

Supplements

Supplemental Table S1: Hyperparameters search space for eXtreme Gradient Boosting.

Hyperparameter	Description	Experimental search space
n_estimators	Number of trees	[50, 100, 150]
max_depth	Maximum depth of each tree	[3, 6, 9]
eta	Learning rate	[0.05, 0.1, 0.3, 0.6]
subsample	Subsample ratio of the training instance	[0.9, 1]

Supplemental Table S2: Metabolites missing data frequency.

	Controls	Cases
Carnitine C12:0	28	33
13-HOTrE	25	24
Prostaglandin-F1a	24	31
9-cis 13-cis-methyl-retinoate	19	37
Cytidine	19	17
9-oxo-ODE	13	8
Hydroxyphenyllactic acid	11	9
Thromboxane-B2	9	4
PCae(22:3)	8	12
Choline phosphate	7	4
Methylmalonic acid	5	2
Dodecanedioic acid	4	4
S-adenosylhomocysteine	5	8
3-phenylpropionic acid	3	6
Adenine	3	5
9(S)-HODE	3	0
3-hydroxy-DL-kynurenine	2	4
Eicosenoic acid	2	1
Hydroxydodecanoic acid	1	4
Indoxyl sulfate	1	2
Caproic acid@9.79-qpneg	1	1
Hexacosanoic acid	1	1
N-acetylglutamine	1	1
Ribose-5-phosphate	1	1
Guanosine	0	2
Taurine	0	1
Stearic acid	0	2
Spermine	0	1
Spermidine	0	1

	Controls	Cases
S-adenosylmethionine	0	4
Putrescine	0	1
Benzoic acid	0	1
Heptadecatrienoic acid	0	1
PCae(20:3)	0	2
PCae(12:0)	0	1
Orotic acid	0	1
Ornithine	0	1
N8-acetylspermidine	0	1
N1-acetylspermidine	0	1
N-acetylputrescine	0	1
N-acetylglutamic acid	0	1
Carnitine C5:0	0	1
PCae(20:5)	0	3

Supplemental Table S3: Metabolites excluded before analyses.

Step	Metabolites excluded
80% rule exclusion	Prostaglandin-F1a 9-cis 13-cis-methyl-retinoate 13-HOTrE Cytidine Carnitine C12:0
Multiple very strongly correlated	5-aminovaleric acid Carnitine C14:2 Heptadecenoic acid 2-oxovaleric acid 2-methylbutyric acid 12(S)-HETE Linoleic acid 9(S)-HODE Ketoisocaproic acid Palmitic acid 4-hydroxy-phenyllactic acid Ketoisovaleric acid Isobutyric acid 9-oxo-ODE
Pairwise very strongly correlated	3-hydroxybutyric acid Indoxyl sulfate 4-hydroxymandelic acid Alpha-tocopherol Caprylic acid Carnitine C10:0 Carnitine C16:0 Eicosenoic acid Gamma-glutamylleucine Hydroxyphenyllactic acid N8-acetylspermidine PCae(15:0) PCae(18:0) Ribose Tyrosomuricholic acid

Supplemental Table S4: Metabolites preselected PLS-DA with VIP>1.2. Metabolites marked with * represent those available also in the external validation dataset.

Metabolites
2-oxoglutaric acid*
3-hydroxyisovaleric acid*
3-methylglutarylcarnitine*
3-methylhistidine*
5-hydroxy-DL-tryptophan
9,10,13-TriHOME
Acetoacetic acid*
Allantoin*
Arabinose*
Arginine*
Capric acid*
Caproic acid*
Carnitine C12:1*
Cholesterol*
Choline*
Citrulline*
Dodecenoic acid*
Erythritol*
Fructose*
Mannose*
Gamma-glutamyllysine
Gamma-glutamylthreonine*
Glucuronic acid*
Glutamic acid*
Glycerol-3-phosphate*
Glycochenodeoxycholic acid*
Glycylglycine
Guanosine*
Hexacosanoic acid
Homoserine
Hyochoic acid*
Hypotaurine*
Inosine*
Isovaleric acid*
Methionine*
Methyl-indole-3-acetic acid
N-acetylglutamic acid*
N-acetylputrescine*
PCae(18:3)
PCae(20:3)

PCae(20:5)
PCae(22:5)
PCee(16:0)
Phosphoric acid*
Propionic acid
Putrescine
Pyruvic acid*
Quinic acid*
S-adenosylhomocysteine*
S-adenosylmethionine
Shikimic acid
Spermidine*
Spermine
Taurochenodeoxycholic acid*
Trigonelline*
Uracil*