

Table SI. m/z of identified metabolites.

No.	MRM	m/z
1	Urea_pos	61.000
2	Glycine_pos	76.000
3	Trimethylamine N-oxide_pos	76.100
4	Cysteamine_pos	78.000
5	Sarcosine_pos	90.000
6	Alanine_pos	90.100
7	Betaine aldehyde_pos	102.000
8	Dimethylglycine_pos	104.070
9	3-Aminoisobutyric acid_pos	104.100
10	Serine_pos	106.000
11	Creatinine_pos	114.100
12	Proline_pos	116.100
13	Guanidinoacetic acid_pos	118.000
14	Indole_pos	118.000
15	5-Aminopentanoic acid_pos	118.090

16	Betaine_pos	118.100
17	Valine_pos	118.100
18	Threonine_pos	120.000
19	L-Homoserine_pos	120.070
20	Purine_pos	121.050
21	Vitamin-B3(Nicotinamide)_pos	123.000
22	Vitamin-B3(Nicotinic acid)_pos	124.000
23	5-Amino-4-carbamoylimidazole (AICA)_pos	127.060
24	L-Pipecolic acid_pos	130.090
25	3-Methyl-2-oxovaleric acid_pos	131.000
26	5-Aminolevulinic acid_pos	132.070
27	Creatine_pos	132.080
28	Leucine_pos	132.110
29	Isoleucine_pos	132.120
30	Ureidopropionic acid_pos	133.060
31	Asparagine_pos	133.100
32	Ornithine_pos	133.100

33	Aspartate_pos	134.000
34	Methylcysteine_pos	136.020
35	Tyramine_pos	138.200
36	Urocanic acid_pos	139.050
37	O-Phosphoethanolamine_pos	142.000
38	Isobutyrylglycine_pos	146.080
39	4-Guanidinobutyric acid_pos	146.100
40	Acetylcholine_pos	147.000
41	Glutamine_pos	147.000
42	Lysine_pos	147.100
43	Na-Methyl-L-ornithine monohydrochloride_pos	147.101
44	Glutamate_pos	148.100
45	Methionine_pos	150.100
46	2-Hydroxyadenine_pos	152.060
47	N1-Methyl-2-pyridone-5-carboxamide_pos	153.070
48	3-Hydroxyanthranilic acid_pos	154.100
49	Histidine_pos	156.100

50	DL-2-Aminooctanoic acid_pos	160.140
51	Carnitine-C0_pos	162.100
52	1,5-anhydroglucitol_pos	165.000
53	7-methylguanine_pos	166.000
54	L-Methionine sulfoxide_pos	166.060
55	Phenylalanine_pos	166.100
56	Hordeine_pos	166.130
57	1-Methylxanthine_pos	167.060
58	3-methoxytyramine (3-MT)_pos	168.100
59	3-Methylhistidine_pos	170.200
60	1-Methylhistidine_pos	170.210
61	N6-formyl_pos	175.100
62	Serotonin_pos	177.100
63	Glucosamine_pos	180.000
64	Nicotinuric acid_pos	181.060
65	Tyrosine_pos	182.100
66	N-Acetylglutamine_pos	189.090

67	Homoarginine_pos	189.100
68	N6-acetyl lysine_pos	189.200
69	5-Methoxytryptamine_pos	191.120
70	5-Hydroxyindoleacetic acid_pos	192.300
71	Dimethyl-L-arginine_pos	203.000
72	NG,NG-Dimethyl-L-arginine (ADMA)_pos	203.150
73	Carnitine-C2_pos	204.100
74	CML_pos	205.100
75	Tryptophan_pos	205.100
76	GALA_pos	205.200
77	N-Acetyl-L-phenylalanine_pos	208.100
78	L-Kynurenine_pos	209.090
79	N-alpha-Acetylarginine_pos	217.120
80	CEL_pos	219.100
81	L-Abrine_pos	219.120
82	N6-lactoyl_pos	219.200
83	N6-oxalyl_pos	219.400

84	Carnitine-C4_pos	232.200
85	Sepiapterin_pos	238.100
86	Cystine_pos	241.300
87	Carnitine-C5:1_pos	244.200
88	Tiglylcarnitine_pos	244.300
89	Vitamin-B7(Biotin)_pos	245.100
90	Carnitine-C5_pos	246.200
91	Isovalerylcarnitine_pos	246.300
92	CEA_pos	247.100
93	gamma-L-Glutamyl-L-valine_pos	247.130
94	Carnitine-C3DC_pos	248.100
95	Carnitine-C4OH_pos	248.101
96	Glycerophosphocholine_pos	258.120
97	3-Methyluridine_pos	259.100
98	Hexanoylcarnitine_pos	260.170
99	Carnitine-C6_pos	260.200
100	Carnitine-C4DC_pos	262.100

101	Carnitine-C5OH_pos	262.200
102	Vitamin-B1(Thiamine)_pos	265.000
103	N6-threonyl_pos	265.200
104	Adenosine_pos	268.110
105	Inosine_pos	269.090
106	3-Hydroxyhexanoylcarnitine_pos	276.170
107	Saccharopine_pos	277.000
108	gamma-Glutamyl-L-methionine_pos	279.100
109	N4-Acetylcytidine_pos	286.110
110	Carnitine-C8:1_pos	286.200
111	Carnitine-C8_pos	288.200
112	gamma-L-Glutamyl-L-phenylalanine_pos	295.130
113	5'-Methylthioadenosine_pos	298.100
114	7-methylguanosine_pos	298.120
115	N2,N2-Dimethylguanosine_pos	312.130
116	Carnitine-C10:2_pos	312.200
117	Carnitine-C10:1_pos	314.100

