

Personalizing Nutrigenomics Research through Community Based Participatory Research and Omics Technologies

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Abstract

Personal and public health information are often obtained from studies of large population groups. Risk factors for nutrients, toxins, genetic variation, and more recently, nutrient–gene interactions are statistical estimates of the percentage reduction in disease in the population if the risk were to be avoided or the gene variant were not present. Because individuals differ in genetic makeup, lifestyle, and dietary patterns than those individuals in the study population, these risk factors are valuable guidelines, but may not apply to individuals. Intervention studies are likewise limited by small sample sizes, short time frames to assess physiological changes, and variable experimental designs that often preclude comparative or consensus analyses. A fundamental challenge for nutrigenomics will be to develop a means to sort individuals into metabolic groups, and eventually, develop risk factors for individuals. To reach the goal of personalizing medicine and nutrition, new experimental strategies are needed for human study designs. A promising approach for more complete analyses of the interaction of genetic makeups and environment relies on community-based participatory research (CBPR) methodologies. CBPR's central focus is developing a partnership among researchers and individuals in a community that allows for more in depth lifestyle analyses but also translational research that simultaneously helps improve the health of individuals and communities. The USDA–ARS Delta Nutrition Intervention Research program exemplifies CBPR providing a foundation for expanded personalized nutrition and medicine research for communities and individuals.

Introduction

ADVANCES IN EXPERIMENTAL TECHNOLOGIES for analyzing genomes, proteins, metabolites, and transcripts are laying the foundation for developing recommendations for personalized nutrition and optimizing medical treatments for each individual. However, current experimental strategies rely on studies that yield the average response of individuals in a population. These “data are reported as the attributable fraction (AF)—“the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure of interest from the population” while other factors remain unchanged (Rockhill et al., 1998). Although many reports explicitly report the data as the attributable fraction specific for that population, the data are often used by the commercial enterprises and the public as an individual risk factor (Vineis and Kriebel, 2006). Because individuals may differ genetically, physiologically,

and nutritionally from the population averages, the AF can only be considered an estimate of the risk for an individual.

Intervention studies also yield information for medical treatments or recommendations for nutritional intakes. A recent example showed an association of three single nucleotide polymorphisms (SNPs) in *IL1A* and *IL1B* with response to a botanical that lowered C-reactive protein (CRP) levels (Kornman et al., 2007). Although nutrigenomic and nutritional intervention studies provide preliminary information about optimum diets, the small number of individuals in many of the studies and their undetermined genetic ancestry precludes using the information to predict responses in other individuals. Epistatic (gene–gene) interactions have been shown to alter the influence of individual SNPs on measured phenotypes (e.g., Adjers et al., 2005; Hamon et al., 2006; Helgadottir et al., 2006; Mannila et al., 2006; Tuo et al., 2006; Smith et al., 2008). These specific examples illustrate the need for developing new approaches to study the interaction of

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genetic makeup and environmental factors. We have previously described challenges to analyzing gene–nutrient interactions that include the genetic diversity of human populations, complexity of diets and cultures, the intricacies of physiological processes that depend on gene–environment interactions (Kaput et al., 2007a, 2007b) and the need for new experimental designs that are not based on population studies (Kaput, 2008). These challenges are reviewed in the context of an emerging strategy for human population studies, the use of community-based participatory research methods that may provide the path for developing recommendations for improving personal and public health.

Genetic Diversity of Human Populations

The sequencing of the human genome, subsequent analyses of human genetic variation and studies that associate gene variants with disease markers or other phenotypic alterations have led to the promise of personalized medicine. Although the first reports described a consensus sequence based on DNA samples from several individuals, the variability observed between overlapping sequences led the HapMap project (Frazer et al., 2007; HapMap Consortium, 2003; 2004a). This international effort resequenced chromosomal segments of 270 individuals, 90 of whom were European, 90 from the Yoruba tribe in Nigeria, 45 Japanese in Tokyo, and 45 Han Chinese in Beijing. The HapMap is a valuable resource of data that has been used as the basis of genotyping platforms (Dalma-Weiszhausz et al., 2006; Steemers and Gunderson, 2005); over 1 million polymorphisms (SNPs) can be interrogated with current array-based technologies. However, the publication of genomic sequences of two individuals of European descent (Craig Venter and James Watson) (Levy et al., 2007; Wheeler et al., 2008) and the known heterogeneity within populations (Li et al., 2008; Tishkoff and Verrelli, 2003), demonstrated a need for analyses of a wider representation of genomes. Hence, the rich HapMap resource represents a small fraction of the total genetic variation in humans. The Human Genome Diversity Project (<http://www.stanford.edu/group/morrinst/hgdp.html>) and Human Variome Project (<http://www.variome.org/>) are expanding analyses of sequence variations by including individuals in many other human populations. Resequencing of more genomes is now possible because new sequencing technologies are reducing the cost and increasing the throughput (Bennett et al., 2005; Shendure et al., 2008). Creating a more in-depth coverage of human genetic diversity is necessary for identifying causative SNPs or other genetic variation and to account for epistasis (see above). New algorithms are being developed that can detect epistatic interactions that affect the expression of gene variants (e.g., see Musani et al., 2007; Sankararaman et al., 2008)).

