National Center for Complementary and Integrative Health

# Strategic Plan

## FY 2021–2025

Mapping a Pathway to Research on Whole Person Health

U.S. Department of Health & Human Services — National Institutes of Health

NCCIH Strategic Plan FY 2021–2025

# Executive Summary

The National Center for Complementary and Integrative Health (NCCIH) was created more than 20 years ago to facilitate the study and evaluation of complementary and alternative health practices. During the past two decades, NCCIH has expanded the scientific knowledge base around these practices and established resources to disseminate this information to the public—ultimately impacting their use. The Center has worked to advance the position that evidence-based complementary therapies should be "integrated" with and not used as an "alternative" to conventional medicine.

NCCIH's new strategic plan for Fiscal Years (FY) 2021–2025 expands the definition of integrative health to include whole person health, that is, empowering individuals, families, communities, and populations to improve their health in multiple interconnected domains: biological, behavioral, social, and environmental. The 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.

**The plan has five major objectives:**

Objective 1: Advance fundamental science and methods development. NCCIH prioritizes research to fill gaps in our understanding of the mechanisms by which complex complementary approaches exert their effects. We also recognize the need for methods development to support rigorous studies of complex botanical products, integrated multicomponent therapeutic systems, health restoration and resilience, and the dissemination and implementation of evidence-based complementary approaches.

Objective 2: Advance research on the whole person and on the integration of complementary and conventional care. NCCIH seeks to support basic, translational, and clinical research on the interaction of multiple physiological systems and the therapeutic effects of multicomponent interventions. The Center is particularly interested in studies conducted in real-world settings and research that focuses on improving health outcomes.

Objective 3: Foster research on health promotion and restoration, resilience, disease prevention, and symptom management. Focused research is needed to understand why people make healthy, unhealthy, or risky choices and to elucidate the impact of these choices on short- and long-term health. Another priority area for NCCIH is expanding the knowledge base about how complementary health approaches may improve resilience, restore health, and manage symptoms in both the short and long term.

"Much progress has been made in the research areas that form the NCCIH portfolio since our last strategic plan was released, and we are now ready to integrate this knowledge into a whole person approach."

**Helene Langevin, M.D.**
NCCIH Director

## Our 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.

## Our Vision

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

Objective 4: Enhance the complementary and integrative health research workforce. 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. The Center will continue to promote strategies to enhance diversity of the workforce, enhance the clinician-scientist career pathway at both the individual and institutional levels, and enhance the transition of Research Career Development (K) awardees to independent research careers.

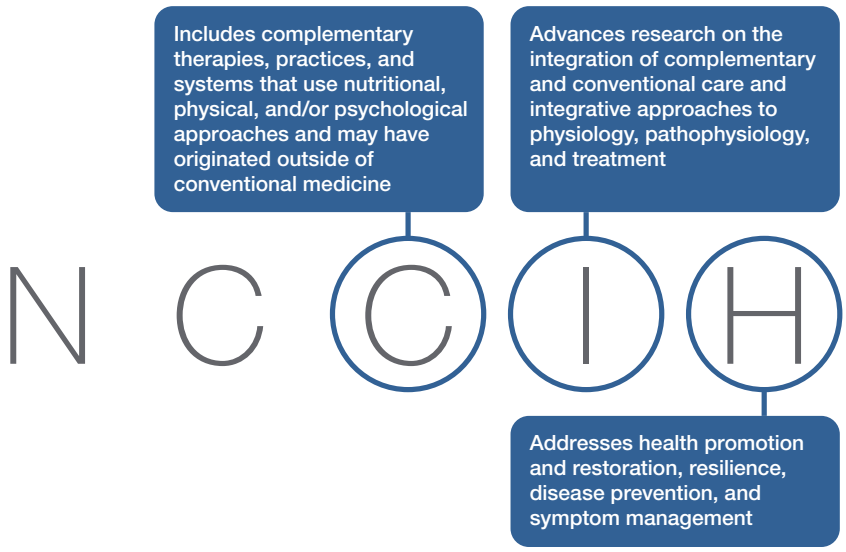
Objective 5: Provide objective evidence-based information on complementary and integrative health interventions. Translating and disseminating scientific information about complementary and integrative health to the public is challenging. Misinformation abounds on these topics, and individuals who use complementary health interventions often do not discuss them with their conventional health care providers. NCCIH will continue to present scientifically objective evidence-based information on complementary and integrative health and to develop methods and resources to enhance the public's understanding of basic scientific concepts to lay a foundation for improved decision making.

In addition to working toward these specific objectives, NCCIH is committed to serving as an efficient and effective steward of public resources:

- To support the goal of improving women's and minority health and eliminating health disparities, NCCIH will fund research with diverse populations and promote a diverse scientific workforce.

- To ensure that research funded by NCCIH contributes to improved public health and health care, NCCIH will set research priorities that 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.

- NCCIH will continue to seek out opportunities to collaborate with other components of the National Institutes of Health (NIH), other Federal agencies, professional societies, patient advocacy groups, and others. Through these collaborations, the Center enhances its research portfolio, expands its multidisciplinary expertise, and incorporates a broader understanding of the health needs and perspectives of the community.




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

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— Advance basic and mechanistic research relevant to nutritional, psychological, and/or physical approaches.

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

— Develop outcome measures to quantify health restoration and resilience.

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

25 **Objective 2:** Advance Research on the Whole Person and on the Integration of Complementary and Conventional Care

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

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

— Foster multicomponent intervention research that focuses on improving health outcomes.

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

31 **Objective 3:** Foster Research on Health Promotion and Restoration, Resilience, Disease Prevention, and Symptom Management

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

— 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.

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

**37 Objective 4:** Enhance the Complementary and Integrative Health Research Workforce

— 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.

— Foster interdisciplinary collaborations and partnerships at individual and institutional levels.

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— 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.

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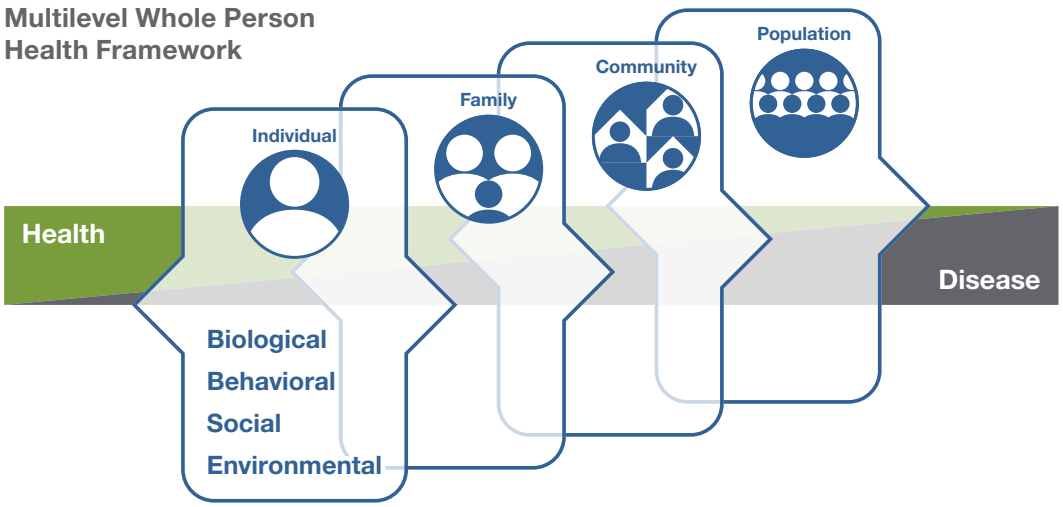
# Director's Message

This unprecedented year has been 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 lifetimes, but Americans have been facing the realities of "noncommunicable epidemics" for some time—opioid abuse, chronic pain, obesity, diabetes, and suicide. These persistent and related public health crises underline the systemic challenges 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 contributing factors such as poor diet, sedentary lifestyle, environmental exposures, and chronic stress—often the consequences of poverty and food and housing insecurity. The domino effect of chronic conditions is seen in the disproportionate toll they take on Latino, Black, American Indian, Alaska Native, 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 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 pharmacologic 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, health restoration through self-care, lifestyle, or behavioral interventions is much less studied. Examples of health restoration, or "salutogenesis," would be the return to health after an acute viral illness or flareup of a chronic condition; normalization of cholesterol, hemoglobin A1C, and/or blood pressure in a patient with metabolic syndrome through lifestyle modification; and return to function and mobility following a musculoskeletal injury. We currently do not know whether salutogenesis consists of "pathogenesis in reverse" or whether it requires some specific salutogenic or healing pathways to be engaged to bring an individual back toward health. Unlike the treatment of disease with drugs that target specific molecular pathways, health restoration through salutogenesis is likely complex and multifactorial and involves the whole person. Advancing research on whole person health will support the investigation of nondrug and noninvasive approaches to improve and restore health.

Meeting this challenge is right up our alley. By its nature, the mission of 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 to bring conventional and complementary approaches together in a safe, coordinated way with the goal of improving clinical care for patients, promoting health, and preventing disease. Now, we are expanding our definition of integrative health to include whole person health, or empowering individuals, families, communities, and populations to improve their health in multiple interconnected domains: biological, behavioral, social, and environmental. This strategic plan, built on the foundation NCCIH has fostered 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 building on current activities and existing collaborations with other NIH Institutes, Centers, and Offices while advancing new strategies and ideas. The objectives and strategies listed here will also be considered through the lens of minority health and health disparities, such that the knowledge they generate is inclusive of populations with the greatest needs.




