

Metabolomics

Biomedical Engineering „Laboratory Techniques“

22.01.2018

Sascha Dammeier, Core Facility for Biomedical Analytics, UKT, Tübingen

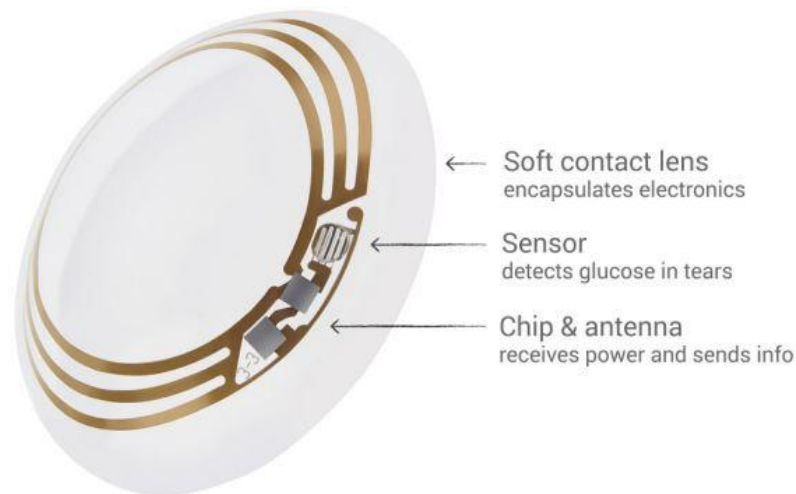
“I have many patients that are managing diabetes, and they described it as having a part-time job. It’s so arduous to monitor,” says Thomas Quinn, who is head of the American Optometric Association’s contact lens and cornea section. “To have a way that patients can do that more easily and get some of their life back is really exciting.”

Google reveals the smart contact lens that can constantly monitor the tears of diabetes sufferers to check their glucose levels

- Lens can monitor the glucose levels of diabetics
- Analyses the glucose level of their tears
- Tiny LED light warn the wearer if levels are low
- Project developed in secretive Google X lab

By MARK PRIGG

PUBLISHED: 00:35 GMT, 17 January 2014 | UPDATED: 13:31 GMT, 17 January 2014



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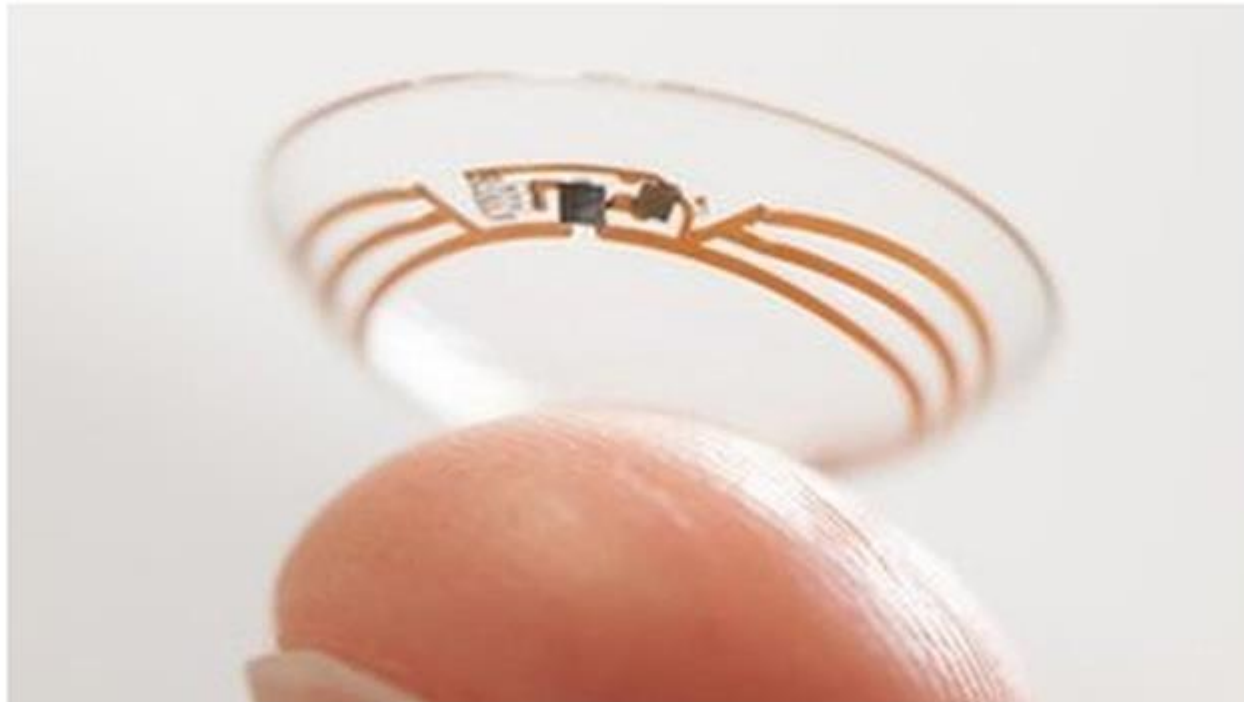
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15 July 2014 Last updated at 18:54 GMT



Google's diabetes 'smart' lens licensed to Novartis



Key Educational Objectives

The students should learn...

- *To explain the importance of metabolites in biomedical research and diagnostics,*
- *To define metabolomics,*
- *To describe the techniques that are required to perform metabolomics, as well as pros and cons,*
- *To define promising clinical applications of metabolomics,*
- *To approach the technical obstacles that must be overcome,*
- *To develop and execute strategies for the successful application of metabolomics in biomedicine.*

Outline

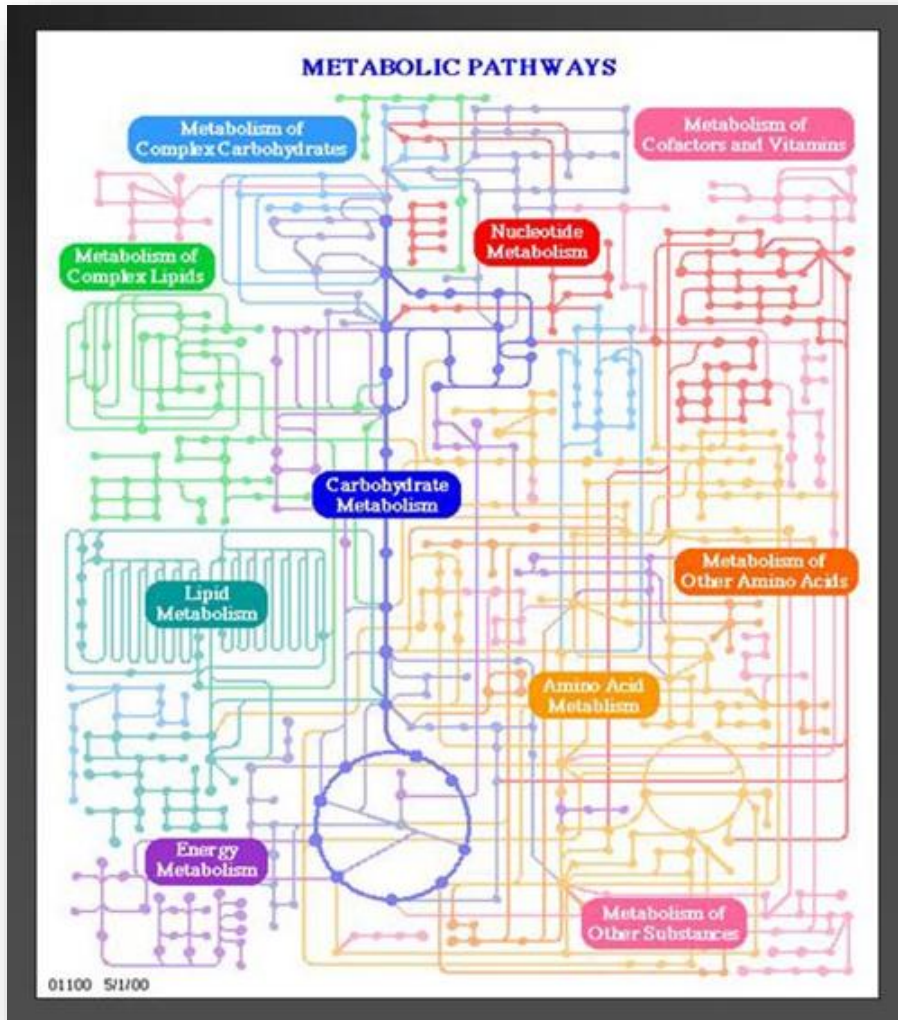
- Definition
- Why Metabolomics?
- Techniques
- Applications
- Examples
- Outlook



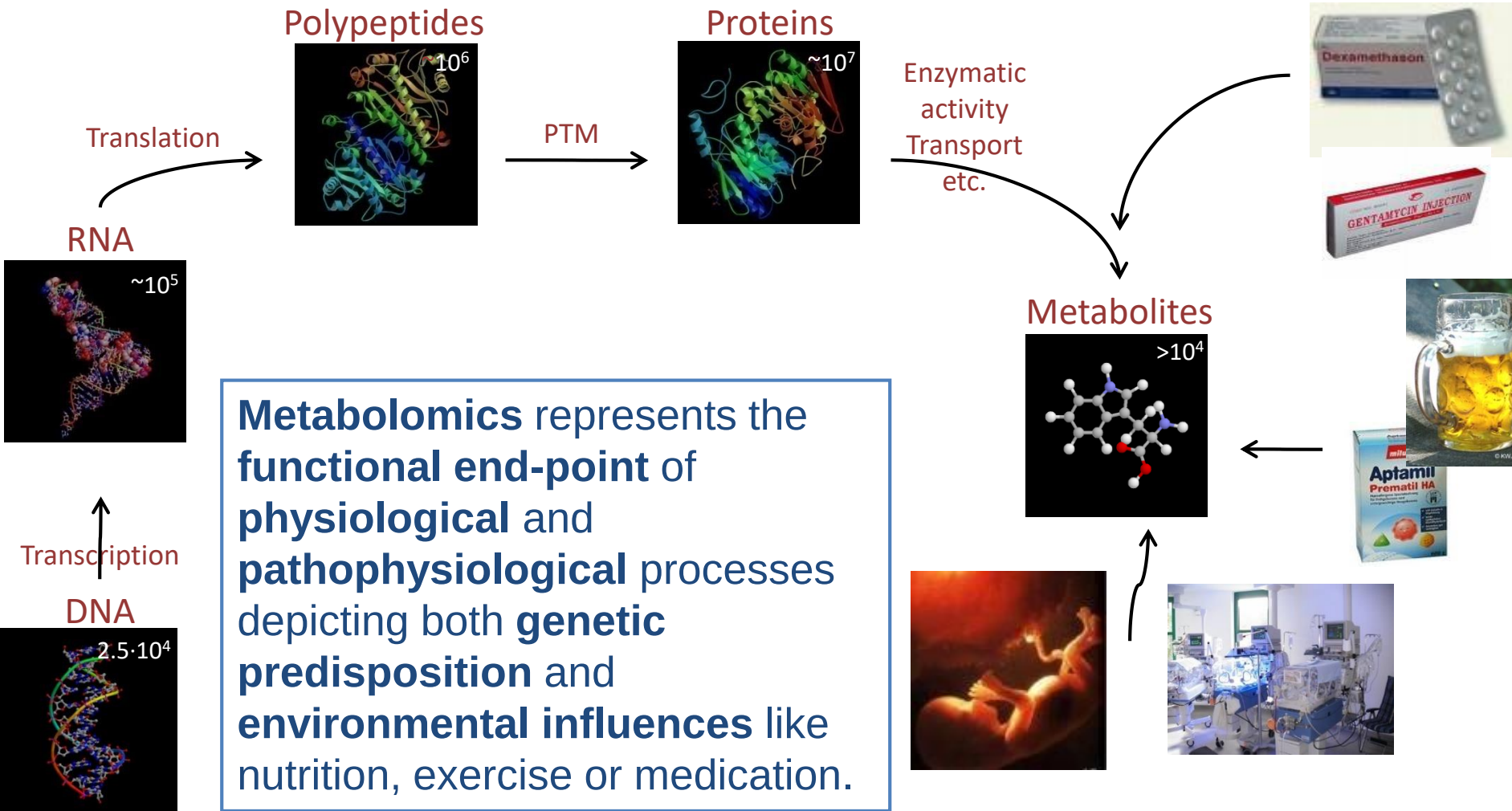
www.ufz.de

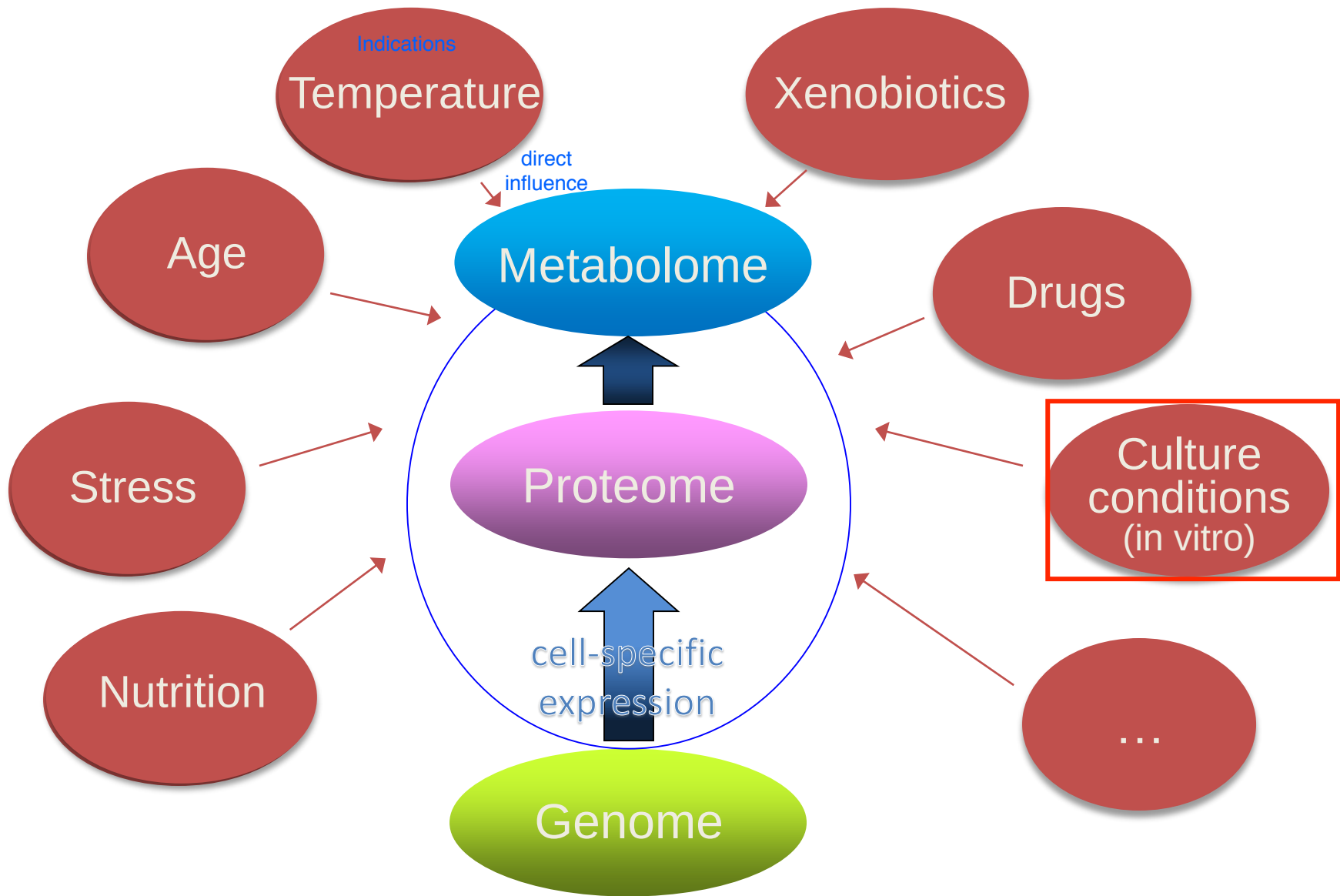
WHAT IS METABOLOMICS?

Definition



Metabolomics is the systematic identification and quantification of all small molecules in a given cellular compartment, cell, tissue or body fluid.





WHY METABOLOMICS?

Metabolites and Human Disease

Lifetime Risk

(12 most common diseases in North America)

same in Europe but
maybe different order

- Common cold/influenza – 100%
- Tooth decay – 92% (sugars) related to small molecules, see brackets!
- Hypertension – 90% (salt, lipids, tobacco)
- Heart disease/Atherosclerosis – 58% (lipids, TMAO, tobacco)
- Cancer – 41% (toxins, mutagens, lipids, tobacco, sugars)
- Obesity – 38% (sugars, lipids)
- Diabetes – 37% (sugars, lipids, BCAAs, amino adipic acid)
- Acid reflux disease – 17% (spices, lipids, sugars)
- Stroke – 15% (lipids, sugars, tobacco)
- Migraine – 10% (sugars, polyphenols, dyes)
- Allergies/Asthma – 9% (various chemicals)
- Alzheimer's disease – 6%

Why Small Molecules Matter...

- > 99% of **food flavours** and **aromas** come from small molecules glutamate
- > 90% of **common clinical tests** measure small molecules
- 89% of all **drugs** are small molecules
- 83% of the **most common diseases** are due to the effects of small molecules
- How many % of all **deaths** in North America and Europe are due to the effects of small molecules?
- > 55% of **drugs** are derived via **natural compounds**

What kind of data do we need to impact therapeutic intervention?

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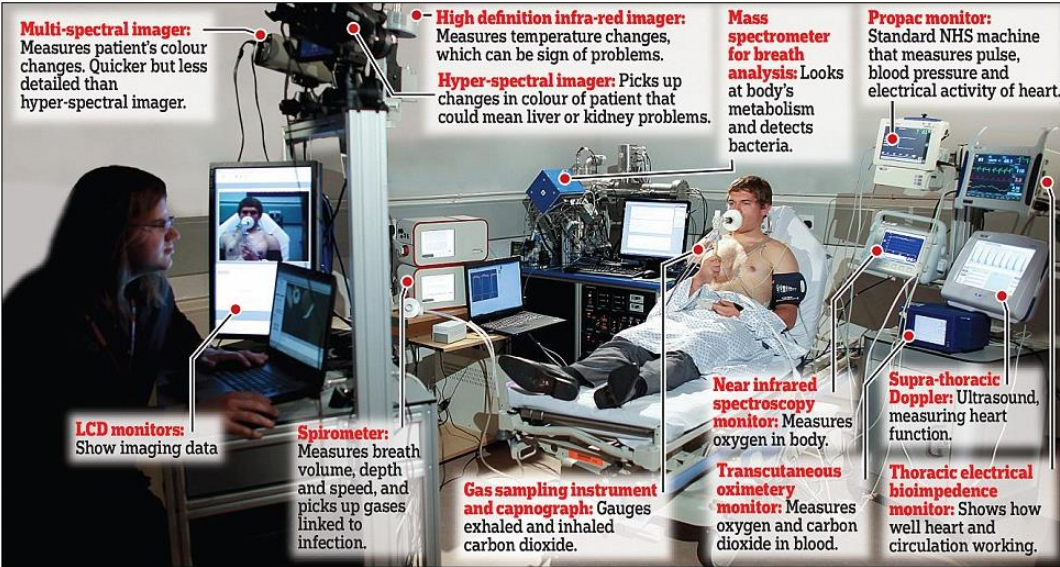
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The space-age sickbay that diagnoses disease without need for tests from sight, smell and 'feel' of disease

By FIONA MACRAE
UPDATED: 15:33 GMT, 1 September 2011

Comments (16) | Share | Tweet | Like

A sickbay that uses space-age technology to diagnose diseases ranging from stomach bugs to cancer has been unveiled at a British hospital. The first of its kind, it contains a bewildering array of equipment, including probes designed for missions to Mars. The gadgets in the million-pound unit can detect illness without the need for painful and invasive tests. They combine information about the sight, smell and 'feel' of a disease to produce a diagnosis.



Multi-spectral imager: Measures patient's colour changes. Quicker but less detailed than hyper-spectral imager.

High definition infra-red imager: Measures temperature changes, which can be sign of problems.

Hyper-spectral imager: Picks up changes in colour of patient that could mean liver or kidney problems.

Mass spectrometer for breath analysis: Looks at body's metabolism and detects bacteria.

Propac monitor: Standard NHS machine that measures pulse, blood pressure and electrical activity of heart.

Near infrared spectroscopy monitor: Measures oxygen in body.

Supra-thoracic Doppler: Ultrasound, measuring heart function.

Transcutaneous oximetry monitor: Measures oxygen and carbon dioxide in blood.

Thoracic electrical bioimpedance monitor: Shows how well heart and circulation working.

Spirometer: Measures breath volume, depth and speed, and picks up gases linked to infection.

