

## **Supplemental Material**

Supplemental Table 1. Protein names and respective Olink® panel sorted in alphabetical order

Protein full name	Entry name	Olink® Panel*	Uniprot ID**
Angiotensin-converting enzyme 2	ACE2	CVD II	Q9BYF1
Adenosine Deaminase	ADA	INF	P00813
Adisintegrin and metalloproteinase with thrombospondin motifs 13	ADAMTS13	CVD II	Q76LX8
ADM	ADM	CVD II	P35318
Agouti-related protein	AGRP	CVD II	O00253
CD166 antigen	ALCAM	CVD III	Q13740
Protein AMBP	AMBP	CVD II	P02760
Angiopoietin-1	ANG1	CVD II	Q15389
Aminopeptidase N	APN	CVD III	P15144
Axin-1	AXIN1	INF	O15169
Tyrosine-protein kinase receptor UFO	AXL	CVD III	P30530
Azurocidin	AZU1	CVD III	P20160
Brain-derived neurotrophic factor	BDNF	INF	P23560
Beta-nerve growth factor	BETANGF	INF	P01138
Bleomycin hydrolase	BLMHYDROLASE	CVD III	Q13867
Bone morphogenetic protein 6	BMP6	CVD II	P22004
Natriuretic peptides B	BNP	CVD II	P16860
Eukaryotic translation initiation factor 4E-binding protein 1	BP1_4E	INF	Q13541
Carbonic anhydrase 5A, mitochondrial	CA5A	CVD II	P35218
Caspase-3	CASP3	CVD III	P42574
Caspase 8	CASP8	INF	Q14790
Eotaxin-1	CCL11	INF	P51671
C-C motif chemokine 15	CCL15	CVD III	Q16663
C-C motif chemokine 16	CCL16	CVD III	O15467
C-C motif chemokine 17	CCL17	CVD II	Q92583
C-C motif chemokine 19	CCL19	INF	Q99731
C-C motif chemokine 20	CCL20	INF	P78556
C-C motif chemokine 22	CCL22	CVD III	O00626
C-C motif chemokine 23	CCL23	INF	P55773
C-C motif chemokine 24	CCL24	CVD III	O00175
C-C motif chemokine 25	CCL25	INF	O15444
C-C motif chemokine 28	CCL28	INF	Q9NRJ3
C-C motif chemokine 3	CCL3	CVD II	P10147
C-C motif chemokine 4	CCL4	INF	P13236
Scavenger receptor cysteine-rich type 1 protein M130	CD163	CVD III	Q86VB7
Natural killer cell receptor 2B4	CD244	INF	Q9BZW8
T-cell surface glycoprotein CD4	CD4	CVD II	P01730
CD40L receptor	CD40	INF	P25942
CD40 ligand	CD40L	CVD II	P29965
T-cell surface glycoprotein CD5	CD5	INF	P06127
T cell surface glycoprotein CD6	CD6	INF	P30203
SLAM family member 5	CD84	CVD II	Q9UIB8
Complement component C1q receptor	CD93	CVD III	Q9NPY3
CUB domain-containing protein 1	CDCP1	INF	Q9H5V8
Cadherin-5	CDH5	CVD III	P33151
Carcinoembryonic antigen-related cell adhesion molecule 8	CEACAM8	CVD II	P31997

Chitinase-3-like protein 1	CHI3L1	CVD III	P36222
Chitotriosidase-1	CHIT1	CVD III	Q13231
Contactin-1	CNTN1	CVD III	Q12860
Collagen alpha-1(I) chain	COL1A1	CVD III	P02452
Carboxypeptidase A1	CPA1	CVD III	P15085
Carboxypeptidase B	CPB1	CVD III	P15086
Macrophage colony-stimulating factor 1	CSF1	INF	P09603
Cystatin D	CST5	INF	P28325
Cystatin-B	CSTB	CVD III	P04080
Chymotrypsin C	CTRC	CVD II	Q99895
Cathepsin D	CTSD	CVD III	P07339
Cathepsin L1	CTSL1	CVD II	P07711
Cathepsin Z	CTSZ	CVD III	Q9UBR2
Fractalkine	CX3CL1	INF	P78423
C-X-C motif chemokine 1 (CVD2)	CXCL1	CVD II	P09341
C-X-C motif chemokine 10	CXCL10	INF	P02778
C-X-C motif chemokine 11	CXCL11	INF	O14625
C-X-C motif chemokine 16	CXCL16	CVD III	Q9H2A7
C-X-C motif chemokine 5	CXCL5	INF	P42830
C-X-C motif chemokine 6	CXCL6	INF	P80162
C-X-C motif chemokine 9	CXCL9	INF	Q07325
Decorin	DCN	CVD II	P07585
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	CVD II	Q16698
Dickkopf-related protein 1	DKK1	CVD II	O94907
Azurocidin	DLK1	CVD III	P80370
Delta and Notch-like epidermal growth factor-related receptor	DNER	INF	Q8NFT8
Epidermal growth factor receptor	EGFR	CVD III	P00533
Protein S100-A12	ENRAGE	INF	P80511
Epithelial cell adhesion molecule	EPCAM	CVD III	P16422
Ephrin type-B receptor 4	EPHB4	CVD III	P54760
Fatty acid-binding protein, intestinal	FABP2	CVD II	P12104
Fatty acid-binding protein, adipocyte	FABP4	CVD III	P15090
Tumor necrosis factor receptor superfamily member 6	FAS	CVD III	P25445
Fibroblast growth factor 19	FGF19	INF	O95750
Fibroblast growth factor 21 (CVD2)	FGF21	CVD II	Q9NSA1
Fibroblast growth factor 23 (CVD2)	FGF23	CVD II	Q9GZV9
Fibroblast growth factor 5	FGF5	INF	P12034
Fms-related tyrosine kinase 3 ligand	FLT3L	INF	P49771
Follistatin	FS	CVD II	P19883
Galectin-3	GAL3	CVD III	P17931
Galectin-4	GAL4	CVD III	P56470
Galectin-9	GAL9	CVD II	O00182
Growth/differentiation factor 15	GDF15	CVD III	Q99988
Growth/differentiation factor 2	GDF2	CVD II	Q9UK05
Growth hormone	GH	CVD II	P01241
Gastric intrinsic factor	GIF	CVD II	P27352
Lactoylglutathione lyase	GLO1	CVD II	Q04760
Granulins	GRN	CVD III	P28799
Gastrotropin	GT	CVD II	P51161
Hydroxyacid oxidase 1	HAOX1	CVD II	Q9UJM8
Proheparin-binding EGF-like growth factor	HBEGF	CVD II	Q99075

Glial cell line-derived neurotrophic factor	HGDNF	INF	P39905
Hepatocyte growth factor	HGF	INF	P14210
Heme oxygenase 1	HO1	CVD II	P09601
Osteoclast-associated immunoglobulin-like receptor	HOSCAR	CVD II	Q8IYS5
Heat shock 27 kDa protein	HSP27	CVD II	P04792
Intercellular adhesion molecule 2	ICAM2	CVD III	P13598
Alpha-L-iduronidase	IDUA	CVD II	P35475
Insulin-like growth factor-binding protein 1	IGFBP1	CVD III	P08833
Insulin-like Growth Factor-Binding Protein 2	IGFBP2	CVD III	P18065
Insulin-like growth factor-binding protein 7	IGFBP7	CVD III	Q16270
Low affinity immunoglobulin gamma Fc region receptor II-b	IGGFCRECEP TORIIB	CVD II	P31994
Interleukin-10	IL10	INF	P22301
Interleukin-10 receptor subunit alpha	IL10RA	INF	Q13651
Interleukin-10 receptor subunit beta	IL10RB	INF	Q08334
Interleukin-12 subunit beta	IL12B	INF	P29460
Interleukin-13	IL13	INF	P35225
Interleukin-15 receptor subunit alpha	IL15RA	INF	Q13261
Pro-interleukin-16	IL16	CVD II	Q14005
Interleukin-17A	IL17A	INF	Q16552
Interleukin-17C	IL17C	INF	Q9P0M4
Interleukin-17D	IL17D	CVD II	Q8TAD2
Interleukin-17 receptor A	IL17RA	CVD III	Q96F46
Interleukin-18 (CVD2)	IL18	CVD II	Q14116
Interleukin-18-binding protein	IL18BP	CVD III	O95998
Interleukin-18 receptor 1	IL18R1	INF	Q13478
Interleukin-1 receptor antagonist protein	IL1RA	CVD II	P18510
Interleukin-1 receptor-like 2	IL1RL2	CVD II	Q9HB29
Interleukin-1 receptor type 1	IL1RT1	CVD III	P14778
Interleukin-1 receptor type 2	IL1RT2	CVD III	P27930
Interleukin-20 receptor subunit alpha	IL20RA	INF	Q9UHF4
Interleukin-27	IL27	CVD II	Q8NEV9
Interleukin-2 receptor subunit alpha	IL2RA	CVD III	P01589
Interleukin-4 receptor subunit alpha	IL4RA	CVD II	P24394
Interleukin-6 (CVD2)	IL6	CVD II	P05231
Interleukin-6 receptor subunit alpha	IL6RA	CVD III	P08887
Interleukin-7	IL7	INF	P13232
Interleukin-8	IL8	INF	P10145
Melusin	ITGB1BP2	CVD II	Q9UKP3
Integrin beta-2	ITGB2	CVD III	P05107
Junctional adhesion molecule A	JAMA	CVD III	Q9Y624
Kidney injury molecule 1	KIM1	CVD II	Q96D42
Kallikrein-6	KLK6	CVD III	Q92876
Latency-associated peptide transforming growth factor beta 1	LAPTGF BETA 1	INF	P01137
Low-density lipoprotein receptor	LDLRECEPTO R	CVD III	P01130
Leptin	LEP	CVD II	P41159
Leukemia inhibitory factor receptor	LIFR	INF	P42702
Lectin-like oxidized LDL receptor 1	LOX1	CVD II	P78380
Lipoprotein lipase	LPL	CVD II	P06858
Lymphotoxin-beta receptor	LTBR	CVD III	P36941
Macrophage receptor MARCO	MARCO	CVD II	Q9UEW3

Myoglobin	MB	CVD III	P02144
Monocyte chemotactic protein 1	MCP1_CVD3	CVD III	P13500
Monocyte chemotactic protein 2	MCP2	INF	P80075
Monocyte chemotactic protein 3	MCP3	INF	P80098
Monocyte chemotactic protein 4	MCP4	INF	Q99616
Matrix extracellular phosphoglycoprotein	MEPE	CVD III	Q9NQ76
Tyrosine-protein kinase Mer	MERTK	CVD II	Q12866
Matrix metalloproteinase-1	MMP1	INF	P03956
Matrix metalloproteinase-10	MMP10	INF	P09238
Matrix metalloproteinase-12	MMP12	CVD II	P39900
Matrix metalloproteinase-2	MMP2	CVD III	P08253
Matrix metalloproteinase-3	MMP3	CVD III	P08254
Matrix metalloproteinase-7	MMP7	CVD II	P09237
Matrix metalloproteinase-9	MMP9	CVD III	P14780
Myeloperoxidase	MPO	CVD III	P05164
NF-kappa-B essential modulator	NEMO	CVD II	Q9Y6K9
Neurogenic locus notch homolog protein 3	NOTCH3	CVD III	Q9UM47
Neurotrophin-3	NT3	INF	P20783
N-terminal prohormone brain natriuretic peptide	NTPROBNP	CVDII	P16860
Osteoprotegerin	OPG_CVD3	CVD III	O00300
Osteopontin	OPN	CVD III	P10451
Oncostatin-M	OSM	INF	P13725
Plasminogen activator inhibitor 1	PAI	CVD III	P05121
Pappalysin-1	PAPPA	CVD II	Q13219
Proteinase-activated receptor 1	PAR1	CVD II	P25116
Poly [ADP-ribose] polymerase 1	PARP1	CVD II	P09874
Proprotein convertase subtilisin/kexin type 9	PCSK9	CVD III	Q8NBP7
Platelet-derived growth factor subunit A	PDGFSUBUNI TA	CVD III	P04085
Platelet-derived growth factor subunit B	PDGFSUBUNI TB	CVD II	P01127
Programmed cell death 1 ligand 1	PDL1	INF	Q9NZQ7
Programmed cell death 1 ligand 2	PDL2	CVD II	Q9BQ51
Platelet endothelial cell adhesion molecule	PECAM1	CVD III	P16284
Peptidoglycan recognition protein 1	PGLYRP1	CVD III	O75594
Elafin	PI3	CVD III	P19957
Polymeric immunoglobulin receptor	PIGR	CVD II	P01833
Perlecan	PLC	CVD III	P98160
Placenta growth factor	PLGF	CVD II	P49763
Paraoxonase (PON 3)	PON3	CVD III	Q15166
Prolargin	PRELP	CVD II	P51888
Brother of CDO	PROTEINBOC	CVD II	Q9BWV1
Serine protease 27	PRSS27	CVD II	Q9BQR3
Prostasin	PRSS8	CVD II	Q16651
Myeloblastin	PRTN3	CVD III	P24158
P-selectin glycoprotein ligand 1	PSGL1	CVD II	Q14242
Pulmonary surfactant-associated protein D	PSPD	CVD III	P35247
Pentraxin-related protein PTX3	PTX3	CVD II	P26022
Receptor for advanced glycosylation end products	RAGE	CVD II	Q15109
Retinoic acid receptor responder protein 2	RARRES2	CVD III	Q99969
Renin	REN	CVD II	P00797
Resistin	RETN	CVD III	Q9HD89
Stem cell factor (CVD2)	SCF	CVD II	P21583

Secretoglobin family 3A member 2	SCGB3A2	CVD III	Q96PL1
E-selectin	SELE	CVD III	P16581
P-selectin	SELP	CVD III	P16109
Serpin A12	SERPINA12	CVD II	Q8IW75
Tyrosine-protein phosphatase non-receptor type substrate 1	SHPS1	CVD III	P78324
SIR2-like protein 2	SIRT2	INF	Q8IXJ6
Signaling lymphocytic activation molecule	SLAMF1	INF	Q13291
SLAM family member 7	SLAMF7	CVD II	Q9NQ25
Superoxide dismutase [Mn], mitochondrial	SOD2	CVD II	P04179
Sortilin	SORT1	CVD II	Q99523
Spondin-1	SPON1	CVD III	Q9HCB6
Spondin-2	SPON2	CVD II	Q9BUD6
Proto-oncogene tyrosine-protein kinase Src	SRC	CVD II	P12931
Sulfotransferase 1A1	ST1A1	INF	P50225
ST2 protein	ST2	CVD III	Q01638
STAM-binding protein	STAMPB	INF	O95630
Serine/threonine-protein kinase 4	STK4	CVD II	Q13043
Tissue factor	TF	CVD II	P13726
Trefoil factor 3	TFF3	CVD III	Q07654
Tissue factor pathway inhibitor	TFPI	CVD III	P10646
Transforming growth factor alpha	TGFALPHA	INF	P01135
Protein-glutamine gamma-glutamyltransferase 2	TGM2	CVD II	P21980
Thrombospondin-2	THBS2	CVD II	P35442
Thrombopoietin	THPO	CVD II	P40225
Angiopoietin-1 receptor	TIE2	CVD II	Q02763
Metalloproteinase inhibitor 4	TIMP4	CVD III	Q99727
Trem-like transcript 2 protein	TLT2	CVD III	Q5T2D2
Thrombomodulin	TM	CVD II	P07204
Tumor necrosis factor	TNF	INF	P01375
TNF-beta	TNFB	INF	P01374
Tumor necrosis factor receptor 1	TNFR1	CVD III	P19438
Tumor necrosis factor receptor 2	TNFR2	CVD III	P20333
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	CVD II	O00220
Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C	CVD III	O14798
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	CVD II	Q9Y6Q6
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	CVD II	O14836
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	CVD III	Q92956
Tumor necrosis factor receptor superfamily member 9	TNFRSF9	INF	Q07011
Tumor necrosis factor ligand superfamily member 13B	TNFSF13B	CVD III	Q9Y275
Tumor necrosis factor ligand superfamily member 14	TNFSF14	INF	O43557
Tissue-type plasminogen activator	TPA	CVD III	P00750
Transferrin receptor protein 1	TR	CVD III	P02786
TNF-related apoptosis-inducing ligand	TRAIL	INF	P50591
TNF-related apoptosis-inducing ligand receptor 2	TRAILR2	CVD II	O14763
TNF-related activation-induced cytokine	TRANCE	INF	O14788
Tartrate-resistant acid phosphatase type 5	TRAP	CVD III	P13686
Tumor necrosis factor (Ligand) superfamily, member 12	TWEAK	INF	O43508
Urokinase-type plasminogen activator	UPA_CVD3	CVD III	P00749
Urokinase plasminogen activator surface receptor	UPAR	CVD III	Q03405
Vascular endothelial growth factor A	VEGFA	INF	P15692
Vascular endothelial growth factor D	VEGFD	CVD II	O43915

