**Table S1:** Stable mass/charge (m/z) values for targeted metabolomics in both positive and negative ionization modes. The list of targeted molecules and their corresponding mass/charge (m/z) for the positive and negative ion modes (Supplementary Table S1) are used to link to the molecular formula and PubChem Identifier (Supplementary Table S2).

| Negative ion mode | | Positive ion mode | |
|---|---|---|---|
| **m/z [M-1]-** | **Name** | **m/z [M+1]+** | **Name** |
| 73 | glyoxylate | 61.1 | Urea |
| 75 | glycolate | 62.1 | ethanolamine |
| 87 | pyruvate | 76.1 | glycine |
| 89 | lactate | 89 | putrescine |
| 101 | 2-oxobutanoate | 90.04 | sarcosine |
| 101.05 | acetoacetate | 90.1 | alanine |
| 103.04 | 3-hydroxybuterate | 102 | betaine aldehyde |
| 105 | glycerate | 104 | choline |
| 111.05 | uracil | 104.01 | 4-aminobutyrate |
| 115 | fumarate | 104.02 | dimethylglycine |
| 115.03 | Maleic acid | 106 | serine |
| 115.05 | 2-keto-isovalerate | 112.1 | cytosine |
| 116.001 | Guanidoacetic acid | 114 | Creatinine |
| 117 | succinate | 116.1 | proline |
| 117.002 | Methylmalonic acid | 118 | indole |
| 119.02 | 3-S-methylthiopropionate | 118.02 | betaine |
| 122 | nicotinate | 118.1 | valine |
| 124 | taurine | 120 | threonine |
| 128 | Pyroglutamic acid | 120.15 | homoserine |
| 129.003 | Citraconic acid | 121 | purine |
| 129.005 | 2-ketohaxanoic acid | 122.1 | cysteine |
| 129.1 | itaconic acid | 123.1 | nicotinamide |
| 130 | N-Acetyl-L-alanine | 127.002 | Imidazoleacetic acid |
| 131 | oxaloacetate | 127.1 | thymine |
| 131 | Gluterate | 130 | DL-Pipecolic acid |
| 131.006 | Hydroxyisocaproic acid | 131.001 | N-Acetylputrescine |
| 133 | malate | 131.9 | N-acetyl-L-alanine |
| 135 | hypoxanthine | 132.003 | creatine |
| 136 | anthranilate | 132.004 | hydroxyproline |
| 136.05 | p-aminobenzoate | 132.1 | leucine-isoleucine |
| 137 | p-hydroxybenzoate | 133 | ornithine |
| 139 | acetylphosphate | 133.1 | asparagine |
| 140 | Carbamoyl phosphate | 134 | aspartate |
| 145 | a-ketoglutarate | 136 | adenine |
| 145.004 | Phenylpropiolic acid | 136.02 | Methylcysteine |
| 147 | 2-oxo-4-methylthiobutanoate | 136.12 | homocysteine |

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|---|---|---|---|
| 147.001 | 2-Hydroxy-2-methylbutanedioic acid | 137.001 | methylnicotinamide |
| 147.1 | 2-hydroxygluterate | 142.1 | histidinol |
| 149.002 | 3-methylphenylacetic acid | 146 | spermidine |
| 151 | xanthine | 147 | lysine |
| 151.004 | Hydroxyphenylacetic acid | 147.1 | glutamine |
| 153 | 2,3-dihydroxybenzoic acid | 148 | O-acetyl-L-serine |
| 155 | orotate | 148.1 | glutamate |
| 157 | dihydroorotate | 149.35 | Mevalonate |
| 157.05 | allantoin | 150.1 | methionine |
| 159 | 2-oxoadipate | 152.2 | guanine |
| 160.001 | Aminoadipic acid | 154.05 | cysteine sulfinate |
| 160.002 | Indole-3-carboxylic acid | 156.1 | histidine |
| 163 | phenylpyruvate | 160 | 2-Aminooctanoic acid |
| 165.004 | Atrolactic acid | 162.1 | carnitine |
| 165.006 | Phenyllactic acid | 166 | Methionine sulfoxide |
| 166 | quinolinate | 166.1 | phenylalanine |
| 167 | phosphoenolpyruvate | 169 | Pyridoxamine |
| 167.001 | Uric acid | 170 | pyridoxine |
| 169 | dihydroxy-acetone-phosphate | 170.1 | 1-Methyl-Histidine |
| 169.05 | D-glyceraldehdye-3-phosphate | 175 | N-acetyl-L-ornithine |
| 171 | sn-glycerol-3-phosphate | 175.02 | arginine |
| 171.1 | glycerol 3-phosphate | 176 | citrulline |
| 173 | shikimate | 176 | N-acetyl-L-aspartic acid |
| 173 | dehydroascorbic acid | 177.05 | N-carbamoyl-L-aspartate |
| 173.05 | aconitate | 180 | glucosamine |
| 175 | allantoate | 182.1 | tyrosine |
| 175.001 | Ascorbic acid | 184.001 | Phosphorylcholine |
| 175.002 | 2-Isopropylmalic acid | 186 | 3-phospho-serine |
| 175.03 | N-carbamoyl-L-aspartate-nega | 188 | N-acetyl spermidine |
| 176.8 | Pyrophosphate | 189.001 | N6-Acetyl-L-lysine |
| 177 | glucono-delta-lactone | 189.002 | Acetyllysine |
| 178.07 | hippurate | 189.1 | N-acetyl-glutamine |
| 179 | myo-inositol | 190.1 | N-acetyl-glutamate |
| 179.05 | hydroxyphenylpyruvate | 203 | Ng,NG-dimethyl-L-arginine |
| 181 | sorbitol | 203.1 | spermine |
| 182 | homocysteic acid | 204 | Acetylcarnitine DL |
| 182.003 | 4-Pyridoxic acid | 205 | tryptophan |
| 185 | 3-phosphoglycerate | 209 | Kynurenine |
| 186 | Indoleacrylic acid | 212 | phosphocreatine |

