

Director's Message

As I write this message, 2020 is drawing to a close. It has been a year like no other and a reminder of the importance of rigorous scientific investigation in ensuring and promoting human health. COVID-19 may be the first major pandemic we have seen in our lifetime, but Americans have been facing the realities of “non-communicable epidemics” for some time—opioid abuse, chronic pain, obesity, diabetes, and suicide. These persistent, and related, public health crises underline the systemic challenges that we must recognize and take on if we are to improve our society’s overall state of health. Multiple chronic conditions in individuals, such as obesity, diabetes, cardiovascular disease, and degenerative joint disease, are not only comorbid with chronic pain, depression, opioid addiction, and suicide, but also share common roots, such as poor diet, sedentary lifestyle, and chronic stress. The domino effect of chronic conditions is seen in the disproportionate toll they take on Hispanic, Black, American Indian, and other communities that are often underserved in our health care ecosystem. We have certainly witnessed the dire consequences of these effects during the COVID-19 pandemic, which illustrates how chronic underlying conditions pose immediate and long-term risks to those infected.

Now, more than ever, we need to look at the multiple factors that promote either health or disease and more scientifically consider the whole person as a complex system in which health and disease are part of a bidirectional continuum. Our current biomedical research model is superb in advancing the diagnosis and treatment of organ-specific diseases with growing precision. This knowledge is based on an increasingly sophisticated understanding of pathogenesis, or the mechanisms by which diseases occur. On the other hand, the reverse of pathogenesis, or salutogenesis—the mechanisms of moving from disease back to health—is much less studied. One reason for the lack of research on salutogenesis is that, while disease can target specific organ systems, health involves the whole person. Because biomedical science, medical specialties, and academic departments, as well as the National Institutes of Health (NIH), have been compartmentalized into either organs or diseases, our current understanding of how these various systems are integrated is lacking, which challenges our ability to maintain and to restore health. And while there have been many advances in science and medicine, they tend to remain siloed within one disease or organ system. A focus on whole person health will bring these scientific disciplines together to treat the whole person and to improve and restore health.

Meeting this challenge is right up our alley. By its nature, the mission of the National Center for Complementary and Integrative Health (NCCIH) includes both integration and health. NCCIH was created more than 20 years ago to facilitate the study and evaluation of complementary and alternative medical practices and to disseminate the resulting information to the public. Over time we incorporated a focus on integrative health research as a way to bring conventional and complementary approaches together in a safe, coordinated way with the goal of improving clinical care for patients, health promotion, and disease prevention. Now, we are expanding our definition of integrative health to include whole person health, or helping individuals improve their health in multiple interconnected domains: social, psychological, and physiological, including connections between organs and systems. This strategic plan, built on the foundation NCCIH has built for two decades, continues to advance our mission through an

effort to better define and map a path to whole person health. We will do this by expanding and building on current activities while advancing new strategies and ideas.

The objectives and strategies presented in this 5-year plan reflect our continued commitment to advancing fundamental science and methods development for both basic and clinical research. We also present strategies to advance research on whole person health and the integration of complementary and conventional care. And with the goal of improving and restoring health rather than just treating disease, we offer strategies to foster research on health promotion and restoration, resilience, disease prevention, and symptom management. As always, we remain committed to enhancing the complementary and integrative health research workforce and disseminating what we learn.

From April 2020 through July 2020, we offered stakeholders several ways to contribute their thoughts and feedback on this plan. This included responding to a request for information (RFI) (<https://grants.nih.gov/grants/guide/notice-files/NOT-AT-20-013.html>) using a web form or by email. The Center broadly disseminated information throughout the process to its many stakeholder groups and individuals. In May 2020, we hosted [Whole Person Health: Mapping a Strategic Vision for NCCIH](#) Webinar and Town Hall in conjunction with the International Congress on Integrative Medicine and Health. In July 2020, a Center-hosted [Town Hall and Public Comment Session](#) invited comments from stakeholders, experts, communities, and members of the public, including but not limited to researchers and trainees across academia, industry, and government; health care providers and health advocacy organizations; nongovernmental, scientific, and professional organizations; and Federal agencies.

The draft strategic plan was posted to the NCCIH website in early 2021, and an RFI was issued for public comment on the draft. The National Advisory Council for Complementary and Integrative Health also received updates during its public sessions in September 2019; February, June, and September 2020; and January 2021.

As Director of the Center, I am confident that our diligence in hearing from all stakeholders has resulted in a set of research priorities guided by attention to public health needs, scientific promise, amenability of topics to rigorous scientific inquiry, potential to impact health care practices, and relationship to use and practice. We know that priorities can change—2020 certainly taught us that—so we must always have our ears to the ground and our eyes on the sky. Priorities and innovation can come through investigator-initiated applications as well as from programmatically directed funding initiatives. We must always be agile and responsive to challenges and opportunities that come our way.

Much progress has been made in the research areas that form the NCCIH portfolio since our last strategic plan was released, but there is still much to do. And as we look forward to the next 5 years, we will continuously think strategically about existing programs and priorities, the growing evidence base, research capacity, scientific opportunities, and public health needs.

Mission

The mission of NCCIH is to determine, through rigorous scientific investigation, the fundamental science, usefulness, and safety of complementary and integrative health approaches and their roles in improving health and health care.

Vision

Scientific evidence informs decision making by the public, health care professionals, and health policymakers regarding the integrated use of complementary health approaches that can include a whole person health framework.

Introduction

The National Center for Complementary and Integrative Health (NCCIH) is the lead Federal agency for scientific research on the fundamental science, usefulness, and safety of complementary and integrative treatments and practices. To address the need for objective evidence on the safety and efficacy of these approaches, NCCIH supports rigorous scientific investigation to better understand how these interventions impact health, for whom, and the optimal methods of practice and delivery.

NCCIH supports research on a diverse group of health practices encompassing dietary, psychological, and physical approaches that may have originated outside of conventional medicine and includes natural products, such as dietary supplements, plant-based products, and probiotics, as well as mind and body approaches, such as yoga, massage therapy, meditation, mindfulness-based stress reduction, spinal/joint manipulation, and acupuncture. In clinical practice, these approaches are often combined into multimodal therapeutic systems, such as traditional Chinese medicine, Ayurveda, and naturopathy, that have an underlying diagnostic and theoretical framework that may be different from that of conventional medicine. These practices and systems are considered complementary because they are used in conjunction with conventional medicine. Integrative health care seeks to bring conventional and complementary approaches together in a safe, coordinated way with the goal of improving clinical care for patients, health restoration, resilience, health promotion, and disease prevention.

NCCIH, formerly known as the National Center for Complementary and Alternative Medicine (NCCAM), was created more than 20 years ago to facilitate the study and evaluation of complementary and alternative medical practices and to disseminate the resulting information to the public. At that time, the use of these practices was growing in popularity and availability, but little was known about their safety and efficacy. In addition, people rarely discussed their use of complementary approaches with their health care providers; many were unaware that certain natural products may interfere with prescribed medications; and some used these approaches as an alternative to conventional medical care. NCCIH was created to address this scientific and public health need. In addition, NCCIH has worked to advance the position that these complementary therapies should be “integrated” with and not used as an “alternative” to conventional medicine. The name of the center was changed in 2014 from NCCAM to NCCIH to reinforce this position. In the last 20 years, the Center has helped build the infrastructure needed to conduct rigorous scientific research of complementary health approaches. The Center has expanded the scientific knowledge base around these practices and established resources to

disseminate this information to the public—ultimately impacting their use. As we look to the future, NCCIH will build upon the foundation established over the last 20 years to propel the field forward.

The impact of long-term scientific investments

Scientific research is a long-term investment with the goal of improving public health and health care. Over the last 20 years, NCCIH has invested in numerous clinical trials, which were built upon countless previous scientific investigations. Here we look back at a few of these trials and evaluate the impacts of those investments.

The AREDS trials: The Age-Related Eye Disease Study (AREDS) began in 1992 before NCCIH was created. This clinical trial was sponsored by the National Eye Institute (NEI) and sought to evaluate the effects of a nutritional supplement, called the AREDS formulation, on the progression of age-related macular degeneration (AMD). AMD is one of the leading causes of visual impairment and blindness in the United States. The results from this study were published in 2001 and showed that the AREDS formulation significantly reduced the risk of advanced AMD and its associated vision loss. These results were exciting and represented the first intervention shown to reduce the risk of advanced AMD. The AREDS formulation contains high doses of vitamin C, vitamin E, beta-carotene and zinc, and while it was shown to be effective there were concerns about the high concentration of beta-carotene. Previous studies had shown that high concentrations of beta-carotene were associated with an increased risk of lung cancer in smokers. So, in 2006 a second clinical trial was launched called AREDS2 to determine if beta-carotene could be removed from the AREDS formulation and still be effective. NCCIH contributed approximately \$1.5 million to this study. The effort was led by NEI and received additional funds from other NIH Institutes. In the AREDS2 trial, the antioxidants lutein and zeaxanthin, which are in the same family of nutrients as beta-carotene were added to the AREDS1 formulation as a substitute for beta-carotene. The study found that lutein and zeaxanthin together appeared to be a safe and effective alternative to beta-carotene. The scientific investments made in the AREDS trials helped identify nutritional supplements that reduced the risk of developing advanced stages of AMD by about 25 percent and the risk of central vision loss by 19 percent in people with high risk of developing the disease. The AREDS1 and 2 formulations have undergone phase 3 clinical trials and are available over the counter in the United States.

The TACT trials: The Trial to Assess Chelation Therapy (TACT) began in 2002. This clinical trial was sponsored by NCCIH and the National Heart, Lung, and Blood Institute (NHLBI). The trial sought to determine the safety and efficacy of disodium EDTA (ethylene diamine tetra-acetic acid) chelation therapy in individuals with coronary artery disease—the leading cause of death for both men and women in the United States. Chelation is a chemical process where a substance is used to tightly bind metals or minerals. The U.S. Food and Drug Administration (FDA) has approved chelation with EDTA for the treatment of lead poisoning or exposure to other heavy metals. Before the TACT clinical trial, some physicians and alternative medicine practitioners were recommending EDTA chelation as a complementary treatment for heart disease, without evidence to support its safety or efficacy and sometimes in lieu of proven conventional therapies. The 5-year TACT study was designed to determine if this practice was safe and effective. The results of this study showed the EDTA chelation therapy resulted in a modest reduction in cardiovascular events overall. However, among participants with diabetes there was an impressive 41 percent reduction in the risk of any cardiovascular event; 52 percent reduction in recurrent heart attacks; and 43 percent reduction in death from any cause. In 2016, NCCIH, NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Environmental Health Sciences (NIEHS) supported a large followup study. The goal of this study, called TACT2, was to repeat the results of the first TACT study—but only in patients with

diabetes and a prior heart attack—to see if the apparent benefit could be replicated. It is anticipated that the TACT phase 3 clinical trial will be complete in FY2023. In total, NCCIH has invested approximately \$54.9 million in the TACT trials. This scientific investment will help the FDA determine whether disodium EDTA chelation therapy should be an approved intervention to reduce the risk of further cardiovascular events in patients with both coronary artery disease and diabetes.

The Cytisine trial: In 2015, NCCIH started a public-private partnership with Achieve Life Sciences, Inc., to advance clinical trials of cytisine, a natural product for smoking cessation. Cytisine is isolated from the plant *Laburnum anagyroides* and has been used as a smoking cessation aid, primarily in eastern European countries, for several decades. Cytisine clinical trials conducted outside of the United States showed promise in helping participants stop smoking, but those studies did not conform to U.S. FDA standards. Clinical trials needed to be conducted under Investigational New Drug (IND) guidelines before cytisine could be made available in the United States. Achieve Life Sciences, Inc., was interested in bringing cytisine to the United States, but was struggling to find private investment to support the preclinical safety and toxicology studies needed to begin U.S. clinical trials. NCCIH decided to help Achieve Life Sciences, Inc., overcome this bottleneck, supported the necessary preclinical trials, and utilized the NIH Blueprint Neurotherapeutic Network to conduct the studies. This approximate \$1.7 million investment enabled FDA acceptance of the IND application for cytisine and for Achieve Life Sciences, Inc., to begin clinical trials and raise private funds in order to conduct them. Since 2015, Achieve Life Sciences, Inc., has successfully completed a phase 2b clinical trial and plans to begin the phase 3 clinical trial in 2021 to complete its New Drug Application (NDA) to the FDA. These investments may lead to the wide availability of a new smoking cessation option to address the major public health issues associated with tobacco use.

