IBMC
Institute of Biomedical Chemistry

HIGHER SCHOOL OF ECONOMICS
NATIONAL RESEARCH UNIVERSITY

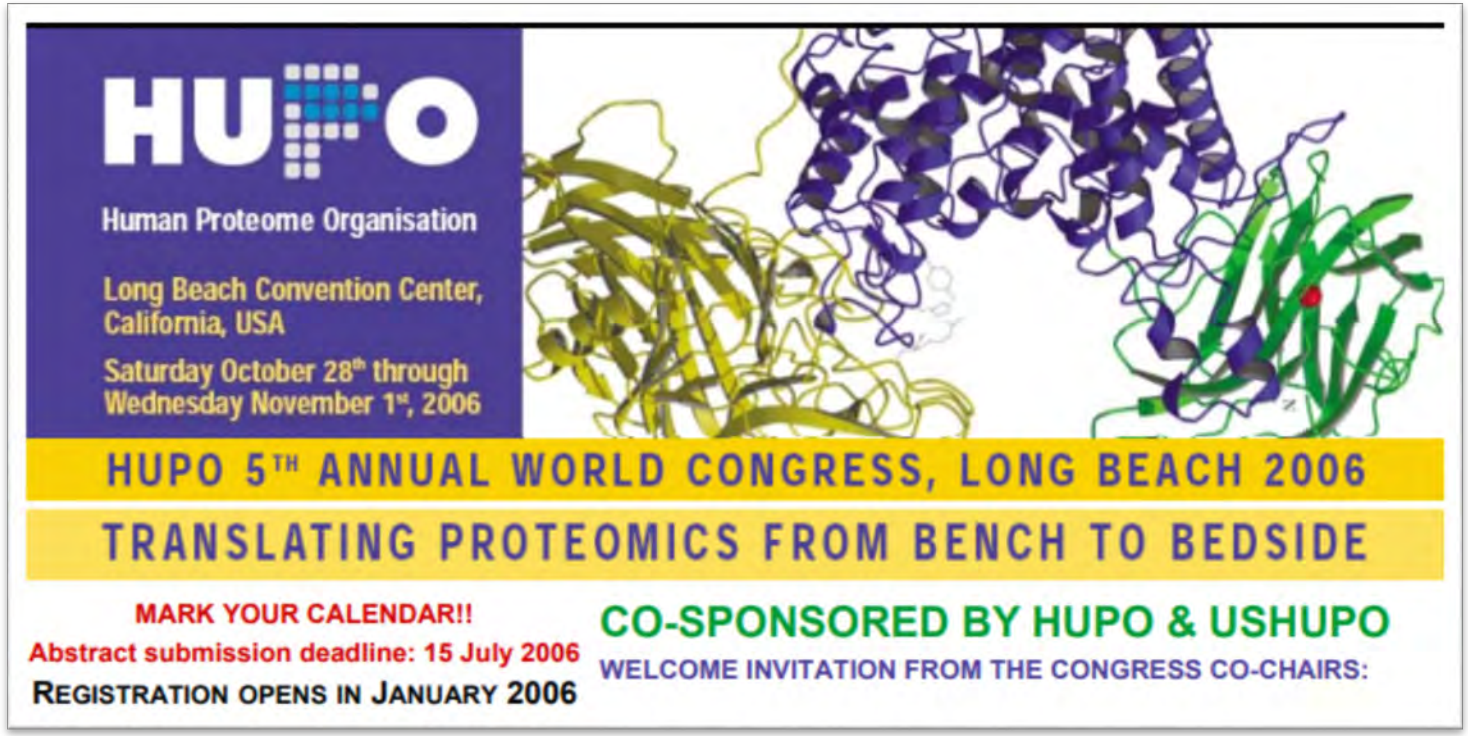
It Was Twenty Years Ago Today: How Omics Have Succeeded in Personalized Medicine

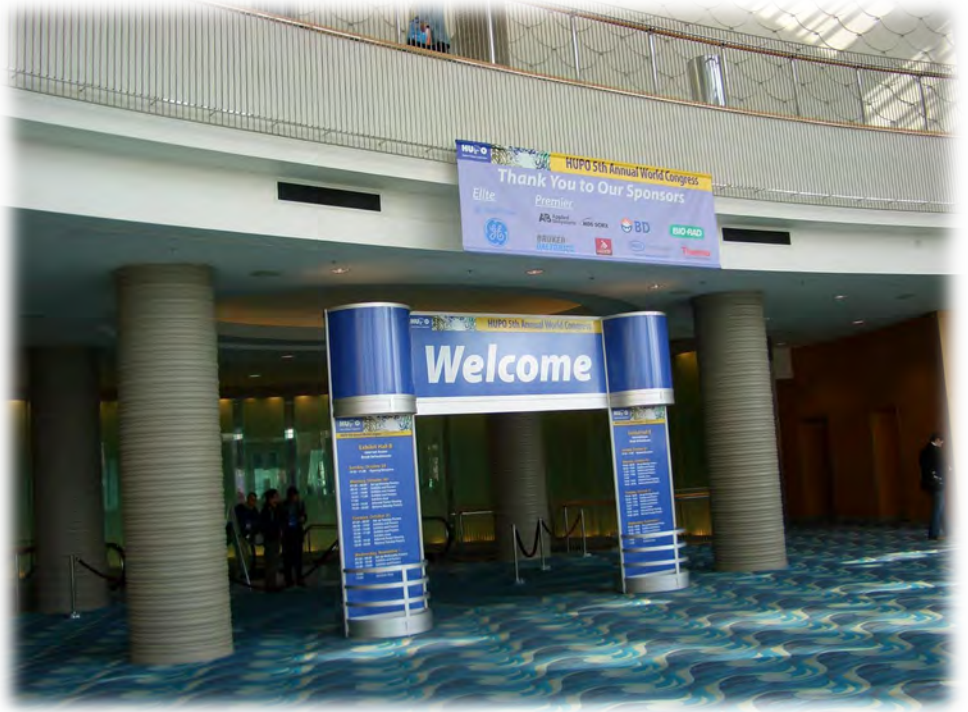
Mikhail Pyatnitskiy, PhD

Bioinformatics.ru

XXIX Symposium on Bioinformatics and Computer-Aided Drug Discovery, 19 Sep

Personalized medicine and omics: from bench to bedside





Proteomics Clin. Appl. 2007, *1*, 107–117 DOI 10.1002/prca.200600229

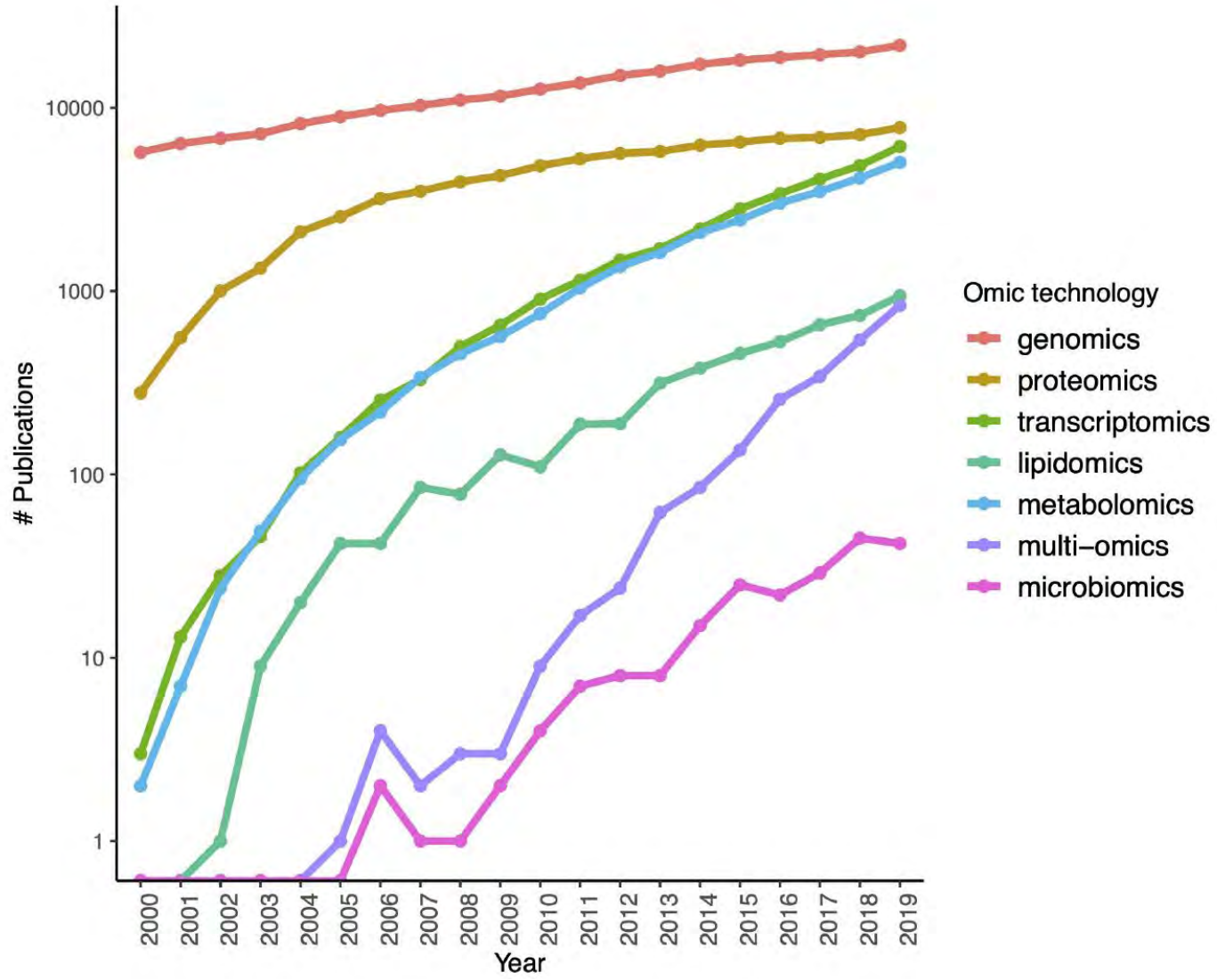
RESEARCH ARTICLE

Acute phase serum amyloid A in ovarian cancer as an important component of proteome diagnostic profiling

Sergei A. Moshkovskii[1], Maria A. Vlasova[1], Mikhail A. Pyatnitskiy[1], Olga V. Tikhonova[1], Metanat R. Safarova[2], Oleg V. Makarov[2] and Alexander I. Archakov[1]

[1] Institute of Biomedical Chemistry, Moscow, Russia
[2] Russian State Medical University, Moscow, Russia

