

Trans-NIH Initiatives

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Trans-NIH Initiatives

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Introduction

The National Institutes of Health (NIH) seeks fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. To achieve these goals, the NIH supports research on the causes, prevention, and treatment of human diseases and disorders; processes in healthy development and aging; and methods for collecting and disseminating data and health information. In addition, the NIH Institutes, Centers, and Offices (ICOs) leverage existing strengths and resources by collaborating in innovative and creative ways, to develop multidisciplinary approaches to answering complex and crucial questions about human health and preventing disease.

Trans-NIH collaborative efforts have led to the development of special initiatives and innovative research programs across the agency. For example, the Accelerating Medicines Partnerships (AMP), a federal and private collaboration, aims to increase the number of available diagnostic tools and therapeutics for major diseases including Type 2 diabetes and Parkinson's disease. The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, a public-private partnership, focuses on innovative technologies which allow researchers to gain a new understanding of the brain to ultimately lead to discoveries in treatments, cures, and preventions for brain disorders. Other examples of trans-NIH collaborative efforts include the NIH Maternal Mortality and Morbidity Task Force, which is focused on increasing support for research on maternal health to reduce disparities and advancing foundational knowledge of the risk factors associated with maternal mortality and morbidity in the United States. The National Institute on Aging (NIA), in collaboration with 23 ICOs across NIH, has made substantial efforts in Alzheimer's disease and related dementia (ADRD) research. Research on ADRD has led to new tools and biomedical knowledge such as expansive data sharing platforms, new disease biomarkers and targets for treatment, and training programs designed to enhance diversity in the research workforce. NIH ICOs have partnered to develop data science, including artificial intelligence, to help NIH meet the challenges ahead by introducing new analytical methodologies and expanded capabilities. This includes the ability to flexibly and automatically analyze images and large datasets for many areas of biomedical research, including diagnostics and precision medicine.

A broad range of expertise focused on basic, translational, and clinical research is needed to guide and support research and related policies across the biomedical enterprise. The Advisory Committee to the Director (ACD) Working Groups, for instance, bring together experts from within NIH and the scientific community to address complex issues, such as ending the culture of sexual harassment and enhancing scientific rigor in animal research. NIH supports early-stage investigators through the Next Generation Researchers Initiative (NGRI). In alignment with the recommendations of the ACD Working Group on the NGRI, NGRI encourages ICOs to prioritize funding opportunities for early-stage investigators, track the impact of that funding on investigator careers and develop policies responsive to the needs of these investigators.

The ultimate example of trans-NIH collaborative efforts came with the emergence of the COVID-19 pandemic. NIH quickly responded to this public health challenge by establishing new multi-ICO programs, including the Accelerating COVID-19 Therapeutics Interventions and Vaccines (ACTIV) partnership and the Rapid Acceleration of Diagnostics (RADxSM) initiative.

Together, these initiatives support the development of promising therapeutic, vaccine, and diagnostic approaches to usher in an end to the pandemic. ACTIV brings together key partners from federal, private, academic, and nonprofit organizations to align efforts and resources across four areas of opportunity: preclinical treatments, clinical therapeutics, clinical trial capacity, and vaccine development. RADx is working to expand the development and distribution of COVID-19 diagnostics with trans-NIH support for promising testing technologies, advancement of existing testing platforms, development of novel approaches to testing, and identification of effective strategies to make testing available to all, especially underserved and/or vulnerable populations. In addition to developing new initiatives, existing trans-NIH efforts quickly shifted to meet the growing emergency and public health need associated with COVID-19. The Helping to End Addiction Long-term (HEALSM) Initiative, a trans-agency effort developed to address the national opioid crisis, leveraged its existing partnerships and research infrastructure to respond to COVID-19 and its intersection with the opioid epidemic by funding research on the best approaches to treat those with opioid use disorder who are at a higher risk of respiratory illnesses and providing additional support to ongoing studies to direct resources to the COVID-19 pandemic. The *All of Us* Research Program leveraged its large and diverse cohort by testing participant samples collected prior to March 2020 for antibodies against SARS-CoV-2, which may indicate if a participant has been exposed. This testing will enhance understanding of when the virus first arrived in the United States and how it has spread since. Participants also are being surveyed on the effect of COVID-19 on their physical and mental health. To help researchers study common symptoms and treatments, the *All of Us* Research Program is also collecting and standardizing electronic health record information of those affected by COVID-19 for secondary analysis.

During FY 2022, NIH will continue to facilitate partnerships across ICOs to leverage infrastructure and scientific strengths and effectively advance biomedical research and public health. Building partnerships and leveraging existing relationships are important for NIH to support and facilitate research discoveries to prevent illness and disease and promote health. By answering the call of urgent public health needs, closing gaps in health disparities, and capitalizing on foundational research investments, NIH will continue turning discovery into health.

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

Program Overview

The COVID-19 pandemic is an unprecedented global crisis that has been met with a swift and extraordinary response. One of the ways the NIH has addressed this public health need with great urgency is by establishing and leading the new public-private partnership, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership,¹⁰⁵ to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines. Announced April 17, 2020, and managed by the Foundation for the National Institutes of Health (FNIH), ACTIV brings NIH together with the Biomedical Advanced Research and Development Authority (BARDA); Centers for Disease Control and Prevention (CDC); Food and Drug Administration (FDA); Department of Defense (DOD); Department of Veterans Affairs (VA); the trans-governmental collaborative effort formerly known as Operation Warp Speed; European Medicines Agency (EMA); and representatives from numerous biopharmaceutical companies, academia, and philanthropic organizations.

The ACTIV governance consists of a Leadership Group, an Executive Committee, and four working groups. The Leadership Group, which includes representatives from all ACTIV partners, meets regularly to review the progress of ACTIV. The Executive Committee, comprised of scientific executives from government and industry, oversees the activities and operations of the working groups, including reviewing recommendations for preclinical testing and therapeutic agents selected to enter ACTIV clinical trials using master protocols. NIH Institute Directors and Deputy Directors, including those from the National Center for Advancing Translational Sciences (NCATS), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), and the Office of the Director (OD), actively participate on the ACTIV Leadership Group, and some also serve on the ACTIV Executive Committee. Four working groups have focused on fast-track areas most ripe for opportunity: preclinical, therapeutics clinical, clinical trial capacity, and vaccines. The working groups include senior scientists from government, industry, academia, and philanthropic organizations.

In an unprecedented timeframe, ACTIV has made numerous accomplishments by developing a collaborative framework for prioritizing candidate therapeutics that fall into four categories (antivirals, immunomodulators, supportive therapies, and neutralizing antibodies), streamlining clinical trials, coordinating regulatory processes, and leveraging assets among all partners to rapidly respond to the COVID-19 and future pandemics.

The preclinical working group was charged with standardizing and sharing preclinical evaluation resources and methods and accelerating testing of candidate therapies and vaccines to support entry into clinical trials.¹⁰⁶ The working group has developed a master inventory of preclinical testing resources, including for nonhuman primates (NHPs), small animal models, and biosafety level 3/4 laboratories. A national strategy for NHP research was developed, which aims to maximize the research value of scarce NHP resources that are needed for preclinical testing of

¹⁰⁵ www.nih.gov/research-training/medical-research-initiatives/activ

¹⁰⁶ www.nih.gov/research-training/medical-research-initiatives/activ/preclinical-working-group

some vaccines and certain therapeutics during the pandemic. The working group has established standard operating procedures for accelerated preclinical agent development in response to a pandemic. They have also completed a prioritization framework for evaluating and prioritizing preclinical compounds for further preclinical testing. Together with the therapeutics clinical working group, the preclinical working group helped to establish an ACTIV COVID-19 Clinical and Preclinical Candidate Compound Survey to collect information for an inventory of potential candidates for preventing or mitigating COVID-19 infection.¹⁰⁷ The preclinical working group has created a virtual preclinical testing network to streamline access to testing resources. They have also created a public database for sharing preclinical data, which will help to facilitate interpretation and comparison of results from multiple experiments on multiple agents that could provide insight on SARS-CoV-2 and treatment approaches not apparent from a single study.¹⁰⁸ As new viral variants have emerged, they are generating a process to assess viral variant effects on vaccines and therapeutics. The working group has published scientific papers related to the group's efforts, including preclinical paths to support rapid development of therapeutics and preclinical models for vaccines and therapeutics.^{109,110}

The therapeutics clinical working group was charged with designing an adaptive master protocol strategy and prioritizing therapeutic agents for testing within clinical trial networks identified by the clinical trial capacity working group.¹¹¹ The working group has developed a process to prioritize clinical agents for rapid testing, evaluated hundreds of publicly available agents, and prioritized promising compounds for clinical testing. Based on the results of several waves of agent prioritization, ACTIV clinical trials have been launched in numerous NIH-supported networks using selected candidates, including monoclonal antibodies, antivirals, immunomodulators, and anticoagulants/anti-platelet agents. These rapid launches were made possible by the development of master protocols by the working group, which allow for the efficient evaluation of multiple investigational agents as they become available and for the standardization of primary endpoints to enable the comparison of trial data. The ACTIV-1 master protocol, led by NCATS and launched in October 2020, tests promising immune modulator compounds, a class of drugs that help minimize the deleterious effects of an overactive immune response to SARS-CoV-2 infection, in a Phase 3 trial of hospitalized patients.¹¹² ACTIV-2, led by NIAID and launched in August 2020, is designed as a Phase 2 trial that can expand seamlessly to Phase 3 testing of monoclonal antibodies and other types of therapeutics in outpatients.¹¹³ ACTIV-3, also led by NIAID and launched in August 2020, is a Phase 3 trial testing monoclonal antibodies and other types of therapeutics in hospitalized patients.¹¹⁴ ACTIV-4, led by NHLBI, consists of three adaptive platform Phase 3 clinical trials to test antithrombotics in three patient populations. The outpatient and inpatient trials were

¹⁰⁷ redcap.ncats.nih.gov/redcap/surveys/index.php?s=DAE87WPTE7

¹⁰⁸ opendata.ncats.nih.gov/covid19/databrowser

¹⁰⁹ [www.cell.com/cell-host-microbe/fulltext/S1931-3128\(20\)30522-9](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30522-9)

¹¹⁰ [www.cell.com/cell-host-microbe/fulltext/S1931-3128\(20\)30521-7](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30521-7)

¹¹¹ www.nih.gov/research-training/medical-research-initiatives/activ/therapeutics-clinical-working-group

¹¹² www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ1

¹¹³ www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ2

¹¹⁴ www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ3

launched in September 2020, and the third trial involving post-hospitalized patients launched in March 2021.¹¹⁵ The ACTIV-5 master protocol, led by NIAID and launched in October 2020, is designed to test other promising therapies in a series of Phase 2 trials of hospitalized patients.¹¹⁶ The ACTIV-6 master protocol, starting in May 2021, will test the efficacy of repurposed medications in an outpatient setting.¹¹⁷ In addition to the ACTIV clinical trials, some of which have yielded results, several ACTIV-associated trials, which are other NIH-funded flagship COVID-19 therapeutic trials of ACTIV-prioritized agents using protocols informed or endorsed by the ACTIV partnership, are underway or complete.¹¹⁸

The clinical trial capacity working group was charged with developing an inventory of clinical trial capacity, including networks from the NIH Institutes and Centers (ICs) and contract research organizations (CROs), to serve as potential settings in which to efficiently implement COVID-19 clinical trials.¹¹⁹ The working group developed and launched a series of clinical trial capacity surveys that included questions designed to identify the capabilities of more than 60 networks, over 700 clinical trial sites, and over 30 CROs and site management organizations. The results of these surveys were combined with geographic mapping, COVID-19 disease incidence data, and visualization capabilities into a unique “geotracking tool” that has enabled the therapeutics clinical working group and trial sponsors to choose the most effective networks and sites to support ACTIV master protocols and associated trials. This effort included multiple NIH ICs involved in the ACTIV partnership, including NCATS, NHLBI, NIAID, and OD. The working group created a reference guide for novel clinical trial innovations along with a resource map of available solutions to help enable the safe and efficient conduct of ACTIV clinical trials under the unique conditions imposed by the COVID-19 pandemic.

The vaccines working group was charged with accelerating the evaluation of vaccine candidates by supporting harmonized clinical efficacy trials and a parallel effort to generate biomarkers and other evidence for more rapid approval/authorization.¹²⁰ The working group coordinated and contributed to the development of harmonized protocols for vaccine evaluation in clinical trials, which allows for the simultaneous assessment of multiple vaccine candidates through analyses of correlates of protection across trials. SARS-CoV-2 vaccine clinical trials using these ACTIV-informed harmonized protocols include Phase 3 trials of the Moderna mRNA-1273 vaccine using a messenger RNA delivery platform, the AstraZeneca AZD1222 vaccine using a non-replicating adenovirus delivery system, the Johnson & Johnson JNJ-78436725 vaccine using a non-replicating adenovirus delivery system, and the Novavax NVX-CoV2373 protein subunit vaccine.¹²¹ The Phase 1/2 trial of the Sanofi/GlaxoSmithKline COVID-19 adjuvanted recombinant protein-based vaccine is also using a harmonized protocol. These trials activated at

¹¹⁵ www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4

¹¹⁶ www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ5

¹¹⁷ clinicaltrials.gov/ct2/show/NCT04885530?term=ACTIV-6&draw=2&rank=1

¹¹⁸ www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ6

¹¹⁹ www.nih.gov/research-training/medical-research-initiatives/activ/clinical-trial-capacity-working-group

¹²⁰ www.nih.gov/research-training/medical-research-initiatives/activ/vaccines-working-group

¹²¹ www.nih.gov/research-training/medical-research-initiatives/activ/sars-cov-2-vaccine-clinical-trials-using-activ-informed-harmonized-protocols

sites that are part of the NIAID COVID-19 Prevention Network (CoVPN).¹²² The vaccine sponsors, ACTIV, and NIH leadership work closely with the networks on recruitment strategies and communication to promote enrollment of a diverse population in the vaccine trials. This working group has developed scientific publications, assessing practical considerations and prerequisites for using controlled human challenge studies to support SARS-CoV-2 vaccine development and potential vaccine-associated enhanced disease in SARS-CoV-2 vaccine development.^{123,124}

Next Steps/Goals

Both the vaccines and clinical capacity working groups officially completed their charges as of July 31, 2020. The vaccines working group continues to meet on an ad-hoc basis to provide recommendations for ongoing vaccine trials. The majority of ACTIV trials are at capacity for agents to be assessed. Therapeutic agents received through the ACTIV COVID-19 Clinical and Preclinical Candidate Compound Survey continue to be considered by the ACTIV preclinical and clinical therapeutics working groups in case additional capacity becomes available in any of the trials.

