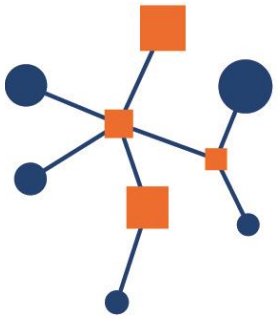
Leiden University
Medical Center

BBMRI Metabolomics Consortium



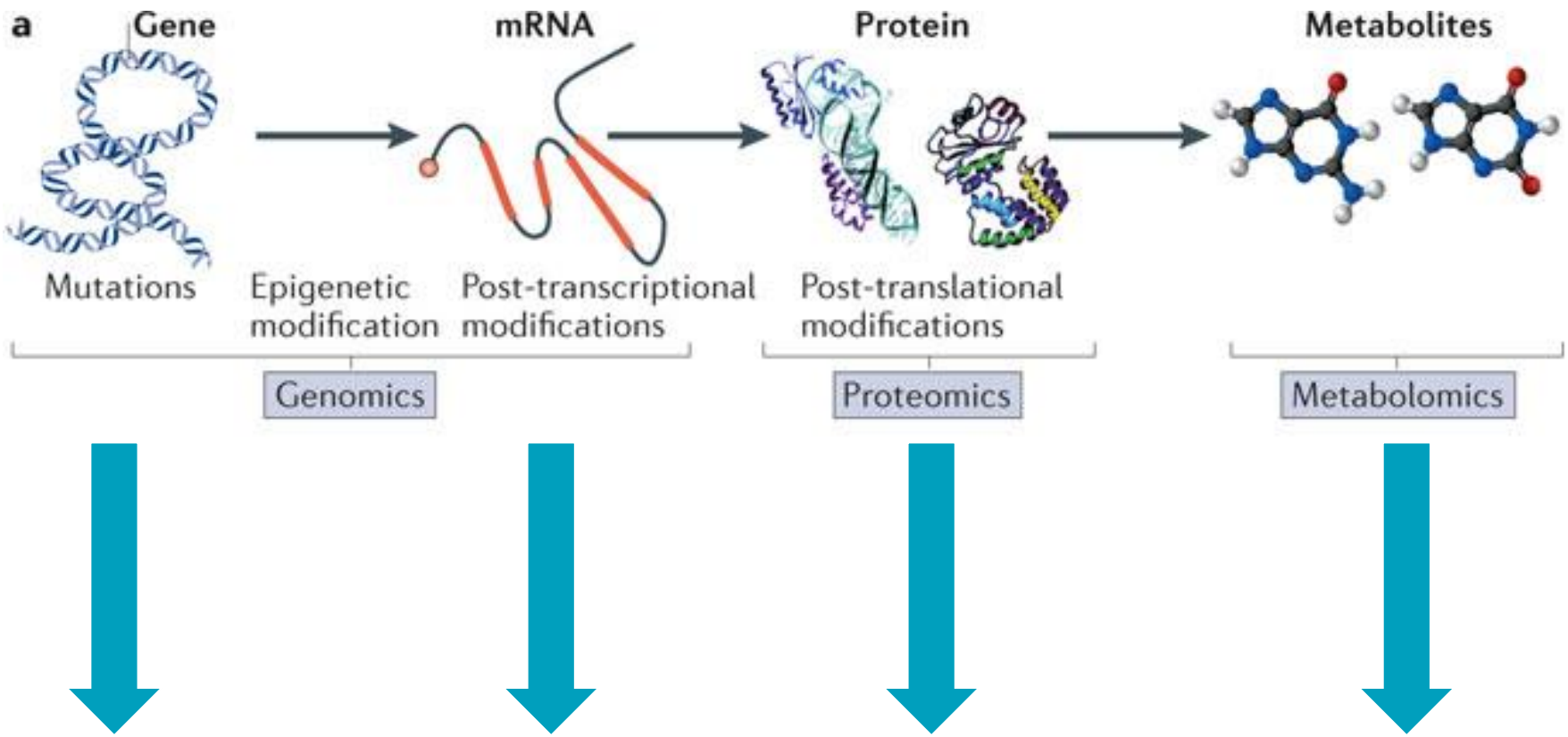
BBMRI.nl

Biobanking and
BioMolecular resources
Research Infrastructure
The Netherlands

Marian Beekman

MOLECULAR EPIDEMIOLOGY, LUMC

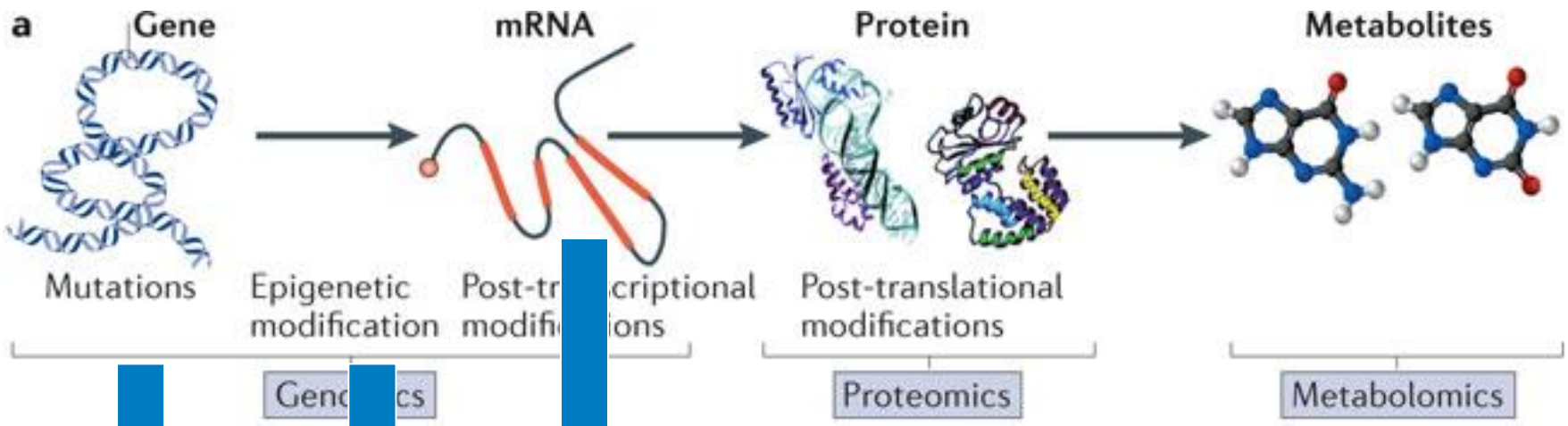
The central dogma of biology



Health and Disease

Nature Reviews Molecular Cell Biology 13, 263-269 (April 2012) | doi:10.1038/nrm3314

