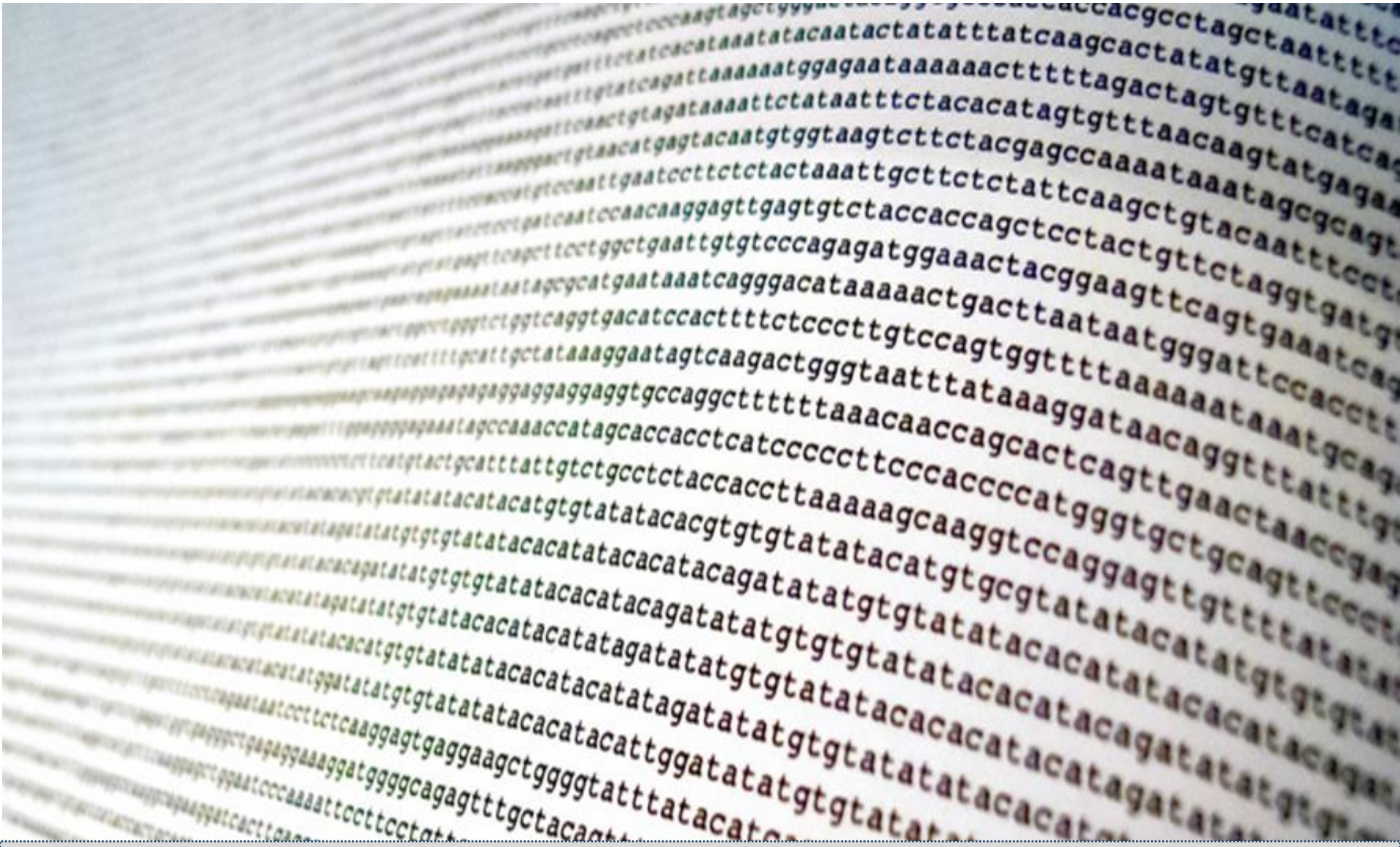
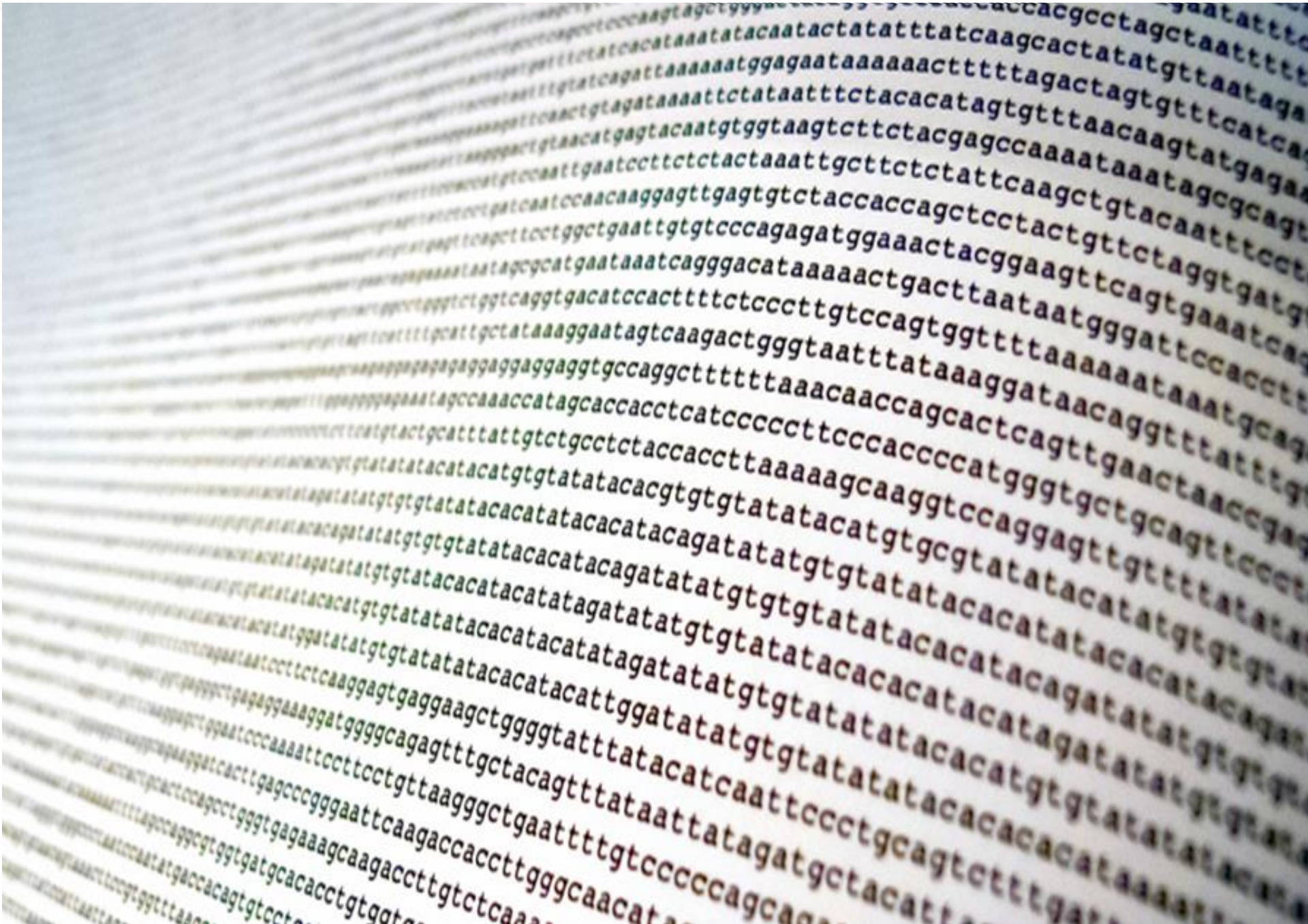
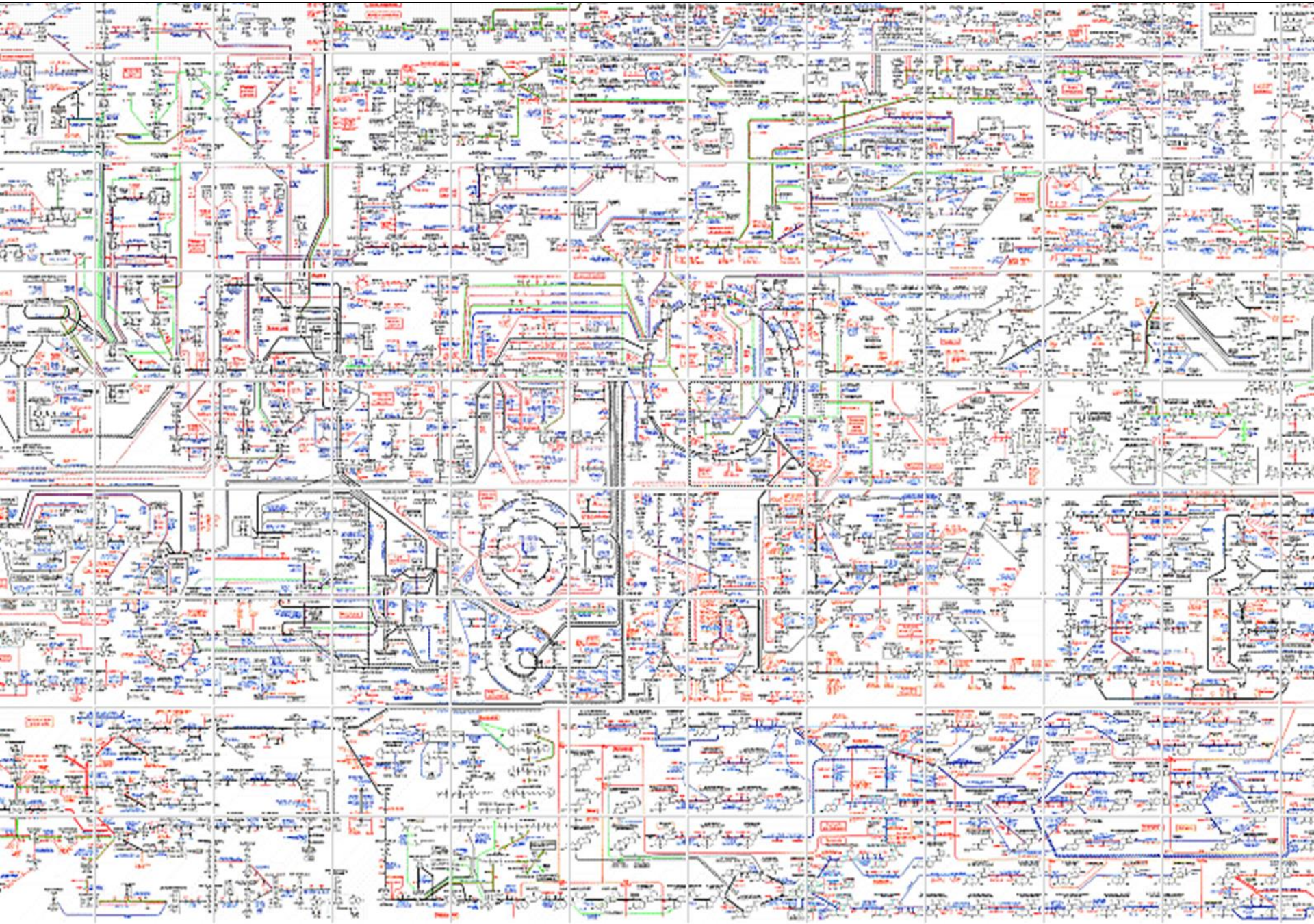
Monty Python´s LIFE OF BRIAN

