

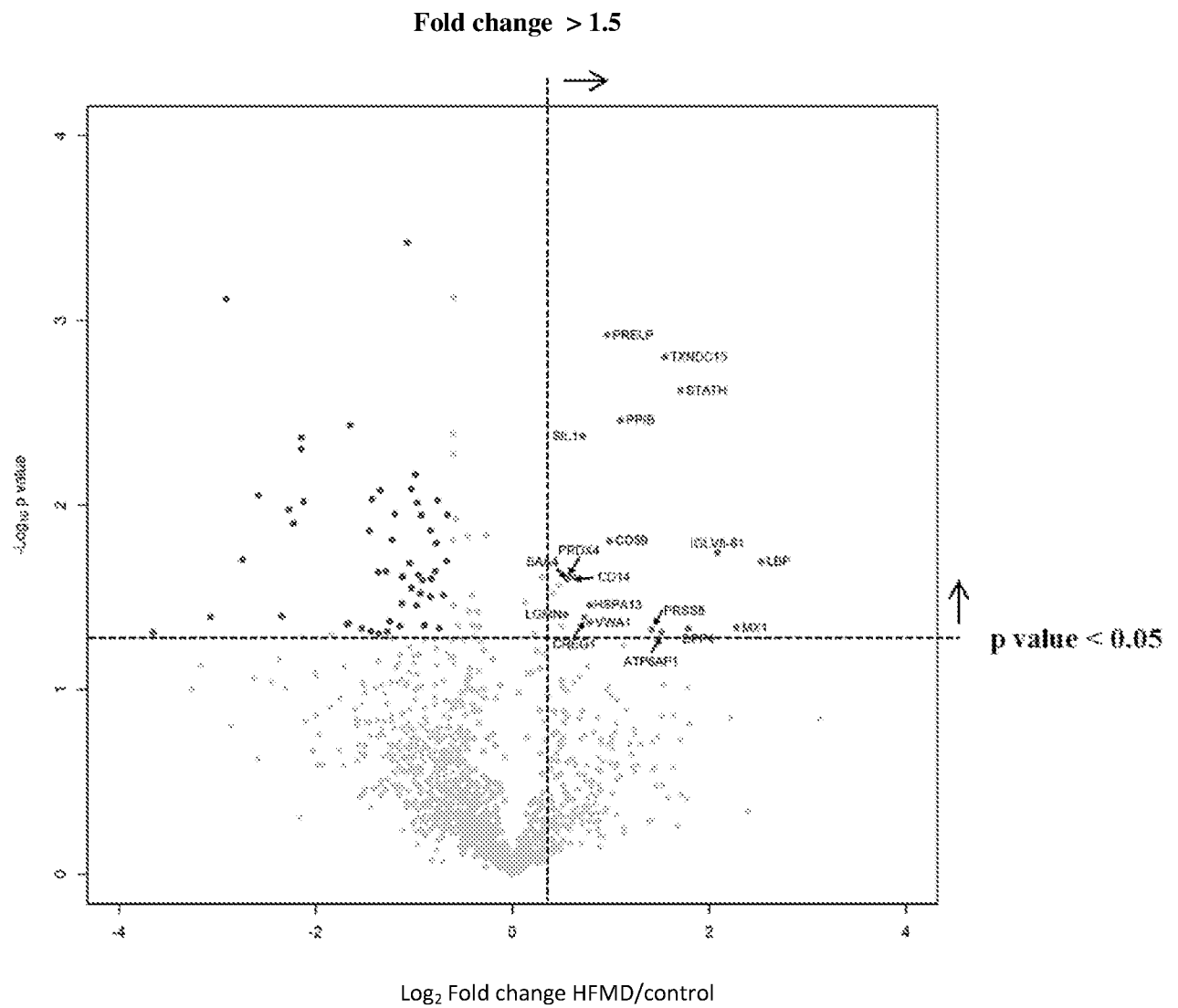


Figure 1

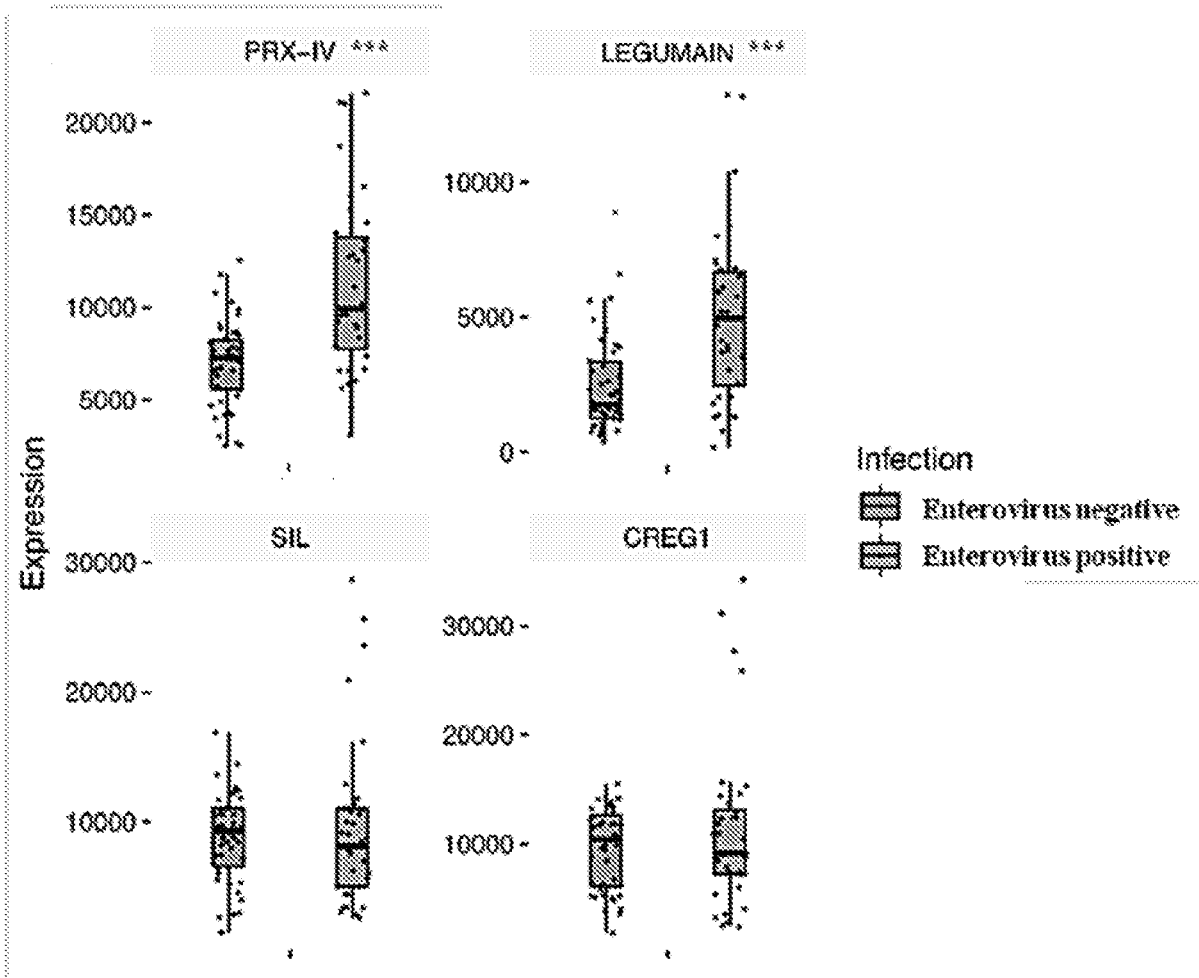


Figure 2

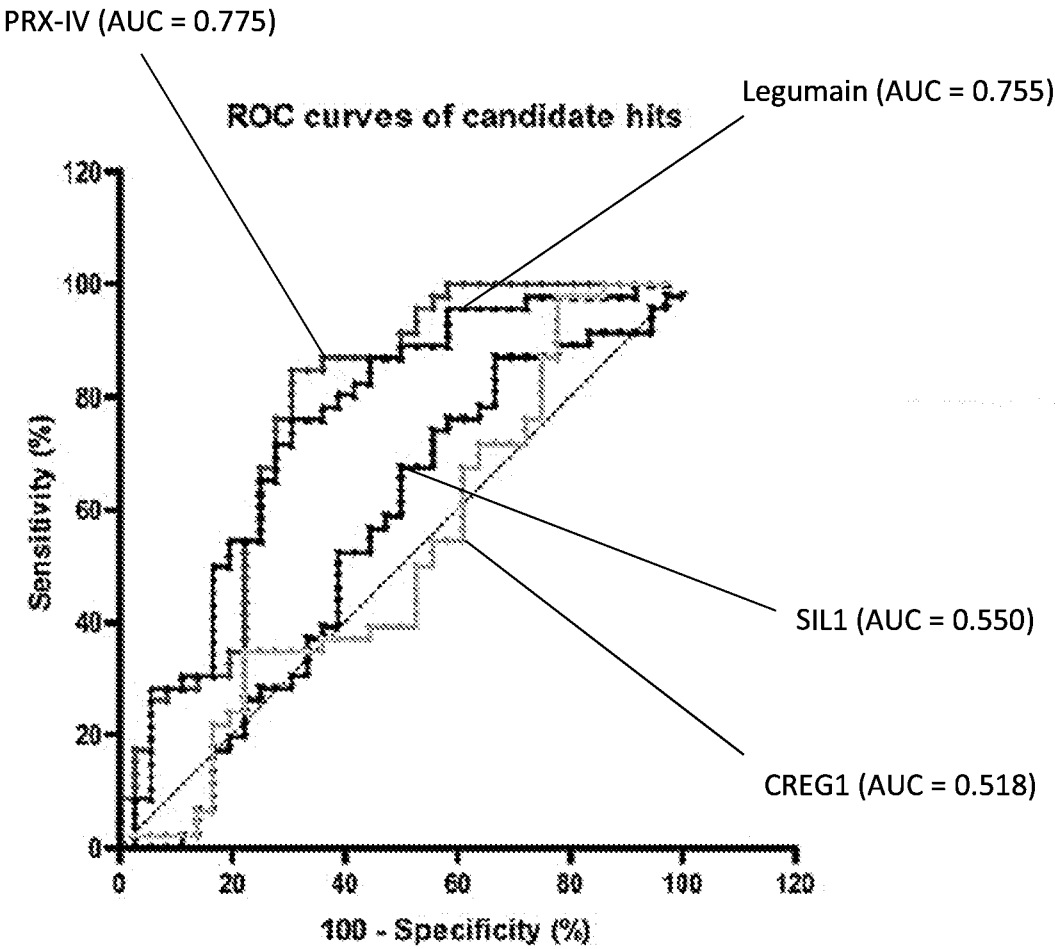


Figure 3

Protein IDs	Protein names	Gene names	n. ratio H/L (D64)	n. ratio H/L (D66)	n. ratio H/L (D68)	Log n. ratio H/L (D64)	Log n. ratio H/L (D66)	Log n. ratio H/L (D68)	P value	Average Log fold change	Average fold change
P18428	Lipopolysaccharide-binding protein	LBP	6.65	3.54	8.24	2.73	1.82	3.04	0.02	2.53	3.3
