

Supplementary materials

Table S1. List of 92 proteins measured by Proseek Oncology lv2 assay

Abbreviation	Protein Name	Uniprot ID.
AM	Adrenomedullin	P35318
AREG	Amphiregulin	P15514
BAFF	B-cell-activating factor	Q9Y275
CA125	Carcinoma antigen 125	Q8WXI7
CAIX	Carbonic anhydrase IX	Q16790
CASP3	Caspase-3	P42574
CCL19	C-C motif chemokine 19	Q99731
CD40L	CD40 ligand	P29965
CD69	Early activation antigen CD69	Q07108
CDH3	Cadherin-3	P22223
CDKN1A	Cyclin-dependent kinase inhibitor 1	P38936
CEA	Carcinoembryonic antigen	P06731
CSF1	Macrophage colony-stimulating factor 1	P09603
CSTB	Cystatin-B	P04080
CXCL10	C-X-C motif chemokine 10	P02778
CXCL11	C-X-C motif chemokine 11	O14625
CXCL13	C-X-C motif chemokine 13	O43927
CXCL5	C-X-C motif chemokine 5	P42830
CXCL9	C-X-C motif chemokine 9	Q07325
EGFR	Epidermal growth factor receptor	P00533
eIF4B	Eukaryotic translation initiation factor 4B	P23588
EMMPRIN	Extracellular matrix metalloproteinase inducer	P35613
EpCAM	Epithelial cell adhesion molecule	P16422
EPO	Erythropoietin	P01588
ErbB2/HER2	Receptor tyrosine-protein kinase erbB-2	P04626
ErbB3/HER3	Receptor tyrosine-protein kinase erbB-3	P21860
ErbB4/HER4	Receptor tyrosine-protein kinase erbB-4	Q15303
EZR	Ezrin	P15311
FADD	FAS-associated death domain protein	Q13158
FAS	Fas cell surface death receptor	P25445
FasL	Fas antigen ligand	P48023
Flt3L	Fms-related tyrosine kinase 3 ligand	P49771
FRalpha	Folate receptor alpha	P15328
FS	Follistatin	P19883
FUR	Furin	P09958

Table S1. List of 92 proteins measured by Proseek Oncology lv2 assay

Abbreviation	Protein Name	Uniprot ID.
GDF-15	Growth differentiation factor 15	Q99988
GH	Growth hormone	P01241
HBEGF	Proheparin-binding EGF-like growth factor	Q99075
HE4	WAP four-disulfide core domain protein 2	Q14508
HGF	Hepatocyte growth factor	P14210
hK11	Kallikrein-11	Q9UBX7
ICOSLG	ICOS ligand	O75144
IFN gamma	Interferon gamma	P01579
IL-12	Interleukin-12	Alpha:P29459/Beta:P29460
IL-17RB	Interleukin-17 receptor beta	Q9NRM6
IL-1ra	Interleukin-1 receptor antagonist protein	P18510
IL-2	Interleukin-2	P60568
IL-6	Interleukin-6	P05231
IL-6RA	Interleukin-6 receptor subunit alpha	P08887
IL-7	Interleukin-7	P13232
IL-8	Interleukin-8	P10145
ILT3	Immunoglobulin-like transcript 3	Q8NHJ6
ITGA1	Integrin alpha-1	P56199
KLK6	Kallikrein-6	Q92876
LAP-TGF-beta-1	Latency-associated peptide-Transforming growth factor-beta-1	P01137
LITAF	Lipopolysaccharide-induced tumor necrosis factor-alpha factor	Q99732
LYN	Tyrosine-protein kinase Lyn	P07948
MCP1	Monocyte chemotactic protein 1	P13500
MIA	Melanoma-derived growth regulatory protein	Q16674
MICA	MHC class I polypeptide-related sequence A	Q29983
MK	Midkine	P21741
MMP-1	Matrix metalloproteinase-1	P03956
MYD88	Myeloid differentiation primary response protein MyD88	Q99836
NEMO	NF-kappa-B essential modulator	Q9Y6K9
NTRK3	NT-3 growth factor receptor	Q16288
PARK7	Parkinson disease protein 7	Q99497
PDGF subunit B	Platelet-derived growth factor subunit B	P01127
PECAM-1	Platelet endothelial cell adhesion molecule-1	P16284
PIGF	Placenta growth factor	P49763
PRL	Prolactin	P01236
PRSS8	Prostasin	Q16651
PTPN22	Tyrosine-protein phosphatase non-receptor type 22	Q9Y2R2