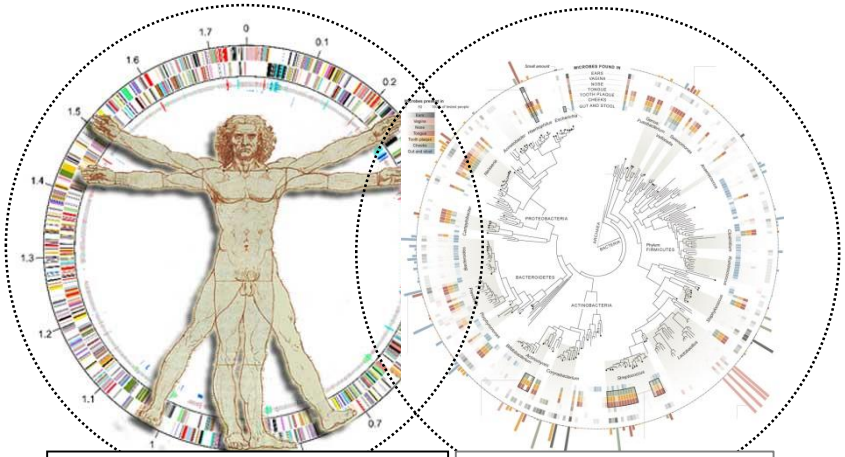
WE ARE ALL INDIVIDUALS



WE ARE ALL INDIVIDUALS

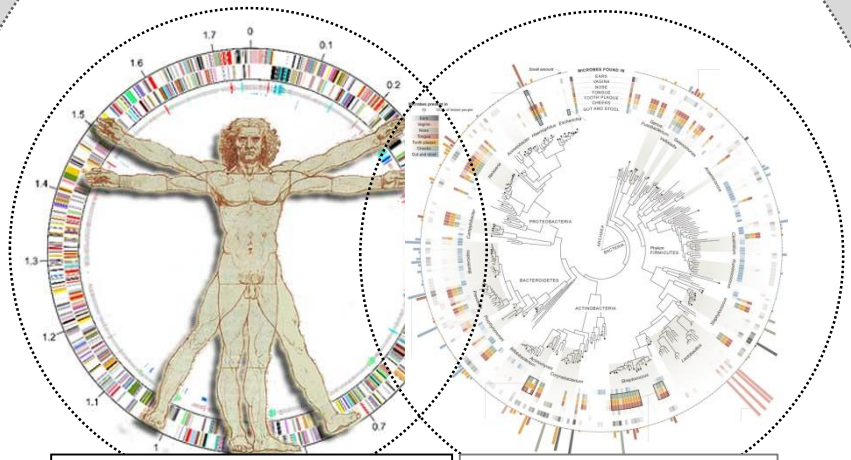






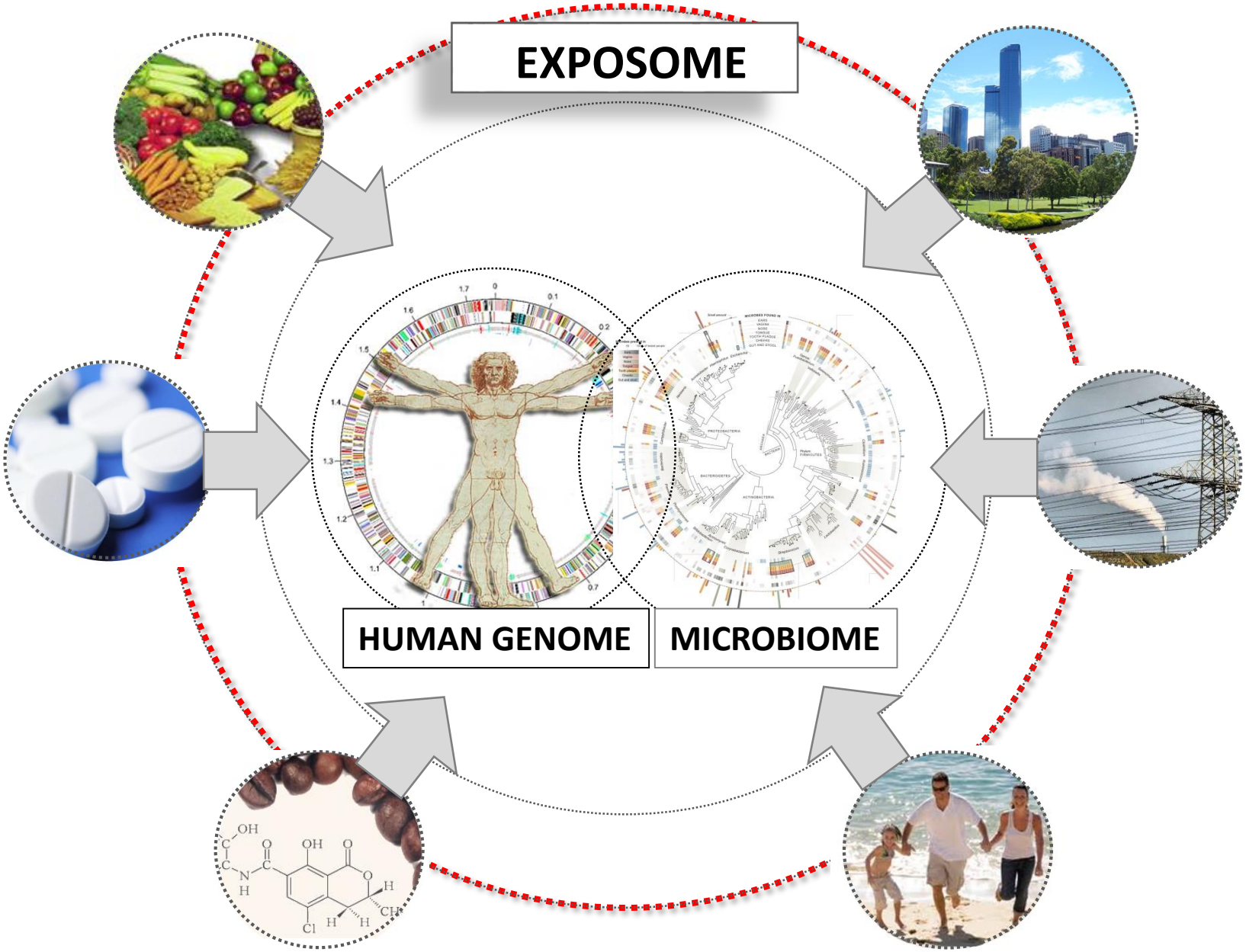
HUMAN GENOME | MICROBIOME

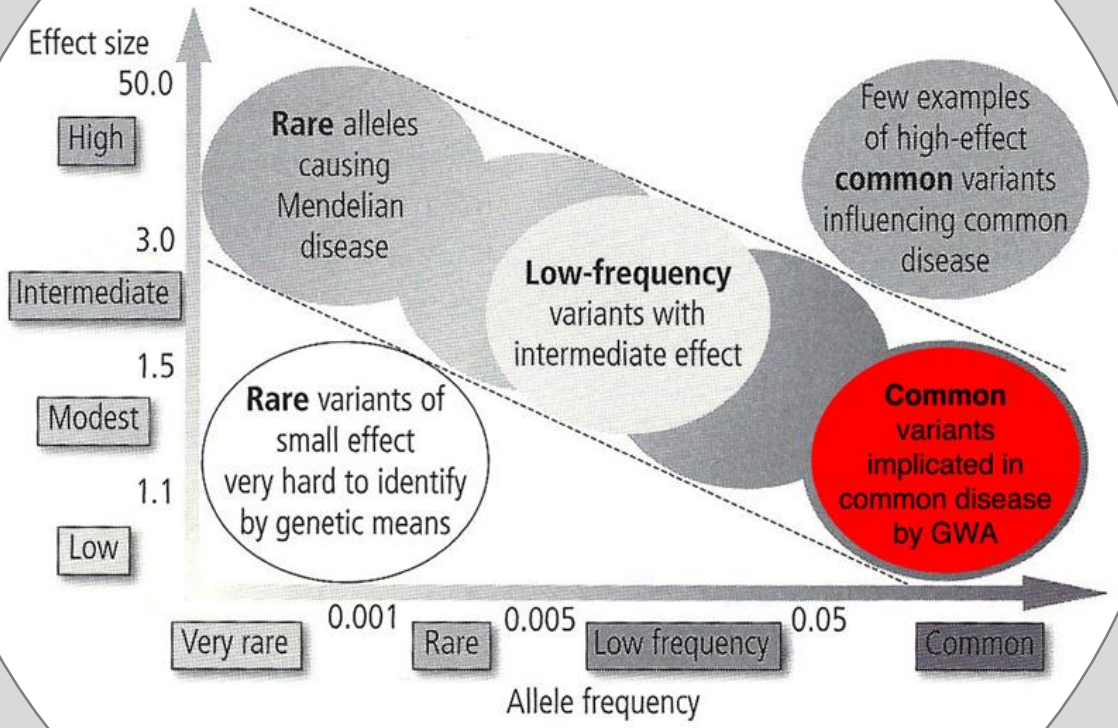
EXPOSOME

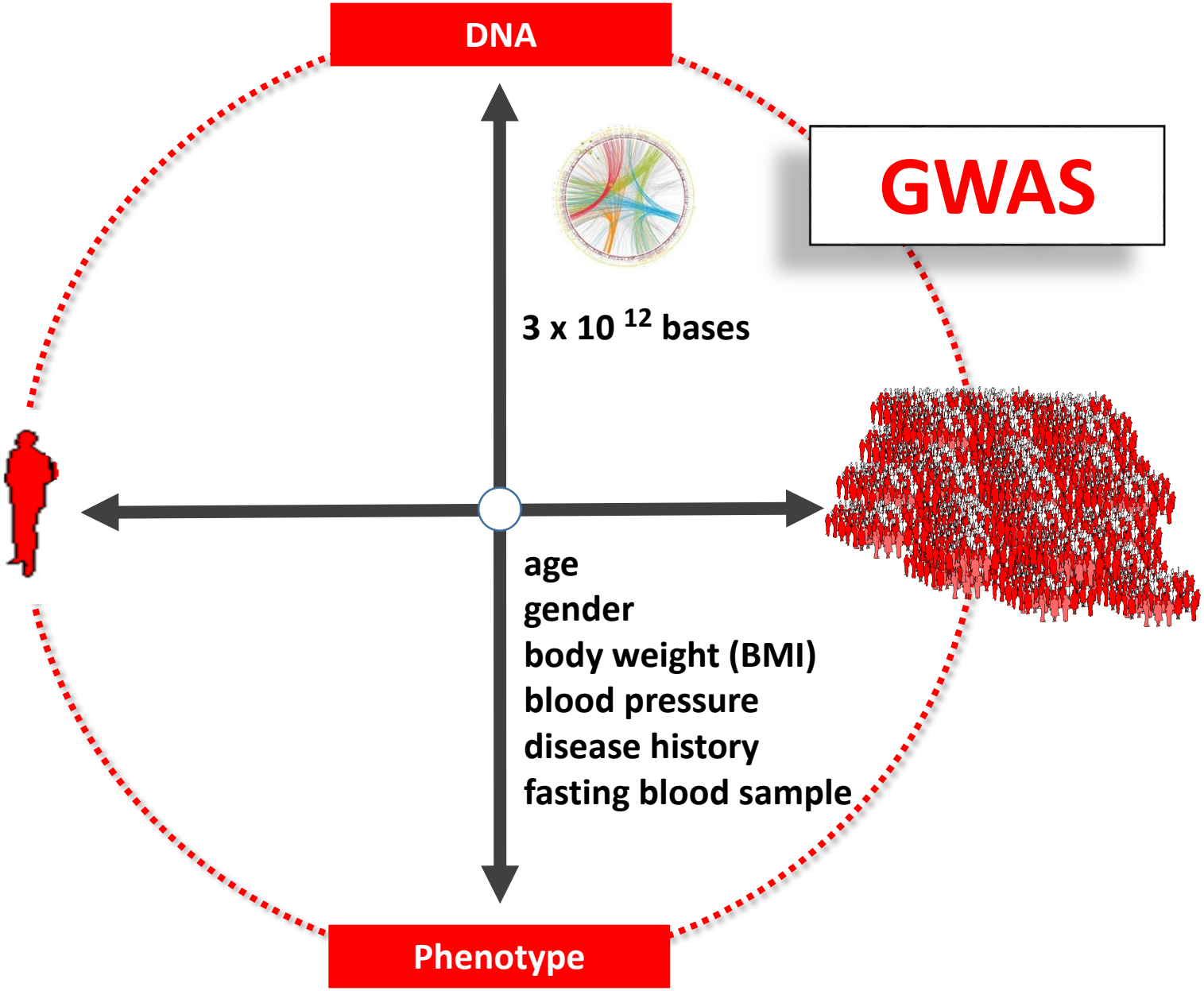


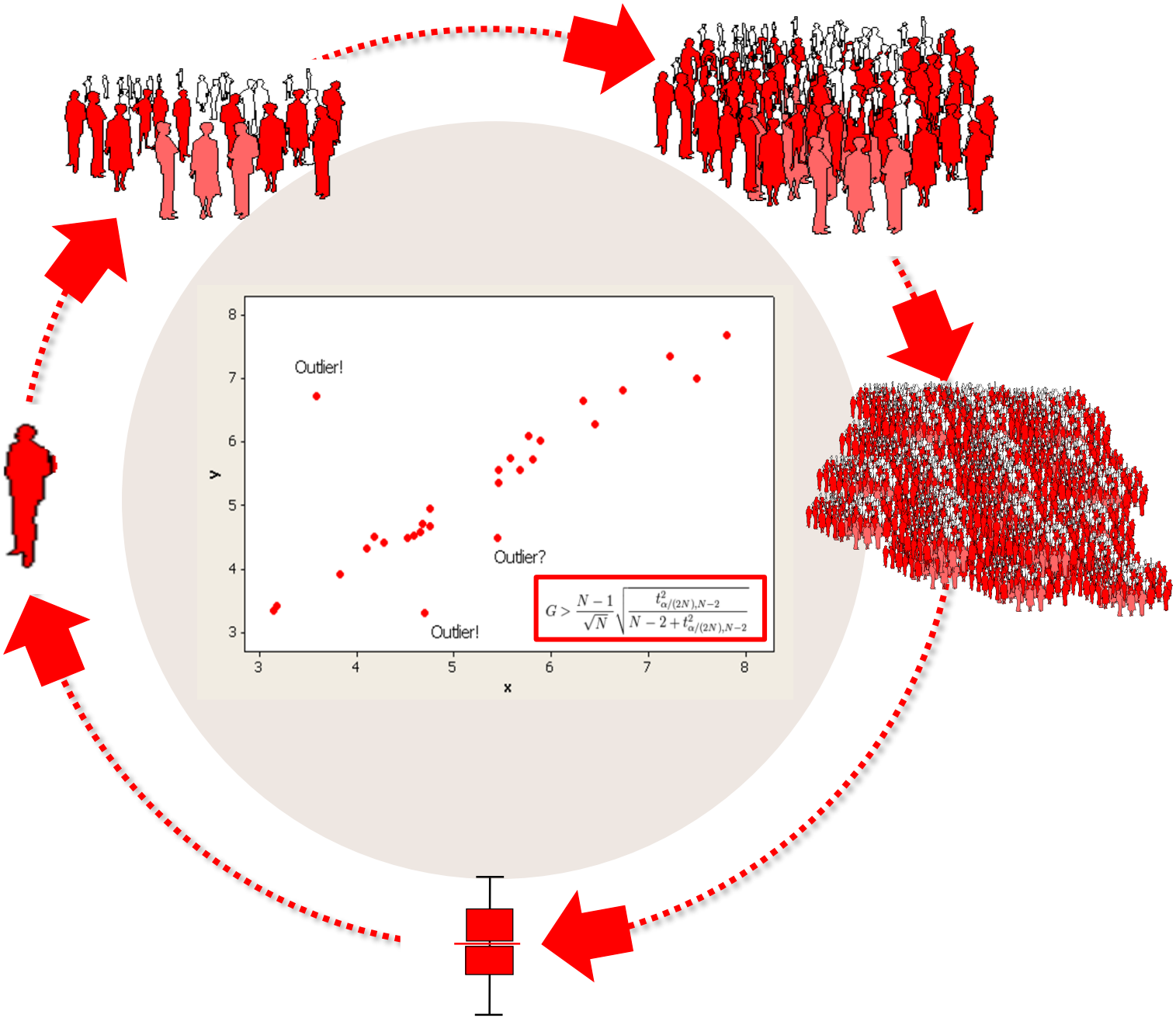
HUMAN GENOME

MICROBIOME


EXPOSOME
HUMAN GENOME
MICROBIOME


Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Rare alleles causing Mendelian disease
Few examples of high-effect common variants influencing common disease
Low-frequency variants with intermediate effect
Rare variants of small effect very hard to identify by genetic means
Common variants implicated in common disease by GWA
Very rare
0.001
Rare
0.005
Low frequency
0.05
Common
Allele frequency


DNA
GWAS
3 x 10 12 bases
age
gender
body weight (BMI)
blood pressure
disease history
fasting blood sample
