Oregon Nutrition Day 2024

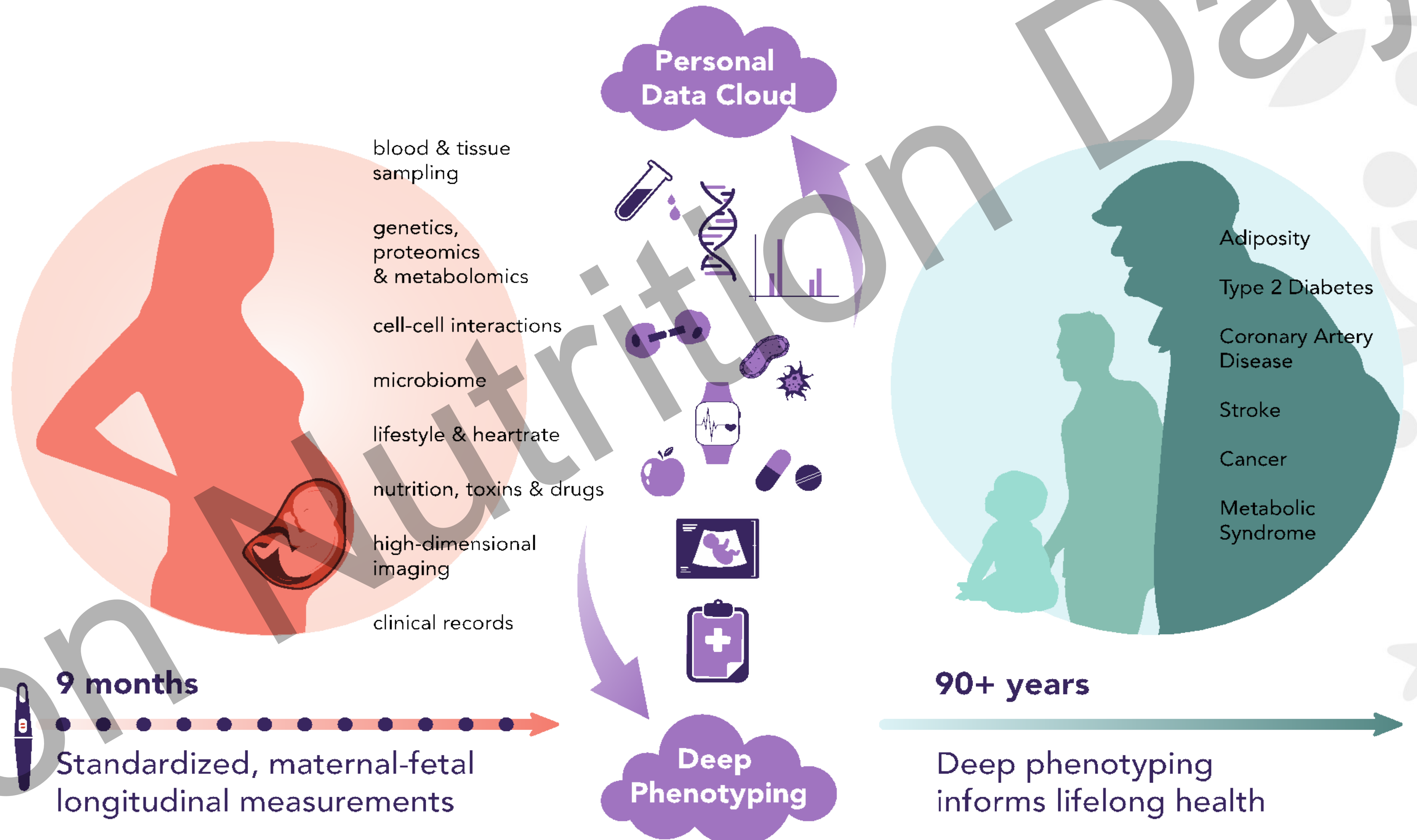
Thorne HealthTech

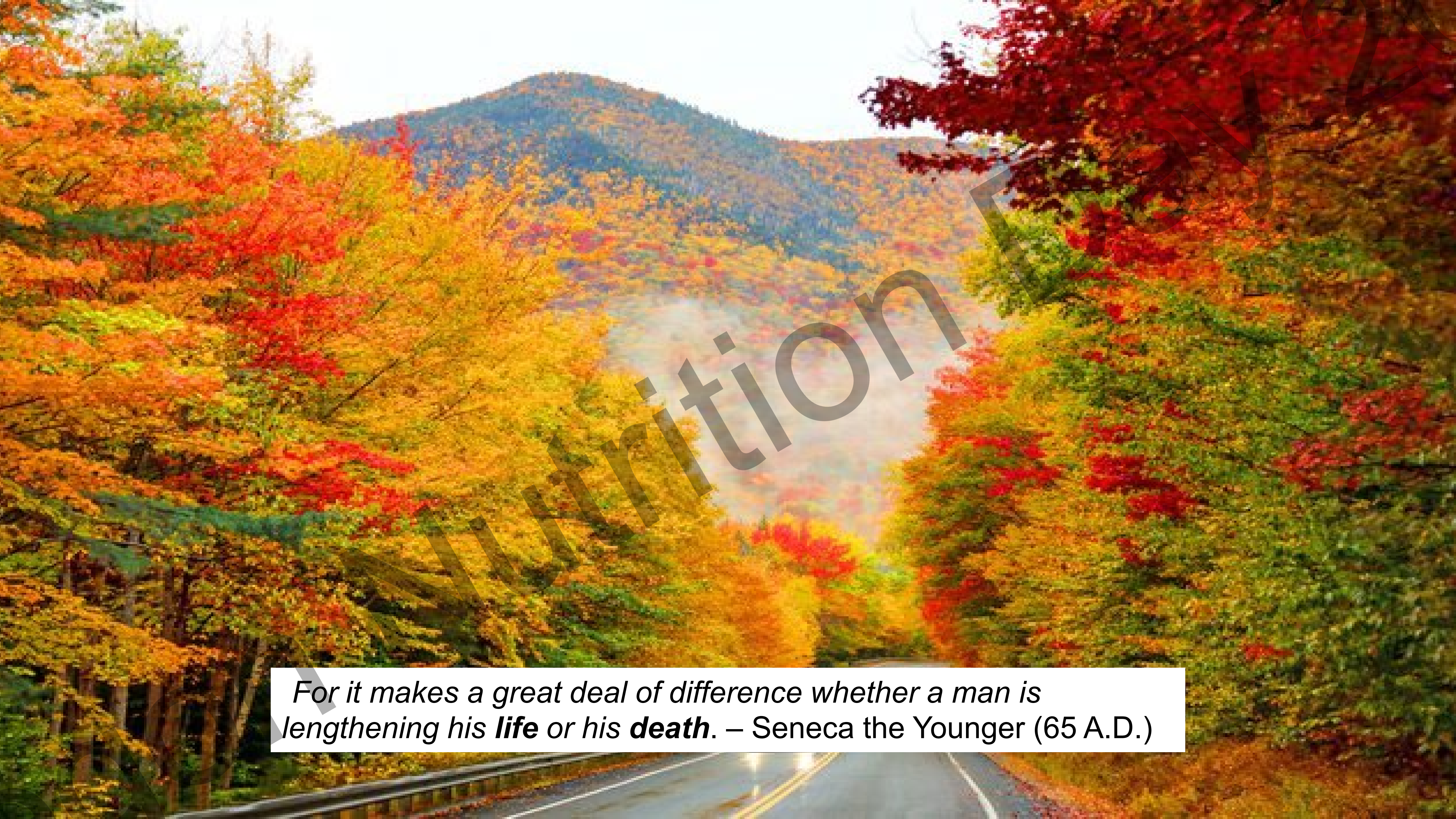
Healthspan Extension and Precision Prevention in the Age of Scientific Wellness

Nathan Price
Chief Scientific Officer, Thorne HealthTech
Professor (on leave), Institute for Systems Biology

ISB

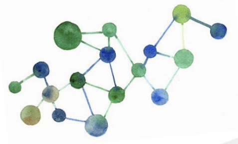
DOHAD: Linking development to lifelong health via deep phenotyping





*For it makes a great deal of difference whether a man is lengthening his **life** or his **death**.* – Seneca the Younger (65 A.D.)

