ILMN_2734729	H2-Aa	14960	3.797
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ILMN_2739760	Prelp	116847	3.152
ILMN_2740465	Il1rap	16180	-5.55
ILMN_2740852	F2r	14062	4.309
ILMN_2740965	Prss8	76560	5.543
ILMN_2741096	Timp3	21859	3.896
ILMN_2741169	Cd8b1	12526	2.9
ILMN_2742075	Cd14	12475	3.762
ILMN_2743013	Ncf4	17972	1.612
ILMN_2743244	Cd86	12524	0.012
ILMN_2744380	Npc2	67963	3.192
ILMN_2744514	Veph1	72789	5.057

ILMN_2746086	Tax1bp3	76281	5.21
ILMN_2746556	Dkk3	50781	0.859
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ILMN_2746895	Gpr120	107221	5.147
ILMN_2749747	2410004L22Rik	76478	5.311
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ILMN_2755660	LOC100044779	1E+08	4.706
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ILMN_2757232	Aqp4	11829	-2.809
ILMN_2757807	BC031353	235493	-4.18
ILMN_2757966	Cxcl4	56744	1.979
ILMN_2758029	Prtn3	19152	1.477
ILMN_2758878	Tmem66	67887	-3.469
ILMN_2759309	Rnase6	78416	2.312
ILMN_2759344	LOC100048733	1E+08	2.915
ILMN_2760105	Olig1	50914	0.18
ILMN_2760979	Tgfbr2	21813	4.694
ILMN_2762944	Ifi27	76933	1.076
ILMN_2764466	Capsl	75568	2.635
ILMN_2764588	Igfbp7	29817	3.092
ILMN_2769567	F2rl1		5.525
ILMN_2769777	Msc	17681	1.081
ILMN_2770066	LOC100044439		3.09
ILMN_2771034	Mfge8		5.463
ILMN_2771182	H2-Q8		-0.248
ILMN_2771641	Aldh8a1	237320	-4.988
ILMN_2772077	Bok		3.879
ILMN_2773113	Capg	12332	3.527
ILMN_2773259	Lum		-0.049
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ILMN_2774572	Crygn		0.194
ILMN_2775660	Myl6		3.843
ILMN_2776087	Rab25	53868	0.006
ILMN_2776278	Ly6e		1.955
ILMN_2776419	Dnclc1		5.564
ILMN_2776431	C1qa	12259	1.102
ILMN_2777359	Serpinh1		2.384
ILMN_2777462	Pnpla3	116939	5.16

ILMN_2777769	H2-DMa	14998	3.043
ILMN_2778151	Sox9		4.628
ILMN_2778655	Vcam1	22329	1.788
ILMN_2781030	Napsa	16541	2.706
ILMN_2789294	Tmem25	71687	-3.905
ILMN_2789948	Arhgdib	11857	1.611
ILMN_2790373	Snn	20621	5.327
ILMN_2791028	App	11820	4.958
ILMN_2791665	Agxt2	268782	-3.889
ILMN_2793522	Tnfrsf19	29820	3.735
ILMN_2794645	Cyr61	16007	4.788
ILMN_2795106	Cyp1a2	13077	-3.581
ILMN_2795412	Tmem176a	66058	2.97
ILMN_2800813	Cabc1	67426	-3.573
ILMN_2801891	Cygb	114886	1.144
ILMN_2803674	S100a9	20202	1.821
ILMN_2804444	Pcdh17	219228	3.371
ILMN_2804487	Aif1	11629	1.498
ILMN_2806159	Tmsb4x	19241	3.291
ILMN_2806439	Slc17a8	216227	-2.374
ILMN_2806700	Cyba	13057	1.833
ILMN_2808811	Gpd1	14555	-2.138
ILMN_2810882	Ppic	19038	3.418
ILMN_2812926	Slc30a10	226781	-5.328
ILMN_2814005	Nid1	18073	4.919
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ILMN_2816180	Lbh	77889	0.835
ILMN_2819558	Bach2	12014	-3.618
ILMN_2820893	Selplg	20345	2.411
ILMN_2821460	Ptpn18	19253	2.292
ILMN_2821850	Nampt	59027	3.585
ILMN_2827081	Sgk2	27219	-2.032
ILMN_2830666	9130409I23Rik	619326	-3.956
ILMN_2831283	Tmem43	74122	4.321
ILMN_2831669	EG240549	240549	-4.099
ILMN_2833163	BC064033	208164	0.599
ILMN_2834379	Tgfbi	21810	0.159
ILMN_2837189	6720467C03Rik	68099	3.72
ILMN_2837671	Fblim1	74202	2.012
ILMN_2838317	Pqlc3	217430	4.973
ILMN_2844829	Prodh2	56189	-3.063
ILMN_2845214	Lrpprc	72416	-4.778

