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WP2 RESEARCH INFRASTRUCTURES

Task 2.3 Unlocking the collaborative potential of EDUC Research Infrastructures

Advancing healthcare using the Research Infrastructure CeSAR of UniCa: Nutrition during the first two years of life

Cagliari, 23th and 24th November 2023

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METABOLOMICS IN THE CLINICAL PRACTICE

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Metabolomics

Studi of "…the complete set of metabolites/low-molecular-weight intermediates, which are context dependent, varying according to the physiology, developmental or pathological state of the cell, tissue, organ or organism…"

Oliver, 2002

A partial list of “-omics” terminologies

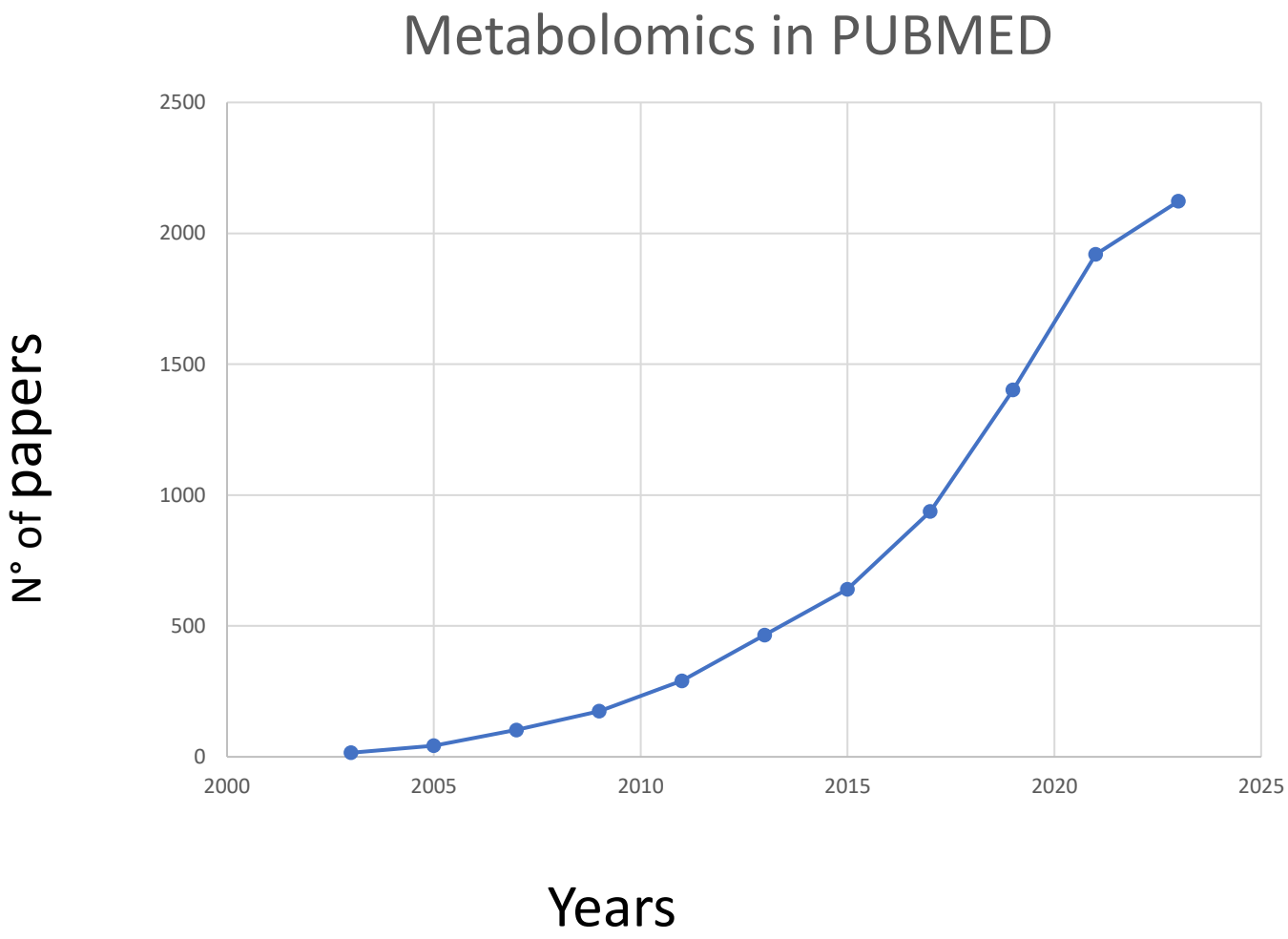
agrigenomics, agronomics, antigenomics, aquagenomics, bacteriomics, behaviouromics,bibliomics, biogenomics, biomics, bionomics, cardiomics, cardioproteomics, chemoproteomics, chomics, choomics, cardiogenomics, cellomics, chemogenomics, chromonomics, chondriomics, chronomics, clinomics, complexomics, cryptomics, crystallomics, crystalomics, cytomics, degradomics, diagnomics, embryogenomics, economics, enzymomics, epigenomics, epitomics, expressomics, fluxomics, foldomics, fragmentomics, functomics, gastrogenomics, genomics, glycomics, glycoproteomics, hybridomics, immunomics, immunoproteomics, inomics, integromics, ionomics, interactomics, kinomics, ligandomics, liganomics, linkomics, lipidomics, lipoproteomics, localizomics, metabolomics, metabonomics, metallomics, metalloproteomics, methylomics, microbiomics, microgenomics, mitochondriomics, neuropharmacogenomics, neuroproteomics, nucleomics, nutragenomics, nutrigenomics, oncogenomics, oncopharmacogenomics, operomics, orfeomics, parasitomics, pathogenomics, peptidomics, pharmacogenomics, pharmacometabolomics, pharmacometabonomics, pharmacomethylomics, pharmacophylogenomics, pharmacoproteomics, phenomics, phosphatomics, phosphoproteomics, phylogenomics, phyloproteomics, physiogenomics, physiomics, phytogenomics, phytoproteomics, postgenomics, predictomics, promoteromics, proteogenomics, proteomics, pseudogenomics, regulomics, resistomics, ribonomics, riboproteomics, Rnomics, saccharomics, secretomics, separomics, sialomics,signalomics, somatonomics, stereomics, systeomics, toponomics, toxicogenomics, toxicomics, toxiconomics, toxicoproteomics, transcriptomics, transgenomics, translatomics transportomics, unknomics, vaccinomics, variomics, virogenomics,viromics

GOOGLE Search

Genomics: 281.000.000

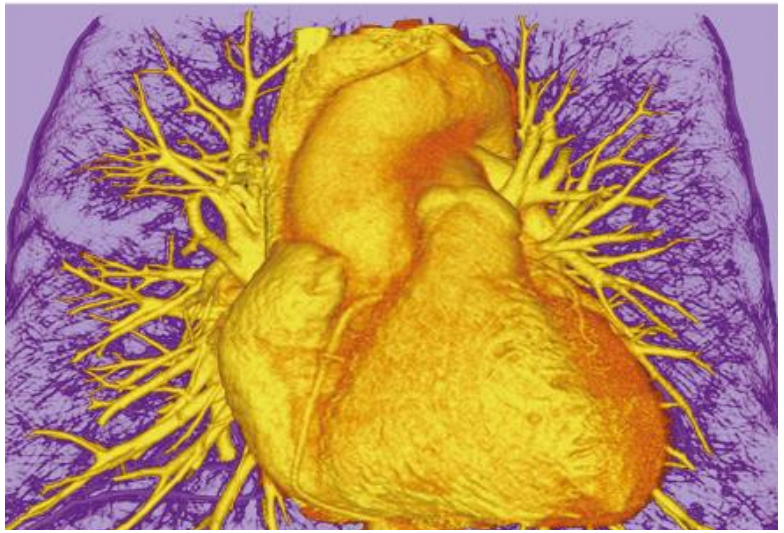
Metabolomics: 42.000.000

Economics: 1.990.000.000


Metabolomics in PUBMED
N° of papers
2500
2000
1500
1000
500
0
2000
2005
2010
2015
2020
2025
Years

nature REVIEWS
November 2011 volume 8 no. 11
www.nature.com/reviews

CARDIOLOGY



Metabolomics as a tool for cardiac research

Julian L. Griffin, Helen Atherton, John Shockcor and Luigi Atzori

Abstract | Metabolomics represents a paradigm shift in metabolic research, away from approaches that focus on a limited number of enzymatic reactions or single pathways, to approaches that attempt to captu the complexity of metabolic networks. Additionally, the high-throughput nature of metabolomics makes it ideal to perform biomarker screens for diseases or follow drug efficacy. In this Review, we explore the role of metabolomics in gaining mechanistic insight into cardiac disease processes, and in the search for nove biomarkers. High-resolution NMR spectroscopy and mass spectrometry are both highly discriminatory for a range of pathological processes affecting the heart, including cardiac ischemia, myocardial infarction, and heart failure. We also discuss the position of metabolomics in the range of functional-genomic approaches, being complementary to proteomic and transcriptomic studies, and having subdivisions such as lipidomics (the study of intact lipid species). In addition to techniques that monitor changes in the total sizes of pools of metabolites in the heart and biofluids, the role of stable-isotope methods for monitoring fluxes through pathways is examined. The use of these novel functional-genomic tools to study metabolism provides a unique insight into cardiac disease progression.

Griffin, J. L. *et al. Nat. Rev. Cardiol.* **8**, 630–643 (2011); published online 20 September 2011; doi:10.1038/nrcardio.2011.138

- KEY POINTS
- Metabolomics enables the parallel assessment of the levels of a broad range of metabolites found within a cell, tissue, biofluid, or organism
- It has been shown to have a great impact in classifying phenotypes, investigation of physiological status, diagnosing diseases, measuring the response to treatment, discovering biomarkers, identifying perturbed pathways due to disease or treatment, and characterisation of natural products.
- No single analytical tool can measure all metabolites within an organism, but NMR and MS can profile wide ranges of metabolites
- Metabolomics is hypothesis-generating rather than hypothesis- based.

Metabolomics is now adult, but….

despite this maturity, the literature is unfortunately saturated with small-scale preliminary-type studies with many suffering from being poor in experimental design and thus any findings are likely to be false as they lack statistical robustness and validity.

Few biomarkers have made it into the clinic.

Is metabolomics already in the clinic?

Table 1
A selection of small molecule biomarkers and their clinical relevance; summarised from an available test list at the Mayo Clinic, US. The biological matrix investigated (U- urine, P-plasma, Sm-serum, Sa-saliva, Se-semen, WB-whole blood, BS-dried blood spot & C-CSF) and the analytical method/test applied is detailed.

Biomarker	Clinical Relevance	Biological Matrix								Analytical Test
		U	P	Sm	Sa	Se	WB	BS	C	
5-Hydroxyindoleacetic acid	Intestinal carcinoid syndrome									LCMS
Acylcarnitines	Fatty acid oxidation disorders, several organic acidurias & new born screening									ESI-MS
Acylglycines	Inborn errors of metabolism									Capillary GCMS
Allo-isoleucine	New born screening: branched-chain amino acids elevations									LCMS
Amino acid (Panel)	Inborn errors of metabolism - evaluation of endocrine & neurological disorders, liver, muscle & neoplastic diseases									LCMS
Aminolevulinic acid	Various acute hepatic porphyrias									LCMS
Bile acids	Liver dysfunction									Enzymatic & LCMS
Carnitines	Organic acidemias, fatty acid oxidation disorder and primary carnitine deficiency									MS
Carotene, Beta	Fat malabsorption									HPLC
Ceramides	Myocardial infarction, cardiovascular disease and mortality within 5 years									LCMS
Cholesterol	Evaluation of cardiovascular risk									Enzymatic
Citric acid	Metabolic diseases									Enzymatic Spectrophotometry
Cortisol	Cushing syndrome & adrenal insufficiency									LCMS & Immunoenzymatic Assay
Creatinine	Renal function									Enzymatic
d-Lactate	d-lactate acidosis									Enzymatic
Ethylmalonic acid	New born screening									LCMS
Fatty acid profiles	Identifying deficiency of essential and other nutritionally beneficial fatty acids									Capillary GCMS
Fructosamine	Glyceamic control									Colourmetric
Fructose	Azoospermia									Qualitative Test
Galactitol	Galactosemia									GCMS
Glucose	Diabetes & carbohydrate metabolism disorders									Photometric
Glutaric Acid	New born screening									LCMS
HDL cholesterol	Cardiovascular risk									Colorimetric & Enzymatic
Hippuric acid	Liver function									LCMS
Histamine	Allergies and mast cell disorders									Immunoenzymatic Assay
Homocysteine	Inherited disorder of methionine metabolism									ESI-MS
Homovanillic acid	Screening children for catecholamine-secreting tumors									LCMS
Hydroxyglutaric acid	New born screening									LCMS
Insulin	Insulinoma									Electrochemiluminescence immunoassay
Lactate	Lactic acidosis & differentiating between bacterial and viral meningitis									Photometric
LDL Cholesterol	Cardiovascular risk									Colorimetric & Enzymatic
Methylmalonic acid	Methylmalonic acidemia									LCMS
Methylsuccinic acid	New born screening									LCMS
Organic acid screen	Inborn errors of metabolism									GCMS
Phenylalanine and tyrosine	Hyperphenylalaninemia									MS
Phospholipids	Ecithin-cholesterol acyltransferase deficiency									Colourmetric
Pipecolic acid	Peroxisomal biogenesis									GCMS
Purines and pyramidines (Panel)	Disorders of purine and pyrimidine metabolism									LCMS
Pyridoxal 5-phosphate	Progressive nerve compression disorders									LCMS
Pyruvate	Disorders of mitochondrial metabolism									Spectrophotometry
Riboflavin vitamin B2	Ariboflavinosis									LCMS
Thiamine	Behavioural change, delierium, dietary concerns									LCMS
Triglycerides	Elevated cholesterol values									Enzymatic
Urea	Renal failure									UV
Uric acid	Acute uric acid nephropathy from other causes of acute renal failure									Enzymatic & Photometric

New Horiz Transl Med. 2017 Mar; 3: 294–305.

Newborn Screening for Metabolic Disorders (IEMs)

- Biotinidase deficiency
- Carnitine uptake defect
- Citrullinemia
- Arginosuccinic aciduria
- Glutaryl-CoA Dehydrogenase deficiency
- HMG-CoA Lyase deficiency
- Isovaleric acidemia
- Long chain 3HA-CoA Dehydrogenase deficiency
- Maple syrup urine disease
- Methylmalonic acidemia
- Phenylketonuria
- Propionic acidemia
- VLAD deficiency
- MCAD deficiency

- *Most countries use metabolomics to screen for treatable metabolic disorders*
- *Screens cover 4-40 different disorders*
- *IEMs account for 90-95% of incidence of monogenic disorders, 10% of all genetic diseases are IEMs*

From David Wishart

Table 2
Potential new metabolite biomarkers discovered and reported since 2000. Various sets of biomarkers have been proposed over the years for a number of diseases based on metabolomic investigations. Studies marked with an asterisk (*) indicates a further validation study that was included in the same publication.

