The National Institute on Aging:

Strategic Directions for Research, 2020-2025

ONLINE ONLY

From the Director

I am pleased to present the strategic directions of the National Institute on Aging (NIA) for 2020-2025.

Today, there are more Americans ages 65 and older — just over 49 million, according to the U.S. Census — than at any other time in history, and we expect these numbers to grow as more Baby Boomers (individuals born between 1946 and 1964) reach retirement age. We can attribute this unprecedented demographic shift to a variety of factors, many of which benefit people of all ages. For example, even within the lifetimes of today's older Americans, infectious diseases that once cut millions of lives short have been largely controlled in the U.S., and public health campaigns and policy changes — for example, smoking cessation efforts and laws mandating seat belt use — have saved many more lives.

Despite these advances, aging itself remains the most significant risk factor for many chronic diseases and conditions, including Alzheimer's disease and related forms of dementia (AD/ADRD), most types of cancer, many types of heart disease, osteoporosis and hip fracture, kidney failure, and diabetes. While these diseases are rarely inevitable, it is probable that as the number of older Americans increases, so too will the number of people with age-related diseases. A significant increase in the number of individuals with serious chronic conditions will have profound social and economic effects on the nation.

NIA is meeting these challenges through its ongoing mission to:
- Support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging.
- Foster the development of research and clinician scientists in aging.
- Provide research resources.
- Disseminate information about aging and advances in research to the public, health care professionals, and the scientific community, among a variety of audiences.

Our primary activities include funding extramural research at universities and research centers across the U.S. and around the world; maintaining an active communications and outreach program; and conducting a vibrant intramural research program at NIA laboratories in Baltimore and Bethesda, Maryland. In addition, as the lead federal agency for research on AD/ADRD, NIA has received an unprecedented influx of funding targeted toward understanding and addressing these conditions over the past seven years, and our plans and priorities reflect this extraordinary opportunity for discovery.

This document presents our scientific priorities for the next five years. Consistent with guidance in the 21st Century Cures Act, we also lay out our goals and objectives with respect to some of the "behind the scenes" activities we conduct in order to support the science. It is our hope that this description of our priorities is useful to you, whether you're an independent researcher, an advocate, or an interested layperson.

For up-to-date information about NIA's activities, priorities, and advances, I invite you to visit our web site at www.nia.nih.gov.

Sincerely,

Richard J. Hodes, M.D.

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The National Institute on Aging: Strategic Directions for Research, 2020-2025

The National Institute on Aging

The National Institute on Aging (NIA) is one of 27 Institutes and Centers of the National Institutes of Health (NIH), a component of the U.S. Department of Health and Human Services. Our mission encompasses basic, translational, and clinical research; training and career support for investigators at all levels; resource allocation; and health communication to a range of audiences. Congress established the NIA in 1974 to lead a national scientific effort to understand the nature of aging in order to promote the health and well-being of older adults. The Institute was subsequently designated as the lead within NIH for research on Alzheimer's disease and related forms of dementia (AD/ADRD). NIA pursues its mission by funding extramural research at universities and medical centers across the U.S. and around the world; maintaining an active communications and outreach program; and conducting a vibrant intramural research program at NIA laboratories in Baltimore and Bethesda, Maryland.

Public Law 93-296 authorizes the establishment of a National Institute on Aging and requires that the institute develop a national comprehensive plan to coordinate the Health, Education, Welfare (HEW) agencies involved in aging research. The Institute's purpose, functions, and certain activities are described in 42 U.S. Code §285e.

About This Document

This document outlines NIA's broad strategic directions. It provides a point of reference for setting priorities and a framework for systematically analyzing the Institute's scientific portfolio and assessing progress. NIA developed and refined these goals over a one-year period, receiving valuable input and feedback from stakeholders in the research community, nongovernmental organizations, partners within NIH and elsewhere within the federal government, and members of the general public via a November 2018 Request for Information. We will update the document as needed as the field of aging research evolves.

Our goals are as follows:

Understanding the Dynamics of the Aging Process

Goal A: Better understand the biology of aging and its impact on the prevention, progression, and prognosis of disease and disability.

Goal B: Better understand the effects of personal, interpersonal, and societal factors on aging, including the mechanisms through which these factors exert their effects.

Improving the Health, Well-Being, and Independence of Adults as They Age

Goal C: Develop effective interventions to maintain health, well-being, and function and prevent or reduce the burden of age-related diseases, disorders, and disabilities.

Goal D: Improve our understanding of the aging brain, Alzheimer's disease, related dementias, and other neurodegenerative diseases. Develop interventions to address Alzheimer's and other age-related neurological conditions.

Goal E: Improve our understanding of the consequences of an aging society to inform intervention development and policy decisions.

Goal F: Understand health disparities related to aging and develop strategies to improve the health status of older adults in diverse populations.

Supporting the Research Enterprise

Goal G: Support the infrastructure and resources needed to promote high-quality research.

Goal H: Disseminate information to the public; scientific and medical communities; stakeholder advocacy, community and older adult-support organizations; the media; and policymakers about research and interventions.

Goal I: Effectively steward public resources.

Our vision is to enable all Americans to enjoy robust health and independence with advancing age.

How Will We Measure Progress?

As a component of the NIH, NIA supports research with the goal of curing disease and improving overall health. However, the path from bench to bedside — that is, from basic scientific discovery to clinical application — is often long and is rarely straightforward. It's the nature of biomedical science that years or even decades worth of incremental advances may be necessary before a basic discovery, however ground-breaking, pays off in the form of new interventions to benefit health. While a direct link can sometimes be drawn between specific funding and an improvement in health, more often the story is complex. Furthermore, with each new breakthrough, science can advance and evolve in unanticipated ways. These new directions also serve as indicators of progress, and we consider them to be a successful outcome of our support, even when direct clinical application is not immediately evident.

With all of this in mind, NIA will use both quantitative and qualitative techniques to measure progress toward the priorities described in this document; analyze the scientific, clinical, and public health impact of its research; and periodically report results to stakeholders. We will do this through regular analysis and evaluation of programs and initiatives that have been developed in support of our priorities. Because no two programs or initiatives are exactly the same, the tools, measures, and approaches we use for each evaluation or analysis will differ. However, we anticipate working with partners across NIH, such as the Office of Portfolio Analysis and the Office of Program Evaluation, Performance, and Reporting to track progress and initiate course corrections where necessary.

Understanding the Dynamics of the Aging Process

Aging is associated with changes in dynamic biological, physiological, environmental, psychological, behavioral, and social processes. Some age-related changes are benign, such as graying hair. Others result in declines in function of the senses and activities of daily life and increased susceptibility to and frequency of disease, frailty, or disability. In fact, advancing age is the major risk factor for a number of chronic diseases in humans.

Studies from the basic biology of aging using laboratory animals — and now extended to human populations — have led to the emergence of theories to explain aging. While there is no single "key" to explain aging, these studies have demonstrated that the rate of aging can be slowed, suggesting that targeting aging will coincidentally slow the appearance and/or reduce the burden of numerous diseases and increase healthspan (the portion of life spent in good health).

To develop new interventions for the prevention, early detection, diagnosis, and treatment of aging-related diseases, disorders, and disabilities, we must first understand their causes and the factors that place people at increased risk for their initiation and progression. NIA-supported researchers are engaged in basic science at all levels of analysis, from molecular to social, to understand the processes of aging and the factors that determine who ages "well" and who is susceptible to age-related disease and disability. Research is also ongoing to identify the interactions among genetic, environmental, lifestyle, behavioral, and social factors and their influence on the initiation and progression of age-related diseases and degenerative conditions.

NIA has established two goals related to the basic science of aging:

> **Goal A: Better understand the biology of aging and its impact on the prevention, progression, and prognosis of disease and disability.**

> **Goal B: Better understand the effects of personal, interpersonal, and societal factors on aging, including the mechanisms through which these factors exert their effects.**

Goal A
Better understand the biology of aging and its impact on the prevention, progression, and prognosis of disease and disability.

Aging is not, in and of itself, a disease. However, aging is the major risk factor for developing many major chronic diseases. Furthermore, many diseases appear to accelerate the aging process — which is manifested as declines in functionality and reduced quality of life.

One of our challenges is to develop a clearer understanding of the basic biology underlying changes that accompany aging, as distinct from the basic biology underlying disease. For example, in response to bacterial infections or wounds, inflammation is an essential part of the recovery and healing process. However, low-level chronic inflammation that appears in the absence of clinically diagnosed infection may increase the susceptibility to and rate of progression of age-related pathologies. Chronic inflammation may also contribute to frailty in ways that are independent of obvious disease.

Another challenge is to take advantage of the most promising opportunities presented by research in laboratory animals and to translate those findings to humans. A few recent discoveries offer possibilities for improved human health in an aging population. For example:

- Interventions that extend lifespan also extend healthspan — the portion of lifespan spent in good health — suggesting that interventions that extend life can reduce the burden of multiple diseases.

- A particularly promising avenue of research involves cellular senescence, a process in which cells lose function, including the ability to divide and replicate, but continue to secrete molecules that damage neighboring cells. Investigators found that when treated with *senolytics*, or compounds that selectively remove senescent cells, mice that had previously been injected with damaging senescent cells regained physical function. Senolytics also extended lifespan and healthspan in naturally aging mice. In addition, investigators have found that clearing senescent cells from the brain preserves cognition in a mouse model of Alzheimer's disease. Several senolytics have recently moved into early-stage human trials.

- Reduction of caloric intake causes normal cells to mount stress-response defenses that cancer cells cannot, a finding that has entered clinical testing as a possible intervention to enhance chemotherapy while also reducing some of its side effects.

- Longevity can be inherited across generations through *epigenetic* changes — that is, changes that affect gene behavior but do not alter the underlying sequence of DNA. This suggests that parental lifespan and even parental behavior can influence the lifespans and healthspans of the next generation through mechanisms other than genetics.

These and newly emerging findings on the basic biology of aging hold great promise for improving health, and NIA is committed to continuing support of this research and translating these discoveries into interventions that support better health.

Goal A objectives:

A-1: Identify genetic, molecular and cellular factors that determine the rate of aging processes.

A-2: Determine how cellular and molecular changes associated with aging contribute to decreased resilience and increased morbidity and influence response to treatment of age-associated physical conditions.

A-3: Determine how cellular and molecular bases of changes associated with aging contribute to the development and course of age-related dementia and treatment response.

A-4: Identify factors associated with successful aging and resilience against disease and dysfunction.

A-5: Understand the sensory and motor changes associated with aging and how they lead to decreased function and increased risk of morbidity.

A-6: Identify and characterize interventions that hold the promise of increasing healthy lifespan.

A-7: Develop and/or identify biomarkers (including genetic, epigenetic, molecular, cellular, immunological, metabolic, and microbiome-related) that are applicable to aging and geroscience research.

A-8: Use comparative biology to understand how adaptations in diverse species ultimately affect aging.

Approach

A-1 Identify genetic, molecular and cellular factors that determine the rate of aging processes. Researchers continue to identify and explain key factors affecting the rate of aging, including the body's response to a variety of stresses; the function of the immune system; the role of cellular senescence; the body's response to macromolecular damage (damage to large molecules such as proteins or lipids), such as that caused by oxidative stress; and protein quality control (proteostasis). Studies of genes and epigenetic mechanisms associated with aging processes, longevity, and age-related diseases, as well as the interplay among genes and environmental influences, also continue to provide insights into disease pathologies and vulnerability. NIA will support research to identify additional factors and to clarify their roles both in animal models of aging and in humans.

A-2 Determine how cellular and molecular changes associated with aging contribute to decreased resilience and increased morbidity and influence response to treatment of age-associated physical conditions. Increasing age is often accompanied by a progressive decline in most physiological functions, resulting in increased susceptibility to disease. At the same time, many people maintain physical function and enjoy robust health well into older age. Together, these findings inform the emerging field of geroscience, which hypothesizes that manipulating basic processes of aging could help to maintain physiological function and might provide an effective way to prevent or treat age-related diseases. NIA will encourage research in both the loss and maintenance of functions during the aging process and will foster studies both in humans and in animal models to investigate the health- and disease-related effects of manipulating aging-related processes at the molecular or cellular level.

A-3 Determine how cellular and molecular bases of changes associated with aging contribute to the development and course of age-related dementia and treatment response. Aging itself is the primary risk factor for the development of Alzheimer's disease and most other forms of dementia, in addition to diseases and conditions (e.g., type 2 diabetes, hypertension, and vascular disease) that are associated with increased dementia risk. However, we do not fully understand the mechanisms through which aging-related changes influence the brain and increase vulnerability to pathological change. NIA will conduct and support research on how aging processes influence the development of neurological disease. In addition, we will test interventions in animal models and ultimately in humans that have been shown to increase lifespan and healthspan in animals to determine their effect on cognitive function.