ILMN_2850233	Elf3	13710	4.033
ILMN_2851671	Myadm	50918	3.974
ILMN_2857957	Mgll	23945	-4.02
ILMN_2860479	Arpc1b	11867	3.402
ILMN_2864309	OTTMUSG00000000971		-1.589
ILMN_2864416	Rtp3	235636	-3.782
ILMN_2866901	Efemp2	58859	1.938
ILMN_2867147	Tyrobp	22177	1.795
ILMN_2870672	Fbln1	14114	1.031
ILMN_2871628	Mapk8ip1	19099	4.472
ILMN_2873750	Gldc	104174	-2.895
ILMN_2874853	Eef1b2	55949	3.147
ILMN_2878071	Lyz	17110	3.01
ILMN_2879588	Lhfp	108927	2.156
ILMN_2885532	Cpt2	12896	-5.177
ILMN_2886896	4632417N05Rik	74032	-5.072
ILMN_2888191	Ccr5	12774	0.227
ILMN_2888940	1810033M07Rik	69187	-4.617
ILMN_2890357	2610027C15Rik	230752	-0.142
ILMN_2894678	H2-T10	15024	-2.883
ILMN_2896601	Icam1	15894	5.224
ILMN_2896768	Cbr3	109857	4.213
ILMN_2901626	Tnfrsf21	94185	-1.831
ILMN_2909150	Ctgf	14219	3.858
ILMN_2910295	Crim1	50766	3.805
ILMN_2910934	Cd52	23833	2.594
ILMN_2911344	Plscr1	22038	4.902
ILMN_2913590	Lonp2	66887	-4.918
ILMN_2914744	Hn1	15374	5.01
ILMN_2915232	Cotl1	72042	1.859
ILMN_2923607	Phlda3	27280	5.507
ILMN_2924505	Gys2	232493	-4.931
ILMN_2925281	Abcd3	19299	-3.699
ILMN_2925947	Abat	268860	-5.213
ILMN_2932164	Notum	77583	-2.279
ILMN_2933887	1200013B08Rik	74131	1.744
ILMN_2939503	Ttc39a	230603	1.974
ILMN_2939681	Lyzs	17105	3.039
ILMN_2941728	Nenf	66208	5.38
ILMN_2941790	Cldn6	54419	1.387
ILMN_2943599	Ngfrap1	12070	4.785
ILMN_2950286	Ankrd1	107765	5.707
ILMN_2951682	Cobl	12808	2.669

ILMN_2954575	Arhgap30	226652	1.771
ILMN_2954868	Oasl2	23962	1.973
ILMN_2959372	Clec4b1	69810	2.342
ILMN_2960044	Cyp4a31	545670	-3.413
ILMN_2964042	Bgn	12111	0.611
ILMN_2964185	H2-M2	14990	4.798
ILMN_2965613	Abca6	76184	-5.384
ILMN_2967266	Fxyd5	18301	3.634
ILMN_2971688	Nrg1	211323	4.334
ILMN_2971816	Gltp	56356	2.583
ILMN_2973156	Esrrg	26381	-2.829
ILMN_2973824	Car14	23831	-3.596
ILMN_2976159	Mreg	381269	-5.561
ILMN_2976211	Cyp2b23	243881	-3.787
ILMN_2981169	Ifit2	15958	4.485
ILMN_2983516	Slc11a1	18173	-0.727
ILMN_2984744	Emp3	13732	1.926
ILMN_2986051	Ccbl1	70266	-4.663
ILMN_2987599	AI317395	215929	-5.772
ILMN_2987709	Slc15a3	65221	-0.581
ILMN_2988143	Plac8	231507	0.478
ILMN_2992232	Mlxipl	58805	-1.723
ILMN_2993314	Clec4n	56620	2.109
ILMN_2994299	Hgfac	54426	-4.257
ILMN_2999329	Serpina5	268591	0.017
ILMN_3000236	F11	109821	-4.447
ILMN_3006219	Fyb	23880	1.148
ILMN_3008361	Bmper	73230	1.24
ILMN_3009910	Rbm13	67920	2.722
ILMN_3033562	OTTMUSG00000017677	574404	2.082
ILMN_3040693	Lamc3	23928	4.131
ILMN_3046836	Suclg2	20917	-3.495
ILMN_3054840	AW061290	381110	-3.904
ILMN_3061070	Slc25a20	57279	-4.265
ILMN_3062267	Acot1	26897	-0.989
ILMN_3067068	Tmsb10	19240	3.81
ILMN_3070469	Entpd5	12499	-4.057
ILMN_3079257	Mup5	17844	-5.08
ILMN_3091003	Ms4a7	109225	5.49
ILMN_3100812	Gpx4	625249	3.656
ILMN_3103896	Timp1	21857	4.894
ILMN_3107059	Espn	56226	4.766
ILMN_3114124	Hsd3b7	101502	-4.573

