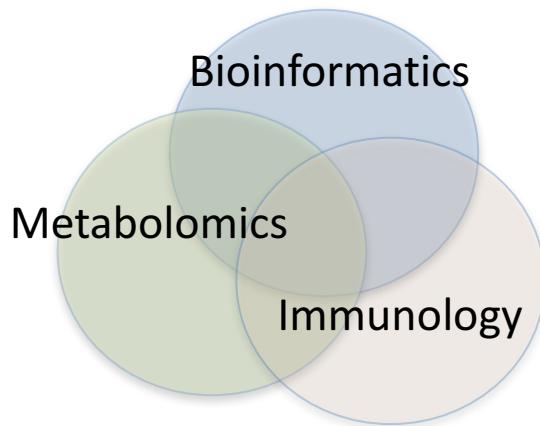




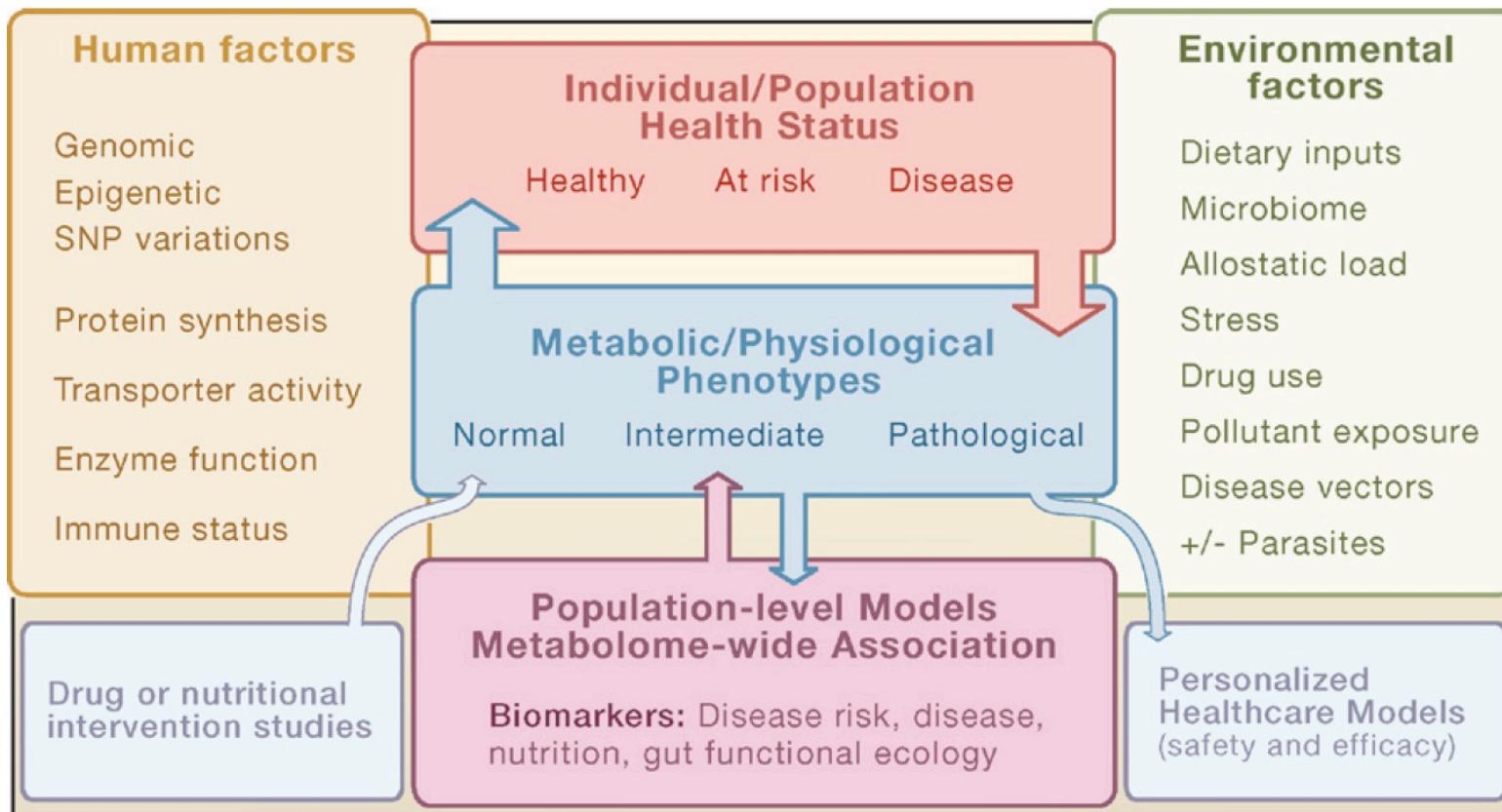
# Metabolomics and Precision Medicine



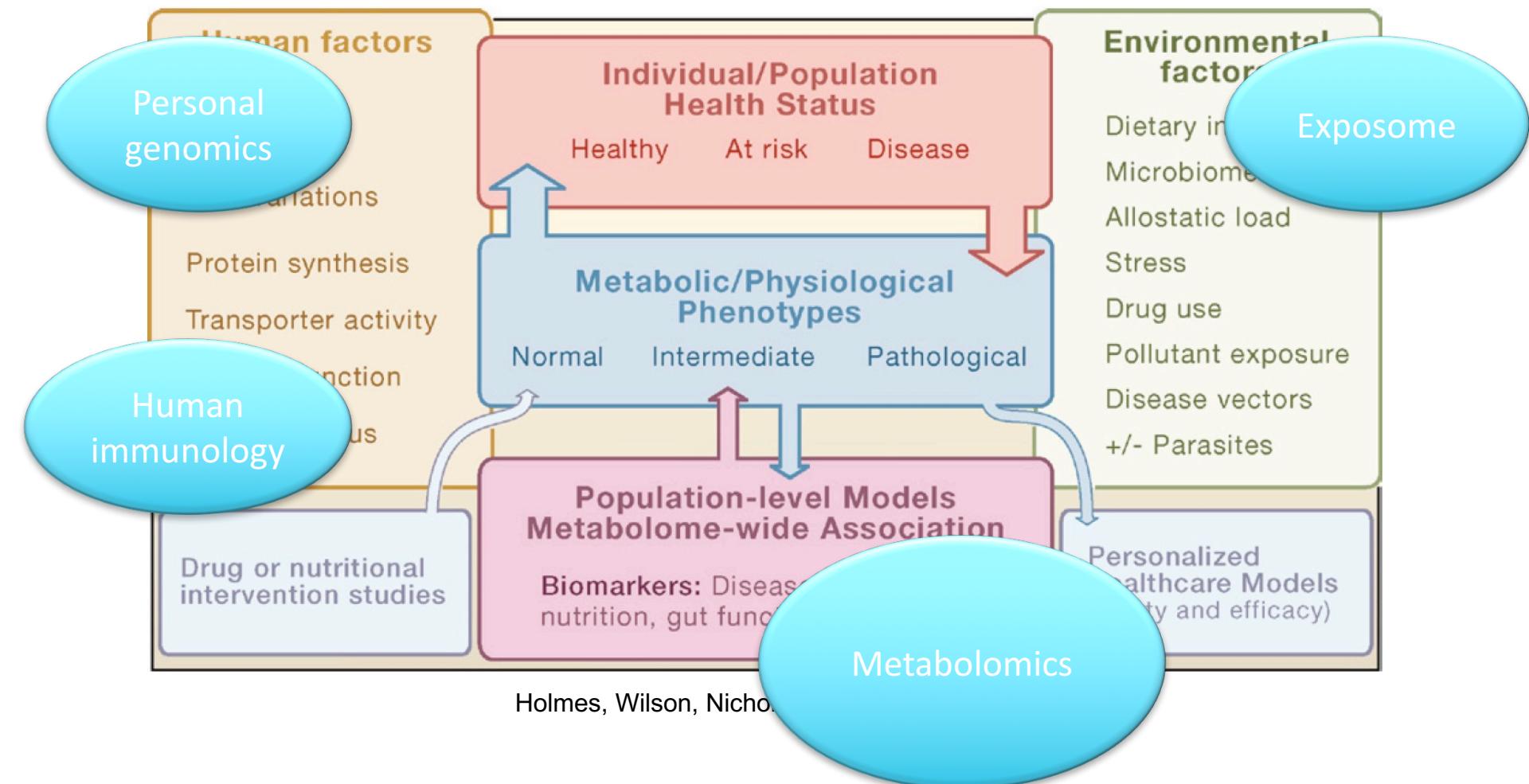
Shuzhao Li, Ph.D  
Assistant Professor  
Department of Medicine  
Emory University  
August 29, 2019

# Modeling systems medicine

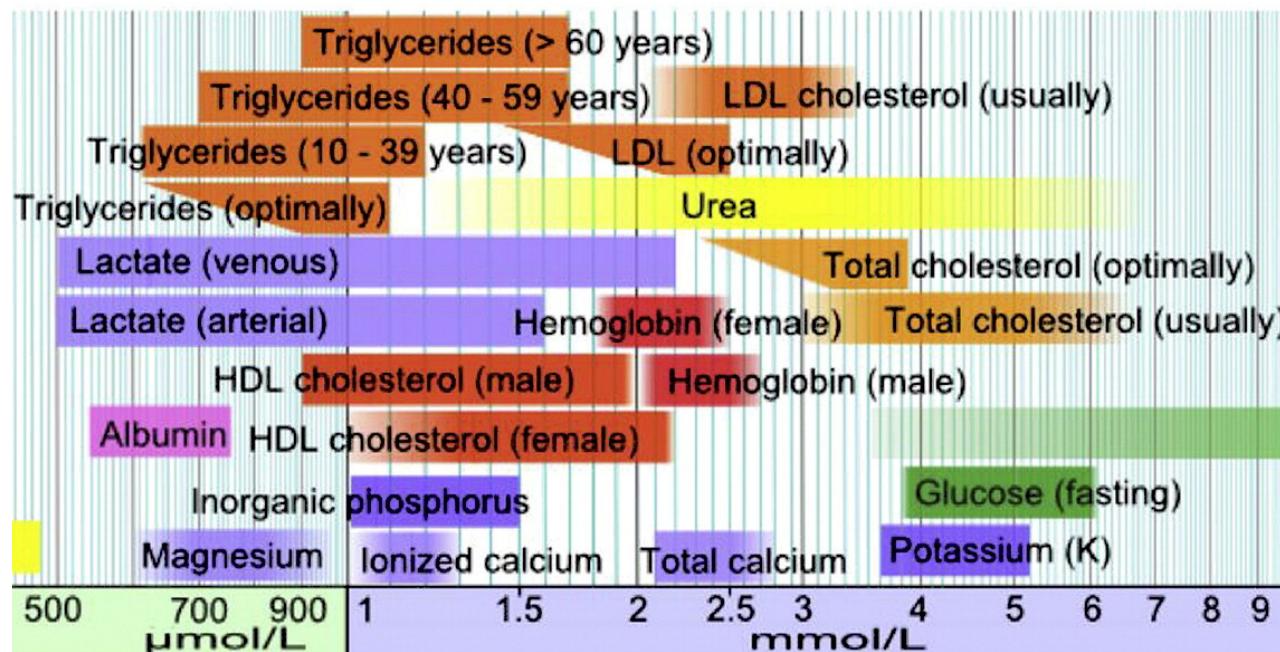
Holmes, Wilson, Nicholson (2008). Cell 134:714