V-set and immunoglobulin domain-containing protein 2	VSIG2	CVD II	Q96IQ7
von Willebrand factor	VWF	CVD III	P04275
Lymphotactin	XCL1	CVD II	P47992

Legend: \*CVII: cardiovascular II; CVIII: cardiovascular III; INF: inflammation panels; \*\*UniProt ID from UniProt Knowledgebase

Supplemental Table 2. Study proteins order by p-value (from lowest to highest in the discovery set) in both discovery and replication phases

Protein name	Discovery (phase 1a)								Replication (phase 1b)							
	Adjusted for matching variables				Adjusted for matching variables and risk factors				Adjusted for matching variables				Adjusted for matching variables and risk factors			
	OR	(95% CI)	P-value	Z	OR	(95% CI)	P-value	Z	OR	(95% CI)	P-value	Z	OR	(95% CI)	P-value	Z
NTPROBNP	1.74	(1.46, 2.06)	<0.0001	6.3	1.79	(1.49, 2.14)	<0.0001	6.3	2	(1.64, 2.44)	<0.0001	6.9	2.06	(1.66, 2.54)	<0.0001	6.6
BNP	1.62	(1.42, 1.86)	<0.0001	7	1.59	(1.37, 1.84)	<0.0001	6.3	1.73	(1.50, 2.01)	<0.0001	7.3	1.77	(1.51, 2.07)	<0.0001	7.1
GDF15	2.74	(2.08, 3.61)	<0.0001	7.2	2.34	(1.72, 3.19)	<0.0001	5.4	1.89	(1.44, 2.47)	<0.0001	4.6	1.55	(1.15, 2.09)	0.0036	2.9
TRAILR2	3.26	(2.32, 4.60)	<0.0001	6.8	2.7	(1.86, 3.92)	<0.0001	5.2	3.22	(2.21, 4.69)	<0.0001	6.1	2.65	(1.72, 4.07)	<0.0001	4.4
CSTB	2.1	(1.67, 2.66)	<0.0001	6.2	1.84	(1.43, 2.37)	<0.0001	4.8	1.3	(1.07, 1.60)	0.0101	2.6	1.16	(0.93, 1.44)	0.1808	1.3
UPAR	2.7	(1.94, 3.75)	<0.0001	5.9	2.27	(1.61, 3.21)	<0.0001	4.6	1.67	(1.23, 2.28)	0.0011	3.3	1.38	(1.00, 1.92)	0.0519	1.9
VEGFA	2.65	(1.91, 3.67)	<0.0001	5.9	2.27	(1.59, 3.22)	<0.0001	4.5	1.52	(1.09, 2.11)	0.0129	2.5	1.27	(0.89, 1.80)	0.1837	1.3
HGF	2.49	(1.78, 3.48)	<0.0001	5.3	2.12	(1.50, 3.01)	<0.0001	4.2	1.5	(1.11, 2.02)	0.0077	2.7	1.29	(0.94, 1.77)	0.119	1.6
CXCL9	1.56	(1.30, 1.87)	<0.0001	4.7	1.52	(1.25, 1.84)	<0.0001	4.2	1.09	(0.89, 1.34)	0.3813	0.9	1.03	(0.83, 1.28)	0.7895	0.3
IL6	1.51	(1.29, 1.78)	<0.0001	5.1	1.42	(1.20, 1.68)	<0.0001	4.1	1.21	(1.03, 1.43)	0.021	2.3	1.09	(0.92, 1.30)	0.3325	1
OPN	2	(1.52, 2.63)	<0.0001	5	1.81	(1.36, 2.41)	<0.0001	4.1	1.5	(1.16, 1.95)	0.0021	3.1	1.36	(1.03, 1.79)	0.0298	2.2
ADM	2.56	(1.82, 3.59)	<0.0001	5.4	2.12	(1.48, 3.05)	<0.0001	4.1	1.8	(1.32, 2.45)	0.0002	3.7	1.41	(1.02, 1.96)	0.0389	2.1
CD40	2.26	(1.68, 3.04)	<0.0001	5.4	1.93	(1.41, 2.66)	<0.0001	4.1	1.27	(0.94, 1.72)	0.1228	1.5	1.05	(0.76, 1.46)	0.7743	0.3
MCP3	1.7	(1.35, 2.15)	<0.0001	4.5	1.61	(1.27, 2.05)	<0.0001	3.9	1.18	(0.89, 1.55)	0.2444	1.2	1.08	(0.81, 1.44)	0.6164	0.5
TFE3	1.61	(1.32, 1.95)	<0.0001	4.8	1.52	(1.23, 1.87)	0.0001	3.9	1.45	(1.15, 1.84)	0.0019	3.1	1.25	(0.96, 1.62)	0.0924	1.7
FABP4	1.82	(1.51, 2.19)	<0.0001	6.2	1.57	(1.25, 1.97)	0.0001	3.9	1.57	(1.29, 1.92)	<0.0001	4.5	1.28	(1.01, 1.61)	0.0383	2.1
OPG_CVD3	2.31	(1.63, 3.27)	<0.0001	4.7	2.05	(1.42, 2.95)	0.0001	3.9	1.45	(1.02, 2.06)	0.0385	2.1	1.25	(0.86, 1.82)	0.2381	1.2
CXCL11	1.34	(1.17, 1.55)	<0.0001	4.1	1.33	(1.15, 1.54)	0.0001	3.8	1.11	(0.96, 1.29)	0.1425	1.5	1.13	(0.96, 1.32)	0.1375	1.5
TNFRSF10A	2.63	(1.88, 3.69)	<0.0001	5.6	2.01	(1.40, 2.88)	0.0002	3.8	2.56	(1.74, 3.77)	<0.0001	4.8	1.98	(1.31, 3.01)	0.0013	3.2
TNFR1	2.4	(1.75, 3.28)	<0.0001	5.5	1.98	(1.38, 2.84)	0.0002	3.7	1.63	(1.23, 2.16)	0.0007	3.4	1.26	(0.92, 1.73)	0.1488	1.4
SPON1	2.25	(1.55, 3.26)	<0.0001	4.3	2.05	(1.40, 2.98)	0.0002	3.7	1.76	(1.16, 2.67)	0.0083	2.6	1.42	(0.91, 2.21)	0.1225	1.5
GAL9	2.96	(1.95, 4.49)	<0.0001	5.1	2.3	(1.48, 3.58)	0.0002	3.7	3.14	(2.01, 4.91)	<0.0001	5	2.59	(1.61, 4.19)	<0.0001	3.9
FGF23	1.7	(1.40, 2.07)	<0.0001	5.3	1.48	(1.20, 1.81)	0.0002	3.7	1.84	(1.44, 2.36)	<0.0001	4.8	1.69	(1.30, 2.20)	<0.0001	3.9
TNFRSF11A	2.09	(1.61, 2.72)	<0.0001	5.6	1.72	(1.28, 2.31)	0.0003	3.6	1.95	(1.47, 2.59)	<0.0001	4.6	1.53	(1.12, 2.11)	0.0085	2.6
IL2RA	1.74	(1.33, 2.28)	<0.0001	4.1	1.66	(1.25, 2.22)	0.0005	3.5	1.42	(1.09, 1.84)	0.0092	2.6	1.26	(0.94, 1.67)	0.1163	1.6
TNFR2	2.11	(1.58, 2.82)	<0.0001	5.1	1.75	(1.27, 2.42)	0.0007	3.4	1.55	(1.20, 2.00)	0.0008	3.3	1.29	(0.98, 1.71)	0.0743	1.8
RETN	1.82	(1.42, 2.33)	<0.0001	4.7	1.58	(1.21, 2.06)	0.0008	3.3	1.37	(1.05, 1.77)	0.0182	2.4	1.22	(0.92, 1.62)	0.1584	1.4
TNFRSF13B	1.74	(1.34, 2.24)	<0.0001	4.2	1.58	(1.21, 2.06)	0.0008	3.3	2.61	(1.82, 3.74)	<0.0001	5.2	2.33	(1.58, 3.44)	<0.0001	4.3
AGRP	1.82	(1.38, 2.40)	<0.0001	4.2	1.64	(1.23, 2.20)	0.0009	3.3	1.9	(1.31, 2.76)	0.0007	3.4	1.62	(1.08, 2.44)	0.0193	2.3
TNFRSF14	2.09	(1.55, 2.82)	<0.0001	4.9	1.76	(1.26, 2.46)	0.0009	3.3	1.52	(1.15, 2.01)	0.0034	2.9	1.26	(0.93, 1.71)	0.1394	1.5
GAL4	1.89	(1.47, 2.42)	<0.0001	5	1.57	(1.19, 2.05)	0.0012	3.2	1.44	(1.10, 1.87)	0.0071	2.7	1.18	(0.89, 1.57)	0.2553	1.1
RARRES2	3.33	(2.02, 5.51)	<0.0001	4.7	2.45	(1.42, 4.23)	0.0014	3.2	2.05	(1.38, 3.05)	0.0004	3.5	1.67	(1.09, 2.56)	0.0183	2.4
ACE2	1.6	(1.27, 2.02)	<0.0001	4	1.48	(1.16, 1.89)	0.0014	3.2	1.52	(1.17, 1.98)	0.0016	3.2	1.4	(1.06, 1.84)	0.0173	2.4
PLGF	2.17	(1.54, 3.06)	<0.0001	4.4	1.86	(1.27, 2.72)	0.0014	3.2	1.95	(1.38, 2.75)	0.0002	3.8	1.61	(1.11, 2.34)	0.0131	2.5
PGLYRP1	1.68	(1.31, 2.15)	<0.0001	4.1	1.53	(1.17, 1.98)	0.0016	3.2	1.36	(1.06, 1.74)	0.0151	2.4	1.2	(0.92, 1.56)	0.1893	1.3
TGFALPHA	1.9	(1.40, 2.59)	<0.0001	4.1	1.66	(1.21, 2.28)	0.0016	3.2	1.38	(1.07, 1.78)	0.0122	2.5	1.23	(0.94, 1.61)	0.1345	1.5
MMP12	1.64	(1.32, 2.03)	<0.0001	4.6	1.42	(1.13, 1.79)	0.0023	3	1.54	(1.23, 1.92)	0.0002	3.8	1.33	(1.04, 1.70)	0.0236	2.3
TIMP4	1.72	(1.32, 2.23)	<0.0001	4	1.54	(1.17, 2.04)	0.0024	3	1.2	(0.93, 1.53)	0.1568	1.4	1.08	(0.83, 1.41)	0.5465	0.6
SLAMF7	1.55	(1.26, 1.91)	<0.0001	4.1	1.41	(1.13, 1.76)	0.0024	3	2.16	(1.52, 3.06)	<0.0001	4.3	2	(1.38, 2.91)	0.0003	3.7
TNFRSF9	1.54	(1.25, 1.90)	<0.0001	4	1.41	(1.13, 1.76)	0.0025	3	1.33	(1.03, 1.72)	0.0318	2.1	1.15	(0.86, 1.53)	0.3411	1
IL1RA	1.54	(1.27, 1.86)	<0.0001	4.4	1.37	(1.11, 1.69)	0.003	3	1.25	(1.07, 1.46)	0.0048	2.8	1.17	(0.99, 1.39)	0.059	1.9
CCL16	1.47	(1.21, 1.79)	<0.0001	3.9	1.37	(1.11, 1.68)	0.003	3	1.72	(1.34, 2.22)	<0.0001	4.2	1.55	(1.18, 2.02)	0.0015	3.2
CD4	2.06	(1.49, 2.85)	<0.0001	4.3	1.67	(1.18, 2.35)	0.0035	2.9	2.17	(1.49, 3.16)	<0.0001	4	1.86	(1.25, 2.77)	0.0021	3.1