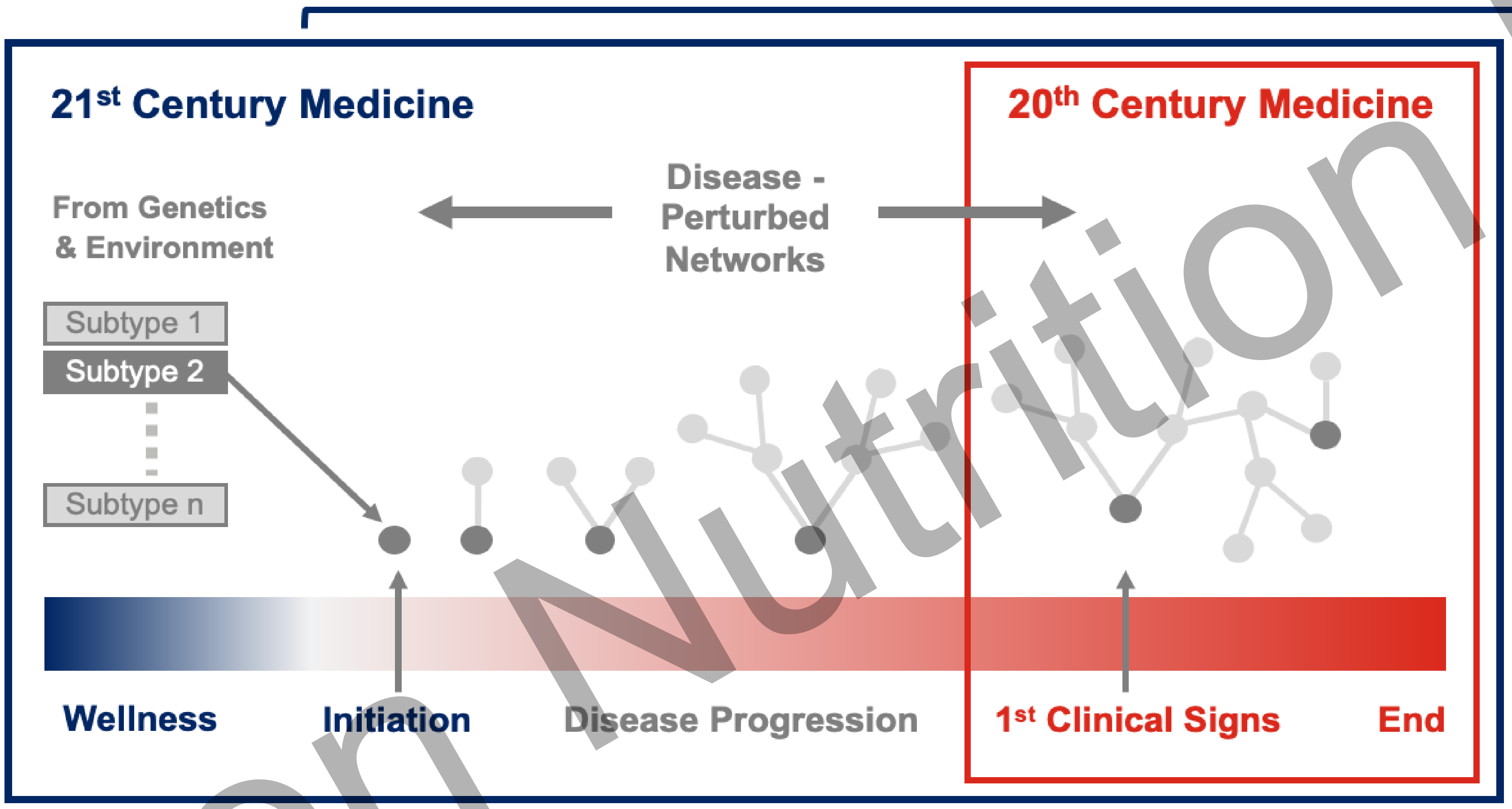
The Age of Scientific Wellness



WHY THE FUTURE OF MEDICINE IS PERSONALIZED, PREDICTIVE, DATA-RICH, AND *IN YOUR HANDS*

Leroy Hood, MD, PhD
Nathan D. Price, PhD

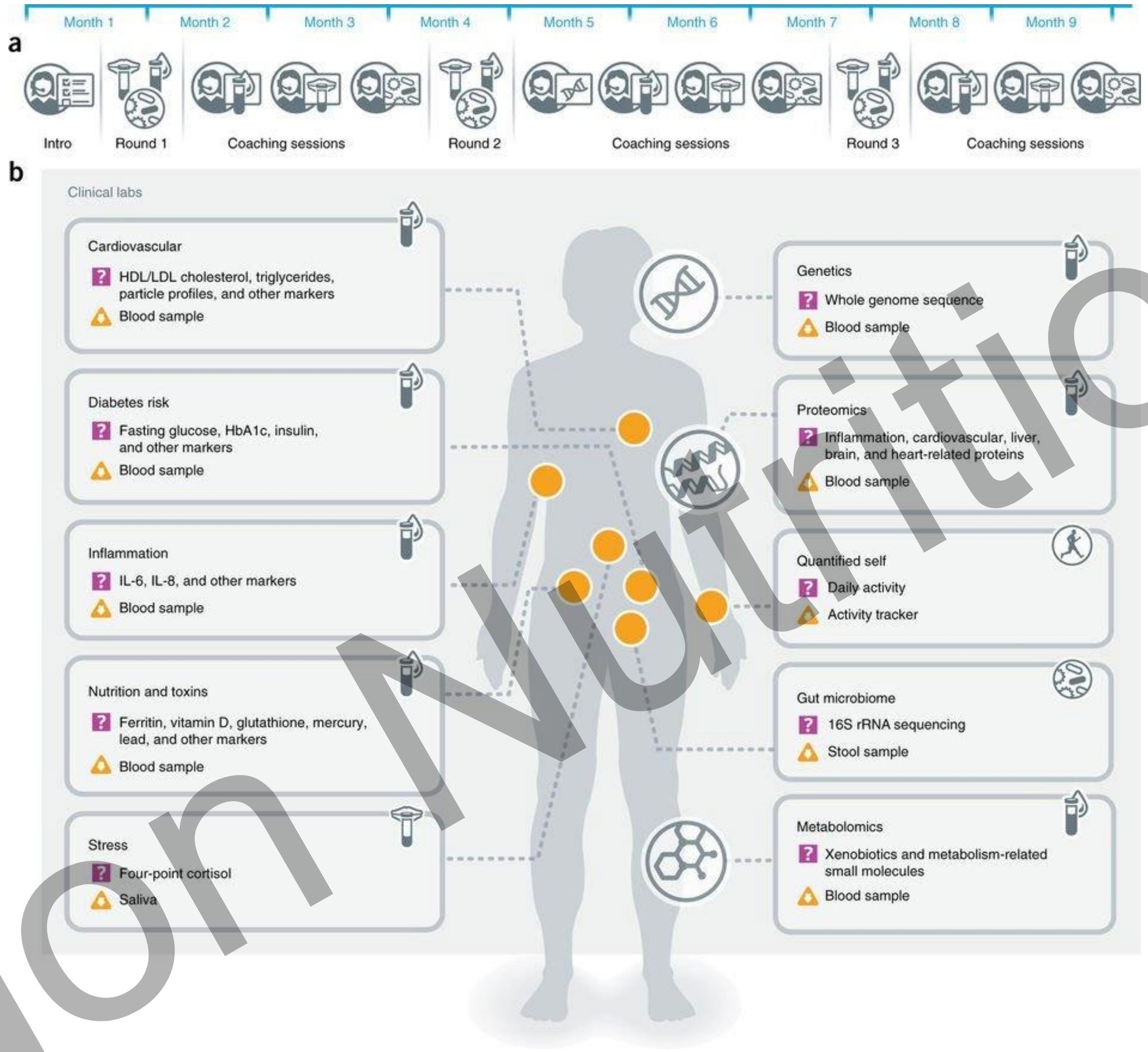
The Challenges, Opportunities, and Technologies of the 21st century Necessitate Wellness-Centric *Health*care and focus on healthy aging

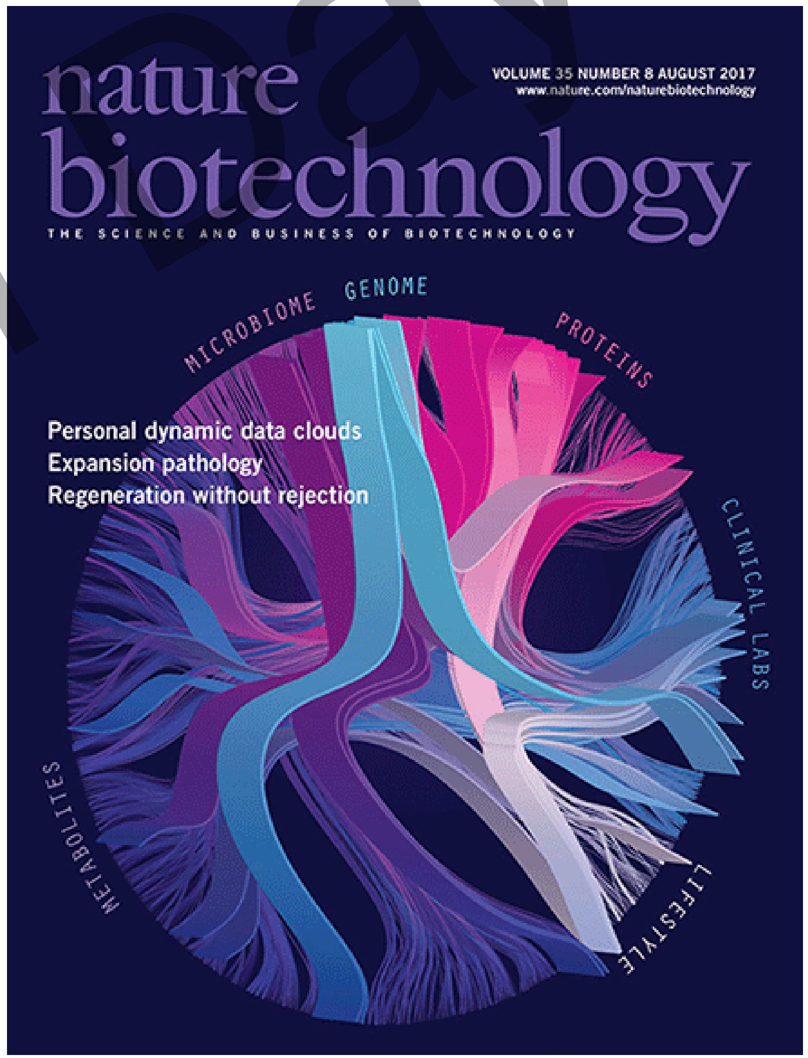


1. Executes scientific wellness and healthy aging
2. Identifies wellness to disease transition and reverses It
3. Manages disease—stratify disease and stratify patients

Scientific Wellness Pilot: Pioneer 100

PIs: Lee Hood and Nathan Price





Price, Magis, Earls…Hood, *Nature Biotechnology*, 2017

Assays / Measurements—108 Pioneers

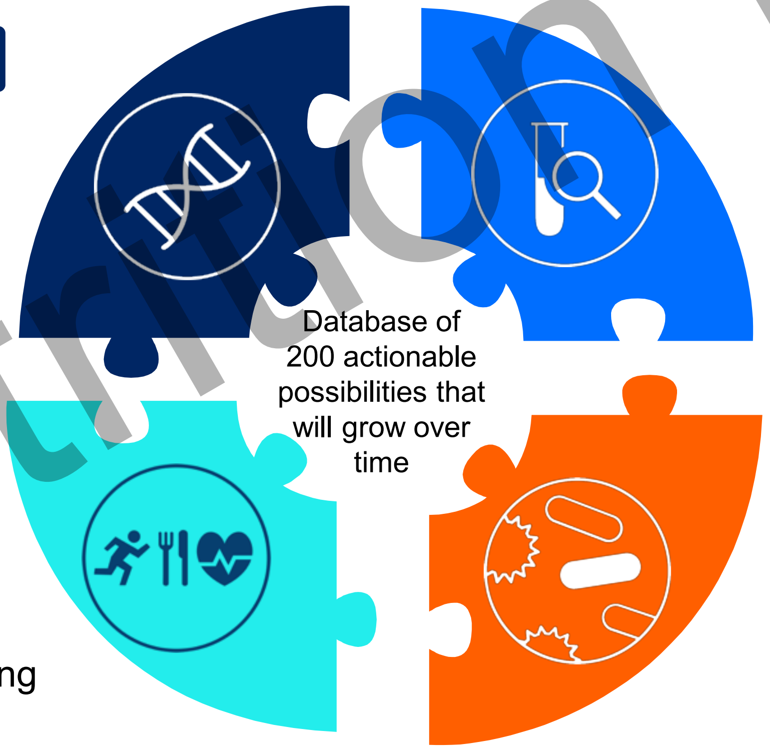
Creating personal, dense, dynamic data (PD3) clouds – “**deep phenotyping**”

GENOME

Whole Genome Sequencing
SNPs Millions

LABS

Detailed lab tests 3x (blood, urine, saliva)
Clinical chem. 150
Metabolites 700
Proteins 400
Almost 1200 analytes



SELF-TRACKING

Continual self-tracking of physiology
& lifestyle monitoring

MICROBIOME

Gut Microbiome
Ratio of microbial species 3x

Price, Magis, Earls…Hood, *Nature Biotechnology*, 2017

Longitudinal datasets from ‘healthy’ population

	DATA TYPE	UNIQUE MEMBERS	TOTAL SAMPLES
Genomic Data	Whole Genome Sequencing	**2,876**	2,876
	SNP Genotyping (MEG/GSA)	**1,948**	1,948
Clinical Data	Clinical Blood Tests	4,879	11,162
	Salivary Cortisol	2,946	4,148
	Weight/BMI	5,722	285,319
	Blood Pressure	4,868	16,955
	Health Assessments	4,946	6,836
Precision Medicine Data (Research)	Gut Microbiome	3,692	5,229
	Blood Metabolomics	1,999	3,223
	Blood Proteomics	2,811	6,014
Digital Health Data	Activity	3,752	3,070,797
	Sleep	3,643	1,491,049
	Heart Rate	3,151	1,385,888

Turning data to insights fuels the future of healthcare

The AI Will See You Now

As medical research produces ever more data about health and disease, doctors are turning to artificial intelligence tools to help them make the best decisions for patients.

By Lee Hood and Nathan Price

By virtue of their medical training, doctors have a wealth of knowledge, experience, wisdom and judgment. Yet even the greatest of human brains can't remember or interpret a tiny fraction of the information now available on human health and disease. Just a few years ago, most medical decisions were based entirely on the knowledge in the head of the doctor at the time the decision was made. Today that is beginning to change, thanks to the rapid development of artificial intelligence.

The evolution that brought the world ChatGPT and similar large language models is making AI one of the most quickly adopted technologies in history, promising profound changes for the way we live and work. Some of the most important will take place in the field of healthcare. As the technology behind these systems progresses, AI will soon be as much a part of our healthcare experience as doctors, nurses, waiting rooms and pharmacies. In fact, it won't be long before AI has mostly replaced or redefined all of these.

A host of AI "decision support systems" are already helping to give physicians access to a wealth of information at the point of care. These systems leverage what computers are naturally good at—storing, recalling and correlating vast amounts of information virtually instantaneously—and link it to the ability of a human expert to reason intuitively and think creatively.

When early so-called "expert systems" were first being developed in the 1980s and 1990s, they were met with hostility by many physicians who worried that computers would soon be in charge of medical decision-making, taking the "doctor's touch" out of the equation and binding the hands of physicians whose opinions differed from the computer's analysis. But that's not what happened. Research has shown that these systems have gotten better and better at helping doctors spot potential outcomes that they might have missed, without taking the ultimate decision-making authority out of their hands.

We are fast approaching a time when "centaur doctors," combining the best parts of human intelligence and AI assistance, will be empowered to make bold medical decisions with far fewer unintended consequences. That's vitally important, because medical mistakes account for about a quarter of a million deaths annually in the U.S. alone. It is not an

Please turn to page C4

EDMON DE HARO

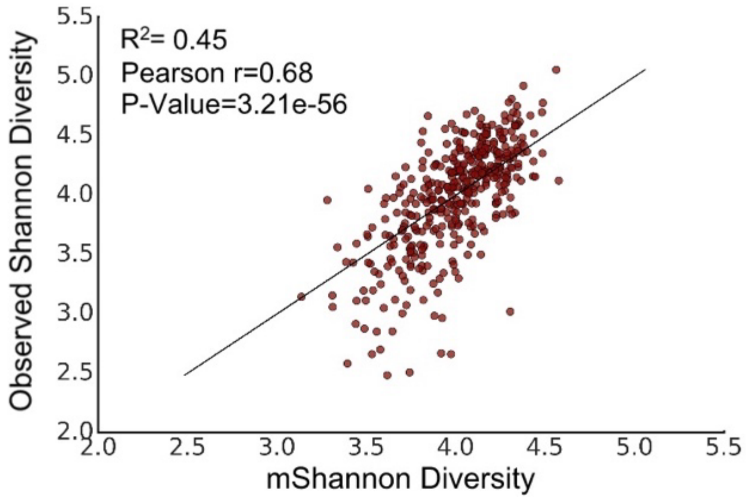
THE WALL STREET JOURNAL.

