

**Supplementary table 1**  
**HCC risk stratification scores and biomarkers (without independent validation)**

Biomarker type	Score/biomarker	Biomarker development phase	Level of evidence (Simon et al./ILCA)	Variables	Study design	Enrollment	Endpoint (HCC)	Major etiology	Region/country	No. subjects	Race/ethnicity	Cirrhosis	Independent validation	Reference (PMID)
Clinical NIS/NIT	US-VA model (HCC risk calculator) for HCV	2	IV/2b	Age, sex, BMI, race/ethnicity, genotype, platelets, AST, ALT, albumin, INR, hemoglobin, cirrhosis, SVR	Cohort	Retrospective	Development	HCV	U.S.	45,810	Caucasian, Black	24%	Internal (cross-validation)	30138686
	US-VA model (HCC risk calculator) for NAFLD and ALD	2	IV/2b	Age, sex, BMI, diabetes, platelets, AST, ALT, Albumin	Cohort	Retrospective	Development	NAFLD, Alcohol	U.S.	23,243	Caucasian, Black	100%	Internal (cross-validation)	31145929
	ASAP model	2	IV/2b	Age, sex, AFP, DCP	Cohort	Retrospective	Development (3/6/9m)	HBV	China	855	Asian	36%	No	34412596
	Neutrophil-to-lymphocyte ratio	2	IV/2b	Neutrophil-to-lymphocyte ratio	Cohort	Retrospective	Development	HBV on NA	China	1,599	Asian	100%	No	34074986
	Degasperi <i>et al.</i>	2	IV/2b	AFP, DCP, diabetes	Cohort	Retrospective	Development (4y)	HCV post-SVR with DAA	Italy	400	n.a.	100%	No	34738664
SNP	Hepatic fat-genetic risk score	3	III/2a	SNPs of <i>PNPLA3</i> , <i>TM6SF2</i> , <i>MBOAT7</i> , <i>GCKR</i> , and hepatic fat content	Cohort	Prospective-retrospective	Development; Recurrence	HCV treated with DAA	Italy	452; 57	n.a.	100%; 100%	No	32762045
Tissue transcriptome	Immune-mediated cancer field signature	1	n.a.	172 mRNAs	Cohort	Prospective-retrospective	Development	HCV	Italy	216	Caucasian	100%	No	31344396
	HSC signature	1	n.a.	122 mRNAs	Cohort	Prospective-retrospective; Retrospective	Development; Recurrence	HCV; HCV, HBV	Italy; Japan	216; 82	Caucasian	100%; 52%	No	26045137
	Activated HSC gene signature	1	n.a.	37 mRNAs	Cohort	Retrospective	Recurrence after curative resection	HBV	China	247	Asian	91%	No	25833323
	HIR gene signature	1	n.a.	233/65 mRNAs	Cohort	Retrospective	Early/late recurrence	HBV	Korea, Hong Kong, China	72 + 96 + 228	Asian	50% + 63% + 93%	Yes, within the study	25536056
	Ectopic lymphoid structure signature	1	n.a.	12 mRNAs	Cohort	Retrospective	Late recurrence after curative resection	HCV, HBV	Japan	82	Asian	52%	No	26502405
Imaging-based	FAST score	3	III/2a	FibroScan, AST	Cohort	Prospective-retrospective	Development	HCV post-SVR	Japan	280	Asian	n.a.	No	32697871

Prospective-retrospective enrollment indicates Prospective sample collection–Retrospective-Blinded Evaluation (PRoBE) design.

No. subjects for training and validation sets are separately shown with "+" in between.

HCC, hepatocellular carcinoma; ILCA, International Liver Cancer Association; HBV, hepatitis B virus; HCV, hepatitis C virus; SVR, sustained virologic response; NAFLD, non-alcoholic fatty liver disease; VA, Veterans Affairs; HSC, hepatic stellate cell; HIR, hepatic injury and regeneration.