Phenotype


Outlier!
Outlier?
Outlier!
y
x
$G > \frac{N-1}{\sqrt{N}} \sqrt{\frac{t^2_{\alpha/(2N),N-2}}{N-2+t^2_{\alpha/(2N),N-2}}}$

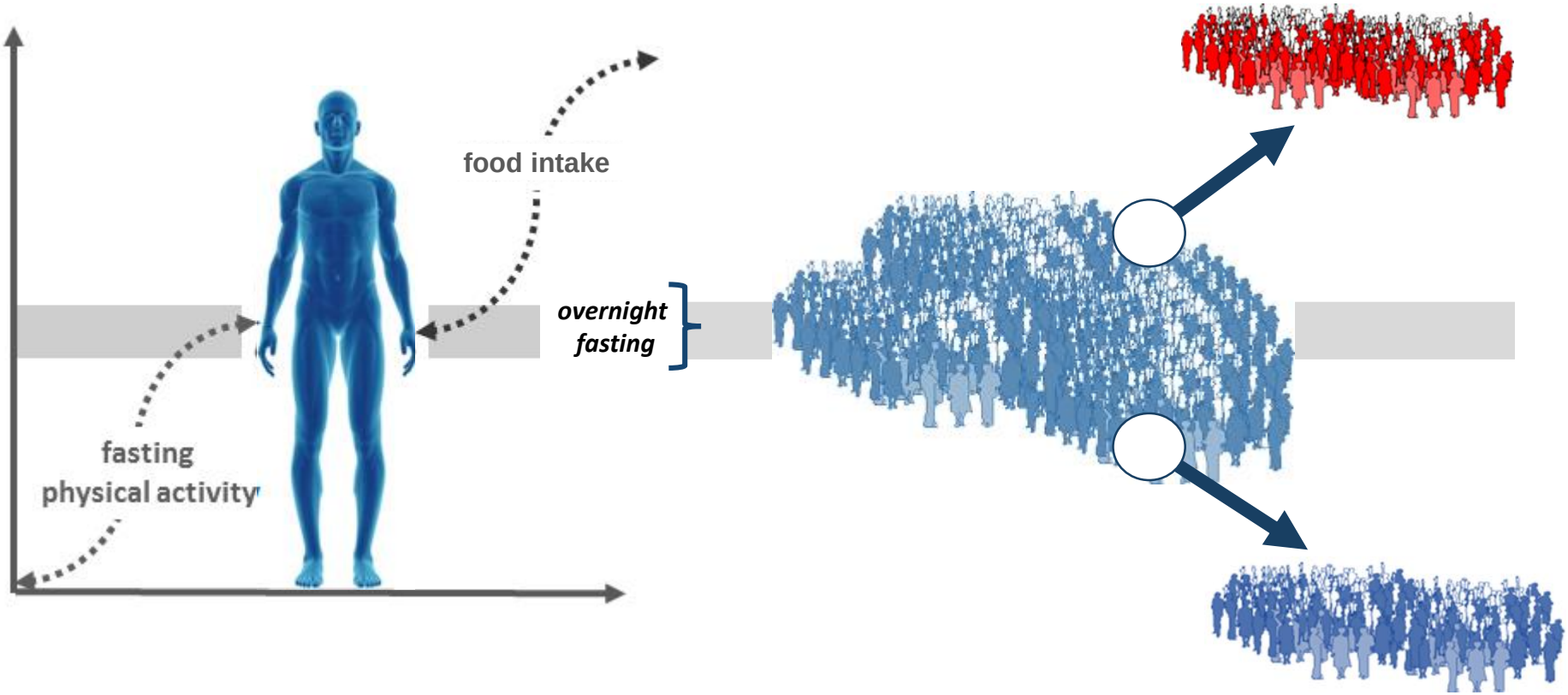
The phenotype is a function of

genome x environment

..... and is highly dynamic

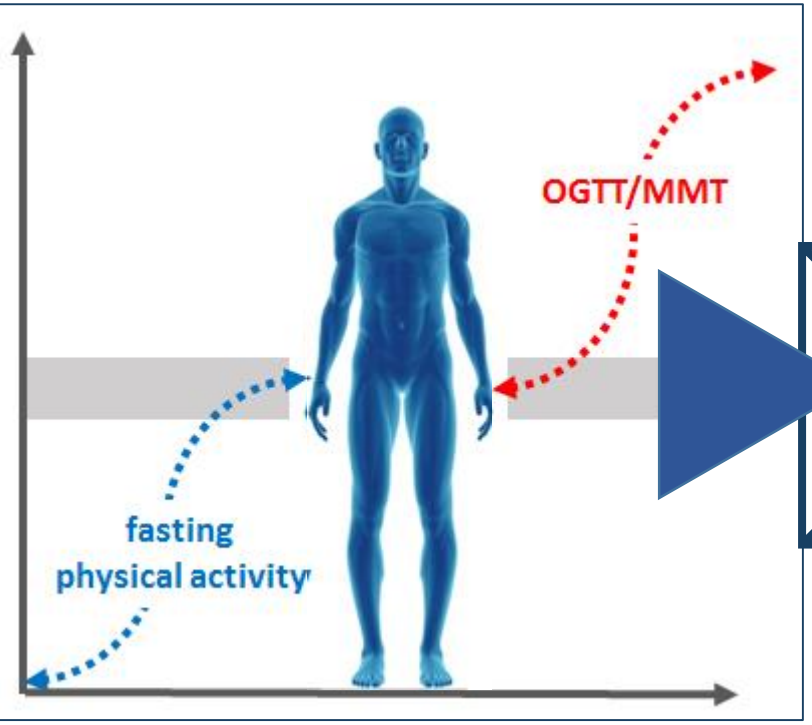
Krug S, et al. Daniel H., FASEB J 26(6):2607-19, 2012
Petersen A, … Daniel H et al. Hum Mol Genet 15;21(6):1433-43, 2012
Rubio-Aliaga I. et al. Daniel H., Metabolomics 7(3):375-387, 2011
Skurk T, et al. Daniel H., Metabolomics 7(3):388-399, 2011
van Ommen B, van der Greef J, Ordovas JM, Daniel H., Genes Nutr 9(5):423, 2014

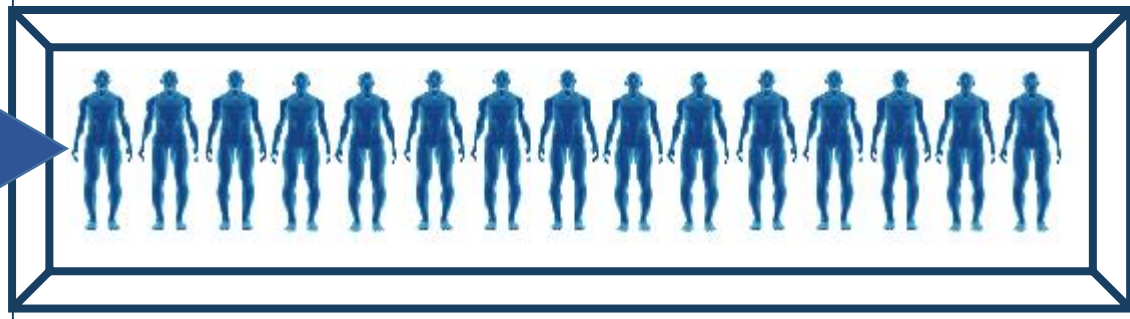
The metabolic phenotype is highly dynamic



Phenotypic flexibility as key factor in the human nutrition and health relationship.
van Ommen B, van der Greef J, Ordovas JM, Daniel H.
Genes Nutr. 2014 Sep;9(5):423. doi: 10.1007/s12263-014-0423-5.

