Metformin treated Wistar rats demonstrate gut microbiome and plasma metabolome alterations

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Metformin

Firstline (oral) drug T2D treatment

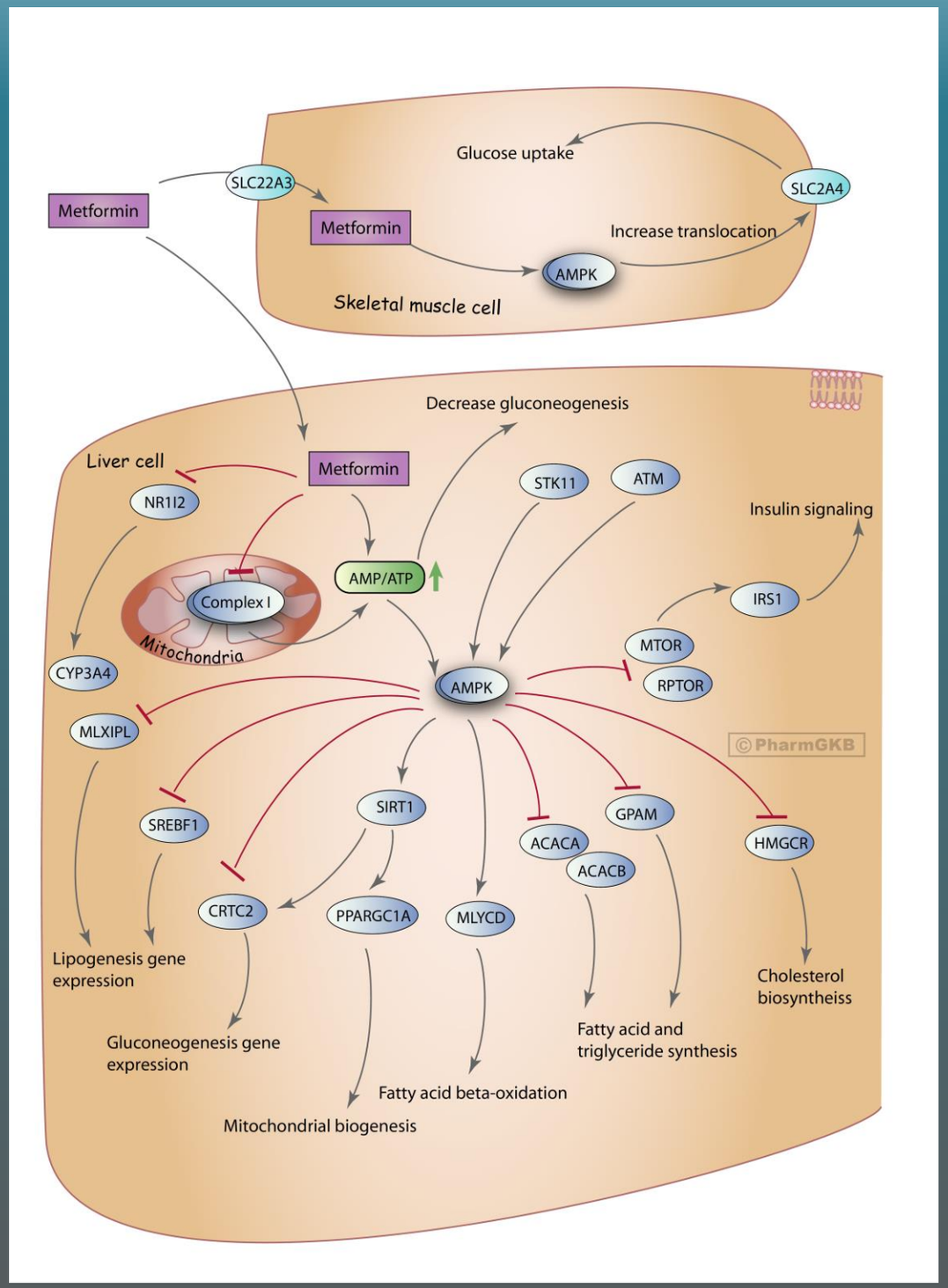
Gestational Diabetes

PCOS

Anti-cancer drug
(occurrence of colon, pancreas, hepatocellular carc)

Anti-ageing (TAME clinical trial)

Metformin Pathway: Pharmacodynamics



[Gong L, Goswami S et al. Pharmacogenet Genomics. 2012]

Metformin & Gut Microbiome Alterations

An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice

Na-Ri Shin,[1] June-Chul Lee,[2] Hae-Youn Lee,[2] Min-Soo Kim,[1] Tae Woong Whon,[1] Myung-Shik Lee,[2] Jin-Woo Bae[1]

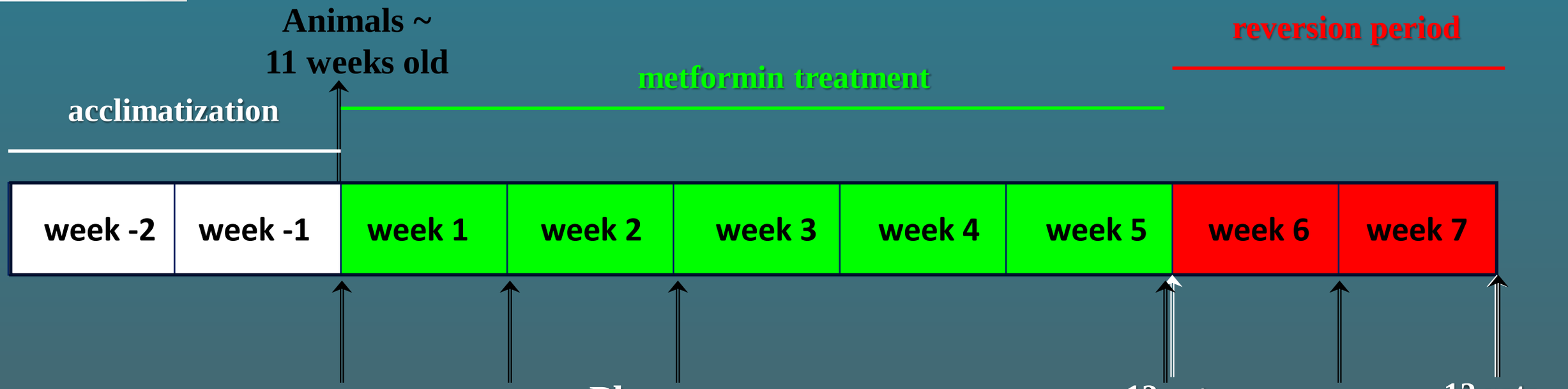
Study Design

n=24 male Wistar Rats (12 x 2 Groups)