**Supplementary table 2**  
**HCC early detection scores and biomarkers (individual studies used for the meta-analyses in Table 2 and studies published after the meta-analyses).**

Biomarker type	Score/biomarker (cutoff)	Biomarker development phase	Level of evidence (Simon et al./ILCA)	Variables	Study design	Enrollment	Major etiology	Region/country	No. subjects	Race/ethnicity	Cirrhosis%, HCC : control	Definition of early-stage HCC	Sensitivity	Specificity	AUROC	Independent validation	Reference (PMID)
Clinical tumor markers	AFP (5 ng/mL)	3	II/2a	AFP	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	36% (any stage)	86% (any stage)	0.70 (any stage)	Yes, independent studies	30153338
	AFP (5 ng/mL)	3	II/2a	AFP	Cohort	Prospective-retrospective	HBV	China	36 (18) : 108 (matched)	Asian	75% : 75%	n.a.	56% (any stage)	88% (any stage)	0.74 (any stage)	Yes, independent studies	27731353
	AFP (20 ng/mL)	3	II/2a	AFP	Cohort	Prospective-retrospective	HBV, HCV	Japan	104 (90) : 104 (matched)	Asian	n.a.	n.a.	12 months prior to HCC: 35% (any stage)	12 months prior to HCC: 86% (any stage)	n.a.	Yes, independent studies	24057163
	AFP (20 ng/mL)	3	II/2a	AFP	Cohort	Prospective-retrospective	HCV	U.S.	39 (24) : 77 (matched)	Caucasian, Black, Hispanic	56% : 57%	n.a.	57% (any stage)	76% (any stage)	0.72 (any stage)	Yes, independent studies	19852963
	AFP-L3% (4%)	3	II/2a	AFP-L3%	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	46% (any stage)	91% (any stage)	0.69 (any stage)	Yes, independent studies	30153338
	AFP-L3% (7%)	3	II/2a	AFP-L3%	Cohort	Prospective-retrospective	HBV, HCV	Japan	104 (90) : 104 (matched)	Asian	n.a.	n.a.	12 months prior to HCC: 34% (any stage)	12 months prior to HCC: 75% (any stage)	n.a.	Yes, independent studies	24057163
	DCP (20 mAU/mL)	3	II/2a	DCP	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	17% (any stage)	83% (any stage)	0.59 (any stage)	Yes, independent studies	30153338
	DCP (32 mAU/mL)	3	II/2a	DCP	Cohort	Prospective-retrospective	HBV	China	36 (18) : 108 (matched)	Asian	75% : 75%	n.a.	39% (any stage)	93% (any stage)	0.57 (any stage)	Yes, independent studies	27731353
	DCP (40 mAU/mL)	3	II/2a	DCP	Cohort	Prospective-retrospective	HBV, HCV	Japan	104 (90) : 104 (matched)	Asian	n.a.	n.a.	12 months prior to HCC: 12% (any stage)	12 months prior to HCC: 94% (any stage)	n.a.	Yes, independent studies	24057163
	DCP (40 mAU/mL)	3	II/2a	DCP	Cohort	Prospective-retrospective	HCV	U.S.	39 (24) : 77 (matched)	Caucasian, Black, Hispanic	56% : 57%	n.a.	63% (any stage)	88% (any stage)	0.83 (any stage)	Yes, independent studies	19852963
Combination of AFP, AFP-L3, or DCP	AFP (5 ng/mL) + AFP-L3% (4%)	3	III/2b	AFP, AFP-L3%	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	66% (any stage)	85% (any stage)	0.78 (any stage)	Yes, independent studies	30153338
	AFP (5 ng/mL) + DCP (20 mAU/mL)	3	II/2a	AFP, DCP	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	46% (any stage)	71% (any stage)	0.61 (any stage)	Yes, independent studies	30153338
	AFP (5 ng/mL) + DCP (32 mAU/mL)	3	II/2a	AFP, DCP	Cohort	Prospective-retrospective	HBV	China	36 (18) : 108 (matched)	Asian	75% : 75%	n.a.	72% (any stage)	82% (any stage)	n.a.	Yes, independent studies	27731353
	AFP (20 ng/mL) + DCP (40 mAU/mL)	3	II/2a	AFP, DCP	Cohort	Prospective-retrospective	HCV	U.S.	39 (24) : 77 (matched)	Caucasian, Black, Hispanic	56% : 57%	n.a.	86% (any stage)	69% (any stage)	0.88 (any stage)	Yes, independent studies	19852963
	AFP (20 ng/mL) + AFP-L3% (10%) + DCP (7.5 ng/mL)	3	II/2a	AFP, AFP-L3%, DCP	Cohort	Prospective-retrospective	HCV, alcohol, NASH	U.S. (VA system)	484	Caucasian, Black, Latino	100%	n.a.	31% (any stage)	91% (any stage)	n.a.	Yes, independent studies	35124267
	AFP (5 ng/mL) + AFP-L3% (4%) + DCP (20 mAU/mL)	3	II/2a	AFP, AFP-L3%, DCP	Cohort	Prospective-retrospective	HBV	Korea	42 (38) : 168 (matched)	Asian	93% : 93%	n.a.	77% (any stage)	66% (any stage)	0.69 (any stage)	Yes, independent studies	30153338
Clinical score	GALAD score (-0.63)	3	III/2a	Gender, Age, AFP, AFP-L3%, DCP	Cohort	Prospective-retrospective	HCV, alcohol, NASH	U.S.	355	Caucasian, Black, Latino	100%	BCLC 0/A	74%	87%	n.a.	Yes, independent studies	34618932
	GALAD score (-0.63)	3	III/2a	Gender, Age, AFP, AFP-L3%, DCP	Cohort	Prospective-retrospective	HCV, alcohol, NASH, NAFLD, alcohol, HCV, others	U.S. (VA system)	484	Caucasian	100%	Single, ≤5 cm	54%	78%	0.75	Yes, independent studies	35124267
Plasma cfDNA/ctDNA	Methylated SEPT9	2	IV/3	SEPT9	Case-control	Retrospective	alcohol, HCV, others	U.S.	60 (49) : 103	n.a.	100% : 100%	n.a.	77% (any stage);	64% (any stage)	n.a.	Yes, independent studies	33765926
	Methylated SEPT9	2	IV/3	SEPT9	Case-control	Retrospective	NASH, alcohol	UK	38 : 103	n.a.	76% : 30%	n.a.	89% (any stage)	82% (any stage)	0.89 (any stage)	Yes, independent studies	33931320

