

Personal Omics for Precision Health

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The convergence of scientific capability and technology that generates vast health data at diminishing cost has generated opportunities, challenges, and anticipation surrounding future data-centric healthcare models. Individualized health data spanning biomolecular, physiological, and environmental dimensions comprise a personal omics profile. Here, we discuss methods and opportunities to bridge genome and dynamic physiology, detect disease at an early stage, and uncover lifestyle and environmental patterns associated with the disease. Significant challenges exist to aggregate, integrate, and protect personal omics data to advance our understanding of the disease, enable data-driven clinical decisions, and motivate individuals to sustain behavioral change.

Since the first sequencing of the human genome in 2003, the relationship between genetic variants and phenotypes has remained a central challenge in medicine. Many diseases including coronary atherosclerosis are polygenic or indeed omnigenic wherein many variants work together to impact a phenotype.¹ Potentially confounding factors and small study population size in comparison to the size of the human genome make it challenging to decipher genetic risk for complex and heterogeneous diseases.

To better understand how genetic variation maps to complex traits, simultaneous measurements that bridge genotype and phenotype are required. This deep phenotyping is the goal of personal omics profiling,² which combines measures of the genome, epigenome, transcriptome, proteome, metabolome, and additional omes (Figure [A]). Rapid advances in sequencing and mass spectrometry drive continued improvement in cost, accuracy, and throughput.^{3,4} Mobile and wearable technologies enable physiological, contextual, and environmental measurements. As we learn more about the symbiotic functions of the microbiome in human health, we also apply multiomic profiling to microbial populations (Figure [B]). Together these measurements provide a holistic profile of dynamic health and facilitate personalized, precision interventions based on predictive models (Figure [E]).

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Linking Genetic Variants With Dynamic Phenotype

Many complex diseases such as type II diabetes mellitus involve both genetic and environmental factors. Modeling the interaction of multiple omic data types facilitates dissecting the effects of environmental and genetic factors.⁵ As a first step toward genotype–phenotype analysis, investigators combined genome sequencing (relatively stable) and metabolomics (highly dynamic). Because of the dynamic nature, it is challenging to interpret metabolomics data when sampled nonsystematically, with examples such as TMAO (trimethylamine N-oxide) that fluctuate with dietary intake.⁶ Metabolomics and genomics integration enables discovery of new genetic variants with metabolic consequences, functions for known genetic variants, early signs of disease and drug response (pharmacogenomics), and penetrance of genetic polymorphisms with presumed metabolic impact.^{7,8} Integrating genotype and dynamic physiology through a whole exome sequencing and global metabolomics study on 80 healthy individuals identified subclinical metabolic imbalances and associated metabolic abnormalities with genetic variants.⁸ Moreover, it was possible to identify novel metabolites for tracking disease risk and health state. With metabolomics now accessible in the clinic, metabolic profiling will complement next-generation sequencing for disease risk analysis, monitoring, and clinical decision-making.

Multiomics Integration and Detecting the Health–Disease Transition

The explosion of multiomics studies over the last decade (Figure [C]) has led to longitudinal multiomic studies over an extended time period to study transitions between health and disease.⁹ Many complex diseases are highly heterogeneous between patients, and longitudinal profiling increases statistical power by allowing each subject to serve as their own control. We conducted an N-of-1 study involving deep longitudinal profiling of single individual >14 months creating an iPOP (Integrative Personal Omics Profile).² We performed whole genome sequencing and periodic measurements of transcriptome, proteome, antibodies, metabolites, and clinical biomarkers profiled at higher temporal resolution during events of infection or illness (Figure [D]). Genomic analysis revealed an increased risk for type II diabetes mellitus. During the course of the study, and following a rhinovirus infection, the participant developed type II diabetes mellitus. Complementing genetic risk prediction, comprehensive profiling across transcriptomic, proteomic, and metabolomic layers enabled early detection and dissection of signaling network rewiring during the transitions from health to disease and back.

