Targeted metabolomics as a tool in discriminating endocrine from primary hypertension

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SUPPLEMENTAL MATERIALS

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**Supplemental table 1. List of metabolites measured with the Absolute/DQ® p180 Kit GAC, Helmholtz Zentrum München**

### Acylcarnitines (40)

| Abbreviation | Full-Name | Abbreviation | Full-Name                  |
|--------------|-----------|--------------|----------------------------|
| C0           | Carnitine  | C10:1        | Decenoylcarnitine          |
| C2           | Acetylcarnitine | C10:2    | Decadienylcarnitine        |
| C3           | Propionylcarnitine | C12     | Dodecanoylcarnitine        |
| C3:1**       | Propenoylcarnitine | C12:1    | Dodecenoylcarnitine        |
| C3-OH*       | Hydroxypropionylcarnitine | C12-DC** | Dodecanediobutyricarnitine |
| C4           | Butyrylcarnitine | C14     | Tetradecanoylcarnitine     |
| C4:1         | Butenoylcarnitine | C14:1    | Tetradecanoylcarnitine     |
| C4-OH (C3-DC) | Hydroxybutrylcarnitine | C14:1-OH | Hydroxytetradecanoylcarnitine |
| C5           | Valeryl carnitine | C14:2   | Tetradecadienylcarnitine  |
| C5:1*        | Tiglylcarnitine | C14:2-OH* | Hydroxytetradecadienylcarnitine |
| C5:1-DC*     | Glutaconylcarnitine | C16     | Hexadecanoylcarnitine      |
| C5-DC (C6-OH)* | Glutaryl carnitine (Hydroxyhexanoylcarnitine) | C16:1 | Hexadecanoylcarnitine      |
| C5-M-DC**    | Methylglutaryl carnitine | C16:1-OH | Hydroxyhexadecanoylcarnitine |
| C5-OH (C3-DC-M)* | Hydroxymalonylcarnitine (Methylmalonylcarnitine) | C16:2* | Hexadecadienylcarnitine  |
| C6 (C4:1-DC)* | Hexanoylcarnitine (Fumarylcarnitine) | C16:2-OH* | Hydroxyhexadecadienylcarnitine |
| C6:1*        | Hexenoylcarnitine | C16-OH* | Hydroxyhexadecanoylcarnitine |
| C7-DC**      | Pimelylcarnitine | C18     | Octadecanoylcarnitine      |
| C8           | Octanoylcarnitine | C18:1   | Octadecanoylcarnitine      |
| C9           | Nonanoylcarnitine | C18:1-OH* | Hydroxyoctadecanoylcarnitine |
| C10          | Decanoylcarnitine | C18:2   | Octadecadienylcarnitine   |

### Amino Acids (21)

| Ala  | Alanine | Lys  | Lysine |
| Arg  | Arginine| Met  | Methionine |
| Asn  | Asparagine| Orn | Ornithine |
| Asp  | Aspartate| Phe  | Phenylalanine |
| Cit  | Citrulline| Pro  | Proline |
| Gln  | Glutamine| Ser  | Serine |
| Glu  | Glutamate| Thr  | Threonine |
| Gly  | Glycine | Trp  | Tryptophan |
| His  | Histidine| Tyr  | Tyrosine |
| Ile  | Isoleucine| Val  | Valine |
| Leu  | Leucine |

### Monosaccharides (1)

| H1   | Sum of Hexoses (including Glucose) |
### Glycerophospholipids (90)