G1: vehicle (purified water)

G2: Metformin (350mg/kg/day)

gavage



Lipid Profiling

Polar Metabolic Phenotyping - HILIC

Bile Acid Profiling

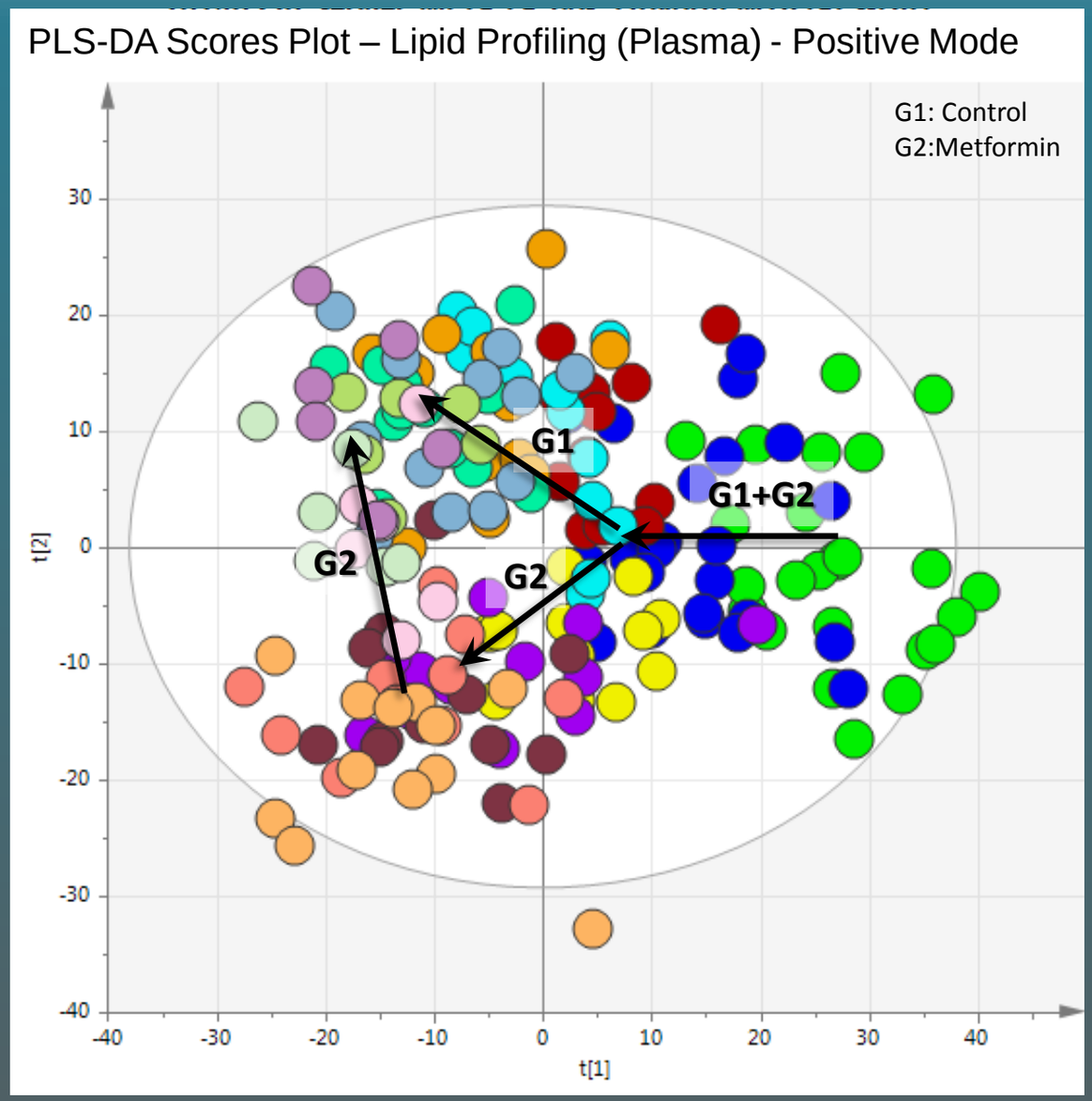
16S RNA gene Sequencing (6 TP)

