



National Institutes of Health
Turning Discovery Into Health

2020–2030 Strategic Plan for NIH Nutrition Research

A Report of the NIH Nutrition Research Task Force





1 Spur Discovery and Innovation through Foundational Research—*What do we eat and how does it affect us?*



2 Investigate the Role of Dietary Patterns and Behaviors for Optimal Health—*What and when should we eat?*



3 Define the Role of Nutrition Across the Lifespan—*How does what we eat promote health across our lifespan?*



4 Reduce the Burden of Disease in Clinical Settings—*How can we improve the use of food as medicine?*

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FOREWORD



What should we eat to stay healthy? Answering this question seems like it should be easy, but each of us knows that it is not. Dietary recommendations issued over past decades have aimed to guide what we eat to promote good health. But for many of us, these one-size-fits-all, “eating right” strategies have been frustrating to figure out and put into practice. We now appreciate the profound differences between individuals in dietary responses along with links between diet and disease risk—as well as fascinating but complex changes in our inner microbial world known as the microbiome. Interpersonal differences, such as these, pervade nearly all biological characteristics and behaviors and have driven NIH’s Precision Medicine approach to improving health overall.

What if each of us had individualized, actionable dietary recommendations that helped us decide what, when, why, and how to eat to optimize our health and quality of life? This is the bold vision of Precision Nutrition, as articulated through this *2020–2030 Strategic Plan for NIH Nutrition Research*, the result of years of hard work from the NIH Nutrition Research Task Force. This Plan outlines an exciting, strategic, and scientifically guided approach to fundamentally transform nutrition science through innovative research on nutrition, dietary patterns, and involvement of the microbiome. It also considers the role of diet in health holistically, across the lifespan and in the context of various diseases. The Plan is infused with strategies that pay close attention to the role of diet in the health of women and children due to the formative role of nutrition in pregnancy and infancy and throughout childhood.

Good nutrition is so central to our livelihood that it is hard to consider it as an isolated area of research, and we must not ignore its broad influence on individual and community health. Diseases linked to poor diet are the most frequent causes of death in the United States, and diet is the leading risk factor for premature death worldwide. Reducing even a fraction of this burden by improving people’s diets would not only save countless lives but also reduce annual health expenditures

by billions of dollars. Addressing these grim statistics is a vital responsibility for NIH and its various stakeholders to shoulder. But through this Plan, I see so much more: Advances in nutrition science will occur through innovative technologies and interdisciplinary teams of scientists that unearth exciting and unexpected discoveries. For example, new alliances between nutrition scientists and data scientists will enable us to process complex, multi-dimensional datasets with the goal of creating predictive nutrition algorithms to support healthy living for individuals from every walk of life. New tools such as artificial intelligence present an unprecedented opportunity to untangle the various roles of whole foods, individual nutrients, sociocultural impacts on eating and lifestyle, and societal infrastructure on the health of individuals and populations.

It is my expectation that this Plan will guide nutrition science over the next 10 years into uncharted, but tremendously exciting, new territory. This new landscape creates a holistic, interdisciplinary investigational approach to nutrition science and will simplify our ability to know what’s best to eat for good health.

Francis S. Collins, M.D., Ph.D.

Director, NIH

EXECUTIVE SUMMARY



The Nutrition Research Task Force Co-chairs (from left): Dr. Gary Gibbons, Dr. Norman Sharpless, and Dr. Diana W. Bianchi, with Chair Dr. Griffin P. Rodgers

Good nutrition is essential for healthy development and basic survival, but it is also integral to well-being and disease prevention. Health conditions linked to poor diet constitute the most frequent and preventable causes of death in the United States and are major drivers of health care costs, estimated in the hundreds of billions of dollars annually.¹ The answer to the seemingly simple question: “What should I eat to be healthy?” is not simple at all, nor is it the same across people of different ages, sizes, food environments, and internal microbial milieus known as the microbiome. Providing individuals with the right answer to this question requires considering dietary patterns, metabolism, microbiome variation, disease, and many factors unique to an individual and his or her environment.

The NIH Nutrition Research Task Force, guided by input from a broad range of stakeholders, conducted a strategic, scientifically guided approach to fundamentally transform nutrition science. This document, the *2020-2030 Strategic Plan for NIH Nutrition Research* (hereafter, “this Plan”) presents a bold, unifying vision emergent as “Precision Nutrition.” An important constituent of Precision Medicine, Precision Nutrition in research and practice considers multiple, synergistic levels of influence: dietary habits, genetic background, health status, microbiome, metabolism, food environment, physical activity, socioeconomic, psychosocial characteristics, and environmental exposures. Understanding the interrelationships among these factors will be critical for developing more targeted and effective dietary interventions to improve and maintain health in an increasingly diverse U.S. population.

As is apparent, nutrition research spans many disciplines and is intertwined with many specific diseases. This plan dovetails with the *National Nutrition Research Roadmap 2016–2021*,² created by the Interagency Committee on Human Nutrition Research, a trans-federal government committee charged with enhancing the coordination and communication among multiple federal agencies engaged in nutrition research. As well, this Plan complements diet-related components of disease-specific research plans previously developed by NIH, such as the *Strategic Plan for NIH Obesity Research*³ and aligns well with the *NIH-Wide Strategic Plan*.⁴ However, this Plan focuses on the impact of diet and nutrition on *all* health conditions and emphasizes the critical role played by interpersonal variation through its core focus on Precision Nutrition. Through a multifaceted approach that spans basic to clinical discovery, this Plan leverages ongoing large cohort-based studies, applies innovative research approaches such as data-science methods, and ensures equitable distribution of research findings to a diverse America.

