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Illinois Initiative for Personalized Nutrition
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Dear Drs. Nicastro and Lynch,

On behalf of the Illinois Initiative for Personalized Nutrition and my colleagues (**Appendix 1**) at the University of Illinois, I would like to thank you for the opportunity to comment on the future needs and priorities in the area of Precision Nutrition. The Illinois Initiative for Personalized Nutrition was recently established in response to a call in the 2018-2023 University of Illinois Strategic Plan, which called out personalized nutrition as an area for strategic investment to enrich interdisciplinary connections and establish new resources and facilities to expand our campus's strength in food, nutrition, energy, health sciences, and cancer. Needless to say, we are delighted that Precision Nutrition has been identified as a focus of the 2020-2030 NIH Nutrition Strategic Plan.

With the release of the 10-year NIH Nutrition Strategic Plan, the upcoming 2020-2025 Dietary Guidelines for Americans and the COVID-19 pandemic, it is no exaggeration to say that field of nutrition is poised to make sorely needed contributions to improving the health of the nation. The links between poor dietary intake and the etiology and severity of non-communicable diseases, which are the major causes of death in the U.S. are clear. The novel coronavirus (SARS-CoV-2) has put a spotlight on the important role of nutrition in supporting the immune system. [1] (**see Appendix 2 for references**) In addition, while all groups are affected by the COVID-19 pandemic, the elderly, underrepresented minorities, and those with underlying medical conditions are at the greatest risk. [2] The high rate of consumption of diets high in saturated fats, sugars, and refined carbohydrates worldwide, contribute to the prevalence of obesity and type 2 diabetes, and could place these populations at an increased risk for severe COVID-19 pathology and mortality. [3, 4] However, it is essential to critically appraise emerging literature for prevention or treatment of COVID-19 by nutrition or probiotic interventions. [5, 6] Precision Nutrition could also be an important component of longitudinal studies designed to examine the long-term impacts of SARS-CoV-2 infection and how patients who recover from infection fare over time.

The increased risk of mortality from COVID-19 in underrepresented populations in the U.S. highlights the dire need for future Precision Nutrition studies to be inclusive, diverse and equitable for several reasons. Gathering this information in order to improve the health of diverse populations is a fundamental human right. Where and how people live, and their genetic/epigenetic backgrounds all affect dietary intake and risk of disease. In addition, many groups of people have not been well represented in prior research, which means that researchers and health care providers know little about their health and their response to

medical or nutrition interventions. Participants should be from different races, ethnicities, age groups, and regions of the country. Participants should also be diverse in gender identity, sexual orientation, socioeconomic status, education, disability, and health status.

There will always be variability in how individuals respond to diet, in both direction and magnitude of the physiological response (e.g. weight gain, postprandial glucose, brain function, immune function, etc.). This interindividual variability has important implications for the efficacy of certain nutrients or dietary patterns in improving or optimizing an individual's health. [7] Over the past 10-20 years, the development of new analytical tools have enabled us to systematically study large quantities of detailed and multidimensional metabolic and health data, providing the opportunity to address current nutrition problems through Precision Nutrition. One of the ultimate goals of Precision Nutrition is to develop more comprehensive and dynamic nutritional recommendations based on shifting, interacting parameters in a person's internal and external environment throughout life. [8, 9] This information will enable the design of tailored nutritional recommendations not only to treat or prevent nutrition-related disorders in individuals or subpopulations, but to enhance health across the lifespan. [10, 11] To that end, Precision Nutrition approaches must go beyond genomics to explore other aspects that drive dynamic gene regulation (e.g. epigenomics, small molecule regulators, transcriptomics), metabolites (e.g. metabolomics, lipidomics, glycomics and proteomics) and the microbiome. [8, 9, 12] In addition, rich metadata cataloging the "exposome" of the individual (e.g. dietary intake, food behavior, physical activity, environmental contaminants, stress, etc.), is necessary to place 'omics data into context and to provide insight into gene-environment interactions within the context of health and disease. [13]

As will be noted below in our responses to the five questions included in the RFI, we believe that the current barriers to translating evidence from 'omics into meaningful dietary advice range from measurement to implementation. First, accurate, precise and minimally- or non-invasive methods for repeated *data collection* from human subjects across the lifespan are lacking. Secondly, adaptive and sophisticated *behavioral intervention* approaches to ensure long-term compliance with dietary or lifestyle interventions are needed. Thirdly, *biostatistical and bioinformatic approaches* for integrating multi-'omic datasets with each other and with demographic, clinical, dietary, and behavioral data are needed to to uncover mechanisms of action and identify robust biomarkers for clinical translation to diverse populations are sorely needed. ***To achieve its full potential, Precision Nutrition will require transdisciplinary collaborations across basic and applied physical (computer science and engineering), biological, behavioral, clinical, statistical, and social sciences.***