| Abbreviation | Full-Name | Abbreviation | Full-Name |
|--------------|-----------|--------------|-----------|
| lysoPC a C14:0 | PC aa C34:1 | PC ae C38:2 |
| lysoPC a C16:0 | PC aa C34:2 | PC aa C42:1 |
| lysoPC a C16:1 | PC aa C34:3 | PC aa C42:2 |
| lysoPC a C17:0 | PC aa C34:4 | PC aa C42:4 |
| lysoPC a C18:0 | PC aa C36:0 | PC aa C42:5 |
| lysoPC a C18:1 | PC aa C36:1 | PC aa C42:6 |
| lysoPC a C18:2 | PC aa C36:2 | PC ae C30:0 |
| lysoPC a C20:3 | PC aa C36:3 | PC ae C30:1* |
| lysoPC a C20:4 | PC aa C36:4 | PC ae C30:2 |
| lysoPC a C24:0** | PC aa C36:5 | PC ae C32:1 |
| lysoPC a C26:0* | PC aa C36:6 | PC ae C32:2 |
| lysoPC a C26:1* | PC aa C38:0 | PC ae C34:0 |
| lysoPC a C28:0** | PC aa C38:1* | PC ae C34:1 |
| lysoPC a C28:1** | PC aa C38:3 | PC ae C34:2 |
| PC aa C24:0* | PC aa C38:4 | PC ae C34:3 |
| PC aa C26:0 | PC aa C38:5 | PC ae C36:0 |
| PC aa C28:1 | PC aa C38:6 | PC ae C36:1 |
| PC aa C30:0 | PC aa C40:1 | PC ae C36:2 |
| PC aa C30:2* | PC aa C40:2 | PC ae C36:3 |
| PC aa C32:0 | PC aa C40:3 | PC ae C36:4 |
| PC aa C32:1 | PC aa C40:4 | PC ae C36:5 |
| PC aa C32:2** | PC aa C40:5 | PC ae C38:0 |
| PC aa C32:3 | PC aa C40:6 | PC ae C38:1 |

### Sphingolipids (15)

| Abbreviation | Full-Name | Abbreviation | Full-Name |
|--------------|-----------|--------------|-----------|
| SM (OH) C14:1 | SM C18:0 | SM (OH) C22:1 | SM (OH) C24:1 |
| SM C16:0 | SM C18:1 | SM (OH) C22:2 | SM C26:0* |
| SM C16:1 | SM C20:2 | SM C24:0 | SM C26:1* |
| SM (OH) C16:1 | SM C22:3* | SM C24:1 |

### Biogenic Amines (21)

| Abbreviation | Full-Name | Abbreviation | Full-Name |
|--------------|-----------|--------------|-----------|
| Ac-Orn | Acetylornithine | PEA* | Phenylethylamine |
| ADMA* | Asymmetric dimethylarginine | cis-OH-Pro* | cis-4-Hydroxyproline |
| alpha-AAA | alpha-Aminoadipic acid | trans-OH-Pro | trans-4-Hydroxyproline |
| Carnosine* | Carnosine | Putrescine | Putrescine |
| Creatinine | Creatinine | SDMA* | Symmetric dimethylarginine |
| DOPA* | DOPA | Serotonin* | Serotonin |
| Dopamine* | Dopamine | Spermidine | Spermidine |
| Histamine* | Histamine | Spermine* | Spermine |
| Kynurenine* | Kynurenine | Taurine | Taurine |
| Met-SO | Methionine sulfoxide | total DMA | Total dimethylarginine |
| Nitro-Tyr* | Nitrotyrosine |

**Notes:** Complete list of the 188 metabolites. With the asterisk (*) are marked the 33 metabolites excluded after selection as described in the method section. With the double asterisk (**) are marked 8 metabolites included in the analyses for which only the variance between batches, but not within the batches, were only slightly above the predetermined cutoff prior normalization.
**Abbreviations:** $C_x:y$ indicates the lipid chain composition where “$x$” is the number of carbons and “$y$” the number of double bonds. LysoPC, lysophosphatidylcholine, PC, phosphatidylcholine; a, acyl; aa, diacyl; ae, acyl-alkyl; SM, sphingomyelin; SM(OH), hydroxysphingomyelin
Supplemental Table 2.1. Table with summary of metabolites with significant difference in the performed statistical tests (wilcoxon rank-sum test, SAM, EBAM, PLS-DA and oPLS-DA). The table is in Excel-Format and in each sheet are represented results with significant metabolite difference for comparison between PHT with CS, PA and PPGL separately as well as EHT as common-group. The analyses were performed for all patients together as well as separately for each sex (female, male) and age group (<50 years and ≥ 50 years).