This Plan consists of four **Strategic Goals** and sub-serving Objectives that will guide us toward Precision Nutrition for optimal health.

Strategic Goal 1.

Spur Discovery and Innovation through Foundational Research—*What do we eat and how does it affect us?*

Research within this Strategic Goal will ensure a strong foundation of basic and methodological research in nutrition science through integrated connections with other fields of study such as bioinformatics, neurobiology, and genomics.

Strategic Goal 2.

Investigate the Role of Dietary Patterns and Behaviors for Optimal Health—*What and when should we eat?*

Research within this Strategic Goal will illuminate how specific dietary patterns influence health outcomes in different ways among individuals, subgroups, and communities—toward determining effective strategies to create and sustain nutrition-related behaviors conducive to optimal health.

Strategic Goal 3.

Define the Role of Nutrition Across the Lifespan—*How does what we eat promote health across our lifespan?*

Research within this Strategic Goal will lead to a better understanding of how nutritional needs and eating behaviors change over time, focusing on three time-windows that have been especially understudied: pregnancy, infancy and toddlerhood, and older adulthood.

Strategic Goal 4.

Reduce the Burden of Disease in Clinical Settings—*How can we improve the use of food as medicine?*

Research within this Strategic Goal will expand knowledge about the role of nutrition in disease. This research will grow evidence toward development of “Food as Medicine” and medical nutrition therapies for improved health.

WHAT IS PRECISION NUTRITION?

For more than 100 years, federally issued nutrition guidelines have aimed to help Americans eat a healthy diet. Prompting these was the 1894 publication in the U.S. Department of Agriculture's *Farmers' Bulletin* "Foods: Nutritive Value and Cost," authored by chemist and pioneer of the study of human nutrition Dr. William Atwater.⁵ The first set of guidelines advocated variety, moderation, caloric content through ingestion of nutrient-rich foods that limited fat, sugar, and starch.⁶ Over the years, conventional nutrition guidelines adhered to similar principles and were adjusted generally for healthy population subgroups. We now know that dietary patterns—not individual nutrients or the "food groups" so familiar to many of us—have a greater influence on human health. Moreover, and in parallel, there has been an explosion of knowledge in nutrition science about the multitude of factors that influence a person's diet not just on a daily or monthly basis, but throughout life. These conceptual shifts have led to the birth of Precision Nutrition: a holistic approach to developing comprehensive and dynamic nutritional recommendations relevant to both individual and population health. To that end, Precision Nutrition is a framework canvassing a wide array of features including genetics, dietary habits and eating patterns, circadian rhythms, health status, socioeconomic and psychosocial characteristics, food environments, physical activity, and the microbiome.

An important distinction between Precision Nutrition and personalized nutrition or nutrigenomics is that the latter considers genomic and other "Omic" contributions to an individual's diet and metabolism that are mainly fixed and thus don't change much across time. Conversely, Precision Nutrition recognizes that humans are inherently different from one another, so *when, why, and how* we eat is likely as important as *what* we eat. The comprehensive and dynamic nature of Precision Nutrition offers a rigorous way to convey advances in nutrition science and related fields into meaningful, clinically relevant, and unbiased nutritional

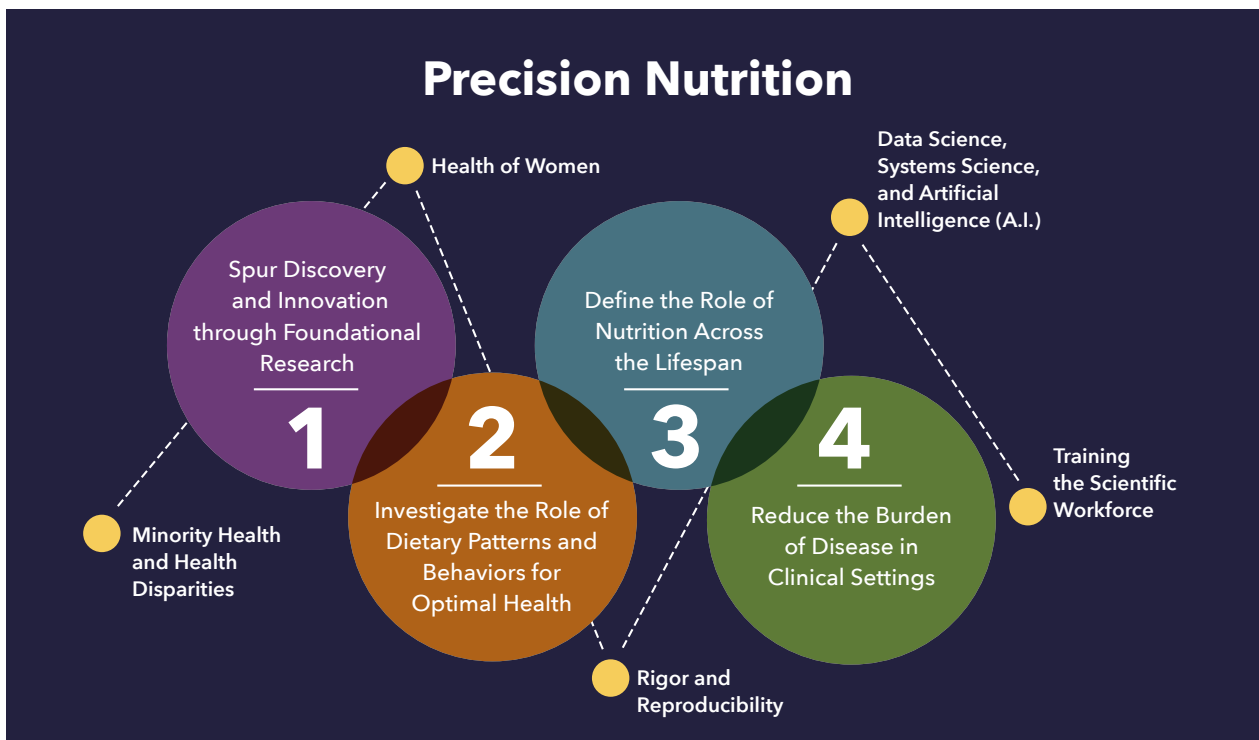
solutions for individuals and population subgroups—with important implications for preventing diet-related diseases like obesity, diabetes, cardiovascular diseases, and cancers. Due to the highly multidisciplinary nature of modern nutrition science, various concepts emerge as Cross-Cutting Research Areas that overlay Precision Nutrition investigations: Minority Health and Health Disparities; Health of Women; Rigor and Reproducibility; Data Science, Systems Science, and Artificial Intelligence; and Training the Nutrition Scientific Workforce. These Cross-Cutting Research Areas are relevant to all Strategic Goals described in this Plan.