¹²² coronaviruspreventionnetwork.org/

¹²³ stm.sciencemag.org/content/early/2020/10/16/scitranslmed.abe0948

¹²⁴ science.sciencemag.org/content/368/6494/948

Alzheimer’s Disease and Related Dementias

Program Overview

In 2020, as many as 5.8 million Americans 65 years and older had Alzheimer’s disease, and the prevalence in the United States is projected to increase to 13.8 million by 2050. Alzheimer’s is the most common dementia diagnosis and the sixth leading cause of death for Americans. In addition, many people have other forms of Alzheimer’s disease related dementias, such as Lewy body disease, frontotemporal dementia, and vascular cognitive impairment/dementia, either alone or more commonly mixed with Alzheimer’s pathology.

Since the passage of the National Alzheimer’s Project Act (NAPA) in 2010, Congress has expressed continuing interest and support of Alzheimer’s research through additional Alzheimer’s-focused legislation including the mandate for an annual professional judgment budget and appropriations report language targeting increased funds for Alzheimer’s research.

NIH leads an ambitious research agenda designed to better understand, diagnose, prevent, and treat these devastating diseases. NIH now progresses more quickly, connects scientific discoveries more precisely, increases the diversity of its research workforce as well as clinical trial participants, and builds new research resources such as extensive data sharing platforms. Indeed, today NIH is pursuing the answers to fundamental questions that could not be addressed just a few years ago. Even with everything learned so far, the path toward effective prevention and treatment remains challenging; however, NIH is unwavering in its commitment to combat these complicated diseases. NIH is poised to build on the current momentum and capitalize on the recent funding increases in this area, which have enabled significant progress in:

Disease Mechanism Studies: NIH investments in research to identify underlying biological mechanisms that cause Alzheimer’s and related dementias are fundamental for the discovery of potential drugs targeting those processes. Today, scientists have identified variants in more than 50 genetic areas that may increase risk for the disease. Ten years ago, we knew of just 10 genes associated with Alzheimer’s disease, and 20 years ago, we knew of only four. These genetic regions appear in clusters that point toward what may be highly relevant molecular pathways and specific biological processes, such as cell trafficking, lipid transport, inflammation, and immune responses. These discoveries are providing researchers with multiple new clues that suggest potential preventions, treatments and cures for Alzheimer’s and related dementias.



Studies of toxic proteins are also providing important clues to possible disease mechanisms underlying Alzheimer's and related dementias. As one example, recent NIH-supported research has demonstrated that the features of abnormal protein folding may contribute to their toxicity and accumulation in brain diseases that cause dementia.^{125,126,127} Specifically, researchers have demonstrated differences in the structure of abnormal tau protein filaments that collect in the brains of people with Alzheimer's versus two other neurodegenerative conditions.

With nearly 100 billion neurons and 100 trillion connections, the human brain remains one of the greatest mysteries in science and one of the greatest challenges in medicine. Advances in basic science research, such as those described above, will produce greater knowledge about disease mechanisms that will have clinical implications and ultimately improve human health. To accelerate progress toward that goal, 10 institutes are collaborating on the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. Launched in 2013, the initial focus has been on understanding the basic mechanisms underlying the function of the healthy brain, often in cellular and animal models. BRAIN Initiative advances are now setting the stage for groundbreaking human neuroscience research aimed at understanding the human brain, including diagnosing and treating its disorders. Over time this project will provide new tools and knowledge to combat human brain diseases, such as Alzheimer's and related dementias.

Biomarker Research: Biomarkers — characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, disease processes, or responses to therapeutic intervention — can facilitate a more accurate diagnosis by helping researchers and clinicians discern between the different diseases that cause dementia. NIH funding has enabled significant recent progress in developing, testing, and validating biomarkers for diagnosing Alzheimer's and related dementias. These technological advances have helped scientists discover that changes in the brain that occur during Alzheimer's are evident long before a person shows outward signs of cognitive impairment or dementia. Emerging research also shows that beta amyloid plaques, tau proteins, and other biomarkers not only are present in the brain and spinal fluid but also circulate in the bloodstream.

In 2019 and early 2020, NIH-supported scientists reported advances in the development of blood-based tests that could enable rapid screening of volunteers who wish to enroll in studies. These blood tests could help detect pathological Alzheimer's in people who are showing signs of dementia or even detect abnormal levels of protein prior to cognitive symptoms. Blood tests that are at the most advanced stage of development detect the accumulation of amyloid or tau proteins. Using blood tests for screening and tracking response to treatment could help reduce the number of research volunteers needing to undergo invasive procedures such as a spinal tap or expensive positron emission tomography (PET) imaging. In the future, improved blood-based biomarkers may help not just researchers but also physicians to detect and diagnose Alzheimer's and related neurodegenerative disorders earlier, when interventions are more likely to be effective. In addition to blood tests, other NIH-supported research projects are designed to look beyond current measures to detect signs of dementia even earlier. These include changes in

¹²⁵ doi: 10.1186/s40478-019-0787-2

¹²⁶ doi: 10.1038/s41586-019-1026-5

¹²⁷ doi: 10.1038/s41586-020-2043-0

vision and pupil responses that may signal Alzheimer's, or a combined decline in memory and walking speed as a sign of dementia. New NIH programs are also working to develop biomarkers for small vessel diseases of the brain and vascular contributions to cognitive impairment and dementia (VCID). The MarkVCID consortium—led by the National Institute of Neurological Disorders and Stroke (NINDS)—has developed and is currently testing 11 different biomarker kits, which include several types of vascular imaging and fluid-based biomarkers, across several clinical research sites.

Translational Research Infrastructure: NIH has been able to augment investments in key research areas necessary for laying the groundwork for a precision medicine approach to treatment and prevention of Alzheimer's and related dementias. To accelerate the discovery of effective treatments that will become broadly available to the public, NIH has developed programs to make data, knowledge, and research tools widely available to all researchers. NIH has launched a number of programs over the past six years to provide researchers with an infrastructure for developing their ideas for medicines and other products, including: the Alzheimer's Disease Sequencing Project, Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD), the Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) consortium, and TaRget Enablement to Accelerate Therapy Development for Alzheimer's Disease (TREAT-AD) consortium. A hallmark of these programs is that every one of them brings together scientists from academia and industry who are working in many different disciplines, from epidemiology and genetics to data science and computational biology, molecular and cell biology, and medicinal chemistry and pharmacology. Working collaboratively, the researchers utilize an open-science/open-source approach to the key steps of the translational process. They are discovering new and better targets for treatment; producing and analyzing comprehensive and shareable sets of molecular data; and developing high quality translational research tools.

Complementing the new translational infrastructure is support for new cross-disciplinary training programs funded through NIH's Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD-Related Dementias, which is designed to support a new and more diverse generation of translational scientists with expertise in biology, data science, engineering, and drug development, who are able to participate and lead team-science programs from target discovery to clinical trials. In addition, the National Institute on Aging (NIA)-funded Alzheimer's Clinical Trials Consortium (ACTC), a clinical trials infrastructure to accelerate and expand studies for therapies in Alzheimer's and related dementias, continues to provide centralized resources and shared expertise to researchers nationwide to hasten the development of effective interventions. In 2020, the ACTC launched the Institute on Methods and Protocols for Advancement of Clinical Trials in Alzheimer's and related dementias (IMPACT-AD) course that aims to educate and promote diversity among research professionals and future researchers in the Alzheimer's field.

Prevention and Treatment Research: Scientists have been able to pursue many avenues simultaneously as they study promising treatments that act upon many different targets. Some approaches do not rely on drugs; rather, they focus on behavior changes and lifestyle choices such as the careful control of high blood pressure, which is an established risk factor for dementia. For example, a previously supported NIH study called SPRINT Memory and

Cognition in Decreased Hypertension (SPRINT MIND) demonstrated that people who intensively control their blood pressure with one or more drugs can significantly reduce their risk of developing mild cognitive impairment (MCI).¹²⁸ This study provided what is perhaps the most promising randomized clinical trial evidence to date supporting a role for active primary prevention in the cognitive trajectory of dementia.

NIH will build on the current momentum by continuing to support a broad range of treatment targets. NIH currently supports approximately 270 clinical trials on Alzheimer's and related dementias, from pilot studies to large-scale trials, on a wide range of interventions for diagnosis, treatment, prevention, care, and caregiving. While amyloid continues to be a target of clinical investigation, 40 of the 57 pharmacological trials supported by NIH are investigating other targets. More than 120 current trials test nonpharmacological interventions, while more than 80 others are aimed at care and caregiving for people living with dementia. NIH has taken significant steps to modernize and speed up trials to test potential interventions earlier in the disease continuum, examine how therapies can be delivered pragmatically in real-world settings, and foster new partnerships with organizations and individuals in the design and operation of trials.

Ensuring greater racial, ethnic, gender, and socioeconomic diversity among participants and researchers is central to these efforts. Inclusion is critical to understanding and addressing disparities in the incidence and prevalence of disease and identifying unique care needs for diverse populations. As part of a broader effort to improve inclusivity, NIA has recently awarded a contract to develop an institute-wide informatics system to track, report, and manage NIA's clinical research data, activities, and portfolio in real time. This system will also enable NIA to better manage clinical research, identify and support sites not able to meet diverse recruitment goals, learn from top-performing sites, and provide transparency regarding its recruitment efforts and successes.

Population Studies and Precision Medicine Research: Because of the accelerated pace of research in recent years, we now know that Alzheimer's and related dementias are complex conditions that stem from the interplay of genetic, lifestyle, and environmental factors. NIH-supported researchers continue to study large, diverse groups of people, to better understand the reasons why some people develop these conditions and others do not, and which genes, lifestyle choices, and other factors seem to be associated with the disease.

Developing a better understanding of how and why many diseases affect diverse communities in different ways is paramount in our search for treatments and prevention for Alzheimer's and related dementias. NIH-supported studies in health disparities have already found that: 1) those who do not graduate from high school are at higher risk; 2) the risk of dementia is highest among African Americans and American Indians or Alaska Natives; intermediate for Latinos, Pacific Islanders, and non-Latino whites; and lowest for Asian Americans; and 3) women are at potentially higher risk of dementia than men, at least in part due to greater overall longevity. These discoveries, paired with knowledge of genetic and other factors, can be used to design clinical trials to test whether these factors truly confer risk or offer protection.

¹²⁸ doi: 10.1001/jama.2019.10551

Care and Caregiver Support Studies: NIH is also committed to enabling better outcomes for people with Alzheimer’s and related dementias, as well as for their caregivers. NIH-supported efforts have led to improved quality of care and quality of life for those living with these conditions and the development of resources designed to help ease burdens on care providers. Our efforts to encourage broad sharing of data and resources include raising awareness about evidence-based social and behavioral interventions. In 2019, NIA expanded its network of Edward R. Roybal Centers for Translational Research on Aging to focus on the development of behavioral interventions for dementia care providers. The Roybal network, which was established in 1993, is designed to translate findings from basic behavioral and social research into evidence-based interventions and programs that can be shared and implemented in the community. The four new centers, called collectively the Roybal Centers for Translational Research on Dementia Care Provider Support, will develop and pilot test dementia-related interventions and their related materials for feasibility, acceptability, and efficacy.

Also in 2019, NIH funded a new effort called the IMbedded Pragmatic Alzheimer’s disease and related dementias Clinical Trials (IMPACT) Collaboratory to meet the urgent public health need to deliver high quality, evidence-based care to people living with dementias and their caregivers. Through this effort, researchers will develop and test care interventions in real world settings such as hospitals, assisted living facilities, nursing homes, and adult day care centers. In general, a “pragmatic clinical trial” means participants are enrolled as part of a real-world setting, rather than selected from a broader community based on narrowly defined criteria.

Additionally, the costs of dementia care and the challenges families face as caregivers continue to be a priority area of research. A recent analysis of Medicare and Medicaid data shows that the costs of health care for people with dementia are much higher than for those without dementia, and the burden of those higher costs falls disproportionately on people with dementia and their families.¹²⁹

Trans-NIH Collaboration

NIA spearheads the NIH effort in Alzheimer’s and related dementias, in close collaboration with NINDS. Many other NIH ICOs also contribute, and major international research summits hosted by NIH contribute significantly to the development of detailed operational plans. These summits focus on 1) treatment and prevention of Alzheimer’s disease (hosted by NIA); 2) treatment and prevention of Alzheimer’s related dementias, including vascular cognitive impairment/dementia, Lewy body dementia (LBD), and frontotemporal dementias (hosted by NINDS); and 3) better approaches to care, services, and support (hosted by NIA). The research summits are held annually with a three-year rotation by topic. The summit focused on treatment and prevention of Alzheimer’s disease took place in April 2021. Extensive summit-related discussion and feedback from a wide range of key stakeholders informs NIH’s future Alzheimer’s and related dementias research efforts. Additionally, representatives from NIA, NINDS, and other NIH ICOs meet annually to discuss opportunities for research collaborations and joint funding initiatives in Alzheimer’s and related dementias. To foster greater collaboration and spur new research ideas, NIA offers Alzheimer’s and related dementias supplement awards to researchers with grants from any of the ICOs, including those focused on non-Alzheimer’s topics. NIA also supports Alzheimer’s and related dementias projects at other ICOs that are within the NIA pay

¹²⁹ doi: 10.1111/jgs.16414

line. In 2019 NIA launched the collaborative intramural Center for Alzheimer's and Related Dementias (CARD) in partnership with NINDS, and also including the National Center for Advancing Translational Sciences, and the NIH Clinical Center. CARD will be housed in newly constructed headquarters on the NIH main campus. The Center will combine the power of NIH intramural science with the work of researchers around the globe to push boldly ahead in basic, translational and clinical AD/ADRD research. CARD will also emphasize teamwork, innovation, transparency, data sharing and advanced technology to speed up the translation of scientific findings into real-world applications.

Next Steps/Goals

NIH has embarked on an ambitious research agenda, making much progress toward better understanding these complex diseases. NIH continues to make significant advances in discovering approaches that may prevent, diagnose, and treat them, while at the same time continuing to advance research on dementia care and caregiving. Future work in this area will focus on a deeper understanding of different forms of dementia, as well as the development of effective prevention approaches and care interventions that can improve quality of life for patients and caregivers. NIH will work toward precision medicine for Alzheimer's and related dementias research, making it possible in the future to treat the right patients with the right drugs at the right time of disease progression.

