Title

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Journal

Critical Reviews in Food Science and Nutrition, 58(17)

ISSN

1040-8398

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Publication Date

2018-11-22

DOI

10.1080/10408398.2017.1348335

Peer reviewed

HHS Public Access

Author manuscript

Crit Rev Food Sci Nutr. Author manuscript; available in PMC 2019 January 05.

Published in final edited form as:

Crit Rev Food Sci Nutr. 2018 ; 58(17): 3004–3015. doi:10.1080/10408398.2017.1348335.

21st Century Toolkit for Optimizing Population Health through Precision Nutrition

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Abstract

Scientific, technological, and economic progress over the last 100 years all but eradicated problems of widespread food shortage and nutrient deficiency in developed nations. But now society is faced with a new set of nutrition problems related to energy imbalance and metabolic disease, which require new kinds of solutions. Recent developments in the area of new analytical tools enable us to systematically study large quantities of detailed and multidimensional metabolic and health data, providing the opportunity to address current nutrition problems through an approach called Precision Nutrition. This approach integrates different kinds of "big data" to expand our understanding of the complexity and diversity of human metabolism in response to diet. With these tools, we can more fully elucidate each individual's unique phenotype, or the current state of health, as determined by the interactions among biology, environment and behavior. The tools of Precision Nutrition include genomics, metabolomics, microbiomics, phenotyping, high-throughput analytical chemistry techniques, longitudinal tracking with body sensors, informatics, data science, and sophisticated educational and behavioral interventions. These tools are enabling the development of more personalized and predictive dietary guidance and interventions that have the potential to transform how the public makes food choices and greatly improve population health.

Keywords

Precision Nutrition; -*omics*; food science & technology; phenotyping, big data

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Precision Nutrition: New Directions for Science and Society

Twentieth century science catalyzed some of the most profound societal transformations in human history. Scientific breakthroughs have enabled humans to reconstruct cultural, commercial and built environments, transforming foods, dietary practices and health. The field of nutrition blossomed by using the tools of analytical chemistry and experimental biology to describe foods in molecular detail, identify essential nutrients and elucidate their biological functions, ultimately leading to the establishment of nutrition recommendations formulated to avoid nutrient deficiencies in entire populations (Harper 1981).

Reductionist 20th century science has been very successful in building scientific knowledge and bringing that knowledge to practice in a wide range of industries. But living organisms are greater than the sums of their parts and exhibit complex emergent phenomena that cannot be adequately described using a reductionist approach. The successful models of 20th century science are ultimately failing to deal with many of the challenges currently facing society in which diversity matters and complexity is pervasive. This is the case for the epidemics of obesity and diabetes. Consumer preferences, together with market forces and one-size-fits-all dietary recommendations, have brought about the development of modern dietary patterns with the potential to promote excess caloric energy stores and elevated blood glucose. But the precise mechanisms responsible for these metabolic imbalances are diverse among affected individuals, and incredibly complex. The inability of many people to maintain a healthy metabolic homeostasis across a wide range of modern lifestyles is affecting quality of life for millions, has made lifestyle-associated diseases top causes of death, and has brought about a crisis of increased healthcare costs. Solving this problem requires increased understanding of the complexity and individuality of human energy metabolism.

Consequently, scientists in the 21st century are faced with the challenge of elucidating diverse and complex dietary effects on metabolic health to provide science-based guidance and healthpromoting food products for the future. Recent advances in technology, informatics, and scientific methods have made a set of tools available with the capacity to address this challenge effectively. The field of genomics and the associated transcriptomics, epigenomics, proteomics, metabolomics, lipidomics, glycomics and microbiomics (the -*omics*) provide myriad measures documenting the interactions of foods, microbes and human bodies in great detail. New technologies are making available more spatially and temporally specific measures, such as longitudinal tracking of measures that fluctuate or change over time with wearable body sensors. Modern informatics and analytics capabilities enable us to harness these complex data in ways that enlighten and inform our understanding of metabolism. Already we are beginning to see how nutrients and non-nutrient components of foods interact with numerous metabolic pathways to influence human health. The application of *-omics* technologies has highlighted the many individual factors that can affect health, including genetics (Carpenter et al. 2015a), lifestyle (Dunstan et al. 2012), microbial diversity (Turnbaugh et al. 2006), insulin sensitivity (Himsworth 1934), and exocrine and glucose transporter activity levels (Gibbs et al. 1995). These developments have led to the concept of "precision nutrition", in which the challenge lies in characterizing the phenotypic differences between individuals that contribute to health status. Achieving

such dynamic precision requires measuring a range of personal characteristics of individuals in sufficient detail and breadth to generate evidence-based knowledge tailored for individual phenotypes. Importantly, this knowledge base facilitates the development and commercialization of health-promoting diets and lifestyle tools capable of targeting specific metabolic pathways to reduce disease progression and risk.

The science of nutrition and the food industry have a unique opportunity to develop analytical platforms that inform intervention strategies prior to disease. To achieve substantial change in population health these analytical platforms and intervention strategies must a) translate to real life situations that are easily comprehended by the public, b) interface with the technologies that individuals use to inform their food and lifestyle choices, and c) utilize the most advanced behavioral science knowledge on motivating and enabling lifestyle change. Providing the public with more personalized and predictive dietary guidance will remove much of the uncertainty that people currently face about how specific food choices are expected to affect their individual health. This level of personal health measurement and management has the potential to ignite a revolution against the non-optimal current state of our health and shift aggregate food demand toward more health-promoting foods.

