

CROSS-CUTTING NIH INITIATIVES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Cross Cutting Initiatives

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INTRODUCTION

The National Institutes of Health (NIH), the Nation's premiere biomedical research agency, is tasked with guiding United States scientific research and development in an ever-changing world. The pace of research and development is continuing to move fast, and the coming years are certain to offer both new scientific opportunities and pose continued serious challenges for human health. As ever, NIH constantly strives to not only meet the current and evolving biomedical needs, but to set the standard for high caliber research and ethical conduct of science.

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 its mission, NIH invests in research programs designed to explore the causes, prevention, and treatments of human diseases and disorders; processes in healthy development and aging; and methods for collecting and disseminating data and health information. In addition, NIH Institutes, Centers, and Offices (ICOs) leverage existing strengths and resources by collaborating in innovative, creative, and multidisciplinary ways to answer complex and crucial questions about human health and disease.

NIH is made up of 27 Institutes and Centers (ICs), each with a specific research agenda and budget, often focusing on particular diseases or body systems. NIH ICs came together to address emerging scientific and clinical questions by contributing to major NIH-wide initiatives in areas such as health disparities and pain research, and by contributing to capacity building. This allows NIH ICs with comparatively smaller budgets (less than \$1 billion) to have a much larger contribution to biomedical research than one might expect from the size of their budgets alone. Building strong research collaborations and partnerships across ICs requires both a diverse scientific workforce and recruitment of diverse research participants to ensure thoughtful methodology can capture the wide variety of human health needs. NIH-wide efforts continue to focus on developing and testing interventions to reduce health disparities, identifying key gaps in science related to health disparities, and promoting targeted research on appropriately tailored public health, clinical, and community preventive services in diverse settings and contexts. For example, the NIH UNITE Initiative, comprised of representatives from across all 27 NIH ICs, was established in 2021 with the goal of identifying and addressing structural racism within the NIH community and the greater biomedical research community.

To tackle some of the most complex questions facing biomedical science currently, NIH leverages crosscutting, multi-ICO initiatives and research programs which bring together diverse experts and leaders from across this and other agencies. The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership involves many ICOs as well as sister agencies in the United States Department of Health and Human Services (HHS) to develop a coordinated research strategy for prioritizing and speeding development of the most promising COVID-19 treatments and vaccines. The NIH Climate Change and Health Initiative also includes multiple ICOs working together toward reducing health threats from climate change across the lifespan to build health resilience in individuals, communities, and nations around the world. A bedrock of cross-cutting, multi-ICO research is exemplified by the NIH Clinical Center, America's research hospital, located on the NIH campus in Bethesda, Maryland. The Clinical Center has supported multidisciplinary, ethical, and efficient clinical research since

1953 to translate laboratory discoveries into state-of-the-art diagnostic, preventive, and therapeutic interventions to improve the nation's health.

Multifaceted questions about human health and disease are best served by inter-Institute, interdisciplinary, collaborative efforts that fully capture the complexities of the research need. For example, the NIH Common Fund Molecular Transducers of Physical Activity Consortium (MoTrPAC) brings together a multidisciplinary team to uncover, at the molecular level, how exercise improves and maintains the health of the body's tissues and organs. Tracking the impact of exercise on biological molecules through time will help MoTrPAC researchers create a map of molecular changes in the body. The Office of Research on Women's Health (ORWH) is another example of how interdisciplinary collaborations can advance research for the health of women and develop evidence-based care and personalized medicine for both women and men by understanding sex and gender differences in many disease conditions. Another important NIH-wide effort that applies expertise and resources from multiple NIH ICOs has been the INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project, that investigates conditions affecting individuals with Down syndrome and the general population, such as Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease and diabetes.

During FY 2024, NIH will continue to facilitate partnerships across ICOs to leverage infrastructure and synergize scientific expertise to effectively turn scientific discovery into improved human health and disease prevention. Building partnerships and leveraging existing relationships are critical to supporting and facilitating scientific and clinical research to prevent illness and disease. NIH will learn from its most recent advances and build on these collaborations going forward. By responding to urgent and evolving health needs, addressing health disparities, building upon previous discoveries, and embracing diversity, equity, and inclusion, NIH will remain a leader in biomedical research and development well beyond FY 2024 and continue to be the steward of medical and behavioral research for the Nation.

ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

Program Overview

While the traditional model of drug discovery and approval takes years to complete, the rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally in early 2020 required immediate action by the U.S. government biomedical research agencies to accelerate development of coronavirus disease 2019 (COVID-19) vaccines, therapeutics, and diagnostics. Responding to this urgent and unprecedented need, in April 2020, NIH established the public–private partnership Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)⁹⁸ to harness the collective scientific power of both public and private sectors and develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines. ACTIV leverages the scientific innovation, knowledge, and biomedical resources of both the U.S. government and the private sector to mitigate COVID-19 morbidity and mortality and to hasten an end to the pandemic.

The ACTIV partnership has enabled the rapid and open exchange of ideas and information among government participants, industry members, and investigators. Coordinated by the Foundation for the National Institutes of Health (FNIH), NIH is joined by its sibling agencies in the Department of Health and Human Services (HHS), including the Biomedical Advanced Research and Development Authority (BARDA), Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA); other government agencies including the Department of Defense (DoD), and Department of Veterans Affairs (VA); the HHS Coordination Operations and Response Element (and formerly Operation Warp Speed); the European Medicines Agency (EMA); and representatives from academic, non-profit and philanthropic organizations, and numerous biopharmaceutical companies.

As a highly collaborative venture, ACTIV governance includes an NIH-led Leadership Group, an Executive Committee, and five working groups. The Leadership Group, comprising representatives from each organization involved in ACTIV, regularly reviews ACTIV’s progress. The Executive Committee includes scientific executives representing both U.S. government agencies and industry, and oversees ACTIV’s activities and operations. Leaders from across NIH, including 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 in the Leadership Group and Executive Committee, as well as collaborate in the five working groups.

The ACTIV working groups are pursuing five fast-track focus areas, with each working group led by senior scientists representing relevant sector partners:

- The Preclinical Working Group focused on development of a collaborative, streamlined forum to identify preclinical treatments^{99, 100}

⁹⁸[nih.gov/research-training/medical-research-initiatives/activ](https://www.nih.gov/research-training/medical-research-initiatives/activ)

⁹⁹[nih.gov/research-training/medical-research-initiatives/activ/preclinical-working-group](https://www.nih.gov/research-training/medical-research-initiatives/activ/preclinical-working-group)

¹⁰⁰ The Preclinical Working Groups completed its charge as of September 2021

- The Clinical Trial Capacity Working Group focused on improvement of clinical trial capacity and effectiveness^{101, 102}
- The Clinical Therapeutics Working Group focused on acceleration of clinical testing of the most promising therapeutics¹⁰³
- The Vaccines Working Group focused on acceleration of the evaluation of vaccine candidates to enable rapid authorization or approval¹⁰⁴
- The ACTIV Tracking Resistance and Coronavirus Evolution (TRACE) Working Group focused on tracking of emerging SARS-CoV-2 variants and coordination of open data and reagent sharing¹⁰⁵

ACTIV ACCOMPLISHMENTS

The ACTIV partnership has been successful in accelerating the development of COVID-19 vaccines, therapeutics, and diagnostics, generating significant findings and results that have informed the care of patients with COVID-19 in the United States and worldwide. Importantly, the ACTIV program has advanced the U.S. government and global preparedness for future emerging infectious disease research response in keeping with the U.S. Government National Security Strategy.

Supporting Preclinical Testing of COVID-19 Therapeutics

Shortly after the start of the pandemic, the ACTIV partnership pulled together leaders from across the government and other sectors to swiftly tackle the need for COVID-specific therapeutics and vaccines. Led by the Preclinical Working Group, ACTIV worked to accelerate preclinical testing of candidate therapies by creating a prioritization framework that facilitated rapid review of potential therapeutic candidates to enter into COVID-19 clinical trials for clinical investigation. NCATS, NIAID, and OD's Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) worked closely with other ACTIV members on triaging and prioritizing preclinical resources. Additionally, the ACTIV Preclinical Working Group standardized and shared preclinical evaluation resources and methods, including a master inventory for preclinical testing resources, development of a centralized process and repository for harmonizing and sharing methods and evaluation animal models,¹⁰⁶ creation of publicly available databases of preclinical studies¹⁰⁷ and COVID-19 related animal studies,¹⁰⁸ and creation of a virtual testing network for triaged drug candidates.

¹⁰¹ [nih.gov/research-training/medical-research-initiatives/activ/clinical-trial-capacity-working-group](https://www.nih.gov/research-training/medical-research-initiatives/activ/clinical-trial-capacity-working-group)

¹⁰² The Clinical Trial Capacity Working Group completed its charge as of July 2020.

¹⁰³ [nih.gov/research-training/medical-research-initiatives/activ/therapeutics-clinical-working-group](https://www.nih.gov/research-training/medical-research-initiatives/activ/therapeutics-clinical-working-group)

¹⁰⁴ [nih.gov/research-training/medical-research-initiatives/activ/vaccines-working-group](https://www.nih.gov/research-training/medical-research-initiatives/activ/vaccines-working-group)

¹⁰⁵ [nih.gov/research-training/medical-research-initiatives/activ/trace-working-group](https://www.nih.gov/research-training/medical-research-initiatives/activ/trace-working-group)

¹⁰⁶ Hewitt JA, et al. ACTIVating Resources for the COVID-19 Pandemic: In Vivo Models for Vaccines and Therapeutics. *Cell Host Microbe*. 2020 Nov 11;28(5):646-659. doi: 10.1016/j.chom.2020.09.016. Epub 2020 Oct 1. PMID: 33152279; PMCID: PMC7528903.

¹⁰⁷ opendata.ncats.nih.gov/covid19/databrowser

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

Conducting Clinical Trials for COVID-19 Vaccines and Therapeutics

In order to expedite clinical trials for testing of COVID-19 vaccines and therapeutics, ACTIV leveraged the existing infrastructure of both NIH and non-NIH clinical trial networks. To support these efforts, the ACTIV Clinical Trial Capacity Working Group developed an inventory of clinical trial capacity to inform implementation of ACTIV trials, including existing NIH trial networks and contract research organizations (CROs) that could be rapidly deployed to test COVID therapeutics.

To support vaccine efforts, the ACTIV Vaccines Working Group accelerated the evaluation of COVID-19 vaccine candidates by supporting harmonized clinical efficacy trials and a parallel effort to generate biomarkers and other evidence for more rapid approval and authorization. They advised on the protocol designs and endpoints to ensure a harmonized approach across multiple vaccine efficacy trials. Several SARS-CoV-2 vaccine trials used harmonized protocols informed by ACTIV.¹⁰⁹

Through the Clinical Therapeutics Working Group, ACTIV has developed a process for evaluating potential therapeutic agents by reviewing publicly available data, submissions from investigators, and information gathered from an online survey and then moving prioritized agents into clinical trials. ACTIV has been able to rapidly deploy potential therapeutics into clinical trials by leveraging existing NIH networks supported by various Institute and Centers (ICs) including NIAID, NCI, National Institute of Neurological Disorders and Stroke (NINDS), NHLBI, and NCATS, allowing for ACTIV agents to be studied in more than 620 trial sites across the United States and internationally. Using this process, ACTIV has evaluated over 800 therapeutic agents and prioritized 33 for testing in ACTIV clinical trials.¹¹⁰

ACTIV clinical trials are examining the effectiveness of multiple therapeutic classes aimed at COVID-19 patients with varying disease severity. By developing and implementing multiple master protocols, which allow coordinated, efficient, and adaptive evaluation of potential therapeutic agents across multiple study sites, ACTIV has been able to nimbly test drug and biological candidates as they became available and to swiftly weed out those that do not demonstrate effectiveness. ACTIV includes six master protocol-driven adaptive clinical trials:

- The ACTIV-1 master protocol was overseen by NCATS and tested promising immune modulator compounds, a class of drugs that helps minimize the deleterious effects of an overactive immune response to SARS-CoV-2 infections, in hospitalized patients with moderate to severe COVID-19 disease.¹¹¹
- Led by NIAID, the ACTIV-2¹¹² and ACTIV-3¹¹³ master protocols examine monoclonal antibody therapies and other therapeutics in two patient populations, with ACTIV-2

¹⁰⁹ [nih.gov/research-training/medical-research-initiatives/activ/sars-cov-2-vaccine-clinical-trials-using-activ-informed-harmonized-protocols](https://www.nih.gov/research-training/medical-research-initiatives/activ/sars-cov-2-vaccine-clinical-trials-using-activ-informed-harmonized-protocols)

¹¹⁰ [nih.gov/activ/nih-funded-activ/activ-associated-clinical-trials](https://www.nih.gov/activ/nih-funded-activ/activ-associated-clinical-trials)

¹¹¹ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ1](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ1)

¹¹² [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ2](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ2)

¹¹³ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ3](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ3)

focusing on non-hospitalized adults and ACTIV-3 on hospitalized patients, including those in critical care.