Faculty Institutional Recruitment for Sustainable Transformation (FIRST)

Program Overview

As our nation's population grows increasingly diverse, there is an urgent need to ensure that scientific talent is nurtured, recognized, and supported in researchers from diverse backgrounds. Fostering inclusive environments in the biomedical research workforce will allow creative minds the opportunity to contribute to realizing our national research and health goals. Efforts to increase the diversity of the biomedical research workforce are anticipated to lead to the recruitment of talented researchers from all backgrounds, enrich the training environment, balance and broaden the perspective in setting research priorities, improve the ability to recruit subjects from all backgrounds into clinical research protocols, and expand the nation's capacity to address and eliminate health disparities.

Despite recognizing the pressing need to enhance diversity in National Institutes of Health (NIH)-funded institutions across the United States, success in accomplishing this goal has largely been limited to trainee populations, leaving biomedical research faculty diversity as an ongoing challenge. Institutional cultures lacking necessary elements of inclusion and equity are an important contributing factor to faculty-level disparities. However, many previous efforts to enhance diversity have focused on the individual and have not addressed the critical issue of institutional culture.

Early indications from the intramural NIH Distinguished Scholars Program,¹³⁰ as well as other cohort-based recruitment programs, suggest that recruitment of a critical mass of investigators committed to diversity and inclusion may foster the institutional changes needed to create meaningful improvement in diversity at the faculty level. Building upon this hypothesis, NIH is launching the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program.¹³¹ FIRST aims to create cultures of inclusive excellence at NIH-funded institutions, to establish and maintain scientific environments that cultivate and benefit from a full range of talent. This goal will be achieved by implementing a set of well-integrated, evidence-based strategies and evaluating their impact on prespecified metrics of institutional culture, inclusion, and diversity. FIRST will establish a faculty cohort model for hiring, mentoring, and professional development; integrated, institution-wide approaches to address faculty equity, mentoring, and work/life issues; and a coordination and evaluation center to conduct independent evaluations of program impacts. Ultimately, successful strategies can be adopted by additional institutions, leading to meaningful improvements in the diversity of biomedical research faculty.

FIRST consists of two independent, but linked, components. The first component is support for institutions in their efforts to develop and implement faculty cohort models for simultaneous hiring of a cohort of research faculty committed to promoting diversity and scientific excellence. Highly-Resourced Institutions and Limited-Resourced Institutions¹³² may apply independently or in a partnership arrangement to develop and implement faculty cohort models for the

¹³⁰ diversity.nih.gov/programs-partnerships/dsp

¹³¹ commonfund.nih.gov/first

¹³² Limited-Resourced Institutions must award doctoral degrees in the health professions or health-related sciences and have received less than \$50 million a verage in annual NIH funds within the three years prior to the time of application. These criteria are also used for the Research Centers in Minority Institutions (RCMI) program.

simultaneous hiring of a diverse cohort of research faculty. Any individual who is competitive for a new tenure track faculty position and who has demonstrated a strong commitment to promoting diversity and scientific excellence is eligible for FIRST faculty support.

Faculty in the cohort will receive multilevel mentoring, sponsorship, and professional and research development embedded within institutions that are actively implementing integrated, systems-level approaches for sustainable culture change. Each institutional cohort is expected to include at least 6 to 10 faculty, and may be comprised of small clusters of scientists (no fewer than 3) within several scientific areas, such as neuroscience, cardiovascular disease, cancer, minority health and health disparities, behavioral, social, or other research area within the NIH mission. FIRST will support three cycles of faculty cohorts; awardee institutions will begin with a planning year in the first year of the award, and then bring new cohort faculty on board in the second year. The first planning year of awards is anticipated in FY 2021, and the first year of faculty cohort support will start in FY 2022.

The second component of the FIRST program is support for a Coordination and Evaluation Center (CEC), which will facilitate evaluation of institutional culture change. The FIRST CEC will establish consortium-wide evaluation plans and develop common metrics of inclusive excellence. Working collaboratively with the individual institutions supporting faculty cohorts, the CEC will coordinate submission of data across institutions and objectively assess progress towards achieving consortium-wide metrics. Evaluation activities will include three levels of analysis: cohort-level, department-level, and institution-wide. The CEC will also coordinate consortium-wide activities and disseminate knowledge generated through FIRST to inform national institutional policies, programs, and practices. The CEC award is expected to start in FY 2021.

The FIRST program is funded through the NIH Common Fund and managed in collaboration with the National Cancer Institute, the National Institute on Minority Health and Health Disparities, the Office of Scientific Workforce Diversity, the National Institute of Neurological Disorders and Stroke, and the National Heart, Lung, and Blood Institute. Additional program management is provided by trans-NIH Working Group members from 17 ICOs. The robust trans-NIH participation in the FIRST program demonstrates that supporting a diverse biomedical research workforce is a high priority across NIH. Fostering a workforce that better reflects the diversity of our nation will advance the missions of all NIH ICOs by ensuring talented individuals from all backgrounds can use their skills and creativity to address current challenges and opportunities in biomedical research.

Harnessing Artificial Intelligence (AI) for Health

Program Overview

Biomedical science has made, and continues to make, enormous progress in studying fundamental components of human biology. The challenge ahead will increasingly be to systematically learn how the components work together—an endeavor in which technological advances will undoubtedly foster progress and expedite discoveries. The extraordinary capability of artificial intelligence (AI) to learn, infer, and make predictions can be harnessed as a powerful tool to advance biomedical science and develop treatments. However, this requires new approaches to data collection, integration, and labeling to create large datasets that are “AI-ready.” It requires dynamic application of algorithms that include detailed model descriptions to enable their transparent interpretation and reuse. As technologies advance, the public will need to be assured that data and algorithms are developed with the highest ethical standards to address bias and transparency and ensure safe and trustworthy adoption in the biomedical research community. To achieve these goals, a well-rounded and multidisciplinary workforce fluent in biomedical and computational challenges and well-versed in ethics, social, and behavioral sciences will be critical. The National Institutes of Health (NIH) is developing new programs that focus on data development and ethics, building training programs that will engage a diverse workforce, and employing AI for a broad array of applications—like addressing public health needs, closing the gaps in disparities, and expanding on fundamental discoveries.

Through the Common Fund’s leadership, NIH assembled an internal group of leaders to start implementing a large subset of the recommendations put forth by the 2018 AI Working Group of the Advisory Committee to the Director.¹³³ The National Human Genome Research Institute (NHGRI), National Institute of Biomedical Imaging and Bioengineering (NIBIB), and National Library of Medicine (NLM) in partnership with the Common Fund are leading the new program, which was approved as a concept at the May 2020 Council of Councils. The new program, Bridge to Artificial Intelligence (Bridge2AI), will be run by a trans-NIH team, which is developing funding announcements and planning for program launch. Bridge2AI is now possible because of extraordinary technological advances in AI and drastic increases in the ability to collect and store massive amounts of biologically relevant data.

FY 2021 appropriations included \$50 million to expand the number of machine learning (ML)-focused grants focused on the use of AI to address chronic diseases. This initiative will leverage NIH Office of Data Science Strategy (ODSS) programs and allow NIH to develop unbiased, ethical, and transparent datasets; link massive datasets together across programs; develop AI algorithms that take advantage of the capabilities of cloud and Industries of the Future-based infrastructures and transparent, explainable models to improve understanding of the causes and early treatments of chronic disease; and to account for important social and behavioral factors that affect health outcomes across heterogeneous populations.

Across NIH, individual institutes and centers continue to support mission-specific AI efforts, several of which are detailed below.

¹³³ acd.od.nih.gov/documents/presentations/12132019AI_Report.pdf

Addressing Urgent Public Health Challenges

Efforts in AI are addressing public health needs with great urgency. Through support from the CARES Act, NIBIB, in collaboration with multiple NIH institutes, launched the Medical Imaging and Data Resource Center¹³⁴ to support rapid analysis and dissemination of coronavirus disease 2019 (COVID-19) related imaging and associated data. This large database will fill several unmet needs, including (1) use of machine intelligence for quality assurance/quality control to ensure optimal image quality, (2) biomedical discovery (radiogenomics, deep learning, and predictive modeling to affect public health), and (3) virtual clinical trials. In other efforts to respond to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the NCI researchers and NVIDIA,¹³⁵ an AI computing company, partnered to develop high-throughput AI classification algorithms for detecting COVID-19 in computerized tomography (CT) scans from patients.

NLM and NIAID are funding research to devise algorithms for chest x-ray screening and visualization.¹³⁶ The algorithms are being applied to detect tuberculosis infections in chest radiography images from children with and without HIV.

The NIAID Tuberculosis Portals¹³⁷ program supports NIAID's efforts to rapidly respond to a potential drug-resistant tuberculosis outbreak in the United States. Through an international partnership, the portal collects tuberculosis case data—including chest x-rays and CT scans—and uses AI and image processing techniques to process, analyze, and organize the images bases on similarity metrics. Other examples include applying natural language processing to medical records and image analysis for TB diagnostics and selection of potential compounds targeting SARS-CoV-2.

Combating Health Disparities

Other AI applications are helping to close the gap in health disparities. For example, the National Eye Institute supported work that led to an FDA-approved AI diagnostic system, IDx-DR. The system analyzes retinal images to screen and detect diabetic retinopathy, an important step in managing a disease that causes vision loss in more than 30 million Americans. As IDx-DR is implemented in clinics and more data are produced, this tool can transform the field by improving access to rural and underserved populations.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is supporting an ML framework to predict severe maternal morbidity.¹³⁸ Severe maternal morbidity, or life-threatening pregnancy complications at delivery, has been increasing steadily, affecting more than 50,000 women in the United States in 2014. Researchers aim to analyze population-based data from Maryland state databases and hospital surveys to develop techniques that can predict maternal risks early. Identifying key predictors of severe maternal

¹³⁴ www.nibib.nih.gov/news-events/newsroom/nih-harnesses-ai-covid-19-diagnosis-treatment-and-monitoring

¹³⁵ www.nature.com/articles/s41467-020-17971-2#Abs1

¹³⁶ reporter.nih.gov/project-details/10016025

¹³⁷ tbportals.niaid.nih.gov/

¹³⁸ projectreporter.nih.gov/project_info_description.cfm?aid=9767258

morbidity can help ascertain health disparities, strengths and weaknesses in obstetric care, and prevent adverse maternal and neonatal outcomes.

Capitalizing on Foundational Investments and Beyond

NCI has hosted multiple innovation labs, or short, intensive opportunities for cross-disciplinary teams to form de novo, rapidly generate novel ideas, and receive pilot funds to jump-start projects. These opportunities bring together diverse expertise to develop new algorithms for application to understanding cancer disease mechanisms, cancer epidemiology, and approaches to cancer care. Recent innovation labs include “Towards Development of a Cancer Digital Twin”,¹³⁹ and “Advancing Cancer Biology at the Frontiers of Machine Learning and Mechanistic Models”.¹⁴⁰

The National Institute of Dental and Craniofacial Research (NIDCR)-supported FaceBase Consortium¹⁴¹ generates, integrates, and distributes diverse data on craniofacial development and associated disorders that researchers can analyze to make new discoveries. For example, FaceBase Consortium researchers combined 3D facial imaging and AI to create a tool to more quickly diagnose children with rare genetic diseases that affect facial features.

National Institute of Mental Health (NIMH) investigators are developing an objective, passive, ML algorithm that uses biosensor data to measure depression symptom severity.¹⁴² The algorithm analyzes biological, physiological, and behavioral data to monitor symptoms in natural settings, allowing clinicians to evaluate patients outside the clinic, and optimize and expedite treatment options.

Progress in AI is in many ways inspired by neuroscience research on how animal and human brains “compute.” Researchers from the National Institute of Neurological Disorders and Stroke (NINDS) and the Brain Research through Advancing Innovative Neurotechnologies® Initiative are increasingly applying AI to help understand the brain and to treat brain diseases. In one recent example, researchers used brain signals recorded from epilepsy patients (whose brain electrical activity was monitored as part of their treatment) to program a computer to mimic natural speech.¹⁴³ This strategy could one day restore the ability of certain patients to communicate.

Unique Challenges

Addressing ethical considerations and training—two key issues in AI—will help enable broad, trustworthy, and ethical application of AI technologies to biomedical and clinical research. Incorporating ethics and training into AI activities will help achieve the broader goal of conducting science in service to society. Several recent activities highlight NIH’s dedication in these areas.

¹³⁹ events.cancer.gov/cbiit/dtwin2020/

¹⁴⁰ www.hub.ki/groups/mechanisticapproachesinnovationlab

¹⁴¹ www.facebase.org/

¹⁴² projectreporter.nih.gov/project_info_description.cfm?aid=9839684&icde=50836319

¹⁴³ www.nature.com/articles/s41586-019-1119-1

In July 2020, ODSS led an International Society for Computational Biology workshop¹⁴⁴ focused on “Ethics, Bias, and the Application of AI in Biomedicine.” Leaders in the field presented and discussed challenges related to trustworthy AI and training a workforce ready to address these challenges with creative solutions. To incorporate lessons from these discussions into practice, ODSS is part of the trans-NIH team developing Bridge2AI initiatives on training and ethics, bias, and transparency in AI data and algorithms.

In the training space, the National Institute of Nursing Research hosted an AI boot camp in August 2020¹⁴⁵ to provide the next generation of nurse scientists with the basic knowledge of AI for use in clinical applications and research to improve health care and health outcomes across diverse patient populations.

In October 2020, the Office of Behavioral and Social Sciences Research (OBSSR) and its partner institutes (NICHD, NIMH, the National Institute on Drug Abuse, the National Institute on Minority Health and Health Disparities, and the National Heart, Lung, and Blood Institute) launched the Training in Advanced Data Analytics for Behavioral and Social Sciences Research program designed to infuse data science training into existing BSSR predoctoral programs and produce a cohort of specialized health-related researchers with competencies intersecting the social sciences and data science.¹⁴⁶

Future directions include continued integration of AI methodologies into biomedical research activities. NIH will also plan events—such as ethics workshops and trainings—to reach more users, diversify the workforce, and increase skill bases. For example, ODSS will collaborate across NIH to place computer science students and professionals in projects focused on using ML for biomedicine or streamlining administrative tasks and will build programs to engage underrepresented communities for future AI-focused codeathons, trainings, and data science bootcamps.