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|---|---|---|---|
| 188 | Kynurenic acid | 222 | N-acetyl-glucosamine |
| 191 | citrate-isocitrate | 223 | Flavone |
| 191.02 | isocitrate | 223 | cystathionine |
| 191.05 | citrate | 235 | 5-methoxytryptophan |
| 193 | 2-dehydro-D-gluconate | 241.002 | Cystine |
| 195 | D-gluconate | 244.1 | cytidine |
| 199 | D-erythrose-4-phosphate | 245 | N-acetyl spermine |
| 204.001 | Xanthurenic acid | 245.1 | biotin |
| 205 | lipoate | 252 | deoxyadenosine |
| 209 | D-glucarate | 255 | Nicotinamide Riboside |
| 213 | deoxyribose-phosphate | 258.1 | Glycerophosphocholine |
| 218 | pantothenate | 259 | acadesine |
| 225 | prephenate | 260 | D-glucosamine-6-phosphate |
| 227 | deoxyuridine | 260.1 | D-glucosamine-1-phosphate |
| 229 | ribose-phosphate | 264 | AL-II |
| 241 | thymidine | 265 | thiamine |
| 243 | uridine | 268 | S-ribosyl-L-homocysteine-posi |
| 243.2 | 2-deoxyglucose-6-phosphate | 268.1 | deoxyguanosine |
| 251 | deoxyinosine | 268.15 | adenosine |
| 253.1 | shikimate-3-phosphate | 281.8 | 1-Methyladenosine |
| 257 | D-glucono-?-lactone-6-phosphate | 284.1 | guanosine |
| 259 | hexose-phosphate | 291 | L-arginino-succinate |
| 259.01 | glucose-1-phosphate | 291.2 | arginosuccinic acid |
| 259.02 | glucose-6-phosphate | 294 | AL-I |
| 259.03 | fructose-6-phosphate | 298 | S-methyl-5-thioadenosine |
| 265 | 1,3-diphopshateglycerate | 298.002 | 7-methylguanosine |
| 265.1 | 2,3-Diphosphoglyceric acid | 301.1 | retinoic acid |
| 266 | S-ribosyl-L-homocysteine-nega | 305 | N-acetylaspartylglutamic acid |
| 267 | inosine | 308 | dCMP |
| 275 | 6-phospho-D-gluconate | 308.1 | glutathione |
| 283 | xanthosine | 323 | dTMP |
| 289 | D-sedoheptulose-1-7-phosphate | 324 | CMP |
| 298.07 | 4-phosphopantothenate | 325 | UMP |
| 300 | N-acetyl-glucosamine-1-phosphate | 332.1 | dAMP |
| 306 | glutathione-nega | 335 | Nicotinamide ribotide |

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|---|---|---|---|
| 307 | dUMP-nega | 339 | aminoimidazole carboxamide ribonucleotide |
| 313 | Geranyl-PP | 345.2 | thiamine-phosphate |
| 319 | O8P-O1P | 348.1 | dGMP |
| 321 | dTMP-nega | 348.15 | AMP |
| 328 | cyclic-AMP | 349 | IMP |
| 339 | fructose-1,6-bisphosphate | 355 | S-adenosyl-L-methioninamine |
| 341 | trehalose-sucrose | 364 | GMP |
| 341.1 | Cellobiose | 365 | xanthosine-5-phosphate |
| 367 | orotidine-5-phosphate | 377 | riboflavin |
| 369 | SBP | 385.1 | S-adenosyl-L-homoCysteine-posi |
| 381 | trans, trans-farnesyl diphosphate | 387.36 | cholesterol |
| 383.1 | S-adenosyl-L-homocysteine-nega | 399.1 | S-adenosyl-L-methionine |
| 386 | dCDP-nega | 442 | folate |
| 389 | 5-phosphoribosyl-1-pyrophosphate | 444.2 | 7,8-dihydrofolate |
| 391.202 | Deoxycholic acid | 460.1 | 5-methyl-THF |
| 399 | OBP | 464 | Adenylosuccinate |
| 401 | dTDP-nega | 525.5 | Diiodothyronine |
| 402 | CDP-nega | 613 | glutathione disulfide-posi |
| 403 | UDP-nega | 664.1 | NAD+_posi |
| 407.2 | Cholic acid | 666.1 | NADH |
| 421 | trehalose-6-Phosphate | 688 | dephospho-CoA-posi |
| 423.1 | Thiamine pyrophosphate | 744.2 | NADP+_posi |
| 426 | adenosine 5-phosphosulfate | 746.15 | NADPH |
| 426.1 | ADP-nega | 768 | coenzyme A-posi |
| 426.12 | dGDP-nega | 786 | FAD |
| 427 | IDP-nega | 810 | acetyl-CoA-posi |
| 442 | GDP-nega | 824.1 | propionyl-CoA-posi |
| 445 | CDP-ethanolamine | 852 | acetoacetyl-CoA-posi |
| 455 | FMN | 854 | malonyl-CoA-posi |
| 465.2 | cholesteryl sulfate | 868.1 | succinyl-CoA-posi |
| 466 | dCTP-nega | 912.17 | HMG-CoA_pos |
| 467 | dUTP-nega | | |
| 481 | dTTP-nega | | |
| 482 | CTP-nega | | |
| 483 | UTP-nega | | |
| 487 | CDP-choline | | |
| 490 | dATP-nega | | |

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|---|---|---|---|
| 498.2 | Taurodeoxycholic acid | | |
| 506.1 | ATP-nega | | |
| 506.12 | dGTP | | |
| 522 | GTP-nega | | |
| 535.4 | UDP-xylose | | |
| 565 | UDP-D-glucose | | |
| 579 | UDP-D-glucuronate | | |
| 588 | ADP-D-glucose | | |
| 602 | guanosine 5-diphosphate,3-diphosphate | | |
| 606 | UDP-N-acetyl-glucosamine | | |
| 611 | glutathione disulfide-nega | | |
| 662 | NAD+_nega | | |
| 664 | NADH-nega | | |
| 686.2 | dephospho-CoA-nega | | |
| 689 | cyclic bis(3->5) dimeric GMP | | |
| 742 | NADP+_nega | | |
| 744 | NADPH-nega | | |

