Phenome HEALTH

The Human Phenome Initiative and Radical Health

How the Human Phenome Initiative Will Transform Healthcare with the Largest Paradigm Change Ever

Data-driven health for individuals
is the strategy

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Phenome Health

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Co-founder, Professor
Institute for Systems Biology, Seattle

Buck
Live better longer.

Crawford Lecture // April 25, 2024

Big Idea: Health underlies and enhances all of basic human nature and spirit—every individual should have access to health

Generate a healthspan for individuals of 90-100 years or more

Big Idea: Think differently about health

Radical Health

WHAT

Catalyze a shift from our current disease-oriented healthcare to one focused on wellness and prevention

WHY

The US healthcare system ranks last among high-income countries* despite spending almost 3 x as much per patient on healthcare than the next closest country

HOW

Data-driven health, using genome and longitudinal phenome analyses, offers a quantified assessment of your health, its projection into the future and how to optimize wellness and prevent transitions to disease for you

Commonwealth Fund: *EC Schneider et al. (2021) “Mirror, Mirror 2021: Reflecting Poorly”

I Participated in Seven Paradigm Changes in Biology/Medicine—1970-2024

All 7 paradigm changes (yellow) began to unravel biological complexity and framed my view of next generation of healthcare

New ideas need new organizational structures*

I cofounded 4 new companies and 5 non-profits to directly catalyze these paradigm changes.

Institute for Systems Biology

Data-Driven Health: the Genome and the Longitudinal Phenome and The Human Phenome Initiative

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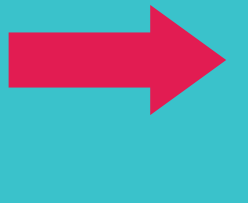
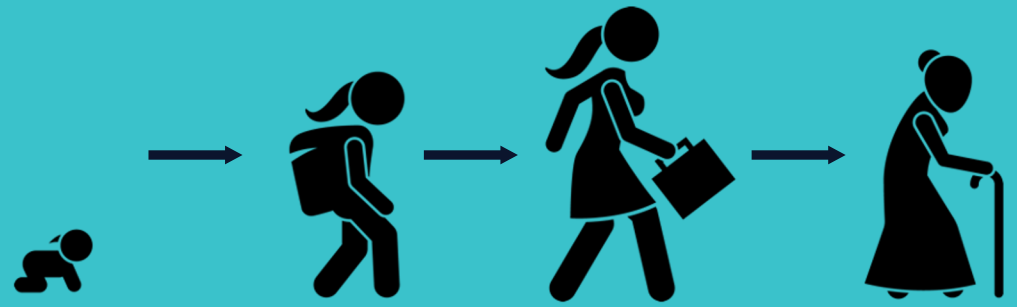
Human Genome Project (HGP)

1 person = 1 genome



Phenotype



1 person = Infinite phenomes across one's longitudinal life trajectory

The phenome allows one to assess the changing phenotype and allows ongoing assessments of the contributions of your genome, your behavior, and your environment (the "phenome") to an individual's always changing phenotype.

A 2nd Human Genome-like Project: The Human Phenome Project (HPP)

Million people over 10 years (genome/phenome)

with return of results

Assess the phenome at one point in time by blood analytes, gut microbiome, brain and body digital health assays,

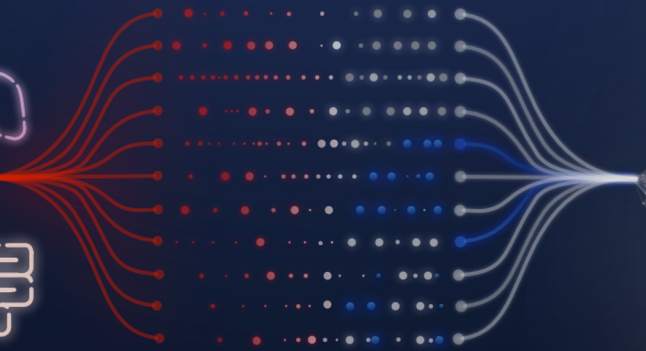
Systems Biology: Blood Is a Window into Health and Disease

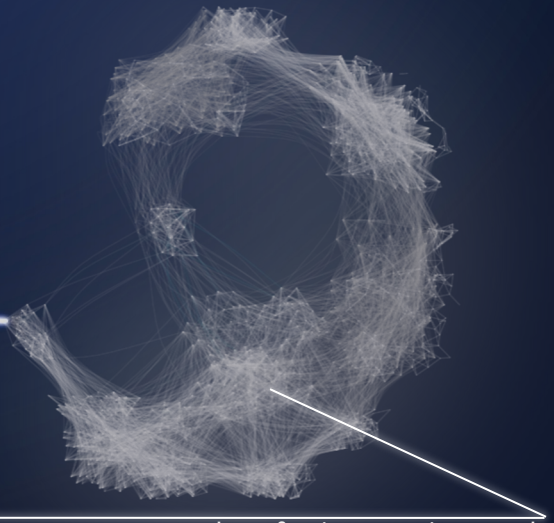
Organs release information-rich analytes into the blood

Features of Systems Biology
- Holistic
- Global
- Dynamical (longitudinal)
- Integrative
- Hierarchial

AI will associate measurements of each individual with health outcomes, health trajectories and the multiorgan dimensionality of disease and wellness