Omics publications: growth continues

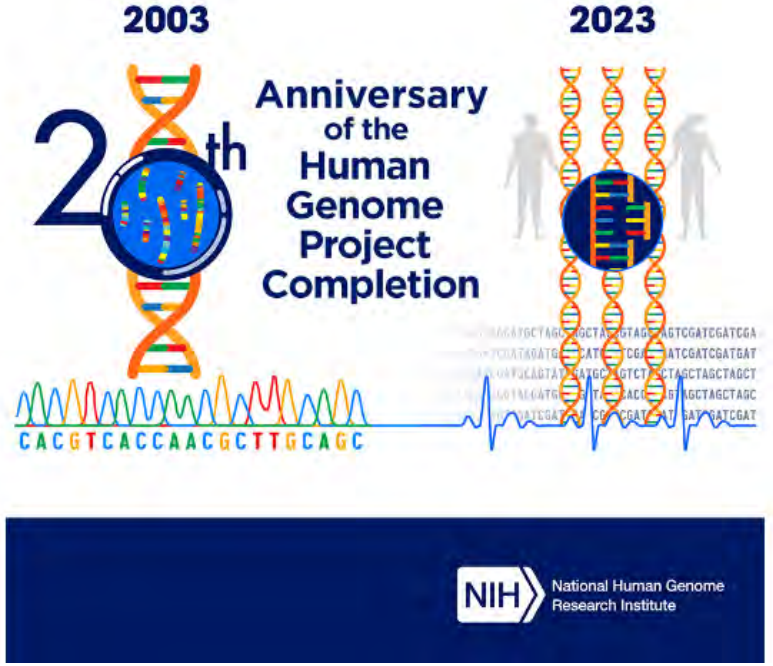


Anda-Jáuregui & Hernández-Lemus, *Front in Oncol,* 2020

Personalized medicine and omics

Systematic analysis of 683 articles containing a definition of personalized medicine:

> *PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics*



Shtchleidgen et al. *BMC Medical Ethics*, 2013
https://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecuture-on-p4-medicine

Personalized medicine is genomics

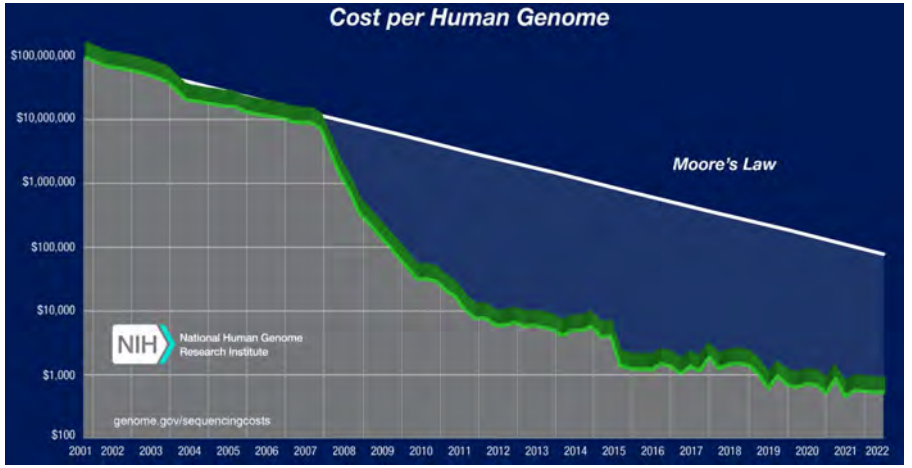
76,326 genetic tests on GTR worldwide

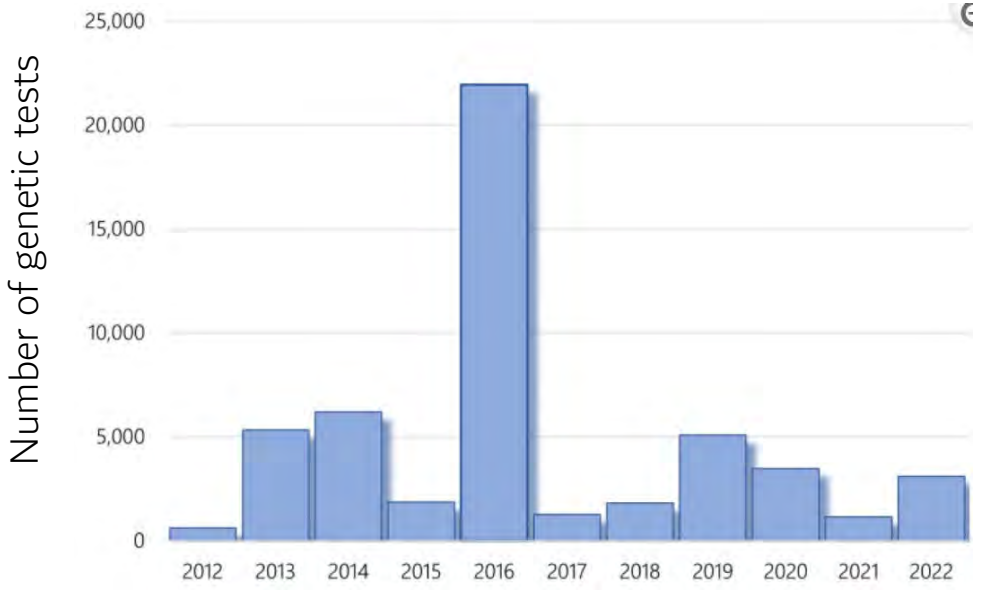
37,289 tests belong to US laboratories

New genetic tests:

- 62% diagnostic.
- 11% risk assessment
- 10% pre-symptomatic testing
- 10% screening