The central dogma of biology



BIOS gene expression

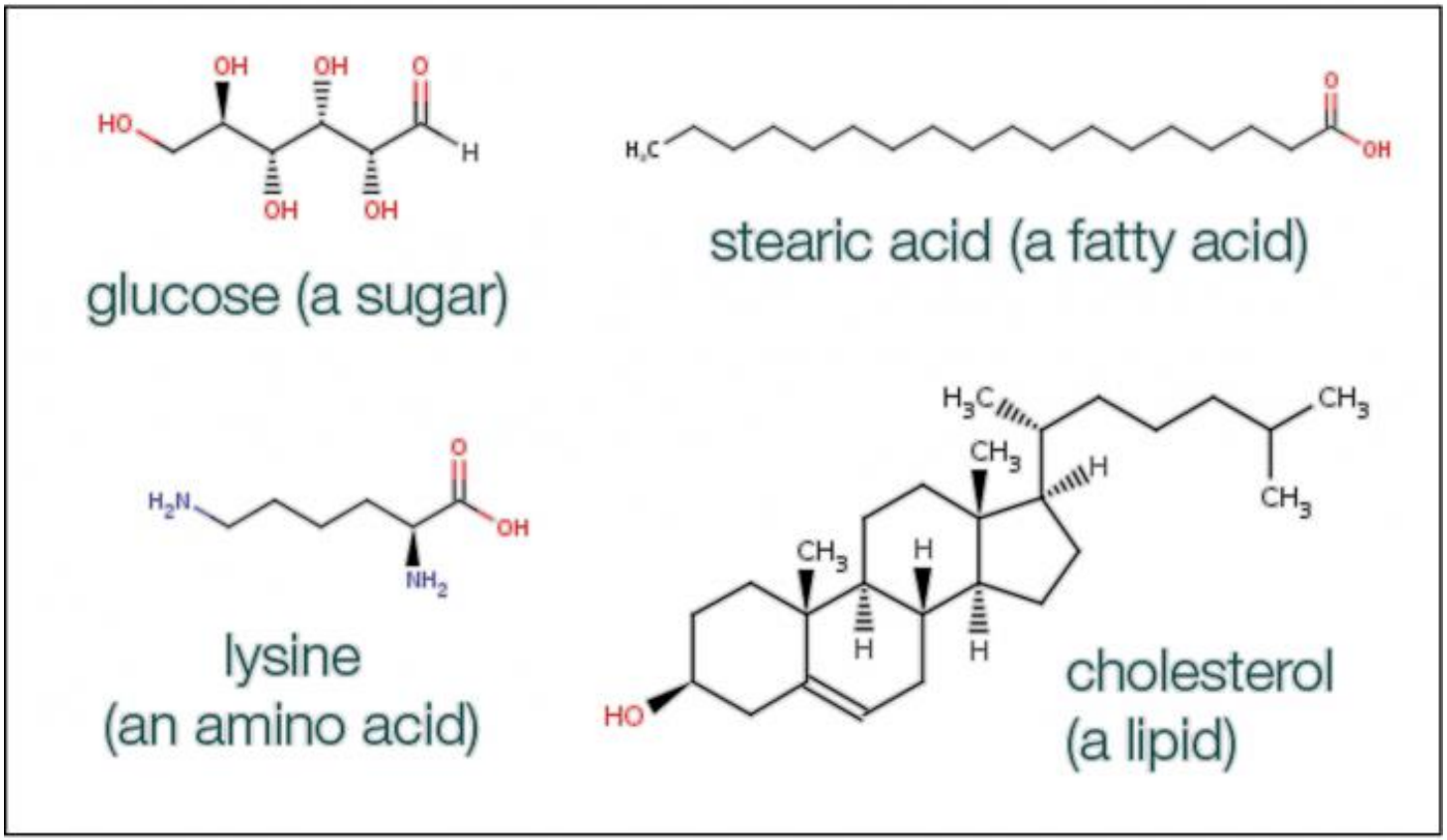
BIOS DNA methylation

Metabolomics Consortium

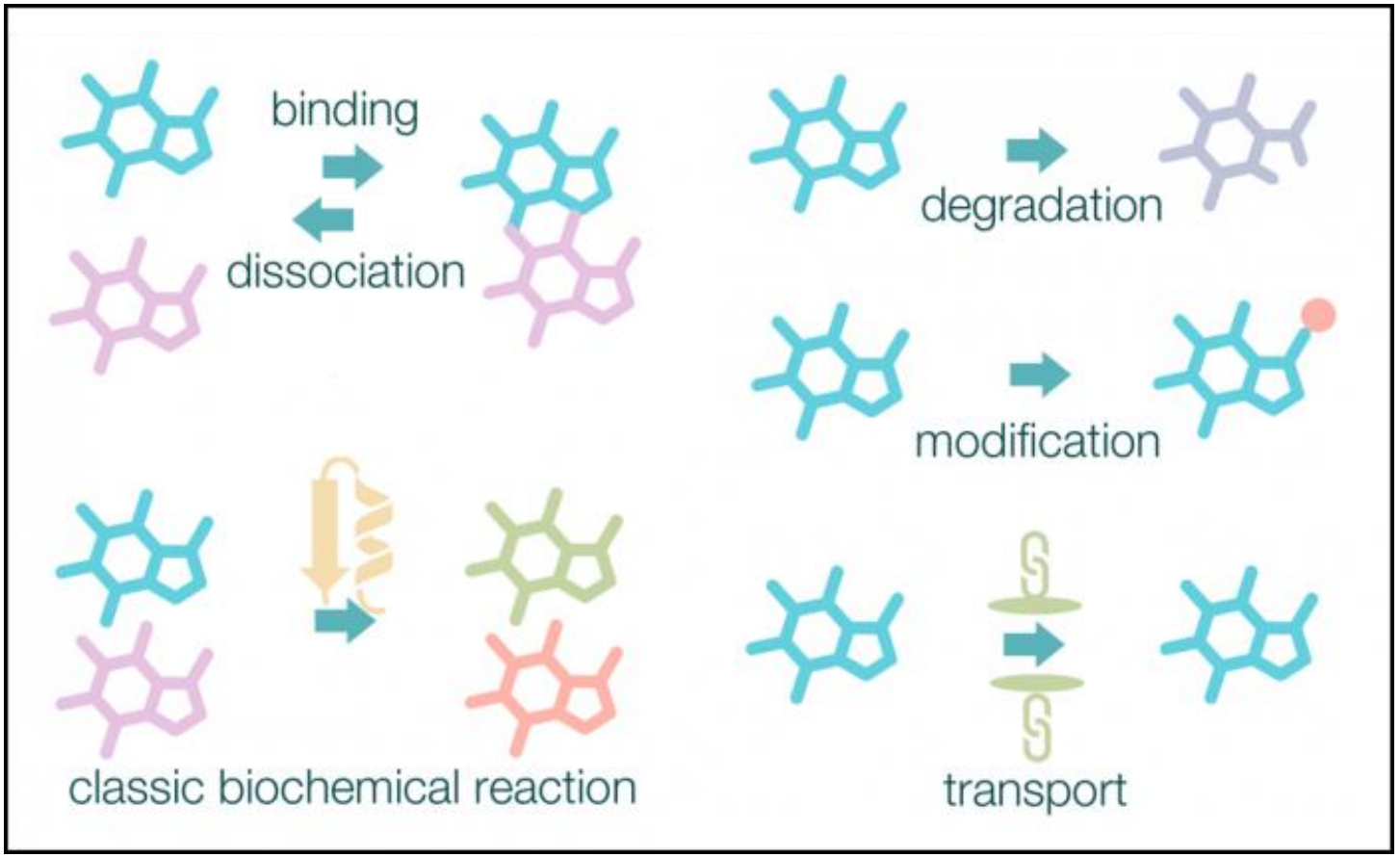
Genome of the Netherlands Go.NL

Nature Reviews Molecular Cell Biology 13, 263-269 (April 2012) | doi:10.1038/nrm3314