**Table S2:** Kyoto Encyclopedia of Genes and Genomes (KEGG) IDs list for targeted metabolites. The list of targeted molecules and their corresponding mass/charge (m/z) are used to link to the molecular formula and PubChem Identifier.

| Metabolite name | formula | PubChem Identifier (KEGG/HMDB) |
|---|---|---|
| 1,3-diphopshateglycerate | C3H8O10P2 | C00236 |
| 1-Methyladenosine | C11H15N5O4 | C02494 |
| 1-Methyl-Histidine | C7H11N3O2 | C01152 |
| 2,3-dihydroxybenzoic acid | C7H6O4 | C00196 |
| 2,3-Diphosphoglyceric acid | C3H8O10P2 | C01159 |
| 2-Aminooctanoic acid | C8H17NO2 | HMDB00991 |
| 2-dehydro-D-gluconate | C6H10O7 | C00629 |
| 2-deoxyglucose-6-phosphate | C6H13O8P | C06369 |
| 2-Hydroxy-2-methylbutanedioic acid | C5H8O5 | C02612 |
| 2-hydroxygluterate | C5H8O5 | C02630 |
| 2-Isopropylmalic acid | C7H12O5 | C02504 |
| 2-ketohaxanoic acid | C6H10O3 | HMDB01864 |
| 2-keto-isovalerate | C5H8O3 | C00141 |
| 2-oxo-4-methylthiobutanoate | C5H8O3S | C01180 |
| 2-oxoadipate | C6H8O5 | C00322 |
| 2-oxobutanoate | C4H6O3 | C00109 |
| 3-hydroxy-3-methylglutaryl-CoA | C27H44N7O20P3S | C00356 |
| 3-hydroxybuteric acid | C4H8O3 | C01089 |
| 3-hydroxybutyryl-CoA | C25H42N7O18P3S | C01144 |
| 3-methylphenylacetic acid | C9H10O2 | HMDB02222 |
| 3-phosphoglycerate | C3H7O7P | C00197 |
| 3-phosphoserine | C3H8NO6P | C01005 |
| 3-S-methylthiopropionate | C4H8O2S | C08276 |
| 4-aminobutyrate | C4H9NO2 | C00334 |
| 4-phosphopantothenate | C9H18NO8P | C03492 |
| 4-Pyridoxic acid | C8H9NO4 | C00847 |
| 5-methoxytryptophan | C12H14N2O3 | HMDB02339 |
| 5-methyl-THF | C20H25N7O6 | C00440 |
| 5-phosphoribosyl-1-pyrophosphate | C5H13O14P3 | C00119 |
| 6-phospho-D-gluconate | C6H13O10P | C00345 |
| 7,8-dihydrofolate | C19H21N7O6 | C00415 |
| 7-methylguanosine | C11H16N5O5 | HMDB01107 |
| acadesine | C9H14N4O5 | D02742 |
| acetoacetate | C4H6O3 | C00164 |
| acetoacetyl-CoA | C25H40N7O18P3S | C00332 |
| Acetylcarnitine DL | C9H18NO4 | C02571 |
| acetyl-CoA | C23H38N7O17P3S | C00024 |
| Acetyllysine | C8H16N2O3 | C02727 |
| acetylphosphate | C2H5O5P | C00227 |
| aconitate | C6H6O6 | C00417 |
| adenine | C5H5N5 | C00147 |
| adenosine | C10H13N5O4 | C00212 |

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|---|---|---|
| adenosine 5-phosphosulfate | C10H14N5O10PS | C00224 |
| ADP-D-glucose | C16H25N5O15P2 | C00498 |
| ADP-nega | C10H15N5O10P2 | C00008 |
| a-ketoglutarate | C5H6O5 | C00026 |
| alanine | C3H7NO2 | C00041 |
| allantoate | C4H8N4O4 | C00499 |
| allantoin | C4H6N4O3 | C01551 |
| Aminoadipic acid | C6H11NO4 | C00956 |
| aminoimidazole carboxamide ribonucleotide | C9H15N4O8P | C04677 |
| AMP | C10H14N5O7P | C00020 |
| anthranilate | C7H7NO2 | C00108 |
| arginine | C6H14N4O2 | C00062 |
| Ascorbic acid | C6H8O6 | C00072 |
| asparagine | C4H8N2O3 | C00152 |
| aspartate | C4H7NO4 | C00049 |
| ATP-nega | C10H16N5O13P3 | C00002 |
| Atrolactic acid | C9H10O3 | HMDB00475 |
| betaine | C5H11NO2 | C00719 |
| betaine aldehyde | C5H12NO | C00576 |
| biotin | C10H16N2O3S | C00120 |
| butyryl-CoA | C25H42N7O17P3S | C00630 |
| Carbamoyl phosphate | CH4NO5P | C00169 |
| carnitine | C7H15NO3 | C00318 |
| CDP-choline | C14H27N4O11P2 | C00307 |
| CDP-ethanolamine | C11H20N4O11P2 | C00570 |
| CDP-nega | C9H15N3O11P2 | C00112 |
| Cellobiose | C12H22O11 | C00185 |
| cholesterol | C27H46O | C00187 |
| cholesteryl sulfate | C27H46O4S | HMDB00653 |
| Cholic acid | C24H40O5 | C00695 |
| choline | C5H14NO | C00114 |
| Citraconic acid | C5H6O4 | C02226 |
| citrate | C6H8O7 | C00158 |
| citrate-isocitrate | C6H8O7 | C00158 |
| citrulline | C6H13N3O3 | C00327 |
| CMP | C9H14N3O8P | C00055 |
| coenzyme A | C21H36N7O16P3S | C00010 |
| creatine | C4H9N3O2 | C00300 |
| Creatinine | C4H7N3O | C00791 |
| CTP-nega | C9H16N3O14P3 | C00063 |
| cyclic bis(3->5) dimeric GMP | C20H24N10O14P2 | C16463 |
| cyclic-AMP | C10H12N5O6P | C00575 |
| cystathionine | C7H14N2O4S | C02291 |
| cysteine | C6H12N2O4S2 | C00491 |
| cysteine sulfinate | C3H7NO4S | C00606 |
| Cystine | C6H12N2O4S2 | C00491 |
| cytidine | C9H13N3O5 | C00475 |