The metabolic phenotype is highly dynamic



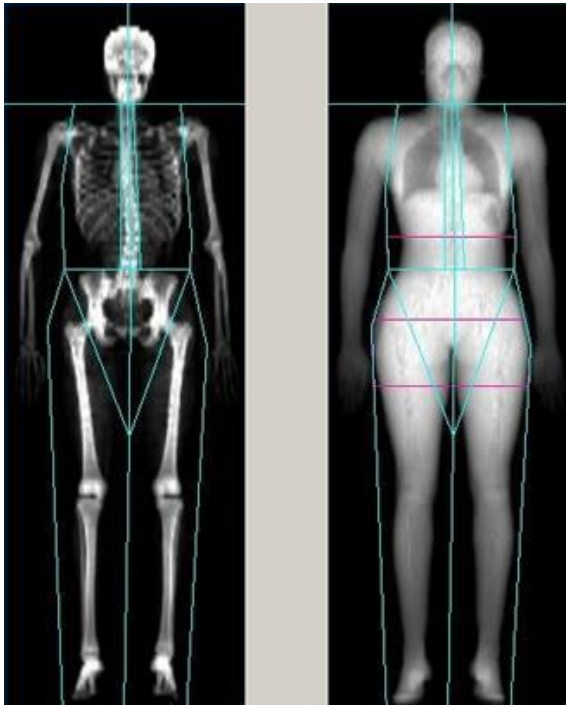


The HuMet study

The HuMet study

Antropometric data

	n	Min.	Max.	Mean	SD	SEM	CV
Age (y)	15	22	33	27.8	2.98	0.77	10.72%
Height (m)	15	1.71	1.92	1.83	0.06	0.02	3.47%
Weight (kg)	15	63.5	90.4	77.5	7.09	1.83	9.14%
BMI	15	20.4	25.5	23.1	1.76	0.45	7.61%
WHR	15	0.8	1	0.89	0.05	0.01	5.12%
Waist (cm)	15	70.5	87.5	80.5	4.59	1.19	5.72%
Hip (cm)	15	84	98	90.1	4.72	1.22	5.24%
Heart rate (1/min)	15	44	84	62	11.37	2.94	18.39%
Blood pressure (syst.)	15	106	160	121.5	12.07	3.12	9.93%
Blood pressure (diast.)	15	70	93	81.9	5.95	1.54	7.26%
Fat mass (kg)	15	8.84	19	14.4	3.32	0.86	23.05%
Fat (%) whole body	15	13.6	23.9	18.7	2.92	0.76	15.67%
Fat (%) trunk	15	12.9	22.3	17.2	3.07	0.79	17.84%
Muscle (kg)	15	47.7	70.4	59.5	5.91	1.53	9.94%
24h-BMR (kcal)	15	1300	2160	1721	223.60	57.73	12.99%
RQ	15	0.78	0.99	0.85	0.06	0.01	6.47%
Body surface area(m^2)	15	1.77	2.19	1.99	0.12	0.03	5.80%



4 days in house in the study center at TUM (2 times 2 days)

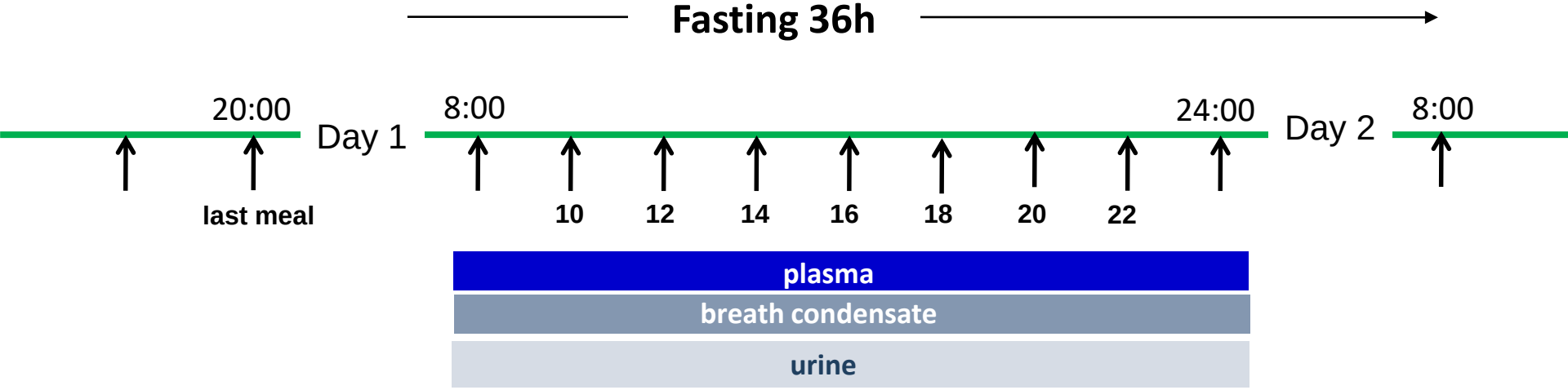
a total of 56 blood samples from each volunteer

a total of 56 breath samples from each volunteer

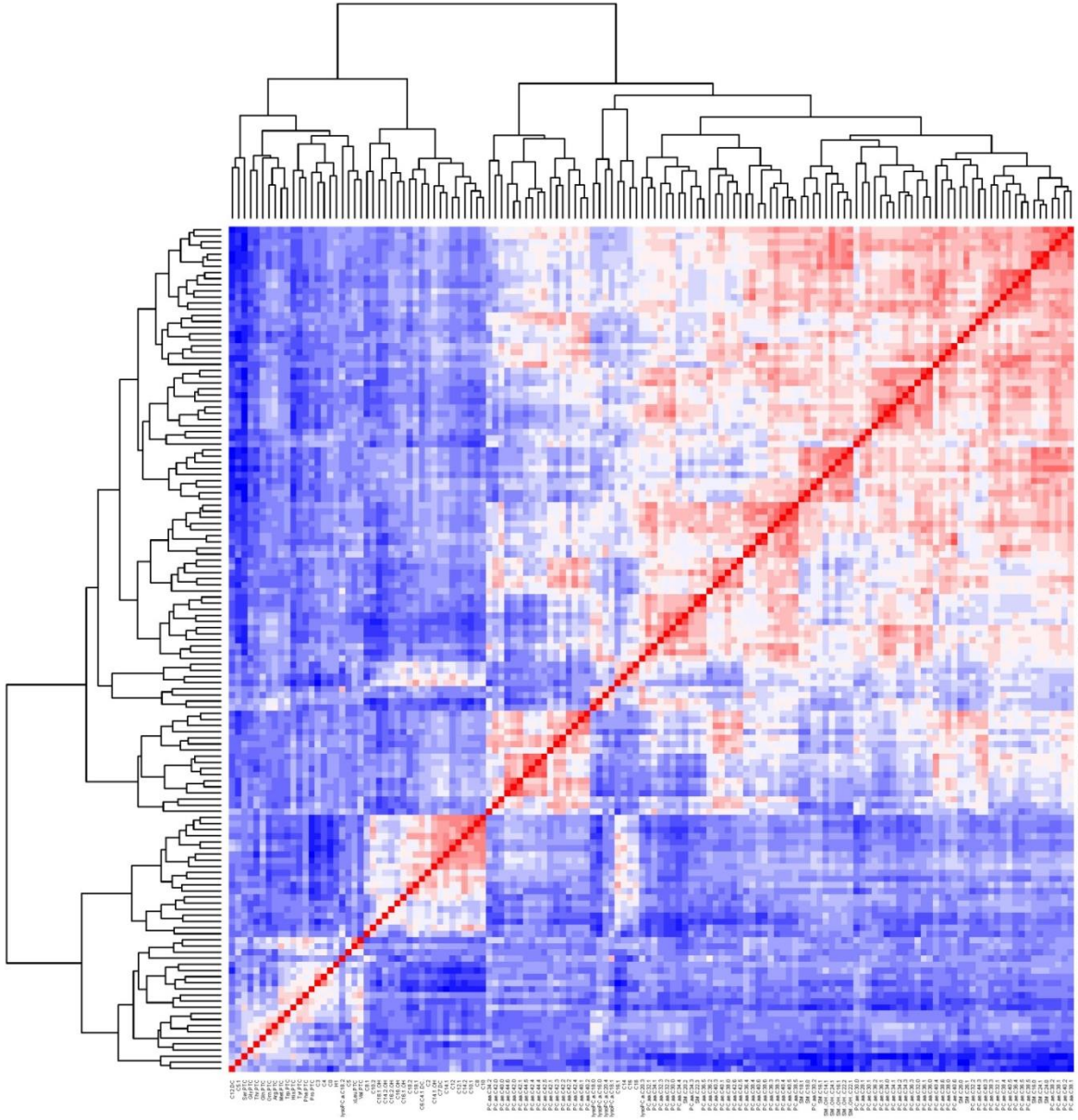
a total of 25 urine samples from each volunteer

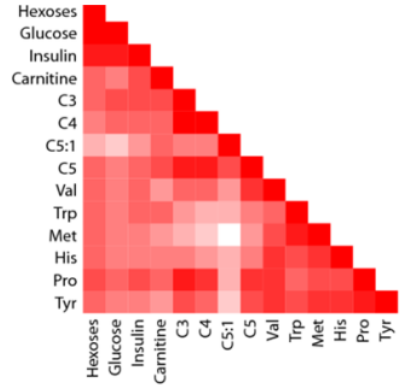
The challenges

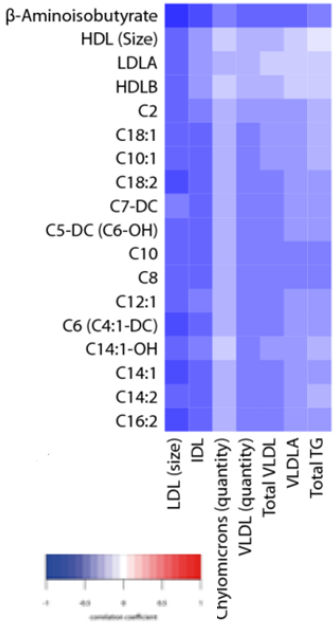

Fasting 36h
Standard liquid diet (SLD)
Oral glucose tolerance test
Standard liquid meal
Cycle ergometer test (Ergo)
Oral lipid load
Cold stress test
Day 1
Day 2
Day 3
Day 4
last meal
plasma
breath condensate
urine
samples
exercise
discharge


Fasting 36h
20:00
Day 1
8:00
24:00
Day 2
8:00
last meal
10
12
14
16
18
20
22
plasma
breath condensate
urine