We expanded the iPOP study to >100 individuals who we have profiled along many omic dimensions through perturbations including weight gain, infection, and vaccination (iHMP

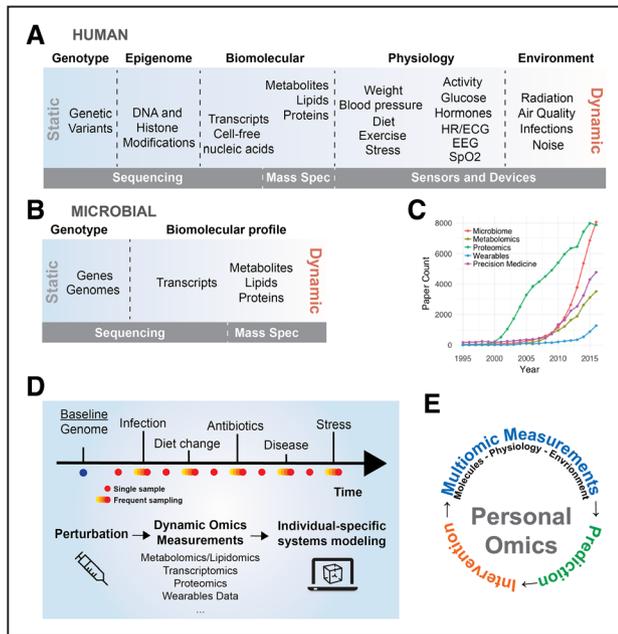


Figure. Overview of personal omics. **A**, Omic measures span genotype, phenotype, and environment and range from mostly static to highly dynamic. Sequencing, mass spectrometry, and smartphone/wearable sensors are principal technologies driving personal omics. **B**, Multiomic measures of human-associated microbes that play a vital role in human health. **C**, The past 2 decades have seen a dramatic increase in NCBI (National Center for Biotechnology Information) PubMed records containing personal omics keywords. **D**, Through regular sampling and high-frequency sampling during health perturbations such as disease progression or infection, personal omics reveals the cause, consequence, and course of health changes. **E**, Personal omics comprises holistic molecular, physiological, and environmental profiling of an individual over time.

[integrative human microbiome project] Consortium).¹⁰ We find some consistent changes across individuals in response to particular perturbations but also that individuals vary greatly in several responses. Developing biomarkers to predict how an individual will react to a perturbation provides a basis for personalized risk assessment and development of personalized behavioral and precision therapeutic interventions. The American Heart Association has launched the American Heart Association Precision Medicine Platform to facilitate multiomics data collection and collaboration between physicians and researchers (<http://precision.heart.org>). Additional ongoing personal omics efforts are summarized in Online Table I.

As wearable and smartphone sensors continue to improve in accuracy, usability, and cost, there is increasing appreciation for the potential clinical value of these sensors. We recently studied wearable sensors for managing health and diagnosing disease.¹¹ We found that physiological parameters can indicate health transitions. We developed an algorithm to correct for individual activity patterns, allowing us to detect when an individual deviated from their healthy baseline. Several study participants experienced infection or illness during the course of the study, including one participant who contracted Lyme disease. Changes in heart rate, skin temperature, and blood oxygen saturation from baseline levels preceded infection and inflammation before symptoms developed (Online Figure I).¹¹

Detecting Environmental and Behavioral Patterns Underlying Chronic Disease

Combining molecular and sensor measurements can uncover lifestyle patterns that impact disease and reveal biomarkers for personalized optimization of dietary or lifestyle habits. Zeevi et al¹² sought to understand intraindividual variability in glucose regulation to personalize diets to minimize blood sugar spikes. Integrating clinical, anthropometric, and microbiome data allowed the authors to develop a machine learning model to predict individualized glycemic responses. This study illustrates the potential for predictive models based on multiomics data to identify beneficial dietary and lifestyle behaviors.

King et al¹³ developed a mobile platform to understand the interplay between motivation, behavior, and health. Three motivational frameworks were tested to reduce sedentary behavior in aging adults and health outcomes were explored. This demonstrates how personal omics data can be leveraged to personalize behavioral health interventions.