Table S1. List of 92 proteins measured by Proseek Oncology lv2 assay

Abbreviation	Protein Name	Uniprot ID.
REG 4	Regenerating islet-derived protein 4	Q9BYZ8
SCF	Stem cell factor	P21583
SELE	E-selectin	P16581
TF	Tissue factor	P13726
TGF-alpha	Transforming growth factor-alpha	Q9UQ91
THPO	Thrombopoietin	P40225
TIE2	Tyrosine kinase with Ig and EGF homology domains-2	Q02763
TNF	Tumor necrosis factor	P01375
TNFR-1	Tumor necrosis factor receptor-1	P19438
TNFR-2	Tumor necrosis factor receptor-2	P20333
TNFRSF-4	Tumor necrosis factor receptor superfamily member 4	P43489
TNFSF-14	Tumor necrosis factor receptor superfamily member 14	Q92956
TR-AP	Tartrate-resistant acid phosphatase type 5	P13686
TRAILR-2	TNF-related apoptosis-inducing ligand receptor-2	O14763
U-PAR	Urokinase plasminogen activator surface receptor	Q03405
VE-statin	Vascular endothelial statin	Q9UHF1
VEGF-A	Vascular endothelial growth factor-A	P15692
VEGF-D	Vascular endothelial growth factor-D	O43915
VEGFR-2	Vascular endothelial growth factor receptor-2	P35968
VIM	Vimentin	P08670

Table S2. Diagnostic performance of 92 protein biomarkers in the discovery set and the validation set

Protein marker	Training set			Validation set		
	Fold change (Case vs. control)	p-value*	AUC (95% CI) †	Fold change (Case vs. control)	p-value*	AUC (95% CI) †
GDF-15	1.68	<0.001	0.78[0.72-0.85]	1.42	<0.001	0.76[0.66-0.88]
AR	1.34	<0.001	0.72[0.66-0.80]	1.32	<0.001	0.79[0.70-0.90]
TRAIL-R2	1.23	<0.001	0.68[0.62-0.76]	1.28	<0.001	0.74[0.64-0.87]
FasL	0.74	<0.001	0.68[0.61-0.76]	1.10	0.906	0.45[0.35-0.57]
IL-6	1.56	<0.001	0.68[0.61-0.77]	1.48	0.014	0.63[0.54-0.79]
EGFR	0.84	<0.001	0.68[0.61-0.76]	0.98	0.723	0.47[0.31-0.62]
AM	1.23	<0.001	0.68[0.61-0.75]	1.28	0.004	0.68[0.56-0.83]
Flt3L	0.83	<0.001	0.65[0.58-0.74]	0.99	0.557	0.50[0.37-0.68]
HE4	1.24	<0.001	0.65[0.59-0.74]	1.19	0.014	0.65[0.53-0.80]
REG4	1.21	<0.001	0.65[0.59-0.73]	1.14	0.229	0.51[0.32-0.69]
TNF-R2	1.21	<0.001	0.64[0.57-0.73]	1.16	0.014	0.64[0.54-0.80]
MK	1.30	<0.001	0.63[0.56-0.73]	1.01	0.772	0.45[0.33-0.59]
ILT-3	1.21	<0.001	0.63[0.56-0.72]	1.14	0.043	0.62[0.51-0.76]
ErbB2-HER2	0.86	<0.001	0.63[0.56-0.72]	1.10	0.285	0.52[0.33-0.70]
ITGA1	0.84	<0.001	0.63[0.57-0.72]	1.08	0.687	0.47[0.34-0.61]
CEA	1.29	<0.001	0.63[0.56-0.72]	1.86	0.000	0.75[0.65-0.89]
VE-statin	1.13	<0.001	0.62[0.55-0.71]	1.14	0.083	0.59[0.50-0.74]
VEGF-A	1.25	0.001	0.61[0.55-0.71]	1.22	0.171	0.54[0.45-0.72]
CXCL9	1.27	0.001	0.61[0.55-0.70]	1.42	0.040	0.60[0.50-0.78]
ErbB3-HER3	0.89	0.001	0.61[0.55-0.71]	1.04	0.462	0.48[0.34-0.64]
CSF-1	1.11	0.001	0.61[0.54-0.70]	1.14	0.083	0.56[0.45-0.74]
TNF-R1	1.17	0.001	0.61[0.55-0.70]	1.24	0.014	0.65[0.54-0.79]
PIGF	1.11	0.001	0.60[0.54-0.69]	1.12	0.083	0.59[0.48-0.75]
EZR	0.89	0.001	0.60[0.54-0.70]	1.14	0.083	0.59[0.49-0.75]
CXCL13	1.21	0.001	0.60[0.54-0.69]	1.14	0.189	0.54[0.41-0.72]
GH	1.89	0.002	0.60[0.53-0.70]	1.37	0.334	0.49[0.34-0.66]
NTRK3	0.90	0.002	0.60[0.53-0.70]	1.10	0.364	0.50[0.35-0.67]
CA-125	1.34	0.003	0.59[0.53-0.69]	1.29	0.218	0.54[0.38-0.72]
EPO	1.03	0.004	0.55[0.51-0.66]	1.00	0.462	0.48[0.37-0.63]
ErbB4-HER4	0.88	0.004	0.59[0.52-0.69]	1.07	0.750	0.45[0.33-0.60]
MMP-1	1.29	0.005	0.59[0.53-0.68]	1.24	0.363	0.49[0.32-0.65]
VEGF-D	0.90	0.005	0.58[0.52-0.68]	1.05	0.596	0.47[0.33-0.63]
HGF	1.14	0.007	0.58[0.51-0.68]	1.27	0.032	0.63[0.53-0.77]
IFN-gamma	1.10	0.009	0.57[0.51-0.67]	1.16	0.129	0.52[0.32-0.70]
EMMPRIN	0.91	0.010	0.57[0.51-0.67]	1.14	0.675	0.47[0.33-0.61]

