Proteome Multimarker Panel for the Early Detection of Hepatocellular Carcinoma: Multicenter Derivation, validation, and Comparison

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LIST OF ABBREVIATIONS:

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; MRM-MS, multiple reaction monitoring-mass spectrometry; CHB, chronic hepatitis B; CHC, chronic hepatitis C; AUROC; area under the receiver operating characteristics curve

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SUPPLEMENTS

SUPPLEMENTARY METHODS

Quantitative MRM-MS analysis

Prior to sample preparation, block randomization was performed to minimize the variance. A volume of 44 µL of each sample was mixed with 176 µL of MARS buffer A (Agilent Technologies, CA) and passed through 0.22-µm Spin-X filters (Corning Costar, NY). The 6 most abundant proteins (albumin, immunoglobulin A, immunoglobulin G, transferrin, haptoglobin, and α1-antitrypsin) were removed from 200 µL of each sample mixture by a Multiple Affinity Removal System Human-6 (MARS Hu-6×100 mm; Agilent Technologies, Santa Clara, CA) column that was loaded onto a high-performance liquid chromatography system (Shimadzu Co., Kyoto, Japan). Five milliliters of each depleted sample were then concentrated on a 3000-Da molecular weight cutoff (MWCO) filter unit (Amicon Ultra-4 3K, Millipore, MA) in a precooled centrifuge at 4°C for 6 hours.

The protein in each depleted sample was quantified by bicinchoninic acid (BCA) assay, in which 2 mg/mL of BSA standard was diluted 1:2 6 times to generate a standard curve. Each sample was diluted 1:20 and 1:40 and loaded onto a 96-well plate. Further, 200 µL of a 1:50 mixture of copper solution and BCA solution was added and incubated at 37°C for 1 hour before scanning.

Samples were digested according to the results of the BCA assay. For a 100-µg digestion, each sample was adjusted with HPLC water to a volume of 20 µL. The adjusted sample was mixed with 20 µL of 0.2% RapiGest, 20 mM DTT, and 100 mM ABC buffer and reacted in 60°C for 1 hour. Next, 10 µL 100 mM iodoacetamide (IAA) was added and stored in the dark at room temperature for 30 minutes, after which 40 µL trypsin (Promega, sequencing-grade modified, Madison, WI) in 50 mM ABC was added to the mixture and incubated at 37°C for 4 hours. Finally, 10 µL 10% formic acid was added and incubated at 37°C to stop the reaction. Supernatants were collected after centrifugation at 15,000 rpm and 4°C.

Prior to the mass spectrometry analysis, each sample was spiked with stable isotope-labeled standard peptide (30% to 70% purity per the manufacturer, JPT, Berlin, Germany) at a 9:1 ratio.

Capillary Liquid Chromatography

MRM-MS analysis was performed on a fully automated online 1260 Capillary-flow liquid chromatography (LC) system (Agilent Technologies, Santa Clara, CA, USA). The autosampler was set to 4 °C, where the LC separation was performed at 40 °C. Sample cleanup was performed using a guard column (2.1 × 15.0 mm, 1.8 µm, 80 Å), and peptides were separated on an analytical column (0.5 × 35.0 mm, 3.5 µm, 80 Å) (both columns from Agilent Technologies, Santa Clara, CA, USA).

Ten microliters of the digested sample were injected onto a guard column at 40 µL/min for a minute in 10% solvent B. Sample flow was directed from the guard to the analytical column after the valves were switched. Then, 10% solvent B was run at a flow rate of 40 µL/min for a minute. To separate the peptides, A linear gradient of 10% to 60% solvent B over 5 mins at 40 µL/min eluted bound peptides from the analytical column. The column wash was held at 90% solvent B for 1 min at 40 µL/min and then equilibrated at 10% solvent B for 4 mins. The switching valve was returned to its original position after a minute of equilibration, while reconditioning performed simultaneously in both guard and analytical columns.

Mass Spectrometry

Quantitative analysis was performed on an Agilent 6490 triple quadrupole (QqQ) mass spectrometer with an Electrospray source (Agilent Technologies, Santa Clara, CA, USA), operated in positive ion, scheduled multiple reaction monitoring (MRM) mode. Gas temperature was set to 250 °C where gas flow as 15 L/min. Sheath gas temperature was set to 350 °C where the gas flows at 12 L/min. The delta electron multiplier voltage (EMV) was set to 200 V, and the cell accelerator voltage and fragment voltage were 5 V and 380 V, respectively.

SUPPLEMENTARY FIGURES

Figure S1. Density plot of the 17 marker peptides in the MRM-MS panel. Density plot of raw and log $(x+10^{-10})$-transformed data on the 17 markers. The less skewed format was used as the final transformation method.

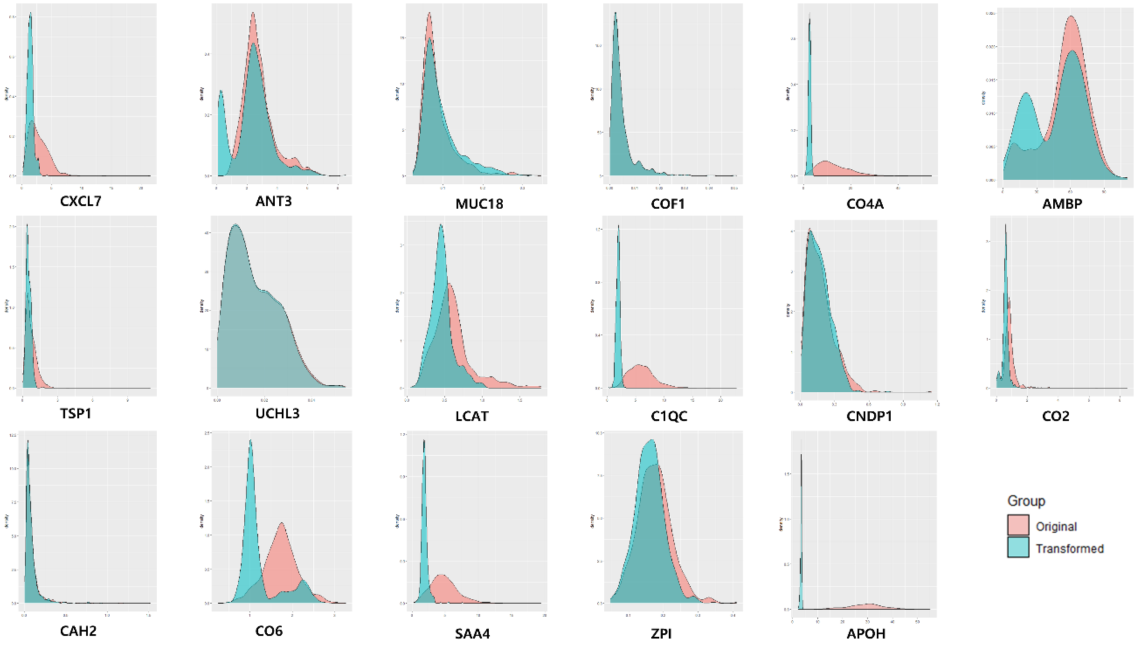


Figure S2. Performance of AFP and the MRM-MS panel excluding general proteins. ROC curves of AFP and the MRM-MS panel with and without the combination of AFP and/or PIVKA-II excluding general proteins in the (A) training, (B) test, and (C) confirmation sets.