Integration of phenomic measurements





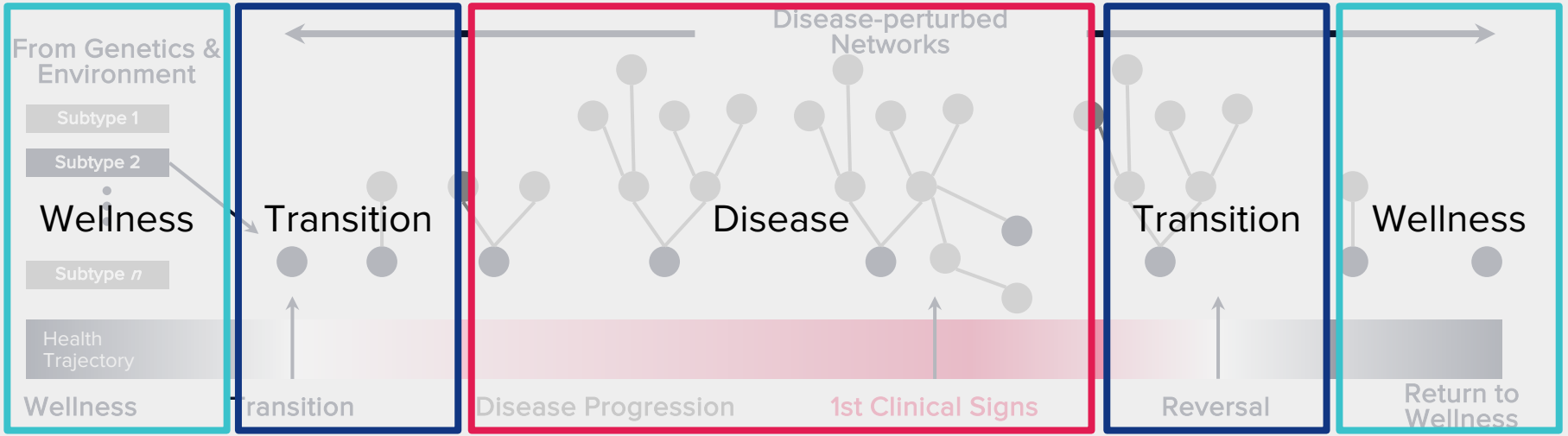
Powered by AI systems approaches for integrative analysis on our state-of-the-art multiomic platform:

- Machine Learning (ML) for classification
- Digital Twins for simulating trajectories& Knowledge Graphs for causality
- Large Language Models (LLMs) for deriving actionable recommendations from incredible biological complexity

A Data-Driven Vision of Health (Genome/Phenome)

Assessing and Optimizing the Health Trajectory of Each Individual

Three stages of health: wellness, disease, and transitions between the two



Improve wellness with actionable recommendations and healthy aging

Identify wellness-to-disease transitions and reverse them years before clinical disease

Manage disease—stratify disease and stratify patients

Data-Driven Health: Largest Paradigm Change in Healthcare Ever

Replace Disease-Focused Healthcare with a Wellness and Prevention

Proof of Principle for the Human Phenome Initiative through a Personalized Population Health (Arivale) Revealing Actionable Possibilities

Arivale (body)

5,000+ deeply analyzed individuals over 4 years—genome and longitudinal phenome analyses
Led to science-driven and data-driven Science of Wellness and Prevention

Gut microbiome

An explosion of research including: Arivale 5000, showing how important this feature is for diet, general health, aging, drug metabolism, metabolic health and more

Assays / Measurements for Arivale 5000 Participants

Creating personal dense, dynamic data clouds

GENOME

Whole Genome Sequencing
SNPs Millions

LABS

Detailed lab tests x2 (blood, urine, saliva)
Clinical chem. 150
Metabolites 1000
Proteins 400