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 the webinar and town hall Whole Person Health: Mapping a Strategic Vision for NCCIH (https://www.nccih.nih.gov/news/events/whole-person-health-mapping-a-strategic-vision-for-nccih-webinar-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 (https://www.nccih.nih.gov/news/events/nccih-strategic-planning-town-hall-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 February 2021, and an RFI was issued for public comment on the draft (https://grants.nih.gov/grants/guide/notice-files/NOT-AT-21-005.html). The National Advisory Council for Complementary and Integrative Health provided input into the strategic planning process and 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 a diverse group of stakeholders has helped us develop 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. 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.

—**Helene Langevin, M.D.**
NCCIH Director

# Introduction

**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 in a whole person health framework.

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 nondrug and noninvasive health practices encompassing nutritional, psychological, and physical approaches that may have originated outside of conventional medicine, many of which are gradually being integrated into mainstream health care. These include 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 multicomponent therapeutic systems, such as traditional Chinese medicine, Ayurveda, chiropractic, osteopathy, and naturopathy, that have distinctive underlying diagnostic and theoretical frameworks. 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, restoring health, promoting resilience, and preventing disease.

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, these practices were 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 evidence-based 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 to conduct rigorous scientific research on 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.

## 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. Integrative health 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 has increasingly become blurred.

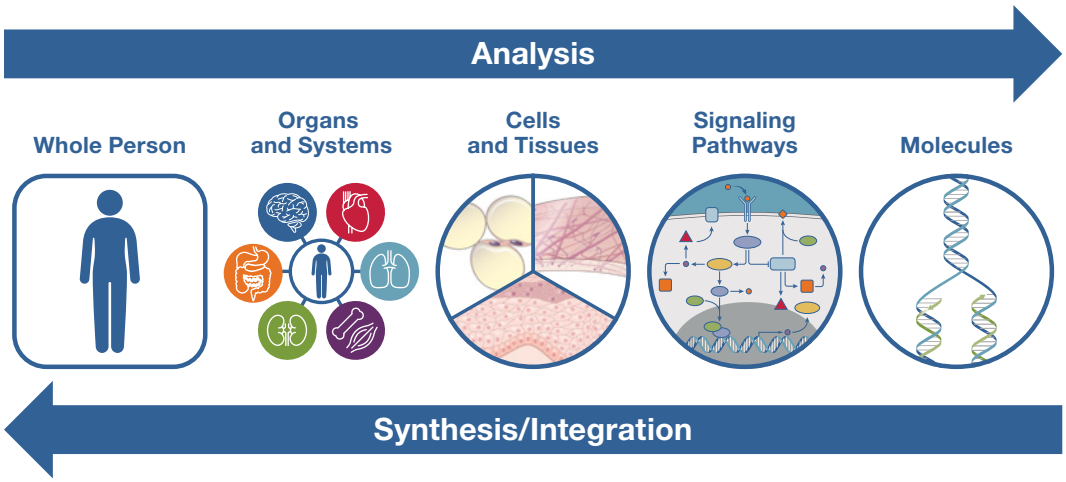
### What Is Whole Person Health?

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 mature 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.

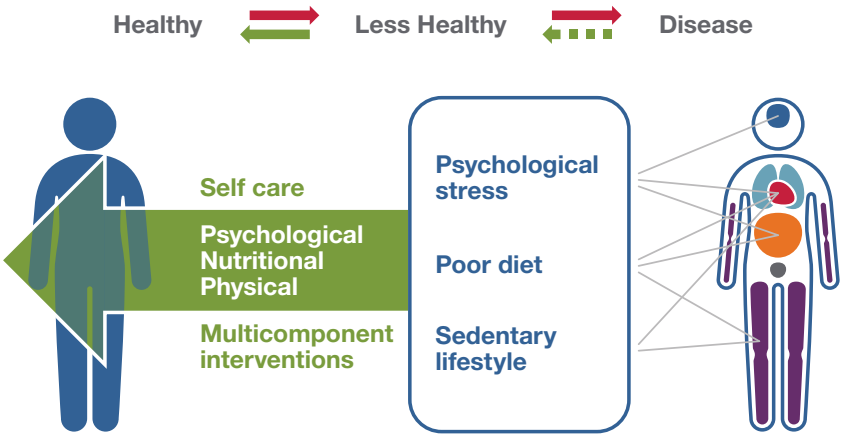
Now is the time for biomedical science to work toward restoring its balance between analysis and synthesis. We can do this by strengthening our efforts toward integration of knowledge across disciplines, focusing on the whole person, and taking a transdisciplinary approach that integrates the natural, 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, such as poor diet, sedentary lifestyle, chronic stress, and poor sleep, as well as social determinants of health (the conditions in which people are born, grow, live, work, and age) 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 across the lifespan. We witnessed this in real time in 2020 and 2021. Although COVID-19 is a respiratory infection, chronic conditions in other body systems (e.g., diabetes, hypertension) as well as social determinants of health 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 biological, behavioral, social, and environmental domains, we can better understand how co-occurring conditions can arise from common, interrelated factors. As a result, we can also examine the potential role of multicomponent behavioral and/or systems-level 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.

**Integrated Approach to Multisystem Health Restoration**




## How To Study Whole Person Health?

Research on whole person health 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 care to develop multicomponent interventions that not only prevent progression to disease but also restore an improved state of health, as well as systems-level interventions to improve access to and/or reimbursement for these interventions. 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.

Strategic plans in the early history of the Center expressed an interest in exploring many paths, including research on systems of care 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 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 for pain, anxiety, and depression, which are some of the main reasons driving the use of complementary therapies. NCCIH also supported methods development for both basic science and clinical trials. The development of methodologies for conducting rigorous pragmatic trials was particularly important and will be invaluable for conducting research on whole person health.

### 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 transitioned to more inclusive definitions to reflect a whole person approach, considering:

- The growing understanding of the overlap of complementary approaches with the conventional nutritional, psychological, and physical categories.

- The increased interest in various types of synthesis or integration in biomedical science, 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 multicomponent interventions that address these problems, and expand how we support patients through the full continuum of their health experience, including the return to health.

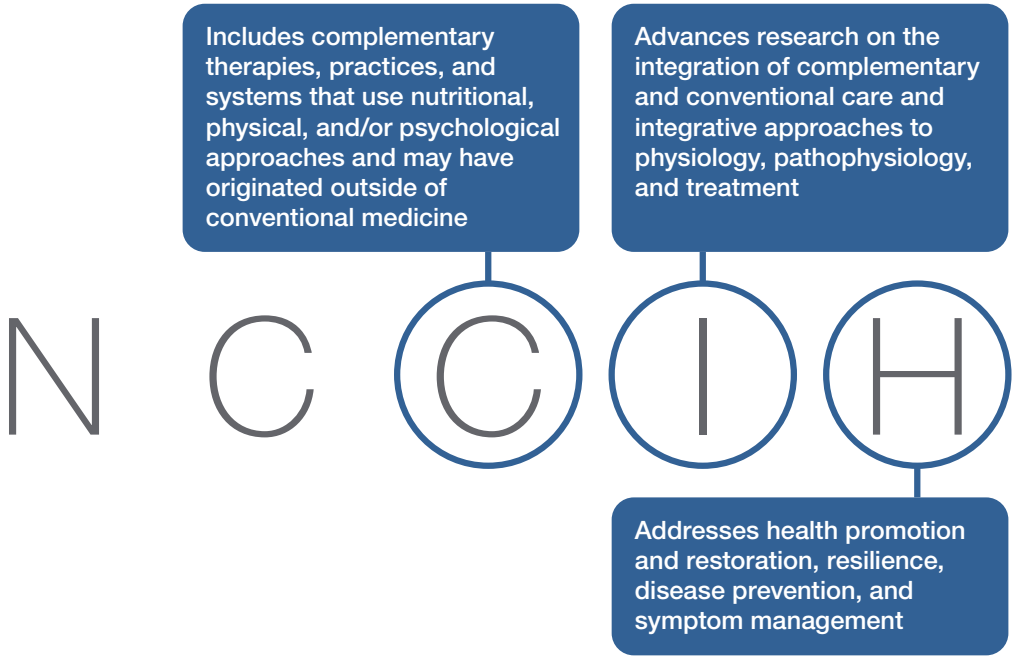
## Reframing How We Think About Natural Products and Mind and Body Practices

Until now, NCCIH has classified its extramural 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: nutritional, psychological, and physical.