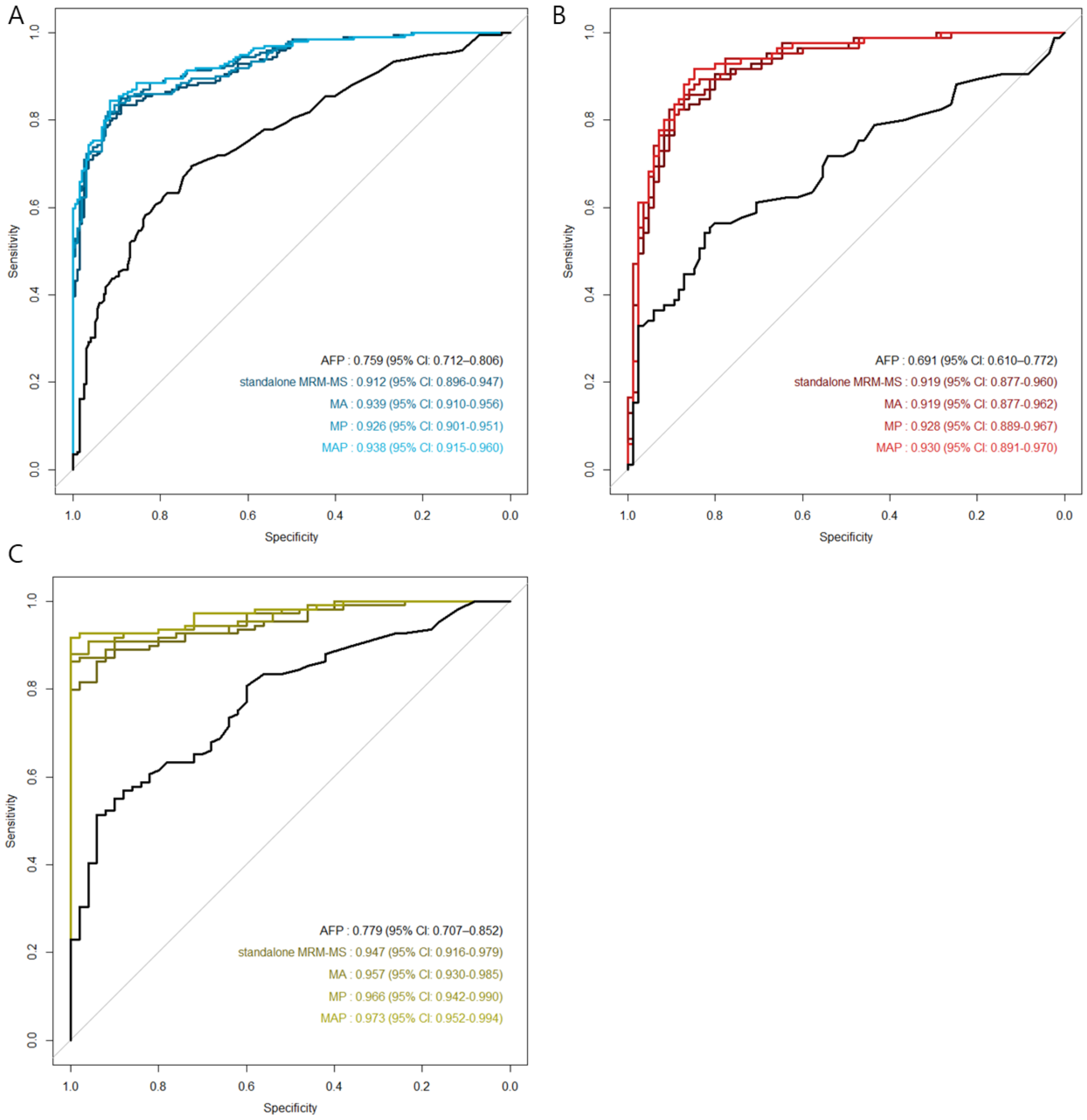


Figure S3. Performance of AFP and the MRM-MS panel with/without combination of AFP and/or PIVKA-II in the test set. (A): ROC curve of AFP and the MRM-MS panel with/without combination of AFP and/or PIVKA-II. (B): ROC curve of AFP and the MRM-MS Panel with/without combination of AFP and/or PIVKA-II in the small(<2cm) single HCC.

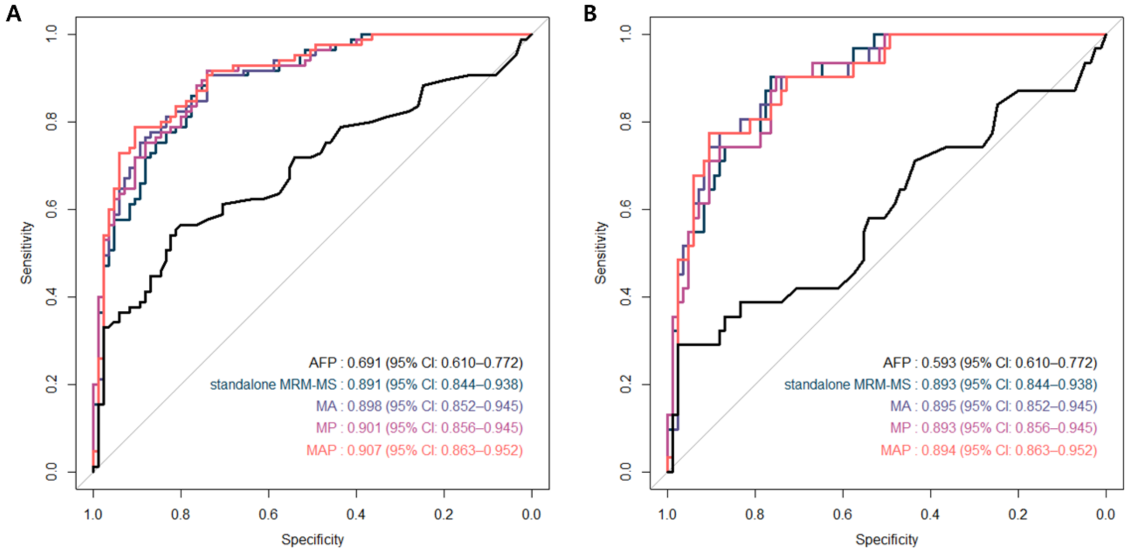


Figure S4. Performance of GALAD score and the MRM-MS panel with and without AFP and PIVKA-II in detecting HCC. ROC curves of the GALAD score, standalone MRM-MS panel, MRM-MS + AFP (MA) panel, MRM-MS + PIVKA-II (MP) panel, and MRM-MS + AFP + PIVKA-II (MAP) panel in the GALAD cohort.

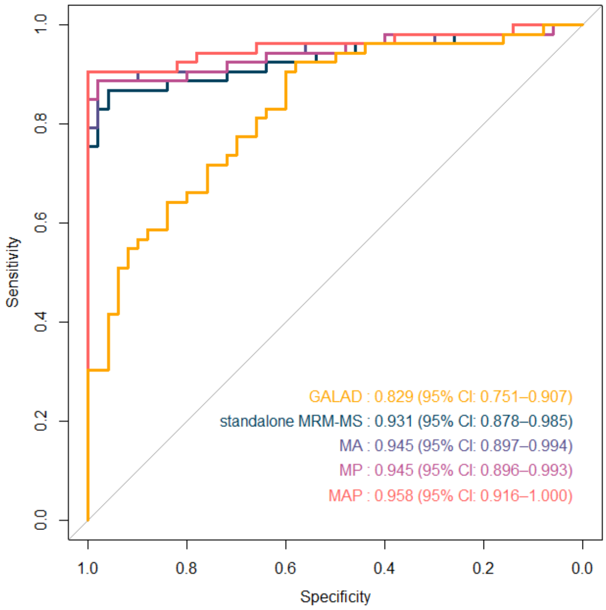
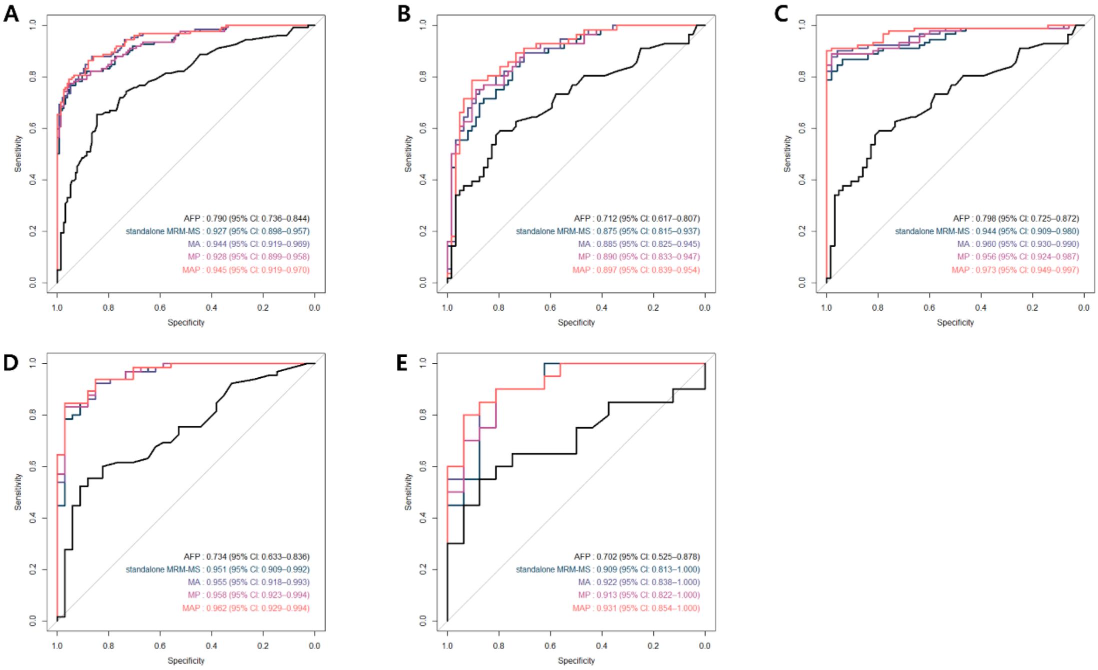


Figure S5. Subgroup analysis of patients with cirrhosis and chronic hepatitis B. ROC curves of AFP, standalone MRM-MS panel, MRM-MS + AFP (MA) panel, MRM-MS + PIVKA-II (MP) panel, and MRM-MS + AFP + PIVKA-II (MAP) panel in the (A) training set, (B) test set, and (C) confirmation set with cirrhosis and in the (D) training set and (E) test set with chronic hepatitis B.



SUPPLEMENTARY TABLES

Table S1. Logistic regression equation (logit [P=HCC]) with selective log transformation for the 17 marker proteins

Protein (gene name)	Peptide sequence	Transformation	Coefficient
(Intercept)			-1.977
PPBP	NIQSLEVIGK	Log $(x+10^{-10})$	1.714
SERPINC1	VWELSK	Normal	-1.48
MCAM	EVTVPVFYPTEK	Log $(x+10^{-10})$	-22.293
CFL1	NIILEEGK	Normal	141.879
C4A	DSSTWLTAFVLK	Log $(x+10^{-10})$	1.175
AMBP	TVAACNLPIVR	Log $(x+10^{-10})$	0.034
THBS1	GTSQNDPNWVVR	Log $(x+10^{-10})$	2.614
UCHL3	YLENYDAIR	Normal	32.042
LCAT	SSGLVSNAPGVQIR	Log $(x+10^{-10})$	-10.386
C1QC	TNQVNSGGVLLR	Log $(x+10^{-10})$	-2.258
CNDP1	AIHLDLEEYR	Log $(x+10^{-10})$	2.839
C2	HAFILQDTK	Log $(x+10^{-10})$	5.261
CA2	SADFTNFDPR	Log $(x+10^{-10})$	22.593
C6	QLEWGLER	Log $(x+10^{-10})$	1.005
SAA4	GPGGVWAAK	Log $(x+10^{-10})$	-2.048
SERPINA10	LFDEINPETK	Log $(x+10^{-10})$	19.721
APOH	ATVVYQGER	Normal	0.078

PPBP, platelet basic protein; SERPINC1, antithrombin-III; MCAM, cell surface glycoprotein; CFL1, cofilin-1; C4A, complement C4-A; AMBP, protein AMBP**;** THBS1, thrombospondin-1**;** UCHL3, ubiquitin carboxyl-terminal hydrolase isozyme L3; LCAT, phosphatidylcholine-sterol acyltransferase; C1QC, complement C1q subcomponent subunit C; CNDP1, Beta-Ala-His dipeptidase; C2, cytochrome c oxidase subunit 2; CA2, carbonic anhydrase 2; C6, complement component C6; SAA4, serum amyloid A-4 protein; SERPINA10, protein Z-dependent protease inhibitor; APOH, beta-2-glycoprotein 1.