This paper addresses this challenge faced by academia, health professionals and the food industry in the coming decades by identifying the specific available tools most important for achieving success. A better knowledge of the interplay of genomes and an understanding of personal phenotypes forms the foundation of future research and the fast growing market for personal health and nutrition. The identification of important cohorts for generating evidence of phenotype-linked nutrient-disease interactions, and implementing interventions with novel bioactive foods or food components within a more comprehensive and customized overall diet, is becoming essential. In parallel, the technologies necessary to isolate, purify and measure food components will enable the development of advanced food products. Indeed, advanced molecular identification and bioinformatics tools will enable a better understanding of human, food and microbial data with the potential to model the intertwined networks of these related systems. Translation of these sciences to the marketplace, the clinic, and the home will maximize the impact for public health in a bottom-up approach starting at the roots of personal diet and phenotype.

Genomics Guidance for Food and Health

Genomics has revolutionized all fields of life sciences by adding immense breadth and depth to the understanding of living organisms. Similarly, genomics will become a core knowledge area of food. There are three genomic categories in which knowledge building is critical: 1) human genomics: a detailed and personalized understanding of the needs for, and responses to, foods and nutrients; 2) commodity plant and animal genomics: a comprehensive understanding of the living organisms and their ecosystems that provide the components of foods; and 3) microbial genomics (e.g. viruses, bacteria, yeasts and molds): understanding of the central role of microbes in food safety and increasingly in all of food and agriculture's quality, sustainability and bioavailability.

Human genomics: Defining in genetic detail our individual needs for and responses to food.

In addition to its most obvious role of elucidating the genetic basis for human physiological functions and disease, the human genome also provides a broad portfolio of tools for establishing the relationships between diet and health. Nutrigenomics is establishing proof-of-principle that much of the variation in human responses to diet is of genetic origin. Just as hair color and height can be assigned to specific genetic sequences, variations in risks of diet-dependent diseases including atherosclerosis, diabetes, obesity and hypertension are, in part, genetically defined. Examples of genetic variations that have been scientifically identified include variations in the sequence and function of intestinal transporters that alter the requirements for essential nutrients (Zeisel 2011), variations in the regulatory mechanisms that guide lipid metabolism (Glaser et al. 2011), and sequence variations in the machinery that controls lipoprotein formation and clearance (Descamps et al. 2011). These seminal findings highlight the variations in human genetics that underlie risk for deviations in health, and point to the need for diets of the future to be personalized to accommodate these differences. The compilation of these genetic variations in human responsiveness forms an essential knowledge base for building the analytical tools required to measure human health, and the composition, structure and function of human diets.

Commodity genomics: Defining the biological organisms that provide the pipeline of agricultural biomaterials that become foods.

The science of plant and animal genomics is starting to revolutionize commodity agriculture (Hamblin et al. 2011), from improving existing traits in traditional crops to recruiting novel plants and animals for production agriculture. However, bringing this knowledge to practice requires the simultaneous characterization of resulting phenotypes (Furbank & Tester 2011). As the task of identifying the various molecules of these organisms continues, the true novelty will be in our ability to interpret ensembles of chemicals as complex living systems, which will require mapping the molecular details of living systems: spatially, temporally and functionally. In this way, chemistry partners with biochemistry, metabolism, physiology, toxicity and the knowledge management tools necessary to interpret such massive information stores (Lange et al. 2007).

Much of the success in increasing agricultural output has been achieved by adopting ever-more productive crops, but at the cost of decreasing overall diversity. Diversity of agricultural crops is necessary for agricultural sustainability, and achieving this diversity calls for broader and deeper chemistry, including mapping the composition of organisms with greater comprehensiveness, quantitative accuracy and biological context. For example, human diets are assembled from a remarkably narrow slice of the diversity of plants and animals available due to demands for agricultural productivity, nutritional quality and safety.

There are two general strategies that plants have used in their interactions with animals, among which of course are humans. One strategy that has emerged in these organisms through evolution is to utilize overt chemical toxicity as a product of secondary metabolism in order to avoid being eaten (Singh et al. 2011). Not coincidentally, the crops that have become agriculturally valuable have either been genetically selected to lose their toxic

pathways or are processed to inactivate the toxins and anti-nutritive factors. Genomics will make a much wider diversity of organisms available as crops by enabling us to better understand, and alter, their strategies for avoiding consumption (Rasmussen et al. 2010). To achieve such breakthroughs requires the chemicals of these organisms be catalogued, but also the consequences of their manipulation to be understood. On the other hand, plants also produce fruits and nuts that are intended to be consumed by animals as a strategy for seed dissemination. Expanding the genomic repertoire of agricultural crops in this category is also a direction for new approaches to improve health. The opportunities to diversify agriculture and recruit completely new organisms and improve existing crops toward a more complex and sustainable system of quality-based agricultural production are compelling.

Microbial genomics: Defining the genetic basis of food safety and quality.