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Table S2. Continued

Protein marker	Training set			Validation set		
	Fold change (Case vs. control)	p-value*	AUC (95% CI) †	Fold change (Case vs. control)	p-value*	AUC (95% CI) †
VEGFR-2	0.91	0.012	0.57[0.51-0.67]	1.03	0.333	0.50[0.32-0.67]
ICOSLG	0.90	0.016	0.57[0.50-0.67]	1.14	0.396	0.49[0.32-0.64]
CXCL11	1.16	0.035	0.56[0.49-0.66]	1.19	0.298	0.50[0.31-0.67]
SCF	0.93	0.041	0.56[0.50-0.66]	1.01	0.675	0.47[0.34-0.62]
Ep-CAM	0.81	0.057	0.55[0.48-0.65]	0.92	0.870	0.44[0.34-0.57]
THPO	0.90	0.074	0.54[0.47-0.64]	1.14	0.171	0.54[0.45-0.71]
CAIX	1.06	0.083	0.55[0.49-0.64]	1.08	0.723	0.48[0.34-0.65]
MCP-1	0.91	0.143	0.53[0.46-0.63]	1.00	0.928	0.45[0.33-0.57]
U-PAR	1.07	0.187	0.52[0.45-0.63]	1.10	0.126	0.57[0.47-0.73]
IL-6RA	1.11	0.187	0.53[0.45-0.63]	1.05	0.189	0.53[0.33-0.71]
MIC-A	1.02	0.187	0.52[0.40-0.62]	1.27	0.209	0.51[0.32-0.70]
IL-17RB	1.10	0.258	0.51[0.38-0.61]	1.26	0.171	0.55[0.44-0.72]
IL-12	1.09	0.258	0.52[0.41-0.62]	1.19	0.332	0.49[0.32-0.66]
PECAM-1	0.96	0.290	0.51[0.40-0.61]	0.95	0.301	0.50[0.31-0.68]
PTPN22	0.89	0.315	0.51[0.39-0.61]	1.41	0.126	0.57[0.45-0.75]
hK11	1.08	0.323	0.50[0.39-0.61]	1.09	0.353	0.51[0.33-0.68]
SELE	0.91	0.327	0.49[0.38-0.59]	1.28	0.032	0.61[0.51-0.78]
CSTB	1.05	0.378	0.50[0.38-0.60]	1.28	0.083	0.60[0.48-0.76]
PARK7	0.94	0.402	0.50[0.40-0.60]	1.10	0.406	0.49[0.33-0.66]
TR.AP	0.96	0.404	0.49[0.39-0.59]	1.05	0.576	0.47[0.33-0.62]
FADD	0.90	0.426	0.50[0.38-0.60]	1.20	0.498	0.49[0.34-0.64]
HB-EGF	1.03	0.426	0.50[0.40-0.60]	1.06	0.723	0.46[0.35-0.61]
CDH3	1.06	0.434	0.50[0.40-0.59]	1.20	0.209	0.55[0.40-0.72]
TF	1.00	0.474	0.50[0.39-0.60]	1.18	0.371	0.50[0.33-0.66]
CXCL10	1.10	0.477	0.50[0.40-0.60]	1.43	0.083	0.56[0.42-0.75]
LYN	0.92	0.482	0.48[0.38-0.58]	0.80	0.218	0.52[0.33-0.70]
TNFSF14	0.89	0.482	0.49[0.38-0.59]	1.04	0.633	0.47[0.35-0.63]
VIM	0.82	0.485	0.49[0.39-0.59]	1.35	0.189	0.55[0.45-0.73]
CXCL5	0.92	0.505	0.49[0.40-0.58]	0.67	0.129	0.57[0.45-0.75]
KLK6	1.03	0.505	0.48[0.39-0.58]	1.11	0.257	0.48[0.29-0.66]
CD40-L	1.01	0.505	0.49[0.40-0.59]	1.16	0.615	0.46[0.34-0.61]
CD69	1.09	0.525	0.49[0.40-0.59]	0.79	0.298	0.51[0.32-0.69]
PDGF-subunit-B	1.05	0.525	0.48[0.39-0.58]	1.01	0.952	0.45[0.34-0.57]
FS	1.05	0.543	0.49[0.40-0.59]	1.14	0.076	0.60[0.48-0.75]
IL-2	1.00	0.543	0.48[0.46-0.55]	1.00	0.952	0.46[0.42-0.55]
MYD88	0.87	0.574	0.48[0.39-0.58]	0.99	0.782	0.46[0.31-0.61]
TNFRSF4	1.00	0.597	0.49[0.40-0.58]	1.14	0.293	0.51[0.35-0.68]