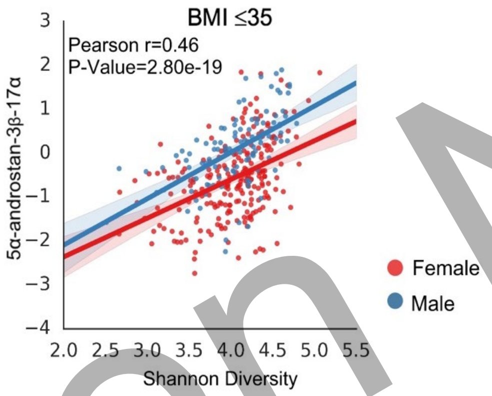
April 2023 (Weekend edition)

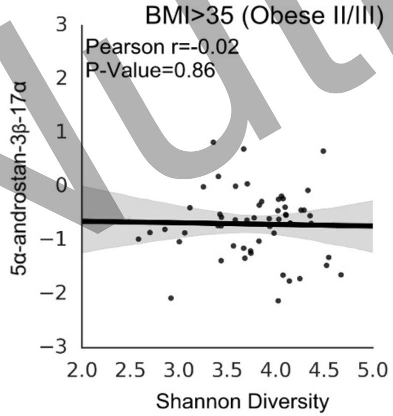
Microbiome health effects reflected in our biochemistry

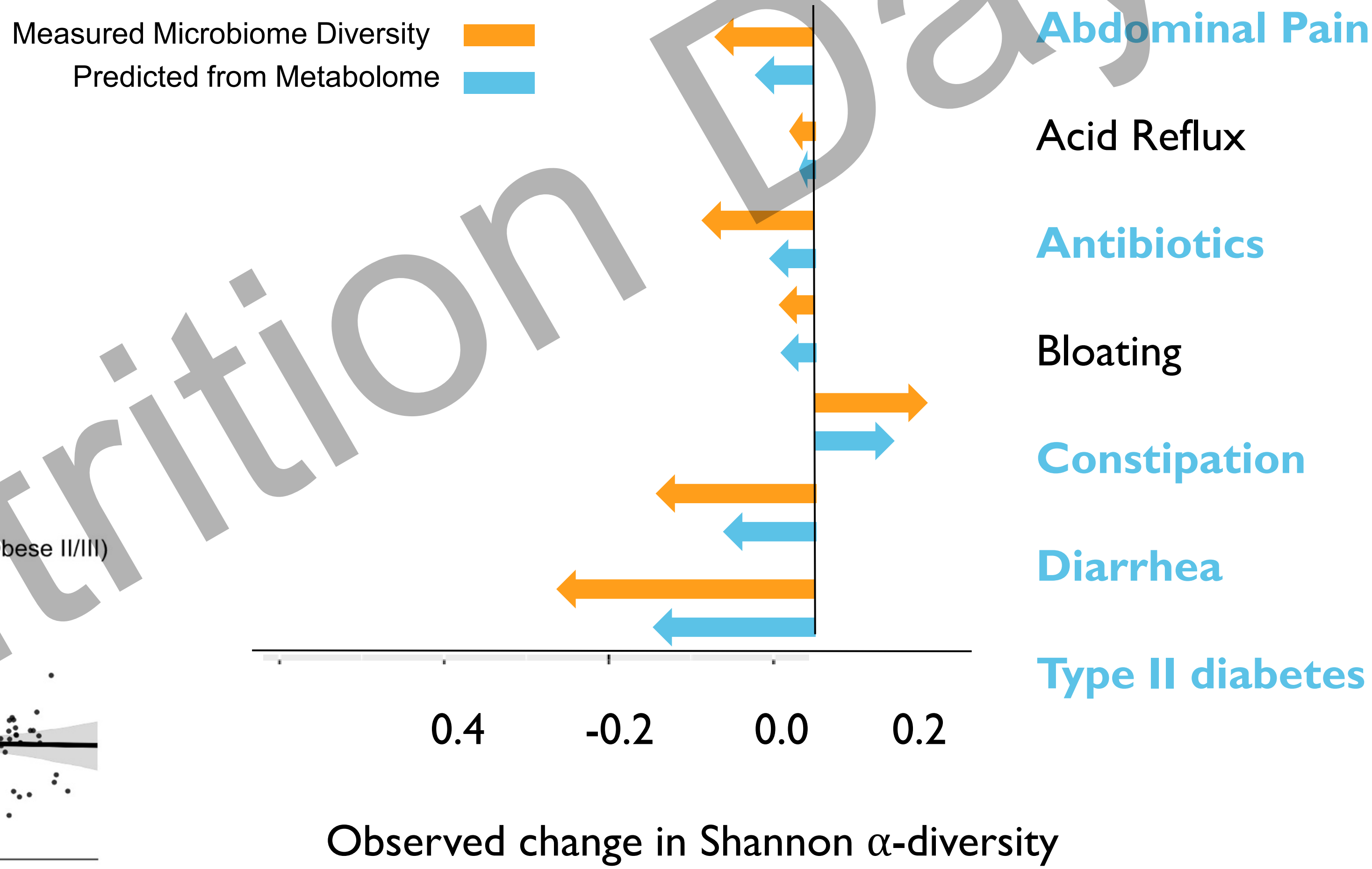
artist: Allison Kudla

Blood Metabolome Predicts Microbiome Diversity in Gut









Wilmanski, Rappaport…Price, *Nature Biotechnology* (2019)

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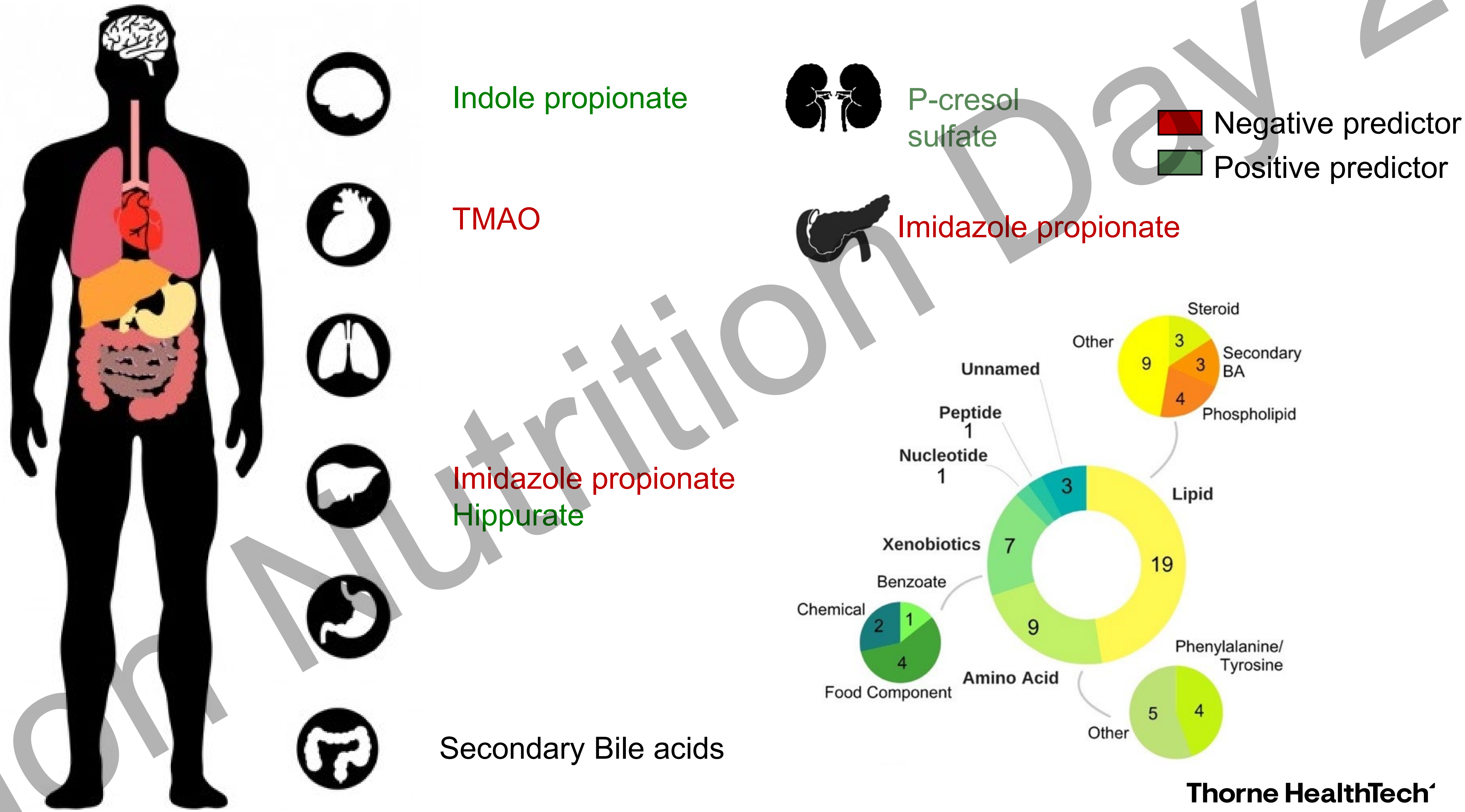
Identified Metabolites Exert Biological Effects in the Host



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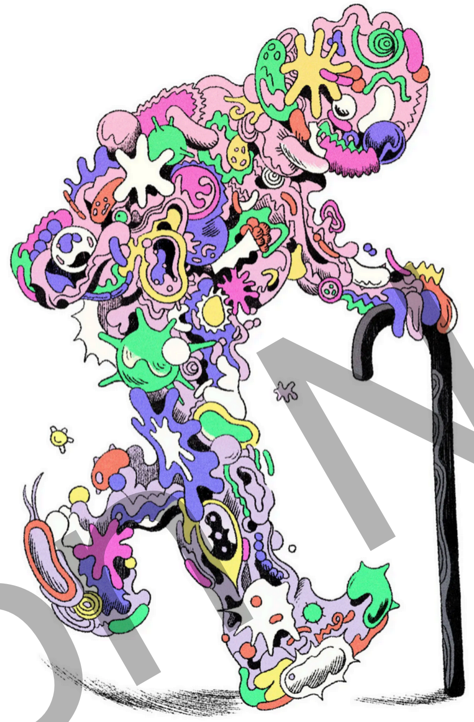
Gut microbiome is important for healthy aging and is highly personalized

The New York Times

A Changing Gut Microbiome May Predict How Well You Age

People whose gut bacteria transformed over the decades tended to be healthier and live longer.



Wilmanski…Price (*Nature Metabolism*, 2021)

Microbiome Uniqueness Increases with Age: *From around age 50, each person's microbiome becomes more distinct, influencing personalized health approaches.*

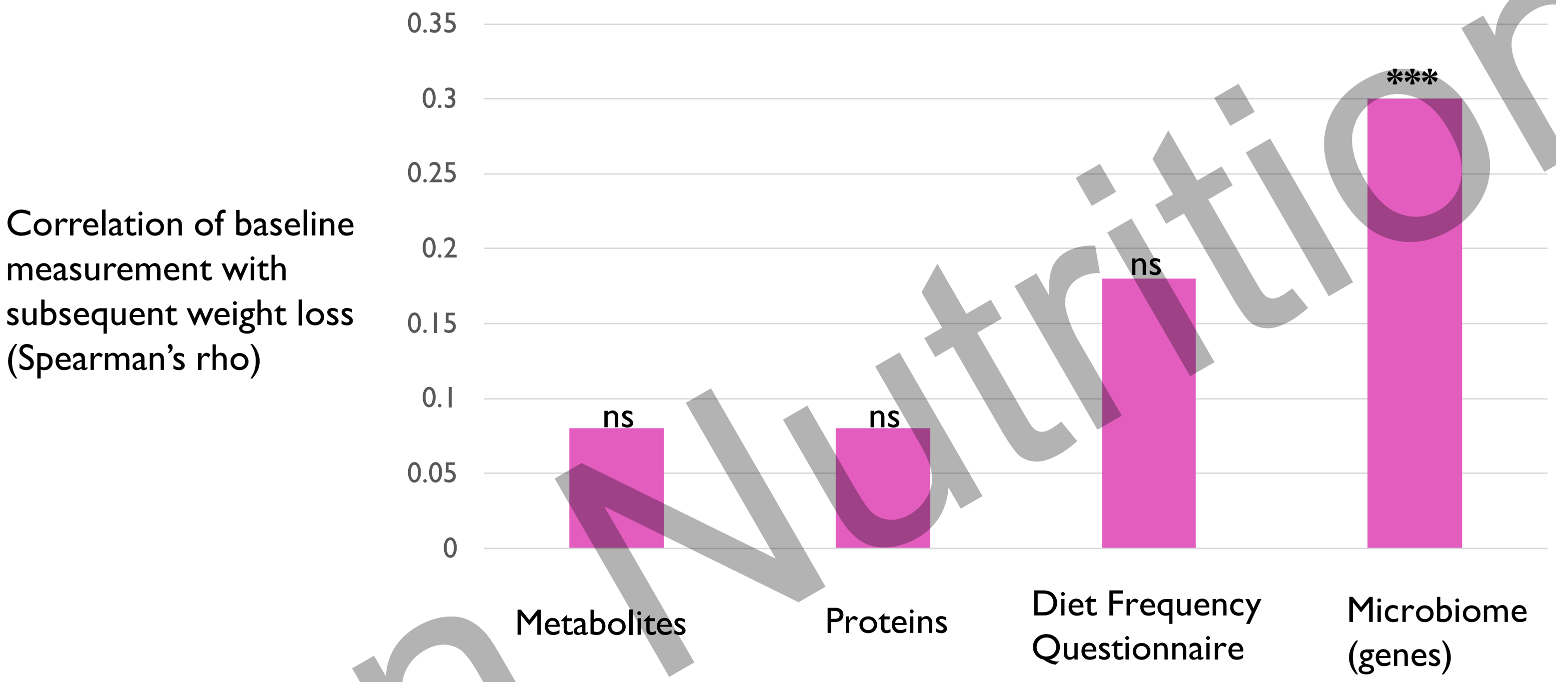
Stable Metabolic Processes in Healthy Aging: *Despite increased uniqueness, key metabolic functions are conserved in those who age healthily.*