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|---|---|---|
| cytosine | C4H5N3O | C00380 |
| dAMP | C10H14N5O6P | C00360 |
| dATP-nega | C10H16N5O12P3 | C00131 |
| dCDP-nega | C9H15N3O10P2 | C00705 |
| dCMP | C9H14N3O7P | C00239 |
| dCTP-nega | C9H16N3O13P3 | C00458 |
| deoxyadenosine | C10H13N5O3 | C00559 |
| Deoxycholic acid | C26H43NO5 | C04483 |
| deoxyguanosine | C10H13N5O4 | C00330 |
| deoxyinosine | C10H12N4O4 | C05512 |
| deoxyribose-phosphate | C5H11O7P | C00673 |
| deoxyuridine | C9H12N2O5 | C00526 |
| dephospho-CoA | C21H35N7O13P2S | C00882 |
| D-erythrose-4-phosphate | C4H9O7P | C00279 |
| dGDP-nega | C10H15N5O10P2 | C00361 |
| D-glucarate | C6H10O8 | C00818 |
| D-gluconate | C6H12O7 | C00257 |
| D-glucono-?-lactone-6-phosphate | C6H11O9P | C01236 |
| D-glucosamine-1-phosphate | C6H14NO8P | C00352 |
| D-glucosamine-6-phosphate | C6H14NO8P | C00352 |
| D-glyceraldehdye-3-phosphate | C3H7O6P | C00118 |
| dGMP | C10H14N5O7P | C00362 |
| dGTP | C10H16N5O13P3 | C00286 |
| dihydroorotate | C5H6N2O4 | C00337 |
| dihydroxy-acetone-phosphate | C3H7O6P | C00111 |
| Diiodothyronine | C15H13I2NO4 | HMDB00582 |
| dimethylglycine | C4H9NO2 | C01026 |
| DL-Pipecolic acid | C6H11NO2 | C00408 |
| D-sedoheptulose-1-7-phosphate | C7H15O10P | C05382 |
| dTDP | C10H16N2O11P2 | C00363 |
| dTMP | C10H15N2O8P | C00364 |
| dTTP | C10H17N2O14P3 | C00459 |
| dUMP | C9H13N2O8P | C00365 |
| dUTP | C9H15N2O14P3 | C00460 |
| ethanolamine | C2H7NO | C00189 |
| FAD | C27H33N9O15P2 | C00016 |
| Flavone | C15H10O2 | C15608 |
| FMN | C17H21N4O9P | C00061 |
| folate | C19H19N7O6 | C00504 |
| fructose-1,6-bisphosphate | C6H14O12P2 | C05378 |
| fructose-6-phosphate | C6H13O9P | C05345 |
| fumarate | C4H4O4 | C00122 |
| GDP-nega | C10H15N5O11P2 | C00035 |
| Geranyl-PP | C10H20O7P2 | C00341 |
| glucono-?-lactone | C6H10O6 | C00198 |
| glucosamine | C6H13NO5 | C00329 |
| glucose-1-phosphate | C6H13O9P | C00103 |

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|---|---|---|
| glucose-6-phosphate | C6H13O9P | C00668 |
| glutamate | C5H9NO4 | C00025 |
| glutamine | C5H10N2O3 | C00064 |
| glutarate | C5H8O4 | C00489 |
| glutathione | C10H17N3O6S | C00051 |
| glutathione disulfide | C20H32N6O12S2 | C00127 |
| glycerate | C3H6O4 | C00258 |
| glycerol 3-phosphate | C3H9O6P | C00093 |
| Glycerophosphocholine | C8H21NO6P | C00670 |
| glycine | C2H5NO2 | C00037 |
| glycolate | C2H4O3 | C00160 |
| glyoxylate | C2H2O3 | C00048 |
| GMP | C10H14N5O8P | C00144 |
| GTP | C10H16N5O13P3 | C00044 |
| Guanidoacetic acid | C3H7N3O2 | C00581 |
| guanine | C5H5N5O | C00242 |
| guanosine | C10H13N5O5 | C00387 |
| guanosine 5-diphosphate,3-diphosphate | C10H11N5O17P4 | C01228 |
| hexose-phosphate | C6H13O9P | C05345 |
| histidine | C6H9N3O2 | C00135 |
| histidinol | C6H11N3O | C00860 |
| HMG-CoA | C27H44N7O20P3S | C00356 |
| homocysteic acid | C4H9NO5S | C16511 |
| homocysteine | C4H9NO2S | C00155 |
| homoserine | C4H9NO3 | C00263 |
| Hydroxyisocaproic acid | C6H12O3 | HMDB00746 |
| Hydroxyphenylacetic acid | C8H8O3 | C05852 |
| hydroxyphenylpyruvate | C9H8O4 | C01179 |
| hydroxyproline | C5H9NO3 | C01157 |
| hypoxanthine | C5H4N4O | C00262 |
| IDP-nega | C10H14N4O11P2 | C00104 |
| Imidazole | C3H4N2 | C01589 |
| Imidazoleacetic acid | C6H8N2O2 | C02835 |
| IMP | C10H13N4O8P | C00130 |
| indole | C8H7N | C00463 |
| Indole-3-carboxylic acid | C9H7NO2 | HMDB03320 |
| Indoleacrylic acid | C11H9NO2 | HMDB00734 |
| inosine | C10H12N4O5 | C00294 |
| isocitrate | C6H8O7 | C00311 |
| itaconic acid | C5H6O4 | HMDB0002092 |
| Kynurenic acid | C10H7NO3 | C01717 |
| Kynurenine | C10H12N2O3 | C00328 |
| lactate | C3H6O3 | C00186 |
| L-arginino-succinate | C10H18N4O6 | C03406 |
| leucine-isoleucine | C6H13NO2 | C00123 |
| lipoate | C8H14O2S2 | C00725 |
| lysine | C6H14N2O2 | C00047 |