LTBR	1.93	(1.40, 2.68)	<0.0001	4	1.7	(1.18, 2.45)	0.004	2.9	1.42	(1.06, 1.90)	0.0203	2.3	1.22	(0.88, 1.68)	0.2287	1.2
IL15RA	2.12	(1.47, 3.05)	<0.0001	4	1.74	(1.18, 2.56)	0.0053	2.8	1.75	(1.07, 2.85)	0.0258	2.2	1.46	(0.86, 2.49)	0.1579	1.4
KIM1	1.41	(1.19, 1.68)	<0.0001	4	1.29	(1.07, 1.55)	0.0065	2.7	1.51	(1.23, 1.84)	<0.0001	4	1.31	(1.05, 1.62)	0.0159	2.4
PLC	2.26	(1.59, 3.21)	<0.0001	4.5	1.77	(1.17, 2.68)	0.0071	2.7	1.76	(1.24, 2.49)	0.0015	3.2	1.43	(0.97, 2.11)	0.0686	1.8
CEACAM8	1.51	(1.22, 1.86)	0.0001	3.8	1.47	(1.18, 1.83)	0.0006	3.4	1.49	(1.19, 1.86)	0.0005	3.5	1.36	(1.08, 1.73)	0.0098	2.6
ICAM2	1.91	(1.37, 2.66)	0.0001	3.8	1.73	(1.22, 2.44)	0.0019	3.1	1.16	(0.86, 1.57)	0.3262	1	1.06	(0.77, 1.45)	0.7229	0.4
EPHB4	1.96	(1.40, 2.76)	0.0001	3.9	1.62	(1.11, 2.37)	0.0121	2.5	1.38	(1.00, 1.91)	0.0499	2	1.19	(0.84, 1.69)	0.3334	1
HSP27	2.13	(1.42, 3.22)	0.0003	3.6	2.03	(1.32, 3.14)	0.0013	3.2	1.32	(1.02, 1.71)	0.0357	2.1	1.27	(0.97, 1.68)	0.0826	1.7
LAPTFGBETA1	1.68	(1.27, 2.22)	0.0003	3.6	1.58	(1.18, 2.12)	0.0021	3.1	1.15	(0.88, 1.49)	0.3102	1	1.11	(0.84, 1.47)	0.4747	0.7
PAR1	1.86	(1.33, 2.60)	0.0003	3.6	1.64	(1.16, 2.31)	0.0048	2.8	1.74	(1.24, 2.45)	0.0014	3.2	1.53	(1.07, 2.19)	0.0186	2.4
TWEAK	0.51	(0.36, 0.73)	0.0003	3.6	0.58	(0.39, 0.85)	0.0052	2.8	0.53	(0.39, 0.71)	<0.0001	4.1	0.58	(0.42, 0.80)	0.0008	3.4
CXCL16	1.95	(1.36, 2.79)	0.0003	3.6	1.66	(1.13, 2.46)	0.0101	2.6	1.29	(0.93, 1.81)	0.1317	1.5	1.12	(0.78, 1.60)	0.5478	0.6
JAMA	1.43	(1.18, 1.73)	0.0003	3.6	1.29	(1.06, 1.58)	0.0122	2.5	1.11	(0.94, 1.32)	0.2257	1.2	1.07	(0.90, 1.28)	0.4462	0.8
IL18BP	1.71	(1.28, 2.29)	0.0003	3.6	1.5	(1.09, 2.07)	0.013	2.5	1.39	(1.06, 1.83)	0.0192	2.3	1.18	(0.87, 1.59)	0.2842	1.1
CCL15	1.51	(1.21, 1.88)	0.0003	3.6	1.29	(1.00, 1.65)	0.0463	2	1.39	(1.08, 1.79)	0.0117	2.5	1.18	(0.89, 1.57)	0.238	1.2
CHI3L1	1.33	(1.14, 1.56)	0.0004	3.5	1.25	(1.06, 1.47)	0.0086	2.6	1.2	(1.01, 1.42)	0.0352	2.1	1.08	(0.90, 1.29)	0.4317	0.8
CSF1	2.27	(1.43, 3.61)	0.0005	3.5	1.91	(1.18, 3.09)	0.0088	2.6	1.37	(0.78, 2.42)	0.2774	1.1	1.05	(0.57, 1.93)	0.8707	0.2
PDL1	1.64	(1.24, 2.16)	0.0005	3.5	1.47	(1.09, 1.98)	0.0107	2.6	1.3	(0.93, 1.81)	0.1215	1.5	0.96	(0.67, 1.39)	0.8473	0.2
PDL2	1.96	(1.34, 2.87)	0.0005	3.5	1.68	(1.13, 2.50)	0.011	2.5	1.77	(1.18, 2.65)	0.006	2.7	1.62	(1.05, 2.50)	0.0287	2.2
FAS	1.78	(1.29, 2.46)	0.0005	3.5	1.49	(1.06, 2.09)	0.0223	2.3	1.52	(1.10, 2.11)	0.012	2.5	1.29	(0.90, 1.84)	0.1601	1.4
GRN	2.09	(1.38, 3.16)	0.0005	3.5	1.66	(1.07, 2.57)	0.0239	2.3	1.41	(0.96, 2.08)	0.0811	1.7	1.16	(0.76, 1.75)	0.4918	0.7
SLAMF1	1.44	(1.17, 1.76)	0.0005	3.5	1.27	(1.02, 1.58)	0.0293	2.2	1.62	(1.23, 2.13)	0.0005	3.5	1.42	(1.06, 1.89)	0.0175	2.4
CTSZ	1.74	(1.27, 2.39)	0.0005	3.5	1.44	(1.03, 2.02)	0.0321	2.1	1.32	(0.97, 1.78)	0.0748	1.8	1.09	(0.79, 1.52)	0.5884	0.5
IGFBP7	1.66	(1.24, 2.23)	0.0006	3.4	1.42	(1.04, 1.94)	0.0259	2.2	1.6	(1.21, 2.11)	0.001	3.3	1.42	(1.05, 1.91)	0.021	2.3
IL16	1.54	(1.20, 1.97)	0.0007	3.4	1.38	(1.06, 1.79)	0.016	2.4	1.46	(1.15, 1.86)	0.0019	3.1	1.34	(1.04, 1.72)	0.0232	2.3
CCL25	1.51	(1.18, 1.94)	0.0009	3.3	1.35	(1.04, 1.75)	0.0234	2.3	0.96	(0.72, 1.29)	0.8091	0.2	0.85	(0.62, 1.17)	0.3243	1
IL12B	1.4	(1.14, 1.72)	0.0011	3.3	1.3	(1.05, 1.62)	0.0173	2.4	1.25	(1.00, 1.56)	0.0476	2	1.12	(0.88, 1.43)	0.3453	0.9
PON3	0.71	(0.58, 0.87)	0.0011	3.3	0.83	(0.66, 1.04)	0.0977	1.7	0.64	(0.51, 0.80)	<0.0001	3.9	0.72	(0.56, 0.91)	0.0064	2.7
IGFBP1	1.26	(1.09, 1.45)	0.0013	3.2	1.41	(1.19, 1.66)	<0.0001	4.1	1.08	(0.92, 1.26)	0.3564	0.9	1.14	(0.95, 1.37)	0.153	1.4
CCL23	1.6	(1.20, 2.14)	0.0014	3.2	1.74	(1.28, 2.37)	0.0005	3.5	1.08	(0.79, 1.47)	0.6256	0.5	0.98	(0.70, 1.37)	0.9144	0.1
DECR1	1.19	(1.07, 1.33)	0.0014	3.2	1.17	(1.04, 1.31)	0.0085	2.6	1.03	(0.93, 1.15)	0.5695	0.6	1.02	(0.91, 1.15)	0.7041	0.4
SPON2	2.86	(1.50, 5.48)	0.0015	3.2	2.66	(1.36, 5.21)	0.0044	2.8	2.4	(1.36, 4.25)	0.0026	3	2.1	(1.16, 3.79)	0.0137	2.5
TM	1.9	(1.27, 2.82)	0.0016	3.2	1.63	(1.07, 2.48)	0.0233	2.3	1.5	(1.03, 2.19)	0.0354	2.1	1.24	(0.85, 1.82)	0.2637	1.1
REN	1.31	(1.11, 1.55)	0.0018	3.1	1.18	(0.98, 1.41)	0.0772	1.8	1.54	(1.29, 1.85)	<0.0001	4.7	1.38	(1.13, 1.68)	0.0014	3.2
MMP3	1.4	(1.13, 1.74)	0.0021	3.1	1.37	(1.09, 1.73)	0.0062	2.7	1.17	(0.94, 1.45)	0.1521	1.4	1.05	(0.83, 1.33)	0.673	0.4
CASP8	1.26	(1.09, 1.47)	0.0021	3.1	1.22	(1.04, 1.43)	0.0126	2.5	1.19	(1.03, 1.37)	0.0148	2.4	1.18	(1.02, 1.37)	0.0286	2.2
TLT2	1.49	(1.16, 1.93)	0.0021	3.1	1.39	(1.06, 1.82)	0.0169	2.4	1.06	(0.80, 1.40)	0.6846	0.4	0.98	(0.73, 1.32)	0.9002	0.1
MMP2	1.64	(1.19, 2.24)	0.0023	3	1.55	(1.11, 2.16)	0.0096	2.6	1.38	(1.01, 1.88)	0.0452	2	1.38	(0.99, 1.91)	0.0553	1.9
IL10RB	1.77	(1.22, 2.56)	0.0024	3	1.56	(1.06, 2.30)	0.0247	2.2	1.27	(0.83, 1.92)	0.2708	1.1	0.92	(0.58, 1.46)	0.7309	0.3
GAL3	1.52	(1.16, 2.00)	0.0025	3	1.44	(1.08, 1.92)	0.012	2.5	1.17	(0.89, 1.54)	0.2714	1.1	1.02	(0.76, 1.37)	0.887	0.1
CD163	1.46	(1.14, 1.87)	0.0025	3	1.35	(1.05, 1.75)	0.0198	2.3	1.07	(0.84, 1.35)	0.581	0.6	0.99	(0.77, 1.27)	0.9236	0.1
VSIG2	1.43	(1.14, 1.81)	0.0025	3	1.24	(0.96, 1.59)	0.0967	1.7	1.76	(1.33, 2.32)	<0.0001	4	1.46	(1.06, 2.01)	0.02	2.3
TR	1.37	(1.12, 1.69)	0.0028	3	1.29	(1.04, 1.61)	0.0202	2.3	1.24	(0.99, 1.55)	0.0663	1.8	1.12	(0.88, 1.43)	0.3645	0.9
CCL20	1.21	(1.07, 1.38)	0.003	3	1.17	(1.02, 1.33)	0.0223	2.3	1.06	(0.94, 1.21)	0.3405	1	1.03	(0.90, 1.18)	0.6877	0.4
NEMO	1.19	(1.06, 1.34)	0.0032	2.9	1.16	(1.02, 1.31)	0.0224	2.3	1.07	(0.93, 1.23)	0.3387	1	1.04	(0.90, 1.21)	0.5799	0.6
IL4RA*	1.52	(1.15, 2.02)	0.0033	2.9	1.42	(1.06, 1.90)	0.0171	2.4	1.62	(1.18, 2.22)	0.0029	3	1.45	(1.03, 2.03)	0.0309	2.2
MERTK	1.66	(1.18, 2.33)	0.0038	2.9	1.6	(1.12, 2.28)	0.0101	2.6	1.38	(0.96, 1.99)	0.0863	1.7	1.29	(0.87, 1.91)	0.2016	1.3
IL17C	1.41	(1.12, 1.77)	0.0038	2.9	1.29	(1.01, 1.65)	0.0398	2.1	1.07	(0.80, 1.44)	0.6416	0.5	1.02	(0.75, 1.39)	0.8845	0.1

CXCL10	1.28	(1.08, 1.52)	0.0042	2.9	1.26	(1.05, 1.51)	0.0116	2.5	1.05	(0.88, 1.25)	0.5963	0.5	1.08	(0.89, 1.29)	0.437	0.8
ENRAGE	1.26	(1.08, 1.47)	0.0042	2.9	1.23	(1.04, 1.46)	0.0137	2.5	1.54	(1.25, 1.90)	<0.0001	4	1.44	(1.15, 1.81)	0.0016	3.2
BETANGF	1.66	(1.16, 2.36)	0.005	2.8	1.38	(0.95, 2.00)	0.0917	1.7	1.15	(0.77, 1.72)	0.4889	0.7	1.06	(0.70, 1.62)	0.7691	0.3
LOX1	1.39	(1.10, 1.76)	0.0054	2.8	1.36	(1.07, 1.74)	0.0129	2.5	1.49	(1.19, 1.86)	0.0005	3.5	1.46	(1.15, 1.86)	0.0018	3.1
MMP10	1.34	(1.09, 1.66)	0.0055	2.8	1.25	(1.00, 1.55)	0.0463	2	0.88	(0.68, 1.14)	0.3391	1	0.76	(0.57, 1.00)	0.0518	1.9
PECAM1	1.51	(1.13, 2.01)	0.0058	2.8	1.41	(1.04, 1.91)	0.0267	2.2	1.05	(0.81, 1.35)	0.7106	0.4	1.06	(0.81, 1.38)	0.6884	0.4
IL10	1.35	(1.09, 1.67)	0.0062	2.7	1.31	(1.05, 1.63)	0.0161	2.4	1.03	(0.84, 1.27)	0.7601	0.3	0.96	(0.78, 1.20)	0.742	0.3
LIFR	1.68	(1.16, 2.45)	0.0067	2.7	1.44	(0.97, 2.14)	0.0679	1.8	1.15	(0.75, 1.76)	0.5178	0.6	0.94	(0.60, 1.49)	0.7975	0.3
HOSCAR	2.11	(1.23, 3.64)	0.0069	2.7	1.93	(1.09, 3.39)	0.023	2.3	1.93	(1.12, 3.32)	0.0175	2.4	1.68	(0.95, 2.97)	0.0764	1.8
IGFBP2	1.35	(1.08, 1.68)	0.0072	2.7	1.55	(1.21, 1.99)	0.0005	3.5	1.25	(0.99, 1.58)	0.0628	1.9	1.35	(1.03, 1.77)	0.0298	2.2
CDCP1	1.34	(1.08, 1.66)	0.0074	2.7	1.26	(1.01, 1.59)	0.0431	2	0.98	(0.76, 1.26)	0.8736	0.2	0.85	(0.65, 1.11)	0.2395	1.2
MCP2	1.36	(1.09, 1.70)	0.0075	2.7	1.35	(1.07, 1.71)	0.0127	2.5	1.13	(0.91, 1.41)	0.2737	1.1	1.11	(0.88, 1.41)	0.3724	0.9
CX3CL1	1.48	(1.11, 1.97)	0.0075	2.7	1.3	(0.96, 1.77)	0.0926	1.7	1.18	(0.87, 1.60)	0.2787	1.1	1.01	(0.72, 1.41)	0.9603	0
PRTN3	1.35	(1.08, 1.68)	0.0081	2.6	1.3	(1.04, 1.64)	0.0238	2.3	1.26	(0.99, 1.59)	0.0557	1.9	1.18	(0.92, 1.51)	0.1911	1.3
AXIN1	1.16	(1.04, 1.29)	0.0085	2.6	1.13	(1.01, 1.26)	0.0403	2.1	0.96	(0.84, 1.10)	0.5615	0.6	0.94	(0.81, 1.09)	0.4114	0.8
MPO	1.43	(1.09, 1.86)	0.009	2.6	1.36	(1.03, 1.79)	0.0323	2.1	1.17	(0.90, 1.51)	0.2337	1.2	1.09	(0.83, 1.43)	0.524	0.6
GT	1.27	(1.06, 1.53)	0.0101	2.6	1.19	(0.97, 1.44)	0.088	1.7	1.3	(1.02, 1.67)	0.037	2.1	1.26	(0.96, 1.65)	0.092	1.7
SORT1	1.93	(1.17, 3.18)	0.0103	2.6	1.99	(1.17, 3.38)	0.0107	2.6	1.68	(1.08, 2.62)	0.0218	2.3	1.8	(1.12, 2.89)	0.0149	2.4
ST1A1	1.16	(1.04, 1.31)	0.0103	2.6	1.13	(1.00, 1.27)	0.0593	1.9	1.02	(0.91, 1.15)	0.7111	0.4	1.01	(0.89, 1.15)	0.8863	0.1
CCL11	1.45	(1.09, 1.93)	0.0104	2.6	1.41	(1.05, 1.91)	0.0242	2.3	1.46	(1.06, 1.99)	0.019	2.3	1.36	(0.97, 1.91)	0.0734	1.8
CST5	1.35	(1.07, 1.70)	0.0113	2.5	1.19	(0.92, 1.54)	0.1858	1.3	1.01	(0.76, 1.35)	0.9334	0.1	0.85	(0.62, 1.18)	0.3325	1
SELP	1.33	(1.07, 1.67)	0.0121	2.5	1.26	(1.00, 1.60)	0.0529	1.9	1.12	(0.91, 1.37)	0.3031	1	1.11	(0.89, 1.39)	0.3584	0.9
BP1_4E	1.17	(1.04, 1.33)	0.0121	2.5	1.14	(1.00, 1.30)	0.0541	1.9	1.17	(1.02, 1.34)	0.0254	2.2	1.12	(0.97, 1.29)	0.135	1.5
SIRT2	1.13	(1.03, 1.24)	0.0131	2.5	1.11	(1.00, 1.22)	0.049	2	1.05	(0.94, 1.17)	0.3818	0.9	1.03	(0.92, 1.15)	0.6376	0.5
ST2	1.37	(1.07, 1.75)	0.0131	2.5	1.25	(0.97, 1.62)	0.0861	1.7	1.42	(1.09, 1.83)	0.0083	2.6	1.33	(1.01, 1.76)	0.0395	2.1
CASP3	1.15	(1.03, 1.28)	0.0133	2.5	1.12	(1.00, 1.26)	0.0486	2	1.04	(0.93, 1.17)	0.4996	0.7	1.02	(0.90, 1.16)	0.7465	0.3
PRSS8	1.62	(1.11, 2.38)	0.0133	2.5	1.39	(0.93, 2.07)	0.1063	1.6	1.3	(1.04, 1.63)	0.0193	2.3	1.21	(0.96, 1.53)	0.1148	1.6
VWF	1.18	(1.04, 1.35)	0.0135	2.5	1.15	(1.00, 1.32)	0.0539	1.9	1.18	(1.03, 1.36)	0.0153	2.4	1.17	(1.01, 1.35)	0.0347	2.1
FGF21	1.15	(1.03, 1.28)	0.0139	2.5	1.08	(0.96, 1.21)	0.2096	1.3	1.15	(1.03, 1.30)	0.0161	2.4	1.07	(0.95, 1.22)	0.272	1.1
TGM2	1.26	(1.05, 1.51)	0.0144	2.4	1.22	(1.01, 1.48)	0.0383	2.1	1.43	(1.18, 1.73)	0.0003	3.6	1.55	(1.25, 1.91)	<0.0001	4
IL1RT1	1.58	(1.09, 2.28)	0.0145	2.4	1.39	(0.94, 2.06)	0.0991	1.6	1.18	(0.86, 1.62)	0.3017	1	1.07	(0.76, 1.49)	0.704	0.4
CD244	1.48	(1.08, 2.04)	0.0154	2.4	1.36	(0.97, 1.90)	0.0737	1.8	0.79	(0.55, 1.12)	0.1841	1.3	0.7	(0.48, 1.02)	0.0603	1.9
MCP1_CVD3	1.27	(1.05, 1.55)	0.0162	2.4	1.23	(1.02, 1.49)	0.0308	2.2	1.14	(0.91, 1.43)	0.265	1.1	1.09	(0.86, 1.38)	0.4702	0.7
CD93	1.6	(1.09, 2.35)	0.0163	2.4	1.38	(0.91, 2.09)	0.1272	1.5	1.62	(1.12, 2.35)	0.0107	2.6	1.44	(0.96, 2.15)	0.0793	1.8
PCSK9	1.43	(1.07, 1.93)	0.0171	2.4	1.32	(0.97, 1.79)	0.0791	1.8	1	(0.74, 1.36)	0.982	0	0.91	(0.66, 1.25)	0.5486	0.6
PI3	1.27	(1.04, 1.54)	0.0174	2.4	1.08	(0.87, 1.35)	0.4985	0.7	1.21	(1.01, 1.45)	0.0384	2.1	1.09	(0.90, 1.32)	0.3972	0.8
IL6RA	1.5	(1.07, 2.10)	0.0192	2.3	1.58	(1.10, 2.25)	0.0126	2.5	1.21	(0.89, 1.63)	0.228	1.2	1.17	(0.85, 1.61)	0.3472	0.9
VEGFD	1.52	(1.07, 2.17)	0.0205	2.3	1.75	(1.19, 2.58)	0.0045	2.8	1.81	(1.29, 2.54)	0.0007	3.4	1.98	(1.36, 2.89)	0.0004	3.6
TNFSF14	1.28	(1.04, 1.57)	0.0212	2.3	1.22	(0.98, 1.52)	0.0795	1.8	1.14	(0.94, 1.38)	0.1775	1.3	1.17	(0.96, 1.44)	0.1236	1.5
ITGB1BP2	1.11	(1.02, 1.21)	0.0213	2.3	1.09	(0.99, 1.19)	0.0842	1.7	1.03	(0.93, 1.14)	0.5949	0.5	1.01	(0.90, 1.12)	0.9105	0.1
FABP2	1.27	(1.03, 1.56)	0.0223	2.3	1.2	(0.97, 1.50)	0.0998	1.6	1.32	(1.06, 1.63)	0.0119	2.5	1.19	(0.95, 1.49)	0.1356	1.5
BLMH	1.44	(1.05, 1.96)	0.0224	2.3	1.5	(1.08, 2.09)	0.0154	2.4	0.79	(0.58, 1.07)	0.1287	1.5	0.83	(0.60, 1.15)	0.2558	1.1
SRC	1.19	(1.02, 1.38)	0.0231	2.3	1.15	(0.99, 1.35)	0.0733	1.8	1.07	(0.92, 1.26)	0.3867	0.9	1.03	(0.87, 1.21)	0.7691	0.3
IL8	1.2	(1.03, 1.40)	0.0232	2.3	1.18	(1.00, 1.39)	0.0508	2	1.13	(0.94, 1.36)	0.2025	1.3	1.1	(0.90, 1.33)	0.3563	0.9
SELE	1.37	(1.04, 1.79)	0.0239	2.3	1.13	(0.85, 1.51)	0.409	0.8	1.31	(0.99, 1.75)	0.0624	1.9	1.18	(0.87, 1.60)	0.2917	1.1
LEP	1.17	(1.02, 1.35)	0.0246	2.2	1.01	(0.84, 1.21)	0.9082	0.1	1.22	(1.04, 1.43)	0.0148	2.4	1.03	(0.83, 1.28)	0.7984	0.3
PSPD	1.22	(1.02, 1.46)	0.0262	2.2	1.27	(1.05, 1.54)	0.0122	2.5	1.29	(1.03, 1.61)	0.0236	2.3	1.32	(1.05, 1.67)	0.0194	2.3
IL18R1	1.42	(1.04, 1.94)	0.0266	2.2	1.2	(0.86, 1.66)	0.2856	1.1	1.2	(0.84, 1.72)	0.3199	1	0.96	(0.65, 1.41)	0.8428	0.2

