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REVIEW

The genomics of micronutrient requirements

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Abstract Healthy nutrition is accepted as a cornerstone of public health strategies for reducing the risk of non-communicable conditions such as obesity, cardiovascular disease, and related morbidities. However, many research studies continue to focus on single or at most a few factors that may elicit a metabolic effect. These reductionist approaches resulted in: (1) exaggerated claims for nutrition as a cure or prevention of disease; (2) the wide use of empirically based dietary regimens, as if one fits all; and (3) frequent disappointment of consumers, patients, and healthcare providers about the real impact nutrition can make on medicine and health. Multiple factors including environment, host and microbiome genetics, social context, the chemical form of the nutrient, its (bio)availability, and chemical and metabolic interactions among nutrients all interact to result in nutrient requirement and in health outcomes. Advances in laboratory methodologies, especially in analytical and separation techniques, are making the chemical dissection of foods and their availability in physiological tissues possible in an unprecedented manner. These omics technologies have opened opportunities for extending knowledge of micronutrients and of their metabolic and endocrine roles. While these technologies are crucial, more holistic approaches to the analysis of physiology and environment, novel experimental designs, and more sophisticated computational methods are needed to advance our understanding of how nutrition influences health of individuals.

Keywords System nutrition · Micronutrient · Omics · N-of-1

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Nutritional phenotype and the complexity of defining health

The description of human physiology based on responses to nutrition is now commonly termed "the nutritional phenotype" (Zeisel et al. 2005; van Ommen et al. 2010a). This phenotype is defined as a "to-be-integrated" set of quantitative genetic, proteomic, metabolomic, functional, and behavioral data that form the basis for the assessment of human nutritional and health status. While the nutritional phenotype is a useful descriptor of those factors to be measured for determining status, it lacks a clear definition of whether that status is healthy for the individual.

The World Health Organization defined health in 1948 as "a condition of complete physical, mental, and social well-being and not merely the absence of disease or

Table 1 Conceptual flow of the manuscript

Step	Concepts
1	Health status is the ability of an individual to adapt and self-manage
2	Micronutrient status and phenotype have an impact on health status
3	Micronutrient nutritional phenotype is determined by differences in genetic-environment interactions that cannot be understood using the one-gene–one-polypeptide approach
4	Micronutrient nutritional phenotype can be characterized by an integrated set of quantitative genetic, proteomic, metabolomics, functional, dietary intake, and behavioral data characterized with extensive metadata
5	Integration of data is possible using computational system modeling
6	N-of-1 trials are studied where each participant is in his/her own control and will metabolically respond to a (micro)nutrient intervention challenge
7	The systematic comparison of phenotypic responses of individuals exposed to different diets using omics approaches may be used to validate and to better understand the role of the diet and micronutrient needs in the etiology of health

infirmity" (WHO 2006). This definition inadvertently contributed to the medicalization of society, including not only medical practice but also nutrient recommendations since (1) "complete" well-being is an unattainable ideal that is itself unmeasurable; (2) individuals may need drugs or treatments to be "completely" healthy; and (3) people with chronic diseases or conditions are automatically defined as ill even if they function well in their personal and social environments (Huber et al. 2011). A new definition of health was proposed as "the ability to adapt and self-manage" (Huber et al. 2011). Health has social, mental, and physical components, each of which incorporates the concept of positively responding to or even reducing stress or challenges. Physiological health can be considered equivalent to metabolic flexibility or adaptability (Storlien et al. 2004; van Ommen et al. 2009, 2014).