Table S2. Characteristics of the GALAD cohort

	HCC (n=53)	Control (n=50)	P value
Age, years	60.0 (52.0–66.0)	57.0 (51.0–61.0)	0.072
Sex, N (%)			<0.001
Female	7 (13.2%)	26 (52.0%)	
Male	46 (86.8%)	24 (48.0%)	
Body mass index, kg/m^2	25.2 (22.5–27.1)	24.4 (23.0–27.9)	0.791
Platelet, x 10^3/μL	162.0 (121.0–192.0)	74.0 (56.0–102.0)	<0.001
Creatinine, mg/dL	0.9 (0.8–1.0)	0.7 (0.6–0.9)	<0.001
Albumin, g/dL	3.8 (3.6–4.1)	3.9 (3.7–4.3)	0.437
ALT, IU/L	22.0 (18.0–37.0)	23.0 (19.0–30.0)	0.685
Total bilirubin, mg/dL	0.6 (0.4–0.8)	1.6 (1.0–2.3)	<0.001
Prothrombin time, INR	1.1 (1.0–1.1)	1.1 (1.1–1.3)	<0.001
Risk factors			0.001
Cirrhosis, N (%)	42 (79.2%)	50 (100.0%)	
Noncirrhotic CHB, N (%)	9 (17.0%)	0	
Noncirrhotic CHC, N (%)	2 (3.8%)	0	
Others, N (%)	0		
Child-Pugh class, N (%)			0.003
A	50 (94.3%)	35 (70.0%)	
B	3 (5.7%)	15 (30.0%)	
Alcoholic, N (%)	4 (7.5%)	6 (12.0%)	0.518
Diabetes mellitus, N (%)	14 (26.4%)	5 (10.0%)	0.058
Hypertension, N (%)	18 (34.0%)	13 (26.0%)	0.506
AFP, ng/mL	6.8 (3.0–58.1)	3.0 (2.3–5.6)	<0.001
PIVKA-II, mAU/mL	68.0 (27.0–241.0)	17.0 (14.0–21.0)	<0.001
Tumor number, N (%)			
1	47 (88.7%)		
2	4 (7.5%)		
3	2 (3.8%)		

Tumor size, cm	2.5 (1.9–3.5)
AJCC stage, n (%)	
IA	17 (32.1%)
IB	30 (56.6%)
II	6 (11.3%)

Data are provided as N (%) or median (interquartile range).

HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; INR, international normalized ratio; CHB, chronic hepatitis B; CHC, chronic hepatitis C; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AJCC, American Joint Committee on Cancer.

Table S3. Performance of AFP and the MRM-MS panel with and without AFP and PIVKA-II compared with GALAD in detecting HCC

	AUROC 95% CI	P value	Sensitivity (%)	Specificity (%)
GALAD	0.718 (0.751–0.907)		52.8	92.0
Standalone MRM-MS panel	0.931 (0.878–0.985)	<0.001*	88.7	82.0
MA panel	0.945 (0.897–0.994)	0.064†	92.5	70.0
MP panel	0.945 (0.896–0.993)	0.013†	88.7	98.0
MAP panel	0.958 (0.916–1.000)	0.009†	90.6	98.0

* AUROC of the standalone MRM-MS panel versus AUROC of GALAD score.

† AUROC of the multimarker panel with AFP and/or PIVKA-II versus AUROC of the standalone MRM-MS panel.

AUROC; area under the receiver operating characteristics curve; AFP, alpha-fetoprotein; MA, multiple reaction monitoring-mass spectrometer + AFP; MP, multiple reaction monitoring-mass spectrometer + protein induced by vitamin K absence or antagonist-II; MAP, multiple reaction monitoring-mass spectrometer + AFP + protein induced by vitamin K absence or antagonist-II.

Table S4A. Subgroup analysis of patients with cirrhosis

	AUROC 95% CI	P value	Sensitivity (%)	Specificity (%)
Training set				
AFP	0.790 (0.736–0.844)		20.2	97.5
Standalone MRM-MS panel	0.927 (0.898–0.957)	<0.001*	76.6	94.9
MA panel	0.944 (0.919–0.969)	0.019†	86.3	87.9
MP panel	0.928 (0.899–0.958)	0.672†	76.6	95.5
MAP panel	0.945 (0.919–0.970)	0.021†	77.4	96.2
Test set				
AFP	0.712 (0.617–0.807)		28.6	96.9
Standalone MRM-MS panel	0.875 (0.815–0.937)	0.005*	76.8	78.1
MA panel	0.885 (0.825–0.945)	0.591†	87.5	70.3
MP panel	0.890 (0.833–0.947)	0.088†	80.4	76.6
MAP panel	0.897 (0.839–0.954)	0.303†	80.4	81.3
Confirmation set				
AFP	0.798 (0.725–0.872)		36.7	96.0
Standalone MRM-MS panel	0.944 (0.909–0.980)	<0.001*	88.9	82.0
MA panel	0.960 (0.930–0.990)	0.005†	92.2	70.0
MP panel	0.956 (0.924–0.987)	0.005†	88.9	98.0
MAP panel	0.973 (0.949–0.997)	0.001†	90.0	98.0

[*] AUROC of standalone MRM-MS panel versus AUROC of AFP.

[†] AUROC of multimarker panel with AFP and/or PIVKA-II versus AUROC of the standalone MRM-MS panel.

AUROC; area under the receiver operating characteristics curve; AFP, alpha-fetoprotein; MA, multiple reaction monitoring-mass spectrometer + AFP; MP, multiple reaction monitoring-mass spectrometer + protein induced by vitamin K absence or antagonist-II; MAP, multiple reaction monitoring-mass spectrometer + AFP + protein induced by vitamin K absence or antagonist-II.

Table S4B. Subgroup analysis of patients with chronic hepatitis B

	AUROC 95% CI	P value	Sensitivity (%)	Specificity (%)
Training set				
AFP	0.734 (0.633–0.836)		13.8	97.1
Standalone MRM-MS panel	0.951 (0.909–0.992)	<0.001*	86.2	85.3
MA panel	0.955 (0.918–0.993)	0.286†	92.3	85.3
MP panel	0.958 (0.923–0.994)	0.085†	87.7	88.2
MAP panel	0.962 (0.929–0.994)	0.111†	84.6	97.1
Test set				
AFP	0.702 (0.525–0.878)		15.0	100.0
Standalone MRM-MS panel	0.909 (0.813–1.000)	0.048*	85.0	87.5
MA panel	0.922 (0.838–1.000)	0.388†	90.0	81.3
MP panel	0.913 (0.822–1.000)	0.843†	85.0	81.3
MAP panel	0.931 (0.854–1.000)	0.298†	85.0	81.3

* AUROC of the standalone MRM-MS panel versus AUROC of AFP.

† AUROC of multimarker panel with AFP and/or PIVKA-II versus AUROC of the standalone MRM-MS panel.

AUROC; area under the receiver operating characteristics curve; AFP, alpha-fetoprotein; MA, multiple reaction monitoring-mass spectrometer + AFP; MP, multiple reaction monitoring-mass spectrometer + protein induced by vitamin K absence or antagonist-II; MAP, multiple reaction monitoring-mass spectrometer + AFP + protein induced by vitamin K absence or antagonist-II.

Table S5. MS Method Information of 383 targets

Protein	Precursor Mz	Precursor Charge	Product Mz	Product Charge	Fragment Ion	Retention Time
A1AG1_NWGLSVYADKPETTK	570.3	3	704.9	2	y13	37.1
A1AG1_SDVVYTDWK	556.8	2	811.4	1	y6	34.5
A1AT_ITPNLAEFAFSLYR	821.4	2	1103.6	1	y9	52.6
A1BG_LELHVDGPPPRPQLR	575.3	3	616.3	2	y11	35.4
A2AP_LGNQEPGGQTALK	656.8	2	771.4	1	y8	26.5
A2AP_LCQDLGPGAFR	617.3	2	604.3	1	y6	35.7
A2AP_QEDDLANINQWVK	524.9	3	674.4	1	y5	43.6
A2AP_DFLQSLK	425.7	2	588.4	1	y5	39.1
A2AP_LFGPDLK	395.2	2	529.3	1	y5	35.3
A2GL_DLLLPQPDLR	590.3	2	725.4	1	y6	43.2
A2GL_GQTLLAVAK	450.8	2	715.5	1	y7	32.0
A2MG_NEDSLVFVQTDK	697.8	2	836.5	1	y7	36.5
A2MG_TEHPFTVEEFVLPK	558.3	3	861.5	1	y7	45.2
A2MG_FEVQVTVPK	523.8	2	770.5	1	y7	37.5
A2MG_QGIPFFGQVR	574.8	2	850.5	1	y7	45.0
A2MG_TGTHGLLVK	309.2	3	412.8	2	y8	25.4
A2MG_AIGYLNTGYQR	628.3	2	1071.5	1	y9	33.9
A2MG_HYDGSYSTFGER	473.5	3	508.3	1	y4	28.6
A2MG_TEVSSNHVLIYLDK	540.0	3	694.4	2	y12	37.9
AFAM_YHYLIR	432.7	2	564.4	1	y4	29.1
ALBU_DLGEENFK	476.2	2	723.3	1	y6	29.2
ALBU_LVNEVTEFAK	575.3	2	937.5	1	y8	35.8
ALBU_SLHTLFGDK	339.9	3	465.8	2	y8	33.1
ALBU_LCTVATLR	467.3	2	660.4	1	y6	30.7
ALBU_DDNPNLPR	470.7	2	596.4	1	y5	25.4
ALBU_YLYEIAR	464.3	2	651.3	1	y5	34.2
ALBU_AAFTECCQAADK	686.3	2	1082.4	1	y9	26.2
ALBU_AACLLPK	386.7	2	630.4	1	y5	29.4
ALBU_LVTDLTK	395.2	2	577.3	1	y5	28.3
ALBU_QNCELFEQLGEYK	553.3	3	645.3	1	b5	42.9
ALBU_FQNALLVR	480.8	2	685.4	1	y6	35.7
ALBU_VPQVSTPTLVEVSR	504.6	3	589.3	1	y5	38.7
ALBU_RPCFSALEVDETYVPK	637.6	3	719.3	1	b6	40.9
ALBU_QTALVELVK	500.8	2	587.4	1	y5	37.7
ALS_ANVFVQLPR	522.3	2	759.5	1	y6	39.3
ALS_NLIAAVAPGAFLGLK	727.9	2	802.5	1	y8	51.4