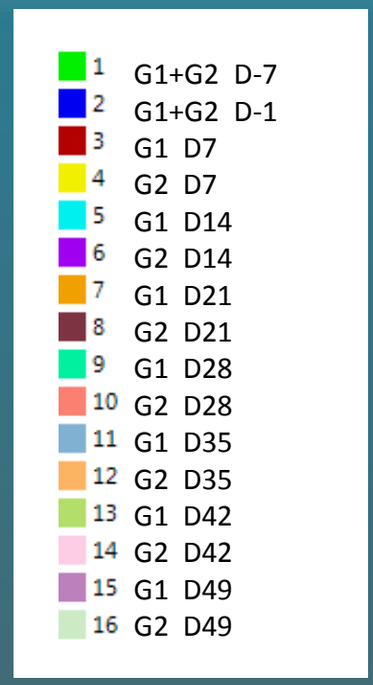
Data Overview

2 valid components

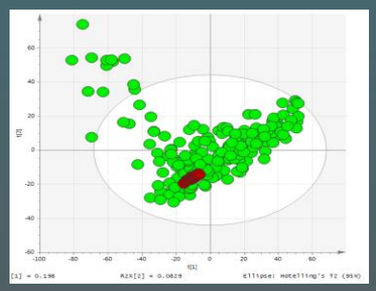
UV Scaling – Total Area Normalised

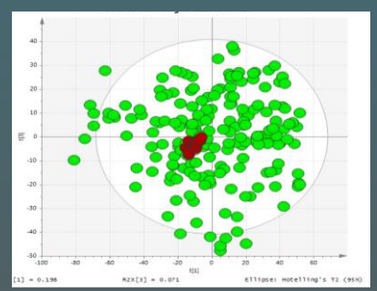
CV-ANOVA p-value= $2x10^{-17}$





Samples Vs QCs



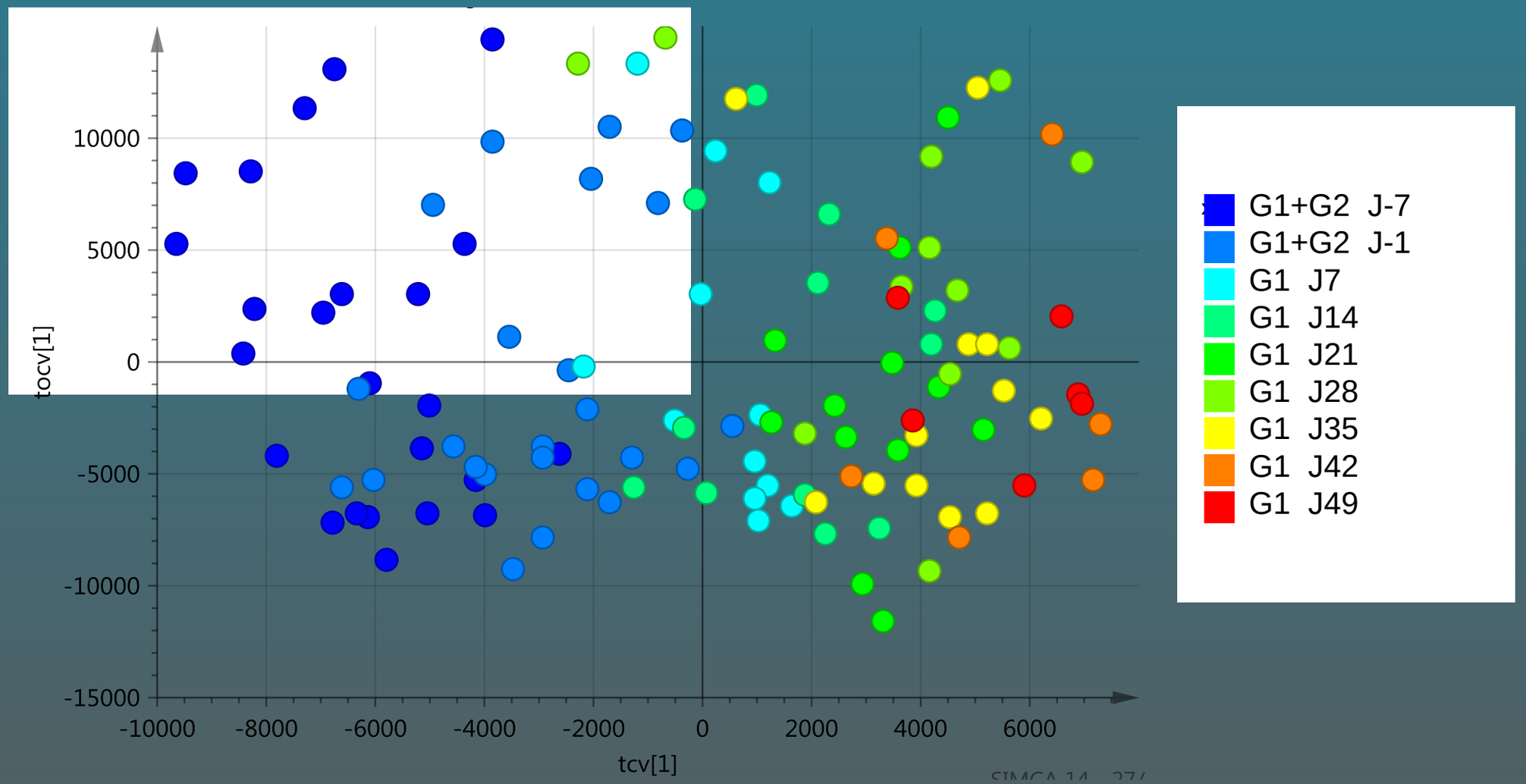