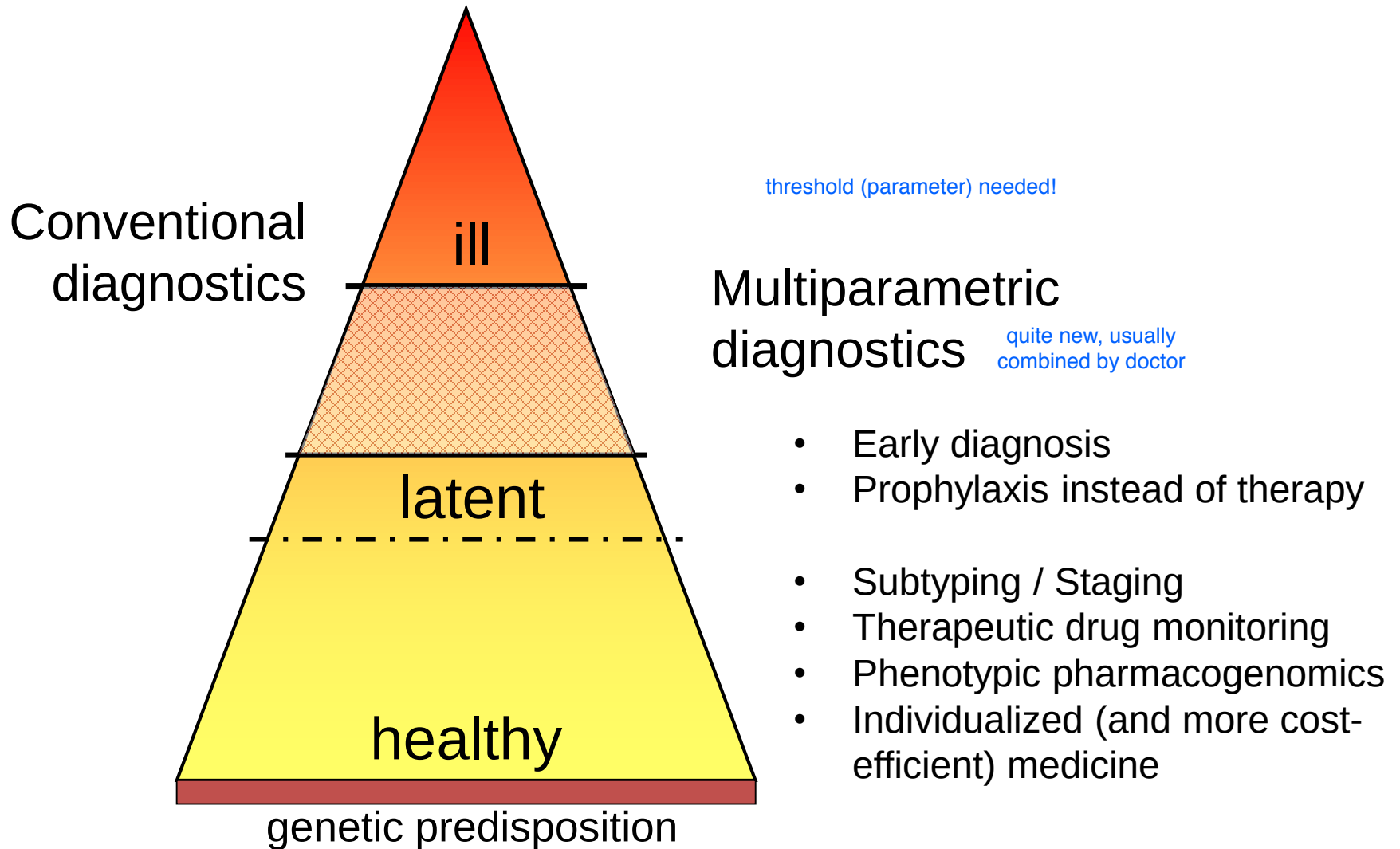
Gas sampling instrument and capnograph: Gauges exhaled and inhaled carbon dioxide.

LCD monitors: Show imaging data

High-tech hospital: It looks like something out of a sci-fi film, but this is the latest sick bay to be unveiled in Britain

The unit is described as the first step towards the tricorder scanners that Star Trek's Dr McCoy waved in front of patients' bodies to diagnose and treat illness in the crew of the Starship Enterprise.

Goals in modern clinical diagnostics



Courtesy of K. Weinberger

Paradigm shift in clinical diagnostics

High-resolution biochemical characterization of body fluids by targeted metabolomics will facilitate a transition...

- from **damage**-oriented diagnostics to **function**-oriented diagnostics
- from **risk factor** assessment to actual (patho-)physiological **phenotyping**
- from **generic** diagnostics of complex diseases to a detailed **sub-typing** and **staging** which will direct personalized therapeutic regimens

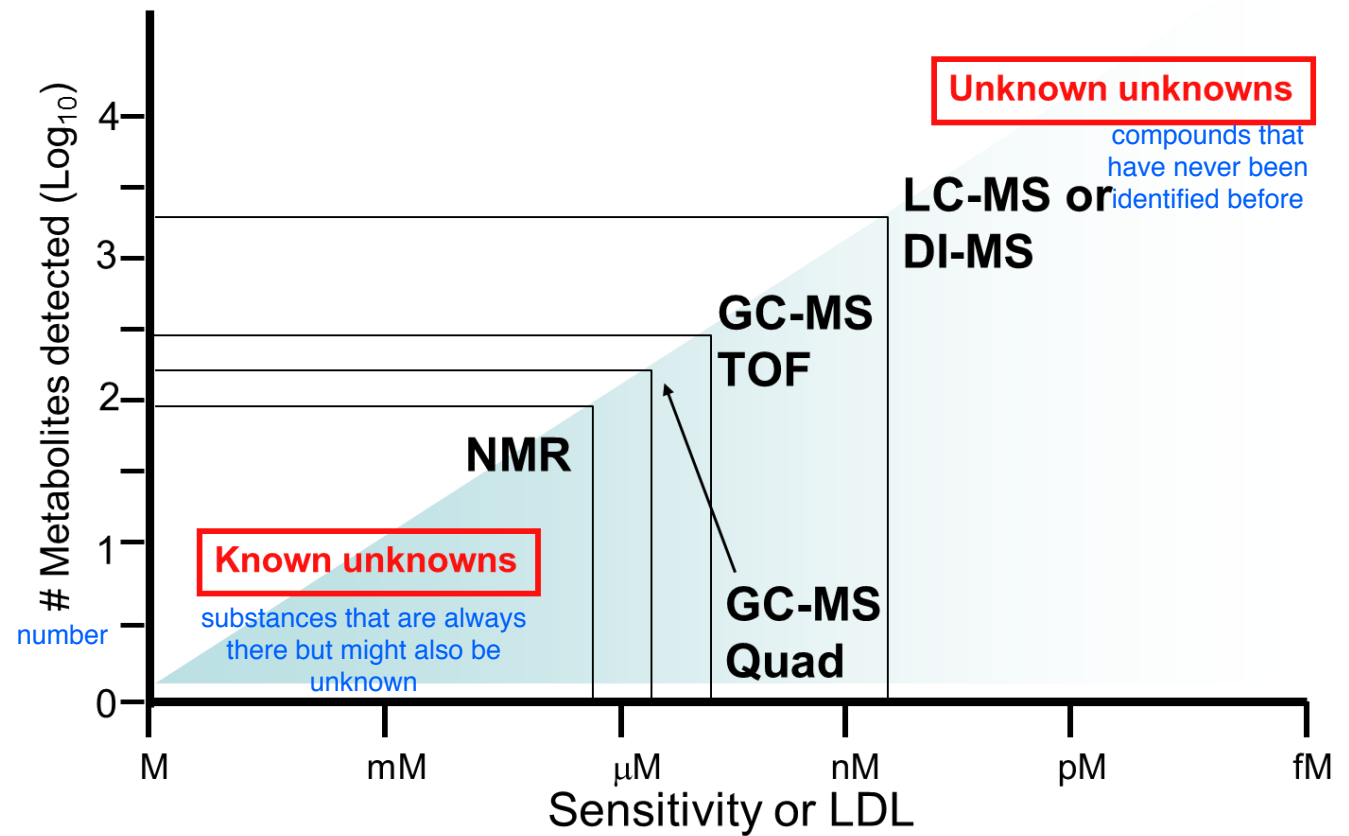
→ Find and identify medically useful **biomarkers!**

careful with this term! only few biomarkers
went into clinical testing, if you do not
search correctly for a biomarker you won't
find it

Type of Biomarkers

- **Diagnostic** fever: body temperature, as a biomarker for inflammation
glucose level: diabetes
 - Do you have a given disease/condition
- **Prognostic** look a praca1 (?) gen for
breast cancer, is there a
mutation etc?
 - How well will you do with this disease/condition
- **Predictive** how aggressive is the cancer?
Caras(?) for colon cancer
 - Odds of getting a given disease/condition
- **Marker of Response or Toxicity** companion diagnostics, are the all the
patients responsive for the drug? eg.
HER2, Herceptin only approved with
diagnostic test with HER2
 - Response to drug/food/toxin intake
- **Marker of Exposure**
 - Indication of drug/toxin/food consumption
also for doping (EPO)

R is limited to
sensitivity -> more



Graph by D. Wishart, University of Alberta, Canada

TECHNIQUES

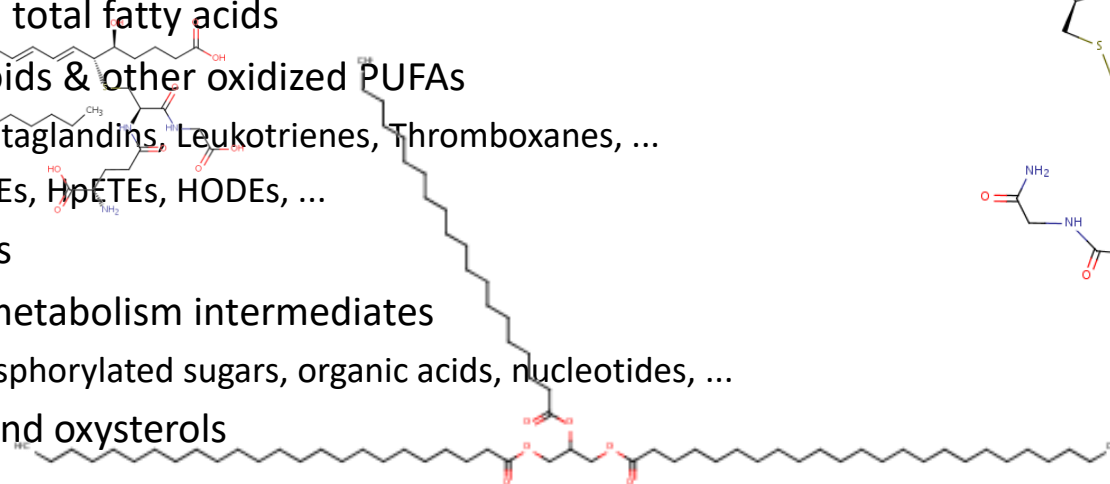
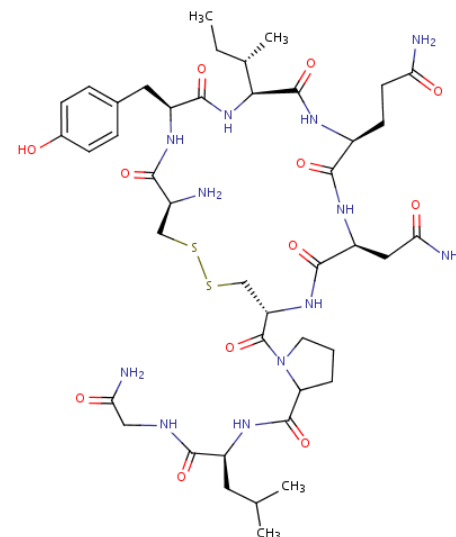
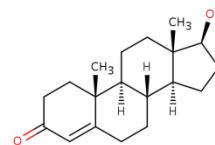
Analytical Challenge

LARGE DIVERSITY!!!!

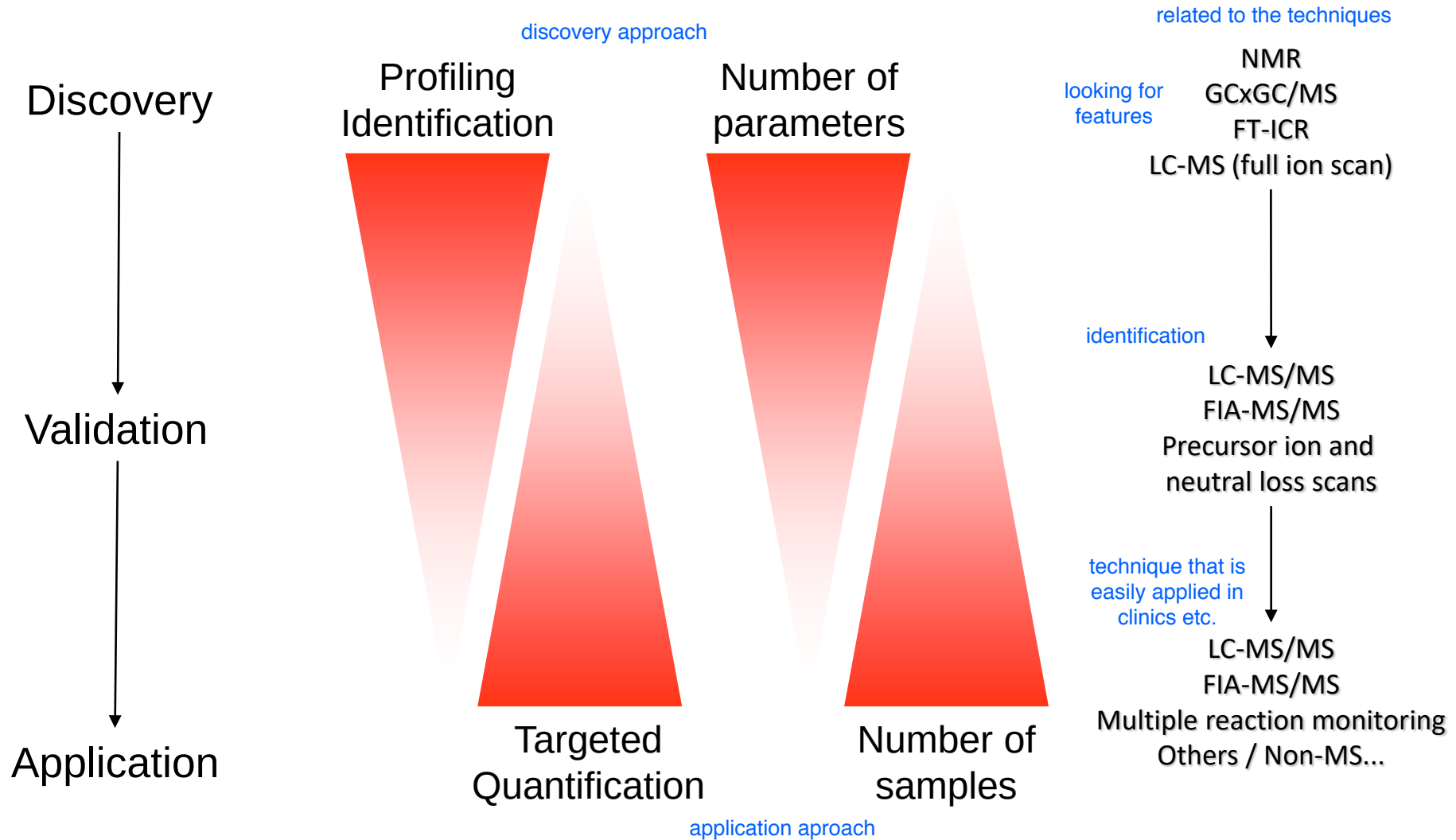
analyse all of them in one measurements, often not
all have to be measured

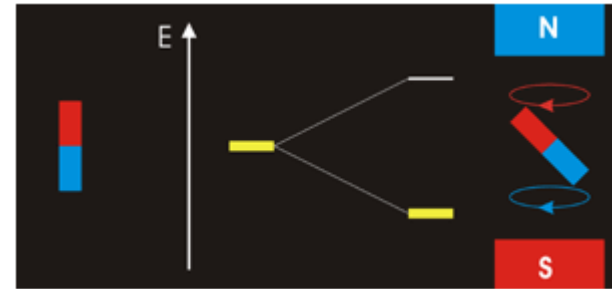
structural and mass differences!
cyclic peptides vs. amino acid

- Primary and secondary amines
 - Proteinogenic and non-proteinogenic amino acids
 - Biogenic amines and polyamines
- FATMO intermediates
 - Acylcarnitines and free carnitine
 - Hydroxy- and dicarboxy-AC
- Reducing mono- and oligosaccharides
- Glycerophospho- and sphingolipids
- Free and total fatty acids
- Eicosanoids & other oxidized PUFAs
 - Prostaglandins, Leukotrienes, Thromboxanes, ...
 - HETEs, HpETEs, HODEs, ...
- Bile acids
- Energy metabolism intermediates
 - Phosphorylated sugars, organic acids, nucleotides, ...
- Sterols and oxysterols
- Vitamins
- ...



Metabolomic Technologies & Biomarkers





Metabolomics Techniques

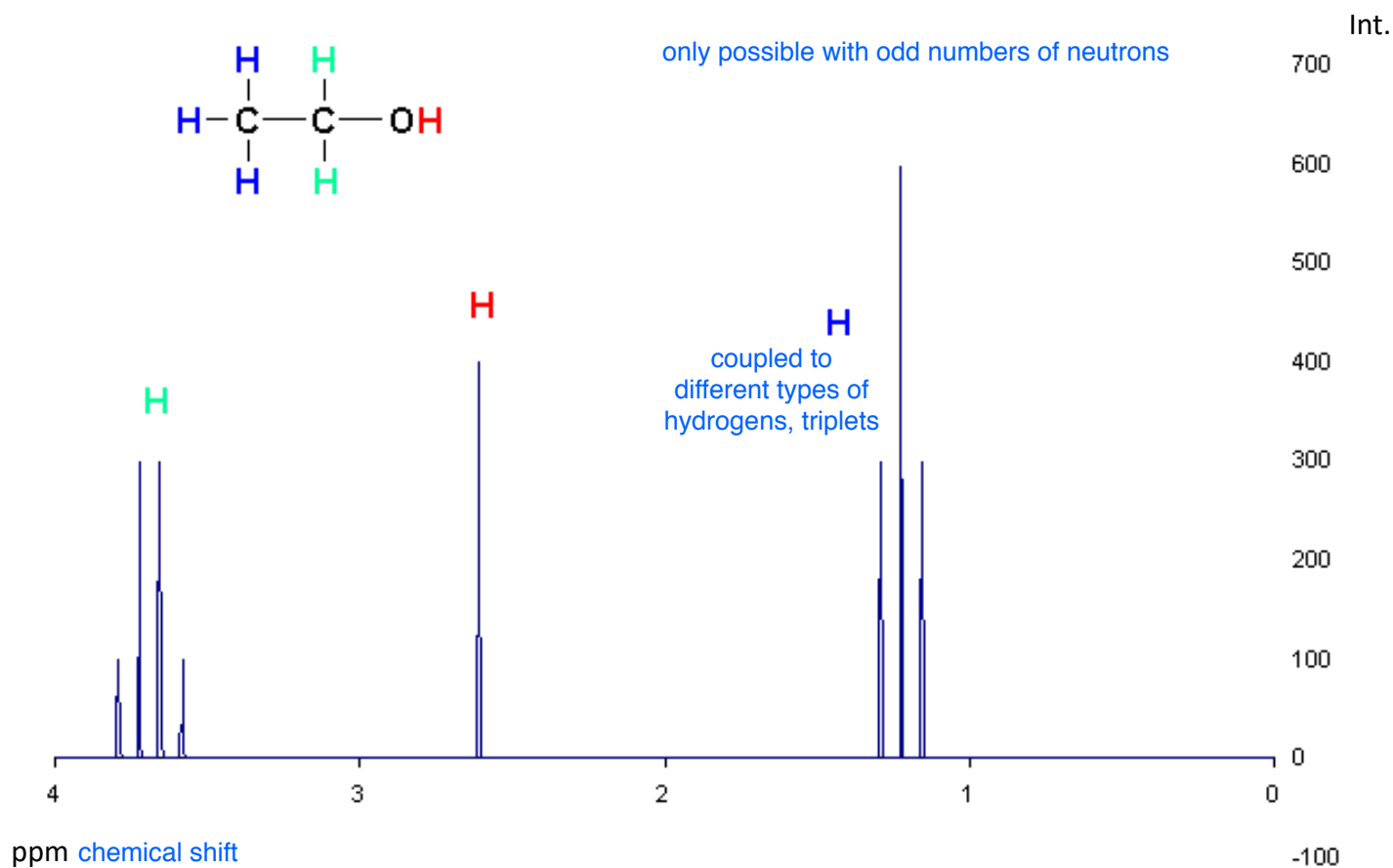
NMR-SPECTROSCOPY

Simple ^1H -NMR Spectrum

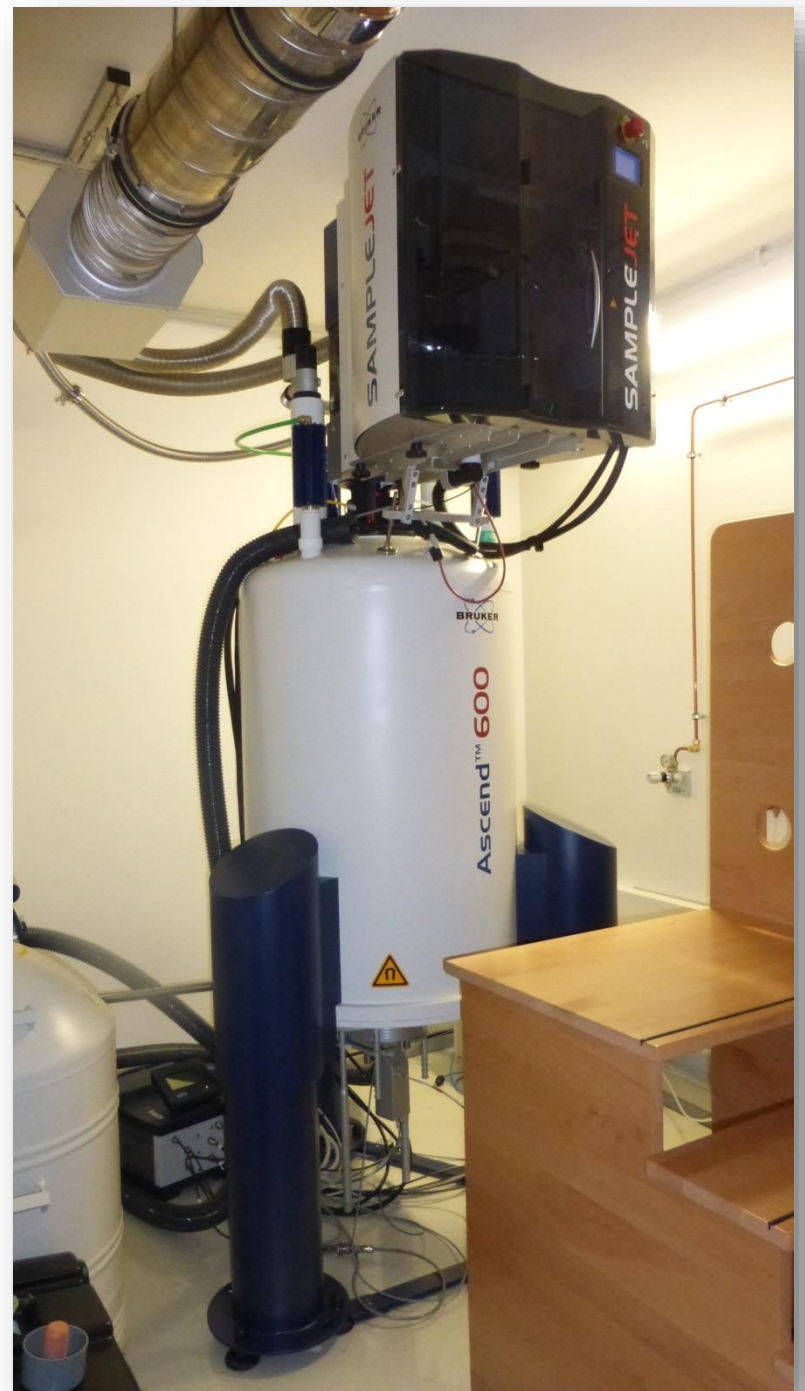
very
characteristic

wikipedia!