- ACTIV-4, which is led by NHLBI, evaluates the safety and effectiveness of several interventions aimed at preventing or treating the blood clots, vascular damage, and host-tissue injury caused by SARS-CoV-2. These interventions range from blood thinners, such as antithrombotics, anticoagulants, and antiplatelets, to vascular/tissue-protective agents, in hospitalized, non-hospitalized, and convalescent participants.¹¹⁴
- ACTIV-5 is led by NIAID and is conducting a series of Phase II trials to look at whether certain approved therapies or investigational products in late-stage clinical development show promise against COVID-19.¹¹⁵
- The NCATS-led ACTIV-6 trial focuses on using repurposed drugs in outpatient settings to see if therapeutics that have been previously approved by the FDA for other diseases are also effective in treating COVID-19.¹¹⁶

Additionally, several NIH-funded trials are testing ACTIV-prioritized agents using protocols informed or endorsed by the ACTIV partnership.¹¹⁷

The ACTIV trials have had significant impact on clinical treatment of COVID-19 patients. For example, initial results from ACTIV-4 on heparin and other anticoagulants have already changed clinical practice. Results from ACTIV-4 showed that heparin improved outcomes in hospitalized moderately ill patients with COVID-19 by increasing the probability of survival to hospital discharge and reducing the need for cardiovascular or respiratory organ support.¹¹⁸ However, ACTIV-4 showed this treatment is not effective for critically ill patients.^{119,21} ACTIV-1 has shown that the immune modulator drugs infliximab and abatacept both substantially improve clinical status and reduce deaths in hospitalized patients, though they do not substantially shorten time to recovery.¹²⁰ Additionally, ACTIV-2 and ACTIV-3 studies have supported the use of monoclonal antibodies in the treatment of COVID-19, with data from ACTIV-2 used to support an application for Emergency Use Authorization (EUA) for a monoclonal antibody combination from Brio Bio (BRII-196/BRII-198).¹²¹ Three products tested in ACTIV trials also received EUAs based on separate, industry-supported trials: the monoclonal antibodies sotrovimab,¹²² bamlanivimab,¹²³ and AZD7442/ Evusheld.¹²⁴ Though some of these EUAs have since been

¹¹⁴ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4)

¹¹⁵ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ5](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ5)

¹¹⁶ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ6](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ6)

¹¹⁷ [nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#ACTIV-Associated](https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#ACTIV-Associated)

¹¹⁸ ATTACC Investigators et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*. 2021 Aug 26;385(9):790-802. doi: 10.1056/NEJMoa2105911. Epub 2021 Aug 4. PMID: 34351721; PMCID: PMC8362594.

¹¹⁹ www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients

¹²⁰ [nih.gov/news-events/news-releases/immune-modulator-drugs-improved-survival-people-hospitalized-covid-19](https://www.nih.gov/news-events/news-releases/immune-modulator-drugs-improved-survival-people-hospitalized-covid-19)

¹²¹ briobio.com/news-detail.php?id=370

¹²² [fda.gov/media/149534/download](https://www.fda.gov/media/149534/download)

¹²³ [fda.gov/media/145802/download](https://www.fda.gov/media/145802/download)

¹²⁴ [fda.gov/media/154701/download](https://www.fda.gov/media/154701/download)

revised due to changes in effectiveness in more recent SARS-CoV-2 variants,^{125, 126} they have served as important clinical tools at varying stages throughout the pandemic.

Equally as important, ACTIV also demonstrated which therapeutics do not have efficacy against SARS-CoV-2, thus informing better clinical practice. For example, ACTIV-6 found that fluticasone furoate has no clinical benefit for patients with mild to moderate COVID-19 symptoms.¹²⁷ ACTIV-6 is also examining the use of ivermectin for patients with mild to moderate COVID-19 disease and showed ivermectin at the lower of two ivermectin doses being tested in the trial did not lower incidence of hospitalization or death among COVID-19 patients with mild to moderate disease.¹²⁸ Results from testing of a higher dose of ivermectin are not yet available. Initial data about three of the monoclonal antibody products tested in ACTIV-3 (Lilly, Bii Bio, and GSK-Vir products) did not support further testing.^{129, 130, 131} The results of ACTIV trials identified new treatment strategies and how these should be applied to specific sets of patients along the spectrum of SARS-CoV-2 infection. Furthermore, these results are critically important to avoid applying ineffective and risky treatments to certain categories of COVID-19 patients and helped focus further clinical trial efforts on other possibilities.

Tracking the Impact of Emerging SARS-CoV-2 Variants on Vaccines and Therapeutics

To ensure patients receive effective vaccines and therapeutics, tracking the evolution of the SARS-CoV-2 virus and its impact on treatments is a critical need. ACTIV's TRACE Working Group is tackling this challenge. ACTIV partners have developed processes and infrastructure for monitoring and testing emerging SARS-CoV-2 variants, and for gathering and publicly sharing variant sequencing and phenotypic data. TRACE is following a multi-step approach to variant monitoring and data sharing: to monitor global emergence and circulation of SARS-CoV-2 mutations; characterize prioritized mutants *in vitro* through critical-path assays; characterize prioritized mutants *in vivo* through critical-path assays; and rapidly share activity data with ACTIV and scientific community.

In collaboration with NCATS, NIAID, and the National Center for Biotechnology Information (NCBI) in the National Library of Medicine (NLM), TRACE is improving the analysis pipeline for COVID-19 variants. Along with a weekly report that summarizes shifting trends in emerging variants based on sequence data deposition to GenBank/SRA¹³², TRACE provides publicly available information on viral variant phenotypic characteristics and overviews of preclinical

¹²⁵ [fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization](https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization)

¹²⁶ [fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab](https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab)

¹²⁷ activ6study.org/wp-content/uploads/2022/07/ACTIV-6_Lay_Summary-Fluticasone_30JUNE20221_508.pdf

¹²⁸ Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Naggie S. Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. medRxiv [Preprint], 2022 Aug 11:2022.06.10.22276252. doi: 10.1101/2022.06.10.22276252. PMID: 35982669; PMCID: PMC9387156.

¹²⁹ [nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies](https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies)

¹³⁰ niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study

¹³¹ [nih.gov/activ/nih-funded-activ/activ-associated-clinical-trials](https://www.nih.gov/activ/nih-funded-activ/activ-associated-clinical-trials)

¹³² ftp.ncbi.nlm.nih.gov/pub/ACTIV-TRACE/

assays used to test them through the Variant Therapeutic Data Summary¹³³ within the NCATS OpenData Portal. These are valuable resources for tracking the changing COVID-19 landscape.

Next Steps/Goals

As the pandemic evolves, so does ACTIV. As new SARS-CoV-2 variants emerge, the TRACE Working Group continues to monitor them and examine their sensitivity to extant COVID therapeutics. The ACTIV Vaccines Working Group determines the implications of the changing variant landscape for current and second-generation vaccination strategies. In parallel, ACTIV will complete its ongoing clinical trials of COVID therapeutics, which include continued tracking of participant outcomes. Current inpatient activities will be transitioned as appropriate to ACTIV's new Strategies and Treatments for Respiratory Infectious Viral Emergencies (STRIVE) Platform. STRIVE will evaluate therapeutic agents and combinations of therapeutics in a strategic manner across disease severity, from those with mild to severe COVID symptoms.

ACTIV is a demonstration of what a team of dedicated experts from across sectors can accomplish and serves as a model for future partnerships. The lessons learned from ACTIV will continue to inform future COVID-19 and other viral disease research and pandemic preparedness.

¹³³ opendata.ncats.nih.gov/variant/summary

INCLUDE (INVESTIGATION OF CO-OCCURRING CONDITIONS ACROSS THE LIFESPAN TO UNDERSTAND DOWN SYNDROME) PROJECT

Program Overview

In FY 2018, NIH launched the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project¹³⁴ in support of a Congressional directive to increase participation of people with Down syndrome (DS) and their families in clinical research, expand knowledge about DS and its links to other health conditions, and improve the health of individuals with DS.

DS is the most common genetic cause of intellectual disability, the most common autosomal trisomy, and one of the most visible and universally recognized genetic syndromes. Each year there are approximately 6,000 babies born in the United States with DS. Within the past 25 years, the average lifespan for a person with DS has doubled from 30 to 60 years, though significant disparities persist among racial and ethnic minority groups. Despite this increase, individuals with DS and their families face serious and changing health challenges. About 50 percent of all babies born with DS are also born with congenital heart disease, and estimates suggest that 50 percent or more of adults with DS will develop dementia due to Alzheimer’s disease (AD). Additional common co-occurring conditions in individuals with DS include intellectual disability, leukemia, sleep apnea, autism, immune disorders, celiac disease and diabetes, and problems with hearing and vision.

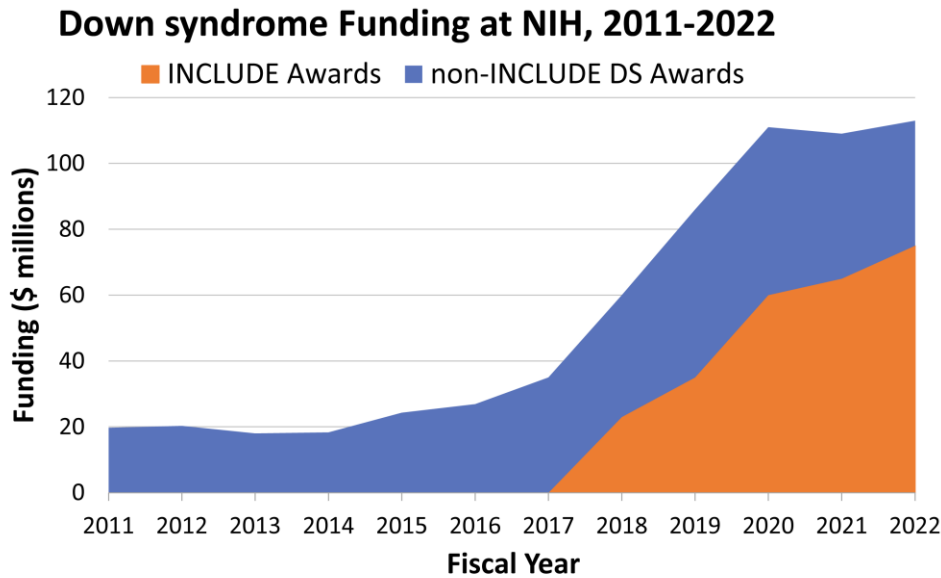


FIGURE 1 DOWN SYNDROME FUNDING AT NIH, FISCAL YEARS 2011-2022. NOTE THAT NON-INCLUDE DS AWARD FUNDING FOR FY 2022 REFLECTS THE PRELIMINARY ACTUAL LEVEL.

¹³⁴ nih.gov/include-project

INCLUDE builds on NIH's creation of the public-private Down Syndrome Consortium¹³⁵ formed in 2011 as outlined in *Down Syndrome Directions: The NIH Research Plan on Down Syndrome*.¹³⁶ INCLUDE has increased its support each year, from \$23 million in FY 2018 to \$35 million in FY 2019 to \$61 million in FY 2020 and to \$65 million in FY 2021. In FY 2022, INCLUDE committed \$75 million in 67 new awards across 12 NIH Institutes and Centers (ICs), including 5 new clinical trials.¹³⁷

INCLUDE aims to understand critical health and quality of life needs for individuals with DS across the lifespan with two goals: (1) to yield scientific discoveries that will improve the health, well-being, and neurodevelopment of individuals with DS and (2) to inform scientific thinking about common conditions they share with individuals who do not have DS. In addition, INCLUDE aims to increase the number and diversity of participants and investigators involved in DS-related research. INCLUDE pursues these goals through three major scientific components:

1. Conduct targeted, high-risk, high-reward basic science studies on chromosome 21. Research has elucidated the roles of individual genes in the DS critical region on chromosome 21 and has provided insights about their roles in cognition and neurodegeneration. INCLUDE funds basic science investigations of promising new cellular, organoid, and animal models with the goal of understanding mechanisms underlying many of the clinical manifestations of DS.
2. Assemble a large study population of individuals with DS. A large cohort of individuals with DS is essential to follow individuals' development over time and perform deep phenotyping, genomic and biomarker analyses, and natural history studies. Enrolling a cross-sectional cohort of individuals with DS at different ages across the lifespan captures the broadest array of phenotypes and ages of onset for the co-existing conditions, as well as the critical windows for interventions.
3. Conduct clinical trials research inclusive of individuals with DS. Despite the relative frequency of DS in the population, very few clinical trials have focused solely on people with DS. INCLUDE funding opportunities offer a compelling route for investigators to conduct such trials and for investigators new to DS to bring their prior trial experience to bear. In conducting these trials, INCLUDE is demonstrating that such research can be conducted safely in individuals with DS, which should lead to inclusion of this population more broadly in clinical research.

Selected Achievements

The Alzheimer's Biomarkers Consortium - Down Syndrome¹³⁸ (ABC-DS), a longitudinal study funded by INCLUDE, the National Institute on Aging (NIA), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), follows a cohort of adults with DS over time to identify early biomarkers that may herald the onset of AD. ABC-DS has

¹³⁵ downsyndrome.nih.gov

¹³⁶ nichd.nih.gov/publications/product/441

¹³⁷ Figures incorporate INCLUDE funding in the NIH Office of the Director as well as contributions from NIH ICs.

¹³⁸ nia.nih.gov/research/abc-ds

enrolled more than 400 adults with DS, plus sibling controls. Early results have identified neuroimaging and blood-based biomarkers that distinguish between cognitive stability and AD in aging adults with DS.¹³⁹ Investigators hope that these biomarkers can be useful to inform clinical trials and improve the quality of life for people with DS and for the general population.

Launched in FY 2020, the INCLUDE Data Coordinating Center¹⁴⁰ (DCC) has created a cloud-based, open digital platform to easily access and share DS data resources to accelerate research. The INCLUDE Data Hub brings information and resources from many sources together in one place. With these tools, scientists and community members can work together more easily and quickly and combine their data to learn about health conditions that impact people with DS. The DCC also advances community access to research by working closely with DS-Connect®: The Down Syndrome Registry,¹⁴¹ which is a resource where people with DS and their families can connect with researchers, health care providers, and study opportunities.

INCLUDE-funded investigators are making strides in both our basic science and clinical understanding of DS. At the basic science level, projects include generating and characterizing rodent models of DS and using cellular models to study heart and brain development. On the clinical side, one study developed a language test to better evaluate possible language interventions for individuals with DS.¹⁴² Another established the need for precise diagnostic tools for attention deficit hyperactivity disorder (ADHD) in children with DS,¹⁴³ and additional work suggests that children with co-occurring DS and ADHD may be more sensitive to certain medications than other children. Ongoing projects include developing better diagnostic tools and novel therapeutic interventions for obstructive sleep apnea syndrome in children with DS. Clinical trials are studying specific treatments for some of these conditions, including ADHD, sleep apnea, and prevention of AD.