A-4 Identify factors associated with successful aging and resilience against disease and dysfunction. Some people seem to be resistant to age-related disease and dysfunction. These "super-agers" may even perform cognitively or physically at levels more often seen in people who are decades younger. NIA will work to illuminate the factors that are associated with this resilience, and to determine whether those factors can be harnessed to increase resilience more broadly across the population.

A-5 **Understand the sensory and motor changes associated with aging and how they lead to decreased function and increased risk of morbidity.** Mobility changes in the aging adult can result from changes in gait, balance, and physical strength, and can negatively influence the number and severity of falls, social participation, and independence. Loss of sensory functions such as vision, hearing, or the ability to taste is also common among older adults. NIA-supported research to better understand the underlying mechanisms of age-associated sensory and motor changes will provide the knowledge base necessary to develop interventions that optimize mobility and sensory function in the later years of life.

A-6 **Identify and characterize interventions that hold the promise of increasing healthy lifespan.** The NIA established and continues to support the Intervention Testing Program to test the reproducibility of candidate interventions that will prolong lifespan and increase healthspan. In this and other research the NIA promotes studies in both female and male organisms. Similar studies are supported in the Caenorhabditis Interventions Testing Program, a multi-institutional study that investigates interventions that might extend lifespan or healthspan using diverse species and strains of the worm *Caenorhabditis*, to explore the impact of genetic diversity on the efficacy of interventions. We support studies on the mechanisms of action of these interventions which will facilitate their translation to benefit healthy aging in humans.

A-7 **Develop and/or identify biomarkers (including genetic, epigenetic, molecular, cellular, immunological, metabolic, imaging, and microbiome-related) that are applicable to aging and geroscience research.** Aging is associated with changes at multiple physiological levels. Research is needed to enable us to predict, identify, and where necessary address these changes.

A-8 **Use comparative biology to understand how adaptations in diverse species ultimately affect aging.** Lifespan is a complex biological trait resulting from multiple genetic interactions. In fact, we have identified roughly 400 genes involved in human lifespan. Comparing processes at the molecular, cellular, structural, and organismal levels across animal species and diverse human populations can provide important information about how these genes interact and illuminate critical molecular pathways that determine both lifespan and healthy function at older ages.

Goal B
Better understand the effects of personal, interpersonal, and societal factors on aging, including the mechanisms through which these factors exert their effects.

Behavioral and psychological factors — for example, physical activity, smoking and other health behaviors, cognitive and social engagement, personality, and psychosocial stress — play a critical role in health across the lifespan. Studies have shown that up to 50% of preventable deaths in the U.S. can be attributed to adverse health behaviors such as smoking as well as unhealthy diet that result in obesity. Social factors, such as social relationships and socioeconomic circumstances, have a similarly important impact on health and well-being. For example, subjective feelings of loneliness are known to be a risk factor for serious functional declines and even death, and converging lines of evidence from multiple cross-national epidemiological studies indicate that social isolation is a major risk factor for morbidity and premature mortality. And the relationship between personality — relatively stable individual differences in dispositions to think, feel, and act in particular ways — and aging-related

outcomes has been well documented: Conscientiousness is related both to longevity and to the development of AD, and neuroticism is linked to health in both positive and negative ways. A more comprehensive understanding of the causal pathways through which behavior, personality, social relationships, and socioeconomic circumstances are associated with health and well-being outcomes may suggest novel targets for intervention.

Furthermore, we now know that behavioral and social factors interact with genetic, molecular, and cellular mechanisms to influence health at older ages. Basic behavioral science is uncovering individual-level psychological, social, and behavioral factors that predict adaptive and healthy aging or confer risk for age-related decline. Evidence suggests that addressing these factors and their interplay are critical to minimizing disease and achieving full potential and vitality as people age. NIA will support and conduct research to verify these linkages and to better understand their underlying mechanisms.

Research supported and conducted by NIA is helping to identify lifestyle factors and health behaviors that directly influence physical, cognitive, sensory, and emotional health and risk of disease as people age, such as research linking work and social engagement to cognition. Scientists are developing and refining recommendations for people of all ages regarding optimal diet, use of dietary supplements, mental stimulation, physical exercise, quality sleep, social engagement, stress reduction, and other practices to increase their likelihood of enjoying healthy old age. Still other researchers are looking for better ways to enhance the physical, mental, and social capacities of older adults and to expand opportunities for them to achieve personal goals and contribute to society in meaningful ways. As investigators more precisely identify the psychological, behavioral, and social processes that influence health and quality of life, we will be able to reinforce prevention efforts, enhance symptom management, and conserve function among older adults.

Goal B objectives:

B-1: Understand the basic behavioral, social, and psychological aspects of aging.

B-2: Illuminate the pathways by which social, psychological, economic, and behavioral factors affect health in middle-aged and older adults.

B-3: Identify developmental, prenatal, early life, and environmental exposures that affect individual differences in trajectories of biological, cognitive, and functional aging; the risk of disease and death; and the capacity for resilience and adaptation.

B-4: Explore the mechanisms that account for the effects of social adversity and disadvantage, including research that focuses on critical periods for reversing such effects and/or the optimal timing of intervention.

B-5: Better understand motivation, decision-making, and mechanisms of behavior change among older adults.

B-6: Consider the role of place in the aging processes, taking into account geography in studies of late-life disability and mortality trends.

Approach

B-1 Understand the basic behavioral, social, and psychological aspects of aging. Along with new physical, social, and emotional challenges, increasing age brings changes in cognition and emotion that have impacts on subjective well-being, social relationships, decision making, and self-control. How individuals respond to these challenges has implications for their independence, cognitive function, social relationships, mental health, physical function, and economic well-being.

NIA will continue to conduct and support basic research in cognition, emotion, and motivation in normal aging, including their neurobiological and genetic bases. We will also explore these factors' relationships to individual differences, social processes, and contextual factors. Finally, NIA will continue research on the interrelationships among emotion, cognition, and brain function; this information will guide the development of new biobehavioral interventions.

B-2 Illuminate the pathways by which social, psychological, economic, and behavioral factors affect health in middle-aged and older adults. Research is needed to help fully establish the pathways through which genes, environments, and behavior interact. We will encourage multilevel and interdisciplinary research on the interactive effects of genes, behavior, biology, and social and physical environments on health and well-being as people age. Finally, we will work to identify important biomarkers that are linked to aging-relevant social and behavioral phenomena, including the integration of neuroimaging data in large-scale surveys and laboratory-based studies with representative samples.

B-3 Identify developmental, prenatal, early life, and environmental exposures that affect individual differences in trajectories of biological, cognitive, and functional aging; risk of disease and death; and the capacity for resilience and adaptation. Exposure to adverse social, interpersonal, and physical environments can exert profound and long-lasting psychological and physical effects on a developing organism, with long-term impacts on adult physical and cognitive health and longevity. Contextual factors such as residential segregation and socioeconomic status may be associated with or compound the effects of these adverse exposures. Conversely, environmental factors such as educational attainment have been associated with a reduced risk of cognitive decline and dementia. NIA will continue to support mechanistic and epidemiological studies to identify such factors and participate in translational studies to find ways to minimize their effects in adults. NIA will also continue to encourage research using a life-course approach to behavioral, psychological, economic, and social explanations for health outcomes that also incorporates the geroscience agenda.

B-4 Explore the mechanisms that account for the effects of social adversity and disadvantage, including research that focuses on critical periods for reversing such effects and/or the optimal timing of intervention. Many outcomes and behaviors in older adults are influenced by events, social relationships, noncognitive character skills, environmental factors, and habits that begin relatively early in life. Subgroups of the population experience disadvantage throughout their lives or for extended periods in life that generate persistent stress, and their patterns of stress reactivity appear to hasten the progression of disease. It is therefore important to elucidate the processes by which these adverse social exposures become biologically and psychologically embedded and contribute risk for disease and distress. In

addition, it is important to examine the malleability of these biobehavioral risk mechanisms in order to identify opportunities for their amelioration. Life-course data connecting childhood circumstances to midlife/old-age outcomes will facilitate research that identifies such mechanisms. Because many health disparities and chronic conditions emerge in midlife, NIA will continue to support research on processes of aging during this life stage to identify optimal timepoints for interventions to reverse or redirect the impact of early-life adversity and cumulative stress exposures on aging processes.

B-5 **Better understand motivation, decision-making, and mechanisms of behavior change among older adults.** As the population ages, it will be important to understand how people make decisions about retirement, lifestyle, social relationships, health, and health care. Age-related changes in the interplay between motivation, cognition, and emotion, along with changes in life circumstances, health status, and social roles, combine to shape how individuals make both everyday choices around health behaviors and major decisions related to life transitions and long-term goals. The ability to make sound decisions is an important component of cognitive health, and deficits in decision-making abilities may be an early warning sign of dementia. NIA seeks to better understand the basic psychological processes involved in decision-making and how they change with aging, how social factors and social networks influence those decisions, and the incentives that motivate middle-aged and older adults to make health-supportive decisions in a wide range of life domains. We will support research in this area along the full spectrum, from neuroeconomic, cognitive and affective research on how aging individuals perceive stimuli and make decisions to social network research.

B-6 **Consider the role of place in aging processes, taking into account geography in studies of late-life disability and mortality trends**. Health and mortality can vary dramatically across geographic regions, localities, census tracts, and even ZIP codes. We will continue to support and conduct research to identify the drivers behind these differences as well as policies and interventions that may close gaps between health and mortality in diverse locales.

The Importance of Longitudinal Data on Aging

NIA supports a number of longitudinal studies in which we have already collected a large amount of data on the participants. Because so much is already known about participants in theses studies, they provide us with a unique "living laboratory" in which to study both risk persistence mechanisms and factors that enhance responsiveness to intervention. New techniques for inferring causality from observational studies and complex data are also enabling us to draw important conclusions about the links between behavior and biology, and about possible behavioral interventions, as a complement to experimental studies and randomized controlled trials.

A cornerstone of our longitudinal data collection efforts continues to be the Health and Retirement Study (HRS), NIA's long-running study of health, retirement, disability, resources, and family support among Americans ages 50 and older. The HRS has been harmonized with similar studies in over a dozen countries in Europe, Africa, South America, and Asia, facilitating partnership and comparative research on aging around the world. HRS has also fielded a cost-effective algorithmic approach to assessing cognitive impairment and dementia, the Harmonized Cognitive Assessment Protocol, that will provide a basis for comparing trends over

time across the U.S. as well as other countries with HRS-like longitudinal studies of aging. We will continue to invest in a robust data collection infrastructure that enables study of the influence of population aging on the health and well-being of older adults.

Finally, we will continue our investments in select studies originally conceived of for other purposes but valuable for the study of early-life and midlife conditions and intergenerational influences on later-life outcomes. Cohorts from studies such as the Wisconsin Longitudinal Study and the Midlife in the U.S. Study, among many others, can be followed as they move through middle age to older adulthood in order to identify early-life risk and protective factors for age-related disease and dysfunction.

Improving the Health, Well-Being, and Independence of Adults as They Age

New insights into lifestyle, psychological, and other environmental influences on health promise to have a profound impact on the ability of older adults to remain physically healthy and cognitively, emotionally, and socially vital into very advanced ages – ideally, for as long as they live. Capitalizing on new insights from basic research, scientists will continue to work from multiple perspectives to develop and test strategies for preempting or reducing the severity of health problems that midlife and older adults experience. We will also work to strengthen the translation of basic findings and cutting-edge technological breakthroughs into practical applications to improve health and well-being at older ages.

NIA has established four goals for improving the health, well-being, and independence of adults as they age.

> **Goal C: Develop effective interventions to maintain health, well-being, and function and prevent or reduce the burden of age-related diseases, disorders, and disabilities.**
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> **Goal D: Improve our understanding of the aging brain, Alzheimer's disease, related dementias, and other neurodegenerative diseases. Develop interventions to address Alzheimer's and other age-related neurological conditions.**
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> **Goal E: Improve our understanding of the consequences of an aging society to inform intervention development and policy decisions.**
>
> **Goal F: Understand health disparities related to aging and develop strategies to improve the health status of older adults in diverse populations.**

Goal C
Develop effective interventions to maintain health, well-being, and function and prevent or reduce the burden of age-related diseases, disorders, and disabilities.

As previously noted, aging is the primary risk factor for an array of diseases and conditions. However, research has shown that health habits and behaviors such as physical activity, proper nutrition, and avoidance of smoking and other health-harming behaviors can help people live longer, postpone the onset of disability, and increase quality of life and function at older ages.

Conversely, unhealthy lifestyle choices may be associated with significant health problems. However, research has shown that it is almost never too late to decrease risk of disease and disability by establishing healthier patterns. Research has also shown that optimizing both the physical and social environment is important to the health and functioning of older adults.