¹⁴⁴ www.iscb.org/cms_addon/conferences/ismb2020/tracks/odss

¹⁴⁵ www.ninr.nih.gov/newsandinformation/events/bootcamp2020

¹⁴⁶ obssr.od.nih.gov/obssr-t32-training-in-advanced-data-analytics-for-behavioral-and-social-sciences-research-grants-awarded/

NIH Helping to End Addiction Long-term (HEAL) Initiative

Program Overview

The crisis of opioid misuse, addiction, and overdose in the United States is a rapidly evolving and urgent public health emergency. In 2019, 70,630 people in the United States died of overdose, including 49,860 dying from opioid overdose (70.6 percent of all drug overdose deaths).¹⁴⁷ More than 2 million Americans have Opioid Use Disorder (OUD) while 10 million Americans misuse opioids, taking them differently than prescribed.¹⁴⁸ An additional 50 million Americans experience chronic pain, putting them at increased risks for opioid use and misuse.^{149,150} The magnitude of the crisis has made clear the need for collaborative and innovative scientific solutions, including the need for safe and effective pain management interventions; additional user-friendly and effective options for the treatment of OUD; and strategies to implement evidence-based interventions for pain and addiction.

In response to this historic crisis, in 2018 NIH launched the Helping to End Addition Long-term (HEAL) Initiative, a trans-NIH effort spanning basic, translational, clinical and implementation science on opioid misuse, addiction, and pain. By the end of FY 2020, HEAL funded over \$1.5 billion in research, representing more than 500 research projects across the United States. These projects aim to identify new therapeutic targets for both pain and opioid use disorder, reduce the risk of opioids through nonpharmacological strategies for pain management, and improve opioid addiction treatment in a variety of settings.

Progress in efforts to reduce opioid overdose and death has been affected by the COVID-19 pandemic, which has fueled increases in opioid use, addiction, and overdose. Since the declaration of a public health emergency for COVID, overdoses increased 42 percent in May 2020 compared to May 2019.¹⁵¹ For patients receiving treatment for addiction and chronic pain, access to support systems, medications to treat opioid use disorder, and mental health care have been significantly interrupted or shifted to virtual platforms. In addition, social support is closely tied to better treatment adherence and recovery outcomes, therefore social distancing measures and the stress of social isolation intensifies challenges for people with pain and addiction, and makes it difficult for individuals to maintain their mental health.

Addressing the Opioid Crisis During the COVID-19 Pandemic

The colliding opioid and COVID crisis is affecting individuals, families and communities in deadly ways. Since the declaration of a public health emergency for COVID, fentanyl and heroin use increased by 32 percent and 13 percent respectively. The use of stimulants and other illicit drugs, together with opioids, is also increasing leading to an overall dramatic rise in

¹⁴⁷ www.cdc.gov/drugoverdose/data/statedeaths.html

¹⁴⁸ Center for Behavioral Health Statistics and Quality (CBHSQ). 2017 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2018.

¹⁴⁹ Collins, Koroshetz, Vo www.cdc.gov/drugoverdose/data/statedeaths.html

¹⁴⁹ Center for IOWA. (2018). Research plan for the HEAL Initiative. *JAMA*, 320(2), 129-130.

¹⁵⁰ Dahlhamer, Lucas, Zelaya, Nahin, Mackey, DeBar, Kerns, Von Korff, Porter, Helmick. (2018). Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. *CDC Morbidity and Mortality Weekly Report*, 67(36);1001–1006. www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm#References

¹⁵¹ ODMAP. (2020). Overdose Detection Mapping Application Program. <http://www.odmap.org/>

overdose and overdose death. Disruptions of treatment and recovery services, limited access to mental health and peer recovery support, and increased stress provide drive this increase and create new barriers to recovery. Economic impacts from job losses may also contribute to despair, and fatalities from misuse relapse, overdose, and suicide. Additional risks face people with OUD such as housing instability and incarceration where social distancing is difficult. Vulnerable and underserved populations, particularly economically disadvantaged, geographically remote, and ethnic minority communities affected by poverty, lack access to adequate prevention, treatment, and recovery resources, putting them at especially high risk.

The COVID pandemic has also complicated efforts to address the need for safe and non-addictive pain management. For the 50 million Americans in chronic pain, significant disruptions to healthcare access occurred as providers moved resources to intensive care units and other critical COVID care sites. Nonurgent needs, such as routine management of chronic pain, or outpatient, elective procedures needed to treat chronic pain, have been delayed to avoid the risk of transmitting the SARS-CoV-2 virus.¹⁵² It is not yet known how this unmanaged and untreated pain has contributed to the rise of opioid misuse, addiction and overdose.

To match the urgency of these combined epidemics, the NIH HEAL initiative is leveraging expertise across NIH Institutes and Centers to approach the crisis from all angles and disciplines. NIH leadership, intramural and extramural investigators, and key stakeholders have collaborated to monitor impact of COVID on communities, provision of treatment services, and available outcome data. Research progress is closely monitored on the impact of COVID. Additionally, NIH has responded by supplementing ongoing research to collect additional measures to understand the impact of COVID on HEAL communities. The initiative is harnessing its collaborative structure to adapt to the COVID crisis while continuing to make progress toward key goals: identifying new therapeutic targets for both pain and opioid use disorder, reducing the risk of opioids through nonpharmacological strategies for pain management, and improving opioid addiction treatment in a variety of real-world settings. Examples of high impact programs are listed below:

Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW). Infants exposed to maternal opioid use while in the womb can experience neonatal opioid withdrawal syndrome (NOWS), which has an estimated frequency of 7 per 1,000 hospital births. Every 15 minutes an infant is born with NOWS.^{153, 154} The NIH HEAL Initiative has funded \$41.7 million of research through *ACT NOW* to identify best practices for the management of NOWS and to improve our understanding of health outcomes of these infants. Specifically, the *ACT NOW Eat Sleep and Console (ESC)* clinical research trial is testing the effects of function-based assessments for NOWS among 864 families over two years. The *ACT NOW Weaning Trial* will test the effectiveness of two different pharmacological treatments for NOWS among over 500 infants. Despite COVID-19's impact, both *ACT NOW* trials began recruitment in 2020. In

¹⁵² Volkow, N. (2020). Collision of the COVID-19 and opioid epidemics. *Annals of Internal Medicine*. doi:10.7326/M20-

¹⁵³ NIH HEAL Initiative. (2020). Advancing clinical trials in neonatal opioid withdrawal. (ACT NOW). heal.nih.gov/research/infants-and-children/act-now

¹⁵⁴ Bremer, A. September 1, 2020 NIH HEAL Multidisciplinary Working Group Meeting (MDWG). Addressing the medical and social needs of children affected by opioids: The ACT NOW Program. heal.nih.gov/files/2020-09/MDWG%20for%20website%20day%202%20v2_0.pdf

addition to the clinical trials, the ACT NOW Longitudinal Study will use neuroimaging to measure the effects of prenatal opioid exposure on neurodevelopment, as well as how maternal and environmental factors interact to influence development and behavior. These efforts complement the HEALthy Brain and Child Development (HBCD) Study, which is a comprehensive study of early brain development to study the impact of opioid exposure together with other environmental factors influencing child development. Additional research is planned to compare the effectiveness of specific pharmacological approaches for treating NOWS. Together, these studies will rapidly provide key evidence to help inform clinical guidance of infants born with NOWS.

New Strategies to Prevent and Treat Opioid Addiction. Through HEAL, NIH has invested \$157 million to date on studies aimed at new prevention and treatments strategies for OUD. This research includes prevention studies for at-risk adolescents and young adults, as well as other groups at the highest risk for opioid initiation and misuse. Prevention research is also underway to test ways to reduce the likelihood that individuals who misuse opioids or those with low-severity OUD progress to more severe OUD. Research on new strategies to treat OUD include studies defining the role of sleep dysfunction in OUD and recovery, an issue highlighted as of special importance to people in treatment for OUD and those with lived experience. Additional research is testing how integrated approaches to mental health and substance use disorder treatment affects outcomes for the 40 percent of patients with OUD who also have a diagnosed mental health condition. This research has been delayed by COVID-related effects on patient recruitment and care, but has benefited from creative approaches in virtual enrollment and engagement of research participants. Together, this research will provide insight into the full experience of addiction during the COVID pandemic, and will open new avenues for novel therapeutic strategies, OUD prevention and treatment approaches, and ways to sustain long-term recovery.

HEALing Communities Study. NIH has devoted \$209.2 million to support the HEALing Communities Study, an unprecedented effort to test the integration of prevention, overdose reversal, and medication-based treatment for OUD, with an ambitious goal of a 40 percent reduction in opioid overdose deaths in select rural and urban communities hit hard by the opioid crisis.¹⁵⁵ During the COVID pandemic, community engagement and coalition building activities in the study were transitioned to a virtual format. Despite these challenges, baseline data were collected, and the first wave communities have selected and begun implementing locally appropriate interventions, such as novel approaches to distribute naloxone for overdose reversal. This research is strengthened by complementary efforts through the Justice Community Opioid Innovation Network (JCOIN) to test approaches to provide evidence-based treatment for OUD within justice settings, and by the Behavioral Research to Improve Medication-Based Treatment (BRIM) program, which tests the use of non-pharmacologic strategies to help individuals stay on lifesaving medications for the treatment of OUD. Together, these programs seek to inform strategies to integrate evidence-based treatments for OUD in specific settings where they will be of the greatest benefit.

¹⁵⁵ NIH HEAL Initiative. (2020). Translation of research to practice for the treatment of opioid addiction. *HEALing Communities Study*. heal.nih.gov/research/research-to-practice/healing-communities

Precision Medicine in Pain Management. NIH has invested \$207 million to date for research in clinical research in pain management. To reduce the risk of opioids and enhance management of pain, HEAL supports Phase III trials on pharmacological and nonpharmacological therapies for pain conditions including post-surgical pain, musculoskeletal pain, osteoarthritis, and cancer pain through the Pain Management Effectiveness Research Network. With the goal of increasing uptake of effective pain treatments, HEAL tests how best to embed effective non-pharmacological treatments for pain into large health care settings, including a virtual intervention to treat chronic low back pain in the Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) program. Chronic low back pain is one of the most common forms of chronic pain among adults worldwide, and there are multiple contributions and treatment interventions. Through the Back Pain Consortium (BACPAC) Research Program, researchers test an iterative model to inform precision medicine using interdisciplinary methods and exploring innovative technologies.¹⁵⁶ Pain is also a common problem in end-stage renal disease and patients receiving hemodialysis. The Hemodialysis Opioid Prescription Effort (HOPE) received an FDA Investigational New Drug (IND) Application for the use of buprenorphine for pain management as part of multidisciplinary approach.¹⁵⁷ Although the COVID pandemic has resulted in some delays in enrollment across study sites, studies that have been able to continue are modifying protocols to increase the use of telehealth where appropriate, as well as alternative means to collaborate through research projects.

Preclinical and Translational Research in Pain. Through a suite of targeted trans-NIH efforts, HEAL research is accelerating the development of safe and effective therapeutics to treat pain with little or no addiction liability. To date, HEAL has invested \$223 million in preclinical research, including programs to validate novel therapeutic targets for non-addictive medications for pain that would reduce reliance on opioids. HEAL research on the translation of promising technologies, such as implanted devices and noninvasive technologies that target areas of the brain associated with pain, will yield next-generation medical devices to diagnose and treat pain. To improve the efficacy of clinical trials for pain treatments, and to increase the chance that new therapeutics will advance along the regulatory path to approval, HEAL tests the development of biomarkers to objectively measure pain, including pain associated with sickle cell disease, musculoskeletal disease, nerve pain and headache. Promising biomarkers identified through this program may advance to clinical validation through the Early Phase Pain Investigation Clinical Network (EPPIC-Net). Findings from these studies could improve quality of life for millions of people in the United States who experience pain daily; however, the COVID pandemic poses a new unprecedented challenge. In many cases, disruptions to research caused by lab closures and long startup times impacted scientific collaboration and data collection. NIH staff closely monitors efforts needed to reestablish these studies and works with investigators to avoid further disruptions.

Medication Development to Treat Opioid Use Disorders and Prevent Overdose. Through the HEAL Initiative, NIH supports over 70 targeted studies to accelerate medication development of treatments for OUD, including novel medications and biologic agents, as well as novel formulations of approved medications to treat OUD and prevent opioid overdose. To date, 16

¹⁵⁶ heal.nih.gov/research/clinical-research/back-pain

¹⁵⁷ heal.nih.gov/research/clinical-research/hemodialysis

Investigational New Drug applications were filed with the FDA and authorized to for human studies. These studies focus on a variety of drug targets, as well as vaccines that could prevent opioids from entering the brain. Despite this success, COVID-19 greatly impacted progress across studies. For example, many of these projects were delayed by closures of labs and clinical facilities, and the pipeline of analgesic candidate development pipeline may be slowed across the portfolio. NIH staff are working closely with investigators to help manage budgets and FDA review processes to accomplish research goals despite COVID-19 delays.

Trans-NIH Collaboration

Through its trans-NIH design, the NIH HEAL Initiative builds on scientific expertise across NIH Institutes and Centers and cross-cutting collaborations across disciplines and sectors. For example, recent HEAL awards will evaluate the best approaches to treat people with both OUD as well as common mental health conditions and/or suicidality. In addition, interdisciplinary HEAL research is addressing stigma as a barrier to treatment of both painful conditions and OUD, as people with chronic pain and people with OUD face stigma from their healthcare providers, family, friends, coworkers, the health care system. HEAL is building collaborations across NIH to enhance ongoing studies to reduce the burden of chronic pain and OUD in vulnerable populations, diversify recruitment in clinical trials to better represent patient populations, and accelerate diversity inclusion policies, processes, and programs.

HEAL Data Ecosystem: As currently funded projects are completed, the HEAL initiative will rapidly disseminate research findings and results to patients, providers, institutions, and organizations so that they can rapidly put them into practice across the United States. A platform for accessing HEAL research data will make studies across HEAL and other NIH datasets accessible for investigators and the public, while protecting the privacy and confidentiality of research participants. HEAL will continue to maximize the availability of publications and the sharing of underlying data to promote dissemination of new knowledge, enhance reproducibility and accelerate the ability of researchers to build upon HEAL research to make new discoveries. This platform will form the foundation for an ecosystem for data management, analysis, and interaction through the HEAL initiative, and accelerate scientific solutions to the opioid crisis.