Diversity, Equity, Inclusion, and Accessibility (DEIA)

NIH is interested in expanding and diversifying both research participants and the DS research workforce. NIH recognizes that there are health disparities among individuals with DS. New INCLUDE funding opportunity announcements require that projects that are enrolling individuals with DS include a Recruitment Plan to Enhance Diversity, and several INCLUDE funding opportunities have direct diversity, equity, inclusion, and accessibility (DEIA) emphases, including:

- R25 awards for creative and innovative short courses to train the next generation of DS researchers in state-of-the-art clinical research skills¹⁴⁴
- R15 awards supporting trainees pursuing small-scale basic and translational DS-specific research projects at institutions that do not receive substantial funding from the NIH¹⁴⁵
- R21 Community-Based Participatory Research (CBPR) initiative focused on reducing health disparities to address diverse representation in research on DS¹⁴⁶

¹³⁹ pubmed.ncbi.nlm.nih.gov/33337378/

¹⁴⁰ includedcc.org

¹⁴¹ dsconnect.nih.gov

¹⁴² pubmed.ncbi.nlm.nih.gov/33827417/

¹⁴³ pubmed.ncbi.nlm.nih.gov/34939724/

¹⁴⁴ grants.nih.gov/grants/guide/pa-files/PAR-22-195.html

¹⁴⁵ grants.nih.gov/grants/guide/notice-files/NOT-OD-22-136.html

¹⁴⁶ grants.nih.gov/grants/guide/notice-files/NOT-OD-22-142.html

INCLUDE also commits significant support to community outreach and engagement to support DEIA efforts through websites, workshops, seminars, conferences, and resources. Among these efforts, in July 2022, the DCC hosted the Data Science for Diverse Scholars in Down Syndrome Research (DS3), an in-person, immersive summer course for graduate students and early-stage postdoctoral fellows from underrepresented groups to provide bioinformatics training and promote their career advancement. In September 2022, INCLUDE held a two-day “Building a Diverse Community for Down Syndrome Research” Workshop, bringing together more than 200 self-advocates, family members, scientists, healthcare and service providers, government and agency partners, and experts in diversity and inclusion to discuss expanding representation among both the DS research community and the DS scientific workforce.

Collaboration Within and Beyond NIH

Appropriate to the multi-organ system involvement of DS and its co-occurring conditions, and in a truly NIH-wide effort, INCLUDE has assembled a team across NIH, leveraging the expertise and resources of at least 20 ICs. INCLUDE is co-chaired by Dr. Tara Schwetz, NIH Acting Principal Deputy Director, Office of the Director (OD), Dr. Diana Bianchi, Director, NICHD, and Dr. Gary Gibbons, Director, National Heart, Lung, and Blood Institute (NHLBI). Other institutes with significant involvement on the INCLUDE Steering Committee include NIA, the National Cancer Institute (NCI), National Human Genome Research Institute (NHGRI), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of General Medical Sciences (NIGMS), and National Institute of Neurological Disorders and Stroke (NINDS). The Steering Committee is complemented by the participation of at least 11 additional ICs across the NIH-wide Down Syndrome Working Group, and program working groups on data coordination and each scientific component. Together, these groups drive the development of funding opportunities, outreach activities, resources, and awareness of emerging needs in the DS research community.

Integral to the program’s goals, collaboration by INCLUDE extends beyond NIH to DS organizations and communities throughout the U.S. The team actively participates in DS-related events and conferences, works closely with major DS organizations through the DS Consortium, and conducts outreach to DS parent organizations and DS clinics. INCLUDE strives to be a true partner to research and participant communities both within NIH and beyond; for example, the September diversity workshop was developed in response to listening sessions for families and researchers held by INCLUDE earlier in FY 2022.

Next Steps / Goals

To reflect the progress made to date and integrate DS efforts across NIH, the agency has developed the 2022 NIH INCLUDE Down Syndrome Research Plan. The plan incorporates input from the DS community, addresses the need for greater diversity among DS research participants, and proposes a roadmap to further expand understanding of health disparities among individuals with DS. It also describes training opportunities to increase the pipeline of new and early-stage investigators conducting DS research.

As part of this roadmap, INCLUDE has developed a communications and outreach plan to further engage communities and investigators and expand the DS-Connect registry, with goals to

increase the number of research teams and trainees engaged in DS research; increase the representation, diversity, and number of participants in DS research; and share results of DS research broadly with the entire DS community.

INCLUDE plans to expand its efforts to create a large cohort of individuals with DS, including those from diverse communities across the lifespan. Accompanying this cohort-building, INCLUDE plans to establish one or more biorepositories that will bank cells, plasma, serum, cerebrospinal fluid, and brain and other tissues to accelerate research into co-occurring conditions. Biorepository data will be integrated with the DCC, as feasible, thereby facilitating rapid, broad data sharing, integration, and analysis. Additionally, to expand research infrastructure, participant diversity, and the investigator pool, INCLUDE will establish or augment collaborations among clinical studies and research networks that conduct research related to DS and its co-occurring conditions.

INCLUDE's investments in high-risk basic science, cohort-building, clinical trial representation, scientific infrastructure, and community engagement are breaking new ground to improve the health and quality of life of individuals with DS and all individuals who are impacted by the condition.

MOLECULAR TRANSDUCERS OF PHYSICAL ACTIVITY IN HUMANS CONSORTIUM (MOTRPAC)

Program Overview

We know that physical activity promotes health in a variety of ways and benefits many different organs of the body. However, very little is known about the specific biological molecules that confer the benefits of physical activity. Additionally, although it is likely that individual differences play a role in response to physical activity, researchers and clinicians do not understand these differences and therefore cannot develop personalized exercise recommendations. The NIH Common Fund is in a unique position to bring together scientists from diverse fields, such as exercise physiology, genetics, biochemistry, and computational biology, to shed light on how physical activity benefits health and how individuals differ in their response to exercise.

The Common Fund's Molecular Transducers of Physical Activity in Humans Consortium (MoTrPAC)¹⁴⁷ aims to uncover, at the molecular level, how exercise improves and maintains the health of the body's tissues and organs. Through a 10-year, \$261 million investment, MoTrPAC will transform our understanding of the health benefits of physical activity by measuring the molecular and physiological changes that occur following endurance and resistance training in hundreds of adults and children so that individual variability in response can be assessed. Tracking the impact of exercise on biological molecules through time will help MoTrPAC researchers create a map of molecular changes in the body. In parallel, extensive preclinical studies in rats are allowing many additional tissue types to be explored, substantially increasing the impact of the program. Researchers will use the molecular map produced by MoTrPAC to better understand how exercise affects diverse people of different ages, sexes, body compositions, and fitness levels. In the future, the map also may enable clinicians to make more tailored recommendations to patients when using exercise as an intervention to improve health.

MoTrPAC – An NIH-wide Collaboration

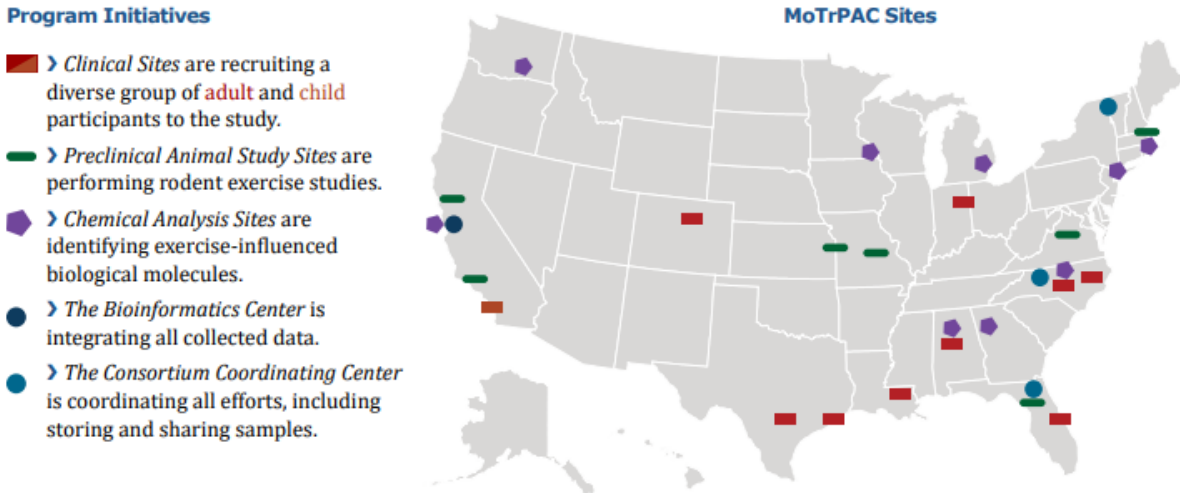
As a Common Fund program, MoTrPAC is managed as a collaboration between the Office of Strategic Coordination (OSC), in the Office of the Director (OD), and many NIH Institutes, Centers, and Offices (ICOs) that have an interest in research on physical activity. MoTrPAC is managed by a cross-NIH Working Group led by OSC, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), and the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK), with representatives from an additional 11 ICOs across NIH.

Current Status of MoTrPAC

MoTrPAC is the largest study of its kind. To undertake this unprecedented study, MoTrPAC supports several coordinated initiatives: 1) adult and pediatric physical activity studies; 2) complementary animal model physical activity studies analyzing both endurance/aerobic exercise and resistance/weight lifting exercise; 3) analysis of biological samples to identify exercise-influenced biological molecules; 4) integration and dissemination of data; and 5) study coordination, including storing and sharing biological samples. The seven Clinical Sites are

¹⁴⁷ commonfund.nih.gov/MolecularTransducers

recruiting a diverse group of adults spanning a wide range of ages (six sites), as well as pediatric participants (one site).



MoTrPAC Adult Studies

Adult exercise studies are asking “What is the molecular profile of adults who exercise regularly?” and “What is the molecular profile of sedentary adults before and after exercise training?” To answer these questions, blood, muscle, and adipose tissue samples are collected from sedentary and highly active adult volunteers performing resistance or aerobic endurance exercises. To investigate the molecular effects of starting a new exercise regimen, sedentary individuals are evaluated before and after 12 weeks of supervised training.

MoTrPAC Pediatric Studies

Pediatric exercise studies are investigating the molecular profiles of children who currently engage in low or high levels of physical activity. In this study, blood samples are collected from sedentary and highly active pediatric volunteers performing aerobic exercises. This study will help identify the molecular differences between children who are highly physically active and those who are not and, in combination with the data generated by MoTrPAC adult studies, will also reveal differences in the response to physical activity between children and adults.

MoTrPAC Preclinical (Animal) Studies

Parallel studies in animals will allow analysis of additional tissue types beyond what is available from humans. These studies are investigating molecular profiles before and after a single bout of endurance exercise and molecular profiles before and after endurance training, in both young (6 months) and old (18 months) rats. Animal studies allow collection and analysis of a wide variety of tissue samples, with sources including adipose tissue, adrenal glands, aorta, bone, colon, several parts of the brain, gonads, heart, kidney, liver, lung, small intestine, and spleen. Additionally, a resistance training protocol has now been developed for the animal studies and could be used in future studies.

Recent Accomplishments of MoTrPAC

While human exercise studies are underway, preliminary results from the animal studies have begun to emerge. In an analysis of animals undergoing 8 weeks of endurance training, researchers identified over 35,000 molecular changes in response to exercise. These changes cluster into networks and pathways that influence a variety of biological functions, such as metabolism, inflammation, and nutrient absorption. Interestingly, approximately half of these clusters have different trajectories in males and females, and many show tissue-specific variation. For example, although both male and female animals demonstrate cardiovascular improvements after exercise training, only males demonstrated reduced whole-body fat content (adiposity), fat cell (adipocyte) size, and abundance of a type of fat found in the blood (triglycerides). Novel findings from the animal studies suggest additional effects of exercise on different organs, including the discovery that exercise increases anti-inflammatory proteins in the kidney and elicits production of bile acid and cholesterol in the liver that could impact digestive health.

Next Steps and Goals

MoTrPAC is continuing to support human and animal physical activity studies and the associated molecular analysis of samples. Although the COVID-19 pandemic paused human studies, all clinical sites have resumed recruitment under enhanced safety protocols, and human samples from pre-COVID-19 cohorts are now undergoing analysis. MoTrPAC will deliver a data-rich map of molecular changes in response to exercise across a variety of tissues by the end of the program in FY 2026. This resource, which will be openly shared with the broad biomedical research community, is expected to stimulate investigator-initiated research that will continue long beyond the lifetime of the MoTrPAC program. By delivering the largest and most detailed data set of its kind, MoTrPAC will provide a key foundational resource to generate new insights into the functional effects of molecules influenced by physical activity, individual differences in the response to exercise, and how tailored exercise recommendations can improve health for all people.

NIH CLIMATE CHANGE AND HEALTH (CCH) INITIATIVE

Program Overview

Climate change elevates threats to human health across a wide range of illnesses, including respiratory diseases, cancers, cardiovascular diseases, mental illnesses and neuropsychiatric disorders, reproductive outcomes, and atypical development. Climate change alters environmental and social stressors that affect well-being, thereby increasing the risk of foodborne diseases and malnutrition, vector-borne and zoonotic diseases, waterborne diseases, and extreme temperature- and weather-related morbidities and mortality. Of particular concern is the disproportionate impact of climate change on communities already experiencing social and environmental inequalities where they live, work, learn, and play, both in the United States and globally. Certain populations are also disproportionately at risk of climate change effects, including children, older adults, pregnant women, persons with disabilities, persons experiencing homelessness, those with mental illness, and others. In the global community, these same populations, as well as all those living in extreme poverty with limited access to health and economic services, experience a higher risk of climate change consequences for health.

Leaders at NIH recognize the urgent need for a concerted, collective effort across NIH Institutes, Centers, and Offices (ICOs) to advance understanding of impacts of climate change on health, identify health co-benefits of reducing exposures to direct and downstream climate events, and provide opportunities to develop and test interventions that can increase the long-term resilience of communities to the effects of climate change. NIH funding support for climate change and health research has historically been concentrated in a few Institutes. However, more than half of the ICOs have funded at least one or more—in several cases, significantly more—relevant projects. The level of funding has increased in the last few years and received a significant boost this year with \$40.0 million in new funding provided for climate change and health research in FY 2023 appropriations.