Metabolites

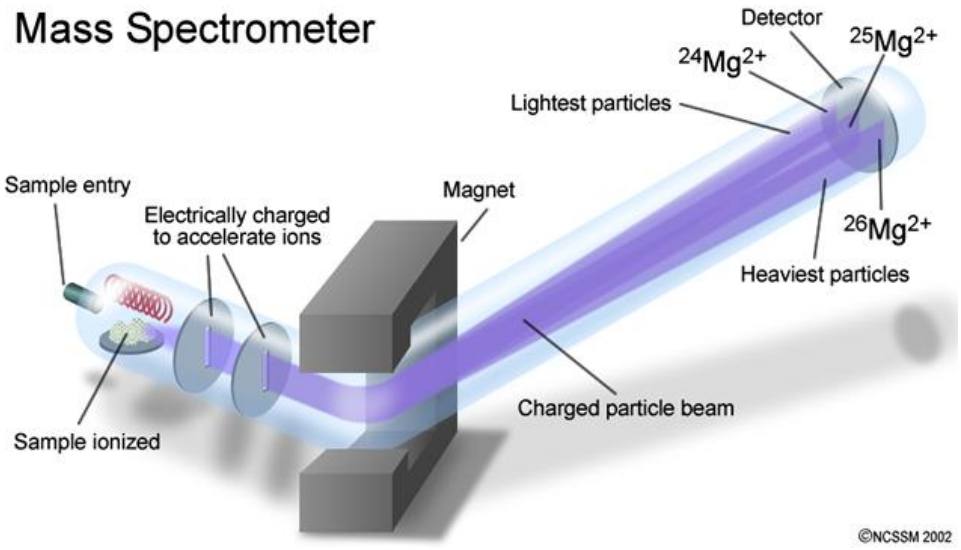


Snaphot in time



Methods to measure metabolomics

- Mass Spectometry (separation on mass)
- Nuclear Magnetic Resonance (separation on the capacities of absorbsion and re-emission of electromagnetic radiation)



Nightingale Health (formerly known as Brainshake)