Next Steps and Goals

Although HEAL research has initiated a remarkably diverse set of scientific programs, there is more work to be done. HEAL has encouraged innovative approaches and bold new research into prevention and treatment interventions for substance misuse and addiction. Examples of planned research areas are summarized below:

Opioid Use in the Context of Polysubstance Use: Seventy percent of drug overdose deaths involved opioids, and the use of illicitly manufactured fentanyl in combination with stimulants is driving a new wave of overdose deaths. There is an urgent need for research to address polysubstance use. Leveraging HEAL infrastructure to accelerate development of safe and effective prevention and treatment interventions, including novel medications and collaborative treatment approaches, will provide much-needed options for individuals who misuse opioids together with psychostimulants such as methamphetamine and cocaine.

Advancing Health Equity: There are wide disparities in provision of care and treatment for pain and addiction, which result in both inappropriate treatment with opioids, increased risk of addiction and overdose, and lack of evidence-based non-pharmacological options for managing pain and lifesaving medications for OUD. Planned expansion to HEAL includes the development and implementation of culturally appropriate interventions for the prevention and management of pain and addiction in diverse populations, with a focus on interventions that target health disparities at multiple levels and those which can be rapidly implemented by healthcare systems.

Coordinated Approach to Pain Management: Research that is guided by individuals and joins together scientists, caregivers, people with lived experience, and other key community partners to build and test approaches for treating pain is essential for long term pain management. HEAL researchers will work in collaboration with clinicians and federal partners to test multi-disciplinary multimodal approach to pain management and uncover successful strategies for managing pain and preventing progression to opioid misuse and addiction.

Harnessing the Power of Innovation to Treat Pain: Recent discoveries in human genetics and molecular biology will be incorporated into the development of a novel team-based platform to rapidly test targets and candidate therapeutics for diverse human pain conditions and share finding with the wider pain research community. This research will address pain systems and allow for a variety of research questions including conditions of chronic analgesic use, other drug use, SUDs and other co-morbid conditions, and will enable and accelerate human gene and cell-based validation of pain therapeutic targets through the HEAL initiative and other pipelines. This will build on existing HEAL research, which has invested \$223 million to date on preclinical and translational research in pain, and ongoing efforts to accelerate the development of novel treatments for pain.

High-Risk, High-Reward Research

Program Overview

Scientific progress often advances in modest steps, building upon a strong foundation of previous research and preliminary data. In contrast, more rapid advances in science can be stimulated by approaches that foster innovation and risk taking, and/or allow investigators flexibility to "follow their noses" to surprising and fortuitous discoveries. Such research is often referred to as "high-risk, high-reward" research. NIH is committed to supporting high-risk research with the potential for exceptionally large impact, balanced with support for incremental, yet extremely important, research that also advances our understanding of human health and disease.

Awards designed to support high-risk research may emphasize different criteria during peer review compared to more traditional grant mechanisms, weighting innovation and potential impact more heavily than feasibility and preliminary data. Thus, these awards provide an opportunity for investigators and projects that might not fare well in typical peer review due to a lack of preliminary data and/or ideas that appear inherently risky. "High risk" in this context refers to the type of science supported, which is often more innovative and paradigm-shifting than traditional research studies. "High risk" does not refer to risks posed to research participants. As with all NIH-funded studies involving people, any risks posed to participants are carefully evaluated by institutional or tribal review boards and explained to participants so that their consent is fully informed.

A major source of support for high-risk, high-reward research is the Common Fund's High-Risk, High-Reward (HRHR) program.¹⁵⁸ The HRHR program supports research projects that span the entire NIH mission, and is managed by a trans-NIH Working Group that includes members from 28 ICOs. The HRHR program consists of the following initiatives:

- NIH Director's Pioneer Award: supports individual scientists of exceptional creativity who propose pioneering or transformative approaches to major challenges in biomedical and behavioral research.
- NIH Director's New Innovator Award: supports promising new investigators proposing highly innovative research that may lack the preliminary data necessary to fare well in traditional peer review.
- NIH Director's Transformative Research Award: supports individual investigators or teams proposing exceptionally innovative and/or unconventional research projects with the potential to overturn fundamental paradigms.
- NIH Director's Early Independence Award: provides a mechanism for exceptional early career scientists to move rapidly into independent research positions and launch innovative research programs as early in their careers as possible by omitting the traditional post-doctoral training period.
- Transformative Research to Address Health Disparities and Advance Health Equity – launched in FY 2021, this initiative supports research in developing, disseminating, or

¹⁵⁸ commonfund.nih.gov/highrisk

implementing innovative and effective interventions that prevent, reduce, or eliminate health disparities and health inequities; it also aims to expand the capacity for health disparities research at minority serving institutions.¹⁵⁹

The HRHR awards often forge new ground, providing foundations upon which future research can build. These awards have supported significant technological breakthroughs that enable a wide range of research questions to be explored. For example, HRHR support contributed to the development of revolutionary techniques that allow researchers to precisely control the activity of neurons (optogenetics)¹⁶⁰ and expand the contents of tissue samples to allow detailed viewing of fine subcellular structures (expansion microscopy).¹⁶¹ HRHR awardees are also advancing public health, including identification of celebrity endorsements and advertisements of unhealthy food and beverages during television programming popular with children and adolescents,^{162,163} and development of a low-cost device based on a children's toy that could be used to diagnose diseases such as malaria.¹⁶⁴ Independent evaluations of the Pioneer¹⁶⁵ and New Innovator¹⁶⁶ Awards concluded that these awards support research that is more innovative and impactful compared to more traditional NIH research awards.

The Common Fund's HRHR program is a trans-NIH endeavor, with Working Group members from across NIH helping to coordinate and oversee the program. In addition to the HRHR awards supported by the Common Fund, ICs may also support HRHR awards that address exciting scientific projects relevant to their missions. Awards can be co-funded by multiple ICs, representing innovative research projects with the potential for high impact across multiple disciplines and subject areas. For example, a Transformative Research Awardee supported by the National Institute on Aging and the National Institute for Neurological Disorders and Stroke found that the ages of cells within multiple organ tissues can vary widely, even within tissues that have high or low overall rates of turnover, providing a fundamentally new characterization of the aging process.¹⁶⁷ In FY 2020, 18 New Innovator, 1 Pioneer, and 3 Early Independence Awards were funded by ICs, and 3 New Innovator awards were co-funded by Common Fund and other ICs or OD offices.

In addition to participating in the Common Fund's HRHR program, many ICs support awards that target exceptionally creative and innovative researchers and high-risk projects within the IC's mission. Some of these awards were launched based on the success of the HRHR program,

¹⁵⁹ commonfund.nih.gov/healthdisparitiestransformation

¹⁶⁰ www.eureka.lert.org/pub_releases/2007-04/su-al040207.php

¹⁶¹ directorsblog.nih.gov/2015/03/26/diaper-compound-brings-change-to-cell-microscopy/

¹⁶² commonfund.nih.gov/earlyindependence/programhighlights#Celebrity

¹⁶³ commonfund.nih.gov/earlyindependence/programhighlights#Unhealthy%20Promotions

¹⁶⁴ commonfund.nih.gov/newinnovator/programhighlights#Paperfuge

¹⁶⁵ commonfund.nih.gov/sites/default/files/HRHR%20PA%20FY%202004-2006%20Outcome%20Evaluation.pdf

¹⁶⁶ commonfund.nih.gov/sites/default/files/HRHR%20New%20Innovator%20Award%20Outcomes%20Evaluation%202007-2009_508%20compliant.pdf

¹⁶⁷ www.salk.edu/news-release/how-old-are-your-organs-to-scientists-surprise-organs-are-a-mix-of-young-and-old-cells/

demonstrating the trans-NIH value of this approach. Examples of IC-supported awards for high-risk, high-reward research include:

- Avant-Garde Award Program for HIV/AIDS and Drug Use Research (National Institute on Drug Abuse):¹⁶⁸ supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers.
- Avenir Award Program (National Institute on Drug Abuse):¹⁶⁹ supports early stage investigators who propose pioneering research approaches to HIV/AIDS/substance abuse research as well as epigenetics research.
- Biobehavioral Research Awards for Innovative New Scientists (BRAINS; National Institute of Mental Health):¹⁷⁰ helps exceptional early-career scientists launch innovative research programs that have the potential to transform mental health research.
- Outstanding New Environmental Scientist (ONES) Program (National Institute of Environmental Health Sciences):¹⁷¹ fosters the careers of outstanding scientists while supporting innovative environmental health research.
- Research Innovations for Scientific Knowledge (RISK; National Institute of Arthritis and Musculoskeletal and Skin Diseases):¹⁷² fosters innovative research by encouraging researchers to pursue unusual observations, test imaginative hypotheses, investigate creative concepts, and build ground-breaking paradigms, all of which deviate significantly from the current prevailing theories or practice.
- Multiple ICs support R35 awards, which aim to provide long term support to an investigator with an outstanding record of research productivity. This support is intended to encourage investigators to embark on long-term projects of unusual potential.

Moving forward, the NIH will continue to support a robust portfolio of high-risk, high-reward research. Within the Common Fund's HRHR program, several new activities aim to increase the diversity of the applicant pool to reflect the investigator and institutional diversity of the nation's research workforce, while maintaining a focus on supporting the best science. Based on recommendations from the Advisory Committee to the Director Working Group on High-Risk, High-Reward Programs¹⁷³ and input from the scientific community, the HRHR program is increasing outreach to underrepresented groups, strengthening language in funding opportunities to encourage applicant diversity, making institutional diversity a program priority, taking steps to mitigate potential bias against some scientific topics, and piloting anonymized review within the Transformative Research Award.¹⁷⁴ Additionally, to address specific pressing public health needs, the HRHR program is supporting two new scientific focus areas in FY 2021: 1) COVID-19-related funding opportunities within the Transformative Research and Early Independence

¹⁶⁸ www.drugabuse.gov/about-nida/organization/offices/aids-research-program-arp/avant-garde-award-hiv-aids-research

¹⁶⁹ www.drugabuse.gov/news-events/subject-area-experts/avenir-award-winners

¹⁷⁰ grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-525.html

¹⁷¹ www.niehs.nih.gov/research/supported/training/ones/index.cfm

¹⁷² www.niams.nih.gov/grants-funding/funding-opportunities/research-innovations-scientific-knowledge-risk

¹⁷³ acd.od.nih.gov/documents/presentations/06132019HRHR.pdf

¹⁷⁴ dpepsi.nih.gov/sites/default/files/CoC_Jan_2020_845_concept_clearance_HRHR_slides.pdf

Awards,^{175, 176} and 2) Accelerating Leading-edge Science in ALS (ALS²) within the Transformative Research Awards.¹⁷⁷

¹⁷⁵ grants.nih.gov/grants/guide/rfa-files/RFA-RM-20-020.html

¹⁷⁶ grants.nih.gov/grants/guide/rfa-files/RFA-RM-20-021.html

¹⁷⁷ grants.nih.gov/grants/guide/notice-files/NOT-RM-20-019.html

Maternal Mortality and Morbidity—Closing the Gap in Health Disparities

Program Overview

An estimated 700 women die each year in the United States from conditions related to or associated with pregnancy or childbirth, and over 50,000 women experience severe maternal morbidity (SMM).¹⁷⁸ Over a 25-year period, the global maternal mortality ratio (MMR) of deaths per 100,000 live births declined from 385 in 1990 to 216 in 2015, a relative decline of 44 percent.¹⁷⁹ In contrast, the MMR increased in the United States during the same period and, at 17.4 per 100,000 in 2018,¹⁸⁰ is currently the highest among developed nations. High rates of maternal mortality (MM) and SMM disproportionately affect specific racial and ethnic minority populations. In particular, African American and American Indian/Alaska Native women are two to four times more likely to die from pregnancy-related or -associated causes compared to White women. Furthermore, African American, Hispanic/Latina, Asian, Pacific Islander, and American Indian/Alaska Native women all have higher incidence of SMM compared to White women.¹⁸¹ Age, disabilities, and geographical disparities also affect MM and SMM, as do social determinants of health, including education, racism, and socioeconomic standing.

One-third of pregnancy-related deaths occur during pregnancy, one-third occur during or in the week after delivery, and one-third occur between one week to one year postpartum.¹⁸² Causes of MM and SMM are multifaceted. In the United States, the leading causes are cardiovascular disease, hemorrhage, and infection. Drug overdose and suicide are major factors, particularly during the postpartum period. Other significant contributing factors include comorbid conditions such as obesity, mental health, and substance use disorders, and structural and health care system characteristics. It is estimated that 60-70 percent of maternal deaths in the United States are preventable.¹⁸³ Therefore, implementing multifaceted strategies to address preventable contributors to pregnancy-related and pregnancy-associated morbidity, particularly MM and SMM in disproportionately affected populations, has the potential to drastically reduce disparities in pregnancy-related maternal deaths and morbidity.

NIH supports a broad portfolio of research on MM and SMM, including research focused on disproportionately affected populations. NIH has taken steps to emphasize the inclusion of disadvantaged and high-risk pregnant and lactating women in clinical studies. In concurrence with recommendations from the Congressionally mandated Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), NIH plans to implement additional

¹⁷⁸ www.cdc.gov/vitalsigns/maternal-deaths/index.html#:~:text=about%201%2F3%20of%20deaths,week%20to%201%20year%20postpartum.

¹⁷⁹ www.unfpa.org/publications/trends-maternal-mortality-1990-2015#:~:text=Estimates%20by%20WHO%2C%20UNICEF%2C%20UNFPA,the%20United%20Nations%20Population%20Division&text=The%20global%20maternal%20death%20ratio.an%20estimated%20303%2C000%20in%202015.

¹⁸⁰ www.cdc.gov/nchs/maternal-mortality/index.htm

¹⁸¹ www.cdc.gov/vitalsigns/maternal-deaths/index.html#:~:text=about%201%2F3%20of%20deaths,week%20to%201%20year%20postpartum.

¹⁸² www.cdc.gov/vitalsigns/maternal-deaths/index.html#:~:text=about%201%2F3%20of%20deaths,week%20to%201%20year%20postpartum.

¹⁸³ www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/mmr-data-brief.html

recommendations from this group to strengthen its efforts.^{184,185} These recommendations highlight the potential for leveraging existing federal resources, implementing systematic data collection, and developing new research tools and strategies, among other key approaches to addressing MM and SMM research. Developing scientifically validated, safe and effective interventions for pregnant and lactating women is difficult, as many researchers routinely exclude these women from clinical research. Researchers often do not consider potential risks of untreated maternal disorders to both the mother or the fetus and worry about safety and exposure of the fetus to experimental treatments. In conducting research on promising therapeutics to be used by pregnant and lactating women, researchers will need to over-sample racial and ethnic minority women to better understand the differential impact of maternal health disorders. NIH clinical research networks have supported extensive research on interventions to reduce maternal morbidity and mortality, with a special emphasis on reducing health disparities. Scientists found that a quality improvement initiative undertaken at 99 California hospitals benefitted African American women more than White women by reducing disparities in the risk of obstetric hemorrhage.¹⁸⁶ Current efforts include clinical research studies and trials on reducing the risk of preeclampsia and prophylactic interventions to prevent postpartum hemorrhage after cesarean delivery.