Data Overview

Temporal Effect

All non-treated Animals

OPLS-Regression
Lipid Profiling



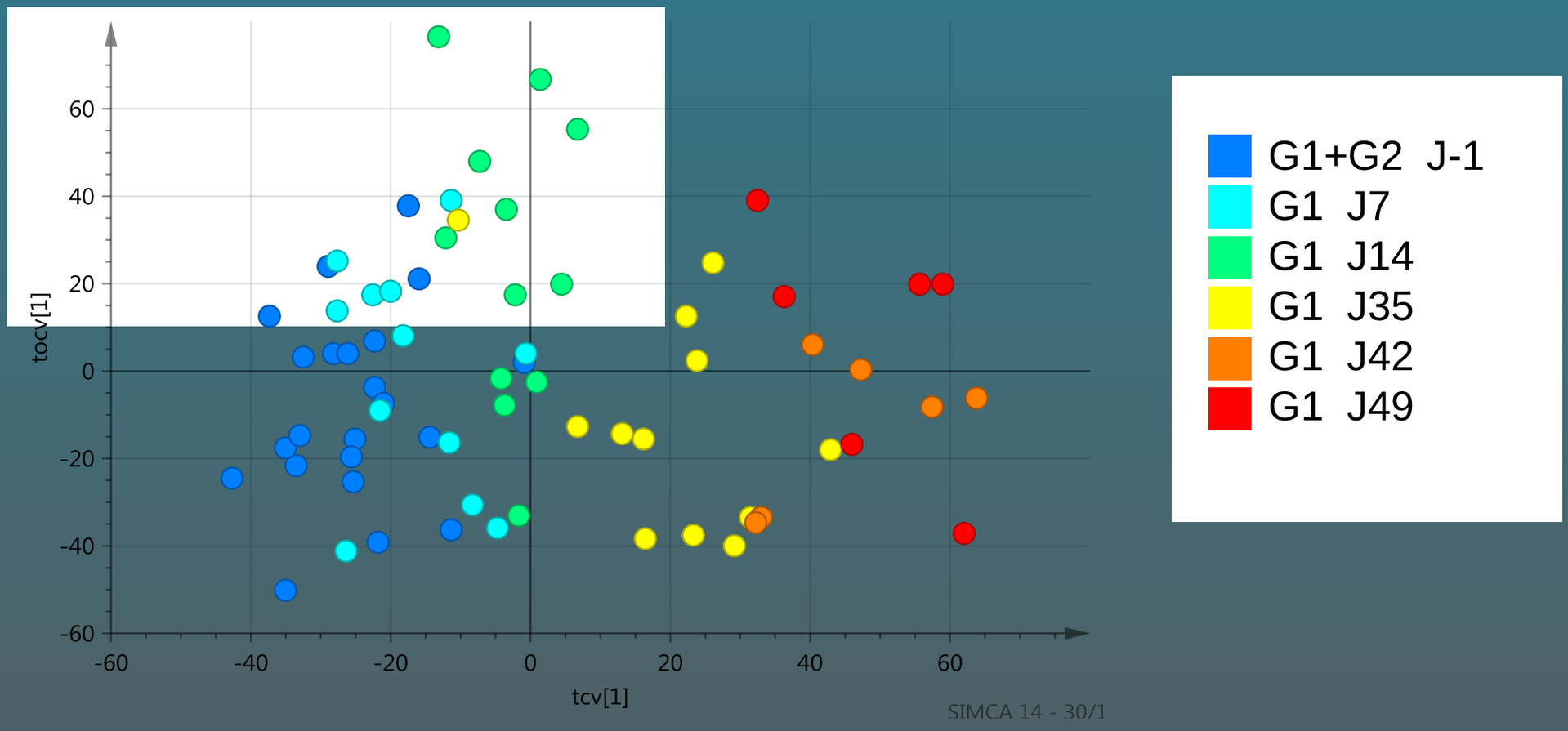
$R^2Y=0.80$ $Q^2Y=0.76$

Data Overview

Temporal Effect

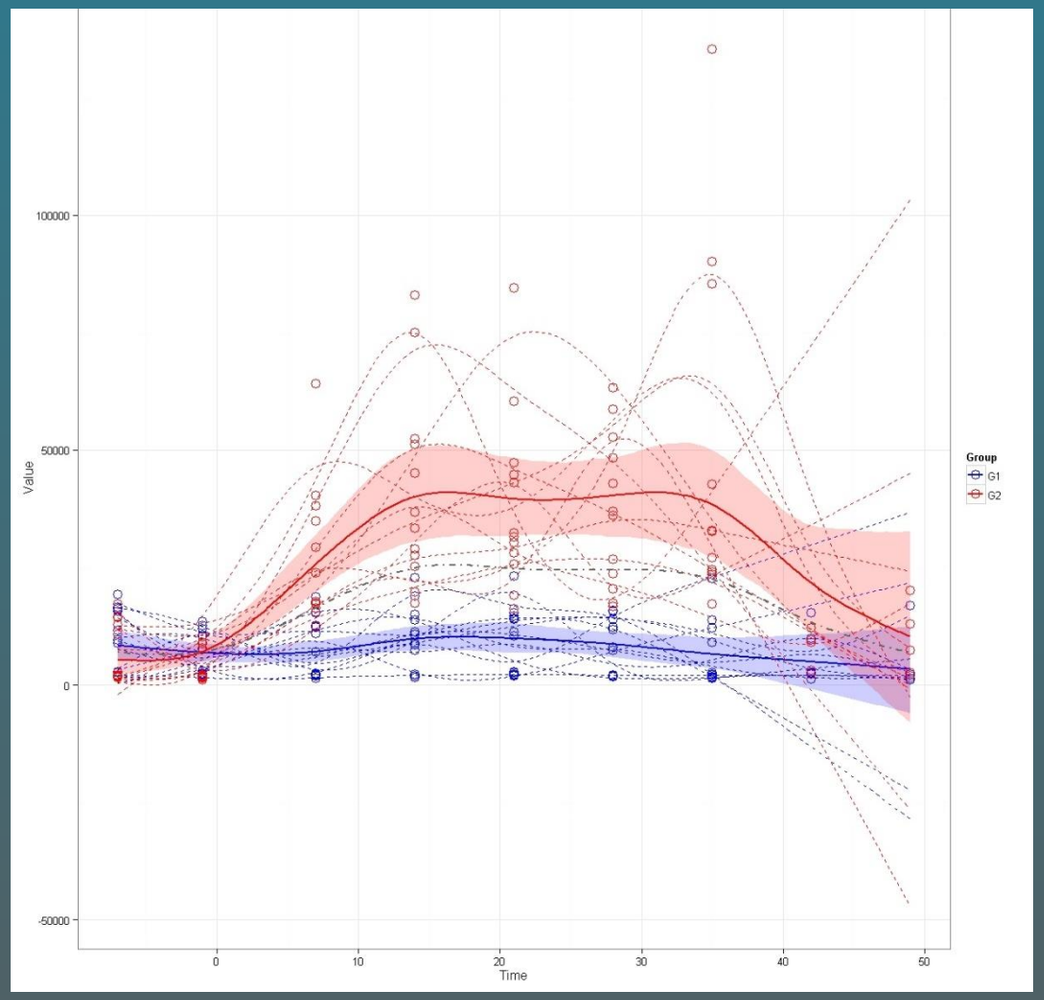
All non-treated Animals

