General disease biomarkers for PA and MMA, from targeted metabolic assays

Supplementary Figure 1
Supplementary Figure 2

General disease biomarkers for PA and MMA (increased), from DI–HRMS analysis

- 2-Methylcitric acid
- 3-Dehydroxycarnitine
- Propionylcarnitine
- Fructoseglycine
- Isoleucyl-Isoleucine
- LysoPC(15:0)
- Glucosamine
- Threonic acid

General disease biomarkers for PA and MMA (decreased), from DI–HRMS analysis

- DL-2-Amino-octanoic acid
- 2-Methyl-3-ketovaleric acid
- Glutamine
- Methionine
- Histidine
Supplementary Figure 3

General disease biomarkers for PA, from DI−HRMS analysis

- Propionylglycine
- Glycine
- 2-Amino-3-phosphonopropionic acid
- 1-(sn-Glycero-3-phospho)-1D-myo-inositol
- LysoPC(17:0)
- Homocysteine
- Isoleucine

General disease biomarkers for MMA, from DI−HRMS analysis

- Methylmalonic acid
- Propionic acid
- 3-Hydroxy-9-hexadecanoylcarnitine
Supplementary Figure 4

PLS-DA, VIP-scores and heatmap for PA samples versus control samples

A) DBS

B) Plasma
Supplementary Figure 5

Plasma, targeted Acute metabolic decompensations

Propionylcarnitine (PL)

Age (y)

Z-score

0 2 4 6 8 10 12 14 16 18 20

0 2 4 6 8 10 12 14 16 18 20

0 2 4 6 8 10 12 14 16 18 20

0 50 100 150 200

0 50 100 150 200

0 50 100 150 200

0 2 4 6 8 10 12 14 16 18 20

0 2 4 6 8 10 12 14 16 18 20

0 2 4 6 8 10 12 14 16 18 20

0 50 100 150 200

0 50 100 150 200

0 50 100 150 200

Age (y)
Supplementary Figure 6

Propionylcarnitine (DI-HRMS)
Supplementary Figure 7

Propionylglycine (DI-HRMS)

- PA, P.14
- MMA, P.01
- MMA, P.06
- PA, P.16
- MMA, P.02
- MMA, P.07
- PA, P.17
- MMA, P.03
- MMA, P.10
- PA, P.19
- PA, P.22
- PA, P.23
- PA, P.24

Acute metabolic decompensations
Dried blood spots
Plasma

Age (y)
Z-score
Supplementary Figure 8

Plasma, targeted Acute metabolic decompensations
Supplementary Figure 9

Glycine (DI–HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma
Supplementary Figure 10

3-Dehydroxycarnitine (DI-HRMS)

Plasma Dried blood spots

Acute metabolic decompensations
Supplementary Figure 11

2-Methylcitric acid (DI–HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma

Plasma
Dried blood spots
Acute metabolic decompensations

Age (y)
Z-score
**Supplementary Figure 12**

**A) DBS**

PLS-DA, VIP-scores and heatmap for MMA samples versus control samples.

**B) Plasma**

PLS-DA, VIP-scores and heatmap for MMA samples versus control samples.
Supplementary Figure 14

Methylmalonic acid (PL)

Age (y)
Supplementary Figure 15

**Methylmalonic acid (DI-HRMS)**

- **Acute metabolic decompensations**
- **Dried blood spots**
- **Plasma**

**Plasma**

**Dried blood spots**

**Acute metabolic decompensations**

- **P.14**
- **P.18**
- **P.16**
- **P.17**
- **P.19**
- **P.22**
- **P.23**
- **P.24**

**Age (y)**

**Z-score**
Supplementary Figure 16

Methylmalonylcarnitine (PL)

Z-score vs. Age (y)

Acute metabolic decompensations
Plasma, targeted
Supplementary Figure 17

Methylmalonylcarnitine (DI–HRMS)

Age (y)
Supplementary Figure 19

Urea (PL)

Z-score vs. Age (y)

Acute metabolic decompensations
Plasma, targeted
Supplementary Figure 20

Ammonia (PL)

- Acute metabolic decompensations
- Plasma, targeted

Z-score vs. Age (y) for different samples:
- PA, P.14
- PA, P.18
- MMA, P.01
- MMA, P.02
- MMA, P.03
- MMA, P.06
- MMA, P.07
- MMA, P.10
- PA, P.16
- PA, P.17
- PA, P.19
- PA, P.22
- PA, P.23
- PA, P.24
Supplementary Figure 21

Biomarkers AMD for PA (increased), from targeted metabolic assays

- Leucine (PL)
- Phenylalanine (PL)
- Valine (PL)
- Isoleucine (PL)
- Lactic acid (U)
- 3−OH−Butyric acid (U)
- Pyruvic acid (U)

Biomarkers AMD for PA (decreased), from targeted metabolic assays

- Glutamine (PL)
- Citrulline (PL)
- Decanoylcarnitine (PL)
- Carnitine (PL)
- Octanoylcarnitine (PL)
- Homovanillic acid (U)
Supplementary Figure 22

Valine (PL)

- PA, P.14
- PA, P.18

MMA, P.01
MMA, P.02
MMA, P.03
MMA, P.06
MMA, P.07
MMA, P.10

PA, P.16
PA, P.17
PA, P.19
PA, P.22
PA, P.23
PA, P.24

Z-score
Age (y)

Acute metabolic decompensations
Plasma, targeted
Supplementary Figure 23

Plasma, targeted Acute metabolic decompensations

Z-score

Age (y)
Supplementary Figure 24

Glutamine (PL)

- PA, P.14
- PA, P.18
- MMA, P.01
- MMA, P.02
- MMA, P.03
- MMA, P.06
- MMA, P.07
- MMA, P.10
- PA, P.16
- PA, P.17
- PA, P.19
- PA, P.22
- PA, P.23
- PA, P.24