Microbiology has been at the center of food safety since food storage began, and microbial food safety is looking to be an increasingly important problem in the future. What is changing is not only the chemistry to understand toxicity but the genetics to understand the biology of pathogenic organisms more broadly. Solutions to the problems of contamination of food by pathogenic microorganisms will never be simple, and multiple, redundant and overlapping strategies must be developed to identify, eliminate and control contaminating pathogens from the food supply at all stages. New food-borne pathogens are emerging constantly due in part to simple evolution and antibiotic resistance {Koluman:2013bz}, and genomics will be vital to understanding these new microorganisms. Indeed, modifying the genomics of specific microorganisms may provide novel and innovative strategies to prevent food spoilage, increase nutritive value and improve food security.

Tantalizingly, as scientists come to understand the biological properties of a wider range of microorganisms opportunities will arise to provide innovative solutions using these diverse microorganisms 'professionally.' Viruses (as bacteriophages), bacteria, archaea, yeast, molds and fungi, have been used traditionally as fermentative microorganisms for centuries. As genomics reveals the details of these life forms their utility will expand dramatically. With the greater use of microorganisms at various points in food processing, the resulting complex ensembles of plant and animal commodities plus microorganisms will place massive demands on chemical tools to analyze all of the molecular and structural transformations that result.

Resident Microbes: A New Level of Complexity in the Human Superorganism

The concept that humans function as a superorganism (Goodacre 2007), or a complex combination of genetic and metabolic pathways of the host as well as of our resident microbiota, particularly the gut microbiota, has forged a fundamental shift in the way health and disease are defined and measured. Our resident microbes metabolize a variety of compounds we ingest, and these *de novo* synthesized microbial metabolites can have local effects in the gut and/or be absorbed and have systemic effects at distal organs. For example, certain saccharolytic microbes produce short chain fatty acids from dietary fermentable carbohydrates, which affect the pH in the colon, shaping the local environment and

microbial ecology (Ferrario et al. 2014). Short chain fatty acids are also absorbed and have systemic effects on blood lipid profiles (Fechner et al. 2014), glucose, energy homeostasis and appetite (Byrne et al. 2015).

In addition to the de novo production of metabolites, gut microbes can also modify compounds that we ingest, potentiating their bioactivity. For instance, certain gut microbes convert the soy isoflavone daidzein to O-desmethylangolensin, also known as equol. This conversion to equol results in the potentiation of the isoflavone as an estrogenic compound that is positively associated with bone mineral density in women (Frankenfeld et al. 2006). Another example is the conversion of linoleic and α-linolenic acid to conjugated linoleic and linolenic acid by gut bacteria including bifidobacteria (Gorissen et al. 2010). Conjugated linoleic acid has been linked with a host of beneficial health effects in animals and humans including effects on hepatic gene expression involving lipid metabolism (McLeod et al. 2004), lipid profiles (Pintus et al. 2013), weight loss (Gaullier et al. 2004), bone metabolism (Kelly et al. 2003), as well as immunomodulatory effects (Draper et al. 2014).

Moreover, certain dietary compounds are metabolized by the gut microbiota and these metabolites are then further metabolized by the host, resulting in the production of microbialhost co-metabolites. One example is the conversion of choline-containing precursors (including carnitine, choline, and phosphatidylcholine) by gut microbes to trimethylamine (TMA), which is readily absorbed and then further metabolized in the liver to trimethylamine-N-oxide (TMAO). Plasma TMAO concentration is independently associated with an increased risk for cardiovascular events even after adjustment for other CVD risk factors (Tang et al. 2013). However, there is high inter-individual variability in TMAO production following dietary choline consumption, which is dependent on the host's background diet; vegans do not produce TMAO whereas omnivores do (Miller et al. 2014). What's striking is that although vegans do not produce TMAO at all after choline ingestion, omnivores are highly variable in their TMAO production ranging from near 0, just as in the vegans, to as high as 30 uM. It is clear that variation in the gut microbiota in association with long-term diet contributes to these differences in TMAO production (Brown & Hazen 2014). However the details of this relationship between the host's background diet, their gut microbial ecology, and hepatic metabolism related to TMAO production have not been fully elucidated. This highlights the complexity of measuring metabolic phenotype and responsiveness to different diets and foods in humans with diverse microbial communities. Precision nutrition will have to account for not just the variability between individuals' genomes but also their microbial genomes in order to measure and understand health status, and also to be able to tailor appropriate diets, foods, and functional ingredients for improving health.

Metabolomics and Personal Phenotyping for Precision Nutrition

Metabolomics involves measuring many small molecules and their fluxes through human metabolism. Research has shown that metabolomic profiles can more accurately identify the complexities of metabolic regulation than measurements of single biomarkers using traditional biochemical methods (Bakker et al. 2010). Metabolites change in every cell and body fluid, notably in response to food intake (Zivkovic et al. 2008; Scalbert et al. 2014;

Zheng et al. 2015); however, metabolic homeostasis is maintained so that the variations in any given metabolite pool are usually minor relative to the overall abundance of the metabolites. Metabolomics is already proving to be very informative in 1) revealing the complex metabolic effects of diet (Zheng et al. 2015; Lai et al. 2015); 2) predicting responders to drugs (Robertson & Reily 2012), changes in body composition during energy restriction (Smilowitz et al. 2013; Longo & Mattson 2014) and inflammatory and metabolic phenotype in response to dietary compounds; and 3) identifying metabolic aberrations associated with disease (Zivkovic et al. 2012; Rasmiena et al. 2013; Gowda et al. 2014; Frye 2015). Limitations of this method still exist, including quantification of metabolites that have overlapping peaks, which can cause quantification bias {Julia:2015dn}, and the sheer complexity and quantity of data produced requires high performance bioinformatics programs to assimilate interpretable data. However, this systems biology approach, in combination with multivariate data analysis, provides new opportunities to understand how metabolism can vary in response to diet and lifestyle.