Building a Path to Whole Person Health

Whole person health is not altogether a new goal. A whole person health perspective has been central to NCCIH’s mission dating back to its origins. The Center’s current definition of “integrative health” refers to treatment of the whole person as opposed to separate organ systems. It also aims for well-coordinated care among different providers and institutions by bringing conventional and complementary approaches together to care for the whole person. Further, one of the Center’s longstanding strategic objectives is to foster health promotion and disease prevention, central tenets of whole person health.

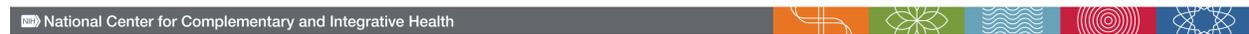
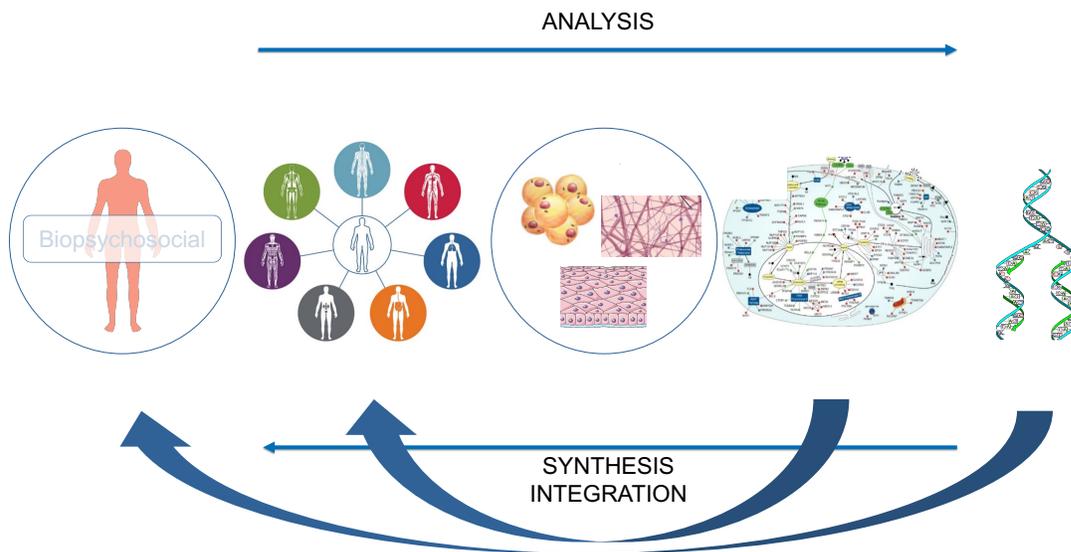
This strategic plan has been informed and shaped by an effort to better define and map a path to whole person health by expanding and building on current activities while advancing new research strategies and ideas to promote its realization. The concept of whole person health will continue to evolve, just as the concept of complementary medicine has changed over time as the line between conventional and complementary medicine is increasingly blurred.

What is Whole Person Health?

Whole person health is a concept and a vision as well as an organizing principle. There are many ways to promote and achieve it, and methods and strategies will evolve as understanding and refinement of this concept matures over time.

Any kind of knowledge base includes both analysis and synthesis: analysis breaks things down into individual components, and synthesis puts them back together to understand the whole. For more than a century, biomedicine has been strongly pulled toward analysis, from its early organization into organ systems in the late nineteenth century to cellular and molecular biology with its increasingly detailed understanding of cells, molecules, genetics, and signaling pathways. In the last few decades, systems biology, derived from ecology, has begun to influence biomedical research, with a greater awareness of how body systems relate to one another, and how networks of genes influence physiological processes. Nevertheless, our predominantly biochemical approach to treatment remains overwhelmingly pharmacologic. And because we tend to think about a specific disease or specific organ system, even when co-occurring conditions are present, we typically treat them separately, sometimes with medications that interfere with one another.

Now is the time for biomedical science to work toward restoring its balance between analysis and synthesis. We can do this by strengthening our efforts toward integration of knowledge across disciplines, focusing on the whole person, taking a transdisciplinary approach that integrates the natural, social, and health sciences and transcends traditional boundaries.



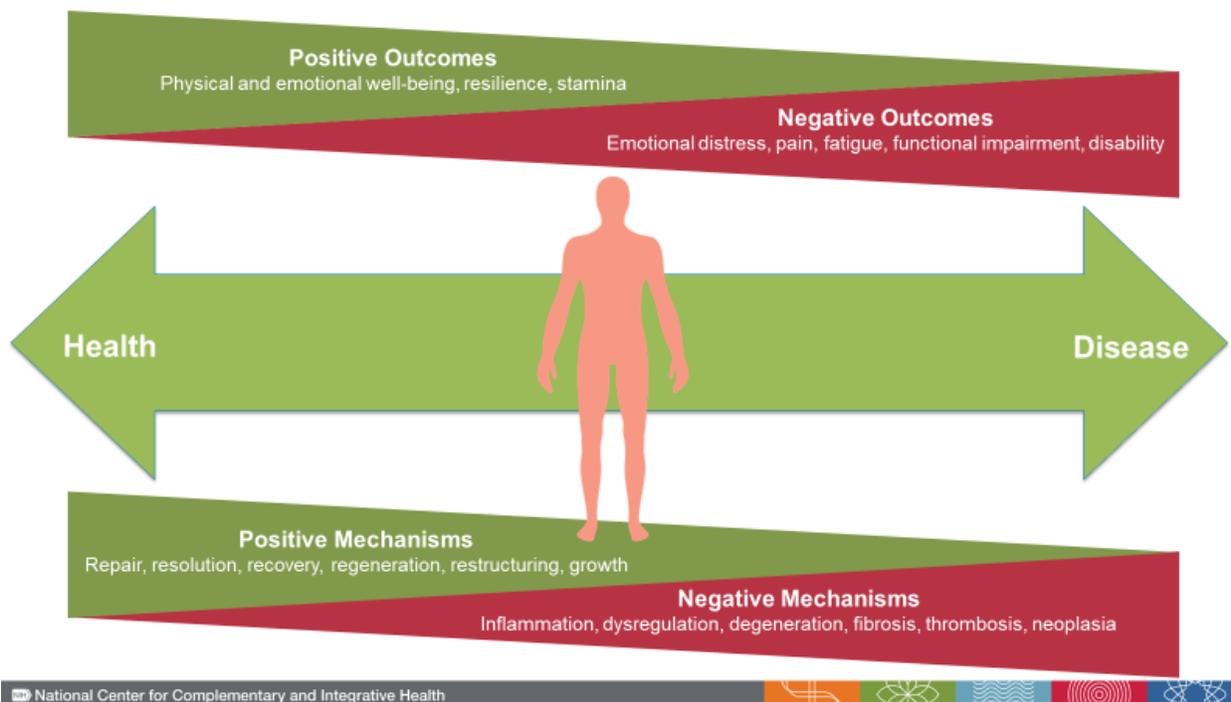
We also need to recognize that health and disease are not separate disconnected states but rather a bidirectional continuum. We know that on the path between health and disease, some unhealthy behaviors and social determinants of health—poor diet, sedentary lifestyle, chronic stress, and poor sleep—can lead to chronic diseases of multiple organ systems, such as diabetes, cardiovascular disease, degenerative joint disease, and depression. Addressing these issues at an early stage can not only prevent multiple diseases, but also restore health and stop progression to disease. We witnessed this in real time in 2020. Although COVID-19 is a respiratory infection, chronic conditions in other body systems

(e.g., diabetes, hypertension) as well as social determinants of health (health disparities, socioeconomic status, mental health, and increased substance use) are important factors in its severity and mortality.

By looking at the entire health/disease spectrum in a bidirectional way, we can expand our understanding of integrative health to include the return to an improved state of health, in addition to disease prevention. By looking at connections across social, psychological, and physical domains, we can better understand how co-occurring conditions arise from interrelated dysfunctional behaviors. As a result, we can also examine the potential role of multimodal behavioral interventions in addressing these problems and restoring health. It is possible that one intervention developed with the whole person in mind could cross several systems, restoring health in all.

Whole Person Health Research

Whole person health research aims to identify the gaps in our knowledge of the progression from health to disease and from disease back to health. It also may identify gaps in integration of multimodal care in order to develop interventions that not only prevent progression to disease, but also restore an improved state of health. The result is a whole person health approach that helps people improve their health in multiple interconnected domains. In addition, complementary health approaches such as yoga, mindfulness meditation, and tai chi impact multiple systems of the body (e.g., respiratory, neural, and musculoskeletal). This makes thinking about health in terms of the whole person important to understanding the role of complementary approaches in promoting health and preventing disease.



How to Study Whole Person Health

Strategic plans in the early history of the Center expressed an interest in exploring many paths, including research on whole health systems such as traditional Chinese medicine, Ayurveda, and naturopathy. This type of research is challenging to conduct, and there were many stumbling blocks along the way. Figuring out the right methods for studying complex interventions was perplexing. As a result, many of the studies funded in these earlier days did not bear fruit.

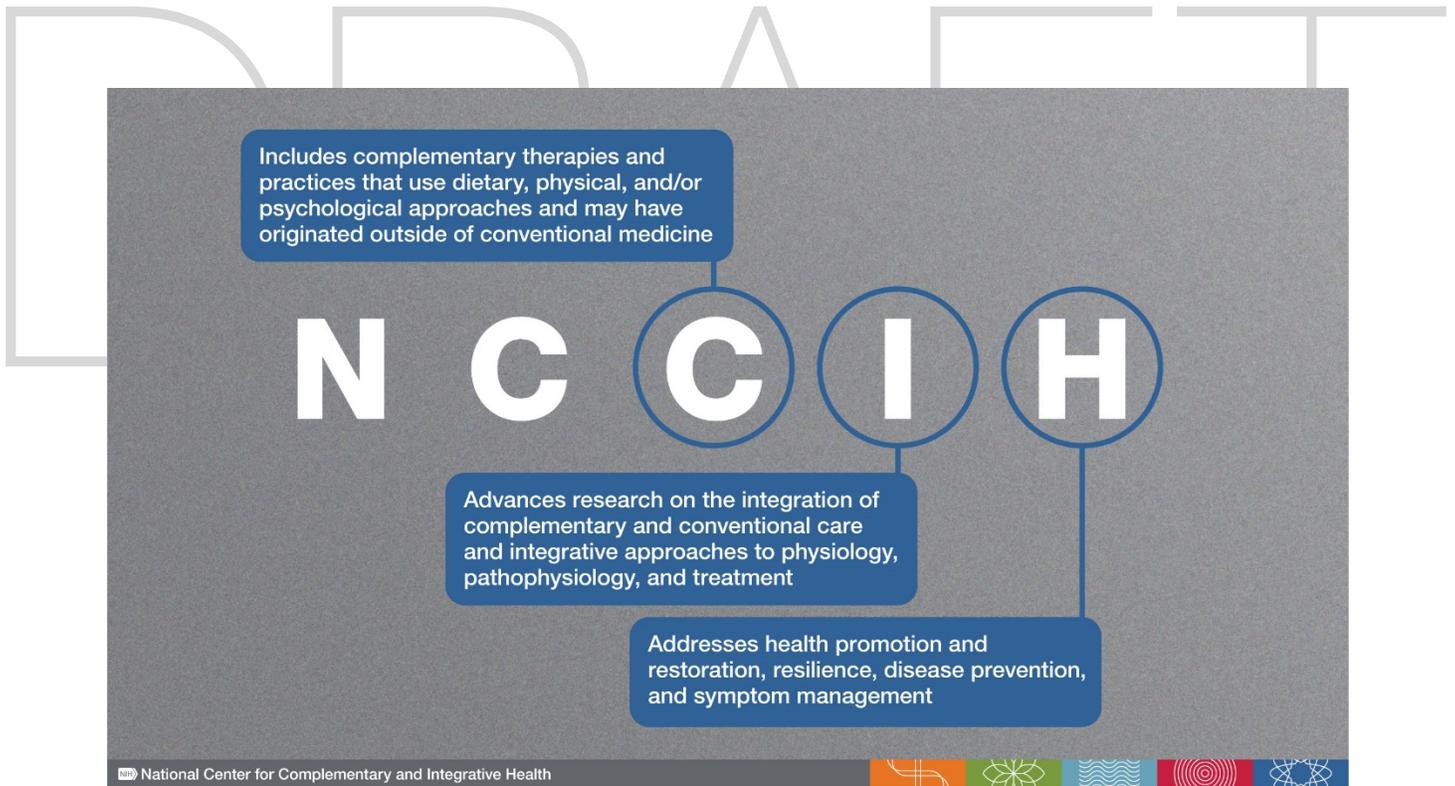
In subsequent years, there was a concerted effort to address this problem by focusing on specific strategically chosen areas, such as natural products and mind and body therapies. There was also a decision to focus on symptom management, especially pain, anxiety, and depression, which are some of the main reasons driving the use of complementary therapies. NCCIH also supported methods development, both in basic science and clinical trials. The development of methodologies for conducting rigorous pragmatic trials was particularly important and will be an invaluable study design for whole person health research.