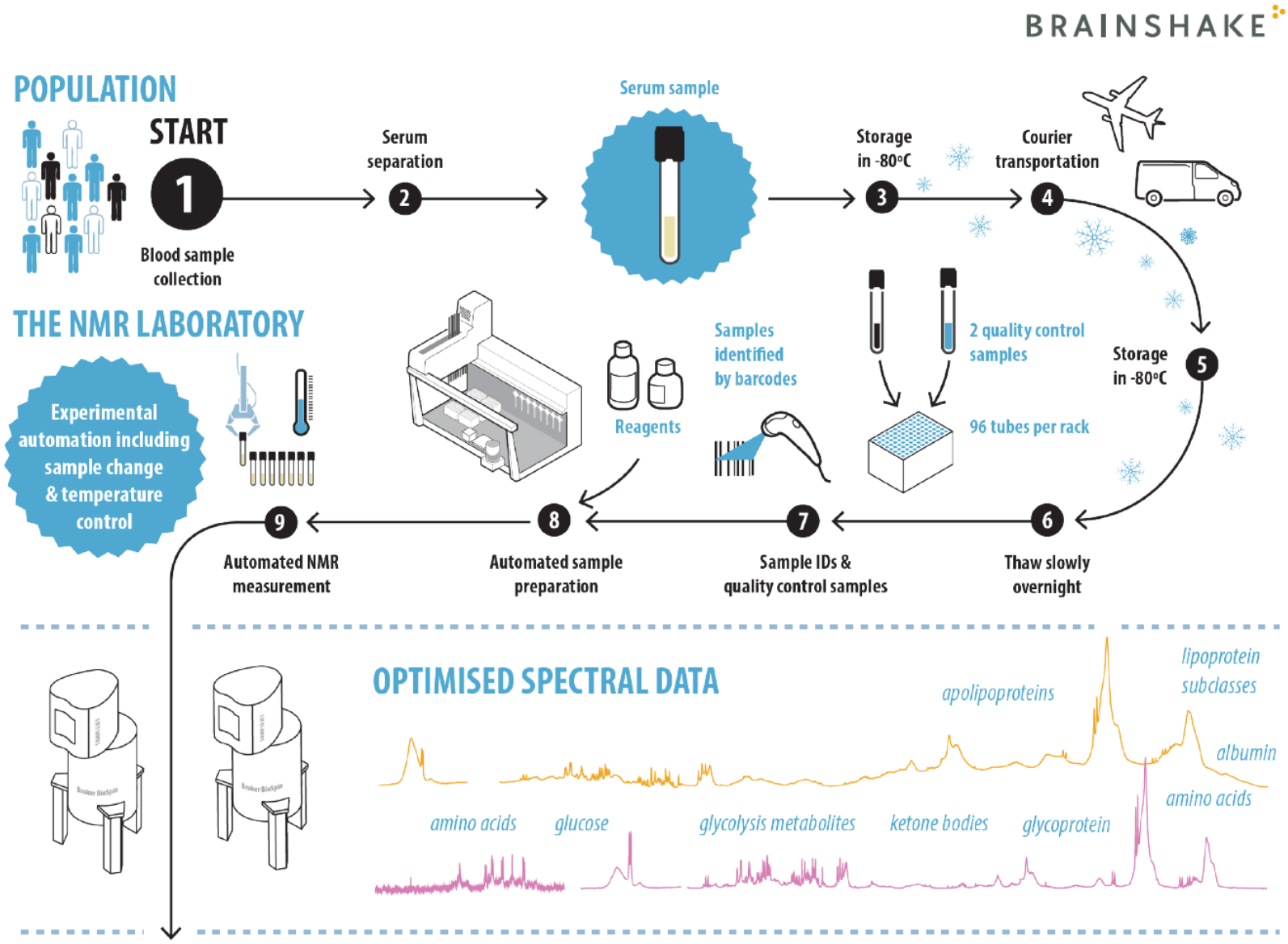
BRAINSHAKE

TRANSFORMING MEDICINE

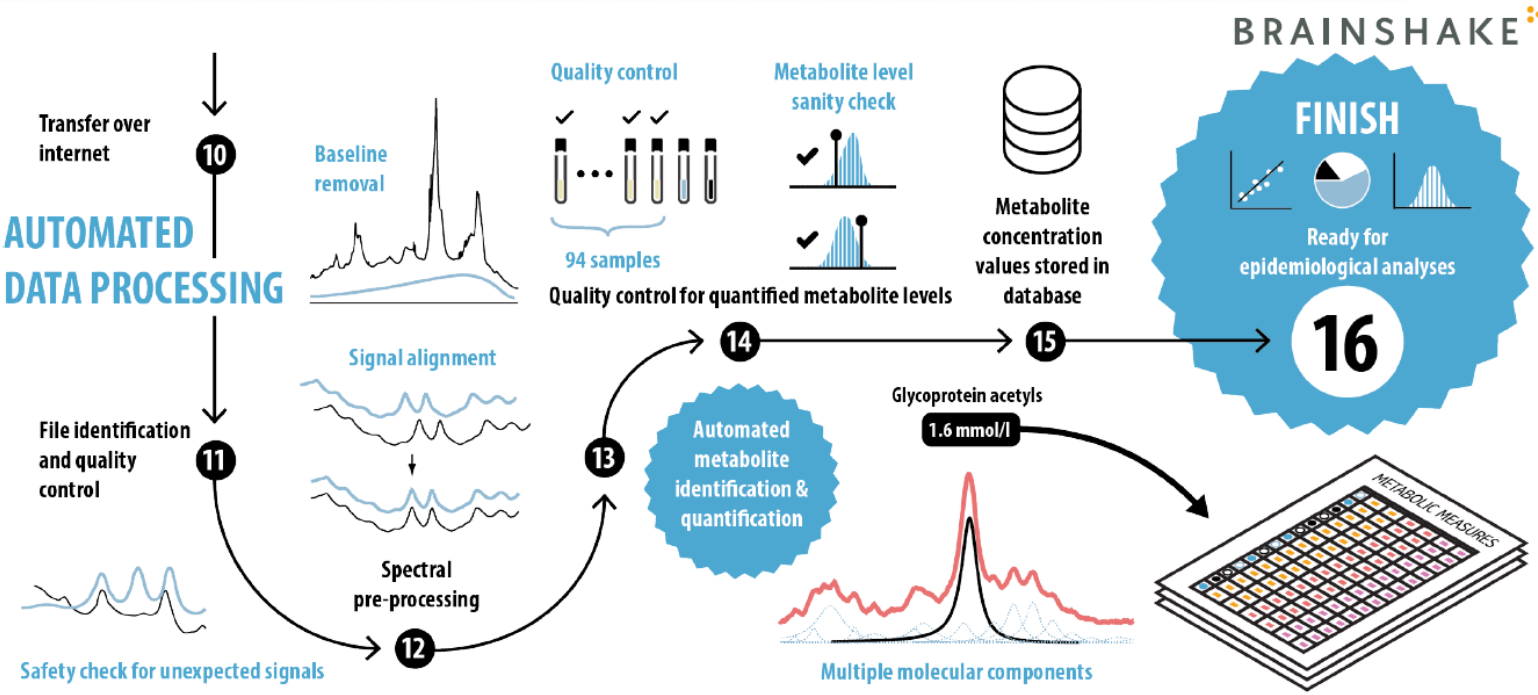
Nightingale

https://nightingalehealth.com/science/biomarkers

Nightingale Health (formerly known as Brainshake)



Nightingale Health (formerly known as Brainshake)

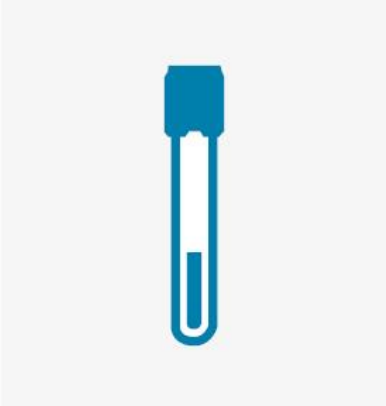


The quantitative molecular output from the serum NMR metabolomics platform:

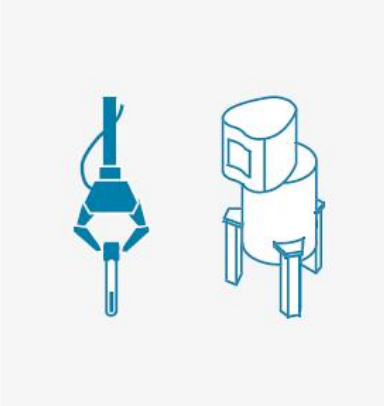
228 metabolic biomarkers measured currently

Nightingale Health (formerly known as Brainshake)

ONE BLOOD SAMPLE



ONE TEST



OVER 200 METABOLIC BIOMARKERS

Lipoprotein particle size

Glycerides & phospholipids

14 lipoprotein subclasses

Fatty acid saturation

Cholesterol

Apolipoproteins

Fatty acids

Ketone bodies

Inflammation

Fluid balance

Amino acids

Glycolysis-related measures

http://www.computationalmedicine.fi/platform#metabolites:glycolysis

Nightingale Health (formerly known as Brainshake)

228 METABOLIC MEASURES

BRAINSHAKE

Ketone bodies (mmol/l)

- Acetate
- Acetoacetate
- 3-hydroxybutyrate

Glycolysis related metabolites (mmol/l)

- Glucose
- Lactate
- Pyruvate
- Citrate
- Glycerol

Inflammation (mmol/l)

- Glycoprotein acetyls

Fatty acids and saturation

- Total fatty acids
- Estimated degree of unsaturation

Fatty acids (mmol/l and % of total FAs)

- ●○ Omega-3 fatty acids
- ●○ Omega-6 fatty acids
- ●○ Polyunsaturated fatty acids
- ●○ Monounsaturated fatty acids; 16:1, 18:1
- ●○ Saturated fatty acids
- ●○ Docosahexaenoic acid; 22:6
- ●○ Linoleic acid; 18:2

Amino acids (mmol/l)

- Alanine
- Glutamine
- Glycine
- Histidine

Branched-chain amino acids

- Isoleucine
- Leucine
- Valine

Aromatic amino acids

- Phenylalanine
- Tyrosine

Cholesterol (mmol/l)

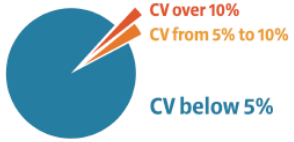
- VLDL cholesterol
- LDL cholesterol
- HDL cholesterol
- HDL_2 cholesterol
- HDL_3 cholesterol
- Cholesterol
- Free cholesterol
- Esterified cholesterol
- Remnant cholesterol

Apolipoproteins (g/l)

- ApoA-I
- ApoB
- ○ ApoB/ApoA-I

Fluid balance

- Creatinine (mmol/l)
- Albumin (signal area)



Glycerides & phospholipids (mmol/l)

- VLDL triglycerides
- LDL triglycerides
- HDL triglycerides
- Triglycerides
- Phosphoglycerides
- ○ Ratio of triglycerides to phosphoglycerides
- Phosphatidylcholine and other cholines
- Sphingomyelins
- Total cholines

Lipoprotein particle size (nm)

- Mean diameter of VLDL particles
- Mean diameter of LDL particles
- Mean diameter of HDL particles

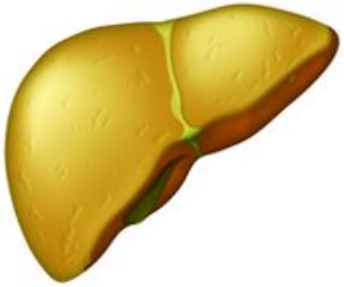
14 LIPOPROTEIN SUBCLASSES

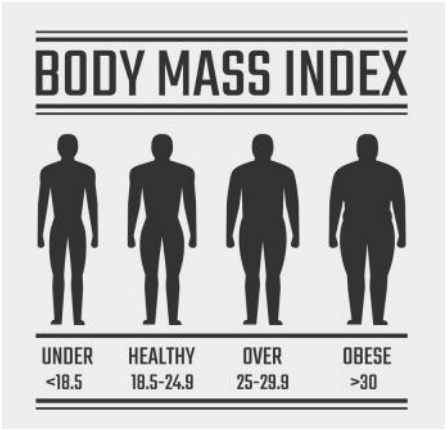
12 lipid measures for each subclass

- ●○ Esterified cholesterol (mmol/l and % of total lipids)
- ●○ Free cholesterol (mmol/l and % of total lipids)
- ●○ Triglycerides (mmol/l and % of total lipids)
- ●○ Phospholipids (mmol/l and % of total lipids
- ●○ Total cholesterol (mmol/l and % of total lipids)
- Total lipids (mmol/l)
- Particle concentration (µmol/l)

https://nightingalehealth.com/science/biomarkers

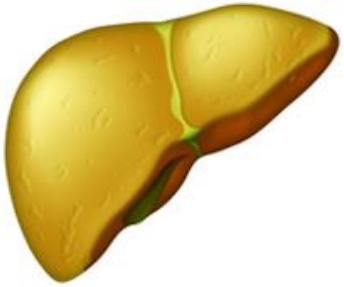
Metabolomics association with disease

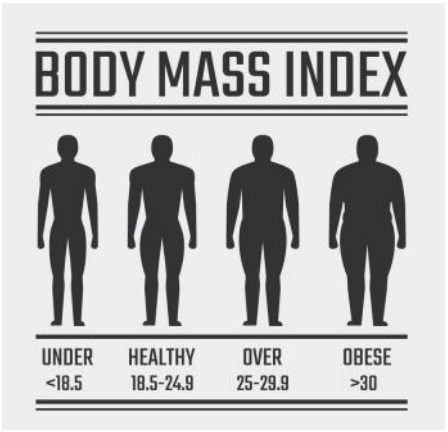




Metabolomics

Metabolomics association with disease





bolomics

Epidemiology and Prevention

Metabolite Profiling and Cardiovascular Event Risk
A Prospective Study of 3 Population-Based Cohorts