While much of our research in this area will promote the most basic and fundamental aspects of health and well-being — a nutritious diet, adequate exercise, and healthy behaviors — we will also aggressively leverage powerful emerging technologies that will result in new and effective ways to maintain health and independence. For example, wearable technologies can help older adults and their health care providers track both activities and health indicators such

as blood pressure and exercise level in real time. Apps linked to a phone or device can assist with medication management. And remote sensors and artificial intelligence can be integrated to facilitate care of older adults, including those with dementia, and may also help older adults remain comfortably within their own homes as they age.

Goal C objectives:

C-1: Develop efficacious and cost-effective strategies for promoting and ensuring adherence to healthy and safe behaviors among older adults.

C-2: Develop improved approaches for the early detection and diagnosis of disabling illnesses and age-related debilitating conditions.

C-3: Develop interventions for treating, preventing, or mitigating the impact of age-related diseases and conditions.

C-4: Find significantly improved and cost-effective ways to reduce caregiver, family, and patient stress and improve older adults' ability to cope with chronic disease.

C-5: Develop strategies to improve the interaction of older adults with the health system.

C-6: Understand and develop strategies to enhance societal roles and interpersonal support for older adults, reduce social isolation, and promote positive caregiving outcomes and supports.

Approach

C-1 Develop efficacious and cost-effective strategies for promoting and ensuring adherence to healthy and safe behaviors among older adults.

- **Build on our understanding of the roles of nutrition, obesity, sleep, and metabolic status to develop more effective health maintenance strategies.** Epidemiological studies — and, in some cases, studies in animals — have shown clear positive effects of lifestyle choices such as healthy diet and physical activity, as well as the negative effects of obesity, malnutrition, and less-than-optimal sleep patterns on health and age-related morbidity. We will use these and other findings to launch clinical trials of dietary and other behavioral measures and adherence strategies for the prevention or delay of disease and disability.

- **Support research on mechanisms of behavior change in midlife and older age.** Behavior change is difficult, yet adherence to healthy lifestyles can reduce the risk of disease and increase healthspan. Having a better understanding of how and why successful behavior change occurs is the key to providing blueprints for effective and efficient behavior interventions that could reliably improve health outcomes. We will support research on the behavioral, psychological, interpersonal, and neurobiological mechanisms that drive healthy behavior change to inform the design of interventions to prevent disease and promote adaptive aging.

- **Use our increased understanding of the underlying science to maximize the positive effect of physical activity on older adults.** Several studies strongly suggest that modest physical activity may have beneficial effects in maintaining health — including mental health — and that these benefits are possible even at advanced ages. For example, weight-bearing exercise can build bone strength, protecting against osteoporosis and

subsequent fragility fractures, and balance exercises such as Tai Ji Quan may help prevent future falls. We will:

o Continue to foster research into the molecular, cellular, and physiological mechanisms by which physical activity improves health.

o Support further research on the effects of physical activity programs on older adults within specific age groups and develop strategies for promoting adherence.

o Continue to disseminate information about the importance of physical activity for older adults.

o Study the effects of physical activity and exercise on mental health and cognition.

o Support basic and translational research on the behavioral, psychological, and interpersonal mechanisms that support initiation and long-term engagement in physical activity over the adult lifespan.

- **Continue to support and conduct research to understand hormone changes in older adults and pursue the development of interventions to address these changes without unwanted side effects.** Counteracting some effects of aging by supplementing hormones such as estrogen, testosterone, human growth hormone, melatonin, and DHEA (dehydroepiandrosterone) is an area of active study, but there are concerns that individuals may be taking such agents before their safety and efficacy have been established. NIA will support studies to understand the biological action of hormonal changes in older men and women, assess whether or not hormone therapy will improve health, investigate the use of compounds to produce the beneficial responses of hormones in the body without detrimental side effects, and determine the potential to regulate hormone production in specific body tissues where increased or decreased amounts of these hormones are favorable to health.

- **Support and conduct research to understand and address the needs of people with multiple chronic health conditions.** Data from the Centers for Disease Control and Prevention show that more than half of Americans ages 65 and older are living with two or more chronic conditions. NIA will support research to identify, test, and disseminate interventions to facilitate optimal management of multiple conditions.

- **Improve the safe use of medications by older adults.** Managing medications can be complex for older adults; their medications are often prescribed by more than one physician, for multiple health problems. Complications include adverse drug interactions and interactions with dietary supplements coupled with the physiological and functional changes associated with aging or age-related diseases. Research supported and conducted by NIA will improve our understanding and maximize the effectiveness of medications, develop new technical aids for physicians to monitor drug use, and provide new technologies and information to enable patients to manage medications better and avoid adverse reactions.

- **Develop strategies to reduce falls and their consequences.** Research supported and conducted by NIA will continue to identify safety risks for older adults in home and work environments, improve screening strategies, and develop and disseminate information important to reducing the risk of falls.

- **Explore new ways to improve safety in the home and community through studies of ergonomics and the built environment.** This will include continuing research to identify cost-effective alterations in design that can reduce injuries and provide a safer environment for older adults, and an environment that encourages physical activity and social engagement.

- **Pursue a better understanding of needs and develop interventions to improve the safety of older drivers.** NIA will continue to support research to identify factors such as visual impairment, hearing, attention, speed of processing, and other cognitive changes that put older drivers at risk of automobile accidents. In addition, we will continue to support the development of tools for assessing visual, cognitive, and other abilities associated with safe driving, interventions to improve the physical and cognitive skills necessary for safe driving, and technology and design changes to accommodate or compensate for the special needs of older drivers. We will also support research to understand the dynamics of making the decision to stop driving, the implications of that decision for the health and well-being of older adults, and alternative transportation options that help older adults maintain as much independence as possible. This research will provide the insights needed to develop guidelines for older adults, their health care providers, and family members.

C-2 Develop improved approaches for the early detection and diagnosis of disabling illnesses and age-related debilitating conditions. NIA will help develop and evaluate improved biochemical, imaging, and other techniques and tools to measure the well-being of older adults as well as symptoms of disease and disability. As new interventions are ready, the institute will disseminate information about the interventions to the public and health care communities, working to help move interventions into mainstream medical practice.

C-3 Develop interventions for treating, preventing, or mitigating the impact of age-related diseases and conditions.

- **Investigate the mechanisms by which lifestyle interventions affect aging-related changes and determine how individuals can maintain function with age or regain that function after loss due to immobility, illness, or trauma.** After peaking in early adulthood, most tissue functions decline with advancing age. This leads to increased risk of developing diseases such as cardiovascular disease and cancer and may lead to declines in overall health and quality of life. Further research is needed on the mechanisms through which common interventions, both medical and behavioral, may slow physical and cognitive decline. NIA will continue to support research into the mechanisms of functional decline and its delay, with the goals of identifying molecular targets for drug interventions and treatments that minimize losses and promote the recovery of function after illness or trauma.

- **Support the development of behavioral interventions based on principles of basic behavioral and social science and designed with an eye to real-world implementation, in line with the NIH Stage Model.** Because behavioral interventions frequently do not move beyond efficacy testing to effectiveness or implementation, NIH has developed a model to define and clarify the activities in behavioral intervention development and to facilitate scientific development of interventions that are both potent and

implementable. NIA will use this model as a guide for developing interventions that will be effective in real-world settings. (For more on the NIH Stage Model, see https://www.nia.nih.gov/research/dbsr/nih-stage-model-behavioral-intervention-development).

- **Identify, characterize, and where appropriate, develop interventions for physiological changes that influence the risk of age-related diseases across the human lifespan.** Studies will include changes that are associated with increased risk of disease and disabling conditions such as sarcopenia (reduced muscle mass), as well as those that are associated with exceptional health and longevity.

- **Conduct clinical studies and encourage the translation of new interventions to the clinical setting.** As mechanisms, pathways, and processes of disease are better defined, and as potential healthspan-extending interventions are validated in model systems, development and testing of clinical applications in humans can begin. We will pursue the use of novel, flexible research designs where appropriate, and we will work with others to facilitate the navigation of barriers to the translation of promising compounds into clinical trials and ultimately approval by the U.S. Food and Drug Administration.

- **Support comparative effectiveness research.** NIA will continue to support research to identify the relative merits of differing interventions for older adults. For example, investigators are testing the effectiveness of different interventions in improving quality and efficiency, eliminating disparities in treatment, and reducing unwarranted variations in expenditures at hospitals. Still others are comparing physical activity interventions and cognitive interventions to determine their relative effectiveness and examining the interactive effects of a combined physical activity/cognitive intervention program.

C-4 **Find significantly improved and cost-effective ways to reduce caregiver, family, and patient stress and improve older adults' ability to cope with chronic disease.** Families and others who care for people with chronic disease frequently face emotional stress as well as physical and financial burdens. At present, the direct economic costs of caregiving to caregivers and society are unknown, and it is not well understood how caregiving impacts the health and well-being of some caregivers and why some caregivers thrive in the experience of caregiving, whereas others experience distress, burden, and unhealthy outcomes of their own. Using approaches grounded in basic behavioral and social science, investigators will continue to develop and evaluate strategies to improve social support, skills training, and assistive services both for those who cope with chronic disease and for their caregivers. These initiatives should result in more effective and implementable approaches for prevention, treatment, and rehabilitation, as well as the ultimate adoption of these approaches in real-world contexts. Research supported and conducted by NIA will clarify needs and patterns of family caregiving and how people make decisions on providing care and inform guidance on support and skills, including a focus on families with diverse ethnic and socioeconomic backgrounds.

- **Develop strategies to help older adults and their families prepare for and manage age-associated changes in health, income, function, and roles.** Older adults and family members are faced with many complex decisions about medical treatment and various aspects of their retirement, finances, and long-term care that can affect their independence and well-being. Issues of concern include the ability of health care delivery systems to support patient and family needs, adherence to a patient's advance

directives, and financial resources to cover out-of-pocket costs for acute and long-term care and assistance needed for maintenance of optimal health. We will support research to develop data resources incorporating work, financial status, health care utilization, and outcomes to allow analyses of pathways to independent healthy aging. We will support the development of principle-based supportive interventions that can be implemented in real-world contexts. Research findings will be useful for people as they plan for later-life transitions as well as to inform policy decisions.

- **Investigate the social aspects of family caregiving and develop and disseminate effective interventions for patient care in family and community settings.**

  o *Assess and evaluate family relationships over time.* This research will help us understand the role of interpersonal processes and the effects of changing relationships and social roles on the health and well-being of older adults.

  o *Address issues centered on the increased demands faced by family caregivers in light of changing patterns of work and family demographics.* We will pay particular attention to the ways in which characteristics such as gender, marital status, income, socioeconomic status, race, and ethnicity influence these demands.

- **Research and develop strategies to improve decision making for long-term and end-of-life care.** There is a pressing need to identify approaches that will ensure quality, affordable long-term care that maintains optimal health and function for older adults. There is also a critical lack of peer-reviewed research on how to improve quality at the end of life. To better address these issues, we will:

  o *Support research to examine component parts of health care delivery systems and their impact on medical, social, functional, and cost outcomes and use this information to test interventions to improve care.* This research will help inform the development of interventions to coordinate care that promotes attention to patient and family preferences, facilitates smooth transitions among care settings, and maximizes independence. We will explore ways to support long-term care including care provided in the home. We will focus on interventions that reduce the burdens of caregivers, with an emphasis on the unique challenges faced by caregivers of patients with dementia.

  o *Understand caregiving patterns and improve the effectiveness of strategies for helping families manage the care needs of the physically frail.* For example, we will support research to identify effective caregiving strategies, environmental modifications, and technological supports for both informal and formal long-term care settings.

  o *Develop strategies to improve the experience of older adults at the end of life.* We will support research to better understand the decision-making process and changing preferences associated with advance care planning; better understand the transitions among end-of-life care settings such as the home, hospital, nursing home, and hospice; assess the benefit of end-of-life therapies and the cost effectiveness of interventions to improve end-of-life care; develop better measures of end-of-life quality for the patient and the family to improve our understanding of

psychosocial issues that impact the end-of-life experience; and understand the social and economic context of caring for an older person who is dying.

C-5 Develop strategies to improve the interaction of older adults with the health system. For older adults and their families, effective health care requires quality communication with and among health care professionals. According to one study, fewer than 40% of people experiencing symptoms associated with heart and circulatory or musculoskeletal systems seek a physician's care. Similarly, women often avoid seeking care for urinary incontinence. We will seek better interventions to help older adults recognize the implications of disease-related signs and symptoms and consult a physician or other health care provider when they first occur. And we will work to find ways to help health care providers coordinate their services to older adults to optimize health status.