ALS_LEYLLLSR	503.8	2	764.5	1	y6	42.7
ALS_LEALPNSLLAPLGR	732.4	2	1037.6	1	y10	48.9
AMBP_TVAACNLPIVR	607.3	2	1013.6	1	y9	36.1
AMBP_EYCGVPGDGDEELLR	854.9	2	1100.5	1	y10	37.8
ANGT_DPTFIPAPIQAK	649.4	2	724.4	1	y7	40.4
ANGT_VLSALQAVQGLLVAQGR	575.0	3	643.4	1	y6	52.2
ANGT_SLDFTELDVAAEK	719.4	2	975.5	1	y9	43.4
ANT3_VWELSK	381.2	2	662.4	1	y5	31.7
ANT3_VAEGTQVLELPFK	715.9	2	746.4	1	y6	45.4
ANT3_LPGIVAEGR	456.3	2	531.3	1	y5	32.0
APOA1_THLAPYSDELR	434.6	3	619.3	1	y5	31.0
APOA2_EPCVESLVSQYFQTVTDYGK	784.0	3	1062.5	2	y18	53.0
APOA2_SPELQAEAK	486.8	2	659.4	1	y6	24.1
APOA4_IDQNVEELK	544.3	2	974.5	1	y8	28.7
APOA4_ISASAEELR	488.3	2	775.4	1	y7	27.8
APOB_EVYGFNPEGK	570.3	2	911.4	1	y8	32.7
APOB_SVSLPSLDPASAK	636.3	2	885.5	1	y9	38.7
APOB_QGFFPDSVNK	569.8	2	659.3	1	y6	36.1
APOB_ALVDTLK	380.2	2	575.3	1	y5	30.9
APOB_SVGFHLPSR	333.9	3	407.2	2	y7	33.6
APOB_SGSSTASWIQNVDTK	790.9	2	1090.6	1	y9	36.0
APOB_LATALSLSNK	509.3	2	833.5	1	y8	32.8
APOB_AQIPILR	405.8	2	498.3	1	y4	35.7
APOB_TSSFALNLPTLPEVK	808.9	2	1010.6	1	y9	49.5
APOB_QIDDIDVR	487.3	2	732.4	1	y6	30.2
APOB_AASGTTGTYQEWK	700.3	2	911.4	1	y7	29.2
APOC2_TAAQNLYEK	519.3	2	865.4	1	y7	25.2
APOC2_TYLPAVDEK	518.3	2	658.3	1	y6	31.9
APOC3_DALSSVQESQVAQQAR	573.0	3	672.4	1	y6	32.8
APOC3_GWVTDGFSSLK	598.8	2	854.4	1	y8	42.9
APOC3_DYWSTVK	449.7	2	620.3	1	y5	32.5
APOC4_ELLETVVNR	536.8	2	717.4	1	y6	35.9
APOC4_AWFLESK	440.7	2	623.3	1	y5	39.6
APOD_IPTTFENGR	517.8	2	824.4	1	y7	29.4
APOE_AQAWGER	409.2	2	514.2	1	b5	29.9
APOF_SGVQQLIQYYQDQK	566.6	3	613.3	1	b6	43.6
APOH_ATVVYQGER	511.8	2	751.4	1	y6	25.1
APOL1_LNILNNNYK	553.3	2	765.4	1	y6	35.0
APOM_SLTSCLDSK	505.7	2	810.4	1	y7	28.9

APOM_AFLLTPR	409.3	2	599.4	1	y5	37.3
ATRN_CTWLIEGQPNR	687.3	2	813.4	1	y7	37.3
BAG6_EHIAASVSIPSEK	456.6	3	460.2	1	y4	31.6
BCDO2_VDIETLEK	473.8	2	732.4	1	y6	32.8
BGH3_DLLNNHILK	360.5	3	426.3	2	y7	36.1
BGH3_GDELADSALEIFK	704.4	2	993.5	1	y9	48.5
BTD_VDLITFDTPFAGR	726.4	2	1011.5	1	y9	49.2
BTD_ILSGDPYCEK	591.3	2	955.4	1	y8	29.6
BTD_LSSGLVTAALYGR	654.4	2	751.4	1	y7	42.6
C1QC_TNQVNSGGVLLR	629.3	2	815.5	1	y8	31.4
C1R_NIGEFCGK	462.7	2	697.3	1	y6	28.0
C1R_YTTEIIK	434.2	2	704.4	1	y6	29.3
C1R_ESEQGVYTCTAQGIWK	928.9	2	1227.6	1	y10	38.2
C1R_GYGFYTK	418.2	2	615.3	1	y5	30.2
C1RL_GSEAINAPGDNPAK	670.8	2	698.3	1	y7	26.0
C4BPA_DTIVFK	361.7	2	506.3	1	y4	30.7
C4BPA_TWYPEVPK	510.3	2	732.4	1	y6	37.1
C4BPB_ALLAFQESK	503.8	2	822.4	1	y7	35.9
CADH1_NTGVISVVTTGLDR	716.4	2	1060.6	1	y10	42.3
CAH1_GGPFSDSYR	493.2	2	627.3	1	y5	29.9
CAH1_YSSLAEAASK	513.8	2	776.4	1	y8	26.3
CAH1_VLDALQAIK	485.8	2	758.4	1	y7	39.0
CAH2_SADFTNFDPR	585.3	2	749.4	1	y6	35.4
CALR_FVLSSGK	369.2	2	491.3	1	y5	27.9
CATA_LFAYPDTHR	373.9	3	625.3	1	y5	31.1
CATA_DAQIFIQK	481.8	2	648.4	1	y5	32.1
CBPB2_YPLYVLK	448.3	2	732.5	1	y6	38.9
CBPB2_DTGTYGFLLPER	684.8	2	831.5	1	y7	43.6
CETP_ASYPDITGEK	540.8	2	759.4	1	y7	29.7
CFAB_DISEVVTPR	508.3	2	787.4	1	y7	32.1
CFAB_STGSWSTLK	483.7	2	778.4	1	y7	29.8
CFAB_VASYGVKPR	488.8	2	806.5	1	y7	23.3
CFAB_VSEADSSNADWVTK	754.8	2	1007.5	1	y9	30.4
CFAB_QLNEINYEDHK	468.2	3	485.2	1	b4	27.7
CFAH_EGWIHTVCINGR	481.2	3	619.3	1	y5	36.9
CFAI_FSVSLK	340.7	2	533.3	1	y5	33.1
CFAI_VFSLQWGEVK	596.8	2	946.5	1	y8	44.4
CHLE_NIAAFGGNPK	494.8	2	761.4	1	y8	29.6
CHLE_TQILVGVNK	486.3	2	742.5	1	y7	31.1

CHLE_IFFPGVSEFGK	614.3	2	967.5	1	y9	47.1
CHLE_AEEILSR	409.2	2	617.4	1	y5	26.2
CHLE_YLTLNTESTR	599.3	2	921.5	1	y8	31.7
CLUS_EIQNAVNGVK	536.3	2	829.5	1	y8	26.5
CLUS_TLLSNLEEAK	559.3	2	903.5	1	y8	39.4
CLUS_IDSLLENDR	537.8	2	846.4	1	y7	31.7
CLUS_ASSIIDELFQDR	697.4	2	922.4	1	y7	50.1
CLUS_RPHFFFPK	359.2	3	411.7	2	y6	33.6
CLUS_EILSVDCSTNNPSQAK	881.9	2	1221.5	1	y11	31.5
CLUS_ELDESLQVAER	644.8	2	802.4	1	y7	32.9
CLUS_ALQEYR	390.2	2	595.3	1	y4	23.5
CNDP1_ALEQDLPVNIK	620.4	2	798.5	1	y7	39.0
CNDP1_AIHLDLEEYR	420.2	3	467.2	1	y3	38.1
CO2_HAFILQDTK	358.2	3	469.3	1	b4	27.9
CO3_VVLVAVDK	421.8	2	644.4	1	y6	31.7
CO3_NEQVEIR	444.2	2	644.4	1	y5	24.6
CO4A_DSSTWLTAFVLK	684.4	2	791.5	1	y7	51.9
CO5_GGSASTWLTAFALR	719.4	2	1078.6	1	y9	50.7
CO6_SEYGAALAWEK	612.8	2	845.5	1	y8	37.3
CO6_ENPAVIDFELAPIVDLVR	670.7	3	811.5	1	y7	53.8
CO6_GFVVAGPSR	445.2	2	487.3	1	y5	30.4
CO6_QLEWGLER	515.8	2	789.4	1	y6	38.0
CO6_TLNICEVGTIR	425.9	3	446.3	1	y4	38.9
CO6A1_VAVVQYSGTGQQRPER	592.3	3	703.8	2	y12	27.6
CO6A2_LFAVAPNQNLK	607.8	2	713.4	1	y6	36.1
CO7_LSGNVLSYTFQVK	728.4	2	985.5	1	y8	44.6
CO7_ELSHLPSLYDYSAYR	605.3	3	774.3	1	y6	42.7
CO7_VLFYVDSEK	550.3	2	887.4	1	y7	37.3
CO7_QNDFNSVEEK	605.3	2	705.3	1	y6	26.0
CO7_AASGTQNNVLR	565.8	2	901.5	1	y8	23.9
CO8B_YEFILK	406.7	2	520.3	1	y4	38.6
CO8B_SGFSFGFK	438.7	2	585.3	1	y5	41.3
CO8B_IPGIFELGISSQSDR	540.3	3	679.3	1	y6	47.4
CO9_VVEESELAR	516.3	2	833.4	1	y7	26.9
CO9_TEHYEEQIEAFK	508.6	3	607.3	1	y5	34.0
CO9_TSNFNAAISLK	583.3	2	716.4	1	y7	36.0
CO9_DVVLTTTFVDDIK	733.4	2	938.5	1	y8	46.2
CO9_AIEDYINEFSVR	728.4	2	751.4	1	y6	45.9
COF1_NIILEEGK	458.3	2	688.4	1	y6	30.6