File name: Supplemental Table 2.1.xlsx

Supplemental Table 2.2. Complete list of metabolite of interest and metabolite ratios of interest in comparison between PHT and CS and their association after including sex (male versus female) and age-group (<50 versus ≥ 50 years) in a regression model

Note: “Red” are marked the metabolites with no significant correlation with the clinical diagnosis.

File name: Supplemental Table 2.2.xlsx

Supplemental Table 2.3. Complete list of metabolite of interest and metabolite ratios of interest in comparison between PHT and PA and their association after including sex (male versus female) and age-group (<50 versus ≥ 50 years) in a regression model

Note: “Red” are marked the metabolites with no significant correlation with the clinical diagnosis.

File name: Supplemental Table 2.3.xlsx

Supplemental Table 2.4. Complete list of metabolite of interest and metabolite ratios of interest in comparison between PHT and PPGL and their association after including sex (male versus female) and age-group (<50 versus ≥ 50 years) in a regression model

Note: “Red” are marked the metabolites with no significant correlation with the clinical diagnosis.

File name: Supplemental Table 2.4.xlsx

Supplemental Table 2.5. Complete list of metabolite of interest and metabolite ratios of interest in comparison between PHT and EHT (as common group) and their association after including sex (male versus female) and age-group (<50 versus ≥ 50 years) in a regression model

Note: “Red” are marked the metabolites with no significant correlation with the clinical diagnosis. “Green” are marked the top 15 metabolites according to the degree of association with the clinical diagnosis.

File name: Supplemental Table 2.5.xlsx
**Supplemental Table 3.1.** List of unique metabolites for: (a) CS-PHT, (b) PA-PHT, (c) PPGL-PHT and (d) EHT (as common group)-PHT for different disease scenarios. The “x” in the columns indicates in which subgroup of patients the variable has been identified.

a) **CS-PHT**

| Variables               | All | Male | Female | <50 | >50 |
|-------------------------|-----|------|--------|-----|-----|
| Sex                     | x   |      |        |     |     |
| C18:1                   | x   | x    | x      | x   |     |
| C18:2                   | x   | x    | x      |     |     |
| C9                      | x   |      | x      |     |     |
| H1                      | x   |      |        |     | x   |
| lysoPC a C16:0          | x   |      |        |     |     |
| Orn                     | x   |      |        |     |     |
| SM C16:1                | x   | x    |        |     |     |
| SM C18:1                | x   | x    |        |     | x   |
| SM C20:2                | x   |      |        |     |     |
| lysoPC a C20:4          |     | x    |        |     |     |
| lysoPC a C16:1          |     | x    |        |     |     |
| lysoPC a C24:0          |     | x    |        |     |     |
| Ala                     |     | x    |        |     |     |
| Asp                     |     | x    |        |     |     |
| Spermidine              |     | x    | x      |     |     |
| PC aa C42:1             |     | x    | x      |     |     |
| PC ae C34:3             |     |     | x      |     |     |
| PC ae C42:0             |     |     | x      |     |     |
| C2                      |     |     | x      |     |     |
| C8                      |     | x    | x      |     |     |
| C16:1-OH                |     |     | x      |     |     |
| PC ae C36:1             |     | x    |        |     |     |
| C12                     |     | x    |        |     |     |
| C7-DC                   |     | x    |        |     |     |
| C14:2                   |     | x    |        |     |     |
| SM (OH) C24:1           |     |     | x      |     |     |
| SM (OH) C16:1           |     |     | x      |     |     |
| PC ae C44:4             |     | x    |        |     |     |
### b) PA-PHT