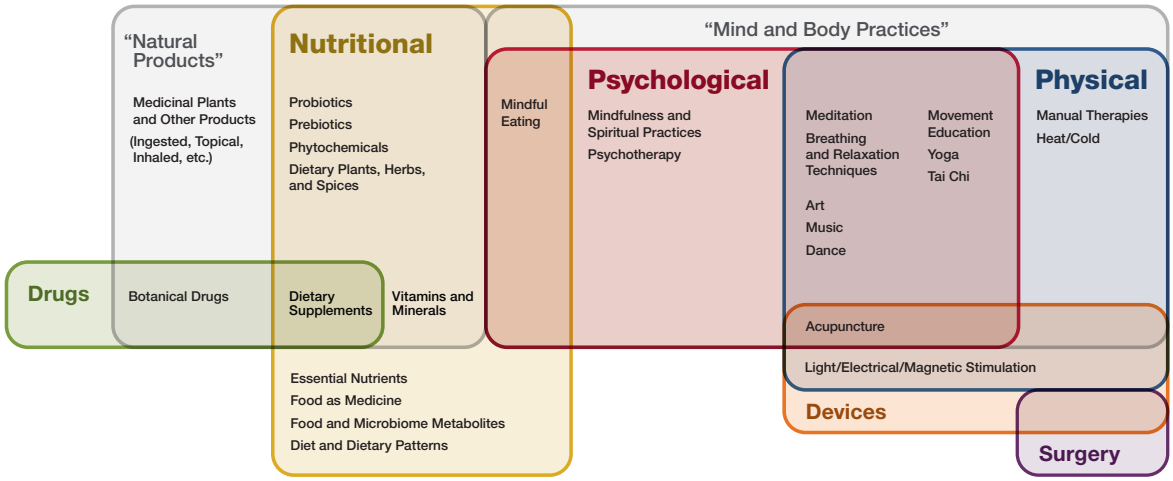
To ensure continuity, the Center is not abandoning its mind and body practices and natural products terminology or research but is recategorizing the approaches that fall within our research mission based on their primary therapeutic input. This categorization illustrates where there are partially overlapping boundaries, including with pharmacologic drugs and devices. For example, a single natural product can be available as a food or food component, dietary supplement, or medication (e.g., niacin). Foods, 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.

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 nutritional categories 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 multicomponent interventions.

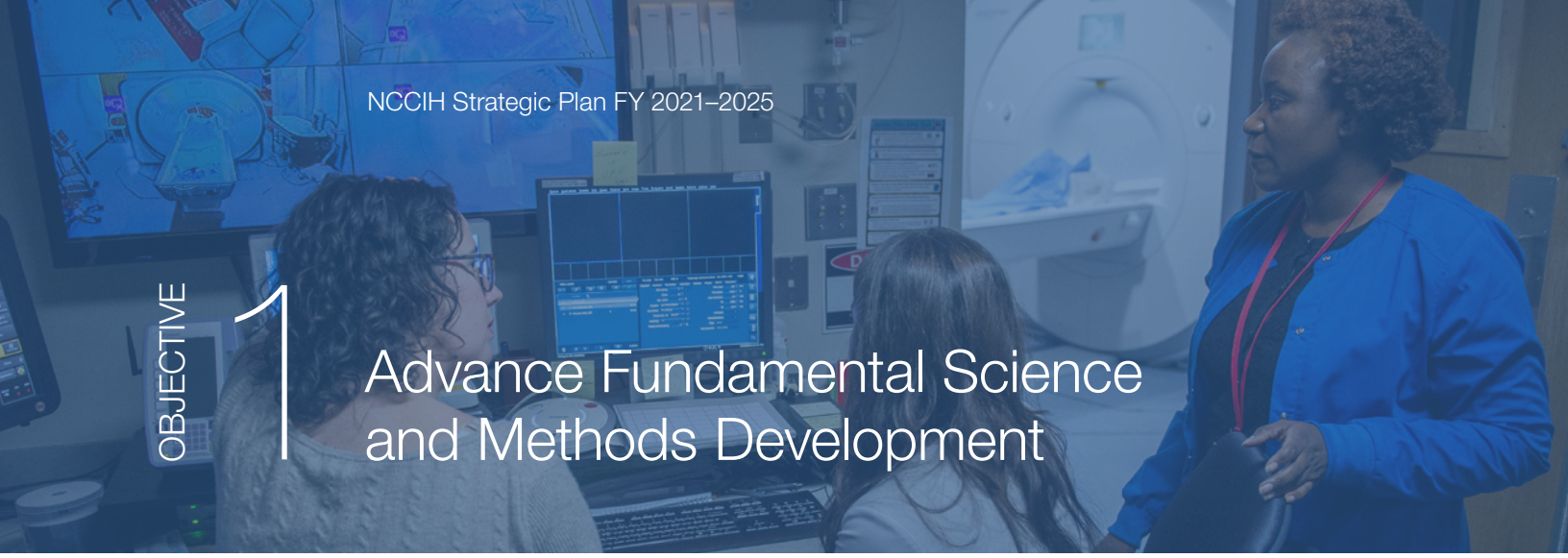


**Illustrative Examples of Therapeutic Input Framework**




This graphic shows the primary therapeutic input of approaches that may be studied within the NCCIH portfolio. The specific modalities are meant to be illustrative of the types of approaches that fall within these categories.

There are both conventional and complementary examples of multicomponent interventions. Conventional cardiac rehabilitation often includes nutritional recommendations, exercise, and a psychological component such as mindfulness-based stress reduction. Tai chi is also increasingly being incorporated into these programs. Although this example illustrates a holistic approach that recognizes interconnectedness of the psychological and physical components, the diagnostic and therapeutic framework under which these combined therapies are used is that of conventional medicine. In contrast, other types of multicomponent therapeutic interventions or systems bring together different modalities using diagnostic and/or therapeutic frameworks that are different from those of conventional medicine. For example, traditional Chinese medicine includes nutritional 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 that the framework that ties each intervention together in traditional Chinese medicine is distinct from those of conventional medicine. It is important to address this from a research perspective to gain more insight into whole person health.



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 experimental models, or with human volunteers. The development of tools, models, measures, and methodologies for performing these investigations is at the cornerstone of NCCIH's mission.

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

## STRATEGIES

### 1 Advance basic and mechanistic research relevant to nutritional, psychological, and/or physical approaches.

**Nutritional approaches**

NCCIH has a broad interest in studying the biological activities of natural products, such as prebiotics, probiotics, dietary 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 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.

## 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 and 2020, new components were 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 and on the development of a new nuclear magnetic resonance (NMR) data repository. These and other innovative approaches will break through existing bottlenecks that have hampered progress in natural products research. These additions have 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.

NCCIH will continue to support research on isolated natural product compounds 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 possibilities of drug interactions, direct toxicities, and contamination with active pharmaceutical agents or environmental chemicals are 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 substances. Interactions may occur among 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 molecular mechanisms of action of the microbiota and potential interactions with pre- and probiotics and their impact on processes in the human body. NCCIH will continue to work closely with other NIH Institutes, Centers, and Offices; the U.S. Food and Drug Administration (FDA); and the U.S. Department of Agriculture to leverage its investments in this research area.

### Psychological and physical approaches

Among complementary physical and psychological approaches are mindfulness-based cognitive therapy, tai chi, yoga, acupuncture, massage, spinal/joint manipulation, art therapy, music therapy, dance, meditation, mindfulness-based stress reduction, and many others. These approaches are widely used by the public and may help meet the need for nondrug approaches for the management of pain and other common, troublesome symptoms, which may benefit from a diversity of interventions that are safer than drugs and have fewer adverse effects. They may also play a role in interventions to optimize health. Included within the physical and psychological approaches are the qualities of patient–provider relationships and patient engagement. However, there are gaps in the understanding of the mechanisms by which these approaches exert their effects, and this has made it difficult to determine whether they are well suited for specific conditions or target populations and for 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, relaxation techniques, 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. This may include rigorous fundamental science on less well-studied aspects of the body (e.g., human biofield, hormesis) that may be relevant to complementary therapies.

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, biophysical, 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), define appropriate dosage, refine the components and system of intervention delivery, determine optimal frequency or duration of the intervention, assess feasibility, and enhance adherence. The Center also supports later stage full-scale efficacy, effectiveness, or pragmatic trials when the evidence base is sufficient to justify them.

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 quantitative and qualitative methodologies for complementary health research, especially those that can be used to assess symptoms, multisystem interactions, patient engagement, health restoration, and resilience. Studies that identify and validate objective endpoints or biomarkers predicting therapeutic response, assess and measure adherence or treatment fidelity, or otherwise strengthen the design of clinical trials of complementary health approaches are particularly important.

NCCIH is also interested in the study of multicomponent 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 systems of care 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 NMR spectroscopy to study materials of natural origin to identify new 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, learn from each other, and 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 practice 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, will 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 techniques to study a system of care, such as traditional Chinese medicine, chiropractic, Ayurveda, homeopathy, or naturopathy, to determine the reliability of its diagnostic methods. 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 | Multicomponent Interventions and Systems |
| --- | --- |
| Nutritional, physical, or psychological approaches<br><br>May have originated outside of conventional medicine | Multicomponent interventions combine multiple approaches that address different aspects of a person<br><br>Multicomponent 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 regarding 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.