Inadequate nutritional phenotype, environmental stressors such as exposures to unclean water, unsanitary conditions, and infectious agents reduce this flexibility and increase susceptibility to chronic disease. Indeed, the impact of subclinical undernourishment and the micronutrient needs of populations in different environments and with diverse cultural, genetic, and agricultural histories are still unknown (Kaput and Morine 2012; Kussmann and Kaput 2014). While policymakers rely almost exclusively on population averages for micronutrient recommendations, the quantitative aspects of human nutrient requirements on the utilization, function, and metabolism of micronutrients at the cellular, organ, and whole biology system level (Young and Scrimshaw 1979) in individuals must be determined. Understanding the complexity of an individual nutrient needs requires more holistic approaches to the analysis of nutritional phenotype and environment, novel experimental designs, and standardized metadata capture and storage (e.g., nutritional phenotype database—van Ommen et al. 2010a) and more sophisticated computational methods to advance our understanding to practice translational nutrition, which constitute the starting point and the conceptual flow of the present review (Table 1).

A further recent concept of translational nutrition and health science is the use of nutritional or functional challenges to homeostasis with subsequent analysis of its restoration. This is best exemplified by the oral glucose tolerance test, a mainstay in diagnosing type 2 diabetes (Leiter et al. 2005). Assessing postprandial changes in metabolic processes using omics technologies is becoming an important tool for assessing metabolic health since flexibility decreases in chronic disease (van Ommen et al. 2014). However, the influence of genetic variation on metabolic flexibility has not yet been analyzed, and the responses to acute challenges have not been adequately correlated with long-term health. In addition, postprandial responses to acute challenges may miss the effects of bioactives that are present in foods at low concentrations and act in the long term (e.g., micronutrients). An approach for analyzing the effects of low-concentration, long-to-act nutrients is a human intervention study providing high but safe concentrations for 4–6 weeks. Analysis of genetic makeup, dietary intake, and multiple physiological parameters is then used to analyze their effects (Monteiro et al. in preparation). The present review also explores a study design called N-of-1 trials, an approach to expand and translate nutritional knowledge.

Quantitative aspects of human nutrient requirements: What do we know?

The field of nutrition science today is evolving from the analysis of a single process or nutrient studied in isolation to a more holistic analysis of the system (Kaput et al. 2014). In the past, researchers and policy makers focused primarily on protein and calories as the cause of infant malnutrition (for example). Focusing on a single nutritional

cause obscured the broader malnutrition that exists in a child with marasmus or kwashiorkor. Growth retardation characteristic of children in low- and middle-income countries (LMIC) was similarly believed to be due solely to the lack of protein and calories despite clear evidence that many micronutrient deficiencies exist and are fundamental part of the growth and development process (Darby 1966).

Micronutrient recommendations are currently based on the amount judged sufficient to meet the requirements of the majority of healthy individuals within a population group (Pavlovic et al. 2007). Such recommendations serve as a basis for regulating national and/or regional nutrition policies, which considers average intake. However, no standard approach exists for deriving micronutrient recommendations (Sheffer and Lewis-Taylor 2008), and requirements vary considerably across countries causing confusion among consumers, food producers, and policy makers. The United States Institute of Medicine (IOM) and the Food and Nutrition Board (FNB) developed the concept of dietary reference intakes (DRIs) which superseded the US recommended daily allowances (RDA) and the Canadian recommended nutrient intakes (RNI). DRIs for micronutrients are regularly updated as new evidence is published. The need to align procedures for creating micronutrient recommendations across Europe was recognized by the European Commission's Directorate General for Research, which funded the EURRECA (EURopean micronutrient RECommendations Aligned) Network of Excellence (NoE). Coordinated by ILSI Europe, the network includes 38 partners with more than 200 individual scientists from 17 European countries and a budget of €13.2 million (2007–2012) (Ashwell et al. 2008; Pijls et al. 2009; Matthys et al. 2010, 2011; Van't Veer et al. 2013).