118	Carnitine-C10_pos	316.100
119	UMP (Uridine 5'-monophosphate)_pos	325.100
120	N-oleoylethanolamine_pos	326.300
121	cAMP_pos	330.100
122	17-OH-Progesterone_pos	331.200
123	Deoxyadenosine monophosphate (dAMP)_pos	332.080
124	Carnitine-C10 OH_pos	332.200
125	GOLA_pos	333.200
126	Carnitine-C12:1_pos	342.300
127	Carnitine-C12_pos	344.300
128	Corticosterone_pos	347.000
129	Cortexolone_pos	347.500
130	Cortisol_pos	363.200
131	Carnitine-C14:2_pos	368.300
132	3, 5-Tetradecadiencarnitine_pos	368.500
133	Carnitine-C14:1_pos	370.300
134	Carnitine-C14_pos	372.300

135	Vitamin-B2(Riboflavin)_pos	377.000
136	S-Lactoylglutathione_pos	380.110
137	Carnitine-C14OH_pos	388.300
138	Carnitine-C16:1_pos	398.300
139	1,25-Dihydroxyvitamin D3_pos	399.300
140	Carnitine-C16_pos	400.300
141	Carnitine-C18:2_pos	424.300
142	Carnitine-C18:1_pos	426.400
143	Carnitine-C18_pos	428.400
144	Lanosterin_pos	444.000
145	DG(16:0/18:3)_pos	591.500
146	DG(16:1/18:2)_pos	591.500
147	DG(16:0/20:5)_pos	615.400
148	DG(16:0/20:4)_pos	617.500
149	DG(18:1/18:1)_pos	621.400
150	DG(16:0/22:6)_pos	641.500
151	DhCer d18:0/24:0_pos	652.900

152	Methylcobalamin_pos	673.000
153	SM 30:1;4_pos	679.500
154	SM 32:2;3_pos	689.600
155	SM 32:1;4_pos	707.600
156	SM 34:1;3_pos	719.500
157	SM 34:0;3_pos	721.600
158	SM 36:0;2_pos	733.600
159	SM 34:1;4_pos	735.600
160	SM 36:3;3_pos	743.500
161	SM 36:2;3_pos	745.700
162	SM 38:1;2_pos	759.600
163	SM 38:0;2_pos	761.600
164	SM 38:2;3_pos	773.600
165	L-Thyroxine(T4)_pos	777.700
166	SM 40:1;2_pos	787.700
167	SM 40:0;2_pos	789.600
168	SM 40:4;3_pos	797.600

169	SM 40:3;3_pos	799.700
170	SM 40:2;3_pos	801.700
171	SM 42:3;2_pos	811.600
172	SM 42:2;2_pos	813.700
173	SM 42:1;2_pos	815.700
174	BMP(18:1/22:6)_pos	838.600
175	SM 44:1;2_pos	843.700
176	SM 44:0;3_pos	861.600
177	TG54:8-FA22:6_pos	875.800
178	TG58:8-FA22:5_pos	931.800
179	Lactamide_pos	90.055
180	N,N-Dimethylaniline_pos	122.096
181	2-Acetylpyrazine_pos	123.055
182	2-Methylindole_pos	132.081
183	Thiazolidine-4-carboxylic acid_pos	134.027
184	2-Phenylacetamide_pos	136.076
185	3-FORMYLINDOLE_pos	146.060

186	DEOXYCARNITINE_pos	146.120
187	Oxypurinol_pos	153.041
188	N-Acetylhistamine_pos	154.097
189	Indole-3-acetaldehyde_pos	160.076
190	N-Methylglutamic acid_pos	162.076
191	Diphenylamine_pos	170.096
192	Caffeine_pos	195.088
193	Ala-Leu_pos	203.139
194	Serylleucine_pos	219.135
195	4-Hydroxybenzoylcholine_pos	224.128
196	Leucylleucine_pos	245.187
197	gamma-Glutamylleucine_pos	261.145
198	gamma-Glutamylglutamine_pos	276.119
199	Phenylalanylisoleucine_pos	279.172
200	Asp-Phe_pos	281.113
201	Oleamide_pos	282.279
202	Hexaethylene glycol_pos	283.175

203	gamma-Glutamyltyrosine_pos	311.124
204	Phytosphingosine_pos	318.299
205	N-Fructosyl phenylalanine_pos	328.139
206	Bilirubin_pos	585.271
207	Urobilinogen_pos	593.334
208	Acetic acid_neg	59.000
209	Malondialdehyde_neg	71.000
210	Propionic acid_neg	73.000
211	Pyruvate_neg	87.000
212	L-Lactate_neg	89.000
213	Acetoacetic acid_neg	101.000
214	2-Ketobutyric acid_neg	101.000
215	Malonic acid_neg	103.000
216	2-Hydroxybutanoic acid_neg	103.100
217	3-Hydroxybutanoic acid_neg	103.100
218	Glyceric acid_neg	105.020
219	p-Cresol_neg	107.000

