

Supplemental Information

TRAINING/TEST DATA SETS

In machine learning 1 data set, training is used to build the model with the computer program. The test data set is used to evaluate the resultant model.

LEAST ANGLE REGRESSION METHOD

With least angle regression, features are selected 1 at a time and evaluated for

predictive performance and goodness of fit at each step. If the new feature improved the performance of the model, it was retained in the panel. If the new feature failed to improve the model's performance, it was removed, and the next-best feature was used. This process repeats until there are no features remaining that satisfy the algorithm's goodness-of-fit requirements. From this

process, the optimal starting panel was chosen at 1 step beyond the point at which the performance of the model plateaued. If the feature with the least predictive contribution had a *P* value $>.05$ via logistic regression, it was removed, and the model rebuilt. This process was repeated until all remaining features were statistically significant.

SUPPLEMENTAL TABLE 4 Initial Discovery Panel With 11 Analytes Included for Testing the Biomarker Panel Highlighted in Gray

Variable	KD	Control	P
α -1-microglobulin (ug/mL)	9.2 (7.325–10.75)	9.55 (7.975–12)	.065
α -1-antitrypsin (mg/mL)	3.3 (3–3.675)	2.7 (2.2–3.225)	<.001
Angiopoietin-1 (ng/mL)	34.5 (23.5–44.75)	19 (15–29)	<.001
Apolipoprotein A-I (ug/mL)	25.5 (13.25–57.75)	52.5 (20–141)	.005
β -2-microglobulin (ug/mL)	2.2 (1.725–2.775)	2.2 (1.7–3)	.563
Brain-derived neurotrophic factor (ng/mL)	6.55 (4.425–9.975)	7.95 (5.575–12)	.082
C-reactive protein (ug/mL)	124 (72.75–209.25)	4.65 (2.7–15.25)	<.001
CD163 (ng/mL)	392 (272.5–502)	369.5 (264.5–552.25)	.844
CD5 antigen-like (ng/mL)	1820 (1450–2212.5)	3180 (2197.5–4375)	<.001
Clusterin (ug/mL)	197 (161.5–225)	248 (208–317)	<.001
Complement C3 (mg/mL)	1.35 (1.125–1.675)	1.3 (1.1–1.6)	.507
Cystatin-C (ng/mL)	913.5 (760.25–1067.5)	827 (709.25–965)	.05
Eotaxin-1 (pg/mL)	131 (99–181)	168 (102–264)	.068
Factor VII (ng/mL)	269 (205.5–346.5)	390 (297.25–507.25)	<.001
Fibrinogen (mg/mL)	0.023 (0.014–0.034)	4.75 (0.56–6.6)	<.001
Free T4 (ng/dL)	1.26 (1.07–1.385)	1.21 (1.07–1.4)	.716
Growth/differentiation factor 15 (ng/mL)	0.35 (0.25–0.552)	0.32 (0.19–0.492)	.168
Haptoglobin (mg/mL)	3.85 (2.625–5.725)	2.35 (1.2–3.6)	<.001
Immunoglobulin A (mg/mL)	1 (0.677–1.7)	1.3 (0.88–1.9)	.124
Immunoglobulin M (mg/mL)	2.35 (1.9–3.375)	2.7 (2–3.225)	.446
Intercellular adhesion molecule 1 (ng/mL)	182 (145.5–222.75)	182 (147–239.5)	.288
Interleukin-1 α (ng/mL)	0.001 (0.001–0.001)	0.001 (0.001–0.001)	.155
Interleukin-1 β (pg/mL)	2.95 (2.95–6.9)	9.6 (7.3–12)	<.001
Interleukin-1 receptor antagonist (pg/mL)	475 (272–917)	472.5 (301.75–816)	.921
Interleukin-12 subunit p40 (ng/mL)	0.55 (0.43–0.67)	0.78 (0.608–0.978)	<.001
Interleukin-12 subunit p70 (pg/mL)	21.5 (21.5–21.5)	21.5 (21.5–21.5)	1.00
Interleukin-17 (pg/mL)	6.4 (3.125–13.5)	3.1 (1.3–4)	<.001
Kidney injury molecule-1 (ng/mL)	0.06 (0.06–0.06)	0.06 (0.06–0.06)	.051
Matrix metalloproteinase-3 (ng/mL)	6 (3.8–9.475)	2 (1.3–3.725)	<.001
Matrix metalloproteinase-9 (ng/mL)	36 (16–46)	309.5 (57–639.5)	<.001
Midkine (ng/mL)	16 (13.25–21.75)	17 (13.75–23.25)	.47
N-terminal prohormone of brain natriuretic peptide (pg/mL)	639.5 (198.5–1722.5)	116.5 (43.5–248.75)	<.001
Osteocalcin (ng/mL)	38 (28.25–51)	73 (52–109.25)	<.001
Osteopontin (ng/mL)	48 (32–69.75)	105.5 (54–151)	<.001
P-selectin (ng/mL)	117.5 (99.5–146.75)	118.5 (91.75–167)	.967
Periostin (ng/mL)	297 (256–338)	319.5 (244–392.5)	.187
Serum amyloid P-component (ug/mL)	13 (12–17)	17 (13–22)	.002
ST2 (ng/mL)	10.5 (5.7–21.5)	9.95 (6.2–20.25)	.853
Stem cell factor (pg/mL)	352 (280–480.5)	425 (327–548)	.016
Thyroid hormone uptake (%)	34 (32–36)	31 (30–33.75)	<.001
Thyroxine-binding globulin (ug/mL)	45 (38.25–50.75)	60.5 (49.75–69)	<.001
Thyroid stimulating hormone (uIU/mL)	1.295 (0.937–2.12)	1.38 (0.931–1.99)	.786
Vascular endothelial growth factor (pg/mL)	494 (341.25–751.25)	381.5 (256–543)	.003
Vitamin D-binding protein (ug/mL)	205 (160–257)	245.5 (171.5–307)	.023
von Willebrand factor (ug/mL)	225 (183–301.5)	239 (149–307)	.66