Complexity of Biological Processes in Disease and Health

Our laboratories (Kaput et al., 2007a, 2007b) and others (Brown et al., 2006; Gardiner, 2004; Wolford et al., 2004) have described the variable physiological mechanisms that produce health or disease states. Such complexity results from the many genes and pathways that make small contributions

to the overall phenotype, the epistatic (gene–gene) interactions that may alter the expression of an analyzed SNP, and epigenetic effects on gene expression caused by variable histone modifications and DNA methylation status. The substrates for epigenetic mechanisms are derived from the one carbon metabolism pathway. Interactions exist between genes of the folate/methionine cycle and cofactors, which are derived from the diet (Blander and Guarente, 2004, 2004b; Eberharther and Becker, 2002; Gellekink et al., 2005; Hsiao et al., 2002; Klerk et al., 2002; Picard et al., 2004; Porto et al., 1998; Rossell et al., 2006; Waterland and Jirtle, 2003). Changes in epigenetic regulation may occur throughout life, but fetuses and developing children may be particularly susceptible to unbalanced nutrition (Dolinoy et al., 2007; Mathers 2007; Szyf, 2007).

Genetic analyses, whether DNA resequencing or genotyping, coupled with “deep” phenotyping (Tracy, 2008) using proteomic (Kussmann, 2007), metabolomic (Gibney, et al., 2005), and transcriptomic (Garosi, et al., 2005) technologies, will generate detailed genetic and physiological data for each individual. The use of these technologies is likely to overcome the diversity of challenges of analyzing human genetic heterogeneity (Kaput et al., 2007a, 2007b) in population-based study designs.

Nutrient Assessments and Study Designs

As the “omic” technologies mature and individual genome data become increasingly available, two fundamental problems challenge the development of an understanding of complex biological processes. The first is the difficulty in measuring food and nutrient intakes that may change during life. The second is that the majority of research strategies are based on population averages. Although assessing nutrient intakes remains a significant challenge (Rutishauser, 2005; Tucker, 2007), new methods, such as photographs of before and after food servings (Kikunaga et al., 2007) and omic analyses linking food exposure to defined biomarkers, may overcome these limitations (see below). Yet a further challenge is an extension of the attributable risk problem: many population-based studies (with the notable exception of longitudinal studies like the Framingham Heart Study; <http://www.nhlbi.nih.gov/about/framingham/>) measure biological complexity at a single point in time using a limited set of biomarkers. These measures may or may not provide an accurate assessment of a given condition or biomarker, essentially because long-term changes in the nutrient, physical, immune, or psychological environment could alter biomarker levels observed at a single time point.

Developing the Path to Personalized Health Interventions

One of us recently proposed a path to personalization based on preselecting phenotypic or metabolic groups (Kaput, 2008). The fundamental concept is based on comparative analyses, because no one population can be considered a reference population. The strategy is to first identify and group individuals with common phenotypes and analyze the genetic differences between them. Alternatively, individuals can be selected based on variations within functional genes