Ethanol

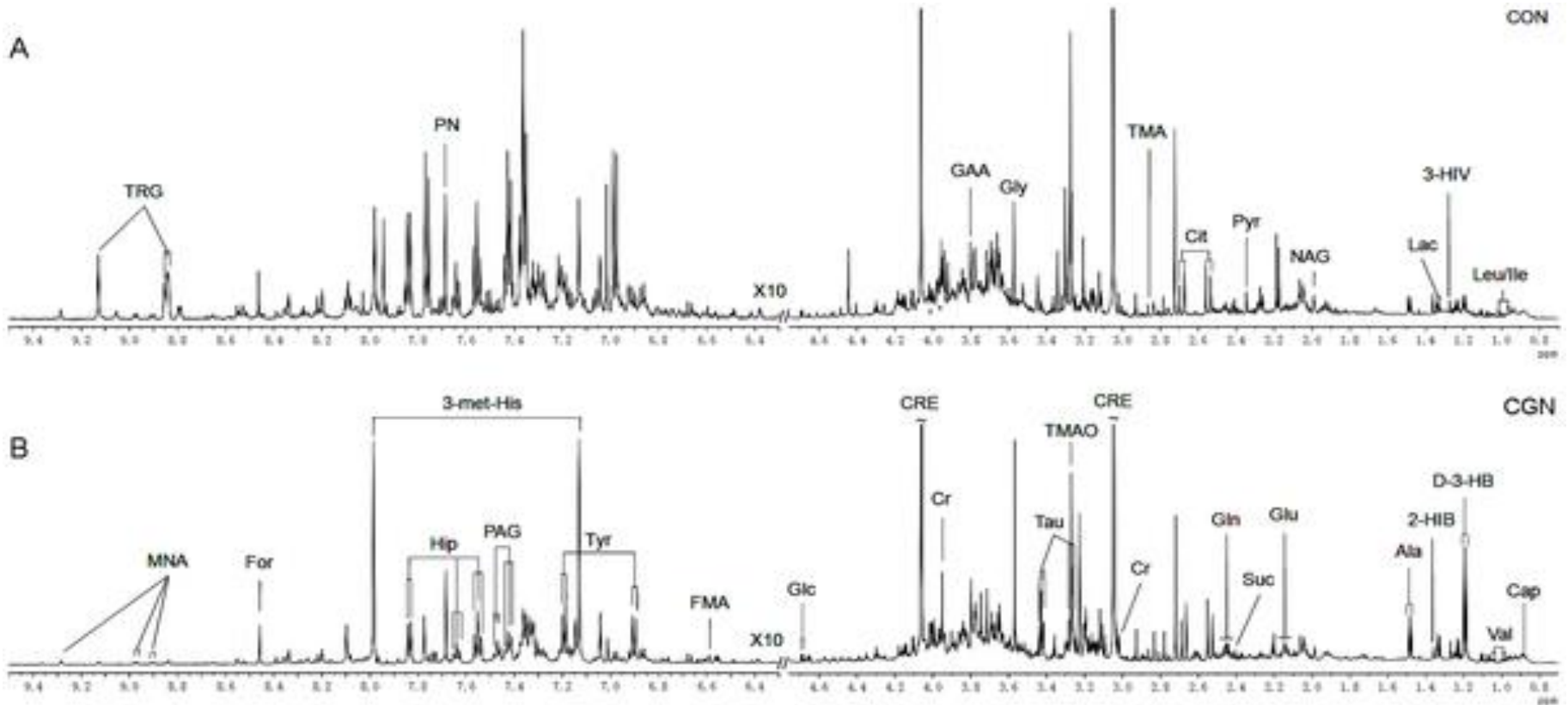


Expensive Instrumentation



Courtesy of AG Pichler, UKT

Representative 600 MHz ^1H NMR spectra of urine from control people and patients with FSGS.

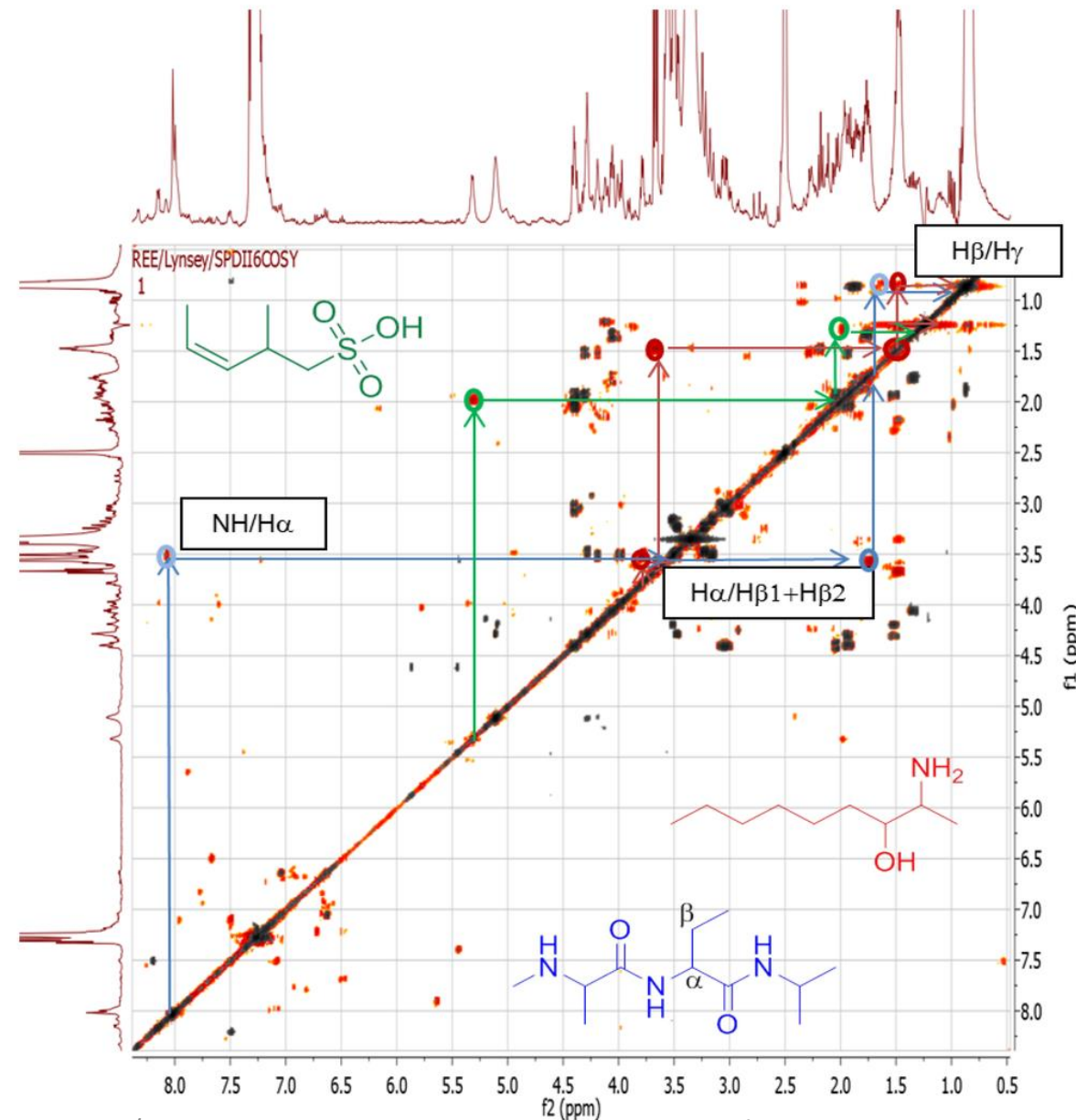


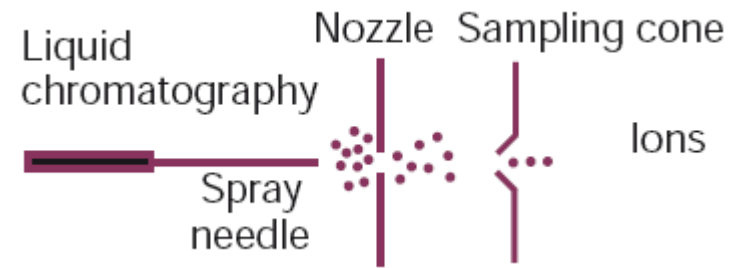
Hao X, Liu X, Wang W, Ren H, et al. (2013) Distinct Metabolic Profile of Primary Focal Segmental Glomerulosclerosis Revealed by NMR-Based Metabolomics. PLoS ONE 8(11): e78531. doi:10.1371/journal.pone.0078531
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0078531>

2D Spectra

no detail!

2D-NMR COSY spectrum of *Bacillus* sp. 4115, overlaid with spectrum from M1 medium. Signals in orange are from the sample and signals in grey are from the medium.





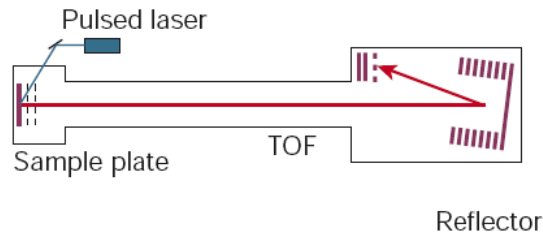
Metabolomics Techniques

MASS SPECTROMETRY

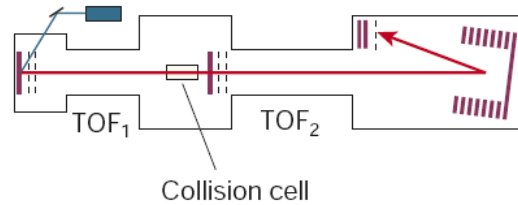
plus GC or LC



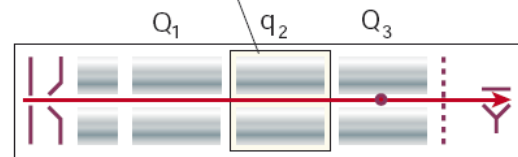
a
Reflector
time-of-flight (TOF)



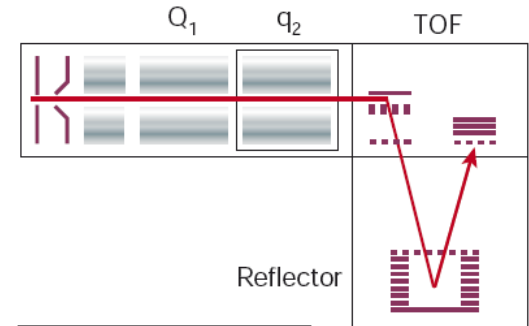
b
Time-of-flight
time-of-flight (TOF-TOF)



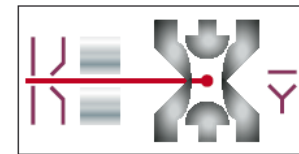
c
Triple quadrupole
or linear ion trap



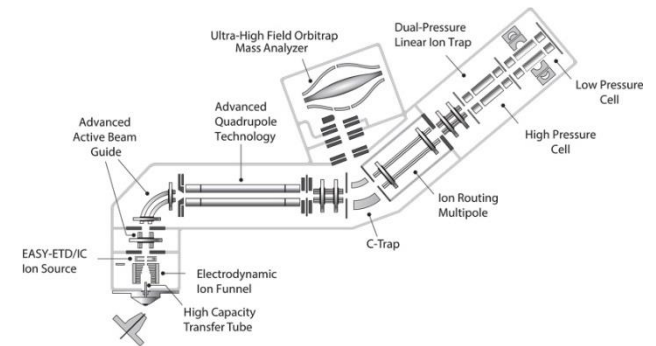
d
Quadrupole
time-of-flight



e
Ion trap

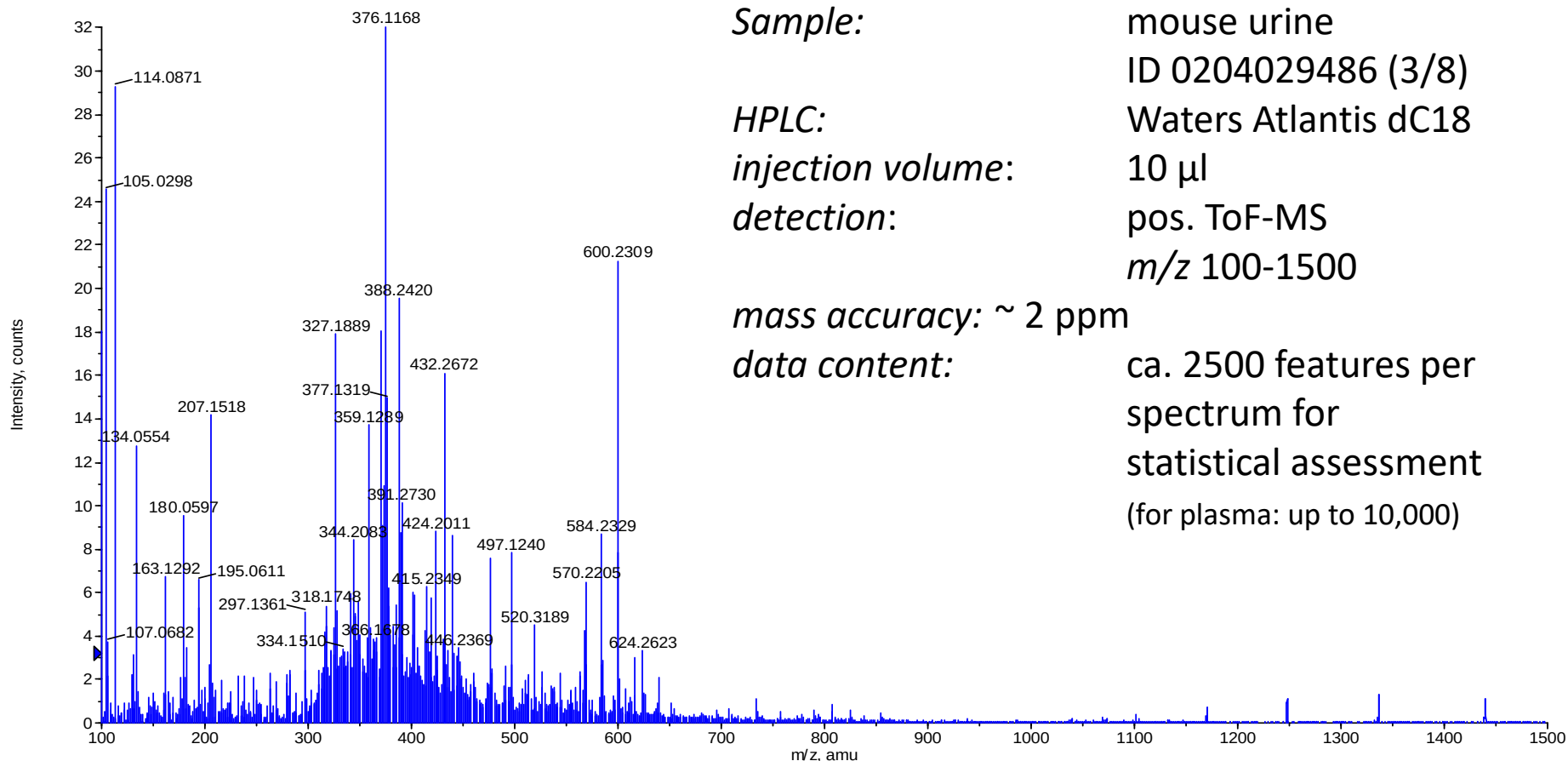


f
Orbitrap



Schemes:
NATURE | VOL 422 | 13 MARCH 2003 | Aebersold
and Mann,
Thermo Fisher Scientific; planetorbitrap.com

HPLC-ESI-ToF-MS of urine samples



Sample:

mouse urine

HPLC:

ID 0204029486 (3/8)

injection volume:

Waters Atlantis dC18

detection:

10 μ l

pos. ToF-MS

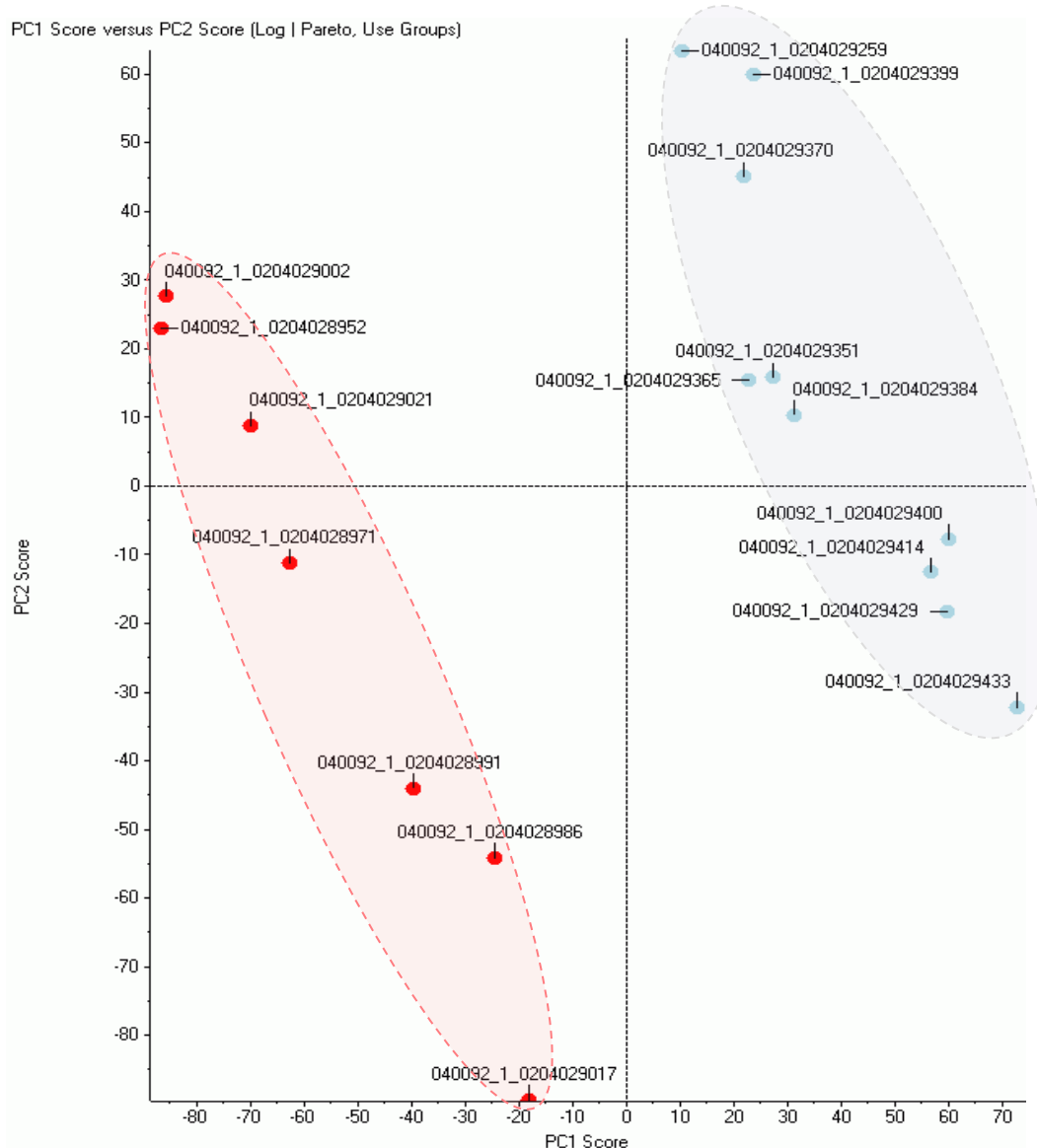
m/z 100-1500

mass accuracy: ~ 2 ppm

data content:

ca. 2500 features per spectrum for statistical assessment (for plasma: up to 10,000)

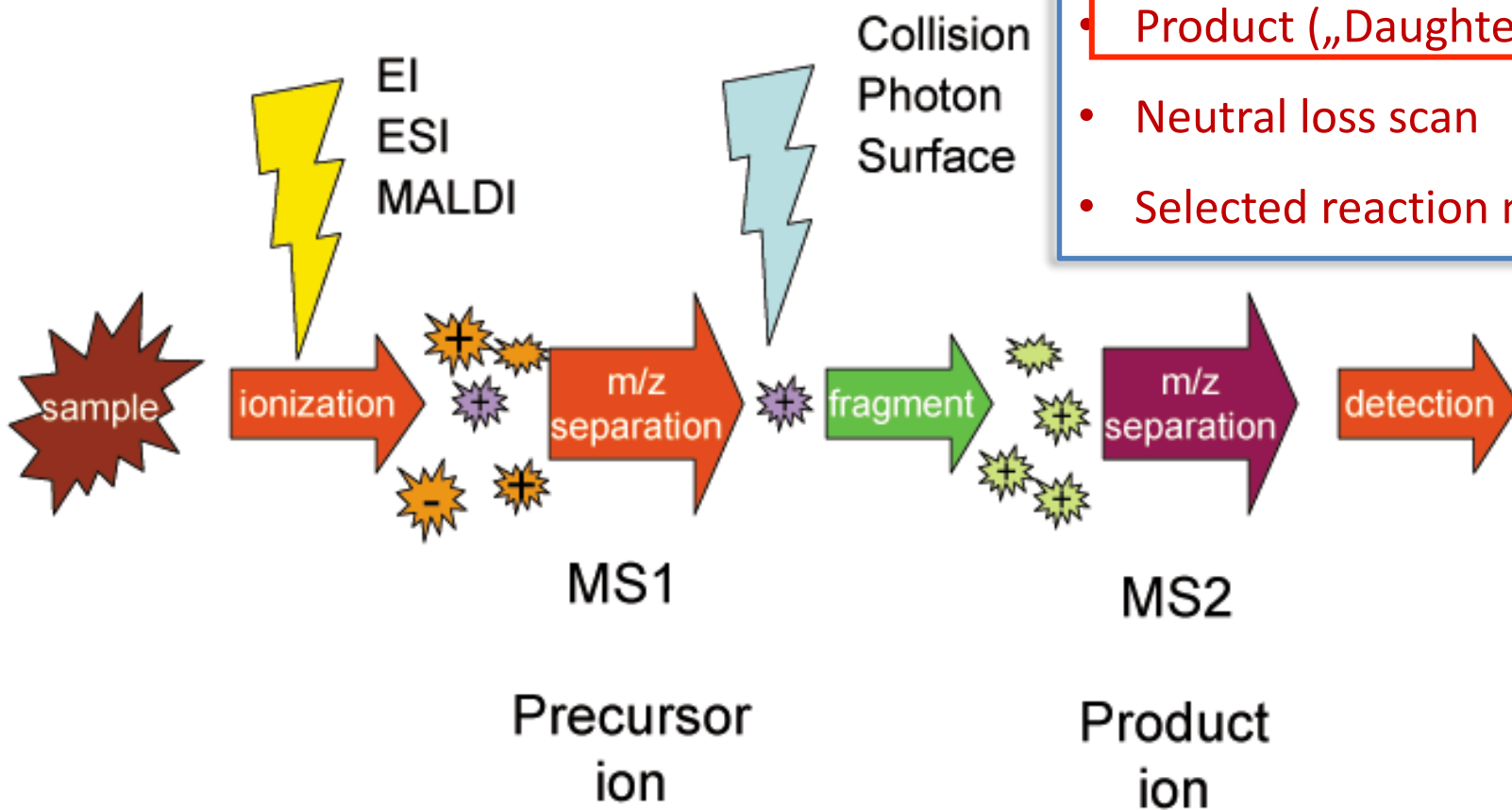
PCA of LC/MS profiling data



- Full separation of **untreated** (red) from **treated** (blue) diabetic mice
- Selection of influential factors from the corresponding loadings plot
- Structural identification?