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Table S2. Continued

Protein marker	Training set			Validation set		
	Fold change (Case vs. control)	p-value*	AUC (95% CI) †	Fold change (Case vs. control)	p-value*	AUC (95% CI) †
IL-7	1.04	0.597	0.47[0.39-0.57]	1.09	0.490	0.49[0.33-0.65]
FUR	1.00	0.597	0.48[0.39-0.57]	1.02	0.584	0.48[0.34-0.64]
NEMO	0.95	0.608	0.48[0.40-0.56]	0.73	0.257	0.51[0.32-0.69]
TNF	1.00	0.609	0.48[0.42-0.58]	1.00	0.729	0.47[0.38-0.62]
CASP-3	0.86	0.661	0.47[0.39-0.55]	0.83	0.219	0.52[0.35-0.70]
LAP-TGF-beta1	1.02	0.663	0.48[0.40-0.56]	1.02	0.490	0.49[0.34-0.65]
FR-alpha	1.02	0.664	0.48[0.40-0.57]	0.94	0.841	0.45[0.32-0.59]
TIE2	1.03	0.686	0.47[0.40-0.56]	1.09	0.129	0.57[0.46-0.73]
CDKN1A	0.99	0.752	0.48[0.40-0.56]	0.79	0.129	0.57[0.47-0.74]
CCL19	0.99	0.752	0.47[0.40-0.55]	1.21	0.229	0.51[0.32-0.68]
eIF-4B	1.02	0.752	0.47[0.40-0.56]	0.99	0.931	0.44[0.33-0.57]
PRL	1.02	0.752	0.48[0.41-0.57]	0.97	0.952	0.44[0.33-0.56]
MIA	1.00	0.765	0.47[0.40-0.54]	1.07	0.334	0.49[0.32-0.66]
IL-8	0.84	0.779	0.46[0.39-0.55]	1.94	0.219	0.54[0.42-0.71]
FAS	1.07	0.821	0.47[0.40-0.56]	1.12	0.108	0.57[0.45-0.74]
LITAF	0.94	0.828	0.47[0.40-0.54]	1.22	0.137	0.56[0.44-0.72]
TGF-alpha	0.98	0.931	0.47[0.40-0.55]	1.30	0.189	0.54[0.41-0.71]
PRSS8	1.03	0.940	0.47[0.40-0.54]	1.29	0.025	0.63[0.51-0.81]
BAFF	0.99	0.942	0.47[0.41-0.54]	1.02	0.396	0.49[0.32-0.65]
IL-1ra	0.96	0.949	0.47[0.40-0.54]	1.26	0.193	0.54[0.41-0.71]

Abbreviation: AUC, area under the curve; CRC, colorectal cancer; 95% CI, 95% confidence interval.