| Variables                        | All | Male | Female | >50 | <50 |
|----------------------------------|-----|------|--------|-----|-----|
| C18:2                            | x   | x    | x      | x   | x   |
| C18:1                            | x   | x    | x      | x   | x   |
| Spermidine                       | x   | x    |        |     |     |
| Orn                              | x   | x    |        |     |     |
| C9                               | x   | x    |        |     |     |
| PC aa C42:1                      | x   |      |        |     |     |
| PC aa C42:4                      | x   | x    | x      |     | x   |
| Thr                              | x   | x    | x      |     |     |
| lysoPC a C20:4                   |     |      |        |     |     |
| Arg                              |     |      |        |     |     |
| PC ae C32:1                      |     | x    | x      |     |     |
| lysoPC a C24:0                   |     |      |        |     |     |
| Age                              |     | x    | x      |     |     |
| PC ae C44:3                      |     |      |        |     |     |
| lysoPC a C16:0                   | x   |      |        |     |     |
| C16                              |     |      |        |     |     |
| C10:1                            |     |      |        |     |     |
| PC ae C38:1                      |     |      |        |     |     |
| Asp                              |     |      |        |     |     |
| C16:1                            |     |      |        |     |     |
| PC aa C32:1                      |     |      |        |     |     |
| PC aa C42:0                      |     |      |        |     |     |
| PC aa C40:1                      |     |      |        |     |     |
| PC aa C34:2                      |     |      |        |     |     |
| PC ae C40:3                      |     |      |        |     |     |
| SM C18:1                         |     |      |        |     |     |
| lysoPC a C18:0                   |     |      |        |     |     |
| C7-DC                            |     |      |        |     |     |
| PC ae C32:2                      |     |      |        |     |     |
### c) PPGL-PHT

| Variables          | All | Male | Female | >50 | <50 |
|--------------------|-----|------|--------|-----|-----|
| C18:1              | x   | x    | x      | x   | x   |
| C18:2              | x   | x    | x      |     |     |
| SM C18:1           | x   |      | x      |     |     |
| C16:1              |     |      | x      |     |     |
| PC aa C32:2        | x   | x    |        |     |     |
| SM C18:0           | x   |      | x      |     |     |
| Age                |     |      | x      |     |     |
| SM C24:1           |     |      | x      |     |     |
| PC aa C36:4        | x   |      |        |     |     |
| Spermidine         | x   | x    |        |     |     |
| lysoPC a C24:0     | x   | x    |        |     |     |
| C14:1              |     | x    | x      | x   |     |
| PC ae C42:0        | x   |      | x      |     |     |
| C10:1              |     |      | x      |     |     |
| lysoPC a C18:2     | x   |      |        |     |     |
| C2                 | x   | x    |        |     |     |
| PC aa C38:6        | x   |      |        |     |     |
| PC aa C36:2        | x   |      |        |     |     |
| PC aa C34:2        | x   |      |        |     |     |
| Orn                | x   | x    |        |     |     |
| PC ae C34:2        | x   |      |        |     |     |
| C14:2              | x   |      |        |     |     |
| C9                 | x   |      |        |     |     |
| H1                 | x   |      |        |     |     |
| Asp                | x   |      |        |     |     |
| Gln                | x   |      |        |     |     |
| alpha-AAA          | x   |      |        |     |     |
| PC aa C40:6        | x   |      |        |     |     |
| Arg                |     | x    | x      |     |     |
| PC aa C36:3        | x   |      |        |     |     |
| PC ae C34:3        |     | x    |        |     |     |
| C8                 |     |      | x      |     |     |
| C16:1-OH           |     |      |        | x   |     |
| PC aa C34:4        |     |      |        |     | x   |
| lysoPC a C20:4     |     |      |        | x   |     |
| lysoPC a C18:0     |     |      |        | x   |     |
| His                |     |      |        |     |     |
### d) EHT-PHT

| Variables       | All | Male | Female | >50 | <50 |
|-----------------|-----|------|--------|-----|-----|
| C18:2           | x   | x    |        | x   | x   |
| C18:1           | x   | x    |        | x   | x   |
| Spermidine      | x   | x    |        |     |     |
| Orn             | x   | x    |        | x   | x   |
| lysoPC a C16:0  | x   | x    |        |     | x   |
| C16:1           | x   |      |        |     |     |
| C9              | x   | x    | x      |     |     |
| PC aa C36:4     |     | x    |        |     |     |
| SM C18:1        | x   |      |        |     |     |
| lysoPC a C20:4  | x   | x    | x      |     |     |
| C10:1           | x   |      |        |     |     |
| lysoPC a C17:0  | x   |      |        |     |     |
| SM C20:2        | x   |      |        |     |     |
| PC ae C42:0     | x   | x    |        |     |     |
| C2              | x   | x    |        |     |     |
| PC aa C34:2     |     | x    |        |     |     |
| C16             |     |      |        |     | x   |
| lysoPC a C24:0  |     |      |        |     | x   |
| Asp             |     | x    |        |     |     |
| Arg             |     |      |        |     | x   |
| lysoPC a C18:2  |     |      |        |     | x   |
| C16:1-OH        |     |      |        |     | x   |
| PC ae C34:2     |     | x    |        |     |     |
| Ser             | x   |      |        |     | x   |
| C12:1           |     |      |        | x   |     |
| H1              |     |      |        |     |     |
| Sex             | x   |      |        |     | x   |
| PC aa C36:2     |     |      |        |     | x   |