COL11_VFIGINDLEK	574.3	2	901.5	1	y8	42.0
CPN2_LSNNALSGLPQGVFGK	801.4	2	989.5	1	y10	44.1
CPN2_GQVVPALNEK	527.8	2	671.4	1	y6	30.6
CRP_ESDTSYVSLK	564.8	2	609.4	1	y5	30.4
CXCL7_NIQSLEVIGK	550.8	2	745.4	1	y7	36.5
CXCL7_GTHCNQVEVIATLK	523.9	3	773.5	1	y7	34.2
DOPO_TPEGLTLLFK	559.8	2	920.5	1	y8	47.3
DSG2_YKPTPIPIK	352.9	3	389.2	1	b3	33.6
ECM1_NLPATDPLQR	562.8	2	897.5	1	y8	33.1
ENPL_GVVDSDDLPLNVSR	743.4	2	1115.6	1	y10	39.1
ENTP5_ALLFEVK	410.3	2	635.4	1	y5	43.4
ESYT1_GSNPHLQTFTFTR	502.6	3	575.8	2	y9	35.7
EXT2_ASVVVPEEK	479.3	2	502.3	1	y4	27.2
FA7_TLAFVR	353.7	2	492.3	1	y4	32.7
FA9_NCELDVTCNIK	455.9	3	635.3	1	y5	33.2
FA9_SALVLQYLR	531.8	2	692.4	1	y5	43.8
FA9_VPLVDR	349.7	2	502.3	1	y4	27.3
FABPL_AIGLPEELIQK	605.9	2	856.5	1	y7	42.6
FAS_WVESLK	381.2	2	502.2	1	b4	30.7
FBLN1_GYHLNEEGTR	392.5	3	462.2	1	y4	24.4
FCG3A_AVVFLEPQWYR	704.4	2	749.4	1	y5	48.1
FCGBP_GNPAVSYVR	481.8	2	694.4	1	y6	27.9
FCGBP_LASVSVSR	409.7	2	634.4	1	y6	26.0
FCN3_GEPGDPVNLLR	583.8	2	711.5	1	y6	38.2
FCN3_SWSSYR	393.2	2	611.2	1	b5	25.1
FETA_GYQELLEK	490.3	2	759.4	1	y6	33.6
FETUA_QYGFCK	401.7	2	511.2	1	y4	26.3
FETUB_LVVLPFPK	456.8	2	700.4	1	y6	44.6
FHR1_TGESAEFVCK	564.3	2	840.4	1	y7	27.1
FHR2_ITCAEEGWSPTPK	738.3	2	772.4	1	y7	32.2
FHR2_TGDIVEFVCK	584.3	2	781.4	1	y6	38.1
FHR5_TGDAVEFQCK	577.8	2	711.3	1	y5	27.5
FIBA_VPPEWK	378.2	2	423.2	1	b4	24.4
FIBA_HPDEAAFFDTASTGK	531.9	3	621.3	1	b6	34.2
FIBA_GSESGIFTNTK	570.8	2	610.3	1	y5	28.9
FIBB_AHYGGFTVQNEANK	512.6	3	703.3	1	y6	28.7
FIBB_YQISVNK	426.2	2	560.3	1	y5	27.3
FIBG_DNCCILDER	597.7	2	965.4	1	y7	30.6
FINC_WSRPQAPITGYR	477.9	3	496.3	1	y4	33.1

FINC_LGVRPSQGGEAPR	441.9	3	605.8	2	y12	24.7
FINC_SYTITGLQPGTDYK	772.4	2	1079.5	1	y10	37.0
FINC_IYLYTLNDNAR	678.4	2	966.5	1	y8	39.0
FINC_FLATTPNSLLVSWQPPR	643.0	3	770.4	1	y6	50.2
FINC_IGDTWR	374.2	2	634.3	1	y5	27.4
FINC_HTSVQTTSSGSGPFTDVR	622.0	3	734.4	1	y6	30.3
FINC_IGDQWDK	431.2	2	748.3	1	y6	26.7
FINC_GEWTCIAYSQLR	495.2	3	503.3	1	y4	41.5
FUCO_DGLIVPIFQER	643.9	2	888.5	1	y7	48.0
G3BP1_INIPPQR	419.3	2	724.4	1	y6	28.7
G6PI_VFEGNRPTNSIVFTK	570.3	3	731.9	2	y13	34.7
GBLP_LWNTLGVCK	545.8	2	791.4	1	y7	37.1
GELS_TGAQELLR	444.3	2	658.4	1	y5	29.2
GPV_TLPAAAFR	423.7	2	632.4	1	y6	32.6
GPV_YLGVTLSPR	503.3	2	729.4	1	y7	37.1
GSHB_LFVDGQEIAVVYFR	552.6	3	584.3	1	y4	32.4
HABP2_GQCLITQSPPYYR	791.9	2	1011.5	1	y8	36.9
HBA_VGAHAGEYGAEALER	510.6	3	617.3	1	y5	29.7
HCDH_LVEVIK	350.7	2	488.3	1	y4	29.9
HEMO_GEFVWK	383.2	2	579.3	1	y4	34.5
HEMO_ELISER	373.7	2	391.2	1	y3	25.1
HEMO_QGHNSVFLIK	381.5	3	520.3	1	y4	32.9
HEP2_GPLDQLEK	450.2	2	632.3	1	y5	32.6
HEP2_GGETAQSADPQWEQLNNK	987.0	2	1156.6	1	y9	32.7
HEP2_LNILNAK	393.2	2	558.4	1	y5	32.5
HEP2_FAFNLYR	465.7	2	712.4	1	y5	42.0
HEP2_YEITTIHNLFR	469.6	3	557.8	2	y9	42.7
HEP2_NFGYTLR	435.7	2	609.3	1	y5	33.5
HEP2_SVNDLYIQK	540.3	2	893.5	1	y7	31.1
HEP2_QFPILLDFK	560.8	2	845.5	1	y7	51.0
HEP2_TLEAQLTPR	514.8	2	814.4	1	y7	31.6
HEP2_EVLLPK	349.7	2	357.2	1	y3	29.9
HEP2_IAIDLFK	410.3	2	706.4	1	y6	43.4
HEXA_TEIEDFPR	503.7	2	776.4	1	y6	32.1
HEXA_IQPDTIIQVWR	684.9	2	1127.6	1	y9	46.0
HGFA_LCNIEPDER	573.3	2	872.4	1	y7	27.5
HGFA_TTDVTQTFGIEK	670.3	2	923.5	1	y8	35.3
HGFA_VANYVDWINDR	682.8	2	818.4	1	y6	41.8
HPT_VGYVSGWGR	490.8	2	562.3	1	y5	33.7

HPT_VTSIQDWVQK	602.3	2	1003.5	1	y8	37.2
IBP3_ALAQCAPPPAVCAELVR	912.0	2	1208.6	1	y11	39.2
IBP3_FLNVLSPR	473.3	2	685.4	1	y6	40.0
IBP3_YGQPLPGYTTK	612.8	2	876.5	1	y8	31.0
ICAM1_VELAPLPSWQPVGK	760.9	2	1108.6	1	y10	45.3
IGF2_GIVEECCFR	585.3	2	900.3	1	y6	32.6
IGHM_YAATSQVLLPSK	639.4	2	1043.6	1	y10	34.2
IGHM_NVPLPVIAELPPK	693.9	2	1173.7	1	y11	46.3
IGHM_QIQVSWLR	515.3	2	561.3	1	y4	40.8
IGHM_QVGSGVTTDQVQAEAK	809.4	2	1090.5	1	y10	28.3
IGJ_IVLVDNK	400.7	2	588.3	1	y5	28.3
IGJ_SSEDPNEDIVER	695.3	2	971.5	1	y8	27.7
IGJ_IIVPLNNR	469.8	2	613.3	1	y5	33.4
IL1AP_LYIEYGIQR	577.8	2	878.5	1	y7	37.7
IL1AP_NEVWWTIDGK	624.3	2	905.5	1	y7	43.3
IPSP_AVVEVDESGTR	581.3	2	892.4	1	y8	26.7
ITB1_IGFGSFVEK	492.3	2	870.4	1	y8	40.1
ITIH1_QAVDTAVDGVFIR	695.9	2	805.5	1	y7	40.5
ITIH1_FAHYVVTSQVVNTANEAR	669.3	3	775.4	1	y7	35.7
ITIH1_EVAFDLEIPK	580.8	2	714.4	1	y6	44.3
ITIH1_AAISGENAGLVR	579.3	2	902.5	1	y9	29.9
ITIH1_LDAQASFLPK	545.3	2	861.5	1	y8	37.1
ITIH1_GSLVQASEANLQAAQDFVR	668.7	3	806.4	1	y7	47.0
ITIH2_VVNNSPQPQNVVFDVQIPK	708.0	3	945.5	1	y8	44.5
ITIH2_VQFELHYQEVK	473.9	3	596.8	2	y9	36.1
ITIH2_IYLQPGR	423.7	2	570.3	1	y5	28.4
ITIH2_AHVSFKPTVAQQR	490.3	3	630.9	2	y11	26.6
ITIH2_TILDDLR	423.2	2	631.3	1	y5	38.1
ITIH2_IQPSGGTNINEALLR	791.9	2	1157.6	1	y11	37.3
ITIH2_FYNQVSTPLLR	669.4	2	686.4	1	y6	40.0
ITIH3_EVSFDVELPK	581.8	2	934.5	1	y8	42.0
K2C1_SLVNLGGSK	437.8	2	674.4	1	y7	30.8
KAIN_VGSALFLSHNLK	429.2	3	593.8	2	y11	36.8
KAIN_LGFTDLFSK	514.3	2	914.5	1	y8	47.5
KAIN_WADLSGITK	495.8	2	733.4	1	y7	37.0
KAIN_FFSAQTNR	485.7	2	676.3	1	y6	27.4
KLKB1_DSVTGTLPK	459.3	2	616.4	1	y6	28.1
KLKB1_VLTPDAFVCR	589.3	2	864.4	1	y7	39.0
KNG1_TVGSDTFYSFK	626.3	2	1051.5	1	y9	38.1