220	Fumarate_neg	115.000
221	Alpha-ketoisovaleric acid_neg	115.050
222	2-Hydroxy-3-methylbutyric acid_neg	117.000
223	Succinic acid_neg	117.090
224	L-Threonine_neg	118.000
225	3-Methylthiopropionic acid_neg	119.020
226	Benzoic acid_neg	121.020
227	Taurine_neg	124.000
228	Pyroglutamic acid_neg	128.000
229	2-Ketohexanoic acid_neg	129.005
230	Ketoleucine_neg	129.060
231	N-Acetyl-L-alanine_neg	130.050
232	Methylsuccinic Acid_neg	131.000
233	Oxaloacetic acid_neg	131.010
234	Hydroxyisocaproic acid_neg	131.070
235	L-Malate_neg	133.000
236	Hypoxanthine_neg	135.000

237	p-Aminobenzoic acid_neg	136.050
238	2-Hydroxybenzoic acid_neg	137.000
239	p-Hydroxybenzoic acid_neg	137.020
240	a-Ketoglutarate_neg	145.000
241	Oxoglutaric acid_neg	145.020
242	Adipic acid_neg	145.100
243	N-acetylserine_neg	146.050
244	Citramalic acid_neg	147.001
245	L-2-Hydroxygluterate_neg	147.030
246	Mevalonic acid_neg	147.070
247	3-methylphenylacetic acid_neg	149.002
248	4-Ethyl-2-methoxyphenol_neg	151.000
249	p-Hydroxyphenylacetic acid_neg	151.040
250	Xanthine_neg	151.110
251	2-Pyrocatechuic acid_neg	153.000
252	2,3-Dihydroxybenzoic acid_neg	153.020
253	Tiglylglycine_neg	156.000

254	4,5-Dihydroorotic acid_neg	157.000
255	Allantoin_neg	157.000
256	L-Dihydroorotic acid_neg	157.020
257	Isovalerylglycine_neg	158.000
258	Aminoadipic acid_neg	160.000
259	Indole-3-carboxylic acid_neg	160.100
260	Phenyllactic acid_neg	165.050
261	Phosphoenolpyruvate_neg	167.000
262	Uric acid_neg	167.020
263	Dihydroxyacetone phosphate_neg	169.000
264	D-Glyceraldehyde 3-phosphate_neg	169.000
265	Glycerol 3-phosphate_neg	171.000
266	Aconitate_neg	173.000
267	Suberic Acid_neg	173.000
268	Shikimic acid_neg	173.150
269	Arginine_neg	173.200
270	N-Acetyl-L-aspartic acid_neg	174.000

271	Citrulline_neg	174.000
272	Allantoic acid_neg	175.000
273	2-Isopropylmalic acid_neg	175.002
274	N-Carbamoyl-L-aspartic acid_neg	175.030
275	Ureidosuccinic acid_neg	175.110
276	L-Ascorbic acid_neg	175.120
277	N-Formylmethionine_neg	176.040
278	Pyrophosphate_neg	176.800
279	Gluconolactone_neg	177.000
280	Hippuric acid_neg	178.200
281	Hexose Pool_neg	179.000
282	Fructose_neg	179.010
283	Inositol_neg	179.020
284	Glucose_neg	179.020
285	Mannose_neg	179.030
286	4-Hydroxyphenylpyruvic acid_neg	179.157
287	Myoinositol_neg	179.160

288	4-Hydroxyphenyllactic acid_neg	181.040
289	Homovanillic acid (HVA)_neg	181.200
290	4-Pyridoxic acid_neg	182.003
291	Azelaic acid_neg	187.100
292	Kynurenic acid_neg	188.000
293	N-Acetylglutamic acid_neg	188.100
294	Isocitrate_neg	191.000
295	Citrate_neg	191.000
296	D-Glucuronic acid_neg	193.030
297	p-Aminohippuric acid_neg	193.100
298	Salicyluric acid_neg	194.100
299	Gluconic acid_neg	195.000
300	Vanillomandelic acid (VMA)_neg	197.000
301	FA(12:0)_neg	199.100
302	Sebacic acid_neg	201.100
303	Cinnamoylglycine_neg	204.000
304	Xanthurenic acid_neg	204.001

305	2-Methylcitric acid_neg	205.000
306	Indoxyl sulfate_neg	212.000
307	Deoxyribose phosphate_neg	213.000
308	Gamma-glutamyl-Alanine_neg	217.000
309	Pantothenic acid_neg	218.000
310	5-Hydroxy-L-tryptophan_neg	219.000
311	FA(14:0)_neg	227.100
312	Alpha-D-Ribose 5-phosphate_neg	229.000
313	Thymidine_neg	241.089
314	Pseudouridine_neg	243.060
315	Uridine_neg	243.060
316	Pyridoxal 5-phosphate_neg	246.040
317	FA(16:2)_neg	251.100
318	Shikimate-3-phosphate_neg	253.100
319	FA(16:1)_neg	253.100
320	FA(16:0)_neg	255.100
321	Gamma-glutamyl-Isoleucine_neg	258.000