Genomics became routine





Halbisen & Lu, *J Pers Med,* 2023

Genomics: key applications

Pharmacogenomics

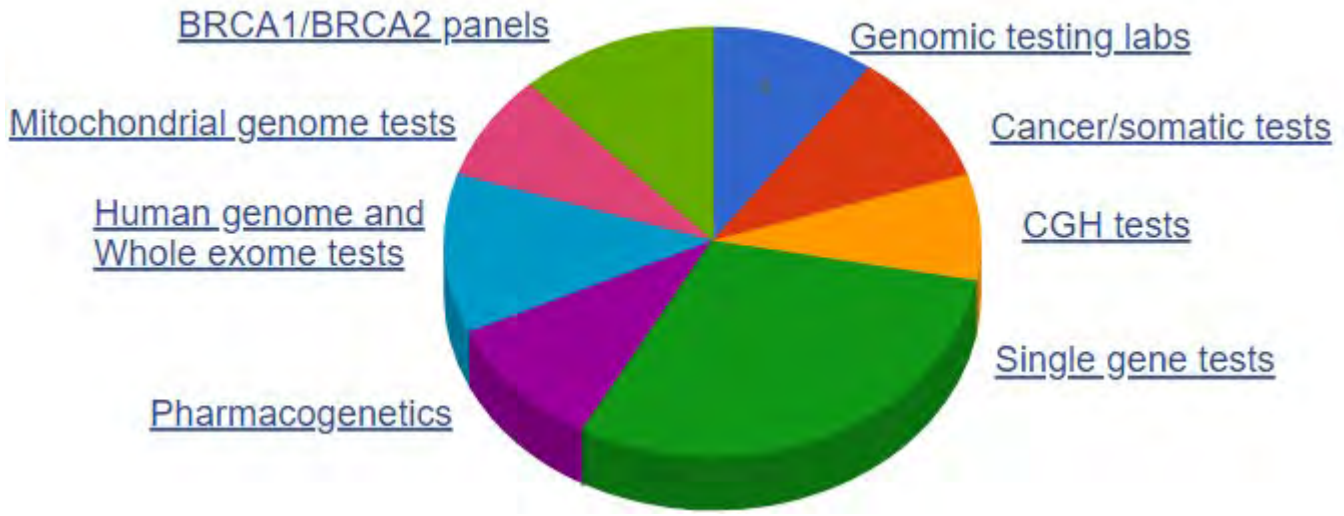
Individualize drug therapy

FDA: 80 biomarkers for 270 drugs

Rare diseases

Uncover previously unknown mutations

25-35% of undiagnosed patients, often with actionable findings



https://www.ncbi.nlm.nih.gov/gtr/

Newborn & inherited disease screening

Detect genetic disorder that may not manifest symptoms immediately

Crucial for family planning

Forensic genomics

Aid in criminal investigations, paternity testing, identifying human remains

Precision Oncology

Most successful area of pharmacogenomics

matching of cancer patients with targeted drugs

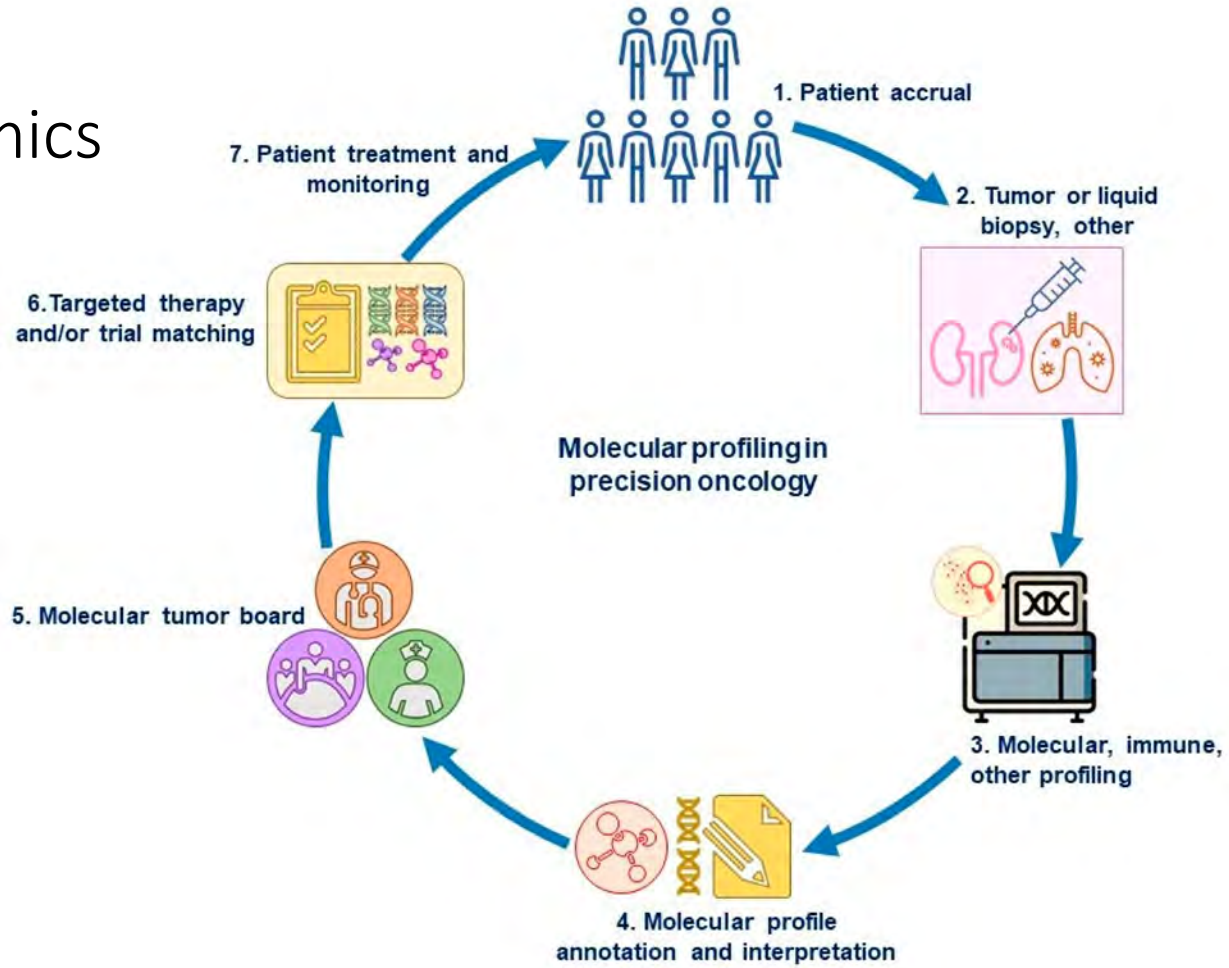
Several NGS-based multigene panels

Oncomine Dx, Foundation One CDx, MSK-IMPACT, PGDx elio

FDA APPROVED

Clinical trials are on the way, results are somewhat mixed

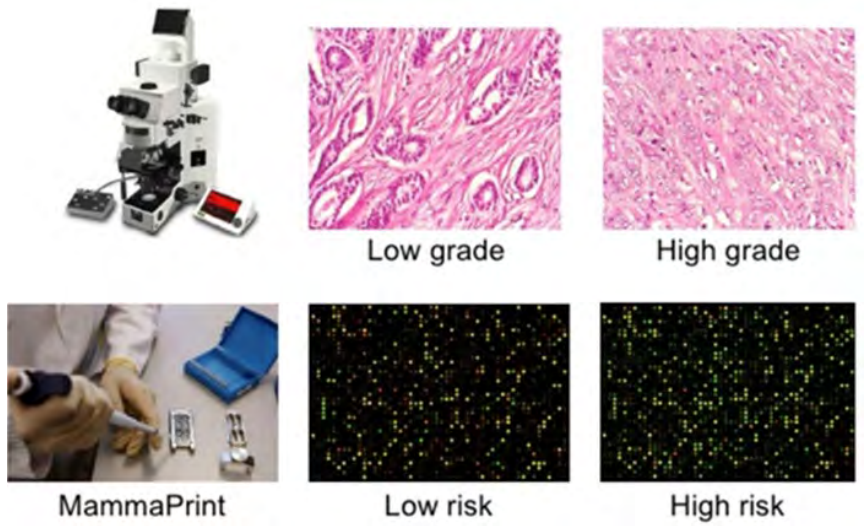
SHIVA, IMPACT2, NCI-MPACT, TAPUR, NCI-MATCH, …

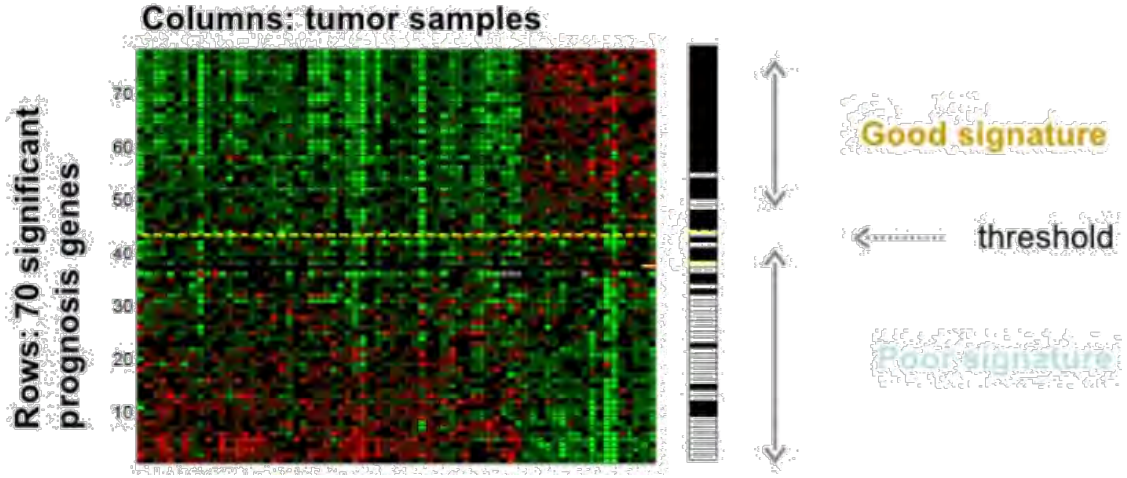


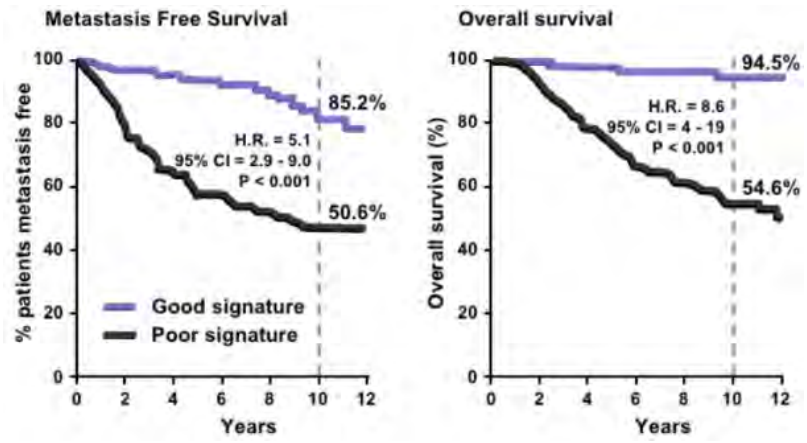
Song et al., *Cancers*, 2023

Transcriptomics success story: MammaPrint®

- Assess the risk that a breast tumor will metastasize in five years
- 70 genes signature, correlation-based classifier
- Microarray, FFPE
- Supported by several clinical trials
- First results in 2002
- Similar tests: Oncotype DX, EndoPredict, Prosigna







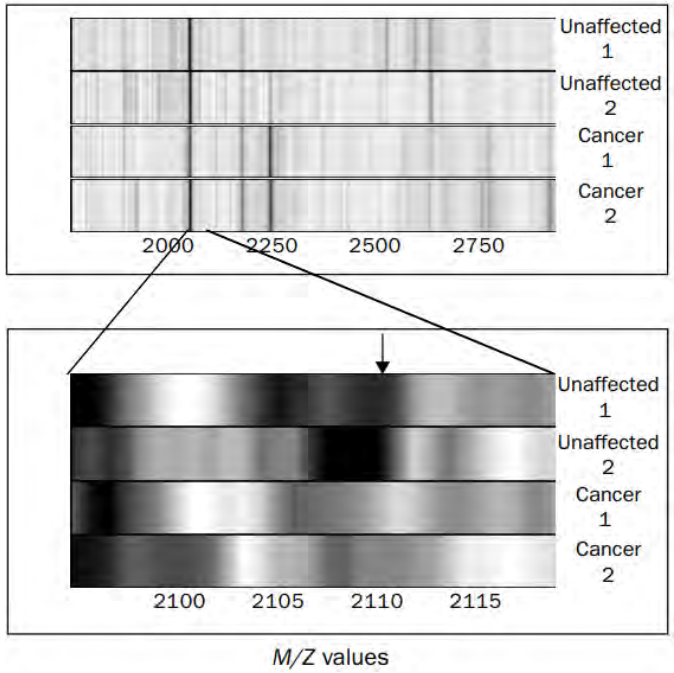
Proteomics as an example of problems in translational medicine

How: use MS-based methods to detect ovarian cancer

Initial findings: several m/z peaks able to provide 100% sens, 95% spec, 94% PPV

Support: Adam et al., 2002; Drake et al., 2003; Petricoin et al., 2002b; Vlahouet al., 2001; Zhu et al., 2003

Planned to market: early 2004



Petricoin et al., *Lancet*, 2002

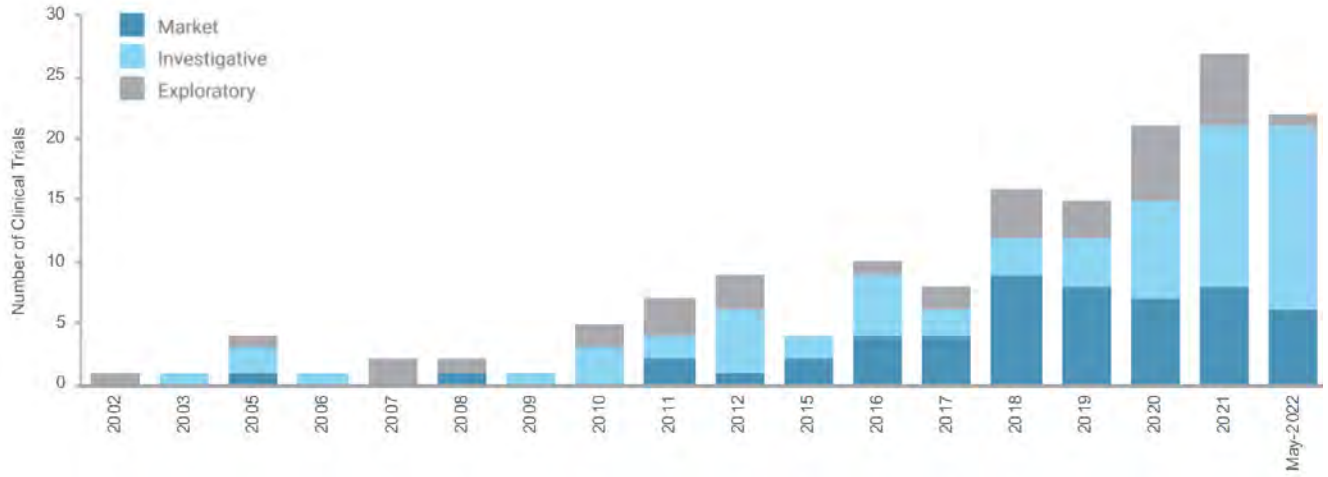
But…

During the past 5 years, a large number of scientists were able to identify candidate protein disease biomarker profiles using patient research study sets and to achieve high diagnostic sensitivity and specificity in blinded test sets (*1*, *2*, *5–8*). Nevertheless, translating these research findings to useful and reliable clinical tests has been the difficult part. Clinical translation of promising ion fingerprints has been hampered by sample collection bias, interfering substances, biomarker perishability, laboratory-to-laboratory instrument variability, SELDI chip discontinuance and surface lot changes, and the stringent dependence of the ion signature on the subtleties of the reagent composition and incubation protocols. These difficulties are exemplified

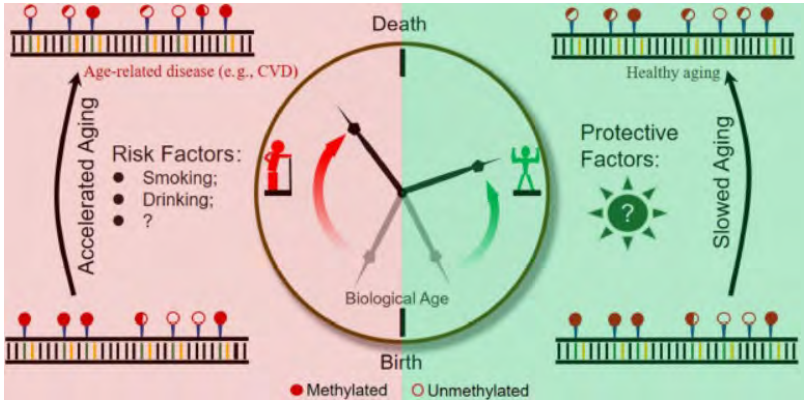
Liotta & Petricoin, *Clin Chemistry*, 2008