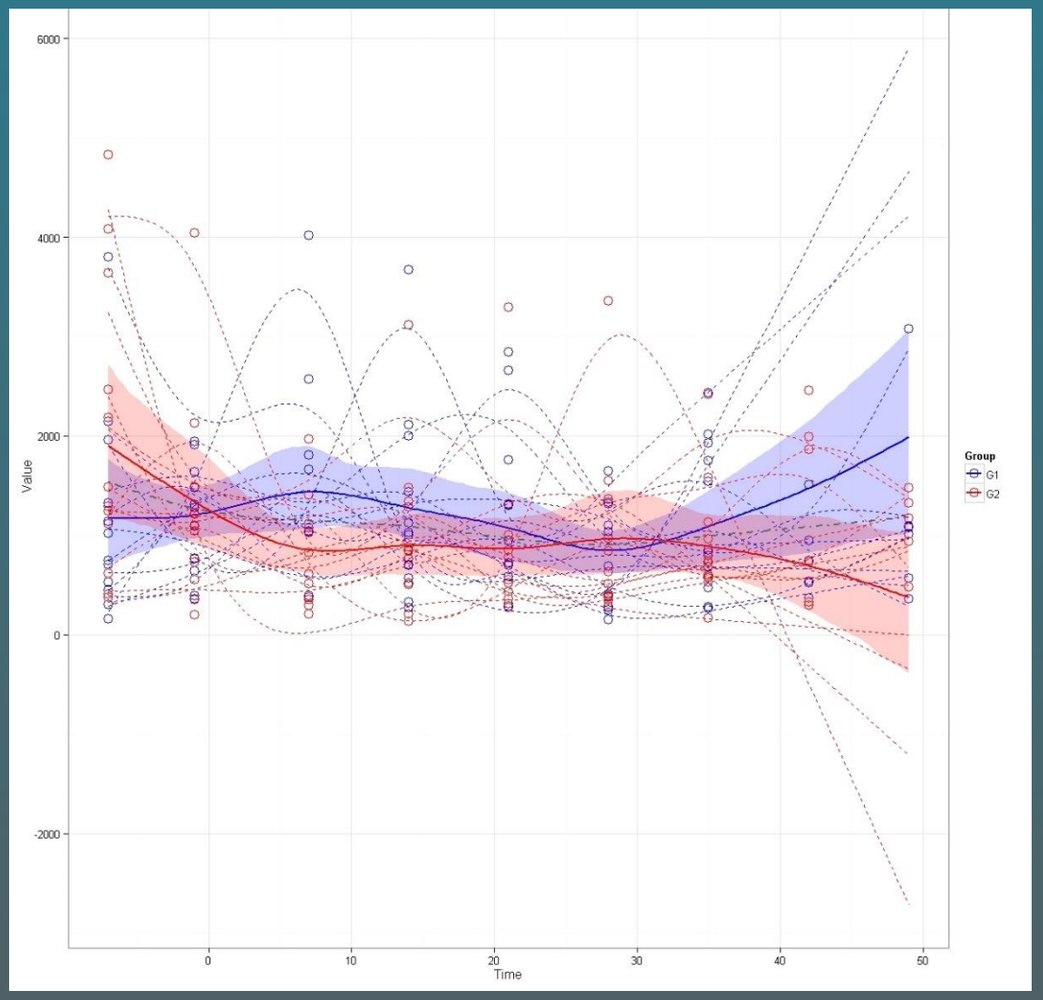
OPLS-Regression
16S rRNA gene



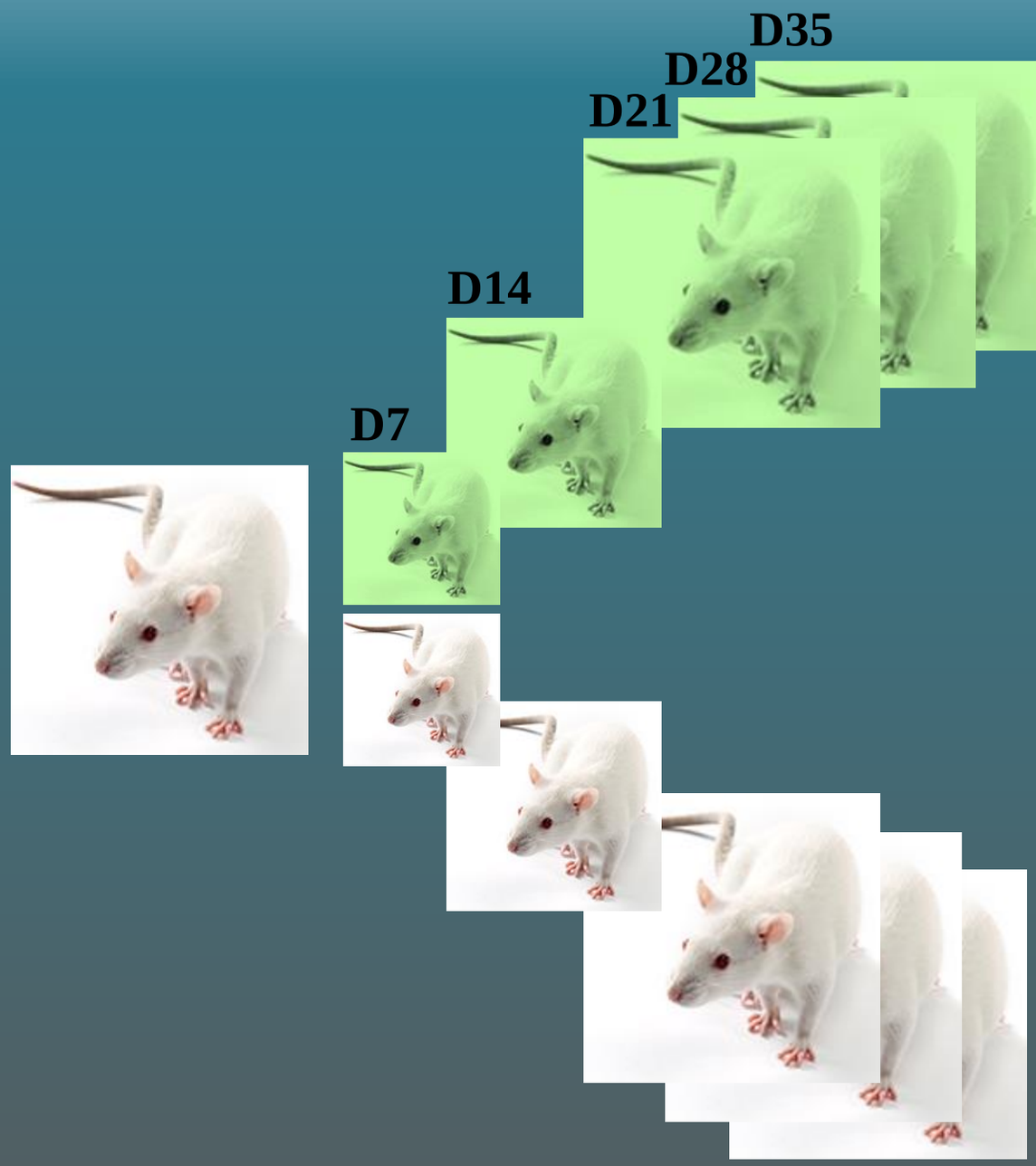
$R^2Y=0.92$ $Q^2Y=0.87$

Time Series Statistical Analysis





Metformin Effect



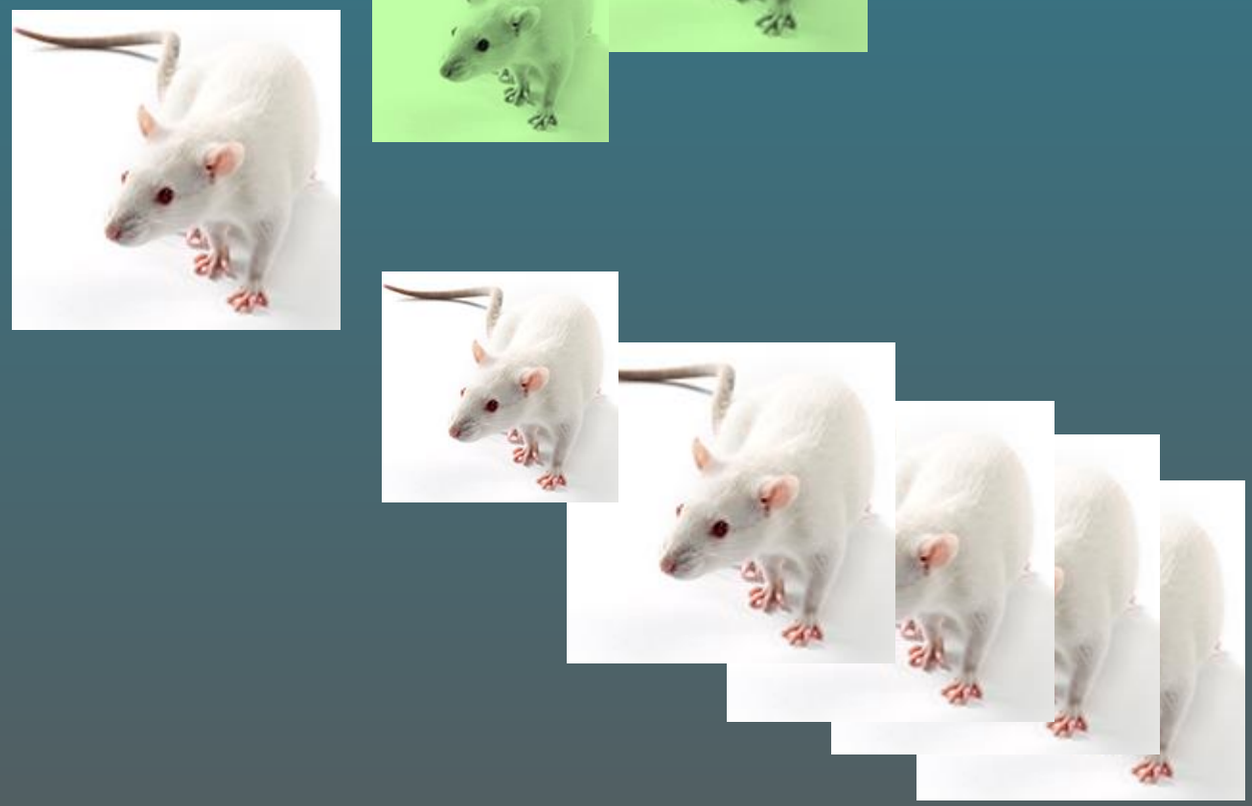
Lipid Profiling

- Phosphatidylcholines (18C/saturated) ↑
- Phosphatidylcholines (20:4,22:6 chains) ↓
- Lysophosphatidylcholines (lysoPC) ↓
- lysoPC(18:0) ↑
- Sphingomyelins ↑
- Ceramides ↑
- Fatty Acids (All lengths & saturation level) ↓

HILIC

- Pantothenic acid ↑
- Creatine ↓
- Pentanoylcarnitine ↓
- **Sugars** ↑
- Ala-containing peptide ↓