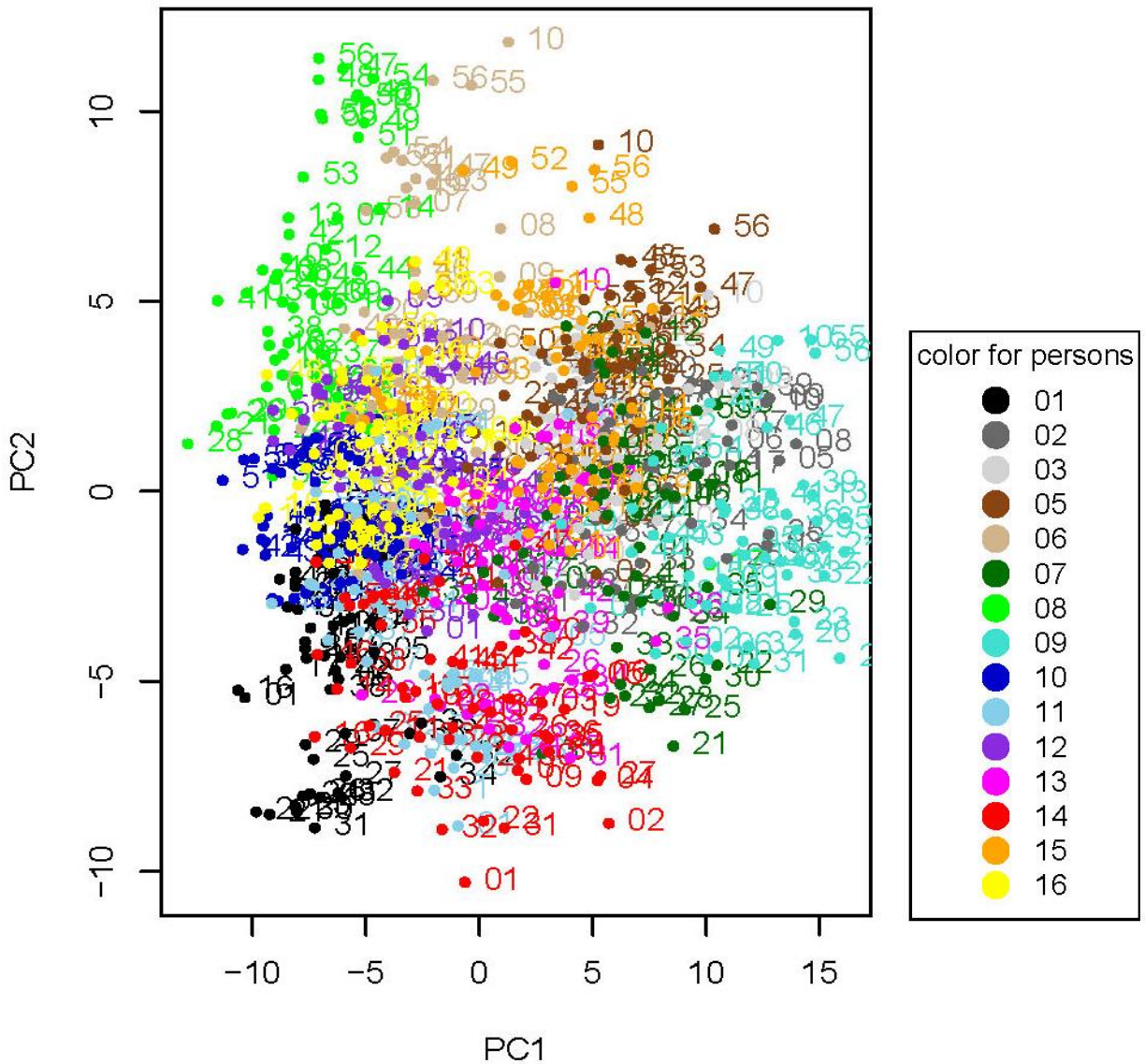
Kendall Correlation amongst metabolites quantified over all challenges



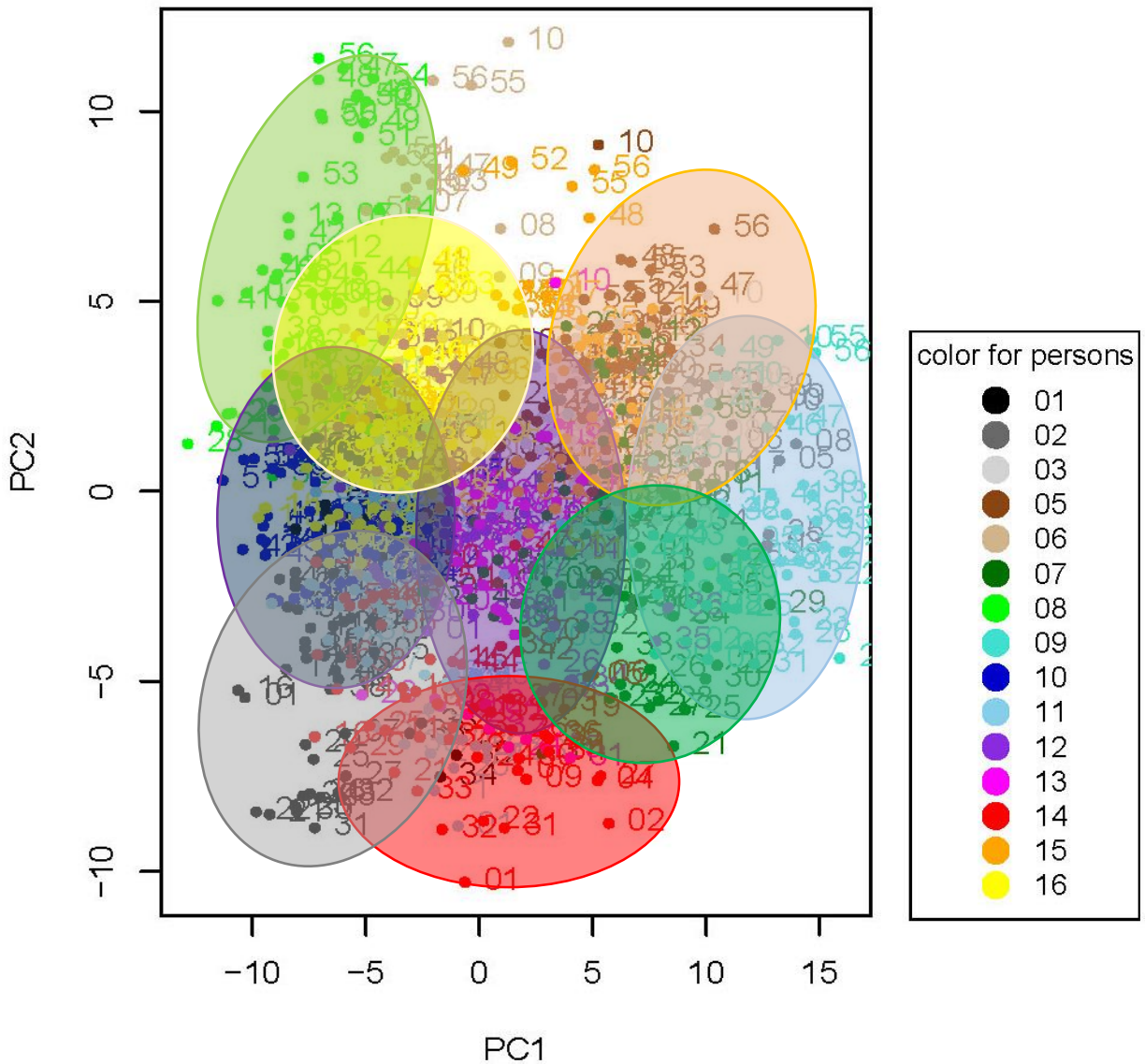


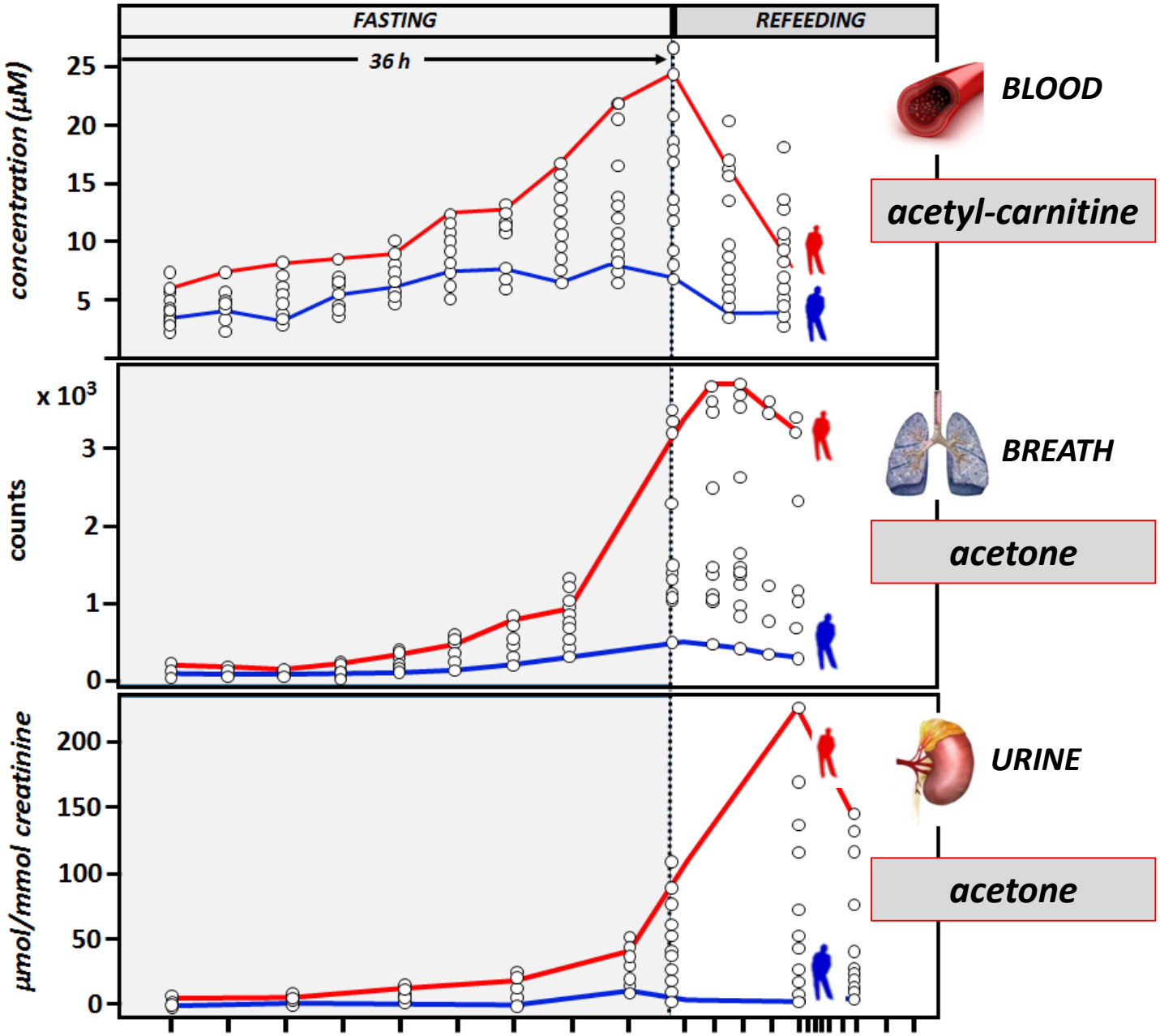


Principal component analysis



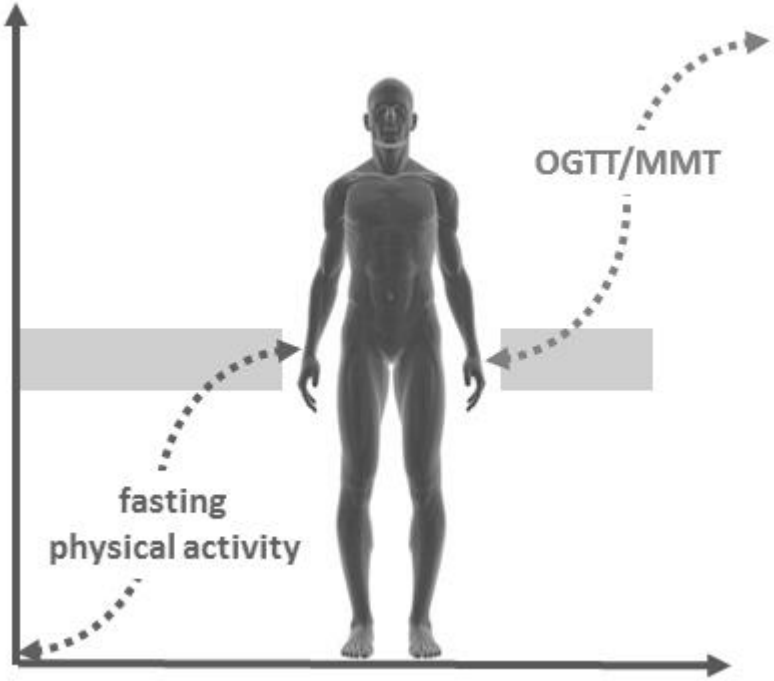
Principal component analysis




FASTING
REFEEDING
36 h
concentration (µM)
25
20
15
10
5
BLOOD
acetyl-carnitine
x 10³
counts
3
2
1
0
BREATH
acetone
µmol/mmol creatinine
200
150
100
50
0
URINE
acetone

How „robust“ is a metabolic phenotype ?