Defining and measuring personal phenotype.

Phenotypes are observable and measureable human characteristics that vary between different individuals, ranging from body composition to behavioral tendencies, from nutrient status to complex metabolite patterns, and from gut microbial composition to DNA methylation profiles. An individual's genetic makeup forms the foundation for their phenotype. However, genotypes have flexibility in their expression, so multiple lifestyle and environmental factors, from *in utero* imprinting to acute dietary intake, combine to shape personal phenotypes. The term *phenotyping* is increasingly used in scientific literature to describe the process of quantifying phenotypic characteristics (Zeisel 2011). The introduction and widespread application of *-omics* technologies has taken phenotyping to a higher level. Metabolomics has been particularly influential by enabling comprehensive measurements of molecular components underlying complex metabolic traits. The term *metabolic phenotype* was coined with the introduction of metabolomics-based research to describe the metabolic state of an individual, which is a product of genetic, dietary, lifestyle, epigenetic and other environmental influences, along with their combined interactions (Zivkovic et al. 2008; Montmayeur et al. 2010).

The concept of precision nutrition originated in genetics-based research; however, with the introduction of advanced phenotyping, researchers began to discover that phenotype alone could be used to evaluate individual health status, establish metabolic targets for preventing and treating diseases, and monitor response to intervention. Phenotyping therefore provides both the input and monitoring system required to make Precision Health a reality. One of the first studies to apply phenotyping in this context with human volunteers showed that urinary metabolomic profiles predicted susceptibility to acetaminophen-induced liver injury (Winnike et al. 2009). In the case of nutrition, instead of a "one size fits all" approach, personalized interventions, including foods, supplements, microbiome and lifestyle modifications, can be used to shape an individual's metabolic phenotype and health status (German et al. 2011). With this goal in mind, the first step in nutrition research was to identify and quantify dietary responder phenotypes. One of the first such studies in the literature identified a vitamin D responsive group using a combination of targeted and

untargeted phenotyping (O'Sullivan et al. 2011). This unique cluster showed beneficial changes in markers of metabolic health following vitamin D supplementation which were not apparent when considering the treatment group as a whole or when vitamin D deficient individuals were isolated (O'Sullivan et al. 2011). Since then several other studies have reported similar variation in response to different nutrients, foods, diet and lifestyle interventions using a variety of phenotyping methodologies (O'Sullivan et al. 2014; Piccolo et al. 2015; Parr et al. 2016). The next generation of studies is focusing on providing precision dietary advice based on phenotype in order to establish the efficacy of precision interventions.

Intensifying phenotyping efforts requires a toolset capable of identifying and accurately quantifying complex phenotypic features and discrete changes in phenotype status. Although the analytical technologies exist to deliver large amounts of phenotypic data (e.g. transcripts, proteins or metabolites) in a relatively short amount of time, analyzing these datasets remains a challenge. For example, in metabolomics the difficulties of identification, quantification and annotations are currently being addressed through expanding and enhanced libraries of metabolite data such as the Human Metabolome Database (HMDB) (http://www.hmdb.ca/), the Food Metabolome Database (FoodDB) (http://foodb.ca/) and Phenol-Explorer (http://phenolexplorer.eu/). Analytical strategies that also incorporate pathway-mapping tools are necessary to move from descriptive to mechanistically linked phenotypes.

Conventional methods should not be overlooked in this move toward intensified phenotyping and personalization. Traditional physiological, immunological and behavioral measurements contribute toward more clearly defined responder phenotypes and will play a major role in designing targeted interventions. As an example, consider phenotyping responders and nonresponders in a weight loss trial. While knowledge of underlying metabolic profiles will be essential in guiding future interventions, the relevance of these findings is lost without showing associated body compositional changes. What's more, incorporating advanced techniques such as whole-body magnetic resonance imaging (MRI) to distinguish patterns of fat deposition could provide critical information about the health or disease risk of a phenotype (Thomas et al. 2009). Opportunities to automate phenotypic data collection are increasingly available. Advances in computing technologies and applications have led to the development of novel phenotyping tools capable of measuring a variety of lifestyle and behavior related traits. New devices have come to market including ambulatory blood pressure monitors, accelerometer-based activity monitors, mobile digital imaging and devices that assess dietary intake in real time. These new measurement tools will make phenotyping less burdensome and more accurate. Most importantly, they will fundamentally change human diet management, making it more empowered, detailed and interactive, and will ultimately develop into a valuable commercial engine for delivering health.

Cohorts characterizing the diversity of phenotypes.