While policymakers, regulators, food producers, and the consumer all rely on the recommendations for the average individual in a population, there is increasing awareness that gender, age, activity, and physiological condition alter nutrient intake requirements and should therefore result in more specific recommendations. Nutrigenomics research over the past two decades has provided examples of inter-individual variation in nutrient responses depending on genetic makeup (e.g., Ordovas 2009; Morine et al. 2014). Nutritional genomics (Kaput and Rodriguez 2004) is the broad term encompassing genetics, epigenomics, and genomics, all of which involve the interactions of environmental factors with genes, which in turn result in phenotypic outcomes, including nutritional requirements and disease risk (Field et al. 2007; Kussmann et al. 2008; Kussmann and Van Bladeren 2011). The conceptual basis of nutritional genomics is inter-individual variability in nutrient requirements. EURRECA acknowledged that genetic variation (e.g., single-nucleotide polymorphisms) would alter micronutrient metabolism, metabolomics, and phenotypic expression (van Ommen et al. 2010b; Bouwman et al. 2012). However, research into variation in (micro)nutrient requirements is still in its infancy, but must be accounted for in determining micronutrient requirements for individuals and for public health.

Aberrant homeostatic systems and micronutrient levels

Loss of homeostasis occurs in chronic diseases and metabolic flexibility (rev. in (van Ommen et al. 2014)). The role of micronutrient levels in chronic diseases has not been analyzed comprehensively. For example, vitamin D together with B group vitamins has been reported to be deficient particularly in morbidly obese individuals (Aasheim et al. 2008; Kaidar-Person et al. 2008; García et al. 2009; Soares et al. 2011). These results suggested that the vitamin content of the diet influences adiposity and body fat content. Obese individuals have also been shown to have a lower level of the antioxidant vitamins C and E (Aasheim et al. 2008). An adequate vitamin C level may contribute to maintenance of body weight, while vitamin E has been shown to impact adipocyte biology, leading to modulation of the secretion of adipokines (Landrier et al. 2009; Amara et al. 2014). However, the causality between low vitamin status and obesity remains difficult to be established, especially in humans. Moreover, vitamins in other chronic diseases are typically studied one at a time instead of comprehensively in a system approach (van Ommen et al. 2008).

Micronutrient requirements and food intake data

Organisms adapt to their environment. Individual's long-term dietary and activity habits influence physiological processes by inducing genes and establishing a homeostasis for that environment. Adapting to a new environment alters expression of genetic information and therefore creates a new homeostasis, reflecting a different series of set points. Acute challenges and intensive short-term interventions are beginning to contribute to our understanding of metabolic health but are still incomplete because of the difficulty in assessing the environmental context of the individual study participants and how those environments may produce different homeostatic conditions. Accurately assessing the environment as a means to understand the homeostatic condition is challenging and indispensably requires information and analysis of dietary intake (Stumbo et al. 2010; Tucker et al. 2013).

Dietary intakes are measured with different methods and vary in precision and sources of error. Food frequency

questionnaires (FFQ) are usually preferred over diet records or 24-h recalls because they are more suitable and accurate in assessing long-term or habitual exposure to specific nutrients (Mason 2003). However, repeated diet records (EDR) or 24-h recalls are commonly used as the reference method for a relative validation process of the FFQ based on correlation and agreement statistical methods (Pauwels et al. 2014). Biomarkers are key for validating and improving the FFQ accuracy (Yoshino et al. 2010), but to date, only a limited number of dietary/nutrient metabolites correlate well with dietary nutrient content (Manach et al. 2009; Pujos-guillot et al. 2012). Metabolomics and proteomics are promising tools for biomarker discovery, with the potential to identify biomarkers of dietary patterns or combinations of nutrients. Many existing and novel computational methods can be used to analyze complex data (Priami and Morine 2015). For example, principal component analysis (PCA) can be used to find different dietary patterns, and partial least squares discriminant analysis can be used to associate different dietary patterns with biomarker profiles. Once the biomarker profile is identified, validation is necessary. The systematic comparison of biomarker profiles of individuals exposed to different diets using omics approaches may be used to validate and to better understand the role of the diet and micronutrient needs in the etiology of health.