322	Gamma-glutamyl-Leucine_neg	258.100
323	Hexose Monophosphate Pool_neg	259.020
324	D-Glucose 1-phosphate_neg	259.020
325	D-Fructose 6-phosphate_neg	259.030
326	Phenylacetylglutamine_neg	263.100
327	2,3-Diphosphoglyceric acid_neg	265.100
328	Estradiol_neg	271.100
329	FA(18:3)_neg	277.200
330	FA(18:2)_neg	279.200
331	FA(18:1)_neg	281.200
332	Guanosine_neg	281.940
333	Xanthosine_neg	282.700
334	FA(18:0)_neg	283.200
335	Sedoheptulose monophosphate_neg	289.040
336	Argininosuccinic acid_neg	289.270
337	13S-hydroxyoctadecadienoic acid_neg	295.300
338	Eicosapentaenoic acid_neg	301.200

339	FA(20:4)_neg	303.200
340	FA(20:3)_neg	305.200
341	FA(20:2)_neg	307.200
342	FA(20:1)_neg	309.200
343	FA(20:0)_neg	311.200
344	Octulose-monophosphate_neg	319.000
345	8-HETE_neg	319.000
346	11,12-Epoxyeicosatrienoic acid_neg	319.000
347	12-HETE_neg	319.000
348	14,15-Epoxy-5,8,11-eicosatrienoic acid_neg	319.000
349	20-Hydroxyeicosatetraenoic acid_neg	319.000
350	11-HETE_neg	319.200
351	15-HETE_neg	319.460
352	Uridine 5-monophosphate_neg	323.100
353	FA(22:6)_neg	327.200
354	Cyclic adenosine monophosphate_neg	328.000
355	FA(22:3)_neg	333.300

356	LTB4_neg	335.000
357	FA(22:2)_neg	335.300
358	11,12-DiHETrE_neg	337.000
359	14,15-DHET_neg	337.000
360	FA(22:1)_neg	337.300
361	D-Fructose 1,6-bisphosphate_neg	338.990
362	Hexose Diphosphate Pool_neg	339.000
363	FA(22:0)_neg	339.300
364	Sucrose_neg	341.110
365	LXA4_neg	351.000
366	Prostaglandin D2_neg	351.000
367	13,14-Dihydro-15-keto PGF2a_neg	353.000
368	PGF2alpha_neg	353.000
369	Cortisone_neg	359.200
370	FA(24:4)_neg	359.300
371	FA(24:2)_neg	363.300
372	Orotidine monophosphate_neg	367.000

373	FA(24:0)_neg	367.300
374	Thromboxane B2_neg	369.300
375	Lithocholic acid_neg	375.300
376	Alloisolithocholic acid_neg	375.300
377	23-Nordeoxycholic acid_neg	377.300
378	Sphingosine 1-phosphate_neg	378.200
379	S-Adenosylhomocysteine_neg	383.117
380	Deoxycytidine diphosphate_neg	386.000
381	6-Ketolithocholic acid_neg	389.300
382	12-Ketolithocholic acid_neg	389.300
383	7-Ketolithocholic acid_neg	389.300
384	Apocholic acid_neg	389.300
385	Chenodeoxycholic acid_neg	391.300
386	Isodeoxycholic acid_neg	391.300
387	Deoxycholic acid_neg	391.600
388	Dioxolithocholic acid_neg	403.300
389	Allocholic acid_neg	407.300

390	beta-Muricholic acid_neg	407.300
391	alpha-Muricholic acid_neg	407.300
392	Hyochoholic acid_neg	407.300
393	Cholic acid_neg	407.600
394	Glyco-ursocholanic Acid_neg	416.317
395	Thiamine pyrophosphate_neg	423.100
396	3a,6a,7a,12a-Tetrahydroxy-5b-cholanoic acid(2a,3a,7a,12a-THBA)_neg	423.300
397	ADP_neg	426.000
398	Folic acid_neg	440.100
399	Chenodeoxyglycocholic acid_neg	448.300
400	Glycochenodeoxycholic acid(GCDCA)_neg	448.300
401	Glycodeoxycholic acid(GDCA)_neg	448.300
402	LPE(16:1)_neg	450.263
403	Lithocholic acid (LCA-S) sulfate_neg	455.247
404	3a,12a, 23-Nordeoxycholic Acid sulfate_neg	457.227
405	Adenylsuccinic acid_neg	462.100

406	Glycocholic acid(GCA)_neg	464.300
407	Deoxycytidine triphosphate_neg	465.800
408	9(11), (5p)-Cholenic Acid-3a-ol-12-one sulfate_neg	467.211
409	3a-Hydroxy-12 Ketolithocholic Acid sulfate_neg	469.227
410	Chenodeoxycholic Acid sulfate_neg	471.242
411	LPE(18:3)_neg	474.263
412	LPE(18:2)_neg	476.278
413	LPE(18:1)_neg	478.293
414	LPE(18:0)_neg	480.310
415	Cholic acid sulfate_neg	487.237
416	2-Deoxyinosine triphosphate_neg	490.900
417	Taurochenodeoxycholic Acid_neg	498.300
418	LPE(20:3)_neg	502.294
419	LPG(18:2)_neg	507.273
420	Glycolithocholic Acid sulfate_neg	512.269
421	Tauro alpha/beta/omega muricholic acid_neg	514.300
422	Taurohyocholic acid_neg	514.300