Methylated <i>SEPT9</i>	2	IV/3	<i>SEPT9</i>	Case-control	Retrospective	HCV, HBV, others	Japan	136 (62) : 45	Asian	50% : 73%	n.a.	63% (any stage)	72% (any stage)	n.a.	Yes, independent studies	32140662
Methylated <i>SEPT9</i>	2	IV/3	<i>SEPT9</i>	Case-control	Retrospective	HBV, HCV	China	64 (23) : 44	Asian	n.a. : 100%	n.a.	n.a.	n.a.	0.66 (any stage)	Yes, independent studies	32945374
Methylated <i>SEPT9</i>	2	IV/3	<i>SEPT9</i>	Case-control	Retrospective	HBV	China	104 (46) : 95	Asian	77% : 66%	BCLC A	77%	83%	0.8	Yes, independent studies	33178361
Methylated <i>SEPT9</i>	2	IV/3	<i>SEPT9</i>	Case-control	Retrospective	HCV, alcohol, NASH, HBV	France, Germany	51 (33) : 135 + 47 (18) : 56	n.a.	100% : 100% + 100% : 100%	BCLC 0/A	France: 94% (any stage) Germany: 85% (any stage) France+Germany: 73%	France: 84% (any stage) Germany: 91% (any stage) France+Germany: 86%	France cohort: 0.94 (any stage) Germany cohort: 0.93 (any stage) France + Germany: 0.86	Yes, independent studies	29627389

Prospective-retrospective enrollment indicates Prospective sample collection–Retrospective-Blinded Evaluation (PRoBE) design.

No. subjects for case-control studies are shown as HCC case (early-stage HCC) : control. No. subjects for training and validation sets are separately shown with "+" in between.