Minority Health and Health Disparities

Certain populations—whether defined by race, ethnicity, socioeconomic status, disability, sex, gender, or geography—are disproportionately affected by many diseases, contributing to disproportionately high mortality rates. Nutrition-related health disparities arise from multiple factors related to biology, behavior, and environment and across several levels of influence that range from individual to interpersonal to community to society. Obtaining a better understanding of how these influences interact is important for mitigating nutrition-related health disparities.

Health of Women

Nutrition plays an important role in many diseases and conditions that primarily affect women or that affect women differently than men. Inherent within this Plan and its implementation are research approaches and activities that address the roles of sex and gender in health and disease; promoting participation of women in clinical nutrition research; and integrating sex as a biological variable in basic, preclinical, and translational nutrition research. Another vitally important area of emphasis is the role of nutrition in pregnancy and lactation.



This Plan is organized around a central unifying vision of Precision Nutrition research. Progress in each of the four Strategic Goals, as well as the five Cross-Cutting Research Areas, are essential to achieve this vision.

Rigor and Reproducibility

NIH is committed to ensuring the highest standards of rigor and reproducibility in all levels of nutrition science investigation. Careful consideration of study design, conduct, analysis, and communication will benefit from including nutrition scientists in these formative processes. Standardizing and harmonizing nutrition research methods, measures, and data capture and description (e.g., through common data elements) will facilitate comparison of results across research studies. These measures may explain variability between individuals or biomedical research studies.

Data Science, Systems Science, and Artificial Intelligence

As with all modern biomedicine, nutrition research will benefit from data-science methods to integrate large, diverse, and complex data from distinct fields. These approaches will help explain the complex associations between diet, nutrition, and disease. Use of artificial

intelligence and its derivatives are likely to provide exciting opportunities toward design of Precision Nutrition algorithms for individuals and populations: in particular, vulnerable groups that are disproportionately affected by the confluence of poor diet and unhealthy food environments.

Training the Nutrition Scientific Workforce

A strong and diverse nutrition workforce is critical to achieve the necessary cultural shifts facing nutrition science. The Strategic Goals described in this Plan point to the need for diverse skill sets and multidisciplinary teams to solve nutrition-related health problems through foundational research about the roles and interactions between nutrients, dietary patterns, and co-occurring diseases. We are at a pivotal time in our understanding of the role of the microbial environment in all these factors. Novel data-science and various integrated research approaches will help to untangle the roles of these many factors in nutrition and health.

STRATEGIC GOALS



Strategic Goal 1. Spur Discovery and Innovation through Foundational Research—*What do we eat and how does it affect us?*

As with all biomedical endeavors, nutrition science requires a strong foundation of basic and methodological research to unearth discoveries and unleash innovation. Moreover, integrated connections with other fields of study such as bioinformatics, neurobiology, and genomics, will undoubtedly accelerate our understanding of the microbiome and its influences on diet and overall health. These new alliances will guide development of individualized, actionable dietary recommendations: Precision Nutrition. Foundational research within this Strategic Goal will fortify cohort studies proposed in Strategic Goal 2, through leveraging existing study populations and data sets.

Objective 1-1. Address Bioinformatic Gaps in Nutrition Related Genes and Pathways

Gaps persist in our understanding of digestion, absorption, distribution, metabolism, excretion, and storage of nutrients throughout the body. Despite extensive rigorous research, we still have incomplete knowledge about the molecular processes that drive these basic body functions. Expanded bioinformatic analyses of a wide range of nutrition-related genes and pathways will help to fill these gaps. One salient example is the large gene family that encodes membrane transporters for nutrients. Proteins encoded by these genes are clinically relevant as potential drug targets and transporters. Additional research in this area will illuminate details about individual variation among ligand and solute

specificity, tissue-specific expression and subcellular localization, as well as epigenetic, transcriptional, and translational control (see text box).