Other research efforts across NIH have made advances in reducing pregnancy-related and -associated morbidity and mortality (PRAMM). Population health researchers supported by NIH were quick to alert the nation to alarming rates of maternal mortality and have continued using large-scale data approaches to shed light on disparities. Researchers found that Black women were particularly at risk for cardiopulmonary complications shortly after delivery, with a risk of postpartum pulmonary edema (fluid in the lungs) and/or acute heart failure more than twice as high as that of Non-Hispanic White women.¹⁸⁷ Results from the NuMoM2b Heart Health Study showed that women who experienced adverse outcomes in a first pregnancy were more likely to have hypertension two to seven years postpartum, compared to women without such pregnancy history.¹⁸⁸ Another study with support from multiple NIH ICOs determined that among women readmitted postpartum for sepsis, 61 percent occurred after six weeks, the normal time for postpartum visits. These results support the need for a flexible continuum of postpartum care for mothers that could extend well beyond the traditional check-in at six weeks after delivery.¹⁸⁹

Although NIH and NIH-supported researchers have made strides in addressing PRAMM and its associated health disparities, the agency recognized the need for a trans-NIH initiative targeted at this issue. In 2020, NIH convened a trans-NIH Maternal Mortality Task Force led by the NIH Immediate Office of the Director, NICHD, and the Office of Research on Women's Health (ORWH) to coordinate collaborative research efforts across NIH to address maternal mortality and drive a new initiative under development at NIH called Implementing a Maternal health and PRenancy Outcomes Vision for Everyone (IMPROVE).¹⁹⁰ IMPROVE aims to use an integrated approach to understanding biological, behavioral, sociocultural, and structural factors

¹⁸⁴ www.nichd.nih.gov/about/advisory/PRGLAC

¹⁸⁵ www.nichd.nih.gov/about/advisory/PRGLAC/recommendations

¹⁸⁶ pubmed.ncbi.nlm.nih.gov/31978432/

¹⁸⁷ pubmed.ncbi.nlm.nih.gov/30786255/

¹⁸⁸ pubmed.ncbi.nlm.nih.gov/31564189/

¹⁸⁹ pubmed.ncbi.nlm.nih.gov/31529451/

¹⁹⁰ www.nih.gov/research-training/medical-research-initiatives/improve-initiative

that affect PRAMM by building an evidence base for improved care and outcomes. IMPROVE is a multipronged innovative research initiative designed to target health disparities associated with PRAMM by 1) implementing and evaluating community-engaged interventions for disproportionately affected women (e.g., African American, American Indian/Alaska Native, advanced maternal age, low socioeconomic status, or rural populations), and 2) identifying risk factors and the underlying biological mechanisms associated with leading causes of PRAMM, including cardiovascular disease, infection and immunity, and mental health.

To address the leading causes of PRAMM during pregnancy, at delivery, and up to one year postpartum, IMPROVE will build on ongoing efforts among federal and other key partners to accelerate progress and maximize reach and impact by leveraging existing resources including previously studied cohorts and archived biospecimens, and developing new studies. IMPROVE will expand and complement existing research efforts that incorporate local community needs and perspectives to address health disparities in PRAMM. Supported projects will develop, implement, and evaluate community-tailored interventions, as well as investigate biological, behavioral, sociocultural, and structural risk factors and mechanisms of the leading causes of PRAMM. Through this multidimensional strategy, IMPROVE aims to create an evidence-based approach to reducing PRAMM and its associated health disparities. In FY 2020, IMPROVE kicked off by supporting 36 supplements to existing research projects that incorporate community partnerships in high-risk areas and populations, expand research on the leading causes of, or build the knowledge base for PRAMM.

Other activities across NIH align with the priorities of IMPROVE and primarily address PRAMM in disproportionately affected populations. The ORWH developed and maintains the Maternal Morbidity and Mortality Web Portal that offers maternal health and pregnancy-related resources to the public.¹⁹¹ NIH also engaged the research community in workshops to consider priorities and gaps in research to address underlying factors that contribute to PRAMM and methods or care models that reduce inequities in maternal health. In FY 2020, multiple NIH institutes supported two projects to target different facets of PRAMM. One included multidisciplinary research to advance the understanding, prevention, and reduction of PRAMM in racial and ethnic minorities and socially disadvantaged populations.¹⁹² The second project will encourage women's health research in Institutional Development Award (IDeA) states that have historically received low levels of NIH funding.¹⁹³ These states often have a large proportion of rural or minority populations that are disproportionately affected by PRAMM.

NIH synergizes its own activities through internal collaborations as well as external collaborations with other agencies within U.S. Department of Health and Human Services (HHS) and other governmental agencies on maternal health topics. Multiple NIH ICOs participate in the HHS Maternal Mortality and Morbidity (MMM) Working Group to address MMM in diverse populations across operating divisions. NIH led the congressionally mandated PRGLAC, which brings together clinical, research, advocacy, public health, regulatory, and pharmaceutical industry leaders to address the significant gaps in research on safety, efficacy, and dosing of medications currently used to manage pregnancy-related and other conditions of pregnant and

¹⁹¹ orwh.od.nih.gov/research/maternal-morbidity-and-mortality

¹⁹² grants.nih.gov/grants/guide/rfa-files/RFA-MD-20-008.html

¹⁹³ grants.nih.gov/grants/guide/notice-files/NOT-GM-20-017.html

lactating women. Plans for implementing the PRGLAC recommendations, published in September 2018, are already underway.¹⁹⁴ NIH also contributed to the Health Resources and Services Administration's Maternal and Child Health Bureau Grand Challenge on Remote Pregnancy Monitoring focused on technology-based solutions for remote health monitoring of pregnant women, and maternal mortality action plans from HHS and the Surgeon General.

Next Steps

In FY 2021, IMPROVE will include a multipronged initiative to accelerate understanding of the impact of structural racism and discrimination in the context of the COVID-19 pandemic on maternal health outcomes and up to one year postpartum¹⁹⁵ and technology-focused initiatives to improve maternal health outcomes.¹⁹⁶ IMPROVE plans will be complemented by other efforts across NIH, including the planned continuation of the NuMoM2b Heart Health Study that will continue follow-up for 6 to 15 years with a cohort of geographically and ethnically diverse group of women enrolled during their first pregnancies to explore the occurrence and mechanisms of cardiovascular disease development in women with and without adverse pregnancy outcomes.¹⁹⁷

¹⁹⁴ www.nichd.nih.gov/sites/default/files/inline-files/PRGLAC_Implement_Plan_083120.pdf

¹⁹⁵ grants.nih.gov/grants/guide/notice-files/NOT-OD-21-071.html

¹⁹⁶ grants.nih.gov/grants/guide/notice-files/NOT-EB-21-001.html

¹⁹⁷ reporter.nih.gov/project-details/9085357

Next Generation Researchers Initiative: Investing in the Future of the Biomedical Workforce

Program Overview

The National Institutes of Health (NIH) has long recognized that the most critical assets in the biomedical research enterprise are the scientists who comprise its workforce. The biomedical research enterprise relies upon a pipeline of highly trained investigators to convey new insights, develop innovative ideas, and advance the translation of scientific research into improved health for all. Intense competition for funding, however, can pose a challenge for researchers trying to embark upon and sustain independent research careers. NIH understands this challenge and, as such, is continuing to invest in the future through initiatives that strengthen and diversify the biomedical research workforce.

In September 2017, with support from the 21st Century Cures Act (P.L. 114-255), NIH launched the Next Generation Researchers Initiative (NGRI) to cultivate and support talent entering the biomedical and behavioral research workforce.¹⁹⁸ This initiative aims to bolster opportunities for early-stage investigators (ESIs).¹⁹⁹ ESIs are defined as those within 10 years of completing their highest advanced research degree or postgraduate clinical training and who have not previously competed successfully for a substantial NIH independent research award. In addition, applications from ESIs are given special consideration during peer review as well as at the time of funding consideration.

NIH Institutes and Centers prioritize funding for ESIs as part of NGRI. The initiative also tracks the impact of funding decisions on ESIs, such as subsequent grant submission and success. As a result of this initiative, NIH has substantially increased support for ESIs – from less than 600 ESIs in 2013 to 1,412 in FY 2020.

Moving forward, NGRI will continue to support novel approaches to expand pathways for funding ESIs. One such pathway is available through the new ESI award named in honor of Stephen I. Katz, M.D., Ph.D., who was profoundly dedicated to mentoring the next



Caption: Dr. Stephen Katz with early career scientists in 2018.

¹⁹⁸ grants.nih.gov/ngri.htm

¹⁹⁹ grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html

generation of scientists.²⁰⁰ Dr. Katz led the National Institute of Arthritis and Musculoskeletal and Skin Diseases from 1995 to his passing in 2018. ESIs may apply for this new opportunity, issued in November 2020, to support their innovative ideas if they are proposing research that is a change in direction from their past work and experience, and for which they have no preliminary data.

In addition to the Katz Award, NIH has several other established programs targeted to those early in their research career, such as:

- NIH Director’s New Innovator Award Program²⁰¹
- Maximizing Investigators’ Research Award²⁰²
- NIH Pathway to Independence Award²⁰³
- NIH Director’s Early Independence Award²⁰⁴
- High Priority, Short-Term Project/Bridge Award²⁰⁵
- Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program²⁰⁶

Also as part of NGRI, NIH is implementing methods to identify and support meritorious investigators (new or established) who are at-risk for losing all NIH funding and who do not have significant research support from other sources. The Advisory Committee to the NIH Director NGRI Working Group also called for special funding consideration for “at-risk” investigators in their December 2018 NGRI report.^{207,208} Early data suggest that, since NGRI began, the outlook for at-risk investigators has improved somewhat in 2018 and 2019, but still their funding rates are lower than those for established investigators who are assured of continuing funding for at least one more fiscal year.²⁰⁹

NGRI also aims to strengthen diversity in the future biomedical workforce. Scientists and trainees from diverse backgrounds and life experiences bring different perspectives and creative approaches to solving the scientific problems we face as a nation. NIH recognizes that its ability to help ensure that the nation remains a global leader in biomedical scientific discovery and innovation is dependent upon a pool of highly talented scientists from diverse backgrounds who will help to further NIH's mission. Today and going forward, NIH will analyze NGRI policies to ensure its efforts continue supporting career development for women and individuals from nationally underrepresented backgrounds in biomedicine.

NIH has several programs aimed at promoting diversity and enhancing progress to an independent career. As an example, the BRAIN Initiative Advanced Postdoctoral Career

²⁰⁰ grants.nih.gov/funding/katz-esi-r01.htm

²⁰¹ commonfund.nih.gov/newinnovator

²⁰² www.nigms.nih.gov/research/mechanisms/mira/pages/default.aspx

²⁰³ grants.nih.gov/grants/guide/pa-files/PA-20-188.html

²⁰⁴ commonfund.nih.gov/earlyindependence

²⁰⁵ grants.nih.gov/grants/funding/r56.htm

²⁰⁶ www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx

²⁰⁷ acd.od.nih.gov/working-groups/nextgen.html

²⁰⁸ acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf

²⁰⁹ nexus.od.nih.gov/all/2020/02/07/whats-happening-with-at-risk-investigators/

Transition Award to Promote Diversity (K99/R00) program enhances biomedical research workforce diversity and fosters a strong cohort of new, highly skilled and well trained, NIH-supported, independent investigators from diverse backgrounds.²¹⁰ The MOSAIC program, referenced earlier, facilitates the transition of cohorts of talented postdoctoral researchers from diverse backgrounds into independent faculty careers in research-intensive institutions.

In addition, NIH has developed and implemented a range of approaches to improve the representation of women in the biomedical research pipeline. NIH implemented automatic extensions of ESI status for childbirth within the ESI period.²¹¹ In FY 2020, an automatic extension of one year was also implemented for childbirth within the four-year K99 eligibility window.²¹² Additionally, NIH offers support for early-career investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.^{213,214}

NIH remains strongly committed to the goals of NGRI to fund more early-career investigators, protect and retain meritorious at-risk scientists, and enhance the diversity of the biomedical research workforce. NIH will continue to incorporate guidance from the Advisory Committee to the NIH Director NGRI working Group and the National Academies of Sciences, Engineering, and Medicine (NASEM) report “The Next Generation of Biomedical and Behavioral Sciences Researchers: Breaking Through” in the future design, testing, implementation, and evaluation of policies and programs to enhance the success of the next generation of talented biomedical researchers.²¹⁵ To address concerns raised in the NASEM report, NIH will continue to collect and analyze workforce-related data to assess workforce trends.

²¹⁰ grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-043.html

²¹¹ grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html

²¹² grants.nih.gov/grants/guide/pa-files/pa-18-592.html

²¹³ grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html

²¹⁴ grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html

²¹⁵ www.nap.edu/catalog/25008/the-next-generation-of-biomedical-and-behavioral-sciences-researchers-breaking

Nutrition Research

Program Overview

The National Institutes of Health (NIH) funds a broad array of basic, clinical, and applied research to further understand nutrition as it relates to health and disease. The goal of the recently released *2020-2030 Strategic Plan for NIH Nutrition Research*,²¹⁶ the first NIH-wide plan for nutrition research, is to advance nutrition research and address diet-related diseases through interventions focused on nutrition across the lifespan, including the use of food as medicine. To elevate attention to and ensure a coordinated approach to nutrition research across NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Office of Nutrition Research (ONR) was moved to the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the NIH OD in FY 2021.

The Strategic Plan for NIH Nutrition Research

The *Strategic Plan for NIH Nutrition Research* was developed by the NIH Nutrition Research Task Force (NRTF),²¹⁷ which coordinated with NIH ICOs. The NRTF completed their work developing the plan in 2020 and its implementation will be overseen by the newly created ONR with the assistance of an NIH-wide Senior Liaison Group and topic-specific Implementation Work Groups.²¹⁸ The strategic plan calls for expanded collaboration across NIH ICOs to accelerate nutrition science and uncover the role of human nutrition in maintaining and

improving public health and reducing diseases that contribute to the top causes of death, disability, and high health care costs in the United States. The strategic plan reflects the wide range of nutrition research supported across NIH—over an estimated \$1.9 billion in FY 2020 (**Figure 1**).