First Steps

As part of the strategic planning process, NCCIH has been examining the meaning of the terms complementary, integrative, and health in the Center's name and has suggested more inclusive definitions to reflect a whole person approach and:

- The growing understanding of the overlap of complementary approaches with the conventional dietary, psychological, and physical domains
- The increased interest in various types of synthesis or integration such as systems biology and integrative physiology
- The recognition of common risk factors for a broad range of co-occurring conditions.

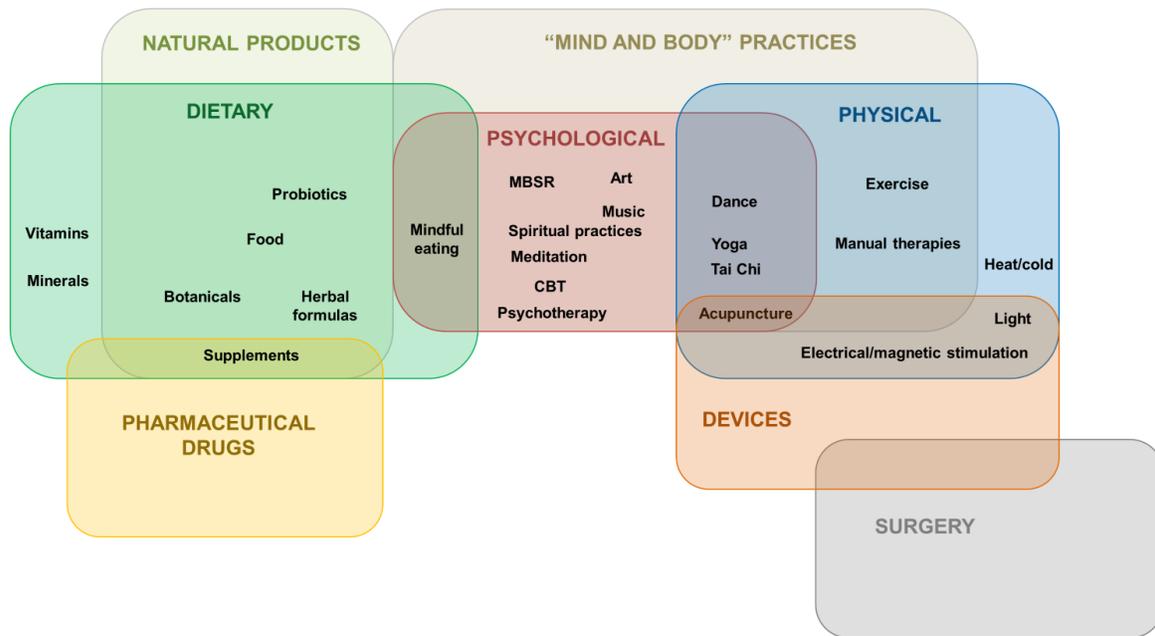
A whole person health framework also provides critical insights and opportunities to expand and build on NCCIH's current research portfolio on natural products and mind and body approaches. By deepening our scientific understanding of the connections that exist across domains of human health, we can better understand how conditions interrelate, define multimodal interventions that address these problems, and expand how we support patients through the full continuum of their health experience, including the return to health.



Reframing How We Think About Natural Products and Mind and Body Practices

Until now, NCCIH has classified its research portfolio into two areas—mind and body practices and natural products. However, the field of complementary and integrative health is expanding and the line between conventional and complementary approaches is blurring. Therefore, we propose that it is time to reframe the way we think about the research we support into new categories: dietary, psychological, and physical.

To ensure continuity, the Center is not abandoning its mind and body practices and natural products terminology or research, but is recategorizing the nonpharmacologic approaches that fall within our research mission based on their primary therapeutic input. This categorization illustrates where there are partially overlapping boundaries, including with pharmacologic drugs and devices. For example, a single natural product can be available as a food, dietary supplement, or a medication (e.g., niacin). Food, probiotics, and dietary supplements, such as fish oil, are often used as part of a healthy diet and are also frequently recommended by practitioners. Mind and body practices, such as mindfulness-based stress reduction, can overlap with more conventional practices like psychotherapy. For example, cognitive behavioral therapy increasingly incorporates relaxation, meditation, and other modalities.



National Center for Complementary and Integrative Health

Many of the mind and body therapies, such as yoga, tai chi, and acupuncture, have both physical and psychological components. There is also an overlap between the psychological and dietary domains in the form of mindful eating.

Looking at complementary therapies one by one is still important and necessary but it is also important to think about how these therapies are used in combinations as multimodal interventions.

There are both conventional and complementary examples of multimodal interventions. Conventional cardiac rehabilitation includes dietary recommendations, exercise, and a psychological component like mindfulness-based stress reduction to help reduce stress. Tai chi is also increasingly being incorporated into these programs. Although these examples illustrate a holistic approach that recognizes that interconnectedness of the psychological and physical components, the diagnostic and therapeutic framework under which these multimodal therapies are used remains that of conventional medicine. In contrast, other types of multimodal therapeutic interventions or systems bring together different therapeutic modalities using diagnostic and/or therapeutic frameworks that are different from those of

conventional medicine. For example, traditional Chinese medicine includes dietary components like herbs and physical components like tai chi, soft tissue manipulation, and acupuncture. The difference between traditional Chinese medicine and conventional cardiac rehabilitation, is the framework that ties each intervention together in a system of care that is distinct from conventional medicine. It is important to address this from a research perspective to gain more insight into whole person health.

Mission and Statutory Authority

In October 1998, Public Law 105-277, the Omnibus Consolidated and Emergency Supplemental Appropriations Act, elevated the status and expanded the mandate of the NIH Office of Alternative Medicine by authorizing the establishment of the National Center for Complementary and Alternative Medicine (NCCAM). In December 2014, Public-Law 113-235, the Consolidated and Further Continuing Appropriations Act, 2015, included a provision to change NCCAM's name to the National Center for Complementary and Integrative Health.

NCCIH Organizational Structure

NCCIH is one of 27 Institutes and Centers of NIH, the Nation's premier biomedical research agency. NIH is the steward of medical and behavioral research for the Nation. The agency is responsible to Congress and the U.S. taxpayers for carrying out its mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability, in a manner that not only facilitates research but does so cost-effectively and in compliance with applicable rules and regulations.

The NCCIH organizational structure includes an Office of the Director (OD), which provides overall leadership for and administration of the Center's components, including the Division of Extramural Research (DER), the Division of Intramural Research (DIR), and the Division of Extramural Activities (DEA).

The NCCIH OD is responsible for planning, directing, and coordinating the programs and activities of NCCIH, including research, training, education, and information dissemination efforts, and providing guidance and policy direction to the offices and divisions of the Center regarding management, program planning, program coordination, and program evaluation. The OD includes the Office of Administrative Management; the Office of Communications and Public Liaison; the Office of Policy, Planning, and Evaluation; and the Office of Clinical and Regulatory Affairs.

The NCCIH DER oversees the planning, development and implementation of scientific programs or areas of science that fulfill NCCIH's mission. DER devises scientific policies, research and training, and career development nationally through grants and contracts to research organizations. The NCCIH DER is organized into two branches based on the type of research being supported. Both the Clinical Research Branch and the Basic and Mechanistic Research Branch oversee studies of complementary health approaches, including natural products, pre/probiotics, manual therapies, meditation, and meditative movement interventions.

The NCCIH DIR, located on the NIH campus in Bethesda, Maryland, conducts basic, clinical, and translational research focusing on the role of the brain in perceiving, modifying, and managing pain. Research projects include investigating the role of the brain in pain processing and control, and how factors such as emotion, attention, environment, and genetics affect pain perception. The program includes research that explores how chronic pain produces changes in the brain that can modify how the brain reacts to pain medications like opioids.

The NCCIH DEA develops, implements, and coordinates extramural programs and policies within NCCIH, other NIH Institutes, and the extramural community. The division, through its Office of Scientific Review, coordinates the receipt, referral, and scientific review of grants, cooperative agreements, and research contracts. The division, through its Office of Grants Management, oversees the processing of grants, cooperative agreements and contracts. The division also coordinates meetings of the National Advisory Council for Complementary and Integrative Health and manages the Center's committee management activities.

Objective 1: Advance fundamental science and methods development

Fundamental scientific inquiry is essential to the progress of biomedical research because it enhances the understanding of how living systems work. This understanding serves as a foundation for translational and clinical studies that can lead to improved approaches for the management, treatment, and prevention of numerous symptoms and conditions and an ultimate restoration of health. NCCIH's basic research seeks to understand the nature and scientific principles of complementary health approaches such as their biology; physiology; and physical, chemical, and behavioral properties. This includes research on basic physiological and pathophysiological mechanisms relevant to complementary and integrative health. It also includes identifying and understanding the active components of a complementary health approach and how these components produce effects. Depending on the question, basic and mechanistic studies may be performed in the laboratory, in animals, or with human volunteers. The development of tools, models, and methodologies for performing these investigations is at the cornerstone of NCCIH's mission.

Methods development is also foundational to NCCIH's mission. From the outset, complementary and integrative research has addressed and met methodological challenges stemming from the recognition that natural products are complex mixtures, to understanding that interventions, such as yoga, involve both contemplative and movement practices. Given the complexity of approaches we study, the development of sound research design and analytic methods are vital to NCCIH's mission.

Strategies

1. *Advance basic and mechanistic research relevant to dietary, psychological, and/or physical approaches*

Dietary approaches

NCCIH has a broad interest in studying the biological activities of natural products, such as prebiotics, probiotics, supplements, botanicals, and vitamins. A strong research emphasis is placed on products for which there is compelling preclinical evidence for potential biological

activity that may lead to a health benefit or treatment intervention, and/or products that are widely used by the American public. Many of the natural products used by individuals are very complex, with multiple molecular constituents that may contribute to their effects. To fully understand the activity of complex mixtures, it is necessary to identify the individual components responsible for a specific activity and determine how those components interact with other components and biological targets. Preclinical model systems are valuable for these studies. Clinical trials of natural products are maximally informative if they incorporate well-formulated biological hypotheses, are built on a sound foundation of basic mechanistic and pharmacologic understanding, and incorporate assessment of defined signatures of biological effects. Thus, the design of maximally informative clinical efficacy trials of natural products requires mechanistic insight as a first step.