Quantifying phenotypic flexibility from time-profiles of metabolite levels in plasma during challenge test



The NuTrTech study

The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

12 weeks (control)

32 participants

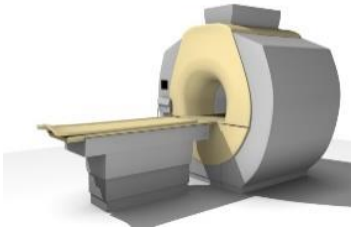
40 participants

12 weeks (intervention)

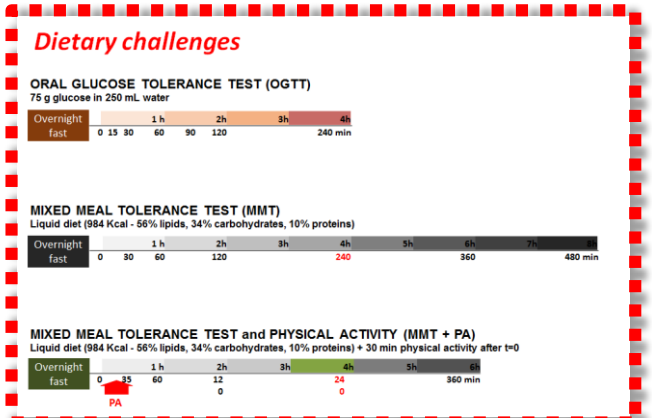
reduction of energy intake by 20%

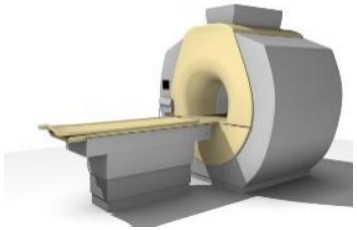
weight loss: around 5,5 kg

72 participants



+ challenge experiments



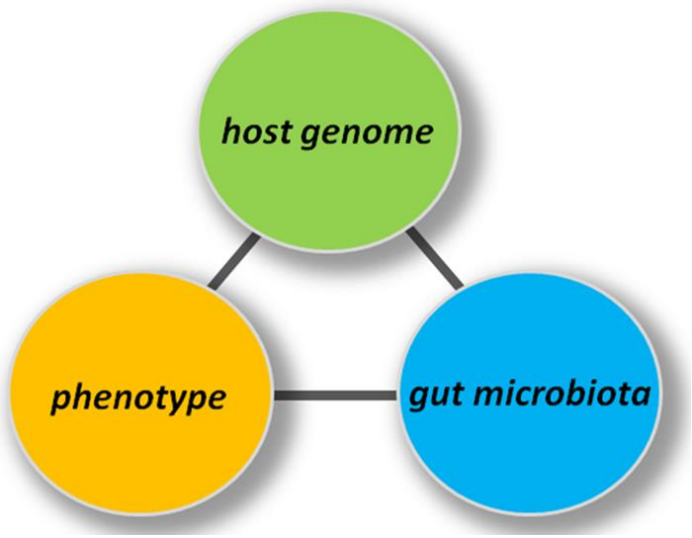


+ challenge experiments

The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

- Exome sequencing
- Muscle & adipose tissue biopsy´s
- PBMC-transcriptome analysis
- Microbiome analysis



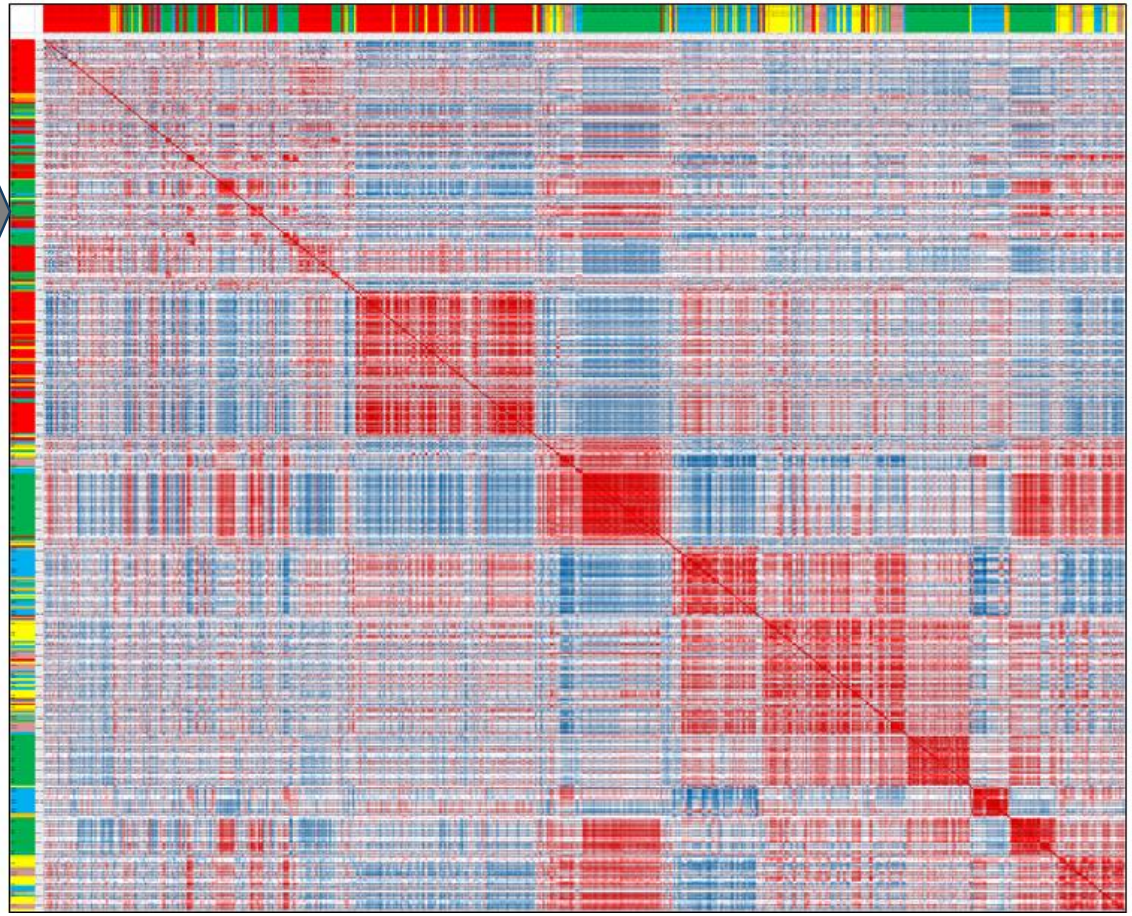
Around 3.000 samples

More than 400 metabolites identified and/or quantified by using LC-MS/MS, GC-MS, NMR and clinical chemistry.

The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

correlation of 664 variables in fasting state



How „robust“ is a metabolic phenotype ?

3 month

72 participants

72 participants

Dietary challenges

ORAL GLUCOSE TOLERANCE TEST (OGTT)
75 g glucose in 250 mL water

Overnight fast | 0 15 30 60 90 120 | 1 h 2h 3h 4h | 240 min

MIXED MEAL TOLERANCE TEST (MMT)
Liquid diet (984 Kcal - 56% lipids, 34% carbohydrates, 10% proteins)

Overnight fast | 0 30 60 120 240 360 480 min | 1 h 2h 3h 4h 5h 6h 7h 8h

MIXED MEAL TOLERANCE TEST and PHYSICAL ACTIVITY (MMT + PA)
Liquid diet (984 Kcal - 56% lipids, 34% carbohydrates, 10% proteins) + 30 min physical activity after t=0

Overnight fast | 0 35 60 12 0 24 0 360 min | 1 h 2h 3h 4h 5h 6h | PA

Around 3.000 samples with more than 300 metabolites identified using LC-MS/MS, GC-MS, NMR and clinical chemistry.