423	Taurocholic acid_neg	514.300
424	LPE(22:6)_neg	524.278
425	LPE(22:5)_neg	526.294
426	Glycodeoxycholic acid sulfate_neg	528.200
427	Glycochenodeoxycholic Acid sulfate_neg	528.264
428	LPE(22:4)_neg	528.310
429	Taurolithocholic acid -3-O-sulfate_neg	562.200
430	Glycocholic Acid sulfate_neg	566.240
431	Dihydroxy bile acid glucuronide_neg	567.300
432	LPC(22:5)_neg	568.362
433	LPI(16:0)_neg	571.289
434	LPI(18:3)_neg	593.273
435	Taurocholic acid-3-O-sulfate_neg	594.200
436	LPI(18:2)_neg	595.289
437	LPI(18:0)_neg	599.320
438	PA(16:0/16:1)_neg	645.400
439	PA(16:0/16:0)_neg	647.486

440	PA(16:0/18:1)_neg	673.501
441	PE(P-18:1/18:2)_neg	724.500
442	CL(18:2/18:2/18:2/18:1)_neg	724.600
443	PG(16:0/18:2)_neg	745.503
444	PG(16:0/18:1)_neg	747.518
445	PG(18:1/18:2)_neg	771.518
446	PG(18:0/18:2)_neg	773.534
447	PG(18:1/18:1)_neg	773.534
448	PC(18:1/18:1)_neg	784.607
449	PG(20:0/18:1)_neg	803.581
450	PI(14:0/18:2)_neg	805.487
451	PI(14:0/18:1)_neg	807.503
452	PI(18:2/16:1)_neg	831.503
453	PI(18:2/22:6)_neg	905.518
454	3-Hydroxybenzaldehyde_neg	121.030
455	Threonic acid_neg	135.030
456	Salicylic acid_neg	137.024

457	4-Nitrophenol_neg	138.020
458	4-Hydroxyquinoline_neg	144.045
459	Indole-3-carboxaldehyde_neg	144.045
460	Cinnamic acid_neg	147.045
461	P-Toluenesulfonic acid_neg	171.012
462	CAFFEIC ACID_neg	179.035
463	2,4-Dinitrophenol_neg	183.005
464	3-Indolepropionic acid_neg	188.072
465	Indolelactic acid_neg	204.067
466	2-Naphthalenesulfonic acid_neg	207.012
467	FA(13:0)_neg	213.186
468	Monoisobutyl phthalate_neg	221.082
469	Pyroglutamyl-Isoleucine_neg	241.119
470	FA(15:0)_neg	241.217
471	Isoleucylisoleucinev_neg	243.172
472	beta-Hydroxymyristic acid_neg	243.197
473	N-Acetyltryptophan_neg	245.093

474	FA(17:0)_neg	269.249
475	N-Acetylneuraminic acid_neg	308.099
476	Octadecanedioic acid_neg	313.238
477	Dodecylbenzenesulfonic acid_neg	325.184
478	Avocadyne Acetate_neg	325.238
479	FA(22:4)_neg	331.264
480	Abietic acid_neg	301.217
481	FA(5:0)_neg	101.130
482	FA(6:0)_neg	115.160
483	FA(8:0)_neg	143.210
484	FA(10:0)_neg	171.260

MRM, multiple reaction monitoring.

Table SII. Top 25 metabolic pathway quantitative enrichment results from metabolite set enrichment analysis.

Description	Total cmpd	Hits	Statistic Q	P-value	FDR
Sphingolipid Metabolism	40	5	24.6900	0.0026	0.2435
Steroid Biosynthesis	48	4	16.0410	0.0273	0.6438
Warburg Effect	58	23	12.9790	0.0451	0.6438
Transfer of Acetyl Groups into Mitochondria	22	8	13.4390	0.0456	0.6438
Citric Acid Cycle	32	12	13.0030	0.0466	0.6438
Folate Metabolism	29	4	12.6590	0.0524	0.6438
Gluconeogenesis	35	14	11.3300	0.0562	0.6438
Pyruvate Metabolism	48	11	10.8980	0.0602	0.6438
Lactose Degradation	9	2	11.3550	0.0677	0.6438
Lactose Synthesis	20	4	11.3420	0.0678	0.6438
Glutathione Metabolism	21	6	7.5311	0.0888	0.7665
Histidine Metabolism	43	9	7.7237	0.1023	0.7672
Porphyrin Metabolism	40	4	6.8452	0.1492	0.7672
Valine, Leucine and Isoleucine Degradation	60	14	6.4807	0.1545	0.7672

Glycolysis	25	10	5.7858	0.1725	0.7672
Pterine Biosynthesis	29	2	6.0160	0.1767	0.7672
Phospholipid Biosynthesis	29	4	5.6532	0.1907	0.7672
Galactose Metabolism	38	8	4.9660	0.2365	0.7672
Starch and Sucrose Metabolism	31	7	4.9645	0.2366	0.7672
Fructose and mannose degradation	32	8	4.9643	0.2366	0.7672
Amino Sugar Metabolism	33	11	4.9558	0.2368	0.7672
Plasmalogen Synthesis	26	1	4.8505	0.2422	0.7672
Bile acid biosynthesis	65	13	4.4303	0.2523	0.7672
Caffeine metabolism	24	2	4.6330	0.2533	0.7672
Tryptophan metabolism	60	15	4.3966	0.2625	0.7672

cmp, compound; FDR, false discovery rate.