Solute-Carrier Transporters. A recent NIH and FDA workshop⁷ revealed scant knowledge about the solute-carrier (SLC) group of membrane-transport proteins that traffic nutrients, metabolites, and drugs in the body. Unbiased, high-throughput bioinformatics methods are necessary to systematically characterize this large set of more than 400 genes that comprise 65 protein families. Some of these have emerged as therapeutic targets or are involved in drug and drug metabolite transport. Therefore, improved characterization of SLC genetic variation, such as allelic and copy-number differences, will be instrumental not only toward developing Precision Nutrition strategies, but for Precision Medicine as well.

Objective 1-2. Improve Understanding of Sensory Nutrition and Ingestive Behaviors

Interactions between what we eat and how we sense our world (e.g., chemosensory and taste reception) trigger both physiological and pathological responses and are thus a gateway for many chronic diet-related diseases. We still do not understand how these receptors and their associated pleasurable or aversive pathways are affected by external, internal, and circadian cues. Nor do we know how they affect food desire and food choice: this is important information for developing new approaches to tailor diet-related behaviors to individual characteristics. Research gaps in this area are diverse, from the neurophysiological level to environmental-level effects on behavior. Emerging research can take advantage of recent advances in conceptual and other behavioral frameworks. As well, genetic and molecular tools can be used in both human and animal models to study the pathways, mechanisms, and substrates responsible for nutrition-related behaviors and food choice. This research should also inform what we know about gut-brain signaling.



Objective 1-3. Investigate Diet-Host-Microbiome Interrelationships

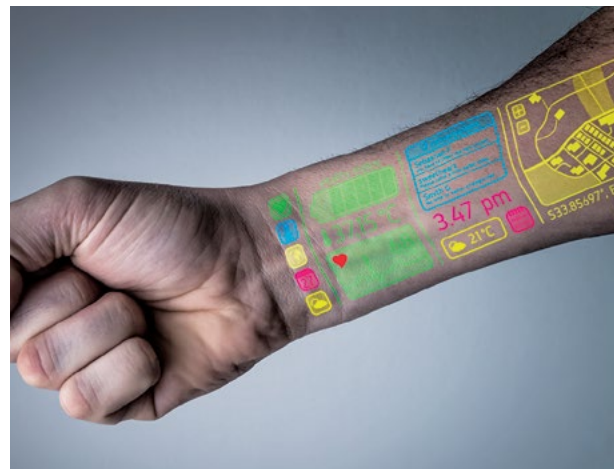
The gut microbiome, which is highly variable between individuals, has been linked to disease susceptibility, as well as to individual variability in behavioral and physiological responses to diet. More study is needed to clarify health roles of gastrointestinal microbiota, including the role of pre- and probiotics and synergistic combinations of the two (synbiotics). The human gastrointestinal microbiota not only influence what nutrients a host can extract from his or her diet, but may also affect that individual's physiology, behavior, and susceptibility to diet-related chronic diseases. Research should explore relationships between host biology and microbiome changes in response to probiotics, specific foods, or dietary pattern challenges.

Imagine a Future where we can measure and adjust fluctuations in our microbiome to tune our diet.

Objective 1-4. Identify and Determine the Effects of Unknown Metabolites Arising from Microbiome and Host Metabolism of Our Food

Advances in metabolomic technologies demonstrate that thousands of uncharacterized metabolites (often apparent on a molecular level as novel mass spectrometric signatures, or nutrition “dark matter”) appear in our bodies after eating, either directly from our food or in response to host and microbiota digestion/metabolism. Scientists want to uncover the molecular identity of these unknown metabolites and understand their function.

Nutrition Dark Matter. Recent NIH-funded mass-spectrometry technology breakthroughs have uncovered previously unrecognized biologically active metabolites that affect physiological or pathological pathways in a host or the host’s microbiome. It remains unclear where this nutrition “dark matter” comes from but knowing its source will pave a path for understanding, and manipulating, both host and microbiome biology. Research in this area conjoins methods from biochemistry and data science and is thus an exciting new frontier for health. Expanding this research area should further “de-orphan” mass spectrometric signatures toward facilitating therapeutic discovery for diseases.



Objective 1-5. Develop New Tools for Microbiome and Precision Nutrition Research

A significant challenge in nutrition research is the difficulty of establishing measurable links between the consumption of specific nutrients or food constituents and biophysiological processes. Moreover, there is substantial interindividual variability in response to dietary exposures—variability that likely stems from microbiome influences. Advancing Precision Nutrition calls for novel point-of-care tools (e.g., swallowable, micro-robotic smart pills or sensors) that can sample the microbiome across the entire gastrointestinal tract as well as continuously monitor nutrients, metabolites, and nutrition-related hormones. Research should leverage biomedical engineering approaches and collaborate with the private sector to adapt and expand current continuous glucose-monitoring technologies for point-of-care assessment of host and microbiome metabolism.

Imagine a Future where we can swallow “smart pills” in the doctor’s office instead of undergoing invasive procedures to investigate the human microbiome, GI physiology, and disease.