ILMN_3117876	Chi3l3	12655	1.781
ILMN_3118707	Sla	20491	1.915
ILMN_3120510	Gvin1	74558	2.462
ILMN_3131679	Usp18	24110	2.427
ILMN_3139405	Hbs1l	56422	-4.753
ILMN_3141801	Wfdc15b	192201	1.919
ILMN_3151149	Cpne8	66871	4.172
ILMN_3152506	Atp11c	320940	-3.922
ILMN_3158499	Mdk	17242	1.533
ILMN_3158698	BC046404	192976	4.558
ILMN_3161652	Clec4a3	73149	0.224

Supplementary Table 2. Functional categories of genes in the SOH signature.

Functional category*	**P value[#]**
Cellular movement	5.41×10^{-21}
Cellular growth and proliferation	7.00×10^{-19}
Cell-to-cell signaling and interaction	4.80×10^{-18}
Cellular function and maintenance	7.61×10^{-18}
Cell death and survival	1.31×10^{-13}
Cellular development	6.02×10^{-13}
Lipid metabolism	3.43×10^{-11}
Small molecule biochemistry	3.43×10^{-11}
Free radical scavenging	2.14×10^{-9}
Protein synthesis	2.80×10^{-7}
Cellular compromise	1.18×10^{-6}
Cellular assembly and organization	1.84×10^{-6}
Cell signaling	2.44×10^{-6}
Post-translational modification	7.99×10^{-6}
Amino acid metabolism	1.11×10^{-5}
Molecular transport	1.39×10^{-5}
Protein trafficking	3.72×10^{-5}
Vitamin and mineral metabolism	9.46×10^{-5}
Protein folding	1.68×10^{-4}
Cell cycle	1.71×10^{-4}

*Functional category was defined by the Ingenuity Knowledge Base database.
[#]Fisher's exact test.

Supplementary Table 3. Canonical Pathways enriched in the SOH signature.

Ingenuity Canonical Pathways	**P values**[#]
Cdc42 Signaling	1.4×10^{-6}
CD28 Signaling in T Helper Cells	1.0×10^{-5}
OX40 Signaling Pathway	1.6×10^{-5}
Nur77 Signaling in T Lymphocytes	9.5×10^{-5}
iCOS-iCOSL Signaling in T Helper Cells	0.0004
Glycine Biosynthesis I	0.0006
Fatty Acid beta-oxidation I	0.001
Glutathione Redox Reactions I	0.001
STAT3 Pathway	0.002
T Cell Receptor Signaling	0.003
Glutamate Degradation III (via 4-aminobutyrate)	0.006
Sphingosine-1-phosphate Signaling	0.006
Signaling by Rho Family GTPases	0.007
IL-10 Signaling	0.007

[#] Fisher's exact test.

Supplementary Table 4. Significant association between the SOH subtype and YAP1 protein expression in HCC.

YAP1 expression	SOH	AH	Total
High	6	13	19
Low	0	13	13
Total	6	26	32

P = 0.02 by χ^2-test

Supplementary Table 5. Univariate and multivariate Cox regression analyses of recurrence-free survival with continuous SOH probability.

	Univariate		Multivariate	
Characteristic	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Patient sex (M or F)	1.4 (0.89–2.18)	0.14	1.2 (0.75–1.9)	0.44
Age (>60 years or not)	0.88 (0.62-1.25)	0.49	0.93 (0.63–1.37)	0.72
AFP (>300 ng/ml or not)	1.25 (0.94–1.67)	0.12	1.0 (0.74–1.37)	0.98
Cirrhosis (yes or no)	1.08 (0.72–1.64)	0.68	1.2 (0.78–1.9)	0.39
Tumor size (>5 cm or not)	1.34 (1.0–1.79)	0.04	1.14 (0.83–1.58)	0.4
Cohort (Korean or FULCI)	1.17 (0.85–1.59)	0.32	1.13 (0.8–1.6)	0.46
BCLC stage (B/C/D or 0/A)	1.74 (1.2–2.3)	< 0.001	1.42 (1.0–2.0)	0.04
SOH signature (continuous)	3.8 (2.1–7.0)	< 0.001	2.9 (1.5–5.7)	0.001

Supplementary Table 6. Univariate and multivariate Cox regression analyses of overall survival.