Funding level alone, however, belies the full NIH contribution to the evolution of the understanding of climate change and health. For decades NIH has provided leadership on the issue of impacts of climate change on health through engagement of its scientists at national and global levels, beginning with the first Intergovernmental Panel on Climate Change (IPCC). In 2010, NIH co-led with the Centers for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA), and National Oceanic and Atmospheric Administration the creation of the first federal climate change and health research needs assessment, titled “A Human Health Perspective on Climate Change.”¹⁴⁸ Over more than a decade of engagement with the U.S. Global Climate Change Research Program, NIH has contributed strong leadership to influential outcomes including the Interagency Crosscutting Group on Human Health and health-focused chapters of multiple National Climate Assessments.

¹⁴⁸ Portier CJ, Thigpen Tart K, Carter SR, Dilworth CH, Grambsch AE, Gohlke J, Hess J, Howard SN, Luber G, Lutz JT, Maslak T, Prudent N, Radtke M, Rosenthal JP, Rowles T, Sandifer PA, Scheraga J, Schramm PJ, Strickman D, Trtanj JM, Whung P-Y. 2010. A Human Health Perspective On Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change. Research Triangle Park, NC:Environmental Health Perspectives/National Institute of Environmental Health Sciences. doi:10.1289/ehp.1002272 Available: www.niehs.nih.gov/climatereport

In 2021, in response to President Biden’s Executive Order 14008: Tackling the Climate Crisis at Home and Abroad, NIH committed to developing an NIH-wide Climate Change and Health (CCH) Initiative to grow the NIH research portfolio and investigator community to address these urgent issues.¹⁴⁹ An Executive Committee comprised of directors from seven NIH Institutes and Centers (ICs) was established to lead the Initiative. These ICs include:

- the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD);
- Fogarty International Center (FIC);
- National Heart, Lung, and Blood Institute (NHLBI);
- National Institute of Environmental Health Sciences (NIEHS);
- National Institute of Mental Health (NIMH);
- National Institute on Minority Health and Health Disparities (NIMHD); and
- the National Institute of Nursing Research (NINR).

Staff of the National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), and National Institute of Aging (NIA) also joined the Initiative through its Steering Committee and Planning and Implementation Team (PIT), which help to guide and execute the Initiative’s Strategic Framework. An NIH Climate Change and Health Working Group comprises more than 140 NIH scientific and programmatic staff across 24 ICs and meets regularly to exchange information on climate change and health topics, host presentations from CCH partners to increase awareness of the field, and provide input on opportunities for member engagement in the Initiative’s work plan.

Goals and Objectives

Members of the CCH Initiative have worked steadily since its establishment to create an infrastructure for the program and begin to implement projects and proposals in support of its goals. The NIH CCH Initiative Strategic Framework¹⁵⁰ was developed with input from a range of stakeholders, including the larger scientific community, clinicians, advocates, and policymakers. It was published in February 2022.

This Strategic Framework outlines the goals of the Initiative, which are to reduce health threats across the lifespan and build health resilience among individuals, communities, and nations around the world, especially among those at highest risk of adverse health impacts. The framework’s four core elements are depicted in Figure 1, and include: health effects research, health equity, intervention science, and training and capacity building. Objectives described in the framework are to:

- **Identify risks and optimize benefits** to the health of individuals, communities, and populations from climate related factors and actions to mitigate or adapt to climate change.

¹⁴⁹ Woychik RP, Bianchi DW, Gibbons GH, Glass RI, Gordon JA, Pérez-Stable EJ, Zenk SN. The NIH Climate Change and Health Initiative and Strategic Framework: addressing the threat of climate change to health. *Lancet*. 2022 Nov 26;400(10366):1831-1833. doi: 10.1016/S0140-6736(22)02163-8. Epub 2022 Nov 4. PMID: 36343650.

¹⁵⁰ National Institutes of Health. NIH Climate Change and Health Strategic Framework. Research Triangle Park, NC: National Institutes of Health; 2022 Feb. 11 p.

- Develop the necessary **research infrastructure and workforce** to enable the generation of timely and relevant knowledge, drawing from the full spectrum of biomedical disciplines.
- **Leverage partnerships** with other scientific and social disciplines and organizations to achieve the most impactful results.
- **Innovate** across the research translation continuum to ensure findings are credible, accessible, and actionable for achieving these goals.

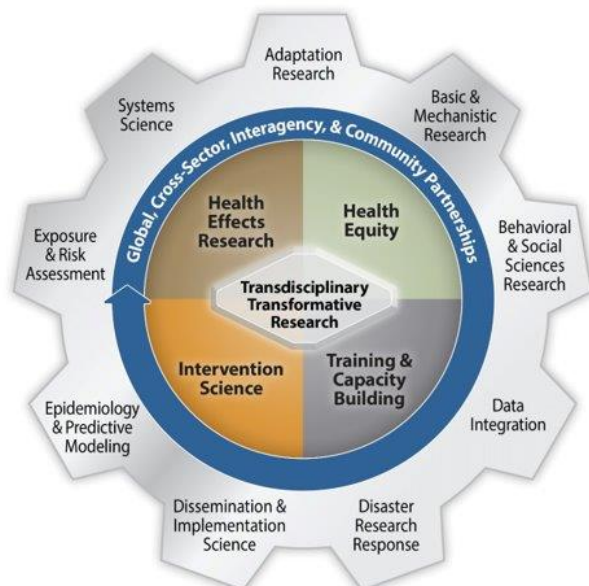


FIGURE 1. NIH CLIMATE CHANGE AND HEALTH STRATEGIC FRAMEWORK

The NIH CCH Executive Committee and Working Group have led the development of new funding opportunities within existing budgets, including:

- **Alliance for Community Engagement-Climate and Health¹⁵¹ (ACE-CH)**. The ACE-CH seeks to empower communities across the United States to participate in community-engaged research, assist to understand factors that contribute to health inequities related to climate change, and develop solutions through health equity. The ACE-CH will collaborate with an NIH-funded Research Coordinating Center (RCC) being established in parallel to manage and support current and future climate change and health research and capacity building efforts. Together, they will help to support the development of an NIH-wide Climate and Health Community of Practice. NHLBI will take the lead for administering the ACE-CH, which has been developed with input and funding support from across NIH.
- **NIH-wide Notices of Special Interest (NOSIs)** (NOT-ES-22-006, NOT-ES-22-009, NOT-ES-22-010) were released in 2022 to encourage investigator-initiated research related to the scientific domains outlined in the strategic framework. ICOs across NIH are participating in these announcements.

¹⁵¹ Research Opportunity Announcement - Alliance for Community Engagement (nih.gov)

- **Climate Change and Health Research Coordinating Center¹⁵²** (RFA-ES-22-003). The Research Coordinating Center (RCC) will support the progress of the NIH CCH Community of Practice by creating opportunities for networking and collaborations among NIH-supported CCH scientists. Working groups led by the RCC will explore contemporary themes in CCH in in-depth, meaningful ways to support future directions of the program.

Highlights of NIH-supported CCH Research Projects

Highlights of ongoing research are below. In addition, NIH grantees have published 43 climate and health related manuscripts since April 2022.

- *Training in Interventions to Improve Outcomes in Chronic Conditions (NINR)*: This research addresses farmworkers' vulnerability to heat hazards and provides evidence-based tools and interventions to maintain worker safety during extreme conditions.
- *Effects of Agricultural Expansion and Intensification on Infections, 2015-2021 (FIC)*: This research demonstrated that temperature increases from climate change will increase the risk of schistosomiasis (river blindness) in parts of the world. These findings can help inform and improve control measures used to reduce the spread of the disease.
- *Assessing and Addressing Heat-Health Vulnerability in Ahmedabad, India, 2015-2017 (FIC)*: Investigators learned that despite substantial risks to heat-related illnesses, health workers did not routinely consider heat effects when making diagnoses. Health workers may have attributed symptoms of heat stroke — such as high fever and altered mental state — to malaria, which is common in the area. Training sessions were held to sensitize health professionals to the signs of heat-related illnesses and best practices for treatment.
- *Research on health risks and resilience in Puerto Rico and the U.S. Virgin Islands after the 2019 Hurricanes Irma and Maria (NIMHD)*: This time-sensitive research looked at how the events impacted social determinants of health in communities with health disparities for several diseases. Additionally, over the past 10 years, NIEHS's grant program has funded rapid response research across the United States on climate-related disasters including hurricanes, wildfires, and floods.
- *Wildfire Smoke (NIMHD, NIEHS)*: In Northern Arizona, researchers are incorporating community input while developing a methodology for exploring health inequities tied to wildfire smoke in Native American populations. (NIMHD) Scientists in California are studying adverse impacts of wildfire smoke on pregnant women and their children (NIEHS), as well as characterizing the chemical composition of air pollution from wildfires in rural and urban settings (NIEHS).
- *Pediatric Health and Extreme Weather - Health Effects of Ambient Temperature (NIEHS)*: Children's vulnerability to heat effects varies by age in ways that are important for public health messaging. Other heat outcomes, such as injury, are an important gap in existing research, which may be missing the bulk of heat-health burden for children.
- *Investigation of Neighborhood Greenspace as Protection Against Development of Childhood Asthma (NIEHS)*: Exposure to vegetated land cover, or "greenspace," particularly in early life, may prevent development of asthma. This study will look at

¹⁵² RFA-ES-22-003: Research Coordinating Center to Support Climate Change and Health Community of Practice (U24 Clinical Trial Not Allowed) (nih.gov)

neighborhood greenspace and asthma incidence in a longitudinal cohort of over 170,000 children living in the Philadelphia metropolitan region.

- *Influence of Temperature on Malaria Transmission and Prospective Vector Control (NIAID)*: Knowing that not all malaria-transmitting Anopheles species feed at night and that night-feeding Anopheles can shift their feeding behavior in response to bed nets, the results show differences in vector competence resulting from biting time with implications for malaria transmission. Shifts towards morning feeding might have little impact as these mosquitoes may have limited capacity to transmit malaria. However, mosquitoes feeding in the early evening could improve vector efficiency.

Partnerships

The NIH CCH Initiative has worked to develop partnerships across federal agencies, non-profits, and academic organizations. Examples of federal partners include HHS (Office of Climate Change and Health Equity Office, Office of the Assistant Secretary for Policy and Evaluation [ASPE], Administration for Strategic Preparedness and Response, Administration for Health Research and Quality [AHRQ], Centers for Disease Control and Prevention, and other operating divisions), National Oceanic and Atmospheric Administration, National Aeronautics and Space Administration, National Science Foundation, and U.S. Global Change Research Program. In a newly funded collaborative project, NIH staff from three ICOs will work with AHRQ and ASPE to develop data integration resources, tools, and systems to support patient and population-based climate change and human health research, specifically around a use case related to wildfires.

Next Steps

The CCH Initiative will expand outreach and engagement at global and domestic conferences to increase awareness of funding and partnership opportunities and build the NIH climate change and health community of practice. Other efforts will target the development of government, academic, and healthcare partnerships with key organizations including the International Society of Environmental Epidemiologists, the American Public Health Association, the American Geophysical Union, the Wellcome Trust, and the Rockefeller Foundation.

MAJOR CONTRIBUTIONS FROM INSTITUTES AND CENTERS WITH BUDGETS LESS THAN \$1 BILLION

Program Overview

All 27 NIH Institutes and Centers (ICs) support research or other activities to achieve the overall NIH mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The breadth and diversity of IC missions enables all ICs to make very significant contributions to improving human health. This section highlights some of the efforts of NIH ICs with budgets under \$1 billion, such as in the areas of chronic pain, whole person health, new innovations, research to benefit everyone, biomedical research stewardship, and capacity building and infrastructure. The ICs included in this section are:

- Fogarty International Center (FIC)
- National Center for Advancing Translational Sciences (NCATS)
- National Center for Complementary and Integrative Health (NCCIH)
- National Eye Institute (NEI)
- National Human Genome Research Institute (NHGRI)
- National Institute on Alcohol Effects and Alcohol-Associated Disorders (NIAAA)¹⁵³
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute on Minority Health and Health Disparities (NIMHD)
- National Institute of Nursing Research (NINR)
- National Library of Medicine (NLM)

Chronic Pain

Nearly 20 percent of United States adults report having pain every day for the previous 3 months. Chronic pain permeates every aspect of a person's life making it difficult to complete day-to-day tasks. Individuals with severe pain have worse health, use more health care, and have more disability than individuals with less severe or no pain. While the National Institute on Neurological Disorders and Stroke (NINDS) has a lead role in supporting research to address chronic pain, many other NIH ICs play a critical role in developing approaches to treating pain.

The NIH Pain Research Center and Pain Management Collaboratory

NCCIH supports several initiatives to address chronic pain. The NCCIH-led Intramural Research Program Pain Research Center, located within the NIH Clinical Center in Bethesda, MD, is a multidisciplinary, trans-NIH initiative that is working to identify specific pain mechanisms, determine the efficacy of non-opioid treatments, and predict individual patient response to therapies and outcomes. The overarching mission of the Pain Research Center is to better understand diverse pain states in order to recommend personalized therapies to better

¹⁵³ The FY 2024 Budget proposes that the National Institute on Alcohol Abuse and Alcoholism be renamed the "National Institute on Alcohol Effects and Alcohol-Associated Disorders."

manage or prevent the development of chronic pain and opioid abuse.¹⁵⁴ NCCIH also supports the Pain Management Collaboratory (PMC), a joint effort between the Department of Defense, Department of Veterans Affairs (VA), and NIH (led by NCCIH). It is composed of 11 large-scale, multi-site, pragmatic clinical trials that are studying nonpharmacological approaches for the management of pain and common co-occurring conditions in Military and Veterans healthcare systems and are supported by a central Coordinating Center.¹⁵⁵ These studies involve 42 Military Health Service and VA facilities with over 8,200 participants enrolled. The PMC mission to improve the capacity, tools, and skills available to health care providers to provide timely, equitable and cost-effective integrated, patient-centered, multimodal and interdisciplinary pain care that incorporates evidence-based nonpharmacological approaches to pain management while reducing the reliance on opioid and other potentially harmful medications and invasive procedures.