Objective 1-6. Develop, Refine, and Integrate Approaches to Capture Dietary Data

Understanding reasons for and effects of dietary patterns on health requires accurate dietary intake information. A significant challenge in nutrition research is the lack of accurate and user-friendly tools to capture information about a person's diet. Current approaches rely primarily on self-reporting, which has inherent limitations that have been well-characterized. New, unbiased data-capture methods are those that minimize measurement error and bias, cost, respondent burden, and subjectivity (see text box). Each should be rigorously evaluated and validated using controlled-feeding approaches.

Dietary-Intake Data Capture. There is a tremendous need to develop inexpensive and customizable dietary intake data-capture tools, including those that meet the needs of vulnerable populations, such as older adults with cognitive challenges, acutely ill patients, and people with eating disorders. Such approaches include mobile devices, as well as innovative biomarkers of dietary intake and exposure. As well, integrated strategies might employ software and statistical models to combine data from multiple, distinct methods of dietary-intake assessment; integrate datasets with nutrient-composition databases; and develop and disseminate statistical approaches to mitigate the effect of measurement error and thus improve accuracy.



Strategic Goal 2. Investigate the Role of Dietary Patterns and Behaviors for Optimal Health—*What and when should we eat?*

Landmark achievements in nutrition research, including that which led to the discovery of essential nutrients and nutritional deficiencies, focused on specific foods and nutrients. Modern nutrition research recognizes the importance of dietary patterns: What, when, why, and how we eat? Advancing knowledge in this area calls for improved tools to capture dietary components and behaviors that drive these patterns. Nutrients are not consumed in isolation and may likely have interactive and synergistic effects in context of diet. Research within this Strategic Goal aims to illuminate

how specific dietary patterns influence health outcomes in different ways among individuals, subgroups, and communities—toward determining effective strategies to create and sustain nutrition-related behaviors conducive to optimal health. One approach to achieve this goal could be to nest an innovative, multi-goal discovery science study within an NIH-funded cohort.

Objective 2-1. Advance Methods for Dietary Pattern Analysis

Achieving the goal of Precision Nutrition hinges on changing the way we think about diet, toward a holistic view that considers and analyzes dietary patterns, not individual nutrients. Dietary patterns are multidimensional, representing both individual behaviors and multi-layered exposures, and they are also dynamic in that patterns vary throughout a person's life. Patterns can be food-based (e.g., describing what foods are eaten such as the Dietary Approaches to Stop Hypertension [DASH]); time-based (e.g.,

Imagine a Future where dietary recommendations are customizable for individuals.

approaches based on meal timing, including periodic fasting or time-restricted feeding patterns that leverage circadian rhythms); and/or amount-based (e.g., a very low-calorie diet). To date, researchers have not adhered to standard dietary-pattern categories, complicating comparison of results across studies. New tools are needed to accomplish this task—both in individuals and for population-based studies—to understand what, when, and how we eat affects health and chronic diseases.

Objective 2-2. Determine the Mechanisms of Interindividual Variability in Responses to Food-based Dietary Patterns

Given the well-known causal links between diet, nutritional status, growth, development, health, and disease, individual differences in dietary intake and nutritional status likely yield substantially different health outcomes between individuals. Such variability may account for the observed lack of reproducibility between biomedical research studies assessing the role of diet in large populations of such individuals. Controlled-feeding study designs in which participants are provided all their food and beverages enables researchers to capture dietary intake in the most accurate way, because it averts potentially unverifiable (and thus, unreliable) information available through self-administration and self-report methods. Such studies could include metabolic assessments/phenotyping, mixed-meal challenge tests, continuous monitoring of metabolites and other biosamples—along with other measures to assess inter-individual variability.

Objective 2-3. Determine the Health Benefits and Mechanisms of Time-based Dietary Patterns

NIH has a long-standing research investment in circadian biology: the study of how sleep-wake cycles affect health. Beyond what we eat, *when* we eat is known to influence our health and well-being. For example, emerging evidence suggests that intermittent fasting



regimens—abstaining from food for periods of time—appears to offer health benefits based upon observed changes in metabolic or chronic disease biomarkers. In addition, routine circadian misalignment in modern society (irregular sleep-wake schedules, bright light exposure at night, eating around the clock, or shift work) are thought to contribute to health problems in different ways between individuals. Mounting evidence links poor circadian health to an array of adverse health conditions including obesity, diabetes, cardiovascular disease, cancer, and gastrointestinal disorders—and meal timing appears to have an effect independent of caloric intake. Adding complexity to this research area is that fundamental mechanisms of eating behavior, appetite/satiety, and metabolism are themselves circadian-variable, as are characteristics and activity of the gut microbiome.

Imagine a Future where individuals can get tailored information in real time about recommendations for what and when to eat to improve health.

Objective 2-4. Discover and Validate Prognostic Chronic Disease Biomarkers

For many individuals, there is a long lag time between dietary pattern exposures and the appearance of a diet-related chronic disease, making it difficult to attribute any specific condition or conditions to dietary factors. New research is needed to detect and track these links earlier than currently possible—which would enable interventions to prevent illness. Identifying and validating surrogate chronic disease biomarkers can come in a range of forms beyond markers in blood. Other means to detect imminent disease might include tissue staining or imaging, measurement of cellular or subcellular components, or physiological measures such as high blood pressure. However, it is critical that any chronic disease biomarkers reflect a biological process, and if used for clinical purposes, satisfy criteria recommended by the National Academies of Science and Engineering.⁸ Research activities could include leveraging future or existing cohort studies that collect longitudinal biosamples or other biological data.