# What has changed (2019)

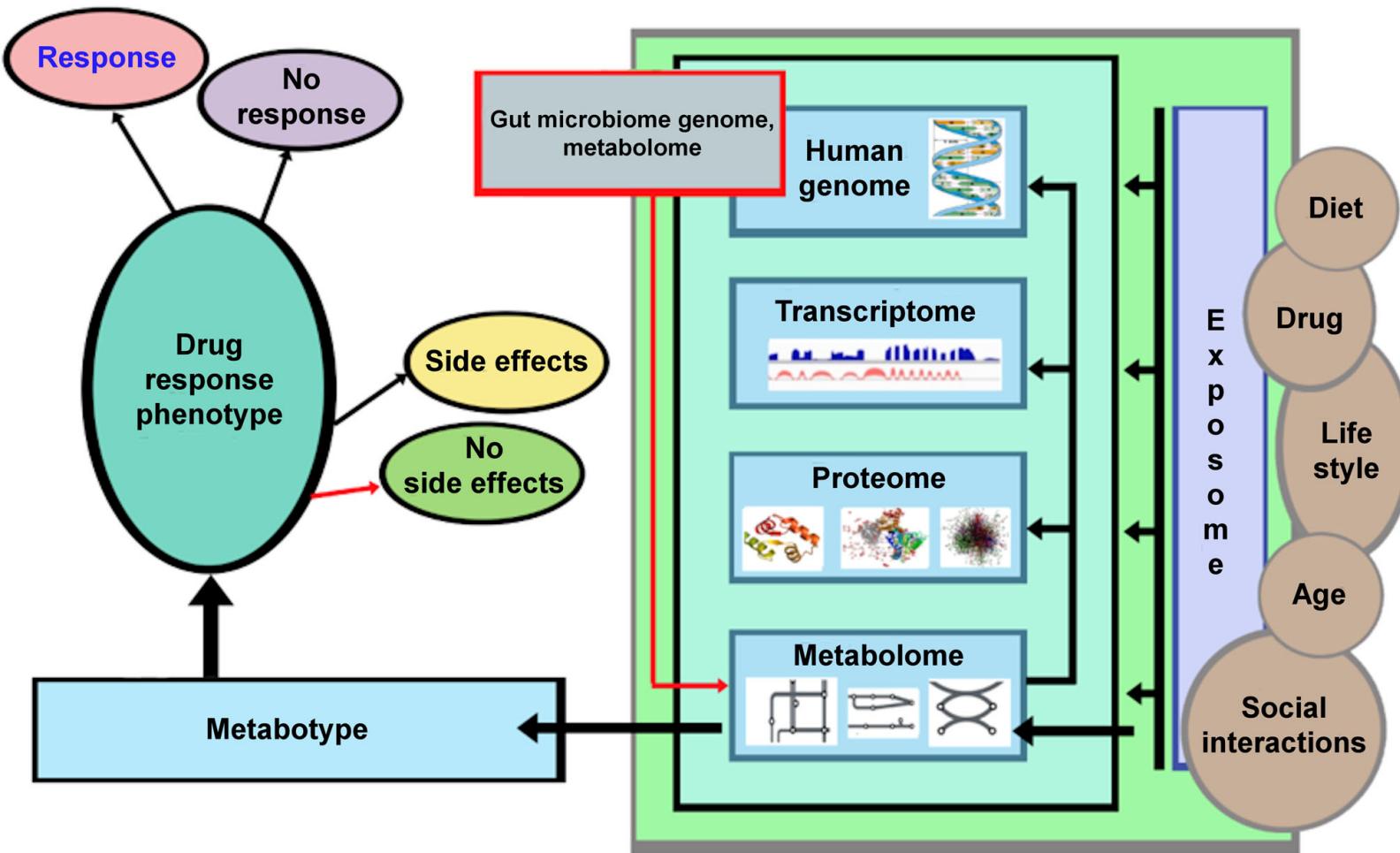


# Examples of blood metabolite concentrations



Adopted from Medical gallery of Mikael Haggstrom 2014.  
*WikiJournal of Medicine*, 1(2), p.1.

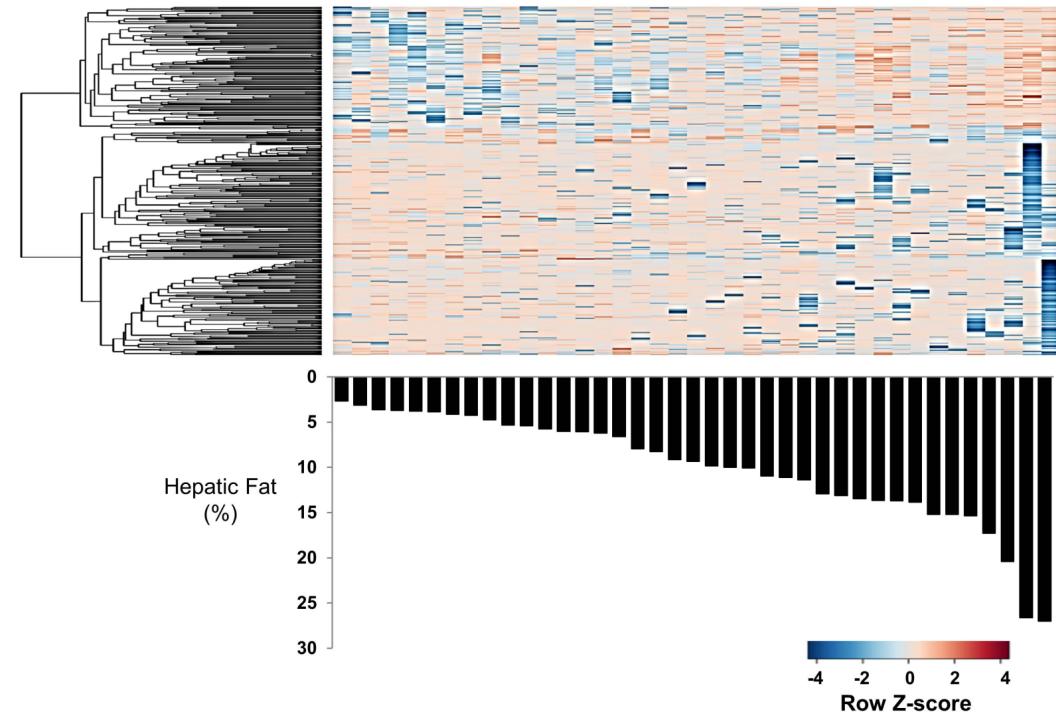
Beger, R.D., Dunn, W., Schmidt, M.A., Gross, S.S., Kirwan, J.A., Cascante, M., Brennan, L., Wishart, D.S., Oresic, M., Hankemeier, T. and Broadhurst, D.I., 2016. Metabolomics enables precision medicine: “a white paper, community perspective”. *Metabolomics*, 12(9), p.149.



# Metabolomics and Precision Medicine: Topics

- MWAS to understand disease risks and pathobiology
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# Metabolome wide association study of NAFLD

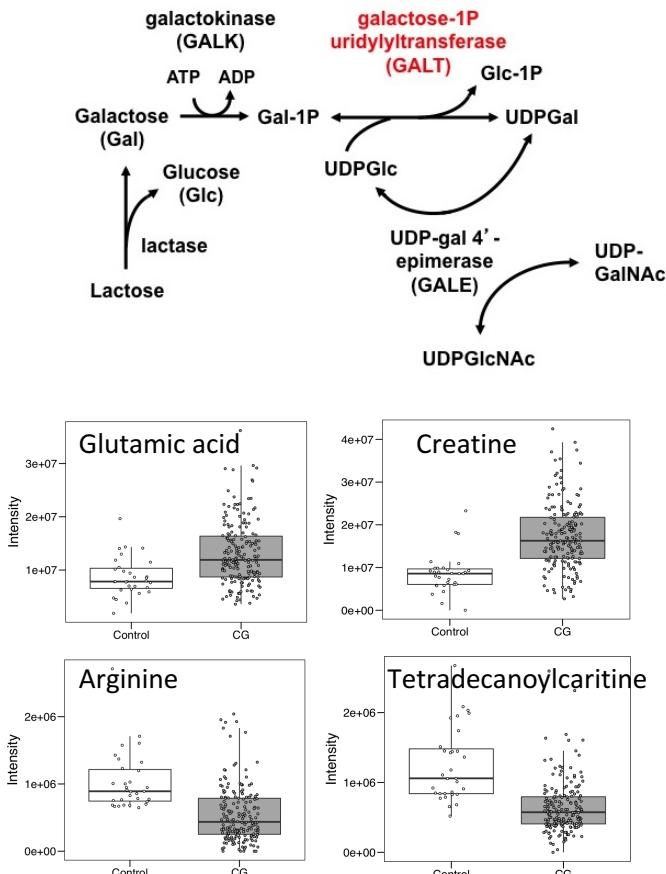


Jin, Banton, et al., 2016.  
*The Journal of pediatrics* 172: 14

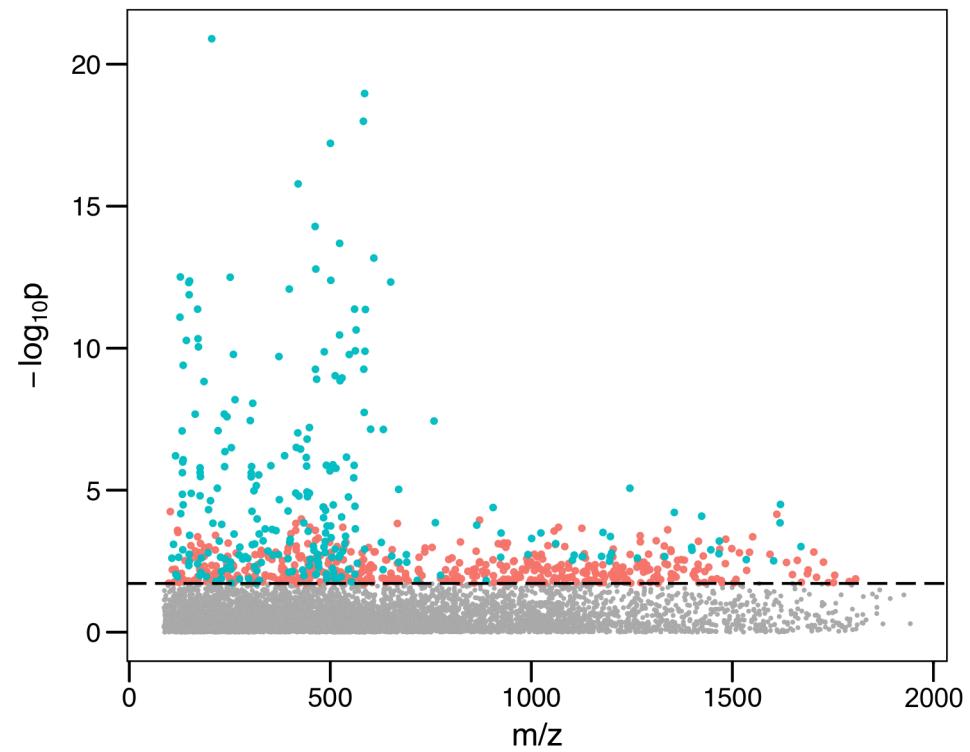
Pathway	Overlap size	Pathway size	Model p-value
Vitamin E metabolism	9	32	0.00095
Drug metabolism - cytochrome P450	8	34	0.00196
Tyrosine metabolism	15	79	0.00202
Vitamin B2 (riboflavin) metabolism	3	6	0.00229
Purine metabolism	10	51	0.00332
Ascorbate (Vitamin C) and Aldarate Metabolism	4	16	0.00773
Vitamin B9 (folate) metabolism	4	18	0.01307
Glutamate metabolism	3	12	0.01834
Methionine and cysteine metabolism	7	42	0.02026
Alanine and Aspartate Metabolism	4	20	0.02159
Biopterin metabolism	3	13	0.02493
Di-unsaturated fatty acid beta-oxidation	3	13	0.02493
Histidine metabolism	4	22	0.03449
Glycine, serine, alanine and threonine metabolism	8	53	0.03499
Valine, leucine and isoleucine degradation	7	46	0.03894