As we become more aware of natural human variation in response to environmental conditions such as diet, efforts are being made to stratify recommendations according to basic phenotypic characteristics. For example, the USDA *MyPlate* and the online

SuperTracker help consumers to personalize and manage the most recent Dietary Guidelines for Americans according to their gender, life stage and personal health goals. While this is an important improvement over past recommendations that did not take these considerations into account, personalizing diets and lifestyle to achieve optimal health will require a much deeper understanding of variations in metabolic pathways, physiology and functional characteristics. Intensified phenotyping efforts require that we identify and measure distinct cohorts to examine discrete phenotypic traits and associated health trajectories. A prime example are very low birth weight premature infants (<1,500 grams) often born with an immature gastrointestinal tract and immune system, leading to a high risk for developing necrotizing enterocolitis (NEC) and late-onset sepsis (Claud & Walker 2001; Lin & Stoll 2006; Stoll et al. 2010). Importantly this infant phenotype responds well to nutritional intervention; premature infants fed human milk, abundant in human milk oligosaccharides, exhibit markedly lower rates of NEC compared to formula fed infants (el-Mohandes et al. 1997). In addition, evidence from intervention studies suggest that manipulating gut microbial composition to include bifidobacteria is important for a number of developmental and health-related functions (Deshpande et al. 2010). These remain the most effective strategies in preventing NEC (Lin et al. 2014). Other examples of particularly vulnerable cohorts include overweight and obese children, groups with diet related metabolic disorders, immune suppressed elderly populations and elite athletes. Characterizing this diversity within our population will provide the biological data necessary to inform phenotype-guided health.

Standardizing procedures for phenotyping research.

For phenotyping efforts to achieve practical personal utility in the general population, assumptions, protocols and reference conditions need to be standardized. Phenotypic data is interpreted on the basis of background information such as the experimental design, the biological parameters measured, and the data acquisition and processing procedures. For this reason, it is essential that all phenotype-based studies are well-designed, incorporate universally accepted standard operating procedures, and have appropriate data storage capabilities. In addition, researchers should carefully consider all potential confounding variables when designing studies. For example, we know that the metabolic profiles of women are affected by menstrual cycle phase (Wallace et al. 2010) and that genetic variation affects response to dietary composition to influence disease risk (Neufeld et al. 2004; Carpenter et al. 2015b). Where possible, these confounding variables need to be identified *a priori*. To further strengthen phenotype information, studies should include measurements that target dynamic and kinetic aspects of metabolism. Combining kinetic measurements of metabolic networks with metabolomic technologies, or expanding to real time imaging technologies, will yield valuable information that will undoubtedly provide the scientific community with a new breadth of knowledge that changes how we understand our food.

Analytical Chemistry Techniques for Developing Health-Promoting Foods

A major limitation of agriculture and food research has been the "one molecule at a time" approach, which limits the ability of nutrition science to examine the effects of total diet on complex biological systems. As we move beyond this reductionist approach, systems-based

approaches will influence scientists and food companies to consider the myriad of nutrients and non-nutrients in foods and their impacts on consumers. Twenty-first century chemistry in the food industry will isolate and characterize the diet as complete biosystems of organisms, adding new layers of complexity to our current understanding of these systems. In many cases the technologies that enabled the isolation of food materials for study in the last century - chromatography, extraction, and purification - will be entirely inappropriate to the successful isolation and study of more complex systems. Instead, bio-friendly isolation technologies will be utilized, with the capacity to manipulate biosystem components in living organisms for research purposes and potential commercial products.

Processing of materials for use in experimental studies.

A major obstacle in redefining the modern food production pathway is resolving the chemical structure of bioactive food components present in foods including proteins, secondary metabolites, complex carbohydrates and live bacteria. In addition to improved isolation and purification techniques, tools that accurately measure the structural dimensions at the nanometer, micrometer and millimeter length scales, in addition to the absolute amounts of bioactive molecules in food, will be required so that the exact composition of native and altered formulations can be determined and documented, validating claims of competitive functionality.

New analytical tools for quality control of materials - the example of milk oligosaccharides.

Mammalian milk contains complex indigestible oligosaccharides with remarkable health effects. Although not used directly as nutrients for the infant, we now know that one of the major health benefits of these complex carbohydrates is to establish a healthy commensal microbiome in the newborn infant gut. In order to more broadly exploit this principle of guiding the health of the host by guiding the population characteristics of the endogenous microbiota with functional food products for all ages, oligosaccharides and oligosaccharide-like components must be discovered and understood in our agriculture products. The first generation of such products will be isolated from industrial milk streams (Zivkovic & Barile 2011).

At present, a combination of extraction methods such as liquid/liquid extraction and solid-phase extraction are used in laboratories to isolate these molecules (Niñonuevo et al. 2005; Ward et al. 2006; Aldredge et al. 2013) following a very specific sequence to separate the oligosaccharides based on their unique chemical properties. Graphitized carbon forms a uniquely attractive surface to this class of molecules and much of the isolation is accomplished by this selectivity (Bier et al. 2008; Aldredge et al. 2013). Once the oligosaccharides have been isolated, their composition can be determined by identifying their diverse structural isomers, which are the products of different enzymatic pathways and display different biological activities. Research has now begun to generate detailed structural information for human milk oligosaccharides and assemble these findings in publicly accessible bioinformatic databases containing enough detail to facilitate subsequent functional characterization (Wu et al. 2011). New methodologies such as microchip liquid chromatography separation and high-performance mass spectrometry (MS) techniques, including time-of-flight and Quadrupole time-of-flight analyzers are also contributing to

progress in the field (Niñonuevo and Lebrilla 2009). These methods are combined with enzymatic assays that allow the full characterization of glycan composition and structure from any food source. Commercially available HPLC chip devices and high performance MS make it possible to use this process to rapidly analyze all isomers in a precise and reproducible manner (Niñonuevo et al. 2005; Niñonuevo et al. 2008; Tao et al. 2009; Wu et al. 2011; Aldredge et al. 2013). This example of elucidating functional complex carbohydrates in human and bovine milk illustrates the path to fully understanding the structure-related health benefits of a complex biopolymer component in food commodities using new high-throughput analytic methods.