Objective 2-5. Develop and Validate Algorithms to Predict What All of Us Should Eat

Knowing what we should eat to be healthy holds great promise for improving wellness, reducing chronic disease, and cutting health care costs. Throughout this plan, we emphasize the vast variation in diet-health relationships among individuals. Powerful new data science approaches offer an extraordinary opportunity to analyze huge data sets with artificial intelligence/machine-learning methods to pick out patterns reflective of individual variation in health outcomes related

Imagine a Future where a nutrition score or “vital sign” is part of the electronic health record to increase attention to diet-related health risks.



to dietary intake, eating behaviors, and innate physiological processes. Once these links are established and verified, these investigations can lead to predictive tools, or algorithms, useful to doctors and patients for improving health and quality of life. Precision Nutrition aspires to offer individuals tools to personalize their dietary and lifestyle practices for optimal health.

Objective 2-6. Leverage Behavioral and Implementation Science to Initiate and Sustain Healthy Eating Behaviors

Making and sustaining dietary changes is often difficult due to the influence and interactions (and even convergence) of numerous factors spanning biological, psychosocial, sociocultural, and environmental domains that create and shape an individual’s “food environment.” Thus, to be effective, nutrition interventions must target multiple levels of the food environment. Recognizing the role of this context and need to better understand how to bring Precision Nutrition interventions to scale, implementation science is an important priority in this Plan to equitably move evidence-based interventions into practice. Interdisciplinary teams can employ multiple designs and methodologies beyond randomized controlled trials of efficacy to conduct this research (e.g., sequential multiple assignment randomized trials and related hybrid study designs).



Strategic Goal 3. Define the Role of Nutrition Across the Lifespan— How does what we eat promote health across our lifespan?

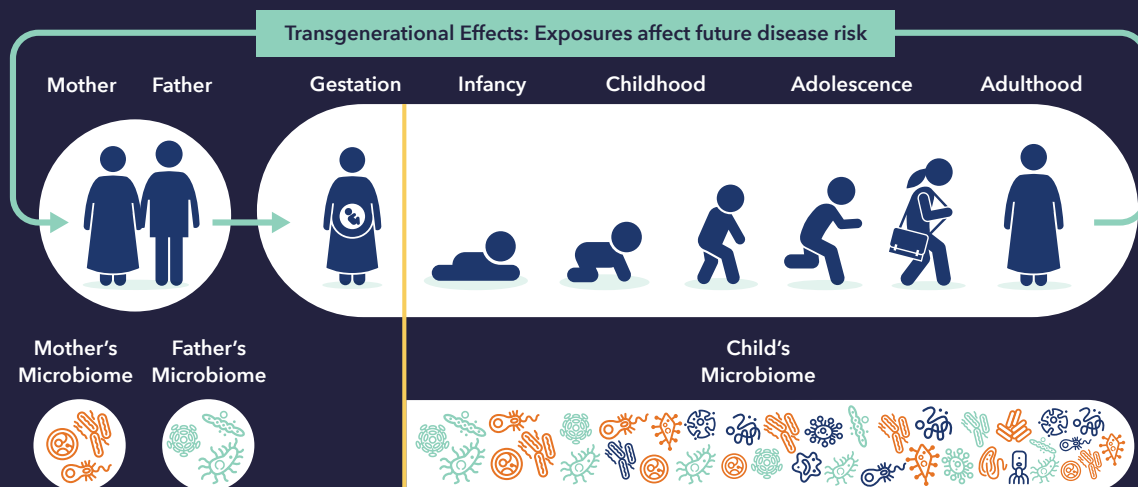
We know that what a person eats—and what they don't—affects their health not only in the near term, but also throughout life. A better understanding of how nutritional needs and eating behaviors change throughout the lifespan will help promote health and prevent disease in individuals, as well as guide strategies for parents and caregivers involved in feeding others. Although gaps in nutrition knowledge exist for all life stages and will continue to be a priority, research within this Strategic Goal will focus on three time-windows that have been especially understudied: pregnancy, infancy, toddlerhood, and older adulthood.

Imagine a Future where dietary interventions in childhood can interrupt or reverse transgenerational health problems stemming from early-life exposures.

Objective 3-1. Examine the Role of Periconceptual and Prenatal Nutrition in Development and Disease Outcomes

We know the effect of an individual's diet and food environment is profound throughout his or her life, but risk for some diet-related diseases (heart disease, obesity, diabetes, cancer, and others) become set even before birth. These exposures often occur within the first trimester of pregnancy before a woman knows she is pregnant, and they can also come from the father. This theory, known as Developmental Origins of Health and Disease (DOHaD), posits a role of epigenetic factors (i.e., "nutritional programming" or "imprinting") as well as that of macro- or micronutrient malnutrition during certain critical windows of brain development. Research is needed to better understand these processes, as well as whether and how changing dietary patterns or taking dietary supplements might modify or reverse nutritional imprinting associated with poor health later in life (see text box).