	Univariate		Multivariate	
Characteristic	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Patient sex (M or F)	1.3 (0.79–2.2)	0.27	1.0 (0.59–1.7)	0.92
Age (>60 years or not)	0.89 (0.15–1.36)	0.6	0.98 (0.62–1.5)	0.94
AFP (>300 ng/ml or not)	1.7 (1.2–2.3)	0.001	1.2 (0.78–1.8)	0.2
Cirrhosis (yes or no)	1.3 (0.8–2.2)	0.25	1.38 (0.8–2.3)	0.23
Tumor size (>5 cm or not)	2.0 (1.4–2.7)	< 0.001	1.6 (1.1–2.0)	0.01
Cohort (Korean or FULCI)	0.97 (0.67–14)	0.9	0.87 (0.58–1.3)	0.53
BCLC stage (B/C/D or 0/A)	2.6 (1.8–3.6)	< 0.001	2.1 (1.5–3.2)	< 0.001
SOH signature (SOH or AH)	2.2 (1.5–3.2)	< 0.001	1.8 (1.2–2.6)	0.003

Supplementary Table 7. Univariate and multivariate Cox regression analyses of overall survival with continuous SOH probability.

	Univariate		Multivariate	
Characteristic	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Patient sex (M or F)	1.3 (0.79–2.2)	0.27	1.0 (0.6–1.7)	0.92
Age (>60 years or not)	0.89 (0.15–1.36)	0.6	1.1 (0.71–1.7)	0.94
AFP (>300 ng/ml or not)	1.6 (1.2–2.3)	0.001	1.2 (0.86–1.8)	0.2
Cirrhosis (yes or no)	1.3 (0.8–2.2)	0.25	1.45 (0.84–2.5)	0.23
Tumor size (>5 cm or not)	2.0 (1.4–2.7)	< 0.001	1.6 (1.1–2.3)	0.01
Cohort (Korean or FULCI)	0.97 (0.67–14)	0.9	0.86 (0.57–1.3)	0.53
BCLC stage (B/C/D or 0/A)	2.6 (1.8–3.6)	< 0.001	2.1 (1.4–3.1)	< 0.001
SOH signature (continuous)	6.6 (3.2–13.6)	< 0.001	4.3 (2.0–9.2)	< 0.001

CI, confidence interval
AFP, alpha-fetoprotein
BCLC, Barcelona Clinic Liver Cancer
SOH, silence of Hippo pathway
AH, active Hippo pathway
FULCI, Fudan University Liver Cancer Institute

SupplementaryTable 8. Drop in concordance index in multivariable analysis

	Drop in concordance index (95% CI)	p-value
Patient sex (M or F)	0.003 (-0.006 to 0.016)	0.29
Age (>60 years or not)	0.004 (-0.005 to 0.023)	0.29
AFP (>300 ng/ml or not)	0.002 (-0.007 to 0.016)	0.37
Cirrhosis (yes or no)	0.003 (-0.016 to 0.016)	0.27
Tumor size (>5 cm or not)	0.002 (-0.007 to 0.016)	0.37
Cohort (Korean or FULCI)	0.007 (-0.007 to 0.03)	0.24
BCLC stage (B/C/D or 0/A)	0.016 (-0.008 to 0.48)	0.12
SOH signature (SOH or AH)	0.02 (-0.001 to 0.056)	0.03

Supplementary Table 9. Concordance of silence of Hippo signature with other prognostic HCC gene expression signatures in the NCI cohort.

Prognostic signature	**SOH**	**AH**	**Total**	**P value***
Number of patients	24	89	113	
NCI HS signature				5.4×10^{-19}
HS (poor)	20	2	22	
HC (good)	4	87	91	
65-gene risk score				3.5×10^{-7}
High (poor)	24	37	61	
Low (good)	0	52	52	

*χ^2-test
SOH, silence of Hippo pathway
AH, active Hippo pathway
HS, hepatic stem cell subtype (formerly known as HB subtype)
HC, hepatocyte subtype

Supplementary Table 10. Characteristics of HCC patients in the MSH cohort, stratified by SOH signature.

Characteristic	**SOH**	**AH**	**Total**	**P value***
No. of patients	22	69	91	
pAKT staining				0.017
Positive	11	16	27	
Negative	10	49	59	
ND	1	4	5	
pIGFR1 staining				0.019
Positive	8	8	16	
Negative	13	49	62	
ND	1	12	13	
pS6 staining				1.4×10^{-4}
Positive	18	22	40	
Negative	4	41	45	
ND	0	6	6	

*χ^2-test
SOH, silence of Hippo pathway
AH, active Hippo pathway
ND, not determined