**Abbreviations:**

Nomenclature Variables: Cx:y indicates the lipid chain composition where “x” is the number of carbons and “y” the number of double bonds. LysoPC, lysophosphatidylcholine, PC, phosphatidylcholine; a, acyl; aa, diacyl; ae, acyl-alkyl; SM, sphingomyelin; SM(OH), hydroxysphingomyelin

CS, cushing syndrome; EHT, endocrine hypertension as common group; PA, primary hyperaldosteronism; PPGL, pheochromocytoma/paraganglioma

**Note:** The order in which the variables were listed corresponds to the most common feature appearing in different classifications on top.
**Supplemental Table 3.2.** Lists of unique metabolite ratios for (a) CS-PHT, (b) PA-PHT, (c) PPGL-PHT and (d) EHT (as common group)-PHT for different disease scenarios. The “x” in the columns indicates in which subgroup of patients the variable has been identified.

### a) CS-PHT

| Variables          | All | Male | Female | >50 | <50 |
|--------------------|-----|------|--------|-----|-----|
| Sex                | x   | x    | x      |     |     |
| Tyr / Phe          | x   | x    | x      | x   | x   |
| Cit / Orn          |     | x    | x      |     |     |
| Orn / Arg          |     | x    | x      |     |     |
| Total DMA / Arg    |     | x    | x      | x   | x   |
| Putrescine / Orn   |     | x    | x      | x   | x   |
| Cit / Arg          |     | x    | x      |     |     |
| Glucogenic AA      |     | x    | x      |     |     |
| Met-SO / Met       |     | x    | x      |     |     |
| Spermidine / Putrescine | x   | x    |        |     |     |
| Age                |     | x    |        |     | x   |
| Total AA           |     | x    |        |     |     |

### b) PA-PHT

| Variables          | All | Male | Female | >50 | <50 |
|--------------------|-----|------|--------|-----|-----|
| Orn / Arg          | x   | x    | x      | x   | x   |
| CPT-I ratio        |     | x    | x      | x   | x   |
| Spermidine / Putrescine | x   | x    | x      | x   | x   |
| Cit / Arg          |     | x    | x      | x   | x   |
| Total DMA / Arg    |     | x    | x      | x   | x   |
| Cit / Orn          |     | x    | x      | x   |     |
| Age                |     | x    | x      |     |     |
| Tyr / Phe          |     | x    | x      |     | x   |
| AAA                |     | x    |        |     | x   |
| Putrescine / Orn   |     | x    |        |     | x   |
| Fisher ratio       |     | x    |        |     |     |
| Essential AA       |     | x    |        |     |     |
| BCAA               |     | x    |        |     | x   |
| Sex                |     |     |        |     | x   |
### c) PPGL-PHT

| Variables                  | All | Male | Female | >50 | <50 |
|----------------------------|-----|------|--------|-----|-----|
| Orn / Arg                  | x   | x    | x      | x   | x   |
| Age                        |     | x    |        |     |     |
| Spermidine / Putrescine    | x   | x    | x      |     | x   |
| Cit / Arg                  | x   |      | x      |     | x   |
| Total DMA / Arg            | x   | x    | x      |     |     |
| Met-SO / Met               | x   |      |        |     | x   |
| Sex                        | x   |      |        |     |     |
| Cit / Orn                  | x   | x    | x      |     |     |
| Glucogenic AA              |     | x    |        |     |     |
| Tyr / Phe                  |     | x    |        |     | x   |
| Putrescine / Orn           |     |      |        |     |     |
| C2 / C0                    | x   | x    |        | x   |     |
| (C2+C3) / C0               |     |      |        |     |     |
| Fisher ratio               | x   |      |        |     | x   |
| CPT-I ratio                |     | x    |        |     | x   |
| Non essential AA           |     |      |        |     | x   |
| Total AA                   |     |      |        |     | x   |

