

Table S1. Proportions of single metabolites and ratios above cutoff limits, and results from applying algorithms according to the Austrian and Heidelberg NBS for cases and controls (n, %).

| | Clinical cases (n=70) | Clinical cases with B12<160 or holoTC<35 pmol/L (n=30) | Matched controls (n=646) | Un-matched controls (n=434) |
|----------------------------------------|--------------------------|-----------------------------------------------------------------|--------------------------------|-----------------------------------|
| C3>97p (4.0 µmol/L) | 1 (1.4%) | 1 (3.3%) | 9 (1.4%) | 28 (6.5%) |
| C3>99p (4.9 µmol/L) | 1 (1.4%) | 1 (3.3%) | 4 (0.6%) | 10 (2.3%) |
| MET<5p (11.7 µmol/L) | 5 (7.1%) | 3 (10%) | 39 (6.0%) | 43 (10%) |
| MET<0.59p (8.9 µmol/L) | 1 (1.4%) | 1 (3.3%) | 6 (0.9%) | 8 (1.8%) |
| MET/PHE<1.75p (0.21) | 3 (4.3%) | 2 (6.7%) | 21 (3.3%) | 21 (4.8%) |
| MET/PHE<5p (0.23) | 5 (7.1%) | 4 (13%) | 39 (6.0%) | 34 (7.8%) |
| MET/PHE>89p (0.44) | 5 (7.1%) | 3 (10%) | 31 (4.8%) | 13 (3.0%) |
| C3/C0>99.3p (0.29) | 0 | 0 | 5 (0.8%) | 11 (2.5%) |
| C3/C2>99.5p (0.21) | 1 (1.4%) | 1 (3.3%) | 1 (0.2%) | 4 (0.9%) |
| C3/C2>99.9p (0.25) | 0 | 0 | 1 (0.2%) | 0 |
| C3/C16>99.2p (1.63) | 2 (2.9%) | 1 (3.3%) | 6 (0.9%) | 1 (0.2%) |
| C3/MET>97p (0.24) | 3 (4.3%) | 2 (6.7%) | 11 (1.7%) | 41 (9.4%) |
| tHcy>6.3 µmol/L | 33 (47%) | 17 (57%) | 195 (30%) | 46 (11%) |
| tHcy>8.6 µmol/L | 13 (19%) | 7 (23%) | 60 (9.3%) | 14 (3.2%) |
| MMA>0.423 µmol/L | 10 (14%) | 4 (13%) | 22 (3.4%) | 115 (26%) |
| MMA>2.35 µmol/L | 1 (1.4%) | 0 | 1 (0.2%) | 0 |
| MCA>0.34 µmol/L | 2 (2.9%) | 1 (3.3%) | 31 (4.8%) | 7 (1.6%) |
| Heidelberg Met pathway | 12 (17%) | 8 (27%) | 89 (14%) | 72 (17%) |
| Heidelberg Met pathway and tHcy>8.6 | 3 (4.3%) | 3 (10%) | 4 (0.6%) | 1 (0.2%) |

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|-----------------------------------|-----------|-----------|-----------|------------|
| Heidelberg C3 pathway | 1 (1.4%) | 1 (3.3%) | 4 (0.6%) | 14 (3.2%) |
| Heidelberg C3 pathway and MMA/MCA | 0 | 0 | 0 | 2 (0.5%) |
| Austrian low C3 pathway | 1 (1.4%) | 1 (3.3%) | 6 (0.9%) | 15 (3.5%) |
| Austrian low C3 and tHcy>6.3 | 1 (1.4%) | 1 (3.3%) | 3 (0.5%) | 1 (0.2%) |
| Austrian low C3 and tHcy>8.6 | 0 | 0 | 1 (0.2%) | 1 (0.2%) |
| Austrian high C3 pathway | 1 (1.4%)* | 1 (3.3%)* | 4 (0.6%)* | 10 (2.3%)* |
| Austrian high C3 and tHcy>6.3 | 1 (1.4%)* | 1 (3.3%)* | 2 (0.3%)* | 1 (0.2%)* |
| Austrian high C3 and tHcy>8.6 | 0 | 0 | 1 (0.2%)* | 1 (0.2%)* |
| Austrian Met pathway | 3 (4.3%) | 2 (6.7%) | 23 (3.6%) | 24 (5.5%) |
| Austrian Met and tHcy>6.3 | 1 (1.3%) | 1 (3.3%) | 4 (0.6%) | 0 |
| Austrian Met and tHcy>8.6 | 0 | 0 | 0 | 0 |

*=overlapping with low C3 pathway, Met=methionine, Phe=phenylalanine, C0=carnitine, C2=acetylcarnitine, C3=propionylcarnitine,

C16=palmitoylcarnitine, tHcy=total homocysteine, MMA=methylmalonic acid, MCA=methylcitric acid.