Osteoarthritis Research

A study supported by NIBIB and NIAMS aims to address osteoarthritis, a challenging problem in aging adults that causes pain and discomfort. As people age, cartilage deteriorates; however, regenerating native cartilage has proven to be difficult, and surgical treatment options can be costly, time-consuming, and unreliable. Researchers have developed a small, biodegradable film with piezoelectric properties that stimulates new cartilage growth. Piezoelectric materials generate electrical signals from pressure or vibrations to the material. The film was evaluated in an osteoarthritis model by implanting the film in rabbits at sites of damaged knee joints.¹⁵⁶ Rabbits that were treated with the piezoelectric film and exercised developed a new layer of cartilage that looked like native tissue which was not seen in untreated rabbits or those that were treated but did not exercise. This biomaterial is easy to scale and manufacture and next steps will be to test in larger animal models and humans.

The Osteoarthritis Initiative is a multicenter, longitudinal, prospective observational study to follow people who either have or are at risk for developing knee osteoarthritis, currently in its 14th year of follow up. This Initiative is a public-private partnership between NIH and private industry that seeks to develop a public-domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression.¹⁵⁷ Within NIH, this effort is led by NIAMS with additional support from NCCIH, NIMHD, NIDCR, and NIBIB, among others. This groundbreaking study is advancing our understanding of how modifiable and non-modifiable risk factors are linked to development and worsening of knee osteoarthritis. Such findings may, in turn, lead to improved strategies for prevention of disease and identification of novel treatment targets, which could result in prevention of later-life disability in individuals with knee osteoarthritis.

Alcohol Use Disorder and Chronic Pain

There is a complex relationship between alcohol misuse and pain. While drinking can help relieve pain in the short term, over time, heavy drinking may cause or exacerbate chronic pain. Withdrawal from alcohol is associated with increased pain and may motivate individuals to drink

¹⁵⁴ www.nccih.nih.gov/research/nih-pain-research-center

¹⁵⁵ painmanagementcollaboratory.org/

¹⁵⁶ pubmed.ncbi.nlm.nih.gov/35020409/

¹⁵⁷ www.niams.nih.gov/grants-funding/funded-research/osteoarthritis-initiative

for pain relief. Heavy drinking to relieve pain can thus drive the development of alcohol use disorder (AUD), and conversely, AUD-related changes in how the brain processes pain may drive the development of chronic pain conditions. NIAAA-funded research is focused on enhancing our understanding of the complex relationship between alcohol and pain, including the interactions between alcohol and opioids in the development and perpetuation of chronic pain.¹⁵⁸

Orofacial Pain

Orofacial pain affects 5 to 12 percent of the population and can have long-reaching effects on the afflicted individual. NIDCR has a robust portfolio in understanding and treating orofacial pain. The Neuroscience of Orofacial Pain and Temporomandibular Disorders Program within NIDCR supports basic, translational, and clinical research on orofacial pain and neuropathies, temporomandibular joint and muscle disorders (TMJD), development of biomarkers for diagnostics and prognostics, and development of therapeutics. Addressing orofacial pain remains a top priority for the Institute. The NIDCR Strategic Plan (2021-2026), “Science: Advancing Oral Health for All,” includes an objective to stimulate and sustain collaborative alliances across the research spectrum to prevent, modulate, and treat dental pain and orofacial neuropathies.¹⁵⁹

NIH HEAL Initiative®

Many NIH ICs, including NIAMS and NCCIH (each received an additional \$5 million in the FY 2023 appropriations omnibus), NIDCR, NIAAA, NCATS, and NINR, support the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®. A major component of the HEAL Initiative® is enhancing pain management including understanding the biological underpinning of chronic pain, developing and advancing non-addictive treatments for pain, and establishing best practices for managing acute and chronic pain. One program supported by the HEAL Initiative® is the Back Pain Consortium Research Program (BACPAC). BACPAC, managed by NIAMS, is a translational, patient-centered effort to address the need for effective and personalized therapies for chronic low back pain. It is examining biomedical mechanisms within a biopsychosocial context by using interdisciplinary methods and exploring innovative technologies.¹⁶⁰ A new program on myofascial pain led by NCCIH aims to develop new technologies to quantify abnormalities of myofascial tissues that likely underlie a wide variety of common musculoskeletal pain conditions including back, neck and shoulder pain, as well as temporomandibular pain and headache.¹⁶¹

Whole Person Health

Whole person health involves looking at the whole person—not just separate organs or body systems—and considering multiple factors that promote either health or disease. It means helping and empowering individuals, families, communities, and populations to improve their health in multiple interconnected biological, behavioral, social, and environmental areas. Instead of treating a specific disease, whole person health focuses on restoring health, promoting

¹⁵⁸ niaaa.scienceblog.com/231/the-complex-relationship-between-alcohol-and-pain/

¹⁵⁹ www.nidcr.nih.gov/sites/default/files/2022-01/NIDCR-Strategic-Plan-2021-2026.pdf

¹⁶⁰ heal.nih.gov/research/clinical-research/back-pain

¹⁶¹ www.nccih.nih.gov/about/offices/od/director/past-messages/entering-a-new-chapter-in-understanding-myofascial-pain

resilience, and preventing diseases across a lifespan.¹⁶² In September 2021, NCCIH held a workshop titled “Methodological Approaches for Whole Person Research Workshop.” The goal of the workshop was to discuss examples of research and explore methodologies potentially appropriate for whole person research. Other ICs collaborating on the workshop include, but are not limited to, NIMHD, NINR, NIBIB, NIEHS, NIDCR, and FIC. Further exemplifying the significance of whole person health, NCCIH’s strategic plan for fiscal years 2021-2025¹⁶³ expanded the definition of integrative health to include whole person health, and NCCIH has indicated research on whole person health is a top priority during this time. Recognizing a greater understanding of whole person health can influence research programs across the agency, other ICs, such as NIAMS, are also committed to the issue.

The environment and environmental exposures have a strong influence on whole person health. Measuring the totality of exposures a person experiences from conception to death along with the associated biological response is referred to as the exposome, a concept that has become increasingly important for discovering environmental causes of disease. One major initiative related to this topic is “Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome.” This initiative is led by NIEHS with support from NIAMS, NINR, NIMHD, and NHGRI, among other ICs and HHS operating divisions. This effort involves expanding and catalyzing the emerging exposomics scientific community to work collaboratively to discover, determine, and design the best ways to operationalize exposomics toward the goal of precision environmental health. NIEHS is working across NIH and multiple scientific disciplines to investigate, identify, and foster key aspects of this critical work, including:

- Tools, Technologies, and Methodologies (measuring the exposome);
- Biological Responses and Impact on Health and Disease, (integrating multi-omics with biomarkers of exposure, response, effect, susceptibility, vulnerability, and resilience);
- Future of Clinical & Prevention Trials, Cohorts and Epidemiology (designing studies, refining methodology, determining statistical power and pooling samples);
- Social and Societal Impacts (integrating social determinants of health, diversity, health disparities, privacy, etc.); and
- Data Infrastructure and Data Analytics (sharing data and harmonizing it; analyzing, interpreting, visualizing, and modeling data).

New Innovations

Remaining at the forefront of scientific discovery is paramount for advancing human health. Most NIH ICs are investing in developing novel technologies that have the potential to change how human diseases are diagnosed or treated. This section highlights programs and initiatives to advance research on artificial intelligence (AI) and machine learning (ML), genetics and genomics, neuroscience, and mobile health.

Artificial Intelligence and Machine Learning

AI and ML have the potential to transform research and clinical care. Multiple ICs, including but not limited to NLM, NEI, NHGRI, NCCIH, NCATS, and NIBIB, are actively involved in supporting AI research through the NIH Common Fund’s Bridge2AI program.¹⁶⁴ The goal of

¹⁶² www.nccih.nih.gov/health/whole-person-health-what-you-need-to-know

¹⁶³ www.nccih.nih.gov/about/nccih-strategic-plan-2021-2025

¹⁶⁴ commonfund.nih.gov/bridge2ai

the program is to tap the potential of AI for revolutionizing biomedical discovery, increasing our understanding of human health, and improving the practice of medicine. The program is assembling team members from diverse disciplines and backgrounds to generate tools, resources, and richly detailed data that are responsive to AI approaches. At the same time, the program will ensure its tools and data do not perpetuate inequities or ethical problems that may occur during data collection and analysis. Through extensive collaboration across projects, Bridge2AI researchers will create guidance and standards for the development of ethically sourced, state-of-the-art, AI-ready data sets that have the potential to help solve some of the most pressing challenges in human health — such as uncovering how genetic, behavioral, and environmental factors influence a person’s physical condition throughout their life.

The AI/ML field currently lacks diversity in its researchers and in data, including electronic health record (EHR) data. These gaps pose a risk of creating and continuing harmful biases in how AI/ML is used, how algorithms are developed and trained, and how findings are interpreted. Critically, these gaps can lead to continued health disparities and inequities for underrepresented communities. Underrepresented communities have untapped potential to contribute new expertise, data, recruitment strategies, and cutting-edge science to the AI/ML field. To close the gaps in the field and to better engage underrepresented communities, NIH has launched the Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) program.¹⁶⁵ Several NIH ICs, including NIMHD and NEI, provide funding for or otherwise participate in the AIM-AHEAD program. This program seeks to increase the participation and representation of the researchers and communities that are currently underrepresented in AI/ML modeling and applications through mutually beneficial partnerships.

The NIH Common Fund’s Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa) program supports data science-related research, including AI and ML. This initiative is led by FIC, NIBIB, NLM, and NIMH with the involvement of many other ICs interested in leveraging these tools to address some of Africa’s most pressing public health problems through a robust ecosystem of new partners from academic, government, and private sectors.

In addition, NIH investigators and extramurally-funded researchers are advancing development and use of AI/ML methods and approaches for discovery and health. For example, NLM investigators have collaborated with the National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), and the National Cancer Institute (NCI) to develop AI algorithms that analyze imaging and non-imaging data in support of HIV, tuberculosis, and sickle cell disease screening; and are designing a novel pipeline for automated localization of possible lesions in dynamic cervical imaging to support cancer research. NLM-funded extramural researchers have applied artificial intelligence and machine learning to predict treatment effectiveness and inform personalized medicine approaches and have developed new AI methods for image and biomedical data analysis.

¹⁶⁵ datascience.nih.gov/artificial-intelligence/aim-ahead

Genetics and Genomics

Understanding the human genome and learning how it can be manipulated is a promising approach for treating a number of diseases and conditions. This section highlights efforts being undertaken by several ICs to better understanding human genomics and to test potential approaches to advance gene therapies and to utilize the power of genomics to improve human health.

New technologies – including the use of viruses to deliver genes to cells that need properly functioning genes – are making gene therapy an increasingly attractive treatment option for individuals with rare genetic diseases. Yet, thousands of these disorders are so rare that companies might be reluctant or unable to invest the years of research and the millions of dollars needed to develop, test, and bring a gene therapy for a very rare disease to market. To address the unmet need for more efficient gene therapy clinical development, NCATS, leading a partnership with NHGRI, NINDS, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), launched the Platform Vector Gene Therapy (PaVe-GT) pilot project in February 2019.¹⁶⁶ The goal of this project is to test the impact of using the same gene delivery system and manufacturing methods in multiple rare disease gene therapy clinical trials. A related example in collaboration with the Foundation for NIH, NCATS, NHGRI, NICHD, NEI, NIDCD, NIDCR, and NIAMS, is the Accelerating Medicines Partnership’s Bespoke Gene Therapy Consortium.¹⁶⁷

The Clinical Genome (ClinGen) Resource, which is primarily funded by NHGRI, is an effort dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.¹⁶⁸ The key goals of the program are aggregating and sharing relevant data about genes; curating a public resource of clinically-relevant genes and variants through the ongoing evolution of data standards; broadly disseminating tools, standards, and expert assertions; and continually evaluating and improving ClinGen resources.

Other NIH genetic data resources, such as the Gene Expression Omnibus (GEO),¹⁶⁹ an open-access repository managed by NLM, support sharing of research outputs for use in subsequent studies. GEO stores gene expression and epigenetic data that describe how different biological conditions or environment can impact biological processes. GEO datasets represent a rich data source which may be further analyzed, mined, and aggregated by interested parties. Researchers use GEO data to extract meaningful information and make new discoveries that accelerate biological and health sciences.

Neuroscience

To develop technologies that treat nervous system disorders, NIBIB has partnered with the NIH Blueprint for Neuroscience consortium of institutes to launch the Blueprint MedTech program. This program is designed to overcome barriers to the commercialization of groundbreaking neurotherapeutic devices. The program will provide support to develop and de-risk technologies

¹⁶⁶ ncats.nih.gov/expertise/pave-gt-pilot-project

¹⁶⁷ fnih.org/our-programs/AMP/BGTC

¹⁶⁸ clinicalgenome.org/about/

¹⁶⁹ www.ncbi.nlm.nih.gov/geo/

to the point where additional investments are warranted from industry partners, investors, and government. One-year pilot project awards of \$100,000 each, along with technical support, have been made. One project is developing a novel method to optimize neurostimulation therapy for treatment of people with mental disorders, including severe depression and anxiety. The system will allow clinicians to select parameters for deep brain stimulation that target specific brain circuits identified as areas of dysfunction and restore patterns of neural activity that are necessary for healthy cognitive function and control.

Mobile Health in LMICs

On behalf of NIH, FIC has coordinated the Mobile Health (mHealth): Technology and Outcomes in Low- and Middle-Income Countries program since 2014.¹⁷⁰ In total, 10 NIH ICOs participate in the program including NEI, NIBIB, NIDCD, NIEHS, and FIC. The purpose of the program is to encourage exploratory/developmental research applications that study the development, validation, feasibility, and effectiveness of innovative mHealth interventions or tools specifically suited for low- and middle-income countries (LMICs) that utilize new or emerging technology, platforms, systems, or analytics. The overall goal of the program is to catalyze innovation through multidisciplinary research that addresses global health problems, develop an evidence base for the use of mHealth technology to improve clinical and public health outcomes, and strengthen mHealth research capacity in LMICs.