Disease/condition	Year of publication	Control subjects	Test subjects	Proposed biomarkers
Abnormal savda	2008 [84]	20	110	Glycochenodeoxycholic acid and bilirubin
Acute coronary syndrome	2009 [90]	10	19	Citric acid, 4-hydroxyproline, aspartic acid, fructose, lactate, urea, glucose and valine
Acute kidney injury	2012 [132]	17	17	Dimethylarginine, pyroglutamate, lysoPC (selection of), acylcarnitine (selection of), phenylalanine, creatinine, homocysteine, methionine, arginine, tryptophan
Advanced liver fibrosis	2016 [165]	30	27	Panel inc: choline, glucose, glutamine, cysteine, histidine, citrate, acetoacetate
Alzheimer's disease	2010 [99]	20	20	Lysophosphocholine, tryptophan, phytosphingosine, dihydrosphingosine, hexadecosphinganine
Alzheimer's disease	2012 [127]	~52	~77	Desmosterol
Alzheimer's disease	2014 [148]	57	57	Arachidonic acid, *N, N*-dimethylglycine, thymine, glutamine, glutamic acid, and cytidine
Alzheimer's disease	2014 [151]	15	15	Alanine and taurine
Alzheimer's disease	2015 [164]	218	256	Sphinganine–1-phosphate, ornithine, phenlyllatic acid, inosine, 3-dehydrocarnitine, hypoxanthine
Asthma	2011 [110]	42	20	Panel inc: Adenosine, alanine, carnitine, formate, fumarate, glucose, histidine, taurine, threonine, succinate
Asthma	2013 [139]	26	39	methionine, glutamine, histidine
Atherosclerosis	2010 [103]	28	16	Palmitate, stearate and 1-monolinoleolglycerol
Autism*	2015 [161]	24	22	Methylguanidine, indoxyl sulfate, glucuronic acid, desaminotyrosine, guanidiosuccinate acid
Autism*	2016 [169]	63	73	Panel inc: decanoylcarnitine, pregnanetriol, uric acid, 9,10 epoxyoctadecanoic acid, docosahexanoic acid, docosapentanoic acid
Bladder cancer*	2011 [125]	16	28	Panel of 50+ differential metabolites
Bladder cancer	2014 [146]	121	138	Succinate, pyruvate, oxoglutarate, carnitine & acylcarnitines, phosphoenolpyruvate
Breast cancer	2010 [97]	50	50	Five unidentified biomarkers
Breast cancer	2012 [134]	34	80 (40 *vs* 40)	Palmitic acid, stearic acid, linoleic acid, FFA
Cardiovascular diseases	2014 [145]	/	67	Medium-and long-chain acylcarnitines, alanine
Chronic heart failure	2013 [143]	15	39	Lactate, creatine, glucose, glycoprotein, lipid species and amino acids
Chronic Hepatitis B	2006 [73]	50	37	Lysophosphatidyl choline and glycochenodeoxycholic acid
Chronic kidney disease	2011 [120]	13	18	Urinary neutrophil gelatinase-associated lipocalin
Chronic widespread musculoskeletal pain	2015 [160]	3736	1191	Epiandrosterone sulfate, dehydroisoandrosterone sulfate, androsterone sulfate, 3-(4-hydroxyphenyl) acetate, nonadecanoate
Colorectal cancer staging	2009 [87]	–	31	Panel inc: fatty acids, organic acids, sugars, steroid, fatty acid ester and pyrimidine nucleoside.
Colorectal cancer*	2010 [94]	110	112	Hydroxylated, polyunsaturated ultra-long-chain fatty acids
Colorectal cancer	2011 [117]	8	42	Free fatty acids and esterified fatty acids
Colorectal cancer	2016 [170]	254	320 (31)	Panel inc: octadecanoic acid, lactic acid, threonic acid, 3-hydroxy butanoic acid, serine, cysteine
Coronary artery disease	2012 [126]		2023	Dicarboxylacylcarnitines, medium-chain acylcarnitines, fatty acids
Coronary heart disease	2009 [88]	25	23	Saturated fatty acids, trans-fatty acid, n3 and n6 poly unsaturated fatty acids
Coronary heart disease*	2014 [41]	897	131	LysoPC (18:1), LysoPC (18:2), MG (18:2), SM (28:1)
Diabetes	2010 [106]	60	40	3-indoxyl sulfate, glycerophospholipids, free fatty acids and bile acids
Diabetic kidney disease	2012 [128]		52 (26 *vs* 26)	Acyl-carnitines, acyl-glycine and metabolites related to tryptophan metabolism
Diabetic mellitus and diabetic nephropathy	2011 [111]	30	120	Non-esterified fatty acids and esterified fatty acids
Diabetic nephropathy and type 2 diabetes	2009 [93]	25	41	Phytospingosine, glycine, lysine, dihydrosphingosine, leucine
Disorders of Propionate Metabolism*	2007 [78]	10	9	Propionyl carnitine, unsaturated acylcarnitine, γ-butyrobetaine, siovaleryl carnitine
Down syndrome	2015 [159]	93	23	Progesterone and dihydrouracil
Endometrial carcinoma	2016 [173]	25	25(10)	Porphobilinogen, acetlycysteine, *n*-acetylserine, urocanic acid, isobutylglycine
Gastric cancer	2016 [166]	40	83	Sucrose, dimethylamine, 1-methylnicotinamide, 2-furoylglycine, *N*-acetyl- serotonin, trans-aconitate, alanine, formate, and serotonin
Gastrointestinal cancer	2012 [129]	12	38	3-hydroxypropionic acid, pyruvic acid, L-alanine, glucuronolactone, L-glutamine
Healthy plasma metabolome	2008 [81]	269	–	300+ unique compounds
Hepatitis B*	2013 [140]	11	13	Tyrosinamide, biotin sulfone, hexanoic acid, 1-aminonaphthalene, 7-dehydroxycholesterol, azelaic acid
Hepatitis E and Hepatitis B	2011 [119]	18	32	Panel inc: L-proline, L-isoleucine, acetone, glycerol, glycine, biopterine, adenosine
Hepatocarcinoma	2011 [121]	38	41	1-methyladenosine
Hepatocellular carcinoma	2009 [92]	20	20	Panel of 18 metabolites inc: glycine, urea, threonine
High altitude pulmonary edema*	2015 [162]	35	35	Methionine, hypoxanthine, inosine, sphingosine, palmitoyl carnitine, C8 carnitine
Human hepatocellular carcinoma	2011 [116]	71	106	Bile acids, histidine, inosine, glycochenodeoxychoclic acid, glycocholic acid, taurocholic acid and

New Horiz Transl Med. 2017 Mar; 3: 294–305.

Table 2 *(continued)*

Disease/condition	Year of publication	Control subjects	Test subjects	Proposed biomarkers
Interstitial cystitis	2016 [172]	21	42	Oleic acid, 2-deoxytetronic acid, saccharic acid, phosphate, trehalose, erthronic acid, oxalic acid, sulfuric acid, cystine, lyxitol, lysine, histidine
Intestinal fistulas	2006 [76]	17	40	Glycochenodeoxycholic acid, glycodeoxycholic acid, taurochenodexycholic acid, taurodeoxycholic acid, lysophosphatidyl choline (C16: 0 and C18:2), phenylalanine, tryptophan and carnitine
IVF	2008 [85]	17	17	Glutamate and alanine/lactate ratios
Lepromatous leprosy	2011 [118]	10	13	Eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid
Liver cirrhosis	2011 [113]	22	37	Lysophosphatidyl cholines, bile acids, hypoxanthine, stearamide, oleamide, myristamide
Liver failure due to Hepatitis B	2010 [104]	16	26	1-Lioleoylglycerophosphocholine or 1-linoleoylphosphatidylcholine
Lung cancer	2010 [108]	12	12	Lysophosphatidylcholines: lyso16:0, sn−2 lysoPC 16:0, sn−1 lysoPC 18:0, sn−1 lysoPC 18:1 and sn−1 lysoPC 18:2
Lung cancer	2011 [122]	29	33	A panel of 23 serum metabolites and 48 tissue specific metabolites
Lung cancer*	2014 [149]	536	469	Creatine riboside, cortisol sulfate, *N*-acetylneuraminic acid
Lung cancer*	2015 [157]	20	18	Maltose, ethanolamine, glycerol, palmitic acid, lactic acid,
Lung cancer	2015 [155]	55	41	Panel inc: trisaccharide phosphate, trihexose, nonanedioic acid, MG (22:2), tetrahexose
Lung cancer	2016 [167]	34	23 (11)	Isobutyl decanoate, putrescine, diethyl glutarate, cysteamine
Major depressive disorder	2012 [135]	25	26	Tryptophan, GABA and lysine
Major depressive disorder*	2015 [153]	59	60	Acyl carnitines, lipid metabolism and tryptophan
Malignant adrenal tumours	2011 [124]	45	102	Panel inc: metabolites from steroid metabolism pathways
Malignant Oligodendroglioma*	2008 [83]	10	24	Alanine, lipids, valine, the total choline compounds, proline, myoinositol, taurine, glutamine, glutamate, GABA, NAA, acetate, and creatine
Melamine-induced nephrolithiasis	2011 [123]	74	73	Proline, 5C-aglycone and hypoxanthine
Multiple sclerosis	2014 [150]	17	15	Choline, myo-inositol, threonate
Multiple sclerosis	2015 [156]	12	13	LPC (18:1), LPC (18:0), LPI (16:0), Glutamate
Muscle respiratory chain deficiencies	2015 [163]	13	24	AMP, *n*-acetyl asparagine, oxoglutaric acid, *n*-succinyl-L-L2.6 diaminopimelate
Nasopharyngeal carcinoma	2011 [115]	40	37	Kynurenine, *N*-acetylglucosaminylamine, *N*-acetylglucosamine and hydroxyphenylpyruvate
Oesophageal cancer	2013 [141]	26	89	Formate, acetate, short-chain fatty acids, GABA
Oesophageal squamous-cell carcinoma	2013 [144]	53	53	Phosphatidylserines, 12-oxo−20-dihydroxy-leukotriene B4, sphinganine 1-phosphate, LysoPC, phosphatidyl ethanolamine, phosphatidyl choline
Onchocerciasis*	2010 [105]	56	76	Panel of 14 inc: hexacosenoic acid, fatty acids, proteins, sterol lipids and phosphorylated sphingolipids
Oral cancer	2014 [152]	50	30	Phenylalanine & leucine
Oral, breast and pancreatic cancer	2010 [95]	87	128	betaine, choline, carnitine, glycerophosphocholine, cadaverine, putrescine, hypoxanthine, ethanolamine, trimethylamine and amino acids
Osteoarthritis*	2010 [98]	299	123	Valine to histidine ratio and leucine to histidine ratio
Ovarian cancer	2011 [112]	27	57	27-nor−5-beta-cholestane−3,7,12,24,25 pentol glucuronide
Ovarian cancer	2011 [114]	12	18	*N*-acetylasparate and *N*-acetyl-aspartyl-glutamate
Ovarian cancer*	2012 [131]	50	50	2-piperidinone, L-tryptophan, lysoPC (18:3), lysoPC (14:0)
Ovarian endometriosis	2012 [133]	52	40	Sphingomyelins and phosphatidylcholines
Paediatric acute liver failure	2009 [89]	20	20	α-NH2-butyric-acid (Aab) and Aab: leucine ratio
Pancreatic cancer	2016 [168]	40	40	Panel inc: palmitic acid, 1,2 dioeoyl GLP Na2, lanosterol, lignorceric acid, 1 oleoyl rac GL, chol epoxide, erucic acid
Parkinson's disease	2008 [79]	25	66	Uric acid and glutathione
Parkinson's disease	2009 [91]	37	43	Pyruvate
Parkinson's disease	2015 [158]	104	297	Cortisol, 11-deocycortisol, 21-deoxycortisol, histidine, urocanic acid, imadazoleacetic acid, hydroxyphenylacetic acid
Periodontal disease	2010 [101]	21	18	Inosine, lysine, putrescine and xanthine
Pre-eclampsia	2005 [72]	87	87	Three unidentified molecules
Pre-eclampsia	2017 [174]	20	20	Panel inc: PC (14:0/0:0), proline betaine, proline
Premature labour*	2010 [107]	16	39	Panel inc: Methyladenine, heptanedioic acid, *N*-acetylglutamine, glycerol, succinic acid, mannose
Prostate cancer	2010 [96]	30	40	Acylcarnitine and arachidonoyl amine
Prostate cancer	2013 [138]	178	331	Panel of 25 metabolites inc top 5: histidine, glycine, alanine, kynurenine, glutamate & glycerol−3-phosphate
Psoriasis	2017 [175]	15	14	Asparagine, aspartic acid, isoleucine, phenylalanine, ornithine, proline, lactic acid & urea
Rectal cancer	2013 [142]	43	127	Lactate, threonine, acetate, glutathione, uracil, succinate, serine, formate, lysine and tyrosine
Renal cell carcinoma	2010 [100]	13	32	Panel inc: acetate, glutamate, glutamine, glucose, tyrosine, histidine, phenylalanine, formic acid, alanine,

New Horiz Transl Med. 2017 Mar; 3: 294–305.

Table 2 *(continued)*

Disease/condition	Year of publication	Control subjects	Test subjects	Proposed biomarkers
				lactate
Rheumatoid arthritis	2010 [102]	51	47	Cholesterol, lactate, acetylated glycoprotein and lipids
Rheumatoid arthritis	2011 [109]	20	25	Panel inc: Glyceric acid, hypoxanthine, histidine, threonic acid, methionine, cholesterol, threonine
Rheumatoid arthritis	2016 [171]	19	46	Arginine, aspartic acid, glutamic acid, phenylalanine, serine, threonine, methlynicotinamide
Schizophrenia	2006 [74]	70	82	Citrate, glutamine, acetate, lactate
Schizophrenia	2007 [77]	–	50	50 lipids including triacylglycerols, free fatty acids, phosphatidylethanolamine.
Schizophrenia*	2013 [137]	62	62	Glycerate, eicosenoic acid, beta-hydroxybutyrate, pyruvate, cysteine
Systemic inflammatory response syndrome (SIRS) & Sepsis	2012 [130]		143 (74 *vs* 69)	Acylcarnitines and glycerophosphatidylcholines (C10:1 and PCaaC32:0)
Type 2 diabetes	2006 [75]	45	78	Non-esterified and esterified fatty acids in plasma
Type 2 diabetes	2008 [80]	28	23	3-hydroxyhippuric acid
Type 2 diabetes	2008 [86]	time course study	75	Citrate, IL–8 and methyl-histidine and branched amino acid degradation products
Type 2 diabetes (T2DM) and Type 2 diabetic coronary heart diseases (T2DM-CHD)	2008 [82]	45	71 and 37 for T2DM & T2DM-CHD	Free fatty acid (C16:0, C18:1 *n*–9 and C18:2 *n*–6)
Type 2 diabetes & impaired fasting glucose	2013 [136]	1897	115 & 192 respectively	Panel inc: amino acids, lipids, carbohydrates (T2D) & panel of lipids, carbohydrates, amino acid plus urate & erythritol (IFG)
Type 2 diabetes mellitus	2015 [154]	300	300	Lipids, hexose sugars, purine nucleotide
Ulcerative colitis (UC) & Crohn's disease (CD)	2014 [147]	17	24 UC & 19 CD	Panel inc: N-acetylated glycoprotein, lactate, methanol, mannose, formate

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Clinical Metabolomics: the new clinical chemistry?

.....or

Medical Principles and Practice

Review

Med Princ Pract 2021;30:301–310
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Published online: December 3, 2020

Metabolomics: The Stethoscope for the Twenty-First Century

Metabolomics of the past

Albus color ut aqua fontis
White as wellwater, i.e. clear

Glaucus color ut cornu lucidum
Light blue/green/grey as lucid horn

Lacteus color ut serum lactis
Milky as whey of milk

Caropos color ut vellus cameli
Bluish-grey as camel skin

Subpallidus color ut succus carnis semi- coctus non remisse
Slightly pale as a not reduced juice of meat

Remissus pallidus ut succus carnis semi- coctus remissi
Reduced pale as reduced juice of meat

Subcitrinus ut pomi subcitrini non remissus
Pale yellow as of a not reduced lemon

Citrinus color ut pomi citrini remissi
Yellow as of a reduced lemon

Subruffus color ut aurum remissum
Slightly ruddy as an alloy of gold

Subrubicundus color ut crocus occidentalis
Slightly red as occidental saffron

Rubeus ut crocus orientalis
Red as oriental saffron

Subrubicundus ut flamma ignis remissa
Slightly red as a lowered flame of fire

Rubicundus ut flamma ignis non remissa
Red as a flame of fire not lowered

Inops color ut epatis animalis
Wine-red as of animal liver

Kyanos color ut vinum bene nigrum
Deep blue as very dark wine

Viridis color ut caulis viridis
Green as green cabbage

Lividus color ut plumbum
Livid as lead

Niger ut incaustum
Black as ink

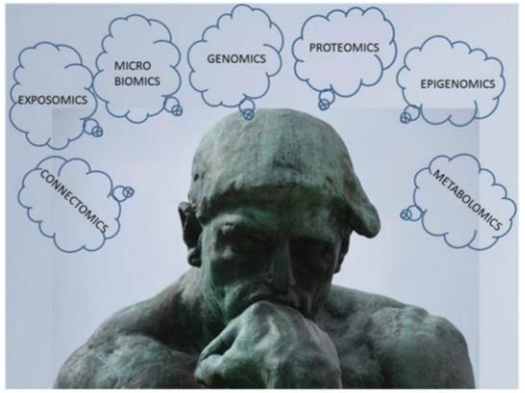
Niger ut cornu bene nigrum
Black as very dark horn

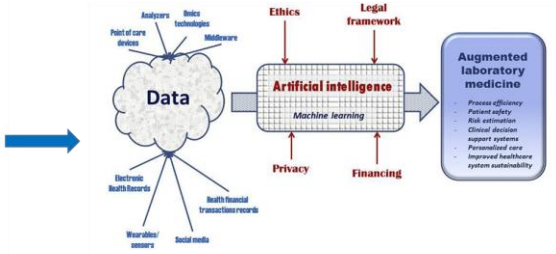
Latin text quoted from: Pinder, Ulrich: "Epiphanie Medicorum ,Nuremberg 1506

Considering the number of metabolites used in a clinical setting as biomarkers of disease onset and/or progression, the picture appears to be rather diverse.

•In **traditional clinical chemistry** a very limited number of small metabolites such as glucose, cholesterol, creatinine, urea, etc., is being used for decades to assess an individual's physiopathological condition.

•In the **new clinical chemistry**, towards precision medicine, there is an urgent need for new/different types of biomarkers. Metabolomics is in principle very well suited to identify and deliver biomarkers for clinical use.





•To treat disease clinicians and health workers require diagnostic indicators of disease, which can be used not only to diagnose disease but also to assess the applicability of therapeutic interventions.

•These indicators are referred to as biomarkers and the NIH definition of a biomarker is:

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Metabolomics has the potential to:

- deliver **diagnostic biomarkers** for the detection and prognosis of diseases, and the prediction of the efficacy and safety of pharmaceutical interventions
- provide **insights into the biochemical mechanisms** of diseases and the modulation by drugs.

It has become clear that health and disease are optimally studied **from a system perspective**. Such an approach will allow a personalized medicine approach and will play an important role in the future to follow the health state of an individual.

At present, there are still significant challenges in answering biological questions.

How does it work?

Different types of breast cancer

- Ductal carcinoma in situ
- Invasive ductal carcinoma
- Invasive lobular carcinoma
- Mucinous carcinoma
- Medullary carcinoma
- Inflammatory breast cancer
- Triple-negative breast cancers
- Paget's disease of the nipple
- Adenoid cystic carcinoma
- Lobular carcinoma in situ
- Papillary carcinoma
- Phyllodes tumor
- Angiosarcoma
- Tubular carcinoma

Is this one Class?

Are they the same Authors?

Giuseppe Arcimboldo

Giuseppe Arcimboldo?

Giuseppe Arcimboldo?

Spiaggia del Principe

Spiaggia Capriccioli

Spiaggia la Celvia

What do we see?

Does it make sense?

Rachel Ruysch: «Natura morta con fiori» (1716)

Rachel Ruysch:
«Natura morta con fiori» (1716)

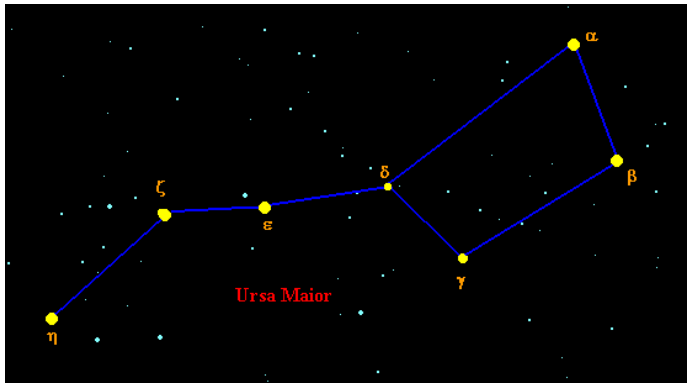
How to look at the stars?

Metabolite targeted analysis →

North Star

How to look at the stars?