Epigenomics: seems promising, but…

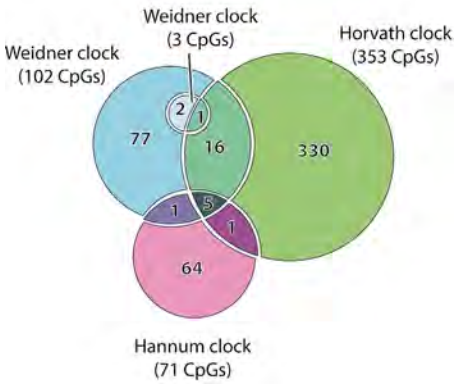
- Most approved assays measure methylation of few genes: Epi proColon (SEPT9), ColoGuard (BMP3, NDRG4)
- Several new promising assays in development: HelioLiver (28 genes), Bladder EpiCheck (15 markers), EPICUP (Illumina 450k)
- Massive increase in number of CTs involving methylation in oncology (focus on colorectal cancer)
- Epigenetic clocks: promising, but still not in clinics



Davalos & Esteller, CA Cancer J Clin, 2023

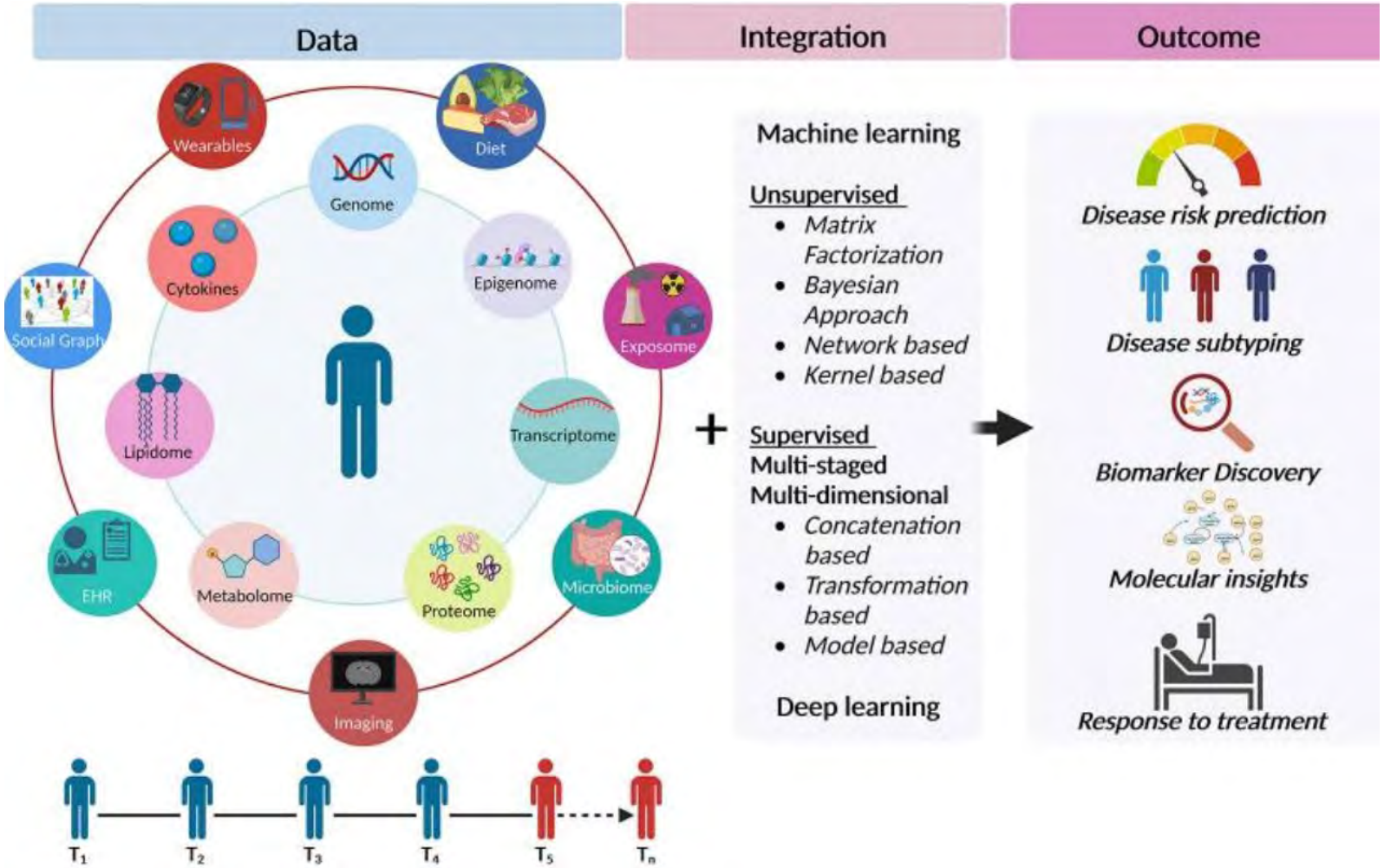


Xiao et al., *Front in Genetics*, 2019



Galkin et al., 2020

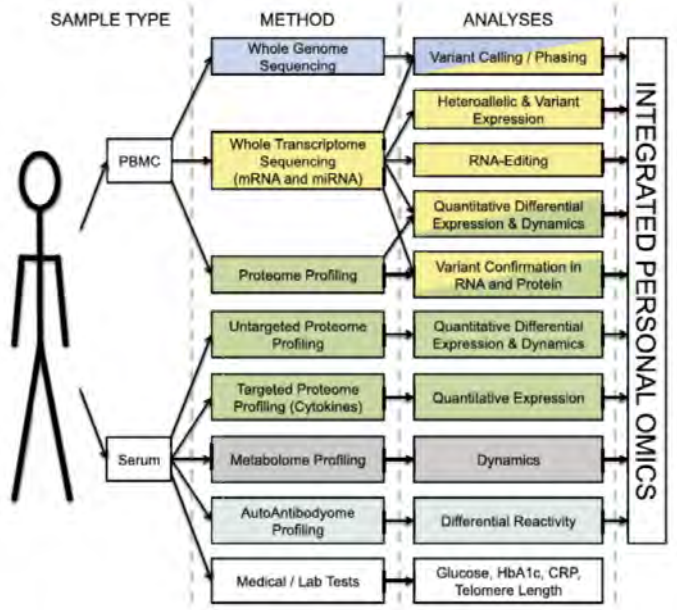
Multiomics: foundation of systems medicine



Babu & Snyder, *Mol Cell Proteomics*, 2023

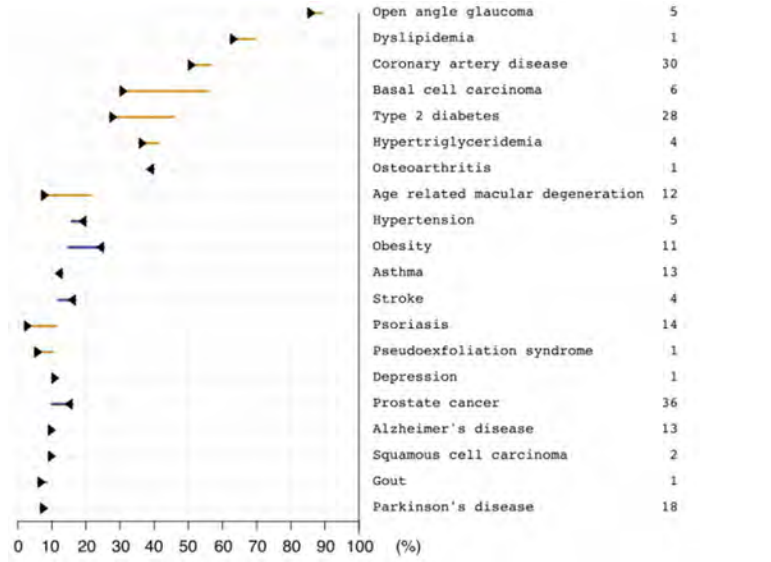
integrative Personal Omics Profile (iPOP aka Snyderome)

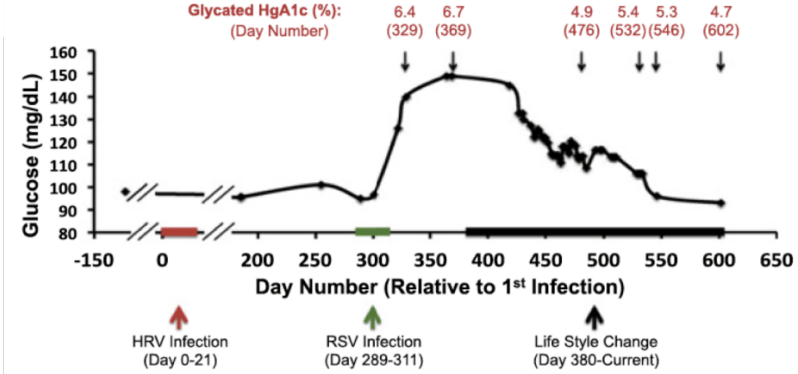
- Multiomics longitudinal profile, 14 months, 20 timepoints for 54 yo Caucasian male, BMI=23.9
- Two viral infections: human rhinovirus (HRV) and a respiratory syncytial virus (RSV)
- Genetic disease risks (RiskOGram algorithm): glaucoma, basal cell carcinoma, hypertriglyceridemia, and Type 2 Diabetes (T2D)



Pre- and post-test probability (after incorporating WGS data)

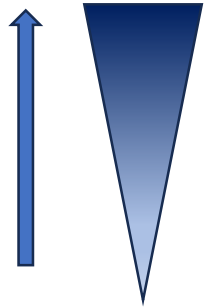
Num disease-associated SNVs for risk calculation





Conclusions:

Clinical utility



continuous glucose monitoring

genomics

transcriptomics, metabolomics

Chen et al., *Cell*, 2012

Pioneer 100 Wellness Project

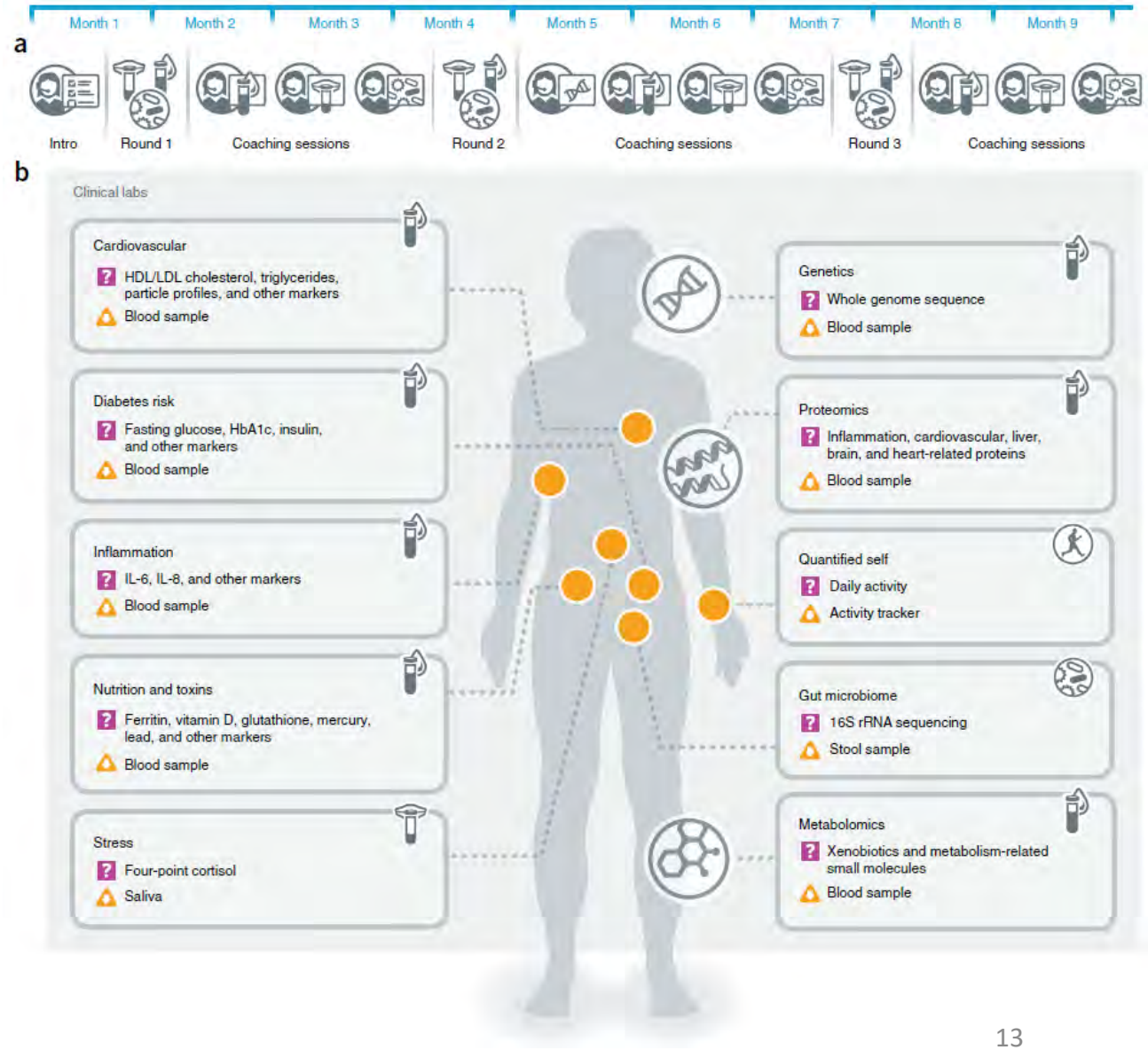
nature biotechnology

ARTICLES

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

Nathan D Price[1,2,6,7], Andrew T Magis[2,6], John C Earls[2,6], Gustavo Glusman[1], Roie Levy[1], Christopher Lausted[1], Daniel T McDonald[1,5], Ulrike Kusebauch[1], Christopher L Moss[1], Yong Zhou[1], Shizhen Qin[1], Robert L Moritz[1], Kristin Brogaard[2], Gilbert S Omenn[1,3], Jennifer C Lovejoy[1,2] & Leroy Hood[1,4,7]

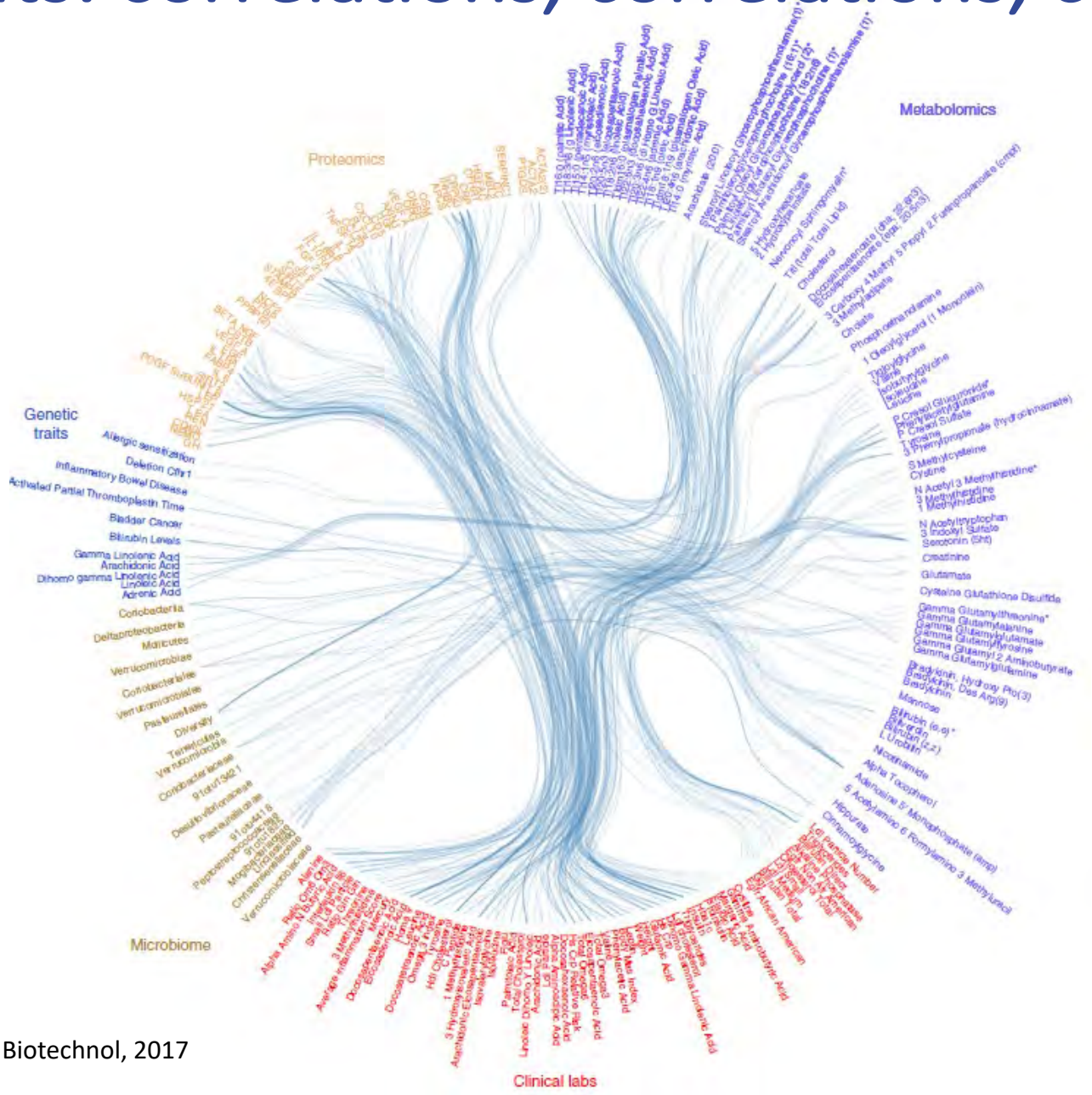
- 108 individuals (ages 21-89), 9 months, 3 rounds followed by coaching sessions
- WGS, proteomics, metabolomics, gut microbiome, wearables
- In each round: 218 lab tests, 643 metabolites, 262 proteins, 127 polygenic scores, 4616 OTUs



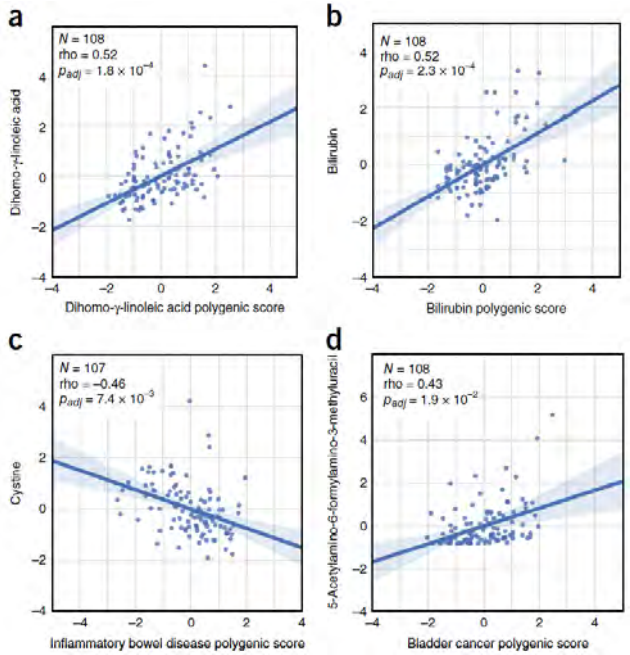
Price et al., Nat Biotechnol, 2017

raw data: dbGaP phs001363.v1.p1

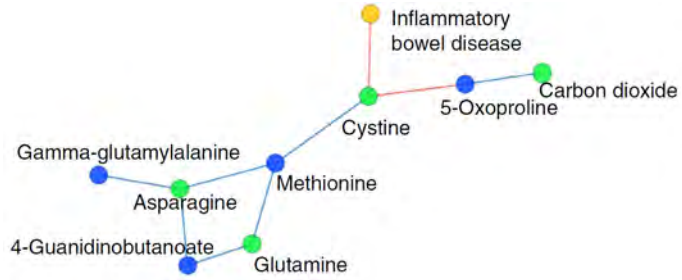
Results: correlations, correlations, correlations



Price et al., Nat Biotechnol, 2017



Polygenic risk scores correlate with blood analytes



The polygenic score for inflammatory bowel disease is negatively correlated with cystine.