Peter Würtz, PhD; Aki S. Havulinna, DScTech; Pasi Soininen, PhD; Tuulia Tynkkynen, PhD; David Prieto-Merino, PhD; Therese Tillin, MBBS; Anahita Ghorbani, MD; Anna Artati, PhD; Qin Wang, MSc; Mika Tiainen, PhD; Antti J. Kangas, MSc; Johannes Kettunen, PhD; Jari Kaikkonen, MSc; Vera Mikkilä, PhD; Antti Jula, MD, PhD; Mika Kähönen, MD, Ph
Terho Lehtimäki, MD, PhD; Debbie A. Lawlor, MD, PhD; Tom R. Gaunt, PhD;

METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 111–121

nature COMMUNICATIONS

ARTICLE

Received 3 Jun 2015 | Accepted 24 Feb 2016 | Published 23 Mar 2016 DOI: 10.1038/ncomms11122 OPEN

Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of *LPA*

Johannes Kettunen *et al.*#

ELSEVIER

Available online at www.sciencedirect.com

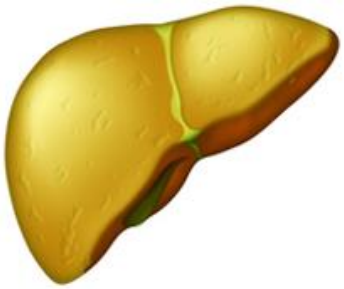
Metabolism

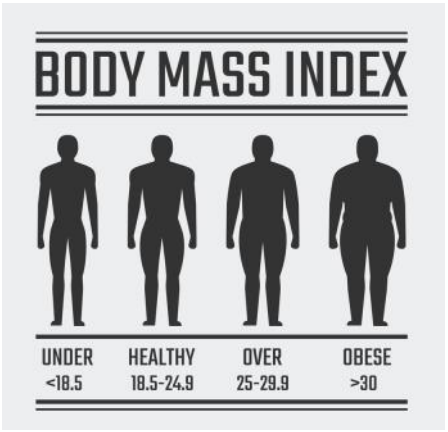
www.metabolismjournal.com

Abdominal obesity and circulating metabolites: A twin study approach

Leonie H. Bogl[a,*,1], *Sanna M. Kaye*[b,1], *Joel T. Rämö*[b,c], *Antti J. Kangas*[d,e], *Pasi Soininen*[d,e], *Antti Hakkarainen*[f], *Jesper Lundbom*[f], *Nina Lundbom*[f], *Alfredo Ortega-Alonso*[c], *Aila Rissanen*[b,g], *Mika Ala-Korpela*[d,e,h,i], *Jaakko Kaprio*[a,c,j,2], *Kirsi H. Pietiläinen*[b,c,k,2]

Metabolomics association with disease





Metabolomics

ORIGINAL ARTICLE

Metabolic Signatures of Insulin Resistance in 7,098 Young Adults

Peter Würtz,[1,2,3] Ville-Petteri Mäkinen,[1,4,5] Pasi Soininen,[1,6] Antti J. Kangas,[1] Taru Tukiainen,[1,2] Johannes Kettunen,[2,7] Markku J. Savolainen,[1,8] Tuija Tammelin,[9] Jorma S. Viikari,[10] Tapani Rönnemaa,[10] Mika Kähönen,[11] Terho Lehtimäki,[12] Samuli Ripatti,[2,7,13] Olli T. Raitakari,[14,15] Marjo-Riitta Järvelin,[3,16,17,18] and Mika Ala-Korpela[1,6,8]

Pathophysiology/Complications

ORIGINAL ARTICLE

Circulating Metabolite Predictors of Glycemia in Middle-Aged Men and Women

Peter Würtz, PhD[1,2,3]
Mika Tiainen, MSc[1,4]
Ville-Petteri Mäkinen, DSc[1,5]
Antti J. Kangas, MSc[1]
Pasi Soininen, PhD[1,4]
Juha Saltevo, MD, PhD[6]
Sirkka Keinänen-Kiukaanniemi, MD, PhD[7,8]
Pekka Mäntyselkä, MD, PhD[9,10]
Terho Lehtimäki, MD, PhD[11]
Markku Laakso, MD, PhD[12]
Antti Jula, MD, PhD[13]
Mika Kähönen, MD, PhD[14]
Mauno Vanhala, MD, PhD[10,15]
Mika Ala-Korpela, PhD[1,3,4,16]

OBJECTIVE—Metabolite predictors of deteriorating glucose tolerance may elucidate the pathogenesis of type 2 diabetes. We investigated associations of circulating metabolites from high-throughput profiling with fasting and postload glycemia cross-sectionally and prospectively on the population level.

Type 2 diabetes is characterized by a long progression period before overt disease onset (1,2). Metabolic perturbations characterizing and contributing to the disease development may be observed already in the prediabetic state (3,4). Knowledge on systemic metabolites associated with deteriorating glucose tolerance may elucidate the pathogenesis of diabetes and holds potential for prevention. Comprehensive metabolic profiling is therefore increasingly used to provide

Pathophysiology/Complications

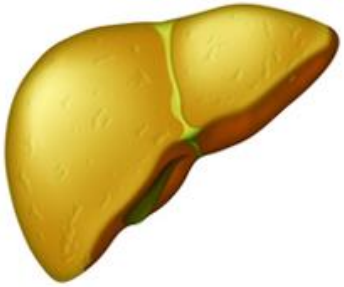
ORIGINAL ARTICLE

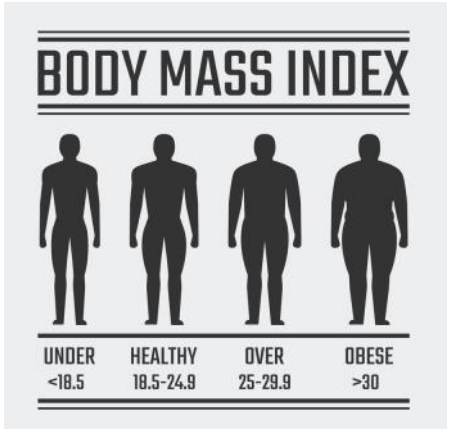
Branched-Chain and Aromatic Amino Acids Are Predictors of Insulin Resistance in Young Adults

Peter Würtz, PhD[1,2]
Pasi Soininen, PhD[2,3]
Antti J. Kangas, MSc[2]
Tapani Rönnemaa, MD, PhD[4]
Terho Lehtimäki, MD, PhD[5]
Mika Kähönen, MD, PhD[6]
Jorma S. Viikari, MD, PhD[4]
Olli T. Raitakari, MD, PhD[7,8]
Mika Ala-Korpela, PhD[2,3]

Furthermore, the circulating concentrations of branched-chain amino acids (isoleucine, leucine, and valine) and aromatic amino acids (phenylalanine and tyrosine) were recently shown to be associated with the risk of future hyperglycemia and overt