1. **Comments or caveats on inputs previously used to develop Precision Nutrition algorithms.**

    a. As noted above, Precision Nutrition approaches to date have included genomics, epigenomics, transcriptomics, metabolomics, lipidomics and proteomics. [14-16] microRNA (miRNA) are strands of RNA made up of around 22 nucleotides that are found inside protective extracellular vesicles called exosomes. By attaching to matching strands of messenger RNA, miRNA can effectively turn mRNA off and on, and alter what proteins are made. miRNA have been studied from the perspective of their presence in the food supply and how dietary intake impacts endogenous miRNAs expression.[17, 18] miRNA in both bovine and human milk are carried in exosomes and are absorbed into the circulation, where they have been shown to modify gene expression and other physiological outcomes in both *in vitro* and animal models. [17, 19] Moreover, emerging data from disease populations support the potential for using miRNA to stratify individuals who are responsive to drug treatments as well as nutritional interventions. [20]

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Recommendations: These analytical techniques are well established and their outputs have been used in many precision medicine and precision nutrition studies and should be retained in future investigations. The potential role(s) of miRNA in personalized nutrition remains unsettled. [21] Therefore, future studies should continue investigate both exosomes consumed in the diet and those endogenously produced miRNA in response to dietary interventions within the context of Precision Nutrition. In addition, improvements in available databases, particularly for metabolites and proteins, that represent more diverse participants and arequantitative rather than relative outputs are needed.

b. The metabolic activity of the gut microbiome is essential in maintaining host homoeostasis and health and its effects extend beyond the gastrointestinal system, influencing immunity, metabolism, and brain function. [7, 21] Studies investigating the role of the gut microbiota in Precision Nutrition typically focus on interindividual variability in response to diet and investigate the potential of the gut microbiota to influence personalized response. [7, 22] Recent findings suggest that the microbiota composition can account for a significant proportion of the variability in the response to a dietary intervention. For example, findings from the PREDICT-1 study showed that the gut microbiota had a greater influence (7.1% of variance) than did meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial glycemia (6.0%). [23] Additionally, the joint study of microbiome and metabolome has been proposed as the most promising approach to evaluate host–microbiome interactions. Visconti and colleagues compared metabolites in the blood (673) and feces (713) of twin human subjects (n=1004) and found metabolic pathways to be associated with 34% of blood and 95% of fecal metabolites, with over 18,000 significant associations. [24] The authors also estimated that the microbiota contributed 15% of blood metabolites and concluded that an intense interplay exists between the gut microbiome and the host. [24]

Recommendations: The gut microbiota is intricately linked to diet and host health. It is no longer sufficient to solely characterize the composition of the microbial community. [25] Thus, future Precision Nutrition studies should include multi-omics approaches that include metagenomic sequencing and microbial metabolomic analyses to advance our understanding of host-microbe interactions. It is important to distinguish the role of the microbiome as a mediator of the effect of diet on metabolism from the potential of the microbiome to be an effect modifier of response to diet. [7] Although these two concepts are inexorably intertwined, they are distinct and require their own independent questions and investigations. Mechanistic investigations link specific microbial metabolic functions with outcomes will be needed in order to manipulate the microbiome through diet or probiotic/prebiotic approaches to enhance beneficial functions or suppress deleterious functions. In addition, studies should consider microbial communities other than the gut/feces, since recent studies have demonstrated interactions between the gut and skin, lung and oral microbiota and host health.

2. **Additional measures that should be considered as inputs to develop Precision Nutrition algorithms**
   a. Glycomics is a rapidly emerging subspecialty of system sciences that evaluates the structures and functions of glycans in biological systems. Moreover, glycomics informs systems glycobiology and personalized glycomedicine, which collectively aim to explain the role of glycans in person-to-person and between-population variations in disease susceptibility and response to health interventions such as drugs, nutrition, and vaccines. [26] Plasma protein N-and O-glycans and glycans in cell membranes have been identified as biomarkers for cardiometabolic risk and cancer. [27, 28] Glycobiology and glycomics have received less attention in precision nutrition, outside of human milk oligosaccharides. [29] Related to glycomics, gut mucin glycoproteins can be source of carbohydrate for gut microbiota. There is growing evidence that microbiota degrading mucin

glycoproteins contributes to mucus layer thinning, leaky gut, inflammation. Composition of the microbiota and their carbohydrate degradation capabilities along with host diet – fiber rich or fiber poor – plays a big role in determining health of gut mucosa. [30]

Recommendations: Future PN studies should consider incorporating glycomics into the 'omics toolbox, given the strong associations with specific patterns of glycation and disease risk, progression and outcomes.