Ursa maior



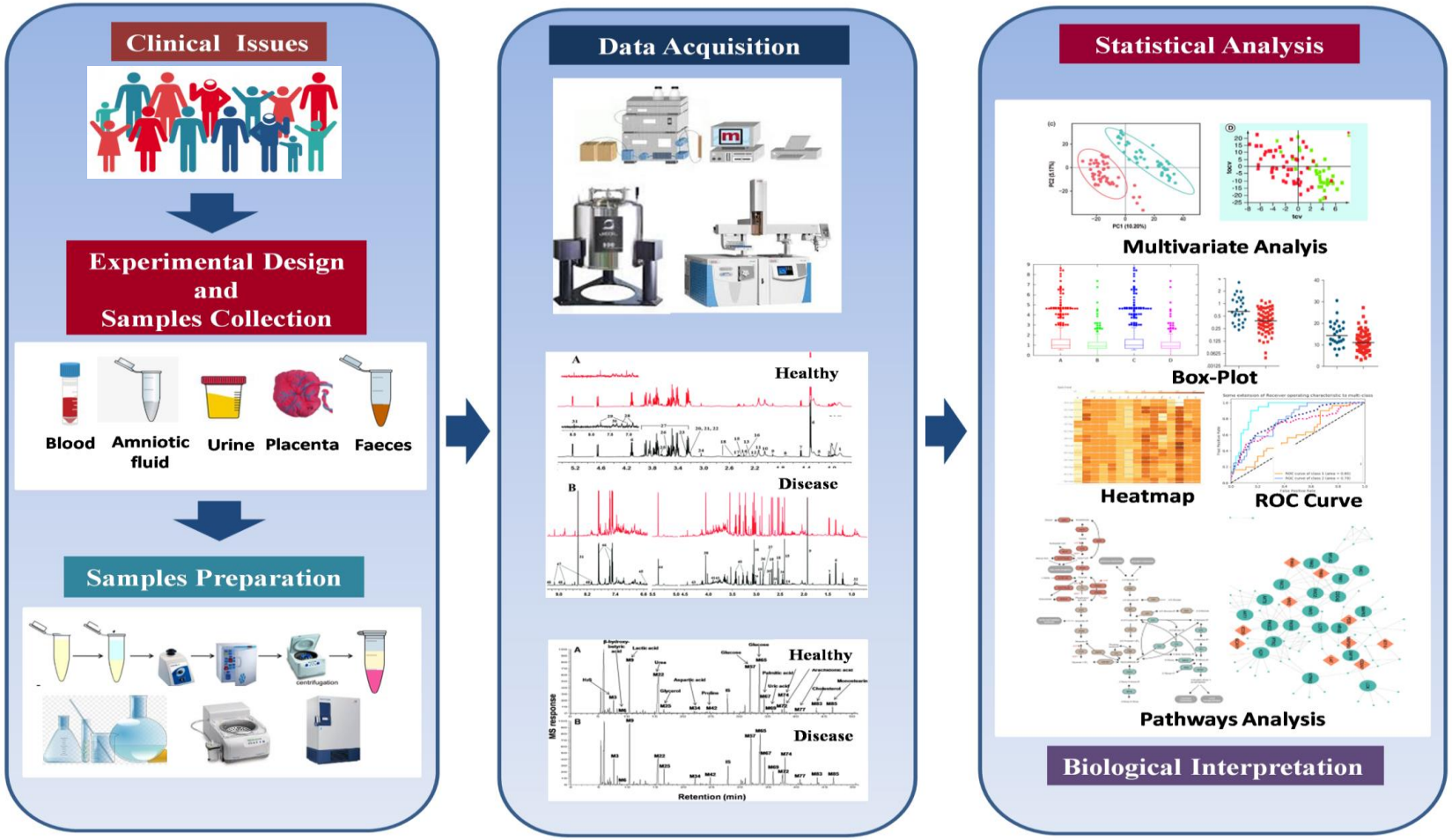
Metabolic profiling →

Metabolic fingerprinting →

Milky Way

Metabolomics Workflow

Workflow Metabolomics



Frontiers in Medicine
June 2021 | Volume 8 | Article 645118

Few examples from the Cagliari experience

to show what we learnt

by using the metabolomic approach

Metabolomic and drug-resistant epilepsy

frontiers in Neurology

ORIGINAL RESEARCH
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Metabolomics As a Tool for the Characterization of Drug-Resistant Epilepsy

Federica Murgia[1], Antonella Muroni[2], Monica Puligheddu[3], Lorenzo Polizzi[2], Luigi Barberini[2], Gianni Orofino[3], Paolo Solla[3], Simone Poddighe[1,4], Francesco Del Carratore[1,5], Julian L. Griffin[6], Luigi Atzori[1†] and Francesco Marrosu[3†]*

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Purpose: Drug resistance is a critical issue in the treatment of epilepsy, contributing to clinical emergencies and increasing both serious social and economic burdens on the health system. The wide variety of potential drug combinations followed by often failed consecutive attempts to match drugs to an individual patient may mean that this treatment stage may last for years with suboptimal benefit to the patient. Given these challenges, it is valuable to explore the availability of new methodologies able to shorten the period of determining a rationale pharmacologic treatment. Metabolomics could provide such a tool to investigate possible markers of drug resistance in subjects with epilepsy.

Methods: Blood samples were collected from (1) controls (C) (n = 35), (2) patients with epilepsy "responder" (R) (n = 18), and (3) patients with epilepsy "non-responder" (NR) (n = 17) to the drug therapy. The samples were analyzed using nuclear magnetic resonance spectroscopy, followed by multivariate statistical analysis.

Key findings: A different metabolic profile based on metabolomics analysis of the serum was observed between C and patients with epilepsy and also between R and NR patients. It was possible to identify the discriminant metabolites for the three classes under investigation. Serum from patients with epilepsy were characterized by increased levels of 3-OH-butyrate, 2-OH-valerate, 2-OH-butyrate, acetoacetate, acetone, acetate, choline, alanine, glutamate, scyllo-inositol (C < R < NR), and decreased concentration of glucose, lactate, and citrate compared to C (C > R > NR).

Significance: In conclusion, metabolomics may represent an important tool for discovery of differences between subjects affected by epilepsy responding or resistant to therapies and for the study of its pathophysiology, optimizing the therapeutic resources and the quality of life of patients.

(12) **United States Patent**
Atzori et al.

(10) **Patent No.: US 10,697,978 B2**
(45) **Date of Patent: Jun. 30, 2020**

(52) U.S. Cl.
CPC *G01N 33/6896* (2013.01); *G01N 33/50* (2013.01); *G01N 33/64* (2013.01); *G01N 33/6812* (2013.01);

(54) **METHOD FOR THE IN VITRO IDENTIFICATION OF DRUG-RESISTANT EPILEPSY**

METHOD FOR DRUG-RESISTANT EPILEPSY IDENTIFICATION

Biomarkers | Metabolomics | Pharmaco-resistant epilepsy | Test

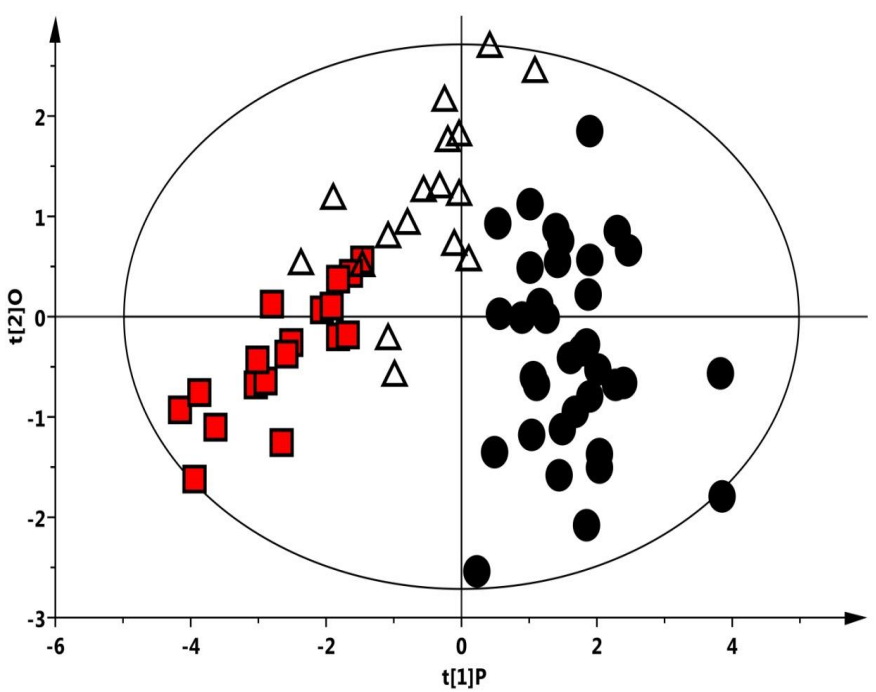
INTRODUCTION

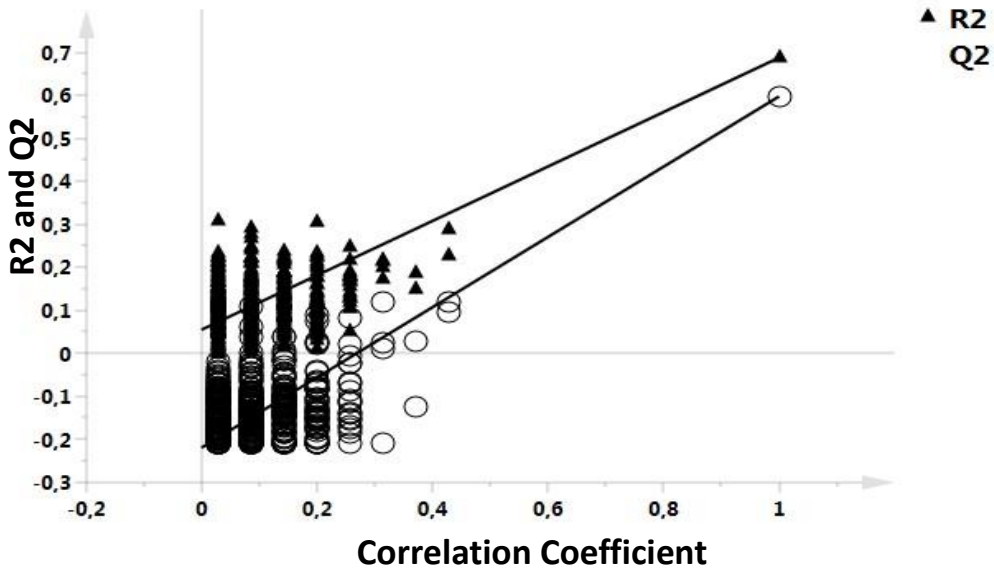
The subjects with pharmaco-resistant epilepsy don't benefit from both the traditional a most recent anticonvulsant drugs. We patented a test allowing for a clear distinction b the group of parmacoresistant subjects and those under pharmacologic control by us same drugs. The metabolomic analysys of pharmacoresistant subjects may address the p towards other solutions, mostly the modern surgical options.

knowledge share PATENTS

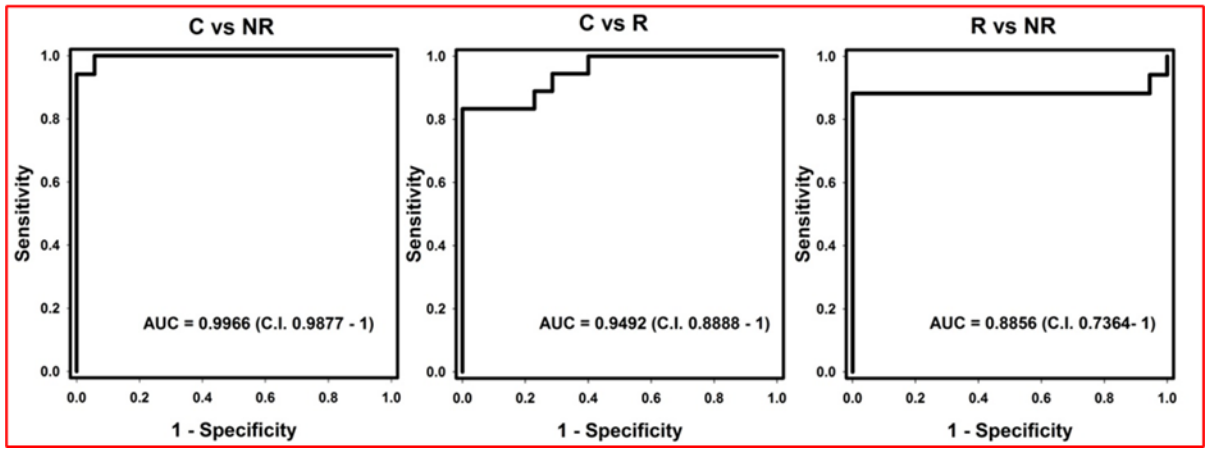
TECHNICAL FEATURES

In our study, we analyzed the metabolic profile of 35 epileptic patients and 35 control p to define the metabolic fingerprint of patients non-responders to therapy. For this aim, samples of the patients were analyzed with nuclear magnetic resonance and the data ol were processed with multivariate statistical analysis. To test the sensitivity and specificity identified biomarkers the Receiver Operating Characteristic (ROC) curves were built b the distance of Mahalanobis. The work of the patent has highlighted a pattern of signi altered molecules (*viz*. 3-hydroxybutyrate, acetoacetate, choline, citrate, glucose, glut lactate, scyllo-inositol, alanine) describing the differences between drug epileptic p resistant to or not to therapy. The identified metabolites could represent the basis construction of a diagnostic test. A validation process is underway on a larger num subjects.

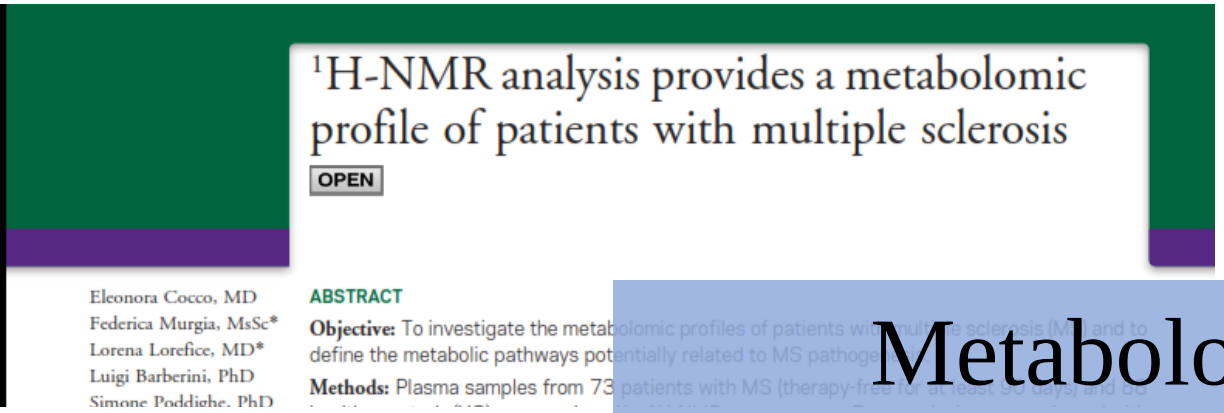




Metabolite	C vs R	C vs NR	R vs NR
Acetate	p<0.001	p<0.001	ns
Acetoacetate	p<0.01	p<0.001	p<0.05
Acetone	p<0.01	p<0.001	p<0.05
Citrate	ns	p<0.05	ns
Glucose	ns	p<0.05	ns
Lactate	ns	p<0.001	p<0.001
Scyllo-inositol	p<0.05	ns	ns



Metabolomic Evaluation of the Pharmacological Treatments in Patients Affected by Multiple Sclerosis



^{1}H-NMR analysis provides a metabolomic profile of patients with multiple sclerosis

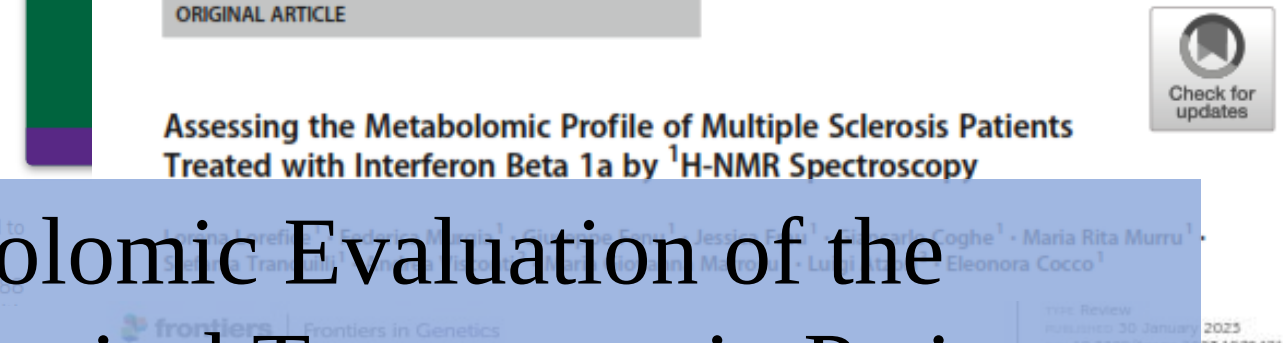
OPEN

Eleonora Cocco, MD
Federica Murgia, MsSc*
Lorena Lorefice, MD*
Luigi Barberini, PhD
Simone Poddighe, PhD

ABSTRACT

Objective: To investigate the metabolomic profiles of patients with multiple sclerosis (MS) and to define the metabolic pathways potentially related to MS pathogenesis.