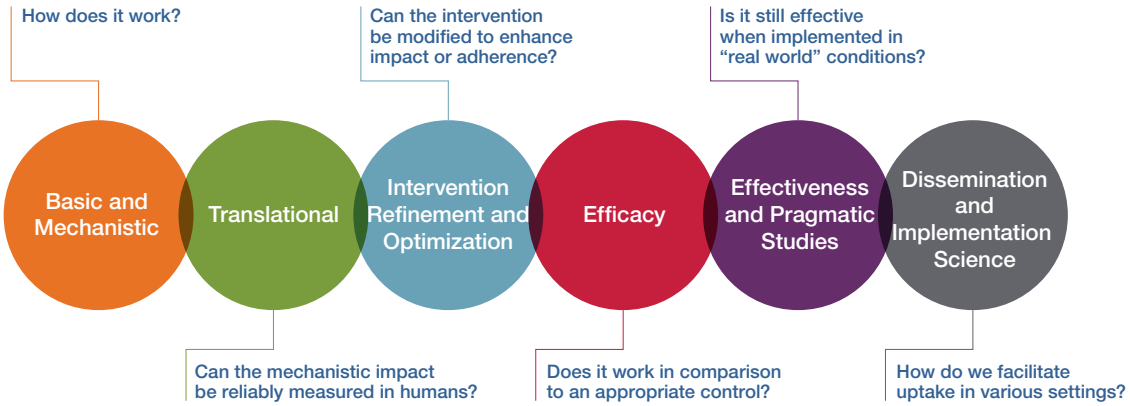
**c. Develop, refine, and test clinical research models and relevant statistical methods for testing multicomponent interventions and systems**

There is a need for research to evaluate multicomponent 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 multicomponent approach in 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 a complex intervention in a clinical trial. Some key aspects that may need further investigation to plan the future trial could include finalizing the multicomponent intervention or system delivery method, the outcome measure(s), or the 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 multicomponent intervention; and the overall feasibility of the trial. Later phase trials can further explore, develop, and test adaptive interventions; optimize or tailor a multicomponent intervention to have a greater impact

on the potential mechanism of action; assess whether the multicomponent intervention can be delivered with fidelity across sites; identify effective ways to recruit 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. This approach may require several stages of research and development from basic science to intervention generation/refinement/modification/adaptation and pilot testing to efficacy, effectiveness, dissemination, and implementation research. In addition, multicomponent 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 multicomponent intervention on multiple systems or composite outcome indices.

There are statistical challenges in studying integrated multicomponent 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 the impact of multicomponent therapies on multiple systems.

**NCCIH Framework for Clinical Research**



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

It is difficult to quantify health, 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, including systems-level research addressing access and reimbursement for interventions. Whereas efficacy and effectiveness studies 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 the Whole Person and on the Integration of Complementary and Conventional Care

Central to the definition of whole person research are studies of integrated multicomponent 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 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 outcomes involving multiple systems (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 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 multicomponent interventions (experimental input or independent variables) on

single or multisystem outcomes (output or 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 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, gastrointestinal, and immune systems) and domains (e.g., biological, behavioral, social, environmental).

NCCIH hopes to expand research on integrated multicomponent 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 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 multicomponent 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. Multicomponent 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 multicomponent interventions that combine conventional and complementary approaches.

There is a fundamental lack of translational research on the mechanisms of resilience and health restoration in humans. In particular, the mechanisms of nutritional, psychological, and physical interventions in restoring health after an acute illness or recovery from a chronic condition are an understudied area that needs a multisystem approach to identify mechanisms and predictive biomarkers that could be used to optimize their effects. 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 promoting 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. This can include identifying the basic elements of health care systems that optimally support the implementation of a patient-centered, multicomponent approach to health care delivery. 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 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–U.S. Department of Defense (DoD)–U.S. Department of Veterans Affairs (VA) Pain Management Collaboratory (PMC).

## Pain Research Supported by NCCIH Through Pragmatic Trials

Pain is the most common medical condition requiring treatment among military personnel. Studies report nearly 45 percent of active-duty military personnel 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 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 DoD, the VA, and seven other Institutes and Centers at NIH to launch the NIH-DoD-VA 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 clinical trials. 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 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 a disability classification 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. The researchers also assess their 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 a disability classification. This early education and referral paradigm could also be adapted to other health care systems.

NCCIH is leading the NIH HEAL (Helping to End Addiction Long-term℠) Initiative's Pragmatic and Implementation Studies for the Management of Pain To Reduce Opioid Prescribing (PRISM) (https://heal.nih.gov/research/clinical-research/prism) program, 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 effectively implement evidence-based interventions and pain management guidelines.

As part of the NIH HEAL Initiative℠, 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.

[1] Nahin RL. Severe pain in veterans: the effect of age and sex, and comparisons with the general population. *Journal of Pain.* 2017;18(3):247-254. (https://pubmed.ncbi.nlm.nih.gov/27884688)

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.

Complementary and integrative health care includes the patient–provider alliance, provider-delivered interventions, and the patient taking ownership of the care. 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. This suggests that access to and utilization of complementary and integrative approaches may empower patients to take charge of their health.

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, including self-care; and elucidate the impact these choices may have on short- and long-term health. New 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 anxiety, headache, insomnia, and back, neck, or joint pain—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 and often do not optimally engage patients in self-

management. 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 technologies of neuroscience, psychoneuroimmunology, psychology, behavioral medicine, physical medicine, and

## 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 [https://www.nccih.nih.gov/research/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 was identified as the intervention target, or a change in emotional well-being was 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 needs 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, racial and ethnic minorities, 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.

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.

## 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 important to health and prevention research. It is also important to consider resilience in relationship to an individual's overall level of stress and allostatic load. 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 to dissemination and implementation science. 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 healthy 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 out 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 underresearched 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.

A more comprehensive approach would look not only at conventional health care settings but also include investigations in other settings such as schools, nursing homes, and community health centers. As the COVID-19 pandemic has shown, the settings in which health care takes place must rapidly evolve to accommodate new and unforeseen situations. Similarly, disasters present “real-life” public health settings in which complementary approaches could be assessed (e.g., meditation or yoga to treat post-traumatic stress disorder in survivors and first responders, or nutritional supplements to mitigate effects of certain exposures).

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 gaps 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 on both the overall effectiveness of the dissemination and implementation strategies and 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 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 levels, 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 include targeted outreach to societies with a focus on individuals from groups that are underrepresented in the biomedical, clinical, behavioral, and social sciences.

## 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 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 minorities or other populations described in the Notice of NIH's Interest in Diversity [https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html]) 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), especially those who are currently underrepresented in biomedical and behavioral scientific research.

- 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 for 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, with the goal of increasing the number of complementary and integrative clinicians included as collaborative partners in research projects. 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 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 also support cross-training opportunities at the mid-career level 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. We will 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 using appropriate performance markers for each activity.

NCCIH will focus on:

- Identifying and addressing barriers to the creation of a highly skilled and diverse research workforce
- Piloting and evaluating new approaches for workforce development
- Exploring approaches to speed the trajectory from trainee status to independent researcher

OBJECTIVE 5

# Provide 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, other 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.

## 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 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. Other studies completed while AREDS was in progress showed that high concentrations of beta-carotene were associated with an increased risk of lung cancer in smokers. So in 2006, a second clinical trial, called AREDS2, was launched to determine if the AREDS formulation could still be effective if beta-carotene was removed. 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 AREDS 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 AREDS and AREDS2 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 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 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; a 52 percent reduction in recurrent heart attacks; and a 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 follow-up 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 TACT2 phase 3 clinical trial will be complete in FY 2023. 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 trials:** 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 used 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 made it possible for Achieve Life Sciences, Inc., to begin clinical trials and raise private funds to conduct them. Since 2015, Achieve Life Sciences, Inc., has successfully completed a phase 2b clinical trial. The company plans to begin the phase 3 clinical trial in 2021 to complete its New Drug Application 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.

# 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, 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 populations, low-income populations, sexual and gender minorities, 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 health disparity populations. NIH-designated health disparity populations include racial and ethnic minorities (Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Asian Americans, and 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 pregnant and lactating women; homeless youth; children with disabilities; children who have experienced abuse; veterans; military personnel; and military families. In addition, we encourage research in these populations through outreach activities. For example, NCCIH cosponsored 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 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 underserved 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 their 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 assessing 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 use 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. Racial and ethnic 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, 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 research will bring these scientific disciplines together to treat the whole person and to improve and restore health.

[2] Murphy SL, Xu J, Kochanek KD, et al. Mortality in the United States, 2017. *NCHS Data Brief.* 2018;(328):1-8. (https://pubmed.ncbi.nlm.nih.gov/30500322)

[3] Woolf SH, Schoomaker H. Life expectancy and mortality rates in the United States, 1959-2017. *JAMA.* 2019;322(20):1996-2016. (https://pubmed.ncbi.nlm.nih.gov/31769830)

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 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 of 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 measure clinical outcomes accurately and effectively 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, nutritional, 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 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.

## 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?

## 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 Physicians guidelines for management of chronic low-back pain include recommendations to consider interventions including mindfulness-based stress reduction, multidisciplinary rehabilitation, tai chi, 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 are examining 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 HEAL. 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.

# Top Scientific Priorities

Research on Whole Person Health

Interoception Research

Health Restoration, Resilience, Disease Prevention, and Health Promotion Across the Lifespan

Implementation Science for Complementary and Integrative Health

Complementary and Integrative Management of Pain

Complex Interactions Involving Nutritional Interventions

Enhancing the Complementary and Integrative Health Research Workforce

Mechanisms and Biomarkers of Mind and Body Approaches

Supporting Impactful Clinical Trials of Complementary and Integrative Health Approaches

Communications Strategies and Tools To Enhance Scientific Literacy and Understanding of Clinical Research

# Research on Whole Person Health

### Introduction and Explanation of Need

Complementary health approaches include a broad range of practices and interventions that may have originated outside of conventional medical care. Complementary approaches can be classified by their primary therapeutic input, which may be nutritional (e.g., special diets, dietary supplements, botanicals, probiotics, and microbial-based therapies), psychological (e.g., meditation, hypnosis, music therapies, relaxation therapies), physical (e.g., acupuncture, massage, manual therapies, devices related to these approaches), a combination of psychological and physical (e.g., yoga, tai chi, dance therapies, some forms of art therapies), or a combination of nutritional, psychological, and physical (e.g., Ayurveda, naturopathy, traditional Chinese medicine). The term integrative health care refers to conventional and complementary approaches used together in a coordinated way. Research on whole person health in the complementary and integrative spheres emphasizes research on multicomponent interventions that aim to improve health in multiple interconnected domains: biological (including multiple organs and systems), behavioral, social, and environmental.