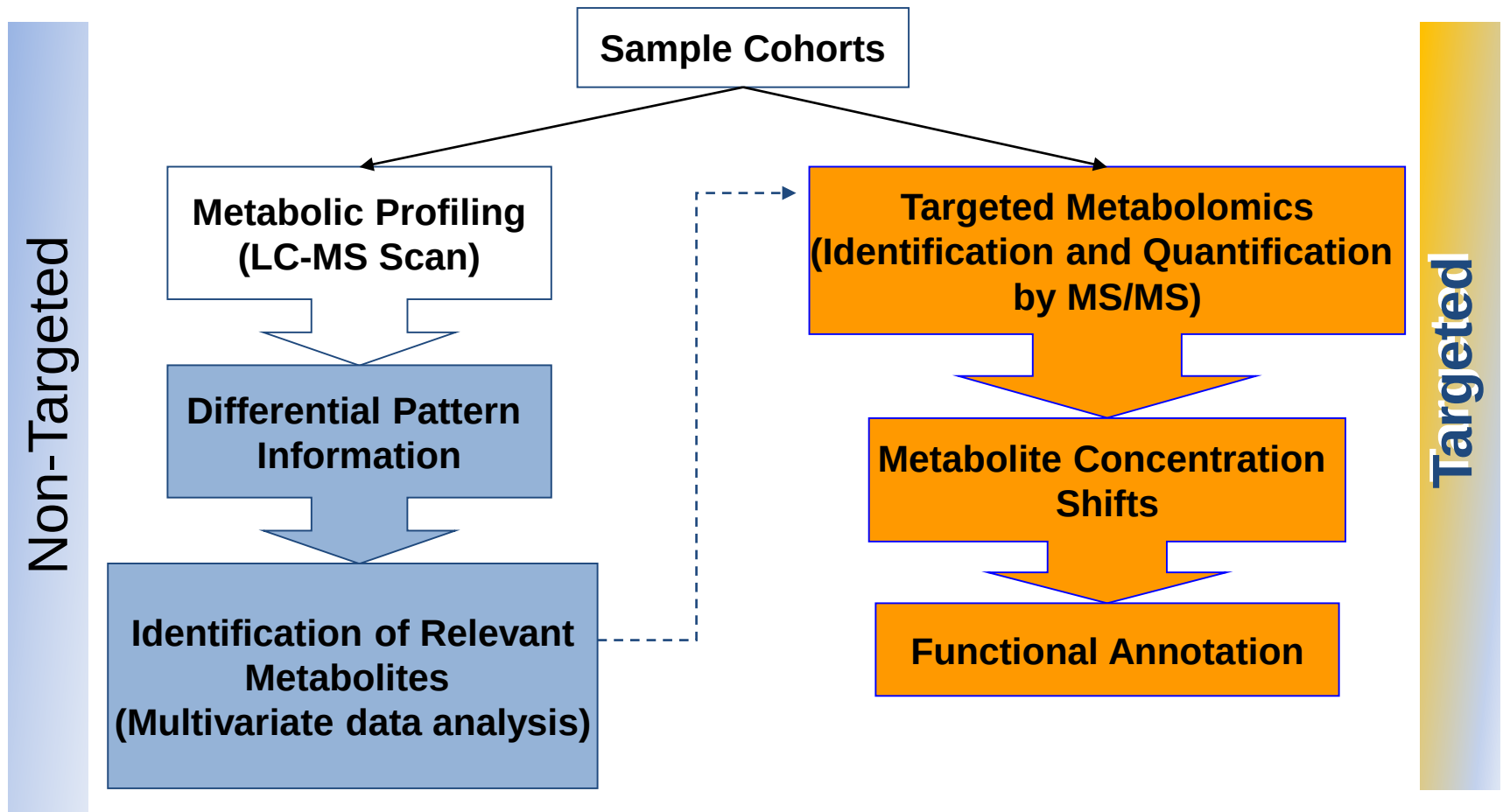
Tandem Mass Spectrometry

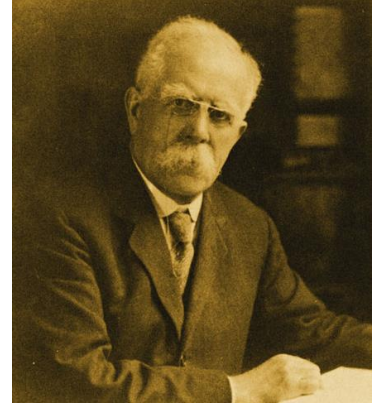
Product scan:
whole fragments that derive from ONE compound!!!
keep MS1 the same, only measure MS2



- Precursor („Parent“) ion scan
- Product („Daughter“) ion scan
- Neutral loss scan
- Selected reaction monitoring

Metabolomics Approaches





Sir Archibald Edward Garrod
1857 – 1936

one disease, one enzyme, not acutal
anymore

APPLICATIONS

Metabolomics

Proof-of-Concept in Neonatology

Newborn screening for inborn metabolic disorders

- replaced expensive monoparametric assays
- simultaneous detection of 40 - 60 metabolites (amino acids, acylcarnitines) [multiparametric diagnostic](#)
- simultaneous diagnosis of 20 - 30 monogenic diseases (AA metabolism, FATMO) with immediate treatment options
- total incidence > 1:2000
- unprecedented sensitivity, specificity, ppv
- millions of newborns screened in Germany
- similar labs worldwide
- Throughput: ~ **140.000 newborns/day**, worldwide [works because there are treatment options!](#)



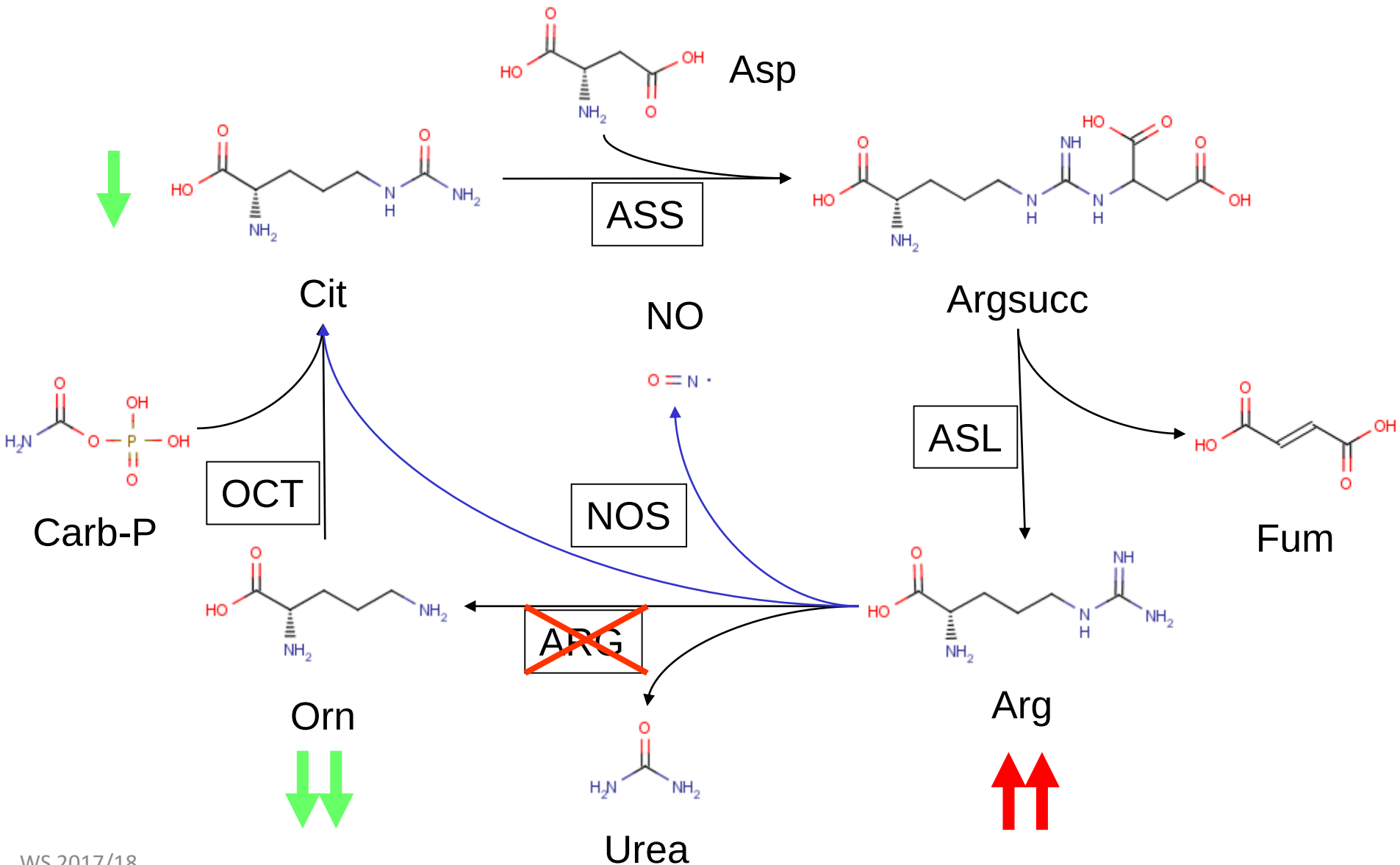
Lessons from newborn screening

- 1) **Quantitative tandem mass spectrometry** (stable isotope dilution) is able to meet the stringent quality criteria for **routine diagnostics**.
- 2) The **concept of multiparametric biomarkers** improving assay sensitivity and particularly specificity is valid.
- 3) MS-based diagnostics can **save costs** despite a wider analytical panel and improved diagnostic quality.

Today, these lessons are also true for therapeutic drug monitoring of immunosuppressants, antidepressants, antiretrovirals, etc.

Pathway mapping of quantitative Mx data

don't learn this!



Metabolomics

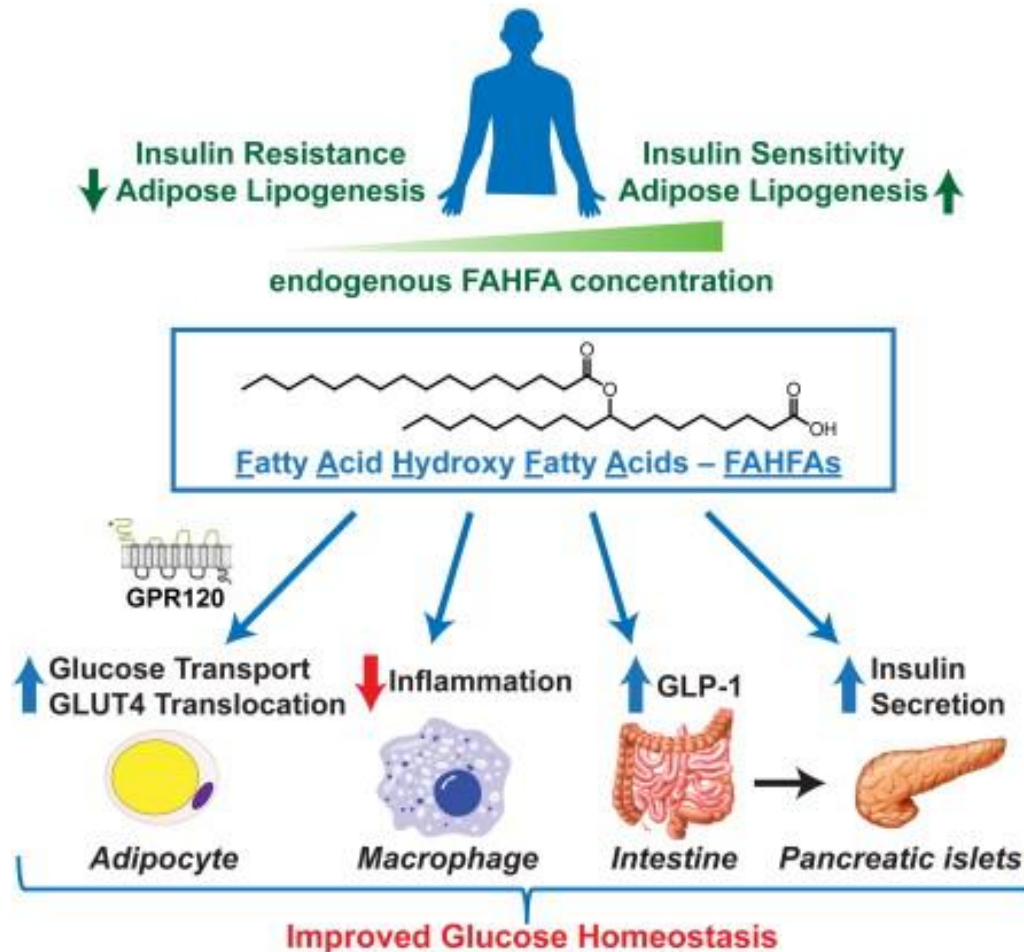
EXAMPLES OF RECENT BIOMEDICAL RESEARCH

Metabolomics Examples

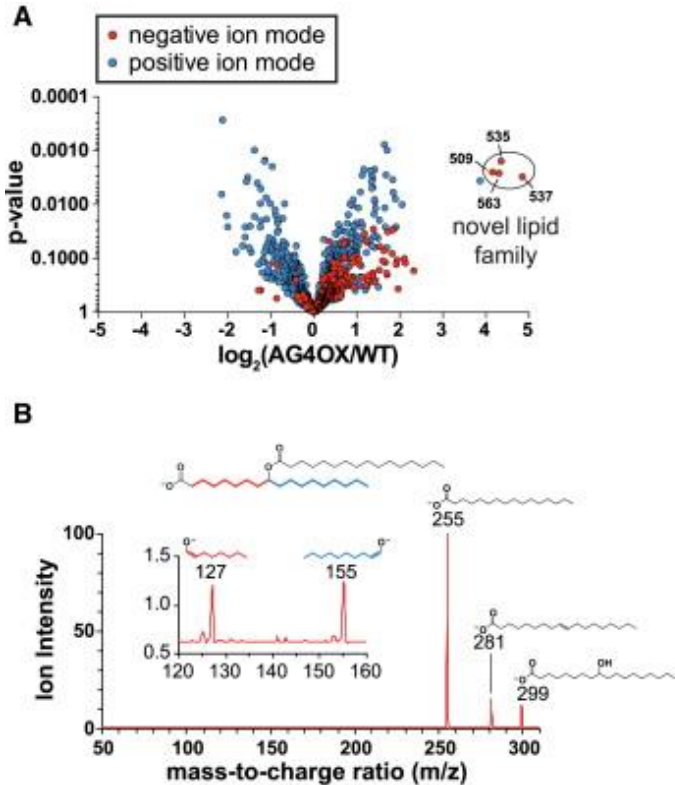
DIABETES

Discovery of a Class of Endogenous Mammalian Lipids with Anti-Diabetic and Anti-inflammatory Effects

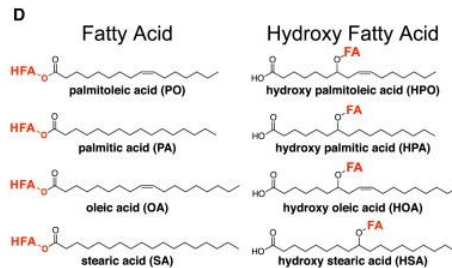
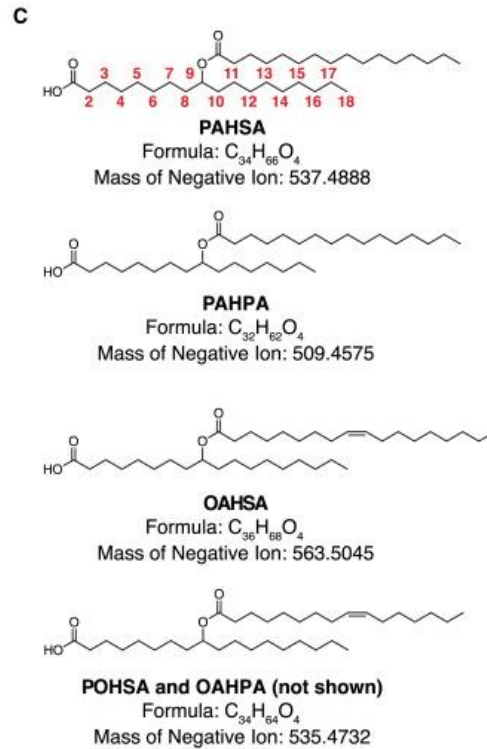
Cell, Volume 159, Issue 2, 2014, 318 - 332



Lipidomics



Structure Elucidation



Targeted Quantification

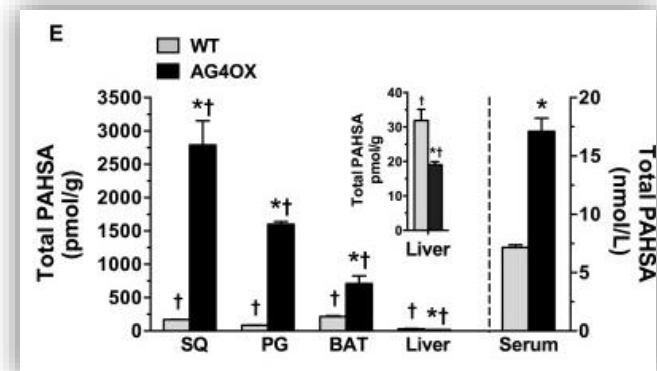


Figure 1 Discovery and Characterization of a Class of Lipids (FAHFAs) (A) Comparative lipidomics of SQ white adipose tissue (WAT) from AG4OX and WT mice reveals the presence of a group of ions at m/z 509 (PAHPA), 535 (POHPA/OAHPA), 563 (OAHPA), and 537 (P...

Metabolomics Examples

NEUROLOGY

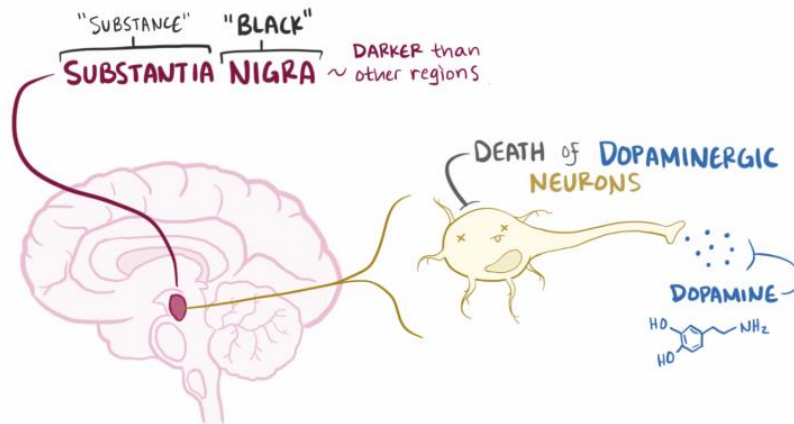
Parkinson's Disease



Illustration of Parkinson's disease by [William Richard Gowers](#), first published in *A Manual of Diseases of the Nervous System* (1886)

CLINICAL FEATURES (CONT.)