# Metabolomics of a genetic disorder

## Classical Galactosemia

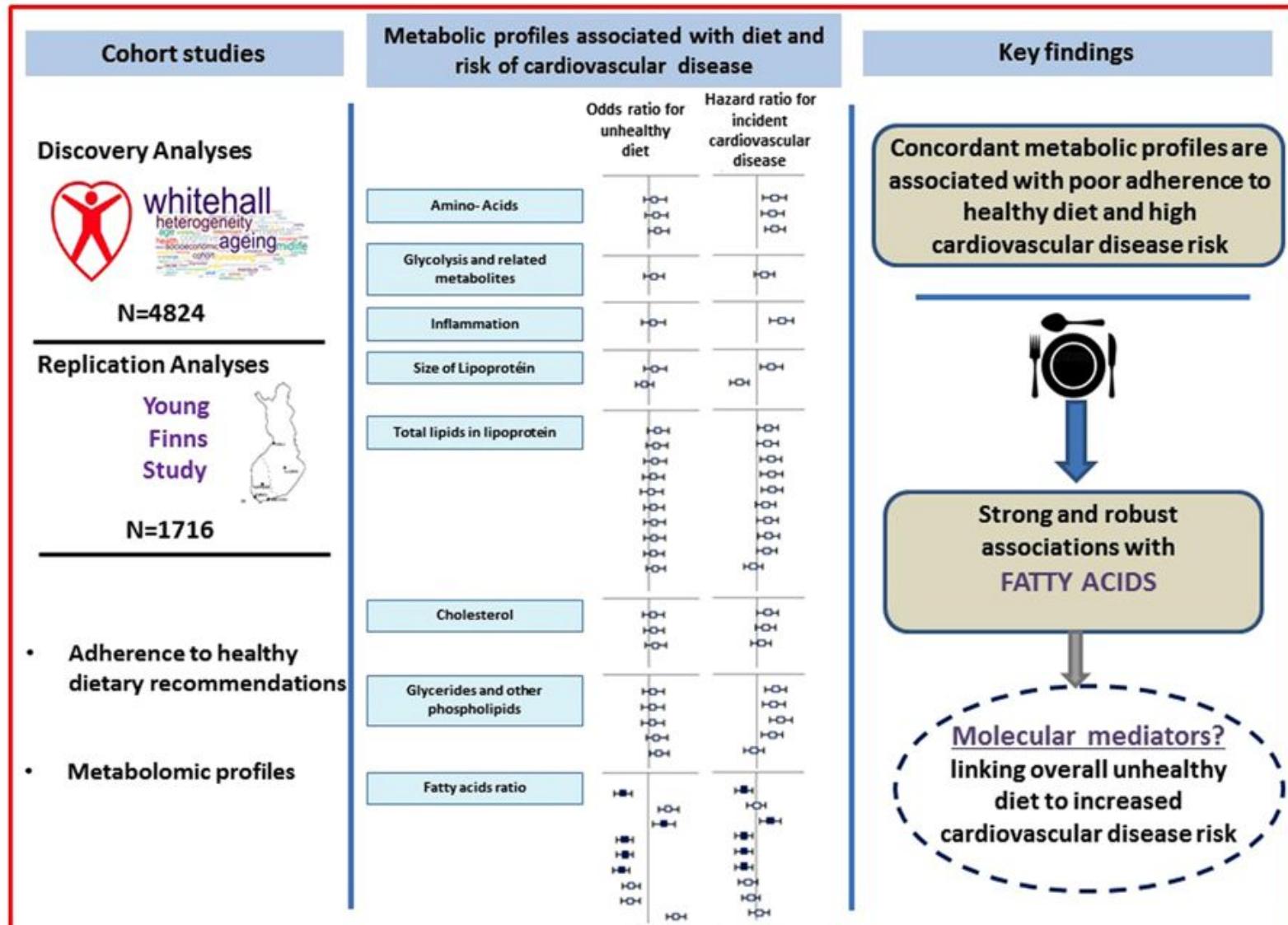


## Patients blood metabolomics (N=138)



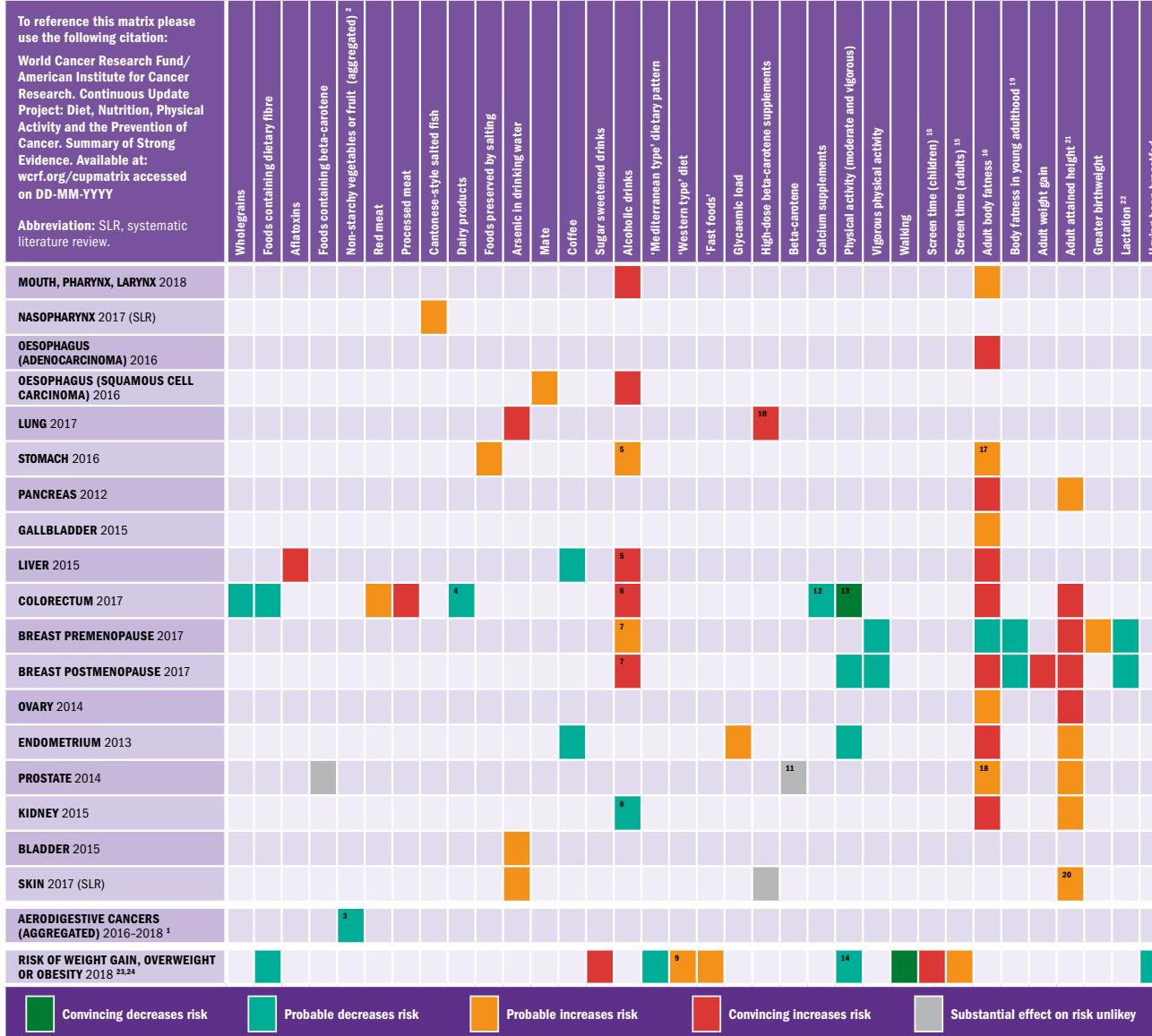
Fischer et al (2019) J Inherit Metab Dis.

# MWAS for epidemiology



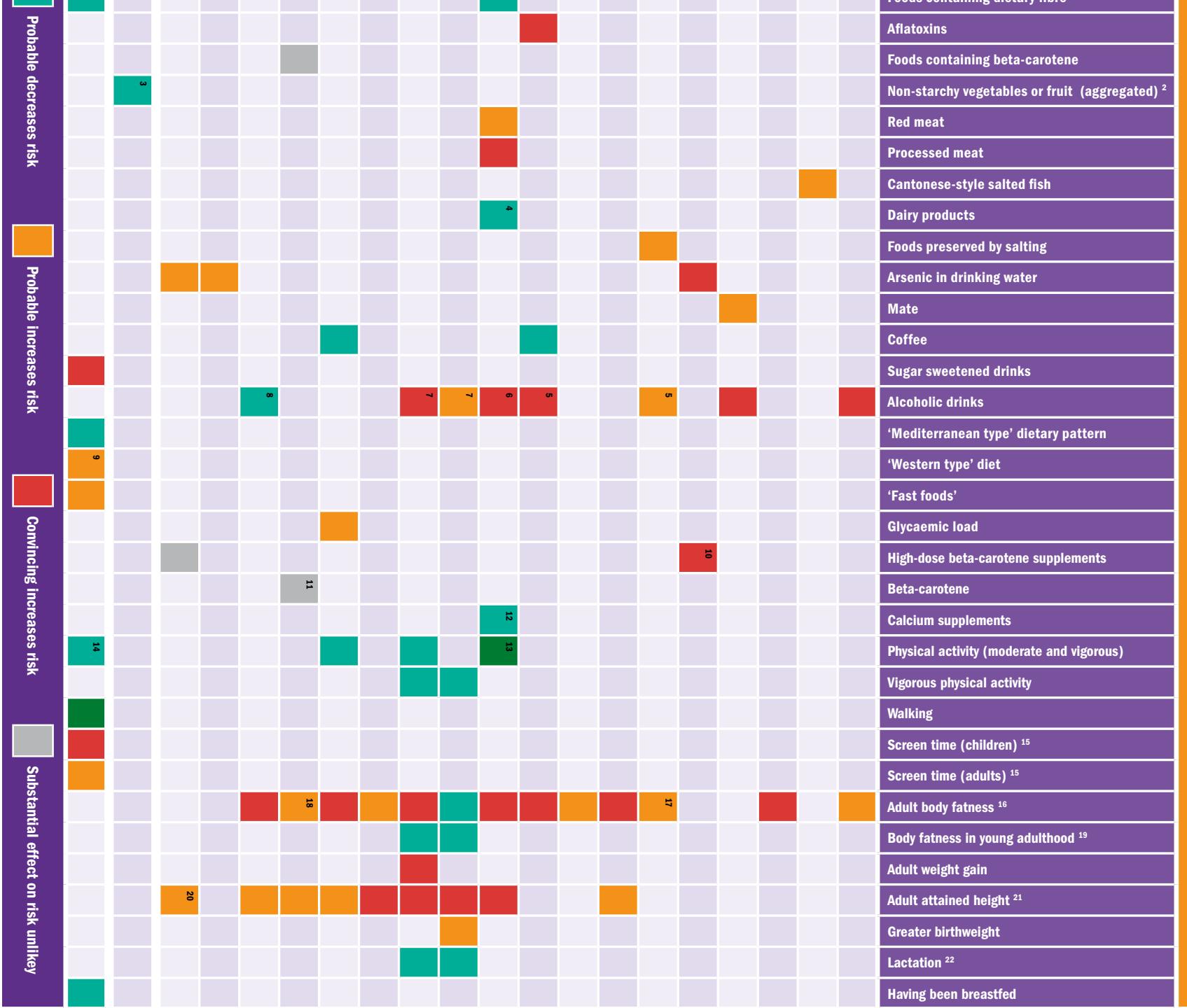
Akbaraly et al. 2018. Association of circulating metabolites with healthy diet and risk of cardiovascular disease: analysis of two cohort studies. *Scientific reports*, 8(1), p.8620.