Informatics and Computation Technologies for Precision Nutrition

Precision nutrition research and development is making a huge leap forward due, in large part, to the burgeoning capability of computers to measure, store, manage, analyze and transmit data, which has enabled scientists to collect and make effective use of the unprecedented depth and breadth of biological data this research requires. Technological advances, including orders of magnitude more data capacity and computing speed than in the recent past, global-scale transmission of data, integration of computers into all manner of instruments and devices, and development of specialized software for specific scientific purposes, are enabling nutrition scientists to record and consolidate a multitude of measures, investigate the broad diversity of differences between individuals, document the dynamic timing of physiological processes, and combine different types of datasets to develop new, interdisciplinary understandings from a systems biology perspective. This data-intensive research has necessitated a paradigm shift in which scientists are increasingly investing in the development of rigorous and robust computing methodologies.

High performance databases for a myriad of measures.

In the laboratory, clinic, and community, instruments and measurement devices are being rapidly introduced that use embedded computers to overcome previous barriers of cost, labor, and invasiveness to efficiently generate large volumes of exquisitely detailed health and diet data. For example, modern sequencing tools can identify tens of thousands of genes in one quick assay and metabolomic technologies such as Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR) Spectroscopy can rapidly identify and quantify large numbers of metabolites in a biological sample. Research data is also being generated by many of the user-friendly and wirelessly-connected personal health devices now available to consumers that measure physical activity, heart rate, blood pressure, brain electrical activity, skin temperature, sweating, body fat percentage, and much more (Topol 2010). Data recorded by individuals, such as these, and other, self-report measures, can easily be aggregated into large population datasets via the internet (while also protecting individual privacy) as has been done by some businesses that sell these consumer devices (Bietz et al. 2016). The wide net cast by the internet also facilitates the identification of sizable cohorts of people with rare diseases or phenotypes (Tweet et al. 2011). Additionally, the electronic medical records of patients at some large healthcare systems have recently been assembled into searchable research databases that include diagnoses, prescriptions, advanced imaging and medical test results (Harris et al. 2009, Ross et al. 2014). These efficient, high-volume

measurement and data aggregation technologies have generated a proliferation of large, multidimensional datasets with potential to transform scientific knowledge of nutrition and health.

These datasets require storage infrastructure in the form of annotated databases with the complex functionalities to be manipulated, integrated and interrogated in the search for relationships between lifestyle and measures of health. Relational databases with unlimited numbers of dimensions, data structures tailored for each data type, and a modular design offer a flexible and extendable solution for this purpose (Lemay et al. 2007). Using the internet, large datasets can now conveniently be stored and backed up on remote servers and public databases can be accessed and queried by scientists everywhere. At present, several large nutrition databases have been created, including the Human Metabolome Database (http://www.hmdb.ca/), the Nutrigenomics Database (http://nutrigenomics.jp), and the long relied-upon USDA Food Composition Databases (https://ndb.nal.usda.gov/ndb/). International efforts are underway to standardize and integrate between datasets and to develop a search engine that can interrogate information from many databases, while retaining the autonomy, data ownership and security of each. Ontologies can also be created that define and name the relationships between different entities, enabling computers to automatically solve problems by applying semantic logic to these datasets (Lange et al. 2007, Puustjarvi et al. 2011).

Advanced analytics and delivering meaning.

Extracting meaningful information from highvolume, multidimensional data is analytically and computationally challenging. In some cases, raw data must be transformed through sophisticated data refinement techniques, such as signal processing or machine learning, into a form that is useful for analysis. The advanced and computationally-intensive statistical methods necessary to summarize and interpret complex data are now widely available to nutrition scientists. These include multivariate methods like principal components analysis, which is used to analyze high-dimensional datasets (Lyalina et al. 2013), and longitudinal methods like multilevel modeling, which is used to analyze time-series data, such as the fluctuation, or change over time, in individual diet, metabolism or other measures (Gollamudi et al. 2016). A recent surge in bioinformatics software has also made available pathway analysis tools for functional interpretation of metabolomics data and increasingly rich open source software options for analysis of biological data, such as can be found in the statistical programming language, R. R offers a large and diverse library of packages for advanced and flexible statistical analyses and elaborate graphical representations of data, and it facilitates the documentation and reproducibility of procedures that is so necessary for carrying out complex analyses (https://cran.r-project.org). Custom software and algorithms can also be designed for specific scientific purposes that partially automate complex analyses. Additionally, computer-based mathematical modeling is greatly enhancing our understanding of complex systems.

Perhaps most exciting, the widespread use of the Internet has generated a new global architecture of health information flows between centralized health web applications and many dispersed individual users. This massive scale transmission of personal health

information is rapidly developing into a mutually beneficial information exchange network among individuals, businesses, clinicians, and researchers. Some online health companies are now utilizing aggregate user data for population research (Eriksson et al. 2010). A few are also exploring the translational application of scientific knowledge to the task of improving the health of individuals by disseminating back to their users meaningful analyses of their personal data and actionable health information and advice, targeted according to each individual's biological profile (Eriksson et al. 2010; Choe et al. 2011). Delivering personally-relevant nutrition information through these channels, in user-friendly or even game-like forms, will make the complexity of selecting a healthy diet easier to navigate and holds great potential to motivate changes in dietary behavior, improve population health, and generate more effective market demand for the health-promoting characteristics of foods.