The use of different FFQs (with different food lists with or without portion sizes and including or omitting specific ethnic foods) and different methodologies of dietary data collection renders quantitative and accurate comparison of data from different studies almost impossible (Stumbo et al. 2010; Tucker et al. 2013). Because of the diversity of dietary methodologies, study-specific quartile rankings for intakes of "favorable" (whole grains, fish, fruit, vegetables, nuts/seeds) and "unfavorable" (red/processed meats, sweets, sugared beverages, and fried potatoes) quality foods are often used. These quartile rankings can be combined to generate a healthy diet score and are sufficient for main effect associations, as has been demonstrated previously with dietary pattern analyses in many studies (Tucker et al. 2013). The primary objectives of a dietary pattern analysis are to characterize the eating habits of a population and to associate diet with health and disease status (Bamia et al. 2005; Waijers et al. 2006).

However, statistical approaches must be enhanced to deal with food intake data in order to define the micronutrient requirements that account for genetic makeup. One approach classifies individuals into mutually exclusive groups according to how (dis)similar they are with respect to their food consumption using (nonparametric) cluster analysis using, for example, the K-means method (Chen et al. 2002). Accounting for covariates and the challenge of comparing different clustering criteria limit the utility of these methods. A finite mixture model (FMM) is analogous to a factor analysis with a categorical latent variable and can be used to create mutually exclusive groups (Fahey et al. 2012). Different clustering methods can also be selected after adjusting for energy intake. Owing to substantial error in food consumption intake reporting, any analysis will usually find some patterns that cannot be validated. However, these mixture models may be useful to identify individuals who underreport food consumption (Fahey et al. 2012).

Given the known limitations of current dietary assessment methods, new approaches for measuring dietary intake are being developed to reduce costs associated with collection and processing of dietary data (Thompson et al. 2010). Examples include a web-based dietary recall for children, mobile phone photography to instantly record consumed foods, a mobile phone application to record intake with voice recognition, and a wearable device to take pictures of food through image recognition (NIH Genes, Environment, and Health Initiative (GEI) 2013—http://tinyurl.com/oh5lh3v). These innovations, along with improvements in biomarkers of dietary intake including metabolomics and other techniques (Vernocchi et al. 2012; Lloyd et al. 2013), hold promise for contributing to improved dietary assessment through advanced technology (Tucker et al. 2013).

Analyzing metabolites delivers metabolic endpoints of the omics cascade and a profile close to the phenotype and may therefore be used to assess the effects of nutritional interventions and validate food intake tools (Manach et al. 2009; Scalbert et al. 2009; Llorach et al. 2012). These chemometrics generate metabolic profiles or patterns of metabolites which can then be associated with food patterns and micronutrient needs (Llorach et al. 2012). However, only the concentration of a few metabolites (e.g., carotenoids) is strongly correlated with dietary intake. This should not be surprising since none of the current methods accounts for variations in half-life of metabolites derived from foods (Thürmann et al. 2002; Landberg et al. 2006; Marklund et al. 2014), and genetic variability in metabolism may produce different metabolomics profiles for the same nutrient(s) intake. Nevertheless, a more integrated approach to the assessment of micronutrient status should involve measurement of multiple biomarkers that are central components, of metabolic, oxidative, inflammatory, and psychological processes and, thereby, of health maintenance. These intermediate markers of metabolism can therefore be considered as surrogate markers of nutritional status and as an important tool to set micronutrient requirements (van Ommen et al. 2009; Bouwman et al. 2012; Dhonukshe-Rutten et al. 2013).

Genetic and epigenetic variability: molecular phenotyping

Although Williams described biochemical and genetic variability at the dawn of the modern era of science (Williams 1956), only the genomics revolution made it possible to characterize the exact genome sequence of individuals. Approximately 228,000 human genomes have been sequenced by the start of 2015, and estimates are that 1.6 million genomes will be sequenced by 2017 (Regalado 2014). Each new genome sequence confirms that individuals are genetically unique (Olson 2012) and hence will have unique responses to environmental factors including diet, lifestyle, and medicines. In addition, epigenetic variation contributes to individuality. Epigenetics is the study of mitotically heritable yet potentially reversible, molecular modifications to DNA and chromatin without alteration to the underlying DNA sequence (Reik et al. 2001; Li 2002).