Database of 200 "actionable possibilities" that will grow over time

SELF-TRACKING

Continual self-tracking (fitbit)
& lifestyle monitoring

MICROBIOME

Gut Microbiome
3x

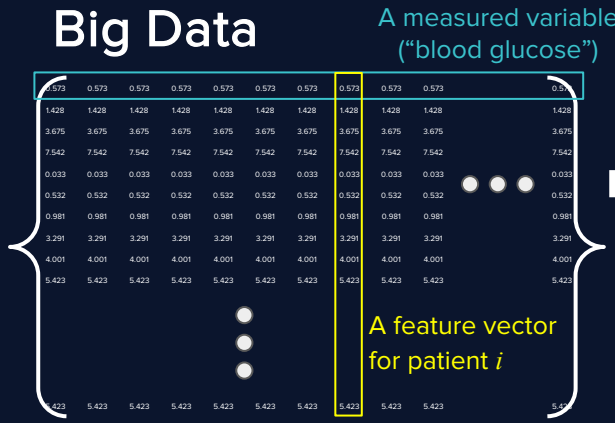
Recent Scientific Publications

	Publication Title	Year	Authors	Journal	PMID/DOI
1	A wellness study of 108 individuals using personal, dense, dynamic data clouds	2017	ND Price et al	*Nature Biotechnology*	28714965
2	Multi-Omic Biological Age Estimation and Its Correlation With Wellness and Disease Phenotypes: A Longitudinal Study of 3,558 Individuals	2019	JC Earls et al	*The Journals of Gerontology, Series A: Biological Sciences*	31724055
3	Genetic Predisposition Impacts Clinical Changes in a Lifestyle Coaching Program	2019	N Zubair et al	*Scientific Reports*	31048771
4	Blood Is a Window into Health and Disease	2019	JT Yurkovich and L Hood	*Clinical Chemistry*	31171530
5	Blood metabolome predicts gut microbiome α-diversity in humans	2019	T Wilmanski et al	*Nature Biotechnology*	31477923
6	Multi-Omics Resolves a Sharp Disease-State Shift between Mild and Moderate COVID-19	2020	Y Su et al	*Cell*	33171100
7	Deep phenotyping during pregnancy for predictive and preventive medicine	2020	AG Paquette et al	*Science Translational Medicine*	31969484
8	A systems approach to clinical oncology uses deep phenotyping to deliver personalized care	2020	JT Yurkovich et al	*Nature Reviews Clinical Oncology*	31619755
9	Atlas of Transcription Factor Binding Sites from ENCODE DNase Hypersensitivity Data across 27 Tissue Types	2020	CC Funk et al	*Cell Reports*	32814038
10	Multiomic blood correlates of genetic risk identify presymptomatic disease alterations	2020	M Wainberg et al	*Proceedings of the National Academy of Sciences*	32817414
11	Longitudinal analysis reveals transition barriers between dominant ecological states in the gut microbiome	2020	R Levy et al	*Proceedings of the National Academy of Sciences*	32471946
12	Untargeted longitudinal analysis of a wellness cohort identifies markers of metastatic cancer years prior to diagnosis	2020	AT Magis et al	*Scientific Reports*	33004987
13	Gut microbiome pattern reflects healthy ageing and predicts survival in humans	2021	T Wilmanski et al	*Nature Metabolism*	33619379
14	The geometry of clinical labs and wellness states from deeply phenotyped humans	2021	A Zimmer et al	*Nature Communications*	34117230
15	Integrated analysis of plasma and single immune cells uncovers metabolic changes in individuals with COVID-19	2021	JW Lee et al	*Nature Biotechnology*	34489601
16	Baseline Gut Metagenomic Functional Gene Signature Associated with Variable Weight Loss Responses following a Healthy Lifestyle Intervention in Humans	2021	C Diener et al	*mSystems*	34519531
17	Multiple early factors anticipate post-acute COVID-19 sequelae	2022	Y Su et al	*Cell*	35216672
18	Manifestations of Alzheimer's disease genetic risk in the blood are evident in a multiomic analysis in healthy adults aged 18 to 90	2022	L Heath et al	*Scientific Reports*	35413975
19	The effect of maternal SARS-CoV-2 infection timing on birth outcomes: a retrospective multicentre cohort study	2022	SN Piekos et al	*Lancet Digital Health*	35034863
20	Genome-microbiome interplay provides insight into the determinants of the human blood metabolome	2022	C Diener et al	Nature Metabolism	36357685
21	Risk factors for severe COVID-19 differ by age for hospitalized adults	2022	S Molani et al	*Scientific Reports*	35484176
22	Heterogeneity in statin responses explained by variation in the human gut microbiome	2022	T Wilmanski et al	*Med*	35690059
23	Personal Dense Dynamic Data Clouds Connect Systems Biomedicine to Scientific Wellness	2022	GS Omenn et al	*Methods Molecular Biology*	35437729
24	Multiomic signatures of body mass index identify heterogeneous health phenotypes and responses to a lifestyle intervention	2023	K Watanabe et al	Nature Medicine	36941332
25	Microbial community-scale metabolic modeling predicts personalized short-chain-fatty-acid production profiles in the human gut.	2023	N Bohmann et al	*bioRxib*	36909644

Story 1 Scientific Wellness, Statistics and Actionable Possibilities

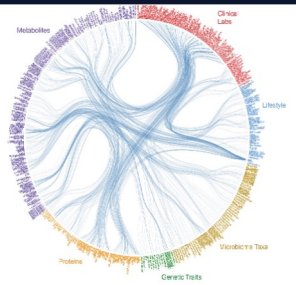
Transforming Individual Big Data* into Actionable Possibilities

108 Individual's 6 types of Big Data



Traditional Data Analysis

Brute force statistical methods |



From statistical correlations go to the literature to find actionable possibilities

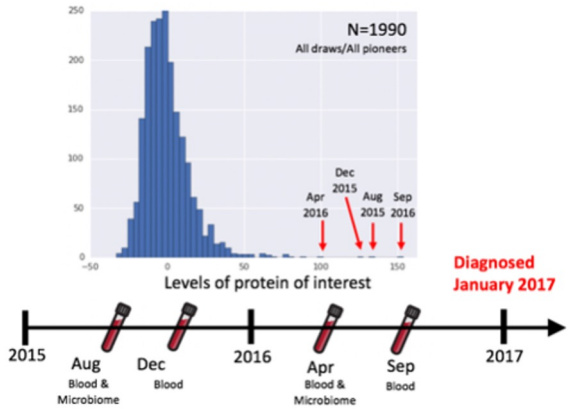
Million person project, estimate 10,000 new actionable possibilities

*Quantification of blood proteins, metabolites and clinical chemistries, gut microbiome, fitbit activity and whole genome sequence

Story 2 Prevention of Chronic Disease through early detection and treatment

State Transitions Open the Possibility of Greatly Reducing Chronic Disease

5000 individual generated 167 transitions from wellness to most chronic diseases



Wellness-to-Disease Transitions for Stage 4 Pancreatic Cancer

Scientific Reports (2020)