One can imagine applying a similar methodology in many contexts where complex and individual-specific environmental patterns may trigger symptoms or conditions such as episodes or relapses in autoimmune disease, food allergies, migraines, asthma, chronic fatigue syndrome, fibromyalgia, or psychological or cardiovascular events. Recently researchers used deep learning to detect cardiac arrhythmias in real time with accuracy exceeding that of physicians.¹⁴ In the future, learning algorithms may also be used to identify triggers of cardiac arrhythmia and other health events that can be addressed to prevent adverse health outcomes. (Online Figure II).

Challenges in Aggregation, Analysis, Integration, and Protection of Personal Omics Data

A major challenge facing multiomics integration is the need for large study populations to enable statistical power and machine learning approaches. Recent mobile health studies have demonstrated novel methods of scaling to population levels. McConnell et al¹⁵ developed the smartphone application MyHeartCounts to gain insights into activity patterns associated with life satisfaction and self-reported disease for 48 000 participants. The study demonstrated the feasibility of consenting and engaging a large population using smartphones and gathering and securely storing data in real time. A related study examined activity patterns in a global study of nearly 800 000 individuals in 111 countries.¹⁶ Overall, 68 million days of physical activity monitoring revealed city and geosocial features associated with health and obesity.¹⁶

With greater reliance on self-collected medical data by individuals using wearable sensors and smartphones, and direct-to-consumer testing services based on, for example, genome and microbiome data (eg, 23andme, Helix, uBiome) it is becoming increasingly feasible to scale health studies to thousands or even millions of participants to identify geographic, demographic, and other population-scale correlates for disease. Large-scale population health studies like the National Health and Nutrition Examination Survey, continue to provide

a rich resource for retrospective population-scale health studies (National Center for Health Statistics).

Genomic and wearable sensor data has value in clinical medicine though it is not possible to store such data in electronic health records. A next-generation electronic health record was tested with 37 families and is being rolled out to 1500 patients across the Stanford hospital system. The modern medical record enables assessment of genetic risk, medication personalization, and monitoring of subclinical risk factors based on genomics and wearables data collected over time.¹⁷

Conclusions

Healthcare is undergoing a period of rapid change because of revolutionary new scientific tools, advances in molecular and physiological measurement technologies, and algorithmic and computing advances enabling real-time analysis and pattern discovery in multimodal and high-dimensional health data. Longitudinal personal omics leveraging these advances facilitates mapping genomic variants to disease regulatory networks, detecting the health–disease transitions based on molecular and physiological metrics, measuring interaction of environment and health outcomes, uncovering complex behavioral and lifestyle patterns linked to symptoms and progression of chronic disease, and scaling health data collection to participant populations spanning diverse geographies and demographics. Continuing this progress will lead to a preventative care model with engaged patients, interoperable health data, cost savings, and improved wellness.

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Disclosures

None.

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Name	Description	References/Link
UK Biobank	Following health and wellbeing of 500,000 study participants aged 40-69 including genotyping, clinical measures, and blood, urine and saliva samples for future analysis.	¹ http://www.ukbiobank.ac.uk/
NIH Precision Medicine Initiative	Launched in 2015 with \$130 million allocated towards establishing a national research cohort of 1 million participants in the U.S followed over several years, and \$70 million allocated for precision medicine in oncology.	² https://allofus.nih.gov/
Genomics England	Generating 100,000 whole genome sequences from NHS patients and families with rare diseases or common cancers.	www.genomicsengland.co.uk
Human Longevity	Genomic sequencing combined with multiomic measurements to discover early signs of disease, including of full-body imaging.	www.humanlongevity.com
Stanford iPOP	Tracking 14 'omes in over 100 individuals during periods of health, stress, infection, and perturbations related to diet and exercise.	³ http://snyderlab.stanford.edu/iPOP.html
100K Wellness project	Study similar to the Stanford iPOP initiative initially focusing on longitudinal multiomic profiles for 100 individuals to study transitions between health and disease.	⁴ www.arivale.com
Project baseline	Coordinated across Stanford, Duke, and Verily Life Sciences and will track 10,000 individuals over at least 4 years. Study participants wear a custom activity watch and collect physiological data via smartphone combined with clinic visits. Goals for the project include testing and developing new tools and technologies to collect, organize, and interpret health information, as well as to understand phenotypic diversity in large populations and identify biomarkers for disease-related transitions.	https://clinicaltrials.gov/ct2/show/NCT03154346
Human Microbiome Project	Ongoing two phase study to characterize the host and microbiome genomics of 1) healthy human subjects at five sites on the body, and 2) three cohorts of microbiome-associated conditions, including pregnancy and preterm birth, inflammatory bowel disease, and type II diabetes	⁵
AHA Precision Medicine Platform	Cloud based resource that allows physicians and researchers to upload cardiovascular and stroke data sets enabling tool development	https://precision.heart.org/

and collaboration.