Values are median (interquartile range). ST2, Suppression of Tumorigenicity 2 protein.

SUPPLEMENTAL TABLE 5 Statistical Comparison by Sample Type (Plasma vs Serum)

Biomarker	Unadjusted <i>P</i> Value	FDR-Adjusted <i>Q</i> -Value	Below Effect Threshold
α -1-antitrypsin (mg/mL)	.744	0.973	
α -1-microglobulin (ug/mL)	.265	0.564	
Angiopoietin-1 (ng/mL)	.002	0.011	TRUE
Apolipoprotein (a) (ug/mL)	.914	0.98	
β -2-microglobulin (ug/mL)	.521	0.85	
Brain-derived neurotrophic factor (ng/mL)	.011	0.04	TRUE
C-reactive protein (ug/mL)	.092	0.243	
CD163 (ng/mL)	.765	0.973	
CD5 antigen-like (ng/mL)	.006	0.028	TRUE
Clusterin (ug/mL)	.022	0.066	TRUE
Complement C3 (mg/mL)	.276	0.564	
Cystatin-C (ng/mL)	.392	0.735	
Eotaxin-1 (pg/mL)	<.001	<.001	TRUE
Factor VII (ng/mL)	<.001	<.001	TRUE
Fibrinogen (mg/mL)	<.001	<.001	TRUE
Free T4 (ng/dL)	.112	0.28	
Growth differentiation factor 15 (ng/mL)	.667	0.968	
Haptoglobin (mg/mL)	.884	0.973	
Immunoglobulin A (mg/mL)	.842	0.973	
Immunoglobulin M (mg/mL)	.764	0.973	
Intercellular adhesion molecule 1 (ng/mL)	.664	0.968	
Interleukin-1 α (ng/mL)	.21	0.471	
Interleukin-1 β (pg/mL)	<.001	0.003	TRUE
Interleukin-1 receptor antagonist (pg/mL)	.447	0.774	
Interleukin-12 subunit p40 (ng/mL)	.779	0.973	
Interleukin-12 subunit p70 (pg/mL)	1.00	1.00	
Interleukin-17 (pg/mL)	.075	0.21	
Kidney injury molecule-1 (ng/mL)	.208	0.471	
Matrix metalloproteinase-3 (ng/mL)	<.001	<.001	TRUE
Matrix metalloproteinase-9 (ng/mL)	<.001	<.001	TRUE
Midkine (ng/mL)	.887	0.973	
N-terminal prohormone of brain natriuretic peptide (pg/mL)	.418	0.752	
Osteocalcin (ng/mL)	.007	0.031	TRUE
Osteopontin (ng/mL)	<.001	<.001	TRUE
P-selectin (ng/mL)	.002	0.011	TRUE
Periostin (ng/mL)	.966	0.988	
Serum amyloid P-component (ug/mL)	.018	0.057	TRUE
ST2 (ng/mL)	.529	0.85	
Stem cell factor (pg/mL)	.018	0.057	TRUE
Thyroxine-binding globulin (ug/mL)	.963	0.988	
Thyroid stimulating hormone (uIU/mL)	.817	0.973	
Thyroid hormone update (%)	.701	0.973	
Vascular endothelial growth factor (pg/mL)	.863	0.973	
Vitamin D-binding protein (ug/mL)	.381	0.735	
von Willebrand factor (ug/mL)	.599	0.929	

All biomarkers with a false discovery rate of >.02 were excluded from our analysis and marked as TRUE in Below Effect Threshold column. ST2, Suppression of Tumorigenicity 2 protein.