Dietary challenges

ORAL GLUCOSE TOLERANCE TEST (OGTT)
75 g glucose in 250 mL water

Overnight fast | 0 15 30 60 90 120 | 1 h 2h 3h 4h | 240 min

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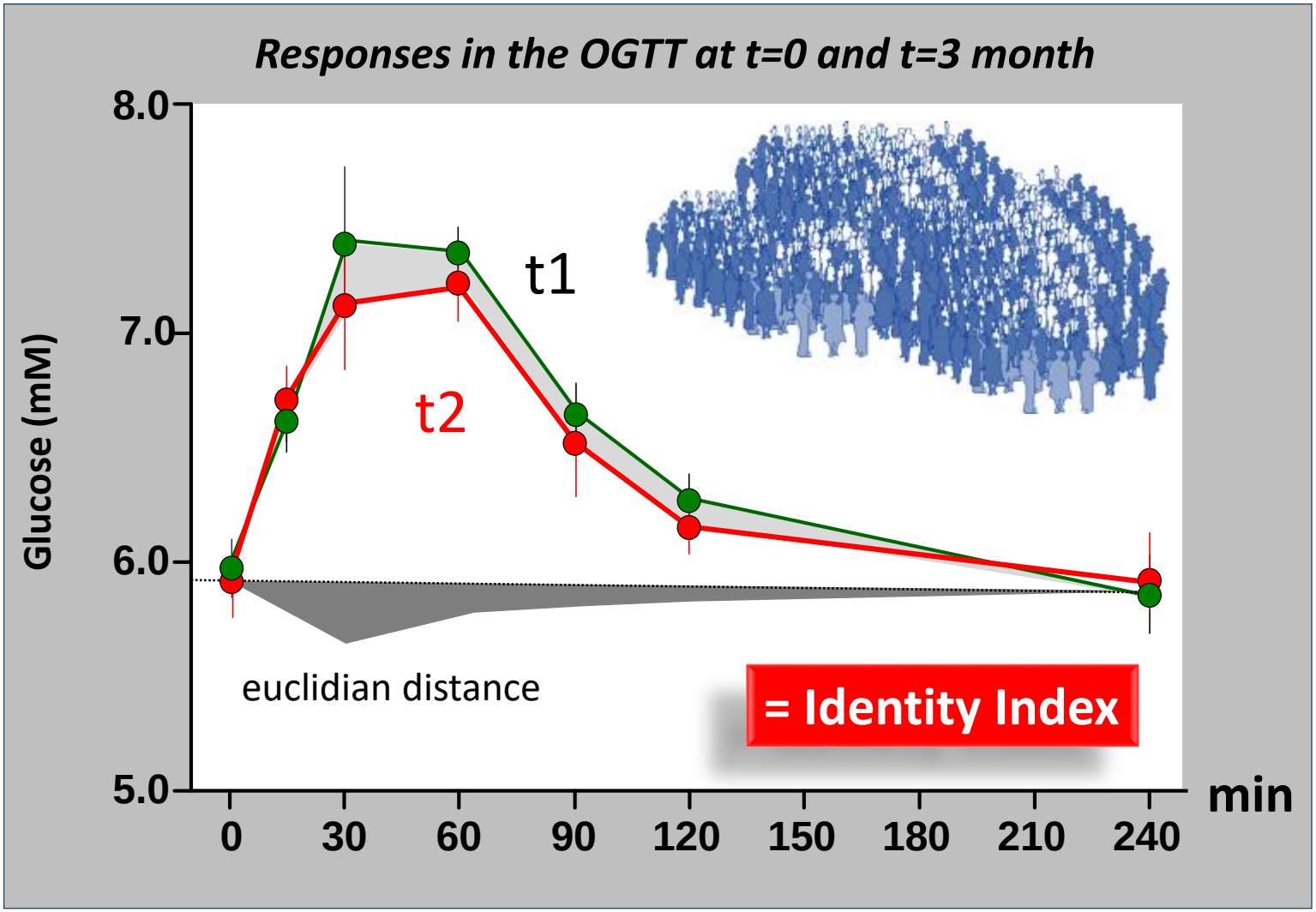
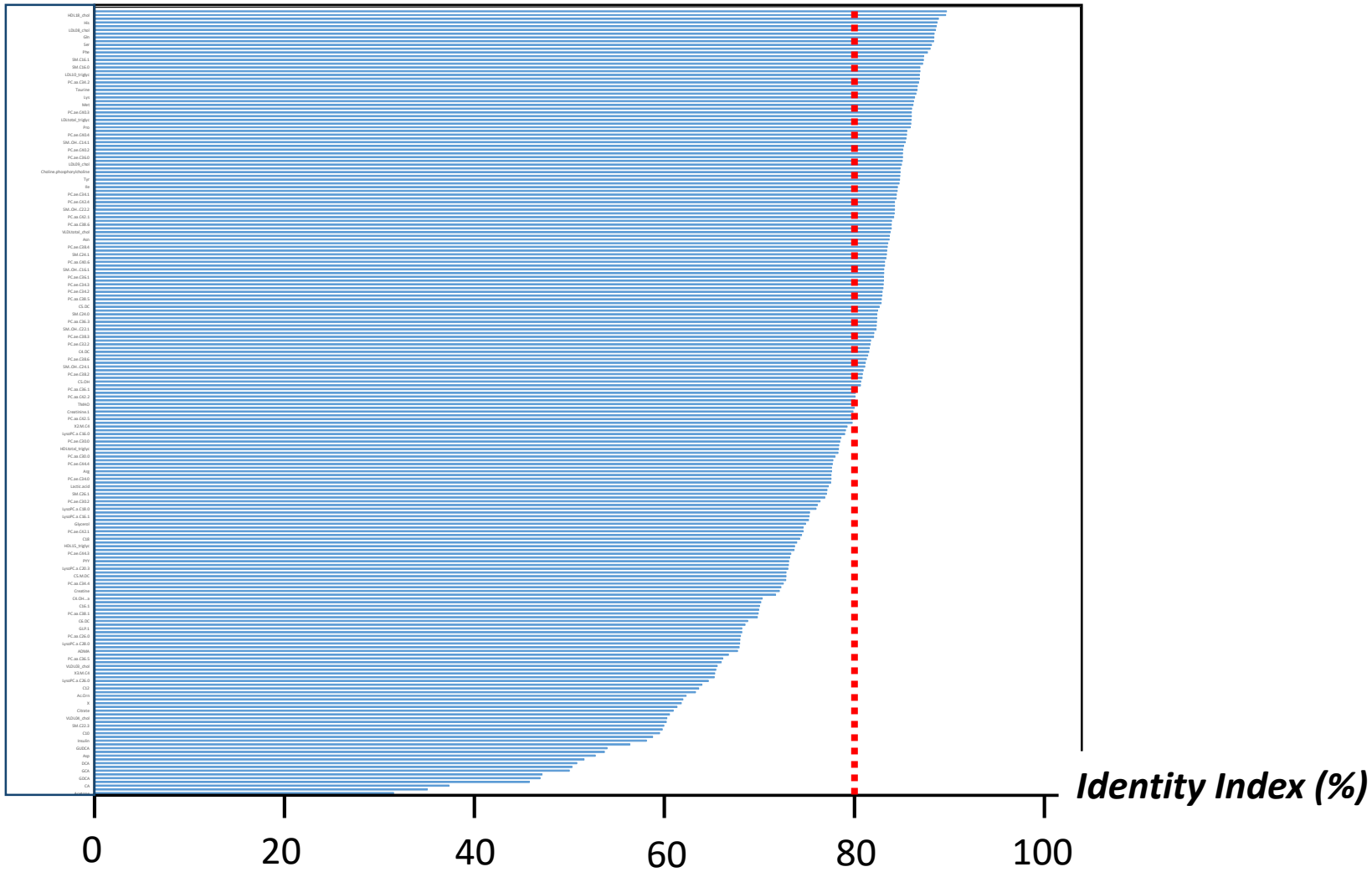
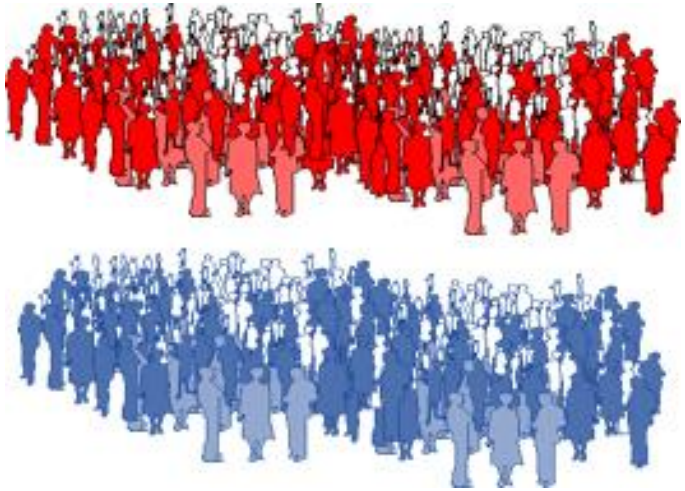

Responses in the OGTT at t=0 and t=3 month
8.0
7.0
6.0
5.0
Glucose (mM)
t1
t2
euclidian distance
= Identity Index
0
30
60
90
120
150
180
210
240
min

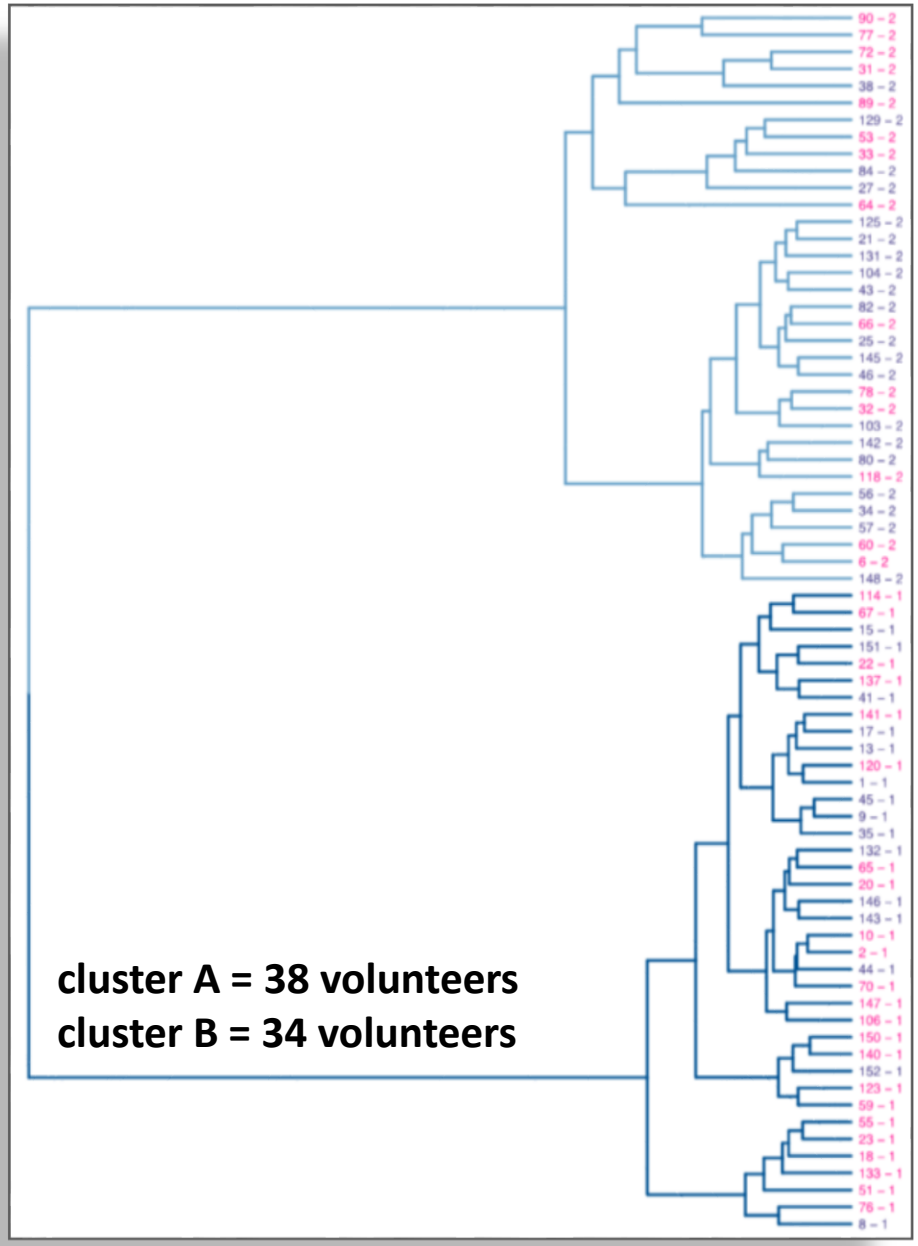
The IDENTITY INDEX of all measured blood parameters in the NutriTech OGTT samples

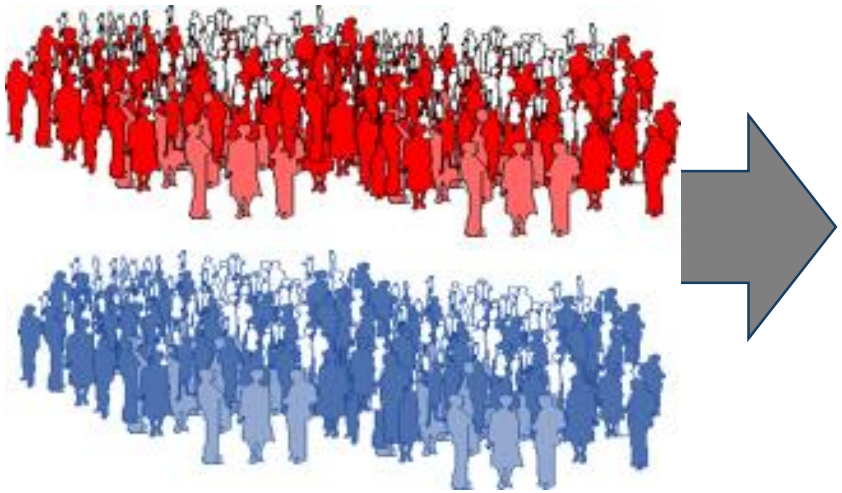
METABOLITES

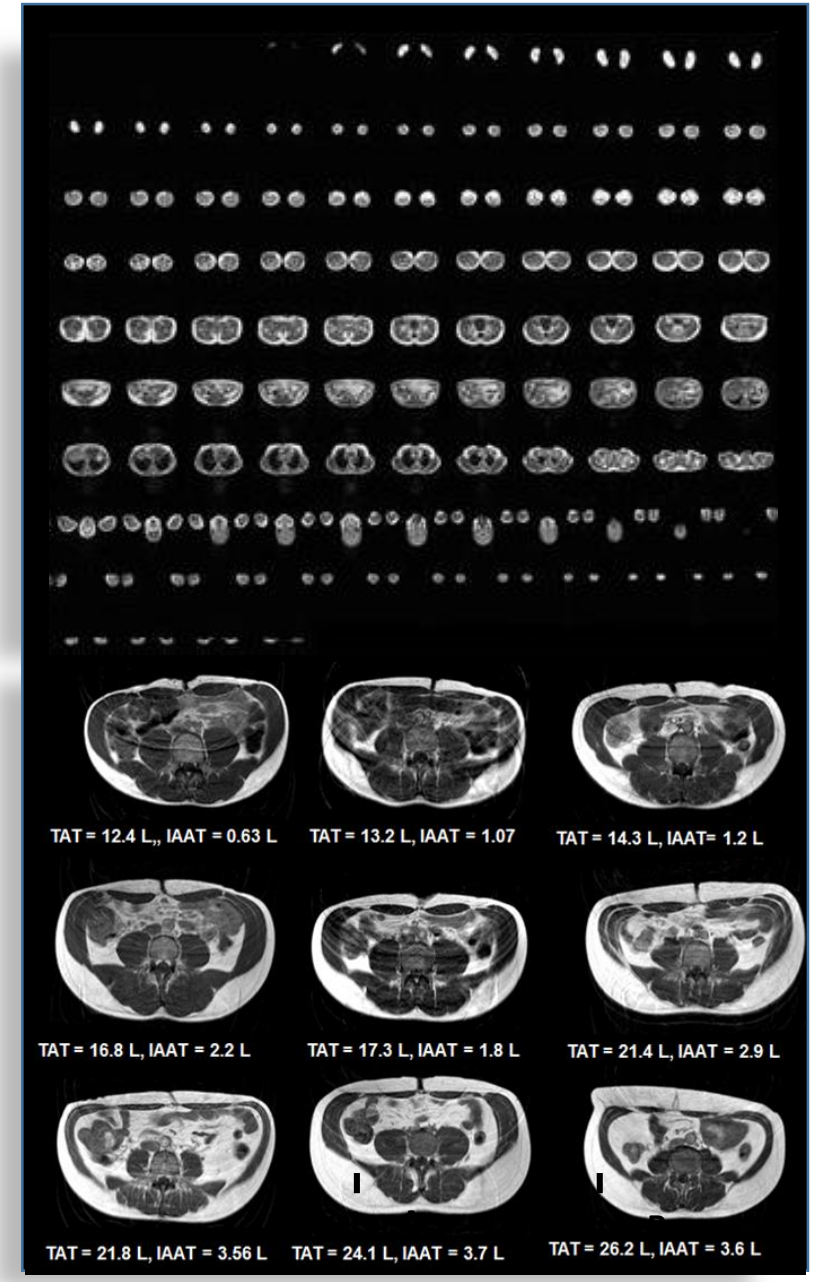


Ranking of metabolites w.r.t. reproducibility of measurements (t=0 and 12 weeks) within the OGTT