* p-values were adjusted by multiple testing (Benjamini-Hochberg method)

† AUCs were adjusted by .632+ bootstrap method, and 95% confidence intervals were derived from 1,000 bootstrap samples.

Table S3. Diagnostic performance of 92 protein biomarkers for detecting advanced adenoma in the validation set

Protein marker	Median (Cq value)		Fold change	p-value*	AUC (95% CI) †
	Advanced adenoma	Free of neoplasm			
AM	7.4	7.2	1.10	0.74	0.50 [0.35-0.63]
AR	3.1	3.0	1.08	0.68	0.53 [0.44-0.66]
BAFF	6.8	6.7	1.02	0.89	0.47 [0.38-0.58]
CA-125	2.5	2.5	1.00	0.93	0.46 [0.38-0.57]
CAIX	2.8	2.8	0.95	0.86	0.45 [0.37-0.56]
CASP.3	12.1	12.1	0.99	0.86	0.46 [0.37-0.56]
CCL19	10.2	10.0	1.15	0.68	0.54 [0.46-0.66]
CD40L	8.3	8.3	1.01	0.93	0.46 [0.38-0.55]
CD69	8.4	8.4	1.00	0.86	0.47 [0.38-0.58]
CDH3	2.3	2.1	1.11	0.68	0.51 [0.37-0.64]
CDKN1A	1.9	1.8	1.08	0.93	0.46 [0.38-0.55]
CEA	2.9	2.7	1.15	0.74	0.50 [0.36-0.63]
CSF-1	8.7	8.7	1.03	0.83	0.47 [0.35-0.59]
CSTB	8.0	7.7	1.21	0.68	0.54 [0.43-0.68]
CXCL10	8.0	8.0	1.00	0.90	0.46 [0.38-0.55]
CXCL11	5.7	5.6	1.04	0.83	0.48 [0.36-0.60]
CXCL13	9.4	9.3	1.05	0.78	0.50 [0.37-0.63]
CXCL5	9.2	9.2	1.02	0.84	0.47 [0.37-0.58]
CXCL9	7.5	7.4	1.06	0.83	0.48 [0.37-0.61]

EGFR	5.8	5.7	1.05	0.98	0.46 [0.38-0.55]
eIF4B	7.5	7.4	1.13	0.75	0.49 [0.36-0.62]
EMMPRIN	7.2	7.1	1.07	0.86	0.46 [0.38-0.57]
Ep-CAM	11.2	11.0	1.15	0.74	0.50 [0.35-0.62]
EPO	0.4	0.4	1.00	0.95	0.47 [0.40-0.56]
ErbB2.HER2	9.1	9.0	1.05	0.83	0.48 [0.36-0.61]
ErbB3.HER3	9.1	9.0	1.06	0.74	0.49 [0.36-0.62]
ErbB4.HER4	6.0	6.0	1.03	0.86	0.47 [0.39-0.57]
EZR	6.3	6.3	1.05	0.83	0.47 [0.37-0.58]
FADD	4.1	3.9	1.15	0.73	0.52 [0.42-0.64]
FAS	9.0	8.8	1.11	0.68	0.51 [0.35-0.65]
FasL	2.6	2.5	1.08	0.84	0.47 [0.36-0.58]
Flt3L	9.2	9.1	1.09	0.98	0.47 [0.38-0.58]
FR-alpha	5.1	5.1	1.00	0.98	0.46 [0.38-0.55]
FS	5.8	5.7	1.08	0.68	0.51 [0.36-0.64]
FUR	7.8	7.7	1.01	0.89	0.46 [0.38-0.57]
GDF-15	9.5	9.3	1.10	0.68	0.52 [0.40-0.65]
GH	8.4	7.9	1.42	0.83	0.48 [0.36-0.60]
HB-EGF	9.1	9.0	1.02	0.86	0.47 [0.38-0.57]