As a relatively new concept, research on whole person health is different from reduction-based research, which mostly focuses on a single intervention's impact on one or at most a few physiological systems as separate processes. Understanding how multiple physiological systems interconnect and interact is one of the key challenges for the success of research on whole person health. Complementary and integrative health approaches often are multicomponent interventions or engage multiple therapeutic systems. Their complexity and heterogeneity may require innovative study designs to fully investigate their fundamental science and therapeutic effects. Furthermore, sophisticated analytic tools and methods may need to be developed to encompass the double complexity of multiple system outcomes and their relationships with multicomponent interventions.

### What Does Success Look Like?

- Expanded research investigating the interaction of multiple physiological systems.
- New methodologies to study multicomponent interventions in an integrative approach or systems science approach.
- New research methods, approaches, and resources to enable integration of multicomponent therapies with multisystem outcomes.

**Priorities**

- Support inclusion of additional systems outcome measures in ongoing research projects as secondary outcomes to build preliminary data for future multisystem studies.

- Encourage development and testing of multicomponent interventions, building on the success of single-component interventions.

- Support research to develop and validate measures and composite indices of multisystem outcomes for whole person health.

- Expand development of protocolized multicomponent treatment interventions that are reproducible and can be rigorously tested in clinical trials.

## Interoception Research

### Introduction and Explanation of Need

Interoception refers to the representation of the internal world of an organism and includes the processes by which the organism senses, interprets, integrates, and regulates signals from within itself. Here, the action of "sensing" denotes communication from other physiological systems to the central nervous system (CNS) through the commonly called ascending pathways, while the action of "regulating" refers to communication from the brain to other physiological systems via descending pathways. The CNS, especially the brain, is primarily responsible for interpreting and integrating these signals into a representation of the internal world. It is important to clarify that the bidirectional communications between other physiological systems and the CNS can be carried through either the peripheral neural pathways or nonneuronal pathways, such as the vascular or lymphatic systems and humoral system (e.g., immune and endocrine). Processes involved in interoception could often serve as therapeutic targets of many complementary and integrative health approaches, including psychological and physical approaches such as meditation, acupuncture, and other manual therapies, as well as nutritional approaches such as natural products.

Because of its potential importance, research on interoception in the context of complementary and integrative health approaches requires a deeper understanding of the connections between brain and body. In addition, tools and methods to probe interoceptive processes, especially in human subject research, are largely limited to self-reports and a handful of measures such as heart rate variability and skin conductance. An expansion of innovative and quantitative methods to study interoception may significantly enhance our understanding of how interoception works. These new tools and methods may also provide novel insights into how complementary and integrative health approaches may modulate the interoceptive processes and interoceptive clinical outcomes.

### What Does Success Look Like?

- Expanded understanding of the mechanisms underlying interoception.
- Improved, innovative tools and methods to probe interoceptive processes, especially in human subjects.
- Increased understanding of the impact of specific complementary and integrative health approaches on interoceptive processes.
- Improved understanding of the efficacy and effectiveness of complementary and integrative health approaches on interoception-related clinical outcomes, especially those related to musculoskeletal and visceral pain.

**Priorities**

- Build on basic interoceptive pathway studies to investigate mechanisms important for complementary and integrative approaches.

- Expand mechanistic research on interoception involving pain, cardiovascular conditions, and digestive conditions.

- Develop translational and clinical efficacy studies supporting development of new tools to probe interoception in humans and animal models.

- Support natural product research related to interoception involving brain-gut interactions and brain-cardiovascular/immune and brain-endocrine pathways, including both neural and nonneural pathways.

- Support mind and body research involving brain-respiratory (meditation), brain-musculoskeletal (acupuncture/manual therapy, movement-based therapies), brain-cardiovascular, brain-endocrine, and vagal/spinal pathways.

# Health Restoration, Resilience, Disease Prevention, and Health Promotion Across the Lifespan

### Introduction and Explanation of Need

There continues to be a growing interest in the use of complementary and integrative health approaches for preventing the onset of mental, emotional, and behavioral disorders, promoting psychological and physical health and well-being, and enhancing cognitive, emotional, and behavioral resilience in people who have experienced stressful or adverse life events. However, there has been limited research to examine the usefulness of these approaches as strategies for early intervention among individuals at increased risk for the purpose of preventing disease progression and supporting health restoration. Research has demonstrated the feasibility of conducting interventions that incorporate complementary and integrative health approaches, especially meditative approaches, for health promotion and disease prevention, particularly among adult populations. Additional research is needed to evaluate the feasibility of a wider range of interventions (e.g., music, guided imagery, qi gong, massage, dietary interventions), including multicomponent interventions (e.g., spinal manipulation combined with meditation), across the full lifespan and in diverse populations and settings.

The evidence base for the efficacy and effectiveness of complementary and integrative approaches in the context of prevention, health promotion, resilience, and health restoration is limited and primarily includes studies of single systems at the individual level. NCCIH-funded studies have shown efficacy primarily for mindfulness-based stress reduction for improving factors related to many physical and mental health conditions in adults, including indices of immune, endocrine, metabolic, and neurological function.

Rigorously designed, developmentally appropriate studies are needed to determine the efficacy and effectiveness of a wider array of complementary and integrative health approaches that include a focus on multiple systems to support whole person health and that address multiple levels of influence (e.g., interpersonal, community, societal) on health outcomes. It is also essential to gain a better understanding of mechanisms related to resilience and health restoration in response to these interventions and to determine what works, for whom, and under what conditions. In fact, there 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 nutritional interventions in restoring health after an acute illness, or reversing the course of a chronic one, is an understudied area that 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 therefore 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 promoting psychological and physical health, resilience, and health restoration.

### What Does Success Look Like?

— NCCIH supports a robust portfolio of efficacy and effectiveness life course–specific studies with a range of complementary and integrative health approaches for health promotion and restoration, resilience, and disease prevention among diverse populations.

— This portfolio includes studies that use multicomponent interventions to study multisystem contributions to health promotion and restoration, resilience, and disease prevention.

— Basic and mechanistic research leads to the discovery of mechanisms and biomarkers of multicomponent interventions for health promotion and restoration, resilience, and disease prevention.

### Priorities

— Encourage research to develop and test the efficacy and effectiveness of complementary and integrative approaches for health promotion and restoration, resilience, and disease prevention in diverse settings[4] and among health disparity and other vulnerable populations[5] across the full lifespan.

— Support research on the use of complementary and integrative health approaches among health disparity and vulnerable populations to overcome the role of social and structural determinants of health.

— Support multicomponent interventions designed to have an impact on a broad array of outcomes and multiple systems and assess the utility of these interventions for improving whole person health.

— Investigate innovative mechanisms of action and identify predictive biomarkers underlying behavioral processes and biological, neurobiological, and psychological mechanisms that are modified by one or multiple interventions across multiple systems.

— Conduct impactful translational research on the mechanisms of multicomponent interventions on health promotion and restoration, resilience, and disease prevention that may be used to optimize the beneficial effects of these interventions.

— Develop and refine innovative technologies (e.g., smartphone apps and wearable activity monitors) that can be used to deliver and measure interventions and outcomes in real time.

[4] Examples of diverse settings include families, schools, Federally Qualified Health Centers, child welfare and juvenile justice systems, and homeless shelters.

[5] NIH-designated health disparity populations include racial and ethnic minorities (Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Asians, and Native Hawaiians and other Pacific Islanders), sexual and gender minorities, socioeconomically disadvantaged populations, and underserved rural populations. Other vulnerable populations include high-risk pregnant women, homeless youth, children with disabilities, children who have experienced abuse, and military families.

# Top Scientific Priorities

## Prenatal Through Young Adulthood

— Develop and test theory-based early interventions for adolescents and young adults at high risk for adverse health outcomes to slow progression of disease, support health restoration, and improve resilience.

— Develop and test complementary and integrative prevention approaches that include the adults most influential in children's lives (e.g., parents, teachers, and other caregivers), with the goal of improving development and well-being of children.

— Test implementation strategies for improving uptake, scale-up, and sustainability of evidence-based interventions for promoting mental, emotional, and behavioral health among children and adolescents in diverse settings.

— Conduct innovative mechanistic studies and identify predictive biomarkers underlying the effects of multicomponent interventions across multiple systems for health promotion, restoration, resilience, and disease prevention in adolescents and young adults.

## Older Populations

— Develop and test nutritional, psychological, and physical interventions focused on older populations,[6] including the general population and those at increased risk for depression, anxiety, and other mental health disorders.

— Perform impactful basic and translational research on the mechanisms of multicomponent interventions in promoting healthy aging, health restoration, resilience, and disease prevention in older populations.

[6] NIH defines an older adult as an individual 65 years of age or older.