| | | |
|---|---|---|
| malate | C4H6O5 | C00149 |
| Maleic acid | C4H4O4 | C01384 |
| malonyl-CoA | C24H38N7O19P3S | C00083 |
| methionine | C5H11NO2S | C00073 |
| Methionine sulfoxide | C5H11NO3S | HMDB02005 |
| Methylcysteine | C4H9NO2S | HMDB0002108 |
| Methylmalonic acid | C4H6O4 | C02170 |
| methylnicotinamide | C7H9N2O | C02918 |
| Mevalonate | C6H12O4 | C00418 |
| myo-inositol | C6H12O6 | C00137 |
| N6-Acetyl-L-lysine | C8H16N2O3 | C02727 |
| N-acetyl spermidine | C9H21N3O | C00612 |
| N-acetyl spermine | C12H28N4O | C02567 |
| N-acetyl-aspartylglutamic acid | C11H16N2O8 | C12270 |
| N-acetyl-glucosamine | C8H15NO6 | C00140 |
| N-acetyl-glucosamine-1-phosphate | C6H14NO8P | C04256 |
| N-acetyl-glutamate | C7H11NO5 | C00624 |
| N-acetyl-glutamine | C7H12N2O4 | HMDB06029 |
| N-Acetyl-L-alanine | C5H9NO3 | C01073 |
| N-acetyl-L-aspartic acid | C6H9NO5 | C01042 |
| N-acetyl-L-ornithine | C7H14N2O3 | C00437 |
| N-Acetylputrescine | C6H14N2O | C02714 |
| NAD+ | C21H27N7O14P2 | C00003 |
| NADH | C21H29N7O14P2 | C00004 |
| NADP+ | C21H28N7O17P3 | C00006 |
| NADPH | C21H30N7O17P3 | C00005 |
| N-carbamoyl-L-aspartate | C5H8N2O5 | C00438 |
| Ng,NG-dimethyl-L-arginine | C8H18N4O2 | C03626 |
| nicotinamide | C6H6N2O | C00153 |
| nicotinamide riboside | C11H15N2O5 | C03150 |
| Nicotinamide ribotide | C11H15N2O8P | C00455 |
| nicotinate | C6H5NO2 | C00253 |
| O8P-O1P (octulose-8-phosphate) | C5H11O8P | |
| O-acetyl-L-serine | C5H9NO4 | C00979 |
| octulose-1,8-bisphosphate (OBP) | C5H11O8P | |
| ornithine | C5H12N2O2 | C00077 |
| orotate | C5H4N2O4 | C00295 |
| orotidine-5-phosphate | C10H13N2O11P | C01103 |
| oxaloacetate | C4H4O5 | C00036 |
| p-aminobenzoate | C7H7NO2 | C00568 |
| pantothenate | C9H17NO5 | C00864 |
| phenylalanine | C9H11NO2 | C00079 |
| Phenyllactic acid | C9H10O3 | C01479 |
| Phenylpropiolic acid | C9H6O2 | HMDB00563 |
| phenylpyruvate | C9H8O3 | C00166 |
| Phosphocreatine | C4H10N3O5P | C02305 |
| phosphoenolpyruvate | C3H5O6P | C00074 |

| | | |
|---|---|---|
| Phosphorylcholine | C5H15NO4P | C00588 |
| p-hydroxybenzoate | C7H6O3 | C00156 |
| prephenate | C10H10O6 | C00254 |
| proline | C5H9NO2 | C00148 |
| propionyl-CoA | C24H40N7O17P3S | C00100 |
| purine | C5H4N4 | C00465 |
| putrescine | C4H12N2 | C00134 |
| Pyridoxamine | C8H12N2O2 | C00534 |
| pyridoxine | C8H11NO3 | C00314 |
| Pyroglutamic acid | C5H7NO3 | C01879 |
| Pyrophosphate | P2H4O7 | C00013 |
| pyruvate | C3H4O3 | C00022 |
| quinolinate | C7H5NO4 | C03722 |
| retinoic acid | C20H28O2 | C00777 |
| riboflavin | C17H20N4O6 | C00255 |
| ribose-phosphate | C5H11O8P | C00117 |
| S-adenosyl-L-homocysteine | C14H20N6O5S | C00021 |
| S-adenosyl-L-methioninamine | C14H23N6O3S | C01137 |
| S-adenosyl-L-methionine | C15H22N6O5S | C00019 |
| sarcosine | C3H7NO2 | C00213 |
| sedoheptulose 1,7-bisphosphate (SBP) | C7H16O13P2 | C00447 |
| serine | C3H7NO3 | C00065 |
| shikimate | C7H10O5 | C00493 |
| shikimate-3-phosphate | C7H11O8P | C03175 |
| S-methyl-5-thioadenosine | C11H15N5O3S | C00170 |
| sn-glycerol-3-phosphate | C3H9O6P | C00093 |
| sorbitol | C6H14O6 | C00794 |
| spermidine | C7H19N3 | C00315 |
| spermine | C10H26N4 | C00750 |
| S-ribosyl-L-homocysteine | C9H17NO6S | C03539 |
| succinate | C4H6O4 | C00042 |
| succinyl-CoA-methylmalonyl-CoA | C25H40N7O19P3S | C00091 |
| succinyl-CoA-posi | C25H40N7O19P3S | C00091 |
| taurine | C2H7NO3S | C00245 |
| Taurodeoxycholic acid | C26H45NO6S | C05463 |
| thiamine | C12H16N4OS | C00378 |
| Thiamine pyrophosphate | C12H19N4O7P2S | C00068 |
| thiamine-phosphate | C12H17N4O4PS | C01081 |
| threonine | C4H9NO3 | C00188 |
| thymidine | C10H14N2O5 | C00214 |
| thymine | C5H6N2O2 | C00178 |
| trans, trans-farnesyl diphosphate | C15H28O7P2 | C00448 |
| trehalose-6-Phosphate | C12H23O14P | C00689 |
| trehalose-sucrose | C12H22O11 | C00089 |
| tryptophan | C11H12N2O2 | C00078 |
| tyrosine | C9H11NO3 | C00082 |
| UDP-D-glucose | C15H24N2O17P2 | C00029 |