# SUMMARY OF STRONG EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND THE PREVENTION OF CANCER



# CANCER RISK FACTORS

## STRONG EVIDENCE ON DIET, NUTRITION, AL ACTIVITY AND THE PREVENTION OF CANCER

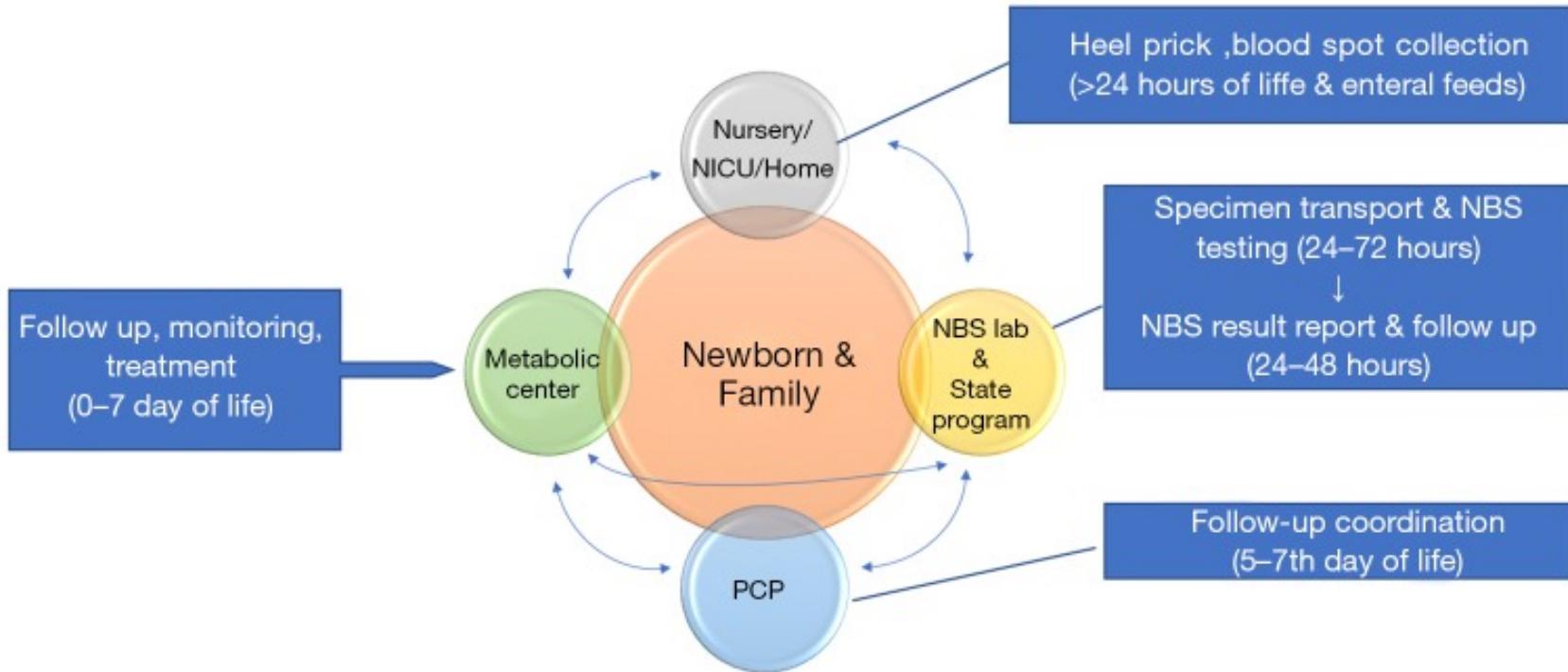


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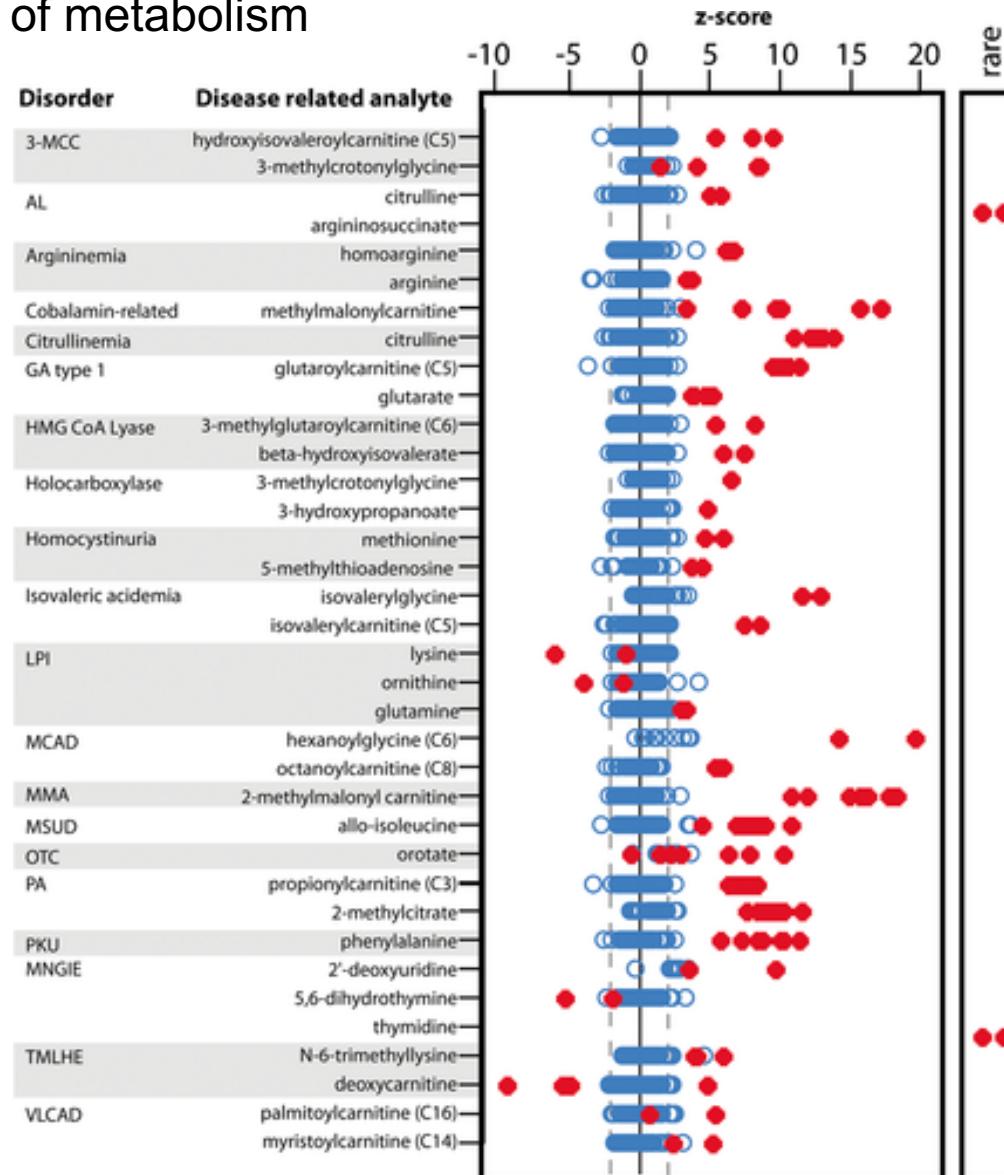
# Newborn screen

## Newborn Screening Workflow



Kanungo et al. Ann Transl Med. 2018 Dec; 6(24): 468.

# Untargeted metabolomic analysis for the clinical screening of inborn errors of metabolism





# Metabolomics and Precision Medicine: Topics

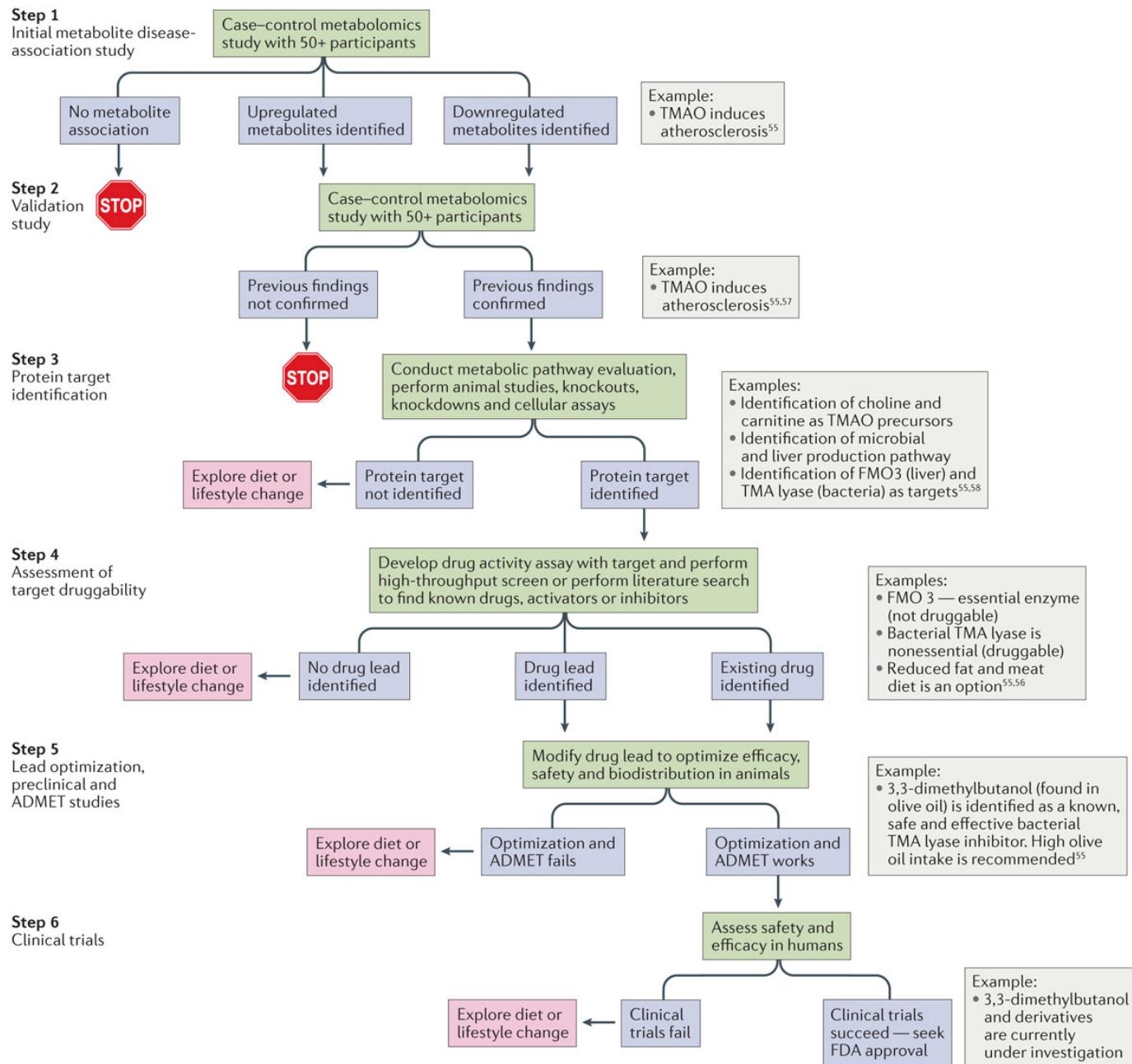
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# Metabolite-based drug discovery and development using atherosclerosis as an example