Methods: Plasma samples from 73 patients with MS (therapy-free for at least 30 days) and 30



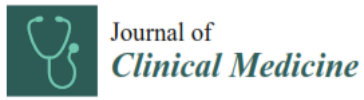
Neurotherapeutics
https://doi.org/10.1007/s13311-019-00721-8

ORIGINAL ARTICLE

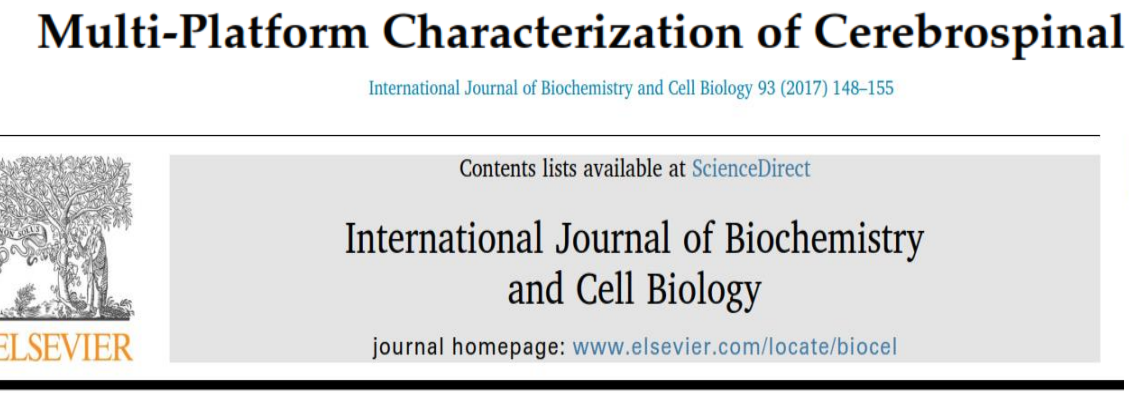
Check for updates

Assessing the Metabolomic Profile of Multiple Sclerosis Patients Treated with Interferon Beta 1a by ^{1}H-NMR Spectroscopy

Maria Rita Murru[1] · Eleonora Cocco[1]



Journal of *Clinical Medicine*



Article

Multi-Platform Characterization of Cerebrospinal

International Journal of Biochemistry and Cell Biology 93 (2017) 148–155

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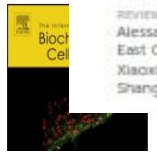

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Omics approaches to understanding the efficacy and safety of disease-modifying treatments in multiple sclerosis

Lorena Lorefice[1]*, Maristella Pitzalis[2], Federica Murgia[3], Giuseppe Fenu[4], Luigi Atzori[1] and Eleonora Cocco[1]

metabolites

MDPI

Metabolomic analysis identifies altered metabolic pathways in Multiple Sclerosis

Simone Poddighe[a,b,*], Federica Murgia[a], Lorena Lorefice[c], Sonia Liggi[a,1], Eleonora Cocco[c], Maria Giovanna Marrosu[c], Luigi Atzori[a,*]

[a] Department of Biomedical Sciences, University of Cagliari, Italy

Article

Metabolomic Changes in Patients Affected by Multiple Sclerosis and Treated with Fingolimod

Federica Murgia [1,†], Lorena Lorefice [2,†], Antonio Noto [1], Martina Spada [1], Jessica Frau [2], Giuseppe Fenu [2], Giancarlo Coghe [2], Antonella Gagliano [3], Luigi Atzori [1,*,‡] and Eleonora Cocco [4,‡]

Metabolomic Evaluation of the Pharmacological Treatments in Patients Affected by Multiple Sclerosis

Basal metabolic profile of disease

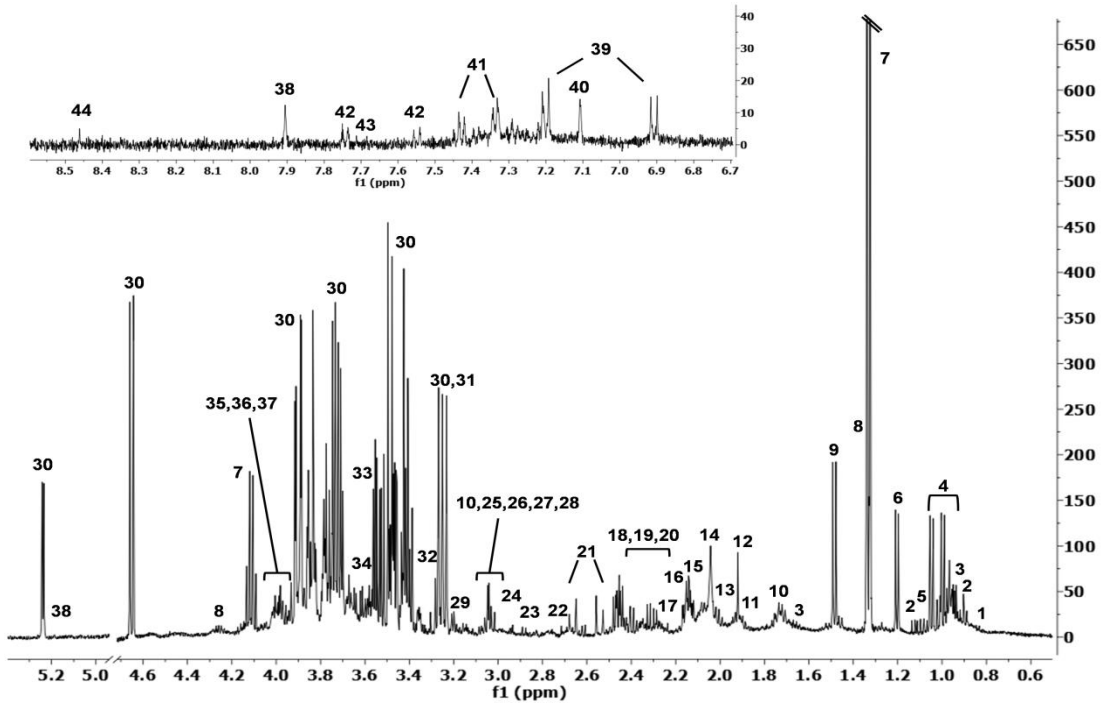
Multiple Sclerosis Phenotypes and Prognosis
- ❑Relapsing-remitting
- ❑ Progressive
- ❑Neuroradiological and clinical features (active and inactive)

Metabolic changes related to the gender and life stage of women
- ❑ Adolescence
- ❑ Maternity
- ❑ Menopause

Metabolic changes related to pharmacological treatments
- ❑INF-β
- ❑Fingolimod
- ❑Ocrelizumab
- ❑Cladribina
- ❑Dymethyl Fumarate
- ❑Teriflunomide

Control *vs* Multiple Sclerosis

1.2-Hydroxyisovalerate; 2. 3-methyl-2-Oxoglutarate; 3. 2-Hydroxybutirate; 4.Branched Aminoacids: Valina, Leucine, Isoleucine, 5. 2-Methylglutarate; 6. 3-Hydroxybutirate; 7. Lactate; 8.Threonine; 9. Alanine; 10. Lysine; 11. Arginine; 12. Acetate; 13. Proline; 14. N-acetyl-Groups; 15. Methionine; 16. Glutamine; 17. Acetone; 18. Glutamate; 19.Pyruvate; 20. Pyroglutamate; 21. Citrate; 22. Dimethylamine; 23. Aspartate; 24. Asparagine; 25. Creatine; 26. Creatine phosphate; 27. Creatinine; 28: Ornithine; 29. Choline; 30. Glucose; 31. Betaine; 32.TMAO; 33. Glycine; 34. Glycerol; 35. Serine; 36. Fructose; 37. Myo-Inositol; 38. Mannose; 39.Tyrosine: 40. Histidine; 41. Phenylalanine; 42. Tryptophan; 43. τ methyl-Histidine; 44. Formate



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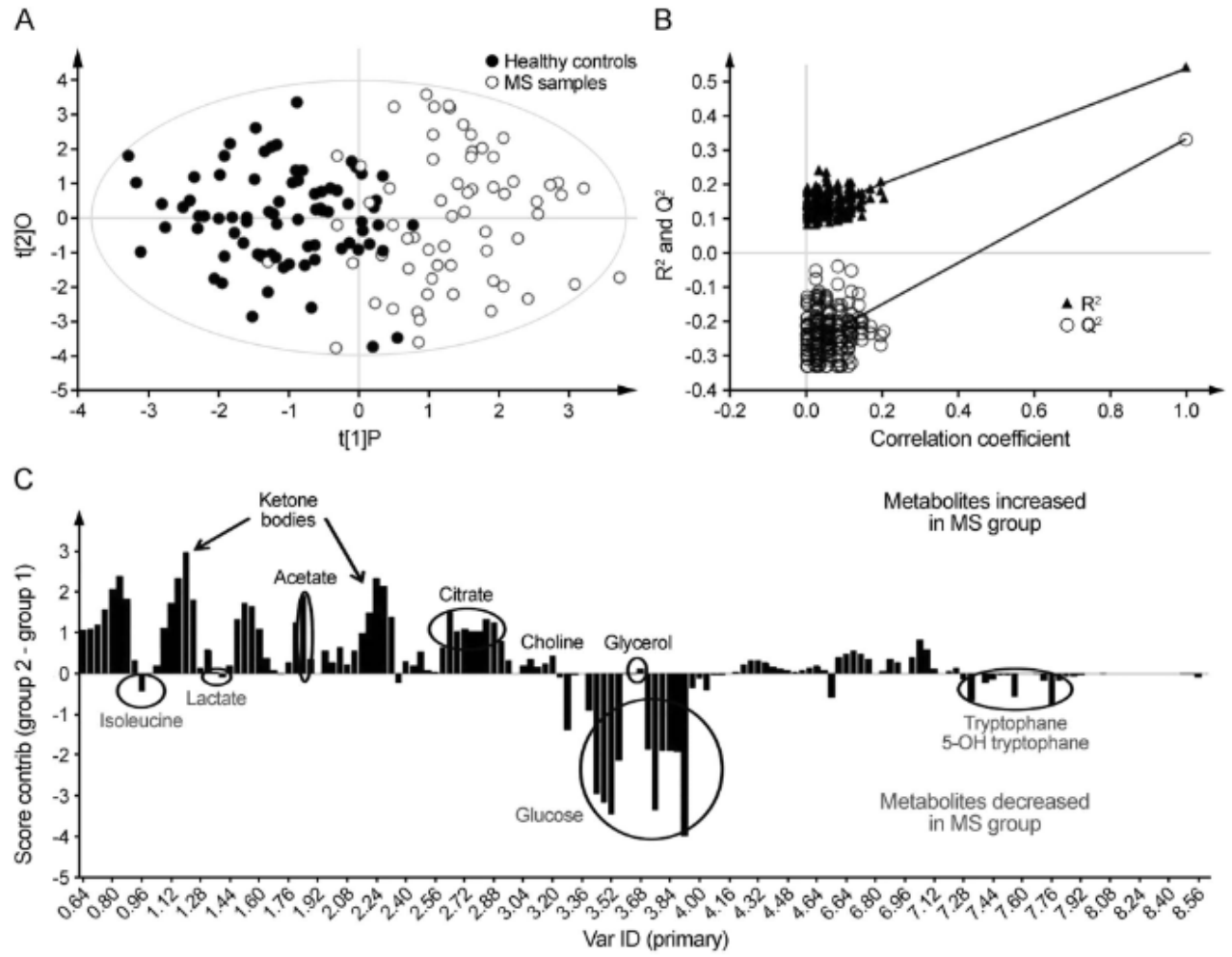
Control *vs* Multiple sclerosis

Figure 1 OPLS-DA model healthy controls vs patients with MS built using bins as variables



(A) Distribution of healthy controls (black circles) and multiple sclerosis (MS) samples (white circles) with orthogonal partial least squares discriminant analysis (OPLS-DA) (R2X = 0.615, R2Y = 0.619, Q2 = 0.476; $p < 0.001$). (B) Validation of the corresponding partial least squares discriminant analysis model via a permutation test. (C) The contribution plot generated by the spectral differences of the 2 groups identified the metabolic changes.

S. Poddighe et al.

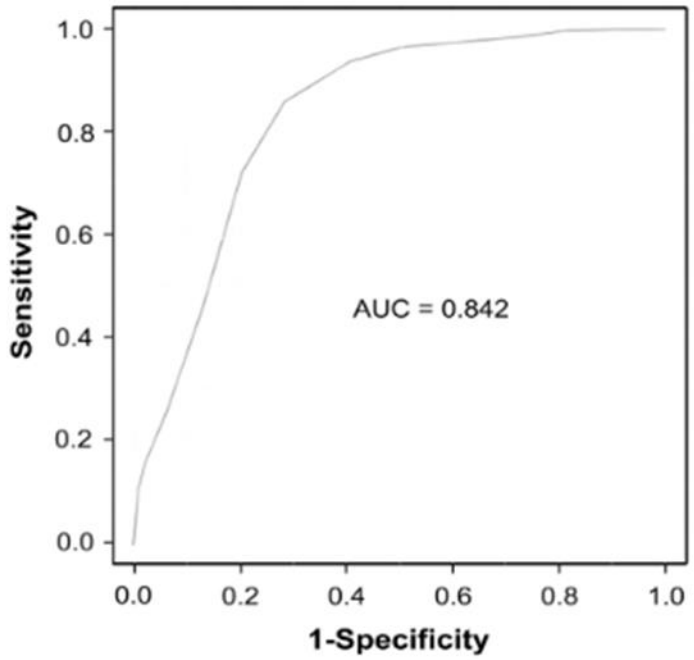
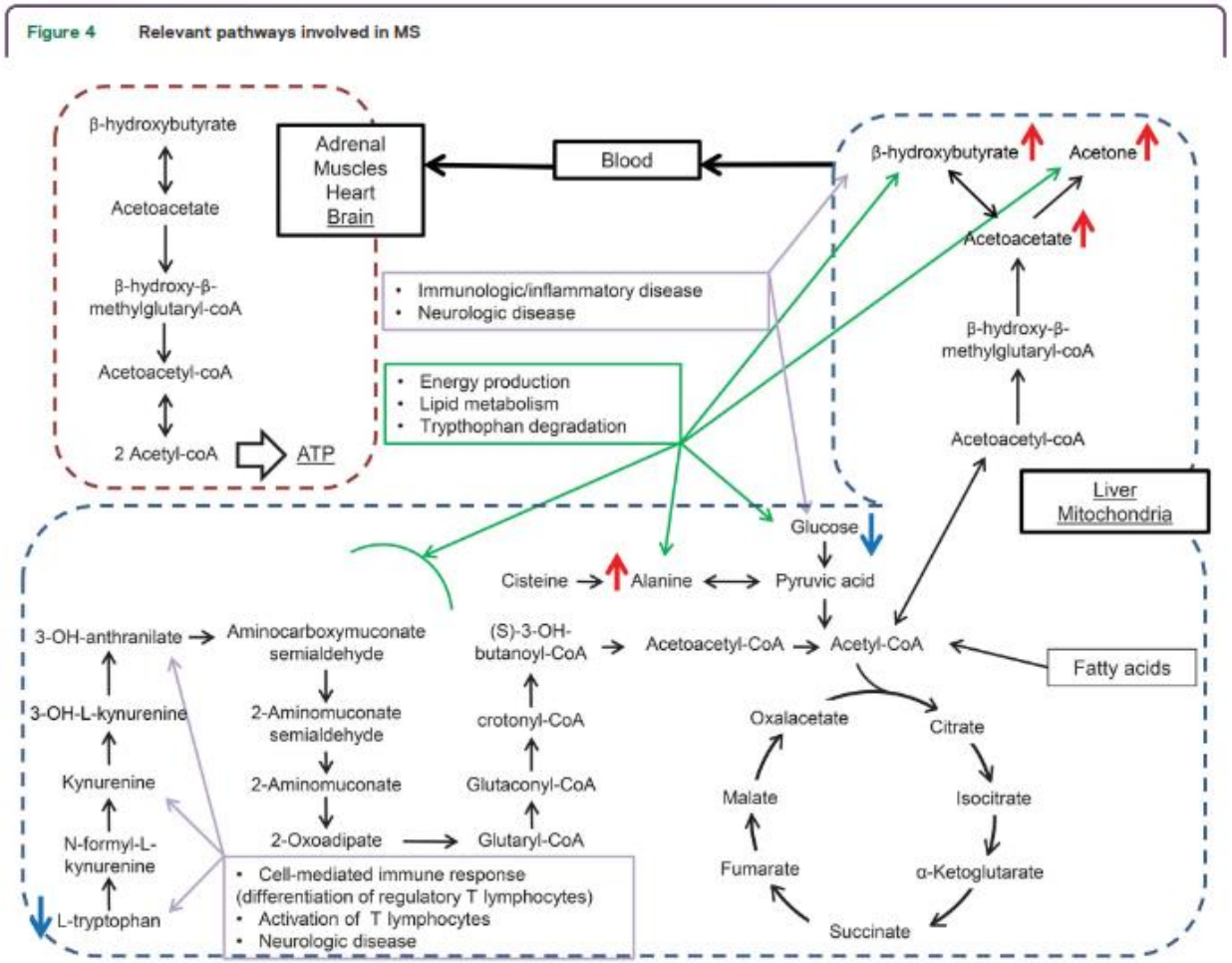


Fig. 3. ROC curve validates the model. ROC curve of generated with the relative concentrations of discriminant metabolites that were significantly different between HC and MS patients (p = 0.01; CI 0.749–1). Only properly identified metabolites were used to build the curves.

Main canonical pathways, biofunction and diseases identified with significant metabolites



Ingenuity Pathway Analysis showed the main canonical pathways, biofunctions, and diseases identified with significant metabolites. Metabolites playing a key role are associated to arrows indicating the relative change in patients with multiple sclerosis (MS) compared with healthy controls (blue arrow: decrease; red arrow: increase). Among the canonical pathways and cellular functions, the tryptophan degradation and the energy production were the most relevant (box and lines in green). Decrease of glucose in patients with MS leads to a decrease in the production of acetyl coenzyme A (acetyl-CoA), a fundamental precursor of the Krebs cycle and the most important pathway in energy production. To overcome the lack of glucose, the β-oxidation of fatty acids in mitochondria is induced. This leads to an increased production of ketone bodies (3-OH-butyrate, acetoacetate, acetone) in patients with MS. Ketone bodies can migrate into the bloodstream for use in peripheral tissues where they are metabolized for the production of ATP, especially 3-OH-butyrate. In particular, tryptophan and some of the intermediaries of this pathway (kynurenine, 3-OH-anthranilate) are implicated in the cell-mediated immune response (differentiation of regulatory T lymphocytes, activation of T lymphocytes). Moreover, the pathways analysis identifies correlation between tryptophan, glucose, and 3-OH-butyrate with immunologic/inflammatory disease and neurologic disease (box and lines in violet).