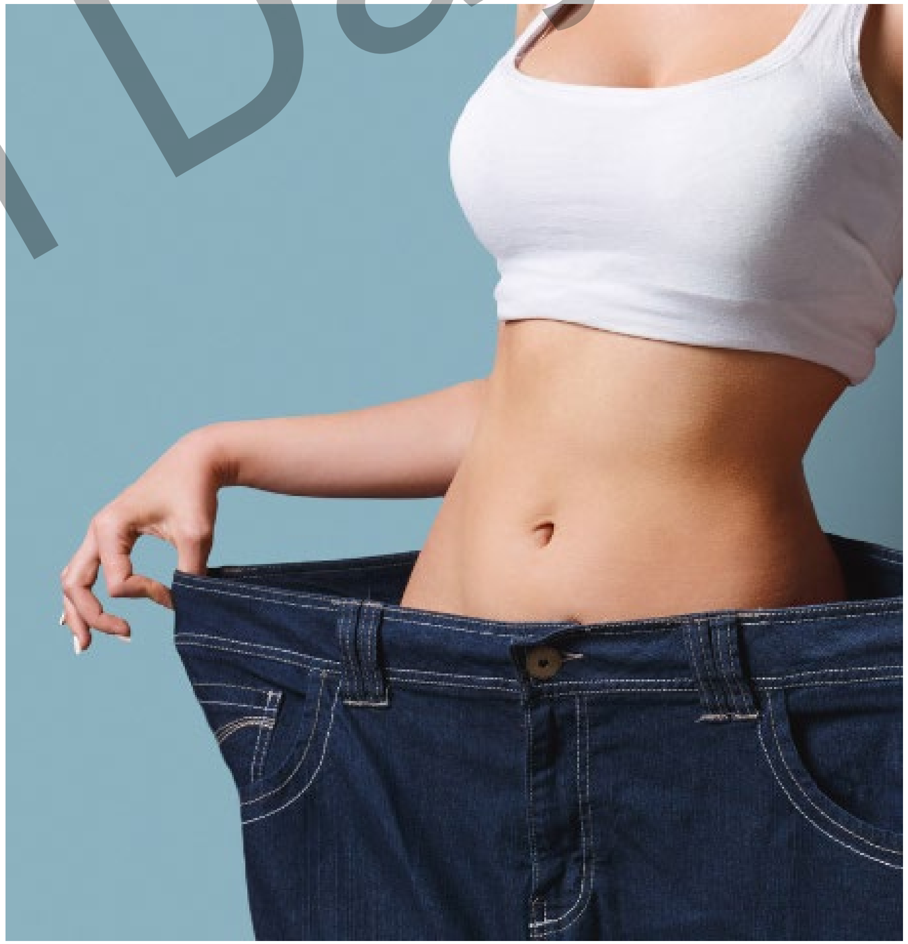
Microbiome Predicts Mortality Risk: *The unique characteristics of an individual's microbiome can predict overall mortality risk in the elderly.*

NAM Catalyst Award

U.S. NATIONAL ACADEMY OF MEDICINE
Healthy Longevity
GLOBAL GRAND CHALLENGE

Microbiome was the most (only) measure predictive of weight loss at baseline independent of BMI





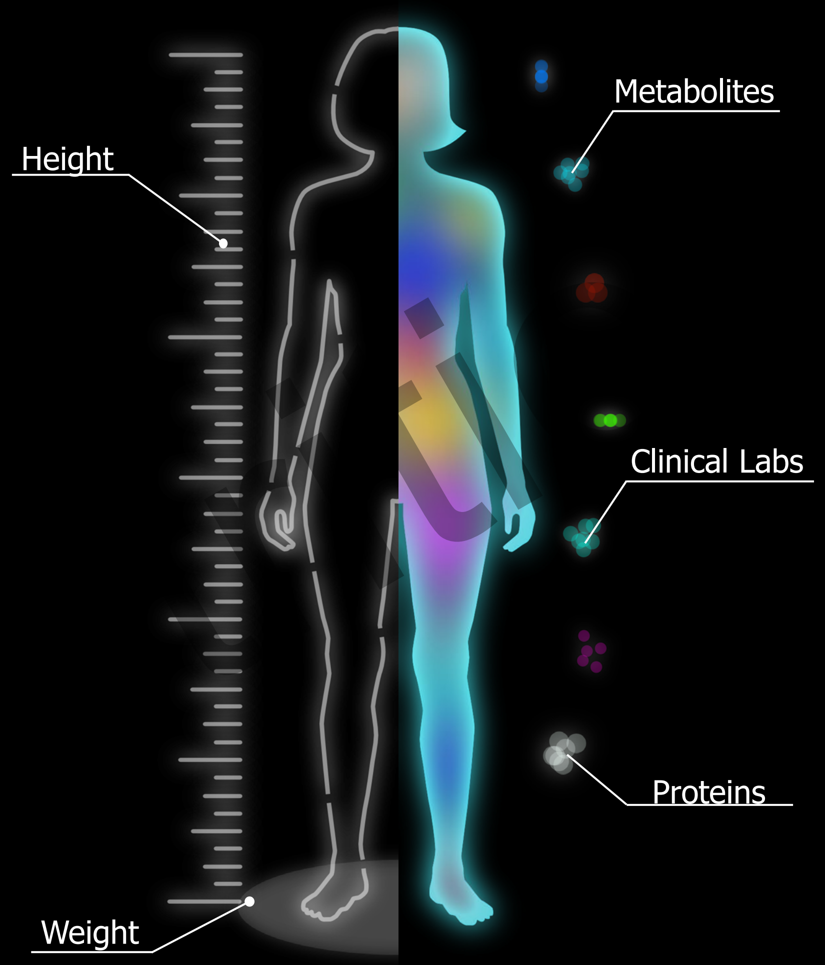
Diener et al., *mSystems*, 2021

Quantifying Metabolic Health Differently

Using phenomics to define data-driven health metrics

Traditional BMI

- Simple metric derived from height and weight
- Correlates with mortality and chronic diseases
- Limited capacity to capture complex metabolic and physiological differences
- Misclassifies up to 30% of people



Biological BMI

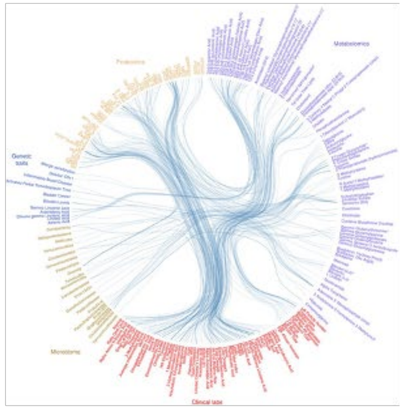
- Integrates various molecular data to capture heterogeneity in metabolic health and gut microbiome structure
- May identify metabolically unhealthy individuals who occupy a normal BMI
- Multidimensional profile of obesity, built on comprehensive profiling that integrates both new and existing biomarkers
- Responsive to lifestyle interventions, offering rapid feedback on metabolic health independent of weight loss

Phenome Health

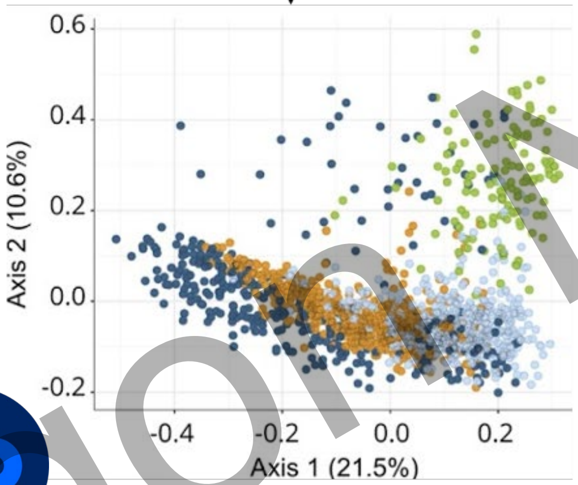
Watanabe… Price, Rappaport, *Nature Medicine*, 2023

Gut microbiome influences statin efficacy

Statins have a *very weak* (but detectable) effect on microbiome composition, while microbiome composition has a strong effect on host *responses* to statins

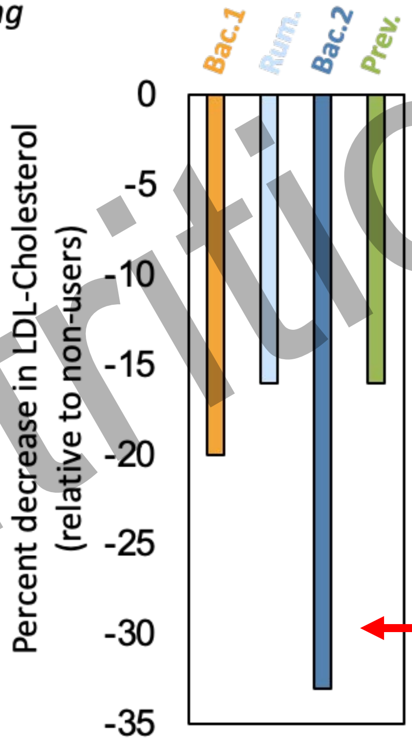


- *Medication and dosage history*
- *Clinical laboratory tests*
- *Plasma Metabolomics*
- *Whole genome sequencing*
- *Gut Microbiome sequencing*



Microbiome Compositional states

Statin on-target effects



Doubled lowering of LDL cholesterol observed with this type of microboime

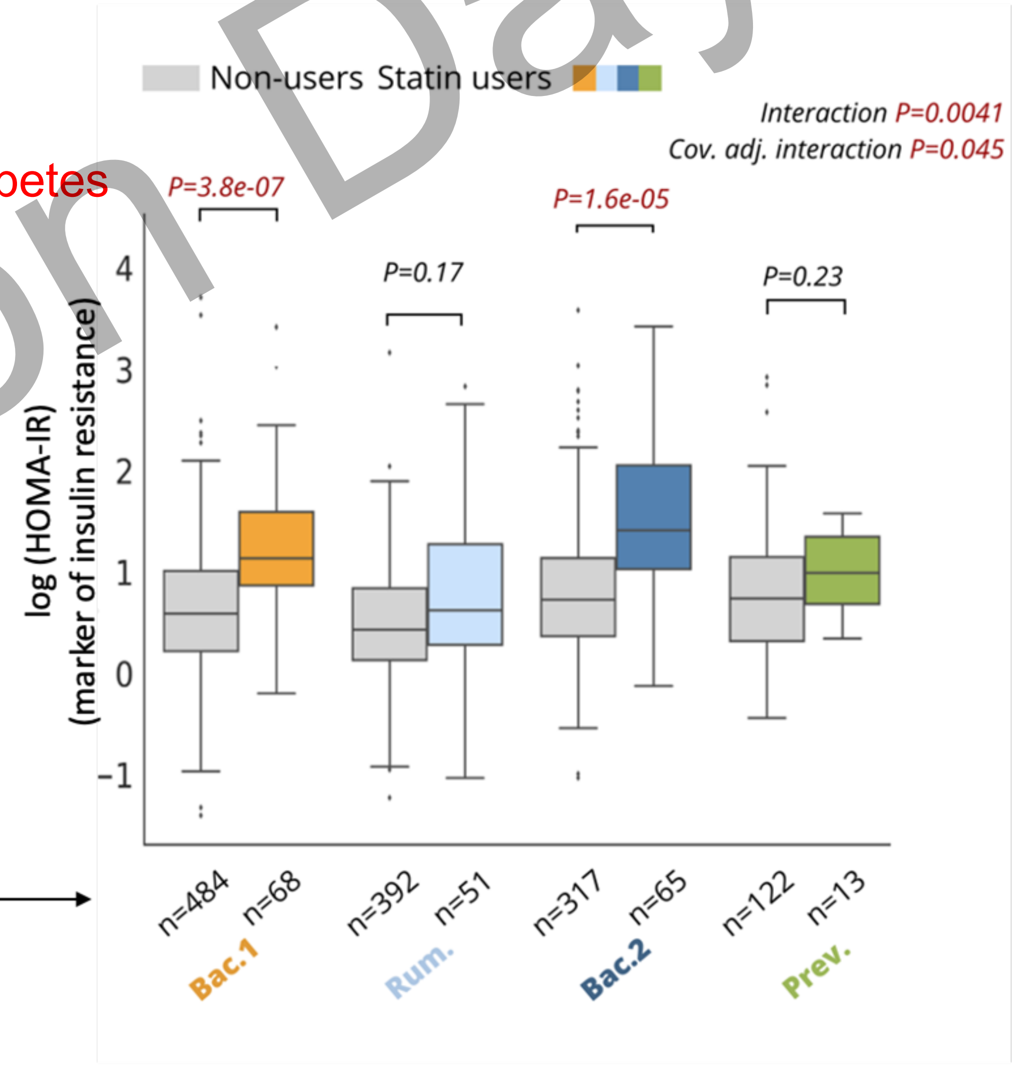
Wilmanski et al., *Med (Cell Press)*, 2022