Research to Benefit Everyone

The entirety of NIH is committed to a scientific enterprise in which everyone can benefit, and everyone can participate. This section highlights just a few of NIH's efforts to minimize health disparities, research on social determinants of health, and efforts to diagnose and treat rare diseases.

Health Disparities

NIMHD is co-leading two NIH-wide research initiatives related to COVID-19. The RADx® Underserved Populations (RADx-UP) initiative supports a consortium of more than 137 research projects to examine testing as an intervention to mitigate disparities in COVID-19 morbidity and mortality for individuals from populations and communities disproportionately affected by the pandemic. The RADx-UP initiative includes participation from 16 ICs along with the NIH Office of the Director. This initiative resulted in a recent peer-reviewed special issue of the *American Journal of Public Health* highlighting interventions to promote testing for SARS-CoV-2 and studies on the social, behavioral, and ethical issues of the pandemic in underserved populations.¹⁷¹ The publication will inform and prioritize key strategies for future public health responses among communities experiencing health disparities. NIMHD has awarded 33 RADx-UP grants that will enable a targeted public health response to COVID-19 through a variety of testing methods among specific populations, areas, and settings. The results will support evidence-based approaches to address disparities in COVID-19 diagnostic testing uptake and effectiveness among populations disproportionately affected by COVID-19. In addition, NIMHD houses and manages the RADx-UP coordination and data collection center, a

¹⁷⁰ www.fic.nih.gov/Programs/Pages/mhealth.aspx

¹⁷¹ pubmed.ncbi.nlm.nih.gov/36265091/; pubmed.ncbi.nlm.nih.gov/36265090/; pubmed.ncbi.nlm.nih.gov/36194852/

centralized hub that provides organizational and analytical infrastructure and expertise, facilitates data integration and analysis, and coordinates across RADx-UP projects.¹⁷²

NIMHD and NHLBI co-lead the Community Engagement Alliance Against COVID-19 Disparities (CEAL) initiative. The initiative promotes diversity and inclusion in COVID-19 prevention, vaccine, and therapeutic trials and conducts urgent community-engaged research and outreach focused on COVID-19 awareness and education. The CEAL teams have been actively working in regions around the United States and its territories to build trusting relationships and share science-based information with the communities most impacted by the COVID-19 pandemic. CEAL partners have developed educational tools, factual materials, and resources in different languages such as Spanish, Chinese, and Korean to broaden CEAL's reach into the affected communities. The CEAL initiative is addressing misinformation and has recently released a guide for healthcare professionals on adapting fact-based information to the needs of communities.¹⁷³ To further its work, the CEAL initiative started a new network for community-engaged primary care research that will: 1) support research on awareness, education, and mistrust around COVID-19, as well as testing and vaccine acceptance; and 2) promote inclusive participation of underserved racial and ethnic minority and rural populations in clinical research.¹⁷⁴

NINR is committed to supporting research that optimizes health and advances health equity. In fact, 34 percent of its budget in FY 2021 and FY 2022 funded research that aims to eliminate health disparities. Focused on identifying solutions, NINR is leading a bold initiative to reduce disparities in severe maternal morbidity and mortality. The Advancing Integrated Models of Care (AIM)¹⁷⁵ to Improve Maternal Health Outcomes among Women Who Experience Persistent Disparities initiative supports intervention research to develop, implement, and evaluate integrated models of supportive care that address structural inequities to prevent adverse maternal health outcomes.

Finally, NIAMS convened a 2-day workshop on health disparities in osteoarthritis in July 2022. The workshop was co-sponsored by NIMHD and the National Institute on Aging. The workshop brought together osteoarthritis investigators with others who have health disparities research expertise to exchange ideas regarding how and why disparities in osteoarthritis treatment outcomes and access to care exist and how they can be addressed. Panelists and speakers highlighted mechanisms through which integration of behavioral and biomedical science can lead to better health in osteoarthritis. Participants were also invited to attend breakout sessions to exchange ideas on how to address and improve issues related to health disparities in osteoarthritis.

Social Determinants of Health

Social determinants of health are the conditions in which people are born, live, learn, work, play, and age that affect health and quality of life for individuals and populations. Social determinants of health include community conditions (e.g., job opportunities, school quality, transportation

¹⁷² nimhd.nih.gov/programs/extramural/investigator-initiated-research/emergency-awards-RADx-UP.html

¹⁷³ covid19community.nih.gov/community-engagement-teams/ceal-teams-resources

¹⁷⁴ covid19community.nih.gov/Network-for-Community-Engaged-Primary-Care-Research

¹⁷⁵ grants.nih.gov/grants/guide/rfa-files/RFA-NR-22-002.html

systems, social cohesion, and green space) and individual and family social and economic circumstances (e.g., income, educational attainment, social isolation, traumatic experiences, nutrition security, and housing) that can have positive or negative influences on health. As co-chair of a new NIH-wide social determinants of health research coordinating committee, NINR, along with NIMHD and the Office of Behavioral and Social Sciences Research, is leading an exciting initiative to accelerate this area of research across NIH – across diseases and conditions, populations, and the life course. The committee has been joined by 15 other NIH Institutes, Centers, and Offices.

NIMHD led the development of the PhenX Toolkit Social Determinants of Health Assessments Collection which enables researchers to develop, disseminate, and use standard data collection measures.^{176,177} The SDOH Collection features a Core collection of 16 measurement protocols designed to create common data elements for cross-study analyses that compare or combine data from different studies that includes elements such as race or ethnicity, age, and gender identity. The Specialty collection has two components. An individual SDOH collection of 22 measurement protocols for researchers collecting information for individuals or their family through elements such as affordability of accessing dental care or prescriptions, discrimination in health care, and housing instability due to affordability. The structural SDOH collection includes 15 measurement protocols at the structural or community level of the socioecological framework with elements such as: minimum wage, neighborhood walking and biking environment, and physical activity-neighborhood environment.

Rare Diseases

While rare diseases are individually rare, collectively they affect about 30 million people in the United States. NCATS is committed to using research to address significant economic burden¹⁷⁸ and the public health crisis presented by rare diseases. Speeding development of treatments for patients requires innovation in science and technology and engaging patients and their support organizations as essential partners. Toward that goal, NCATS supports several programs on research to treat or prevent rare diseases. The Rare Diseases Clinical Research Network (RDCRN) program, involving NCATS and several other ICs, is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing.¹⁷⁹ Through the RDCRN Consortia, physician scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation. The NCATS Division of Preclinical Innovation's Therapeutics for Rare and Neglected Diseases (TRND) program supports preclinical development of therapeutic candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application.¹⁸⁰ In addition to these innovative research programs, NCATS also provides resources to people with rare diseases¹⁸¹ and hosts an

¹⁷⁶ www.nimhd.nih.gov/resources/phenx/

¹⁷⁷ www.phenxtoolkit.org/collections/view/6

¹⁷⁸ ncats.nih.gov/news/releases/2021/nih-study-suggests-people-with-rare-diseases-face-significantly-higher-health-care-costs

¹⁷⁹ ncats.nih.gov/rdcrn

¹⁸⁰ ncats.nih.gov/trnd

¹⁸¹ ncats.nih.gov/engagement

annual Rare Disease Day to raise awareness about rare diseases, the people they affect, and NIH collaborations that address scientific questions and advance research for new treatments.¹⁸²

Biomedical Research Stewardship

NIH is committed to funding the highest priority biomedical research while also maintaining stewardship of taxpayer investments. ICs such as NHGRI, NLM, NIDCR, NCCIH, and NINR are making great strides in ensuring that research is conducted in a way that continually improves agency operations and research programs.

Ethical, Legal, and Societal Implications Research Program

The NHGRI Ethical, Legal, and Societal Implications (ELSI) Research Program fosters basic and applied research on the ethical, legal and social implications of genetic and genomic research for individuals, families and communities.¹⁸³ Since its creation in 1990, the ELSI Research Program has supported a large body of research on a wide range of topics. ELSI research addresses the new and sometimes unexpected ways that genomics interacts with many aspects of daily life, from how healthcare is designed and delivered to the ways individuals, families and communities understand such basic concepts as belonging and what it means to be human. Of particular interest are studies that explore these issues with and within communities that have been underrepresented and/or underserved in biomedical research and healthcare. The ELSI Research Program is often at the forefront of newly arising issues such as the appropriate use and implementation of genomics in diverse communities or the ELSI concerns of citizen science. The information gained from this program can be used to inform research and policy across the agency.

Development of Common Data Elements

NIH continues to develop novel approaches to enhance the scientific rigor of the research it funds. NLM is providing leadership and coordination in a trans-NIH effort to improve research rigor through the use of common data elements (CDEs) across NIH-funded research. NLM is also making CDEs findable through NIH's Common Data Elements (CDE) Repository, a freely available source of standard, structured, machine-readable definitions of data elements, standard variables, and measures used in NIH-funded clinical research.¹⁸⁴

The National Dental Practice-Based Research Network

NIDCR supports clinical studies conducted in a practice-based research setting. The National Dental Practice-Based Research Network (PBRN) is a nationally coordinated program committed to advancing knowledge of dental practice and ways to improve it.¹⁸⁵ Essentially, it is research done in the “real world” of daily clinical practice. The goals of the National Dental PBRN are to support national oral health research studies in dental practices on topics of importance to practitioners and their patients, to provide evidence useful in daily patient care, and to facilitate the translation of research findings into clinical practice. This real-world evidence can inform NIH-funded research as well as improve clinical practice.

¹⁸² ncats.nih.gov/news/events/rdd

¹⁸³ www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program-ethical-legal-social-implications

¹⁸⁴ cde.nlm.nih.gov/home

¹⁸⁵ www.nidcr.nih.gov/grants-funding/grant-programs/clinical-practice-based-research-program/more

Community Partnerships to Advance Science for Society

NINR and the Common Fund are partners in the newly launched “Community Partnerships to Advance Science for Society (ComPASS) Program.”¹⁸⁶ The goals of ComPASS are to:

- Develop, share, and evaluate community-driven structural health equity interventions that leverage partnerships across multiple sectors to reduce health disparities.
- Develop a new health equity research model for community-led, multisectoral structural intervention research across NIH and other federal agencies.

The program will enable communities and researchers to work collaboratively as equal partners in all phases of the research process to enhance the quality of interventions and to advance health disparities research.

Capacity Building and Research Infrastructure

Investing in capacity building and research infrastructure helps to ensure that NIH, and its funded institutions, are prepared to address pressing issues. A few examples of those efforts are highlighted here.

Capacity Building in LMICs

FIC leads the Global Brain Disorders Research program in partnership with NIEHS, NEI, and NIDCD, among others, to support research and capacity building on brain and nervous system disorders relevant to LMICs.¹⁸⁷ Since its start in 2002, the program has supported innovative collaborations that contribute to the long-term goals of building and strengthening sustainable neuro-health research capacity in LMICs to address brain, nervous system and neuromuscular development, function and impairment throughout life and to lead to diagnostics, treatments, prevention and implementation strategies. The program also supports the development of research networks and aims to inform evidence-based policy beyond specific research projects.

FIC also leads the Chronic, Noncommunicable Diseases and Disorders Across the Lifespan International Research Training (NCD-Lifespan) program in partnership with NIA, NIAAA, NIDCR, and NCCIH, among others.¹⁸⁸ Since 2011, the program has helped strengthen research capacity in institutions in LMICs by supporting the training of in-country experts to conduct research on chronic, noncommunicable diseases and disorders. The ultimate goal of this program is to help countries implement evidence-based interventions for conditions such as mental health disorders, cardiovascular disease, diabetes, and many more.

Through both programs, FIC leverages its expertise in global health and research coordination to enhance the infrastructure in LMICs, which can have significant impacts in the health and quality of life in these regions.

SARS-CoV-2 Variant Tracking

NLM, in collaboration with NCATS, NIAID, and NHLBI as well as other U.S. government agencies, continued to participate in the ACTIV Tracking Resistance and Coronavirus Evolution (TRACE) project to develop processes and infrastructure to evaluate submitted SARS-CoV-2 sequence data using standardized methods to identify variants and mutations and to publicly

¹⁸⁶ commonfund.nih.gov/compass

¹⁸⁷ www.fic.nih.gov/Programs/Pages/brain-disorders.aspx

¹⁸⁸ www.fic.nih.gov/Programs/Pages/chronic-lifespan.aspx

disseminate analysis results.¹⁸⁹ In FY 2022, NLM refined data processing and analysis methods to support tracking frequency of SARS-CoV-2 sequence mutations and variants and to predict their impact on vaccine and biologic interventions. As part of this effort, NLM also provided results of this standardized analysis in a lightweight variant report format available through a cloud-based open data platform, through an extensive table that supports findability of individual samples and large-scale analysis across the entire dataset, and through a website interface.

Conclusion

The work highlighted in this section demonstrates that important impacts, resources, and scientific advances to benefit researchers and human health come from across NIH including Institutes and Centers with budgets under \$1 billion. More information on the important work and priorities of all ICs is available in their sections of the Congressional Justification.

¹⁸⁹ www.ncbi.nlm.nih.gov/activ

UNITE INITIATIVE

Program Overview

NIH launched the UNITE Initiative¹⁹⁰ at a special meeting of the Advisory Committee to the Director (ACD)¹⁹¹ on February 26, 2021, with the goal of identifying and addressing structural racism within the NIH community and the greater research community. UNITE is an NIH-wide, collaborative effort comprised of five workstreams—U, N, I, T, and E—with distinct but coordinated objectives to tackle the problem of racial and ethnic equity in science while developing data-driven methods to promote diversity, equity, and inclusion across the biomedical and behavioral enterprise. To thoroughly address structural racism that may exist within the enterprise, UNITE works across three domains of the enterprise—Health Disparities and Minority Health Research (HD/MH), internal NIH workforce, and external biomedical and behavioral research workforce (Fig. 1). Data gathering and analysis are central to all activities, and therefore evidence drives the work of UNITE.