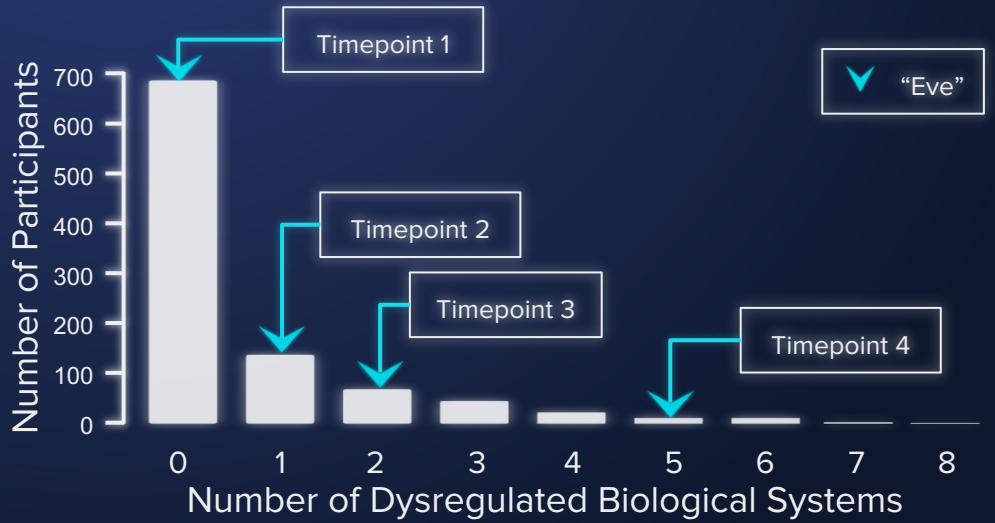
- 10 individuals with cancer transitions and all with abnormal proteins 1-4 years before clinical diagnosis
- With million person project over 10 yrs will estimate 200,000 transitions—validate blood biomarkers for each chronic disease

Key to Prevention

- Health annual budget: $4.4 T and 86% of annual budget for chronic diseases

Network analysis of Eve shows an exponential increase in network complexity with disease progression

Testing 9 potential disease-perturbed networks relevant to pancreatic cancer



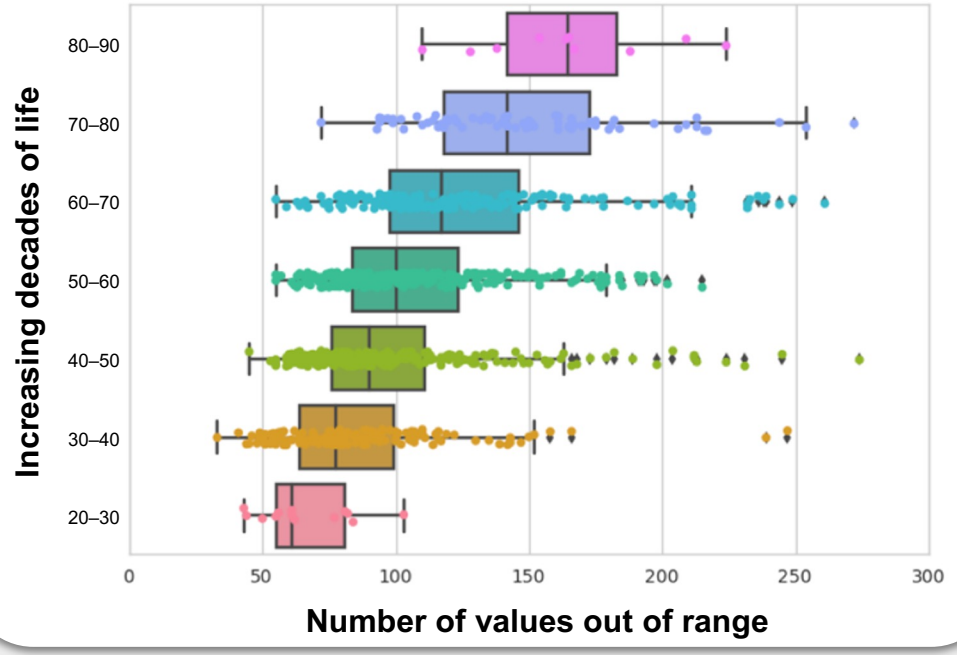
Eddy et al. (2010), *PLOS Computational Biology*

Story 3 Healthy Aging and Healthspan

Defining Biological Age from Phenomic Data

A Metric for Wellness: Biological Age (BA)

- Women lost 1.5 years and men lost 0.8 years of BA per year in the program (Arivale)
- Metric can be tailored to specific organs
- Helps optimization of BA for individuals
- Diseases increased BA
- A metric reflecting one's wellness



Earls et al. (2019), *Journal of Gerontology*

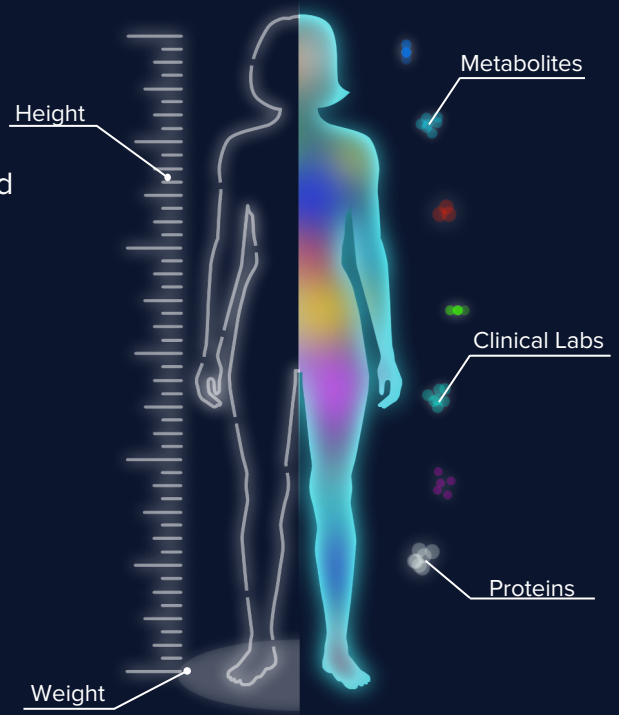
Story 4 Metabolic BMI

Quantifying Metabolic Health Differently

Using phenomics to define data-driven health metrics

Traditional BMI (body mass index)

- 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
- Identified metabolically unhealthy individuals who display a normal traditional 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 independence of weight loss

Watanabe… Hood, Rappaport, Nature Medicine, 2023

Story 5 Brain Health

Brain Health

- 40 digital health measurements have been developed for 25 aspects of brain cognition—e.g., reaction time, depth of field, memory, etc.
  (Posit and Brain HQ)

- Developmental trajectory of cognition for a human reaches a maximum in the mid-30s and declines there after. Many 80-yr olds can be restored in cognitive abilities equivalent to what they should have been in 30s Digital management of brain optimization for wellness and for disease

- More than 250 clinical trials on more than 10,000 individuals carried out on brain wellness and brain conditions or diseases—detection depression, drug addiction proclivity, schizophrenia, PTSD, TBI,. etc. Can do early detection and in some cases brain management (improvement).