Gut microbiome also associated with side effects

Two types of microbiome showed signs of diabetes increase, while two did not

Statins have a *very weak* (but detectable) effect on microbiome composition, while microbiome composition has a strong effect on host *responses* to statins

Statin off-target effects



Wilmanski et al., *Med (Cell Press)*, 2022

Gut microbiome: Innovations in collections and analysis

New "Microbiome Wipe"

Hua, H. et al, Frontiers in Immunology (2022)

Most Innovative Companies 2023

STEP 1

Read the instruction booklet

STEP 2

Collect Stool Sample with Wipe

STEP 3

Place wipe in container and shake until dissolved

STEP 4

Release saline into lower container

STEP 5

Place container in specimen bag and shipper envelope

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Where we are headed: At home measurements coupling microbiome and metabolome at scale

FDA CLEARED

International Organization for Standardization ISO 13485 Quality Management System

OneDraw is placed on the upper arm

→

Blood stabilized in removable-cartridge

→

Cartridge inserted into transport sleeve

- 150uL sample volume
- Stable Transport
- 5 min average collection time
- No cold-chain necessary
- Near pain-free

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Implications for the future

We should evaluate the contributions of the microbiome based on reflections in the host – especially in the metabolome

We will need to map how diet and microbiome interact to fill in health-enhancing niches

Microbiome is a key component in healthy aging – and becomes increasingly unique to each individual

Microbiome wipe should provide a much-improved sample collection experience – and making measurements easier and cheaper is key

Microbiome is initiated at birth and largely passed from mother to child

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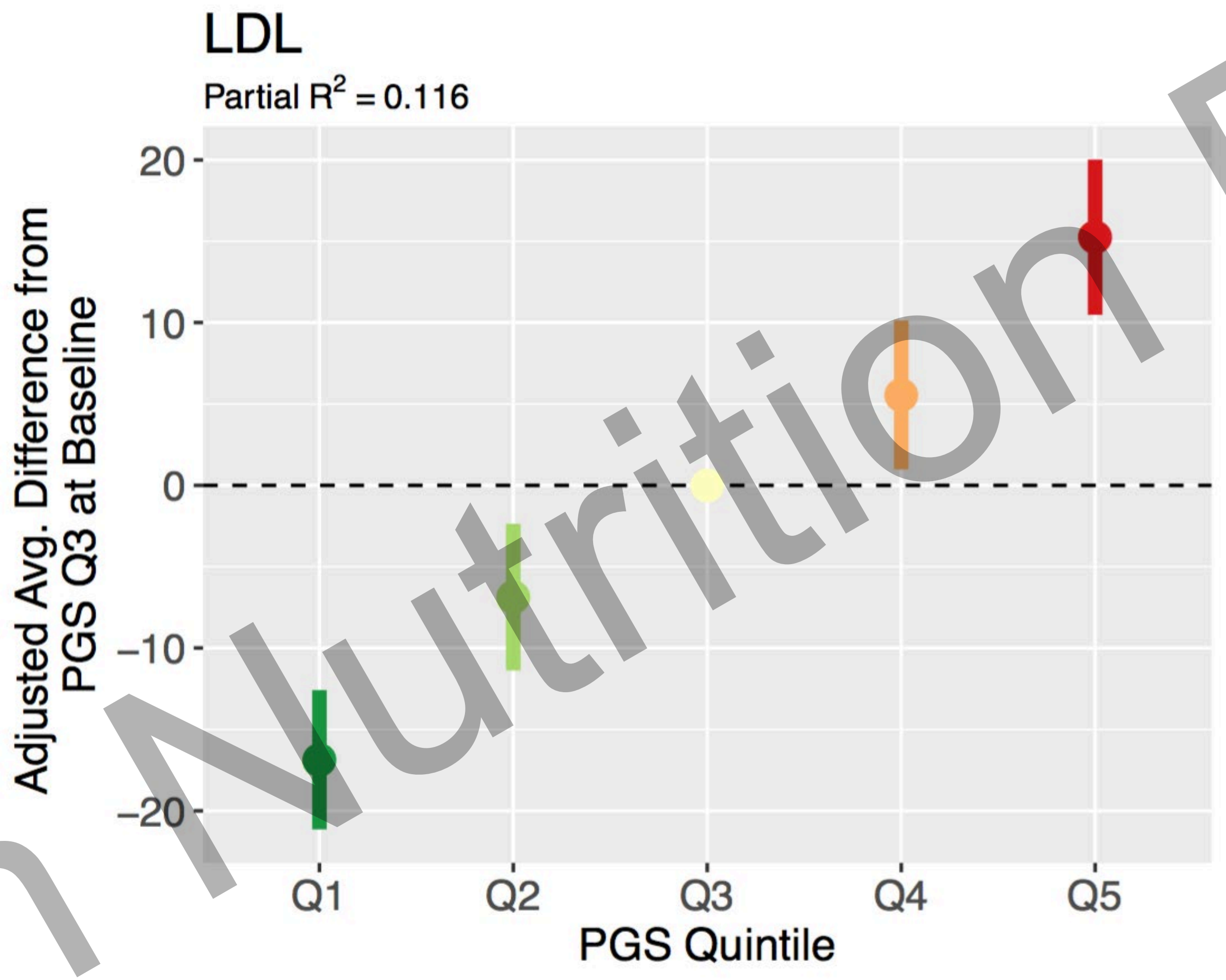
Can genomics predict the outcome of lifestyle interventions?

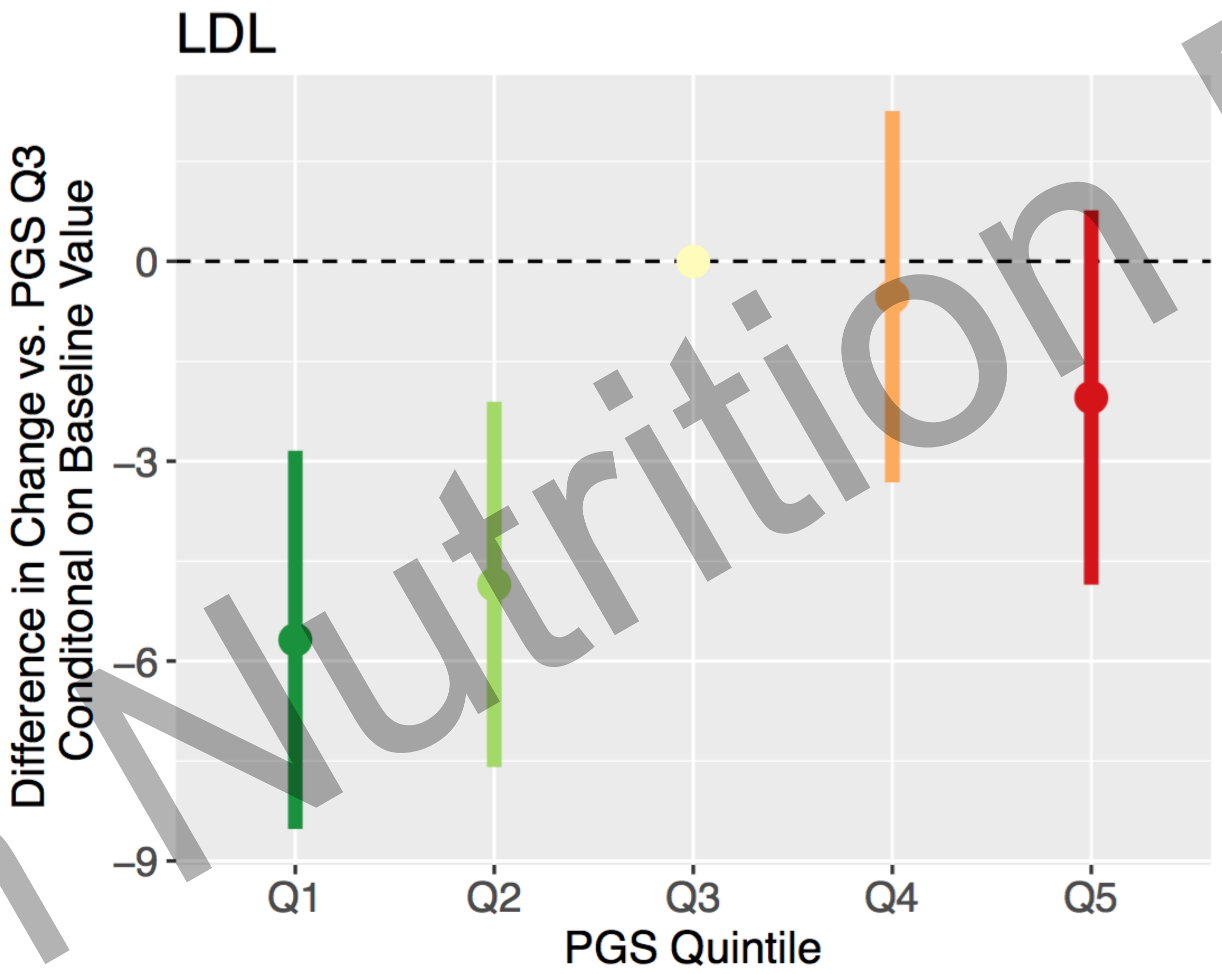
Genetics affects likely level of LDL cholesterol in the blood



PGS = polygenic score

Zubair N et al, *Scientific Reports* (2019)

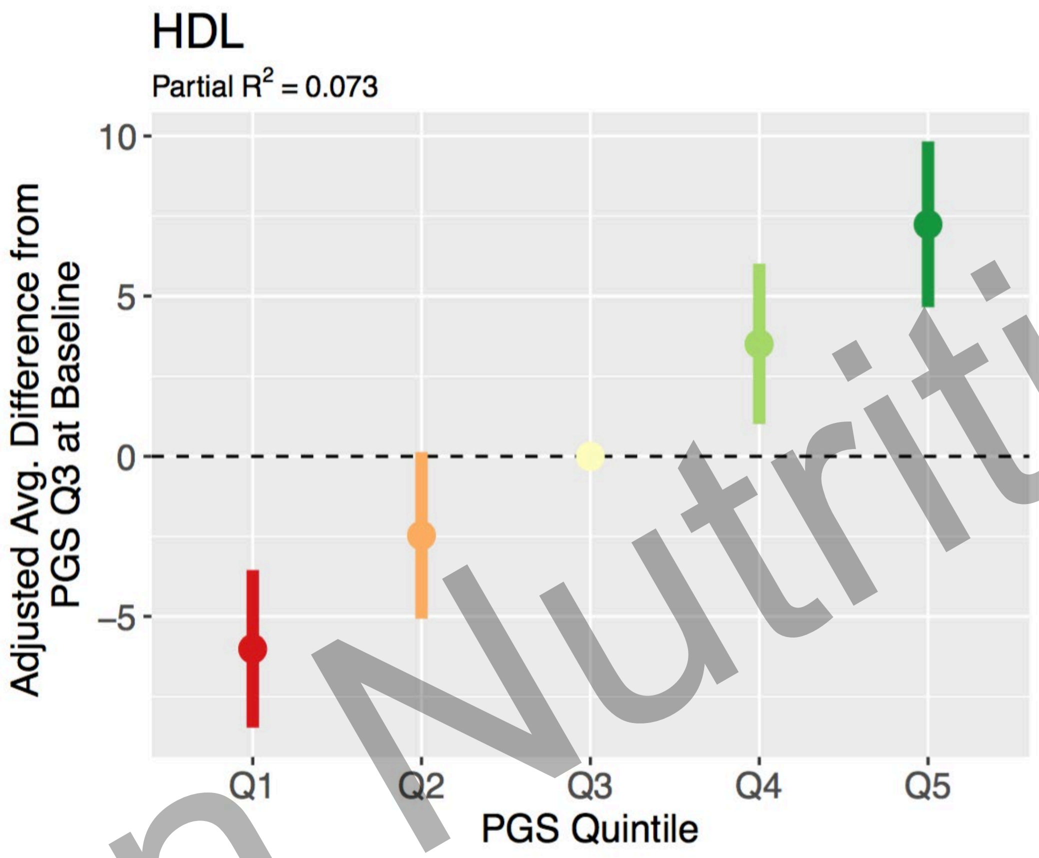
Genetics predicts success or failure in lowering LDL-C through lifestyle intervention