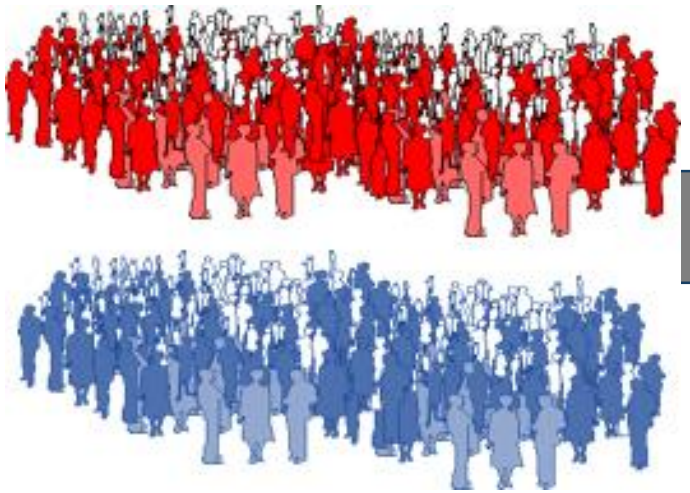


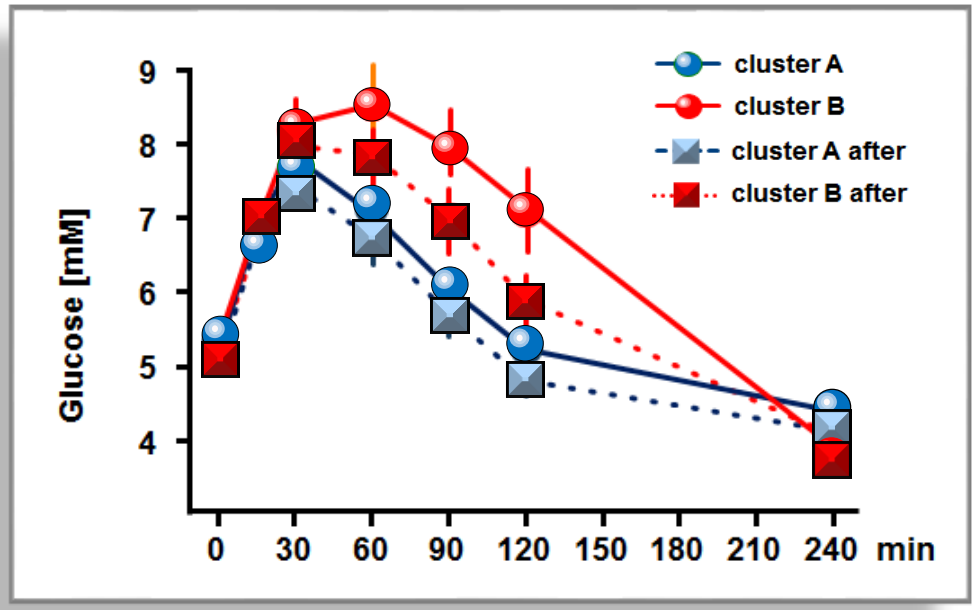

cluster A = 38 volunteers
cluster B = 34 volunteers

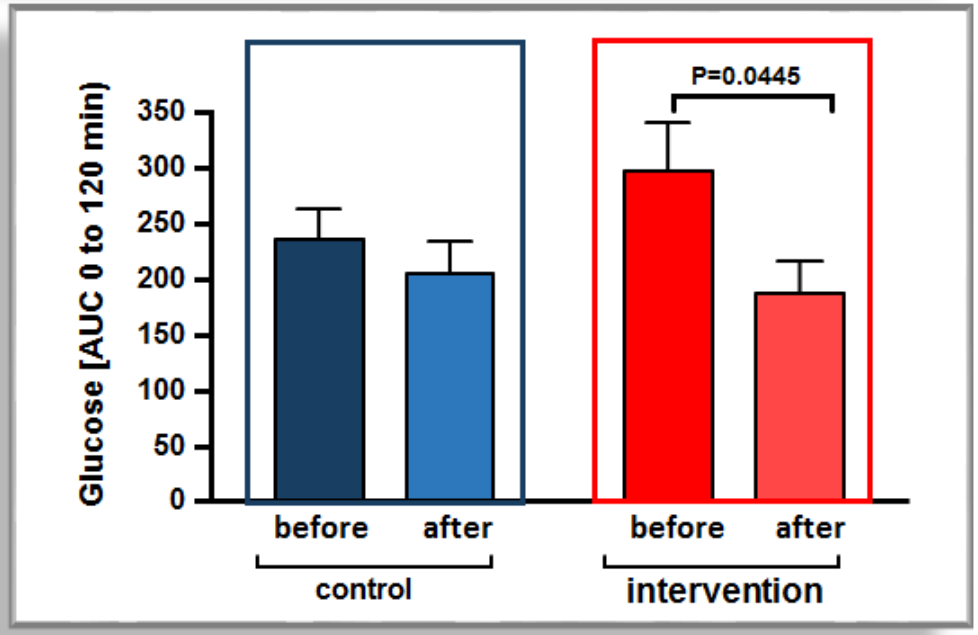




data are mean ± SEM, n=38 and n=34



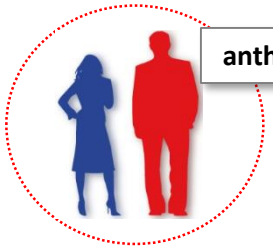




data are mean ± SEM, n=38 and n=34

… taking it into concepts of INDIVIDUALIZED NUTRITION

INPUT



anthropometrics

food intake

physical activity

metabotype

genotype

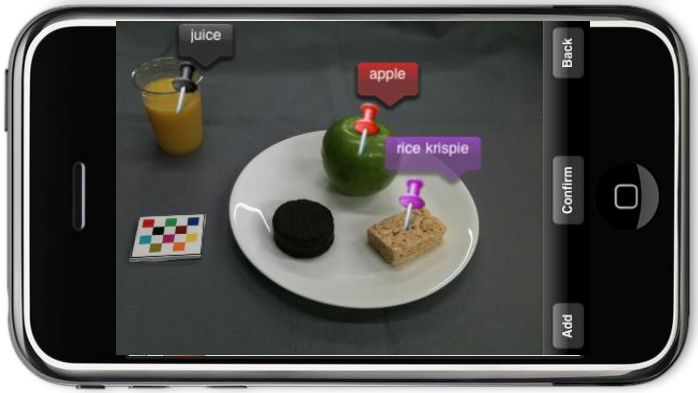
Developments

Genotyping

Body functions

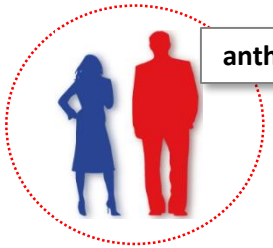
Advice systems

Food intake assessment



food4me.org

INPUT



anthropometrics

food intake

physical activity

metabotype

genotype

OUTPUT

advice systems

data centre

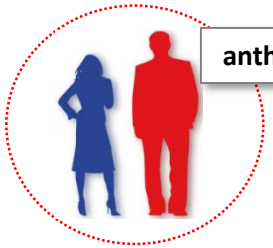
ALGORITHMS

personalized menus

1.607 participants

food frequency questionaire
physical activity monitoring
anthropometric measurements
DNA from buccal swaps
dry blood spots for LC/GC-MS analysis

INPUT



anthropometrics

food intake

metabotype

genotype

ADVISE LEVEL

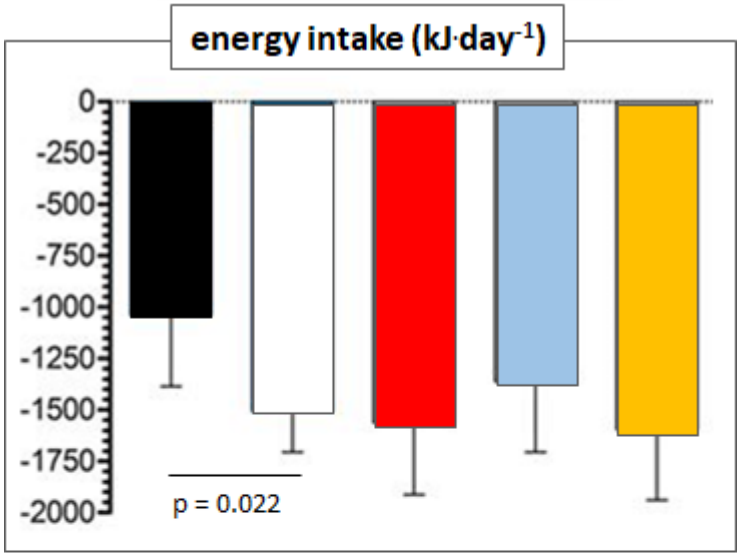
generic

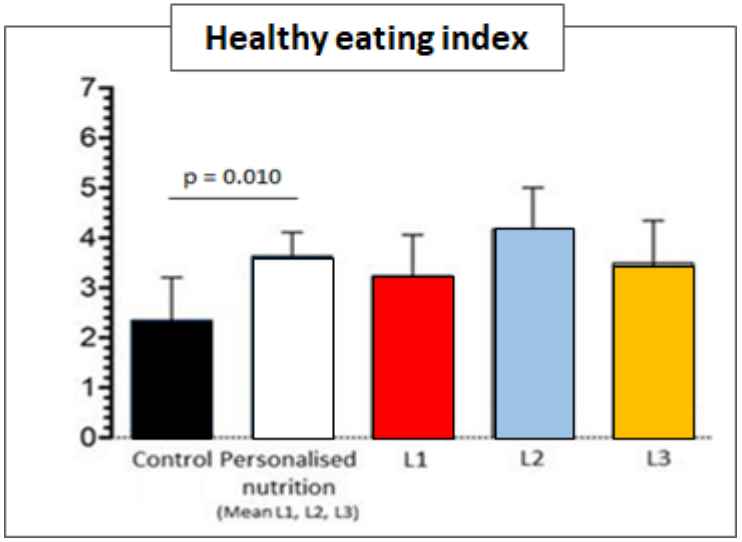
food intake based

food intake+metabotype

food intake+metabotype+genotype

EFFECT-SIZE





WHAT IS HABIT?

Habit is a science-based, personalized nutrition solution to help you eat with confidence and feel your best.

Take home message

- The genome x diet interaction is in essence unexplored.
- Findings from GWAS studies explain only a small fraction of human metabolic diversity and measure only against a very small set of phenotypic parameters.
- Human metabolism is highly dynamic and most phenotyping studies lack the time-dimension of response.
- There are „robust metabotypes“ in healthy populations
- These „metabotypes „ can be targeted for mproving health via individualized advise systems and treatments

THANK YOU ALL