Developmental Origins of Health and Disease



Epigenetic events arising from nutrition, microbiome, and environmental exposures periconceptually through early life may have lifelong and transgenerational consequences for disease risk.

Developmental Origins of Health and Disease (DOHaD).

Nutrition science studies nested within ongoing NIH-funded cohort studies could illuminate how nutrition and feeding practices periconceptually, during pregnancy, and postnatally (especially the first 2 years of life) affect development, future diet-related disease susceptibility, and food preferences. This research could also investigate the clinical significance of microbiome differences between breastfed and formula-fed infants and assess the influence of probiotics and medications—such as antibiotics—on long-term health.

Objective 3-2. Enhance Knowledge of Human Milk Composition and the Translational Roles of its Components

Although human milk is considered the ideal food for infants—and is the food upon which infant formulas are based—we know strikingly little about how it affects immune function and healthy development in the first few years of life. Human milk contains many bioactive and nutritive substances including carbohydrates, fats, hormones, genetic material, and tiny sacs called exosomes. The composition of human milk varies dramatically between women—dependent on age, previous childbirth, genes, and diet—and changes over time (over the course of a day, week, month, or even during a single breastfeeding session). Such changes are poorly understood but may have clinical relevance for optimizing formula as well as for understanding the role of various milk nutrients in health and disease (see text box). Research is needed to understand the role of the microbiome during infancy. For example, are there microbiome differences between

breastfed and formula-fed infants? Do medications (such as antibiotics) or pre- and probiotics have any effect on child development and future health?

Human Milk Composition. The extraordinary interindividual variation in human milk composition provides a “laboratory” for Precision Nutrition research that can benefit both breastfed and formula-fed infants, since formula manufacturing is based on constituents in human milk. Building upon existing DOHaD research, we aspire to develop a reference data set to quantify the nutritional and bioactive components of human milk in a diverse population of mothers. Doing so will likely clarify interrelationships between diet, genes, environment, as well as in maternal and infant microbiomes.

Objective 3-3. Assess the Influence of Diet and Nutritional Status on Infant Developmental and Health Outcomes

The first 2 years of life are a critical period in childhood, yet it remains unclear how diet and feeding patterns affect optimal physical growth, neurological development, and health. Unanswered research questions include defining the influence of infant feeding practices, maternal diet, and other exposures on health of the body and brain, susceptibility to food allergies and intolerances, and impacts on an individual’s microbiome. Other research could investigate psychosocial influences on breastfeeding—as well as how the timing, order, type, and quantity in which foods are provided to children affects food preferences, allergies, and intolerances.

Objective 3-4. Develop Predictive Epigenetic Tools

Nutritional imprinting, or programming, is thought to occur mainly through epigenetic gene modifications. Such changes do not affect gene sequences and are typically unique to specific body tissues. Yet despite

intense research, we still don’t understand how early-life epigenetic modifications in various tissues lead to observed effects of dietary components or eating patterns on health outcomes later in life. We also don’t know how to interpret epigenetic “signatures:” when do they matter, and when are they silent? Answering these questions is critical for developing predictive tests—ideally, measured via blood samples for the effect of diet on health throughout life. Artificial intelligence methods may guide development of computational tools to predict which epigenetic changes influence gene expression, as well as which have health consequences.

Imagine a Future in which targeted dietary interventions promote healthy aging, staving off physical and cognitive decline.

Objective 3-5. Assess the Role of Nutrition in Older Adults to Promote Healthy Aging

Many aging-related factors such as cognitive decline, mental health disorders like depression, and social isolation contribute to changes in eating behaviors. Compromised nutrition can put older adults at risk for falls and injuries, reduced mobility, cognitive impairment, and even premature death. Inadequate protein intake and insufficient intake of vitamins and minerals can lead to loss of muscle mass and other physical ailments: Some individuals, such as post-menopausal (or post-hysterectomy) women may suffer ill effects from too much iron in the body. Many older adults have one or more chronic diseases or conditions and take multiple medications and dietary supplements, which can alter how the body processes food. We need more research with older adults to examine relationships and interactions between disease status, changing dietary intake, inadequate physical activity, chronic or acute inflammation, and medication use, among other factors.



Strategic Goal 4. Reduce the Burden of Disease in Clinical Settings—How can we improve the use of food as medicine?

Many Americans have medical conditions that alter their responses to diet or nutritional requirements. Disease-associated malnutrition accounts for \$15.5 billion in U.S. health care spending each year.⁹ For example, a 2016 study reported that more than one-third of admitted hospital patients were either malnourished or became malnourished during their inpatient stay.¹⁰ Research within this Strategic Goal aims to expand knowledge about the role of nutrition in disease treatment. The findings will grow evidence toward development of medical nutrition therapies and “medical foods” to improve health outcomes as well as reduce the incidence of co-occurring diseases.

Imagine a Future where management of clinical procedures is standardized through evidence-based nutrition support.

Objective 4-1. Identify Interactions Between Drugs, Disease States, and Nutrition to Improve Clinical Care and Test Strategies to Improve Clinical Outcomes

Some medical conditions or medications affect nutritional requirements or are themselves affected by diet and nutritional status. It is well known, for example, that many medicines interact with grapefruit juice to affect drug levels in the body. In some people, anatomical or biochemical problems limit chewing, swallowing, digestion, and absorption of food. We also know that a range of conditions affect either hunger or the desire to eat, and still others necessitate dietary interventions with specialized medical foods, dietary supplements, or probiotics. Dietary counseling can help modify food consumption and guide administration of these products, but more research is needed to understand the links between nutrition and diseases. We need to understand whether dietary interventions (such as medically tailored meals) or nutrient imbalances have measurable effects on long-term health outcomes.