- Acute metabolic decompensations
- Plasma, targeted

Age (y)
Supplementary Figure 25

Citrulline (PL)

- Z-score

Acute metabolic decompensations
Plasma, targeted

Age (y)
Supplementary Figure 26

Free carnitine (PL)

PA, P.14
PA, P.18
MMA, P.01
MMA, P.02
MMA, P.03
MMA, P.06
MMA, P.07
MMA, P.10
PA, P.16
PA, P.17
PA, P.19
PA, P.22
PA, P.23
PA, P.24

Age (y)
Z-score

Acute metabolic decompensations
Plasma, targeted
Supplementary Figure 27

Lactate (U)

Z-score vs. Age (y)

Acute metabolic decompensations
Urine, targeted

PA, P.14
PA, P.18
MMA, P.01
MMA, P.02
MMA, P.03
MMA, P.06
MMA, P.07
MMA, P.10
PA, P.16
PA, P.17
PA, P.19
PA, P.22
PA, P.23
PA, P.24
Supplementary Figure 28

Plasma, targeted Acute metabolic decompensations

Lactate (PL)
Supplementary Figure 29

3-Hydroxybutyric acid (U)

Age (y)

Z-score

Urine, targeted

Acute metabolic decompensations

PA, P.14

PA, P.18

MMA, P.01

MMA, P.02

MMA, P.03

MMA, P.06

MMA, P.07

MMA, P.10

PA, P.16

PA, P.17

PA, P.19

PA, P.22

PA, P.23

PA, P.24
Supplementary Figure 33

Correlation to Ammonia in plasma, from DI–HRMS analysis

- 2-Methylcitric acid (PL): $R^2 = 0.69$
- Alanyl-Isoleucine (PL): $R^2 = 0.66$
- 3-Hydroxyisovaleric acid (PL): $R^2 = 0.65$
- 3-Methyl-2-oxovaleric acid (DBS): $R^2 = 0.56$
- Isobutyrylglycine (PL): $R^2 = 0.56$
- Indole-5,6-quinone (DBS): $R^2 = 0.53$
- Propionylglycine (DBS): $R^2 = 0.52$
- 3-OH-Phenylacetic acid (PL): $R^2 = 0.51$
- Indole-5,6-quinone (PL): $R^2 = 0.51$
- Pyrocatechol sulfate (DBS): $R^2 = -0.65$
- Threonic acid (DBS): $R^2 = -0.6$
- Trimethylamine N-oxide (DBS): $R^2 = -0.59$
- Stearoylcarnitine (DBS): $R^2 = -0.58$
- Methylmalonic acid (DBS): $R^2 = -0.57$
- Ergothioneine (DBS): $R^2 = -0.55$
Supplementary Figure 34

Plasma, targeted Acute metabolic decompensations

Histidine (PL)

Z-score

Age (y)
Supplementary Figure 35

LysoPC(15:0) (DI−HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma

Z-score vs. Age (y)

PA, P.14 vs. PA, P.18
PA, P.16 vs. PA, P.17 vs. PA, P.19
PA, P.22 vs. PA, P.23 vs. PA, P.24

Plasma, Dried blood spots, Acute metabolic decompensations
Supplementary Figure 36

LysoPC(17:0) (DI–HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma

Age (y) vs. Z-score

Plasma
Dried blood spots
Acute metabolic decompensations
Supplementary Figure 37

2-Amino-3-phosphonopropionic acid (DI-HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma

Plasma

Dried blood spots

Acute metabolic decompensations
Supplementary Figure 38

Propionic acid (DI-HRMS)

- Acute metabolic decompensations
- Dried blood spots
- Plasma

Plasma
Dried blood spots
Acute metabolic decompensations

Z-score vs. Age (y)
Supplementary Figure 39

Leucine (PL)

Z-score vs. Age (y)

Acute metabolic decompensations
Plasma, targeted

PA, P.14
PA, P.18

MMA, P.01
MMA, P.02
MMA, P.03

MMA, P.06
MMA, P.07
MMA, P.10

PA, P.16
PA, P.17
PA, P.19

PA, P.22
PA, P.23
PA, P.24
Supplementary Figure 40

Phenylalanine (PL)

- PA, P.14
- PA, P.18

- MMA, P.01
- MMA, P.02
- MMA, P.03

- MMA, P.06
- MMA, P.07
- MMA, P.10

- PA, P.16
- PA, P.17
- PA, P.19

- PA, P.22
- PA, P.23
- PA, P.24

Z-score vs. Age (y) for acute metabolic decompensations.
Supplementary Figure 41

Pyruvate (U)

Z-score

Age (y)

Acute metabolic decompensations

Urine, targeted

PA, P.14

MMA, P.01

MMA, P.06

PA, P.16

MMA, P.02

MMA, P.07

PA, P.17

MMA, P.03

MMA, P.10

PA, P.19

PA, P.22

PA, P.23

PA, P.24
Supplementary Figure 42

Pyruvate (DI–HRMS)

MMA, P.01

MMA, P.02

MMA, P.03

MMA, P.06

MMA, P.07

MMA, P.10

PA, P.14

PA, P.18

PA, P.16

PA, P.17

PA, P.19

PA, P.22

PA, P.23

PA, P.24

Acute metabolic decompensations

Dried blood spots

Plasma
Supplementary Figure 43

PLS-DA, VIP-scores and heatmap for AMD samples versus no AMD samples, for PA and MMA

A) DBS

B) Plasma
Supplementary Figure 44

PLS-DA, VIP-scores and heatmap for AMD samples versus no AMD samples, for PA only

A) DBS

B) Plasma