Nahum M, Lee H, Merzenich MM (2013) Principles of neuroplasticity-based rehabilitation. Prog Brain Res. 207:141-71. doi: 10.1016/B978-0-444-63327-9.00009-6.PMID
Merzenich MM, Van Vleet TM, Nahum M (2014) Brain plasticity-based therapeutics. Front Hum Neurosci 8:385. doi: 10.3389/fnhum.2014.00385. eCollection 2014.PMID: 25018719

Brain, gut and body health are intimately coordinated, and each enhances the other

Two complementary kinds of wellness

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“Traditional” Wellness

- Exercise
- Diet
- Sleep
- Stress management

BIG-Data-Driven Scientific Wellness

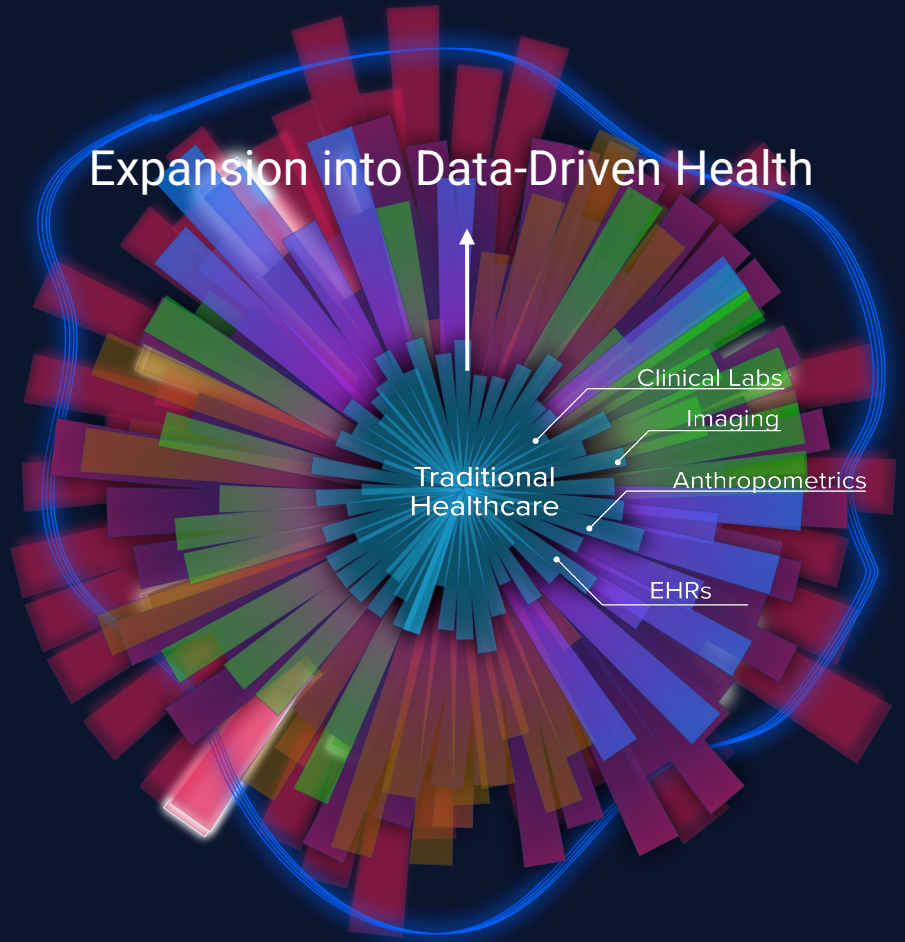
New dimensions that complement *Traditional Wellness* come from generating actionable possibilities

- **From the genome**
  - Known and actionable variants (ACMG set) (82)
  - Pharmacogenomics (100s)
  - Mendelian & Rare diseases (7000 each)
  - 100 polygenic scores for disease phenotypes
  - Hundreds of variants affect athletic performance and injury
  - Ancestory (families!)
- **From the phenome**
  - Identify nutrient and supplement deficiencies
  - Correct abnormal clinical chemistries
  - Identify and eliminate environmental toxicities
  - Identify & target *pre-symptomatic* disease transitions and reverse (blood analytes and polygenic scores (genetic risk)
  - Follow and optimize biological age and metabolic-BMI
  - 200 wellness actionable possibilities identified with 10,000 more to come from million person project
- **Integration of different data types**

  Vitamin D and genetic defects for Vitamin D uptake—requires mega doses of D

Data-driven wellness will add specificity to traditional wellness.