Table SIII. Top 25 enriched metabolic pathways identified by Metabolite Pathway Analysis.

Description	Total compd	Hits	P-value	FDR
Sphingolipid metabolism	21	4	0.0099	0.4678
Terpenoid backbone biosynthesis	18	1	0.0272	0.4678
Glyoxylate and dicarboxylate metabolism	32	11	0.0456	0.4678
Citrate cycle (TCA cycle)	20	11	0.0466	0.4678
Alanine, aspartate and glutamate metabolism	28	15	0.0469	0.4678
Glycolysis / Gluconeogenesis	26	12	0.0564	0.4678
Pyruvate metabolism	22	9	0.0605	0.4678
Riboflavin metabolism	4	1	0.0655	0.4678
One carbon pool by folate	9	1	0.0658	0.4678
Fatty acid degradation	39	1	0.0959	0.5413
Porphyrin and chlorophyll metabolism	30	4	0.0975	0.5413
Histidine metabolism	16	5	0.1015	0.5413
Valine, leucine and isoleucine biosynthesis	8	8	0.1518	0.6825
Valine, leucine and isoleucine degradation	40	8	0.1519	0.6825
Aminoacyl-tRNA biosynthesis	48	18	0.1600	0.6825

Folate biosynthesis	27	2	0.1767	0.7068
Primary bile acid biosynthesis	46	8	0.2363	0.7468
Amino sugar and nucleotide sugar metabolism	37	4	0.2366	0.7468
Caffeine metabolism	10	2	0.2533	0.7468
Tryptophan metabolism	41	7	0.2645	0.7468
Synthesis and degradation of ketone bodies	5	2	0.3020	0.7468
Butanoate metabolism	15	5	0.3054	0.7468
beta-Alanine metabolism	21	3	0.3062	0.7468
Ether lipid metabolism	20	1	0.3259	0.7468
Vitamin B6 metabolism	9	2	0.3285	0.7468

cmp, compound; FDR, false discovery rate.

Table SIV. Top 30 significantly enriched pathways associated with differential metabolites identified by KEGG analysis.

Description	Metabolite ratio	P-value	q-value	KEGG ID	Rich factor	Up	Down
Central carbon metabolism in cancer	3/13	0.0002	0.0017	C00062/C00311/C00158	26.76	2	1
Fc gamma R-mediated phagocytosis	2/13	0.0002	0.0017	C06124/C00165	82.5	2	0
Apelin signaling pathway	2/13	0.0003	0.0017	C06124/C00165	73.33	2	0
Biosynthesis of amino acids	4/13	0.0004	0.0017	C05378/C00062/C00311/C00158	10.31	2	2
Neuroactive ligand-receptor interaction	3/13	0.0004	0.0017	C06124/C01829/C00780	19.04	2	1
Calcium signaling pathway	2/13	0.0005	0.0017	C06124/C00165	60	2	0
Phospholipase D signaling pathway	2/13	0.0005	0.0017	C06124/C00165	60	2	0
Gap junction	2/13	0.0005	0.0017	C00165/C00780	60	1	1
Thyroid hormone signaling pathway	2/13	0.0005	0.0017	C00165/C01829	60	2	0
Amoebiasis	2/13	0.0006	0.0021	C00062/C00165	50.77	1	1
Sphingolipid signaling pathway	2/13	0.0009	0.0026	C06124/C00165	44	2	0
Citrate cycle (TCA cycle)	2/13	0.0016	0.0042	C00311/C00158	33	2	0
Thyroid hormone synthesis	2/13	0.0017	0.0043	C00165/C01829	31.43	2	0
cAMP signaling pathway	2/13	0.0024	0.0057	C00165/C00780	26.4	1	1

Glucagon signaling pathway	2/13	0.0026	0.0058	C00311/C00158	25.38	2	0
Taste transduction	2/13	0.0040	0.0077	C00158/C00780	20.62	1	1
Pathways of neurodegeneration - multiple diseases	2/13	0.0040	0.0077	C00062/C00165	20.62	1	1
Carbon metabolism	3/13	0.0043	0.0078	C05378/C00311/C00158	8.68	2	1
Inflammatory mediator regulation of TRP channels	2/13	0.0048	0.0082	C00165/C00780	18.86	1	1
EGFR tyrosine kinase inhibitor resistance	1/13	0.0061	0.0099	C00165	165	1	0
Serotonergic synapse	2/13	0.0068	0.0106	C00165/C00780	15.71	1	1
NF-kappa B signaling pathway	1/13	0.0091	0.0119	C00165	110	1	0
Th1 and Th2 cell differentiation	1/13	0.0091	0.0119	C00165	110	1	0
Autoimmune thyroid disease	1/13	0.0091	0.0119	C01829	110	1	0
ErbB signaling pathway	1/13	0.0121	0.0119	C00165	82.5	1	0
mTOR signaling pathway	1/13	0.0121	0.0119	C00062	82.5	0	1
Natural killer cell mediated cytotoxicity	1/13	0.0121	0.0119	C00165	82.5	1	0
Th17 cell differentiation	1/13	0.0121	0.0119	C00165	82.5	1	0
T cell receptor signaling pathway	1/13	0.0121	0.0119	C00165	82.5	1	0
B cell receptor signaling pathway	1/13	0.0121	0.0119	C00165	82.5	1	0

KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table SV. Spearman's correlation analysis between differential metabolites and clinical indicators.