Performance metrics for early-stage HCC within 6 months of diagnosis are presented in cohort studies unless indicated otherwise.

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; AUROC, area under receiver operating characteristic curve; ILCA, International Liver Cancer Association; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease;

BCLC, Barcelona clinic liver cancer; AJCC, American Joint Committee on Cancer; DCP, des-gamma-carboxy prothrombin; VA, Veterans Affairs; GALAD, Gender, Age, AFP-L3%, AFP, and DCP; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.

**Supplementary table 3**

**Studies used for meta-analysis of GALAD score for early HCC detection.**

First author	Biomarker development phase	Level of evidence (Simon et al./ILCA)	Study design	Enrollment	Major etiology	Region/country	No. subjects	Race/ethnicity	Cirrhosis (HCC : control)	Definition of early-stage HCC	Sensitivity	Specificity	AUROC	Reference (PMID)
Chalasan (cohort 1)	2	IV/3	Case-control	Retrospective	HCV, NASH, alcohol, HBV	U.S., France, Germany, Italy, Spain, Taiwan, Thailand	136 (81) : 404	Caucasian, Black, Asian	96 : 93	BCLC 0/A	67%	86%	0.83	34391922
(cohort 2)	2	IV/3	Case-control	Retrospective	HCV, NASH, alcohol, HBV	U.S., France, Germany, Italy, Spain, Taiwan, Thailand	156 (78) : 245	Caucasian, Black, Asian	97 : 92	BCLC 0/A	71%	93%	0.89	34391922
Lin	2	IV/3	Case-control	Retrospective	HBV, others	China	122 (37) : 125	Asian	37 : 37	AJCC I/II	65%	94%	0.84	35244350
Schotten	2	IV/3	Case-control	Retrospective	HCV, HBV, others	Germany	196 (n.a.) : 377	n.a.	83 : 33	n.a.	88% (any stage)	95% (any stage)	0.97 (any stage)	34451832
Best	2	IV/3	Case-control	Retrospective	NASH	Germany	125 (29) : 231	n.a.	76 : 21	BCLC 0/A	72%	95%	0.92	31712073
Yang (Mayo cohort)	2	IV/3	Case-control	Retrospective	HCV, NAFLD, alcohol, HBV	U.S.	111 (60) : 180	Caucasian, Asian	98 : 86	BCLC 0/A	82%	86%	0.82	30464023
(EDRN cohort)	2	IV/3	Case-control	Retrospective	HCV, HBV, others	U.S.	233 (10) : 412	Caucasian, Asian	100 : 100	BCLC 0	80%	79%	0.86	30464023
Berhane (Japan cohort)	2	IV/3	Case-control	Retrospective	HCV, HBV, others	Japan	1514 (888) : 2962	n.a.	n.a. : n.a.	Within Milan	61%	96%	0.91	26775025
(Germany cohort)	2	IV/3	Case-control	Retrospective	HBV, HCV, others	Germany	275 (n.a.) : 1003	n.a.	n.a. : n.a.	n.a.	88% (any stage)	89% (any stage)	0.94 (any stage)	26775025
Singal	3	III/2a	Cohort	Prospective-retrospective	HCV, alcohol, NASH	U.S.	42 (24) : 355	Caucasian, Black, Latino	100 : 100	BCLC 0/A	54%	87%	0.78	34618932
Tayob	3	III/2a	Cohort	Prospective-retrospective	HCV, alcohol, NASH	U.S.	49 (34) : 497	Caucasian	100 : 100	Single, ≤5 cm	62%	79%	0.79	35124267

Prospective-retrospective enrollment indicates Prospective sample collection–Retrospective-Blinded Evaluation (PRoBE) design.

No. subjects for case-control studies are shown as HCC case (early-stage HCC) : control. No. subjects for training and validation sets are separately shown with "+" in between.

Performance metrics for early-stage HCC are presented unless indicated otherwise.

For phase 3 studies, performance metrics for early-stage HCC within 24 months of diagnosis or anytime before diagnosis are presented.