Since its launch, UNITE has endeavored to identify and address challenges associated with addressing racial and ethnic equity in science. Consequently, four focus areas have emerged as priorities for UNITE actions. Accomplishments associated with each focus area below were the result of ideas brought forth by UNITE workstreams and implemented by Institutes, Centers, and Offices (ICOs). By addressing these priority areas, UNITE is working to ensure health for all, build and inspire the next generation of scientists, support the development of targeted preventions and cures, and overall promote the public good.

Focus Area 1: Elevating Health Disparities and Minority Health Research

Fundamental to the NIH's role as the "Federal focal point for health research" and the "steward of medical and behavioral research for the Nation"¹⁹² is the agency's ability to conduct research pertaining to HD/MH. Led by the National Institute of Minority Health and Health Disparities (NIMHD), UNITE works to bolster this role by recommending multiple efforts to encourage prioritization of HD/MH research across the NIH. For example, in FY 2021 NIH launched the Common Fund Transformative Research to Address Health Disparities and Advance Health

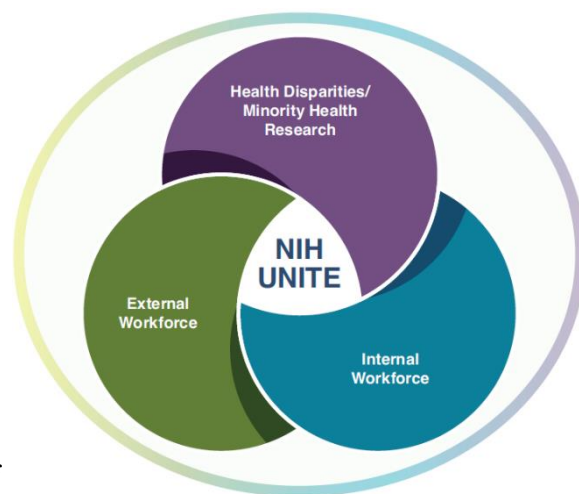


Fig. 1. UNITE's Role Intersecting HD/MH and Internal/External Workforces. In order to address entrenched issues of structural systematic racism in the scientific enterprise, UNITE works across three intersecting domains that are typically singularly focused on by other NIH DEIA-related entities. This design enables greater transparency, accountability, and communications across the NIH and the biomedical research community.

¹⁹⁰ www.nih.gov/ending-structural-racism/unite

¹⁹¹ acd.od.nih.gov/meetings.html

¹⁹² www.nih.gov/about-nih/what-we-do/nih-almanac/about-nih

Equity Initiative.¹⁹³ This initiative has dedicated approximately \$58 million over 5 years to support research projects to prevent, reduce, or eliminate HDs, advance health equity (HE), and expand HD research, including at minority-serving institutions (MSIs). Eleven grants have been issued, five of which were awarded to MSIs.

Based on UNITE recommendations to enhance research on interventions for HDs, in 2022, the Common Fund's Community Partnerships to Advance Science for Society (ComPASS) Program¹⁹⁴ was established and approved for a 10-year research investment of approximately \$400 million. ComPASS is led by NIMHD, the National Institute on Mental Health (NIMH), the National Institute of Nursing Research (NINR), the Office of Research on Women's Health (ORWH), and the Tribal Health Research Office (THRO). The initiative aims to catalyze, develop, and assess community-led HE structural interventions to advance health equity that leverage partnerships across multiple sectors to reduce health disparities, and develop a new HE research model for community-led, multisectoral structural intervention research across NIH and other federal agencies. As of October 2022, NIH has released two funding opportunity announcements (FOAs) (OTA-22-007 and RFA-RM-23-001)^{195,196} associated with the ComPASS program.

Focus Area 2: Funding Extramural Research to Enhance Diversity and Inclusion of Underrepresented Groups (URGs)

Scientific innovation and progress are driven by a workforce that is diverse, inclusive, and equitable. Based on recommendations from UNITE, NIH has implemented several strategies to reduce disparities and enhance diversity, equity, and inclusion (DEI) throughout the external workforce:

Enhance and maintain cultures of inclusive excellence in the biomedical research community: In FY 2021 the Common Fund set aside up to \$241 million over 9 years to launch the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program.¹⁹⁷ FIRST supports extramural institutions in building a self-reinforcing community of scientists through recruitment of early-career faculty committed to inclusive excellence.

Support educational opportunities that complement or enhance workforce training: As of FY 2022 17 NIH ICOs signed on to expand the Science Education Partnership Awards (SEPA) program¹⁹⁸ to provide opportunities for students from underserved communities to consider careers in basic or clinical research, give teachers professional development in science content creation, and improve community health literacy.

Encourage institutional cultural change at extramural institutions: Through the efforts of UNITE, NIH is establishing a Diversity, Equity, Inclusion, and Accessibility (DEIA) Prize Competition.¹⁹⁹ The goals of this prize are to 1) recognize institutions of higher education that

¹⁹³ www.commonfund.nih.gov/healthdisparitiestransformation

¹⁹⁴ commonfund.nih.gov/compass

¹⁹⁵ commonfund.nih.gov/sites/default/files/OTA-22-007.pdf

¹⁹⁶ grants.nih.gov/grants/guide/rfa-files/RFA-RM-23-001.html

¹⁹⁷ commonfund.nih.gov/first

¹⁹⁸ nihsepa.org/

¹⁹⁹ diversity.nih.gov/blog/2022-05-03-requesting-your-input-development-deia-prize-competition

have implemented successful, innovative interventions for enhancing faculty and student DEIA and 2) identify and highlight evidence-based best practices proven to create more inclusive environments for students and faculty. This effort is expected to launch in FY 2023.

Support Extramural DEIA Efforts and Enhance MSI Capacity: In FY 2023 NIH anticipates releasing FOAs based on four concepts approved by the National Institute of General Medical Sciences (NIGMS) and NIMHD Councils for funding in FY 2024. These FOAs will provide institutions support for 1) assessment of institutional climate and achieving DEIA culture change, 2) principal investigators (PIs) who have demonstrated excellence in promoting DEIA in biomedical research to continue their research program and DEIA efforts, 3) low-resource MSIs to increase capacity through instrumentation grants, and 4) MSIs to assess and develop research and training capacity.

Focus Area 3: Creating & Sustaining an Equitable NIH Workplace & Organizational Culture

NIH's mission to solve many of the world's health and well-being challenges relies on the contributions of thousands of diverse staff and researchers internal to NIH. UNITE works to promote equity in the internal NIH workforce through role-modeling the expectations of the external biomedical ecosystem and bolstering NIH's culture of inclusive excellence. To recognize the contributions of all NIH staff and engender a spirit of inclusion across NIH, UNITE launched The Power of an Inclusive Workplace Recognition Project (Fig. 2).²⁰⁰ Spearheaded by Dr. Sadhana Jackson²⁰¹ a National Institute of Neurological Disorders and Stroke (NINDS) and National Cancer Institute (NCI) tenure-track scientist, NIH Distinguished Scholar²⁰² and T Committee Co-Chair, the initiative endeavored to diversify the portraiture within NIH buildings and digital spaces to recognize the contributions of all NIH staff and acknowledge the rich diversity of our NIH workforce.



Fig. 2. The Power of an Inclusive Workplace Recognition Imagery.

The artwork in shared or public spaces encodes an institution's values and sends messages to its members about belonging. Unveiled in November 2021, the Power of an Inclusive Workplace Recognition Project includes portraits, murals, and inspirational quotes, that celebrate NIH staff from various career paths and identities. The Recognition Project is designed to increase feelings of belonging and inclusion across the NIH.

Across NIH, each ICO and the Office of the Director (OD) developed and began implementing racial and ethnic equity plans (REEPs) in April and June of 2022, respectively. ICs applied a

²⁰⁰ www.nih.gov/ending-structural-racism/power-inclusive-workplace-recognition-project

²⁰¹ www.statnews.com/2022/04/11/the-power-of-inclusion-overturning-the-white-wall-standard/

²⁰² diversity.nih.gov/programs-partnerships/dsp

racial and ethnic equity lens to each IC's workforce, structure, and systems, to identify and address any racial or ethnic disparities that may exist in the IC's workforce, and enhance racial and ethnic equity and diversity. As REEP implementation continues, UNITE anticipates that each IC may modify IC-specific policies and procedures based on what is learned during this process, and that any changes will benefit all NIH employees.

Focus Area 4: Improving Accuracy and Transparency of Racial and Ethnic Equity Data

The NIH is committed to standing against structural racism in biomedical and behavioral research²⁰³ by identifying and correcting scientific policies and practices that may have helped to perpetuate structural racism. Foundational to these efforts is strengthening the accuracy and transparency of racial and ethnic equity data. Since its launch UNITE has continuously gathered data to inform its activities. UNITE developed a request for information (RFI)²⁰⁴ for public comments and suggestions to advance racial equity, diversity, and inclusion within the biomedical research workforce, and expand research to eliminate or lessen HDs. UNITE utilized emerging themes from the RFI to inform planning and activities.

Another facet of data gathering was a series of 14 listening sessions with external stakeholders,²⁰⁵ e.g., Minority-Serving Colleges and Universities, Faith-based Organizations and Houses of Worship, Health Centers and Systems, etc. Topics of interest included but were not limited to changing culture to promote equity, inclusivity, and justice; improving policies, transparency, and oversight; and ensuring fairness in review and funding deliberations (Fig. 3).

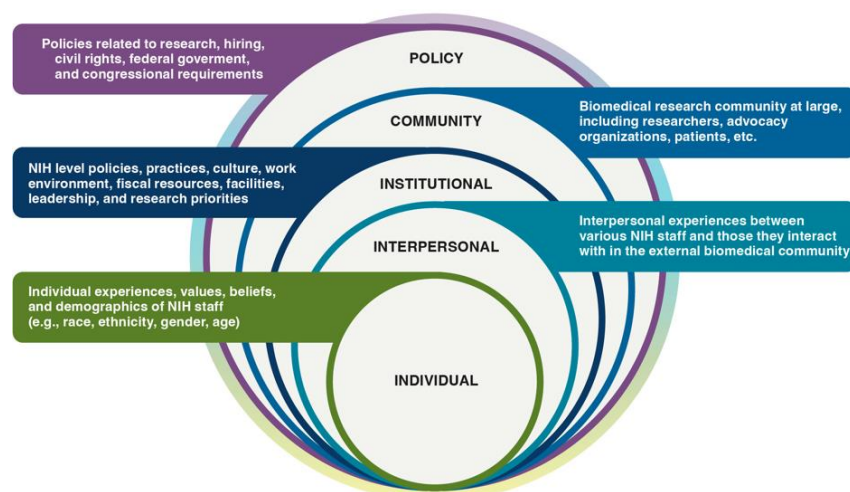


Fig. 3. Socioecological model approach to external listening sessions. The UNITE U Committee drew on the social-ecological model to inform its approach to the extramural listening sessions. The model accounts for factors at the individual, interpersonal, institutional, community, and policy levels, and considers the interplay between the levels. The overlapping nature of these levels emphasizes the need to act across multiple levels at the same time in order to have a sustained and broad impact.

Like the RFI, insights from these sessions provided valuable information on the full range of issues and challenges facing diverse talent that informed the development of UNITE priorities.

To improve transparency and accountability with the public UNITE launched the UNITE Data Dashboard²⁰⁶ to provide information on aggregated, public-facing facts and figures regarding diversity, equity, and inclusion-related data and analyses from the NIH. UNITE efforts made

²⁰³ www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-stands-against-structural-racism-biomedical-research

²⁰⁴ grants.nih.gov/grants/guide/notice-files/NOT-OD-21-066.html

²⁰⁵ www.nih.gov/ending-structural-racism/unite-events

²⁰⁶ www.nih.gov/ending-structural-racism/data-dashboard

data more accessible for the NIH intramural researcher demographics, the NIH-funded extramural workforce, and NIH health disparities research funding.

NIH Cross-Cutting Collaboration

UNITE is spearheaded by the Immediate Office of the Director and co-chaired by the Chief Officer for Scientific Workforce Diversity, the Deputy Director of Management, and the Acting Principal Deputy Director. As of FY 2023 an IC Director is joining as a co-chair of UNITE. The five workstreams of UNITE have more than 80 members from across the NIH workforce with representation from each of NIH's 27 Institutes and Centers and the Office of the Director and across all staff levels. Members of UNITE work collaboratively to recommend and support the implementation of actions at appropriate ICOs and throughout NIH.

UNITE works in collaboration with several NIH key stakeholders including the Office of Equity, Diversity, and Inclusion, the Chief Officer for Scientific Workforce Diversity Office, the Office of Human Resources, the Civil Program, the Office of Communications and Public Liaison, the Division of Program Coordination, Planning, and Strategic Initiatives, and others. Additionally, UNITE goals and charges are aligned with fundamental tenets of the NIH-Wide Strategic Plan for 2021–2025,²⁰⁷ the NIH Minority Health and Health Disparities Strategic Plan 2021–2025,²⁰⁸ and the NIH-Wide DEIA Strategic Plan for 2022–2026, released in December of 2022. The UNITE Initiative reports to the NIH Steering Committee and reports out to the NIH Advisory Committee to the Director (ACD).

The collaborative structure described here allows UNITE to receive input from across NIH, at all levels, and supports the generation of proposals and concepts that receive NIH-wide support.