(and not just variants used for genetic mapping) and phenotypes can be compared subsequently. Because the full spectra of human genetic and phenotypic variation has not been well characterized, the first groups tested would often be those most different in phenotypes or genetic makeups—that is, to determine the extent of the range of variation within the human population. The key aspect of this concept is that membership in the group at each extreme is based on some quantitative measure of phenotype or genotype. Once maximum differences among phenotypes or among genotypes are determined, groups between the extremes can be determined. Although many if not all biological traits are continuous with no discrete breaks in the phenotypic or genetic continuum, such “binning” is a standard for medical practice, which uses clinical measurements to group individuals into treatment options and for statistics that rely on tertiles, quartiles, quintiles, etc., to determine structure within experimental data. This approach differs from standard population study designs in that the binning is done prior to physiological analyses if the genetic variation is predetermined or prior to genetic analyses if different phenotypes are identified. Many human studies discern the groups after experimental data are acquired. A variation of this comparative strategy demonstrated its utility: Holmes et al. (2008) showed that individuals from different ethnic populations could be clustered based on urinary metabolite levels and blood pressure measurements. Although genetic analyses (e.g., Jorde and Wooding, 2004; Tishkoff et al., 2003) have shown that variation is greater within ancestral populations (e.g., within Europe) compared to between populations (European vs Asian), the predominant “nutrient”—related alleles (i.e., genes involved in nutrient metabolism) in a population coupled with local cultural food availability and habits may explain the ability to cluster individuals into groups specific to an environment. Hence, creating bins of similar metabolic responses appears feasible.

Developing this strategy requires novel approaches to individualize research findings. An experimental strategy to implement this comparative approach has historical roots in the 1940s, but has been emerging from medical practice and from sociological/nutritional research efforts. Participatory research has evolved from a continuum of similar but slightly different approaches (Cornwall and Jewkes, 1995). Some have termed these approaches as community-based participatory research (e.g., Boyer et al., 2005; Horowitz et al., 2008; O’Fallon et al., 2000), participatory action research, academic–community-based participatory research, or primary care research (e.g., Beasley et al., 2007; Hueston et al., 2006; Mold and Peterson, 2005). The differences largely reflect the degree of control and involvement of community residents in all phases of the research process. The lowest level of community involvement is termed contractual, in which the researcher brings the proposal to the community and asks them to participate with no or little input or decision making authority while the researcher is in full control (Cornwall and Jewkes, 1995). At the next level (consultative), the researcher asks for the community’s input and adopts some of the input, but the researcher retains full control. The third level is termed collaborative, wherein the community and researchers work together to design and implement the study, but the overall process is managed by researchers.

This is a shared control model and is the most frequently found model in today’s community based participatory research (CBPR). The fourth model is termed collegiate, wherein all parties work together drawing upon different skills while mutual learning takes place. In this desirable but seldom achieved model, the community is in full control (Cornall and Jewkes, 1995). The collegiate model is found most often when community residents are well trained in research methods and have had previous experience in research studies.

Although CBPR has been gaining much interest in the social and nutritional sciences fields ((Chen et al., 2006; Plumb, 2008) (see Table 1), relatively few studies have used this method for biomedical research (Boyer et al., 2007; Wells et al., 2006). CBPR is a cyclic process whereby the participants provide information and biological samples on an ongoing basis, and the biomedical researcher provides existing knowledge as well as results from the ongoing study. The community and biomedical partners continually inform each other as the research is conducted and applied. Collaborations are formed between and among the participants and the biomedical partners to design, implement, evaluate, and publish the research. The concept underlying this strategy is that the research can become “personalized,” because one individual is assessed and informed. The applications are therefore more immediate than population-based methods and targeted to the community and individual. Because genetic and omic data developed from population studies cannot yet be reliably associated with health outcomes in individuals, the initial information flows between researcher and community collaborator focused on nutritional assessments and dietary advice. As more gene–nutrient or omic–nutrient associations are proven, the information flow will include biomedical data and results.

Community-based participatory research differs from the more commonly found community-placed research method in that CBPR includes the community members equitably and actively in decision making, development of the research question and design, in implementation and monitoring of the intervention, interpretation of data analysis, and dissemination of findings. This means that community members are not merely the objects of research but highly engaged in the research process (Ndirangu et al., 2008). Unlike community-placed research, CBPR requires a collaborative assessment with key informants and representation from across the community (Ndirangu et al., 2007). CBPR is a slower process than the more traditional intervention research methods but has gained in momentum because developing trusting relationships and enhancing empowerment or ownership promises to be a more sustainable and therefore more effective approach to promoting health through behavioral changes (Israel, 1998, 2003; Kone, 2000).

The development of relationships among researcher and community is challenging but of critical importance for those who have typically been excluded from research studies or those who suffer from culturally-based health disparities (Boyer et al., 2007; Chen et al., 2006; Plumb et al., 2008; Wells et al., 2006). Individuals in these socio-economically disadvantaged populations will not benefit from the advances in health research unless their genotypes and cultural environments are included in biomedical research studies.