3. **Validated mobile apps, instruments (e.g. surveys or questionnaires), or other well-validated technologies that are available to capture these input measures (Question 2), either in clinical settings or remotely in large scale studies**

a. Accurate assessment of dietary intake and physical activity is a vital component for quality research in public health, nutrition, and exercise science. However, accurate and consistent methodology for the assessment of these components remains a major challenge. Classic methods primarily use self-report to capture dietary intake and physical activity in healthy adult populations. However, these tools, such as questionnaires or food and activity records and recalls, are known to be associated with systematic biases and measurement error in self-report that can lead to over- or underreporting consumption of total energy, foods and nutrients. Statistical methods to correct for measurement error have been developed, but require large-scale calibration studies that are not feasible to conduct in all populations. Nutrient biomarkers can be used as an objective marker of dietary intake, but their utility is limited due to issues related to sensitivity to intake, time-integration, cost and that they are not available for all nutrients.

Recommendations: NIH should fund research to develop, optimize and validate dietary data collection via Apps that include manual entry, selection entry (e.g. choose from a list), semi-automatic (scanning), voice-to-text, photo entry, digital receipts from restaurants or stores, and sensing of eating-related activities through wearables and non-wearables.[31] A desirable feature of Apps vs. more traditional dietary data collection will be a "push" feature, which can automatically prompt data entry. However, response to the push declines over time. [32] Thus, enhancing technology acceptance, [33] conducting comprehensive evaluation of app quality, [34] and determining the reliability and validity of dietary apps as matched to the study purpose (e.g. individual data or population-based data, dietary change or monitoring) are important. [35] Expanding dietary data collection to include several data collection features would enhance data validity. In addition, NIH should fund studies focused on nutrient biomarker discovery through methods such as metabolomics as well the improvement of existing nutrient biomarkers. Development of new and the strengthening of existing approaches that incorporate multiple methods of assessment (i.e. FFQs, diet records/24h and biomarkers) to accurately estimate dietary intake are also recommended Complete feeding studies that manipulate only the food item or food form under study should be utilized when appropriate [36-38] and objective measures of physical activity, including actigraphy are recommended. Precision Nutrition research should also leverage the resources available in The PhenX toolkit, which is a catalog of high-priority measures for consideration and inclusion in genome-wide association studies (GWAS) and other large-scale genomic research efforts. (https://www.phenxtoolkit.org).

b. The success of Precision Nutrition investigations will be dependent upon longitudinal tracking of the exposome and host biological fluids using biosensors. Ideally, the biosensors should incorporate sample collection in addition to monitoring, data fidelity and reproducibility. While approaches such as genome sequencing, RNA-seq, qRT-PCR are powerful and sensitive, their protocols are time-intensive and complex. Precision Nutrition research would benefit from

biomolecular analysis techniques that can be implemented in point-of-use settings, and in some cases integrated with personal mobile devices, to enable interfacing with cloud-based service systems. Nutrition biomarkers that can be easily and frequently quantified from noninvasively obtained bodily fluids (blood fingerstick, saliva, urine, perspiration) can complement wearable sensors that monitor physiological status (heart rate, activity/motion, oximetry, sleep quality) to provide a holistic view of how an individual's environment, diet, sleep, and exercise all contribute to their well-being.

Recommendations: NIH should support transdisciplinary collaborations between computational, engineering, clinical, biological and behavioral scientists to develop novel sensors to collect physiological, dietary and behavioral data in real time with limited burden to participants.

c. Informatics and data science. With advances in technologies, investigators are increasingly generating and using large, complex, and diverse datasets. Managing and analyzing each 'omic data set can be challenging, but approaches to integrate multiple data sets (e.g. host genomics and microbiome) within the context of Precision Nutrition inputs, which can have very different data structures, is relatively underexplored.