David S. Wishart (2016) Emerging applications of metabolomics in drug discovery and precision medicine. *Nature Reviews Drug Discovery* 15, 473–484

ADMET, absorption, distribution, metabolism, excretion and toxicity; FDA, US Food and Drug Administration; FMO3, flavin monooxygenase 3; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

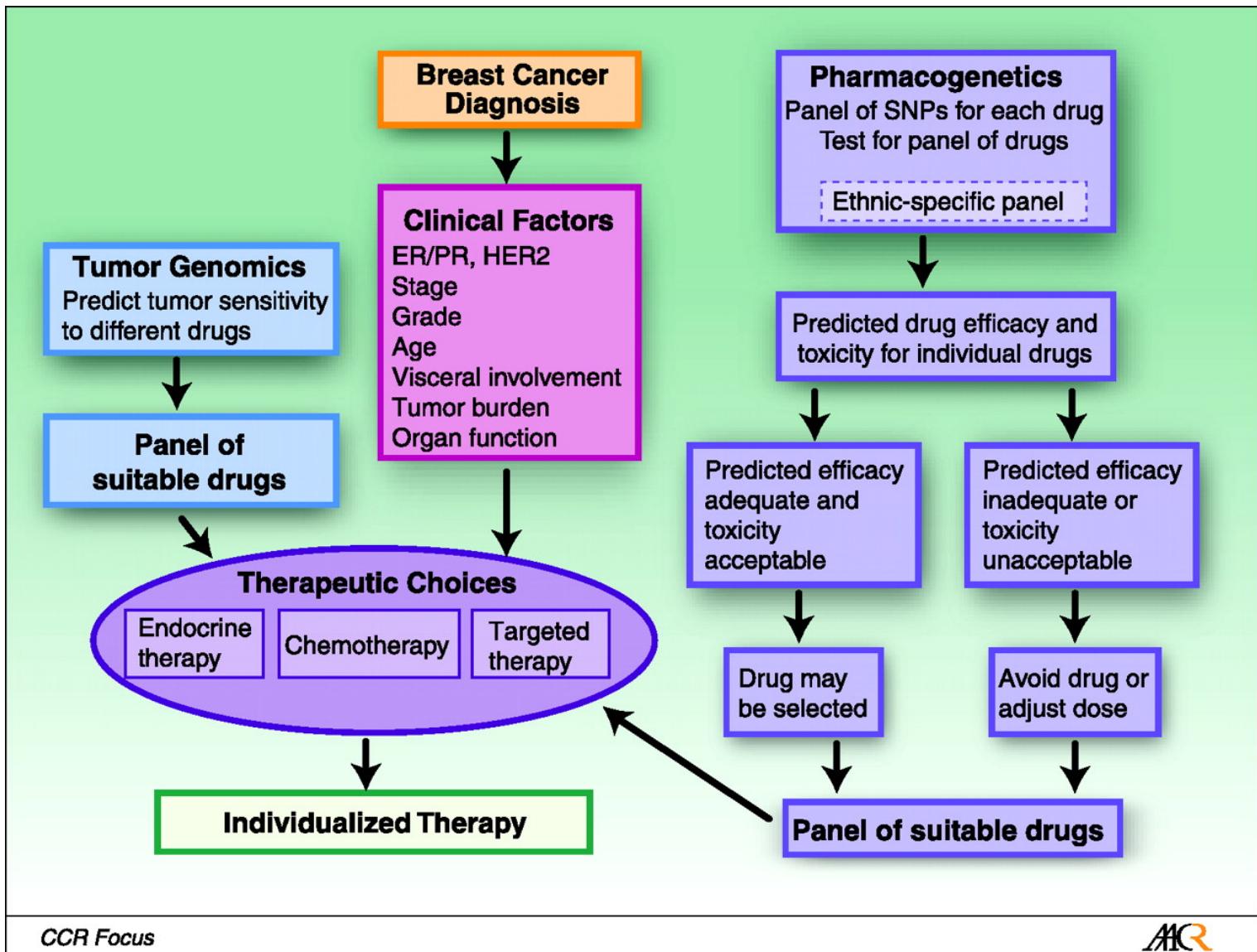
Drug development steps or processes are marked in green, outcomes in blue and alternative actions in red.



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# Treatment decision making



## IMPRECISION MEDICINE

For every person they help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

**1. ABILIFY** (aripiprazole)  
Schizophrenia



**2. NEXIUM** (esomeprazole)  
Heartburn



**3. HUMIRA** (adalimumab)  
Arthritis



**4. CRESTOR** (rosuvastatin)  
High cholesterol



**5. CYMBALTA** (duloxetine)  
Depression



**6. ADVAIR DISKUS** (fluticasone propionate)  
Asthma



**7. ENBREL** (etanercept)  
Psoriasis



**8. REMICADE** (infliximab)  
Crohn's disease



**9. COPAXONE** (glatiramer acetate)  
Multiple sclerosis



**10. NEULASTA** (pegfilgrastim)  
Neutropenia



# Drug efficacy

Schork, N.J., 2015.  
*Nature*, 520, p.609.

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# Cancer therapies

**Therapeutic efficacy and related toxicities of drugs developed for cancer treatment.**

Therapeutic strategy	Target	Clinical benefit	Toxicity	Reference
<b>IMMUNOTHERAPY</b>				
Ipilimumab	Anti-CTLA-4	Increased OS from 6.4 to 10 months	15% had grade 3 or 4 AE	(55)
Pembrolizumab	Anti-PD-1	Response rate of 38%	Grade 1 or 2 AE	(56)
Ipilimumab + Nivolumab	Anti-CTLA-4 plus Anti-PD-1	Objective response 53%	50% had grade 3 or 4 AE	(57)
BMS-93655	Anti-PD-L1	Objective response 6%–17%	9% had grade 3 or 4 AE	(58)
<b>MONOCLONAL ANTIBODIES</b>				
Trastuzumab	Anti-HER2/neu	Increased OS from 20.3 to 25.1 months	27% had cardiac toxicity	(59)
Bevacizumab	Anti-VEGF	Increased OS from 15.6 to 20.3 months	Grade 3 hypertension	(60)
Rituximab	Anti-CD20	Clinical remission in 46% of patients	Grade 1 or 2 AE	(61)
<b>VACCINES</b>				
Provenge	PAP plus GM-CSF	Increased OS from 21.7 to 25.8 months	Grade 1 or 2 AE	(62)
Gardasil	HPV type 6, 11, 16, and 18	Efficacy was 98%	Grade 1 or 2 AE	(63)
Pemetrexed	MAGE-A3 + TLR4 + TLR9	No difference in OS	9% had grade 3 or 4 AE	(64)
Synthetic long-peptide	HPV-16 E6 plus HPV-16 E7	Response rate of 79%	Grade 1 or 2 AE	(65)
<b>ADOPTIVE CELL TRANSFER</b>				
T-cells	MART-1 or gp100	Response rate of 46%	Autoimmune events	(66)
Naïve T-cells	LY6K-177 peptides	Response rate of 22%	Grade 1 or 2 AE	(67)
Memory T-cells	MCF-7 cell lysate antigen	Increased OS to 33.8 months	No toxicity noted	(68)
CAR therapy	Modified CD19	Response rate of 90%	Cytokine release syndrome	(69)
CAR therapy	GD2 antigen	Median OS 931 days	15% had grade 1 or 3 AE	(70)

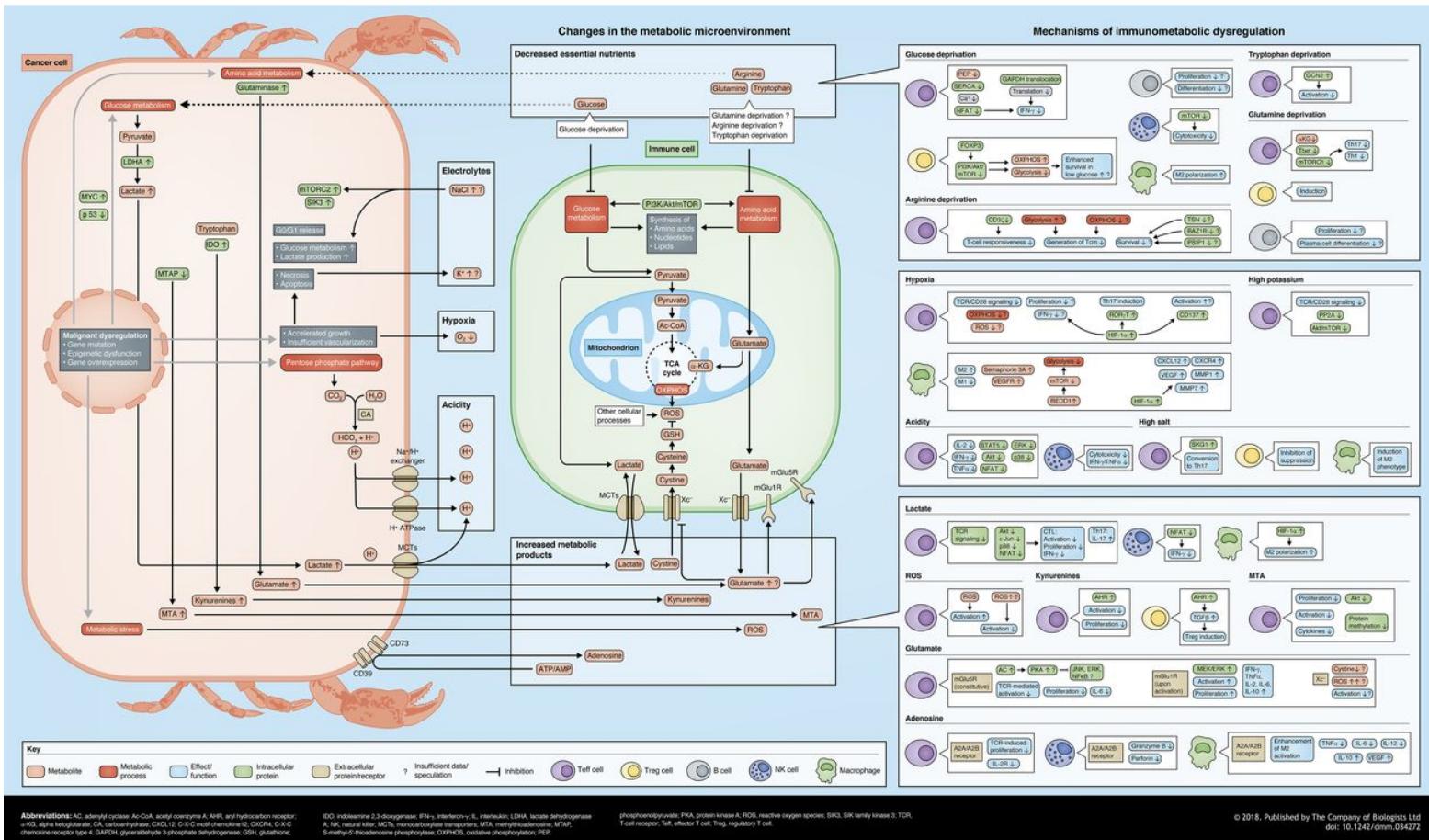
AE, adverse event; HPV, human papillomavirus; OS, overall survival; PAP, prostatic acid phosphatase.