C-6 Understand and develop strategies to enhance societal roles and interpersonal support for older adults, reduce social isolation, and promote positive caregiving outcomes and supports. Despite negative stereotypes, millions of older adults work productively, contribute to society, and place a high value on retaining their independence. Research suggests that social support and continued involvement in useful activities foster positive effects on physical and mental health and on longevity. This effort is especially important for older adults who are at increased risk for multiple diseases, disability, and functional limitations that may keep them from fully engaging in the world around them. NIA will continue to support and conduct research to:

- **Identify ways for older adults to retain valued roles and maintain independence.** Older men and women often continue to work in paid jobs, perform meaningful work as volunteers, maintain their own households, and/or support children and grandchildren. Research supported and conducted by NIA will seek and apply technological, social, and behavioral findings to interventions that help extend the ability of older adults to remain independent, active, and productive.

- **Understand and develop strategies to address self-neglect, adverse social relationships, and susceptibility to physical, emotional and financial abuse among older adults.** NIA will support basic research on the individual, interpersonal, and social environmental risk and protective factors for elder mistreatment and abuse. These efforts will help to inform the design of preventive interventions in individuals at risk for these outcomes. We will continue to partner with other agencies to identify the best ways to detect and address financial fraud and abuse facing older adults, promote adaptive self-care and care of others, and develop strategies to identify and support vulnerable elders in our communities.

Goal D
Improve our understanding of the aging brain, Alzheimer's disease, related dementias, and other neurodegenerative diseases. Develop interventions to address Alzheimer's and other age-related neurological conditions.

A better understanding of how the brain ages can provide important information on which to base strategies for maintaining and enhancing cognitive, emotional, sensory, and motor function. For example, studies have shown that, contrary to what scientists believed for decades, new neurons form in certain regions of the brain even in adulthood. This

phenomenon, known as *neurogenesis*, suggests that we may be able to develop medical and behavioral approaches to stimulate formation of new neurons to compensate for the loss and functional decline of neurons with aging, disease, or traumatic injury.

NIA will continue to support research to identify age-related neural changes and mechanisms the older brain uses to maintain optimal learning, memory, and other cognitive functions. We will continue to support research to clarify the interactions between the brain and the peripheral nervous, endocrine, blood and circulatory, cardiovascular, and immune systems. In addition, we will support the development of preventive and therapeutic approaches to maintaining health in cognition, emotion, sleep function, sensory processes, and motor function.

Research on Alzheimer's Disease and Related Dementias

NIA is the lead federal agency for research on Alzheimer's disease and related forms of dementia (AD/ADRD), and our portfolio reflects this important responsibility. In fact, since 2012, funding for AD/ADRD research has increased such that today, over one-half of our grants research budget is dedicated to research on various forms of dementia. These funds support a broad range of projects, from basic molecular and cellular studies of the aging brain, to large-scale clinical trials of interventions to prevent symptoms of dementia from taking hold, to development of a robust infrastructure for discovery, to demographic studies of AD/ADRD in different geographic, racial and ethnic, and socioeconomic populations.

Strategic planning for AD/ADRD research is handled through its own dedicated process, and therefore many of the goals and objectives outlined here are necessarily broad. For more information on specific goals, milestones, and plans for AD/ADRD research, please see:

AD/ADRD Milestones Database: This database contains detailed information about research implementation plans and progress toward the goal of effectively treating or preventing AD/ADRD by 2025. www.nia.nih.gov/research/milestones

Bypass Budget for AD/ADRD Research: NIH annually submits to the President and then to Congress a professional judgment budget that estimates the additional funding, above the base for AD/ADRD, needed to effectively treat and prevent these disorders by 2025. The estimate — often referred to as a "bypass budget" because it is presented without modification through the traditional federal budget process — also summarizes NIH-funded research and promising research opportunities.

www.nia.nih.gov/about/bypass-budget-proposal-archive

Goal D objectives:

D-1: Understand the mechanisms involved in normal brain aging; the role of plasticity and resilience in maintaining brain function; the role of cognition and sleep in everyday functioning; and protective factors for sensory, motor, emotional, cognitive, and sleep function.

D-2: Identify and understand the genetic, molecular, and cellular mechanisms underlying the pathogenesis of AD/ADRD and other neurodegenerative disorders of aging.

D-3: Improve assessment and diagnostic tools for distinguishing people with normal brain aging from those who will develop mild cognitive impairment (MCI), Alzheimer's disease, and related conditions.

D-4: Translate basic discovery into effective treatment and/or prevention strategies for AD/ADRD and other age-related neurological conditions.

D-5: Better understand and develop interventions to address the special caregiving needs of patients with AD/ADRD, as well as the needs of their caregivers.

D-6: Track epidemiologic trends in AD/ADRD, including incorporating new measures into national surveys.

Approach

D-1 Understand the mechanisms involved in normal brain aging; the role of plasticity and resilience in maintaining brain function; the role of cognition and sleep in everyday functioning; and protective factors for sensory, motor, emotional, cognitive, and sleep function.

- **Improve our understanding of normal brain aging.** Changes in brain structure and function may continue throughout life, and studies in model organisms and humans are helping to define the normal trajectory of changes in the brain over the adult lifespan. Structural neuroimaging and anatomical studies of brain have shown declines in total gray and white matter, along with shrinkage or atrophy and synaptic changes in certain regions of the brain in aging. Functional imaging studies are defining the workings of large-scale neural and cognitive networks in the aging human brain. Human and animal studies suggest that adaptive or resilient processes (i.e., brain plasticity) may be needed for maintenance of brain structure and function during normal aging. At the molecular and cellular level of analysis in animal models, brain aging is associated with changes in gene and epigenetic expression, mitochondrial and energy metabolism, calcium regulation, protein homeostasis, glia, and neural plasticity and synaptic function. We will continue to work to elucidate the processes that occur during "normal" brain aging and to identify and find ways to activate the cellular processes that protect the brain from damage and promote its repair.

- **Identify the behavioral, psychological, and neural mechanisms and processes that confer successful aging and resilience to cognitive impairment.** A subset of older adults remain asymptomatic, despite the presence of amyloid plaques and tau tangles — pathological hallmarks of AD/ADRD — in the brain. We don't fully understand the protective factors that prevent these individuals from cognitive decline or symptoms of dementia. We will support research to identify the cellular, molecular, behavioral, psychological, and social/environmental factors associated with cognitive resilience and, where possible, to use this knowledge as the basis for development of preventive interventions.

- **Determine how genetic, molecular, cellular, and social/environmental factors interact for optimal brain health and functioning, including in the oldest old (people ages 85 and older).** The overall integrity of brain structure and many neural systems is largely preserved in normal aging, whereas in age-related diseases, specific brain cell types and

their connections are damaged or lost. NIA will work to gain a greater understanding of the many factors that interact to maintain brain structure and function, including compensatory mechanisms and adaptive or dynamic changes. For example, we will:

o Continue to pursue a greater understanding of the interaction among genetic factors that underlie normal cognitive, emotional, sensory, motor, and sleep function as well as abnormal decline and the interactions between genetics and the environment.

o Investigate epigenetic changes, which can significantly influence the structure, function, and expression of genes and molecular pathways within the cell.

o Support research to better understand the neurological and behavioral effects of environmental factors, both early and later in life.

In addition, we will continue to investigate the changes in brain structure and function that take place in people 85 or older. In the absence of disease, many of these individuals continue to lead healthy and productive lives even into unusually old age. Others, however, suffer from health conditions that can contribute to cognitive decline and dementia, emotional dysfunction, motor instability, and/or sensory deficits. NIA will work to identify and address the conditions that most affect brain health in this group in order to find ways to maintain function as long as possible.

- **Understand the role of cognition, emotion, and motivation in everyday functioning.** NIA will support research to examine the influence of contexts — behavioral, social, cultural, and technological — on older adults' cognitive and emotional functioning; investigate the effects of age-related changes in motivation, cognition, and emotional well-being on activities of daily living, social relationships, and health status; and develop strategies for improving everyday functioning through various interventions such as cognitive training, stress reduction, and social and cognitive engagements.

- **Understand the role of sleep and other restorative processes in supporting everyday functioning.** There is increasing recognition that positive psychological functioning influences health above and beyond negative psychological functioning (including depression, anxiety, and loneliness). Most research on the relationship between psychological factors and health to date has focused on deteriorative biological processes and related health outcomes. Significantly less is known about restorative biological processes such as sleep, physical activity, and other restorative processes that may support optimal well-being and everyday physical and psychological functioning.

D-2 Identify and understand the genetic, molecular, and cellular mechanisms underlying the pathogenesis of AD/ADRD and other neurodegenerative disorders of aging.

- **Refine our knowledge of genetic, molecular, and cellular changes involved with the development of AD and other dementias of aging.** Studies of the neurobiology of aging have given us increasing insight into the ways brain aging itself is associated with the development of AD/ADRD. However, key questions remain. We will encourage a systems-based approach to investigate the pathological changes associated with the preclinical development of AD/ADRD, including accumulation of abnormal proteins, loss of synapses, and death of neurons. We will also explore the impact of genetic and

inflammatory processes on the development of AD. We will promote further characterization of these pathological changes in tissue culture, animal models, and humans.

- **Refine our knowledge of the cognitive and behavioral changes associated with the development of AD and other forms of dementia.** Our research will also address the behavioral and psychological changes associated with the development of AD as well as psychiatric conditions such as clinical depression.

- **Investigate the relationship between systemic factors and brain function during preclinical AD.** Systemic risk factors such as obesity, diabetes, hypertension, infection with the human immunodeficiency virus (HIV), and heart disease during midlife are associated with accelerated age-related cognitive decline and with increased risk for AD, particularly among individuals with three or more of these risk factors. We will continue to support research to examine the mechanisms by which these risk factors may influence the transition between normal brain aging and AD, and whether the negative impact of metabolic and vascular risk factors on brain aging can be counteracted through behavioral and lifestyle changes. We will also continue to support research that examines brain-body interactions in AD and overall health, especially interactions mediated by stress and other hormones. For example, short sleep — less than an average of six hours per night — has been associated with hormonal and metabolic changes associated with obesity, diabetes, hypertension, cardiovascular disease, and cognitive decline.

- **Understand the role of sleep in brain function and neurodegenerative disorders of aging.** Sleep and circadian clock disruption affect age-related brain function and alter the expression and course of neurodegenerative diseases. We will support research on the molecular and cellular underpinnings of age-related changes in quality and quantity of sleep and deterioration of circadian function. We will continue efforts to determine the effects of sleep deficiency on the brain and behavior, as well as the association between sleep and circadian disruption and neurodegenerative disease.

D-3 Improve assessment and diagnostic tools for distinguishing people with normal brain aging from those who will develop mild cognitive impairment (MCI), Alzheimer's disease, and related conditions. Successfully distinguishing people who are aging normally from those who will develop MCI — often a precursor to AD — and AD itself is critical to promoting healthy aging behaviors and the prevention, early detection, diagnosis, and treatment of disease. A critical step in accomplishing this goal is to clearly delineate changes that occur with aging in people who do not develop MCI or AD until very late in life. This knowledge can help in the identification of biomarkers of the transition from normal function to cognitive impairment and disease. NIA will continue to support research to:

- **Identify and establish links among neuroimaging, biological, and clinical markers for early detection of cognitive decline, MCI, and AD and for understanding the progression from normal cognitive aging to MCI to early AD.** Biomarkers may be helpful in earlier and more accurate diagnosis of disease and in tracking disease progression and treatment response in clinical trials, which can decrease the time and cost of trials. The Alzheimer's Disease Neuroimaging Initiative has achieved considerable success in developing sensitive and precise tools for detecting AD at its earliest stages

and following the disease's progression through the use of a combination of biomarkers. These results are also supporting the development of measures to assess the effectiveness of potential interventions. Future efforts will include continued collection of biomarkers to fill critical gaps in our understanding of the biomarker trajectories of AD and aging.

- **Improve neuropsychological, functional, and passive assessment of cognitive function.** Despite remarkable advances in neuroimaging, neuropsychological assessment of cognitive function continues to be the gold standard by which AD is diagnosed. We will continue to support the development and translation of tools for assessing cognitive function in the clinic, in the primary care setting, and in the home environment.

- **Improve methods for assessing changes in sensory and motor systems as markers of age-related change and AD and decrease the frequency of late and misdiagnoses.** Age-related changes in sensory systems occur in both normal individuals and those with AD. We will continue to examine how the use of sensory testing to predict early neurodegeneration could assist in clinical diagnoses. We will also continue research to explore possible correlations between changes in sensory perception and AD. For example, we will investigate how changes in a person's ability to navigate visually through the environment or changes in a person's sense of smell may predict the development of AD. Finally, we will develop new methods to detect subtle changes in cognition or behavior that could herald the onset of AD/ADRD, including mobile technology and devices.