Metabolite	Age	BMI	CAT	mMRC	EOS	NLR	PLR	FEV1% pred	PF	BP	GH	MH	RE	RP	SF	VT	HT
Sphingosine 1-phosphate	0.03	-0.03	0.39 ^{ab}	0.64 ^{ab}	-0.02	0.21	0.28	-0.28	-0.68 ^{ac}	0.04	-0.35	0.16	-0.19	-0.35	-0.11	-0.11	-0.22
Pyroglutamyl-Isoleucine	0.12	0.27	0.55 ^{ab}	0.43 ^{ab}	-0.29	0.18	0.05	-0.09	-0.49 ^{ac}	-0.08	0.06	-0.05	-0.26	-0.46 ^{ac}	-0.43 ^{ac}	-0.46 ^{ac}	-0.06
L-2-Hydroxyglutarate	0.09	0.17	0.57 ^{ab}	0.51 ^{ab}	0.03	0.10	-0.01	-0.12	-0.45 ^{ac}	-0.38 ^{ac}	-0.11	0.21	-0.06	-0.33	-0.34	-0.29	-0.24
13S-hydroxyoctadecadienoic acid	0.22	-0.08	0.39 ^{ab}	0.44 ^{ab}	0.07	0.03	0.01	-0.20	-0.54 ^{ac}	-0.24	0.02	-0.04	-0.35	-0.38 ^{ac}	-0.42 ^{ac}	-0.30	-0.23
Hexanoylcarnitine	-0.06	0.17	0.48 ^{ab}	0.27	0.17	0.07	-0.09	0.05	-0.40 ^{ac}	-0.13	-0.24	0.02	-0.15	-0.18	-0.26	-0.19	-0.12
Carnitine-C6	-0.03	0.14	0.45 ^{ab}	0.20	0.19	-0.03	-0.19	0.11	-0.35	-0.18	-0.20	0.01	-0.21	-0.13	-0.25	-0.18	-0.13
Carnitine-C18:2	0.07	0.01	0.34	0.24	-0.02	0.23	0.10	-0.21	-0.49 ^{ac}	-0.24	-0.28	0.15	-0.04	-0.26	-0.18	-0.07	-0.14
Carnitine-C18:1	0.01	-0.12	0.32	0.15	0.01	0.20	0.02	-0.10	-0.34	-0.34	-0.28	0.02	-0.07	-0.08	-0.29	-0.05	-0.14
DG (16:0/20:5)	-0.12	0.04	0.53 ^{ab}	0.43 ^{ab}	-0.15	0.46 ^{ab}	0.22	-0.07	-0.48 ^{ac}	-0.07	-0.38 ^{ac}	0.03	0.11	-0.36	-0.29	-0.30	-0.28
DG (16:0/20:4)	0.06	0.06	0.29	0.20	-0.03	0.14	0.01	-0.25	-0.37 ^{ac}	-0.13	-0.17	0.12	-0.17	-0.23	-0.20	-0.17	-0.18
Cinnamic acid	0.23	-0.05	0.25	0.18	-0.13	0.17	0.27	-0.04	-0.26	-0.50 ^{ac}	-0.11	0.13	-0.07	-0.25	-0.15	-0.17	-0.17
3-(Methylthio)propionic acid	-0.30	0.23	0.25	0.26	0.42 ^{ab}	-0.18	-0.12	-0.01	-0.42 ^{ac}	-0.05	-0.03	0.09	0.06	-0.16	-0.08	0.00	0.00
L-Thyroxine	0.05	0.03	0.22	0.22	-0.07	0.45 ^{ab}	0.45 ^{ab}	-0.22	-0.29	-0.05	-0.35	-0.09	-0.14	-0.15	-0.22	-0.07	-0.01
Citrate	0.16	-0.19	0.33	0.13	0.16	-0.10	0.18	-0.01	-0.18	-0.42 ^{ac}	-0.09	0.25	0.09	-0.11	-0.31	-0.24	-0.05
Citramalic acid	0.10	0.07	0.29	0.31	0.05	0.05	-0.03	-0.11	-0.39 ^{ac}	-0.30	0.06	0.18	-0.11	-0.29	-0.11	-0.11	-0.24