P20591	Interferon-induced GTP-binding protein Mx1	MX1	4.17	2.88	9.51	2.06	1.53	3.25	0.05	2.28	4.3
A0A075B6I0			6.22	3.82	3.21	2.64	1.94	1.68	0.02	2.09	4.2
P27487	Dipeptidyl peptidase 4	DPP4	1.99	4.42	4.74	0.990	2.14	2.24	0.05	1.79	3.5
P02808	Statherin	STATH	3.26	2.97	3.63	1.70	1.57	1.86	0.00	1.71	3.3
Q96J42	Thioredoxin domain-containing protein 15	TXNDC15	2.70	3.01	3.10	1.43	1.59	1.63	0.00	1.55	2.9
Q15904	V-type proton ATPase subunit S1	ATP6AP1	2.72	4.45	1.93	1.44	2.15	0.948	0.05	1.51	2.9
Q16651	Prostasin	PRSS8	2.39	4.10	1.95	1.26	2.04	0.965	0.05	1.42	2.7
P23284	Peptidyl-prolyl cis-trans isomerase B	PPIB	2.34	2.02	2.08	1.23	1.01	1.06	0.00	1.10	2.1
E9PNW4	CD59 glycoprotein	CD59	2.21	1.67	2.12	1.15	0.743	1.08	0.02	0.991	2
P51888	Prolargin	PRELP	1.90	1.91	2.04	0.925	0.936	1.03	0.00	0.964	2