Diet can alter epigenetic programming since many of the precursors and substrates for methylation reactions are derived from food (Kussmann et al. 2010; Crider et al. 2012). Specific patterns of epigenetic modifications, particularly to DNA but also to chromatin, are postulated to underly the developmental origin of diseases (Barker et al. 1993; Gluckman et al. 2009). That is, unbalanced nutrition during key developmental windows, including those occurring in utero, produce an epigenetic profile that contributes to the development of chronic diseases such as cardiovascular or metabolic disorders in adulthood. Hence, the epigenetic profile is mismatched for adults in some (but not all) environments. The distinction that the environment should be considered in understanding health is crucial to broaden the concept that metabolic destiny is solely determined by the effects of maternal environment.

The functional elements of the human genome, including variations in DNA sequence, methylation, and regulatory elements, are being analyzed by the Encyclopedia of DNA Elements (ENCODE—http://genome.ucsc.edu/ENCODE/) consortium (Feingold et al. 2004; Birney et al. 2007; Myers et al. 2011; Schaub et al. 2012). The ENCODE data may aid in the interpretation of the genetic variations identified in genome-wide association studies (GWAS). Although GWAS provide a list of SNPs (http://www.genome.gov/gwastudies/) that are statistically associated with a phenotype of interest, causality can only be inferred from the data. The ENCODE project identifies the functional domains in relationship to these genomic variations (SNPs and other) (Schaub et al. 2012). However, a limitation of the ENCODE data is that much of it was obtained from immortalized cells grown in culture.

System nutrition and micronutrient requirements: the role of N-of-1 trials—study designs

Two major scientific concepts of twentieth century have inadvertently impacted the development of personalized medicine and nutrition, including the development of individual requirements for (micro)nutrients. The first is the insistence on randomization for clinical studies, and the second is the reductionist's approach used to study complex systems. While randomization was essential for pregenomic era research (Fisher 1971), the ability to characterize individuals at the genetic, proteomic, and metabolomic level demonstrated that this statistical approach—also by definition—masks inter-individual variation in response not only to nutrients but also to drugs (Guyatt et al. 1990; Lillie et al. 2012; Kaput and Morine 2012). Similarly, the one-gene–one-polypeptide concept best exemplified by Beadle and Tatum's 1941 analysis of auxotrophy in *Neurospora sp.* (Beadle and Tatum 1941) promoted a reductionist approach to biomedical science. A single biochemical pathway cannot be used as the benchmark for the effects of nutrient deficiency or supplementation since only a few components of a much more complex system are studied in isolation. A paradigm shift (Kuhn 1962) in nutrition research is necessary for analyzing dynamics of biological processes in response to changing environmental exposures rather than trying to reduce this complexity to artificial levels that may be less meaningful for real-life situations.

Micronutrient research should therefore investigate how genomic and epigenomic individuality predisposes to health and disease and how an individual's genome expresses itself at different omic levels (proteomics, metabolomics, lipidomics) in response to environment, including nutrition and physical activity. This more comprehensive strategy requires extensive molecular phenotyping of humans, which includes analysis of environmental, genomic, microbiological, and epidemiological factors (Kaput et al. 2005; Kaput and Morine 2012; Kussmann et al. 2013; Kaput et al. 2014). Measuring all of an individual's complexity in diverse environments can of course not be done, but refined phenotyping at molecular level will greatly help explain the mechanisms involved in determining micronutrient requirements.

Developing new experimental approaches also requires an expansion beyond the classical case–control designs to analyze individual response. One reasonable approach has been classified as "N-of-1" studies, i.e., detailed study of one individual over time and in response to environment. Sidman first described this design in the psychological literature in 1960 (Sidman 1960). Since then, N-of-1 trials have been used in a variety of disciplines (Nikles et al.