KNG1_AATGECTATVGK	583.3	2	922.4	1	y9	22.4
KNG1_DFVQPPTK	466.2	2	669.4	1	y6	28.9
LCAT_SSGLVSNAPGVQIR	692.9	2	941.5	1	y9	34.8
LCAT_STELCGLWQGR	653.8	2	876.4	1	y7	39.4
LDHA_ISGFPK	324.7	2	535.3	1	y5	27.9
LG3BP_VEIFYR	413.7	2	598.3	1	y4	34.3
LG3BP_SLGWLK	352.2	2	503.3	1	y4	37.4
LG3BP_SDLAVPSELALLK	678.4	2	870.5	1	y8	47.2
LG3BP_AVDTWSWGER	603.8	2	634.3	1	y5	38.2
LG3BP_SQLVYQSR	490.8	2	765.4	1	y6	25.6
LMNB1_EYEAALNSK	512.8	2	532.3	1	y5	27.9
LUM_NNQIDHIDEK	409.2	3	435.2	2	y7	24.1
LUM_SLEDLQLTHNK	433.2	3	549.3	2	y9	31.2
LUM_SLEYLDLSFNQIAR	834.9	2	1063.6	1	y9	49.6
LUM_LPSGLPVSLLTLYLDNNK	653.0	3	766.4	1	y6	53.4
MBL2_FQASVATPR	488.8	2	701.4	1	y7	28.4
MMSA_AISFVGSNK	461.8	2	738.4	1	y7	26.4
MUC18_GATLALTQVTPQDER	533.9	3	644.3	1	y5	36.0
MUC18_EVTVPVFYPTEK	704.9	2	980.5	1	y8	42.1
MVP_LAQDPFPLYPGEVLEK	606.0	3	771.4	1	y7	49.1
NHRF1_LGVQVR	336.2	2	558.3	1	y5	26.5
P5CS_DEILLANK	458.3	2	471.2	1	b4	31.5
PEDF_GQWVTK	359.7	2	471.2	1	b4	24.4
PERM_VVLEGGIDPILR	640.9	2	840.5	1	y8	43.6
PHLD_VAFLTVTLHQGGATR	524.3	3	570.8	2	y11	39.7
PHLD_IADVTSGLIGGEDGR	730.4	2	1061.5	1	y11	37.0
PLGA_DVVLFEK	425.2	2	635.4	1	y5	36.1
PLMN_VYLSECK	449.7	2	636.3	1	y5	25.5
PLMN_WELCDIPR	544.8	2	773.4	1	y6	40.9
PLMN_HSIFTPETNPR	433.6	3	487.3	1	y4	29.8
PLMN_LFLEPTR	438.3	2	615.3	1	y5	35.3
PLMN_LSSPAVITDK	515.8	2	830.5	1	y8	30.6
PLMN_EAQLPVIENK	570.8	2	699.4	1	y6	33.2
PLMN_YEFLNGR	449.7	2	606.3	1	y5	33.1
PLTP_TGLELSR	388.2	2	504.3	1	y4	27.9
PON1_EVQPVELPNCNLVK	819.9	2	1282.7	1	y11	39.4
PON1_SFNPNSPGK	474.2	2	599.3	1	y6	23.8
PON1_STVELFK	412.2	2	635.4	1	y5	33.9
PON1_IFFYDSENPPASEVLR	628.6	3	868.5	1	y8	46.4

PON1_IQNILTEEPK	592.8	2	943.5	1	y8	34.6
PRDX2_ATAVVDGAFK	489.8	2	806.4	1	y8	30.6
PRDX2_TDEGIAYR	462.7	2	708.4	1	y6	25.7
PROC_ELNQAGQETLVTGWGYHSSR	745.0	3	874.9	2	y16	38.9
PROC_TFVLNFIK	491.3	2	733.5	1	y6	47.5
PROS_SFQTGLFTAAR	599.8	2	836.5	1	y8	39.8
PROS_FSAEFDFR	509.7	2	784.4	1	y6	40.3
PROS_NNLELSTPLK	564.8	2	787.5	1	y7	35.8
PROZ_ENFVLTTAK	511.8	2	533.3	1	y5	33.1
PSMD1_VSTAVLSITAK	545.3	2	731.5	1	y7	35.7
PVR_SVDIWLR	444.8	2	702.4	1	y5	40.2
QSOX1_SFYTAYLQR	574.8	2	751.4	1	y6	39.4
QSOX1_LAGAPSEDPQFPK	678.8	2	1044.5	1	y9	33.5
RET4_YWGVASFLQK	599.8	2	849.5	1	y8	47.5
RET4_LLNLDGTCADSYSFVFSR	689.0	3	742.4	1	y6	50.0
RET4_DPNGLPPEAQK	583.3	2	669.4	1	y6	26.3
S10AD_SLDVNQDSELK	624.3	2	833.4	1	y7	30.0
SAA4_GPGGVWAAK	421.7	2	688.4	1	y7	28.1
SAA4_FRPDGLPK	310.5	3	573.3	1	b5	28.4
SAE2_ESVLQFYPK	555.8	2	795.4	1	y6	39.7
SAMP_IVLGQEQDSYGGK	697.4	2	1068.5	1	y10	30.4
SEPP1_QPPAWSIR	477.8	2	729.4	1	y6	33.6
SEPP1_DDFLIYDR	528.8	2	566.3	1	y4	39.5
SEPP1_VSLATVDK	416.7	2	733.4	1	y7	28.3
SHBG_TSSSFEVR	456.7	2	637.3	1	y5	26.1
SHBG_TWDPEGVIFYGDTNPK	613.6	3	941.4	1	y8	46.7
SHBG_QVSGPLTSK	458.8	2	689.4	1	y7	24.9
SHBG_IALGGLLFPASNLR	721.4	2	804.4	1	y7	51.4
SHBG_QAEISASAPTSLR	665.9	2	889.5	1	y9	31.9
SHBG_DIPQPHAEPWAFSLDLGLK	712.0	3	953.5	2	y17	51.1
SODE_AGLAASLAGPHSIVGR	492.9	3	618.3	2	y13	37.2
SPRC_YIPPCLDSELTEFPLR	650.7	3	837.4	2	y14	50.2
SSRP1_ELQCLTPR	508.8	2	646.3	1	y5	29.6
SYEP_LLSVNIR	407.8	2	588.3	1	y5	35.2
TFR1_VEYHFLSPYVSPK	522.6	3	690.4	1	y6	40.1
THBG_NALALFVLPK	543.3	2	787.5	1	y7	49.7
THBG_GWVDLFVPK	530.8	2	817.5	1	y7	50.1
THRB_SEGSSVNLSPPLEQCVPDR	1036.0	2	1210.6	1	y10	38.8
THRB_ELLESYIDGR	597.8	2	710.3	1	y6	39.9

THRB_SPQELLCGASLISDR	823.4	2	978.5	1	y9	43.7
THRB_ETWTANVGK	503.3	2	589.3	1	y6	28.8
TRFE_DGAGDVAFVK	489.7	2	735.4	1	y7	31.4
TRFE_EFQLFSSPHGK	426.2	3	612.3	1	y6	36.7
TRFE_SASDLTWDNLK	625.3	2	776.4	1	y6	37.8
TRFE_EGYYGYTGAFR	642.3	2	771.4	1	y7	36.8
TRFE_NPDPWAK	414.2	2	501.3	1	y4	27.6
TRFE_YLGEEYVK	500.8	2	724.4	1	y6	33.4
TSP1_SITLFVQEDR	604.3	2	793.4	1	y6	39.8
TSP1_DLASIAR	373.2	2	517.3	1	y5	29.7
TSP1_TIVTTLQDSIR	623.9	2	933.5	1	y8	41.6
TSP1_GTSQNDPNWVVR	686.8	2	770.4	1	y6	31.9
TTC37_DFNCWESLGEAYLSR	616.3	3	738.4	1	y6	46.8
TTHY_VLDAVR	336.7	2	460.3	1	y4	25.0
TTHY_AADDTWEPFASGK	697.8	2	921.4	1	y8	48.3
UCHL3_YLENYDAIR	578.8	2	880.4	1	y7	33.8
VCAM1_NTVISVNPSTK	580.3	2	845.5	1	y8	29.3
VCAM1_LTAFPSESVK	539.8	2	646.3	1	y6	33.0
VIGLN_INIPPPSVNR	553.8	2	766.4	1	y7	32.2
VIME_SSVPGVR	351.2	2	527.3	1	y5	23.0
VTDB_FPSGTFEQVSQLVK	522.9	3	574.4	1	y5	45.8
VTDB_VCSQYAAYGEK	638.3	2	1016.5	1	y9	26.8
VTDB_LCDNLSTK	475.7	2	837.4	1	y7	25.0
VTDB_VLEPTLK	400.2	2	458.3	1	y4	30.1
VTNC_CTEGFNVDK	535.2	2	909.4	1	y8	27.1
VTNC_GQYCYELDEK	652.8	2	956.4	1	y7	30.6
VTNC_DVWGIEGPIDAAFTR	823.9	2	1076.5	1	y10	50.9
VTNC_GSQYWR	398.7	2	524.3	1	y3	26.4
VTNC_FEDGVLDPDYPR	711.8	2	875.4	1	y7	38.5
VTNC_QPQFISR	438.2	2	522.3	1	y4	27.8
VTNC_VDTVDPPYPR	579.8	2	629.3	1	y5	31.2
VWF_AVSPLPYLR	508.3	2	548.3	1	y4	40.0
VWF_VTVFPIGIGDR	587.3	2	727.4	1	y7	43.9
ZA2G_SSGAFWK	391.7	2	608.3	1	y5	31.1
ZPI_LFDEINPETK	603.3	2	945.5	1	y8	36.0