- (1) TREMOR
- (2) RIGIDITY
- (3) BRADYKINESIA
or HYPOKINESIA
or AKINESIA
- (4) POSTURAL INSTABILITY
- * NO WEAKNESS
T



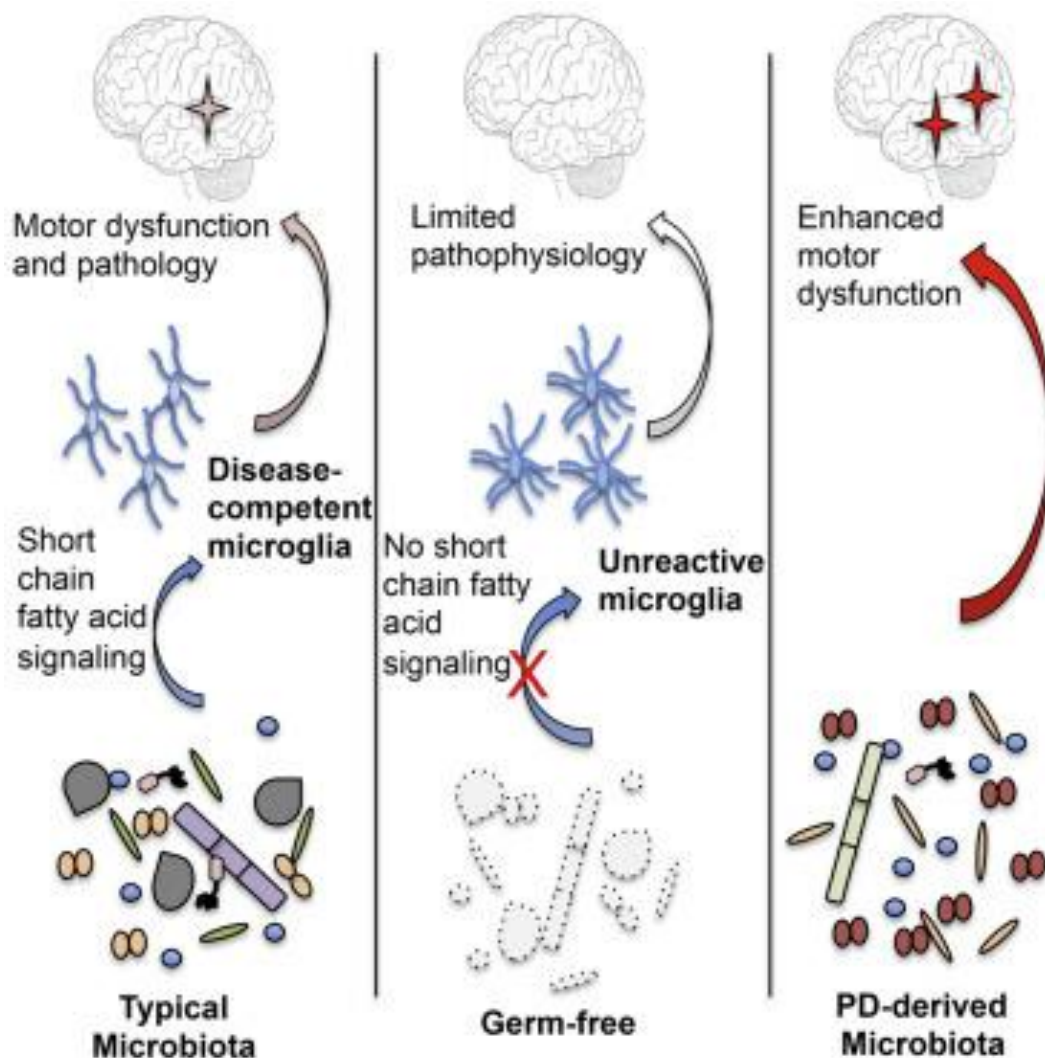
https://upload.wikimedia.org/wikipedia/commons/thumb/e/e5/Parkinsons_disease.webm/290px--Parkinsons_disease.webm.jpg

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Timothy R. Sampson, Justine W. Debelius, Taren Thron, Stefan Janssen, Gauri G. Shastri, Zehra Esra Ilhan, Collin Challis, Catherine E. Schretter, Sandra Rocha, Viviana Gradinaru, Marie-Francoise Chesselet, Ali Keshavarzian, Kathleen M. Shannon, Rosa Krajmalnik-Brown, Pernilla Wittung-Stafshede, Rob Knight, Sarkis K. Mazmanian

Cell, Volume 167, Issue 6, 2016, 1469–1480.e12

Short-chain fatty acids:
Acetate, propionate, butyrate



Metabolomics Examples

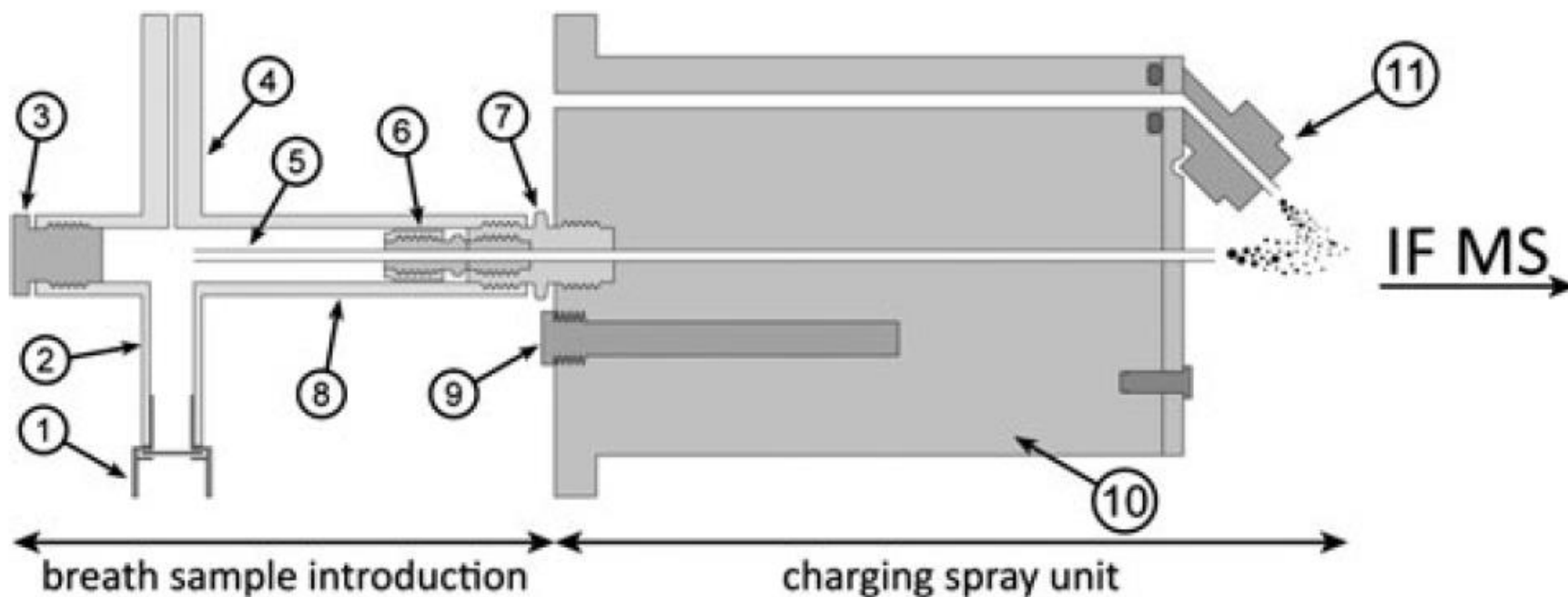
ONCOLOGY



© Xue Li / ETH Zürich

EXHALED BREATH ANALYSIS

SESI-MS



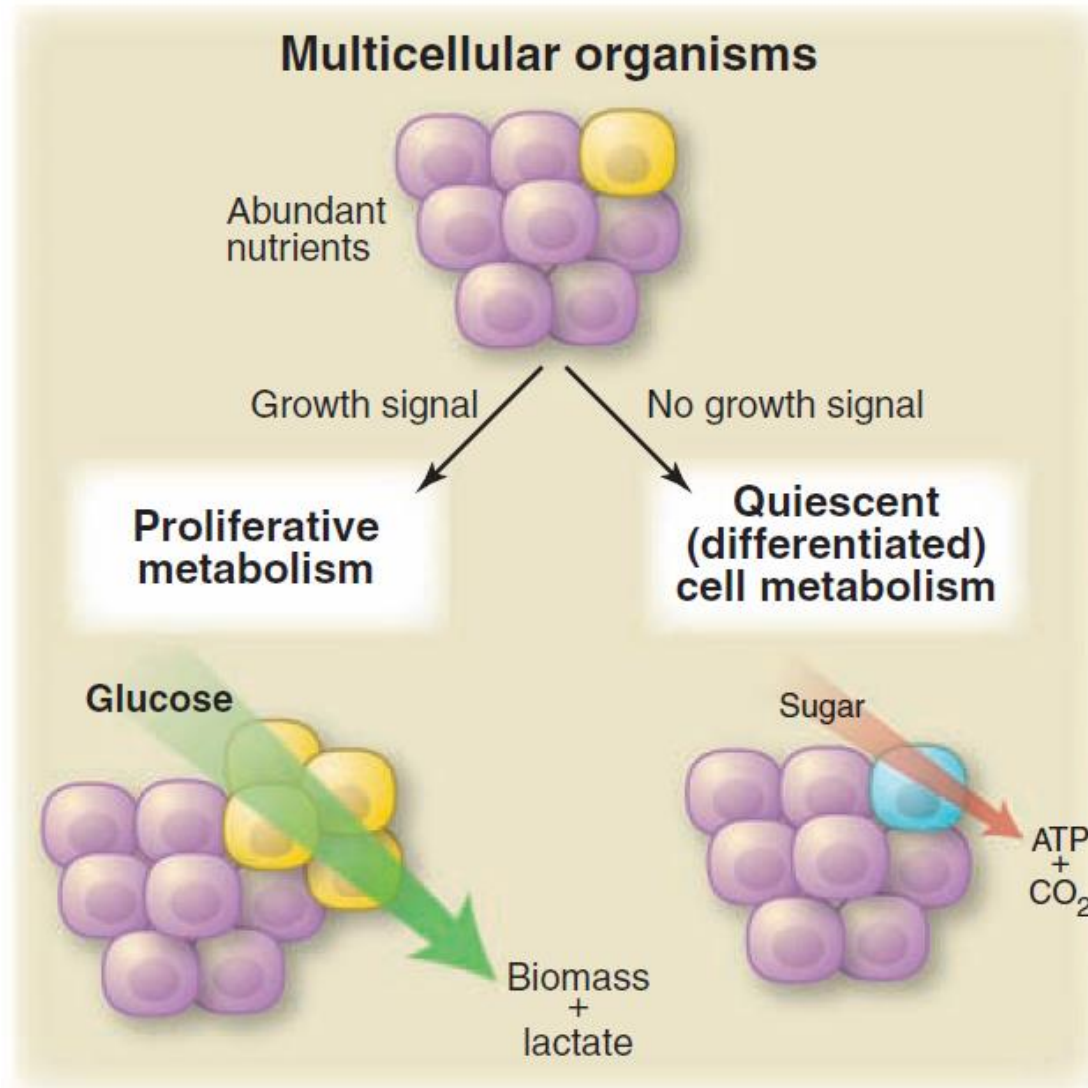
The breath interface: (1) mouth piece with non-return valve; (2) aluminum breath inlet (id 9 mm, od 12 mm); (3) stainless steel plug to allow for easy cleaning of breath interface; (4) aluminum breath outlet (id 2 mm, od 12 mm); (5) stainless steel capillary (id 1 mm, od 1.3 mm); (6) Swagelok union to mount (5); (7) aluminum adapter to connect breath interface with charging spray unit; (8) aluminum breath sampling tube (id 9 mm, od 15 mm); (9) heating cartridge; (10) heated charging spray unit; (11) charging sprays.

Press Release

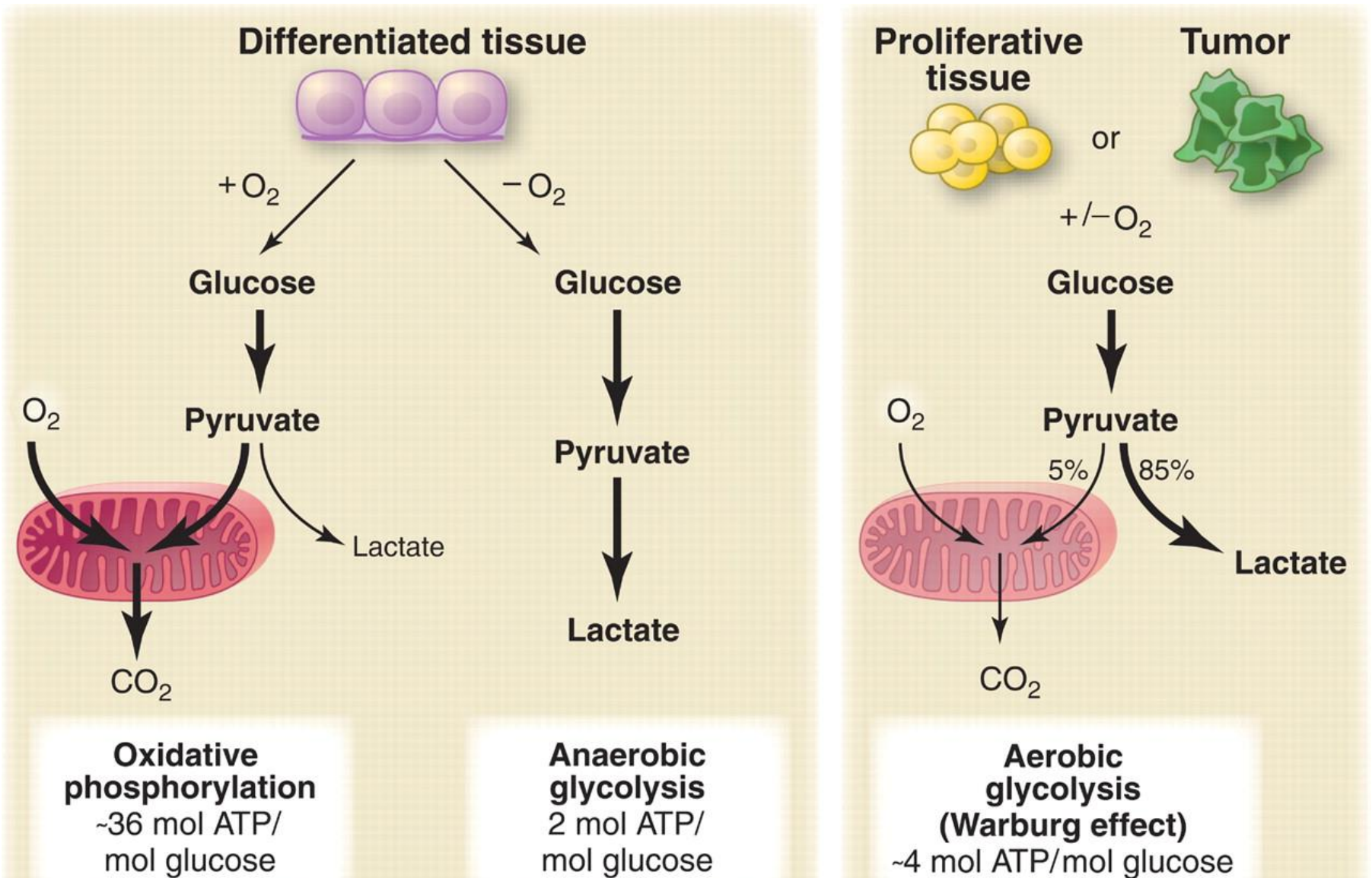
Dec 5, 2012 <http://www.genengnews.com>

“A simple breath analysis could be used for **colorectal cancer screening**, according to researchers at the University Aldo Moro of Bari. Cancer tissue has different metabolism compared to normal healthy cells and produces some substances that can be detected in the breath of these patients.”

Tumor Metabolism



Warburg-Effect



Press Release, continued

Dec 5, 2012 <http://www.genengnews.com>

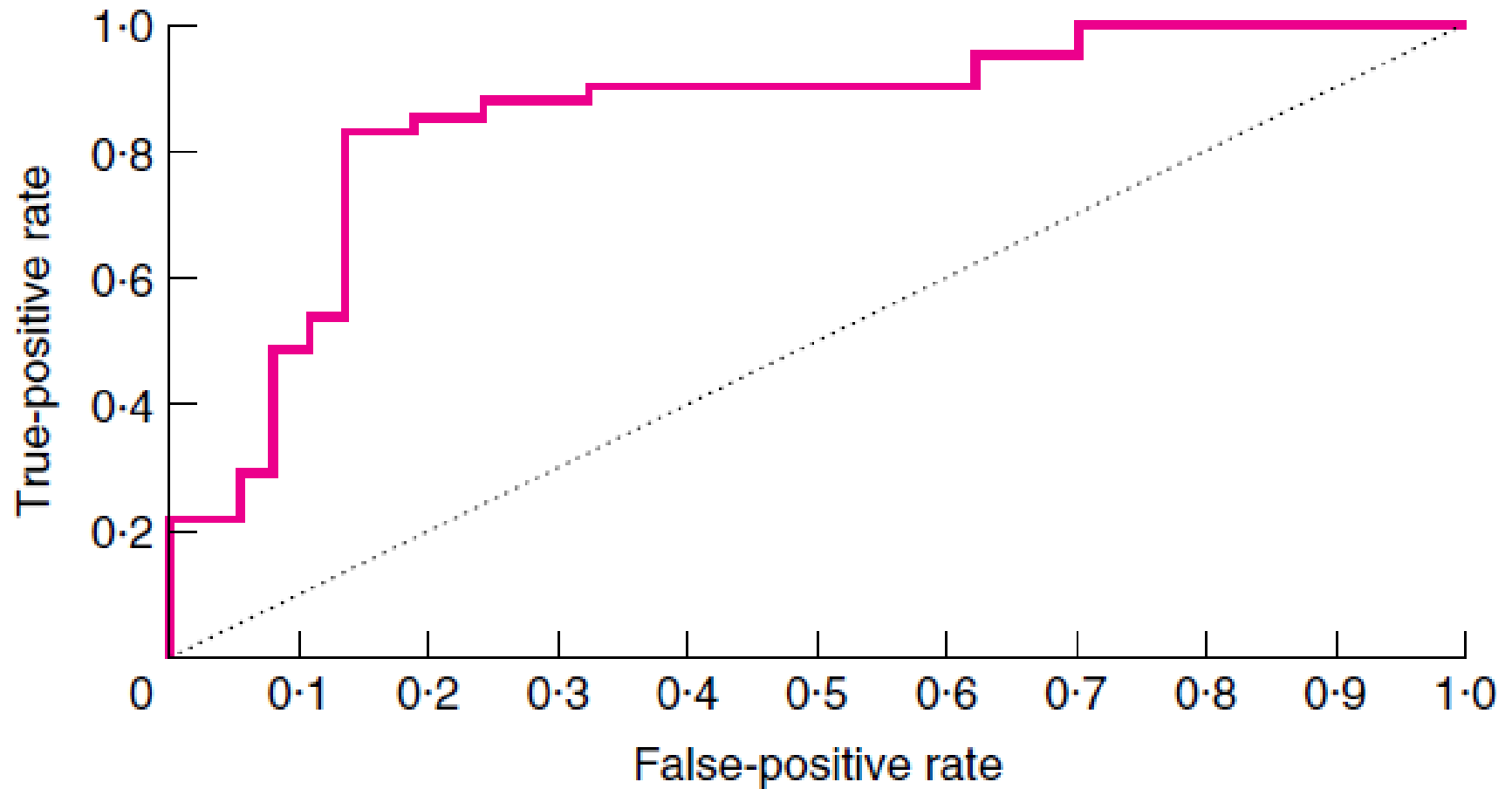
“The research team collected exhaled breath from 37 patients with colorectal cancer and 41 healthy controls, which was processed offline to evaluate the volatile organic compound (VOC) profile. VOCs of interest had been identified and selected, and VOC patterns able to discriminate patients from controls set up.”