Supplementary Table I. Ongoing personal omics efforts.

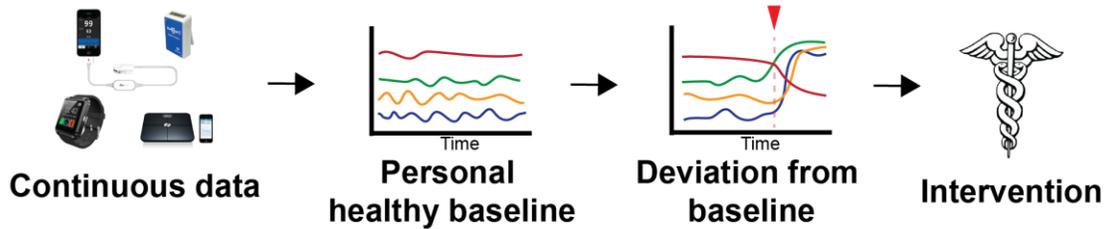


Figure I. Wearables reveal environmental impact on health. Smartphone and wearable sensors provide continuous data about an individual’s physiology. By establishing a personal baseline for sensor values in a healthy state, it becomes possible to detect when sensor readings deviate from this baseline, potentially indicating an environmental perturbation. Li, et al. as able to detect subclinical infection and physiological effects of air travel based on deviation from users’ heart rate, skin temperature, and accelerometer data from healthy baseline values.

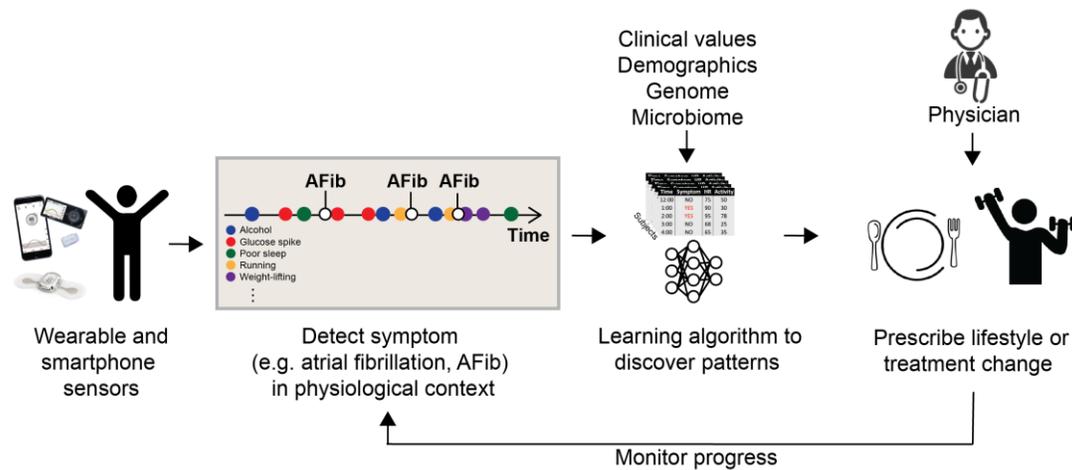


Figure II. Dissecting lifestyle patterns underlying chronic disease. Here we consider a hypothetical scenario of identifying complex behavioral triggers of atrial fibrillation (AFib) episodes. Smartphone and wearable sensors measure both occurrence of atrial fibrillation episodes and lifestyle features including activity, sleep, stress, and diet. Machine learning algorithms can identify lifestyle patterns that precede atrial fibrillation. This approach could be applied widely to identifying lifestyle habits underlying a range of complex immune, metabolic, neurological, cardiovascular and psychological conditions.

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