- **Improve methods for assessing changes in affective processes as markers of normal age-related change, risk for AD, or signs of early psychological changes associated with AD/ADRD.** Aging is also associated with changes in emotion, motivation, and stress resilience. We will continue to support research to advance understanding of normal age-related changes in these processes, the interconnections between these processes and cognitive changes with aging, and how dysfunction in these processes might manifest in MCI and the early stages of AD/ADRD, and/or account for any of the neuropsychiatric symptoms observed in these disorders. Such studies may identify novel targets for interventions or prevention efforts or provide clues to intervention strategies that might normalize emotion dysregulation or strengthen resilience in people with and without AD/ADRD.

D-4 Translate basic discovery into effective treatment and/or prevention strategies for AD/ADRD and other age-related neurological conditions. Studies supported and conducted by NIA have tested both cognitive training and drug treatments, alone and in combination, to improve memory in patients with dementia. Other NIA supported and conducted trials focus on slowing the progression of cognitive symptoms in dementia and on strategies to manage behavioral symptoms. Still others focus on preventing the early stages of cognitive decline. NIA supported and conducted translational studies apply the findings of basic science on brain mechanisms in healthy aging and in disease to the identification and preclinical testing of new prevention and treatment strategies as a precursor to testing in human clinical trials. NIA will continue to:

- **Stimulate translational research aimed at discovery and preclinical development of new candidate drugs and biologics.** By supporting early steps of the drug discovery and development process, we can play a critical role in facilitating the often long, difficult,

and enormously expensive process of translating the wealth of basic science discoveries into successful therapeutics.

- **Support clinical trials for drug interventions to prevent, treat, and delay the onset and progression of cognitive decline, MCI, AD, and other dementias.** We will continue to test promising new and repurposed drugs in clinical trials with the intention of moving them rapidly into clinical practice. We will examine ways to streamline the drug discovery, drug development, and clinical trial processes that advance the development for promising prevention and treatment targets.

- **Support clinical trials for nonpharmacologic interventions to prevent, treat, and delay the onset and progression of cognitive decline, MCI, AD, and other dementias.** Some evidence suggests that diet, physical activity, and other lifestyle factors may promote cognitive health and forestall decline. We will support studies to determine the effects of these and other factors and develop evidence-based communications to share with the public regarding the efficacy of such interventions.

D-5 Better understand and develop interventions to address the special caregiving needs of persons with AD/ADRD, as well as the needs of their caregivers. A number of recent studies have demonstrated that caring for a family member with dementia can have lasting psychological and even physical effects on the caregiver. For example, sleep-wake patterns are altered in AD patients, often leading to chronic sleep deprivation for patient and caregiver. Research has shown that caregivers of AD patients have an increased risk of depression, elevated stress levels, increased vulnerability to influenza, and poor wound healing. NIA will continue to:

- **Conduct research on the family and economic impacts of AD and other dementias.** We will support research at several levels, including studies on the mechanisms through which the stress of caregiving affects physical and mental health. Because formal and informal care for older adults with dementia is a major cost for families, private insurers, and the public sector, we will support other studies to help us to quantify and understand the economic impacts associated with care provision and quality of care.

- **Develop better strategies for the care of patients with MCI and AD and for their caregivers.** NIA-supported investigators have developed multifaceted, personalized interventions that can significantly improve the quality of life for people with dementia and their caregivers. New technologies such as location tracking devices, socially assistive robots, communications devices, and medication management tools, are also facilitating care of older adults with dementia. We will continue to develop and test other interventions of this type to support implementation in the real-world contexts in which they are needed. In addition, we will research the needs of spousal caregivers following the death of their spouses and support development of post-bereavement interventions.

D-6 Track epidemiologic trends in AD/ADRD, including incorporating new measures into national surveys. Longitudinal, demographic, and community-based studies of aging and AD are becoming progressively more sophisticated. Traditional interviews, clinical evaluations, and routine laboratory tests are increasingly complemented by advanced imaging and other technologies to identify risk factors and protective factors and to relate them to specific biological mechanisms.

- **Explore possible additional risk and protective factors for brain health and function, cognitive decline, MCI, and AD through epidemiological and other population studies.** NIA will place a special emphasis on research that elucidates the pathways by which behavioral and social factors confer risk for cognitive decline, MCI and AD/ARDR. We will leverage community-based studies, including studies in racial and ethnic minority populations in sufficient numbers to study sources of variation within groups, capable of linking early life or midlife factors with late-life cognitive decline or impairment. We will include studies of the ways that multiple factors such as stress, discrimination, mental health, education, social engagement, complex work, lifestyle, genetics, comorbid diseases, sleep, or sensory or motor dysfunction interact to cause disease or contribute to cognitive decline. We will also support international comparative research on risk factors, incidence, and prevalence of cognitive impairment and dementia.

Goal E
Improve our understanding of the consequences of an aging society to inform intervention development and policy decisions.

While the increased longevity and improved health at older ages seen in many parts of the world represent one of the crowning achievements of the 20th century, these trends also present significant challenges. Societal aging can affect economic growth, patterns of work and retirement, the way that families function, the ability of governments and communities to provide adequate resources for older adults, and the prevalence of chronic disease and disability.

At the same time, the U.S. lags behind other developed nations with respect to health, longevity, and other key indicators. For example, gains in life expectancy over the past 30 years have not kept pace with those in other developed nations. Since 1980, Americans have, on the average, gained five years in life expectancy from birth, while individuals living in comparable nations have gained eight.[1]

NIA will continue to support research on the social, economic, and demographic consequences of the aging population in the U.S. and other countries. We will support research to better understand the impact of the changing age composition of the population and economic factors across the lifespan that affect health and well-being.

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[1] http://kff.org/slideshow/life-expectancy-in-the-u-s-and-how-it-compares-to-other-countries-slideshow/

Goal E objectives:

E-1: Understand how population aging and changes in the social, economic, and demographic characteristics of cohorts reaching old age affect the health and well-being of older adults in the U.S. and other countries.

E-2: Understand how social and economic factors throughout the lifespan affect health and well-being at older ages.

E-3: Conduct research aimed at modifying organizational or individual behaviors in order to improve important health outcomes among members of population groups at older ages.

E-4: Understand and address the reasons the U.S. is falling behind other countries in health and mortality.

Approach

E-1 Understand how population aging and changes in the social, economic, and demographic characteristics of cohorts reaching old age affect the health and well-being of older adults in the U.S. and other countries.

- **Identify, analyze, and track changing patterns of disability and mortality for older adults and better understand factors contributing to these patterns.** Research supported and conducted by NIA will address disability dynamics at several levels, including longitudinal research to understand the determinants of onset, severity, and recovery from disabling conditions. At the population level, we will foster research to understand the pathways to disability and the causes of change in mobility and function over time as well as subgroup disparities. We will also invest in research on more sensitive measures of functional disability that are needed to better track these changes.

- **Analyze the effects of social and demographic factors on health and well-being at older ages.** For example, educational attainment is one of the strongest correlates of physical health and cognitive functioning at older ages. We will support research to unravel the reasons for such connections, help project health and long-term care needs, and devise ways to intervene and to reduce disparities.

- **Assess the impact of changing family structures on health and caregiving.** NIA will support research on the ways the evolution of the American family structure will affect the well-being of older adults. Changing kinship systems in modern American society and unprecedented demographic changes have profound implications for living arrangement options for older adults, cost of living, cost of health care, caregiving, retirement, and Social Security. Researchers will need to examine how the availability of home- and community-based services (e.g., adult day services, home visits, and assisted living) influences the experience of family caregiving.

- **Encourage comparative analyses to evaluate the impact of institutions and networks on population and individual well-being and foster longitudinal studies on aging.** Other countries have larger proportions of their populations at older ages than the U.S., and some of those with currently younger populations are aging at a much more rapid rate. We will support comparative research on the effects of these changes on behavior,

and we will evaluate institutional reform efforts to gain insights useful both in the U.S. and elsewhere for enhancing population health.

- **Examine the bases for individual and societal attitudes toward older adults and develop effective strategies to improve them.** Older adults may hold negative attitudes about their own aging or be the target of inaccurate and negative stereotypes and discrimination. We will support research to explore the causes of these negative attitudes and develop strategies to counter them with behavioral, community, and other interventions. For example, engaging older adults in meaningful volunteer work may prove to be a "win-win" situation, replacing the image of dependence with one of active and productive citizenship. Understanding the individual, interpersonal and institutional drivers of both positive and negative attitudes toward aging can help identify malleable targets for intervention.

- **Continue research on the measurement of subjective well-being in a policy-relevant framework.** Measurement of subjective and psychological well-being in population-based surveys and in intervention studies holds potential for understanding how older adults' lives are affected by major challenges of aging, including retirement, caregiving, living with disability, onset of illness and impending death, and for ensuring that interventions promote not only better health, but better quality of life at older ages.

E-2 Understand how social and economic factors throughout the lifespan affect health and well-being at older ages. Individual differences in potential for a healthy and secure old age emerge in midlife. For example, chronic conditions and disability influence work and employment decisions for many older and even middle-aged individuals. NIA will continue to:

- **Support and conduct research on how middle-aged and older adults manage the multiple health-related decisions imposed by increasing longevity.** NIA will support research to better understand the social determinants of health and well-being of older adults, including incentives and supports provided by public and private programs that have an impact on health outcomes. Such research will include the measurement of the economic value of good health.

- **Support research on the consequences of changes in older Americans' experience of work and retirement.** Age at retirement in the U.S. has been rising over the last few decades, primarily as a consequence of changes in women's labor force participation, changes in pension plans, and increasing education. Still, most workers today can expect to spend two decades in retirement; some may be retired for three or more decades. The intersection of implications of changes in working life for the health and well-being of older adults during retirement remains an important area of investigation that can inform intervention and policy decisions.

- **Support and conduct research that models and measures the economic risks of old age with the potential for developing interventions to protect against these risks and adverse health consequences.** Demographic and retirement income trends lead to expanding economic risks among older Americans and associated impact on health. Many Americans will require long-term care, but few purchase private insurance to support formal care expenses. We will support research to understand the behavioral

aspects of demand for insurance against these older-age risks as well as alternative models to support efficacious long-term care.

- **Promote the development of data resources to support the development of effective interventions.** Measures of time use, experience sampling, and in-home sensor-based technologies also offer potential for new insights for understanding and designing interventions to promote healthy aging.

E-3 Conduct research aimed at modifying organizational or individual behaviors in order to improve important health outcomes among members of population groups at older ages. Research examining the cognitive effects of work and retirement as well as changing environmental defaults to influence health-related aging outcomes have generated findings with enormous practical implications. Country comparisons available through harmonized surveys have revealed the role of a longer work/career life in maintaining cognitive function. Recent evidence also suggests that changes in the economic incentives within the Medicare program increase the use of preventive services. We will support research to better understand the factors in the health care system that support prevention and the successful management of disease. Through support of research that identifies institutional mechanisms that affect health, NIA will encourage institution-level interventions involving economic, organizational, and systemic interventions to promote better health and reduce health disparities.

E-4 Understand and address the reasons the U.S. is falling behind other countries in health and mortality. The current pattern of increased "active life expectancy," the average number of years an individual will live without a limiting disease or disability in parallel with increased length of life, is threatened by increases in obesity and disability rates among younger Americans. Likewise, longevity rates in the U.S. are lagging relative to other developed nations. We will support research to understand and address the reasons for these trends.

Goal F
Understand health disparities related to aging and develop strategies to improve the health status of older adults in diverse populations.

Health Disparities are differences in any health-related factor — disease burden, diagnosis, response to treatment, quality of life, health behaviors and access to care, to name only a few — that exist among population groups. Health disparities are associated with a broad, complex, and interrelated array of factors, and may reflect:

- Age
- Race
- Ethnicity
- Socioeconomic status
- Disability status
- Identity and expression* (e.g., gender, racial, ethnic)
- Geographic location (e.g., rural or urban environment)
- Education

- Health care (e.g., access, quality)

- Culture (e.g., norms, traditions, collective responses)

- Health behaviors (e.g., smoking, violence, substance abuse)

- Biological (e.g., sex, chronic inflammation, telomere attrition, cellular senescence)

- Or a combination of these

In 2015, NIA developed and adopted its new "NIA Health Disparities Research Framework" (https://ethndis.org/edonline/index.php/ethndis/article/view/39/63) to stimulate the study of environmental, sociocultural, behavioral, and biological factors that influence health disparities related to aging. Many of these factors are broad, complex, and interrelated.

To address the contribution of these factors to health disparities related to aging, NIA has supported research, for example, that found Alzheimer's disease to be more prevalent among African Americans and Hispanics than among other ethnic groups in the U.S. Other studies have found that lower socioeconomic status is associated with poorer health and reduced lifespan in the U.S. Scientists have also observed sex differences in health and longevity. For example, overall women live longer than men, but are more likely to develop osteoporosis or depressive symptoms or to report functional limitations as they age; men, on the other hand, are more likely to develop heart disease, cancer, or diabetes.