With a focus on precision nutrition, the plan is a multifaceted approach—spanning basic to clinical discovery—toward developing comprehensive and dynamic nutrition recommendations relevant to both individual and population health.

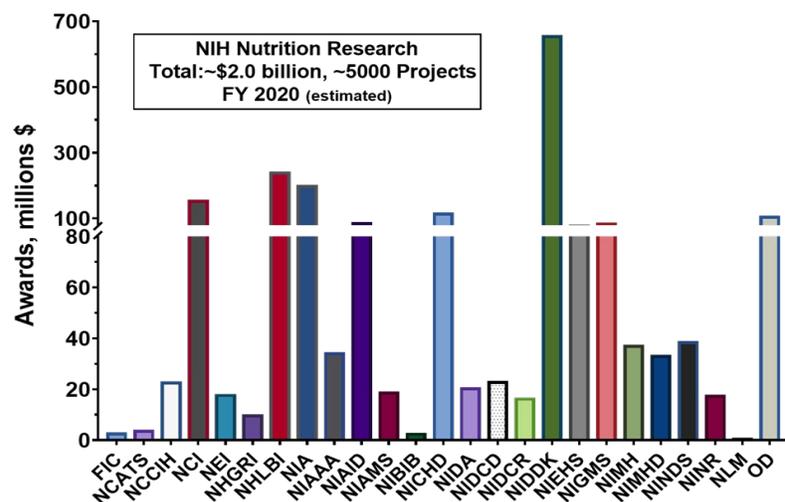


Figure 1. Estimated Nutrition Research Funding, Fiscal Year (FY) 2020.

²¹⁶ dpcpsi.nih.gov/onr/nih-nutrition-report

²¹⁷ dpcpsi.nih.gov/onr/nutrition-research-committees-and-working-groups

²¹⁸ dpcpsi.nih.gov/onr/iwg

NIH is implementing the strategic plan and will monitor and encourage progress. ONR, along with ICO partners, is pursuing opportunities to advance the priorities identified in each of the strategic plan goals and cross-cutting research areas and catalyze nutrition research at NIH-funded universities and institutions and in NIH labs. The ONR will continue to develop new concepts to implement the strategic plan, such as a Human Milk Informatics and Longitudinal Composition Initiative, to characterize components of human milk in a diverse population, and the Developmental Origins of Health and Disease Initiative, to evaluate parents and offspring for contributions of early nutrition to future health and disease.

As the plan is put into action, NIH will continue to seek input from the nutrition community and others. For example, in January 2021, NIDDK, the National Heart, Lung, and Blood Institute (NHLBI), and the DPCPSI Office of Disease Prevention (ODP) held a related workshop²¹⁹ to identify research gaps and opportunities in precision nutrition.

In addition to activities related to the strategic plan, NIH supports ongoing nutrition research studies, which will be coordinated and leveraged to advance nutrition science. Examples of new nutrition advances are in the NIH Nutrition Research Report, 2017-2019.²²⁰

Nutrition for Precision Health, powered by the *All of Us* Research Program

Designed to implement aspects of the strategic plan, the new Common Fund program, Nutrition for Precision Health,²²¹ is powered by the *All of Us* Research Program.²²² Research is needed to provide more precise and dynamic nutritional recommendations than currently possible through population-wide guidance. This in turn will facilitate a deeper understanding of how individual human biological systems and molecular pathways interact with or mediate the relationships among dietary patterns, environmental, social, and behavioral factors to influence health status.

The Nutrition for Precision Health program aims to catalyze precision nutrition research by establishing predictive algorithms to inform targeted dietary approaches. Plans for phase 1 of the program will leverage the *All of Us* Research Program by recruiting a subset of 10,000 participants—the largest precision nutrition study to date (**Figure 2**). Subsets of these individuals will be asked to undergo more detailed dietary regimens and analyses. Each module will involve assessment of social, community, and other behavioral and contextual factors that could be sources of individual variability in dietary responses, along with microbiome, physiological, proteomic, and metabolomic assays. The diverse study population in the *All of Us* Research Program will illuminate important insights into diet-related health disparities. Artificial intelligence and other data science tools will be used to generate predictive dietary intervention algorithms that may be useful for patients and doctors for improving health and quality of life. If successful, a second stage of the program would support studies to validate

²¹⁹ www.niddk.nih.gov/news/meetings-workshops/2021/Precision-Nutrition-Workshop

²²⁰ www.niddk.nih.gov/about-niddk/strategic-plans-reports/nih-nutrition-report

²²¹ commonfund.nih.gov/nutritionforprecisionhealth

²²² allofus.nih.gov/

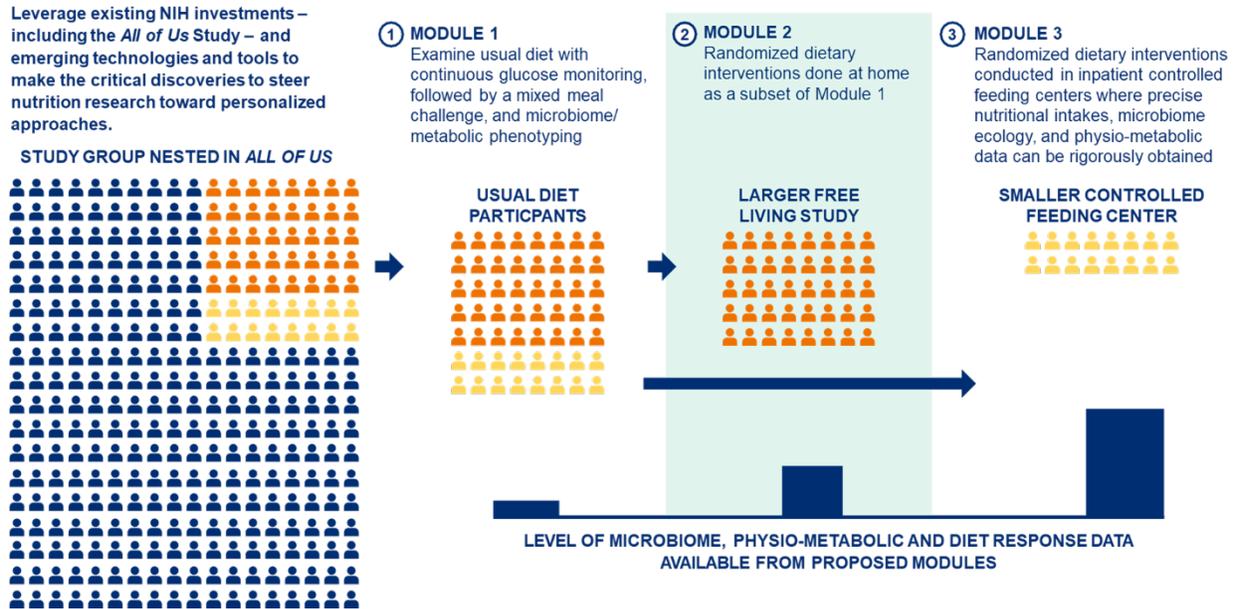


Figure 2. The Nutrition for Precision Health, powered by the *All of Us* Research Program. The Nutrition for Precision Health program aims to use data collected from the large, diverse *All of Us* Research Program cohort to determine what individuals should eat to stay healthy. In phase 1, participants will be divided into modules involving usual diet, controlled feeding, and/or domiciled studies.

those algorithms that predict responses to diet. Although funded by the Common Fund, the Nutrition for Precision Health program will be managed by 17 ICOs collaborating across NIH.

Next Steps and Goals for Nutrition Research at NIH

To fully realize the vision of the strategic plan, the new DPCPSI ONR will undertake a number of research initiatives, workshops, and other activities designed to implement the goals of the strategic plan.

One way to maximize the impact of ONR is to launch time-limited goal-driven programs focused on nutrition. Common Fund programs represent strategic investments in biomedical and behavioral research designed to achieve high impact goals and catalyze discovery within a defined timeframe not to exceed 10 years. These programs address challenges and opportunities that are of high priority for NIH as a whole and include an emphasis on project management to track attainment of milestones and to ensure that goals are met. The 10-year limit to funding ensures a constant churn of funds that enables new programs to be established.

Past examples of transformative programs that informed nutrition research include the Human Microbiome Project (HMP), supported by the Common Fund from 2007-2016, which developed numerous research resources to enable the study of the microbial communities that live in and on the human body and the roles these communities play in health and disease. The gut microbiome, which is highly variable between individuals, has been linked to disease susceptibility, as well as to individual variability in behavioral and physiological responses to diet. The human gastrointestinal microbiota not only influence what nutrients an individual can extract from one's diet, but may also affect that individual's physiology, behavior, and

susceptibility to diet-related chronic diseases. The Nutrition for Precision Health program will build upon this knowledge to advance our understanding of the microbiome and its influences on diet and overall health at the individual and population level. In addition, the Common Fund Metabolomics Program has developed nationwide capabilities to measure metabolic responses and to identify metabolites. This will be essential for the Nutrition for Precision Health program.

The Common Fund itself supports a continuously changing set of topics and would not be able to support repeated projects devoted to the same topic, such as nutrition. However, coordinating Common Fund-like programs through ONR will provide a tested research strategy for repeatedly delivering transformation in the nutrition field.

Rapid Acceleration of Diagnostics (RADx) — Answering the Call of COVID-19

Program Overview

The coronavirus pandemic has presented a significant challenge to public health and safety across the United States. To stem the spread of the novel coronavirus (SARS-CoV-2), communities must have access to efficient and reliable diagnostic testing. In response to this urgent public health need, the Rapid Acceleration of Diagnostics (RADxSM) initiative, a major effort coordinated through the NIH OD, was launched in April 2020. This initiative is a national call for scientists and engineers to present innovative ideas to speed the development, validation, commercialization, and implementation of COVID-19 testing and ensure fast and accurate testing to support nation-wide efforts to reduce the spread of COVID-19 and return to normal activities. With the goal of making millions of tests available each week, the RADxSM initiative is also pursuing opportunities to study and refine testing methods and approaches for distribution through engagement with underserved and vulnerable communities, with a special focus on those at higher risk of COVID-19.

NIH launched the RADxSM initiative in partnership with several other federal agencies, including the Office of the Assistant Secretary of Health (OASH), Department of Defense (DOD), the Biomedical Advanced Research and Development Authority (BARDA), U.S. Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC).

The RADxSM initiative consists of five programs uniquely designed to meet the need of COVID-19 testing:

- **RADx Tech**: NIH established the RADx Tech program to quickly identify, validate, and scale up production of promising new technologies for point-of-care and laboratory COVID-19 testing. The RADx Tech program invited bioengineers and entrepreneurs to submit ideas for testing technologies that could be rapidly developed and deployed. This program is an accelerated milestone-driven approach that, through vigorous vetting, identifies the most promising solutions in which to invest. Experts help awardees simultaneously address technical, regulatory, clinical, and commercialization requirements throughout the phased approach.

The program expanded on the Point-of-Care Technologies Research Network (POCTRN), established by NIH's NIBIB in 2007, which uses a flexible, rapid process to support promising technologies at key stages of development to advance technologies with clinical applications.

- **RADx-ATP**: The RADx Advanced Technology Platforms (RADx-ATP) program seeks to enhance testing capacity and throughput by identifying existing and late-stage testing technologies ready to be scaled up or expanded to increase their geographic reach. This two-year effort began in 2020 by leveraging the established RADx Tech proposal review process and market research infrastructure to identify high-potential applicants. RADx-ATP has placed special emphasis on different testing technologies with the capability to distinguish between SARS-CoV-2 and influenza infections and has built collaborations with key industry partners.

To date, RADx Tech and RADx-ATP have provided support and funding to 150 organizations with promising testing technologies. Projects chosen for advancement through the phased selection process represent a broad range of test types, including both point-of-care and laboratory-based tests. The tests utilize a range of sample types, methods, and technologies all of which have or are near to receiving FDA authorization. Diversifying the available diagnostic tests enhances the ability to develop effective tests for many environments.

- RADx-rad: The RADx Radical (RADx-rad) program supports research and development for new, innovative techniques and new applications of existing approaches to address current gaps in COVID-19 testing. The goal of RADx-rad is to enhance the usability, accessibility, and accuracy of novel COVID-19 testing. Non-traditional approaches supported by RADx-rad include community wastewater analysis and surveillance, sensory detection for early disease, and integration of artificial intelligence systems with digital health technologies for screening and prognostics. RADx-rad has supported 49 projects to address gaps in SARS-CoV-2 testing through technology platforms that can be used in future outbreaks of COVID-19 and that could be applicable to other, yet unknown, infectious organisms.

RADx-rad is coordinated by a trans-NIH committee with partnerships across 25 NIH ICOs. A RADx-rad data coordination effort (RADx Data Hub) will assure harmonized data collection, storage, management and access, and linkages to data from other RADx initiatives, which will provide opportunities for secondary analysis to further explore early findings and identify promising approaches to understand the novel SARS Co V-2 virus. Beyond the current crisis, the technologies advanced through RADx-rad will likely be applicable to the early identification and prevention of other, as yet unknown, infectious disease agents.

- RADx-UP: As part of the NIH-wide effort to address the COVID-19 pandemic, the RADx Underserved Populations (RADx-UP) program was developed to enable and expand COVID-19 testing for underserved and vulnerable populations. RADx-UP addresses the increased burden of COVID-19 on populations with health disparities, particularly African Americans, Hispanics or Latinos, and American Indians/Alaska Natives, older adults, pregnant women, those in underserved rural or urban communities, the homeless, and those who are incarcerated. To partner with these communities, RADx-UP created a consortium of community-engaged research projects designed to evaluate and implement effective COVID-19 interventions. RADx-UP established a collaborative network of clinical research projects to examine COVID-19 infection patterns and efforts to increase access and effectiveness of diagnostic methods. These two-year research projects seek to examine COVID-19 transmission patterns, assess the use and effectiveness of COVID-19 diagnostic tools, and ultimately enable rapid, accurate COVID-19 testing within underserved and vulnerable populations that have been disproportionately affected by the COVID-19 pandemic. In FY 2021, RADx-UP plans to expand this testing network to include studies that focus on testing in the context of vaccination, a new emphasis on testing strategies to safely return children and staff to the in-person school setting, and ways to leverage and build partnerships between RADx-UP and other aligned NIH programs focused on underserved and vulnerable populations.