NCCIH will continue to support research on compounds isolated from natural products, as well as on the complex mixtures from which they originate. Studies may also focus on both the potential beneficial and harmful effects of natural products, including their interactions with medications. NCCIH-supported studies may also include the characterization of novel natural products or discovering the biological activity of chemical constituents in a complex mixture.

The possibility of drug interactions, direct toxicities, and contamination with active pharmaceutical agents is among the safety concerns about dietary and herbal supplements. Although there is a widespread public perception that herbs and botanical products in dietary supplements are safe, research has demonstrated that these products may carry the same dangers as other pharmacologically active compounds. Interactions may occur between prescription drugs, over-the-counter drugs, dietary supplements, and even small molecules in food—making it a daunting challenge to identify all interactions that are of clinical concern. While studies in human subjects are the only way to establish definitive evidence of a clinically relevant drug interaction, the justification for the investment in such a trial is often built on *in vitro* data.

For example, NCCIH is supporting a Center of Excellence for Natural Product Drug Interaction Research that is focused, in part, on conducting rigorous human subject studies to establish the clinical relevance of interactions for selected natural products. NCCIH also supports rigorous screening of natural product libraries in assays with clear relevance to human metabolism for evidence of pharmacokinetic interactions. The data generated will provide additional information on potential interactions and will help inform prioritization strategies regarding which natural products may warrant future investments in clinical studies.

NCCIH will also continue to support research to elucidate the effects of probiotics and prebiotics on the microbiota naturally present in the human body. NCCIH seeks to address fundamental knowledge gaps, including those pertaining to microbiota molecular mechanisms of action and potential interactions with pre- and probiotics and their impact on processes in the human body. NCCIH aligns its probiotics research programs with trans-NIH microbiome initiatives such as the Human Microbiome Project. NCCIH will continue to work closely with other NIH

Institutes, Centers, and Offices; the U.S. Food and Drug Administration; and the United States Department of Agriculture to leverage its investments in this research area.

The CARBON Program

Plants and plant-derived products are widely consumed for basic nutrition, to promote health and well-being, and for medicinal purposes, worldwide and in the United States. Despite this prevalent use, the mechanisms of action and efficacy of many of these products have not been rigorously evaluated, and, the challenges of doing research on these complex materials continue to slow progress toward understanding their contributions to public health. The Consortium for Advancing Research on Botanicals and Other Natural Products (CARBON) Program was launched in 1999 to support research into the safety, effectiveness, and mechanisms of action of botanical dietary supplements that have a high potential to benefit human health.

The CARBON program had its origins with a small number of Botanical Research Centers funded originally in 1999 in response to a Congressional mandate to the Office of Dietary Supplements (ODS) to initiate a program to support botanical research. NCCIH has been a partner on this program from the beginning. Together NCCIH and ODS funded Botanical Research Centers that were tasked with identifying and characterizing botanicals, assessing the chemical components of botanicals, exploring their mechanisms of action, conducting preclinical and clinical evaluations, and training the next generation of scientific researchers. NCCIH and ODS continue to shape the program to tackle the scientific gaps in the field while also addressing shared research priorities. In 2015, a new component was added to the program focusing on development of novel technology looking at how natural products can affect the many features of cells and specific proteins. These and other innovative approaches will break through existing bottlenecks that hampered progress in natural products research. This addition has ushered in a more collaborative environment for the program where the Centers work closely with each other on specific projects.

In the 20-year history of the program, the Centers have provided rigorous scientific data on the usefulness of a wide range of botanical products, generated research resulting in hundreds of peer-reviewed publications and trained numerous early-stage scientists. Many of the botanical supplements studied in these Centers—such as black cohosh, bitter melon, chasteberry, fenugreek, grape seed extract, hops, maca, milk thistle, licorice, and valerian—are among the top 100 supplements consumed in the United States based on sales data. The data generated from these and other studies have helped expand our knowledge of natural products. Research results from the Centers are summarized and available for the public on the NCCIH website, the ODS website, and through NCCIH's mobile app, HerbList.

Psychological and physical approaches

Among complementary physical and psychological approaches are mindfulness-based cognitive behavioral therapy, tai chi, yoga, acupuncture, massage, spinal/joint manipulation, art therapy, music therapy, dance, mindfulness-based stress reduction, and many others. These approaches are widely used by the public and may help meet the need for nonpharmacologic approaches for the management of pain and other common, troublesome symptoms that may benefit from a diversity of interventions that are safer with fewer adverse effects. They may also play a role in interventions to optimize health. However, there are gaps in the understanding of the mechanisms by which these approaches exert their effects, and this has made it difficult to

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determine whether they are well suited for specific conditions or target populations and differentiating responders from nonresponders. The complexity of many physical and psychological approaches has also been a barrier to understanding their effects. NCCIH seeks to support the investigation of the fundamental science relevant to physical and psychological approaches, including mind/brain-focused practices (e.g., meditation, hypnosis), body-based approaches (e.g., acupuncture, massage, spinal/joint manipulation/mobilization), meditative exercise (e.g., yoga, tai chi, qi gong), art and music therapies, or integrative approaches combining several components.

Mechanistic research on mind and body approaches can address three key aspects. The first is the approach itself: What components impact the biological system or subjective experience? The second is the biological system potentially targeted by the approach: What cellular systems or hormonal, genetic, or neural mediators, for example, are influenced by the intervention? The third is the mechanisms: What are the key processes (i.e., biological and/or behavioral) by which the approach exerts its effects?

2. *Develop methods, tools, and technologies to study complementary health diagnostic, treatment, and prevention modalities and systems*

NCCIH's clinical research currently supports trials of both natural products and mind and body interventions and includes early- and mid-phase testing to assess biological signatures of these interventions in humans (and replication of these effects), defining appropriate dosage, refining intervention delivery, determining optimal frequency or duration of the intervention, assessing feasibility, and enhancing adherence. The Center also supports later-stage full-scale efficacy, effectiveness, or pragmatic trials when the evidence base is enough to justify the trials.

Rigorous research on complementary health approaches requires well-established methodologies, including valid, reliable, and relevant research tools and outcome measures. NCCIH seeks to support the development of improved methodologies for complementary health research, especially those that can be used to assess symptoms, multi-system interactions, health restoration, and resilience. Studies that identify and validate objective endpoints or biomarkers predicting therapeutic response, assess and measure adherence or treatment fidelity, or will otherwise strengthen the design of clinical trials of complementary health approaches are particularly important.

NCCIH is also interested in the study of multimodal systems including those with diagnostic and therapeutic frameworks different from those of conventional medicine. Studying these systems is more difficult than studying individual treatment modalities. However, if done with appropriate scientific rigor, it could help inform or complement areas of conventional medicine, as well as the whole health systems themselves. Research on this topic might begin with studies to test the reliability and validity of complementary diagnostic systems. The development of rigorous and reproducible treatment protocols is also needed for use in clinical trials to assess their efficacy.

Catalyze advances in natural products methodology

Natural products have a long and impressive history as sources of medicine and as important resources for biological research. However, many of the techniques for studying complex mixtures of natural products have remained unchanged for many years and have yet to leverage advances in biological and chemical methodologies.

To move the field forward, NCCIH is emphasizing research to overcome methodological and technological hurdles that hinder advances in natural products research. For example, omics-based and other high-throughput technologies may help researchers evaluate the validity of hypothesized additive or synergistic effects that are at the core of many traditional herbal medicines. In addition, the use of network pharmacology—the study of the web of biologic targets for any bioactive substance—will enable researchers to investigate the complex effects of natural products on multiple targets in ways that were not possible before.

NCCIH is supporting the Natural Products Magnetic Resonance Database (NP-MRD), an electronically accessible data repository allowing key information about the world's natural products to be openly shared and rapidly queried by the global scientific community. It will be particularly important for those scientists using Nuclear Magnetic Resonance spectroscopy to study natural products to study or discover new natural products that may one day be used to improve health or cure disease. The NP-MRD will become an important hub for natural product chemists around the world, allowing them to share their data, to learn from each other, and to accelerate the translation of their discoveries to improve health.

Support development of technologies and instruments for clinical research on physical and psychological approaches

The goal of many studies of mind and body interventions is to optimize their practices and delivery to maximize efficacy. This may be accomplished through technological innovation to monitor and possibly facilitate relevant underlying processes associated with these interventions. For example, NCCIH is interested in the development and/or pilot testing of devices to provide biofeedback or optimize practice, wireless technologies for real-time data collection and monitoring of brain activity or other physiological signals, biochemical or epigenetic monitoring devices, and electrodermal monitors. It is also important to optimize and pilot test components of physical and psychological approaches for their mechanistic effects on biological processes. The development of a patient-report measure to assess aspects of the healing context such as beliefs expectations, perceptions of the patient-provider relationship, and other aspects of the overall healing environment will advance research on complementary and integrative health approaches, shed light on understudied phenomena such as placebo responses, and may ultimately contribute to improvement in research trial design. With the increase in telehealth over the past year, NCCIH is also interested in the development and optimization of technologies for home-based and remote delivery of physical and/or psychological approaches.

a. Test the reliability and validity of complementary diagnostic systems

Complementary diagnostic systems may be different than those of conventional medicine and focus more on the prevention of disease and restoration of health. While it is important to study specific therapies, it is also important to develop the techniques to study a system of care, such as traditional Chinese medicine, chiropractic, Ayurveda, or naturopathy, to determine the reliability of the diagnostic methods used in these systems of care. Research design must account for complexity if the diagnostic system will attempt to personalize results or recommend interventions based on individual characteristics and be validated with rigorous, reproducible studies. Validation of these diagnostic systems may involve the use of omics-based technologies to define the cellular, molecular, and immune changes in response to treatments. Retrospective studies may be important to determine the extent to which key principles of complementary diagnostic systems are implemented in practice.

COMPLEMENTARY
THERAPIES

Dietary, physical, or
psychological approaches

May have originated outside of
conventional medicine

MULTIMODAL
INTERVENTIONS
AND SYSTEMS

Multimodal interventions combine
multiple approaches that address
different aspects of a person

Multimodal systems may use
diagnostic and therapeutic
frameworks that are different from
those of conventional medicine

b. Define treatment algorithms for complementary interventions and systems and establish their fidelity and reproducibility

Studying complementary systems is going to require the development of reproducible intervention models, new methodologies, and outcome assessment measures for study in rigorous clinical trials. This process can also be termed “manualization,” where a treatment manual is developed through collaboration between practitioners and researchers. The manual provides guidelines for diagnosis and treatment using complementary systems. This approach allows for standardization of the system and facilitates analysis and reproducibility. Different approaches to analysis of outcomes may need to be employed in research on complementary systems. For example, the real-world perception of an individual to the benefits of treatment

may be important in this context. NCCIH is interested in pragmatic efficacy or effectiveness trials to test the effects of a manualized intervention.

c. Develop, refine, and test clinical research models and relevant statistical methods for testing multimodal interventions and systems

There is a need for research to evaluate multimodal interventions as they are used and delivered to determine whether they are safe and effective. For clinical trials to address this need they must be well designed and test hypotheses that will guide decisions about the inclusion of a multimodal approach into the delivery of health care for a specific condition. To that end, it is typically necessary to conduct a series of early-phase clinical trials to gather the multiple types of preliminary data needed to design subsequent large and rigorous efficacy or effectiveness studies. Although the scientific literature may provide the rationale for conducting an efficacy or effectiveness trial, investigators often lack critical information about key variables needed to implement such a complex intervention in a clinical trial. Some key aspects that may need further investigation to plan the future trial could include finalizing the multimodal intervention or system delivery method, the outcome(s), or recruitment strategy necessary to design an efficacy or effectiveness trial. Early phase clinical trials can fill this information gap, thereby improving study design and knowledge of whether a complex intervention can be implemented in a trial with fidelity and reproducibility; whether participants will adhere to the multimodal intervention; and the overall feasibility of the trial. Later phase trials can further explore, develop, and test adaptive interventions; optimize or tailor a multimodal intervention to have a greater impact on the potential mechanism of action; assess whether the multimodal intervention can be delivered with fidelity across sites; recruitment of sufficient participants from relevant populations across sites; or determine the optimal duration or frequency of the intervention to be used in the future multisite trial. Multimodal interventions and systems may require innovative trial designs and advanced statistical methods to explore which components are necessary and/or sufficient for a clinical effect; and to look at the impact of the multimodal intervention on multiple systems or composite outcome indices.