| | | |
|---|---|---|
| UDP-D-glucuronate | C15H22N2O18P2 | C00167 |
| UDP-N-acetyl-glucosamine | C17H27N3O17P2 | C00043 |
| UDP-nega | C9H14N2O12P2 | C00015 |
| UDP-xylose | C14H22N2O16P2 | C00190 |
| UMP | C9H13N2O9P | C00105 |
| uracil | C4H4N2O2 | C00106 |
| Urea | CH4N2O | C00086 |
| Uric acid | C5H4N4O3 | C00366 |
| uridine | C9H12N2O6 | C00299 |
| UTP-nega | C9H15N2O15P3 | C00075 |
| valine | C5H11NO2 | C00183 |
| xanthine | C5H4N4O2 | C00385 |
| xanthosine | C10H12N4O6 | C01762 |
| xanthosine-5-phosphate | C10H13N4O9P | C00655 |
| Xanthurenic acid | C10H7NO4 | C02470 |

**Table S3:** Percentage of molecules with a coefficient of variation (CV) less than noted in the column header. Corrected represents drift-corrected signal values, and 'processed' represents final signal values used for downstream statistical analysis after preprocessing.

Lipids

| CV% | <5 | <10 | <15 | <20 | <25 | <30 | <35 | <40 | <50 | <60 | <70 | <80 | <90 | <100 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Raw | 0.00 | 0.43 | 4.72 | 9.01 | 13.7 | 21.5 | 34.8 | 44.6 | 56.7 | 62.7 | 69.1 | 73.4 | 79.4 | 83.3 |
| Corrected | 0.43 | 6.87 | 12.9 | 24.5 | 36.9 | 45.9 | 53.2 | 63.1 | 71.2 | 82.0 | 91.0 | 97.0 | 100 | 100 |
| Processed | 89.5 | 98.8 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

Metabolites

| CV% | <5 | <10 | <15 | <20 | <25 | <30 | <35 | <40 | <50 | <60 | <70 | <80 | <90 | <100 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Raw | 3.1 | 21.8 | 39.6 | 46.7 | 59.6 | 66.2 | 74.2 | 80.0 | 87.6 | 93.3 | 97.3 | 97.8 | 97.8 | 97.8 |
| Corrected | 25.8 | 43.6 | 63.1 | 76.0 | 82.2 | 90.2 | 93.3 | 96.9 | 99.1 | 99.5 | 100 | 100 | 100 | 100 |
| Processed | 96.3 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

To assess the potential existence of technical confounders in our lipidomics and metabolomics studies we calculated the coefficient of variation (CV) for the pooled quality control samples at each preprocessing step. After processing, 100 percent of the metabolites and 98.8 percent of the lipids had a CV of less than 10 percent.

**Table S4:** List of input molecules for each stage of systems analysis

| Pathway Analysis using MetaboAnalyst Metabolites (n=51) | Pathway Analysis using LIPEA lipids (n=26) | OBaNK Interaction Analysis Multi-omics (n=109; l=26; m=51; p=32) | SVM and Cluster Analysis (n=25; l=8; m=15; p=2) |
|---|---|---|---|
| 1-Methyladenosine | PC(36:7e) | PC(36:7e) | PC(36:7e) |
| 1,3-diphopshateglycerate | PE(16:1e)(22:6) | PE(16:1e)(22:6) | PE(18:0)(20:3) |
| 2-deoxyglucose-6-phosphate | BiotinylPE(32:5) | BiotinylPE(32:5) | CerP(d36:3+O) |
| 2-hydroxygluterate | PIP2(31:6e) | PIP2(31:6e) | PE(16:1e)(20:4) |
| 2-oxo-4-methylthiobutanoate | DG(8:0)(12:2) | DG(8:0)(12:2) | SM(d38:2) |
| 2,3-Diphosphoglyceric acid | DG(4:0)(10:3) | DG(4:0)(10:3) | PC(32:1e) |
| 3-hydroxybuterate | DG(4:0)(11:3) | DG(4:0)(11:3) | PC(32:0e) |
| 3-methylphenylacetic acid | PC(17:0)(14:1) | PC(17:0)(14:1) | PC(35:1) |
| 7-methylguanosine | PC(16:1e)(18:1) | PC(16:1e)(18:1) | deoxyadenosine |
| acadesine | CL(15:0)(18:1)(15:0)(18:1) | CL(15:0)(18:1)(15:0)(18:1) | shikimate |
| Acetyllysine | PE(40:5e) | PE(40:5e) | indoleacrylic acid |
| alanine | DG(6:0)(11:3) | DG(6:0)(11:3) | S-adenosyl-L-homocysteine |
| anthranilate | ChE(20:4) | ChE(20:4) | 1,3-diphopshateglycerate |
| arginine | DG(18:3e) | DG(18:3e) | methylnicotinamide |
| asparagine | PI(18:0)(20:4) | PI(18:0)(20:4) | anthranilate |
| aspartate | TG(16:0)(16:0)(17:0) | TG(16:0)(16:0)(17:0) | N-acetyl spermidine |
| Carbamoyl phosphate | TG(6:0)(6:0)(14:1) | TG(6:0)(6:0)(14:1) | glucose-6-phosphate |
| D-gluconate | TG(12:1e)(6:0)(6:0) | TG(12:1e)(6:0)(6:0) | hydroxyphenylacetic acid |
| D-glucono-delta-lactone-6-phosphate | PE(18:0)(22:6) | PE(18:0)(22:6) | 7-methylguanosine |
| D-sedoheptulose-1-7-phosphate | CerP(d36:3+O) | CerP(d36:3+O) | S-ribosyl-L-homocysteine |
| deoxyadenosine | PE(16:1e)(20:4) | PE(16:1e)(20:4) | fructose-6-phosphate |
| deoxyinosine | PC(32:0e) | PC(32:0e) | 2,3-Diphosphoglyceric acid |
| deoxyribose-phosphate | PC(32:1e) | PC(32:1e) | N-Acetylputrescine |
| dGMP | PE(18:0)(20:3) | PE(18:0)(20:3) | ACAN |
| dihydroxy-acetone-phosphate | SM(d38:2) | SM(d38:2) | CFL1 |
| dTTP | PC(35:1) | PC(35:1) | |
| fructose-6-phosphate | | 1-Methyladenosine | |
| glucose-6-phosphate | | 1,3-diphopshateglycerate | |
| guanine | | 2-deoxyglucose-6-phosphate | |
| homoserine | | 2-hydroxygluterate | |
| hydroxyphenylacetic acid | | 2-oxo-4-methylthiobutanoate | |
| Indoleacrylic acid | | 2,3-Diphosphoglyceric acid | |
| Kynurenine | | 3-hydroxybuterate | |
| Methylmalonic acid | | 3-methylphenylacetic acid | |