TABLE 1. EXAMPLES OF THE PARTICIPATORY RESEARCH PROGRAMS IN THE UNITED STATES

<i>Location</i>	<i>Program</i>	<i>Populations</i>	<i>Focus</i>	<i>Partners</i>	<i>Ref</i>
Chicago, IL	REACH CSEDCAAC	African American Latino	Community-based participatory research	Six provider organizations Three provider/professional organizations Three government agencies Seven community based organizations One Religious group Two Business Groups One Consumer Group Yukon-Kuskowim Health Corporation	(Giachello et al., 2003)
Alaska	CANHR	Native Americans SW Alaska	Community-based participatory research		(Boyer et al., 2005)
Little Rock, AR	Arkansas Special Populations Access Network	Delta, Central AR, and NW AR	Community-based network for cancer control activities	National Cancer Institute University of Arkansas Medical School	http://crchd.cancer.gov/spn/aspan-spcn-publication.html
Marvell, AR	Delta Nutrition Intervention Research Initiative	Lower Mississippi Delta	Community-based intervention, blood pressure and diabetes among other diseases	Scientists from: Alcorn State University Arkansas Children's Hospital Research Institute Pennington Biomedical Research Center, Southern University and A&M College The University of Arkansas at Pine Bluff, The University of Southern Mississippi Agricultural Research Service (ARS) of USDA, Little Rock, AR.	http://www.ars.usda.gov/main/site_main.htm?modecode=62-51-05-00

Detroit, MI	REACH Detroit Partnership	African American Latino	Community planning for participatory	Six community-based organizations Detroit Health Department Henry Ford Health System University of Michigan School of Public Health	(Kieffer et al., 2004)
Detroit, MI	ESVHWP-HEED	Eastside area	Prevent/delay T2DM	Detroit Department of Health and Wellness Promotion Eastside Parish Nurse Network Friends of Parkside Henry Ford Health System Islandview Development Corporation Village Health Workers Warren/Conner Development Coalition University of Michigan School of Public Health	(Schulz et al., 2005)
Los Angeles, CA	CHIC	Low income LA	Public participation, Assessment of the community context, Practical trial methods and health information	Robert Wood Johnson (sponsor)	(O'Fallon, et al., 2000; Wells et al., 2006)
Minnesota	IDEAL	Statewide	Diabetes prevention	Minnesota Department of Health Health Partners (managed care)	(Desai et al., 2003)

REACH—Racial and Ethnic Approaches to Community Health. (<http://healthy lifestyles.ssw.umich.edu/>).

CSEDCAC—Chicago Southeast Diabetes Community Action Coalition.

CANHR—Center for Alaska Native Health Research (<http://www.alaska.edu/canhr/index.htm>).

ESVHWP—East Side Village Health Worker Partnership (<http://www.sph.umich.edu/urc/projects/esvhwp.html>).

HEED—Healthy Eating and Exercising to Reduce Diabetes Program (<http://www.sph.umich.edu/urc/projects/esvhwp.html#HEED>).

CHIC—Community Health Improvement Collaborative.

IDEAL—Improving Diabetes Care Through Empowerment, Active Collaboration and Leadership.

A Review of the USDA–ARS Delta Nutrition Intervention Research Initiative (NIRI) Community-Based Participatory Research Project

The USDA Delta Nutrition Intervention Research Initiative (Delta NIRI) developed a CBPR (O'Fallon et al., 2000) with the individuals living in and around Marvell and with the Boys, Girls, and Adults Community Development Center (BGACDC) over an 11-year period (Ndirangu et al., 2008; Yadrick et al., 2001). CBPR is a method that simultaneously conducts research while applying existing scientific knowledge to improve prevention practices and healthcare among the participants and their community.

Initiating the Biomedical Research Dialogue.

Rural populations, and particularly rural minority populations, have seldom been included in national surveys of health, nutrition, and physical activity—a prime example is the National Health and Nutrition Examination Survey (NHANES- http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm). The first obstacle in developing effective intervention plans for a rural population is the lack of data. The Delta NIRI began as a consortium of six universities in 36 counties and parishes of three U.S. states: Arkansas, Mississippi, and Louisiana (Fig. 1). The counties and parishes were selected on the basis of being contiguous to the Mississippi River and having high rates of poverty and unemployment. The charge to this consortium was to improve the health of Delta residents through nutrition intervention research, but the first step was to collect data on which to base interventions. Through bus tours of the region and fact finding meetings with community leaders, a key informant study of 500 community residents and a review of literature on the health status of the Delta residents (Harrison, 1997; Smith et al., 1999; Yadrick et al., 2001) the process of documentation of need began. The findings showed geographic differences in the prevalence of hypertension, food insecurity, poor health status, and ability to pay for health insurance, providing preliminary information that these groups were in particular need of targeted interventions (Casey et al., 2004; Stuff et al., 2004a, 2004b).