### d) EHT-PHT

| Variables                  | All | Male | Female | >50 | <50 |
|----------------------------|-----|------|--------|-----|-----|
| Orn / Arg                  | x   | x    | x      | x   | x   |
| Spermidine / Putrescine    | x   | x    | x      |     | x   |
| Cit / Arg                  | x   |      | x      |     | x   |
| CPT-I ratio                | x   |      | x      |     | x   |
| Cit / Orn                  | x   | x    | x      |     |     |
| Sex                        | x   |      |        |     | x   |
| Total DMA / Arg            | x   | x    | x      |     |     |
| Tyr / Phe                  | x   |      |        |     | x   |
| Glucogenic AA              |     | x    |        |     |     |
| Age                        |     |      |        |     |     |
| Putrescine / Orn           |     | x    |        |     |     |
| Fisher ratio               | x   |      |        |     |     |
| C2 / C0                    |     |      |        |     |     |

**Abbreviations:**

Nomenclature Variables: Cx:y indicates the lipid chain composition where “x” is the number of carbons and “y” the number of double bonds. LysoPC, lysophosphatidylcholine; PC, phosphatidylcholine; a, acyl; aa, diacyl; ae, acyl-alkyl; SM, sphingomyelin; SM(OH), hydroxysphingomyelin

CS, cushing syndrome; EHT, endocrine hypertension as common group; PA, primary hyperaldosteronism; PPGL, pheochromocytoma/paraganglioma

**Note:** The order in which the variables were listed corresponds to the most common feature appearing in different classifications on top.
**Supplemental Figure 3.3 a-d.** Representing the diagnostic performance of EHT-PHT classification for subgroups of 3a) female, 3b) male, 3c) subset of age $\geq$ 50, 3d) and < 50 years, through confusion matrices and ROC curves

File names: *Supplemental Figure 3.3a, Supplemental Figure 3.3b, Supplemental Figure 3.3c, Supplemental Figure 3.3d*
4.1 Joint heatmap for classical approach (CA) and machine learning (ML) showing selected metabolites in comparison between PHT and EHT (as common group) for all, sex (male versus female) and age-group (<50 versus ≥ 50 years) subsets.