# Implementation Science for Complementary and Integrative Health

### Introduction and Explanation of Need

NCCIH supports the full continuum of the biomedical research pipeline, whereby a complementary nutritional, psychological, and/or physical health intervention moves from basic and mechanistic research through efficacy trials and through dissemination and implementation research. Currently, NCCIH's research portfolio reflects a range of research to rigorously answer the question, "What complementary and integrative health interventions work?" However, once the evidence for an intervention has been demonstrated, there is a delay before its widespread uptake and adoption. Dissemination and implementation research is a field of science dedicated to decreasing this delay by asking, "How can we help these evidence-based interventions reach the people who would benefit from them?" Dissemination and implementation research, the final steps in the research continuum, 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.

Understanding the difference between implementation science and dissemination science is key for successfully moving interventions through the research pipeline from the laboratory to clinical practice settings. Dissemination research is the scientific study of targeted distribution of information and intervention materials to a specific public health or clinical practice audience. The intent is to understand how best to spread and sustain knowledge and the associated evidence-based interventions. Implementation science research is the scientific study of strategies to adopt and integrate evidence-based health interventions into clinical and community settings to improve patient outcomes and benefit population health.

### What Does Success Look Like?

- An expansion of the NCCIH dissemination and implementation research portfolio to study and test strategies that facilitate uptake and adoption of complementary and integrative health interventions of proven effectiveness in real-world settings.

- Support of research that uses implementation/effectiveness hybrid designs—these studies are designed to simultaneously demonstrate the effectiveness of the intervention in real-world settings and test strategies to increase adoption and uptake of the intervention.

- Promotion of a research framework that encourages investigators to start thinking about effective implementation strategies to scale up an intervention once the intervention has been determined to have sufficient evidence.

- Support of implementation science research evaluating how complementary and integrative health approaches can be used to de-implement drugs or other interventions that may be inappropriately used in clinical care, have significant side effects, or for which potential harms outweigh potential benefits.

# Top Scientific Priorities

**Priorities**

— Develop a robust portfolio of implementation science research for dietary, psychological, and physical complementary interventions.

— Examine potential differences in the use of implementation science frameworks (Consolidated Framework for Implementation Research [CFIR], Reach Effectiveness Adoption Implementation [Re-AIM], alone or in combination) for nutritional, psychological, and physical complementary interventions.

— Conduct research on the adaptation of implementation science frameworks to increase the use and reach of evidence-based complementary and integrative health interventions in multiple settings (schools, communities, health care, mobile health [mHealth]).

— Develop a balanced portfolio of implementation science and effectiveness—implementation hybrid designs that combine elements of clinical effectiveness and implementation research (i.e., hybrid type I, II, and III trials) of complementary and integrative health interventions where there is enough evidence and for which multiple independent research studies have been conducted. Investigators are encouraged to use the NCCIH clinical research framework. (see page 23)

— When appropriate, promote the use of innovative study designs (randomized cluster trials, stepped-wedge designs, pragmatic trials) in implementation science and hybrid effectiveness trials for complementary and integrative health interventions.

— Increase implementation science studies that address disparities and evaluate strategies that make evidence-based complementary health interventions, including mHealth, available to health disparity and other vulnerable populations.

— Conduct research focused on tools and methods development specific for implementation science on complementary and integrative health approaches.

— Increase NCCIH training and career development opportunities in implementation science for complementary and integrative health researchers.

# Complementary and Integrative Management of Pain

### Introduction and Explanation of Need

Chronic pain is the condition for which adults in the United States most often use complementary and integrative health approaches. Under normal circumstances, pain is an important physiological response that serves as a warning of actual or potential tissue damage. Chronic pain can indicate ongoing tissue damage, such as inflammation, or can persist due to central nervous system sensitization resulting from increased neuronal and circuit activation in nociceptive pathways even after the tissue has healed. As a chronic syndrome, pain adversely affects function and psychological and social well-being. Pain is most often treated with pharmacologic and/or surgical interventions. However, these treatments are often associated with adverse outcomes, including tissue damage following surgery and harmful side effects associated with pharmacologic treatment, such as risk of misuse and addiction, particularly in the case of treatment with opioids. Complementary and integrative health approaches to pain management may offer safer, more effective, and cost-efficient options.

NCCIH has focused on research related to chronic pain since the publication of its last strategic plan in 2016. Several programs have been initiated and led by NCCIH alone (e.g., the Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes program) or in collaboration with other NIH Institutes and Centers (e.g., the Trans-NIH Natural Products and Pain Working Group). NCCIH also participates in large trans-NIH and trans-agency pain initiatives, such as the NIH-DoD-VA Pain Management Collaboratory and HEAL, the latter of which aims to help stem the national opioid public health crisis by evaluating innovative therapies for pain management and improving treatment for opioid misuse and addiction. Although research evaluating the impact of complementary and integrative approaches on pain remains a priority for NCCIH, a deeper understanding of the mechanisms by which complementary approaches exert their effects and identification of therapeutic biomarkers are needed to optimize treatments and to predict those individuals or groups most likely to respond to specific treatments. Rigorous basic, mechanistic, translational, clinical efficacy, and implementation research is needed before complementary health approaches for pain management can become an integral component of standard care.

### What Does Success Look Like?

— Advanced understanding of multisystem pain mechanisms and phenotypes (e.g., myofascial pain) and common comorbidities.

— Elucidation of mechanisms underlying overlapping pain conditions.

— Increased focus on health disparities in pain and greater inclusion of women, racial and ethnic minorities, and underserved populations in clinical trials/studies on pain.

— Expanded evidence base on the efficacy and effectiveness of complementary and integrative approaches for pain management.

— Increased understanding of the multisystem mechanisms underlying the effects of complementary and integrative approaches on pain.

— Leveraging HEAL and other trans-NIH and trans-agency programs to identify therapeutic biomarkers for complementary and integrative health approaches on pain.

— Improved methods for incorporating effective complementary and integrative approaches into standard care to treat pain and decrease the unnecessary use of opioids.

### Priorities

#### Basic and Mechanistic Research

— Expand preclinical research elucidating the mechanisms of physical and/or psychological interventions for pain.

— Explore peripheral tissue mechanisms underlying the impact of complementary and integrative health approaches on acute and/or chronic pain management.

— Conduct research to elucidate the myofascial components of chronic pain as potential targets for complementary and integrative health interventions, such as force-based interventions (e.g., manual and movement-based therapies).

— Conduct basic research to elucidate mechanisms underlying musculoskeletal pain.

— Identify novel, nonaddictive dietary supplement candidates to manage pain.

— Conduct basic research to elucidate the biological mechanisms that underlie the analgesic properties of natural products and their derivatives.

— Develop an understanding of how complementary health approaches impact multiple biological systems that may be involved in chronic pain conditions (e.g., brain-gut-microbiome, myofascial tissue—brain).

— Study behavioral, psychological, social, and physiological mechanisms underlying complementary and integrative health interventions for pain management in specific populations, including underserved populations and those underrepresented in research (e.g., people with sickle cell disease pain, children, older adults, women, military personnel/veterans).

—Identify mechanistic targets for complementary and integrative health approaches to treat acute pain conditions and prevent development of chronic pain.

### Biomarkers

—Develop and validate biomarkers that assess therapeutic responsiveness to complementary and integrative health interventions or predict efficacy of these approaches in the treatment of pain, leveraging HEAL and other trans-NIH and trans-agency programmatic efforts.

—Develop and validate diagnostic and prognostic biomarkers with potential applications for complementary and integrative health approaches in selected populations (e.g., minorities, women, underserved populations, children, older adults).

—Develop quantitative evaluations and biomarkers of myofascial pain.

### Clinical Research

—Expand clinical research to determine the analgesic potential of natural products.

—Conduct clinical research on complementary and integrative health approaches in selected populations (e.g., minorities, children, women) to address pain disparities.

—Examine interactions of multicomponent nonpharmacologic interventions (e.g., meditation and probiotics), alone or in combination with pharmaceuticals, to optimize efficacy.

—Expand implementation research to study how to integrate complementary approaches with a strong evidence base into clinical and community settings.

## Complex Interactions Involving Nutritional Interventions

### Introduction and Explanation of Need

Nutritional interventions have millennia of history as therapeutic agents. They commonly include the phytochemicals found in fruits and vegetables, fermented foods containing probiotic cultures, other natural products, and traditional medicine practices that rely heavily on plants. In all cases, the interventions are delivered as complex mixtures and are thought to act across multiple biological systems. Despite this, there is relatively little research on the use of complex mixtures for their health-promoting effects or on the study of how natural products impact multiple biological systems. In part, this is due to the difficulty in systematically studying the complexity of multicomponent and multisystem interactions. Despite the advances in all areas of medicine, scientists still struggle to rigorously study complex multisystem interactions.

Given the difficulty of assessing complex interactions with current approaches, innovative strategies are needed to further elucidate how nutritional interventions, whether in the form of botanicals, probiotics, or dietary constituents, may have health benefits. The potential benefits of these complex interactions could manifest themselves in multiple ways. This includes multiple components of a dietary intervention acting on a single biological system (e.g., nervous or digestive), a single component acting on multiple systems (e.g., omega-3 fatty acids), or multiple components acting on multiple systems (e.g., traditional herbal medicine, probiotics). It also includes the possibility that these complex interactions produce more than additive (i.e., synergistic) effects. Cocktail approaches are used increasingly in modern medicine, as evidenced by current approaches in chemotherapy and antiretroviral and antimicrobial regimens. While the principle of complex interactions and synergy is mentioned often to justify research on natural products, rigorous efforts to quantify these multicomponent and multisystem activities in nutritional interventions is lacking. Classic pharmaceutical development seeks to identify a single active compound that acts at a single target site. This has been a very successful endeavor, as evidenced by the high percentage of pharmaceuticals derived from natural products, but it might not readily apply to the study of multisystem and multicomponent interactions involving nutritional interventions. Thus, a deeper understanding of the systems-level interactions of natural products with human biology, including the microbiome, is needed to answer fundamental questions regarding their health-promoting effects.