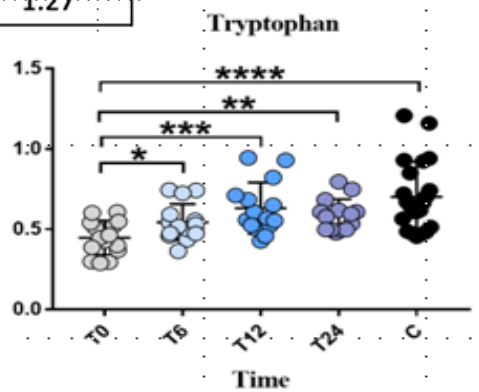
Pathways analysis

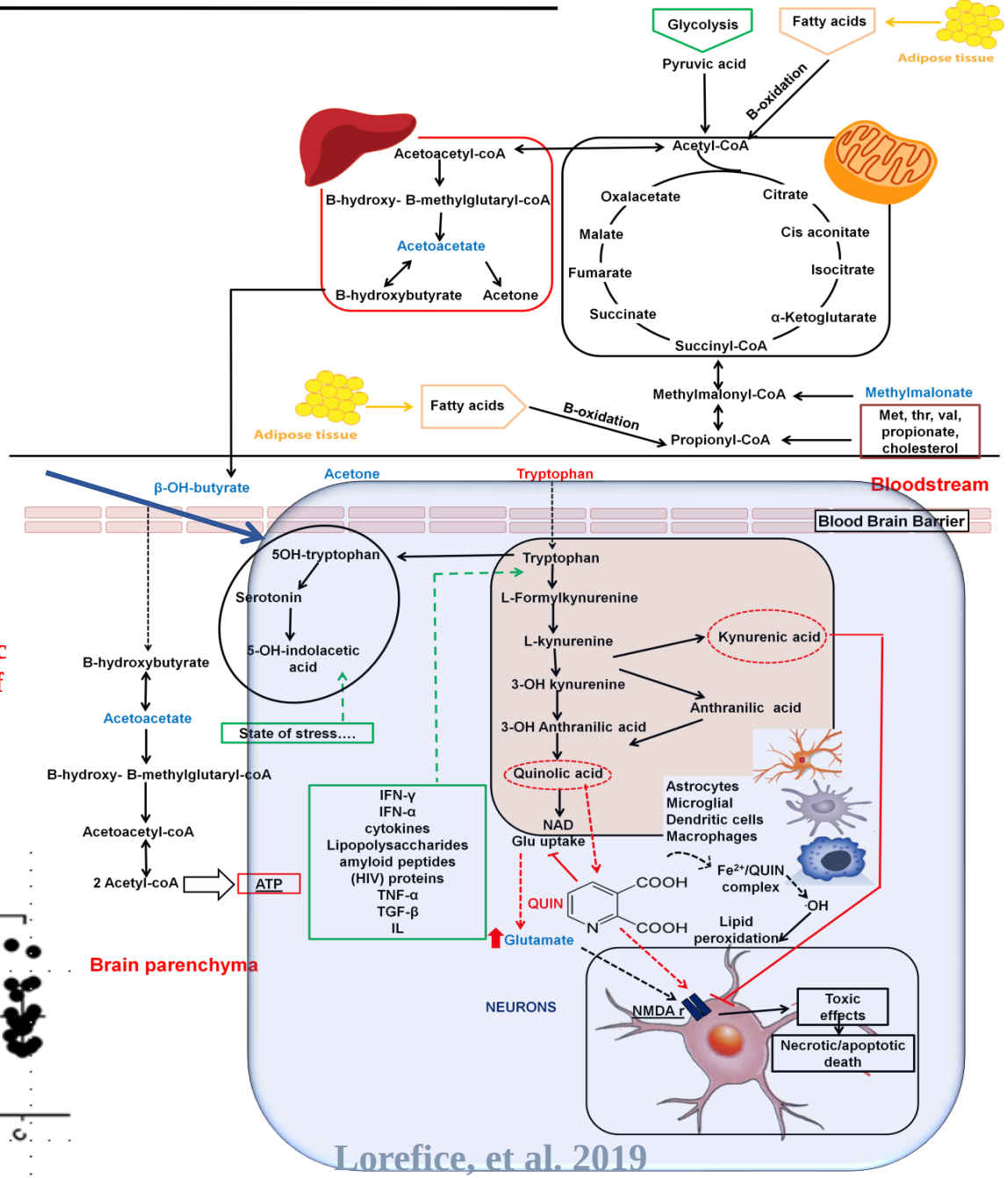
The catabolism of tryptophan to immunosuppressive and neuroactive kynurenines is a key metabolic pathway regulating immune responses and neurotoxicity

This pathway if over-activated leads to the generation of neurotoxic compounds such as quinolinic acid. Moreover a direct effect of the tryptophan has been observed on the immune system and in particular on the Treg, suggesting its pyvotal role in immune sistem regulation

METABOLITES	FOLD CHANGE
5-Hydroxytryptophan	-1.77
Glucose	-1.15
Tryptophan	-2.40
3-Hydroxybutyrate	1.45
Acetoacetate	3.57
Acetone	9.34
Alanine	1.5
Choline	1.27

Basal metabolic profile of MS





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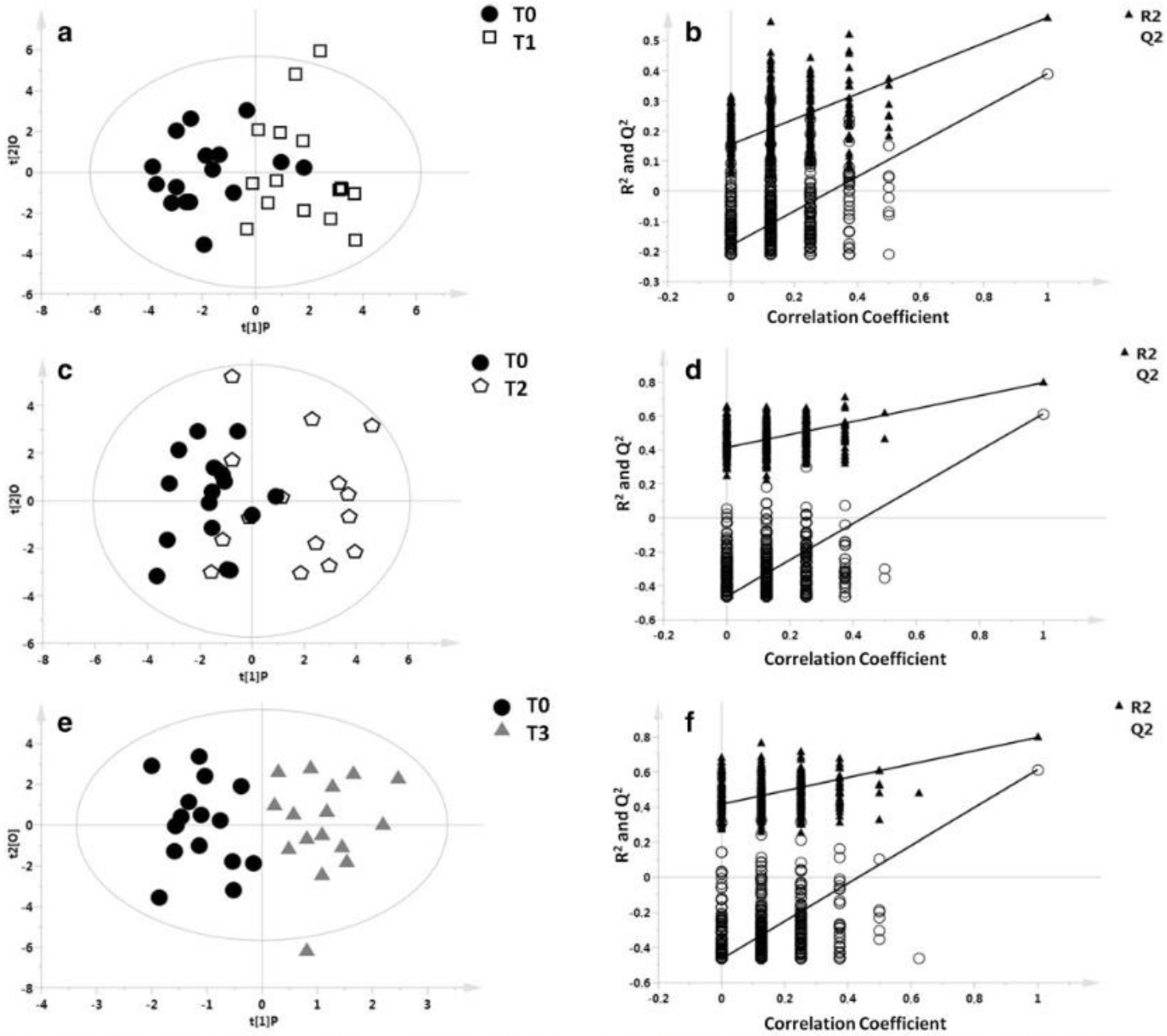
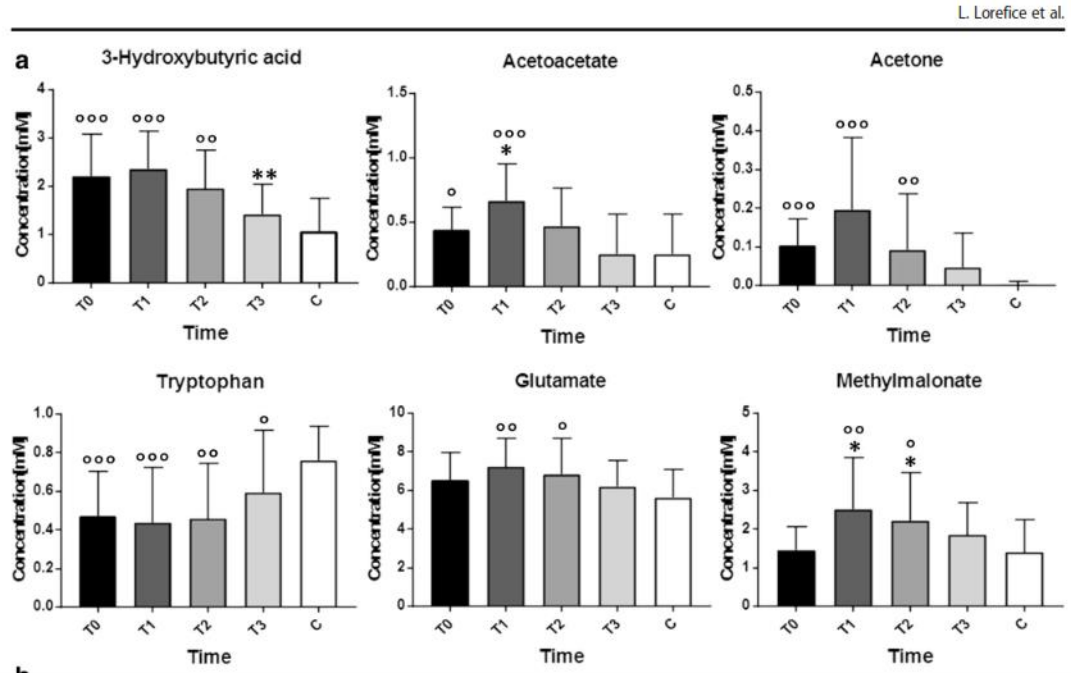


Fig. 1 OPLS-DA models with the respective permutation tests obtained by comparing T0 *vs* T1, T0 *vs* T2, and T0 *vs* T3 samples for each patient. Blood samples were collected at baseline (T0) and then at 6 (T1), 12 (T2), and 24 (T3) months of IFN ß treatment. OPLS-DA models with the respective permutation test indicated a differential distribution of the T0 *vs* T1 sample (A, B), $R^2X = 0.697$, $R^2Y = 0.576$, $Q^2 = 0.391$, $p = 0.006$); T0 *vs* T2 sample (C, D), $R^2X = 0.725$, $R^2Y = 0.450$, $Q^2 = 0.247$, $p = 0.09$); and T0 *vs* T3 sample (E, F), $R^2X = 0.812$, $R^2Y = 0.797$, $Q^2 = 0.613$, $p = 0.003$)

Assessing the Metabolomic Profile of Multiple Sclerosis Patients Treated with Interferon Beta



Responder vs Non- responder at T0 after Interferon beta

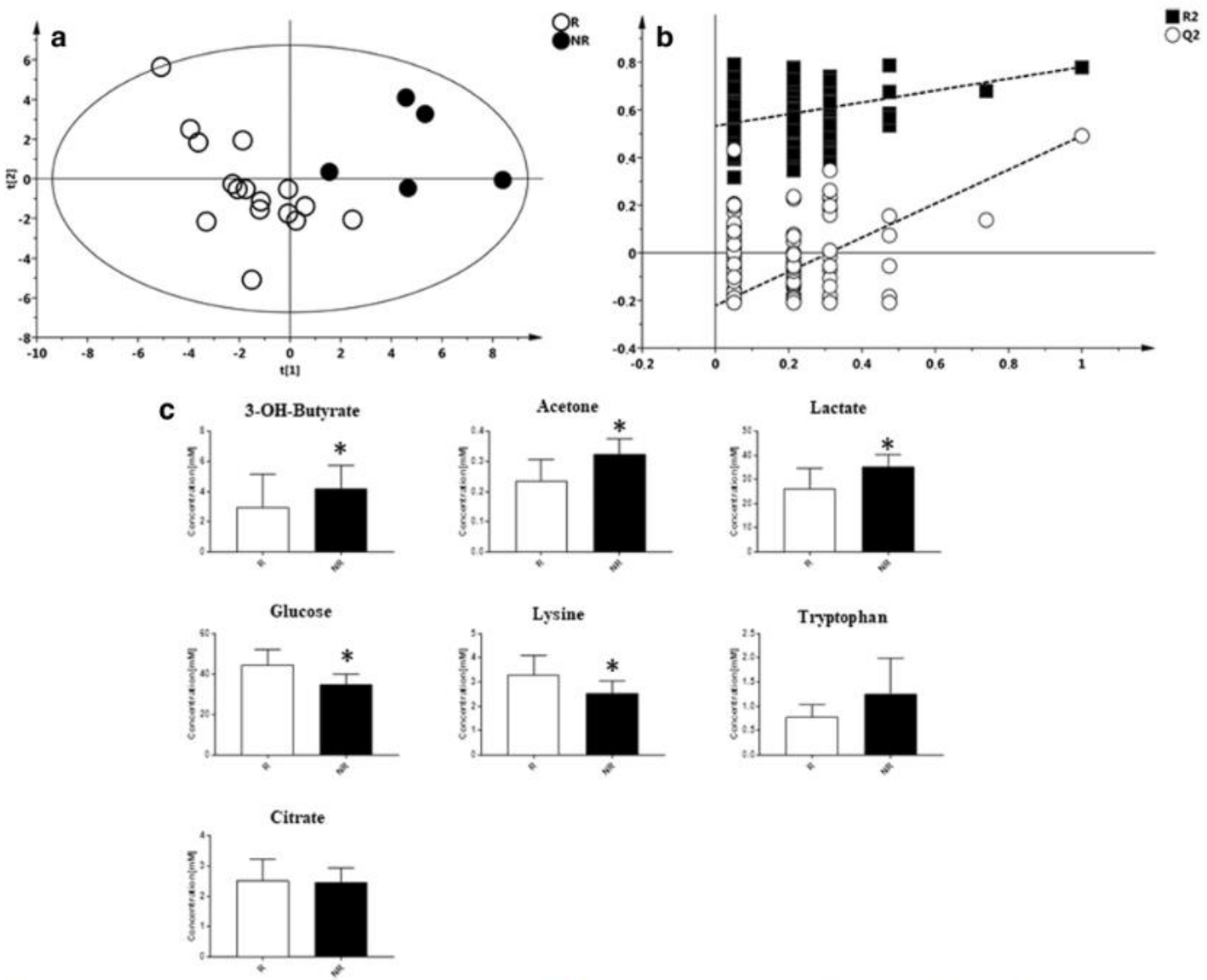


Fig. 4 PLS-DA model with the respective permutation tests obtained by comparing the T0 samples of R *vs* NR patients to IFN ß treatment. (A) PLS-DA model obtained from 21 plasma samples of MS patients at time point T0. Patients were classified as responders (R) and nonresponders (NR) after IFN ß treatment, according to NEDA 3 definition. Statistical parameters were $R^2X = 0.440$, $R^2Y = 0.768$, $Q^2 = 0.532$, $p = 0.01$. (B) Validation of the model by permutation test. (C) Bar graph of the most important metabolites resulting from the multivariate model of R and NR patients

Metabolomic profiles in the patients with hyperthyroidism and hypothyroidism after treatment

International Journal of Biochemistry and Cell Biology 93 (2017) 119–128

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Metabolomic profile in hyperthyroid patients before and after antithyroid drug treatment: Correlation with thyroid hormone and TSH concentration

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ARTICLE INFO

Keywords:
Metabolomics
Hyperthyroidism
Biomarkers
^{1}H NMR
Multivariate statistical analysis

ABSTRACT

Hyperthyroidism (HT) is characterized by an intense metabolic impact which affects the lipid, carbohydrate and amino acids metabolism, with increased resting energy expenditure and thermogenesis. Metabolomics is a comprehensive technique that allows ... molecular and pathophysiological states. The aim of the present prospective study was to identify a distinct metabolomic profile in HT patients using ^{1}H NMR spectroscopy before and after antithyroid drug treatment. This prospective study included 15 patients (10 female, 5 male) who were newly diagnosed hyperthyroidism. A nuclear magnetic resonance (^{1}H ...) ... at diagnosis ($HypT_0$) and when they ... euthyroidism ($HypT_1$). The case groups were compared with a control group of 26 healthy volunteers (C). Multivariate statistical analysis was performed with Partial Least Squares-Discriminant Analysis (PLS-DA). PLS-DA identified a distinct metabolic profile between C and untreated hyperthyroid patients (R^2X 0.638, R^2Y 0.932, Q^2 0.783). Interestingly, a significant difference was ... between C and euthyroid patients after treatment (R^2X 0.510, R^2Y 0.838, Q^2 0.607), while similar cluster emerged comparing $HypT_0$ vs $HypT_1$ patients. This study shows that metabolomic profile is deeply influenced by hyperthyroidism and this alteration persists after normalization of thyrotropin (TSH) and free thyroid hormone (FT3, FT4) concentration. This suggests that TSH, FT3 and FT4 assays may not be insufficient to detect long lasting peripheral effects of the thyroid hormones action. Further studies are needed to clarify whether and to what extent the evaluation of metabolomics profile may provide relevant information in the clinical management of hyperthyroidism.