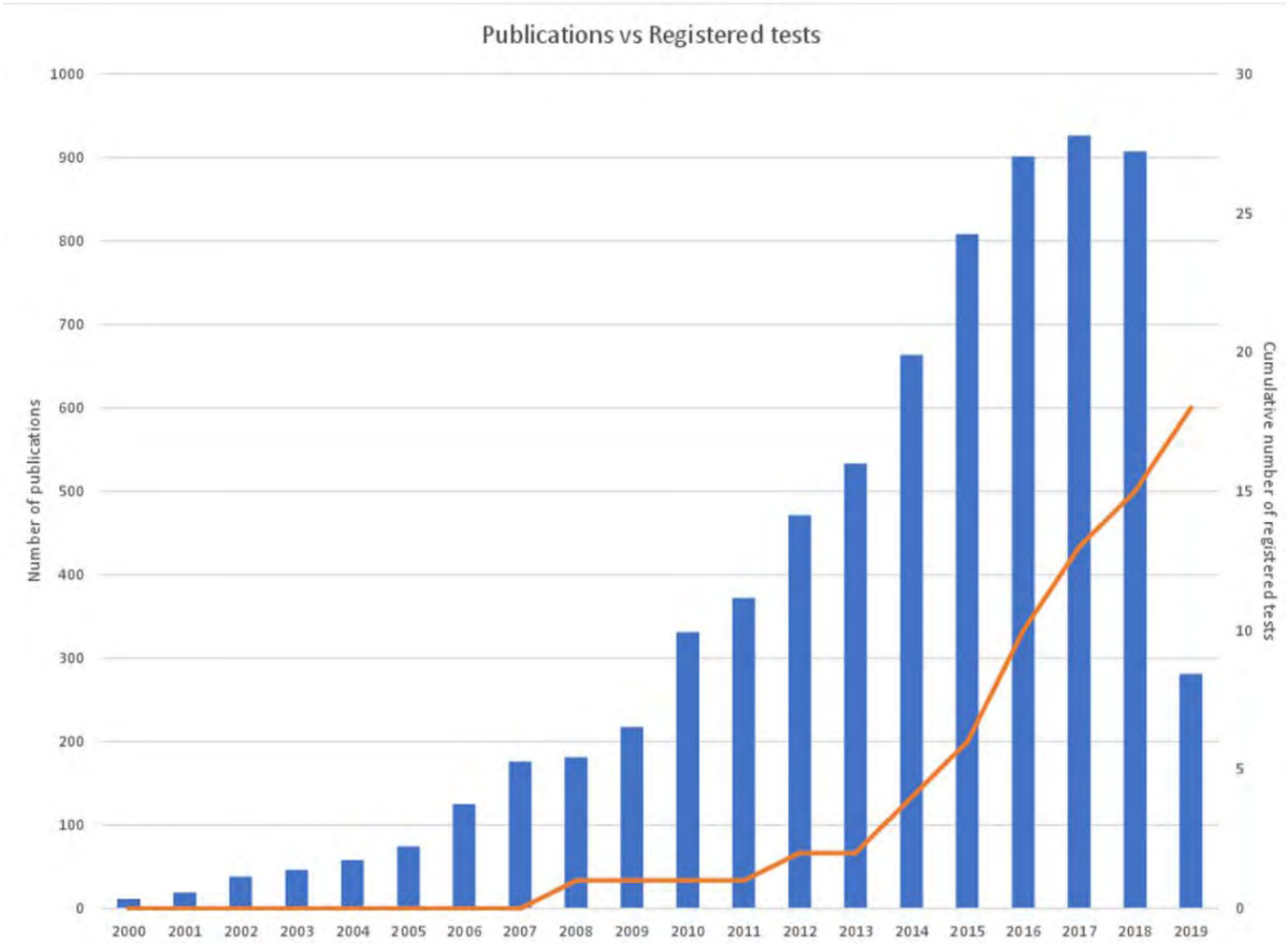
Actionable findings: almost none

Clinical laboratory test		Changes in labs in participants out-of-range at baseline		
Health area	Name	*N*	Δ per round	*P*-value
Nutrition	Vitamin D	95	+7.2 ng/mL/round	7.1×10^{-25}
Nutrition	Mercury	81	−0.002 mcg/g/round	8.9×10^{-9}
Diabetes	HbA1c	52	−0.085%/round	9.2×10^{-6}
Cardiovascular	*LDL particle number (Quest)*	*30*	*+130 nmol/L/round*	9.3×10^{-5}
Nutrition	Methylmalonic acid (Genova)	3	−0.49 mmol/mol creatinine/round	2.1×10^{-4}
Cardiovascular	LDL pattern (A or B)	28	−0.16 /round	4.8×10^{-4}
Inflammation	Interleukin-8	10	−6.1 pg/mL/round	5.9×10^{-4}
Cardiovascular	Total cholesterol (Quest)	48	−6.4 mg/dL/round	7.2×10^{-4}
Cardiovascular	LDL cholesterol	57	−4.8 mg/dL/round	8.8×10^{-4}
Cardiovascular	LDL particle number (Genova)	70	−69 nmol/L/round	1.2×10^{-3}
Cardiovascular	Small LDL particle number (Genova)	73	−56 nmol/L/round	3.5×10^{-3}
Diabetes	Fasting glucose (Quest)	45	−1.9 mg/dL/round	8.2×10^{-3}
Cardiovascular	Total cholesterol (Genova)	43	−5.4 mg/dL/round	1.2×10^{-2}
Diabetes	Insulin	16	−2.3 IU/mL/round	1.5×10^{-2}
Inflammation	TNF-alpha	4	−6.6 pg/mL/round	1.8×10^{-2}
Diabetes	HOMA-IR	19	−0.56 /round	2.0×10^{-2}

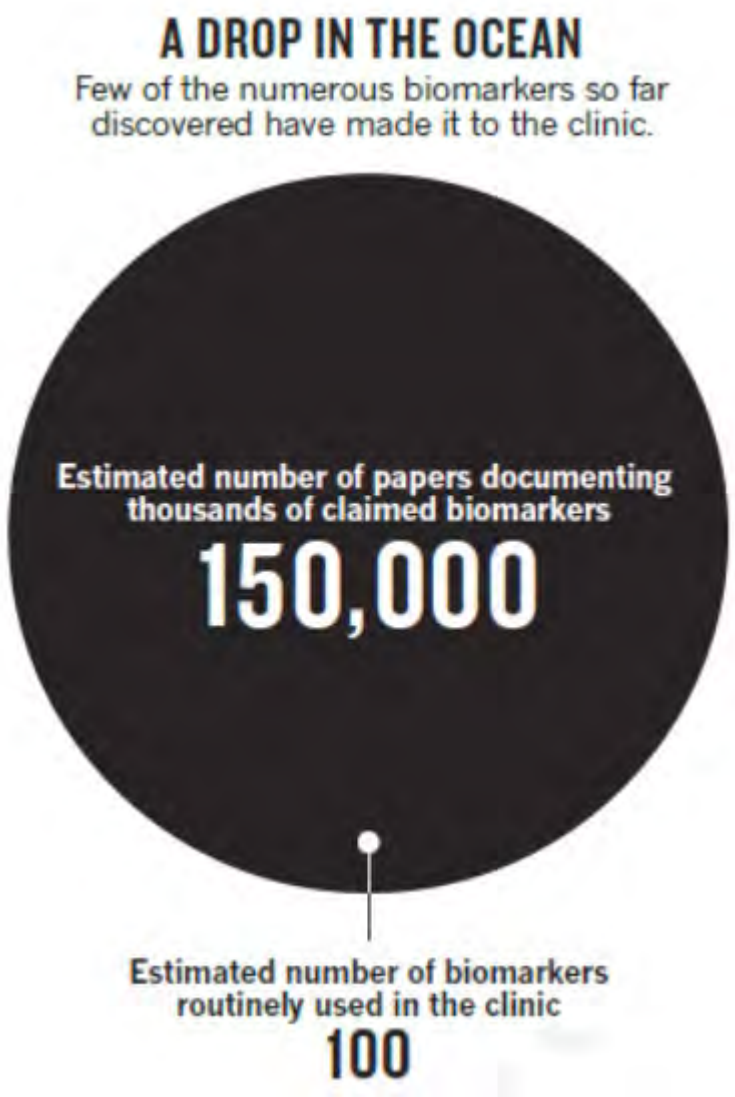
- For each out-of-range measurement the coach would recommend lifestyle changes
- Individual recommendations categories: diet, exercise, stress management, dietary supplements, or physician referral
- Most signif. improvements: vitamin D, mercury, HbA1c, total cholesterol, IL-8

Ex: 65-year-old male, revealed high ferritin level in blood, homozygous for *HFE* C282Y, the primary risk factor for hereditary hemochromatosis. Therapeutic phlebotomy recommended. Ferritin level remained normal throughout the remainder of the study

Translational omics: seems we are not very good



Davalos & Esteller, CA Cancer J Clin, 2023



G. Poste, *Nature*, 2011

Maybe we're searching in the wrong place

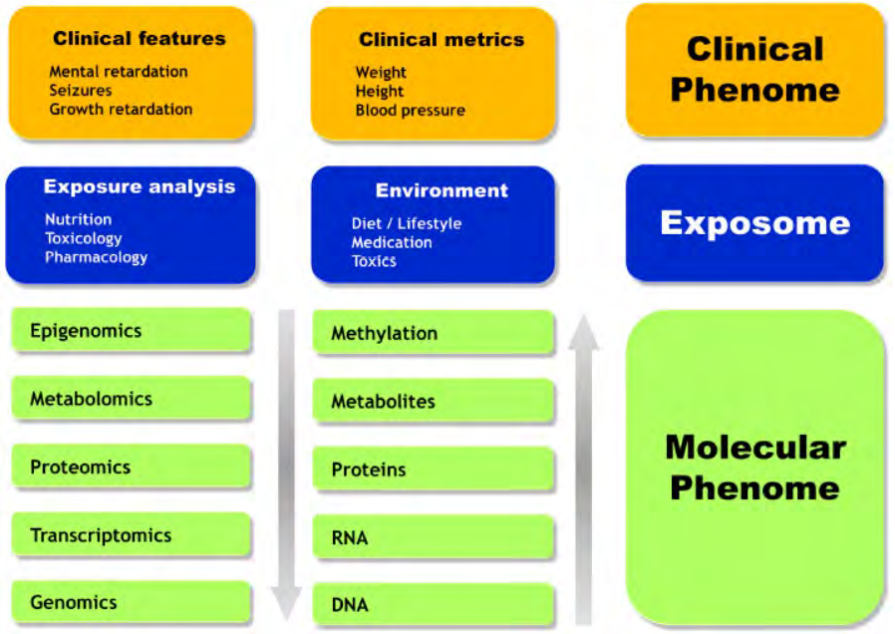
"Biomedical scientists are addicted to data like alcoholics are addicted to cheap booze"

Director, MIT Center for Precision Cancer Medicine

Prof. M. Yaffe

- Focus on deep phenotyping? Lifestyle and environment are very important

- Not only cancer?

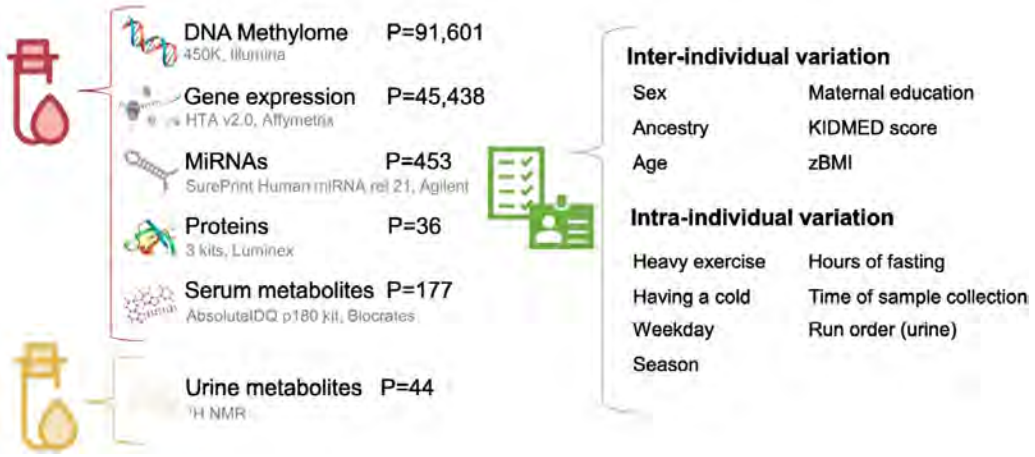


McMoll et al., *Clin Pharm & Ther.*, 2019
Tebani et al., *IJMS*, 2016

Variability of omics profiles

Multi-omics profiles measured 6 months apart in 156 healthy children from 5 countries