SOD2	2.01	(1.08, 3.73)	0.0274	2.2	2.3	(1.20, 4.42)	0.0122	2.5	1.46	(0.87, 2.45)	0.1539	1.4	1.53	(0.88, 2.66)	0.1353	1.5
NT3	1.37	(1.04, 1.82)	0.0274	2.2	1.29	(0.96, 1.74)	0.0929	1.7	0.95	(0.74, 1.23)	0.7178	0.4	1	(0.76, 1.30)	0.986	0
BMP6	1.23	(1.02, 1.47)	0.0278	2.2	1.17	(0.97, 1.42)	0.1076	1.6	1.09	(0.91, 1.31)	0.3624	0.9	1.08	(0.88, 1.31)	0.4708	0.7
APN	1.53	(1.05, 2.23)	0.0279	2.2	1.37	(0.92, 2.04)	0.1161	1.6	0.96	(0.68, 1.34)	0.7958	0.3	0.92	(0.64, 1.32)	0.6636	0.4
STK4	1.13	(1.01, 1.26)	0.0285	2.2	1.1	(0.98, 1.24)	0.0908	1.7	1.06	(0.94, 1.20)	0.3107	1	1.04	(0.92, 1.18)	0.5008	0.7
AMBP	1.98	(1.07, 3.64)	0.0285	2.2	1.63	(0.85, 3.12)	0.1424	1.5	2.48	(1.35, 4.55)	0.0034	2.9	1.86	(0.97, 3.53)	0.06	1.9
IL27	1.46	(1.04, 2.05)	0.0303	2.2	1.57	(1.10, 2.26)	0.014	2.5	1.83	(1.22, 2.74)	0.0036	2.9	1.77	(1.15, 2.72)	0.0095	2.6
CTSL1	1.49	(1.04, 2.13)	0.0314	2.2	1.51	(1.03, 2.20)	0.0331	2.1	1.31	(0.95, 1.79)	0.0972	1.7	1.26	(0.90, 1.76)	0.1822	1.3
TNFSF13B	1.45	(1.03, 2.05)	0.0322	2.1	1.35	(0.94, 1.94)	0.1018	1.6	1.04	(0.76, 1.42)	0.819	0.2	1.04	(0.75, 1.44)	0.8279	0.2
MMP1	1.13	(1.01, 1.28)	0.0346	2.1	1.1	(0.97, 1.24)	0.1339	1.5	1.1	(0.96, 1.25)	0.158	1.4	1.06	(0.92, 1.22)	0.398	0.8
SHPS1	1.38	(1.02, 1.86)	0.0347	2.1	1.14	(0.83, 1.58)	0.4173	0.8	1.19	(0.91, 1.54)	0.1971	1.3	1.07	(0.81, 1.42)	0.6111	0.5
MMP7	1.18	(1.01, 1.39)	0.0352	2.1	1.12	(0.95, 1.32)	0.1941	1.3	1.1	(0.96, 1.25)	0.1669	1.4	1.1	(0.96, 1.26)	0.1809	1.3
IL18	1.21	(1.01, 1.45)	0.0366	2.1	1.16	(0.97, 1.41)	0.1113	1.6	1.27	(1.07, 1.51)	0.0074	2.7	1.24	(1.03, 1.49)	0.0239	2.3
STAMPB	1.14	(1.01, 1.29)	0.0367	2.1	1.11	(0.97, 1.26)	0.1225	1.5	1.03	(0.89, 1.20)	0.6566	0.4	1	(0.86, 1.18)	0.9529	0.1
TF	1.44	(1.02, 2.03)	0.0385	2.1	1.24	(0.86, 1.78)	0.2487	1.2	1.55	(1.05, 2.31)	0.0285	2.2	1.35	(0.89, 2.05)	0.159	1.4
ITGB2	1.38	(1.02, 1.87)	0.0387	2.1	1.31	(0.95, 1.81)	0.0988	1.7	1.02	(0.79, 1.31)	0.8783	0.2	1.01	(0.77, 1.33)	0.9216	0.1
OSM	1.19	(1.01, 1.41)	0.0395	2.1	1.18	(0.99, 1.41)	0.0644	1.8	1.19	(1.01, 1.40)	0.0334	2.1	1.14	(0.96, 1.36)	0.1331	1.5
XCL1	1.26	(1.01, 1.57)	0.0403	2.1	1.18	(0.94, 1.49)	0.1584	1.4	1.33	(1.04, 1.70)	0.0235	2.3	1.26	(0.97, 1.64)	0.0808	1.7
CCL19	1.16	(1.01, 1.34)	0.0403	2.1	1.08	(0.93, 1.26)	0.3193	1	1.23	(1.04, 1.47)	0.0164	2.4	1.21	(1.01, 1.45)	0.0414	2
DKK1	1.27	(1.01, 1.61)	0.0443	2	1.27	(0.99, 1.63)	0.0579	1.9	1.19	(0.97, 1.46)	0.0952	1.7	1.21	(0.97, 1.51)	0.091	1.7
ALCAM	1.42	(1.00, 2.02)	0.0486	2	1.33	(0.92, 1.92)	0.126	1.5	1.1	(0.79, 1.52)	0.5788	0.6	1.03	(0.73, 1.46)	0.8773	0.2
PTX3	1.25	(0.99, 1.58)	0.0597	1.9	1.24	(0.97, 1.59)	0.0816	1.7	1.31	(0.97, 1.78)	0.0778	1.8	1.43	(1.03, 1.97)	0.0302	2.2
IL17D	1.38	(0.99, 1.94)	0.06	1.9	1.37	(0.96, 1.95)	0.0816	1.7	1.22	(0.79, 1.89)	0.3631	0.9	1.28	(0.80, 2.03)	0.3057	1
HGDNF	1.3	(0.98, 1.72)	0.0687	1.8	1.05	(0.78, 1.43)	0.7318	0.3	1.17	(0.80, 1.72)	0.4178	0.8	1.02	(0.68, 1.54)	0.9082	0.1
CXCL6	1.17	(0.99, 1.38)	0.069	1.8	1.18	(0.99, 1.40)	0.0677	1.8	0.99	(0.84, 1.18)	0.9326	0.1	1.01	(0.84, 1.21)	0.9013	0.1
FGF19	1.15	(0.99, 1.35)	0.0722	1.8	1.14	(0.97, 1.35)	0.1164	1.6	0.93	(0.78, 1.10)	0.387	0.9	0.89	(0.74, 1.08)	0.2396	1.2
IL17A	1.25	(0.98, 1.61)	0.0779	1.8	1.18	(0.91, 1.53)	0.2225	1.2	0.93	(0.67, 1.30)	0.6714	0.4	0.94	(0.67, 1.33)	0.7287	0.3
IGGFCRECEPTORIB	1.23	(0.98, 1.54)	0.0784	1.8	1.25	(0.98, 1.58)	0.0672	1.8	1.18	(0.86, 1.60)	0.3064	1	1.13	(0.81, 1.57)	0.466	0.7
PARP1	1.13	(0.99, 1.29)	0.0805	1.7	1.1	(0.95, 1.27)	0.2035	1.3	1.16	(1.00, 1.36)	0.0535	1.9	1.19	(1.00, 1.40)	0.0435	2
IDUA	1.26	(0.97, 1.64)	0.0834	1.7	1.25	(0.95, 1.64)	0.1091	1.6	1.03	(0.82, 1.30)	0.7905	0.3	0.94	(0.74, 1.21)	0.6409	0.5
PDGFSUBUNITB	1.12	(0.98, 1.27)	0.0855	1.7	1.13	(0.99, 1.29)	0.0757	1.8	1.09	(0.94, 1.27)	0.2374	1.2	1.09	(0.93, 1.28)	0.2947	1
CD40L	1.1	(0.99, 1.23)	0.0899	1.7	1.09	(0.97, 1.23)	0.1281	1.5	1.07	(0.96, 1.20)	0.2244	1.2	1.09	(0.97, 1.23)	0.1406	1.5
TNFRSF10C	1.26	(0.96, 1.64)	0.0925	1.7	1.09	(0.83, 1.45)	0.5284	0.6	1.22	(0.94, 1.59)	0.1351	1.5	1.12	(0.85, 1.48)	0.4103	0.8
CTSD	1.28	(0.96, 1.70)	0.0931	1.7	1.06	(0.78, 1.43)	0.7145	0.4	1.06	(0.81, 1.38)	0.6892	0.4	0.93	(0.70, 1.24)	0.6154	0.5
NOTCH3	1.3	(0.96, 1.75)	0.0936	1.7	1.17	(0.85, 1.61)	0.3379	1	1.1	(0.82, 1.49)	0.5157	0.7	1.1	(0.80, 1.51)	0.5684	0.6
MB	1.21	(0.97, 1.50)	0.0947	1.7	1.02	(0.80, 1.30)	0.894	0.1	0.98	(0.78, 1.22)	0.8252	0.2	0.85	(0.66, 1.09)	0.1947	1.3
CD5	1.25	(0.96, 1.63)	0.0956	1.7	1.11	(0.84, 1.48)	0.4591	0.7	1.28	(0.91, 1.79)	0.1504	1.4	1.08	(0.75, 1.55)	0.6754	0.4
TPA	1.21	(0.97, 1.50)	0.0975	1.7	1.11	(0.88, 1.41)	0.3743	0.9	0.99	(0.82, 1.20)	0.9333	0.1	0.96	(0.78, 1.17)	0.6772	0.4
PAPPA	1.22	(0.96, 1.55)	0.0995	1.6	1.28	(1.00, 1.65)	0.0535	1.9	1.15	(0.88, 1.50)	0.2964	1	1.32	(0.99, 1.75)	0.0579	1.9
COL1A1	1.29	(0.95, 1.75)	0.0996	1.6	1.11	(0.81, 1.54)	0.5109	0.7	1.16	(0.84, 1.61)	0.3769	0.9	1.1	(0.78, 1.56)	0.5765	0.6
IL7	1.17	(0.97, 1.41)	0.1021	1.6	1.19	(0.98, 1.45)	0.086	1.7	0.96	(0.78, 1.17)	0.6572	0.4	0.96	(0.78, 1.19)	0.7271	0.3
CCL4	1.16	(0.96, 1.40)	0.1143	1.6	1.14	(0.94, 1.39)	0.1714	1.4	0.98	(0.81, 1.19)	0.8406	0.2	0.96	(0.78, 1.18)	0.7178	0.4
SCF	0.73	(0.50, 1.08)	0.115	1.6	0.73	(0.48, 1.09)	0.1228	1.5	1.3	(0.93, 1.82)	0.1216	1.5	1.25	(0.88, 1.77)	0.2118	1.2
CA5A	1.13	(0.97, 1.31)	0.1184	1.6	0.99	(0.84, 1.16)	0.8755	0.2	1.08	(0.90, 1.31)	0.4065	0.8	0.95	(0.77, 1.16)	0.6048	0.5
PRELP	1.58	(0.89, 2.82)	0.1185	1.6	1.36	(0.74, 2.49)	0.321	1	3.17	(1.55, 6.49)	0.0016	3.2	2.79	(1.31, 5.94)	0.008	2.7
FS	1.29	(0.93, 1.78)	0.1237	1.5	1.24	(0.88, 1.73)	0.2173	1.2	1.4	(1.02, 1.92)	0.039	2.1	1.37	(0.98, 1.91)	0.0637	1.9
CCL17	1.11	(0.97, 1.28)	0.1284	1.5	1.12	(0.97, 1.29)	0.1299	1.5	1.2	(1.04, 1.38)	0.0144	2.4	1.22	(1.04, 1.42)	0.0131	2.5
HBEGF	1.27	(0.92, 1.74)	0.1412	1.5	1.25	(0.90, 1.75)	0.1831	1.3	1.29	(0.99, 1.67)	0.0569	1.9	1.34	(1.01, 1.77)	0.04	2.1