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https://doi.org/10.1007/s40618-020-01434-y

ORIGINAL ARTICLE

Analysis of metabolomics profile in hypothyroid patients before and after thyroid hormone replacement

C. Piras[1] · M. Pibiri[1] · V. P. Leoni[1] · A. Balsamo[1] · L. Tronci[1] · N. Arisci[2] · S. Mariotti[2] · L. Atzori[1]

Received: 13 August 2020 / Accepted: 24 September 2020

Abstract

Purpose The serum metabolic changes occurring during the transition from hypothyroidism to euthyroidism are not known. This study aimed to determine the metabolomic profile in hypothyroid patients before ($HypoT_0$) and after ($HypoT_1$) euthyroidism achieved through levothyroxine (L-T4) treatment.

Methods Eighteen patients with overt primary hypothyroidism were recruited for the study. All patients were treated with L-T4 ... thyroxine (FT4), free triiodothyronine (FT3) and metabolomics pro... treatment. The euthyroid control group consisted of 28 healthy volunteers. Metabolomics analysis was performed using Nuclear Magnetic Resonance (NMR) spectroscopy.

Results ^{1}H NMR-based metabolomics profile of patients with newly diagnosed hypothyroidism ($HypoT_0$) showed signifi... ...inositol and serine, and lower levels of proline and taurine compared to controls. Interestingly, some metabolic changes were persistent three months after pharmacological treatments, despite normal serum TSH and thyroid hormone concentrations ($HypoT_1$). When an Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) model was built to evaluate possible differences in the metabolic profile between $HypoT_0$ and $HypoT_1$, the data obtained were not significantly different.

Conclusion These results suggest that metabolic changes in the patients with hypothyroidism may persist after normalization of serum levels of FT3, FT4, and TSH, which currently represent the gold standard in laboratory testing for diagnosis and evaluation of thyroid pathology. So, the metabolomics approach may contribute to integrate classical hormone assays and to determine the euthyroid status achievement with greater efficacy.

Metabolic changes in the patients with hyperthyroidism and hypothyroidism may persist after normalization of serum levels of FT3, FT4, and TSH, which currently represent the gold standard in laboratory testing for diagnosis and evaluation of thyroid pathology. This suggests that TSH, FT3 and FT4 assays may not be sufficient to detect long lasting peripheral effects of the thyroid hormones action.
So, the metabolomics approach may contribute to **integrate classical hormone assays and to determine the euthyroid status achievement with greater efficacy**.

Inflammatory bowel diseases and microbiome

SCIENTIFIC REPORTS

OPEN

Cross sectional evaluation of the gut-microbiome metabolome axis in an Italian cohort of IBD patients

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Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract of uncertain origin, which includes ulcerative colitis (UC) and Crohn's disease (CD). The composition of gut microbiota may change in IBD affected individuals, but whether dysbiosis is the cause or the consequence of inflammatory processes in the intestinal tissue is still unclear. Here, the composition of the microbiota and the metabolites in stool of 183 subjects (82 UC, 50 CD, and 51 healthy controls) were determined. The metabolites content and the microbiological profiles were significantly different between IBD and healthy subjects. In the IBD group, Firmicutes, Proteobacteria, Verrucomicrobia, and Fusobacteria were significantly increased, whereas Bacteroidetes and Cyanobacteria were decreased. At genus level *Escherichia*, *Faecalibacterium*, *Streptococcus*, *Sutterella* and *Veillonella* were increased, whereas *Bacteroides*, *Flavobacterium*, and *Oscillospira* decreased. Various metabolites including biogenic amines, amino acids, lipids, were significantly increased in IBD, while others, such as two B group vitamins, were decreased in IBD compared to healthy subjects. This study underlines the potential role of an inter-omics approach in understanding the metabolic pathways involved in IBD. The combined evaluation of metabolites and fecal microbiome can be useful to discriminate between healthy subjects and patients with IBD.

metabolites

MDPI

Article

Modulatory Effect of Nicotinic Acid on the Metabolism of Caco-2 Cells Exposed to IL-1β and LPS

Maria Laura Santoru *, Cristina Piras, Federica Murgia, Martina Spada, Laura Tronci, Vera Piera Leoni, Gabriele Serreli, Monica Deiana and Luigi Atzori

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check for updates

Abstract: Inflammatory bowel diseases (IBD) are the most common gastrointestinal inflammatory pathologies. Previous work evidenced a lower content of nicotinic acid (NA) in feces of IBD patients compared to healthy subjects. In the present study, we aimed to understand the effects of NA on intestinal inflammation, as several studies reported its possible beneficial effect, and investigate its influence on inflammation-driven metabolism. NA was tested on a Caco-2 in-vitro model in which inflammation was induced with interleukin-1β (IL-1β) and lipopolysaccharide (LPS), two mayor proinflammatory compounds produced in IBD, that stimulate the production of cytokines, such as interleukin 8. A metabolomics approach, with gas chromatography–mass spectrometry (GC-MS) and nuclear proton magnetic resonance (^{1}H-NMR), was applied to study the metabolic changes. The results showed that NA significantly reduced the level of IL-8 produced in both LPS and IL-1β stimulated cells, confirming the anti-inflammatory effect of NA also on intestinal inflammation. Moreover, it was demonstrated that NA treatment had a restoring effect on several metabolites whose levels were modified by treatments with IL-1β or LPS. This study points out a possible use of NA as anti-inflammatory compound and might be considered as a promising starting point in understanding the beneficial effects of NA in IBD.

[illegible] omics; IBD; nicotinic acid

Metabolomics (2018) 14:140
https://doi.org/10.1007/s11306-018-1439-4

ORIGINAL ARTICLE

CrossMark

Italian cohort of patients affected by inflammatory bowel disease is characterised by variation in glycerophospholipid, free fatty acids and amino acid levels

Antonio Murgia[1,2] · Christine Hinz[2] · Sonia Liggi[2] · Júlia Denes[2] · Zoe Hall[2] · James West[2] · Maria Laura Santoru[3] · Cristina Piras[3] · Cristina Manis[1] · Paolo Usai[4] · Luigi Atzori[3] · Julian L. Griffin[2] · Pierluigi Caboni[1]

Received: 8 June 2018 / Accepted: 5 October 2018

Abstract

Background Inflammatory bowel disease is a group of pathologies characterised by chronic inflammation of the intestine and an unclear aetiology. Its main manifestations are Crohn's disease and ulcerative colitis. Currently, biopsies are the most used diagnostic tests for these diseases and metabolomics could represent a less invasive approach to identify biomarkers of disease presence and progression.

Objectives The lipid and the polar metabolite profile of plasma samples of patients affected by inflammatory bowel disease have been compared with healthy individuals with the aim to find their metabolomic differences. Also, a selected sub-set of samples was analysed following solid phase extraction to further characterise differences between pathological samples.

Methods A total of 200 plasma samples were analysed using drift tube ion mobility coupled with time of flight mass spectrometry and liquid chromatography for the lipid metabolite profile analysis, while liquid chromatography coupled with triple quadrupole mass spectrometry was used for the polar metabolite profile analysis.

Results Variations in the lipid profile between inflammatory bowel disease and healthy individuals were highlighted. Phosphatidylcholines, lyso-phosphatidylcholines and fatty acids were significantly changed among pathological samples suggesting changes in phospholipase A_2 and arachidonic acid metabolic pathways. Variations in the levels of cholesteryl esters and glycerophospholipids were also found. Furthermore, a decrease in amino acids levels suggests mucosal damage in inflammatory bowel disease.

Conclusions Given good statistical results and predictive power of the model produced in our study, metabolomics can be considered as a valid tool to investigate inflammatory bowel disease.

REVIEW ARTICLE - BASIC SCIENCE

Metabolic Alteration in Plasma and Biopsies From Patients With IBD

Maria Laura Santoru, PhD, Cristina Piras, PhD,* Federica Murgia, MSc,* Vera Piera Leoni, PhD,* Martina Spada, MSc,* Antonio Murgia, PhD,† Sonia Liggi, PhD,* Maria Antonia Lai, MD,† Paolo Usai, MD,§ Pierluigi Caboni, PhD,† Aldo Manzin, MD,* and Luigi Atzori, MD, PhD**

Background: Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract, with periods of latency alternating with phases of exacerbation, and include 2 forms: Crohn disease (CD) and ulcerative colitis (UC). Although the etiology of IBD is still unclear, the identification and understanding of pathophysiological mechanisms underlying IBD could reveal newly targeted intestinal alterations and determine therapeutic approaches.

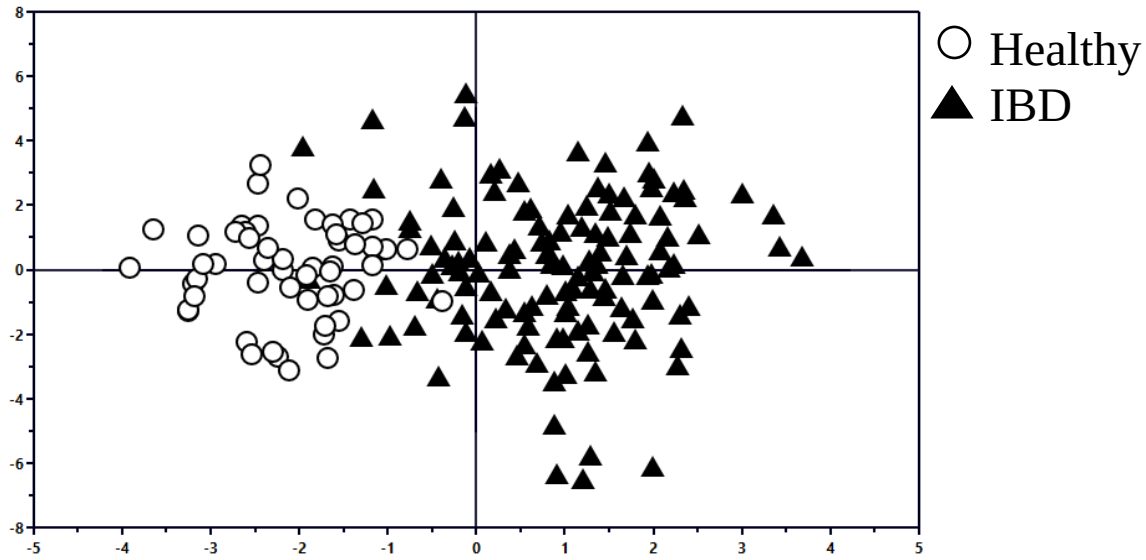
Methods: In this study, by using gas chromatography-mass spectrometry, we characterized plasma and biopsies from the metabolomics profiles of patients with IBD compared with those of a control group.

Results: The results showed a different metabolomics profile between patients with CD (n = 50) and patients with UC (n = 82) compared with the control group (n = 51). Multivariate statistical analysis of the identified metabolites in CD and UC showed changes in energetic metabolism, and lactic acid and ornithine in particular were altered in both plasma and colon biopsies. Moreover, metabolic changes were evidenced between the normal ileum and colon tissues. These differences disappeared when we compared the inflamed ileum and colon tissues, suggesting a common metabolism.

Conclusions: This study showed how the metabolomics profile could be a potential tool to identify intestinal alterations associated with IBD and may have application in precision medicine and for better defining the pathogenesis of the disease.

Inflamm Bowel Dis • Volume 27, Number 8, August 2021

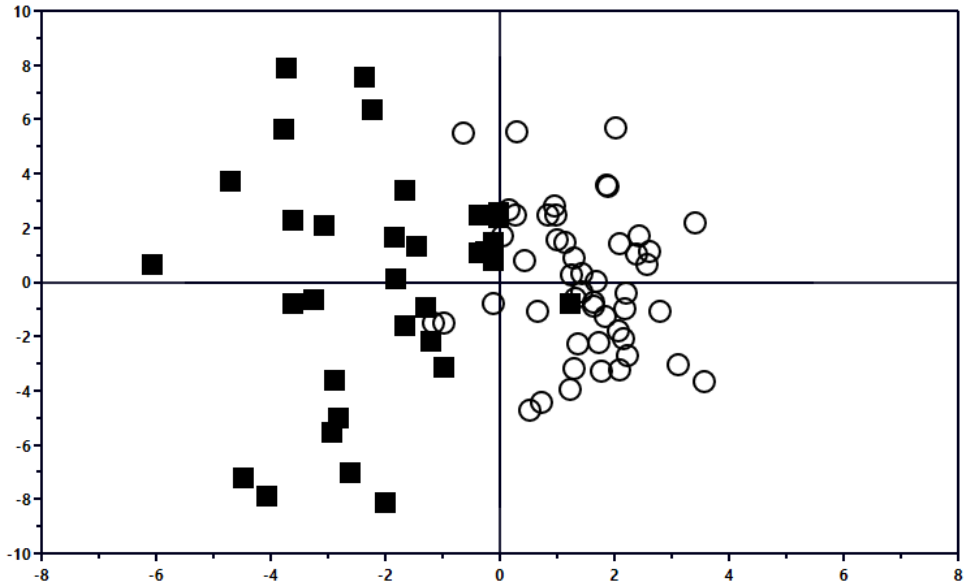
PLASMA ANALYSIS



OPLS-DA model: $R^2X=0,2$; $R^2Y=0,632$; $Q^2=0,563$

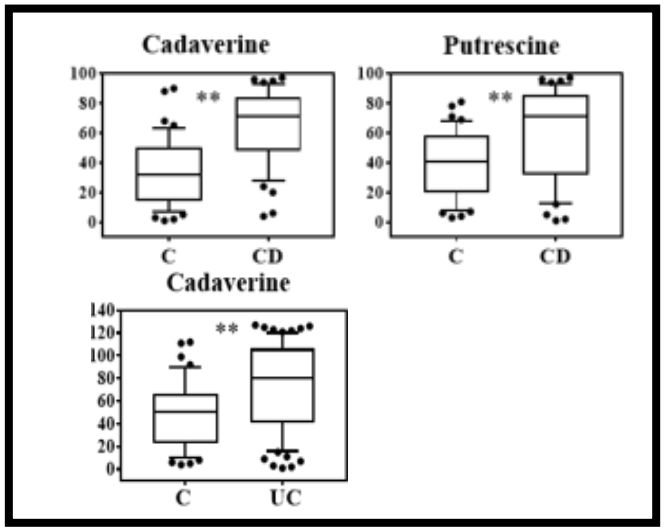
The altered metabolites in IBD plasma were all involved in the energetic metabolism as part of different metabolic pathways such as ***glycolysis***, ***ketone bodies***, ***purine metabolisms***, *the* ***tricarboxylic acid (TCA) cycle***, *and the* ***urea cycle***

BIOPSIES ANALYSIS



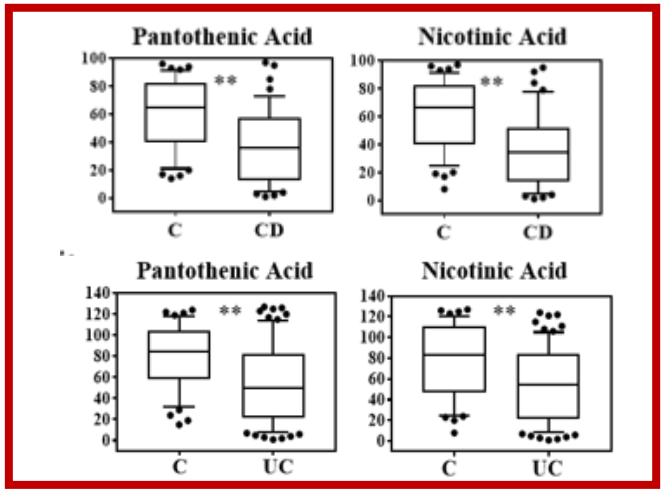
The biopsies metabolomic profile was different:

- Between inflamed and normal colon biopsies from **UC** patients
- Inflamed and normal colon biopsies and inflamed and normal ileum biopsies in **CD** patients



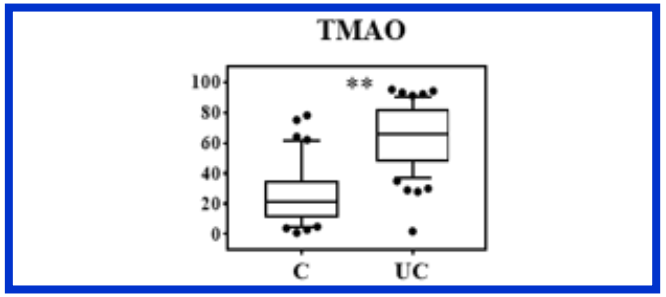
Biogenic amines

- Produced both by the host and by intestinal flora bacteria
- Elevated levels of polyamines seem to have a toxic effect and are associated with several diseases
- Oxidative stress caused by polyamines catabolism



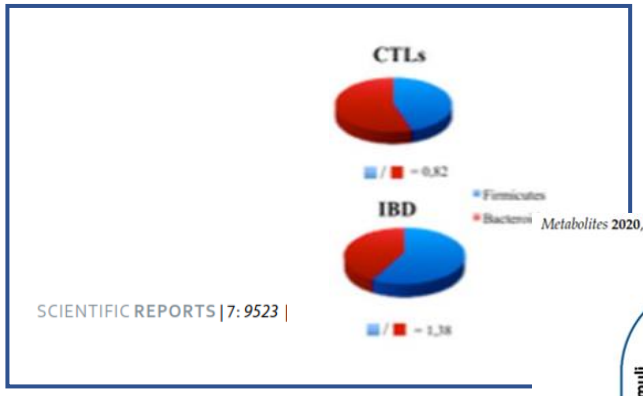
B group vitamins

- Nicotinic acid (vitamin B3) may exert a beneficial effect on the mucosa of the colon, reducing inflammation
- Pantothenic acid (vitamin B5) may have a protective effect against oxidative stress in mammalian tissues



Trimethylamine N-oxide (TMAO)

- Generated by anaerobic bacteria
- One previous study has found that TMAO promotes inflammation by recruiting leukocytes



SCIENTIFIC REPORTS | 7: 9523 |

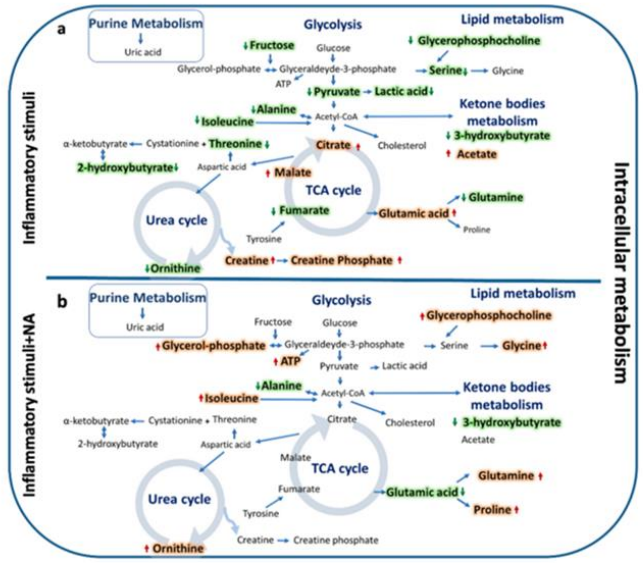


Figure 5. Relevant metabolic pathways that were found significantly altered after treatment with proinflammatory stimuli (LPS and IL-1β) (**a**) and after treatment with proinflammatory stimuli in combination with NA (**b**) in Caco-2 cells at the intracellular level. Increased and decreased metabolites are highlighted in red and green, respectively.