Metabolomics association with disease





Metabolomics

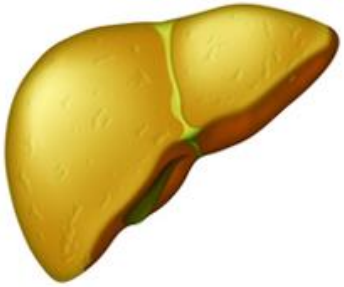
OPEN ACCESS Freely available online

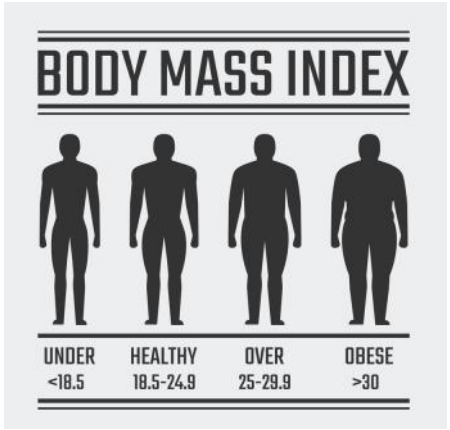
PLOS | MEDICINE

Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons

Krista Fischer[1☯*], Johannes Kettunen[2,3,4☯], Peter Würtz[2,4☯*], Toomas Haller[1], Aki S. Havulinna[3], Antti J. Kangas[4], Pasi Soininen[4,5], Tõnu Esko[1,6,7,8,9,10], Mari-Liis Tammesoo[1], Reedik Mägi[1], Steven Smit[1], Aarno Palotie[2,6,11], Samuli Ripatti[2,11], Veikko Salomaa[3], Mika Ala-Korpela[4,5,12¶], Markus Perola[1,2¶], Andres Metspalu[1,13¶]

Metabolomics association with disease





Metabolomics

Liver INTERNATIONAL

Liver International ISSN 1478-3223

Cell Systems
Report

The Biomarker GlycA Is Associated with Chronic Inflammation and Predicts Long-Term Risk of Severe Infection

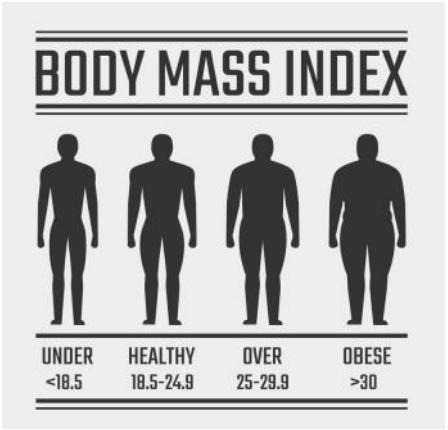
Scott C. Ritchie,[1,2] Peter Würtz,[4] Artika P. Nath,[1,3] Gad Abraham,[1,2] Aki S. Havulinna,[5,6] Liam G. Fearnley,[1,2] Antti-Pekka Sarin,[6] Antti J. Kangas,[4] Pasi Soininen,[4,7] Kristiina Aalto,[8] Ilkka Seppälä,[9] Emma Raitoharju,[9] Marko Salmi,[5,8] Mikael Maksimow,[5,8] Satu Männistö,[5] Mika Kähönen,[10] Markus Juonala,[11,12] Samuli Ripatti,[6,13] Terho Lehtimäki,[9] Sirpa Jalkanen,[8] Markus Perola,[5,6] Olli Raitakari,[14,15] Veikko Salomaa,[5] Mika Ala-Korpela,[4,7,16,17,18] Johannes Kettunen,[4,5,7,19,*] and Michael Inouye[1,2,3,19,*]

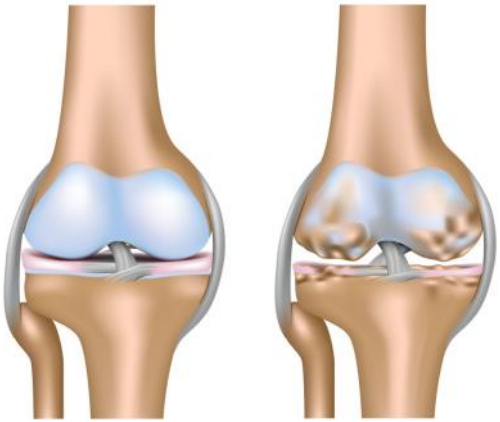
NAFLD/NASH

Ketone body production is differentially altered in steatosis and non-alcoholic steatohepatitis in obese humans

Ville T. Männistö[1], Marko Simonen[1], Jenni Hyysalo[2], Pasi Soininen[3,4], Antti J. Kangas[3,4], Dorota Kaminska[5], Ananda K. Matte[5], Sari Venesmaa[6], Pirjo Käkelä[6], Vesa Kärjä[7], Johanna Arola[8], Helena Gylling[5,9], Henna Cederberg[1], Johanna Kuusisto[1], Markku Laakso[1], Hannele Yki-Järvinen[2], Mika Ala-Korpela[3,4,10] and Jussi Pihlajamäki[5,11]