ADA	1.21	(0.93, 1.57)	0.1589	1.4	1.11	(0.85, 1.46)	0.4453	0.8	0.84	(0.62, 1.13)	0.2553	1.1	0.83	(0.61, 1.14)	0.256	1.1
MMP9	1.12	(0.96, 1.30)	0.1601	1.4	1.11	(0.95, 1.31)	0.1942	1.3	1.21	(1.04, 1.41)	0.0135	2.5	1.18	(1.00, 1.39)	0.048	2
PAI	1.12	(0.96, 1.31)	0.1612	1.4	1.07	(0.91, 1.27)	0.4117	0.8	1.02	(0.87, 1.21)	0.7794	0.3	0.99	(0.83, 1.18)	0.9022	0.1
GIF	0.92	(0.81, 1.04)	0.165	1.4	0.94	(0.83, 1.07)	0.3446	0.9	1.1	(0.96, 1.27)	0.1642	1.4	1.12	(0.97, 1.30)	0.1313	1.5
FGF5	1.33	(0.89, 1.97)	0.1654	1.4	1.15	(0.76, 1.75)	0.5134	0.7	0.95	(0.61, 1.50)	0.8408	0.2	0.88	(0.55, 1.43)	0.6127	0.5
FLT3L	1.23	(0.92, 1.66)	0.1682	1.4	1.18	(0.86, 1.61)	0.2983	1	1.05	(0.76, 1.45)	0.7568	0.3	0.96	(0.68, 1.35)	0.82	0.2
DCN	1.28	(0.90, 1.82)	0.1728	1.4	1.15	(0.79, 1.67)	0.4694	0.7	1.43	(1.02, 2.02)	0.0391	2.1	1.33	(0.93, 1.91)	0.1236	1.5
CHIT1	1.08	(0.97, 1.20)	0.1769	1.4	1.08	(0.96, 1.20)	0.1908	1.3	1.01	(0.91, 1.12)	0.8861	0.1	1.01	(0.90, 1.13)	0.8693	0.2
CPB1	1.13	(0.94, 1.36)	0.18	1.3	1.1	(0.90, 1.34)	0.3452	0.9	1.15	(0.95, 1.40)	0.1547	1.4	1.1	(0.89, 1.36)	0.4001	0.8
CCL3	1.1	(0.95, 1.27)	0.1882	1.3	1.05	(0.90, 1.22)	0.5275	0.6	1.13	(0.91, 1.39)	0.2599	1.1	1.05	(0.84, 1.30)	0.6787	0.4
CD84	1.23	(0.90, 1.67)	0.1894	1.3	1.28	(0.93, 1.77)	0.1285	1.5	1.12	(0.81, 1.55)	0.5086	0.7	1.17	(0.83, 1.66)	0.3731	0.9
UPA_CVD3	1.22	(0.90, 1.65)	0.1925	1.3	1.2	(0.88, 1.63)	0.251	1.1	1.05	(0.75, 1.47)	0.7792	0.3	1.06	(0.74, 1.53)	0.7324	0.3
AXL	1.23	(0.90, 1.70)	0.1933	1.3	1.15	(0.82, 1.62)	0.4106	0.8	1.14	(0.85, 1.54)	0.388	0.9	1.08	(0.79, 1.48)	0.6297	0.5
TFPI	1.26	(0.87, 1.82)	0.2131	1.2	1.25	(0.85, 1.84)	0.2569	1.1	0.98	(0.71, 1.35)	0.8866	0.1	0.96	(0.68, 1.35)	0.8106	0.2
SCGB3A2	1.09	(0.95, 1.26)	0.216	1.2	1.09	(0.94, 1.27)	0.2515	1.1	1.04	(0.89, 1.22)	0.6438	0.5	0.99	(0.83, 1.17)	0.8647	0.2
ANG1	1.08	(0.95, 1.24)	0.2223	1.2	1.09	(0.95, 1.25)	0.2388	1.2	1.06	(0.92, 1.21)	0.4174	0.8	1.08	(0.93, 1.26)	0.302	1
EGFR	0.77	(0.50, 1.18)	0.2258	1.2	0.83	(0.53, 1.31)	0.4258	0.8	0.77	(0.53, 1.10)	0.1504	1.4	0.8	(0.55, 1.18)	0.2607	1.1
DNER	0.8	(0.56, 1.15)	0.2294	1.2	0.85	(0.58, 1.25)	0.4125	0.8	0.41	(0.25, 0.67)	0.0003	3.6	0.43	(0.26, 0.72)	0.0012	3.2
HO1	1.23	(0.88, 1.72)	0.2335	1.2	1.41	(0.99, 2.01)	0.0587	1.9	1.02	(0.73, 1.41)	0.9233	0.1	1.01	(0.71, 1.43)	0.9632	0
TRANSC	0.88	(0.70, 1.10)	0.2543	1.1	0.89	(0.70, 1.12)	0.3111	1	0.83	(0.64, 1.08)	0.1626	1.4	0.78	(0.59, 1.04)	0.0863	1.7
PIGR	1.44	(0.76, 2.73)	0.2581	1.1	1.6	(0.82, 3.13)	0.1693	1.4	1.89	(1.05, 3.39)	0.0333	2.1	1.9	(1.01, 3.57)	0.048	2
PDGFSUBUNITA	1.09	(0.93, 1.26)	0.2869	1.1	1.11	(0.95, 1.31)	0.1923	1.3	1.03	(0.89, 1.18)	0.7228	0.4	1.06	(0.91, 1.23)	0.4793	0.7
THPO	1.18	(0.87, 1.60)	0.2963	1	1.18	(0.86, 1.63)	0.2984	1	1.09	(0.80, 1.50)	0.5843	0.5	1.11	(0.80, 1.56)	0.5249	0.6
CTRC	0.91	(0.77, 1.09)	0.3048	1	0.94	(0.78, 1.13)	0.496	0.7	0.99	(0.83, 1.19)	0.9303	0.1	1.03	(0.85, 1.26)	0.7581	0.3
CNTN1	0.85	(0.62, 1.16)	0.3131	1	0.86	(0.62, 1.19)	0.3602	0.9	0.75	(0.54, 1.02)	0.0654	1.8	0.76	(0.54, 1.05)	0.0996	1.6
CXCL5	1.05	(0.96, 1.15)	0.3253	1	1.03	(0.94, 1.14)	0.4934	0.7	1	(0.90, 1.11)	0.9813	0	1	(0.89, 1.12)	0.9958	0
IL17RA	1.1	(0.90, 1.35)	0.3346	1	1.1	(0.89, 1.36)	0.3577	0.9	0.95	(0.74, 1.23)	0.7123	0.4	0.93	(0.71, 1.22)	0.6185	0.5
PROTEINBOC	1.19	(0.83, 1.71)	0.3396	1	1.17	(0.81, 1.71)	0.4024	0.8	1.54	(1.02, 2.32)	0.0385	2.1	1.59	(1.02, 2.48)	0.0402	2.1
THBS2	1.26	(0.78, 2.05)	0.3475	0.9	1.11	(0.67, 1.83)	0.6897	0.4	2.47	(1.51, 4.03)	0.0003	3.6	2.33	(1.39, 3.90)	0.0013	3.2
MCP4	1.1	(0.89, 1.37)	0.3822	0.9	1.07	(0.85, 1.34)	0.5679	0.6	0.97	(0.78, 1.20)	0.7668	0.3	0.99	(0.79, 1.24)	0.9367	0.1
HAOX1	1.05	(0.93, 1.18)	0.4242	0.8	1.01	(0.89, 1.14)	0.918	0.1	0.91	(0.80, 1.04)	0.1691	1.4	0.87	(0.76, 1.00)	0.0571	1.9
ADAMTS13	0.79	(0.43, 1.44)	0.4457	0.8	1.08	(0.57, 2.04)	0.8111	0.2	1.32	(0.76, 2.31)	0.3298	1	1.61	(0.86, 3.03)	0.1348	1.5
GLO1	1.07	(0.89, 1.29)	0.4772	0.7	1.05	(0.86, 1.27)	0.64	0.5	1.11	(0.90, 1.37)	0.348	0.9	1.07	(0.85, 1.34)	0.5722	0.6
TRAIL	1.14	(0.79, 1.65)	0.4776	0.7	1.12	(0.77, 1.64)	0.5556	0.6	0.45	(0.29, 0.69)	0.0003	3.6	0.42	(0.26, 0.67)	0.0003	3.6
GH	0.97	(0.89, 1.06)	0.4806	0.7	0.99	(0.90, 1.09)	0.8655	0.2	1.05	(0.95, 1.16)	0.3226	1	1.1	(0.99, 1.23)	0.0665	1.8
RAGE	1.12	(0.82, 1.53)	0.4918	0.7	1.2	(0.85, 1.68)	0.3013	1	1.25	(0.90, 1.74)	0.1809	1.3	1.31	(0.91, 1.88)	0.1528	1.4
PSGL1	1.09	(0.84, 1.41)	0.5312	0.6	1.12	(0.84, 1.48)	0.4478	0.8	1.39	(0.92, 2.09)	0.117	1.6	1.48	(0.95, 2.30)	0.0795	1.8
MARCO	0.9	(0.64, 1.27)	0.5512	0.6	0.96	(0.66, 1.38)	0.8067	0.2	1.09	(0.86, 1.38)	0.467	0.7	1.06	(0.83, 1.35)	0.6562	0.4
IL13	1.11	(0.79, 1.55)	0.5531	0.6	1.22	(0.86, 1.72)	0.2701	1.1	0.95	(0.62, 1.45)	0.8094	0.2	0.92	(0.59, 1.42)	0.6948	0.4
CCL28	1.09	(0.81, 1.46)	0.5589	0.6	1.11	(0.82, 1.51)	0.5044	0.7	1	(0.78, 1.30)	0.9758	0	1.09	(0.83, 1.44)	0.5345	0.6
CXCL1	1.04	(0.91, 1.19)	0.566	0.6	1.03	(0.89, 1.19)	0.7054	0.4	1.05	(0.89, 1.24)	0.5851	0.5	1.05	(0.88, 1.25)	0.6141	0.5
GDF2	0.95	(0.78, 1.16)	0.613	0.5	1.03	(0.83, 1.27)	0.8145	0.2	1.01	(0.81, 1.26)	0.9631	0	1.1	(0.87, 1.40)	0.4238	0.8
AZU1	1.06	(0.85, 1.32)	0.618	0.5	1.06	(0.85, 1.34)	0.6042	0.5	1.07	(0.91, 1.25)	0.4075	0.8	1.07	(0.90, 1.26)	0.4452	0.8
MEPE	1.07	(0.83, 1.38)	0.6191	0.5	0.95	(0.72, 1.26)	0.7171	0.4	0.94	(0.72, 1.23)	0.663	0.4	0.8	(0.60, 1.08)	0.1525	1.4
IL20RA	0.9	(0.56, 1.44)	0.6494	0.5	0.94	(0.57, 1.54)	0.7927	0.3	1.14	(0.46, 2.81)	0.784	0.3	1.39	(0.54, 3.57)	0.496	0.7
LPL	0.93	(0.67, 1.29)	0.6713	0.4	0.96	(0.68, 1.35)	0.8206	0.2	0.99	(0.75, 1.30)	0.9345	0.1	1	(0.75, 1.34)	0.9738	0
LDLRECEPTOR	0.96	(0.78, 1.18)	0.6782	0.4	0.97	(0.78, 1.20)	0.7566	0.3	0.89	(0.70, 1.13)	0.3295	1	0.85	(0.66, 1.09)	0.1969	1.3
KLK6	1.06	(0.79, 1.42)	0.7023	0.4	0.99	(0.71, 1.38)	0.9555	0.1	0.9	(0.70, 1.14)	0.3731	0.9	0.82	(0.62, 1.09)	0.1705	1.4

CDH5	1.06	(0.79, 1.41)	0.7034	0.4	0.97	(0.71, 1.32)	0.8371	0.2	1.06	(0.80, 1.42)	0.6711	0.4	1.02	(0.75, 1.38)	0.9126	0.1
TIE2	1.07	(0.73, 1.58)	0.721	0.4	1.07	(0.72, 1.61)	0.7347	0.3	1.41	(0.90, 2.20)	0.137	1.5	1.35	(0.85, 2.14)	0.2	1.3
SERPINA12	1.02	(0.93, 1.12)	0.7294	0.3	0.99	(0.90, 1.09)	0.8486	0.2	1.15	(0.98, 1.36)	0.0826	1.7	1.14	(0.96, 1.35)	0.127	1.5
IL1RL2	0.95	(0.72, 1.26)	0.732	0.3	0.94	(0.71, 1.26)	0.7027	0.4	1.24	(0.90, 1.72)	0.1842	1.3	1.24	(0.88, 1.74)	0.2277	1.2
IL10RA	1.06	(0.74, 1.53)	0.7411	0.3	1.12	(0.76, 1.63)	0.5672	0.6	1.14	(0.59, 2.21)	0.7014	0.4	1.3	(0.65, 2.60)	0.4622	0.7
EPCAM	0.98	(0.86, 1.12)	0.7485	0.3	0.96	(0.84, 1.11)	0.6088	0.5	0.97	(0.83, 1.14)	0.7455	0.3	0.94	(0.79, 1.11)	0.4395	0.8
TNFB	0.96	(0.73, 1.27)	0.7851	0.3	0.98	(0.73, 1.32)	0.9046	0.1	0.83	(0.62, 1.12)	0.222	1.2	0.84	(0.61, 1.14)	0.263	1.1
DLK1	1.02	(0.84, 1.26)	0.812	0.2	0.88	(0.71, 1.11)	0.2825	1.1	1.1	(0.87, 1.38)	0.4338	0.8	0.96	(0.75, 1.25)	0.7821	0.3
TRAP	0.97	(0.71, 1.32)	0.8421	0.2	0.98	(0.71, 1.35)	0.8888	0.1	0.86	(0.65, 1.14)	0.3037	1	0.8	(0.60, 1.08)	0.1446	1.5
TNF	1.02	(0.75, 1.39)	0.8775	0.2	1.05	(0.76, 1.44)	0.7876	0.3	0.99	(0.69, 1.41)	0.9465	0.1	1.03	(0.71, 1.51)	0.8614	0.2
CCL24	0.99	(0.85, 1.15)	0.8876	0.1	1.04	(0.89, 1.21)	0.6233	0.5	0.97	(0.82, 1.14)	0.6845	0.4	0.96	(0.81, 1.15)	0.668	0.4
BDNF	1	(0.96, 1.05)	0.9166	0.1	1.01	(0.96, 1.05)	0.8295	0.2	1.03	(0.98, 1.09)	0.2125	1.2	1.05	(0.99, 1.11)	0.095	1.7
CPA1	1.01	(0.85, 1.20)	0.918	0.1	1	(0.83, 1.20)	0.9837	0	1.06	(0.88, 1.28)	0.5252	0.6	1.02	(0.84, 1.25)	0.8099	0.2
CD6	0.99	(0.79, 1.24)	0.9181	0.1	1.04	(0.82, 1.31)	0.7607	0.3	0.91	(0.70, 1.19)	0.5062	0.7	0.91	(0.69, 1.22)	0.5401	0.6
IL1RT2	1.01	(0.77, 1.34)	0.9375	0.1	0.99	(0.74, 1.32)	0.9496	0.1	0.97	(0.72, 1.30)	0.8275	0.2	0.92	(0.67, 1.26)	0.6147	0.5
CCL22	1	(0.89, 1.14)	0.9398	0.1	1.01	(0.89, 1.15)	0.8543	0.2	1.03	(0.88, 1.19)	0.7421	0.3	1.07	(0.91, 1.25)	0.4181	0.8
PRSS27	1.01	(0.77, 1.32)	0.9562	0.1	0.88	(0.66, 1.17)	0.3814	0.9	1.4	(1.01, 1.94)	0.0443	2	1.3	(0.92, 1.85)	0.1386	1.5

\*FDR 1% threshold in the discovery phase

Supplemental Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for the selected proteins (significant in both discovery and replication sets with a false discovery rate of 1%) after adjustment for the matching variables (age, sex, and follow-up time), clinical risk factors (smoking, diabetes, coronary artery disease, serum creatinine, body mass index, heart rate, anti-hypertensive medication use) and correction for multiple comparisons in both discovery and replication sets

Protein name	Discovery			Replication		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
BNP	1.59	(1.38, 1.84)	<0.0001	1.78	(1.52, 2.08)	<0.0001
NTPROBNP	1.79	(1.50, 2.14)	<0.0001	2.05	(1.66, 2.53)	<0.0001
TRAILR2	2.70	(1.86, 3.92)	<0.0001	2.65	(1.72, 4.06)	<0.0001
TNFRSF13B	1.58	(1.21, 2.07)	0.0008	2.30	(1.56, 3.39)	<0.0001
GAL9	2.30	(1.48, 3.57)	0.0002	2.46	(1.53, 3.94)	0.0002
FGF23	1.48	(1.21, 1.82)	0.0002	1.71	(1.31, 2.22)	<0.0001
TNFRSF10A	2.02	(1.41, 2.90)	0.0001	2.00	(1.32, 3.03)	0.0010
REN	1.17	(0.98, 1.41)	0.0798	1.36	(1.12, 1.66)	0.0019
TNFRSF11A	1.73	(1.29, 2.32)	0.0002	1.54	(1.12, 2.11)	0.0074
GDF15	2.34	(1.72, 3.19)	<0.0001	1.58	(1.18, 2.12)	0.0024
FABP4	1.56	(1.24, 1.96)	0.0001	1.29	(1.03, 1.63)	0.0290
SLAMF7	1.42	(1.14, 1.77)	0.0019	2.02	(1.39, 2.93)	0.0002
CCL16	1.37	(1.11, 1.68)	0.0028	1.57	(1.20, 2.05)	0.0009
TWEAK	0.60	(0.41, 0.87)	0.0075	0.58	(0.42, 0.80)	0.0008
KIM1	1.30	(1.08, 1.55)	0.0050	1.33	(1.07, 1.65)	0.0093
CD4	1.67	(1.18, 2.35)	0.0034	1.82	(1.23, 2.70)	0.0026
VSIG2	1.25	(0.97, 1.60)	0.0857	1.46	(1.06, 2.00)	0.0196
PON3	0.83	(0.66, 1.03)	0.0962	0.72	(0.57, 0.91)	0.0070
PLGF	1.86	(1.28, 2.72)	0.0013	1.61	(1.11, 2.34)	0.0119
MMP12	1.43	(1.14, 1.80)	0.0019	1.35	(1.06, 1.72)	0.0168
ADM	2.10	(1.46, 3.02)	<0.0001	1.40	(1.01, 1.94)	0.0408
RARRES2	2.42	(1.41, 4.18)	0.0015	1.69	(1.10, 2.58)	0.0158
CEACAM8	1.47	(1.18, 1.83)	0.0006	1.37	(1.09, 1.74)	0.0081
SLAMF1	1.28	(1.03, 1.59)	0.0254	1.43	(1.07, 1.90)	0.0142
TNFR1	1.98	(1.38, 2.84)	0.0002	1.27	(0.93, 1.74)	0.1353
AGRP	1.65	(1.23, 2.21)	0.0008	1.66	(1.11, 2.48)	0.0139
TNFR2	1.75	(1.27, 2.42)	0.0007	1.29	(0.97, 1.70)	0.0779
IGFBP7	1.44	(1.05, 1.96)	0.0219	1.43	(1.06, 1.92)	0.0183
UPAR	2.27	(1.61, 3.21)	<0.0001	1.39	(1.01, 1.93)	0.0464
PAR1	1.65	(1.17, 2.33)	0.0040	1.53	(1.08, 2.19)	0.0176
PLC	1.78	(1.17, 2.70)	0.0065	1.42	(0.97, 2.08)	0.0743
ACE2	1.49	(1.17, 1.89)	0.0012	1.41	(1.08, 1.86)	0.0131
IL16	1.39	(1.07, 1.80)	0.0131	1.34	(1.04, 1.72)	0.0219
TFF3	1.52	(1.23, 1.87)	0.0001	1.26	(0.97, 1.63)	0.0834
OPN	1.81	(1.36, 2.40)	<0.0001	1.36	(1.03, 1.79)	0.0304
SPON2	2.64	(1.35, 5.18)	0.0047	2.04	(1.14, 3.66)	0.0166
IL4RA	1.42	(1.07, 1.90)	0.0164	1.45	(1.04, 2.02)	0.0299
TNFRSF14	1.77	(1.26, 2.47)	0.0009	1.26	(0.93, 1.71)	0.1309

Legend: same as in figure 1.