# ImmunoMetabolism



# Immunometabolism in Cancer at a Glance

Katrin Singer, Wan-Chen Cheng, Marina Kreutz, Ping-Chih Ho and Peter J. Siska



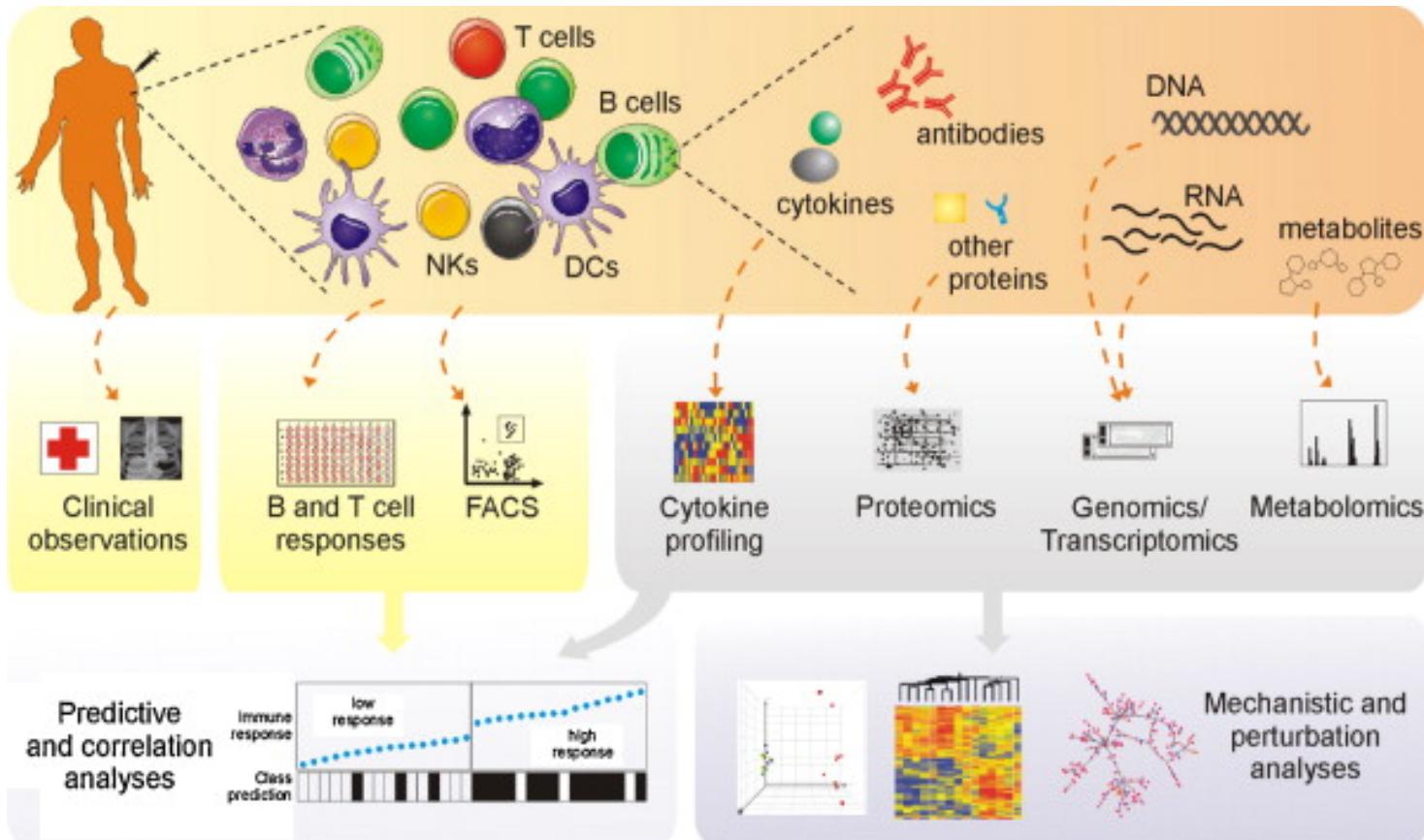
Katrin Singer et al. Dis. Model. Mech. 2018;11:dmm034272



# Metabolomics and Precision Medicine: Topics

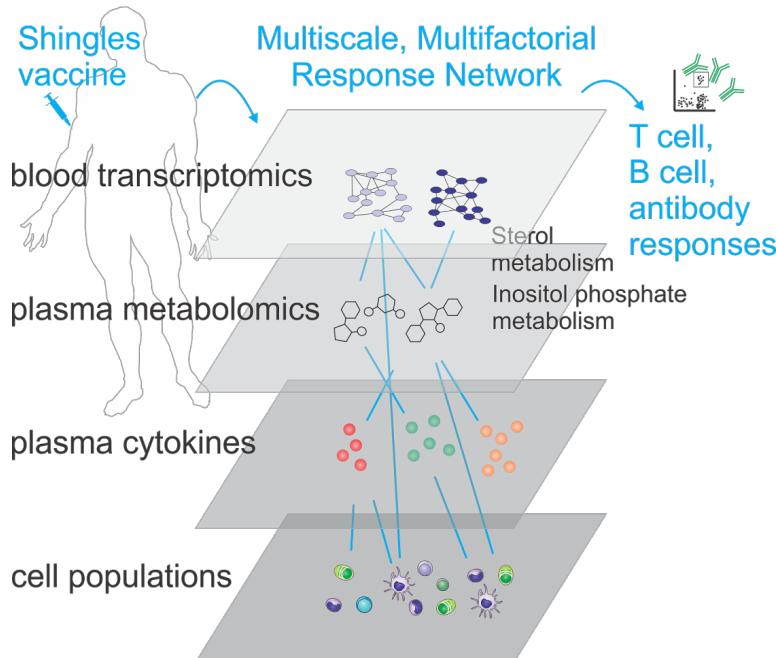
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# Systems biology to understand vaccine efficacy



Li et al. 2013. Seminars in Immunology 25:209

# Metabolic Phenotypes of Response to Vaccination in Humans



Li et al., 2017. *Cell* 169, 862–877

## Lessons learned:

- Early molecular events in peripheral blood are predictive of later adaptive responses
- Strong connections found btw plasma metabolomics and blood transcriptomics during immune response
- Metabolic phenotype affects immune outcome
- Blood metabolites can precede gene activity in the cells
- Orthogonal omics data can cross validate one another

# Metabolomics and Precision Medicine: Topics

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# M Snyder: integrative personal omics profile

## Resource

### Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Rui Chen,<sup>1,11</sup> George I. Mias,<sup>1,11</sup> Jennifer Li-Pook-Than,<sup>1,11</sup> Lihua Jiang,<sup>1,11</sup> Hugo Y.K. Elana Miriami,<sup>1</sup> Konrad J. Karczewski,<sup>1</sup> Manoj Hariharan,<sup>1</sup> Frederick E. Dewey,<sup>3</sup> Yong Hogene Im,<sup>1</sup> Lukas Habegger,<sup>6,7</sup> Suganthi Balasubramanian,<sup>6,7</sup> Maeve O'Huallachain,<sup>1</sup> Sara Hillenmeyer,<sup>1</sup> Rajini Haraksingh,<sup>1</sup> Donald Sharon,<sup>1</sup> Ghia Euskirchen,<sup>1</sup> Phil Lacroute,<sup>1</sup> Maya Kasowski,<sup>1</sup> Fabian Grubert,<sup>1</sup> Scott Seki,<sup>2</sup> Marco Garcia,<sup>2</sup> Michelle Whirl-Carrillo,<sup>1</sup> Maria A. Blasco,<sup>9</sup> Peter L. Greenberg,<sup>4</sup> Phyllis Snyder,<sup>1</sup> Teri E. Klein,<sup>1</sup> Russ B. Altman,<sup>1</sup> Mark Gerstein,<sup>6,7,8</sup> Kari C. Nadeau,<sup>2</sup> Hua Tang,<sup>1</sup> and Michael Snyder<sup>1,\*</sup>

<sup>1</sup>Department of Genetics, Stanford University School of Medicine

<sup>2</sup>Division of Systems Medicine and Division of Immunology and Allergy, Department of Pediatrics