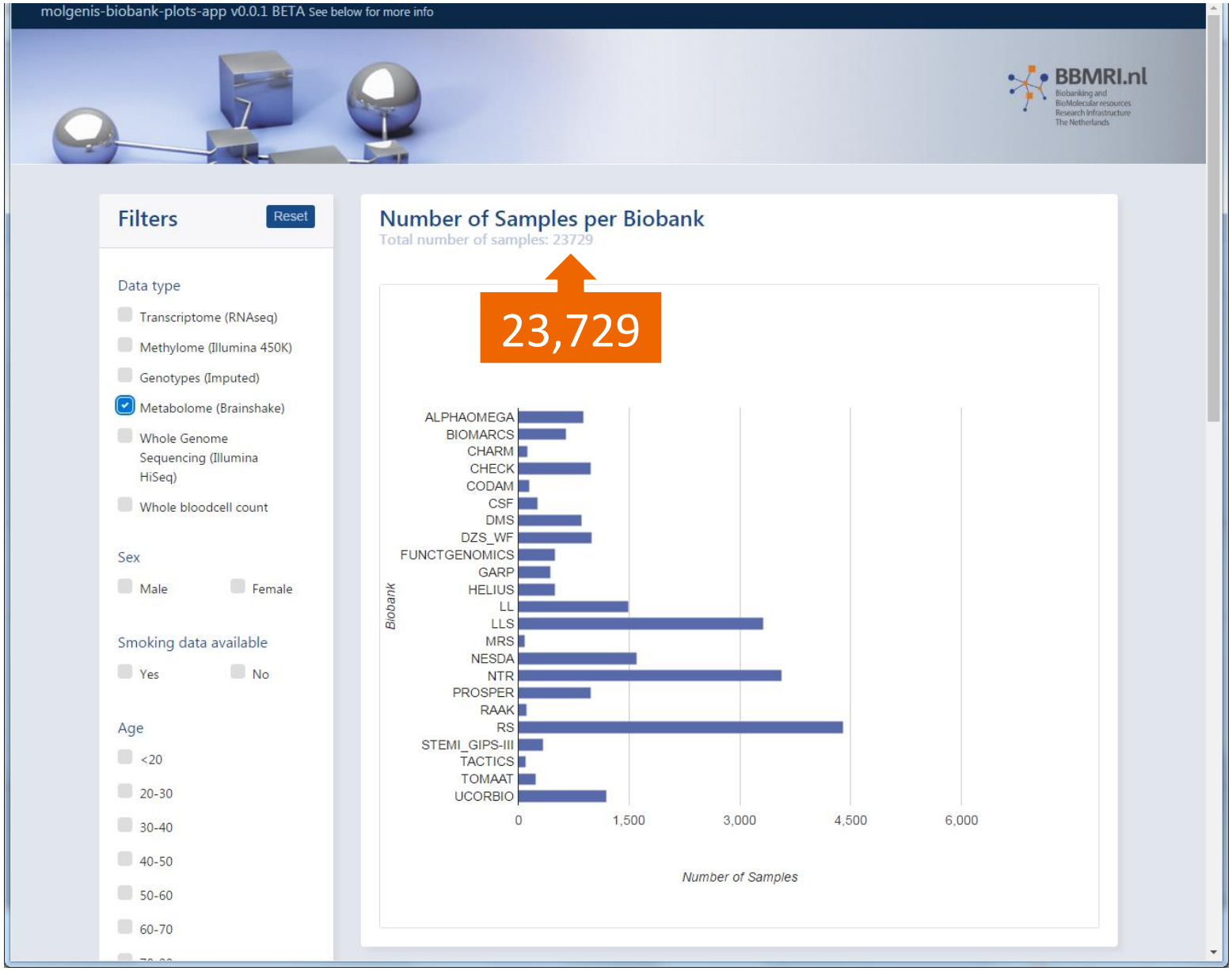
Metabolomics association with disease



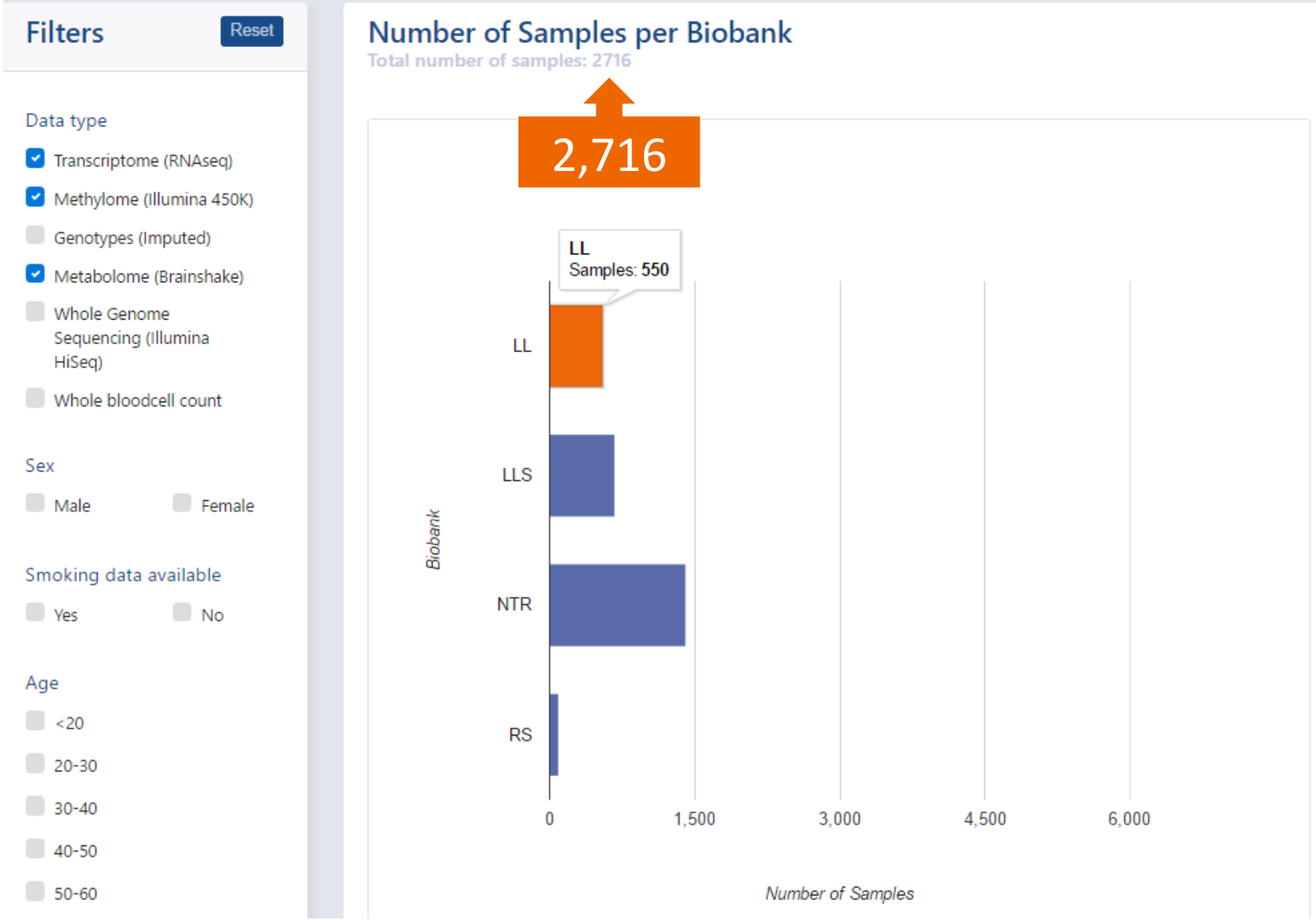


Metabolomics

Overview of participating cohorts at BBMRI.nl/Omics



Overlap Metabolome, Transcriptome, Methylome



Brainshake metabolomics

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Diseases and phenotypes

GWAS

Metabolomics

Genetic loci

Gene expression

DNA methylations sites

GWAS: Brainshake metabolomics

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Research Infrastructure
The Netherlands

ARTICLES

nature genetics

Genome-wide association study identifies multiple loci influencing human serum metabolite levels

Johannes Kettunen[1,2,37], Taru Tukiainen[1,3–5,37], Antti-Pekka Sarin[1,2], Alfredo Ortega-Alonso[1,6], Emmi Tikkanen[1,2], Leo-Pekka Lyytikäinen[7], Antti J Kangas[5], Pasi Soininen[5,8], Peter Würtz[1,3,5], Kaisa Silander[1,2], Danielle M Dick[9], Richard J Rose[6,10], Markku J Savolainen[11,12], Jorma Viikari[13], Mika Kähönen[14], Terho Lehtimäki[7], Kirsi H Pietiläinen[1,15,16], Michael Inouye[17,18], Mark I McCarthy[19,20], Antti Jula[2], Johan Eriksson[21–24], Olli T Raitakari[25,26], Veikko Salomaa[2], Jaakko Kaprio[1,6,27], Marjo-Riitta Järvelin[3,12,28–30], Leena Peltonen[36], Markus Perola[1,2,31], Nelson B Freimer[32], Mika Ala-Korpela[5,8,11,12], Aarno Palotie[1,33–35] & Samuli Ripatti[1,2,33]