Recommendations: NIH should support transdisciplinary collaborations between computational, clinical, biological and behavioral scientists and biostatisticians to develop novel integrative analytical approaches that are robust and reproducible to ultimately support biomarker identification. Furthermore, advanced statistical machine learning algorithms have been developed to quantify dynamics of microbiome composition. [39] However, the effectiveness and robustness of such strategy often rely on the availability of large data repositories. This effort could capitalize upon the NIH Common Fund investment in the **NIH Big Data to Knowledge (BD2K**) initiative https://commonfund.nih.gov/bd2k, which aims to enable biomedical scientists to capitalize more fully on the big data sets being generated by research communities. Precision Nutrition should also capitalize on the new NIH investment in the **Artificial Intelligence for BiomedicaL Excellence (AIBLE)** initiative on artificial intelligence (AI) and machine learning (ML) in biomedicine. Lastly, continuous monitoring (**see comment 3b**) will also generate large amounts of data, which will produce challenges for data storage, analysis and comparison with appropriate standards (for clinical outcomes). It would be ideal for NIH to support a centralized repository for Precision Nutrition data that could be accessed by researchers. This could be similar to **The Cancer Genome Atlas (TCGA)** cancer genomics program supported by the NCI (https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga).

4. To rigorously and feasibly study the basis of individual variability in response to different challenge diets in a sufficient number of participants, controlled-feeding with a cross-over intervention design and short exposure periods (e.g., two weeks) could be used.

a. Randomized clinical trials (RCTs) are considered the gold standard in medical research, because they avoid confounding, and intervention assignment is under the control of the investigator, thus potentially reducing misclassification

b. However, in practice, randomizing diet poses special challenges:

i. Participants are typically not blinded to treatment

ii. If the macronutrient ***content*** of isocaloric diets is manipulated, then only one can be held constant, which can confound causality (e.g. a low fat diet is typically higher in carbohydrate)

c. Cross-over studies help to control for interindividual differences in genetics, epigenetics and microbiome composition. For some outcomes, short-term studies may be sufficient and will increase compliance. However, not all outcomes can be addressed with short-term studies, which will require prospective cohort studies (e.g. development of non-communicable diseases) (**see Question 5**)

d. People typically do not eat isolated foods or individual nutrients. Dietary patterns**,** foods, and nutrients are inexorability linked: dietary patterns comprise foods, and foods deliver nutrients. A dietary pattern is defined as the quantity, variety, or combination of different foods and beverage in a diet and the frequency with which they are habitually consumed. Foods are typically consumed in meals and snacks and those eating events tend to reflect a dietary pattern that we grew up with, which captures cultural or familial food practices. Stressors around meals should also be considered, including food insecurity and emotional or disordered eating. Consistent evidence indicates that, in general, a plant-based dietary pattern is more health-promoting than the current average U.S. diet, however, in most cases underlying mechanisms of action have not been ascribed to dietary patterns as a whole. Thus, more research is warranted in this area.

e. Humanized animal models enable the fundamental understanding of individual variabilities at genomic, epigenomic, metabolic, microbial, and medical levels. Data obtained from animal models can be fed into large scale computational programs for Precision Nutrition. Utilizing algorithms for machine learning (ML), programs can integrate computer science and biostatistics to "fit" individuals with specific dietary needs (Precision Nutrition).

Recommendations: Focusing on dietary patterns vs. manipulation of individual nutrients or macronutrient proportions is consistent with the approach taken by the Dietary Guidelines for Americans Advisory Committees in 2010, 2015 and 2020. Precision Nutrition investigations should apply the most appropriate experimental design to address the hypothesis under study. Intervention studies allow researchers to standardize the dietary stimulus, providing every participant the same amount (or relative amount) and type or quality of ingredients. Shorter-term, randomized, cross-over studies can provide a robust approach for controlling for intra-individual responses to dietary interventions. Baseline characterization of the genome (e.g. SNP's) and microbiome of participants will strengthen the analytical frameworks. For example, preintervention measurements of the microbiome may be used as effect modifiers in an analysis whereas postintervention measurements of the microbiome may serve as mediators. This distinction helps to avoid the circular logic of the effect of the diet on the gut microbiome and the effect of the gut microbiome in response to diet. [7] Animal models are appropriate for asking mechanistic questions, particularly using gnotobiotic or other 'humanized' models.

5. **Advantages and disadvantages of nesting such research within an NIH-funded, longitudinal cohort study**

a. Prospective cohort studies are characterized by the selection of the cohort and the measurement of risk factors or exposures before the outcome occurs, thus establishing temporality, an important factor in determining causality.

b. Our understanding of diet-health interactions has been informed by prospective cohort studies. Because the exposure is identified before the outcome, prospective cohort studies are considered to provide stronger scientific evidence than other observational studies, such as case-control studies. A fundamental characteristic of the prospective study approach is that at the starting

point, subjects are identified and exposure to particular risk factors is assessed. These studies are often sufficiently powered to detect outcomes with relatively low incidence.