Exhaled volatile organic compounds identify patients with colorectal cancer

	Recognition capability (%)
Nonanal	80
4-Methyl-2-pentanone	88
Decanal	92
2-Methylbutane	87
1,2-Pentadiene	95
2-Methylpentane	87
3-Methylpentane	87
Methylcyclopentane	80
Cyclohexane	94
Methylcyclohexane	92
1,3-Dimethylbenzene	96
4-Methyloctane	80
1,4-Dimethylbenzene	80
A (4-methylundecane, RT = 11.3)	59
B (trimethyldecane, RT = 13.2)	72

Altomare et al., BJS 2012

Sensitivity 86% high, multiparametric
Specificity 83% diagnostic



Altomare et al., BJS 2012

Peroxide Generation in Cell Membranes

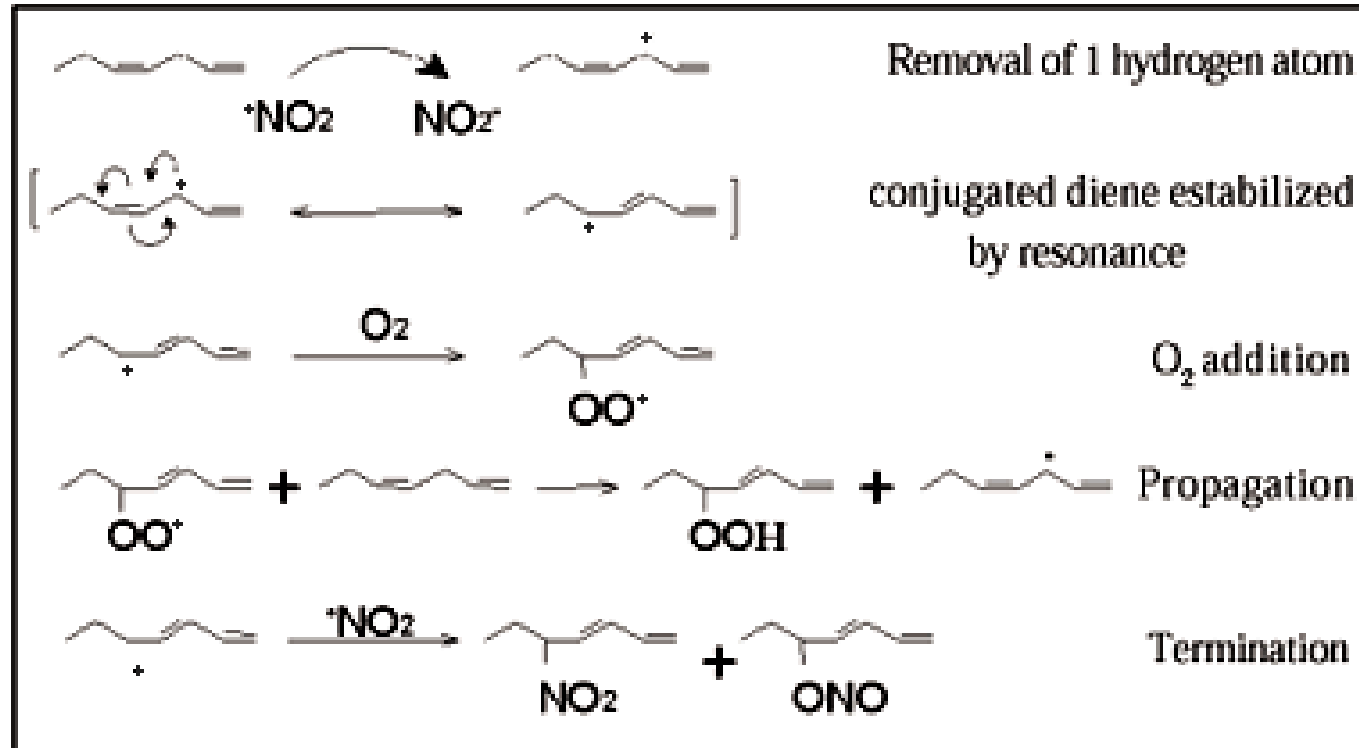
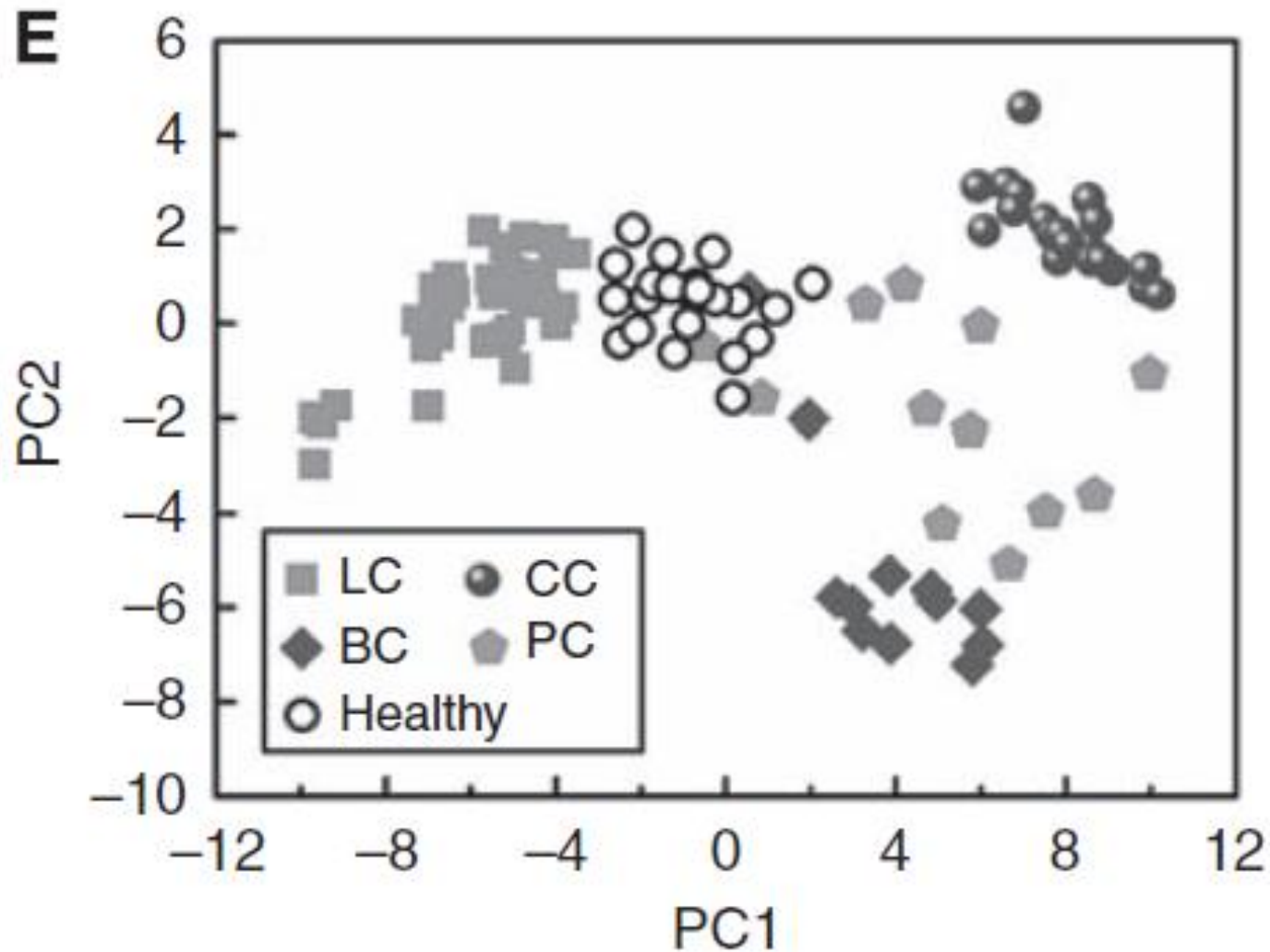


Fig. 2 - Process of lipid peroxidation induced by $\text{NO}_2^\bullet$. The $\text{NO}_2^\bullet$ radical initiates removal of 1 hydrogen atom from a polyunsaturated fatty acid, resulting in a conjugated diene that reacts with an oxygen molecule, forming lipid peroxide. The lipid peroxide removes 1 hydrogen atom from a second fatty acid, forming a lipid hydroperoxide and a second conjugated diene. The conjugated diene may react with the $\text{NO}_2^\bullet$ radical, forming nitrated products.

Subtyping of Cancers from Exhaled Breath





Source: wikipedia

INTRAOPERATIVE ANALYSIS

Application of desorption electrospray ionization mass spectrometry imaging in breast cancer margin analysis

David Calligaris^{a,1}, Diana Caragacianu^{a,b,c,1}, Xiaohui Liu^{a,2}, Isaiah Norton^a, Christopher J. Thompson^d, Andrea L. Richardson^{e,f}, Mehra Golshan^c, Michael L. Easterling^d, Sandro Santagata^{e,f}, Deborah A. Dillon^e, Ferenc A. Jolesz^b, and Nathalie Y. R. Agar^{a,b,f,3}

Departments of ^aNeurosurgery, ^bRadiology, ^cSurgery, and ^dPathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115; ^eBruker Daltonics, Billerica, MA 01821; and ^fDepartment of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215

Edited by Jerrold Meinwald, Cornell University, Ithaca, NY, and approved August 28, 2014 (received for review May 6, 2014)

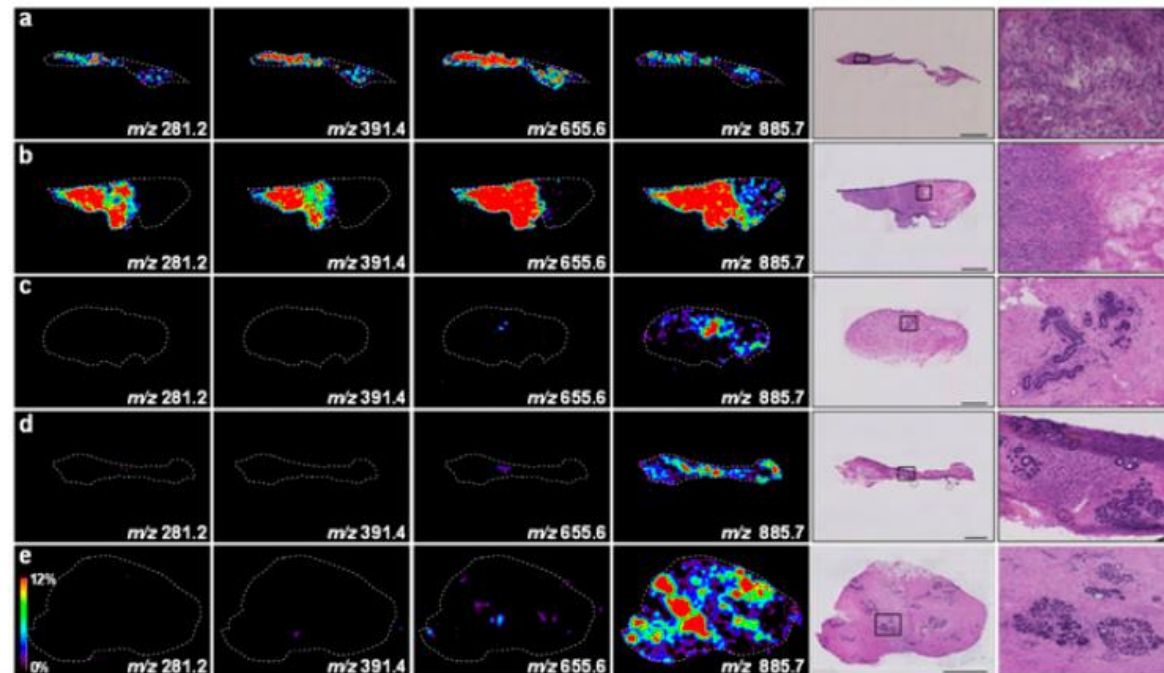
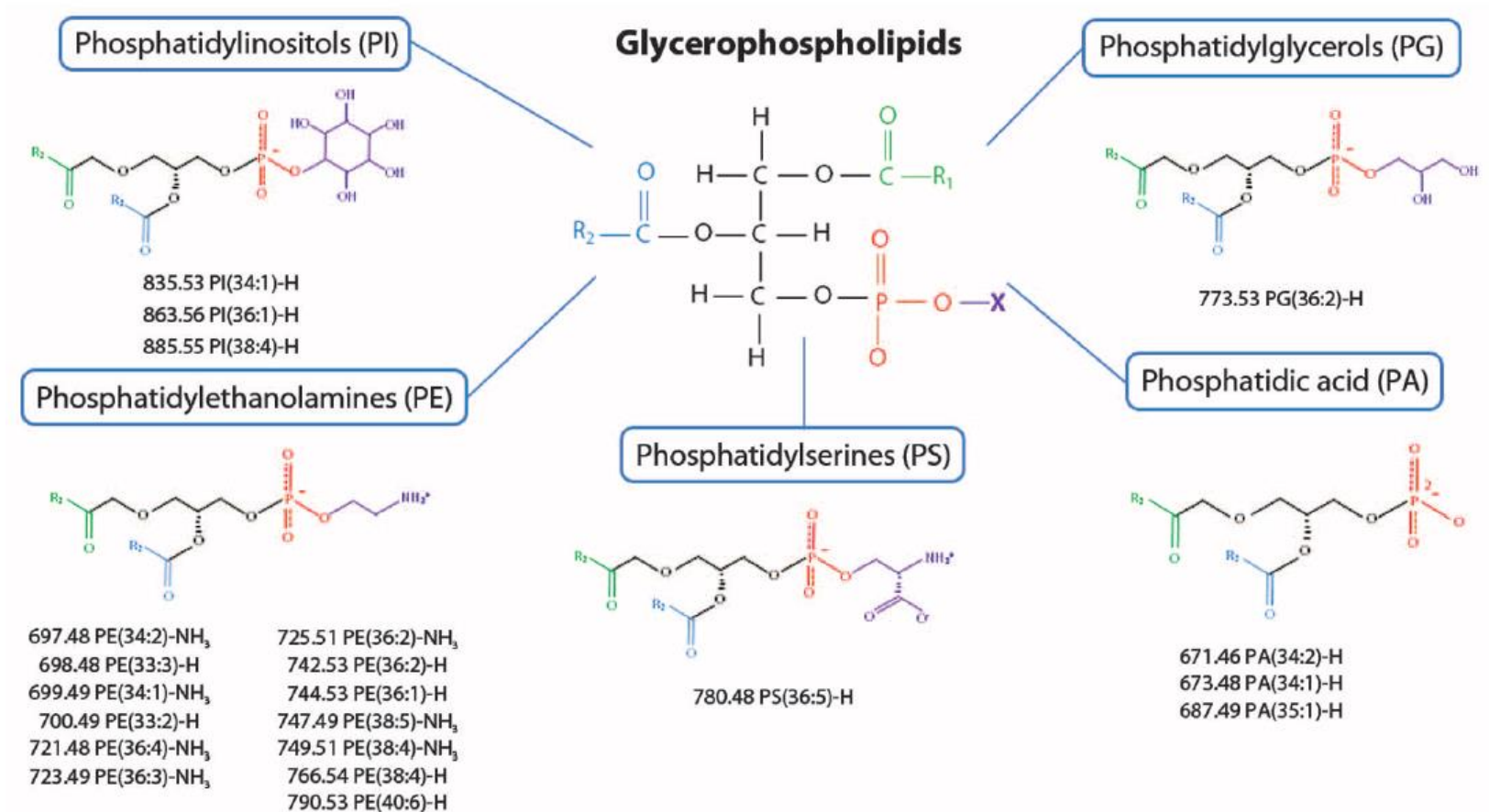


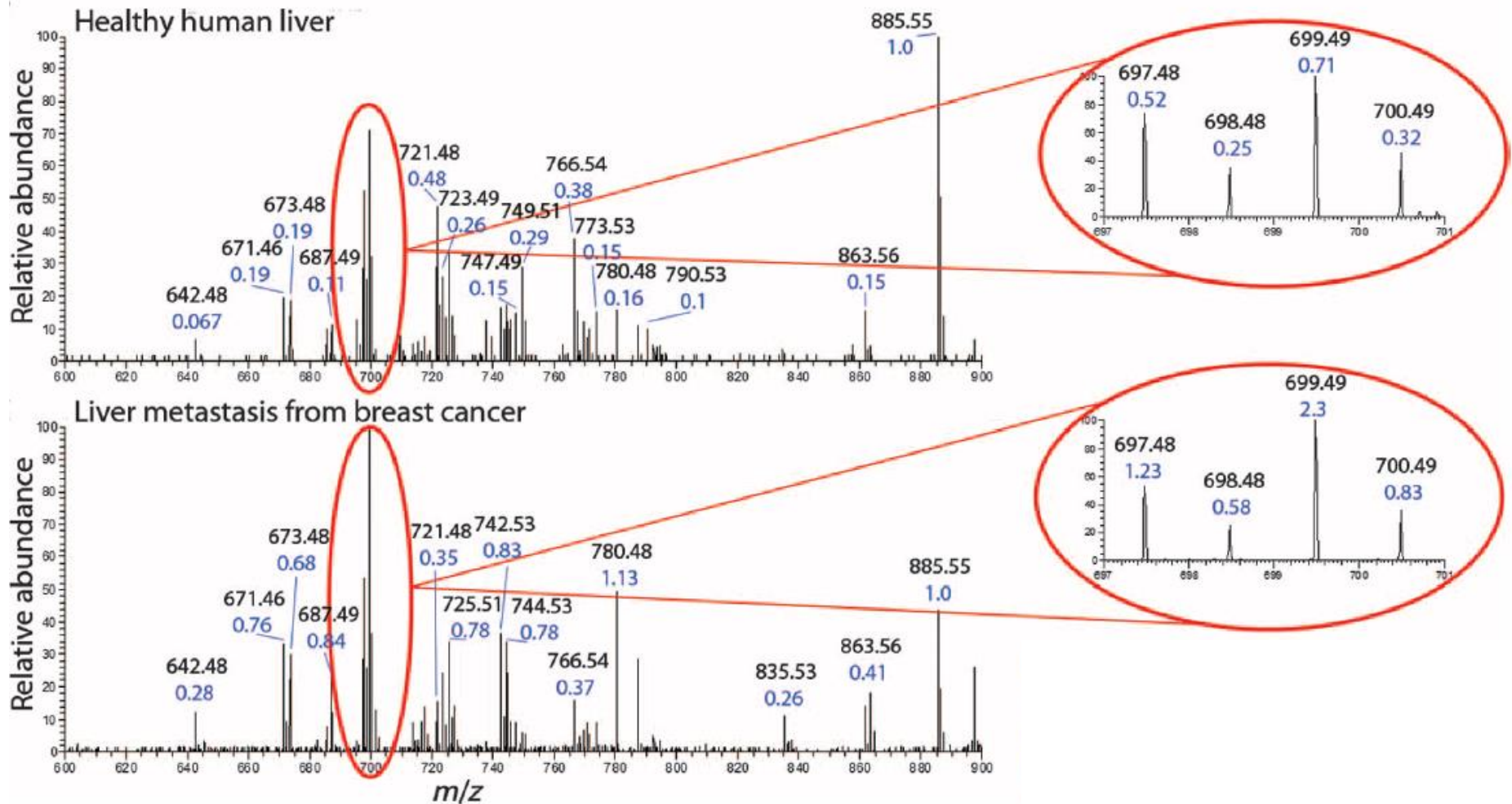
Fig. 3. DESI MS images from the tumor center (A), the tumor edge (B), 2 cm away from the tumor (C), 5 cm away from the tumor (D), and contralateral side (E) tissue sections from research subject 9 showing the distributions of ions at m/z 281.2, m/z 391.4, m/z 655.6, and m/z 885.7. (Right) Light microscopy images of the H&E-stained sections are shown. (Scale bars, 2 mm.)

The Markers

LIPIDS

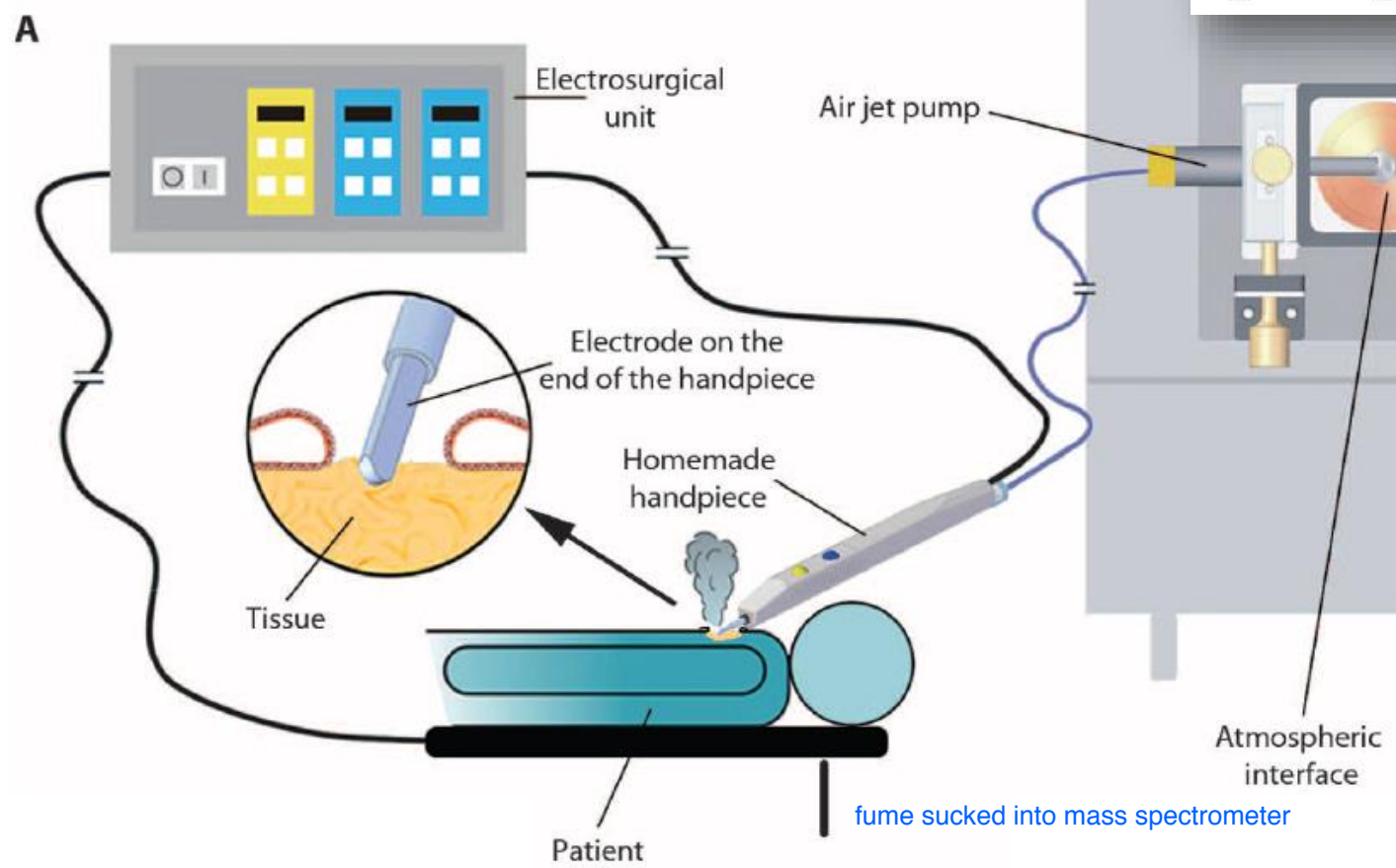
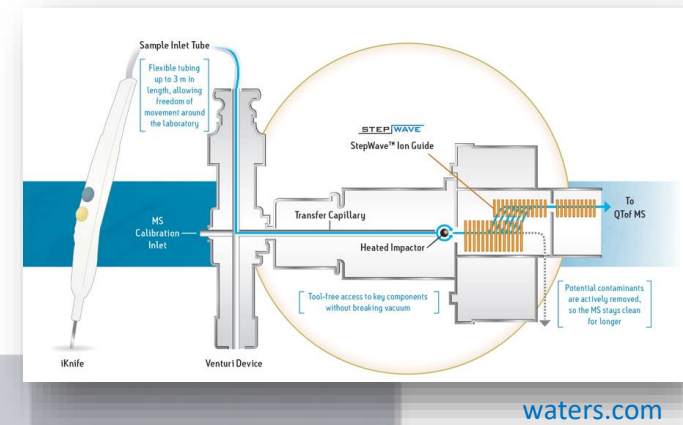