Social environmental factors such as residential segregation, discrimination, immigration, social mobility, work, retirement, education, income, and wealth can also have a serious impact on health and well-being. Economic circumstances can determine whether an individual can afford quality health care and proper nutrition from early life into old age. Individual and family financial resources and health insurance often determine whether an older adult enters an assisted living facility or nursing home or stays at home to be cared for by family members.

The causes of health disparities are dynamic and multidimensional, and to address them adequately, NIA will consider environmental, social cultural, behavioral, and biological factors. For this reason, NIA will use an integrative approach to motivating health disparities research related to aging.

Goal F objectives:

F-1: Identify and understand environmental, social, cultural, behavioral, and biological factors that create and sustain health disparities among older adults.

F-2: Develop strategies to promote active life expectancy and improve the health status of older adults in diverse populations.

F-3: Develop and implement strategies to increase inclusion of underrepresented populations in aging research.

F-4: Support research on women's health, including studies of how sex and gender influence aging processes and outcomes.

Approach

F-1 Identify and understand environmental, social, cultural, behavioral, and biological factors that create and sustain health disparities among older adults. Many complex and interacting factors can affect the health and quality of life of older adults. For example:

- *Environmental factors* related to income, education, occupation, retirement, and wealth may have a serious impact on key determinants of health over the life course and ultimately the health and well-being of older adults.

- *Social factors* such as individual and structural forms of discrimination and bias can shape the everyday experience of individuals from minority or vulnerable populations.

- *Cultural factors* can have a tremendous influence on approaches for managing stress, diet and food preferences, attitudes toward physical activity, and other critical health/coping behaviors.

- *Behavioral factors* and psychological processes represent major pathways by which environmental and social factors affect health. Optimism, pessimism, and sense of control serve as risk or resilience factors for impacting health, while chronic stress exposure can enhance vulnerability.

- *Biological factors* that are influenced by environmental and sociocultural factors — and transduced through behavioral processes — may alter the course, severity and acceleration of disease and disability.

All these factors and their interconnections must be understood to develop and implement effective interventions to address health disparities among various population groups. NIA will support and conduct research across diverse population groups to:

- **Gather data to further distinguish patterns of health disparities and causes.**

  o *Gather and analyze data on burdens and costs of illness, healthy life expectancy, longevity, and mortality trajectories.* Determining the health burden and other costs of specific illnesses has always been difficult due to the lack of adequate data on incidence and prevalence as well as inconsistencies in calculating health and monetary costs. These difficulties are compounded across populations by differences in use of formal medical care and informal family caregiving. Projections of future healthy life expectancy, longevity, and mortality depend on assumptions about how groups of individuals will change over time, particularly as recent immigrants become culturally assimilated. This research will be archived in the best interest of all populations and will provide valuable information for projecting the specific needs for health care services within various population groups.

  o *Support the development and wide sharing of data resources that are needed to conduct health disparities research related to aging.* Research to understand health disparities requires that data from multiple sources be accessible in standard formats to researchers on a national level. NIA will continue to support and expand surveys of health disparity populations in order to provide the data needed by researchers and public policy makers, including cross-national, comparative, and

historic research. We will provide access to these and related data for use in health disparities research and to inform policy development.

- o *Develop comparable databases — including cross-national databases — on health outcomes, risk factors, and determinants of health disparities.* Although many of the disparities in adult health and life expectancy across national, racial/ethnic, and social class boundaries are well documented, causal mechanisms are less well understood. Research to understand these differences will be critical to the development of behavioral and public health interventions.

- o *Use ongoing data collection programs to oversample health disparities populations.* These data will provide important information on socioeconomic factors, health care needs, collective cultural responses, social network characteristics, perceptions of stress and resilience, risk/coping behaviors, genetic stability, and other important factors.

- **Track and analyze reduced life expectancy and disease prevalence in diverse older adult populations.**

  - o *Identify the determinants of disparities in the prevalence of diseases and conditions such as heart disease, obesity, hypertension, frailty, diabetes, comorbidities, and certain types of cancer.* Researchers will explore the influence of contextual factors such as residential segregation, stress, education, language, and access to health care and how these may link with genetic, molecular, and cellular mechanisms to sustain differences across populations.

  - o *Determine the reasons for variation in the prevalence of cognitive decline and AD/ADRD across population groups.* NIA will support research to better understand the differences in the prevalence of AD and related dementias among African Americans, Asians, and Hispanics compared to non-Hispanic whites. We will continue to examine a range of possible causes of these disparities, including the impact of comorbidities such as hypertension, cardiovascular disease, and diabetes; health behaviors; and disease processes. This research will draw on culturally appropriate and standardized measures to better understand these differences and to suggest culturally appropriate interventions.

- **Understand differences in aging processes across diverse populations.** We will characterize normal and accelerated processes of aging in diverse populations to increase our understanding of the course of disease and disability and to identify similarities and differences.

- **Understand how environmental, sociocultural, behavioral, and biological factors lead to disparities in health at older ages and develop interventions to reduce those disparities.** Health disparities persist within and across diverse racial, ethnic, and socioeconomic groups. Research is needed to understand the causes of these disparities and how they relate to relevant factors. Examination of cross-national research opportunities has the potential to provide increased knowledge of natural experiments in divergent aging experiences and aging policy developments that would inform a more general understanding in aging societies.

- **Explore mechanisms through which the effects of environmental and sociocultural factors manifest themselves, as well as critical periods for reversing such effects and/or the optimal timing of intervention.** Specific groups of the U.S. population experience chronic socioeconomic disadvantage throughout their lives or for extended periods in life that generate persistent, chronic stress. The patterns of stress reactivity appear to hasten the progression of disease. It is therefore important to invest in research on the effects of discrimination, bias, stigma, and stereotypes, particularly the mechanisms through which these environmental and sociocultural factors become biologically embedded to influence health disparities.

- **Determine how environmental, sociocultural, behavioral, and biological determinants interact to increase risk of disease and disability.** Environment, socioeconomic factors, and risk behaviors can all interact to influence biological influences and accelerate aging as well as the development, progression, and outcome of disease in populations groups. NIA will support research to learn more about risk factors for disease and preventive factors contributing to good health by researching these influences individually and in concert. We will place a special emphasis on longitudinal data to untangle the multitude of factors that affect health and well-being.

- **Determine the effects of early-life factors on health disparities among older adults.** Differences in childhood socioeconomic status, stress exposure, risk/coping behaviors, disease incidence, environmental exposure, and health care in fetal development and early life can affect disease and disability in later life. NIA will support research to identify these early-life factors, as well as the mechanisms through which they influence health in later life. These findings can then be used to inform clinical and even policy interventions to reverse the effects of childhood disadvantage among older adults.

F-2 Develop strategies to promote active life expectancy and improve the health status of older adults in diverse populations. Life expectancy has increased among all population groups; however, notable disparities remain. For example, African American men have the lowest life expectancy of all racial/gender population groups in the U.S. In addition, more adults are living with one or multiple chronic conditions that may not affect length of life but may dramatically affect quality of life, and significant disparities have been observed in this area, as well. For example, African Americans suffer disproportionately from hypertension and prostate cancer, and Hispanics suffer more from diabetes. NIA will continue to:

- **Support research to better understand effective strategies for communicating health messages that are appropriate in diverse populations.** Because of language, educational, and cultural differences, disproportionately affected populations do not always receive important information about healthy behaviors. Research on communication with specific audiences will assist the development of appropriate health messages and dissemination channels; we will continue to communicate with diverse audiences in various ways.

- **Develop appropriate strategies for disease, illness, and disability prevention and healthy aging among the underserved.** Aging Americans need understandable, culturally appropriate tools they can use to maintain and improve their well-being. For example, diet and physical activity recommendations may need to be adjusted to take

into account religious, ethnic, and cultural sensitivities. To address these concerns, researchers will:

- o Develop and promote culturally appropriate interventions to improve healthy behaviors along with strategies to increase the likelihood that these interventions will be initiated and maintained.

- o Design and promote interventions appropriate for older adults in diverse populations to more effectively prevent, diagnose, or reduce the effects of disease.

- o Design and promote evidence-based and culturally appropriate strategies for self-management of chronic diseases.

- o Investigate the factors affecting medication misuse and culturally appropriate strategies for enhancing proper use and compliance with medication regimens.

- **Develop and disseminate interventions to improve culturally appropriate health care delivery.** NIA will promote better access to appropriate preventive care and clinical treatment, earlier diagnosis, improved outcomes, and reduced health care costs in diverse populations by supporting the development, usage, and clinical translation of research findings.

  - o Develop interventions that build long-term and meaningful relationships among community leaders and members to create trust and to understand the cultural limitations of interventions.

  - o Develop interventions to reduce health disparities and inequities associated with poor provider-patient interactions. Recent studies have revealed that how older adults are diagnosed and treated is as much a function of who they are, who is treating them, and where care is provided as it is a function of the symptoms they present. NIA will investigate ways to ensure that each individual is treated with appropriate evidence-based interventions regardless of race, ethnicity, sexual orientation/gender identity, place of birth, or cultural background.

- **Develop training programs to prepare culturally proficient researchers.** We will facilitate training of researchers in the biomedical, behavioral, and social sciences working with older adults to help them better understand the medical implications of the growing diversity of our population. Training programs will help prepare the next generation of health professionals by incorporating new materials sensitive to these issues and preparing a cadre of culturally competent health care providers prepared to assist with patient decision making.

F-3 Develop and implement strategies to increase inclusion of underrepresented populations in aging research. The ability to recruit and retain research participants that are representative of the total U.S. population is essential to the conduct of rigorous health disparities research related to aging. However, specific racial, ethnic and socioeconomic population groups have been underrepresented in health-related research, including clinical trials and population-based research. NIA will:

- **Continue to support training for clinical and research staff in message development, recruitment strategies, and community and media outreach.** NIA will explore effective ways to mitigate the difficulties associated with enrollment of health disparities

populations in research studies and clinical trials. For example, Community Based Participatory Research methods may be used to address cultural and language barriers and encourage effective communication about the potential benefits of studies and trials that seek to address health disparities and improve public health in priority communities.

- **Investigate novel approaches for increasing recruitment and retention of underrepresented researchers pursuing careers in science, particularly health disparities research.** NIA will work to identify the best strategies for training and attracting a diverse workforce of new, midcareer, and senior researchers. This may be important for evaluating important strategies — including those that account for cultural and geographic factors — to enhance the recruitment of underrepresented groups into aging research. We will continue programs to train high-quality researchers through flexible mechanisms that reflect the rapidly changing needs of science and provide cross-disciplinary training. NIA will also work to tap the talents of all groups of society by encouraging degree-granting institutions to establish and improve programs for identifying, recruiting, and training diverse groups of individuals for careers in biomedical science.

- **Engage broad segments of the U.S. population in research on Alzheimer's disease and related dementias.** As funding for AD/ADRD has increased, the need for more people to participate in relevant research has grown. In particular, an urgent need exists to engage underrepresented communities. Today's participants in AD/ADRD research are mostly white, non-Hispanic, well-educated, heterosexual, and married, with a spouse study partner. However, studies point to significant differences between rates of AD in specific populations, for whom factors like diet, culture, genetic influences, geography, and medical conditions may play a role. Broadly diverse participation in both observational and clinical studies will help us to better define and address racial, ethnic, gender, and other differences so that interventions can be better tailored to communities and individuals. We will continue to provide resources and support to facilitate widespread engagement in our research studies.

F-4 Support research on women's health, including studies of how sex and gender influence aging processes and outcomes. Older women outnumber older men in the U.S., and the proportion of the population that is female increases with age. In 2014, women accounted for 56% of the population ages 65 and older and for 66% of the population ages 85 and older. Despite living longer, however, older women are more likely to report depressive symptoms or limitations in physical function, are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), and live in poverty at a disproportionately high rate. American women also lag significantly behind their counterparts in other higher-income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared to that in other industrialized countries.

NIA supports a diverse portfolio of research on older women's health, including studies on sex differences in the basic biology of aging; hormonal influences on cognitive health; women's health across the life course, with a particular emphasis on the menopausal transition; sex and gender-related demographic disparities in older age; economic implications of sex and gender at older ages; and age-related diseases and conditions that

are unique to or more common in women, such as osteoporosis, breast and ovarian cancer, and urinary tract dysfunction. In addition, we support initiatives to ensure that women are fully represented in NIH-supported research, including the Sex as a Biological Variable (SABV) and Inclusion Across the Lifespan policies. As part of our commitment to supporting research on women's health, NIA will:

- **Encourage research to understand sex and gender differences in health and disease at older ages.** Sex differences in health, longevity, and response to various preventive and treatment interventions are well documented. For example, many of the compounds tested through the Interventions Testing Program demonstrate differential effects on male and female mice. We will accelerate research on the basic biology driving health differences between sexes. In addition, recent demographic and economic trends have gender-specific implications for health and well-being at older ages. Unmarried women, for example, are less likely than unmarried men to have accumulated assets and pension wealth for use in older age, and older men are less likely to form and maintain supportive social networks. We will support research to explain how these and other factors may contribute to the differences in life expectancy and disability rates among men and women at older ages.