Figure 4

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O75629	Protein CREG1	CREG1	1.73	1.95	1.36	0.788	0.962	0.444	0.04	0.732	1.7
P48723	Heat shock 70 kDa protein 13	HSPA13	1.41	1.82	2.01	0.500	0.867	1.01	0.03	0.792	1.7
Q6PCB0	von Willebrand factor A domain-containing protein 1	VWA1	1.47	2.17	1.61	0.555	1.12	0.687	0.04	0.786	1.7
Q9H173	Nucleotide exchange factor SIL1	SIL1	1.54	1.65	1.72	0.626	0.724	0.786	0.00	0.712	1.6
A0A096LPE2	Serum amyloid A-4 protein	SAA4	1.45	1.65	1.33	0.540	0.720	0.410	0.03	0.557	1.5
P08571	Monocyte differentiation antigen CD14	CD14	1.36	1.72	1.54	0.444	0.786	0.620	0.02	0.617	1.5
Q13162	Peroxisomal protein 4	PRDX4	1.32	1.57	1.61	0.397	0.653	0.690	0.02	0.580	1.5
Q99538	Legumain	LGMN	1.66	1.27	1.46	0.728	0.346	0.549	0.04	0.541	1.5
P14314	Glucosidase 2 subunit beta	PRKCSH	0.674	0.656	0.576	-0.569	-0.607	-0.797	0.01	-0.658	0.6
O75083	WD repeat-containing protein 1	WDR1	0.553	0.667	0.681	-0.855	-0.585	-0.554	0.02	-0.665	0.6

Figure 4 (Continued)

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F8VUJ3	Polypeptide N-acetylglucosaminyl-transferase 4	POC1B-GALNT4	0.723	0.603	0.536	-0.467	-0.731	-0.899	0.03	-0.699	0.6
P63261	Actin, cytoplasmic 2	ACTG1	0.732	0.491	0.593	-0.450	-1.03	-0.754	0.05	-0.743	0.6
Q5T6W5	Heterogeneous nuclear ribonucleoprotein K	HNRNPK	0.559	0.655	0.563	-0.838	-0.611	-0.829	0.01	-0.759	0.6
P13010	X-ray repair cross-complementing protein 5	XRCC5	0.648	0.602	0.513	-0.627	-0.732	-0.963	0.02	-0.774	0.6
O43707	Alpha-actinin-4	ACTN4	0.529	0.541	0.686	-0.919	-0.887	-0.543	0.02	-0.783	0.6
B4DY09	Interleukin enhancer-binding factor 2	ILF2	0.589	0.473	0.647	-0.765	-1.08	-0.629	0.03	-0.824	0.6
P68032	Actin	ACTC1	0.679	0.473	0.556	-0.559	-1.08	-0.847	0.03	-0.829	0.6
Q2VIR3	Eukaryotic translation initiation factor 2 subunit 3	EIF2S3	0.627	0.572	0.496	-0.674	-0.806	-1.01	0.01	-0.831	0.6
Q9Y3D6	Mitochondrial fission 1 protein	FIS1	0.569	0.417	0.660	-0.813	-1.26	-0.599	0.04	-0.892	0.5

Figure 4 (Continued)

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D6R9P3	Heterogeneous nuclear ribonucleoprotein A/B	HNRNPAB	0.642	0.450	0.518	-0.639	-1.15	-0.949	0.03	-0.914	0.5
P11586	C-1-tetrahydrofolate synthase, cytoplasmic	MTHFD1	0.604	0.495	0.487	-0.728	-1.01	-1.04	0.01	-0.927	0.5
Q14764	Major vault protein	MVP	0.616	0.553	0.418	-0.698	-0.854	-1.26	0.03	-0.936	0.5
Q00610	Clathrin heavy chain 1	CLTC	0.420	0.576	0.571	-1.25	-0.795	-0.808	0.02	-0.951	0.5
Q01518	Adenylyl cyclase-associated protein 1	CAP1	0.480	0.585	0.478	-1.06	-0.773	-1.07	0.01	-0.965	0.5
Q9Y262	Eukaryotic translation initiation factor 3 subunit L	EIF3L	0.629	0.403	0.525	-0.670	-1.31	-0.930	0.04	-0.971	0.5
B7Z645	Heterogeneous nuclear ribonucleoprotein Q	SYNCRIP	0.450	0.532	0.536	-1.15	-0.911	-0.900	0.01	-0.988	0.5
P45974	Ubiquitin carboxyl-terminal hydrolase 5	USP5	0.445	0.424	0.626	-1.17	-1.24	-0.676	0.03	-1.03	0.5
Q9Y333	U6 snRNA-associated Sm-like protein LSM2	LSM2	0.476	0.557	0.448	-1.07	-0.845	-1.16	0.01	-1.03	0.5
Q9Y2Z0	Suppressor of G2 allele of SKP1 homolog	SUGT1	0.512	0.395	0.563	-0.964	-1.34	-0.829	0.02	-1.04	0.5