2011). The first N-of-1 trials were multicycle, double-blind, and controlled crossover trials using standardized measures of effect. However, no standard design is appropriate for all experimental questions. The ultimate benefits of N-of-1 trials may derive from the reality that interventions of whatever type rarely work in everyone (March et al. 1994; Nikles et al. 2006; Elobeid et al. 2009). N-of-1 trials explore this variability in an objective way while simultaneously leading to an informed decision about the best way to treat an individual patient with their own data (Bacchetti et al. 2011; Lillie et al. 2012; Gardeux et al. 2014; Nikles et al. 2014; Morine et al. 2014). From a global economic and healthcare perspective, one cannot perform one trial per each subject or patient in order to intervene and treat in a personalized fashion. Rather, one recruits cohorts of participant reflecting similar genetic and environmental backgrounds, analyzes each participant longitudinally, and then bins these participants into similar physiological trajectories. The consumer and patient space can thereby be stratified into groups of people sharing disposition and exposure, and these groups are then scientifically and economically amenable to targeted lifestyles, interventions, and treatments.

Following this N-of-1 approach, we used a middle-out (as opposed to top-down or bottom-up) procedure (Monteiro et al. 2014) to analyze genotype data by defining and testing associations of single-nucleotide polymorphisms of genes involved in micronutrient metabolism, related gene networks, and their protein–protein interactions (Morine et al. 2014). Topological partitioning and enrichment analysis identified modules (subnetworks) enriched in genes encoding proteins that participate or regulate pathways associated with micronutrients. Specifically, a pattern of metabolites (met_PC1) that included the ratio SAM/SAH, Hcy, and five vitamins in erythrocytes was significantly associated with: (1) single-nucleotide polymorphisms; (2) levels of plasma proteins; and (3) multilocus genotypes coding for gastrointestinal and immune functions, as identified in a global network of metabolic/protein–protein interactions (Morine et al. 2014). The data used for this analysis were obtained in a community-based participatory research (CBPR) setting, in which the same study subject was repeatedly monitored over time. CBPR is translational research in which the participants provide information and biological samples on an ongoing basis, and the biomedical researcher in return provides existing knowledge as well as results from the study to the participants. Research is "personalized" since one individual is assessed and informed even in the community setting. Translation of knowledge is more immediate than population-based methods and is targeted to the community and individual (McCabe-Sellers et al. 2008; Kaput and Morine 2012; Monteiro et al. 2014).

Statistics and computational system biology: data leverage

A significant challenge for modeling health and disease processes is the integration of the many different environmental, genetic, and omic datasets. A prerequisite of this approach is the capture, management, and storage of not only these experimental datasets, but also detailed metadata of where and how the data were obtained (van Ommen et al. 2010a). Modeling of metabolic networks is a powerful approach to allow a better understanding of nutrient behavior in cells both in normal and in pathogenic states. The data used for modeling are often derived from experiments conducted in vitro, while epidemiological and physiological data usually quantify metabolites and other biomolecules in blood, urine, or other accessible biological fluids. Biochemical pathway maps are examples of how detailed reactions can be amalgamated from independent experiments to generate the appearance of a dynamic system (Rozenblit and Keil 2002). System modeling is a similar mapping tool to organize and display information, but contains additional sets of information such as protein–protein interactions and directionality of regulation or interaction. However, neither pathway nor system maps provide causal explanations for a phenotype. Biomarkers predicted or discovered by system analysis need to be validated in order to inform preventive or therapeutic treatments (Nijhout et al. 2008; Reed et al. 2008) and to set dietary reference intakes for essential nutrients (Scotti et al. 2013). A variety of different statistical and computational methods are used or developed to address this experimental data complexity of system biology (Scotti et al. 2013). Regardless of the choice of methods, the challenge is to translate omic and other phenotypic data into micronutrient requirements using functional analysis.

Micronutrients and bioactives: Are they ready to be recommended?