Supplemental Table 4. Spearman correlation between the clinical risk score variables and the selected biomarkers

	<b>AGE</b>	<b>SMK</b>	<b>DM</b>	<b>CAD</b>	<b>HTN</b>	<b>BMI</b>	<b>HR</b>	<b>CR</b>
<b>BNP</b>	0.12	0.02	-0.02	0.18	0.06	-0.03	-0.12	0.08
<b>NTPROBNP</b>	0.13	-0.02	-0.07	0.18	0.07	-0.08	-0.13	0.06
<b>TRAILR2</b>	0.12	0.10	0.08	0.09	0.07	0.08	-0.01	0.27
<b>TNFRSF13B</b>	0.00	0.10	0.07	-0.01	0.03	0.09	-0.05	0.13
<b>GAL9</b>	-0.10	0.18	0.05	-0.04	-0.03	0.14	-0.07	-0.02
<b>FGF23</b>	0.00	-0.03	0.05	0.06	0.11	0.12	-0.03	0.16
<b>TNFRSF10A</b>	0.01	0.06	0.08	0.06	0.06	0.14	-0.01	0.10
<b>REN</b>	0.04	0.06	0.19	0.08	0.18	0.12	-0.02	0.17
<b>TNFRSF11A</b>	0.08	0.04	0.10	0.06	0.09	0.16	-0.06	0.22
<b>GDF15</b>	0.15	0.04	0.13	0.09	0.15	0.03	-0.01	0.31
<b>FABP4</b>	-0.01	-0.04	0.07	-0.02	0.16	0.36	0.05	0.04
<b>SLAMF7</b>	-0.04	0.02	0.11	0.04	0.04	0.08	0.00	0.10
<b>CCL16</b>	-0.02	0.03	0.01	0.00	0.10	0.08	-0.01	0.20
<b>TWEAK</b>	-0.01	0.02	-0.11	-0.04	-0.12	-0.04	-0.10	-0.05
<b>KIM1</b>	0.02	0.03	0.16	0.02	0.09	0.08	0.00	0.12
<b>CD4</b>	-0.11	0.20	0.10	-0.01	-0.06	0.10	-0.05	0.00
<b>VSIG2</b>	0.03	0.11	0.15	0.00	0.03	0.00	-0.07	0.14
<b>PON3</b>	-0.05	0.07	-0.08	-0.13	-0.18	-0.26	-0.08	-0.11
<b>PLGF</b>	0.13	0.05	0.03	0.08	0.04	0.05	-0.05	0.34
<b>MMP12</b>	0.09	0.12	0.07	0.15	0.12	-0.01	-0.03	0.20
<b>ADM</b>	0.05	0.07	0.03	0.05	0.07	0.20	-0.04	0.16
<b>RARRES2</b>	-0.01	0.06	0.00	-0.03	0.09	0.12	0.00	0.14
<b>CEACAM8</b>	0.17	-0.07	-0.02	0.06	0.12	0.06	0.03	0.19
<b>SLAMF1</b>	-0.08	0.10	0.09	0.03	0.01	0.13	-0.04	0.15
<b>TNFR1</b>	0.10	0.06	0.06	0.00	0.10	0.10	-0.04	0.28
<b>AGRP</b>	0.10	-0.05	0.05	0.10	0.08	-0.02	-0.02	0.22
<b>TNFR2</b>	0.05	0.09	0.05	0.00	0.07	0.06	-0.05	0.20
<b>IGFBP7</b>	0.05	0.03	0.06	0.01	0.08	0.03	-0.07	0.18
<b>UPAR</b>	0.07	0.04	0.01	0.03	0.08	0.04	-0.02	0.09
<b>PAR1</b>	-0.05	0.17	0.09	-0.08	-0.08	0.07	-0.01	0.01
<b>PLC</b>	0.12	-0.03	0.00	0.03	0.11	0.13	-0.06	0.33
<b>ACE2</b>	-0.09	0.12	0.10	0.03	-0.04	0.08	-0.03	0.02
<b>IL16</b>	0.00	0.08	0.03	-0.04	0.02	0.14	-0.05	0.03
<b>TFF3</b>	0.08	0.02	0.06	0.02	0.16	-0.06	0.01	0.24
<b>OPN</b>	0.01	0.14	0.00	0.03	0.00	0.01	-0.07	0.08
<b>SPON2</b>	-0.16	0.22	0.04	-0.06	-0.14	0.04	-0.12	-0.09
<b>IL4RA</b>	-0.04	0.15	0.06	-0.01	-0.10	0.01	-0.10	0.01
<b>TNFRSF14</b>	0.11	0.05	0.06	0.00	0.09	0.03	-0.01	0.25

Legend: SMK, smoking, DM, diabetes mellitus; CAD, coronary artery disease; HTN, hypertension; BMI, body mass index; HR, heart rate; CR, creatinine.

Supplemental Table 5. Final adjusted stepwise forward model starting with the 39 proteins independently selected in both discovery and replication sets (discovery and replication sets “pooled” for this analysis)

<b>Biomarker</b>	<b>OR (95%CI)</b>	<b>P-value</b>
BNP	1.43 (1.25-1.64)	<0.0001
TWEAK	0.38 (0.28-0.50)	<0.0001
NTPROBNP	1.39 (1.17-1.66)	<0.0001
REN	1.28 (1.10-1.49)	0.001
TRAILR2	1.56 (1.13-2.15)	0.007
PON3	0.78 (0.65-0.94)	0.008
CCL16	1.27 (1.06-1.53)	0.008
SLAMF1	1.24 (1.01-1.52)	0.036

Model adjusted for matching variables (age, sex, cohort, phase, follow-up time) and clinical variables (smoking, diabetes, history of coronary artery disease, serum creatinine, body mass index, systolic blood pressure, use of antihypertensive medication, and heart rate (the clinical model) with a p-value for inclusion set at 0.05.

AUC clinical model =0.68; AUC clinical model + final protein selection =0.78 ( $\Delta$ AUC p-value <0.001).

Legend: BNP, brain natriuretic peptide; TWEAK, tumor necrosis factor (Ligand) superfamily, member 12; NTPROBNP, N-terminal prohormone brain natriuretic peptide; REN, renin; TRAILR2, TNF-related apoptosis-inducing ligand receptor 2; PON3, paraoxonase; CCL16, C-C motif chemokine 16; SLAMF1, signalling lymphocytic activation molecule.



Supplemental Table 6. Nodes of induced network linking the top proteins to incident heart failure.

Level	Name (sorted by)	Uniprot ID	Protein / Gene	Cluster
seed	ACE2	Q9BYF1	Angiotensin-converting enzyme 2	Blood pressure regulation
seed	ADM	P35318	Adrenomedullin	Blood pressure regulation
seed	AGRP	O00253	Agouti-related protein	Metabolism
seed	BNP	P16860	Natriuretic peptides B / N-terminal prohormone brain natriuretic peptide	Blood pressure regulation
seed	CCL16	O15467	C-C motif chemokine 16	Inflammation and apoptosis
seed	CD4	P01730	T-cell surface glycoprotein CD4	Inflammation and apoptosis
seed	CEACAM8	P31997	Carcinoembryonic antigen related cell adhesion molecule 8	Extracellular matrix remodelling, angiogenesis and growth
seed	FABP4	P15090	Fatty acid-binding protein, adipocyte	Metabolism
seed	FGF23	Q9GZV9	Fibroblast growth factor 23	Blood pressure regulation
seed	GAL9	O00182	Galectin-9	Extracellular matrix remodelling, angiogenesis and growth
seed	GDF15	Q99988	Growth/differentiation factor 15	Extracellular matrix remodelling, angiogenesis and growth
seed	IGFBP7	Q16270	Insulin-like growth factor-binding protein 7	Inflammation and apoptosis
seed	IL16	Q14005	Pro-interleukin-16	Inflammation and apoptosis
seed	IL4RA	P24394	Interleukin-4 receptor subunit alpha	Inflammation and apoptosis
seed	KIM1	Q96D42	Kidney injury molecule 1/Hepatitis A virus cellular receptor 1	Inflammation and apoptosis
seed	MMP12	P39900	Matrix metalloproteinase-12	Extracellular matrix remodelling, angiogenesis and growth
seed	OPN	P10451	Osteopontin	Extracellular matrix remodelling, angiogenesis and growth
seed	PAR1	P25116	Proteinase-activated receptor 1 / Coagulation Factor II Thrombin Receptor	Blood pressure regulation
seed	PLC	P98160	Perlecan	Extracellular matrix remodelling, angiogenesis and growth
seed	PLGF	P49763	Placenta growth factor	Extracellular matrix remodelling, angiogenesis and growth
seed	PON3	Q15166	Paraoxonase 3	Metabolism
seed	RARRES2	Q99969	Retinoic acid receptor responder 2	Metabolism
seed	REN	P00797	Renin	Blood pressure regulation
seed	SLAMF1	Q13291	Signaling lymphocytic activation molecule	Inflammation and apoptosis
seed	SLAMF7	Q9NQ25	SLAM family member 7	Inflammation and apoptosis
seed	SPON2	Q9BUD6	Spondin 2	Extracellular matrix remodelling, angiogenesis and growth
seed	TFF3	Q07654	Trefoil factor 3	Inflammation and apoptosis
seed	TNFR1	P19438	Tumor necrosis factor receptor 1	Inflammation and apoptosis
seed	TNFR2	P20333	Tumor necrosis factor receptor 2	Inflammation and apoptosis

Level	Name (sorted by)	Uniprot ID	Protein / Gene	Cluster
seed	TNFRSF10A	O00220	Tumor necrosis factor receptor superfamily member 10A	Inflammation and apoptosis
seed	TNFRSF11A	Q9Y6Q6	Tumor necrosis factor receptor superfamily member 11A	Inflammation and apoptosis
seed	TNFRSF13B	O14836	Tumor necrosis factor receptor superfamily member 13B	Inflammation and apoptosis
seed	TNFRSF14	Q92956	Tumor necrosis factor receptor superfamily member 14	Inflammation and apoptosis
seed	TRAILR2	O14763	TNF-related apoptosis-inducing ligand receptor 2	Inflammation and apoptosis
seed	TWEAK	O43508	Tumor necrosis factor (Ligand) superfamily, member 12	Inflammation and apoptosis
seed	UPAR	Q03405	Urokinase plasminogen activator surface receptor	Extracellular matrix remodelling, angiogenesis and growth
seed	VSIG2	Q96IQ7	V-set and immunoglobulin domain-containing protein 2	Inflammation and apoptosis
intermediate	AGT	P01019	Angiotensinogen	Blood pressure regulation
intermediate	Angiotensin I		Angiotensin I	Blood pressure regulation
intermediate	Angiotensin II		Angiotensin II	Blood pressure regulation
intermediate	CERCAM	Q5T4B2	Inactive glycosyltransferase 25 family member 3 / Cerebral endothelial cell adhesion molecule	Extracellular matrix remodelling, angiogenesis and growth
intermediate	CIP2A	Q8TCG1	Cancerous inhibitor of PP2A	Inflammation and apoptosis
intermediate	DNAJA1	P31689	DnaJ homolog subfamily A member 1	Inflammation and apoptosis
intermediate	ERAP1	Q9NZ08	Endoplasmic reticulum aminopeptidase 1	Inflammation and apoptosis
intermediate	FAP	Q12884	Prolyl endopeptidase FAP	Extracellular matrix remodelling, angiogenesis and growth
intermediate	FAS	P25445	Fas Cell Surface Death Receptor/ Tumor necrosis factor receptor superfamily member 6	Inflammation and apoptosis
intermediate	FBLN1	P23142	Fibulin 1	Extracellular matrix remodelling, angiogenesis and growth
intermediate	FBN1	P35555	Fibrillin-1	Extracellular matrix remodelling, angiogenesis and growth
intermediate	FUT11	Q495W5	Fucosyltransferase 11	Extracellular matrix remodelling, angiogenesis and growth
intermediate	GALNT18	Q6P9A2	Polypeptide N-Acetylgalactosaminyltransferase 18	Extracellular matrix remodelling, angiogenesis and growth
intermediate	GHRL	Q9UBU3	Ghrelin	Metabolism
intermediate	GRN	P28799	Granulin/Epithelin	Inflammation and apoptosis /Extracellular matrix remodelling, angiogenesis and growth
intermediate	HIF1A/ARNT	/	Hypoxia-inducible factor 1-alpha/Aryl hydrocarbon receptor nuclear translocator complex	
intermediate	HNF1B	P35680	Hepatocyte nuclear factor 1-beta	
intermediate	KRT18	P05783	Keratin, type I cytoskeletal 18	Inflammation and apoptosis
intermediate	LAMA1	P25391	Laminin Subunit Alpha 1	Extracellular matrix remodelling, angiogenesis and growth
intermediate	LARGE1	O95461	LARGE xylosyl- and glucuronyltransferase 1	Extracellular matrix remodelling, angiogenesis and growth
intermediate	LTA	P01374	Lymphotoxin Alpha	Inflammation and apoptosis
intermediate	NAGLU	P54802	N-Acetyl-Alpha-Glucosaminidase	Extracellular matrix remodelling, angiogenesis and growth
intermediate	NFkB	/	Nuclear factor NF-kappa-B complex	Inflammation and apoptosis