Increasingly powerful technologies are creating tremendous opportunities to advance precision nutrition by accelerating scientific discovery, expanding our understanding of the complexity of the human body, and providing individually-targeted health information to the public. Most of the potential gains from currently available technologies are still yet to be realized.

Educating and Informing the Public to Optimize Food Choices

As outlined above, a sophisticated set of scientific, industrial and computational tools is beginning to produce new breakthroughs in food, agriculture and health that will benefit generations to come. But precision nutrition is not only driven by advances in science and technology; the major motivation is the state of our population's health. True progress depends on developments that ultimately translate to a healthy population (Khoury 2014, Khoury 2016). As precision tools and platforms develop in scope and accessibility, more targeted interventions will become available that can shape the metabolic phenotype and health status of individuals with increasing effectiveness (Gollamudi 2016; Dunstan 2012; Bietz 2016; Lupton 2012; Schaefer 2015; Schaefer 2016; Smilowitz, 2013; Eriksson et al. 2010; Choe et al. 2011; Khoury 2016, German et al. 2011). Foods and diets will be available that are designed and selected to regulate gene expression and metabolism, altering people's health trajectories. As diets become increasingly tailored to meet specific health needs and respond to highly individualized health goals (German et al. 2011), consumer awareness and demand for personalized diet and lifestyle solutions will expand as well.

The wearable technology industry is making it easy for consumers to measure a growing array of personal health metrics like physical activity, caloric balance, heart rate, blood pressure, sleep, stress level, and mood. 70% of U.S. adults now monitor measures of their health or lifestyle (Fox 2013). The availability of consumer tools capable of easily recording continuous, objective lifestyle data and characterizing personal health phenotypes is sparking data-driven movements and health trends, such as The Quantified Self movement (http://quantifiedself.com). The greatest potential lies in tools that use standardized and well-validated measures, and that integrate multiple measures or data sources on each person, so as to allow individuals to examine their own unique relationships between different interacting lifestyle and health variables and to manipulate these through self-experimentation. The data recorded by these consumer devices and applications can serve

the dual purposes of providing a basis for personalized feedback to individuals and also contributing to aggregate population datasets when it is donated for research. Personalized health information and advice is increasingly being provided through accessible consumer formats, like user-friendly dashboards, apps and games, that guide and motivate health behavior based on high-precision phenotyping (Choe et al. 2011; Lupton 2012; Schaefer et al. 2016). The same information can also provide the basis for new information tools for clinicians to help them tailor treatments and therapies for individual patients.

Although first generation health devices and "apps" did not necessarily incorporate proven behavior change techniques or have evidence of efficacy at changing behavior, the sophistication of these platforms is rapidly improving as they mature (Moller, et al. 2017). Behavior change is hard, but some functions and features that have been observed to be able to influence behavior include measuring the desired behavior, making the behavior easier to do, creating accountability, connecting users to a supportive social community, making the behavior more rewarding, and providing relevant data or information. When it comes to providing consumers with high impact data and information analytics, the incorporation of scientific findings learned through precision nutrition research has transformative potential. Disease risks that are longterm, and of uncertain relevance to the individual, are not compelling for many people (Barlow, et al. 2016), but precision nutrition research generates information that is highly personalized and can yield immediate, or short-term, benefits on some of the health outcomes people care about most. For example, continuous time-series measurements of diet and the severity of fluctuating symptoms can be used to identify person-specific temporal relationships between the two, potentially revealing which foods are personal triggers of symptom flare-ups. This is incredibly useful knowledge for people managing chronic conditions, and it cannot be obtained from crosssectional population datasets. In some cases, precision nutrition may be able to predict the probability of specific long-term disease outcomes for a particular individual by identifying early signs of metabolic change. This predictive information enables people to focus their behavior change efforts on the specific lifestyle practices most important for them, a more realistic goal than trying to get everyone to do all recommended health practices. The personal relevance, immediacy, predictiveness and exquisite detail of precision nutrition data gives it the potential to be a highly motivating driver of behavior change (Hood et al. 2012).

Dietary habits for life are established during childhood. So as personal health becomes increasingly data-driven, education will also be an important avenue for establishing the population's long term and foundational health skills and understanding. As phenotyping technologies find their way into classrooms, young people will have new ways of quantifying insights into important biological processes, from the transfer of biomaterials to foods and the composition of these foods, to their interactions within the human body and the resulting health effects. Researchers are examining the power of data-driven approaches in facilitating learning a range of subjects in and out of the classroom (Lupton 2012; Lee 2013; Catford 2011; Carter Ching et al. 2014; Schaefer et al. 2015; Schaefer et al. 2016; Carter Ching et al. 2016). New solutions call for interdisciplinary approaches to integrate information in meaningful ways to optimize child learning and the development of precision health skills (Schaefer et al. 2016; Lee 2013; Carter-Ching 2016 et al.; Baranowski et al. 2008; Ito 2009; Baranowski & Frankel 2012). Applied in these ways, precision health

education can greatly benefit the population by strengthening individual agency for personal health management starting in childhood.