Several elements are required for a nutrient or food component to be evaluated for a dietary recommendation. First, the data must demonstrate that the effects of the food component of interest can be attributed to a health impact, including a plausible mechanism of action. Second, accurate intake assessment is needed, with biomarkers of exposure and/or validated food assessment methods required, including the ability to distinguish the effects of the background diet. An important public health question is whether intake recommendations should shift the focus from disease risk reduction to maintenance of normal physiological function. Moving beyond classic nutrient–disease biomarkers and having holistic view of nutrition

Table 2 Challenges along the path to system nutrition-based, personalized dietary and nutrient recommendations

Challenge/obstacle	References
The bioavailability and bioactivity of micronutrients and bioactives differ widely according to chemical structure. Intake from dietary supplements and foods differ in content, matrices, and dose	Gaine et al. (2013)
The micronutrient and bioactive content of plant foods is influenced by numerous plant-related factors (e.g., sun, ripeness, storage, preparation, processing), making accurate assessment of their intake difficult	Gaine et al. (2013)
Errors in intake measurement: accuracy of food composition databases and reliability of FFQs, and intake amounts do not always equate to bioavailable doses	Gaine et al. (2013)
The health benefits of micronutrients and bioactives in the current literature are often based on surrogate biomarkers of effect rather than actual health outcomes (endpoints), such as disease incidence or mortality	Gaine et al. (2013)
Classical case/control designs of human clinical/nutritional intervention studies should be complemented by crossover, longitudinal studies, in which every subject is its own case and control	Kaput and Morine (2012)
Homeostasis varies among individuals. Challenging homeostasis may identify individual health trajectories	van Ommen et al. (2009)
The funding required in undertaking a formal federal review of micronutrient and bioactive intake has not been viewed as a priority	Gaine et al. (2013)

and metabolism are essential in the development of dietary recommendations of micronutrients and bioactives (Gaine et al. 2013).

Lack of food composition data, insufficient knowledge of actual intake amounts, and limited information on micronutrient absorption and metabolism are still gaps to be filled in order to set dietary recommendations. In reality, micronutrients and bioactives differ in their quantities in foods, bioavailability, metabolites produced, and (potential) health effects because of different genetic backgrounds of individuals (Gaine et al. 2013). Advancing dietary recommendations of micronutrients and bioactive components will require more system nutrition approaches and evidence-based scientific data. The significant challenges and obstacles along this path are summarized in Table 2. Nutritional genomics and quantitative omics must be incorporated into studies that aim to determine these nutrient requirements. Although these technologies are rapidly progressing in terms of data generation, quantitative capture and monitoring of the human environment, including diet, lifestyle, and socioeconomic status, have lagged behind and must catch up (Kaput et al. 2014).

Conclusions

High-throughput technologies are enabling scientists to profile genomes, transcriptomes, proteomes, and metabolomes at an unprecedented scale and rate. Combining "omics" data with clinical research to set personalized dietary recommendations remains a challenge, but is also the ultimate goal of nutritional research. The recently published "field guide to genomic research" (Bild et al. 2014) succinctly summarizes the key steps of biomedical research: (a) specify clear objectives; (b) outline analytical approaches that will be used to meet the objectives; (c) anticipate potential confounding variables; (d) stay true to your original experimental design; (e) understand how statistical and computational methods should be applied to meet the objectives; (f) repeat the study design in different populations but with the same analytical and statistical approaches and also perform in silico and/or mechanistic validations; (g) describe methods in sufficient detail that others can apply them; (h) make raw and processed data available in public repositories like Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/), Database of Genotypes and Phenotypes (http://www.ncbi.nlm.nih.gov/gap), or Sequence Read Archive (http://www.ncbi.nlm.nih.gov/sra). To this common sense, we add the need for (1) a system nutrition approach to understand the complexity of gene–environment interactions, (2) N-of-1 study designs to determine individual responses, (3) community-based participatory research to translate results for improving personal and public health, and (4) standardized study storage including metadata capture, e.g., as intended with the nutritional phenotype database (dbNP).

Conflict of interest Jacqueline Pontes Monteiro has no conflict of interest, Jim Kaput works for Nestlé Institute of Health Sciences, and Martin Kussmman works for Nestlé Institute of Health Sciences.

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