| | | | |
|---|---|---|---|
| methylnicotinamide<br>N-acetyl spermidine<br>N-acetyl-glutamate<br>N-Acetylputrescine<br>N6-Acetyl-L-lysine<br>Nicotinamide Riboside<br>ornithine<br>Phenylpropiolic acid<br>ribose-phosphate<br>S-adenosyl-L-homocysteine-nega<br>S-ribosyl-L-homocysteine<br>SBP<br>shikimate<br>succinate<br>trehalose-sucrose<br>uracil<br>uridine | | 7-methylguanosine<br>acadesine<br>Acetyllysine<br>alanine<br>anthranilate<br>arginine<br>asparagine<br>aspartate<br>Carbamoyl phosphate<br>D-gluconate<br>D-glucono-delta-lactone-6-phosphate<br>D-sedoheptulose-1-7-phosphate<br>deoxyadenosine<br>deoxyinosine<br>deoxyribose-phosphate<br>dGMP<br>dihydroxy-acetone-phosphate<br>dTTP<br>fructose-6-phosphate<br>glucose-6-phosphate<br>guanine<br>homoserine<br>Hydroxyphenylacetic acid<br>Indoleacrylic acid<br>Kynurenine<br>Methylmalonic acid<br>methylnicotinamide<br>N-acetyl spermidine<br>N-acetyl-glutamate<br>N-Acetylputrescine<br>N6-Acetyl-L-lysine<br>Nicotinamide Riboside<br>ornithine<br>Phenylpropiolic acid<br>ribose-phosphate<br>S-adenosyl-L-homocysteine-nega<br>S-ribosyl-L-homocysteine | |

| | | | |
|---|---|---|---|
| | | SBP<br>shikimate<br>succinate<br>trehalose-sucrose<br>uracil<br>uridine<br>ACAN<br>CFL1<br>CXCL11<br>H2AFZ<br>MUC1<br>NAMPT<br>INS<br>CD97<br>ICOS<br>PARK7<br>FAM107B<br>CD38<br>NGF<br>PPIF<br>THPO<br>DCN<br>MICA<br>HAPLN1<br>PRKCA<br>PTPN6<br>IGFBP2<br>FSTL1<br>CTSD<br>PROC<br>CCL28<br>CHRDL1<br>MSN<br>MMP14<br>CCL2<br>CXCL6<br>GNLY<br>CTSV | |

**Table S5**: Functional analysis of lipids at the system level using LIPEA. The eighteen pathways included at least one input lipid.

| Pathway name | Total | Hits | Lipids |
|---|---|---|---|
| Sphingolipid signaling pathway | 9 | 1 | Sphingomyelin |
| Linoleic acid metabolism | 25 | 1 | Phosphatidylcholine |
| alpha-Linolenic acid metabolism | 23 | 1 | Phosphatidylcholine |
| Autophagy - animal | 4 | 2 | Phosphatidylinositol, **Phosphatidylethanolamine** |
| Glycerophospholipid metabolism | 26 | 4 | Phosphatidylinositol, Cardiolipin, Phosphatidylcholine, **Phosphatidylethanolamine** |
| Glycosylphosphatidylinositol (GPI)-anchor biosynthesis | 3 | 2 | Phosphatidylinositol, **Phosphatidylethanolamine** |
| Necroptosis | 4 | 1 | Sphingomyelin |
| Sphingolipid metabolism | 21 | 1 | Sphingomyelin |
| Arachidonic acid metabolism | 75 | 1 | Phosphatidylcholine |
| Phosphatidylinositol signaling system | 11 | 1 | Phosphatidylinositol |
| Autophagy - other | 3 | 2 | Phosphatidylinositol, **Phosphatidylethanolamine** |
| Inositol phosphate metabolism | 9 | 1 | Phosphatidylinositol |
| Ferroptosis | 11 | 2 | 1-Octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-**phosphoethanolamine**, 1-Octadecanoyl-2-(7Z,10Z,13Z,16Z-docosatetraenoyl)-sn-glycero-3-**phosphoethanolamine** |
| Pathogenic Escherichia coli infection | 1 | 1 | **Phosphatidylethanolamine** |
| Tuberculosis | 5 | 1 | Phosphatidylinositol |
| Kaposi's sarcoma-associated herpesvirus infection | 3 | 1 | **Phosphatidylethanolamine** |
| Retrograde endocannabinoid signaling | 8 | 2 | Phosphatidylcholine |
| Choline metabolism in cancer | 5 | 1 | Phosphatidylcholine |

Total: number of lipids in the pathway. Hits: lipids significantly different between delirium and control groups that are in the pathway. Lipids: Main lipid category and KEGG identifier returned by LIPEA.