<sup>3</sup>Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine

<sup>4</sup>Division of Hematology, Department of Medicine

<sup>5</sup>Department of Bioengineering

Stanford University, Stanford, CA 94305, USA

<sup>6</sup>Program in Computational Biology and Bioinformatics

<sup>7</sup>Department of Molecular Biophysics and Biochemistry

<sup>8</sup>Department of Computer Science

Yale University, New Haven, CT 06520, USA

<sup>9</sup>Telomeres and Telomerase Group, Molecular Oncology

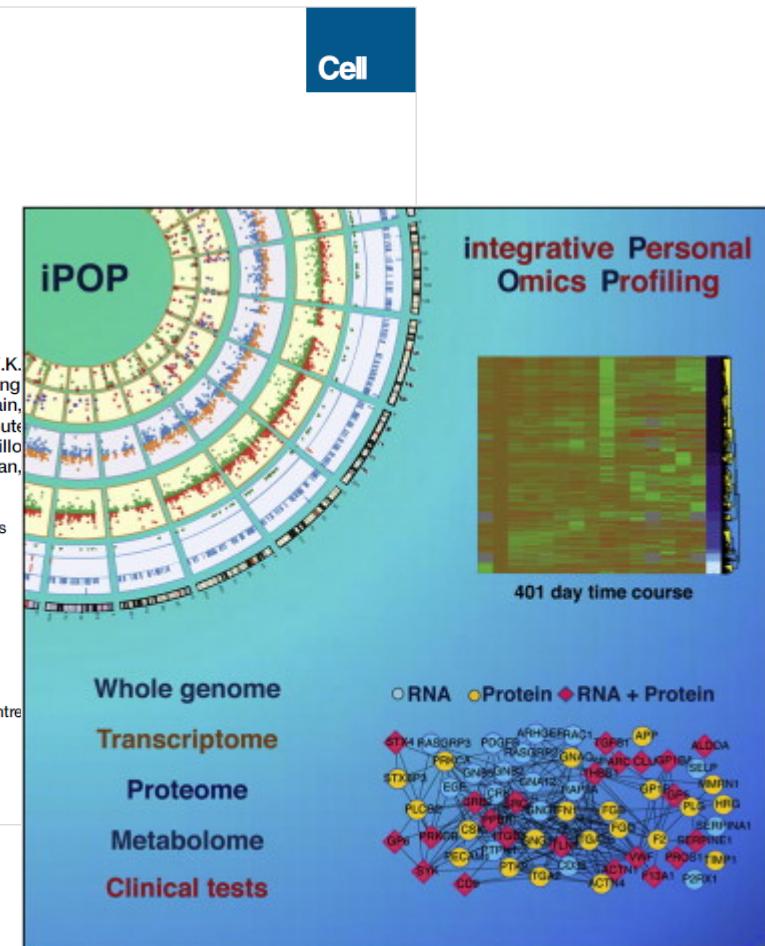
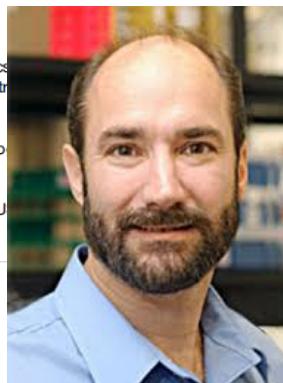
<sup>10</sup>Life Length, Madrid E-28003, Spain

<sup>11</sup>These authors contributed equally to this work

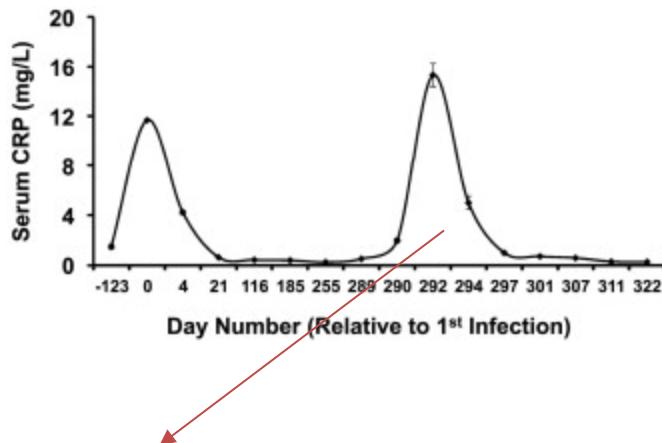
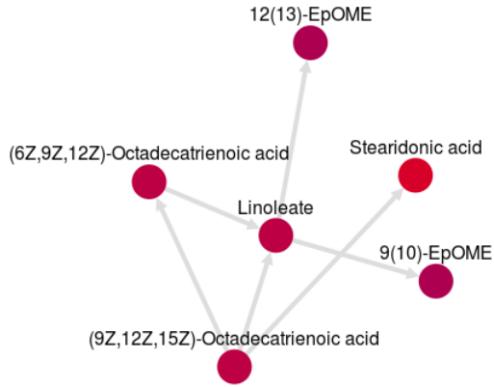
<sup>12</sup>Present address: Personalis, Palo Alto, CA 94301, USA

\*Correspondence: mpsnyder@stanford.edu

DOI 10.1016/j.cell.2012.02.009

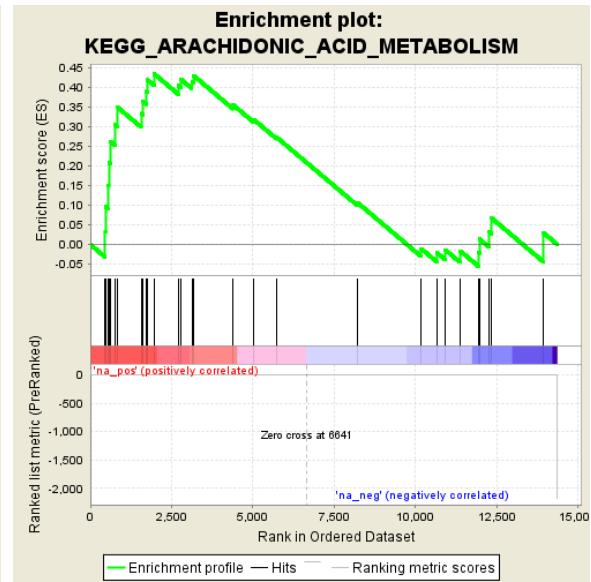
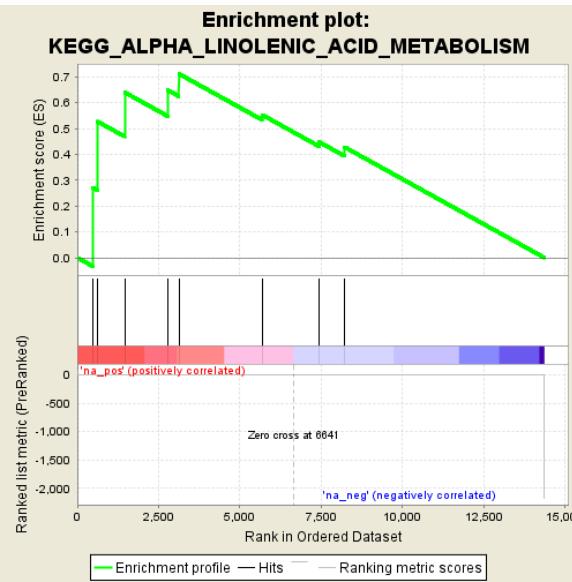
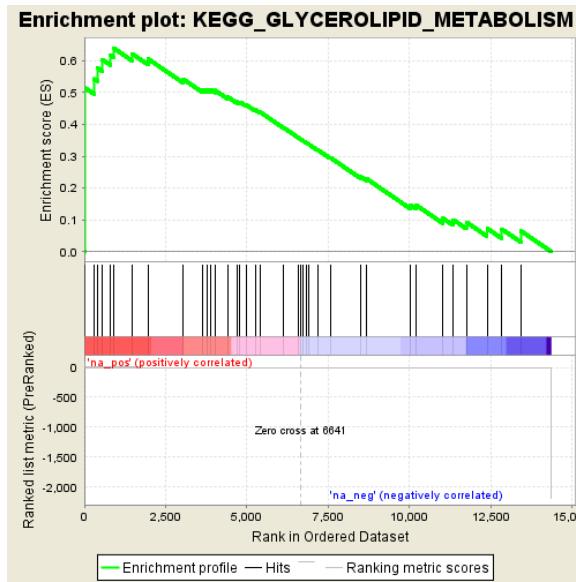


# *Mummichog* interpretation of Snyder metabolome



Pathways	overlap_size	pathway_size	p-value (raw)	p-value
Linoleate metabolism	8	10	3e-05	0.00635
Glycerophospholipid metabolism	7	19	0.04285	0.01085
Porphyrin metabolism	5	16	0.15234	0.03058