A Precision Nutrition Case Study

A recent publication (Zeevi, et al. 2015) demonstrates a novel and exciting method of precision nutrition research and intervention by using metabolic phenotyping to provide personalized dietary advice. Zeevi, et al. examined 1) variation in glycemic response to standardized and "real-life" meals, 2) the potential for phenotyping to predict postprandial glycemic response, and 3) the potential for individually tailored interventions to improve glycemic response. Intra- and inter-individual variation in postprandial glycemic response was measured over 7 days in a cohort of 800 participants using continuous glucose monitoring. The investigators analyzed this data using machine learning and developed a phenotyping algorithm that successfully predicted individuals' postprandial glycemic responses to meals using a combination of biochemical, anthropometric, dietary intake, physical activity and gut microbiota data, which they subsequently validated in a new cohort of 100 subjects (Zeevi et al. 2015). The next phase of the study involved a smaller group of new participants (n=26) who were offered individually tailored dietary advice from a clinical dietitian based on expert opinion or based on the predictive model. Participants in each arm consumed meals with a low postprandial glycemic response for one week and meals with a high postprandial glycemic response for one week. Glycemic response to the predicted meal plans was the same as the expert meal plans. They also reported improvements in glycemic response following the precision dietary intervention (Zeevi et al. 2015).

This study illustrates the power of continuous data streams from large cohorts to elucidate the variations between different people in the complex temporal dynamics of metabolism. It provides proof of concept and highlights the major advantages of precision methods for both research and clinical outcomes. As technologies for data measurement and analysis continue to advance, more interventions like this one, using metabolic phenotype-based predictive modeling will become possible. The predictive algorithms produced by this type of data intensive research also have the potential to be incorporated into consumer health technologies, provided to clinicians and used by educators so as to disseminate personalized health information to the public to guide their lifestyle choices.

Conclusion: Precision Nutrition to Optimize Population Health

The health of the population is in crisis, but a 21st century tool set for precision health and nutrition is available with the capability of developing transformative solutions by elucidating human diversity in genetics, environment and lifestyle choices. New scientific methods, devices, and technologies are giving researchers, clinicians, and the public powerful new ways to measure and use detailed, multidimensional data and to communicate and collaborate on a massive scale. We provide a diagrammatic overview of the Precision Nutrition process of research and intervention in Figure 1 illustrating the mechanisms through which it will accelerate scientific discovery and improve public health. Food quality and safety is going to be guided by a detailed understanding of the genetics and phenotypes of microbes. Detailed measurements of personal phenotype from clinics to classrooms will

enable personalized diets that guide the development of optimized health trajectories for the population. These tools are at hand, and we need not wait for a revolution to move us forward. Opportunities to elevate the health of the population, the value proposition of the food supply and the sustainability of both are now available in the science, technology, engineering and computation tools of the 21st century.

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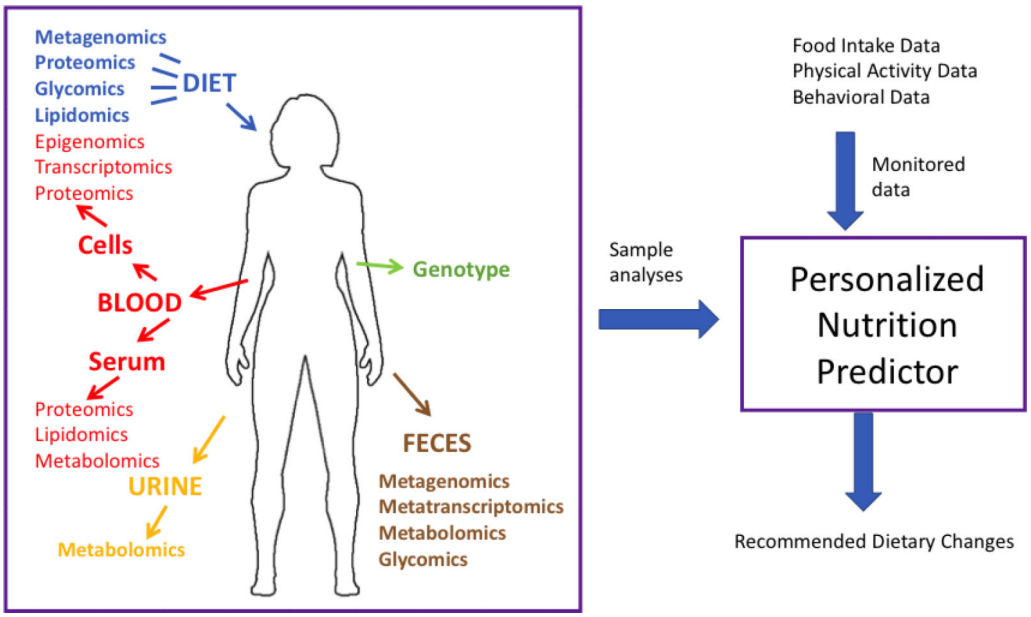

Figure 1.

Overview of Precision Nutrition research and intervention.Data sets arising from analyses of human clinical samples, genetics, electronic medical records, and monitoring of dietary intake, physical activity and behavior are used to develop personal nutrition predictive algorithms. Modeling of observations from thousands of people is used to predict expected health outcomes for new subjects and determine what dietary changes should be recommended based on each person's individual data and phenotype.