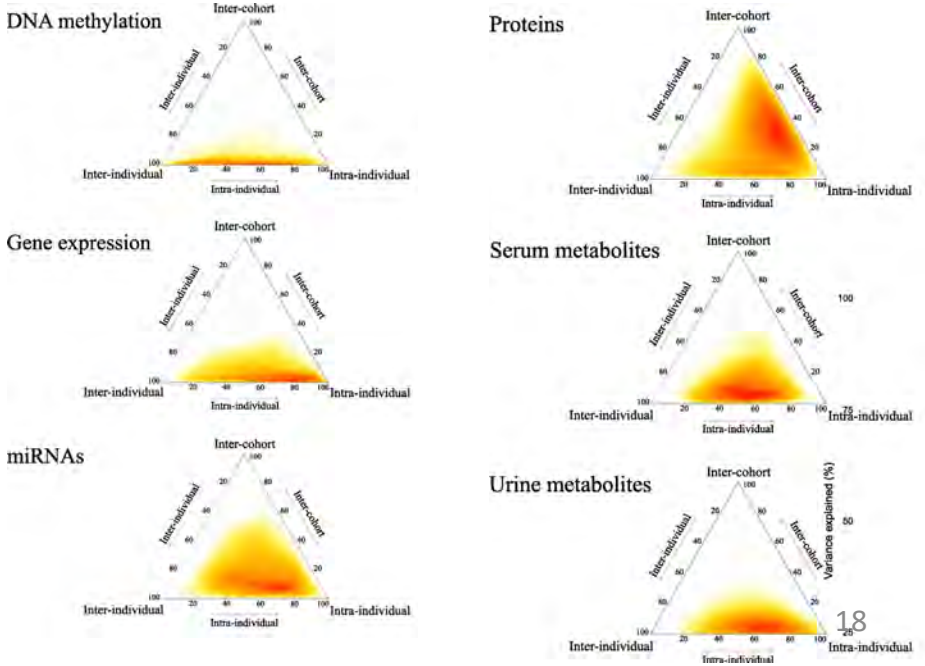
Adjusting for various explanatory variables for inter-individual and intra-individual variation



Conclusions:

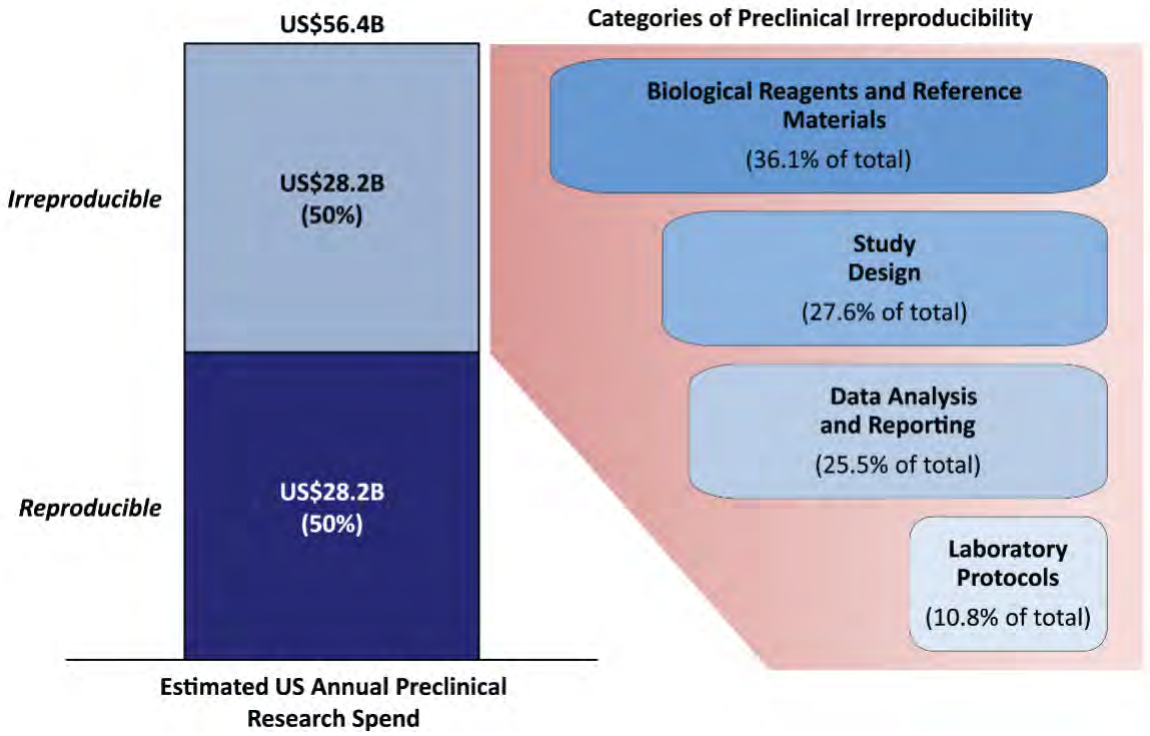
- Intra-individual variation accounts for the largest part of total variation
- The less stable omics: gene expression. Should be used to assess individual trajectories
- More stable omics: DNA methylation and serum metabolites. Should be used as biomarkers

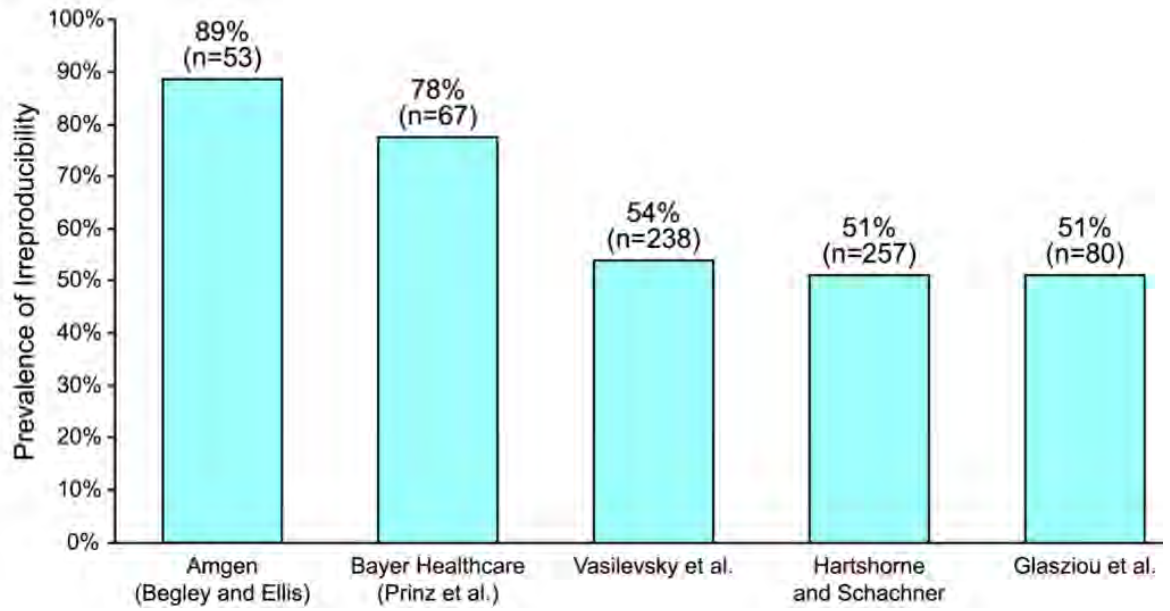
Variability of omics profiles in healthy populations remains under-studied