The RADx-UP Social, Ethical, and Behavioral Implications (SEBI) research program will identify, analyze, and address the social, ethical, and behavioral factors likely to influence access to and uptake of COVID-19 testing in underserved and vulnerable populations. RADx-UP will strengthen the available data on infection rates, disease progression and outcomes, and identify strategies to reduce disparities seen in COVID-19 diagnostics.

The RADx-UP Coordination and Data Collection Center will serve as a national resource to coordinate research activities, guide administrative operations and logistics, and provide analytical infrastructure and expertise for COVID-19-related research activities. RADx-UP also supports the application of technological advances emerging from other RADx efforts to underserved and vulnerable populations in real-world settings, such as distributing home diagnostic kits.

- **Data Management:** In support of these and other COVID-19 related efforts, NIH is constructing an infrastructure to support coordination of the data management needs of COVID-19 efforts. The goal of this effort is to develop a platform to integrate data on individuals and populations from a variety of sources, including testing results, self-reported symptoms, and electronic medical record data. All RADxSM initiatives will be undergirded by a data coordinating effort, which will intake and collect data from the various RADx projects through project-focused coordination centers. This effort will also work with the project coordination centers, to develop and implement common data elements and models, and facilitate harmonized data sharing on a secure cloud-based data platform.

Trans-NIH Collaboration

The RADxSM initiative has overarching trans-NIH governance, including the RADx Executive Committee, specific governance mechanisms for each initiative, and trans-NIH working groups to utilize diverse subject matter expertise from across the agency. RADx also includes collaborations across HHS, including BARDA, FDA, and CDC. These collaborations are a priority for tracking and routing NIH-supported projects, coordinating efforts, implementing review processes, and coordinating communications strategies.

Next Steps

The RADx programs are developing opportunities to expand and support ongoing and new COVID-19 diagnostic research activities. Through the RADxSM initiative, the NIH will continue to evolve and adapt efforts to meet the changing circumstances of the COVID-19 pandemic.

UNITE Initiative

Program Overview

The NIH has spent over a year addressing the COVID-19 pandemic, which has made painfully clear that health disparities and inequities continue to contribute to morbidity and mortality in our nation. In addition, the events of 2020 highlighted our nation's continued struggle with systemic and structural racism. As a science agency, the NIH understands that bringing diverse perspectives, backgrounds, and skillsets to complex scientific problems enhances scientific productivity. NIH is committed to instituting new ways to support diversity, equity, and inclusion, and identifying and dismantling any policies and practices that may harm the NIH workforce and its ability to make important discoveries that improve health and save lives.

NIH launched the UNITE Initiative at a special meeting of the Advisory Committee to the Director (ACD) on February 26, 2021²²³ with the goal of identifying and addressing structural racism within the NIH community and the greater biomedical research community. UNITE²²⁴ is comprised of five workstreams with separate but coordinated objectives to tackle the problem of racism and discrimination in science, while developing methods to promote diversity and inclusion across the biomedical enterprise. These workstreams include:

- U - Understanding stakeholder experiences through listening and learning
- N - New research on health disparities, minority health, and health equity
- I - Improving the NIH culture and structure for equity, inclusion and excellence
- T - Transparency, communication, and accountability with our internal and external stakeholders
- E - Extramural research ecosystem: changing policy, culture and structure to promote workforce diversity

Through this NIH-wide, collaborative effort, UNITE will work to address challenging issues stemming from structural racism with which the NIH is currently grappling.

Attracting and Retaining Scientists from Underrepresented Groups: The NIH will be instituting several efforts to attract and retain scientists from underrepresented groups including expanding the Distinguished Scholars Program²²⁵ to Senior Investigators hired with tenure, and enhancing recruitment of researchers from underrepresented groups as candidates for open tenure-track investigator positions. This program is led through a collaboration between the Office of Scientific Workforce Diversity (SWD) and the Intramural Research Program.

Addressing Disparities in the Success Rates for Grants Supporting Black Scientists: In 2011, Ginther et al. reported a significant racial gap apparent in NIH R01 funding.²²⁶ The funding rate for R01 applications from Black/African American scientists was 10 percentage points lower than for all other groups. This urged NIH and the biomedical community to look closely at

²²³ acd.od.nih.gov/meetings.html

²²⁴ www.nih.gov/ending-structural-racism/unite

²²⁵ diversity.nih.gov/programs-partnerships/dsp

²²⁶ www.ncbi.nlm.nih.gov/pmc/articles/PMC3412416/

individual and systemwide potential contributors and solutions, codified in 13 recommendations by the NIH ACD.²²⁷ Today, there are still far too few Black applicants and applicants from other groups underrepresented in the biomedical workforce (Figure 1). While success rates for receipt of R01 equivalent grants from Black applicants have increased slightly,²²⁸ further work remains to eliminate the well-documented funding gap.

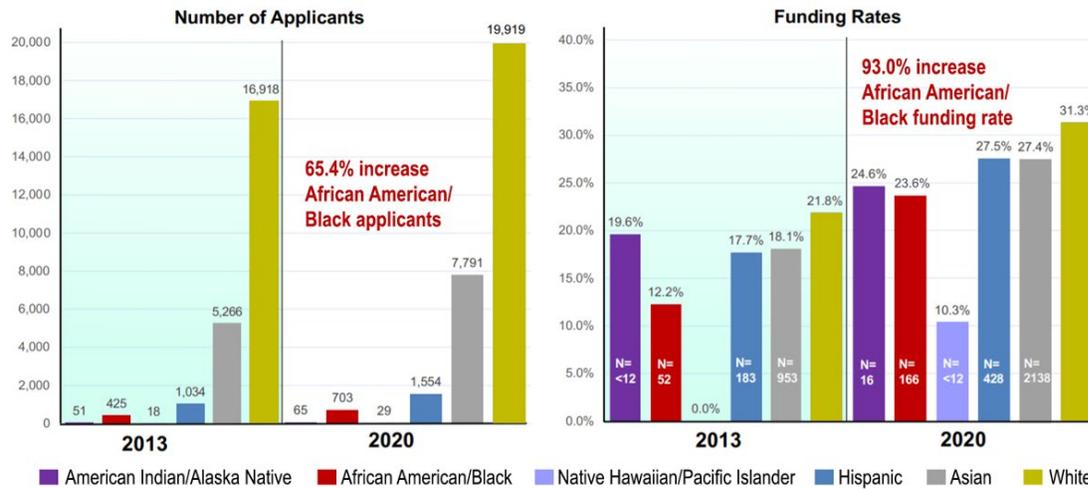


Fig. 1. Disparities in NIH R01 Grant Application and Funding Rates. Disparities in number of applicants and funding rates between NIH R01 grants that support non-White investigators and NIH R01 grants that support White investigators. From 2013 to 2020, both application and funding rates for grants that support African American/Black investigators increased, but differences with White investigators still remained.

Improving Transparency of Race-Based Demographic Data: The NIH workforce is composed of both an extramural scientific workforce of division directors, program officers, policy analysts, etc. and an intramural scientific workforce of lab heads, biologists, trainees, as well as a clinical center running clinical trials. In the scientific workforce, disparities have been identified based on race and ethnicity (Figure 2).

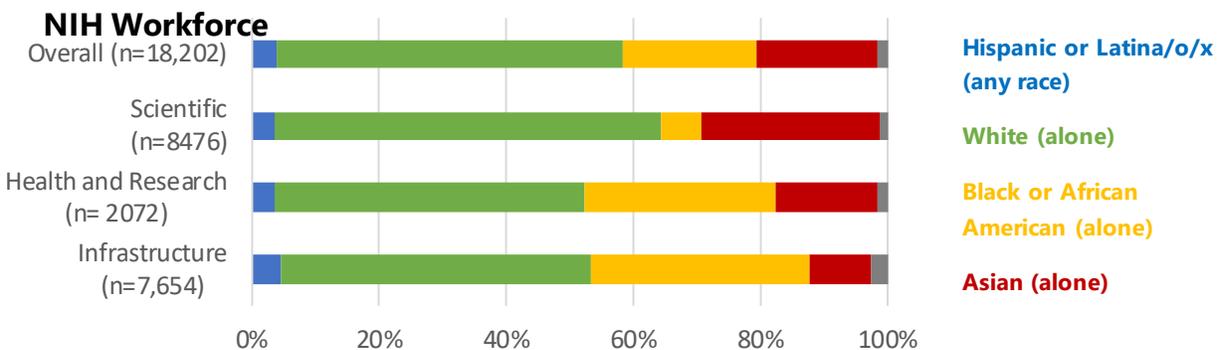


Fig. 2. Demographics of NIH FTE Workforce. This figure demonstrates the NIH’s current FTE workforce data. Scientific Workforce leads or has oversight over research (e.g., investigator, staff scientist, health science administrator); Health and Research Workforce supports research (e.g., nurse, lab technician); and Infrastructure Workforce undergirds the scientific enterprise but not “scientific” or “health and research” (e.g., program analyst, grants management, IT). Disparities in the Scientific Workforce are seen in the underrepresentation of Black/African Americans and American Indian, Alaska Native,

²²⁷ acd.od.nih.gov/documents/reports/DiversityBiomedicalResearchWorkforceReport.pdf

²²⁸ diversity.nih.gov/sites/coswd/files/images/docs/SWD_Progress_2021_Infographic.pdf

Native Hawaiian, Pacific Islander, and Two or More Races compared to the overall workforce demographics where Whites are overrepresented.

In addition, when examining NIH Leadership positions (IC Directors, Deputy Directors, Scientific Directors, Clinical Directors, and Executive Officers), data indicate a disparity with the overall NIH workforce in that Whites are overrepresented compared to others (Figure 3). NIH's goal is to develop a sustainable, systematic process to gather and make public demographic data for both the intramural and extramural biomedical research workforces, extending across all job categories to better empower the work of NIH.

NIH Senior Leadership (n=157)

IC Director, Deputy Dir, Scientific Dir,
Clinical Dir, Executive Officer

Hispanic or Latina/o/x (any
race)

White (alone)

Black or African American
(alone)

Asian (alone)

American Indian, Alaska

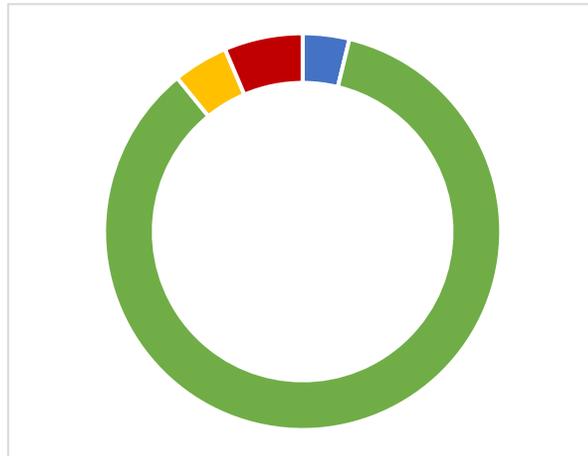


Fig. 3. Demographics of NIH FTE Workforce.

This figure demonstrates the NIH's current Senior Leadership demographic data. This indicates an underrepresentation of Black/African Americans and American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and two or More Races compared to the overall workforce demographics where Whites are overrepresented.

Increasing Funding of Research for Minority Health, Health Disparities, and Health Equity:

All NIH institutes and centers, led by the National Institute of Minority Health and Health Disparities (NIMHD), will seek to expand and enhance research on health disparities and health equity. As part of this, the NIH Common Fund, led by DPCPSI, has announced a new 5-year, \$60 million program to support innovative investigator-initiated projects aimed at reducing health disparities and inequalities.²²⁹ Emphasis will be placed on projects aimed at developing effective interventions, and institutions that serve minority populations will be prioritized for select awards. NIH is also providing robust support to the NIMHD funding opportunity announcement,²³⁰ *Understanding and Addressing the Impact of Structural Racism and Discrimination on Minority Health and Health Disparities*, announced on March 23, 2021, with 22 ICOs signed on with their support.

Addressing Racism in the NIH Workplace:

The NIH has identified accounts of racism in the workplace reported by people of color throughout the biomedical research enterprise both through personal accounts and through

²²⁹ grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-021.html and grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-022.html.

²³⁰ grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-004.html

Notification and Federal Employee Antidiscrimination and Retaliation (NoFEAR) Act data collected and shared by the Office of Equity, Diversity, and Inclusion (EDI).²³¹ To address racism in the NIH workplace, NIH will publicly identify and correct any NIH policies or practices that may have helped to perpetuate structural racism. This includes revisiting and revising NIH manual chapters. Additionally, input was sought from the public and stakeholder organizations through a Request for Information that was issued on March 1, 2021 and remained open through April 23, 2021.²³² Other opportunities to gather feedback from both the extramural community and the internal NIH workforce through listening sessions, focus groups, and town halls are in development. NIH will also ensure that each of its 27 ICs appoint a diversity, equity, and inclusion officer who will have direct access to the institute or center director, and who, among other things, will track the institute or center's diversity and inclusion efforts.

NIH-wide Collaboration

UNITE is spearheaded by the Immediate Office of the Director and co-chaired by the Acting Chief Officer for Scientific Workforce Diversity, the Deputy Director for Management, and the Principal Deputy Director. The five interrelated, but distinct, workstreams of UNITE have nearly 80 members from across the NIH workforce with representation from each of NIH's 27 ICs as well as the OD. Members of UNITE were nominated by NIH ICO Leadership. UNITE works in collaboration with a number of NIH key stakeholders including EDI, SWD, the Office of Human Resources (OHR), OHR/Civil Program, the Office of Communications and Public Liaison, DPCPSI, and others. The UNITE Initiative reports to the NIH Steering Committee and reports its findings and activities to the NIH ACD.

Next Steps/Goals

This is just the beginning of a multifaceted effort to achieve racial equity across the biomedical enterprise. These efforts to improve recruitment and retention of scientists from underrepresented groups; address funding disparities; ensure transparency of race-based demographic data; increase research for minority health, health disparities, and health equity; and address racism in the NIH workplace will take time but will propel NIH's work in biomedical research and discovery. The NIH mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." Ensuring that this fundamental knowledge includes diverse perspectives, backgrounds, and skillsets to address complex research questions not only enhances innovation and scientific productivity but is also key to enhancing the health of our nation.

²³¹ edi.nih.gov/no-fear-act

²³² grants.nih.gov/grants/guide/notice-files/NOT-OD-21-066.html