Profiling



Rapid Evaporative Ionization Mass Spectrometry

REIMS 1

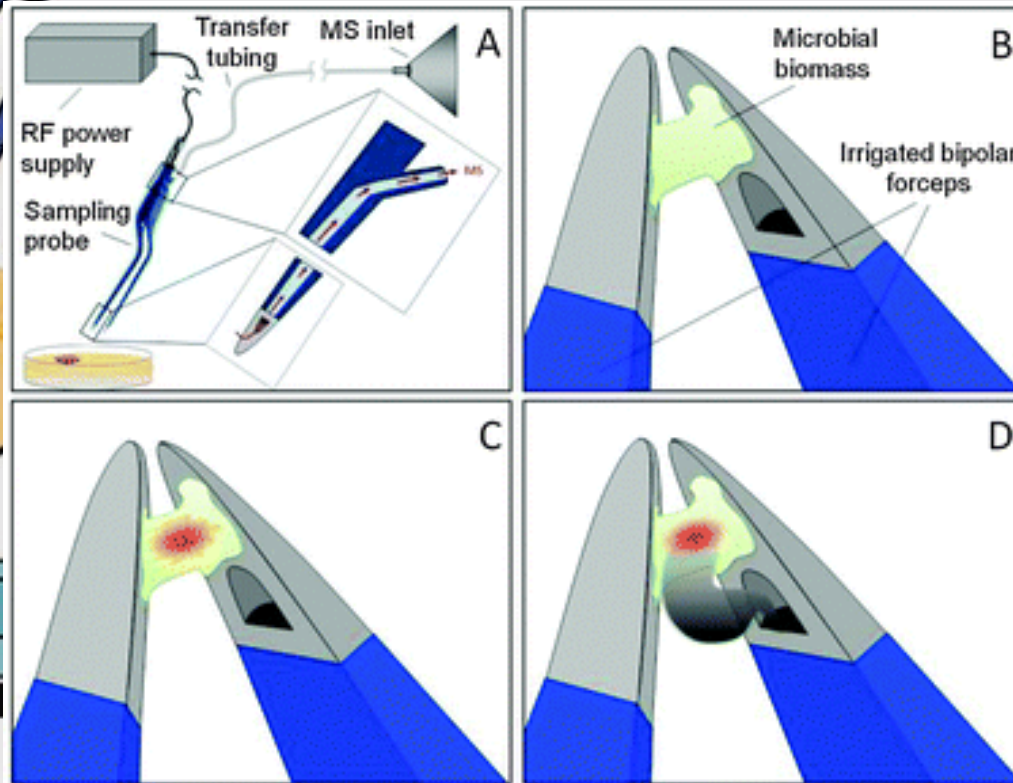
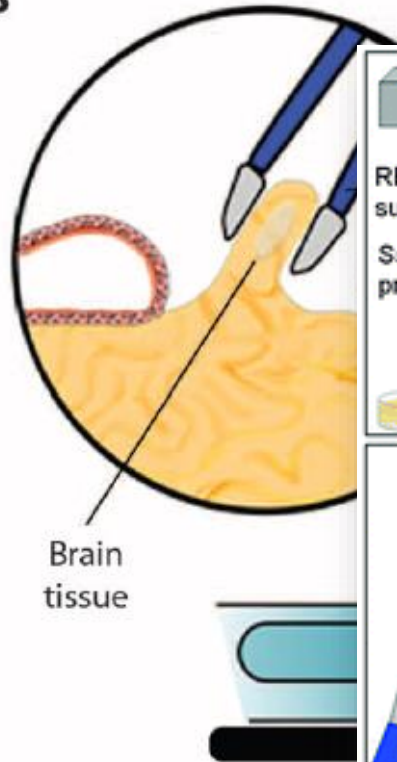


waters.com

Rapid Evaporative Ionization Mass Spectrometry

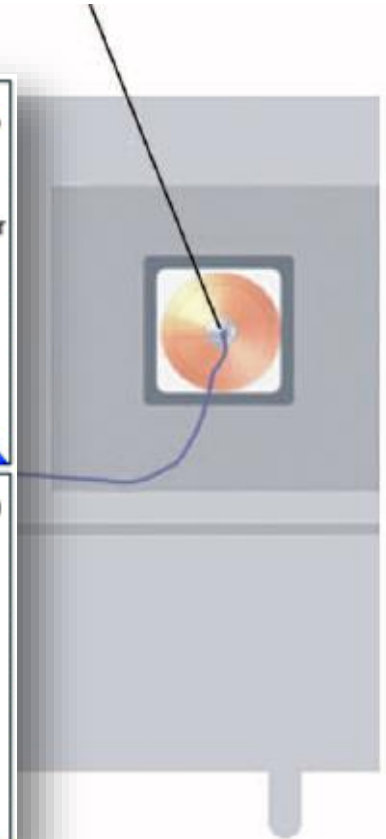
REIMS 2

B

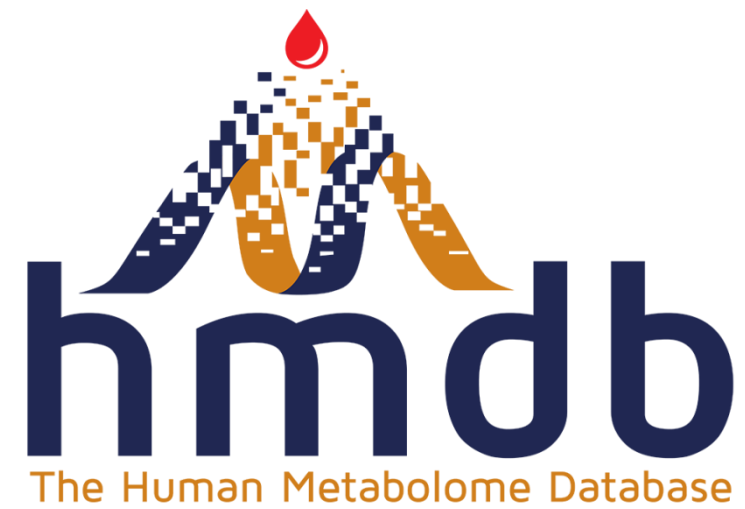


Strittmatter et al., Chem Commun (Camb). 2013 Jul 14;49(55):6188-90

Teflon tubing



skip until slide 70



RESOURCES

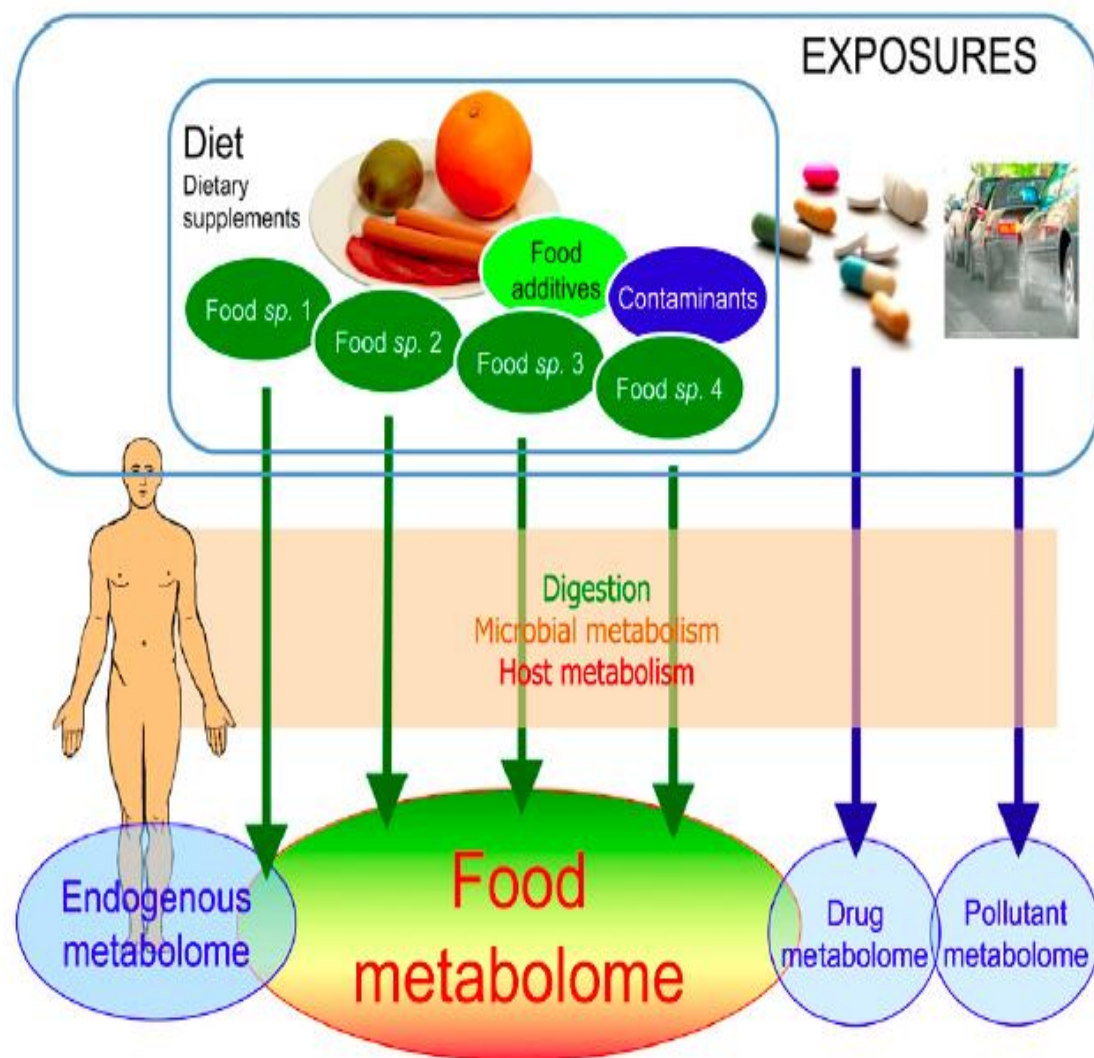
Metabolomics Software

SELECTED METABOLOMICS SOFTWARE

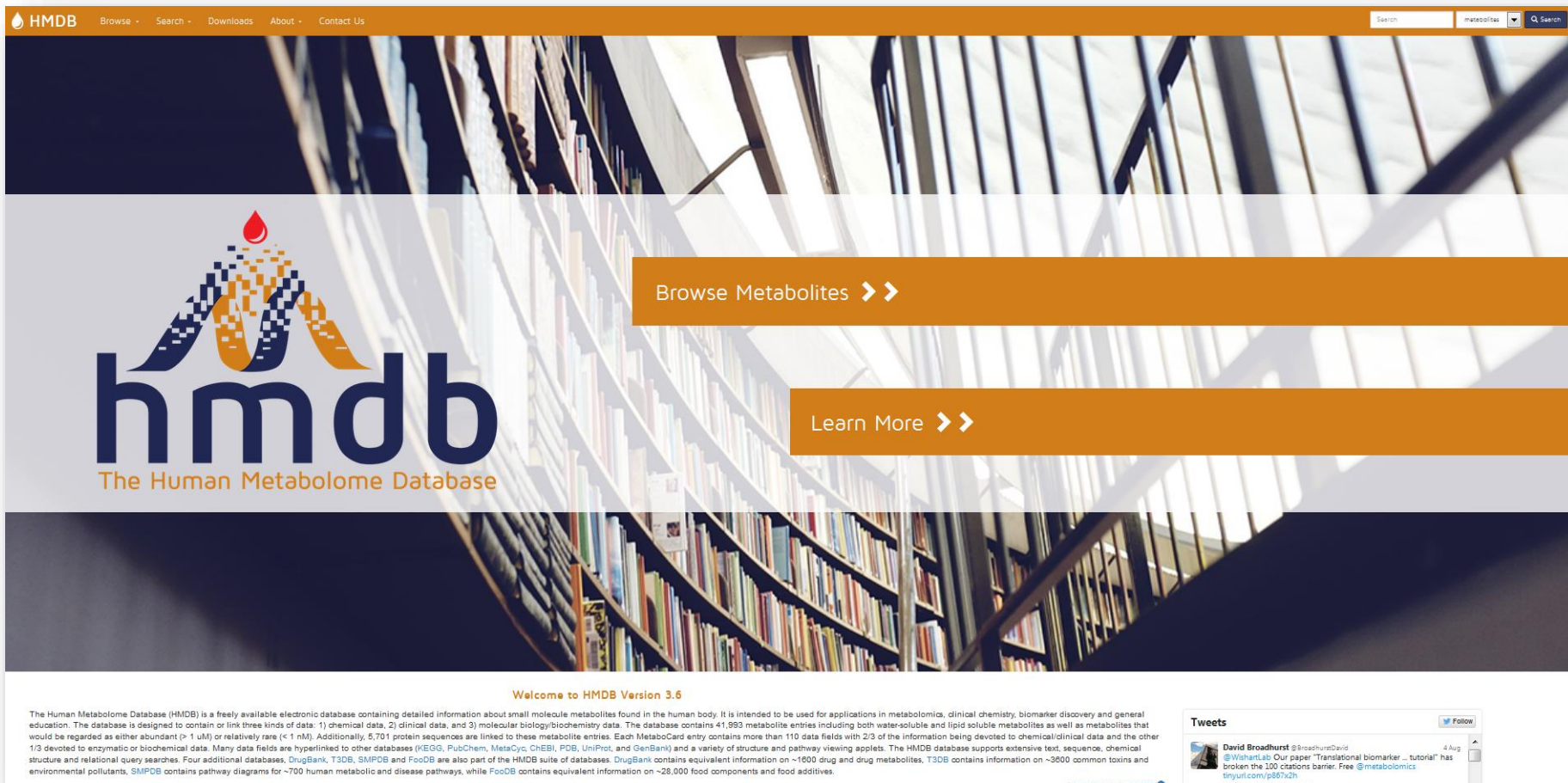
Name	Description
Human Metabolome Database	Free database of metabolites in the human body, including details relevant to chemical profiles, molecular biology and clinical chemistry. Links to pathway and structure-viewing tools and to other databases.
KEGG Pathway	Visualization tool linked to a collection of manually drawn pathway maps (KEGG database) with ability to locate and colour specific metabolites and pathways.
LipidBlast	A tandem-mass-spectral database for lipid identification.
MapMan	Tool for converting large data sets, such as those from gene-expression arrays, into metabolic pathway diagrams. Focuses on plant metabolomics.
MetaboAnalyst	Complete workflow for metabolomics data processing and analysis for both mass spectrometry and nuclear magnetic resonance data with common statistical analyses and heat-map visualizations.
Metabolites Biological Role (MBRole)	A server that integrates chemical and biological annotations from a handful of databases to identify potentially important metabolites and other molecules.
MS-Dial	Downloadable program that spots and identifies peaks in mass-spectrometry data, developed for small molecules.
OpenMS	Open-source library for C++-based data analysis and management that includes infrastructure for software development. Mainly for processing raw data.
XCMS Online	Cloud-based platform for metabolite profiling from raw liquid-chromatography and mass-spectrometry data and for data sharing.
Yeast Metabolome Database	Manually curated collection of yeast metabolites and their chemical properties, with links to spectral and chemical databases.

The Human Metabolome(s)

The complete collection of small molecules found in humans – including endogenous and exogenous compounds



www.hmdb.ca



The screenshot shows the homepage of the Human Metabolome Database (HMDB). The header is orange with the HMDB logo and navigation links: Browse, Search, Downloads, About, and Contact Us. A search bar is on the right. The main banner features a background image of a library with curved bookshelves. On the left is the HMDB logo, which includes a stylized flame above the text 'hmdb' and 'The Human Metabolome Database' below it. On the right are two orange buttons: 'Browse Metabolites >>' and 'Learn More >>'. Below the banner is a section titled 'Welcome to HMDB Version 3.6' containing a detailed paragraph about the database's scope and content. At the bottom right is a 'Tweets' widget showing a tweet from David Broadhurst.

HMDB Browse Search Downloads About Contact Us Search metabolites Search

hmdb
The Human Metabolome Database

Browse Metabolites >>

Learn More >>

Welcome to HMDB Version 3.6

The Human Metabolome Database (HMDB) is a freely available electronic database containing detailed information about small molecule metabolites found in the human body. It is intended to be used for applications in metabolomics, clinical chemistry, biomarker discovery and general education. The database is designed to contain or link three kinds of data: 1) chemical data, 2) clinical data, and 3) molecular biology/biochemistry data. The database contains 41,893 metabolite entries including both water-soluble and lipid soluble metabolites as well as metabolites that would be regarded as either abundant ($> 1 \mu\text{M}$) or relatively rare ($< 1 \text{ nM}$). Additionally, 5,701 protein sequences are linked to these metabolite entries. Each MetaboCard entry contains more than 110 data fields with 2/3 of the information being devoted to chemical/clinical data and the other 1/3 devoted to enzymatic or biochemical data. Many data fields are hyperlinked to other databases (KEGG, PubChem, MetaCyc, ChEBI, PDB, UniProt, and GenBank) and a variety of structure and pathway viewing applets. The HMDB database supports extensive text, sequence, chemical structure and relational query searches. Four additional databases, DrugBank, T3DB, SMPDB and FoodDB are also part of the HMDB suite of databases. DrugBank contains equivalent information on ~1600 drug and drug metabolites, T3DB contains information on ~3600 common toxins and environmental pollutants, SMPDB contains pathway diagrams for ~700 human metabolic and disease pathways, while FoodDB contains equivalent information on ~28,000 food components and food additives.

Tweets

David Broadhurst @broadhurstDavid
@WishartLab Our paper "Translational biomarker ... tutorial" has broken the 100 citations barrier. Free @metabolomics tinyurl.com/p867x2h

Browsing metabolites

Filter by metabolite status:
☐ Detected and quantified
 ☐ Detected but not quantified
 ☐ Expected but not quantified

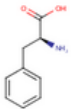
Filter by biofluid:
☐ Other Fluids
 ☐ Saliva
 ☐ Cerebrospinal Fluid
 ☐ Urine
 ☐ Blood

Filter by origin:
☐ Plant
 ☐ Microbial
 ☐ Cosmetic
 ☐ Toxin/Pollutant
 ☐ Food
 ☐ Drug
 ☐ Exogenous
 ☐ Endogenous
 ☐ Drug Metabolite

Displaying metabolites 1 - 25 of 41993 in total

HMDB ID CAS Number	Name	Structure	Formula Average Mass Mono Mass	Biofluid Location
HMDB00001 332-90-9	1-Methylhistidine		C₇H₁₁N₃O₂ 169.1811 169.085126611	Blood Cerebrospinal Fluid (CSF) Saliva Urine
HMDB00002 109-76-2	1,3-Diaminopropane		C₃H₁₀N₂ 74.1249 74.08439833	Blood Urine
HMDB00005 600-15-0	2-Ketobutyric acid		C₄H₆O₃ 102.0886 102.031694058	Blood Cerebrospinal Fluid (CSF) Saliva Urine
HMDB00008 600-15-7	2-Hydroxybutyric acid		C₄H₆O₃ 104.1045 104.047344122	Blood Cerebrospinal Fluid (CSF) Saliva Urine

Showing metabocard for L-Phenylalanine (HMDB00159)

Identification Taxonomy Ontology Physical properties Spectra Biological properties Concentrations Links References XML	
enzymes (17) transporters (2) Show 19 proteins Show Metabolites with Similar Structures	
Record Information	
Version	3.6
Creation Date	2005-11-16 15:48:42 UTC
Update Date	2015-10-26 19:52:40 UTC
HMDB ID	HMDB00159
Secondary Accession Numbers	HMDB00612
Metabolite Identification	
Common Name	L-Phenylalanine
Description	Phenylalanine is an essential amino acid and the precursor for the amino acid tyrosine. Like tyrosine, it is the precursor of catecholamines in the body (tyramine, dopamine, epinephrine and norepinephrine). The psychotropic drugs (mescaline, morphine, codeine, and papaverine) also have phenylalanine as a constituent. Phenylalanine is a precursor of the neurotransmitters called catecholamines, which are adrenalin-like substances. Phenylalanine is highly concentrated in the human brain and plasma. Normal metabolism of phenylalanine requires biotin, iron, niacin, vitamin B6, copper and vitamin C. An average adult ingests 5 g of phenylalanine per day and may optimally need up to 8 g daily. Phenylalanine is highly concentrated in high protein foods, such as meat, cottage cheese and wheat germ. A new dietary source of phenylalanine is artificial sweeteners containing aspartame. Aspartame appears to be nutritious except in hot beverages; however, it should be avoided by phenylketonurics and pregnant women. Phenylketonurics, who have a genetic error of phenylalanine metabolism, have elevated serum plasma levels of phenylalanine up to 400 times normal. Mild phenylketonuria can be an unsuspected cause of hyperactivity, learning problems, and other developmental problems in children. Phenylalanine can be an effective pain reliever. Its use in premenstrual syndrome and Parkinson's may enhance the effects of acupuncture and electric transcutaneous nerve stimulation (TENS). Phenylalanine and tyrosine, like L-dopa, produce a catecholamine effect. Phenylalanine is better absorbed than tyrosine and may cause fewer headaches. Low phenylalanine diets have been prescribed for certain cancers with mixed results. Some tumors use more phenylalanine (particularly melatonin-producing tumors called melanoma). One strategy is to exclude this amino acid from the diet, i.e., a Phenylketonuria (PKU) diet (compliance is a difficult issue; it is hard to quantify and is under-researched). The other strategy is just to increase phenylalanine's competing amino acids, i.e., tryptophan, valine, isoleucine and leucine, but not tyrosine. (http://www.dcnutrition.com).
Structure	 Q MOL SDF PDB SMILES InChI View Structure
Synonyms	(-)-beta-Phenylalanine (L)-Phenylalanine (S)-(-)-Phenylalanine (S)-2-amino-3-phenylpropanoate (S)-2-amino-3-phenylpropanoic acid (S)-2-Amino-3-phenylpropionate (S)-2-Amino-3-phenylpropionic acid (S)-alpha-Amino-benzenepropanoate (S)-alpha-Amino-benzenepropanoic acid (S)-alpha-Amino-beta-phenylpropionate (S)-alpha-Amino-beta-phenylpropionic acid (S)-alpha-Aminobenzenepropanoate (S)-alpha-Aminobenzenepropanoic acid (S)-alpha-Aminohydrocinnamate (S)-alpha-Aminohydrocinnamic acid (S)-Phenylalanine