In addition to a lack of data, a second obstacle was the lack of nutritional assessment tools and methods suitable to this rural, minority, impoverished population with low levels of educational attainment. The feasibility and validity of a telephone-administered 24-h dietary recall had to be determined before a large representative regional survey could be conducted to assess nutritional adequacy in the region (Bogle et al., 2001; Casey et al., 1999). A survey instrument of food security was also administered to older children to determine the prevalence of food insecurity and hunger as perceived by children (Connell et al., 2004). The first regional representative survey to assess dietary intakes, self-reported health status, and food insecurity of Delta residents was the Foods of Our Delta Study: FOODS 2000 (Champagne et al., 2004, 2007; Goolsby et al., 2006; HapMap Consortium 2004b; McCabe-Sellers et al., 2007; Stuff et al., 2004a,b). While these measurements focused on individual dietary habits and effects, the costs and availability of foods also influence food choices and food purchasing. Two studies were conducted in 2001 to address these important is-

sues. One was a regional food store survey to determine availability and quality of 102 food items in 62 supermarkets, 77 small/medium grocery stores, and 86 convenience stores located in 18 counties/parishes randomly selected to represent the region (Connell et al., 2007). These three food store types sold different percentages of healthy food. Although supermarkets carried a large percentage of items surveyed, the number of supermarkets in this region is limited. Hence, community residents with limited transportation to reach supermarkets may experience limited food supply adequacy. While these results may appear unrelated to omic research, comparison of gene–nutrient interactions in different populations must account for food availability in analyzing health status. While the focus of many nutrigenomic studies has been on individual nutrients or classes of nutrients (e.g., polyunsaturated vs. monounsaturated vs. saturated fatty acids; for a review see Corella and Ordovas, 2005), the adequacy of the overall diet may influence the omic biomarker measurements or associations with phenotypes. The second 2001 Delta NIRI study was a series of focus groups held in 9 of the same 18 counties/parishes of the food store survey to identify perceptions of factors influencing healthy food consumption behaviors (McGee et al., 2008). The findings demonstrated additional sources of experimental variation for omics research: food choice was influenced by health concerns, family influence, and the need for and availability of nutrition information. The expressed interest of participants in learning about healthy eating, food preparation skills, and portion control may provide guidance for developing intervention studies linked with biomedical research programs.

Dietary assessment of individuals and groups over a longer time period typically uses a food frequency questionnaire (FFQ) that must, by necessity, include the specific foods consumed by the population being studied (Gibson, 2005). From the 24-h dietary recall data of FOODS 2000, a Delta NIRI Adult Food Frequency Questionnaire was developed, applied, and validated (Talegawkar et al., 2007, 2008; Carithers et al., 2005; Tucker et al., 2005). Not surprisingly, regional food use patterns differ from national patterns and furthermore differ between African–American and European–American adults in the lower Mississippi Delta. Individuals in this region ate grits, turnip greens, okra, ham hocks, chit-terlings, crawfish, catfish, cracklings, jambalaya, potato logs, chicken and dumplings, and sweet potato pie, which are not normally eaten in other parts of the United States. The Delta NIRI Adult FFQ was also designed to add four portion sizes for each food item, presented as questions, rather than in grid format. Another unique factor of the FFQ was that quantities consumed or portions were asked after each food rather than after larger food groups as in most food frequency questionnaires (Tucker et al., 2005). Importantly, two separate studies have assisted in the validation of this instrument by comparing total α -tocopherol and carotenoid intakes with serum α -tocopherol carotenoid concentrations in a sample of the population of interest (Talegawkar et al., 2007)

In 2003, a CBPR program addressing nutrition intervention research was implemented in three rural communities, one of each in Arkansas, Louisiana, and Mississippi. This program focused on developing a local collaborative effort among community residents, universities, and the United