### What Does Success Look Like?

- NCCIH supports a robust portfolio of research focused on the study of nutritional interventions, including individual plants/probiotics as well as multibotanical and multistrain formulas, and their potentially synergistic interactions with single or multiple biological systems.

- Enhanced multisystem research approaches that tie together various cellular, gut microbial, and genetic contributors to health restoration and disease prevention.

- Substantial development or application of cutting-edge multidisciplinary approaches, including bioinformatic and data sciences, to uncover contributions from multiple constituents that may produce subtle changes individually yet yield outsized benefits across multiple biological systems in combination.

— Translation of innovative mechanistic studies from *in vitro* and animal models into human efficacy and effectiveness studies with a strong focus on multisystem outcomes.

**Priorities**

Botanicals

— Use phenotypic models (e.g., cellular, invertebrate, rodent) to study the potential of multiple components in botanical mixtures to act through multiple mechanisms and produce better outcomes than individual constituents.

— Explore innovative multisystem mechanistic interactions (e.g., between the digestive system and the brain or between immune and musculoskeletal or myofascial systems) of botanicals.

— Investigate the theoretical framework underlying the roles of individual components in multibotanical formulae, including how they contribute to activity, bioavailability, and/or toxicity.

Dietary Phytochemicals

— Investigate phytochemicals abundant in fruits and vegetables and how their diverse individual activities interact in combination and across multiple systems.

— Develop and test a unifying hypothesis to explain the broad activity of polyphenols.

Probiotics

— Explore spatial and temporal dynamics of biological activities of probiotics in the gastrointestinal tract.

— Investigate novel mechanisms underlying multisystem effects (e.g., interlinking the gastrointestinal tract, immune system, and brain) of probiotics.

— Conduct systematic and mechanistic studies of how the gut microbiome influences interactive effects of probiotics with other dietary interventions.

— Explore discrete combinations of plants and/or plant constituents with probiotic strains to ascertain how their combined activities differ from either individually.

Methods Development

— Develop and validate computational models to predict the presence of synergistic components in complex dietary interventions.

— Develop and test advanced prognostic and diagnostic systems with a combination of biosensors and artificial intelligence to monitor and predict host physiological status improved by probiotics and complex dietary interventions.

— Compare and validate various traditional diagnostic and prognostic medical systems in contrast to analogous contemporary Western medical diagnostic and prognostic systems.

— Develop and validate *in vitro* and/or *in vivo* models capable of simultaneously assessing multiple biological systems.

— Develop and validate innovative systems biology models incorporating diverse phytochemical inputs and their interaction with multiple biological systems.

**Low-Priority Topics**

— Studies on combinations of macronutrients (fats, carbohydrates, proteins) for their nutritional effects.

— Studies on vitamins, minerals, or amino acids individually or in combination for their nutritional effects or to address nutritional deficiencies.

— Broad epidemiological studies of correlations between dietary patterns and health outcomes.

— Research in humans using dietary constituents individually or in combination for treatment or prevention of chronic disease conditions specifically within the mission of other NIH Institutes and Centers (e.g., cancer, diabetes, cardiovascular disease).

— Studies on mechanisms already well established or known for a natural product or a category of natural products.

# Enhancing the Complementary and Integrative Health Research Workforce

### Introduction and Explanation of Need

NCCIH is committed to training researchers with the expertise needed to conduct successful basic, mechanistic, translational, clinical, and implementation studies on complementary and integrative health approaches. Researchers from many different scientific disciplines possess critical knowledge and technologies required for in-depth investigation of the basic biological, physiological, and clinical effects and safety of complementary health approaches and their integration into conventional medicine. As detailed on our training webpage (https://www.nccih.nih.gov/training), NCCIH supports a range of research training and career development programs aimed at increasing the number and diversity of well-prepared, skilled investigators with knowledge and expertise in both complementary and integrative health interventions and state-of-the-art research methods. The 2021–2025 NCCIH Strategic Plan includes Objective 4: Enhance the Complementary and Integrative Health Research Workforce, with two primary 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.

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

NCCIH supports training and career development of investigators pursuing research topics that are well aligned with our scientific strategic objectives. We seek to support trainees across career stages pursuing basic, mechanistic, translational, and clinical science on natural products, mind and body practices, and/or multicomponent approaches. We are particularly committed to the development of a complementary and integrative health research workforce that is representative of the diversity in American society, in support of NIH's Interest in Diversity (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html). In addition to enhancing the diversity of our research workforce, the Center is also focused on supporting career development of clinician-scientists, including conventionally trained physicians, complementary health practitioners, and other health care professionals (e.g., clinical psychologists, nurses) who are interested in complementary and integrative health research. This includes both individual-level training for clinician-scientists and fostering institutional-level interdisciplinary partnerships to facilitate cross-training and interdisciplinary research teams. We also seek to promote the success of NCCIH-funded trainees as they progress to the next steps of their scientific careers and to identify best practices to continually improve our training and career development portfolio.

**What Does Success Look Like?**

— Increased diversity of researchers engaging in complementary and integrative health research to enhance participation of individuals from groups that are underrepresented in the biomedical, clinical, behavioral, and social sciences, as described in the Notice of NIH's Interest in Diversity (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html).

— An expansion of clinician-scientists in the NCCIH training and career development portfolio representing a diverse range of clinical training expertise.

— Support of institutional-level interdisciplinary collaborations that support cross-training and development of interdisciplinary teams focused on complementary and integrative health research.

— An improved career pipeline that produces more NCCIH-funded trainees, fellows, and early career development awardees who successfully compete for subsequent NIH or other Federally funded research awards.

— The NCCIH training and career development portfolio spans all career stages of basic, mechanistic, translational, and clinical science, as well as research training in natural products, mind and body practices, and/or multicomponent approaches.

— NCCIH evaluates its training and career development activities and retools any underperforming activities.

**Priorities**

- Enhance outreach and communication activities to promote existing and new training and career development funding opportunities to a variety of communities (e.g., complementary and integrative health clinical institutions, minority-serving institutions, trainees from backgrounds underrepresented in biomedical research, interdisciplinary professional organizations).

- Support training and career development funding opportunities that align with NIH's Interest in Diversity (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html) (e.g., participation in trans-NIH efforts to promote diversity, such as the Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program (https://www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx); enhancements to existing administrative supplement programs; development of new initiatives).

- Support training and career development funding opportunities for clinician-scientists at several levels of career development (e.g., participation in trans-NIH efforts to support clinician-scientists; expansion of existing NCCIH-specific administrative supplement programs, such as the KL2 administrative supplement [https://grants.nih.gov/grants/guide/notice-files/NOT-AT-20-010.html]).

- Support funding opportunities to establish institutional collaborations that facilitate research training and the development of interdisciplinary research teams (e.g., participation in trans-NIH efforts to create cohorts of interdisciplinary scientists, such as the NIH Common Fund Faculty Institutional Recruitment for Sustainable Transformation (FIRST) (https://commonfund.nih.gov/FIRST) program; development of new initiatives such as the creation of virtual resource centers to facilitate research collaborations between complementary and research-intensive institutions).

- Develop materials (e.g., blogs, enhancements to the NCCIH website) and hold workshops to support NCCIH-funded trainees as they transition from one career stage to the next.

- Promote applications in specific topic areas to balance the training and career development portfolio across career stages (e.g., encourage fellowship applications from trainees interested in mind and body clinical research that uses secondary data analyses and/or proposes an experience within a mentor's clinical study to enrich translational science training and career development proposals).

- Perform regular evaluations of training and career development activities (e.g., regular evaluation of application rates, funding rates, and appropriate performance markers for all training and career development activities).

# Mechanisms and Biomarkers of Mind and Body Approaches

### Introduction and Explanation of Need

Complementary and integrative health approaches include a broad range of practices and interventions that may have originated outside of conventional medicine and are gradually being integrated into mainstream health care. These approaches can be classified by their primary therapeutic input, which may be nutritional, psychological, and/or physical. Psychological and/or physical approaches encompass what have been commonly considered mind and body approaches. Commonly used psychological approaches include meditation and cognitive behavioral therapy, while physical approaches include acupuncture, other manual therapies (soft tissue manipulation, massage, spinal and joint manipulation, and related devices), and physical exercise. Some approaches, such as yoga and tai chi, comprise both psychological and physical components. Psychological and/or physical approaches have been generally used by the public to treat or manage disorders and symptoms such as pain, sleep disturbance, stress, and anxiety, as well as to support general health.

The majority of the mechanistic studies of psychological and physical approaches focus on the neural system (human adult) and psychological and social systems, while other physiological systems, organs, and tissues (e.g., immune, microbial, cardiovascular, musculoskeletal, endocrine, respiratory, metabolic, digestive, reproductive) remain understudied. Similarly, mechanistic studies involving combined multicomponent approaches (e.g., yoga, massage) are scarce compared to studies evaluating single interventions. Fundamental animal and human research on mechanisms impacting multiple domains (biological, behavioral, social, environmental) that underly psychological and physical interventions, as well as research on potential biomarkers to predict intervention efficacy or treatment responses, are critical for developing strategies to optimize the beneficial effects of these interventions. Such studies are scientifically challenging due to individual heterogeneity (e.g., variability in genetic and epigenetic makeup or psychosocial and environmental factors) and the current lack of optimal tools and technologies to evaluate mechanistic and clinical effects. Nevertheless, recent advances in genomics, neuroscience, stem cells, systems biology, neuroimaging, and predictive computational modeling offer promising technological and conceptual resources and opportunities for innovative and impactful mechanistic studies of physical and psychological approaches.