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Table S3. Continued

Protein marker	Median (Cq value)		Fold change	p-value*	AUC (95% CI) [†]
	Advanced adenoma	Free of neoplasm			
HE4	7.5	7.4	1.08	0.68	0.52 [0.39-0.65]
HGF	8.3	8.2	1.12	0.83	0.48 [0.37-0.60]
hK11	5.8	5.7	1.02	0.83	0.48 [0.38-0.60]
ICOSLG	4.2	4.1	1.06	0.83	0.47 [0.38-0.59]
IFN-gamma	1.6	1.5	1.07	0.86	0.48 [0.38-0.59]
IL12	8.7	8.5	1.12	0.74	0.49 [0.36-0.61]
IL17RB	2.3	2.2	1.07	0.86	0.47 [0.38-0.58]
IL1ra	7.2	7.1	1.07	0.68	0.51 [0.37-0.64]
IL2	1.0	1.0	1.00	0.93	0.46 [0.45-0.53]
IL6	4.8	4.5	1.22	0.68	0.50 [0.35-0.64]
IL6RA	7.4	7.4	1.04	0.74	0.49 [0.36-0.62]
IL7	1.6	1.6	1.01	0.86	0.47 [0.38-0.58]
IL8	8.0	8.0	1.04	1.00	0.46 [0.38-0.55]
ILT3	3.0	3.0	0.99	0.76	0.50 [0.37-0.63]
ITGA1	7.9	7.8	1.04	0.86	0.46 [0.38-0.57]
KLK6	5.8	5.8	1.03	0.93	0.46 [0.39-0.57]
LAP-TGF-beta.1	6.9	6.9	0.97	0.95	0.46 [0.37-0.56]
LITAF	2.3	2.1	1.15	0.83	0.48 [0.37-0.61]
LYN	3.2	3.4	0.89	0.83	0.47 [0.37-0.60]
MCP1	10.5	10.5	1.02	0.93	0.47 [0.39-0.57]

MIA	5.1	5.1	1.00	0.83	0.48 [0.37-0.60]
MICA	4.2	4.2	0.96	0.86	0.48 [0.38-0.60]
MK	8.1	8.1	1.00	0.89	0.46 [0.38-0.56]
MMP1	8.5	8.4	1.12	0.86	0.46 [0.38-0.56]
MYD88	2.9	2.8	1.08	0.74	0.51 [0.37-0.63]
NEMO	6.6	6.4	1.14	0.83	0.48 [0.37-0.59]
NTRK3	7.9	7.8	1.05	0.83	0.47 [0.37-0.58]
PARK7	8.5	8.5	1.01	0.84	0.47 [0.37-0.58]
PDGFsubunit.B	8.6	8.5	1.01	0.98	0.46 [0.38-0.55]
PECAM1	7.5	7.5	1.00	0.95	0.46 [0.38-0.56]
PIGF	7.0	6.9	1.09	0.73	0.50 [0.36-0.63]
PRL	5.1	5.1	1.00	0.83	0.49 [0.37-0.60]
PRSS8	9.5	9.3	1.13	0.68	0.51 [0.35-0.64]
PTPN22	4.8	4.5	1.30	0.68	0.52 [0.39-0.65]
REG4	4.6	4.5	1.05	0.83	0.49 [0.37-0.61]
SCF	8.5	8.4	1.03	0.84	0.47 [0.38-0.57]
SELE	7.5	7.5	1.04	0.86	0.47 [0.38-0.59]
TF	5.9	5.6	1.16	0.68	0.51 [0.35-0.64]
TGFalpha	4.3	4.3	1.00	0.83	0.48 [0.36-0.59]

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Table S3. Continued

Protein marker	Median		Fold change	p-value*	AUC (95% CI) [†]
	Advanced adenoma	Free of neoplasm			
THPO	3.2	3.1	1.09	0.83	0.47 [0.36-0.59]
TIE2	6.1	6.0	1.05	0.76	0.49 [0.36-0.61]
TNF	0.3	0.3	1.00	0.83	0.49 [0.41-0.60]
TNFR1	12.2	12.0	1.11	0.73	0.50 [0.36-0.62]
TNFR2	5.5	5.4	1.08	0.73	0.51 [0.36-0.64]
TNFRSF4	3.7	3.5	1.11	0.68	0.54 [0.41-0.67]
TNFSF14	3.5	3.5	0.97	0.93	0.46 [0.38-0.55]
TRAP	6.4	6.3	1.07	0.83	0.47 [0.37-0.58]
TRAILR2	4.5	4.3	1.09	0.68	0.52 [0.40-0.65]
UPAR	10.6	10.5	1.03	0.83	0.48 [0.37-0.60]
VEstatin	0.0	0.0	1.02	0.83	0.47 [0.37-0.59]
VEGFA	10.7	10.7	0.99	0.84	0.47 [0.37-0.58]
VEGFD	6.8	6.8	0.98	0.86	0.47 [0.38-0.58]
VEGFR2	8.1	8.0	1.08	0.68	0.51 [0.36-0.64]
VIM	5.7	5.8	0.99	0.93	0.46 [0.38-0.55]

Abbreviation: AUC, area under the curve; CRC, colorectal cancer; 95% CI, 95% confidence interval.