Spectra				
Spectra	Spectrum Type	Description	Splash Key	
	GC-MS	GC-MS Spectrum - GC-EI-TOF (Pegasus III TOF-MS system, Leco; GC 6890, Agilent Technologies) (2 TMS)	splash10-4zd0000000-a37fbccaf826443ef70c	View in MoNA
	GC-MS	GC-MS Spectrum - GC-EI-TOF (Pegasus III TOF-MS system, Leco; GC 6890, Agilent Technologies)	splash10-7zg0000000-537e2725d621246630c1	View in MoNA
	GC-MS	GC-MS Spectrum - GC-EI-TOF (Pegasus III TOF-MS system, Leco; GC 6890, Agilent Technologies) (2 TMS)	splash10-zod0000000-ead0919fa19d2352d80	View in MoNA
	GC-MS	GC-MS Spectrum - GC-MS (1 TMS)	splash10-9z10000000-cb2d6dc4bf9515150328	View in MoNA
	GC-MS	GC-MS Spectrum - GC-MS (2 TMS)	splash10-8zn0000000-f77489792f0852dd5613	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - Quattro_QQQ 10V, Positive (Annotated)	splash10-0z00000000-0f3b994108b8a9fd2a56	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - Quattro_QQQ 25V, Positive (Annotated)	splash10-az00000000-c14d44c8a67621757f3d	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - Quattro_QQQ 40V, Positive (Annotated)	splash10-zd00000000-08c842dab7f49c00da43	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-7dce1e473976f7d2143e	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-zq00000000-711557391093b0d8500a	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-0c25a5c116eac7bb059b	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-2804f79084ac4e67e155	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-8a71bb1f8424064d7caf	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-zv00000000-e027ff6bb67ce55e80a5	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-9f8185e9c7d54189f389	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Positive	splash10-0z00000000-df5f72fe2bba91742427	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Negative	splash10-3zyrffj84-bac229222fe7b52812a8	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Negative	splash10-0z00000000-453477dec847a3672ffe	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Negative	splash10-0071zod000-079a66bf710f8778bceb	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-ITFT (LTQ Orbitrap XL, Thermo Scientific) , Negative	splash10-000000z000-62dbe98de4ecde484fb3	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 10V, Negative	splash10-0z00000000-80558c17dc1845663c85	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 20V, Negative	splash10-dz00000000-e1ee31d41e48824e84b7	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 30V, Negative	splash10-zm00000000-cc11290a37815f24e16e	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 50V, Negative	splash10-z000000000-1a6020bce0e1a9a14832	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 40V, Negative	splash10-z300000000-38c044a112152626962e	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 10V, Positive	splash10-1z00000000-96908abfcb63153d80b3	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 20V, Positive	splash10-8z00000000-3ba5964e151bb1d56188	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 30V, Positive	splash10-8z00000000-20a7d24da0281f5b3b78	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 40V, Positive	splash10-lz00000000-1800642a835b49f3398a	View in MoNA
	LC-MS/MS	LC-MS/MS Spectrum - LC-ESI-QQ (API3000, Applied Biosystems) 50V, Positive	splash10-zf00000000-f262384c85fb843f8a11	View in MoNA
	1D NMR	¹ H NMR Spectrum	Not Available	
	1D NMR	¹³ C NMR Spectrum	Not Available	
	2D NMR	[¹ H, ¹ H] 2D NMR Spectrum	Not Available	
	2D NMR	[¹ H, ¹³ C] 2D NMR Spectrum	Not Available	
Biological Properties				
Cellular Locations	- Cytoplasm - Extracellular			

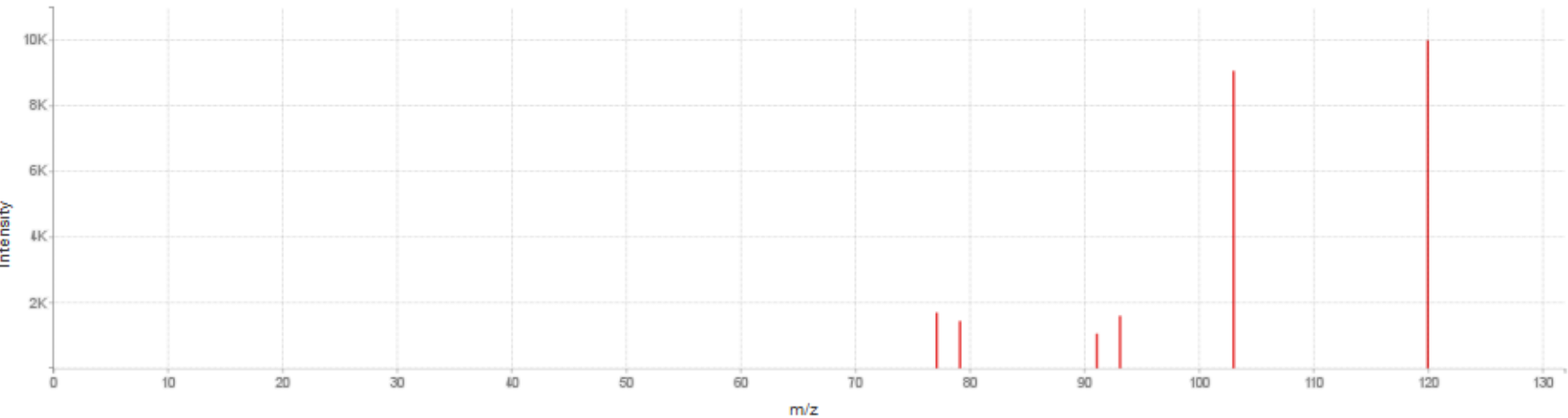
LC-MS/MS Spectrum - Quattro_QQQ 25V, Positive (Annotated) (HMDB00159)

Spectrum Details

HMDB ID: HMDB00159
Compound name: L-Phenylalanine
Spectrum type: LC-MS/MS Spectrum - Quattro_QQQ 25V, Positive (Annotated)
Splash Key: splash10-az00000000-c14d44c8a67621757f3d [View in MoNA](#)

Spectrum View

Image Viewer



Experimental Conditions

Sample Mass: 1.0 mg
Sample Assessment: Excellent
Spectrum Assessment: Excellent
Instrument Type: Quattro_QQQ
Collision Energy Level: med
Collision Energy Voltage: 25
Ionization Mode: Positive

Other...

welcome to



T3DB

the toxin and toxin-target database

The *Toxin and Toxin Target Database* (T3DB) is a comprehensive database of detailed toxin data with chemical structures, toxicity data, and information on pesticides, drugs, and food. It also includes a toxin record (ToxCard) of interactions, and medical books, and scientific literature.

The focus of the T3DB is on records that are interactively linked to chemical structure, and potential applications of the data are applicable to various fields.

Citing the T3DB:

1. Wishart D, Arndt D, Lim E, Pon A, Djafarzadeh S, et al. (2018) The Toxin and Toxin Target Database (T3DB): A Comprehensive Database of Toxin-Target Interactions. *Nucleic Acids Res.* 46:D1234-D1245.
2. Lim E, Pon A, Djafarzadeh S, et al. (2018) The Toxin and Toxin Target Database (T3DB): A Comprehensive Database of Toxin-Target Interactions. *Nucleic Acids Res.* 46:D1234-D1245.

FooDB

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FooDB is the world's largest and most comprehensive resource on food constituents, chemistry and biology. It provides information on both macronutrients and micronutrients, including many of the constituents that give foods their flavor, color, taste, texture and aroma.

Each chemical entry in the FooDB contains more than 100 separate data fields covering detailed compositional, biochemical and physiological information (obtained from the literature). This includes data on the compound's nomenclature, its description, information on its structure, chemical class, its physico-chemical data, its food source(s), its color, its aroma, its taste, its physiological effect, presumptive health effects (from published studies), and concentrations in various foods.

DrugBank

Drug & Drug Target Database

DrugBank Version 5.0

The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. The database contains 8250 drug entries including 2016 FDA-approved small molecule drugs, 229 FDA-approved biotech (protein/peptide) drugs, 94 nutraceuticals and over 6000 experimental drugs. Additionally, 4344 non-redundant protein (i.e. drug target/enzyme) sequences are linked to these drug entries. Each DrugCard entry contains more than 200 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data.

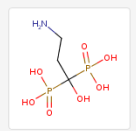
[More about DrugBank](#)

DrugBank is offered to the public as a freely available resource. Use and re-distribution of the data, in whole or in part, for commercial purposes (including internal use) requires a license. We ask that users who download significant portions of the database cite the DrugBank paper in any resulting publications.

Citing DrugBank:

Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. *DrugBank: a comprehensive resource for in silico drug discovery and exploration*. *Nucleic Acids Res.* 2006 Jan 1;34(Database issue):D668-72. [16381955](#)

Drug of the day: **Pamidronate**



Pamidronic acid (INN) or pamidronate disodium (USAN), marketed as pamidronate disodium pentahydrate under the brand name Aredia, is a bisphosphonate. [Wikipedia]

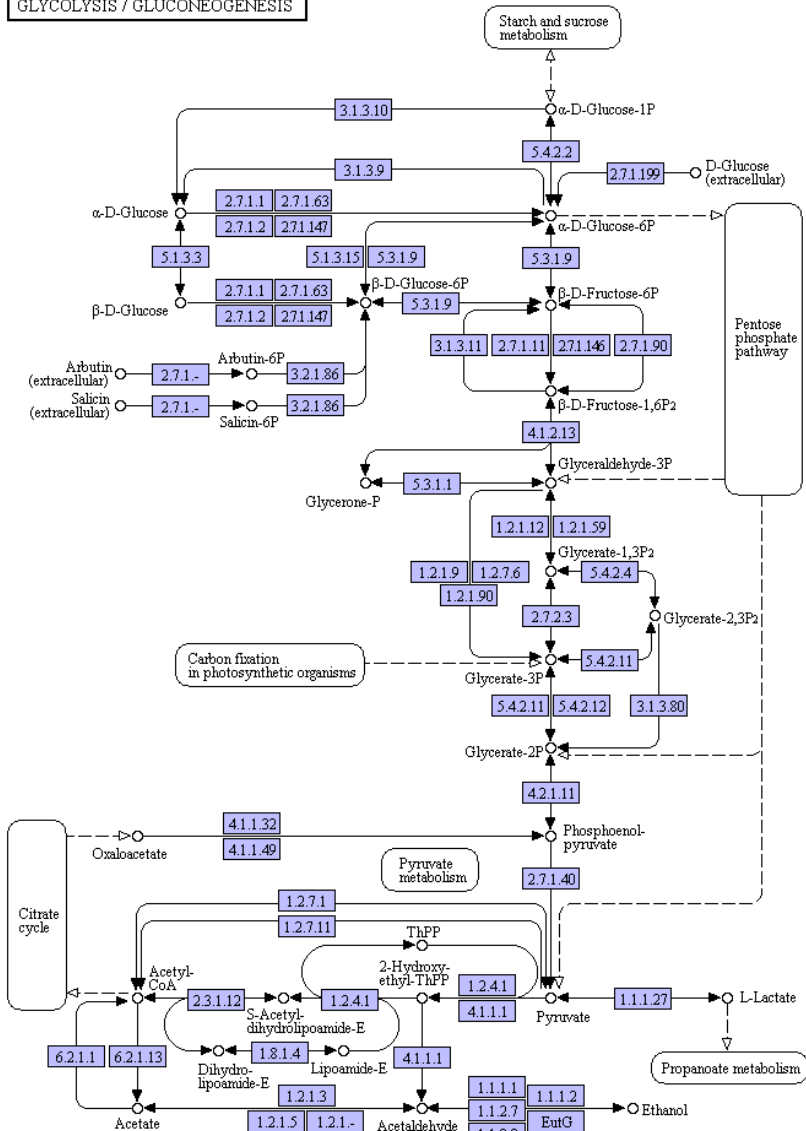
For the treatment of moderate or severe hypercalcemia associated with malignancy

[Learn more about Pamidronate](#)

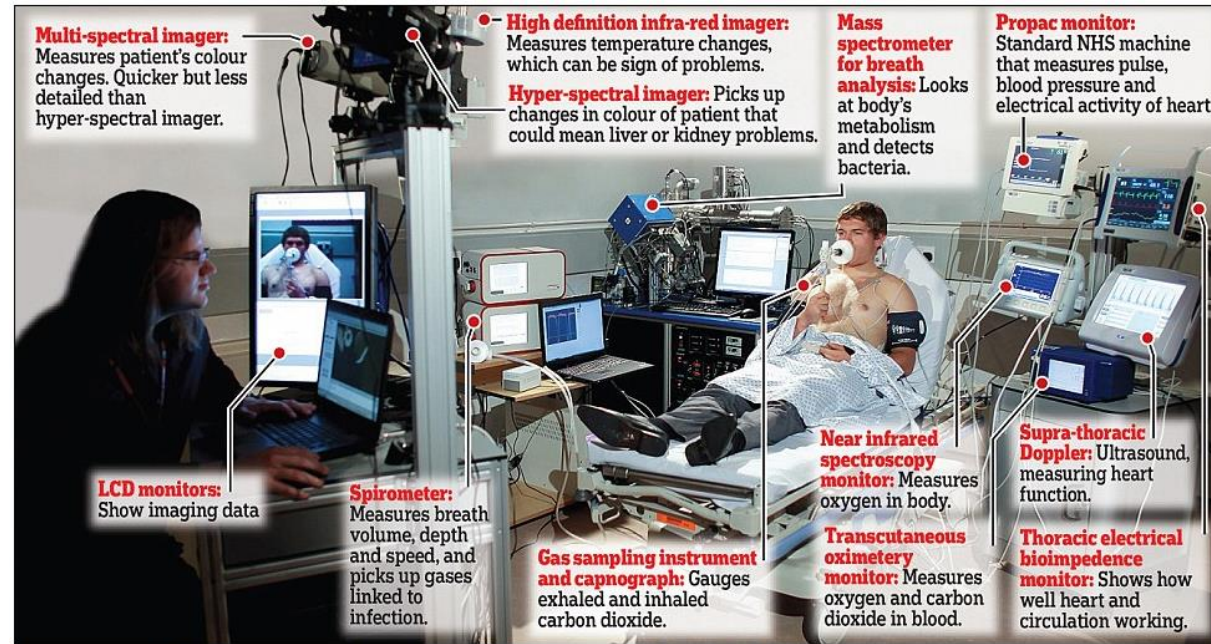
<http://www.drugbank.ca>

KEGG Pathways

GLYCOLYSIS / GLUCONEOGENESIS



- Manually drawn
- Linked to
 - Reference number (ortholog groups)
 - EC number
 - Reaction identifier



High-tech hospital: It looks like something out of a sci-fi film, but this is the latest sick bay to be unveiled in Britain

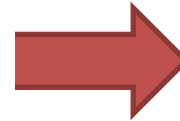
will not happen

OUTLOOK



Bench

\$500,000 instrument, \$200/test



Bedside

\$1000 instrument, \$2/test

TURNING SCIENCE FICTION INTO SCIENCE REALITY

The \$10 million global competition to put healthcare in the palm of your hand

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**CONGRATULATIONS TO
OUR WINNERS!**

Final Frontier Medical Devices' DxtER dubbed first "real-life" Tricorder prototype

DxtER

by Final Frontier Medical Devices

THE DEVICE

The system pulls together data from a patient's personal and family medical history, physical exam, and multiple sensors to make a quick and accurate assessment.

THE TEAM

- Family team led by brothers Dr. Basil Harris, an emergency medicine physician, and George Harris, a network engineer
- Basil Leaf Technologies
- From Pennsylvania

DeepQ Kit

by Dynamical Biomarkers Group

THE DEVICE

The system incorporates innovative technologies for artificial intelligence, physiologic signal analysis, image processing, and biomarker detection in a user-friendly process.

THE TEAM

- Multidisciplinary team of clinicians, scientists, and engineers
- Sponsored by HTC
- From Taiwan and Massachusetts

CONCLUSION

What kind of data is mandatory to impact therapeutic intervention?

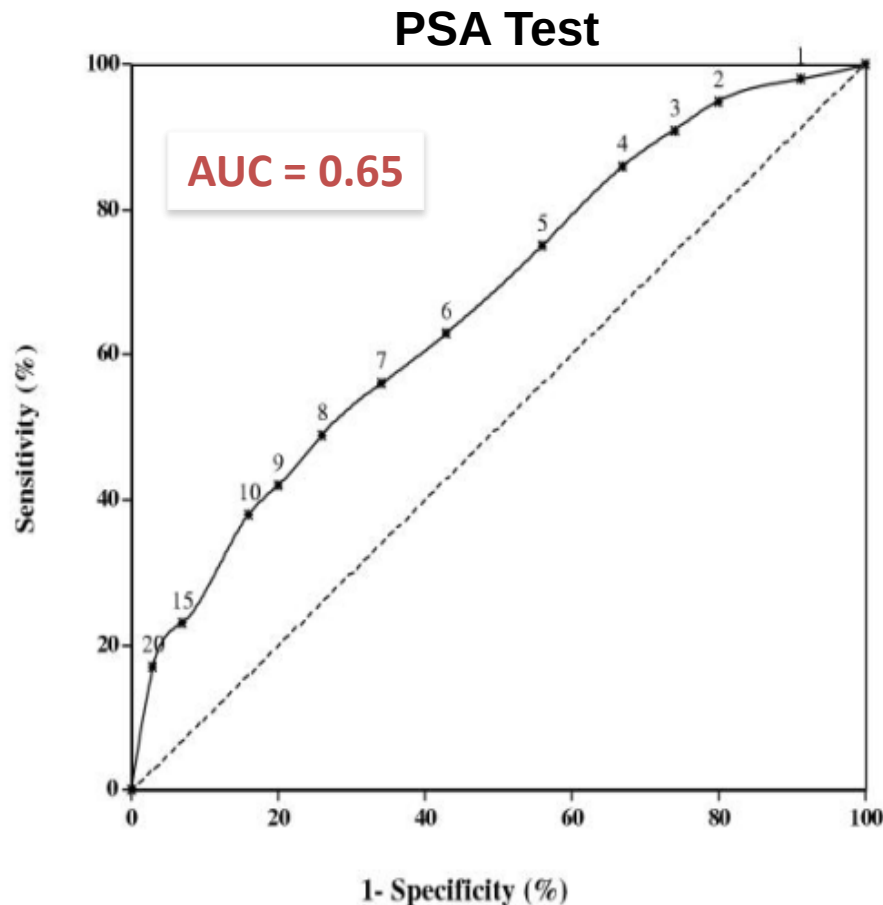
- MS (NMR) in clinical setting with **acceptable** response rate
- Quantitative / rel. quantitative clinical data
- On-demand Mx for differential diagnosis (uncertain cases)

Example for current standard in some hospitals:

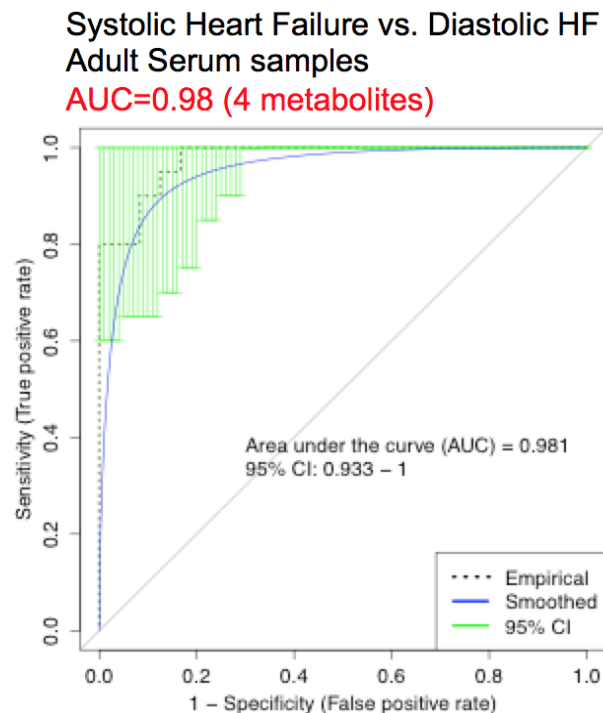
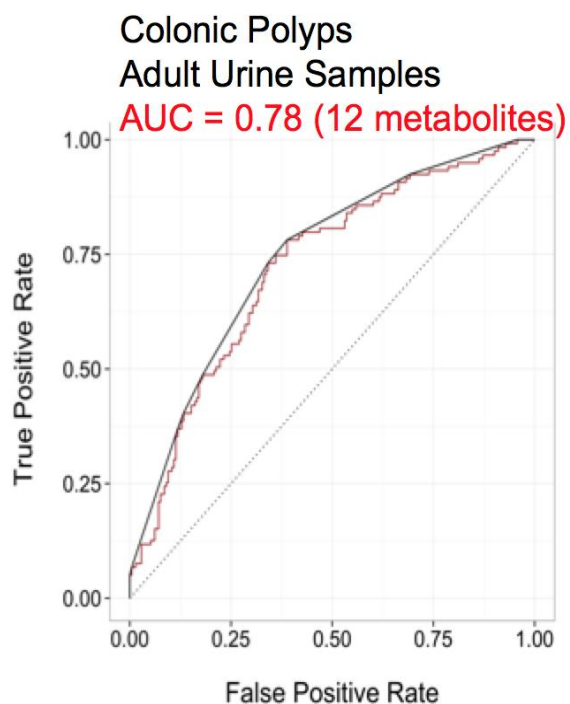
TDM psychoactive drugs, TDM immunosuppressives, clinical microbiology, metabolite analysis in pediatrics, newborn screening, glucose monitoring

Conventional Biomarker Performance

metabolomics often better, see next slide



Metabolomic Biomarker Performance



Vision

- *Personalized Medicine*-patient stratification,
- Microanalytics (biopsy, tears etc.),
- Multiparametric diagnostics,
- „online“ Diagnostics, e.g. breath analysis,
- Intraoperative analyses,
- Single-cell Mx in research,
- Democratization of metabolomics.

optogenetic manipulation of metabolism