Emphasizing Wellness through Data-Driven Personalization



Identify Personalized Phenomic Risk Signature

Dimensionality Reduction

- Genome
- Microbiome
- Metabolome
- Proteome
- Wearable data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HEALTH
The Human
Phenome Initiative
Implementing Data-driven Health

Profiling the Human Phenome

New technologies enable new depth of insights—that need to be integrated into clinical practice

Genetics

Whole genome Sequencing

Social Determinants, Self-reporting by Patients

Stress and Environment

Electronic Health Records (EHRs)

Longitudinal Clinical History

Self-Tracking & Self-Reporting

Wearables, Questionnaires, & Assessments

Blood

Clinical Chemistries
Metabolomics
Proteomics
Deep Immune Phenotyping- transcriptomes of 5000 WBCs/blood draw
Epigenetics WBC DNA
Cell-Free DNA/RNA

Brain

Cognitive Assessments
Psychiatric Assessments
Imaging, Sell Reporting

Microbiome

Gut Microbiome
Community Composition
Metagenomics

Data-driven metrics

1. Biological Age
2. Metabolic BMI
3. Blood metabolic assessment of Gut Microbiome alpha diversity
4. Organ-specific blood proteins

The Human Phenome Initiative Platfrom

An ecosystem of organizations spearheaded by Phenome Health united to transform healthcare

Phenome HEALTH · Buck Live better longer. · Guardian Research Network Translating data into cures. · {tech:nicity/} · brainHQ from Posit Science · Google · ISB

A World-class Board

Jeff Wilke
Chairman and co-founder,
Re:Build Manufacturing

Former CEO Worldwide Consumer,
Amazon

Maria Klawe, PhD
President,
Math for America

Former President
Harvey Mudd College

Roger Perlmutter, MD, PhD
President, CEO, and Chairman,
Eikon Therapeutics

Former President,
Merck Research Laboratories

Backed by Industry-Leading Advisors

George Church, PhD
Professor, Harvard Medical School
Technology & Genetics

Gil Omenn, MD, PhD
Director, University of Michigan
Computational Medicine

Ralph Snyderman, MD
Executive Director,
Duke Health

Bill Hait, MD, PhD
Global Head, J&J Innovation

Esther Dyson
Healthcare Inventor

Michelle Williams, SciD
Dean, Harvard TH Chan
School of Public Health

Mostafa Ronaghi, PhD
Former CTO, Illumina

Edward D. Lazowska
Former Chair,
Computer Science, UW

Larry Smarr, PhD
Founder, Calit2
UC San Diego

Short term

- Individual phenomics/actionable possibilities—to millions within 5-10 years
- Data-rich chronic disease observational and interventional clinical trials: first diabetes then Alzheimer's disease
- Interesting 15-20 year old diabetes cohorts from biobanks
- Data-rich approach to observational trials of normal human physiology—pregnancy
- Asked to submit an Arpa-H proposal on phenomics

Long term—a 2nd genome-like initiative

- The 10-year, million-person genome/phenome initiative

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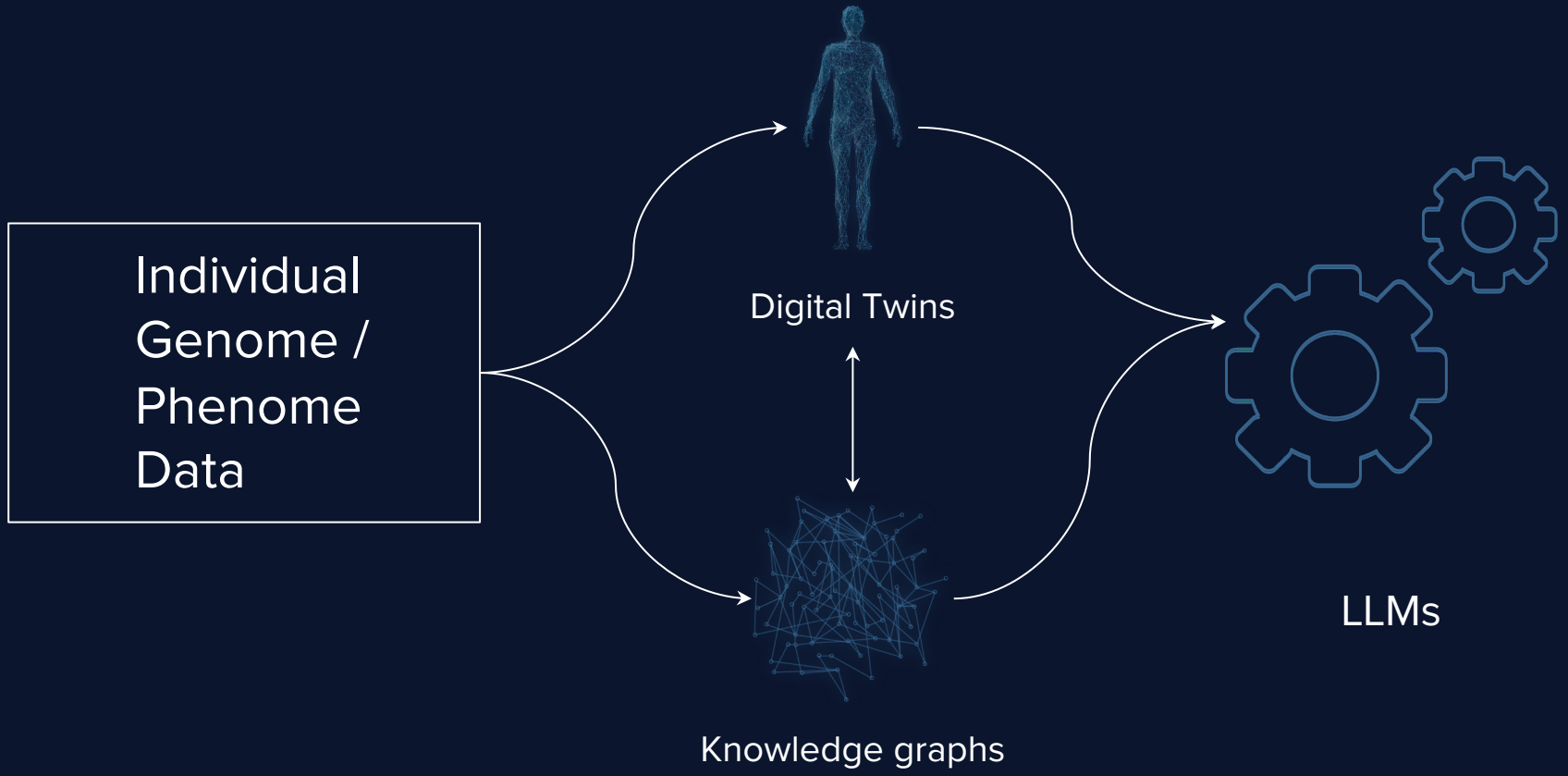
The Human Phenome Initiative