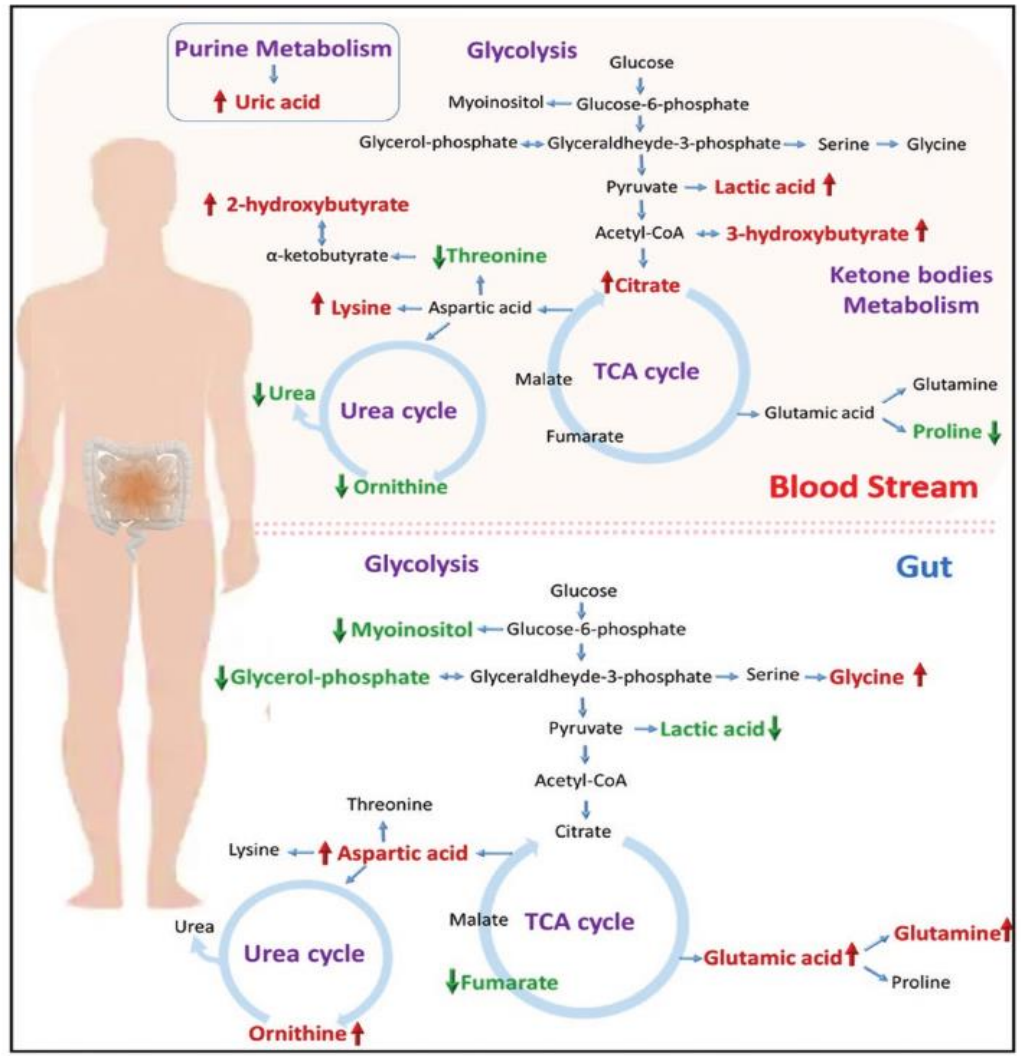
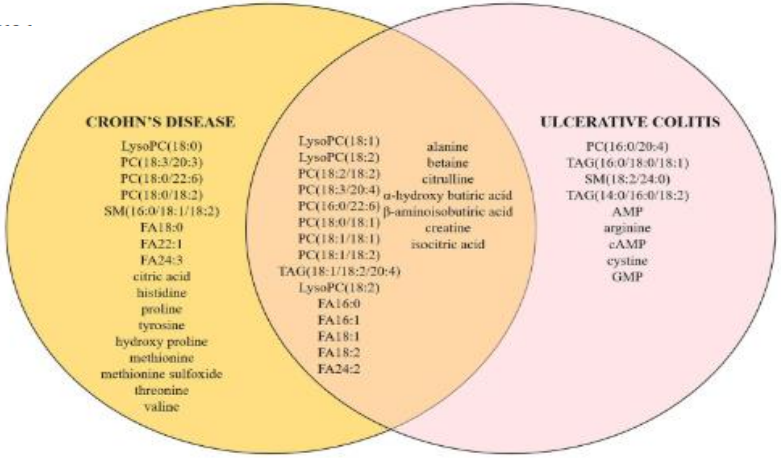


FIGURE 5. Relevant metabolic pathways involved in IBD, obtained from analysis of metabolites in plasma and colon biopsy samples. Increased and decreased metabolites are highlighted in red and green, respectively.

the most discriminant compounds of both untargeted and targeted analysis for the main two pathological classes: Crohn's disease and ulcerative colitis



Metabolomic profiles in cardiovascular disorders

Nature Review Cardiology **8,** 630–643 (2011)

Metabolomics as a tool for cardiac research

Julian L. Griffin, Helen Atherton, John Shockcor and Luigi Atzori

Abstract | Metabolomics represents a paradigm shift in metabolic research, away from approaches that focus on a limited number of enzymatic reactions or single pathways, to approaches that attempt to capture the complexity of metabolic networks. Additionally, the high-throughput nature of metabolomics makes it ideal to perform biomarker screens for diseases or follow drug efficacy. In this Review, we explore the role of metabolomics in gaining mechanistic insight into cardiac disease processes, and in the search for novel biomarkers. High-resolution NMR spectroscopy and mass spectrometry are both highly discriminatory for a range of pathological processes affecting the heart, including cardiac ischemia, myocardial infarction, and heart failure. We also discuss the position of metabolomics in the range of functional-genomic approaches, being complementary to proteomic and transcriptomic studies, and having subdivisions such as lipidomics (the study of intact lipid species). In addition to techniques that monitor changes in the total sizes of pools of metabolites in the heart and biofluids, the role of stable-isotope methods for monitoring fluxes through pathways is examined. The use of these novel functional-genomic tools to study metabolism provides a unique insight into cardiac disease progression.

Deidda *et al. J Transl Med (2015) 13:297*
DOI 10.1186/s12967-015-0661-3

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Metabolomic approach to profile functional and metabolic changes in heart failure

Martino Deidda[1*], Cristina Piras[2], Christian Cadeddu Dessalvi[1], Emanuela Locci[2], Luigi Barberini[3], Federica Torri[1], Federica Ascedu[1], Luigi Atzori[2] and Giuseppe Mercuro[1]

Deidda *et al. J Transl Med (2017) 15:112*
DOI 10.1186/s12967-017-1215-7

Journal of Translational Medicine

Open Access

Blood metabolomic fingerprint is distinct in healthy coronary and in stenosing or microvascular ischemic heart disease

Martino Deidda[1,5*†], Cristina Piras[2†], Christian Cadeddu Dessalvi[1], Damiana Congia[3], Emanuela Locci[1], Federica Ascedu[1], Gianfranco De Candia[4], Mauro Cadeddu[4], Giorgio Lai[4], Raimondo Pirisi[4], Luigi Atzori[2‡] and Giuseppe Mercuro[1‡]

SCIENTIFIC REPORTS

OPEN

Metabolomic fingerprint of coronary blood in STEMI patients depends on the ischemic time and inflammatory state

Received: 23 January 2018
Accepted: 15 November 2018
Published online: 22 January 2019

Martino Deidda[1], Cristina Piras[2], Giulio Binaghi[3], Damiana Congia[3], Alessandro Pani[3], Alberto Boi[4], Francesco Sanna[4], Angelica Rossi[4], Bruno Loi[4], Christian Cadeddu Dessalvi[1], Luigi Atzori[2], Maurizio Porcu[3] & Giuseppe Mercuro[1]

In this study we investigated whether the metabolomic analysis could identify a specific fingerprint of coronary blood collected during primary PCI in STEMI patients. Fifteen samples was subjected to metabolomic analysis. Subsequently, the study population was divided into two groups according to the peripheral blood neutrophil-to-lymphocyte ratio (NLR), a marker of the systemic inflammatory response. Regression analysis was then applied separately to the two NLR groups. A partial least square (PLS) regression identified the most significant involved metabolites and the PLS-class analysis revealed a significant correlation between the metabolic profile and the total ischemic time only in patients with an NLR > 5.77.

International Journal of Cardiology 241 (2017) 401–406

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

ELSEVIER

Distinctive metabolomic fingerprint in scleroderma patients with pulmonary arterial hypertension

Martino Deidda [a,1,2], Cristina Piras [b,1,2], Christian Cadeddu Dessalvi [a,1,2], Emanuela Locci [a,1], Luigi Barberini [a,1], Susanne Orofino [c,1], Mario Musu [a,1], Mario Nicola Mura [d,1], Paolo Emilio Manconi [a,1], Gabriele Finco [a,1], Luigi Atzori [b,1,2], Giuseppe Mercuro [a,*,1,2]

Metabolic fingerprint of healthy coronary arteries is considerably different from that of artherosclerotic vessels.

In addition, the **metabolic profile of microvascular dysfunction is distinguishable from that of stenotic disease,** despite of the presence of comparable cardiovascular risk factors suggesting different underlying pathways or their different modulation.

This approach may hep to discover new biomarkers and therapeutics target to modulate endothelial response and affect the progress of the CAD (i.e. coronary stent eluting specific metabolites with demonstrated anti-atherogenic effects on endothelium).

Evidence of correlation between metabolomic changes and heart failure severity.

This data may help to clarify the reason for different individual susceptibility to the development of atherosclerosis and the mechanims of heart failure progression.

OPEN ACCESS Freely available online

PLOS ONE

Metabolomics Analysis and Modeling Suggest a Lysophosphocholines-PAF Receptor Interaction in Fibromyalgia

Pierluigi Caboni[1], Barbara Liori[1], Amit Kumar[2,3], Maria Laura Santoru[2], Shailendra Asthana[2], Enrico Pieroni[3], Antonella Fais[1], Benedetta Era[1], Enrico Cacace[4], Valeria Ruggiero[4], Luigi Atzori[2]*

1 Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy, 2 Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy, 3 Biomedicine Department, CRS4, Cagliari, Italy, 4 Department of Medical Sciences "Mario Aresu", University of Cagliari, Caglia

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Metabolomics and fibromyalgia

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OPEN

Metabolomics analysis of plasma samples of patients with fibromyalgia and electromagnetic sensitivity using GC–MS technique

Cristina Piras[1], Monica Pibiri[1], Stella Conte[2], Gabriella Ferranti[2], Vera Piera Leoni[1], Sonia Liggi[3], Martina Spada[1], Sandro Muntoni[1], Pierluigi Caboni[4] & Luigi Atzori[1]

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OPEN

Metabolomics and psychological features in fibromyalgia and electromagnetic sensitivity

Cristina Piras[1], Stella Conte[2], Monica Pibiri[1], Giacomo Rao[3], Sandro Muntoni[1], Vera Piera Leoni[1], Gabriele Finco[4] & Luigi Atzori[1]

The application of a metabolomic approach discriminated FMS patients from controls, with an increase of PC(14:0/0:0) and PC(16:0/0:0) compounds in the metabolic profiles. These results and the modeling of metabolite-PAFr interaction, allowed us to hypothesize that lipids oxidative fragmentation might generate lysoPCs in abundance, that in turn will act as PAF-like bioactivators.

If this is the case:

- New Biomarkers?
- Potential therapeutical targets

antioxidants

MDPI

Article

Glutamine Starvation Affects Cell Cycle, Oxidative Homeostasis and Metabolism in Colorectal Cancer Cells

International Journal of Molecular Sciences

MDPI

Article

Metabolomic Alterations in Thyrospheres and Adherent Parental Cells in Papillary Thyroid Carcinoma Cell Lines: A Pilot Study

Metabolomics and mechanisms of cell growth in cultured cells

antioxidants

MDPI

Article

Vitamin C Cytotoxicity and Its Effects in Redox Homeostasis and Energetic Metabolism in Papillary Thyroid Carcinoma

metabolites

MDPI

Article

Crosstalk between Metabolic Alterations and Altered Redox Balance in PTC-Derived Cell Lines

Laura Tronci [1,†,*], Paola Caria [1,†], Daniela Virginia Frau [1], Sonia Liggi [1,2], Cristina Piras [1], Federica Murgia [1], Maria Laura Santoru [1], Monica Pibiri [1], Monica Deiana [1], Julian Leether Griffin [2], Roberta Vanni [1] and Luigi Atzori [1]

What is the “control”?