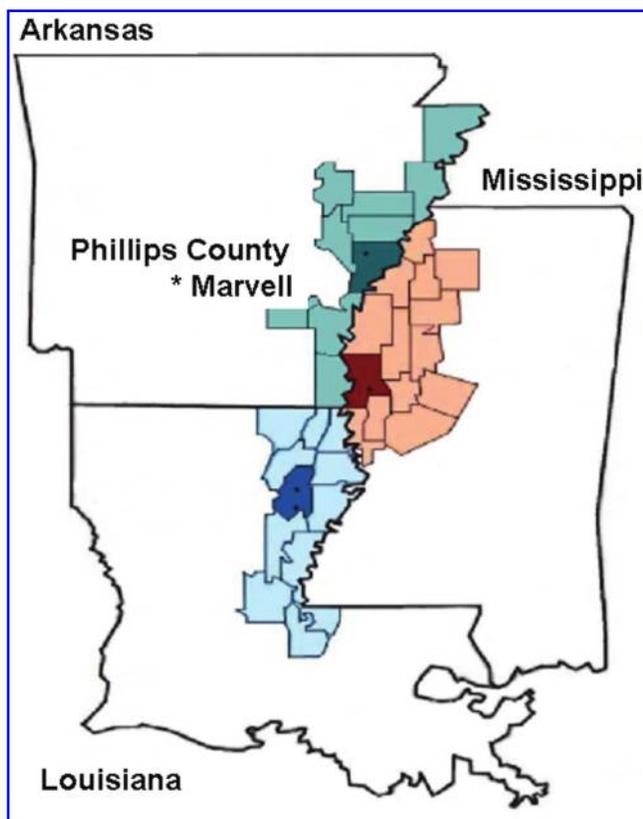


FIG. 1. The map and participants of the delta nutrition intervention research initiative. Shaded areas are the counties involved in the program, and dark shades are the “hubs” of each local.

States Department of Agriculture, Agricultural Research Service that would build capacity of community residents to become full and equitable partners in all phases of the nutritional research identified by the community as priorities. Community members were trained in principles of CBPR methods through the application of the Comprehensive Participatory Planning and Evaluation Model (CPPE), which produced three major nutrition-related problems the communities wanted to address (Ndirangu et al., 2007). Four initial pilot studies in Arkansas consisted of a Walking Club, Walking Trail Focus Group, Obesity Prevention Summer Day Camp, and a WillTry nutrition intervention approach to encourage eating fruits and vegetables (http://www.ars.usda.gov/research/projects/projects.htm?ACCN_NO=407162&fy=2007). Community residents participated in training in basic research principles, institutional review board (IRB) issues, and the Health Insurance Portability and Accountability Act (HIPAA). Additionally, some participated in training to be data collectors, interviewers, and to perform anthropometric measurements according to standardized protocols. These research assistants from the community further served as liaisons between the potential study participants and the researchers because of the greater willingness to address questions to and be reassured about the research by one of their own. From the exposure to and participation in nutrition research studies, the residents of this pilot re-

search community have a basic understanding of the importance of being involved in research studies. This introduction to research established the foundation for more extensive participation in biomedical research, particularly nutrition, genetic, and omic studies. Additional education, further development of trusting relationships, and gradual exposure to risks and benefits of genetic research will be needed to fully proceed in investigating nutrigenomics in this rural population.

Applications to Personalizing Research for Personal Healthcare

The major challenges to developing personalized nutrition and medicine applications are the genetic diversity of human populations, complexity of diets and cultures, and the intricacies of physiology dependent on gene–nutrient interactions that differ among individuals. In this report, we specifically underscore the need for, and the challenge of, creating new experimental designs for human studies (Kaput, 2008). Importantly, the traditional nutritional or genetic population-based designs identify risk factors that may not necessarily apply to the individual. An approach to reach the goal of personalizing healthcare is to identify groups within populations with similar metabolic profiles based on similar genetic profiles. Identifying these groups and characterizing them with omic technologies (i.e., deep phenotyping) may yield an understanding of the full range of genetic and phenotypic variation in the human population. Community-based participatory research and primary care research provides a path to that goal. While any one community or primary care facility will not encompass the full range of genetic makeups or phenotypes, replicating this approach in populations throughout the world and using harmonized study designs will allow for combined and comparative data analyses. While major challenges must be addressed, particularly measurements of total dietary intake and not simply individual nutrients, the global research communities are realizing that such cooperation is necessary to understand the complex biology of health and disease processes (e.g., see Kaput et al., 2005).

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Author Disclosure Statement

The author declares there are no conflicts of interest.

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