### What Does Success Look Like?

Successful mechanistic studies of psychological and physical approaches include two separate but interoperable accomplishments in model systems/organisms and/or human/clinical populations across the lifespan:

- Identification of predictive markers or biomarkers that can differentiate responders from nonresponders to psychological and physical approaches.

- Identification of novel mechanisms of action underlying psychological and physical approaches that may shed new insights into the fundamental science of these approaches or be used to optimize the beneficial effects of these approaches alone or in combination with other therapies.

**Priorities**

- Develop or use innovative (1) humanized cellular or organ systems or (2) transgenic or preclinical animal models to investigate the mechanisms relevant to psychological and physical approaches.

- Elucidate the mechanisms underlying multisystem effects (e.g., physical and psychological) or the effects of combined multicomponent interventions (e.g., yoga and massage) in humans.

- Elucidate the mechanistic effects of psychological and physical interventions combined with conventional medical approaches (pharmacologic and surgical interventions).

- Identify and validate potential biomarkers that predict the therapeutic response to or efficacy of psychological and physical interventions.

- Elucidate the innovative mechanisms of psychological and physical interventions for symptom management (e.g., stress, anxiety, sleep disorders, pain) and health promotion, restoration, and disease prevention across the lifespan (e.g., children, older adults) or in underrepresented populations (e.g., women, underserved, veterans).

- Assess multisystem mechanisms and their interactions underlying psychological and physical interventions (e.g., musculoskeletal-immune, cardiovascular-endocrine, genetic-social, brain-gut).

- Ascertain the interactions of physiological systems (e.g., neural, musculoskeletal, immune) and psychosocial factors in response to force-based interventions (e.g., acupuncture, massage therapy, spinal and/or joint manipulation) in animal models or human subjects.

- Investigate the mechanisms of relatively less studied psychological and physical interventions, such as exercise-based (e.g., stretching, yoga, tai chi, qi gong), stimulatory (nerve stimulation, transcranial magnetic stimulation, neuromodulation), and art-based (music therapy, dance, visual art) interventions.

- Investigate the mechanisms by which psychological contextual factors and social/environmental interactions (e.g., at the family or community level) modulate psychological and physical interventions.

- Develop and validate tools and technologies for mechanistic studies of psychological and physical approaches.

# Supporting Impactful Clinical Trials of Complementary and Integrative Health Approaches

### Introduction and Explanation of Need

To achieve the NCCIH mission 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, NCCIH supports clinical trials to assess the safety, efficacy, and effectiveness of these approaches. NCCIH defines impactful clinical trials as those that 1) provide evidence to inform clinical practice guidelines and health care policies or 2) provide sufficient preliminary data to inform the design of and ability to conduct fully powered clinical trials. Fully powered trials must be rigorously performed using randomized controlled designs with adequate study power to test the primary hypothesis. To enhance generalizability and meet NIH policy requirements, it is important that fully powered trials recruit participants from different geographic regions and include a diverse sample of participants that reflects the U.S. patient population with the condition being studied.

NCCIH has developed a framework for human subjects research that describes the range of research supported from basic and mechanistic studies through dissemination and implementation science studies (see page 23). Within the framework, NCCIH prioritizes the need for preliminary feasibility and acceptability data from the literature or a feasibility study to have confidence that a fully powered efficacy or effectiveness study can be conducted. For this priority area, NCCIH is emphasizing the support of clinical trials that will inform clinical guidelines and health care policy decisions. NCCIH also has interest in supporting randomized pragmatic clinical trials that enroll a generalizable population from real-world settings and leverage data from electronic health records. It is important that the interventions proposed for pragmatic and implementation trials have demonstrated efficacy or effectiveness.

### What Does Success Look Like?

- Trials supported by NCCIH provide strong evidence for clinical guideline development and health care policy decisions.

- The clinical portfolio comprises a range of clinical trials to assess the impact of nutritional, psychological, and physical approaches, including feasibility trials, randomized controlled efficacy trials, randomized controlled effectiveness trials, randomized controlled pragmatic trials, and dissemination and implementation studies.

- Interventions found to be feasible in early-stage trials are moved into multisite clinical trials to assess their safety and efficacy or effectiveness, and then interventions with demonstrated efficacy or effectiveness are evaluated in pragmatic trials conducted in health care systems, as well as dissemination and implementation studies.

- When appropriate, the portfolio includes trials with innovative designs to address unique hypotheses about which complementary health approaches are most effective, for whom, and under what conditions.

- NCCIH issues notices for clinical trials in specific scientific areas based on scientific need and as funds allow.

**Priorities**

Intervention Translation and Development

— Support trials of natural products, including probiotics, to assess whether the impacts of these products on biological signature(s) are reproducible.

— Support development of manualized intervention manuals of integrated multicomponent therapies and systems and feasibility testing of these manualized interventions.

Intervention Refinement and Feasibility Testing

— Encourage multisite pilot studies to demonstrate an intervention is feasible across sites.

Intervention Testing

— For nutritional approaches: Support fully powered randomized controlled efficacy trials when preliminary data demonstrate the nutritional intervention (e.g., natural product) produces a reproducible impact on a biological signature(s).

— For research on psychological and/or physical approaches: Support fully powered randomized controlled efficacy or effectiveness trials when preliminary data demonstrate the single or multicomponent intervention(s) can be delivered with fidelity and participant adherence across sites.

— Encourage pragmatic clinical trials of nutritional, psychological, and/or physical interventions that have demonstrated efficacy or effectiveness to determine whether the interventions remain effective when they are integrated into health care systems.

— When research hypotheses call for it, use innovative or adaptive study designs.

Dissemination and Implementation Studies

— Support research studies to determine how to disseminate or implement complementary health approaches that have established efficacy into clinical or community-based care settings, using dissemination and implementation science methodology (see Implementation Science priority topic for more information).

## Communications Strategies and Tools To Enhance Scientific Literacy and Understanding of Clinical Research

### Introduction and Explanation of Need

Surveys conducted in the United States reveal that many citizens do not have a firm grasp of basic scientific facts and concepts, nor do they understand the scientific process. Without an understanding of the science of health, many consumers will continue to value anecdotes over evidence, believe excessive claims made by supplement manufacturers or TV doctors touting the latest "miracle cure," and potentially make unwise and unsafe decisions about their health. Those who do possess basic knowledge of the science of health have the capacity to obtain, process, and understand basic information about scientific research needed to make appropriate decisions about their health. Given the current health policy and research emphasis on shared decision making with patients, enhanced patient understanding of the science of health is also a system-level priority. Health care professionals will bear a growing onus to explain and engage in dialogue with patients about treatment options. Promoting understanding of the science of health among a broad consumer base may ultimately make those discussions and decisions easier.

There is also a particular need for an improved understanding of the science of health for those who use complementary and integrative health approaches. Because many of these approaches are readily available in the marketplace and because so many individuals choose self-care options for their health, NCCIH sits at the crossroads between research and real-world consumer use. Further, to enhance the value and impact of NCCIH's efforts in disseminating information, consumers need a basic understanding of the research enterprise.

### What Does Success Look Like?

- Continuing to build on and expand the existing Know the Science effort to educate the public about the importance of understanding biomedical research so people can make informed, evidence-based decisions about their health.

- A successful strategic effort includes qualitative and quantitative evaluation, usability testing, expanded content development (e.g., new topics, to include bias and causation versus correlation), support for scientific spokespeople, and outreach and dissemination.

### Priorities

- To collaborate with partners within and external to the Federal Government committed to enhancing consumers' understanding of the science of health and addressing misinformation that persists on the internet and in popular media and advertising.

- To develop and evaluate easy-to-understand materials in a variety of platforms and for diverse audiences.

- To promote the use of these materials among the general public via direct outreach and by targeting influential stakeholders.

### Areas of Low Programmatic Priority

— Development of content with the specific goal of improving clinical trial recruitment.

— Dissemination of materials and content at various reading levels for people with low literacy skills.

— Development of communications strategies pertaining to the understanding of medical brochures, physician instructions, and consent forms, and to the ability to navigate complex health care systems.

# Appendix

## 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 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.

## 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 the webinar and town hall Whole Person Health: Mapping a Strategic Vision for NCCIH (https://www.nccih.nih.gov/news/events/whole-person-health-mapping-a-strategic-vision-for-nccih-webinar-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 (https://www.nccih.nih.gov/news/events/nccih-strategic-planning-town-hall-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. Both NCCIH and NIH staff also provided input to the development of the strategic plan throughout the process.

The draft strategic plan was posted to the NCCIH website in February 2021, and an RFI (https://grants.nih.gov/grants/guide/notice-files/NOT-AT-21-005.html) was issued for public comment on the draft.

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

# For more information

National Center for Complementary and Integrative Health
nccih.nih.gov

National Institutes of Health
nih.gov

U.S. Department of Health & Human Services
hhs.gov

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