DOI: 10.1021/acs.analchem.5b03078
Anal. Chem. 2016, 88, 7921−7929

analytical chemistry

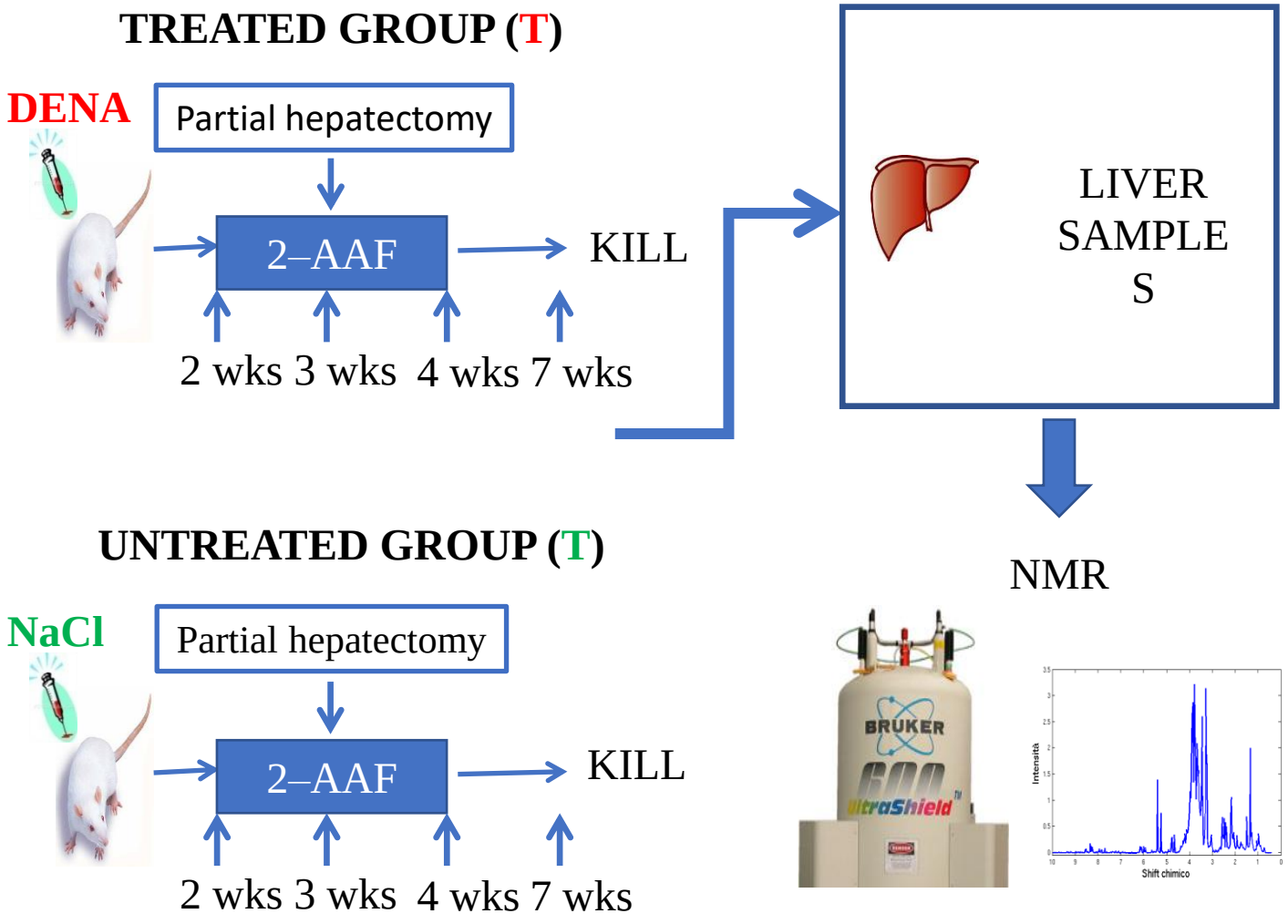
Article

pubs.acs.org/ac

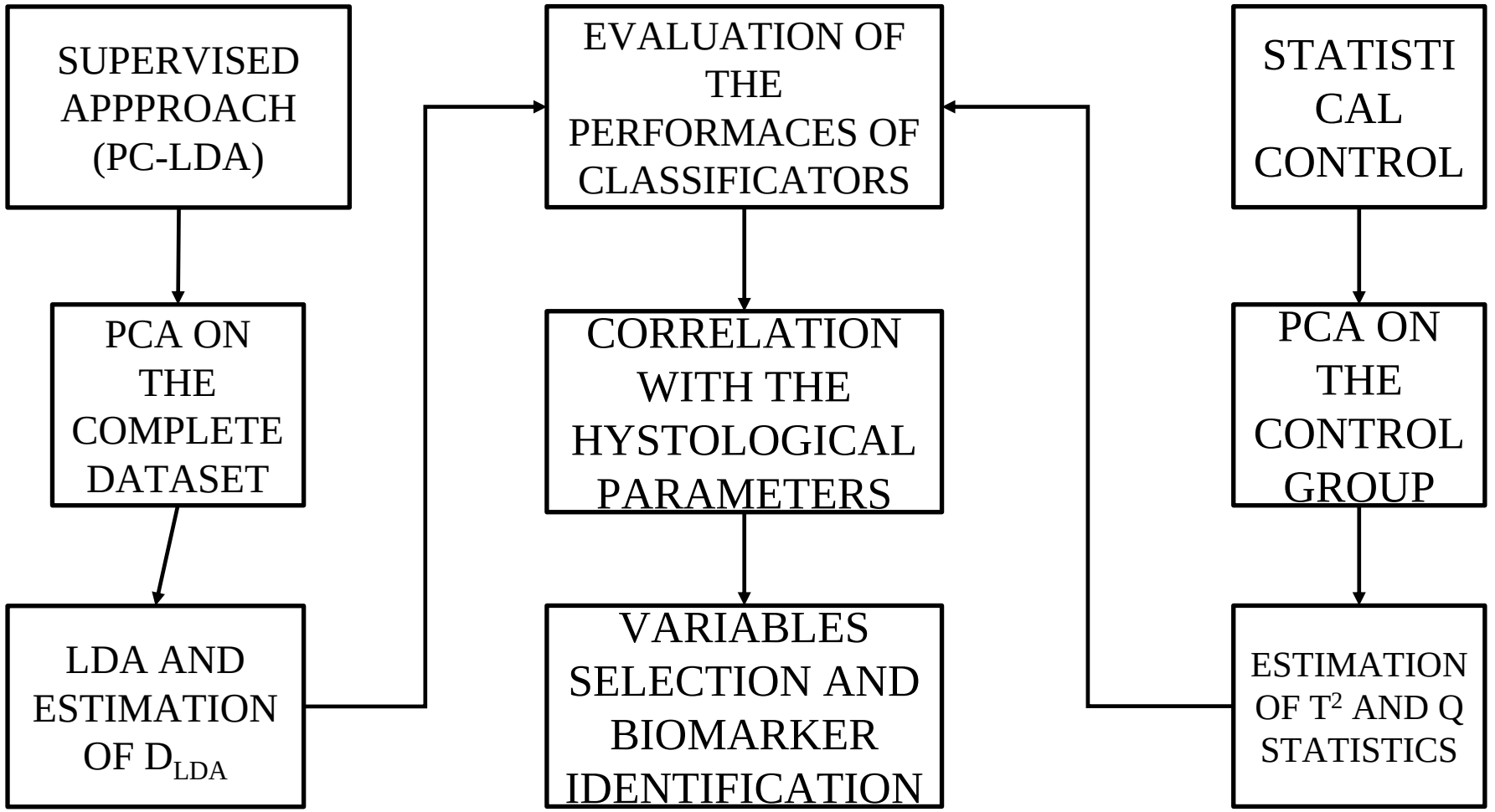
Statistical Health Monitoring Applied to a Metabolomic Study of Experimental Hepatocarcinogenesis: An Alternative Approach to Supervised Methods for the Identification of False Positives

Francesco Del Carratore,[†,⊥,▽] Milena Lussu,[†,⊥] Marta Anna Kowalik,[†] Andrea Perra,[†] Julian Leether Griffin,[‡] Luigi Atzori,[*,†,⊥] and Massimiliano Grosso[*,§,⊥]

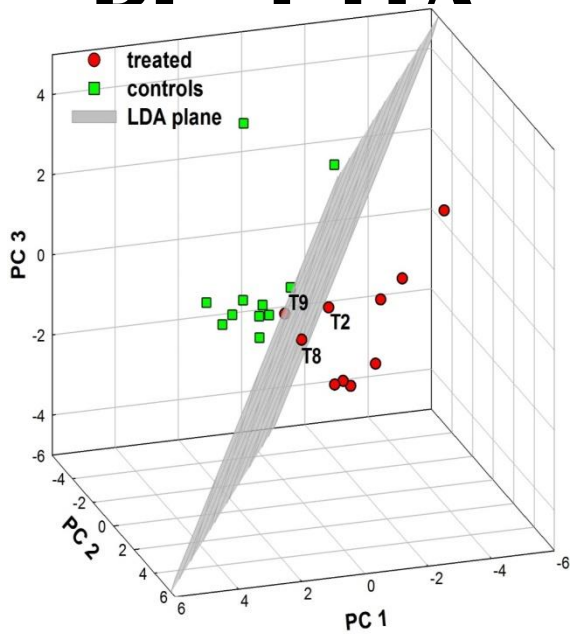
EXPERIMENTAL PROTOCOL



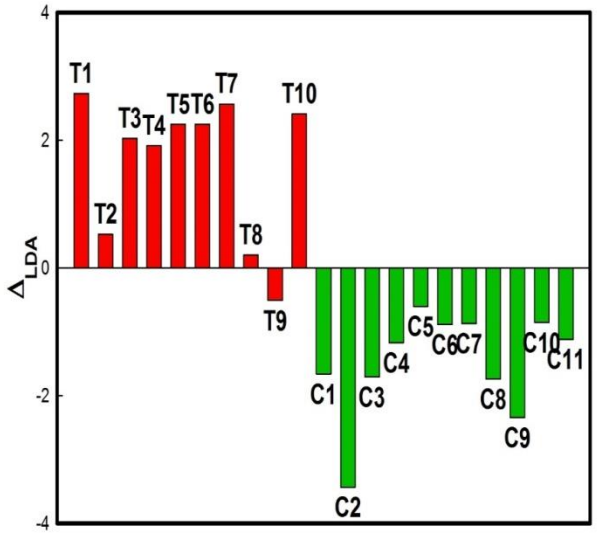
FLOW SHEET

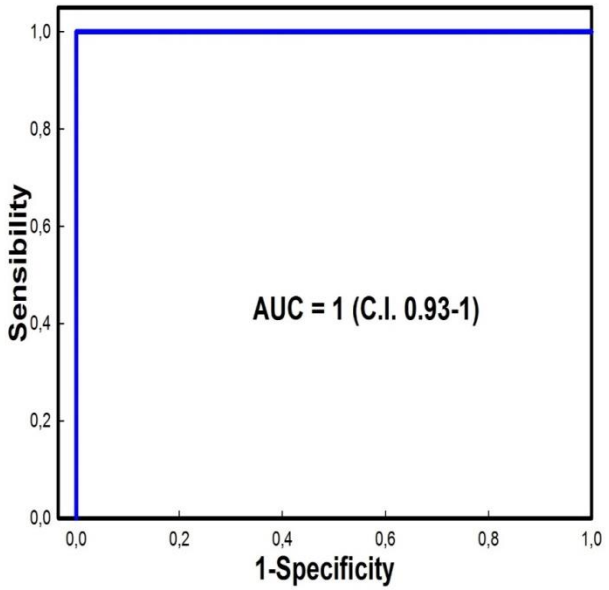

SUPERVISED APPPROACH (PC-LDA)
PCA ON THE COMPLETE DATASET
LDA AND ESTIMATION OF D_{LDA}
EVALUATION OF THE PERFORMACES OF CLASSIFICATORS
CORRELATION WITH THE HYSTOLOGICAL PARAMETERS
VARIABLES SELECTION AND BIOMARKER IDENTIFICATION
STATISTI CAL CONTROL
PCA ON THE CONTROL GROUP
ESTIMATION OF T^2 AND Q STATISTICS

PC LDA



The Linear Discriminant Analysis generates the plane reported in figure. One should notice that only one treated sample is wrongly classified (T9) and the two samples T8 and T2 are very close to the separation plane. The distance of each sample was used to build a two class classifier.





As one can see from the ROC curve, the distance from the plane (Δ_{LDA}) allows to build a very good classifier.

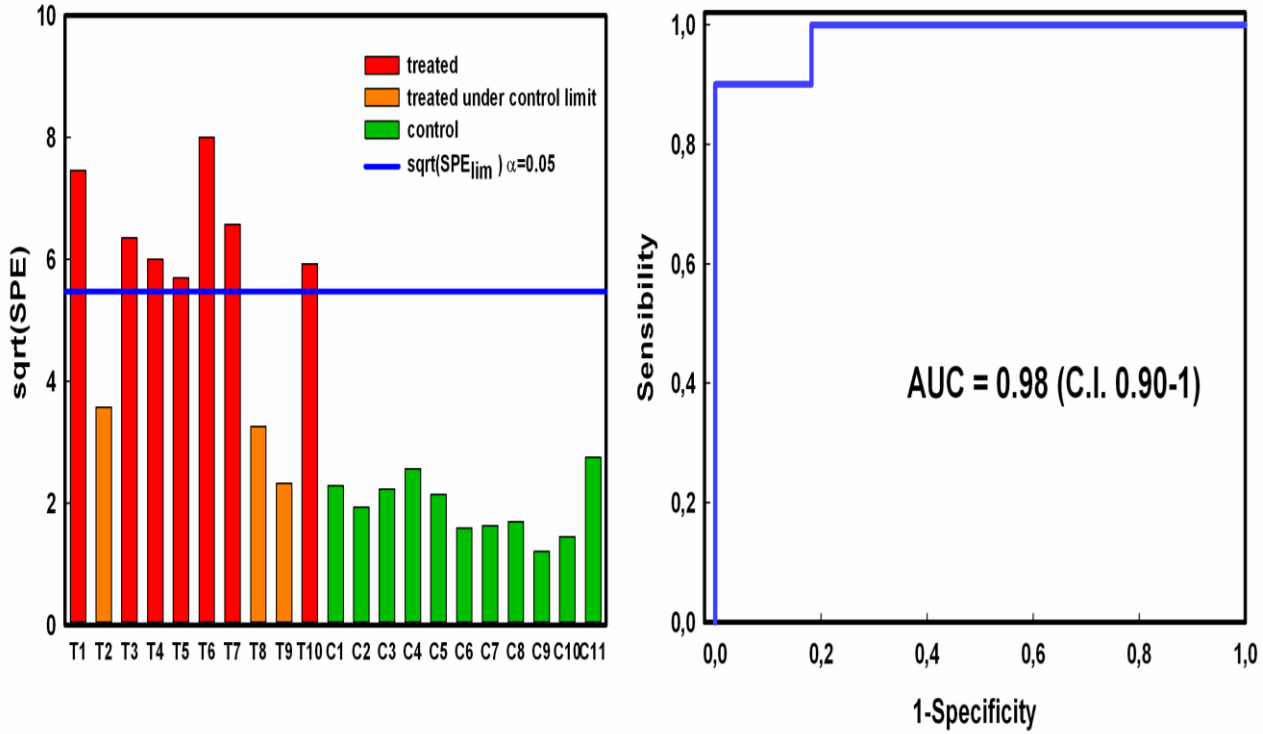
number	metabolites	increase/decrease
1	glycine	+
2	succinate	+
3	glutamate	+
4	glutathione	+
5	phosphoethanolamine	+
6	UDP glucose	+
7	acetate	+
10	choline	-
11	alanine	-
9	carnitine	-
8	glycerol	-
14	betaine	-
12	phosphocholine	-
13	inosine	-
15	AMP	+
16	ADP	-
17	1,7dimethylxanthine	+
18	dimethylurate	-
19	glutamine	-
20	cadaverine	+
21	lactate	+
22	glycocholate	+

Two Class VARIABLES SELECTION

It is important to understand that a supervised approach forces the separation between the members of the two classes. Occurrence of false positive (false negative) may influence the variable selection. **Indeed, when dealing with false positive, variables not related to the treatment may be incorrectly chosen in order to force the separation.**

STATISTICAL CONTROL
Square Prediction Error statistics

Using the SPE statistics leads to a quite good binary classifier classifier.



Looking to the ROC curve one can say that the supervised approach works better, but T2, T8 and T9 are false positives!

Individual
VARIABLES SELECTION

SPE

number	metabolite	T6	T1	T7	T3	T4	T10	T5	T2	T8	T9
1	glycine	+	+	+	+	+	+	+	+	+	+
2	succinate	+	+	+	+	+	+	+	+	+	+
3	glutamate	+	+	+	+	+	+	+	+	=	=
4	glutathione	+	+	+	+	+	+	+	=	=	=
5	phosphoethanolamine	+	+	+	+	+	+	+	=	=	=
6	UDP-glucose	+	+	+	+	+	+	+	=	=	=
7	acetate	+	+	=	+	+	+	=	=	=	=
8	choline	-	-	-	-	-	-	-	-	-	=
9	alanine	-	-	-	-	-	-	-	-	-	=
10	carnitine	-	-	-	-	-	-	-	-	=	=
11	glycerol	-	-	-	-	-	-	-	=	=	=
12	betaine	-	-	-	-	=	-	-	=	=	=
13	phosphocholine	-	=	-	-	-	-	=	=	=	=
14	inosine	=	-	-	-	=	-	-	-	-	=
15	AMP	+	=	=	=	+	+	+	=	=	=
16	ADP	=	=	=	=	-	=	-	=	=	=
17	1,7dimethylxanthyne	=	+	+	+	-	=	+	+	=	=
18	dimethylurate	=	=	-	=	=	=	-	=	-	=
19	glutamine	=	=	=	+	=	=	=	-	-	=
20	cadaverine	=	+	=	=	=	=	=	=	=	=
21	lactate	=	+	=	=	=	=	=	=	=	=
22	glycocholate	=	+	+	+	+	=	=	=	=	+
23	sarcosine	=	-	-	=	=	=	=	=	=	=
24	aspartate	=	-	=	=	=	=	=	-	=	=
25	tyrosine	=	-	=	=	=	=	=	=	=	=
26	pyridoxine	=	=	-	=	=	=	=	=	=	=
27	carnosine	=	=	=	=	+	=	=	=	=	=
28	uridine	+	=	=	=	+	=	+	=	=	=
29	dimethylamine	=	+	=	=	=	=	=	=	=	=

A different set of important variables for each sample. The first 22 metabolites reported on the table were identified also with the class approach, however it is easy to understand that not all these metabolites are important for all the samples in the treated group.

SWOT Analysis

Strenghts, weakness, opportunities, threats of metabolomics

Strenghts

- Robust platform
- Minimally invasive
- Holistic approach
- Low cost per samples
- Final product evaluation

Weakness

- Multiple platform
- Sensitivity
- Complex analysis
- High starting cost

Opportunities

- -omics integration
- Central lab approach
- Sharing data
- Multidisciplinary approach

Threat

- Disadvantage of central lab
- Non-hypothesis driven studies
- Different clinical chemistry approach
- Lack of trained scientists

Conclusions

Table 1. Potential applications associated with the definition of the individual metabotype in clinical practice.

Healthy subjects	Diseased patients	Biomarkers discovery and drug development
• Assessing the individual risk of acute and chronic diseases	• Defining the pathogenesis and the molecular mechanisms of the disease	• Searching and testing candidate biomarkers for the disease diagnosis, prognosis, and follow-up
• Defining healthy status, wellness and preserving good health	• Assessing the response to the therapeutic treatment	• Discovering novel drug targets based on the metabolic cause of the disease
• Defining and maintaining healthy aging	• Tailoring drug treatment	• Elucidating mechanisms of action of new drugs
• Modulating lifestyle on the basis of individual metabolic data	• Assessing the risk of patient adverse outcomes	• Identification of gut microbiota co-metabolites for developing industrial microbial strains
• Applying foodomics and nutrimetabolomics	• Patients' stratification in clinical trials based on drug response	
• Defining physical activity protocols and agonistic performances	• Investigating the impact of gut microbiota on therapy and on drugs pharmacokinetics and pharmacodynamics (Pharmacomicrobiomics)	
• Assessing the individual susceptibility to xenobiotics and environmental toxicants	• Optimizing therapeutic treatment based on medical foods and dietary supplements	
• Assessing the effects on metabolic changes due to alterations in the gut ecosystem	• Tracking drug patient compliance or adherence to the therapeutic protocol	
	• Tracking dietary patient compliance	

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REVIEW

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Slotting metabolomics into routine precision medicine

Michele Mussap [a], Antonio Noto [b], Cristina Piras [c,a], Luigi Atzori [c] and Vassilios Fanos [a]

The metabolomic approach:

1. To identify significantly altered metabolic pathways in diseases
2. To classify pathological conditions
3. Metabolic changes can be used to predict the prognosis
4. To identify specific alterations in the metabolic profile of different pathological conditions and correlate them with the microbiome
5. After treatment with different drug, we can identify metabolic changes between responders and non –responder at T0 and later
6. Clinical response to the drug does not necessarily mean similar metabolomic profile to the control
7. Metabolic changes suggest possible treatment
8. All together these data may lead to the development of new strategies for the early disease prediction and promote the development of novel targeted therapies

- Metabolomics represent a paradigm shift in metabolic research and clinical chemistry, away from approaches that focus on a limited number of reactions or single pathways, to approaches that attempt to capture the complexity of metabolic networks.

- It is reasonable to expect that the metabolomics approach, together with functional genetics and proteomics, will have substantial impact on disease classification and prevention, developing therapeutics and biotechnology drugs in a more personalised manner.

- In addition to reducing times and costs of research and experimentation with new drugs, metabolomics may predict new indications for drugs already in production based on the individual metabolic profile.

- Finally, metabolomics is hypothesis-generating rather than hypothesis-based. Therefore, one has to be really open-minded about the results obtained.

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