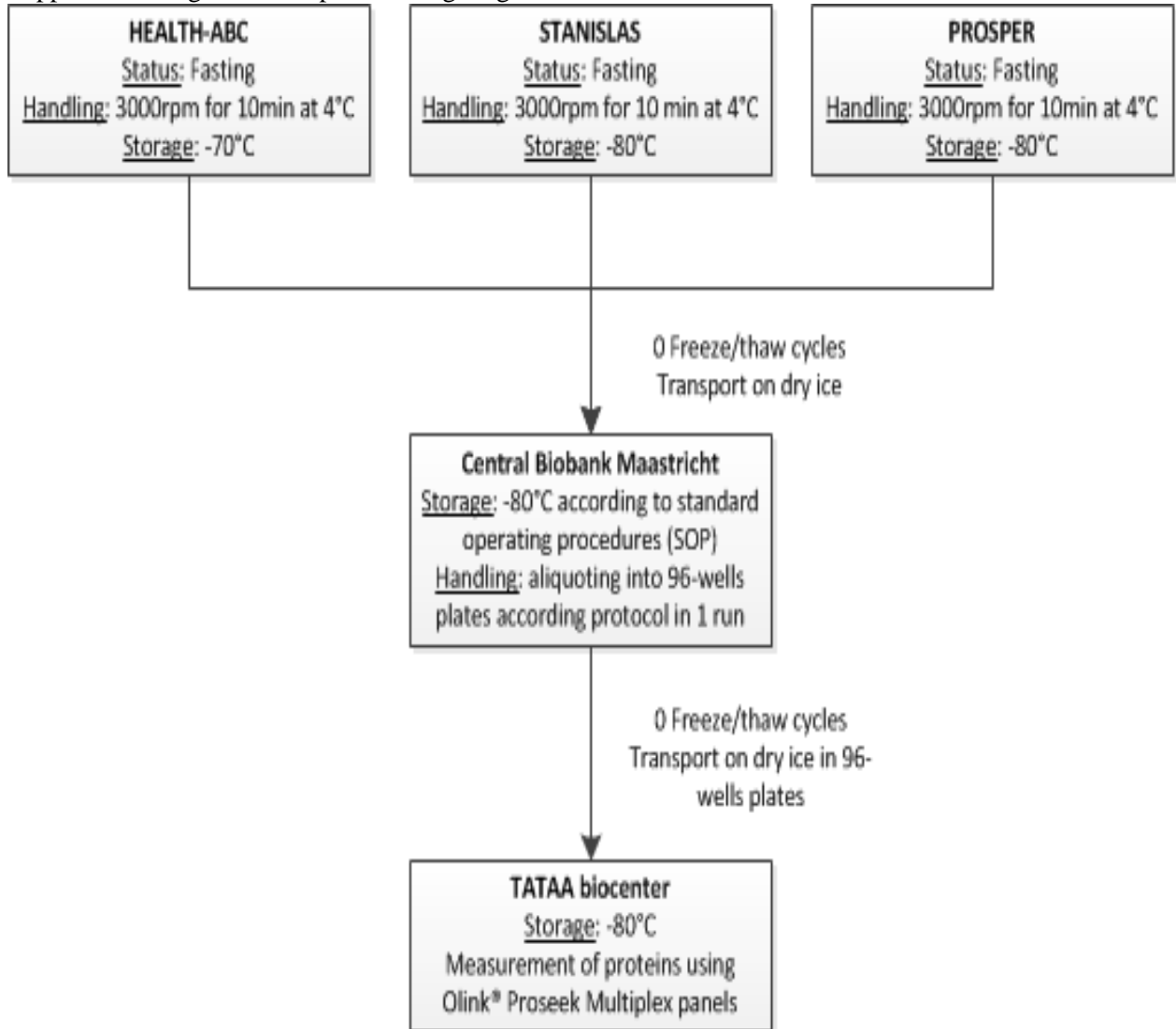
<b>Level</b>	<b>Name (sorted by)</b>	<b>Uniprot ID</b>	<b>Protein / Gene</b>	<b>Cluster</b>
intermediate	NID1	P14543	Nidogen 1/Entactin	Extracellular matrix remodelling, angiogenesis and growth
intermediate	NID2	Q14112	Nidogen 2/Osteonidogen	Extracellular matrix remodelling, angiogenesis and growth
intermediate	S100A10	P60903	S100 Calcium Binding Protein A10	Inflammation and apoptosis
intermediate	SERTAD3	Q9UJW9	SERTA domain-containing protein 3	
intermediate	SLC1A1	P43005	Excitatory amino acid transporter 3	Inflammation and apoptosis
intermediate	SSR4	P51571	Translocon-associated protein subunit delta	Inflammation and apoptosis
intermediate	STAT6	P42226	Signal Transducer And Activator Of Transcription 6 dimer	
intermediate	TNFRSF25	Q93038	TNF Receptor Superfamily Member 25	Inflammation and apoptosis
intermediate	TNFSF10	P50591	TNF Superfamily Member 10	Inflammation and apoptosis
intermediate	TNFSF13	O75888	Tumor Necrosis Factor (Ligand) Superfamily, Member 13	Inflammation and apoptosis
intermediate	TP53	P04637	Tumor Protein P53	
intermediate	TP73	O15350	Tumor Protein P73	
intermediate	TRADD	Q15628	Tumor necrosis factor receptor type 1-associated DEATH domain protein	Inflammation and apoptosis
intermediate	TRAF2	Q12933	TNF Receptor Associated Factor 2	Inflammation and apoptosis
intermediate	TRAF3	Q13114	TNF Receptor Associated Factor 3	Inflammation and apoptosis
intermediate	TRAF5	O00463	TNF receptor-associated factor 5	Inflammation and apoptosis
intermediate	VEGFA	P15692	Vascular Endothelial Growth Factor A	Extracellular matrix remodelling, angiogenesis and growth

Supplemental Table 7. Results of overrepresentation analysis on GO for selected top proteins against all measured proteins as background.

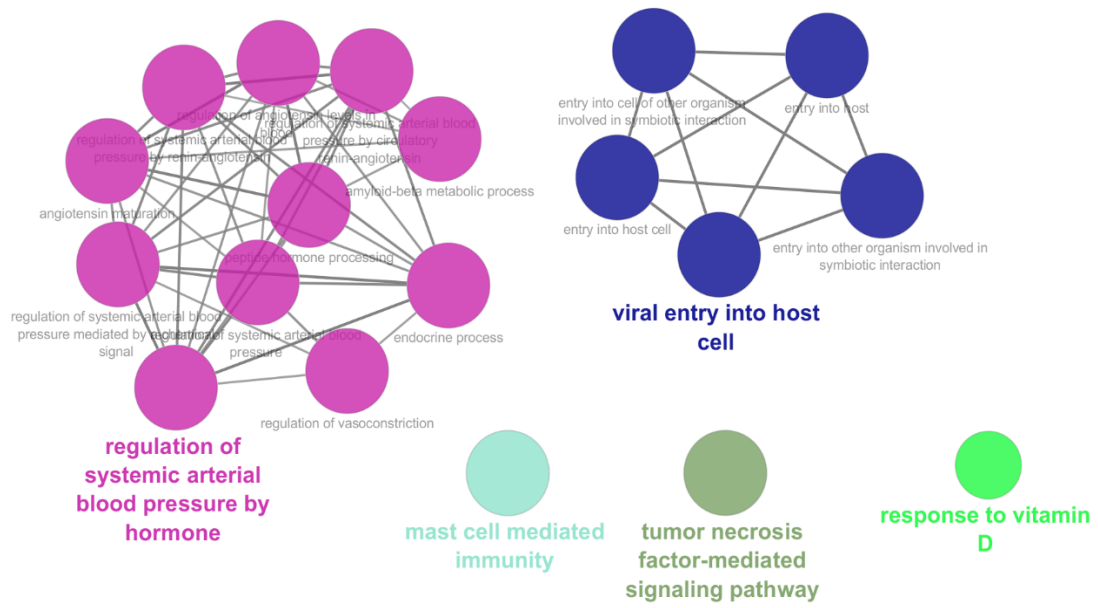
GO process and function	Number of proteins in GO item	Number of proteins on OLINK panel	Proteins in GO process on OLINK panel (with Entrez Gene ID)	Number of selected proteins	Selected proteins (with Entrez Gene ID)	p-value
<i>death receptor activity (GO:0005035)</i>	11	5	7132 TNFRSF1A : TNF receptor superfamily member 1A 7133 TNFRSF1B : TNF receptor superfamily member 1B 8792 TNFRSF11A : TNF receptor superfamily member 11a 8797 TNFRSF10A : TNF receptor superfamily member 10a 8764 TNFRSF14 : TNF receptor superfamily member 14	5 (100.0%)	7132 TNFRSF1A : TNF receptor superfamily member 1A 7133 TNFRSF1B : TNF receptor superfamily member 1B 8792 TNFRSF11A : TNF receptor superfamily member 11a 8797 TNFRSF10A : TNF receptor superfamily member 10a 8764 TNFRSF14 : TNF receptor superfamily member 14	5.47E-05
<i>tumor necrosis factor-activated receptor activity (GO:0005031)</i>	9	4	7132 TNFRSF1A : TNF receptor superfamily member 1A 7133 TNFRSF1B : TNF receptor superfamily member 1B 8792 TNFRSF11A : TNF receptor superfamily member 11a 8764 TNFRSF14 : TNF receptor superfamily member 14	4 (100.0%)	7132 TNFRSF1A : TNF receptor superfamily member 1A 7133 TNFRSF1B : TNF receptor superfamily member 1B 8792 TNFRSF11A : TNF receptor superfamily member 11a 8764 TNFRSF14 : TNF receptor superfamily member 14	0.000409
<i>renal system process (GO:0003014)</i>	116	5	133 ADM : adrenomedullin 2149 F2R/PAR1 : coagulation factor II thrombin receptor 4879 NPPB : natriuretic peptide B 5155 PDGFB : platelet derived growth factor subunit B 5972 REN : renin	4 (80.0%)	133 ADM : adrenomedullin 2149 F2R/PAR1 : coagulation factor II thrombin receptor 4879 NPPB : natriuretic peptide B 5972 REN : renin	0.001827

<b>GO process and function</b>	<b>Number of proteins in GO item</b>	<b>Number of proteins on OLINK panel</b>	<b>Proteins in GO process on OLINK panel (with Entrez Gene ID)</b>	<b>Number of selected proteins</b>	<b>Selected proteins (with Entrez Gene ID)</b>	<b>p-value</b>
<i>regulation of systemic arterial blood pressure (GO:0003073)</i>	91	8	133 ADM : adrenomedullin 1522 CTSZ : cathepsin Z 2149 F2R/PAR1 : coagulation factor II thrombin receptor 4879 NPPB : natriuretic peptide B 5155 PDGFB : platelet derived growth factor subunit B 5972 REN : renin 6648 SOD2 : superoxide dismutase 2 59272 ACE2 : angiotensin I converting enzyme 2	5 (62.5%)	133 ADM : adrenomedullin 2149 F2R/PAR1 : coagulation factor II thrombin receptor 4879 NPPB : natriuretic peptide B 5972 REN : renin 59272 ACE2 : angiotensin I converting enzyme 2	0.002169

Supplemental Figure 1. Sample handling diagram



Supplemental Figure 2. The two major clusters inflammatory/apoptosis and blood pressure regulation were also detected as the main groups using the ClueGO network analysis



## Supplemental addenda 1. Material and Methods for the Olink® technology

Proteins were measured using the Olink® CVDII, CVDIII, and Inflammation panels\* (Olink Proteomics AB, Uppsala, Sweden) according to the manufacturer's instructions. The Proximity Extension Assay (PEA) technology used for the Olink protocol has been well described (Assarsson et al, 2014; accessible at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0095192>), and enables 92 analytes to be analyzed simultaneously, using 1µL of each sample. In brief, pairs of oligonucleotide-labeled antibody probes bind to their targeted protein, and if the two probes are brought in close proximity the oligonucleotides will hybridize in a pair-wise manner. The addition of a DNA polymerase leads to a proximity-dependent DNA polymerization event, generating a unique PCR target sequence. The resulting DNA sequence is subsequently detected and quantified using a microfluidic real-time PCR instrument (Biomark HD, Fluidigm). The resulting Ct-data is then quality controlled and normalized using a set of internal and external controls. The final assay read-out is presented in Normalized Protein eXpression (NPX) values, which is an arbitrary unit on a log<sub>2</sub>-scale where a high value corresponds to a higher protein expression. The four internal controls are designed to mimic and monitor the different steps of the PEA. They consist of two non-human proteins with matching antibody-probes that functions as incubation/immuno controls, an IgG antibody with two matching probes attached to it that functions as an extension control and a complete double-stranded amplicon that function as detection control. The internal controls are introduced to all samples as well as to the external controls. The external controls consist of a triplicate of negative controls used to calculate the limit of detection (LOD), as well as a triplicate of interplate controls (IPCs) containing 92 sets of antibodies with both matching probes for each assay attached to them that are used for normalization. For each sample and assay NPX is calculated by the following equations: 1.  $Ct_{(analyte)} - Ct_{(extension\ control)} = dCt_{(analyte)}$  (to decrease technical variation) 2.  $dCt_{(analyte)} - Ct_{(median\ IPC)} = ddCt_{(analyte)}$  (to improve inter plate variation) 3.  $Correction\ factor_{(analyte)} - ddCt_{(analyte)} = NPX_{(analyte)}$  (for more intuitive data). The correction factor is a set variable unique for each assay and reagent lot.

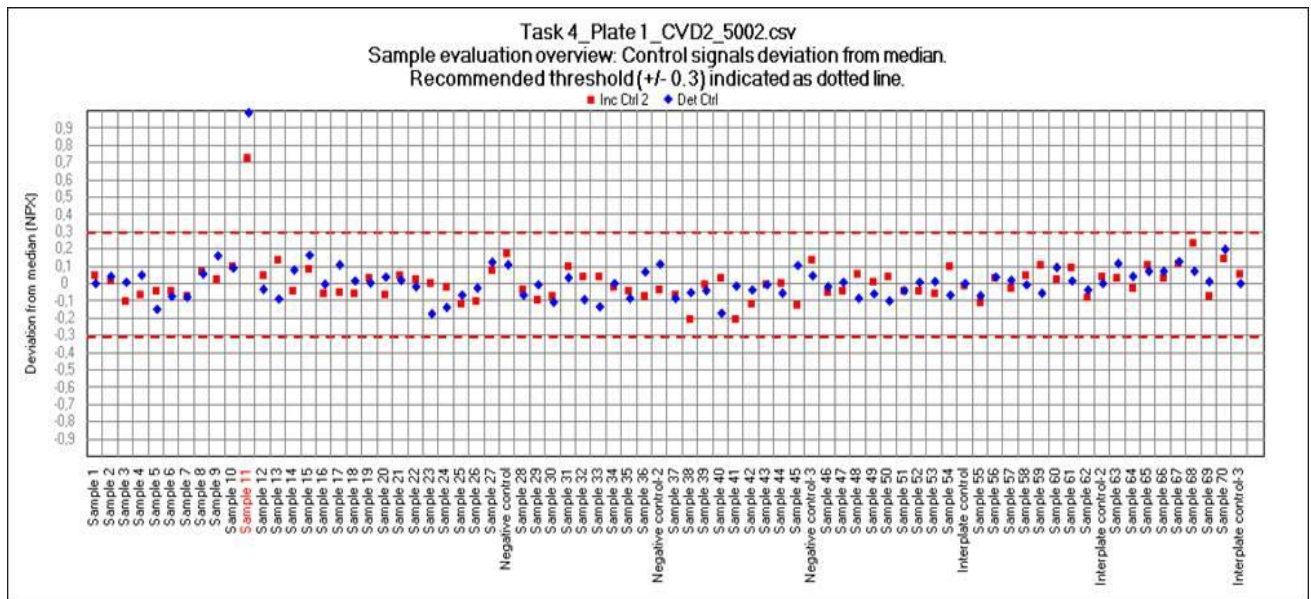
Quality control of the data is performed in two steps: First, the standard deviation for each of the incubation/immuno controls and the detection control is calculated for each run. A run will only pass quality control if the standard deviation for each of the controls is below 0.2. Secondly, each sample is quality controlled using incubation control 2 and the detection control. The run median of each of the controls is calculated and all samples within the run is compared to that. Samples that fall more than +/- 0.3 NPX from the plate median with regards to these two controls will fail the quality control and receive a QC warning in the data output file.

All assay validation data (detection limits, intra- and inter-assay precision data, etc.) are available on manufacturer's website ([www.olink.com](http://www.olink.com)).

\* Previously branded as Olink® Multiplex panels.

An example of a QC-plot is provided below:





## Technical description Olink Proximity Extension Assay

### Overview

Olink Proteomics has developed a unique protein detection system called Proximity Extension Assay (PEA), which enables highly specific and sensitive multiplex immunoassays for the detection of 92 different proteins in 90 samples simultaneously, generating 9260 data points in a single run. These proteins can be measured in a large variety of human sample types using as little as one microliter volume of sample. To date, >25 different biological matrices have been tested, all of which have proven compatible with PEA. Olink Proteomics currently offers assays for more than 977 proteins. During PEA, protein targets are ID-tagged by unique DNA amplicons that are subsequently detected and quantified by real-time PCR using Fluidigm's BioMark HD system. In doing so, the platform harnesses the highly parallel nature of Fluidigm's Dynamic Array IFC (Integrated Fluidic Circuit) technology, bringing the assays to the high throughput, reproducibility and superior sensitivity realm of the BioMark HD.

Measurements performed with the Proseek<sup>®</sup> Multiplex assays are semi-quantitative, where changes in protein levels in one group or population are quantified relative to another. The assays generate quantitation cycle (Cq) values that are then normalized and converted to Olink's arbitrary Normalized Protein eXpression (NPX) unit, which can be used for further statistical analyses. NPX gives relative quantification. NPX is on a log<sub>2</sub> scale. NPX should be compared between samples for each assay separately.