* p-values were adjusted by multiple testing (Benjamini-Hochberg method)

[†] AUCs were adjusted by .632+ bootstrap method, and 95% CIs were derived from 1000 bootstrap samples

Table S4. Diagnostic performance of multi-marker panels for detecting colorectal cancer in the test set stratified by sex

Gender	Marker	AUC (95% CI) [†]	Sensitivity (95% CI) [†]	
			at 90% specificity	at 80% specificity
Male	(a) CRC vs. participants free of neoplasm			
	4 protein panel	0.76 (0.64-0.86)	34.5 (10.3-69.0)	55.2 (31.0-79.3)
	4-protein panel + anti-TP53	0.80 (0.67-0.89)	57.1 (14.3-71.4)	57.1 (39.2-78.6)
	(b) advanced adenomas vs. free of neoplasm			
	4 protein panel	0.57 (0.45-0.68)	17.9 (7.1-37.5)	28.6 (28.6-44.6)
	4-protein panel + anti-TP53	0.63 (0.51-0.74)	32.6 (11.6-46.5)	34.9 (20.9-55.8)
Female	(a) CRC vs. free of neoplasm			
	4 protein panel	0.83 (0.67-0.95)	58.3 (25.0-91.0)	75.0 (41.7-100.0)
	4-protein panel + anti-TP53	0.83 (0.67-0.95)	63.6 (27.3-90.9)	72.7 (45.5-100.0)
	(b) advanced adenomas vs. free of neoplasm			
	4 protein panel	0.57 (0.46-0.67)	10.0 (2.0-24.0)	18.0 (6.0-42.0)
	4-protein panel + anti-TP53	0.57 (0.45-0.68)	17.9 (2.6-30.8)	20.5 (7.7-41.0)

Abbreviation: AUC, area under the curve; CRC, colorectal cancer; 95% CI, 95% confidence interval.

[†] AUCs were adjusted by .632+ bootstrap method, and 95% confidence intervals were derived from 1,000 bootstrap samples.

Table S5. Diagnostic performance of multi-marker panel for detecting colorectal cancer in the test set from a screening setting stratified by age

Age	Marker	AUC (95% CI) [†]	Sensitivity (95% CI) [†]	
			at 90% specificity	at 80% specificity
<65 years	(a) CRC vs. free of neoplasm			
	4 protein panel	0.82 (0.70-0.92)	50.0 (27.8-72.2)	61.1 (33.3-88.9)
	4-protein panel + anti-TP53	0.85 (0.75-0.94)	47.1 (23.5-82.3)	76.5 (41.2-94.1)
	(b) advanced adenomas vs. free of neoplasm			
	4 protein panel	0.61 (0.52-0.70)	13.2 (5.9-23.5)	23.5 (8.8-52.9)
	4-protein panel + anti-TP53	0.63 (0.52-0.73)	15.4 (5.8-40.4)	38.5 (13.5-57.7)
≥ 65 years	(a) CRC vs. free of neoplasm			
	4 protein panel	0.77 (0.64-0.88)	30.4 (8.7-69.6)	60.9 (21.7-82.7)
	4-protein panel + anti-TP53	0.77 (0.63-0.88)	45.5 (18.2-81.8)	63.6 (36.4-86.4)
	(b) advanced adenomas vs. free of neoplasm			
	4 protein panel	0.55 (0.42-0.67)	18.4 (2.6-36.8)	31.6 (10.5-47.4)
	4-protein panel + anti-TP53	0.57 (0.41-0.71)	30.0 (0-53.3)	36.7 (20.0-60.0)

Abbreviation: AUC, area under the curve; CRC, colorectal cancer; 95% CI, 95% confidence interval.

[†] AUCs were adjusted by .632+ bootstrap method, and 95% confidence intervals were derived from 1,000 bootstrap samples.