nature COMMUNICATIONS

ARTICLE

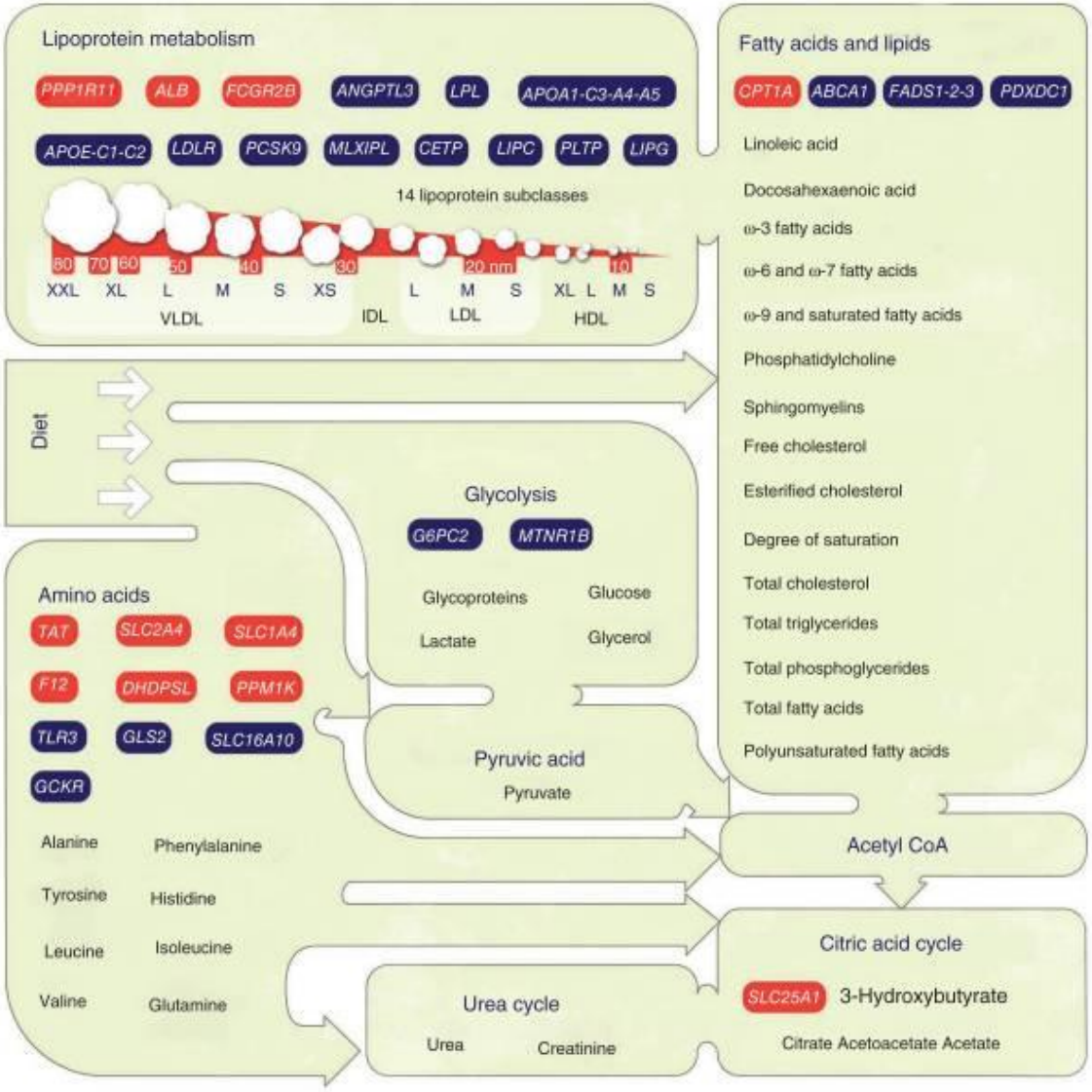
Received 3 Jun 2015 | Accepted 24 Feb 2016 | Published 23 Mar 2016

DOI: 10.1038/ncomms11122 OPEN

Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of *LPA*

Johannes Kettunen *et al.*#

GWAS: associating genetic loci



Brainshake metabolomics

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The Netherlands

Diseases and phenotypes

Metabolomics

GWAS

TWAS

EWAS

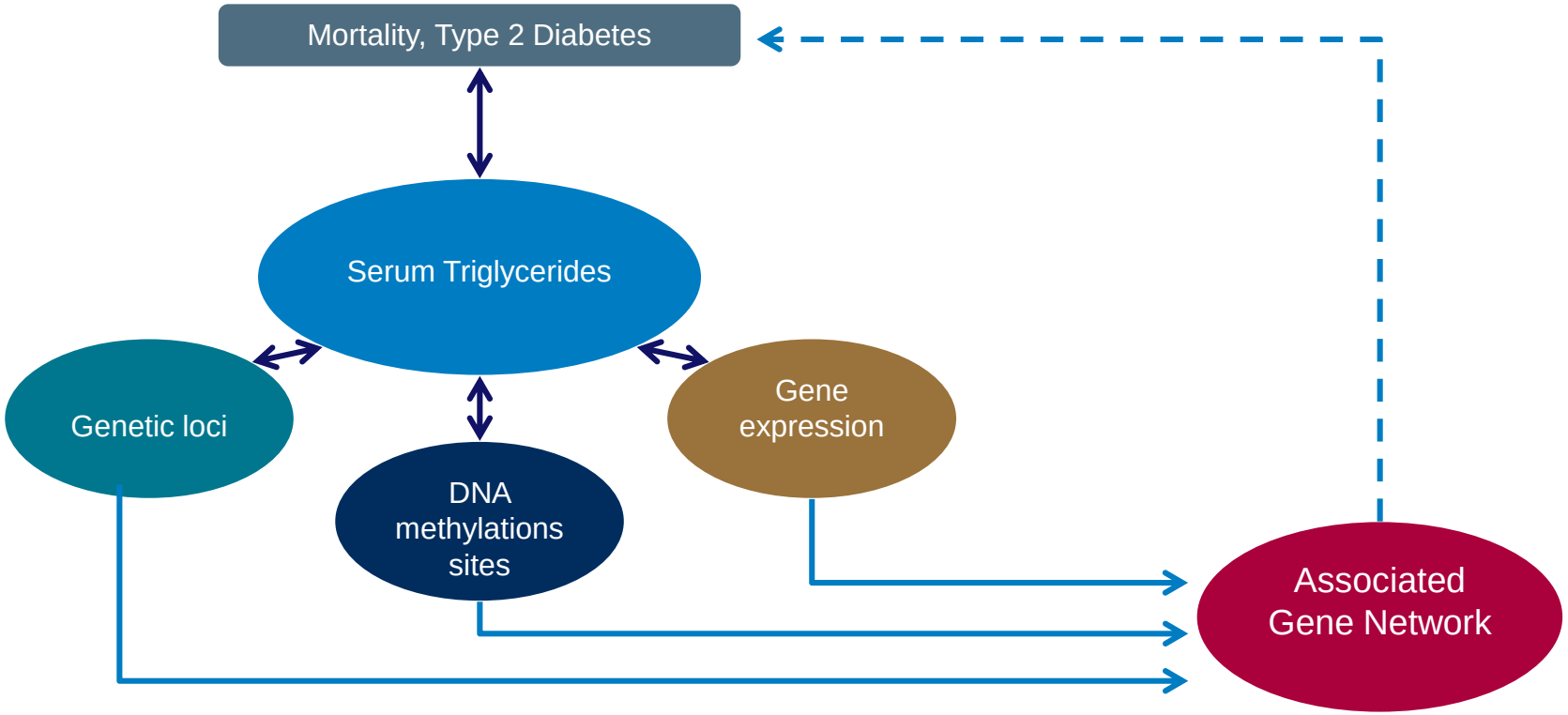
Genetic loci

Gene expression

DN methyla sites

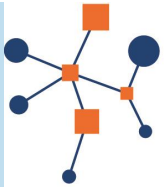
Practical of today

- Introduction to analysis of ^{1}H-NMR based Metabolomics
- The additive information from other BBMRI omics data resources and how that may contribute to the unravelling of the molecular pathways linking the fluctuations in biomarker levels to the outcome



Leiden University Medical Center

Acknowledgements



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Biobanking and BioMolecular resources Research Infrastructure The Netherlands

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Eline Slagboom

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Marleen van Greevenbroek

Marije Doppenberg-Oosting

Nightingale Health

Peter Würtz

Molecular Epidemiology, LUMC

Maarten van Iterson

Erik van den Akker

Koen Dekkers