There are statistical challenges of studying integrated multimodal therapies and systems. Composite scales, such as the Charlson comorbidity index or measures of health-related quality of life, can be helpful in assessing treatments in longitudinal studies. Composite scales do not necessarily require larger sample sizes. Factor analysis and principal component analysis can also be used in scale development. Real-world, observational “big” data can be used for scale development, guideline development, clinical trial design, and hypothesis generation but are not suited for evaluating causal relationships. Machine learning using big data has potential for classifying and clustering patients, including identifying subpopulations of complex patients who may benefit from targeted care management strategies. The development of systems science and integrative physiology methods will also be important to further understanding of the impact of multimodal outcomes on multiple systems.

3. *Develop outcome measures to quantify health restoration and resilience*

It is difficult to quantify health restoration and resilience. Validated outcome measures are needed if research is to advance in this area. Many scales to measure resilience have been published, and it is important to further examine these and to develop new outcome measures to quantify both physical and psychological resilience. The development of outcome measures for health restoration must consider what is important to each person in terms of restoring their own health. Also important is the development of technology and outcome measures for mechanistic studies (e.g., data from wearables could be used to determine the relationship to subjective self-report measures).

4. *Develop methods to conduct implementation science and effectiveness research on complementary and integrative health approaches*

Published results of efficacy and effectiveness studies on complementary health approaches should lead to widespread uptake of evidence-based practices, but too often, the scientific pathway ends prematurely, before the best ways to improve adoption, implementation, and sustainability can be determined. NCCIH supports the full continuum of the research pipeline, whereby a complementary health intervention moves from basic and mechanistic research, through efficacy trials, and through dissemination and implementation. Whereas efficacy and effectiveness research are designed to answer the question, “which intervention(s) should we use?” dissemination research asks, “are the relevant clinicians and target population aware of the novel evidence-based intervention(s)?” Implementation science focuses on “how can these novel evidence-based intervention(s) be more widely and rapidly used in practice?” It should be noted that for complementary and integrative health, the novel evidence-based intervention may be an existing intervention used in a novel setting (e.g., use of acupuncture in a hospital emergency department). The goal is to decrease the time between establishing the evidence base of interventions and the widespread uptake and adoption of these interventions. The development of methods to conduct implementation science and effectiveness research on complementary and integrative health approaches is a high priority for NCCIH.

Objective 2: Advance research on whole person health and on the integration of complementary and conventional care

Central to the definition of whole person health research are studies of integrated multimodal therapies and interconnected systems. These address multiple aspects of a person and may involve diagnostic and therapeutic frameworks different from those of conventional medicine. Whole person health research includes three components: exploring the fundamental science of interconnected systems, investigating multicomponent interventions or therapeutic systems, and examining the impact of these interventions on multisystem or multiorgan outcomes.

The current NCCIH portfolio includes research on natural products as well as mind and body approaches (both psychological and physical). Currently, much of the mind and body portfolio studies single systems (e.g., nervous system) while the natural products portfolio focuses more on multisystem outcomes (e.g., digestive, metabolic, immune).

With this objective, NCCIH plans to support the development of methodologies to better understand how to study interconnected systems, how to investigate multicomponent interventions or therapeutic systems and their integration, and how to examine the impact of these interventions on multisystem or multiorgan outcomes.

Strategies

1. *Promote basic and translational research to study how physiological systems interact with each other*

Over the years much of the NCCIH research portfolio has evolved to become somewhat homogeneous—for example, research on meditation, mindfulness, and yoga, all of which remain important. However, exciting opportunities are emerging to carefully explore new paths toward whole person health research. This will require both fundamental science and methods development using a range of approaches to address multiple aspects of a person or animal model. Mechanistic research may, as appropriate, study the impact of single or multimodal interventions (independent variables) on single or multisystem outcomes (dependent variables). Rigorous methods (e.g., factorial designs, principal component analyses) will be needed to support these variably complex study designs. The use of artificial intelligence to analyze multidimensional datasets offers exciting new opportunities that can be applied to whole person health research, including identifying temporal changes in multisystem physiological patterns and defining the phenotypes of individuals more or less likely to respond to a treatment.

A comprehensive program in whole person research can collectively support a balance of analytical and synthetic approaches to elucidate individual mechanisms and understand how these mechanisms interact.

2. *Conduct clinical and translational research on multicomponent interventions, and study the impact of these interventions on multiple physiological systems (e.g., nervous system, gastrointestinal, immune) and domains (e.g., biological, psychological, social)*

NCCIH hopes to expand research on integrated multimodal therapies. One challenge in clinical research on complex interventions is that researchers may want to tailor the interventions to specific populations, study individual components, or change the intervention to make it more convenient, but these modifications may make replication difficult and reduce the effect size of the intervention. It is important to have a reproducible intervention or algorithm of care that can be consistently delivered by different clinicians at different sites in order to conduct multisite trials to assess efficacy or effectiveness of the multicomponent intervention. Another challenge is how to power a study for multiple primary outcomes. NCCIH is also interested in the development of innovative strategies to evaluate multiple outcomes in a single trial.

3. *Foster multimodal intervention research that focuses on improving health outcomes*

NCCIH-supported research has demonstrated that mind and body therapies are effective at improving symptoms in conditions such as pain and anxiety. While these therapies have shown promise, the efficacy of any single modality treatment is typically modest, and finding a way to

enhance the effect size of clinical outcomes is a crucially important goal. Multimodal strategies may enhance the benefit to individuals by simultaneously targeting multiple pathways and may be more effective than a treatment used in isolation. It is also important to study multimodal interventions that combine conventional and integrative approaches.

There also is a fundamental lack of translational research on the mechanisms of resilience and health restoration in humans. In particular, the mechanisms of physical, psychological, and dietary interventions in restoring health after an acute illness or recovery from a chronic condition is an understudied area, which needs a multisystem approach to identify mechanisms and predictive biomarkers that could be used to optimize and predict the beneficial effects of the interventions. NCCIH seeks to support research that could expand the mechanistic and evidence base on complementary health approaches for preventing mental, emotional, and behavioral disorders, and for the promotion of psychological and physical health, resilience, and health restoration.

4. *Conduct studies in real world settings, where interventions are routinely delivered to test the integration of complementary approaches into health care*

NCCIH is particularly interested in studies on the efficacy and effectiveness of complementary and integrative health approaches aimed at managing pain, anxiety, and depression. The Center has invested in pragmatic research to study pain management.

Many research organizations, including NIH, support learning health care systems in which research is embedded into the delivery of care. In this type of system, data are collected every time a patient receives care, and over time, the system “learns” whether and how well the care worked. Whenever something is learned with this approach, it can be quickly applied and adopted.

Embedded pragmatic trials within a health care system are often challenging. Research and patient care have long been conceptualized as separate activities that take place in different locations under different types of oversight, and the types of recordkeeping used in clinical care, including electronic health records, may not always meet research needs. However, these challenges are beginning to be overcome, and innovative approaches continue to be developed allowing for informative research to be conducted in the actual settings where integrative health care is practiced. These approaches include pragmatic trials that employ rigorous experimental designs.

Given the widespread use of complementary health approaches, opportunities exist to employ clinical outcomes and effectiveness research methodologies to collect real world evidence about the use of specific complementary approaches for health care, health promotion, resilience, and health restoration. Pursuing this type of research requires creative collaboration with those who provide care in settings where integration of complementary health approaches could be studied. The real world settings for such research could be quite varied, and may include schools, nursing homes, hospices, safety net clinics, federally qualified health care centers,

cancer treatment facilities, and settings that provide care for military personnel and veterans. NCCIH is continuing to build on initiatives such as the NIH Health Care Systems Research Collaboratory and the NIH-VA-DoD Pain Management Collaboratory.

Pain Research Supported by NCCIH through Pragmatic Trials

Pain is the most common medical condition requiring treatment for military personnel. Studies report nearly 45 percent of soldiers and 50 percent of veterans experience pain on a regular basis, and there is significant overlap among chronic pain, post-traumatic stress disorder (PTSD), and persistent post-concussive symptoms. Data from the 2010–2014 National Health Interview Survey show that American veterans experience a higher prevalence of pain and more severe pain than nonveterans.¹ Although opioids are often prescribed to treat chronic pain, there is no evidence to suggest that they are effective, and they are often associated with severe adverse effects and may lead to drug addiction, overdose, and death. Therefore, there is a need for nondrug approaches to complement current strategies for pain management and to reduce the need for, and hazards of, excessive reliance on opioids.

In 2017, NCCIH partnered with the Department of Defense (DoD), the Department of Veterans Affairs (VA) and seven other Institutes and Centers at the NIH to launch the NIH-DoD-VA Pain Management Collaboratory (PMC) (<https://painmanagementcollaboratory.org/>). The PMC seeks to support the development, implementation, and testing of cost-effective, large-scale, real-world research on nonpharmacologic approaches for pain management and related conditions in military and veteran health care delivery organizations. The PMC is currently supporting 11 pragmatic, large-scale clinic trials within military and veteran health care delivery organizations. Of these trials, NIH is supporting six, the DoD is supporting four, and the VA is supporting one. Examples of interventions being investigated for their effectiveness in pain management include cognitive behavioral therapy delivered by phone, stepped-care management, behavioral health consultation in primary care, manual therapy such as chiropractic care, and percutaneous peripheral nerve stimulation. NIH is also supporting a coordinating center that provides technical, design, and other support to the research teams during this demonstration phase and will disseminate collaboratory-endorsed policies, best practices, and lessons learned from the demonstration projects.

All of the studies supported by the PMC will not only assess if specific nonpharmacologic approaches are effective for pain management, but also how they can be integrated into a health care system. For example, researchers at Yale University are investigating the effect of early resource education on pain management. The investigators in this study are enrolling veterans when they are seeking disability for a pain condition and educating them on the different types of pain medications. In addition, they inform the veterans of the importance of treating both physical and psychological aspects of pain and connect the veterans with the services available to them. Researchers also assess the risk for substance use disorders and depression and refer the veterans to the appropriate treatment. If this intervention is successful, it can be quickly scaled up and made available nationwide to veterans seeking disability. This early education and referral paradigm could also be adapted to other health care systems.

NCCIH is also leading the NIH HEAL (Helping to End Addiction Long-TermSM) Initiative's [Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing](#) (PRISM) program,

¹ Severe pain in veterans: the impact of age and sex, and comparisons to the general population. *J Pain*, 2017.

which seeks to take interventions and treatment guidelines that have already been shown to work for specific pain conditions and integrate them into health care delivery systems. Recent decades have seen an overreliance on the prescription of opioids for chronic pain, which has contributed to an epidemic of opioid overdose deaths and addiction. Research has shown that nonopioid pain management interventions can be effective for treating acute and chronic pain. More support is needed to assess the impact of evidence-based health care strategies and clinical practices and procedures when they are included in health care systems. Pragmatic and implementation trials could identify strategies to most effectively implement evidence-based interventions and pain management guidelines.

As part of the NIH HEAL InitiativeSM, NCCIH is also leading the Behavioral Research to Improve Medication-Based Treatment (BRIM) program, which supports research that assesses whether behavioral interventions can improve outcomes of medication-based treatment. Specifically, the BRIM program seeks to test the effectiveness of combining medications with a wide range of evidence-based behavioral interventions in diverse groups of patients, including veterans, young adults, low-income individuals, and Latina and Native American women. The behavioral interventions include yoga and mindfulness, cognitive behavioral therapy, multidisciplinary rehabilitation, and mobile health technology. This study will determine whether using these interventions in combination with medication improves adherence to medication, improves treatment outcomes, and reduces relapse in individuals seeking treatment for opioid use disorder.