Figure 4 (Continued)

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Q9NYL9	Tropomodulin-3	TMOD3	0.491	0.469	0.471	-1.03	-1.09	-1.09	0.00	-1.07	0.5
O60763	General vesicular transport factor p115	USO1	0.350	0.581	0.477	-1.52	-0.785	-1.07	0.03	-1.12	0.5
P30101	Protein disulphide-isomerase A3	PDIA3	0.463	0.372	0.570	-1.11	-1.43	-0.811	0.02	-1.12	0.5
Q99460	26S proteasome non-ATPase regulatory subunit 1	PSMD1	0.556	0.321	0.522	-0.846	-1.64	-0.937	0.05	-1.14	0.5
Q16543	Hsp90 co-chaperone Cdc37	CDC37	0.518	0.386	0.417	-0.948	-1.37	-1.26	0.01	-1.19	0.4
E9PEZ3	Protein diaphanous homolog 1	DIAPH1	0.530	0.386	0.384	-0.917	-1.38	-1.38	0.02	-1.22	0.4
Q14166	Tubulin--tyrosine ligase-like protein 12	TTLL12	0.414	0.310	0.586	-1.27	-1.69	-0.772	0.04	-1.25	0.4
D6RD69	GTP-binding protein SAR1a/b	SAR1A/B	0.326	0.356	0.619	-1.62	-1.49	-0.693	0.05	-1.27	0.4
Q13838	RNA helicases DDX39A/B	DDX39A/B	0.532	0.389	0.334	-0.910	-1.36	-1.58	0.02	-1.29	0.4
P61981	14-3-3 protein gamma	YWHA3	0.350	0.466	0.378	-1.52	-1.10	-1.40	0.01	-1.34	0.4

Figure 4 (Continued)

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P27797	Calreticulin	CALR	0.384	0.305	0.505	-1.38	-1.71	-0.986	0.02	-1.36	0.4
Q07960	Rho GTPase-activating protein 1	ARHGAP1	0.263	0.403	0.560	-1.92	-1.31	-0.836	0.05	-1.36	0.4
O60784	Target of Myb protein 1	TOM1	0.366	0.443	0.318	-1.45	-1.18	-1.65	0.01	-1.43	0.4
P48047	ATP synthase subunit O, mitochondrial	ATP5O	0.392	0.242	0.530	-1.35	-2.05	-0.917	0.05	-1.44	0.4
Q9NSC7	Alpha-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1	ST6GALNAC1	0.335	0.315	0.464	-1.58	-1.67	-1.11	0.01	-1.45	0.4
P84077	ADP-ribosylation factor 1/3	ARF1/3	0.317	0.241	0.543	-1.66	-2.05	-0.882	0.05	-1.53	0.3
Q16270	Insulin-like growth factor-binding protein 7	IGFBP7	0.365	0.308	0.290	-1.45	-1.70	-1.79	0.00	-1.65	0.3
F8W651	Coatmer subunit zeta-1	COPZ1	0.318	0.204	0.484	-1.65	-2.30	-1.05	0.04	-1.67	0.3
Q8WXI7	Mucin-16	MUC16	0.484	0.313	0.202	-1.05	-1.68	-2.31	0.04	-1.68	0.3
H0YF78		VPS13A	0.287	0.175	0.242	-1.80	-2.52	-2.05	0.01	-2.12	0.2

Figure 4 (Continued)