Metformin Effect



Bile Acids

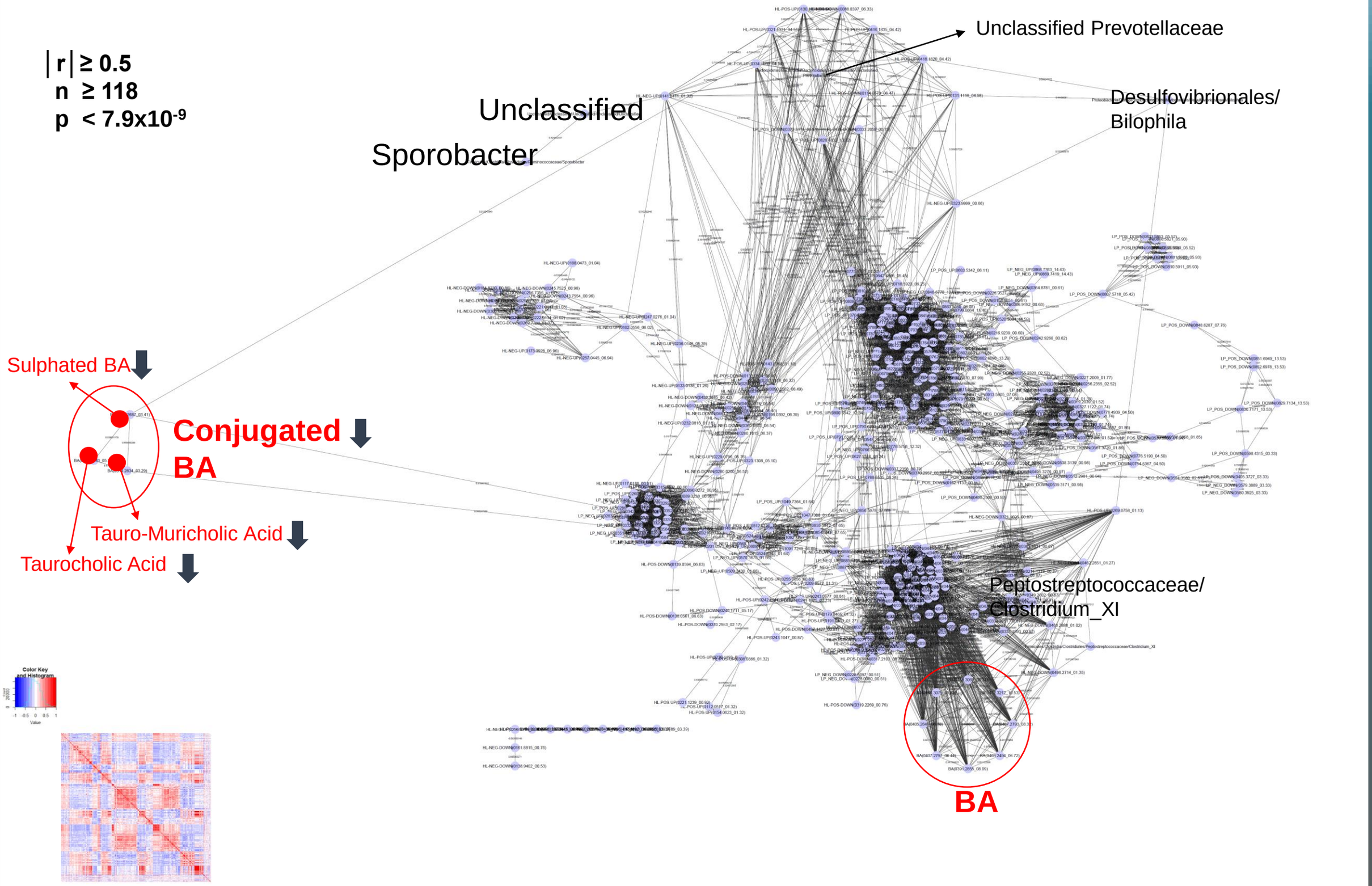
- Taurohyodeoxycholate ⬇
- β-muricholate ⬇
- Sulfated BA ⬇

Gut Microbiome

- Unclassified Prevotellaceae ⬇
- Desulfovibrionaceae ⬆
  Bilophila
- Peptostreptococcaceae ⬇
  Clostridium XI

Correlation Analysis

$|r| \geq 0.5$
$n \geq 118$
$p < 7.9 \times 10^{-9}$



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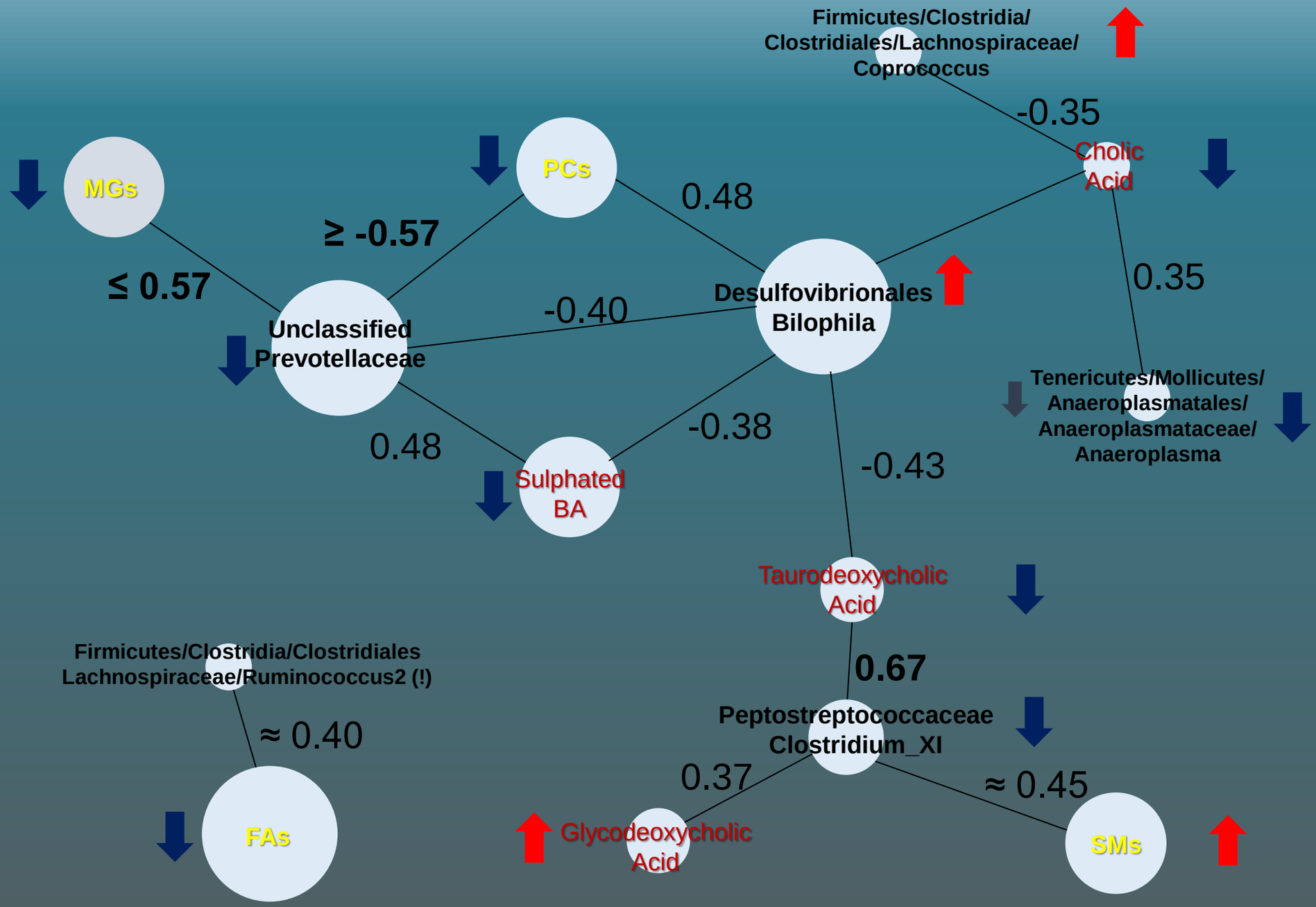