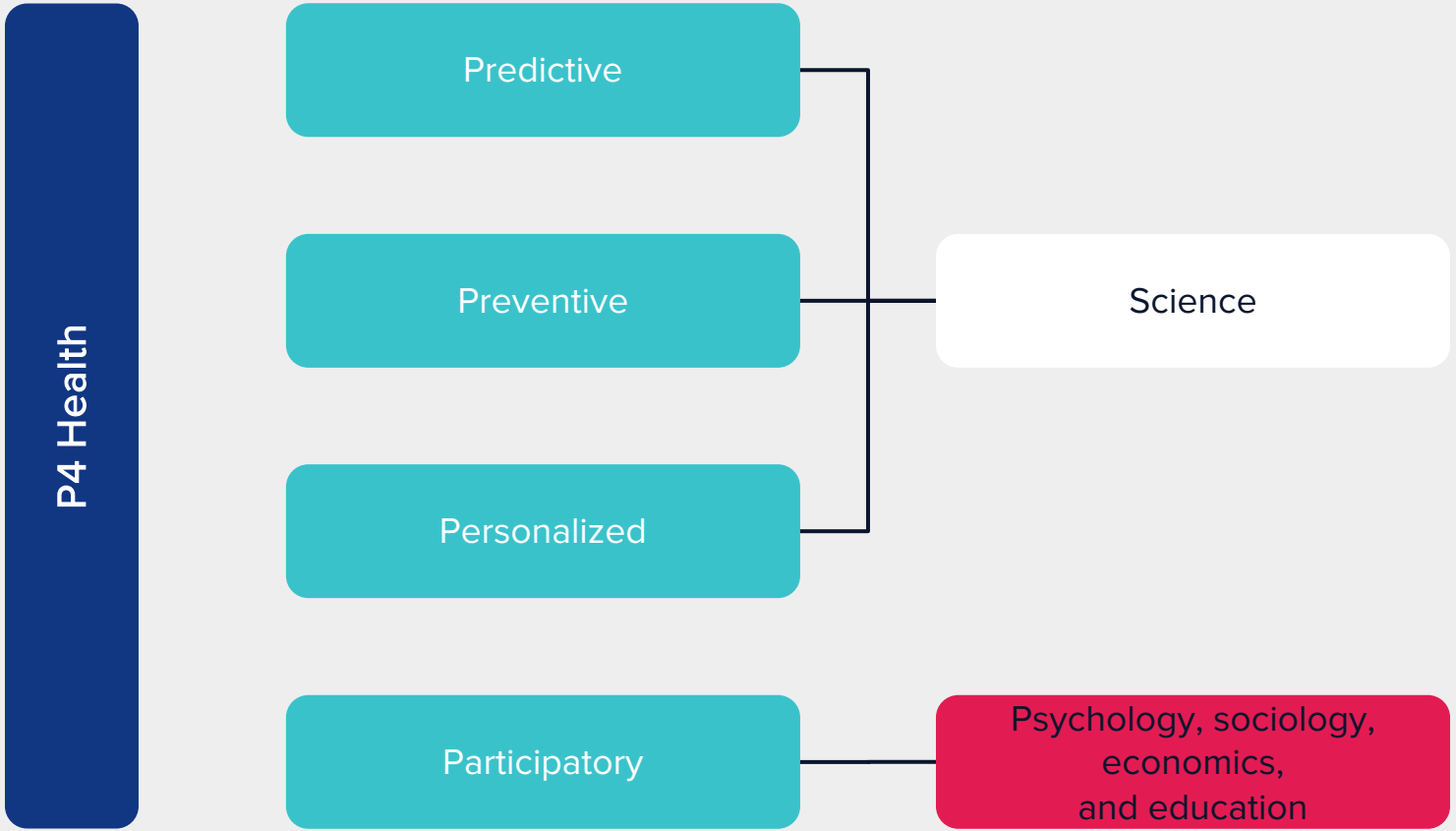
Implementing Data-driven Health

Physician/AI Partnerships and Superdocs



Education

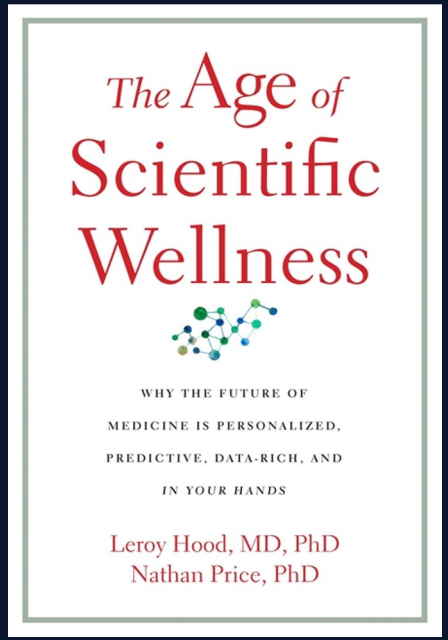
The 4 Ps of Healthcare



Education for Data-Driven Medicine

- Systems Biology and Systems Medicine textbook—med school, community college
- Integrating new thinking into K-12 science curricula—year-long, 4-module course on Systems Medicine and P4 Healthcare for high school students
- “The Transition from Genomics to Phenomics in Personalized Population Health” Nature Genetics Reviews, 2023
- Partnership with Scientific American—special issue on the New Science of Wellness and future issue on Healthspan & Healthy Aging: production of podcasts, meetings, etc. Supported by Google
- Scientific Wellness, 90-min documentary film—Wellness over the last 5000 years—”The Phenome Age: A Quest for Wellness”