The analytical performance is thoroughly validated during product development to ensure the highest standards of sensitivity, precision, specificity and dynamic range. Since traceable calibrators are not yet available for all proteins in Olink's portfolio, performance is evaluated by using full length recombinant proteins as well as well characterized normal and diseased plasma/serum samples.

Repeatability of the measurements is reflected by an average intra-assay variation of 5-10% CV, and inter-assay variation 10-20% CV.

Multiple head-to-head comparisons have been performed against golden-standard single-plex ELISA assays in clinical settings (e.g. NT-pro-BNP, OPN, ST2). So far, these tests have demonstrated strong positive correlation, and have indicated similar, and sometimes superior, levels of sensitivity for Olink's PEA-based assays.

The real strength of Olink's technology is that it offers a high-throughput capacity coupled to a growing list of analytes, therefore placing the platform in a strong position for biomarker selection. Furthermore, the development of new multiplex assays is very rapid thanks to a conjugation procedure that works well on all antibody subtypes tested so far, universal incubation conditions and minimal probe concentrations used in our assays. Olink Proteomics currently offers 12 pre-designed 92-plex panels.

### **Detailed technical description**

#### Measurements

##### 1. Accuracy and reproducibility of the measurements:

Olink's multiplex assays are validated following the standard procedure for immunoassays. Proseek® Multiplex measurements are semi-quantitative, where changes in protein levels are determined and compared for each protein separately. Due to the nature of relative quantification, no calibration standards are needed leaving room for more biological samples on the plate and, thus, higher throughput.

The output from the Proseek Multiplex protocol is in quantitation cycles (Cq) produced by the BioMark's Real-Time PCR Software. To minimize variation within and between runs, the data is normalized using both an internal control (Extension Control) and an Inter-Plate Control (IPC), and data is transformed using a pre-determined correction factor. The pre-processed data will be in the arbitrary unit NPX (Normalized Protein eXpression), which can be used for further statistical analyses.

##### 2. Volume:

As little as 1  $\mu$ l of sample is required to analyse 92 proteins in a single measurement. The amount of data generated increases proportionally with the volume of analysed sample, so that 2  $\mu$ l produces data for 184 proteins and so forth.

##### 3. Number of proteins:

92 proteins are quantified for each sample in a single run.

##### 4. Sample types:

Proseek® Multiplex assays are designed for detection of proteins in complex human biofluids. Proseek® Multiplex assays are validated using both EDTA plasma and serum samples. Furthermore, a wide range of additional sample types are compatible with the technology, such as citrate and heparin plasma, CSF, urine, saliva, tissue and cell lysates, cell culture media, dried blood spots and

many more. See Table 1 at the end of this document for information about some of the sample types that have been analyzed so far. Olink is open to discussion and exploration of untested sample types.

#### 5. Correlation and agreement:

Correlation studies have been carried out for a subset of proteins to compare Olink's Proseek® Multiplex assays to commercial singleplex ELISA/conventional analyses in clinical settings. Olink assays have so far displayed high correlations with these established tests, both in Olink's own Service Laboratory and external, customer-led evaluations, demonstrating the accuracy and parallelism of the PEA technology. PEA is described by a peer-reviewed publication in PLOS one: Homogenous 96-Plex PEA Immunoassay Exhibiting High Sensitivity, Specificity, and Excellent Scalability. Assarsson and Lundberg *et al.*, 2014.

#### 6. Validation:

During the validation procedure, Olink analyzes matched plasma (three different anti-coagulants) and serum samples, and reports their respective protein levels relative to the measurements in EDTA plasma. This varies for each biomarker and is presented in the Validation Data package for each panel. Intra- and inter-assays precision values are also determined for each protein and presented in the Validation Data Packages which can be found on <http://www.olink.com/proseek-multiplex/>.

In a recent pilot wellness study, EDTA plasma was taken from 88 well-characterized individuals at three different time points (every 3 months) and each sample was analyzed using multiple Proseek® Multiplex panels. A large proportion of biomarkers correlated significantly well across the different time points for each individual, while some proteins revealed distinct expression patterns that varied with time. It is also worth mentioning that the inflammation panel was able to identify the signs of infection and single out an individual who had been suffering from illness during one of the three time points (data not shown).

These data further strengthen the case for the robustness of the technology and its potential for future longitudinal studies.

#### 7. Information:

The platform was recently used to investigate the effects of freezer storage, chronological age at sampling, season and month of the year on the abundance levels of 108 proteins in 380 plasma samples collected from 106 Swedish women: "Effects of Long-Term Storage Time and Original Sampling Month on Biobank Plasma Protein Concentrations" Enroth *et al.*, 2016.

The study found that storage time can explain 4.8-34.9% of the observed variance, and that the chronological age at sample collection after adjustment for storage-time explains 1.1-33.5% of the observed variance.

Another recent study performed at the Karolinska Institute, using samples from the BBMRI BioBank in Stockholm, found that proteins are stable for consistent measurements by PEA, even after 8 short, successive freeze-thaw cycles (manuscript in preparation).

The first Olink panel was launched on the 1<sup>st</sup> of March 2013 and since then the technology has been used to analyse over 235 000 samples. This has so far led to 57 publications, in the form of technology reviews and customer applications, demonstrating that Olink's semi-quantitative approach for measuring biomarker levels is approved by referees. More publications are in the pipeline as Olink continues to analyse protein biomarkers for life science researchers around the world. For a complete list of publications see; <http://www.olink.com/data-you-can-trust/publications/>

Olink will work closely with customers to produce smaller and focused custom panels, to support the future development of diagnostic tools based on clinically relevant protein signatures.

Finally, with the help of bio-informatics tools, Olink proteomics is currently developing ways of extending the biological information provided about the proteins in each panel. In doing so, Olink intends to go beyond the simple provision of technology and reagents by simultaneously catering knowledge for the field of protein biomarker discovery. Olink Proteomics provides first-class support to our customers. With our unparalleled experience and skills working with Proseek® Multiplex panels, the support team quickly delivers the best assistance, free of charge. Olink Proteomics also offers professional statistical analysis services. Our in-house team of biostatisticians can help you with customized statistical analyses tailored to your requirements.

All assay validation data (detection limits, intra- and inter-assay precision data, etc) are available on manufacturer's website ([www.olink.com](http://www.olink.com)).

## **Instrumentation**

### 1. Automation:

The Fluidigm BioMark HD combined with a controller or Juno is able to load all reagents into the microfluidic circuits and can be left to operate protocols unattended during the run. The Dynamic Arrays have an integrated network of channels, chambers and valves that automatically combine the reactions, conserving time, reagents and sample volumes. Initial pipetting is needed to pipette samples and reagents into the micro-well section of the dynamic arrays. Automatic sample and assay mixing of Fluidigm integrated fluidic circuit (IFCs) reduces pipetting by 95% compared to conventional PCR microplate-based systems. The IFC is subsequently placed in the controller (either HX or Juno). The samples do not come in contact with the interface plate which is within the controllers. However, it is possible to remove the interface plate and clean with 70% Ethanol as an additional measure between runs. Furthermore, it is possible to automate this using liquid handling instruments as the dynamic arrays have a Society for Biomolecular Sciences (SBS)-compatible format enabling manual and/or 384-well plate format handling and standard dispensing equipment.

By using Fluidigm 96.96 IFCs it is possible to analyse 90 samples + 6 controls in a single run on the BioMark HD. At a rate of 3 to 4 IFCs per day, the platform is largely capable of supporting the proposed scale of proteomic studies. Dedicated staff can achieve up to 360 samples per day (4 IFCs), which translates into  $4 \times 9216 = 36864$  data points in one day per BioMark HD system.

## 2. Accuracy and Reproducibility:

The repeatability and reproducibility of Olink multiplex assays is determined by using spiked and unspiked serum and plasma samples. These reference samples are generated to cover a wide concentration range for each protein target in order to mimic large biological variation, and are analysed by several (external) operators/service providers. Olink assays display an average intra-assay variation of 5-10% and a 10-20% inter-assay variation. The variation between runs is naturally slightly higher, with the highest variation observed for assays that measure samples close to the Limit of Detection (LOD).

### Sample types:

Table 1. Assay detectability in different sample types: Number of proteins detected in healthy blood donors

Sample Type	Panels				
	CVD II	CVD III	ONC II	INF I	NEU I
Whole blood	NT	NT	NT	NT	NT
Plasma EDTA	AS 99% in >75% of samples	AS 98% in >75% of samples	AS 100% in >75% of samples	AS 80% in >75% of samples	AS 100% in >75% of samples
Plasma Heparin	AS	AS	AS	AS	AS
Plasma Citrate	AS	AS	AS	AS	AS
Serum	AS 97% in >75% of samples	AS 99% in >75% of samples	AS 100% in >75% of samples	AS 82% in >75% of samples	AS 98% in >75% of samples
Urine	NT	NT	NT	AS 37% in >75% of samples	NT
PBMC	NT	NT	NT	AS 73% in >75% of samples	NT

Additional sample-types include, but are not limited to:

<b>CSF</b>	AS 70% in >75% samples	AS 61% in >75% samples	AS 76% in >75% samples	AS 62% in >75% samples	AS 85% in >75% samples
<b>Exosomes</b>	AS 48% in >75% samples (plasma origin)	AS 38% in >75% samples (plasma origin)	AS 37% in >75% samples (cell origin)	AS 27% in >75% samples (cell origin)	NT
<b>Saliva</b>	NT	NT	NT	AS 63% in >75% of samples	NT
<b>Synovial fluid</b>	AS 46% in >75% of samples	NT	NT	AS 41% in >75% of samples	NT
<b>Cell lysates</b>	AS 33% in >75% of samples	AS 34% in >75% of samples	AS 41% in >75% of samples	AS 38% in >75% of samples	NT
<b>Tissue lysates</b>	NT	NT	NT	AS 79 % in >75% samples	AS 86% in >75% samples
<b>Cell culture supernatants</b>	NT	NT	AS 34% in >75% of samples	AS 47% in >75% samples	NT
<b>Dried blood spots</b>	NT	NT	NT	AS 73% in >75% of samples	AS 54% in >75% of samples

AS - Run in Analysis Service

NT - Not Tested

## References

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## NPX, QC and CV

### Calculation of NPX

Normalization of the Ct values derived from the qPCR detection step improves precision and makes data more intuitive (higher value = higher protein concentration). NPX (Normalized Protein eXpression) represents the relative signal (on log<sub>2</sub> scale) and is used for downstream statistical analyses.

1. Extension Control:

$$Ct_{\text{analyte}} - Ct_{\text{Ext Ctrl}} = dCt_{\text{analyte}}$$

2. Interplate Control:

$$dCt_{\text{analyte}} - dCt_{\text{Interplate Ctrl}} = ddCt$$

3. Normalization against a correction factor:

$$\text{Correction factor} - ddCt = \text{NPX}$$

- Protein expression changes are measured for each protein separately by relative quantification
- Even if two different proteins have the same NPX values, their actual concentration may differ
- NPX should be compared between samples within a run for each assay separately
- NPX cannot be directly compared between runs

## Quality control

Olink has built-in quality controls in all multiplex panels. Each 92-plex panel contains 96 assays. Four of those are internal controls that allow for an in-process quality control designed to monitor different steps of the protocol: immuno reaction, extension and amplification/ detection.

- The two incubation controls consist of two different non-human antigens measured with PEA assays: Incubation Control 1 and 2. These controls monitor potential variation in all three steps of the reaction.
- The Extension Control is an antibody coupled to both DNA-tags (hence always in proximity). This control monitors the extension and amplification/detection step.
- The Detection Control is a complete double stranded DNA amplicon which does not require any proximity binding or extension step. This control monitors the amplification/detection step.

The internal controls are used for both sample and run QC. The quality control of data is performed separately for each sample plate.

### **Sample QC**

Each of the internal controls are spiked into the samples in the same concentration. The signal for these are therefore expected to be the same over the plate. Sample QC is performed using the Detection Control and Incubation Control 2. Within each run, the levels of these controls are monitored for each sample and compared against the median of all samples. If either of the controls deviate more than the acceptance criteria allow (see below), the sample is flagged.

The Extension Control is used in the normalization step and in generation of NPX, and hence not included in the quality control of data.

The IPC cannot flag on the Detection control. This function was removed already from the start, as the large number of extensions that is required for the IPC made the IPC to always be a bit behind the rest of the samples. I.e., the IPC would always flag on the Detection control. It is however always constant, and flagging on the Detection control was therefore excluded.

Acceptance criteria for passing a sample:

- Incubation Control 2 and Detection Control deviates  $< \pm 0.3$  NPX from plate median.

### **Run QC**

The internal controls are used also in the run QC. This QC assesses the variation over the plate for each of the Incubation Controls 1 and 2 and the Detection Control. If the variation for one of the controls is too large (see below) the entire run is considered unreliable.

Acceptance criteria for passing a run:

- Standard deviation of Incubation Control 1 & 2 and Detection Control:  $< 0.2$  NPX.
- Number of flagged samples:  $\leq 1/6$  of total number of samples (i.e.  $\leq 16$  in a full plate).

### **Correction factor**



The correction factor is calculated during the validation of the panels. It is a pre-determined value, a fixed background, used to shift signals to a more intuitive value. Several runs during the validation process is used for this. Data from all assays are used but only IPC and negative control are needed from the samples. A minimum of 12 runs is performed. All runs should have at least three IPCs and three negative controls. Median is used in the final steps of the calculations to make the analysis less sensitive for extreme values.

Calculation of correction factor

1. Normalize using extension control:

$$Ct_{\text{sample assay (x)}} - Ct_{\text{sample assay (ext ctrl)}} = dCt_{\text{sample assay (x)}}$$

2. Normalize using median IPC (per experiment):

$$dCt_{\text{sample assay (x)}} - \text{Median } dCt_{\text{IPC assay (x)}} = ddCt_{\text{sample assay (x)}}$$

3. Calculate average value for background (per experiment):

$$\text{Average } (ddCt_{\text{background assay(x)}}) = Bg \text{ IPC}_{(x)}$$

4. Calculate median value for the background of all assays:

$$\text{Median } (Bg \text{ IPC}_{(x)})$$

Since the background is shifting within an interval, this interval is usually estimated by assuming normal distribution and selecting which interval to use. Olink uses a confidence interval of 99% (+/- 3xSD from the background). As the customer is recommended to run only three background samples in every run, this will not be enough to exactly calculate the standard deviation for the background. Therefore, we have a fixed value for this, which is selected from the same data as the Correction Factor. In contrast to the correction factor, fixed SD has a function and impact on the data.

Normalization

Olink NPX Manager has three available methods for data normalization and minimization of systematic biases between sample plates. These methods are described below. An important concept when deciding on normalization procedure is randomization, which in this context applies to the sample placement across the plates. For randomized studies with more than one plate, intensity normalization is the default normalization. For other studies, IPC normalization is default.

### **IPC normalization**

Three inter-plate controls (IPC) are included on each plate and run as normal samples. The inter-plate control is a pool of 92 antibodies, each with one of the pairs of unique DNA tags on it positioned in fixed proximity (i.e. 92 Extension Controls).

The median of the three IPCs is used as normalizer for each assay, and this compensates for potential variation between runs/plates. This method is completely independent on the samples included on the plate and is therefore recommended for projects where complete randomization of samples cannot be guaranteed.

### **Intensity normalization**

The intensity normalization adjusts the data so that the median NPX for a protein on each plate is equal to the overall median. Each plate is adjusted so that the median of all assays is the same on all plates.

This method requires that the true median of each plate is the same. One way of ensuring this is to randomize the samples beforehand. If there is total randomization, this method outperforms other normalization methods. If there are specific types of samples that are only available on certain plates, this normalization method should not be used.

### **Control normalization**

The control normalization works in the same way as the IPC normalization, but with one addition. While the IPC adjusts each protein to the level of a reference, the control normalization also adjusts the total intensity of entire plates. This is useful if you have plates or projects that differ on average in a way that cannot be explained biologically. Control normalization can be used to reduce systematic variation in non-randomized studies. This normalization method requires the addition of at least two control samples on each plate.

NOTE This is an optional normalization method that should only be used when standard normalizations are not sufficient.

### **Coefficient of variation**

%CV is calculated using linear NPX values from replicate control samples, for assays detected above LOD.

Intra-CV represents the CV within a plate and inter-CV represents the CV between plates. The reported %CV is the mean %CV over all assays.

Coefficient of Variation = (Standard Deviation / Mean) \* 100

- Reference value for Inter %CV: < 25%
- Reference value for Intra %CV: < 15%