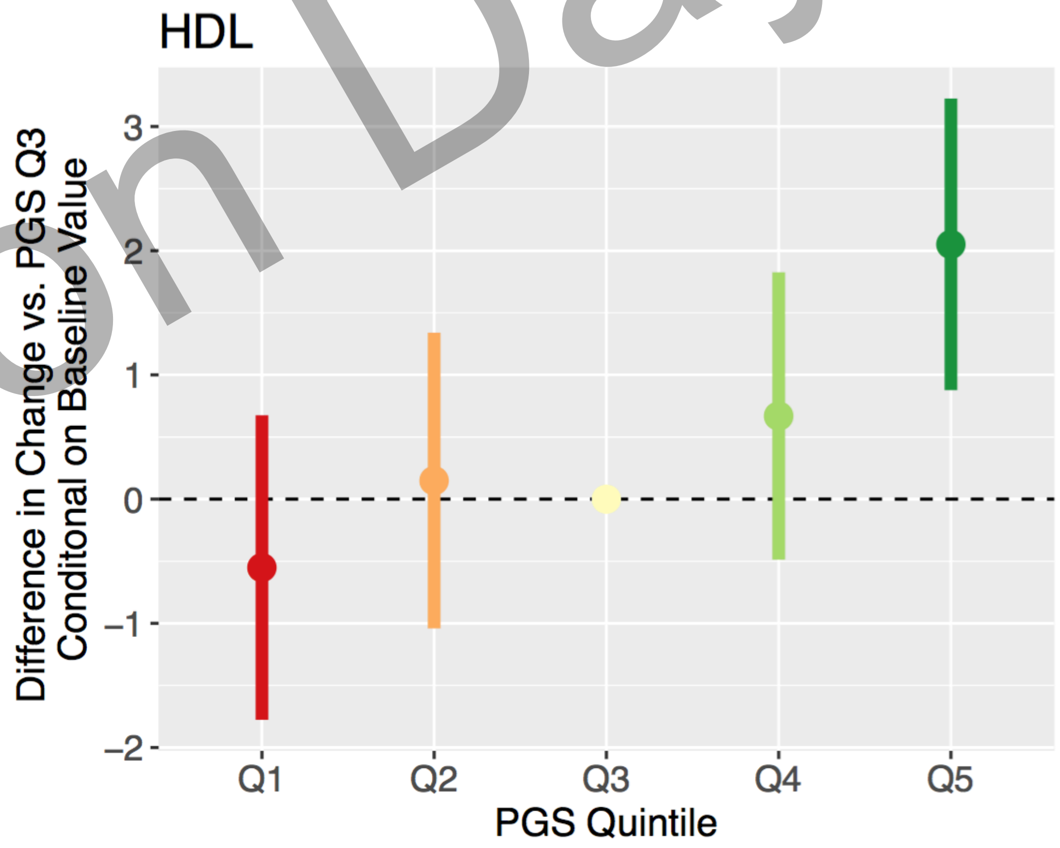


PGS = polygenic score

Zubair N et al, *Scientific Reports* (2019

Genetics predicts success or failure in elevating HDL-C through lifestyle intervention





Zubair N et al, *Scientific Reports* (2019)

PGS = polygenic score

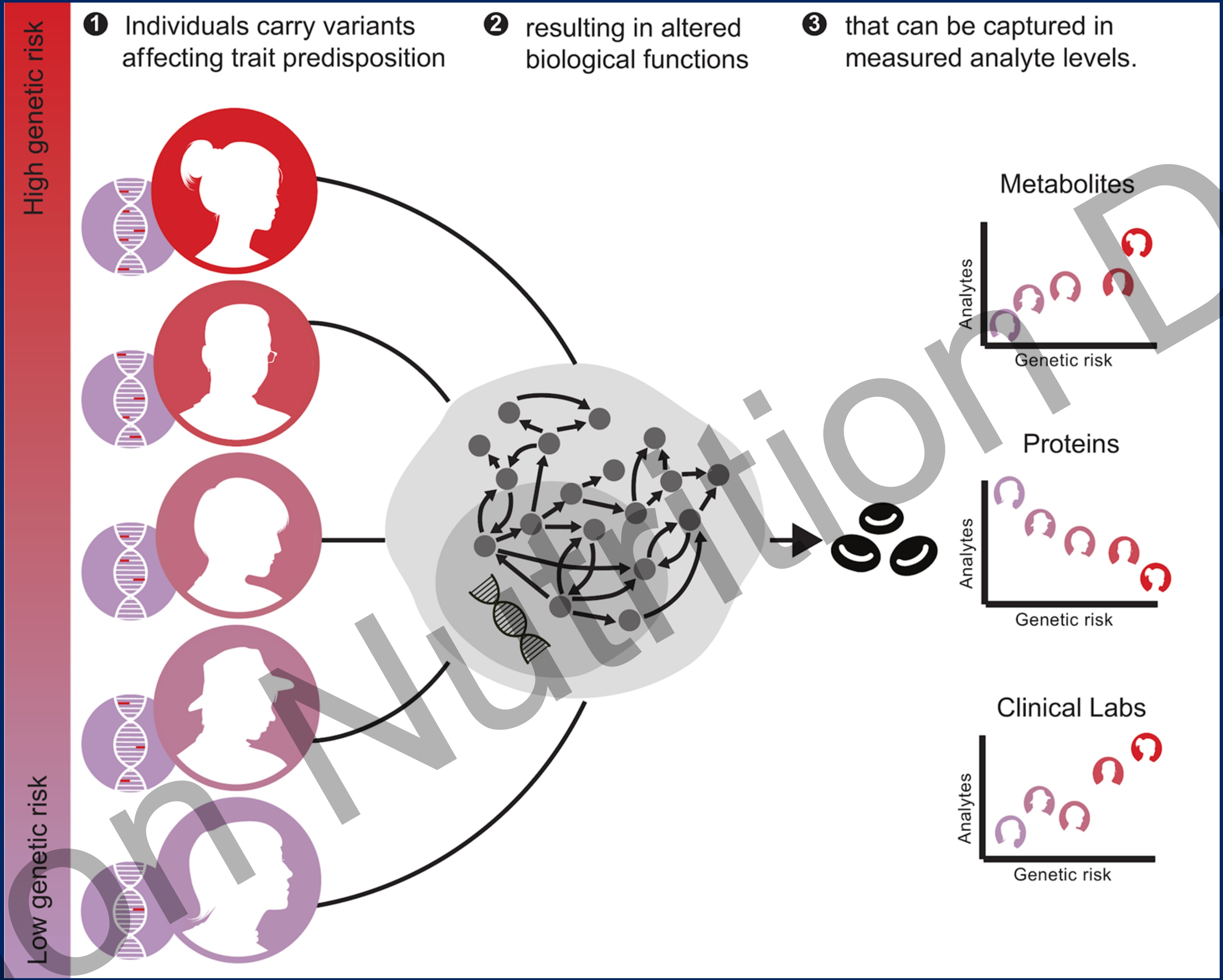
Implications for the future

Genetics are not destiny, but they quantitatively affect the outcomes for lifestyle interventions

We can design health strategies for people that highlight the areas where the most progress is likely – where they would be working with their genes rather than against