Objective 3: Foster research on health promotion and restoration, resilience, disease prevention, and symptom management.

NCCIH's research investments in understanding the role of complementary and integrative health approaches in health promotion and restoration, resilience, disease prevention, and symptom management are, in part, informed by data on the complementary products and practices that people use. These data include what groups of people use them, why they use them, how their use has changed over time, and how their use relates to health outcomes.

Survey data have revealed that people who use complementary and integrative approaches for wellness differ in significant ways from those who use them to treat an illness. For example, an analysis of National Health Interview Survey data showed that wellness-oriented users of complementary approaches were generally healthier, had a lower rate of conventional health services use, and had healthier behaviors overall, including greater physical activity and a lower likelihood of obesity, than those who used complementary approaches to treat illness.

Surveys are only a first step in gaining knowledge about health-related behavior. More focused research is needed to understand why people make healthy, unhealthy, or risky choices; find out what choices people are making on a day-to-day basis; and elucidate the impact these choices may have on short- and long-term health. Ever-changing technologies, such as wearables, have improved the ways in which data can be obtained to measure a variety of behaviors. Current studies can also harness state-of-the-art technologies and approaches from the neurobiological, biomechanical, and biological sciences to elucidate biological effects and identify mechanisms of action of behaviors and interventions of interest. Researchers may also leverage existing databases to provide real world insights into health and health care.

Managing symptoms—particularly recurring or chronic symptoms such as back, neck, or joint pain, anxiety, headache, and insomnia—is challenging. Symptoms may change over time, and patients may experience multiple symptoms in clusters (e.g., pain, sleep difficulties, and mood changes) rather than a single symptom in isolation. Current approaches to symptom management often have limitations. Despite medical treatment, some patients continue to experience troublesome levels of symptoms and a diminished quality of life. Moreover, medications used to treat symptoms may have significant risks and side effects.

Expanding the knowledge base about how complementary health approaches may improve symptom management in both the short and long term is a priority for NCCIH. There is a growing body of basic and clinical research on complementary health approaches for symptom management that employs the methods, tools, and technology of neuroscience, psychoneuroimmunology, psychology, behavioral medicine, physical medicine, and biomechanics. For example, research studies have revealed that interventions such as meditation and acupuncture affect central mechanisms of pain perception and processing, regulation of emotion and attention, and placebo responses. Although not yet fully understood, these effects point toward scientifically plausible mechanisms—often unrelated to traditional explanations or hypotheses concerning their mechanisms of action—by which these interventions might be effective.

Emotional Well-Being

In April 2018, NCCIH and the Office of Behavioral and Social Sciences Research (OBSSR), in collaboration with other NIH Institutes, Centers, and Offices (National Institute on Aging, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute on Drug Abuse, National Institute of Mental Health), sponsored a roundtable discussion with the following goals: (1) to gain a deeper insight into the existing research on the role of emotional well-being in health; (2) to advance research in this area and create a trans-NIH research program focused on developing, testing, and implementing intervention strategies to promote emotional well-being. [View the roundtable meeting report—[Emotional Well-Being: Emerging Insights and Questions for Future Research](#).]

The roundtable participants presented and discussed 10 models of success that produced better health outcomes through promotion of emotional resilience. They included cases in which a component of emotional well-being is identified as the intervention target, or a change in emotional well-being is found to be a mediator of a change in health. They also included interventions in which improvement of some aspect of emotional well-being itself was the desired outcome. Some examples of models of success include Cultivating Awareness and Resilience in Education (CARE) for teachers, active experiencing training for episodic memory recall, the Strong African American Families program (SAAF), and the Health Enhancement Program (HEP).

Through workshop presentations and discussion, research gaps and opportunities were noted that included a need to (1) increase the understanding of the fundamental constituents of well-being across the lifespan and among various subgroups, (2) refine and implement scientifically based prevention strategies to enhance emotional well-being, and (3) develop measurement methodologies to optimize and scale up well-being interventions for treatment and prevention of burnout, stress, pain, and mental health symptoms in at-risk populations (e.g., caregivers, military personnel, minority groups, individuals with substance abuse), as well as children and adolescents.

NCCIH is supporting the development of transdisciplinary research networks designed to advance research on emotional well-being in the social, behavioral, psychological, biological, and neurobiological sciences.

Strategies

1. *Advance the understanding of mechanisms through which complementary and integrative health approaches affect health restoration, resilience, and well-being*

Because our health care system is generally oriented toward disease rather than toward health, mechanistic research tends to focus on mechanisms of disease and disease prevention, rather than health restoration. As part of NCCIH's goal to address the bidirectional health-disease continuum, NCCIH seeks to support basic and mechanistic research on salutogenesis—restoration of health, either after an acute illness, or over the course of a chronic or relapsing condition. This particularly applies to predisease states (e.g., prediabetes, prehypertension) when functional or biochemical abnormalities are manifest but still reversible.

The concept of resilience—the capacity to resist, adapt, recover, or grow from a challenge—is also important to health and prevention research. The study of resilience can help scientists learn why some people are better able than others to resist disease risks posed by stressful or adverse experiences, and it may lead to the development of approaches that will help individuals adapt in a more positive manner to negative life events.

Emotional well-being has been defined as an overall positive state of one's emotions, life satisfaction, sense of meaning and purpose, and ability to pursue self-defined goals. Elements of emotional well-being include a sense of balance in emotion, thoughts, social relationships, and pursuits. The relative importance of each construct will vary across subpopulations and developmental stages. Individuals who report a greater sense of well-being may be more likely to engage in behaviors that lead to improved health and resiliency. Currently, fundamental understanding of the components of emotional well-being as well as the interventions that promote well-being, as a mediator or as an end, is lacking.

A state of physical well-being is not just the absence of disease. It includes lifestyle behavior choices to ensure health, avoid preventable diseases and conditions, and live in a balanced state of body, mind, and spirit.

NCCIH has identified a need to increase the understanding of the fundamental constituents of both physical and emotional well-being across the lifespan and among various subgroups, refine and implement scientifically based prevention strategies to enhance well-being, and develop measurement methodologies to optimize and scale up well-being interventions for treatment and prevention of burnout, stress, pain, sleep disturbance and mental health symptoms in at-risk populations (e.g., caregivers, military personnel, racial and ethnic minorities, individuals with substance abuse), as well as children and adolescents. The Center seeks to support research on complementary health approaches and how they can affect resilience and well-being across the continuum from basic and mechanistic studies. These efforts will build upon

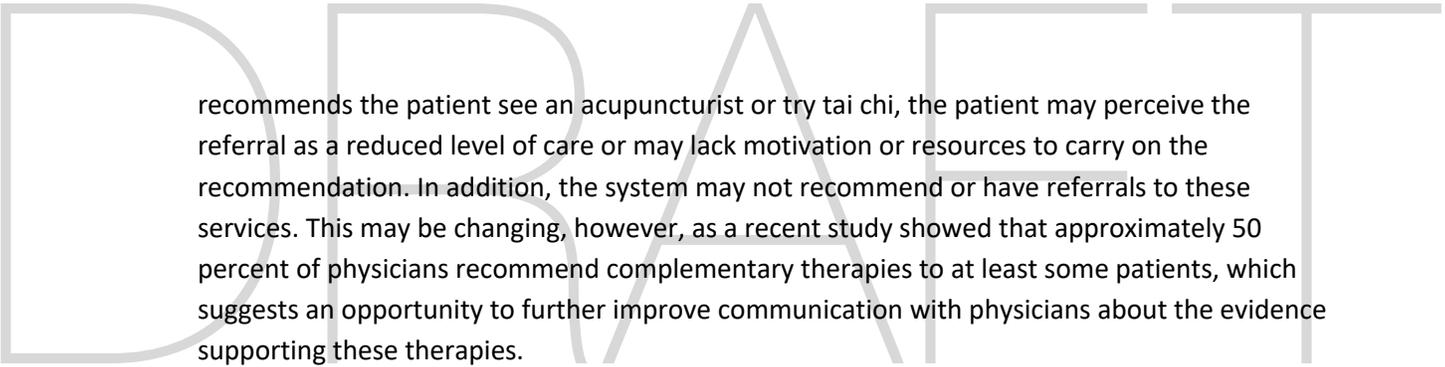
extant data involving mind and body practices such as mindfulness-based stress reduction or meditation. Future studies will help determine the value of complementary health approaches in enhancing cognitive, emotional, behavioral, and physical resilience and well-being in people who are subjected to stressful or adverse circumstances. NCCIH is also interested in the mechanisms of how natural products may work to increase resilience to psychological and environmental stressors, such as sleep disruption, pain, unhealthy diet, exposure to pathogens, or inflammation. There also is a need to understand mechanisms by which managing psychological stress and improving sleep may counteract pathological processes such as inflammation and restore healthier immune, endocrine, and metabolic responses. Similarly, the potential role of the microbiome in the development and maintenance of resilience is of interest to NCCIH.

2. *Investigate the safety and efficacy of complementary health approaches and integrative treatment strategies for health promotion and restoration, resilience, disease prevention, and symptom management in diverse populations and settings*

NCCIH seeks to foster research to develop, test, and refine interventions and to adapt interventions to meet the needs of different populations, including those most vulnerable (e.g., disadvantaged children and youth—resulting from poverty or other adversities, rural populations, individuals with low socioeconomic status, and racial and ethnic minorities). The Center plans to foster research that examines the potential contributions of complementary approaches and integrative treatment strategies in promoting health behaviors, preventing disease, and restoring health across the lifespan. The use of complementary health approaches in the United States is mostly aimed at improving general health and well-being, but much of the research to date has focused on the application of these approaches to specific conditions or symptoms. Although scientific and operational challenges are significant, compelling opportunities exist to explore the potential role of complementary health approaches and integrative treatment strategies for health promotion and restoration, resilience, and disease prevention, as well as symptom management.

3. *Conduct rigorous clinical studies on the effectiveness, dissemination, and implementation of complementary health approaches into health care*

It is important that the lessons learned from NCCIH-supported research are relevant to inform and improve the quality of health, delivery of services, and utilization and sustainability of evidence-based tools and approaches. Research publications often do not lead to widespread uptake of evidence-based practices. There is a gap in the research pipeline to determine the best ways to improve adoption and implementation of evidence-based approaches. Implementing complementary health treatments and practices into the conventional health care system is not without barriers. One such barrier is that some empirically supported complementary health interventions may not be reimbursed by insurance. Patient characteristics and expectations, and the health care system itself, are barriers that may have an impact on implementation. When patients visit a physician, they may expect to receive a prescription or undergo medical tests or procedures. However, if the physician instead



recommends the patient see an acupuncturist or try tai chi, the patient may perceive the referral as a reduced level of care or may lack motivation or resources to carry on the recommendation. In addition, the system may not recommend or have referrals to these services. This may be changing, however, as a recent study showed that approximately 50 percent of physicians recommend complementary therapies to at least some patients, which suggests an opportunity to further improve communication with physicians about the evidence supporting these therapies.

Moreover, underserved and under-researched populations have special considerations in implementation science approaches. Members of these populations are most likely to respond to advice from someone who looks like them, speaks their language, and meets them at their level. Barriers that can affect all populations, such as copays, transportation issues, and getting time off work for appointments and treatments, may be magnified in low-income communities.

Implementation research methods often combine the study of effectiveness and implementation in hybrid designs. In addition, pragmatic trials designed to evaluate the effectiveness of interventions in real-life routine practice conditions can produce results that can be generalized and applied in routine practice settings. In the context of increased interest and investment in intervention trials that will help to determine the optimal interventions to be used in clinical and community settings, it is essential that practitioners (e.g., health care providers, public health practitioners), consumers, families, caregivers, community (e.g., workplace, school, place of worship) health care practice settings, and policymakers are equipped with empirically supported strategies to integrate scientific knowledge about complementary and integrative health approaches and effective health interventions into everyday use.