**Table S6:** Leave-one-out-cross-validation (L1OXV) accuracy and area under curve (AUC) of the receiver's operating curve (ROC) for eight data sets used for regularized logistic regression with the elastic net analysis. AUC_L and AUC_U represent the lower and upper bounds for the 95% confidence interval for AUC. We applied the logistic regression with elastic net analysis on 8 data sets: (i) 26 lipids and (ii) 51 metabolites found to be significantly associated with delirium in this study, (iii) 32 proteins that are identified in Dillon et al., (iv) combination of these 3 sets (109 molecules), and 1.5 tFC cut-off applied to the sets (i-iii), which rendered (v) 8 lipids, (vi) 15 metabolites, (vii) 2 proteins, and (viii) 25 molecules that is the combination of (v-vii). For each data set, we calculated leave-one-out-cross-validation accuracy and the AUC of ROC.

| | **L1OXV** | **AUC** | **AUC_L** | **AUC_U** |
|---|---|---|---|---|
| **25 Molecules** | **73.33** | **0.8622** | **0.6303** | **0.9593** |
| **8 Lipids** | 43.33 | 0.5733 | 0.2858 | 0.7418 |
| **15 Metabolites** | 76.67 | 0.7911 | 0.5269 | 0.9353 |
| **2 Proteins** | 26.67 | 0.3733 | 0.1603 | 0.5976 |
| **109 Molecules** | 70 | 0.8089 | 0.5846 | 0.9286 |
| **26 Lipids** | 63.33 | 0.6933 | 0.4465 | 0.866 |
| **51 Metabolites** | 70 | 0.7067 | 0.4696 | 0.8707 |
| **32 Proteins** | 56.67 | 0.7244 | 0.5028 | 0.8839 |

**Table S7**: Metabolites common between plasma and CSF.

Comparison of metabolites that are associated with delirium based on (a) HiPOR CSF analysis at PREOP, (b) SAGES plasma analysis at PREOP, (c) SAGES plasma analysis at POD2. Metabolites common to all three are denoted in yellow, common in POD2 plasma and CSF denoted in grey, and common to PREOP plasma and CSF in green.

(a) CSF Preoperative (PREOP)

| Metabolites | Nom-p | tFC |
|---|---|---|
| **D-gluconate** | 0.0481 | 1.26 |
| **S-ribosyl-L-homocysteine** | 0.0069 | 1.57 |
| **1-methyladenosine** | 0.0128 | 1.40 |
| **Acetyllysine** | 0.0345 | 1.25 |
| **Deoxyinosine** | 0.0481 | 1.25 |
| **D-glucono-Δ-lactone-6-phosphate** | 0.0481 | 1.48 |
| **D-sedoheptulose-1-7-phosphate** | 0.0182 | 1.18 |
| **Isocitrate** | 0.0481 | 1.14 |
| **S-adenosyl-L-homocysteine** | 0.0005 | 1.95 |
| **DL-pipecolic acid** | 0.0481 | 1.10 |
| **N-acetyl-glutamate** | 0.0007 | 1.24 |
| **Nicotinamide riboside** | 0.0385 | 1.46 |
| **Uracil** | 0.0075 | 1.41 |

(b) Plasma Preoperative (PREOP)

| Metabolites | Avg-p | tFC |
|---|---|---|
| **D-gluconate** | 0.03 | 0.92 |
| **S-ribosyl-L-homocysteine** | 0.01 | -0.86 |
| **DL-pipecolic acid** | 0.03 | -0.94 |
| **N-acetyl-glutamate** | 0.02 | -1.03 |
| **Nicotinamide riboside** | 0.07 | 0.74 |
| **Uracil** | 4.2E-03 | -1.32 |

(c) Plasma Postoperative Day 2 (POD2)

| Metabolites | Avg-p | tFC |
|---|---|---|
| **D-gluconate** | 0.01 | 0.99 |
| **S-ribosyl-L-homocysteine** | 0.03 | 1.11 |
| **1-methyladenosine** | 0.01 | 1.55 |
| **Acetyllysine** | 0.02 | 1.54 |
| **Deoxyinosine** | 1.4E-03 | 1.90 |
| **D-glucono-Δ-lactone-6-phosphate** | 0.03 | 0.81 |
| **D-sedoheptulose-1-7-phosphate** | 0.03 | 1.06 |
| **Isocitrate** | 2.1E-03 | 1.52 |
| **S-adenosyl-L-homocysteine** | 0.03 | 1.02 |

**Table S8**: Quality Control Measures Applied to Instrumentation

| Lipidomics | Metabolomics |
|---|---|
| The platform identifies an average of ~1500 unique lipid species per sample though this number changes based on sample quantity, complexity and purity. The identification are based not only on masses alone but also on MS/MS spectra that are searched against the LipidMaps and LipidSearch internal software databases. The spectra are graded with a letter designation and a mScore. Only scores above 5.0 are accepted and only grades A-C are accepted as these have fragment ions that match the fatty acid chains, head groups and various backbone for each lipid class. In addition, only precursor masses and fragment masses less than 8 ppm to the identified lipid are accepted. In most cases, the mass accuracy match is less than 2 ppm. A set of lipid standards that cover 5 different lipid classes are run on a daily basis for platform accuracy and quality control. | The targeted metabolomics platform used selected reaction monitoring (SRM) with positive/negative polarity switching to target 305 polar metabolites. Q3 fragment ion peak areas are calculated for identification and quantification. In short, the mass for each metabolite of interest is first filtered in Q1 by intact mass and then a specific and unique fragment ion is further filtered in Q3 after being fragmented in Q2. This method has very high specificity as all compounds were compared to known standards and chromatographic retention time is also used for identification accuracy. The end result is not a spectrum in the traditional sense but just a single fragment peak representing the analyte of interest. A cell extract that contains al targeted metabolites is run daily to assure platform accuracy and quality control. |