# *Mummichog* interpretation of Snyder metabolome

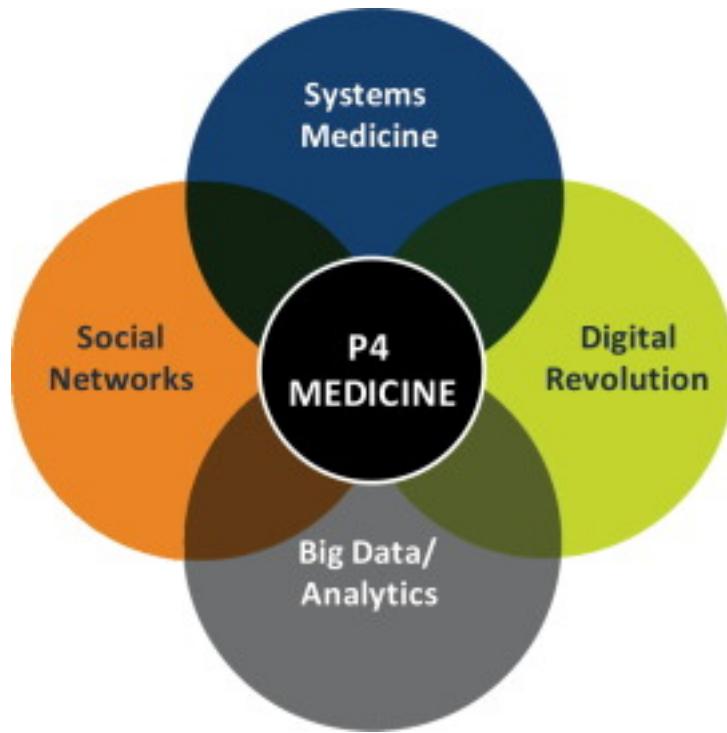


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# L. Hood: P4 Medicine

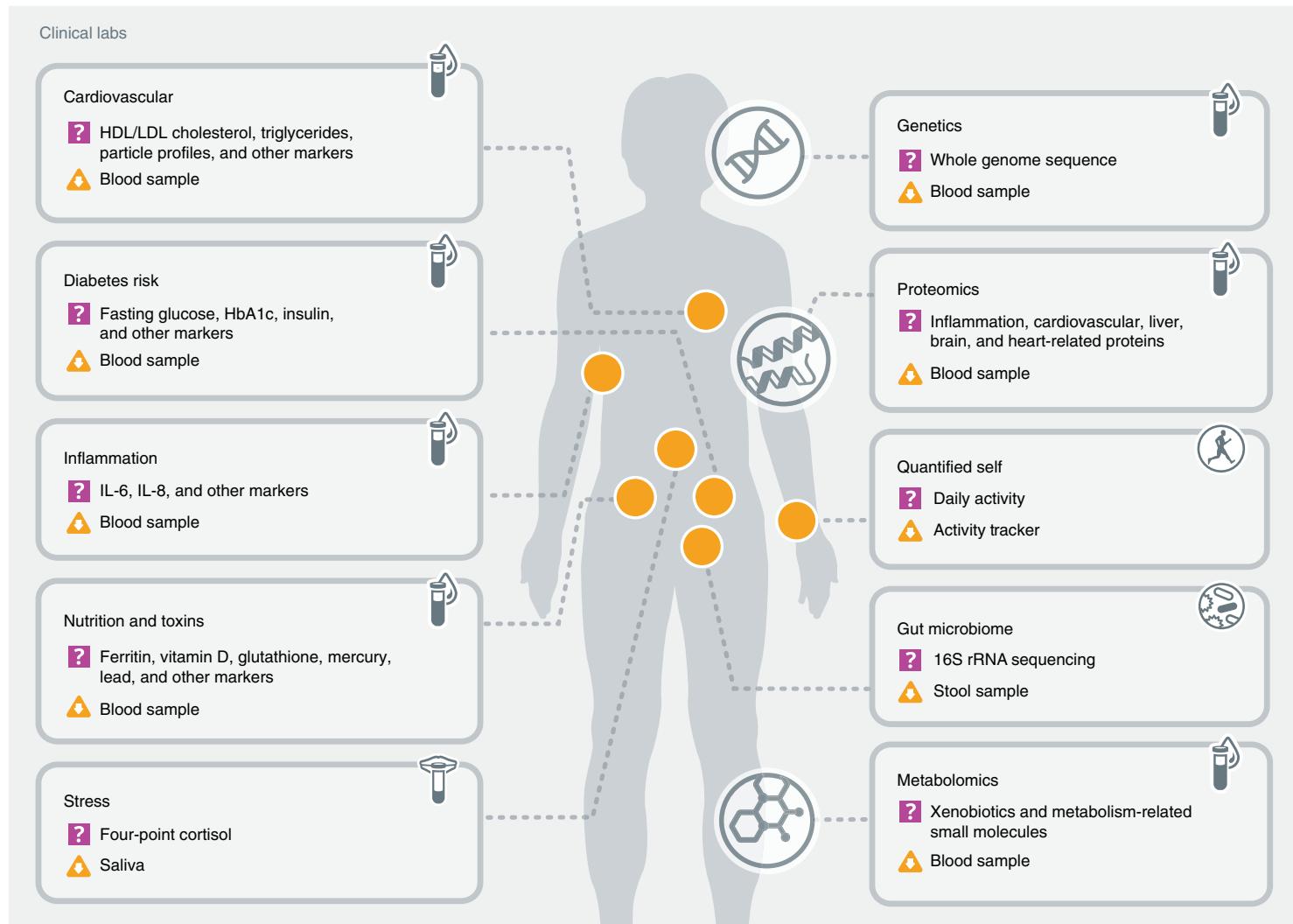


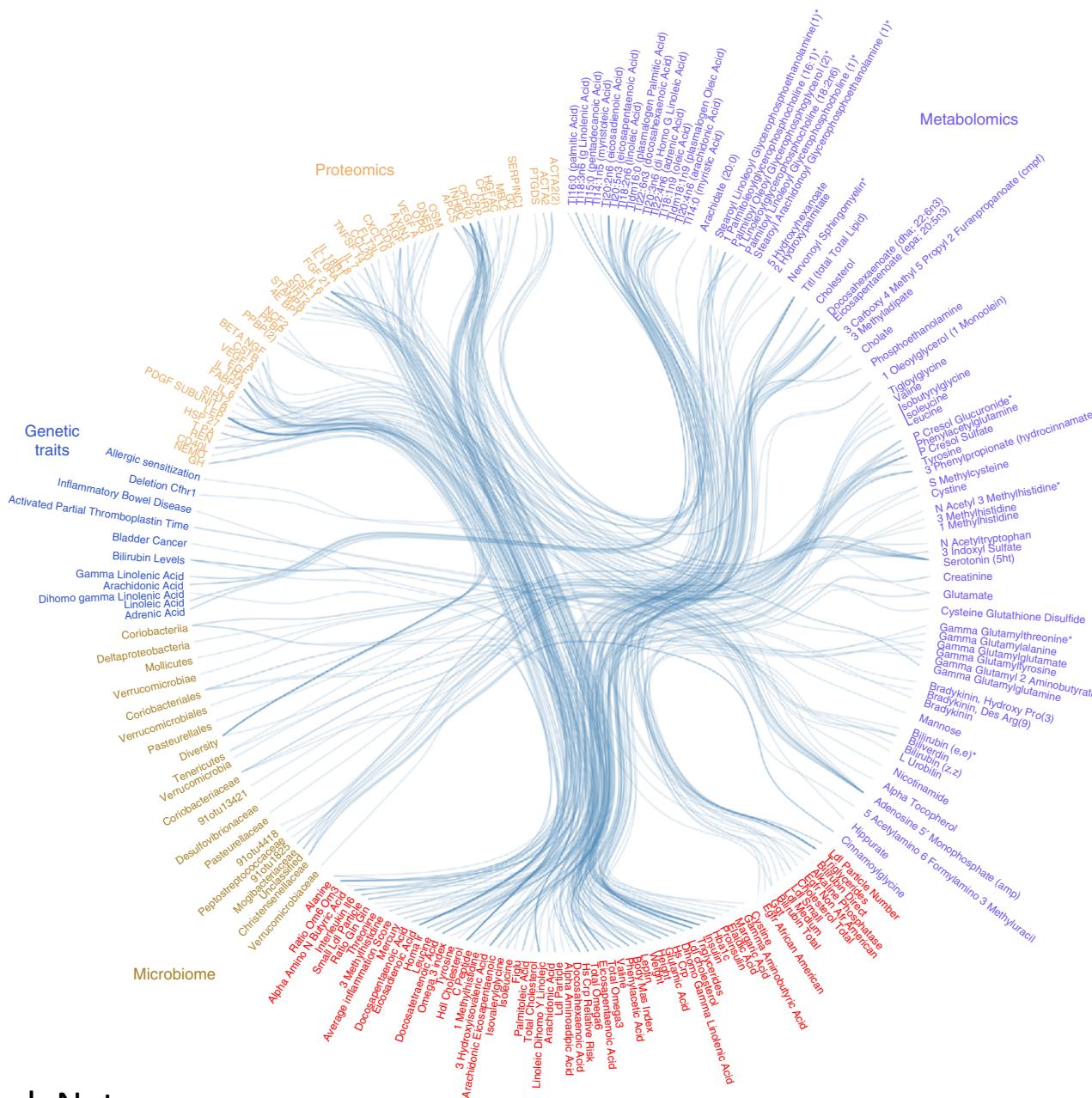
*Systems medicine* is the systems approach to disease (including new technologies and systems-driven strategies). This concept led to the idea that healthcare should be predictive, preventive, personalized, and participatory (P4). Moreover, we realized that *P4 healthcare* should have two major thrusts—wellness and disease, whereas wellness is almost entirely ignored by the conventional 20th-Century Medicine

- Hood. Genomics, Proteomics & Bioinformatics, Volume 16, Issue 1, 2018, pp. 1-9

# A wellness study of 108 individuals using personal, dense, dynamic data clouds

Price et al. Nature Biotechnology 35, pages 747–756 (2017)





Price et al. Nature Biotechnology 35, pages 747–756 (2017)

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# Draft human genome (2000)



Craig Venter, Bill Clinton, Francis Collins

# The post-genomics era?



J. Craig Venter, Bill Clinton, Francis Collins

# The case for a US prospective cohort study of genes and environment

Francis S. Collins

*National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, MSC 2152, 31 Center Drive, Bethesda, Maryland 20892-2152, USA (e-mail: fc23a@nih.gov)*

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Information from the Human Genome Project will be vital for defining the genetic and environmental factors that contribute to health and disease. Well-designed case-control studies of people with and without a particular disease are essential for this, but rigorous and unbiased conclusions about the causes of diseases and their population-wide impact will require a representative population to be monitored over time (a prospective cohort study). The time is right for the United States to consider such a project.

Collins, 2004. Nature, 429:475



# The case for a US study of genes and disease

Francis S. Collins

National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-2152, USA (e-mail: fc23a@nih.gov)

**Information from the Human Genome Project will be needed to identify the genetic variants that contribute to health and disease. Well-designed studies of particular diseases and their causes are essential for this, but rigorous prospective studies of the population-wide impact of variants and their effects on health and disease will require a large-scale, prospective cohort study. The time is right for the United States to lead this effort.**

Collins, 2004. Nature, 429:475

Perspective

## A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“**T**onight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015

President Obama has long expressed a strong conviction that science offers great potential for improving health. Now, the President has announced a research initiative that aims to accelerate progress toward a new era of precision medicine ([www.whitehouse.gov/precisionmedicine](http://www.whitehouse.gov/precisionmedicine)). We believe that the time is right for this visionary initiative, and the National Institutes of Health (NIH) and other partners will work to achieve this vision.

The concept of precision medicine — prevention and treatment strategies that take individual variability into account — is not new<sup>1</sup>; blood typing, for instance, has been used to guide blood

transfusions for more than a century. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. What is needed now is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice.

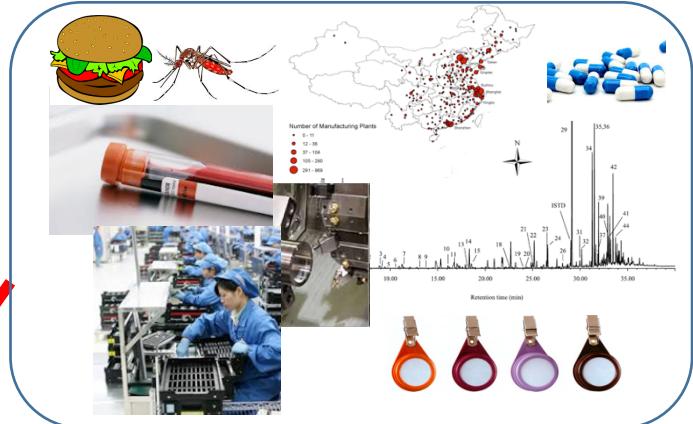
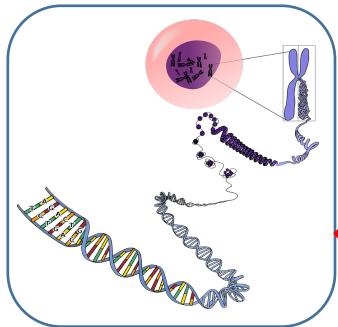
The proposed initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics. Furthermore, the initiative taps into converging trends of increased connectivity, through social media and mobile devices, and Americans’ growing desire to be active partners in medical research.

Oncology is the clear choice for enhancing the near-term impact of precision medicine. Cancers are common diseases; in the aggregate, they are among the leading causes of death nationally and worldwide, and their incidence is increasing as the population ages. They are also especially feared, because of their lethality, their symptoms, and the often toxic or disfiguring therapies

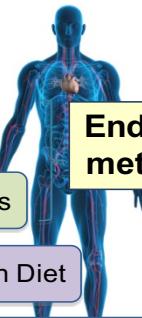
# G × M × E

# Environment

## Genome



## Gene function



Core Biological Metabolome

Microbiome-related Chemicals

Non-nutritive Chemicals in Diet

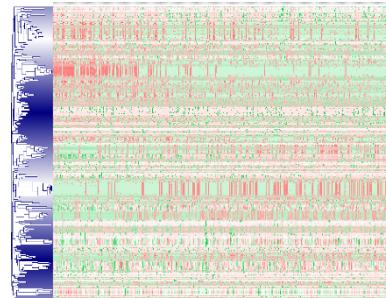
Supplements and Pharmaceuticals

**Environmental metabolome**

Commercial Products

Environmental Chemicals

## Molecular response



## Metabolome

## Body burden

## Recommended reading on metabolomics and precision medicine:

Beger, R.D., Dunn, W., Schmidt, M.A., Gross, S.S., Kirwan, J.A., Cascante, M., Brennan, L., Wishart, D.S., Oresic, M., Hankemeier, T. and Broadhurst, D.I., 2016. Metabolomics enables precision medicine: “a white paper, community perspective”. *Metabolomics*, 12(9), p.149.

Wishart, D.S., 2016. Emerging applications of metabolomics in drug discovery and precision medicine. *Nature reviews Drug discovery*, 15(7), p.473.