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P12277	Creatine kinase B-type	CKB	0.211	0.278	0.197	-2.25	-1.85	-2.34	0.00	-2.15	0.2
P22695	Cytochrome b-c1 complex subunit 2, mitochondrial	UQCRC2	0.189	0.230	0.265	-2.40	-2.12	-1.92	0.00	-2.15	0.2
B5MCP9	40S ribosomal protein S7	RPS7	0.300	0.167	0.196	-1.74	-2.58	-2.35	0.01	-2.22	0.2
P25705	ATP synthase subunit alpha, mitochondrial	ATP5A1	0.169	0.184	0.286	-2.56	-2.45	-1.80	0.01	-2.27	0.2
P01861	Ig gamma-4 chain C region	IGHG4	0.115	0.364	0.183	-3.13	-1.46	-2.45	0.04	-2.34	0.2
Q05707	Collagen alpha-1(XIV) chain	COL14A1	0.132	0.232	0.152	-2.93	-2.11	-2.71	0.01	-2.58	0.2
E5RI99	60S ribosomal protein L30	RPL30	0.257	0.119	0.109	-1.96	-3.07	-3.20	0.02	-2.74	0.1
P06576	ATP synthase subunit beta	ATP5B	0.144	0.137	0.119	-2.80	-2.86	-3.07	0.00	-2.91	0.1
Q8IVF2	Protein AHNAK2	AHNAK2	0.218	0.154	0.050	-2.20	-2.70	-4.31	0.04	-3.07	0.1
P08118	Beta-microseminoprotein	MSMB	0.222	0.076	0.030	-2.17	-3.71	-5.08	0.05	-3.65	0.1

Figure 4 (Continued)