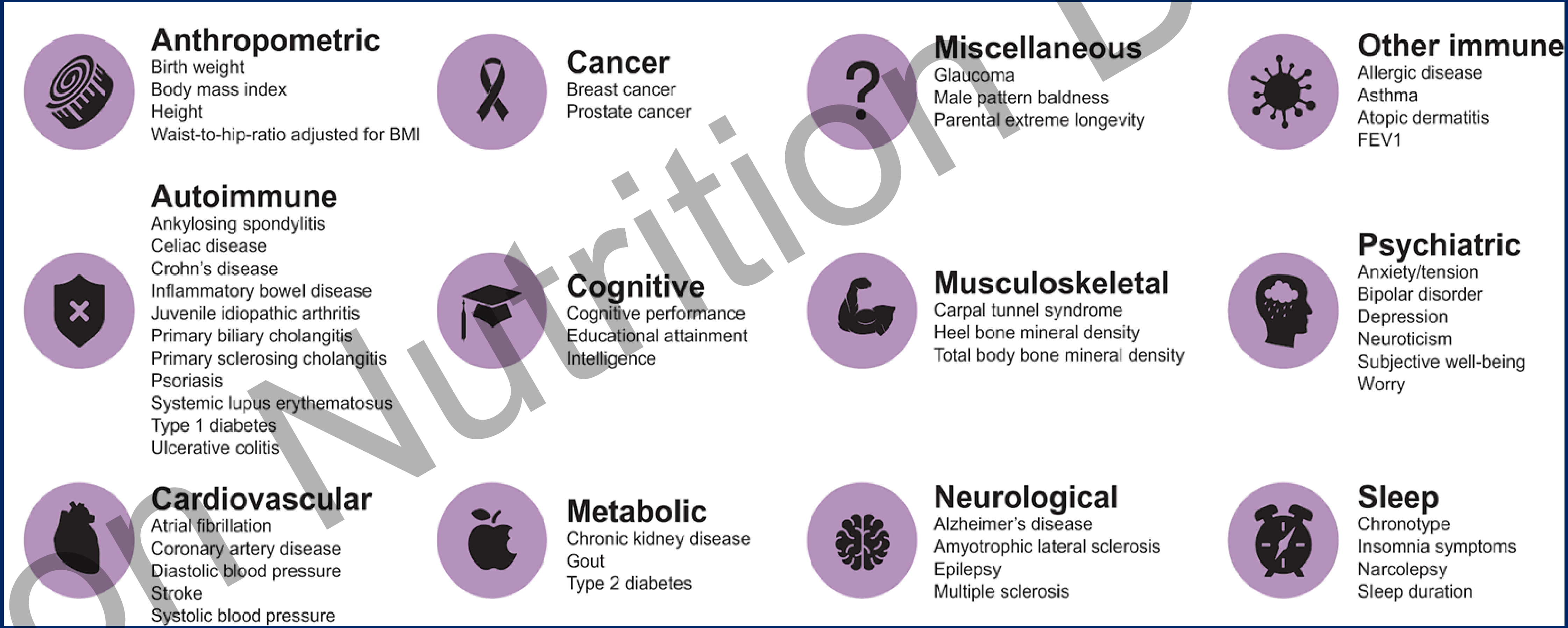
Combined with previous sectoin

Deep Phenotyping Reveals How Genetic Risk Manifests in the Body



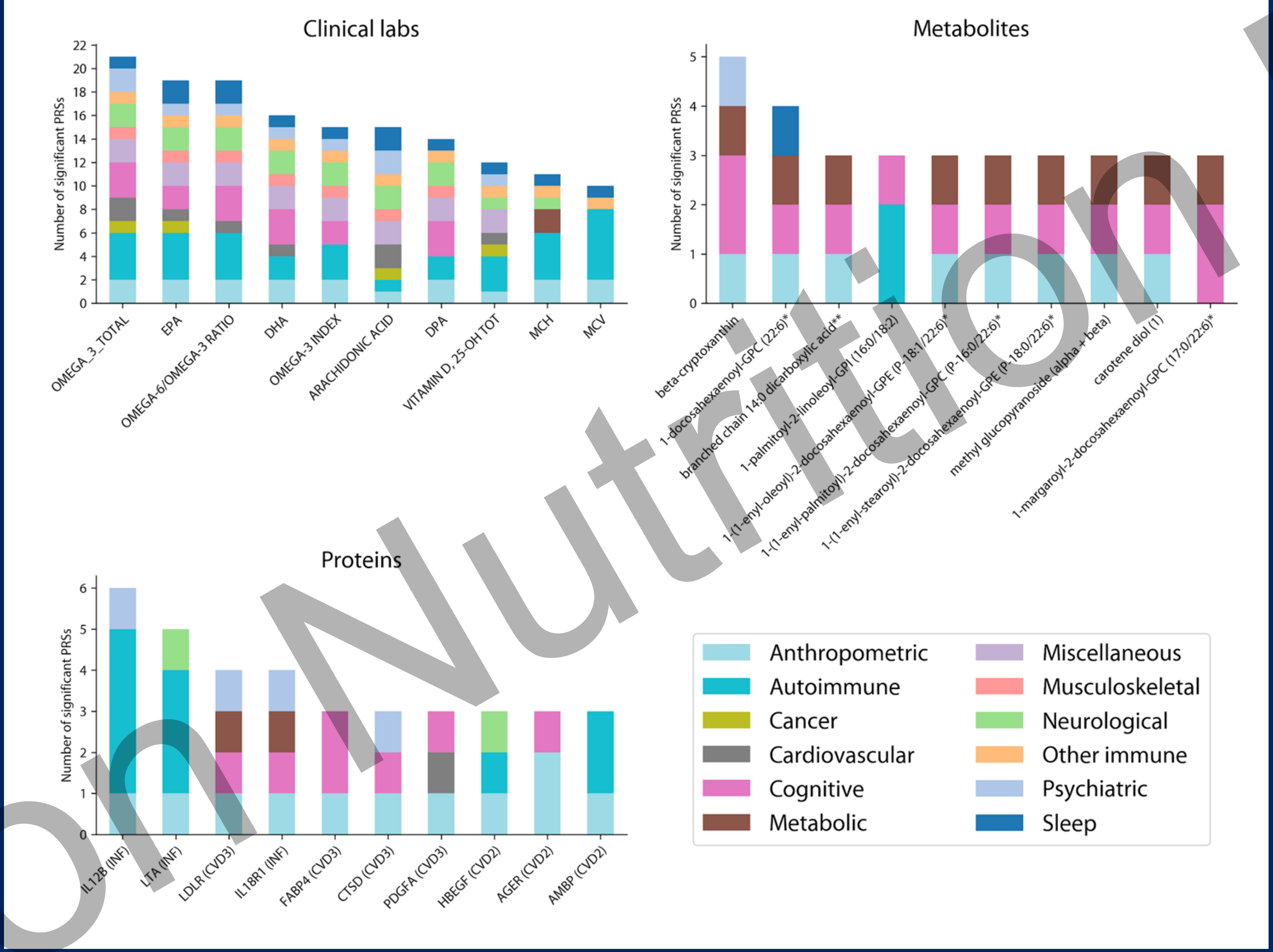
Wainberg…Hood, Price, *PNAS* (2020)

Interesting traits with well-powered GWAS (N = 54):



Wainberg…Hood, Price, *PNAS*(2020)

Which analytes correlate with the most polygenic risk scores?



Wainberg…Hood, Price, *PNAS* (2020)

Selected associations with literature evidence (4/756)

Trait	Analyte	Direction	Notes
ALS	**Total Ω-3s, EPA, DHA**	**+**	**Omega-3 hastened and Omega-6 delayed neurodegeneration in an ALS mouse model** (Boumil et al. *Open Neurol J* 2017)
	Total Ω-6s	**-**	
ALS	**EDTA**	**-**	**Synthetic chelating agent; only association is with ALS. Heavy metal exposure associated with increased ALS risk.** (Bozzoni et al. *Funct Neurol* 2016; Ash et al *Toxicological Sciences* 2018)
Asthma	**IL-33**	**+**	**IL-33's only association. LOF variant in *IL33* associated with halved asthma risk** (Smith et al. *PLOS Genet* 2017)
Coronary artery disease	**LDL, LDL particle number, small LDL, PCSK9**	**+**	**PCSK9 is the sole proteomic association with CAD.**

Implications for the future

Depending on a person's individual genetic profile and dynamic measures can provide a prioritization of health-related choices

We may be able to map out the most genetically at-risk people for disease and tailor approaches to reduce chances of manifesting the disease

Combining with previous section, we can map for both what is highest risk AND what is most likely changeable

Genetics is a bridge between health outcomes, deep phenotyping, and development

How could deep phenotyping and DOHAD intersect?

Research paper

Towards early risk biomarkers: serum metabolic signature in childhood predicts cardio-metabolic risk in adulthood

Xiaowei Ojanen, Ph.D[1,2,3,**], Runtan Cheng, Msc[1,2,**], Timo Törmäkangas, Ph.D[3], Noa Rappaport, Ph.D[4], Tomasz Wilmanski, Ph.D[4], Na Wu, Msc[1], Erik Fung, M.B.Ch.B., Ph.D[5,6,7], Rozenn Nedelec, MSc[8], Sylvain Sebert, PhD[8], Dimitris Vlachopoulos, Ph.D[9], Wei Yan, Ph.D[1], Nathan D. Price, Ph.D[4], Sulin Cheng, Ph.D[1,2,3,10,*], Petri Wiklund, Ph.D[2,3,*]

ELSEVIER

EBioMedicine

- Three childhood metabolic biomarkers (GlycA, L-HDL-PL, ApoB/ApoA) associated with increased adult cardio-metabolic risk.
- Associations confirmed in multiple cohorts, both sexes, from adolescence to older adulthood.
- Bidirectional causal relationship suggested between biomarkers and cardio-metabolic risk from childhood to adulthood.
- Metabolic signature reflects atherogenic lipoproteins, reduced cholesterol efflux, and chronic inflammation, potentially causing early vascular changes.
- Metabolomics panel could identify children at risk for future cardiovascular disease, allowing preventive measures and follow-up.

Why pregnancy is ideal for prototyping P4 medicine of the future

- Pregnancy is one of the most important times in life, with major implications for lifetime health
- Major outcomes can be seen in a relatively short period of time, 9 months or less
- It is generally a time of higher engagement with the healthcare system
- It is a difficult period for the development of novel drugs, and so “scientific wellness” intervention strategies may be particularly attractive
- We can study disease trajectories from the earliest transitions, and hopefully reverse/slow them to the point they are no longer problems
  - Importantly – disease trajectories can be unique!

P4 Medicine

Predictive

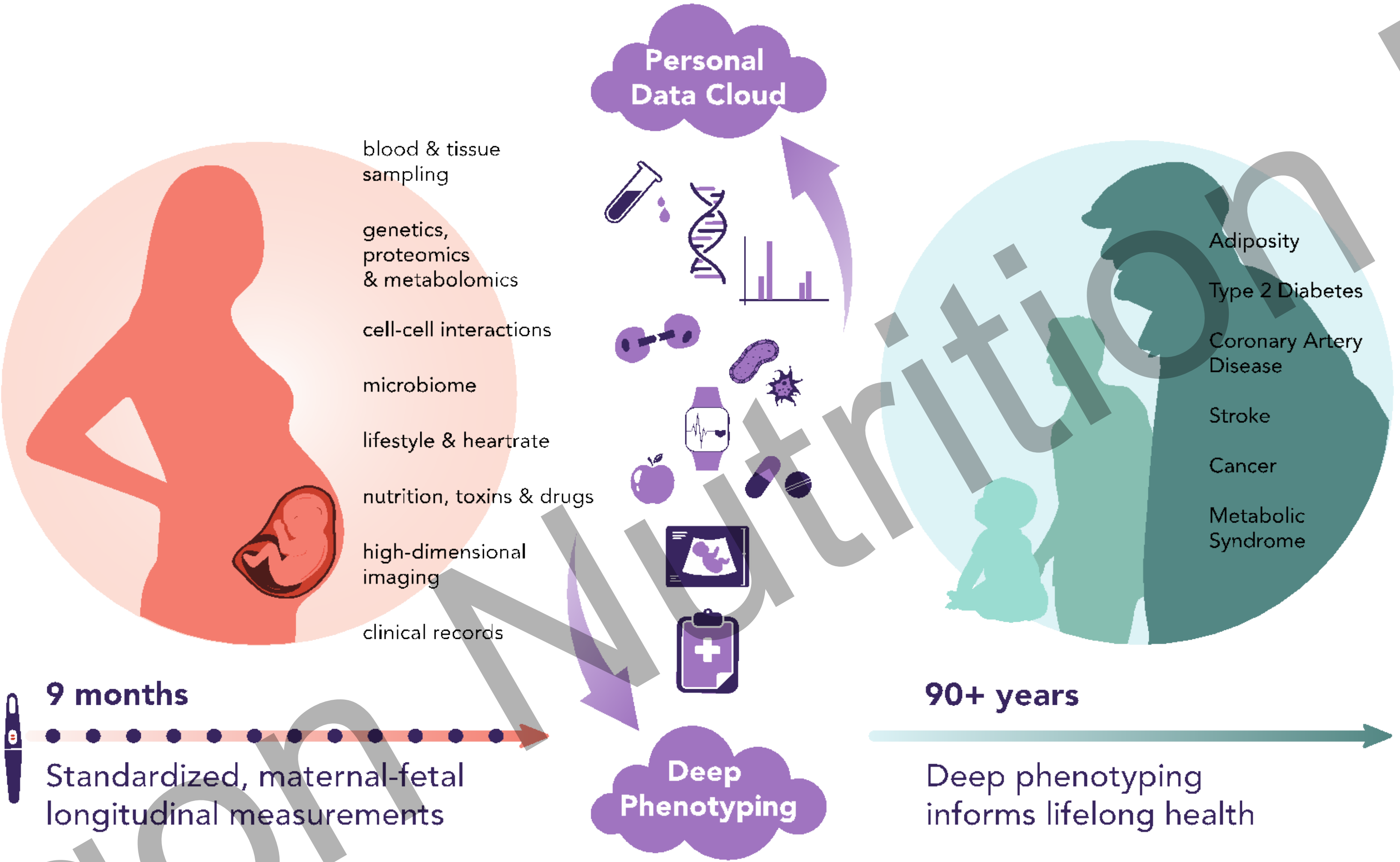
Preventive

Personalized

Participatory

Paquette, Hood, Price, Sadovsky, *Science Translational Medicine* (2020)

The Pregnancy ‘Pioneer 200’