Table S6. AFP, PIVKA and 17 protein value for multimarker panel development

Group	AFP	PIVKA	CXCL7	ANT3	MUC18	COF1	CO4A	AMBP	TSP1	UCHL3	LCAT	C1QC	CNDP1	CO2	CAH2	CO6	SAA4	ZPI	APOH
1	17.6	40564	0.94	0.72	0.06	0.01	3.01	22.43	0.32	0.03	0.64	1.44	0.35	0.26	0.10	2.19	2.44	0.23	35.83
1	1.3	102	1.46	0.44	0.10	0.00	3.32	20.70	0.37	0.03	0.40	1.53	0.24	0.51	0.02	2.40	2.91	0.14	25.55
1	2	22	1.86	0.97	0.12	0.01	2.79	25.83	0.47	0.03	0.69	1.54	0.22	0.33	0.09	2.48	2.08	0.23	31.09
1	236.4	572	2.43	0.43	0.11	0.00	1.70	27.25	0.58	0.02	0.48	1.34	0.10	0.35	0.29	2.41	2.08	0.14	38.00
1	2.9	566	2.36	0.76	0.03	0.02	2.50	27.85	0.61	0.05	0.67	1.49	0.31	0.44	0.14	2.16	1.08	0.24	35.42
1	89.9	44	0.52	0.39	0.13	0.00	2.44	0.68	0.49	0.03	0.37	1.55	0.36	0.76	0.76	1.74	2.49	0.11	24.56
1	11.3	216	1.87	0.69	0.11	0.01	2.11	31.06	0.50	0.03	0.76	1.59	0.34	0.55	0.14	2.32	2.20	0.30	40.23
1	1.3	68	1.17	0.90	0.12	0.00	2.21	23.20	0.40	0.03	0.69	1.62	0.12	0.27	0.08	2.35	1.72	0.18	34.64
1	31.8	19	0.87	0.46	0.16	0.01	2.33	20.82	0.43	0.04	0.69	1.58	0.17	0.09	0.08	2.01	2.34	0.21	22.95
1	3.8	69	1.79	0.76	0.13	0.01	2.95	28.10	0.41	0.04	0.76	1.62	0.26	0.45	0.11	2.41	2.32	0.17	31.53
1	1.5	20	2.60	0.35	0.12	0.03	2.35	21.04	0.86	0.03	0.40	1.38	0.08	0.80	0.29	2.30	2.59	0.17	32.29
1	3.4	36	2.71	0.54	0.05	0.00	3.60	29.53	0.67	0.03	0.53	1.68	0.24	1.18	0.06	2.44	2.26	0.29	39.47
1	1.5	148	1.96	0.89	0.10	0.02	2.51	14.68	0.48	0.03	0.72	1.49	0.28	0.54	0.07	2.30	2.08	0.14	28.54
1	11.7	83	2.74	0.39	0.13	0.00	3.09	32.67	0.90	0.01	0.40	1.64	0.24	0.73	0.06	2.54	2.09	0.19	25.32
1	1.9	26	1.08	0.52	0.17	0.00	2.85	0.95	0.46	0.01	0.35	1.32	0.29	0.99	0.48	2.07	2.68	0.23	38.03
1	275.6	78	1.72	1.03	0.05	0.01	2.41	29.70	0.54	0.04	0.78	1.30	0.32	0.31	0.10	2.32	3.41	0.26	29.53
1	58.4	56	2.44	0.36	0.13	0.01	2.77	18.34	0.68	0.03	0.52	1.74	0.33	2.25	0.40	2.29	3.25	0.21	36.52
1	187.6	4833	2.13	0.28	0.11	0.00	3.25	30.40	0.80	0.03	0.35	1.62	0.21	0.77	0.11	2.23	2.34	0.22	45.87
1	37.7	26	1.51	0.84	0.12	0.00	1.92	26.00	0.41	0.04	0.75	1.61	0.35	0.45	0.07	2.53	1.98	0.21	39.54
1	533.4	307	2.41	0.71	0.08	0.01	2.54	25.15	0.69	0.03	0.45	1.62	0.39	1.12	0.21	2.42	1.53	0.23	40.72
1	3.6	552	1.10	0.39	0.11	0.01	2.96	1.20	0.61	0.03	0.47	1.23	0.22	1.22	0.78	2.32	2.50	0.24	26.41

1	2.4	1890	1.87	0.26	0.16	0.00	1.96	17.12	0.58	0.01	0.35	1.72	0.16	0.73	0.05	2.21	3.32	0.17	34.22
1	2.7	241	2.85	0.35	0.06	0.00	2.09	30.08	0.70	0.02	0.48	1.52	0.18	1.16	0.08	2.53	1.33	0.14	28.80
1	32.4	68	2.39	0.37	0.16	0.00	3.29	29.49	0.69	0.02	0.45	1.70	0.06	0.85	0.04	2.47	2.55	0.29	41.91
1	70.2	21	1.87	0.97	0.07	0.02	2.69	24.94	0.51	0.04	0.63	1.71	0.27	0.32	0.09	2.37	1.69	0.22	35.95
1	2.8	39	1.82	0.75	0.07	0.01	2.75	28.83	0.48	0.04	0.75	1.52	0.33	0.41	0.08	2.48	1.90	0.29	39.91
1	37.8	32	2.70	0.42	0.16	0.01	3.23	27.56	0.70	0.04	0.33	2.03	0.14	1.30	0.13	2.39	1.97	0.21	41.15
1	72.6	2201	1.66	0.64	0.08	0.01	1.92	27.33	0.53	0.03	0.76	1.63	0.25	0.49	0.14	2.41	2.01	0.20	30.01
1	5	33	2.67	0.39	0.12	0.01	3.21	20.78	0.77	0.03	0.36	1.62	0.11	0.76	0.16	2.33	1.86	0.19	35.04
1	2.8	2087	1.95	0.40	0.12	0.01	1.96	21.14	0.54	0.01	0.36	1.50	0.23	1.10	0.09	2.22	2.81	0.20	29.94
1	68.3	221	1.41	0.77	0.09	0.01	2.18	28.35	0.28	0.02	0.71	1.38	0.17	0.42	0.16	2.82	2.10	0.23	28.06
1	11.3	27	2.06	0.56	0.11	0.01	2.23	29.42	0.59	0.02	0.29	1.92	0.10	1.00	0.15	2.26	2.95	0.20	33.05
1	1.8	30	2.77	0.53	0.11	0.00	2.80	27.24	0.85	0.01	0.44	1.55	0.34	0.89	0.10	2.66	2.09	0.17	40.10
1	2	35	2.93	0.26	0.09	0.00	1.89	24.86	0.75	0.02	0.50	1.78	0.36	0.22	0.11	2.20	2.93	0.24	37.58
1	1.6	922	1.32	0.73	0.07	0.01	1.49	29.91	0.38	0.03	0.76	1.59	0.23	0.53	0.07	2.69	2.55	0.21	29.98
1	43.5	29	1.28	1.05	0.09	0.01	1.64	34.14	0.36	0.04	0.75	1.53	0.19	0.68	0.08	2.57	3.30	0.21	28.37
1	1.8	20	1.97	0.42	0.08	0.00	2.42	28.85	0.46	0.03	0.49	1.22	0.24	1.00	0.08	2.32	2.54	0.20	41.19
1	682.3	43	2.40	0.27	0.23	0.00	1.66	14.94	0.76	0.02	0.30	1.80	0.08	1.36	0.03	2.06	1.59	0.12	30.22
1	1.2	62	2.80	0.40	0.08	0.00	2.30	27.51	0.58	0.02	0.46	1.40	0.29	0.95	0.13	2.42	2.17	0.15	36.38
1	10.6	136	2.80	0.44	0.07	0.00	3.04	24.13	0.74	0.01	0.50	1.35	0.33	0.84	0.07	2.39	3.11	0.22	41.53
1	2.9	27	1.58	0.72	0.09	0.02	3.35	9.98	0.35	0.03	0.59	1.52	0.20	0.28	0.11	2.20	7.57	0.16	23.84
1	5.8	19	1.69	0.48	0.10	0.01	2.07	27.46	0.41	0.02	0.71	1.56	0.21	0.19	0.12	2.30	2.43	0.20	32.28
1	3.3	412	1.18	0.53	0.07	0.01	2.31	22.86	0.28	0.02	0.64	1.52	0.27	0.34	0.08	2.31	2.12	0.19	26.08
1	1.9	24	0.26	0.79	0.07	0.00	2.22	22.66	0.27	0.03	0.64	1.49	0.10	0.13	0.09	2.17	2.59	0.20	25.60