- **Support research on sex and gender differences in cognitive decline and AD/ADRD etiology, presentation, prevention, and treatment.** Recent estimates suggest that nearly two-thirds of individuals diagnosed with AD are female. At the same time, most studies conducted in the U.S. have not observed sex differences in the incidence of Alzheimer's disease — that is, in the rate of developing the disease. This may be in part because women, on average, live longer than men. Other potential reasons for this are complex and may include differences in brain structure; possible differential effects of the APOE ε4 genotype, which is the most common genetic risk factor for late-onset disease; differences in education between men and women in the age cohorts currently at greatest risk; and effects of sex steroid hormones on the brain. NIA will continue to study possible AD/ADRD risk and protective factors in both men and women, the mechanisms through which estrogen and other sex hormones work on the brain, and the effects of different forms of menopausal hormone therapy on cognition.

- **Solicit and support research on topics that are uniquely relevant to the health of older women.** Some age-related health issues — for example, menopause and certain types of cancer — are unique to women. Others, such as osteoporosis, are significantly more common in women than in men. We will support research designed to understand and address these conditions, with an additional focus, where appropriate, on how common diseases manifest and respond differently to treatment in women and men.

- **Support initiatives designed to ensure that women are fully represented in basic, translational, and clinical research.** Data from the NIH Office of Research on Women's Health suggests that women now account for roughly half of all participants in NIH-supported clinical research. However, basic and preclinical biomedical research frequently focuses on male animals and cells, which may obscure understanding of key sex influences on health processes and outcomes. NIH has adopted a stringent "Sex as a Biological Variable" policy stating that the organism's sex will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. NIA will

continue to support this and other policies designed to ensure full representation of women in all levels of research.

- **Track, monitor, and report on participation of women in NIA-supported research, including adherence to the NIH SABV policy.** We will continue to report on progress in this domain through programs currently active across the NIH.

Supporting the Research Enterprise

Goal G

Support the infrastructure and resources needed to promote high-quality research.

The availability of the infrastructure, resources, and training needed to support present and future research, program management, and information dissemination is critical to the NIA mission. NIA will provide resources to develop a skilled interdisciplinary research workforce, ensure that scientists have access to the technology and equipment they need to perform the research, promote clinical research participation, and facilitate the dissemination of research results to scientists, health professionals, and the public.

Goal G objectives:

G-1: Foster interdisciplinary exchange and encourage collaborative research across disciplines.

G-2: Engage in partnerships within and among institutions and organizations, including patient and advocacy groups.

G-3: Train and attract the workforce necessary for rigorous research on aging, including new, midcareer, and senior investigators.

G-4: Attract and train more researchers from diverse scientific and cultural backgrounds.

G-5: Develop, maintain, and share research resources.

G-6: Develop the necessary infrastructure to encourage translation of research between basic discovery and intervention development.

Approach

G-1 Foster interdisciplinary exchange and encourage collaborative research across disciplines.

- Support workshops and conferences that bring scientists from various disciplines together for discussion and planning.
- Provide funding opportunities that encourage interdisciplinary efforts and/or partnerships across two or more institutions or organizations.
- Facilitate dialogue with researchers and professional organizations.

G-2 Engage in partnerships within and among institutions and organizations as well as patient and advocacy groups.

- Work closely with other NIH Institutes and Centers, other government agencies, and the private sector to collaborate across the continuum of research from basic science through translational research to clinical studies.
- Partner with other government agencies, professional organizations, private funders of research, and international research groups to collect data and other resources to facilitate understanding of science on a global level.

- Continue to participate in trans-NIH efforts such as the NIH Common Fund and the NIH Blueprint for Neuroscience Research.

- Partner with other government agencies, professional organizations, and advocacy groups to ensure that research results are translated into public health programs and medical practice and used to inform public policy.

- Collaborate with public and private partners to make results of research and other findings on successful patient recruitment strategies, including strategies targeted to minority and special populations, widely available to the research community.

G-3 Train and attract the workforce necessary for rigorous research on aging, including new, midcareer, and senior investigators.

- Develop and promote flexible mechanisms to meet the rapidly changing needs of science and prepare scientists, clinicians, and communicators to work effectively in interdisciplinary team environments across the continuum of research.

- Develop partnerships with academia, professional organizations, and other entities to establish and improve programs for identifying, recruiting, and training scholars for careers in research on aging.

- Participate in NIH efforts to improve recruitment, training, and retention of scientists across the full spectrum of research on aging.

- Expand bioethics training for investigators to address issues specific to older adults in research.

G-4 Attract and train more researchers from diverse scientific and cultural backgrounds.
Participate in NIH efforts to narrow the racial gap in grant approval. Work to recruit, train, and retain scientists from underrepresented groups, including people of diverse racial and ethnic backgrounds; gender identities; ages; and socioeconomic, geographic, and disability status.

G-5 Develop, maintain, and share research resources.

- Support colonies of aged animal models that are necessary for research on aging processes and specific age-related diseases.

- Make available cell cultures and tissue, cell, and blood banks for basic and epidemiological research.

- Create and make available DNA resources for genetic studies on aging and disease.

- Support access to imaging and other advanced technologies in shared facilities for examining aging biological systems.

- Support the development of population-based datasets, especially from longitudinal studies, suitable for analysis of biological, behavioral, and social factors affecting health, well-being, and functional status through the life course.

- Support data archiving and data sharing. Consider innovative means for cost-effectively sharing data that expand research use while reducing disclosure risk.

- Support the development of internationally harmonized biological, social, and behavioral longitudinal data on aging to foster cross-national research.

- Support computer technologies to record and analyze interdisciplinary research findings on basic biological studies and long-term, population-based data.

- Implement efforts to encourage older adults, including individuals from traditionally underrepresented groups, to participate in research and increase the numbers of participants in clinical trials.

- Support candidate drug evaluation programs, facilities, and related resources for animal and clinical studies.

- Develop innovative changes in the design, planning, and implementation of clinical trials and social and behavioral studies on the health and well-being of older adults.

G-6 Develop the necessary infrastructure to encourage translation of research between basic discovery and intervention development. Translational research links scientific discoveries with their application in medical practice and public health. For research on aging, basic discoveries typically begin with studies at the molecular or cellular level that help us understand the mechanisms of normal aging and disease or with basic behavioral or social science that uncovers potential mechanisms driving differences in aging processes across individuals, groups, and geographical regions. New knowledge gained in the laboratory or field may then take a variety of paths to human intervention. Equally important, however, are the basic and mechanistic insights gained in the context of intervention development and testing. Several NIH initiatives are focusing on ways the biomedical and behavioral science community can more successfully support translational activities that embody this process of back-and-forth translation. NIA will continue to:

- **Identify and optimize opportunities for moving new knowledge from basic discovery to intervention development and back.** We will continue to support promising preclinical studies, and community as well as health systems research. We will also work to ensure that new technologies such as advanced imaging and bioinformatics and other resources needed for effective translational research are accessible to scientists and clinicians.

- **Support a robust clinical trials infrastructure to facilitate the translation of basic research to human application in age-related diseases and vice versa.** This support will include technical assistance for patient recruitment and retention of older adults in clinical trials.

- **Foster communication and partnerships with other NIH Institutes and Centers and with other federal agencies as well as with other national and international research organizations.** NIA will continue to collaborate with other NIH Institutes and Centers on projects with a multidisciplinary focus such as the NIH Common Fund, the GeroScience Interest Group, and the NIH Blueprint for Neuroscience Research. We will continue to participate in partnerships with outside organizations to share resources, support collaborative research, eliminate barriers to drug development, and communicate research findings to the public.

Goal H

Disseminate information to the public; scientific and medical communities; stakeholder advocacy, community and older adult-support organizations; the media; and policymakers about research and interventions.

Communication efforts play a critical role in educating the public about research advances to improve health and well-being in later life. Health communication activities can increase the public's awareness of a specific aging issue, problem, or solution; reinforce knowledge, attitudes, or health behaviors; dispel misconceptions about aging; and encourage individual or collective action. Health education programs, activities, and materials can also inform, influence, and motivate the public.

Communicating effectively about health can be challenging because such information is often complex and technical. Moreover, the information may be inconclusive, controversial, contradictory, or subject to change as new research findings are released. Health information may also conflict with long-held personal beliefs. In addition, developments in technology are quickly and dramatically shifting the landscape for communicating health information. To succeed, health communication programs and materials must be based on an appreciation of the needs, interests and capabilities of the target audience, often with special considerations for physical and cognitive changes that come with age that may affect how information is received.

Large scale, multiyear, multimedia efforts engaging community organizations, such as ongoing NIA efforts to promote healthy aging and clinical trials participation, are needed to inform, persuade, convince, and guide behavior change. Such efforts may include engaging key representatives of health care providers, aging-related networks, and community services, advocates in aging and age-related diseases, the media, and others.

NIA communications are directly focused as well on professional audiences in research, clinical care and service delivery, and policy/legislation. These constituencies are interested not only in evidence-based health information, but also in NIA's budget, grants and review policies and practices, funding opportunities, emerging research programs and priorities, and more. NIA will continue to engage these communities in the planning and conduct of research as appropriate and in the dissemination of research results, and we will work to ensure that research directions and study results are communicated as widely as possible.

Goal H objectives:

H-1: Increase awareness and promote adoption of evidence-based strategies to improve health and quality of life of older adults.

H-2: Disseminate information to the public; scientific and medical communities; stakeholder advocacy, community, and older adult-support organizations; the media; and policymakers about research and interventions.

Approach

H-1 Increase awareness and promote adoption of evidence-based strategies to improve health and quality of life of older adults.

- **Develop, test, and conduct health communication programs and outreach activities to inform the public about the interventions and health-related progress validated by the results of research on aging.** We will craft and deliver messages and materials based on research to understand how the various audiences perceive and react to health messages, how the public is persuaded to change behavior, and how people in general — and older adults in particular — respond to various tactics.

- **Explore successful networks for the transfer of research knowledge and to evaluate interventions for older adults.** NIA will continue to work with other NIH Institutes and Centers, federal agencies, state and local governments, and both the private for-profit and not-for-profit sectors to ensure information about research and findings on diagnostics, treatment, prevention strategies, and behavioral and community interventions are widely shared, and that strategies are developed and embraced for effective impact on policies and programs. We will develop and maintain relationships with key journalists through both traditional and evolving media, providing evidence-based information and access to experts on aging and AD/ADRD research.

- **Provide information that supports training for people who work with older adults.** We will provide professional societies, community organizations, and academic institutions with research-based information that can be used in training geriatricians, social workers, counselors, and other community professionals and volunteers to work effectively with older adults and to implement evidence-based interventions.

- **Promote the importance of exercise and physical activity, nutrition, and cognitive health among older adults.** NIA will continue to use its website, social media, print, and other communications tactics to provide information and motivation for a diverse audience of older adults about the role of exercise/physical activity, nutrition, and cognitive health in healthy aging.

H-2 Disseminate information to the public; scientific and medical communities; stakeholder advocacy, community, and older adult-support organizations; the media; and policymakers about research and interventions.

- **Develop appropriate materials and programs for a variety of target audiences.** We will continue to work to overcome age, gender, cultural, and language barriers to the effective communication of health information, always considering the best format(s) for transmitting this information. We will continue to provide print materials for older adults who do not have access to digital and online resources. As older adults become increasingly adept at using digital and online resources, we will continue to employ mobile-friendly/responsive design and web analytics to enhance and expand use of new technologies — such as voice search capabilities — for health information.

- **Rapidly and effectively disseminate information to the medical community.** We will make widely available the latest advances in geriatric medicine, research on aging, and related health data through publications, professional education materials, public

service announcements, videos, as well as new and emerging communications platforms and technologies.

- **Make available health information and reports of research activities and findings on the NIA website and through other communications channels.** The NIA website will continue to serve as our institute's information hub for the public, researchers, health professionals, stakeholder organizations, journalists, and policymakers interested in health, aging, and research. Mobile applications, social media, and other resources will enable our information to reach our audiences directly and invite them to learn more via our website. NIA recognizes the different needs of these audiences, and to the extent possible, will continue to tailor the information it shares using a variety of outreach channels to enhance communications. These include the *Inside NIA* blog for researchers and stakeholders, webinars, videos, social media postings, meetings with stakeholder groups and organizations, staff and leadership presentations, and more. NIA will continue to proactively explore ways to maintain and upgrade communications with both established and new audiences.