Yoel Sadovsky, MD

UPMC
MAGEE-WOMENS
HOSPITAL

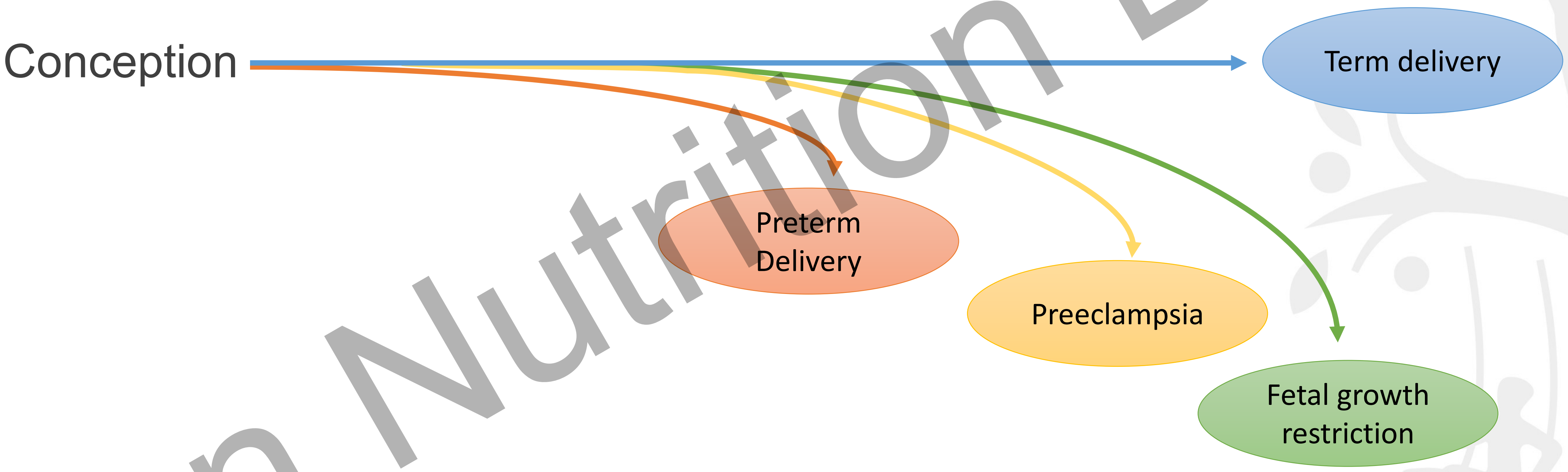
Lee Hood, MD, PhD

Alison Paquette, PhD

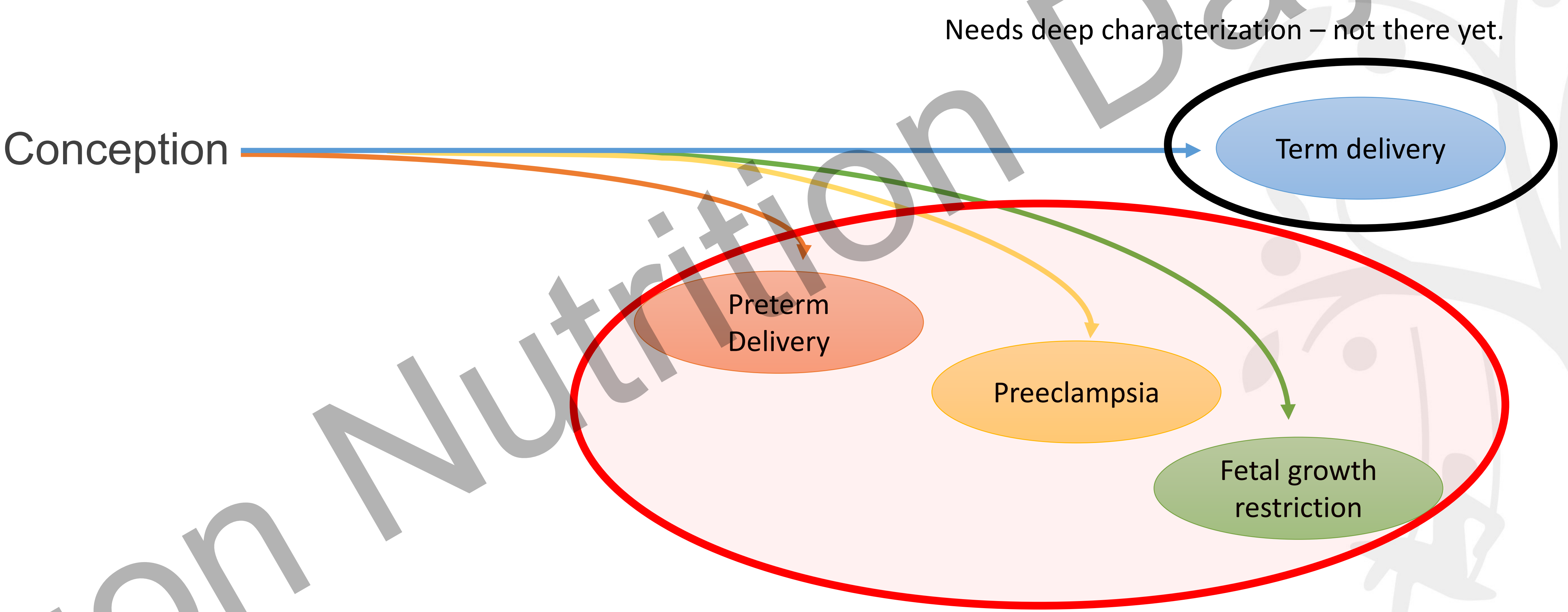
ISB

Paquette, Hood, Price, and Sadovsky, *Science Translational Medicine* (2020)

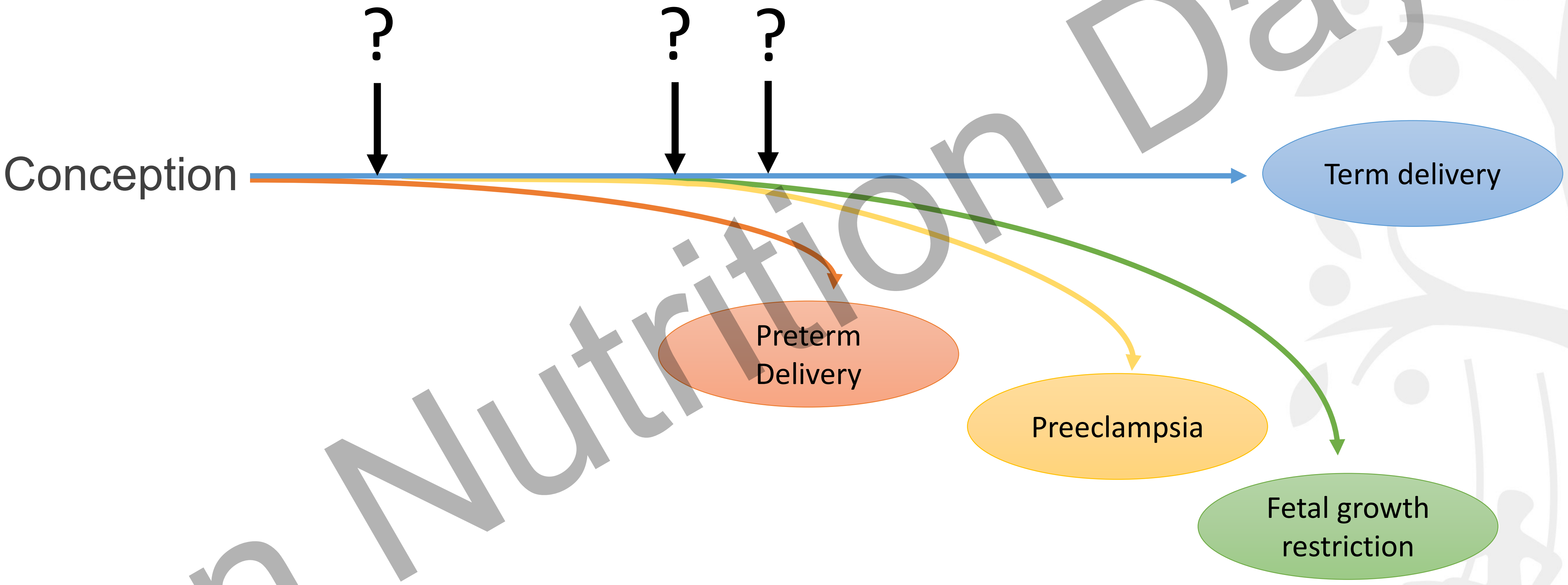
Needs deep characterization – not there yet.



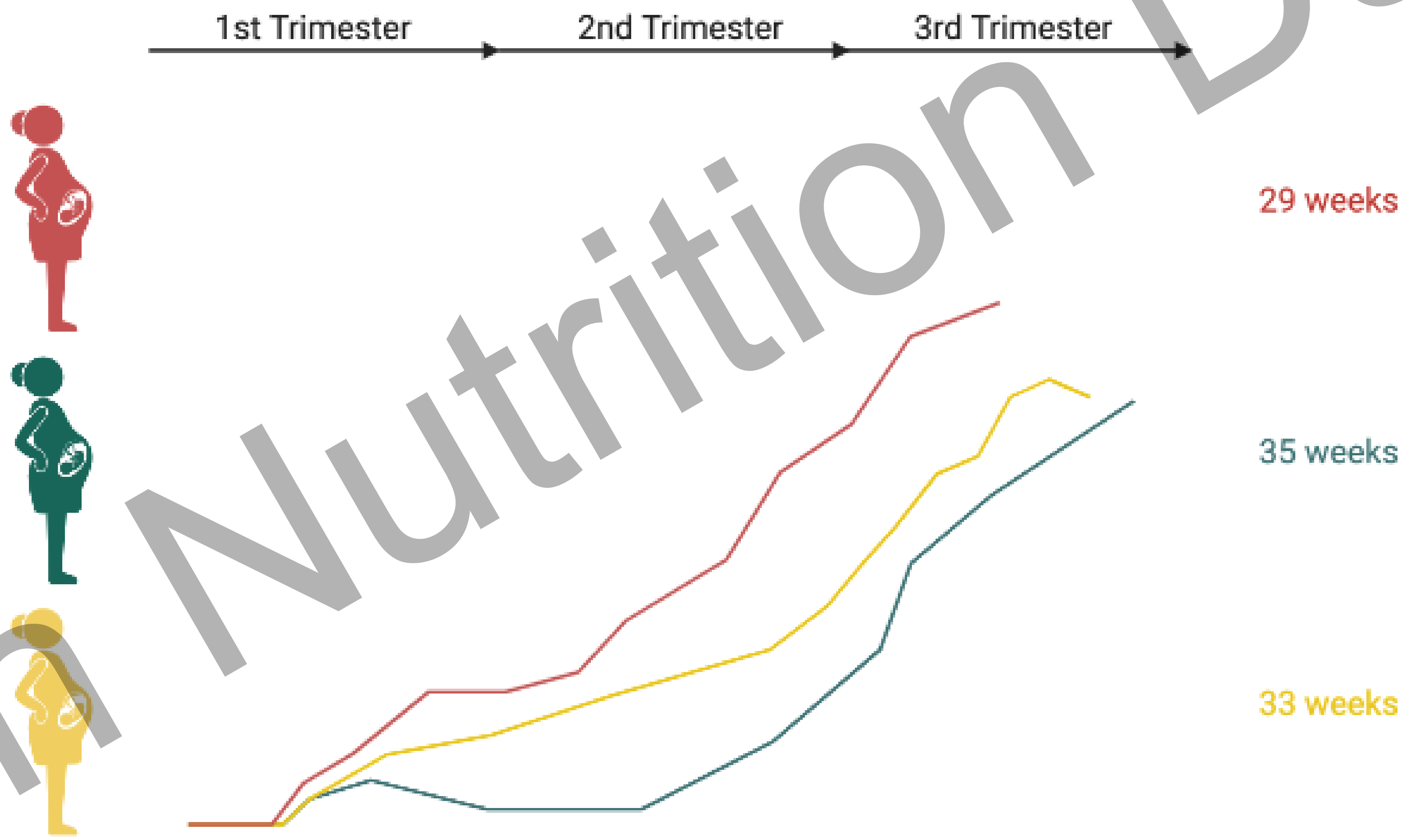
What Is The Difference?



When Is The Point Of Deviation?



What is the underlying cause for each negative pregnancy outcome?



MAGEE-WOMENS RESEARCH INSTITUTE

Collecting Dense, Deep-Phenotypic Data

Questionnaires
- Diet
- Stress
- Depression
- Nausea

Fitbit
- Physical Activity
- Sleep
- Heart Rate

EHR
- Physical Activity
- Blood pressure, heart rate, weight, etc.
- Clinical Labs
- ICD-10 codes
- Free Text

Environmental
- Personal PM monitor
- EPA (Home address)
- Water Samples
  - Nitrate
  - DBP
  - Metals (lead, mercury, etc.)

Blood
- Whole Genome Sequencing
- Transcriptomics
- Proteomics (~1500)
- Metabolomics (~1000)

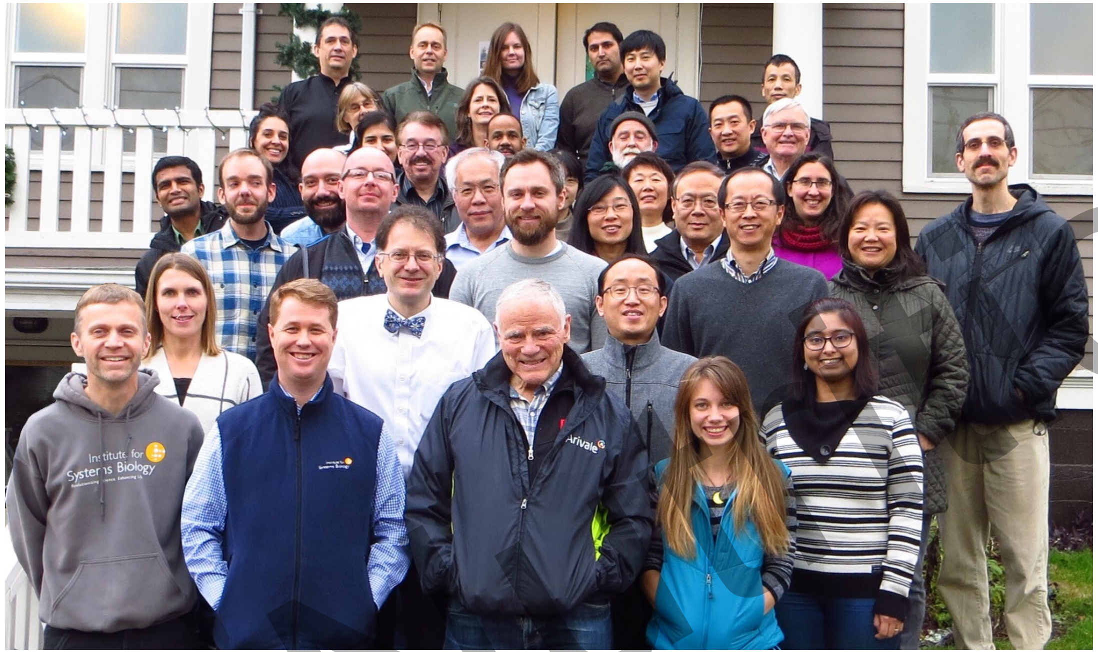
Urine
- Metabolomics (~1000)

Microbiome
- Gut
- Vagina

Summary

- New capabilities are giving us unprecedented access to studying health and the transition states to disease, enabling scientific wellness
- Longitudinal deep phenotyping studies are uncovering numerous interactions across systems and gaining in predictive power
- DOHAD is highly relevant to virtually all of these modalities -- from genetics to the microbiome – and provides a fertile ground for discovery

Integrated Lab for Systems Biomedicine
PIs: Lee Hood and Nathan Price



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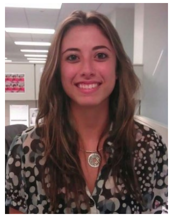

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Thank You!

Thorne HealthTech

If interested, feel free to reach out:

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