Phenome HEALTH.org



Leroy E. Hood & Nathan D. Price
Harvard University Press

James T. Yurkovich, Simon J. Evans, Noa Rappaport, Jeffrey L. Boore, Jennifer C. Lovejoy, Nathan D. Price, & Leroy E. Hood. "The transition from genomics to phenomics in personalized population health." Nature Reviews Genetics (2023).

Potential New Roles for Nurses in Data-Driven Healthcare

- **Intrepreting Data:** Nurses now begin to interpret data-driven actionable possibilities to enhance patient care.
- **Delivering Data-Driven Insights—Health Navigators:** They deliver actionable possibilities to patients, integrating insights from genomics and phenomics.
- **Big-Data Clinical Trials—small and large:** Nurses manage both big-data observational and interventional clinical trials, playing a crucial role in the advancement of medical research and insights into how to deal early with the challenges of chronic diseases.
- **Educational Involvement in data-driven health:** They could be integral to the educational process for individuals across all levels of healthcare. Play a leadership role.

Possible New Courses for Modern Nursing

- **Systems Biology and P4 Healthcare**: Understanding how systems underpin personalized medicine.
- **Personalized vs. Traditional Population Health**: Bridging new methodologies together with traditional approaches to population health.
- **AI and Healthcare**: Leveraging artificial intelligence to improve care delivery and outcomes.
- **Technologies in Healthcare**: Exploring new technologies that are reshaping healthcare delivery.
- **Sociology, Psychology, and Economics of P4 Healthcare**: Examining the broader societal, psychological, and economic impacts of personalized healthcare.

HPI Offers Solutions for Five Challenges of Contemporary Healthcare

(with Enormous Potential Cost Savings)

Quality
Rapidly Expanding Aging Population
Explosion of Chronic Diseases
Diversity, equity and inclusion
Exponentially increasing costs

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Long term—a 2nd genome-like initiative

- The 10-year, million person, return of results, genome/phenome project—
- validate
  - individual wellness increased
  - striking cost savings
  - technology eventually for inexpensive home phenomics

The Human Phenome Initiative

Implementing Data-driven Health

What are the benefits of data-driven health, a radical health?

Shifts healthcare from current disease focus to wellness and prevention health

Democratization of healthcare bringing data-driven health to all individuals

Fourth Industrial Revolution—AI analyses of individual patients' data and bring the resulting actionable possibilities to physicians (and patients) in an acceptable form

About us

The Phenome Health Leadership Team

Phenome Health is a 501(c)(3) nonprofit organization headquartered in Seattle, WA

Our vision is to deliver innovation that drives a paradigm shift from disease-focused to wellness-focused healthcare

A unique team of interdisciplinary professionals with extensive expertise spanning business strategy, medicine, biotechnology & bioinformatics, implementation management, AI & machine learning, and cybersecurity

Lee Hood, MD, PhD
CEO

Tim Yeatman,
MD
Medicine

Simon Evans,
MBA, PhD
Operations

James Yurkovich,
PhD
Innovation

Jeff Boore,
PhD
Technology

BJ Yurkovich,
MS
Cybersecurity

Noa Rappaport,
PhD
Data Science

Jennifer Lovejoy,
PhD
Translational Science

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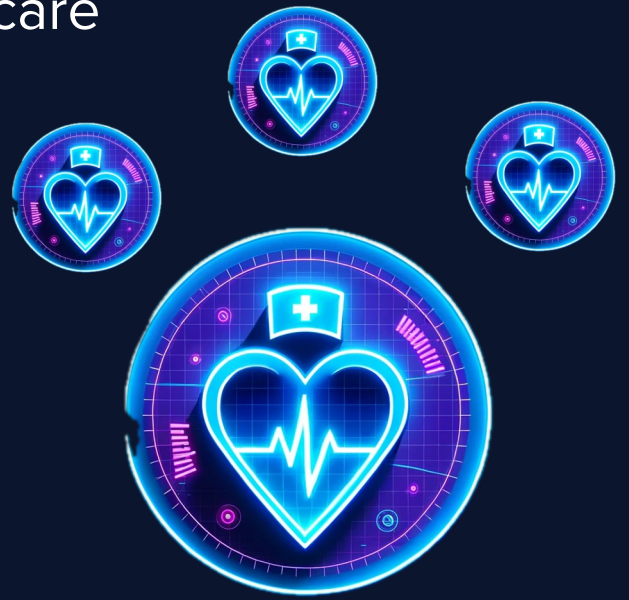
Potential New Roles for Nurses in P4 Healthcare



- **Interpreting Data:** Nurses now interpret data-driven actionable possibilities to enhance patient care.
- **Delivering Data-Driven Insights:** They deliver actionable possibilities to patients, integrating insights from genomics and phenomics.
- **Clinical Trials:** Nurses manage both big-data observational and interventional clinical trials, playing a crucial role in the advancement of medical research and insights into how to deal early with the challenges of chronic diseases.
- **Educational Involvement:** They could be integral to the educational process (P4) for individuals across all levels of healthcare.
- **Lead the Data-Driven Change for Wellness and Prevention.** For patients, physicians and the healthcare system.