Objective 4-2. Improve Assessment of Energy, Protein, and Micronutrient Malnutrition to Improve Clinical Outcomes

It has been reported that U.S. hospital readmissions are 54% higher for malnourished patients: the average cost of readmission per patient is approximately \$17,000.¹¹ It is expected that defining and correcting nutrient deficiencies will reduce readmission rates and associated healthcare costs—as well as decrease co-occurring diseases and improve treatment responses and recovery times. Although there is no single objective measure for assessing malnutrition, nutritional scoring systems based on a variety of measures are often used in clinical practice. Research is needed to identify and validate sensitive, specific, reliable, and cost-effective biomarkers for energy, protein, and micronutrient-related malnutrition or imbalances. Further research—for example, pragmatic trials or natural experiments—should inform standardization of malnutrition-screening practices.

Imagine a Future where physicians prescribe evidence-based “medical foods” or specific eating patterns instead of medications for certain health conditions.

Objective 4-3. Identify Clinical Criteria for Initiating and Ceasing Medical Nutrition Interventions for Patients

Many medical conditions put patients at risk for malnutrition, in part due to insufficient intake of nutrients. In such cases, to assure appropriate and adequate nutrient intake, patients often receive liquid dietary supplements (either by mouth or intravenously) or probiotics/prebiotics/synbiotics (including microbiota-directed therapeutic foods). One example might be use of a specific pre- or probiotic intervention to improve quality of care for pediatric malnutrition or infectious diarrhea. However, these interventional efforts, either in the hospital or at home, are challenging, since evidence guiding such practices is limited. Standardized and/or core measures are needed to evaluate clinical nutrition support practices as well as to determine what impact they have on health outcomes. Interindividual variation affected by age, body mass index, nutritional status, and other characteristics most certainly affects health status and thus should be considered regarding treatment decisions.



LOOKING TO THE FUTURE

The 2020–2030 NIH Strategic Plan for Nutrition Research lays out a bold vision for achieving Precision Nutrition: a framework for accelerating progress in nutrition science and for developing individualized, actionable dietary recommendations. As the NIH Nutrition Research Task Force undertakes the implementation phase of this Plan, NIH program staff will meet regularly to monitor progress and to coordinate and discuss opportunities to advance Objectives identified in each of the Strategic Goals, as well as to ensure appropriate emphasis on the Plan’s Cross-Cutting Research Areas.

We envision that investigator-initiated projects will continue to be the major driver of progress in nutrition research, as is the case for most NIH-supported biomedical research. Through periodic analyses, the Task Force will track progress relevant to the Strategic Goals and Objectives identified in this Plan. Over the next 10

years, the Task Force will continue to engage with the nutrition research community through workshops and other means to discuss this Plan’s Strategic Goals within the ever-changing scientific landscape.

By pursuing current and emerging opportunities coalescing around Precision Nutrition research, as outlined in this Plan, NIH and the broad biomedical research community can truly transform nutrition science. This exciting research agenda promises to deepen understanding of the interactions between what, when, why, and how we eat; how our body systems process our diet and influence the microbiome; as well as how food environments influence health and disease. The promise of Precision Nutrition is in view: precise, targeted approaches and interventions guiding us to a much clearer and precise answer to the question, “What should we eat?”



ENDNOTES

- 1 <https://www.cdc.gov/chronicdisease/about/costs/index.htm>.
- 2 Interagency Committee on Human Nutrition Research. *National Nutrition Research Roadmap 2016–2021: Advancing Nutrition Research to Improve and Sustain Health*. Washington, DC: Interagency Committee on Human Nutrition Research; 2016.
- 3 National Institutes of Health, Obesity Research Task Force (2011). *Strategic Plan for NIH Obesity Research*. Retrieved from <https://obesityresearch.nih.gov/about/strategic-plan.aspx>.
- 4 NIH-Wide Strategic Plan, Fiscal Years 2016–2020: Turning Discovery Into Health. <https://www.nih.gov/about-nih/nih-wide-strategic-plan>.
- 5 <https://archive.org/details/CAT87201446/page/n1/mode/2up>.
- 6 <https://archive.org/stream/principlesofnutr00atwa#page/n4/mode/2up>.
- 7 <https://www.fda.gov/drugs/pediatric-ontogeny-ready-incorporation-modeling-pediatric-drug-development>.
- 8 National Academies of Sciences, Engineering, and Medicine. 2017. Guiding principles for developing Dietary Reference Intakes based on chronic disease. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24828>.
- 9 <https://www.modernhealthcare.com/article/20160923/NEWS/160929940/malnutrition-causes-15-5-billion-in-healthcare-spending-per-year>.
- 10 <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0161833>.
- 11 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb218-Malnutrition-Readmissions-2013.pdf>.

ON-LINE APPENDIX

A link to the on-line Appendix to this report that describes the process and contributors can be found at:
<https://content.niddk.nih.gov/about-niddk/strategic-plans-reports/strategic-plan-nih-nutrition-research#publications>



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