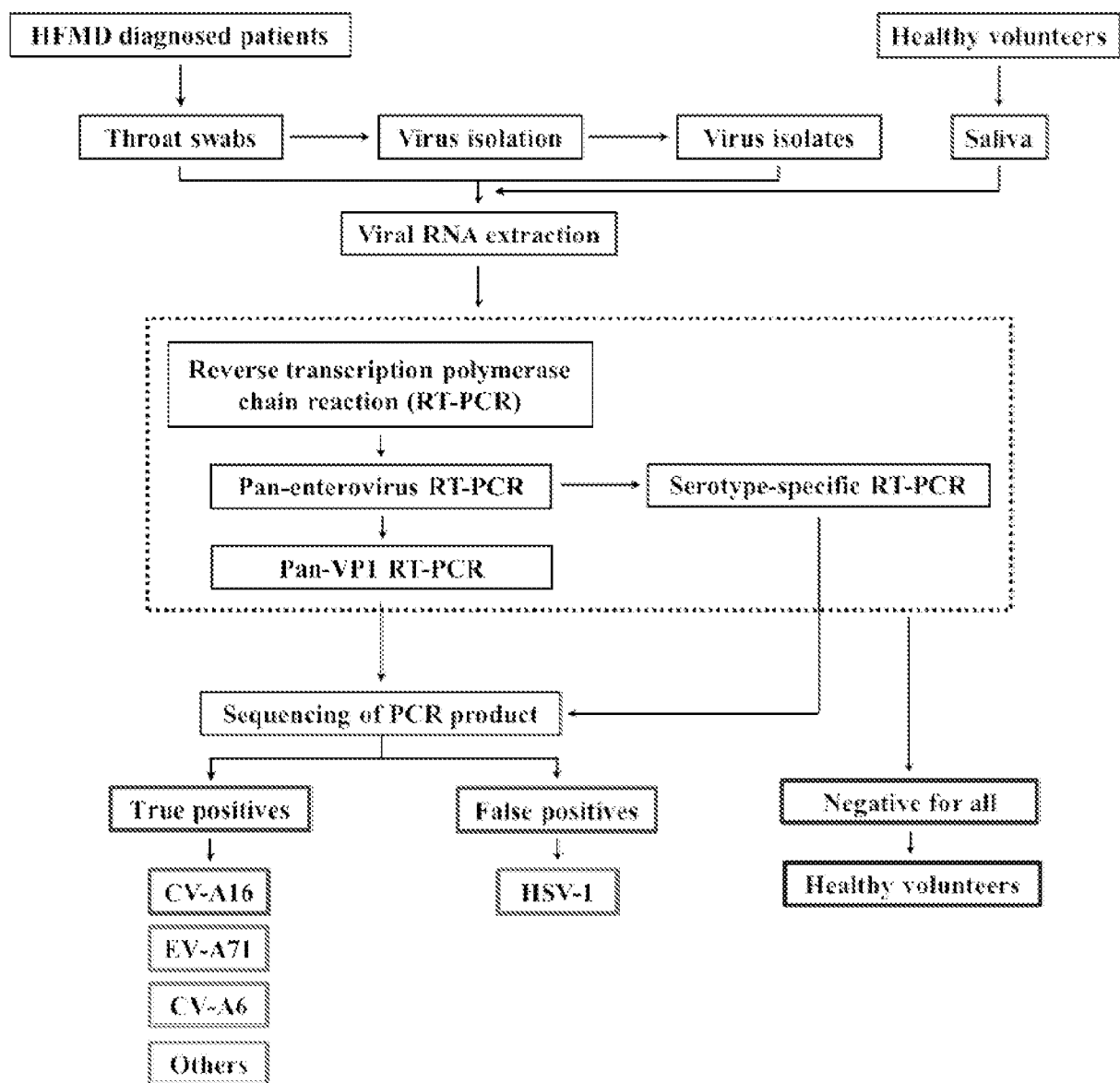


Figure 5

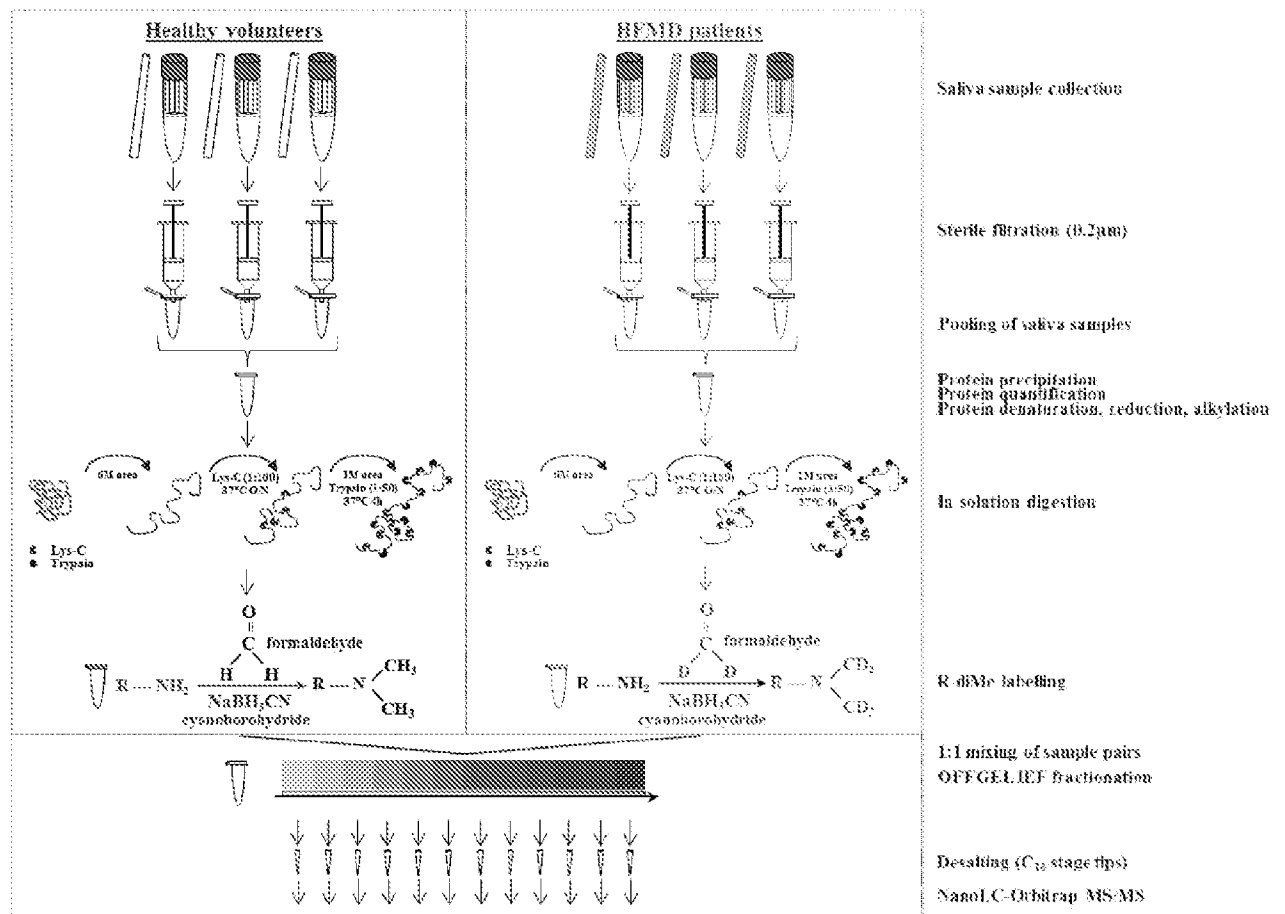


Figure 6

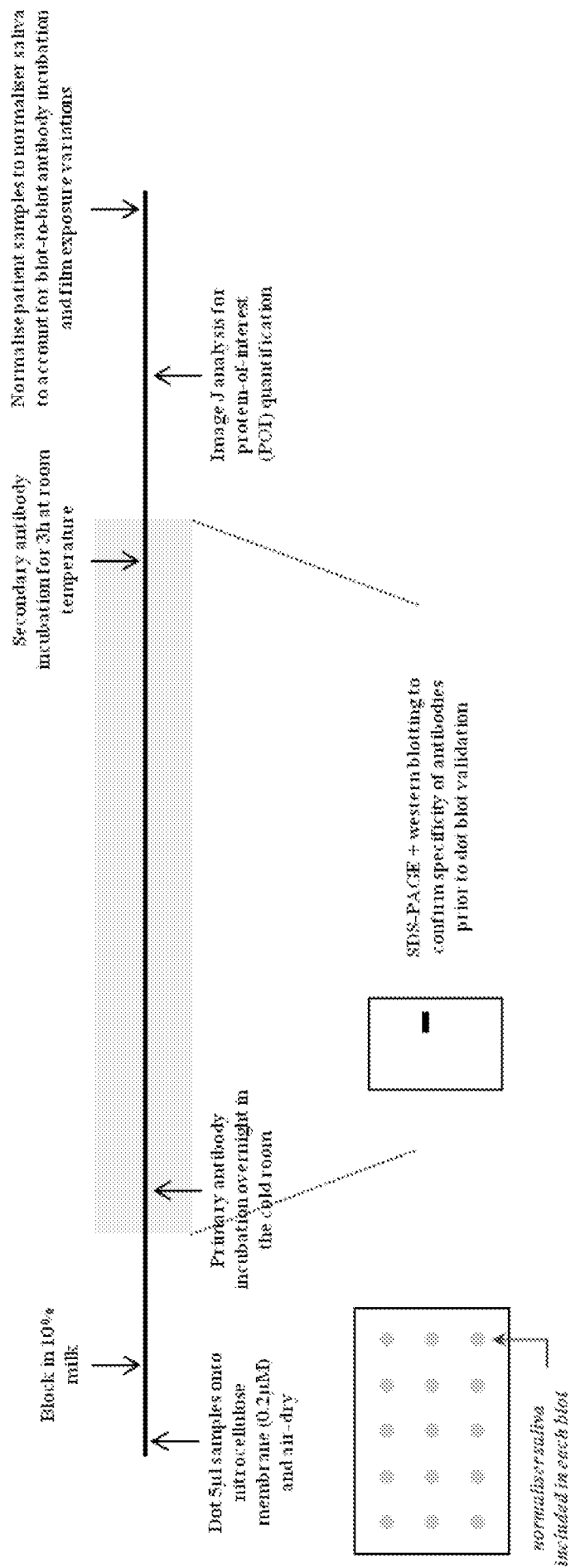


Figure 7

Table 1 | Assessment of candidate salivary biomarkers.

Salivary protein	Cases	Minimum dot intensity	Median dot intensity	Maximum dot intensity	AUC (of ROC)*
PRX-IV	HFMD	3,102	9,927	21,600	0.775
	Healthy	2,504	7,268	12,550	
Legumain	HFMD	178.2	4,965	13,240	0.755
	Healthy	399.6	1,765	8,874	
SIL1	HFMD	2,603	8,127	28,670	0.550
	Healthy	1,518	9,286	16,890	
CREG1	HFMD	2,507	9,176	34,250	0.518
	Healthy	1,896	10,420	15,510	

*AUC measures the discriminative power of the prospective biomarker, where an AUC of 1 indicates a perfect diagnostic test while an AUC of 0.5 indicates a non-discriminating diagnostic

Figure 8

Table 2 | Assessment of combinatory candidate salivary biomarkers using radial basis function kernel function analyses.

Combinations	AUC of ROC
PRX-IV + legumain	0.625
PRX-IV + SIL1	0.813
PRX-IV + CREG1	0.750
Legumain + SIL1	0.688
Legumain + CREG1	0.563
PRX-IV + legumain +	0.688
PRX-IV + SIL1 +	0.813
Legumain + SIL1 +	0.688
PRX-IV + legumain +	0.750

Figure 9