1	1.3	24	0.72	0.63	0.05	0.01	2.69	27.13	0.28	0.04	0.72	1.56	0.14	0.40	0.13	2.41	3.10	0.21	28.76
1	7.9	193	1.63	0.79	0.09	0.01	1.85	24.25	0.36	0.02	0.72	1.79	0.20	0.38	0.09	2.14	3.28	0.17	37.68
1	391	32	1.40	0.89	0.09	0.01	2.59	23.29	0.44	0.03	0.64	1.38	0.20	0.23	0.08	2.08	1.81	0.19	30.96
1	8.6	14	2.46	0.38	0.08	0.00	3.34	21.79	0.53	0.02	0.45	1.50	0.29	1.03	0.03	2.28	2.78	0.18	30.69
1	21.6	184	2.38	0.32	0.04	0.00	2.40	29.32	0.64	0.02	0.45	1.01	0.24	2.01	0.10	2.42	2.28	0.26	33.81
1	2.2	389	2.64	0.31	0.10	0.01	2.72	17.51	0.61	0.01	0.27	1.54	0.06	1.03	0.25	2.26	2.20	0.22	39.26
1	568.5	184	0.28	0.67	0.09	0.02	1.45	0.66	0.35	0.02	0.31	1.21	0.30	0.87	0.55	1.63	1.53	0.19	33.07
1	62886.4	1137	0.69	0.24	0.09	0.00	2.99	0.68	0.62	0.02	0.32	1.39	0.20	0.75	0.38	1.86	2.74	0.13	23.81
1	1.2	19	2.21	0.25	0.10	0.00	2.76	27.01	0.67	0.02	0.37	1.66	0.27	0.72	0.05	2.25	2.26	0.17	31.56
0	5.3	21	1.62	0.31	0.19	0.00	2.36	17.54	0.47	0.00	0.22	1.38	0.11	0.19	0.09	1.88	1.40	0.08	19.43
0	1.6	27	2.36	0.24	0.17	0.00	2.11	13.94	0.42	0.01	0.21	1.03	0.06	0.16	0.06	1.93	1.93	0.09	18.99
0	5.6	17	1.61	0.13	0.16	0.00	1.94	12.43	0.46	0.00	0.25	1.32	0.17	0.16	0.04	1.78	2.12	0.13	19.31
0	2.6	7	1.71	0.11	0.31	0.00	1.95	11.70	0.40	0.00	0.23	1.85	0.10	0.07	0.05	1.80	1.26	0.09	13.62
0	2.6	15	2.06	0.18	0.19	0.00	1.51	17.26	0.42	0.02	0.18	1.36	0.13	0.09	0.05	1.89	1.57	0.11	21.05
0	1.1	11	1.48	0.22	0.27	0.00	1.63	15.37	0.30	0.00	0.24	1.43	0.13	0.07	0.04	1.68	5.55	0.09	21.81
0	0.8	16	1.61	0.17	0.15	0.00	2.57	19.79	0.39	0.00	0.27	1.31	0.09	0.21	0.06	2.00	1.86	0.13	19.14
0	2.9	17	1.89	0.23	0.15	0.00	1.23	15.78	0.43	0.02	0.30	1.51	0.19	0.04	0.03	1.79	1.96	0.13	24.01
0	1.6	11	1.73	0.23	0.18	0.00	2.31	18.47	0.31	0.01	0.26	1.46	0.14	0.13	0.04	1.90	1.31	0.14	23.30
0	63.8	79	1.28	0.17	0.22	0.00	1.16	9.08	0.28	0.00	0.13	2.16	0.08	0.05	0.03	1.32	2.15	0.10	8.96
0	1.3	15	1.69	0.16	0.17	0.00	2.18	15.44	0.37	0.00	0.20	1.01	0.12	0.16	0.03	1.75	1.55	0.06	18.63
0	1.3	26	1.72	0.22	0.20	0.00	2.32	14.97	0.41	0.00	0.26	1.30	0.11	0.02	0.03	1.71	1.72	0.09	15.90
0	1.8	15	1.78	0.19	0.13	0.00	2.24	17.21	0.35	0.01	0.34	1.31	0.20	0.14	0.07	1.78	2.65	0.13	9.33
0	1.8	12	1.50	0.20	0.14	0.00	1.80	15.94	0.36	0.02	0.26	1.26	0.06	0.07	0.03	1.79	1.42	0.10	18.89

0	1	16	1.54	0.23	0.28	0.00	2.27	15.73	0.38	0.01	0.23	1.39	0.13	0.28	0.03	1.84	2.68	0.07	16.44
0	0.7	38	1.22	0.29	0.25	0.00	2.64	15.45	0.32	0.01	0.19	1.61	0.15	0.03	0.02	1.69	3.18	0.08	17.33
0	1.9	17	1.91	0.16	0.22	0.00	2.19	16.44	0.34	0.01	0.36	1.35	0.21	0.18	0.03	2.18	1.70	0.15	25.07
0	2.2	7	1.46	0.12	0.24	0.00	1.41	10.43	0.39	0.02	0.13	1.56	0.08	0.15	0.02	1.70	1.09	0.08	13.74
0	6.5	29	1.35	0.14	0.19	0.00	1.94	12.61	0.34	0.01	0.18	1.72	0.07	0.22	0.04	1.55	1.69	0.08	7.38
0	3.5	21	1.59	0.18	0.21	0.00	0.24	15.10	0.47	0.01	0.33	1.42	0.15	0.15	0.05	1.83	2.26	0.09	21.50
0	1.9	24	1.56	0.24	0.19	0.00	1.16	15.17	0.31	0.01	0.30	1.53	0.19	0.14	0.07	1.77	2.29	0.08	18.13
0	10.4	19	1.32	0.26	0.22	0.00	1.50	14.00	0.38	0.01	0.24	1.62	0.07	0.09	0.06	1.76	2.99	0.12	20.53
0	1.6	14	1.77	0.23	0.21	0.00	2.44	19.54	0.39	0.00	0.33	1.50	0.25	0.24	0.08	1.79	2.23	0.16	24.56
0	1.2	19	1.09	0.32	0.19	0.00	1.99	17.98	0.22	0.01	0.24	1.43	0.06	0.07	0.03	1.86	2.22	0.10	25.70
0	1.9	20	1.13	0.37	0.20	0.00	2.05	14.85	0.33	0.01	0.23	1.59	0.10	0.14	0.03	2.20	1.55	0.12	13.57
0	30.5	23	1.86	0.20	0.19	0.00	1.77	12.90	0.35	0.01	0.18	1.49	0.13	0.13	0.05	1.31	1.96	0.14	16.88
0	2.2	13	0.45	0.22	0.18	0.00	1.60	0.53	0.15	0.01	0.18	1.55	0.08	0.18	0.10	1.52	1.23	0.06	17.01
0	1.8	16	1.54	0.17	0.16	0.00	1.97	14.47	0.21	0.00	0.20	1.31	0.11	0.09	0.02	2.09	2.32	0.12	17.03
0	14.2	19	0.85	0.10	0.17	0.00	1.94	1.13	0.42	0.01	0.25	1.01	0.19	0.02	0.05	1.68	2.09	0.11	13.84
0	2.3	18	1.28	0.21	0.21	0.00	2.32	16.77	0.32	0.00	0.23	1.39	0.04	0.13	0.05	1.90	1.60	0.09	22.51
0	1.8	14	1.75	0.17	0.16	0.00	2.64	11.47	0.40	0.00	0.26	1.27	0.16	0.33	0.07	1.68	2.06	0.10	14.73
0	7.4	16	1.43	0.21	0.17	0.00	2.22	8.61	0.35	0.00	0.20	1.31	0.10	0.21	0.06	1.59	1.45	0.10	9.04
0	4.4	17	1.83	0.18	0.20	0.00	1.82	10.41	0.45	0.00	0.21	1.16	0.11	0.04	0.08	1.62	1.52	0.12	16.61
0	1.7	18	1.89	0.19	0.16	0.00	1.76	16.42	0.36	0.01	0.24	1.21	0.06	0.19	0.02	1.98	1.22	0.11	17.02
0	1.8	19	0.50	0.13	0.19	0.00	0.80	0.58	0.29	0.02	0.14	1.45	0.05	0.17	0.05	1.52	1.22	0.06	14.66
0	3.6	12	1.38	0.15	0.22	0.00	2.45	8.26	0.27	0.00	0.21	1.52	0.14	0.40	0.11	1.38	1.42	0.05	15.63
0	7.1	14	1.41	0.12	0.22	0.00	1.89	16.14	0.43	0.01	0.26	1.47	0.10	0.03	0.02	1.56	1.42	0.08	16.72

0	2.7	13	1.84	0.22	0.19	0.00	1.10	19.53	0.40	0.01	0.35	1.34	0.26	0.13	0.05	1.93	2.75	0.12	18.05
0	5.9	17	2.21	0.17	0.19	0.00	2.24	15.16	0.44	0.01	0.19	1.41	0.07	0.04	0.07	1.74	2.80	0.08	15.16
0	2.4	13	1.21	0.23	0.21	0.00	2.45	11.80	0.34	0.00	0.28	1.75	0.06	0.13	0.04	1.48	2.00	0.07	14.59
0	2.7	15	1.76	0.11	0.23	0.00	2.39	14.33	0.45	0.01	0.19	1.47	0.05	0.13	0.04	1.71	2.20	0.11	20.94
0	5.8	89	1.99	0.11	0.32	0.00	2.07	8.87	0.54	0.00	0.05	1.88	0.11	0.44	0.10	0.67	0.89	0.05	10.56
0	3.2	24	1.30	0.23	0.16	0.00	1.37	11.38	0.31	0.00	0.18	0.67	0.10	0.08	0.03	1.77	2.06	0.12	13.10
0	1.5	18	1.60	0.21	0.19	0.00	2.04	16.86	0.34	0.00	0.27	1.38	0.13	0.05	0.05	2.04	1.90	0.09	15.13
0	5.4	17	1.52	0.21	0.21	0.00	2.15	14.15	0.34	0.01	0.26	1.80	0.14	0.23	0.08	1.66	0.72	0.10	18.03
0	1.2	22	1.40	0.21	0.13	0.00	2.56	17.24	0.38	0.00	0.21	1.64	0.05	0.24	0.07	2.16	2.50	0.15	20.63
0	2.4	11	1.12	0.14	0.19	0.00	1.88	13.48	0.25	0.00	0.20	0.94	0.06	0.11	0.02	1.63	1.74	0.07	13.63
0	4.3	24	1.90	0.13	0.21	0.00	2.08	11.26	0.32	0.01	0.18	1.33	0.12	0.13	0.08	1.56	0.60	0.11	14.73
0	8.3	10	1.56	0.18	0.22	0.00	2.21	16.02	0.36	0.00	0.24	1.47	0.18	0.03	0.03	1.79	1.39	0.12	23.14
0	9.5	11	1.80	0.22	0.18	0.00	1.90	11.44	0.44	0.00	0.29	1.38	0.04	0.32	0.03	1.66	2.50	0.13	14.42