Dissemination and implementation science research intends to bridge the gap between research, practice, and policy by building a knowledge base about how health information, effective interventions, and new clinical practices, guidelines, and policies are communicated and integrated for public health and health care service use in specific settings. Studies of dissemination or implementation strategies of complementary and integrative health interventions with proven efficacy should build knowledge both on the overall effectiveness of the dissemination and implementation strategies, as well as how and why they work. Data on mechanisms of action, moderators, and mediators of dissemination and implementation strategies will greatly aid decision making on which strategies work for which interventions, in which settings, and for what populations.

Objective 4: Enhance the complementary and integrative health research workforce

Researchers from many different biomedical and behavioral disciplines are key to further advancing basic, mechanistic, translational, and clinical research in complementary approaches and their integration into health care. Over the years, NCCIH has also targeted resources to attract well-trained and experienced scientists and clinicians into complementary and integrative health research supporting

their development as scientific leaders in the field. NCCIH will continue to promote strategies to enhance diversity of the workforce, enhance the clinician scientist pathway at both the individual and institutional level, and enhance the transition of Research Career Development (K) Awardees to an independent research career.

NCCIH supports research training and career development programs to increase the number and diversity of well-trained scientists to conduct rigorous complementary and integrative health research. We have special opportunities for individuals from groups who are underrepresented in scientific research (e.g., racial and ethnic minority populations) throughout the continuum from high school to faculty. In addition, we support workshops at NIH and at scientific conferences to help students and fellows connect to NIH funding opportunities, understand how to interact with NIH staff to develop research proposals, navigate the NIH peer-review process successfully, develop resilience to overcome career roadblocks, and develop plans for a successful research career. We attend a wide variety of scientific conferences that includes targeted outreach to minority-oriented societies.

Strategies

1. *Support research training and career development opportunities to increase the diversity and number of well-trained scientists conducting rigorous, cutting edge research on complementary and integrative health practices*

NCCIH supports a range of research training and career development programs aimed at increasing the number, quality, and diversity of well-prepared, skilled investigators with knowledge and expertise in both complementary and integrative health and state-of-the-art research methods. Because complementary and integrative health approaches include a wide variety of modalities, NCCIH's training strategies must include innovative approaches that incorporate an understanding of this diversity to ensure that future research workforce needs for the various modalities as well as combinations of these modalities are met.

In particular, the Center will focus on:

- Individuals from groups who are underrepresented in biomedical, clinical, or behavioral and social science research (e.g., racial and ethnic minority populations or other populations described in the [Notice of NIH's Interest in Diversity](#)) and are interested in careers in complementary and integrative health research.
- Clinician-scientists, including conventionally trained physicians, complementary health practitioners, and other professionals (e.g., clinical psychologists, nurses, physical therapists, occupational therapists, art and/or music therapists) who conduct research across a wide range of complementary and integrative health approaches.
- Scientists trained in key biomedical and behavioral research disciplines necessary for rigorous, state-of-the-art scientific investigation of complementary and integrative health approaches, practices, and disciplines.

2. *Foster interdisciplinary collaborations and partnerships at individual and institutional levels*

As science has advanced, the research enterprise has become increasingly interdisciplinary, requiring teams of investigators with different areas of expertise. Clinician-scientists with both clinical and research expertise play an important role in advancing translational science and provide unique perspectives to biomedical research informed by patient care. However, the path toward becoming a clinician-scientist is not easy and may be particularly challenging for complementary and integrative health clinicians because of diverse credentialing standards and varying opportunities to engage in research prior to/during clinical training.

At the individual level, NCCIH supports multiple interdisciplinary opportunities that support training of clinician-scientists. For example, NCCIH has partnered with the National Center for Advancing Translational Sciences (NCATS) to provide a research career development pathway for complementary and integrative health clinician-scientists to join career development cohorts of other types of clinician-scientists and will continue to support this.

To promote interdisciplinary collaborations at the institutional level, NCCIH is exploring models to support partnerships across different complementary and integrative institutions, disciplines, and systems with research-intensive institutions. For example, we are discussing the creation of a virtual resource center (university without walls) to provide research support (e.g., networking, mentoring, conceptual grant development, central Institutional Review Board, statistical and research design) to investigators based at complementary and integrative health institutions, such as schools of acupuncture, chiropractic, osteopathy, naturopathy, physical therapy, and music and art therapy.

In addition to focusing on interdisciplinary collaborations to promote the clinician-scientist pathway, NCCIH encourages interdisciplinary training opportunities within our funded training and career development awards. We support cross-training opportunities at the mid-career level as well to promote the development of interdisciplinary research teams. NCCIH will also foster interdisciplinary research collaborations between research-intensive institutions and institutions that have a historical mission or a demonstrated commitment to educating students from groups underrepresented in the biomedical research workforce.

3. *Identify best practices to continually improve the quality of NCCIH workforce development activities*

Evidence-based approaches should be used by programs to monitor and improve the recruitment and training of complementary and integrative health scientists at all levels. NCCIH encourages funded research training and education programs to develop and evaluate their practices. To ensure maximum return on its research training investment, the Center encourages programs to disseminate training practices that have proven to be effective. We will perform regular evaluations of NCCIH-led training and career development activities utilizing appropriate performance markers for each activity.

NCCIH will focus on:

- Identifying and addressing barriers to the creation of a highly skilled and diverse workforce
- Pilot and evaluate new approaches for workforce development
- Explore approaches to speed the trajectory from trainee status to independence.

Objective 5: Disseminate Objective Evidence-Based Information on Complementary and Integrative Health Interventions

It is vital that the public, health care providers, researchers, and policymakers be informed and knowledgeable about the safety and effectiveness of complementary and integrative health interventions. They also should have access to information about NCCIH's research results across the full continuum of the research pipeline, as well as ongoing research at the Center, including an awareness of whole person research, which examines the connections that exist across domains of human health. Access to information about NCCIH's scientific priorities and funding initiatives is also important.

The challenges of translating and disseminating complex scientific information about complementary and integrative health interventions to an interested and engaged public are twofold. First, the landscape of complementary and integrative health is inundated with information and misinformation—some of it overtly promotional, and much of it either not based on evidence or of questionable quality and reliability. Second, there is evidence that individuals who use complementary health interventions often do not discuss their use with their conventional health care providers. Instead, they rely on other sources, including family and friends, and information gleaned from the Internet, popular media, and advertising.

Strategies

1. *Disseminate evidence-based information on complementary and integrative health interventions, as well as information about ongoing research, including whole person research, that examines the connections that exist across domains of human health*

NCCIH will continue to ensure that its presentation of evidence-based information on complementary and integrative health interventions is scientifically objective, appropriately balances what is known and not known about their safety and effectiveness, and provides context in the landscape of conventional treatment approaches.

2. *Continue to develop methods and approaches to enhance public understanding of basic scientific concepts and biomedical research*

NCCIH must continue to develop methods and approaches to enhance the public's understanding of basic scientific concepts and biomedical research to lay a foundation of knowledge for the better understanding of information and improved decision making. Importantly, NCCIH must provide information that is engaging, accessible, and of value to the public, health care providers, researchers, and policymakers, given the flood of information and misinformation in the public domain and the frequent self-care use of complementary health interventions.

Serving as an Efficient and Effective Steward of Public Resources

Improving Women's Health and Minority Health, and Eliminating Health Disparities

Women and underserved groups, including racial and ethnic minorities, and sexual and gender minorities (SGM), have distinct health needs and often experience disparities in health outcomes. Individuals with low socioeconomic status, or who live in rural communities, also often experience such disparities. NCCIH maintains that women, racial and ethnic minorities, rural, low income, SGM, and other populations experiencing health disparities should be included in all relevant research, such that there is sufficient representation of each population to conduct relevant analyses. Inclusivity in research generates more broadly applicable information and improves scientific understanding of the health and well-being of specific population groups.

NCCIH is committed to funding research with diverse populations and promoting a diverse scientific workforce. We support training, career development, and research opportunities directed at minority health and health disparities.

Health Disparities Research

NCCIH seeks to expand the research we support involving understudied, underrepresented and underreported populations. We participate in initiatives targeted toward these populations and are currently supporting research to explore the development, feasibility, optimization, and efficacy of complementary and integrative health interventions within minority, low socioeconomic, rural, urban, and gender-specific populations. NIH-designated health disparity populations include racial and ethnic minorities (Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Asians, Native Hawaiians and other Pacific Islanders), sexual and gender minorities, socioeconomically disadvantaged populations, and underserved rural populations. Other vulnerable populations of interest to NCCIH include high-risk pregnant women; homeless youth, children with disabilities; children who have experienced abuse, and military families. In addition, we encourage research in these populations through outreach activities. For example, NCCIH co-sponsored the NIH 2019 Traditional Medicine Summit with the NIH Tribal Health Research Office. The goals of this summit were to identify approaches to respectful collaboration between traditional medicine practitioners and health researchers; explore the relationships between traditional medicine and health care services; and connect younger generations of American Indian/Alaska Native people to traditional medicine, integrative health research, and academic research. We plan to continue expanding these efforts.

Specifically, NCCIH will:

- Support community-engaged research on the efficacy and effectiveness of complementary and integrative health approaches for improving minority health and eliminating disparities in health conditions such as mental, emotional, and behavioral health, obesity, and pain
- Promote research on the use of complementary and integrative health approaches for health promotion and restoration, resilience, disease prevention, and symptom management to address the role of social and structural determinants of health

- Conduct research to test implementation strategies aimed at improving uptake, scale-up, and sustainability of evidence-based interventions among health disparity populations and in low-resource settings
- Foster research collaborations between research-intensive institutions and institutions that have a historical mission or a demonstrated commitment to educating students from groups underrepresented in the biomedical research workforce
- Facilitate research collaborations among health disparities researchers and complementary and integrative health researchers
- Partner with other NIH Institutes, Centers, and Offices to support interventions that address multiple levels of influence (e.g., individual, community, societal) on health outcomes and target co-occurring conditions among health disparity populations
- Serve as a catalyst in the dissemination of innovative and evidence-based health disparities research and scientific opportunities to our stakeholders.

Women's Health Research

Signed into law on December 13, 2016, the 21st Century Cures Act (Public Law No. 114-255) reaffirms NIH's commitment to women's health. Specifically, the Act endorses the importance of including women in clinical research and considering sex as a biological variable in research using humans and nonhuman vertebrate animals. Further, the Act requires that people of all ages be represented in clinical research, expands sex- and gender-based and race- and ethnicity-based results reporting requirements for phase 3 clinical trials, and incorporates changes to encourage research collaboration among NIH Institutes, Centers, and Offices, with the goal of improving the health of all people (<https://www.nih.gov/research-training/medical-research-initiatives/cures>).

The 2017 National Health Interview Survey showed that women were more than twice as likely to use yoga compared with men (19.8 percent versus 8.6 percent). Women were also more likely than men to use meditation (16.3 percent versus 11.8 percent) and see a chiropractor (11.1 percent versus 9.4 percent). Women may also use natural products to improve their health during the lifespan, including during pregnancy and lactation.

NCCIH will continue to further research on women's health and sex as a biological variable by:

- Developing and testing interventions using complementary health approaches for managing symptoms such as perinatal and postpartum depression, stress, anxiety, pain, and sleep disturbance and assess their impact on maternal health outcomes
- Supporting research on the use of complementary health approaches to support pregnant and parenting women with opioid use disorder
- Supporting research on the contributions of sex, gender, and the intersection of sex and gender on the mechanisms of action of complex interventions including various mind and body approaches and natural products
- Conducting research that investigates the influence of sex and gender on utilization of complementary health approaches to improve health outcomes among diverse populations, including gender diverse populations.

Foster Discovery and Innovation by Setting Priorities and Enhancing Stewardship

NCCIH strives to invest in research that will drive new discoveries to lead to improved public health and health care. The Center’s research priorities reflect public health needs, scientific promise, amenability of topics to rigorous scientific inquiry, potential to impact health care practices, and relationship to use and practice.