| Metabolite       | All CA | Male CA | Female CA | Age <50 CA | Age ≥50 CA | All ML | Male ML | Female ML | Age <50 ML | Age ≥50 ML |
|------------------|--------|---------|-----------|------------|------------|--------|---------|-----------|------------|------------|
| **Acylcarnitines** |        |         |           |            |            |        |         |           |            |            |
| C2               |        |         |           |            |            |        |         |           |            |            |
| C3-DC C4-OH      |        |         |           |            |            |        |         |           |            |            |
| C9               |        |         |           |            |            |        |         |           |            |            |
| C10:1            |        |         |           |            |            |        |         |           |            |            |
| C12:1            |        |         |           |            |            |        |         |           |            |            |
| C16              |        |         |           |            |            |        |         |           |            |            |
| C16:1            |        |         |           |            |            |        |         |           |            |            |
| C16:1-OH         |        |         |           |            |            |        |         |           |            |            |
| C18:1            |        |         |           |            |            |        |         |           |            |            |
| C18:2            |        |         |           |            |            |        |         |           |            |            |
| **Amino Acids**  |        |         |           |            |            |        |         |           |            |            |
| Arg              |        |         |           |            |            |        |         |           |            |            |
| Asp              |        |         |           |            |            |        |         |           |            |            |
| Glu              |        |         |           |            |            |        |         |           |            |            |
| Ser              |        |         |           |            |            |        |         |           |            |            |
| **Biogenic Amines** |       |         |           |            |            |        |         |           |            |            |
| Spermidine       |        |         |           |            |            |        |         |           |            |            |
| **Glycerophospholipids** |    |         |           |            |            |        |         |           |            |            |
| lysoPC a C16:0   |        |         |           |            |            |        |         |           |            |            |
| lysoPC a C17:0   |        |         |           |            |            |        |         |           |            |            |
| lysoPC a C18:2   |        |         |           |            |            |        |         |           |            |            |
| lysoPC a C20:4   |        |         |           |            |            |        |         |           |            |            |
| lysoPC a C24:0   |        |         |           |            |            |        |         |           |            |            |
| lysoPC a C28:1   |        |         |           |            |            |        |         |           |            |            |
| PC aa C34:2      |        |         |           |            |            |        |         |           |            |            |
| PC aa C36:2      |        |         |           |            |            |        |         |           |            |            |
| PC aa C36:4      |        |         |           |            |            |        |         |           |            |            |
| PC aa C38:6      |        |         |           |            |            |        |         |           |            |            |
| PC aa C40:1      |        |         |           |            |            |        |         |           |            |            |
| PC aa C40:5      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:0      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:1      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:2      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:3      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:4      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:5      |        |         |           |            |            |        |         |           |            |            |
| PC aa C42:6      |        |         |           |            |            |        |         |           |            |            |
| PC ae C32:2      |        |         |           |            |            |        |         |           |            |            |
| PC ae C34:2      |        |         |           |            |            |        |         |           |            |            |
| PC ae C40:3      |        |         |           |            |            |        |         |           |            |            |
| PC ae C40:5      |        |         |           |            |            |        |         |           |            |            |
| PC ae C42:0      |        |         |           |            |            |        |         |           |            |            |
| PC ae C42:1      |        |         |           |            |            |        |         |           |            |            |
| PC ae C42:2      |        |         |           |            |            |        |         |           |            |            |
| PC ae C44:3      |        |         |           |            |            |        |         |           |            |            |
| PC ae C44:4      |        |         |           |            |            |        |         |           |            |            |
| PC ae C44:6      |        |         |           |            |            |        |         |           |            |            |
| **Sphingolipids** |        |         |           |            |            |        |         |           |            |            |
| SM C16:1         |        |         |           |            |            |        |         |           |            |            |
| SM C18:0         |        |         |           |            |            |        |         |           |            |            |
| SM C18:1         |        |         |           |            |            |        |         |           |            |            |
| SM C20:2         |        |         |           |            |            |        |         |           |            |            |
| SM C24:1         |        |         |           |            |            |        |         |           |            |            |
| SM OH C22:2      |        |         |           |            |            |        |         |           |            |            |
| **Monosaccharides** |       |         |           |            |            |        |         |           |            |            |
| H1               |        |         |           |            |            |        |         |           |            |            |
| **Other**        |        |         |           |            |            |        |         |           |            |            |
| Sex              |        |         |           |            |            |        |         |           |            |            |
### 4.2 Joint heatmap for classical approach (CA) and machine learning (ML) showing selected metabolite ratios in comparison between PHT and EHT (as common group) for all, sex (male versus female) and age-group (<50 versus ≥ 50 years) subsets.

| Metabolite Ratio                        | All   | Male     | Female   | Age <50 | Age ≥50 |
|-----------------------------------------|-------|----------|----------|---------|---------|
|                                          | CA ML | CA ML    | CA ML    | CA ML   | CA ML   |
| Citrulline / Arginine                   |       |          |          |         |         |
| Citrulline / Ornithine                  |       |          |          |         |         |
| CPT-I ratio                             |       |          |          |         |         |
| Met-SO / Met                            |       |          |          |         |         |
| Ornithine / Arginine                    |       |          |          |         |         |
| Putrescine / Ornithine                  |       |          |          |         |         |
| Spermidine / Putrescine                 |       |          |          |         |         |
| Total DMA / Arginine                    |       |          |          |         |         |
| Tyrosine / Phenylalanine                |       |          |          |         |         |
| Glucogenic AA                           |       |          |          |         |         |
| Fisher ratio                            |       |          |          |         |         |
| C2 / C0                                 |       |          |          |         |         |
| **Other**                               |       |          |          |         |         |
| Sex                                     |       |          |          |         |         |
| Age                                     |       |          |          |         |         |