c. Since prospective cohort studies play an important role in identifying associations that can be subsequently tested in intervention trials in human subjects or in preclinical animal studies to determine causality. Thus, there are advantages to keeping prospective (and retrospective) study designs in Precision Nutrition research.

d. However, there are significant disadvantages to nesting Precision Nutrition research within *EXISTING* longitudinal cohort studies as none have been specifically designed to capture the complexity of the inputs needed to fully comprehend the contributions that shape Precision Nutrition outcomes.

   i. **Environmental influences on Child Health Outcomes (ECHO)** program. https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program The goals of this 7-year study are similar to those of the former National Children's Study, however, its approach is different. ECHO supports multiple, synergistic, longitudinal studies using existing study populations, called cohorts, to investigate environmental exposures, including physical, chemical, biological, social, behavioral, natural and built environments, on child health and development. The 5 key outcomes are highly pertinent to Precision Nutrition (Pre-, peri-, and postnatal outcomes; Upper and lower airway diseases; Obesity; Neurodevelopment; Positive Health), but questions related to nutrition are not addressed in most of the cohort studies and fecal microbiome is only assessed in a few studies. Therefore, additional measures would need to be incorporated into these cohorts for them to be pertinent to Precision Nutrition. However, most ECHO cohorts are well-established, thus critical baseline information would not be available or would be dependent upon retrospective recall.

   ii. **All of Us Research Program** https://allofus.nih.gov/ This program has the potential to address questions pertinent to Precision Nutrition. The program is enrolling one million people across the U.S. with the goal of building one of the most diverse health databases in history. The goal is to the data to learn how our biology, lifestyle, and environment affect health. However, a cursory review of the study protocol shows that blood and urine samples are being collected at a single time point and not from all participants. In addition, fecal samples are not being collected. In addition, it appears that little or no information of dietary intake is being collected. To date, only ~1/3 of the participants have been recruited, therefore there is an opportunity to incorporate additional measures. However, as noted above this cohort is not designed to address Precision Nutrition hypotheses.

   iii. The **Health Professionals Follow-Up Study** (HPFS) https://sites.sph.harvard.edu/hpfs/. This >30 year study aims to evaluate a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease, and other vascular diseases. The all female **Nurses' Health Study** https://www.nurseshealthstudy.org/ examines similar hypotheses. The Nurses Health Study III is recruiting both male and female nurses and has added MICRObiome Among Nurses (MICRO-N) to the protocol. These studies are sponsored by the Harvard School of Public Health and are funded by the National Cancer Institute. The advantages of these studies are that establishing links between diet and disease was one of the primary aims and an extensive database on individual characteristics, biobanked samples and long-term follow-up data are currently available for study.

Recommendations: Existing cohort studies were not designed to investigate all potential Precision Nutrition inputs and outcomes, thus, **we recommend that NIH consider funding new cohort(s) across the lifespan** to investigate how individual variability affects responses to diet and health outcomes rather than trying to adapt existing cohorts. These cohorts should include all ages as there are unanswered questions across the lifespan. The cohorts must reflect all aspects of ethnic diversity, socioeconomic status and other social determinants of health. In addition, prospective cohort studies should also consider **Mendelian randomization**, which is a method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in observational studies. The design provides a method for obtaining unbiased estimates of the effects of a putative causal variable without conducting a traditional randomized trial. The design has a powerful control for reverse causation and confounding, which often impede or mislead epidemiological studies.

In closing, we appreciate the opportunity to assist NIDDK in identifying the needs and priorities for Precision Nutrition research. Descriptive and mechanistic studies using state-of-the-art epidemiology, food intake registration, genomics and other 'omic technologies, advanced biostatistics/bioinformatics, imaging, calorimetry, cell biology, challenge tests (meals, exercise, etc.), and integration of all data by systems biology, will be necessary to provide insight on a much higher level than is available today. The ultimate success of Precision Nutrition will require transdisciplinary collaborations across physical, biological, clinical, social and behavioral sciences. We also recommend that NIH consider how to leverage the work of several groups including the International Society for Nutrigenetics and Nutrigenomics and the Nutrigenomics Organisation (NuGo; www.nugo.org) that have been considering for nearly a decade how to conduct precision nutrition studies [40, 41] and the needs for a "nutritional phenotype database (dbNP)". [42] As has been stated by others, we need a "***Moonshot for Nutrition***" to improve the long-term health of the nation [43] and the new NIH Strategic Plan for Nutrition provides the ideal launchpad!

Thank you for considering our comments. If we can be of any further assistance, please contact me at sdonovan@illinois.edu or 217-333-2289.

Sincerely yours,

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Appendix 1. Contributors to the RFI Response:

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Appendix 2: References Cited

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