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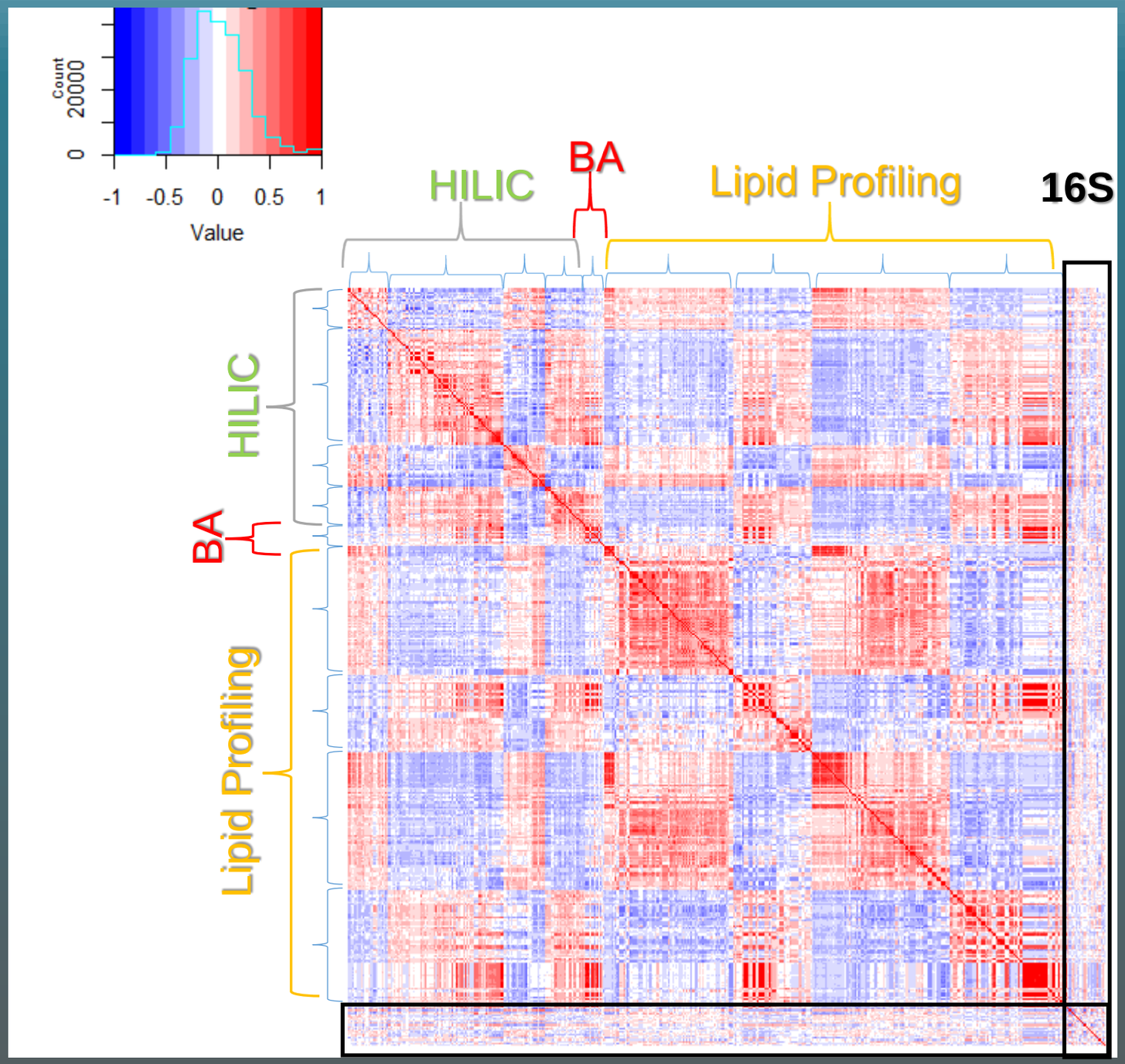

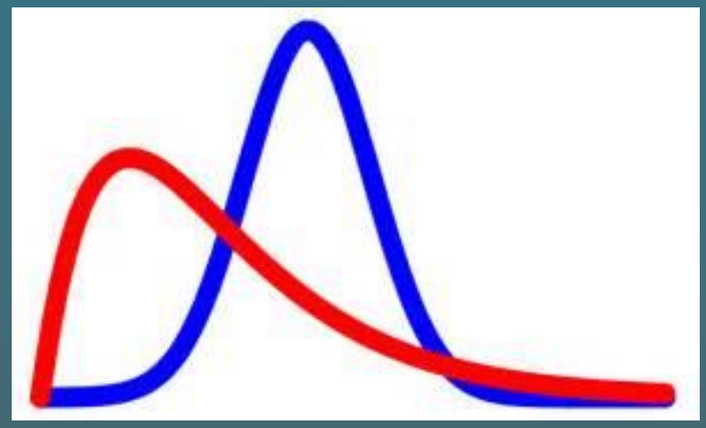

Summary

Metformin alterations in gut microbiome

Rapid alterations in (secondary) bile acid metabolism

Followed by alterations in plasma metabolome

Lipid metabolism

Inflammation, apoptosis

Different functions in non-disease model

Provide insights in the relation of metabolome – gut microbiome

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Thank you

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