- **Maintain and promote the NIA Alzheimer's Disease Education and Referral (ADEAR) Center.** Through this NIA information center — the federal government's premier public information on Alzheimer's disease and age-related cognitive change — the institute will continue to provide and expand evidence-based materials about these conditions, related research, participation in clinical trials, and caregiving.

- **Facilitate and support recruitment for Alzheimer's and aging clinical trials and inclusion of older adults in research.** NIA will continue to convene experts and develop resources to enhance older adult participation in research, including but not limited to maintaining, evolving, and promoting the NIA Alzheimer's & Dementia Outreach, Recruitment & Engagement (ADORE) resources. ADORE contains hundreds of resources on topics related to the engagement, recruitment, and retention of participants in clinical trials and studies on Alzheimer's disease and related dementias. NIA will continue to develop this website to help researchers better engage with their research communities. In addition, we will continue with related recruitment strategy and public outreach efforts through tactics such as testimonial videos.

- **Develop materials for special audiences and diverse populations.** These may include non-English language materials and materials for those with limited literacy.

- **Support national education efforts to encourage healthy practices among older adults.** These may include collaborations with other federal agencies, as well as state and community efforts.

Goal I
Effectively steward public resources.

As a federal agency, NIA is responsible for ensuring that we efficiently and effectively use taxpayer funds to the ultimate benefit of all Americans. This requires, among other things, that we establish a solid foundation for discovery that includes informed planning and priority setting; consistent, expert review and management of grant applications; and a competent, flexible workforce that is capable of meeting the challenges presented by a rapidly changing

scientific milieu. This charge also demands transparency within the limits imposed by privacy and the ethical conduct of research.

Goal I objectives:

I-1: Optimally manage research funds through careful planning and priority-setting, scientific review, and evaluation of investments.

I-2: Encourage innovation across all areas of our mission.

I-3: Ensure timely and accurate reporting of funding for AD/ADRD and in other scientific categories.

I-4: Recruit and retain a highly qualified and diverse workforce.

I-5: Identify and effectively manage risks that may affect the research enterprise.

Approach

I-1 Optimally manage research funds through careful planning and priority-setting, scientific review, and evaluation of investments.

- **Establish realistic scientific goals and priorities based on thorough understanding of the current state of the science**. This will involve regular communication via multiple channels with our various constituencies, including the scientific, medical, and advocacy communities and private industry.

- **Optimize scientific review of funding applications.** NIA receives thousands of applications for funding each year but can only fund a limited number of the applications it receives. We will continually identify and recruit expert reviewers and where necessary revise processes to ensure efficient, seamless grant review and award.

- **Regularly evaluate outcomes of major initiatives.** Regular evaluation will ensure that our long-running initiatives continue to produce results consistent with our level of investment and will allow us to revise our strategies when our goals are not being met.

How NIA Sets Scientific Priorities

NIA routinely engages in activities to assess research needs, gauge progress in meeting those needs, set priorities for future research, and plan new initiatives. The primary goals of our science planning and priority setting activities are to:

- Identify new and emerging areas of scientific opportunity, identify research gaps, and propose new research directions.

- Integrate and align science planning and priority setting with resource allocation decisions.

- Maintain the kind of flexibility that will enable institute programs to keep pace with rapid scientific and technological progress.

In establishing scientific priorities, NIA must carefully balance public health **need** with scientific **opportunity**. This assessment begins at the program level within NIA's four scientific Divisions and the Intramural Research Program, where experts in a broad variety of disciplines, from

molecular biology to population research, maintain ties with the greater scientific community through regular attendance at conferences and vigilant tracking of the scientific literature. Once this knowledge base is established, priorities emerge from:

- Periodic reviews of NIA programs conducted by members of the National Advisory Council on Aging for extramural divisions and the Board of Scientific Counselors for the Intramural Research Program. The reports from these reviews are used extensively to inform future planning.

- Twice-monthly meetings of NIA senior staff (the Planning Group) to guide and coordinate future directions and activities and support the NIA Director in making decisions on a variety of topics.

- Twice-yearly planning retreats as forums for wider participation by institute staff in presenting and discussing needs, opportunities, and priorities for moving the field of research on aging forward.

- Working groups on special aging-related topics to coordinate the implementation of initiatives that are cross-cutting to NIA programs.

I-2 Encourage innovation across all areas of our mission. Addressing the issues faced by our aging society will require focus, passion, and creativity. NIA is committed to supporting innovation in research and developing new ways of viewing and managing age-related changes at both the individual and societal levels.

A key driver of innovation is NIA's Small Business Innovation Research (SBIR) and Small Business Technology Transfer Programs (STTR). All NIA research divisions participate in these programs, which offer funding up to $2.5 million to commercialize products addressing aging and aging-related diseases and conditions, AD/ADRD, and the special challenges and needs of older Americans. The SBIR-STTR programs target early-stage research and development (R&D) and encompass a broad range of research topics and types, including translational and secondary R&D. All applicants are expected to develop, implement, and test the effectiveness of their products and services. NIA will:

- Continue to support a robust SBIR/STTR program that attracts high-quality applications and supports innovators in commercializing their technologies.

- Participate in trans-NIH initiatives to leverage new modalities, methodologies, and technologies to enhance health and wellness in the American population.

- Develop and maintain initiatives that facilitate innovation in aging research, including initiatives that are relevant to AD/ADRD.

I-3 Ensure timely and accurate reporting of funding for AD/ADRD and in other scientific categories. Our constituencies, including members of the American public, should be able to determine how we're spending taxpayer funds and to feel confident in those figures' accuracy and completeness. We will:

- Work with NIH-level experts to optimize tools for categorizing research, including defining and refining disease-based categories, Minority Health/Health Disparities, Women's Health, basic versus applied research, and others.

- Ensure that reporting in all categories is complete, timely, and accurate.

I-4 Recruit and retain a highly qualified and diverse workforce. Every member of NIA's staff, from the Director to the newest student volunteer, makes an important contribution as we strive daily to turn discovery into health. To carry out our mission, we need staff who are expert, creative, dedicated, and energetic, and who represent a diversity of background and experience. We recognize the importance both of recruiting new staff with new skills and insights and retaining seasoned employees who have extensive experience and strong institutional memory. We will:
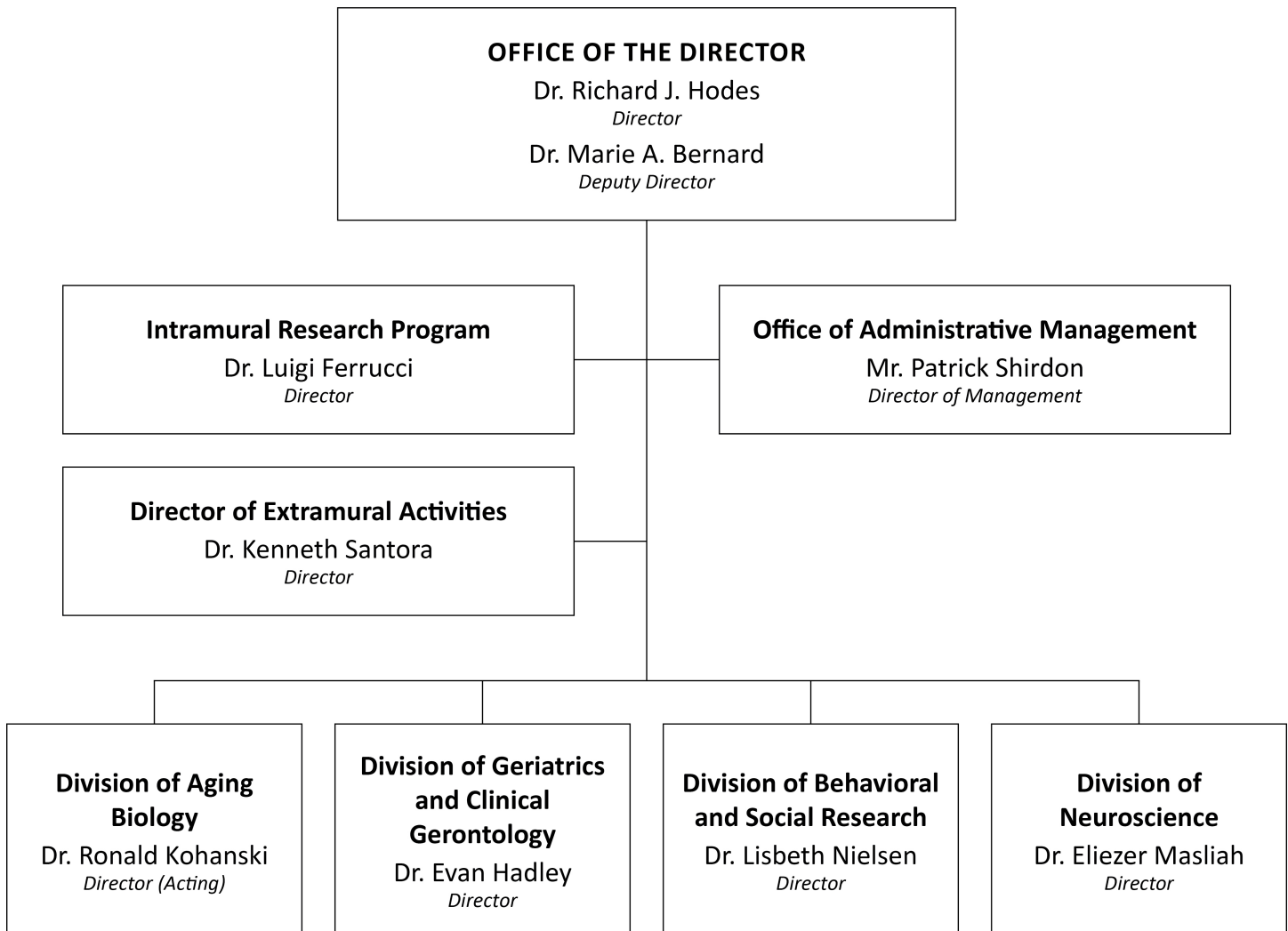
- Continually assess and evaluate the institute's evolving workforce needs and develop and implement plans to address those needs.

- Provide training and other critical tools to enable NIA staff to conduct the nation's business efficiently and effectively.

- Support workflow efficiency by appropriate management of administrative burden on staff.

- Regularly assess employee performance and provide opportunities for growth.

- Maintain a safe and supportive working environment.

- Take steps to ensure equality of opportunity for employment and advancement within NIA.

- Facilitate succession planning to ensure continuity of operations.

I-5 Identify and effectively manage risks that may affect the research enterprise. NIA's risk management activities are designed to proactively identify and mitigate risks to help promote the achievement of our objectives, strategy, and mission. All staff work to identify risks across programs and operations so that appropriate actions can be taken to address them. NIA will continue to:

- Develop and implement appropriate, cost effective management controls for results-oriented management.

- Assess the adequacy of internal controls in programs and operations.

- Identify needed improvements and take corresponding corrective action where appropriate.

Appendices

Appendix 1: NIA Organizational Chart

OFFICE OF THE DIRECTOR
Dr. Richard J. Hodes
Director

Dr. Marie A. Bernard
Deputy Director

Intramural Research Program
Dr. Luigi Ferrucci
Director

Office of Administrative Management
Mr. Patrick Shirdon
Director of Management

Director of Extramural Activities
Dr. Kenneth Santora
Director

Division of Aging Biology
Dr. Ronald Kohanski
Director (Acting)

Division of Geriatrics and Clinical Gerontology
Dr. Evan Hadley
Director

Division of Behavioral and Social Research
Dr. Lisbeth Nielsen
Director

Division of Neuroscience
Dr. Eliezer Masliah
Director

Appendix 2: Setting Strategic Directions

This document was developed over approximately eighteen months (beginning in June 2018) by staff in the NIA Office of Planning, Analysis, and Evaluation (OPAE). The process began with a series of meetings with senior institute staff to review the existing Strategic Directions, discuss advances in science, and brainstorm potential new priorities to be outlined in the new document. These meetings were followed by presentations at several conferences, including the Gerontological Society of America national conference in November 2018, to encourage members of the scientific community to contribute their insights to the process.

A cornerstone of the process was a Request for Information (RFI) that NIA issued in November 2018. The RFI was spotlighted on the NIA blog and on social media, and between these mechanisms we received thoughtful responses from over 20 organizations, researchers, and community members. This valuable input informed the development of new content for the current document.

OPAE staff used all these sources, along with internal assessments and evaluations, to draft the current document. The document then underwent several rounds of internal review as well as final review by the National Advisory Committee on Aging.