Gallego-Pauls et al., *BMC Medicine*, 2021

Reproducibility crisis

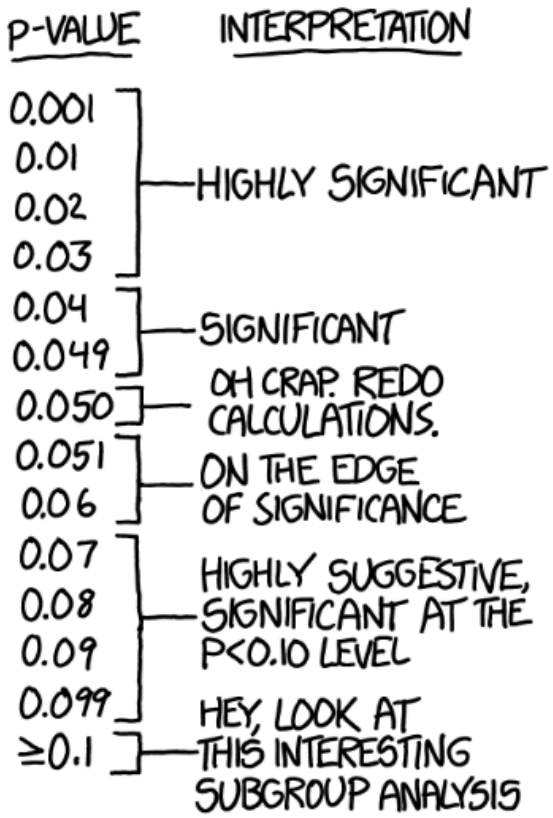




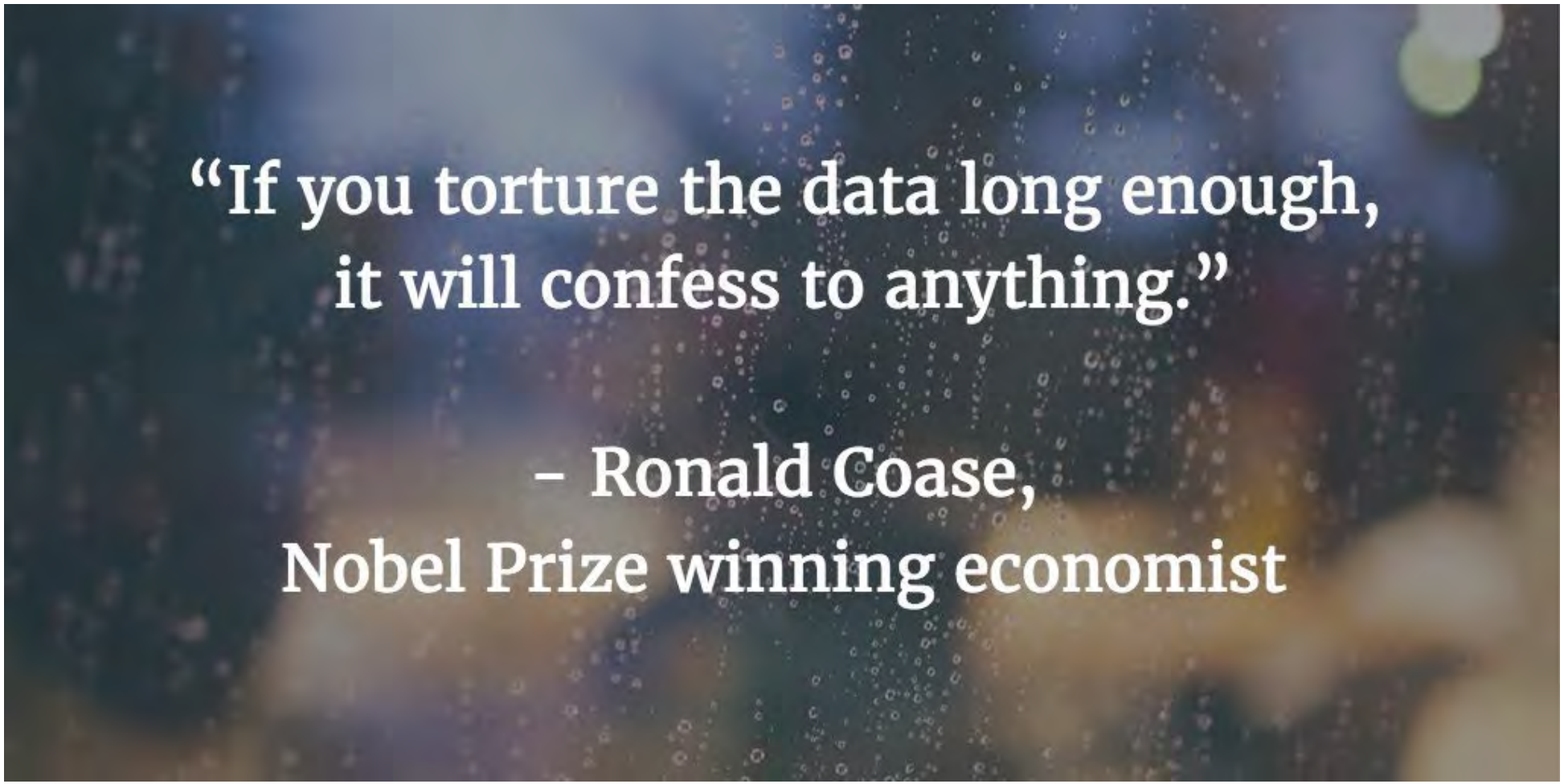
Freedman et al, Plos Biol, 2015

How to cheat with your analysis: some bad advices

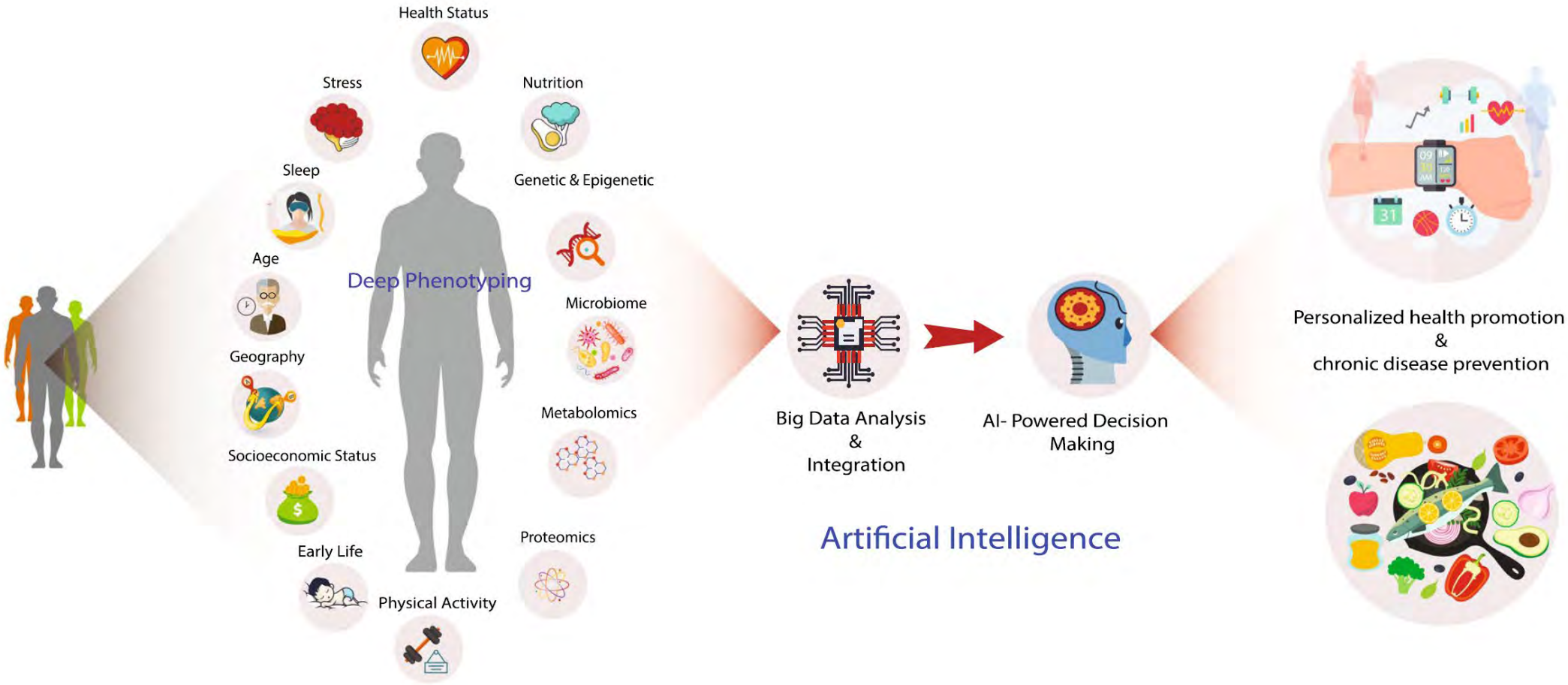
- Remember, everybody (editors, reviewers, investors) prefers positive results.
- Always be your own judge, jury and executioner (the self-assessment trap)
- P-hacking is great: your boss will stay satisfied
- Diffuse author's responsibility ("brotherly graves")
- Do not disclose intricacies of the conducted analysis



https://xkcd.com/1478/


“If you torture the data long enough,
it will confess to anything.”
– Ronald Coase,
Nobel Prize winning economist

AI is our new hope



Subramanian et al., J Transl Med., 2020

Although AI sometimes may also fail…

IBM's Watson supercomputer recommended 'unsafe and incorrect' cancer treatments, internal documents show

By CASEY ROSS @casey

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02 Apr 2019 | 15:00 GMT

How IBM Watson Overpromised and Underdelivered on AI Health Care

A STAT INVESTIGATION

IBM pitched its Watson supercomputer as a revolution in cancer care. It's nowhere close

By CASEY ROSS @caseymross and IKE SWETLITZ @ikeswetlitz / SEPTEMBER 5, 2017

customers' assessments of Watson for Oncology that say it produced "often inaccurate" recommendations that pose "serious questions about the process for building content and the underlying technology."

"While Watson for Oncology provides safe treatment options, treatment decisions ultimately require the involvement and clinical judgement of the treating physician… No technology can replace a doctor and his or her knowledge about their individual patient."

https://spectrum.ieee.org/biomedical/diagnostics/how-ibm-watson-overpromised-and-underdelivered-on-ai-health-care
https://www.statnews.com/2018/07/25/ibm-watson-recommended-unsafe-incorrect-treatments/
https://www.statnews.com/2017/09/05/watson-ibm-cancer/

Characteristics of successful omics studies

Glaab et al., *BMJ Open*, 2021

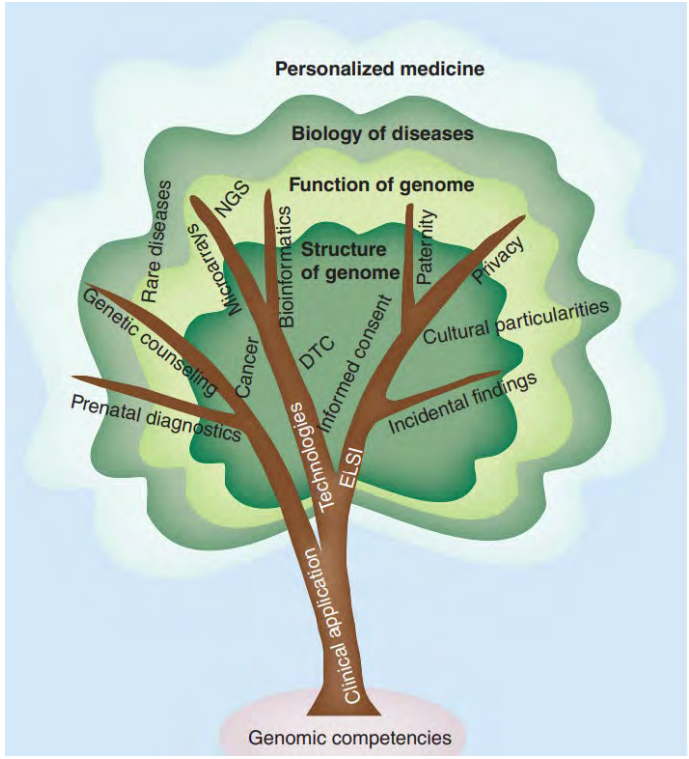
Scoping review of 352 biomarker discovery studies using ML analysis of omics data

- **Study design & sample size**: statistical power, balanced groups, batch effect avoidance
- **Statistical evaluation:** cross-validation, external cohorts, multiple testing correction
- **Clarity of scope & goals:** inclusion/exclusion criteria, primary/secondary outcome
- **Documentation:** reproducible method description
- **Model interpretability:** biological plausibility, human-interpretable models
- **Integration of prior knowledge:** pathways & networks, clinical and real-world data

Name	Test approval type	Purpose (data type used for discovery)
MammaPrint	FDA-cleared Assay	Breast cancer risk-of-recurrence assessment (DNA microarray gene expression data).
ColoPrint	LDT	Colon cancer development of distant metastasis prediction (DNA microarray gene expression data).
Prosigna assay/PAM50	FDA-cleared Assay	Breast cancer risk of distant recurrence prediction (DNA microarray gene expression data).
Oncotype DX	LDT	Breast cancer risk-of-recurrence assessment (DNA microarray gene expression data).
Decipher	LDT	Prostate cancer metastatic risk prediction (DNA microarray gene expression data).
Cancer Type ID	LDT	Predict tumour type for cancers of unknown / uncertain diagnosis (DNA microarray gene expression data).
Afirma Gene Expression Classifier	LDT	Discriminate between benign and cancerous thyroid nodules (DNA microarray gene expression data).
Foundation One Heme	LDT	Test for haematologic malignancies, sarcomas or solid tumours (RNA and DNA sequencing data).
PGDx Elio Tissue Complete	FDA-cleared Assay	Test to assess somatic mutations and tumour mutation burden for solid tumours (DNA sequencing data).
AlloMap Heart	FDA-cleared Assay	Identifying heart transplant recipients with risk of cellular rejection (DNA microarray gene expression data).
Corus CAD	LDT	Identify obstructive coronary artery disease (DNA microarray gene expression data).
Vectra DA	LDT	Multibiomarker blood test for rheumatoid arthritis (immunoassay+clinical data, 396 candidate biomarkers derived from integrative data analysis).
Helix Laboratory Platform & Health Risk App for Late-onset Alzheimer's	FDA-cleared medical device	Whole exome sequencing constituent device based for reporting and interpreting general genetic health risks (DNA sequencing data).

Some conclusions

- Early promises turned out to be overly optimistic (as usual). Seems most low-hanging fruits are already picked.
- There should be clinical evidences of whether -omics approach is better than traditional methods.
- There should be more -omics in medical education.
- A bright future lies ahead, let's get to work!



Callier et al., *Per Med*, 2014