Isocitrate	0.31	-0.02	0.29	0.31	0.02	0.04	0.10	-0.22	-0.36	-0.21	0.06	0.27	-0.13	-0.16	-0.21	-0.01	-0.01
2-Hydroxy-3-methylbutyric acid	-0.21	0.42 ^{ab}	0.29	0.03	0.26	-0.15	-0.22	0.23	-0.10	-0.10	-0.05	0.12	0.04	-0.01	0.02	0.00	-0.03
LPG (18:2)	0.19	0.12	0.23	0.18	-0.19	0.11	-0.01	0.01	-0.27	-0.14	0.03	-0.15	-0.04	-0.25	-0.31	-0.42 ^{ac}	-0.16
FA (24:0)	-0.02	-0.16	0.13	-0.08	0.13	-0.05	-0.16	0.16	-0.05	-0.21	-0.17	0.13	0.03	0.19	-0.10	0.01	-0.09
Mevalonic acid	-0.17	0.15	-0.48 ^{ac}	-0.31	0.38 ^{ab}	-0.41 ^a	-0.16	-0.04	0.26	0.15	0.38 ^{ab}	0.17	0.20	0.25	0.12	0.41 ^{ab}	0.18
D-Fructose 1,6-bisphosphate	-0.11	-0.23	-0.45 ^{ac}	-0.40 ^{ac}	0.14	-0.44 ^{ac}	-0.17	0.17	0.51 ^{ab}	0.09	0.28	0.05	0.14	0.39 ^{ab}	0.20	0.47 ^{ab}	0.29
Threonate	0.15	0.25	-0.08	-0.15	-0.17	0.08	0.00	0.05	0.24	0.08	0.06	-0.23	-0.12	0.28	0.13	-0.04	0.53 ^{ab}
Arginine	0.10	-0.25	-0.34	-0.13	0.03	0.01	0.18	-0.26	0.27	0.42 ^{ab}	0.21	0.18	0.15	0.28	0.37 ^{ab}	0.52 ^{ab}	0.30
Inosine	-0.21	0.05	-0.17	-0.31	0.31	-0.18	-0.10	0.22	0.34	0.22	0.14	0.05	0.22	0.15	0.21	0.21	-0.08
Serotonin	0.14	0.00	-0.09	-0.05	-0.23	-0.18	0.07	0.19	0.26	0.13	0.20	0.11	0.22	0.30	0.18	0.09	0.12

Values in the table represent the rs values from Spearman's correlation analysis. ^aP<0.05, ^bpositive correlation, and ^cnegative correlation. FA, fatty acid; DG, diacylglycerol; BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; mMRC, modified Medical Research Council; EOS, eosinophil; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; FEV1% pred, forced expiratory volume in 1 sec; PF, physical functioning; BP, bodily pain; GH, general health; MH, mental health; RE, role emotional; SF, social functioning; VT, vitality; HT, health transition.

Table SVI. Receiver operating characteristics analysis of differential metabolites.

Metabolite	AUC	P-value	FC
D-Fructose 1,6-bisphosphate	0.8711	0.0002	0.2559
L-2-Hydroxygluterate	0.8489	0.0010	-0.4133
Arginine	0.8356	0.0007	0.4276
DG (16:0/20:5)	0.8267	0.0043	-1.2148
DG (16:0/20:4)	0.8178	0.0063	-1.0147
Carnitine-C18:2	0.8044	0.0026	-0.6261
Cinnamic acid	0.8000	0.0119	-0.3093
FA (24:0)	0.7911	0.0175	-1.5099
Sphingosine 1-phosphate	0.7822	0.0032	-0.3288
Threonate	0.7822	0.0070	0.7370
Citramalic acid	0.7733	0.0120	-0.3224
2-Hydroxy-3-methylbutyric acid	0.7733	0.0179	-0.6460
Pyroglutamyl-Isoleucine	0.7511	0.0234	-0.3811
Carnitine-C18:1	0.7422	0.0238	-0.5692
13S-hydroxyoctadecadienoic acid	0.7333	0.0295	-0.5713

Isocitrate	0.7244	0.0322	-0.3527
Inosine	0.7067	0.0230	0.9277
Citrate	0.7022	0.0459	-0.2754
LPG (18:2)	0.6978	0.0381	-0.2149
L-Thyroxine	0.6978	0.0434	-0.4030
3-(Methylthio)propionic acid	0.6933	0.0436	-0.4454
Serotonin	0.6933	0.0326	0.5813
Mevalonic acid	0.6844	0.0272	0.4201
Hexanoylcarnitine	0.6844	0.0477	-0.7658
Carnitine-C6	0.6800	0.0459	-0.7043

DG, diacylglycerol; FA, fatty acid; AUC, area under curve; FC, fold change.

Table SVII. Characteristics and clinical indicators of the patients in the external cohort.

Variable	COPD-NE (n=10)	COPD-FE (n=10)	P-value
Age, years	70.5 (4.0)	70.0 (7.0)	0.667 ^a
Male	8 (80.0%)	6 (60.0%)	0.329
BMI, kg/m ²	22.1(4.0)	23.7 (3.8)	0.234 ^a
Smoking history			
Never smoked	2 (20.0%)	3 (30.0%)	0.806
Current smoker	3 (30.0%)	1 (10.0%)	
Former smoker	5 (50.0%)	6 (60.0%)	
FEV1/FVC%	52.2 (7.2)	53.5 (10.4)	0.488 ^b
FEV1% pred	51.0 (19.0)	50.8 (9.8)	0.881 ^a
Medication			
LAMA	6 (60.0%)	6 (60.0%)	0.666
ICS	3 (30.0%)	1 (10.0%)	
ICS/LABA	1 (10.0%)	2 (20.0%)	
ICS/LABA + LAMA	0 (0.0%)	1 (10.0%)	
None	0 (0.0%)	0 (0.0%)	

Continuous variables were analyzed using ^atwo-tailed unpaired Student's t test under assumptions of normality and variance homogeneity, otherwise ^bMann-Whitney U test. Categorical variables were tested with Fisher's exact test. Continuous variables are presented as the median (IQR); categorical variables are presented as counts (%). FEV1% pred, predicted value of forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist; LAMA, long-acting muscarinic antagonist; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FE, frequent exacerbation; NE, non-frequent exacerbation; IQR, interquartile range.