The relative burden of a disease or condition on human health and well-being is an important consideration for priority setting. According to the Institute for Health Metrics and Evaluation, the top five leading causes of years lived in less than ideal health include low-back and neck pain, other musculoskeletal disorders, depressive disorders, and anxiety disorders. Complementary and integrative health approaches have shown promise in treating and managing these conditions, but additional research is needed to identify and optimize beneficial interventions.

The U.S. population at large is in an alarmingly poor overall state of health and is seeing a decline in life expectancy,² with many people suffering from co-occurring chronic diseases such as obesity, diabetes, cardiovascular disease, and degenerative joint disease. Many of these chronic diseases are not only linked to the “epidemics” of chronic pain, depression, opioid addiction, and suicide, but also share common roots, such as poor diet, sedentary lifestyle, and chronic stress. Minorities are often diagnosed with many of these chronic diseases at a higher rate than non-Hispanic Whites.³ In the COVID-19 pandemic, we saw in real time an example of why this is important: although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory infection, it is clear that chronic conditions in other body systems (e.g., diabetes, hypertension) are important factors in its severity and mortality. And while there have been many advances in science and medicine, they tend to remain siloed within one disease or organ system. A focus on whole person health will bring these scientific disciplines together to treat the whole person and to improve and restore health.

NCCIH has also made pain management a major emphasis in its research efforts. Pain is a major public health problem and is the most common reason why Americans use complementary and integrative health practices. Data from the 2012 National Health Interview Survey estimated that 126.1 million adults reported some pain in the previous 3 months, with 25.3 million adults (11.2 percent) suffering from daily (chronic) pain and 23.4 million (10.3 percent) reporting a lot of pain. Conventional care often fails to manage chronic pain effectively and other approaches to relieve or reduce pain and increase functional ability are needed. Research studies have shown that some complementary health modalities may reduce pain associated with some chronic conditions: examples include massage, spinal manipulation, and yoga for chronic back pain, and tai chi for fibromyalgia pain.

Scientific Plausibility and Rigor

NCCIH strives to invest in research that will drive new discoveries and focuses on areas that will have the greatest impact by prioritizing research topics that show scientific opportunity and promise and are

² <https://www.cdc.gov/nchs/products/databriefs/db328.htm>

³ Woolf SH, Schoomaker H. Life Expectancy and Mortality Rates in the United States, 1959-2017. *JAMA*. 2019;322(20):1996-2016.

amenable to rigorous scientific inquiry. No matter how interesting an approach may be, if the evidence favoring it is too limited to support the scope and direction of a proposed study, or if reliable, rigorous methods of measurement do not exist, that topic is not suitable for a full-scale investigation.

As a responsible steward of its publicly provided resources, NCCIH is highly selective in the choice of topics for major clinical trials. Decisions about which large-scale trials to support must be based on the strength, reliability, and reproducibility or signals from clinical experience and preliminary, smaller pilot studies, as well as on evidence of scientific plausibility obtained from mechanistic studies. Adequate methods and tools to accurately and effectively measure clinical outcomes are equally important to sound research design. Objective, validated measurement tools are essential, and so are processes and procedures to ensure quality control, whether the intervention is physical, psychological, dietary-based, or a combination. For example, NCCIH has developed a strict natural product integrity policy to ensure that natural products used in research supported by the Center are fully identified, characterized, and standardized.

Priority Setting Framework

NCCIH is committed to funding research in areas that will have an impact on health and health care. When considering funding a potential research project, the Center assesses whether it is reasonably likely that the results of the research could lead to changes in the health practices of individuals or

Priority Setting

1. Scientific Promise

- Does a reasonable body of evidence support the potential of the proposed research to lead to improved (1) options or strategies to treat health conditions or symptoms or (2) approaches to promote disease prevention, health promotion, resilience, or health restoration?
- Is evidence sufficient to support the scope and directions of the proposed research? If not, what research is needed to establish such evidence?

2. Amenability to Rigorous Scientific Inquiry

- Are the key research goals achievable, and are the key research questions amenable to rigorous scientific investigation, given needed and available methods for measurement, translational tools, and technologies?
- Are potential approaches feasible and scientifically plausible? Do they lend themselves to rigorous quality control? If not, does the proposed research focus appropriately on developing needed methods, tools, and technologies?

3. Potential to Change Health Practices

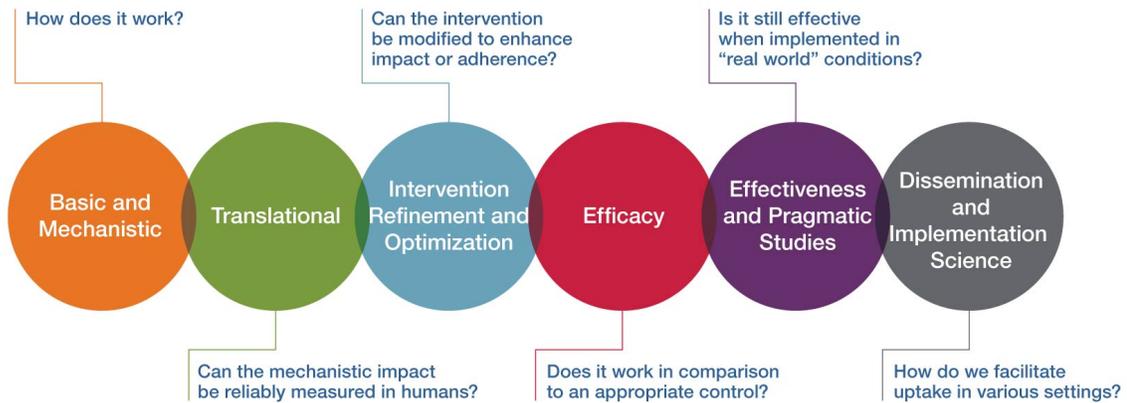
- Is it reasonably likely that the results of the research or program could lead to changes in the health practices of individuals or health care providers or in the decisions of health policymakers?

4. Relationship to Use and Practice

- Does the proposed project address an important public health concern or scientific information need regarding the fundamental mechanism, efficacy, safety, or public use of complementary health approaches?

health care providers or in the decisions of health policymakers. The Center also considers whether the research addresses an important public health concern or need for scientific information regarding the mechanism of action, safety, efficacy, or effectiveness of complementary and integrative health approaches.

NCCIH Framework for Clinical Research



Research Partnerships

To fulfill its mission and leverage its research investments, NCCIH collaborates with other NIH Institutes, Centers, and Offices; other Federal agencies; professional societies; patient advocacy groups; and organizations with an interest in furthering our understanding of complementary approaches and their integration into health care with the goal of improving health. Through these collaborations, NCCIH enhances its research portfolio, expands its multidisciplinary expertise, and incorporates a broader understanding of the health needs and perspectives of the community.

NCCIH partnership with SAMHSA to combat opioid use disorder

More than 4 million people in the United States report using opioids for nonmedical purposes in the past month, and almost 2 million report symptoms consistent with an opioid use disorder (OUD). Fewer than half of those with an OUD receive treatment and even fewer receive treatment of adequate duration. The number of drug overdose deaths involving opioids has quadrupled between 1999 and 2015, to more than 33,000 annually.

Chronic pain is an important comorbidity in patients with OUD. Twenty to 30 percent of U.S. adults report chronic pain. Treatment of acute and chronic pain conditions with opioids is contributing to the OUD epidemic. Patients at increased risk of developing OUD are those with pain that is inadequately controlled, those exposed to opioids during acute pain episodes, and/or those with chronic pain and a

history of substance abuse. Among patients with OUD treatment and chronic pain, barriers to actively engaging in treatment include fear of inadequately treated pain and depression. Many behavioral interventions have shown value for management of chronic pain. Recent American College of Physician guidelines for management of chronic back pain include recommendations to consider interventions including mindfulness-based stress reduction, multidisciplinary rehabilitation, meditative exercise such as tai chi and yoga, progressive relaxation, operant therapy, and cognitive behavioral therapy. However, there are relatively few studies evaluating their effectiveness for the comorbidity of OUD and chronic pain. In addition, despite the proven effectiveness of medication-assisted treatment (MAT) for OUD, approximately 50 percent of people who begin methadone maintenance therapy, for example, discontinue within 12 months, and 50 percent of people retained have an opioid relapse within 6 months. Research also suggests that pain, which is highly prevalent, may be an important contributor to MAT dropout, opioid relapse, and opioid overdose.

NCCIH has partnered with the Substance Abuse and Mental Health Services Administration (SAMHSA) to study the impact of behavioral interventions for primary or secondary prevention of OUD, or as a complement to MAT of OUD. Researchers will examine whether select behavioral interventions such as mindfulness meditation, cognitive behavioral therapy, or multidisciplinary rehabilitation improve adherence to and retention in MAT or reduce resumption of drug use in individuals with OUD. NCCIH has awarded six research grants, totaling \$9.4 million over 3 years. In addition to support from NCCIH, funding for these awards will come from the NIH's HEAL (Helping to End Addiction Long-termSM) Initiative. The NCCIH-administered grants will support research around the treatment supported by the \$1 billion SAMHSA State Targeted Response (STR) to the Opioid Crisis Grants initiative, also known as Opioid STR grants.

As part of the 21st Century Cures Act, Opioid STR grants have been distributed to all 50 U.S. states, U.S. territories, and free-associated states to expand access to evidence-based prevention, treatment, and recovery support services; reduce unmet treatment needs; and help prevent opioid overdose death. The six research awards supported by NCCIH will examine the impact of behavioral and complementary health interventions within the context of states' plans for use of Opioid STR grant funds. As such, each of the funded research projects includes relevant state agency staff to ensure adequate input on study design from the SAMHSA-funded projects. The overarching idea of this collaboration is that researchers, health professionals, and community members all have a role in implementing evidence-based prevention and treatment strategies for OUD. In addition, this collaboration provides an opportunity to study, in a clinical setting, whether complementary approaches in combination with certain psychosocial interventions and medications can further improve treatment outcomes and/or help manage co-occurring pain.

Risk Management

The NCCIH Office of Administrative Management leads the Center in identifying and proactively managing risks, improving strategic decision making, increasing efficiency and effectiveness, and promoting accountability and integrity. The Center created a Risk Management Council in 2020 to ensure that we are considering risks from across the Center and developing appropriate ways to mitigate them.

Assessing Programs, Processes, Outcomes, and Impact

NCCIH uses a variety of approaches, including monitoring, performance measurement, analysis, and evaluation, to assess the progress and effectiveness of its programs, policies, and operations, and to

generate information for decision making. NCCIH will follow NIH guidance in the implementation of the Foundations for Evidence-Based Policymaking Act to further develop its data-driven, results-oriented culture.

The NCCIH Office of Policy, Planning, and Evaluation often conducts portfolio analyses and evaluation of NCCIH's programs. The Center works in conjunction with partners across NIH, including the Office of Portfolio Analysis, Office of Evaluation, Performance, and Reporting, and other NIH components.

Description of the Strategic Planning Process

From April 2020 through July 2020, stakeholders were offered several ways to contribute their thoughts and feedback. This included responding to a request for information (RFI) (<https://grants.nih.gov/grants/guide/notice-files/NOT-AT-20-013.html>) using a web form or by email. The Center broadly disseminated information throughout the process to its many stakeholder groups and individuals. In May 2020, the Center hosted [Whole Person Health: Mapping a Strategic Vision for NCCIH](#) Webinar and Town Hall in conjunction with the International Congress on Integrative Medicine and Health. In July 2020, NCCIH hosted a [Town Hall and Public Comment Session](#) at which the Center invited comments from stakeholders, experts, communities, and members of the public, including but not limited to researchers and trainees across academia, industry, and government; health care providers and health advocacy organizations; nongovernmental, scientific, and professional organizations; and Federal agencies.

The draft strategic plan was posted to the NCCIH website in early 2021, and an RFI was issued for public comment on the draft.

The National Advisory Council for Complementary and Integrative Health was also provided with updates during their public meeting sessions in September 2019; February, June, and September 2020; and January 2021.