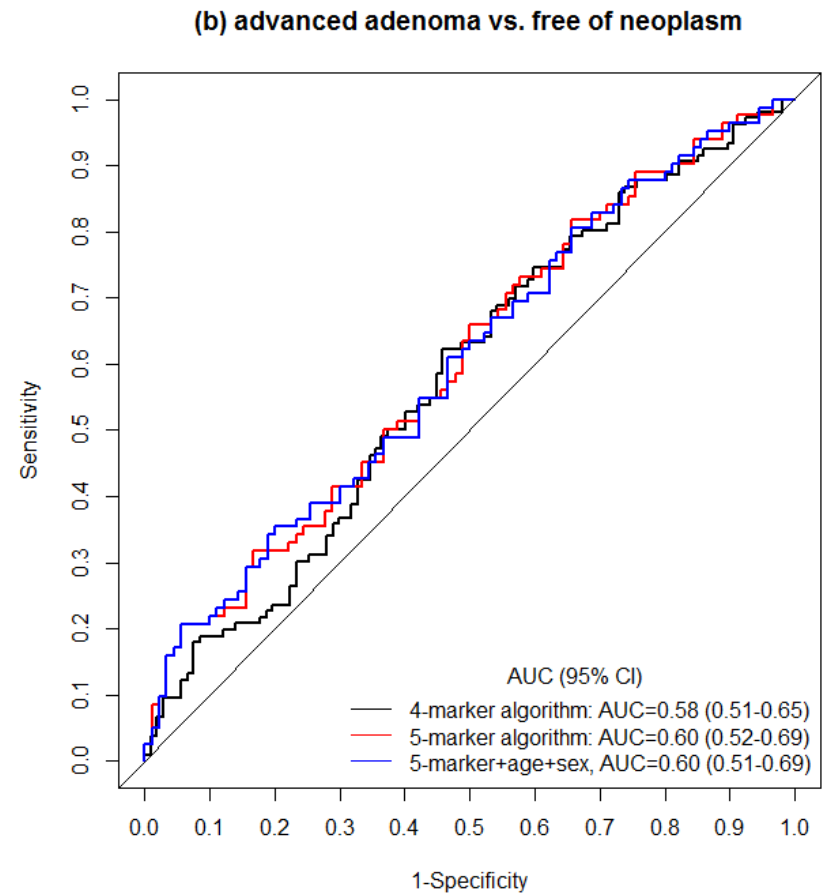
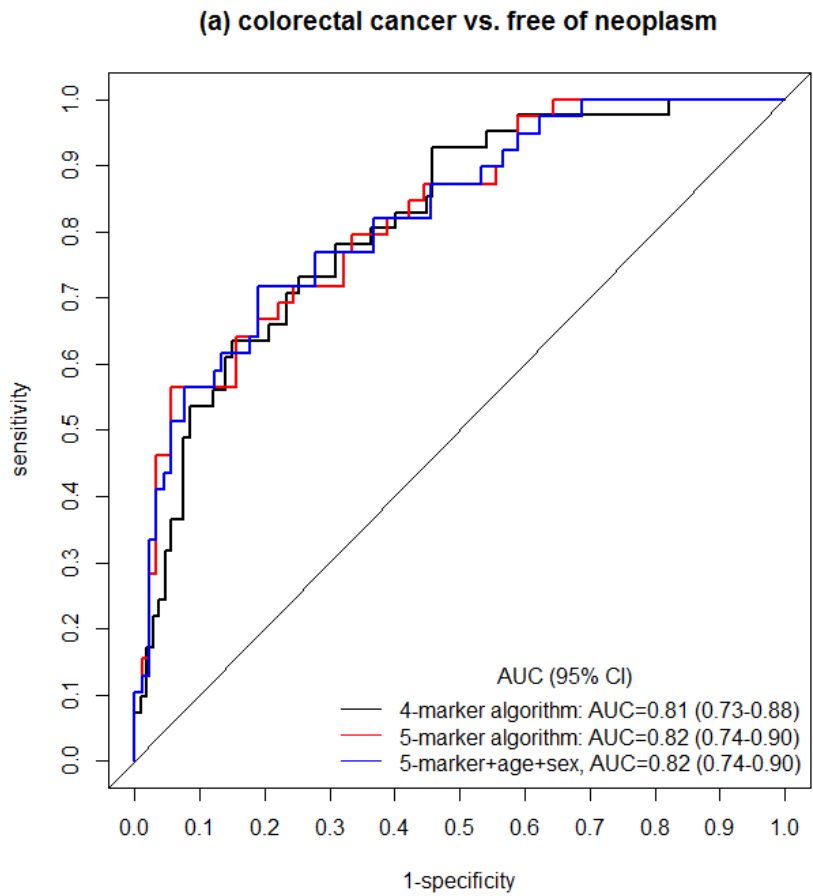


Figure S1. Receiver operating characteristics curves comparing different models (four-marker panel, five-marker panel, and five-marker panel combined with age and sex) for detecting a) colorectal cancer vs. free of neoplasm s; b) advanced adenomas vs. free of neoplasm.