Next Steps/Goals

While NIH understands that achieving racial and ethnic equity in the biomedical and behavioral research enterprise will take time, the agency believes doing so will propel its work in biomedical and behavioral research and discovery. Recommendations put forward by UNITE for next steps within the four focus areas include but are not limited to:

Focus Area 1: Elevating Health Disparities and Minority Health Research

Develop additional FOAs that focus on IC-specific diseases or topic areas in health disparities and minority health research

Focus Area 2: Funding Extramural Research to Enhance Diversity and Inclusion of Underrepresented Groups

Expand Sponsored Program Administration (SPAD) services and activities

Focus Area 3: Creating & Sustaining an Equitable NIH Workplace & Organizational Culture

Support ICOs in implementing and proposing action steps for REEPs

Focus Area 4: Improving Accuracy and Transparency of Racial and Ethnic Equity Data

Continue listening and learning from internal and external stakeholders

²⁰⁷ www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2021-2025-508.pdf

²⁰⁸ www.nimhd.nih.gov/docs/nimhd-strategic-plan-2021-2025.pdf

WOMEN'S HEALTH

Program Overview

Improving the health of women benefits all members of our society. Support for research on the health of women has produced significant returns on investment. The 2019–2023 Trans-NIH Strategic Plan for Women's Health Research sets an ambitious vision for a world in which the biomedical research enterprise thoroughly integrates sex and gender influences; every woman receives evidence-based disease treatment and prevention tailored to her own needs, circumstances, and goals; and all women in scientific careers reach their full potential.²⁰⁹ The NIH Office of Research on Women's Health (ORWH) is well positioned to drive progress in each of these areas as part of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH Office of the Director. ORWH coordinates and collaborates with all NIH Institutes, Centers, and Offices (ICOs) to set the NIH agenda for research on the health of women, address critical gaps in knowledge about the health of women across the lifespan by stimulating interdisciplinary and innovative research approaches, and launch the careers of promising women's health researchers. These programs set the stage for improved health for women and their families and career opportunities and advancement for a diverse biomedical workforce.

NIH Collaborations

NIH ICOs support research relevant to the health of women, from the laboratory to the clinic, generating new knowledge to inform better treatment of diseases unique to women as well as diseases that may affect women differently. For example, in response to a FY 2021 Congressional request, ORWH and the NIH Advisory Committee on Research on Women's Health (ACRWH) co-hosted "Advancing NIH Research on the Health of Women: A 2021 Conference."²¹⁰ Subsequently, the ACRWH outlined opportunities for future NIH research related to maternal morbidity and mortality (MMM), rising rates of chronic debilitating conditions in women (CDCW) and stagnant cervical cancer survival, emphasizing the importance of an intentional approach and enhanced efforts on female-specific conditions and diseases as well as strategic clinical research relevant to the health needs of women.²¹¹

Maternal Health and Health Disparities

In the United States, there is a growing MMM crisis and thousands of women experience severe maternal morbidity (SMM), which are unexpected outcomes of labor and delivery that result in significant short- or long-term health consequences. This crisis disproportionately affects African American and American Indian/Alaska Native, women who are two to three times more likely to die from pregnancy-related causes compared with non-Hispanic White women; they also have a higher incidence of SMM compared to non-Hispanic White women.²¹² ²¹³ NIH is committed to advancing research in this space to lower poor pregnancy-related and -associated

²⁰⁹ orwh.od.nih.gov/about/trans-nih-strategic-plan-womens-health-research

²¹⁰ orwh.od.nih.gov/research/2021-womens-health-research-conference

²¹¹ orwh.od.nih.gov/sites/orwh/files/docs/ORWH-WHC-Report-508C.pdf

²¹² cdc.gov/reproductivehealth/maternal-mortality/disparities-pregnancy-related-deaths/infographic.html

²¹³ Gray KE, Wallace ER, Nelson KR, Reed SD, Schiff MA. Population-based study of risk factors for severe maternal morbidity. *Paediatr Perinat Epidemiol.* 2012 Nov;26(6):506-14. doi: 10.1111/ppe.12011. PMID: 23061686; PMCID: PMC3498497.

outcomes and to reduce maternal health disparities. Among the activities that NIH has recently led are the following:

Implementing a Maternal Health and PRegnancy Outcomes Vision for Everyone (IMPROVE)

IMPROVE is an NIH-wide effort coordinated by the NIH Coordinating Committee for Maternal Morbidity and Mortality, which is co-led by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), ORWH, and the National Institute of Nursing Research (NINR) with participation from 30 other NIH ICOs.²¹⁴ IMPROVE seeks to address the leading causes of maternal mortality and morbidity in the United States – cardiovascular disease, infection, and immunity – as well as other health conditions and social factors, such as mental health and substance use. The initiative addresses structural and health system factors and community engagement in implementation of interventions for pregnancy-related complications particularly for populations experiencing health disparities. Recent projects supported with IMPROVE funding include one that will examine the impact of structural racism and discrimination on perinatal mental health during the COVID-19 pandemic.²¹⁵

Understudied, Underrepresented, and Underreported (U3) Populations Interdisciplinary Research Administrative Supplement

The U3 framework was developed by ORWH to address persistent disparities in women’s health and healthcare, support research to address this gap, and highlight how intersectional experiences and social determinants of health interact to contribute to different health outcomes.²¹⁶

Investigators who have been awarded a grant from one of the 21 participating NIH ICOs can apply for a U3 supplement to their grant. The U3 Supplement Program provides support for scientists from different disciplines who are conducting preclinical, clinical, behavioral, or translational research addressing health disparities among women from one or more NIH-designated health disparity populations. Supplements focus on many aspects of maternal health, including the role of inflammation and possible biomarkers for risk of gestational diabetes among Native Hawaiian and other Pacific Islander women.²¹⁷

Women’s Health Research in Institutional Development Award (IDeA) States

The IDeA program builds research capacity in states with historically low levels of NIH funding.²¹⁸ ORWH and the National Institute of General Medical Sciences (NIGMS) expanded research on women’s health and health disparities, including maternal and infant morbidity and mortality,²¹⁹ through supplemental funding and a new Women’s Health Research Center of Biomedical Research Excellence (COBRE) to strengthen research infrastructure and investigator competitiveness.^{220 221} One recent publication supported by the administrative supplements for women’s health research in IDeA states reported the development of a novel, noninvasive

²¹⁴ nichd.nih.gov/research/supported/IMPROVE

²¹⁵ reporter.nih.gov/search/q4mKX5AkrEKHRnaHQzjwTQ/project-details/10392594

²¹⁶ orwh.od.nih.gov/womens-health-research/interdisciplinary-research/u3-interdisciplinary-research/orwh-u3

²¹⁷ reporter.nih.gov/project-details/10387025

²¹⁸ [nigms.nih.gov/capacity-building/division-for-research-capacity-building/institutional-development-award-\(idea\)](https://nigms.nih.gov/capacity-building/division-for-research-capacity-building/institutional-development-award-(idea))

²¹⁹ nigms.nih.gov/News/results/Pages/20201009.aspx

²²⁰ grants.nih.gov/grants/guide/notice-files/NOT-GM-21-018.html

²²¹ grants.nih.gov/grants/guide/notice-files/NOT-GM-21-056.html

diagnostic and predictive assay for preeclampsia, a high blood pressure disorder that can occur during pregnancy which is a leading cause of maternal and fetal morbidity.²²²

Chronic Debilitating Conditions and Women’s Health Across the Lifespan

Pregnancy complications like gestational diabetes and preeclampsia are associated with increased risk of Type 2 diabetes and hypertension, that can last a lifetime.²²³ Chronic debilitating conditions such as these pose a significant burden on the health and quality of life of women. These conditions include diseases and disorders that occur across the lifespan, many of which predominantly affect women, including: cardiovascular disease, arthritis, depression, dementia, and osteoporosis. Lower socioeconomic status and education are risk factors for multimorbidity, particularly for underrepresented populations. NIH supports several collaborative efforts employing a life course approach to address chronic debilitating conditions in women of all ages, including the following:

Accelerating Medicines Partnership (AMP®)

The AMP Autoimmune and Immune-mediated Diseases (AMP-AIM) public-private partnership seeks to better understand cellular and molecular interactions that lead to inflammation and autoimmune diseases, frequently seen in women, and develop new research tools in rheumatoid arthritis, systemic lupus erythematosus, psoriasis/psoriatic arthritis, and Sjögren’s disease.²²⁴

Study of Women’s Health Across the Nation (SWAN)

SWAN is a multi-site longitudinal, epidemiologic study on physical, biological, psychological, and social mid-life changes women experience.²²⁵ It includes diverse participants from a variety of racial and ethnic groups (Black, Chinese, Hispanic, Japanese, and White) at designated research centers. SWAN has generated new knowledge informing midlife women’s health care for example, weight gain and menopause symptom management, as well as heart disease and osteoporosis risk. SWAN, co-sponsored by ORWH and several ICs, began in 1994 and has enrolled 3,302 participants providing critical insights into important differences among diverse populations of women.

Funding Opportunities for Basic, Clinical and Behavioral Research on Sex & Gender Influences in CDCW

ORWH leads several funding opportunities in collaboration with NIH ICOs to advance biomedical research on sex and gender influences on health and disease, including CDCW to inform and improve the health of women across the lifespan. The Specialized Centers of Research Excellence in Sex Differences is an innovative interdisciplinary research and training program that supports groundbreaking research integrating basic, clinical, and behavioral research approaches focused on major medical conditions, including chronic debilitating conditions affecting women such as HIV, kidney disease, and irritable bowel syndrome.²²⁶ The

²²² Cheng S, Banerjee S, Daiello LA, Nakashima A, Jash S, Huang Z, Drake JD, Ernerudh J, Berg G, Padbury J, Saito S, Ott BR, Sharma S. Novel blood test for early biomarkers of preeclampsia and Alzheimer’s disease. *Sci Rep.* 2021 Aug 5;11(1):15934. doi: 10.1038/s41598-021-95611-5. PMID: 34354200; PMCID: PMC8342418.

²²³ nhlbi.nih.gov/news/2022/hypertensive-pregnancy-disorders-linked-future-cardiac-events

²²⁴ niams.nih.gov/grants-funding/niams-supported-research-programs/accelerating-medicines-partnership-amp

²²⁵ swanstudy.org/

²²⁶ orwh.od.nih.gov/womens-health-research/interdisciplinary-research/specialized-centers-of-research-excellence-on-sex-differences-u54-clinical-trial-optional

Intersection of Sex and Gender Influences on Health and Disease R01 is an initiative that targets gaps in knowledge regarding the influence and intersection of sex and gender on disease, including CDCW such as asthma and substance use disorder, to improve our understanding of factors and mechanisms underlying sex differences in health.²²⁷ The Research on Sex/Gender Influences is an NIH-wide administrative supplement program that catalyzes new insights by accelerating consideration of sex as a biological variable and gender as a social construct across a wide array of scientific disciplines and throughout the research spectrum from the laboratory to the clinic.²²⁸ Over the last ten years, ORWH/NIH has supported over 1,400 investigators from 19 NIH ICOs for a total investment of more than \$42 million under the umbrella of this program.

Women’s Health Research and Career Development Programs

The fourth goal of the FY 2019-2023 Trans-NIH Strategic Plan for Women’s Health Research, *Promote Training and Careers*, focuses on attracting, retaining, and advancing women in biomedical science careers; building interdisciplinary research careers in women’s health; and training scientists and health professionals on sex and gender influences in health and disease. Many NIH-wide collaborative activities support a diverse and robust workforce to accelerate the translation of research findings into improved health care for women.

Programs to Promote Careers in Women’s Health Research

The Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) program was established by ORWH and collaborating NIH ICOs in 2000, and since its inception has supported more than 750 BIRCWH Scholars who are junior faculty matched with several research mentors.²²⁹ Most of the Scholars achieve productive careers in women’s health research, successfully compete for at least one NIH research grant and generate impactful publications. The ORWH funding level for FY 2022 included \$4 million for the BIRCWH program to support additional fellows at existing sites to increase the diversity of the scholars and research areas. The Women’s Reproductive Health Research (WRHR) Program was established in 1998 by NICHD, with support from ORWH. The focus of this institutional career development program is to create a cohort of clinically trained junior obstetrics/gynecologic investigators representing several subspecialties and emerging areas with expertise in women’s reproductive health research at academic settings across the United States.²³⁰

Career Development Opportunities to Advance Women in Biomedical Research

The Research Supplements to Promote Re-Entry and Re-integration into Health-Related Research Careers program provides mentored research training experience for scientists to re-enter or re-integrate into an active research career after an interruption due to family responsibilities or having been adversely affected by unsafe (e.g., sexual harassment) or discriminatory environments.²³¹ Between FY 2012-2021, 80 percent of the applicants were women and the most cited reason for hiatus was childrearing. The Continuity Supplements program for NIH-mentored career development and research program grant awardees aims to

²²⁷ grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-028.html

²²⁸ orwh.od.nih.gov/research/funded-research-and-programs/administrative-supplements

²²⁹ orwh.od.nih.gov/career-development-education/building-interdisciplinary-research-careers-in-womens-health-bircwh

²³⁰ nichd.nih.gov/research/supported/wrhr

²³¹ orwh.od.nih.gov/career-development-education/research-supplements-promote-reentry-and-reintegration-health-related

retain investigators facing critical life events such as childbirth, adoption, or primary caregiving responsibility for an ailing immediate family member as they transition to the first renewal of their first independent research project grant award or transitioning from career development grants to R01s.^{232 233} In the first 2 years, the success rate for both programs was around 65 percent and a majority of the awardees have been women. The most frequently cited critical life event was childbirth, and the funds were used to hire additional personnel to continue the research. The Advancing Gender Inclusive Excellence (AGIE) initiative seeks to investigate institutional strategies enabling, and barriers preventing, women to attain leadership positions in Science, Technology, Engineering, Mathematics, and Medicine (STEMM) research, leading to expanded dissemination to additional institutions so more women can benefit from these opportunities.²³⁴ The NIH Prize for Enhancing Faculty Gender Diversity recognized organizations achieving sustained improvements and ORWH shared success strategies for broad application.²³⁵

NIH Working Groups Supporting Career Development

The ORWH and NIH Directors co-chair the Working Group on Women in Biomedical Careers which has membership from multiple NIH ICOs and develops innovative strategies and actions to promote sustained advancement of women in biomedical and research careers, within NIH and throughout the extramural community.²³⁶ Initiatives advanced by the Working Group include the NIH Prize for Enhancing Faculty Gender Diversity, and the Continuity Supplements.²³⁷ The Women of Color Research Network was created to provide women of color and supporters of their advancement in the biomedical sciences with information about NIH grants process, career development, and a forum for sharing information.²³⁸

ORWH-NIAMS Team Science Leadership Scholars Program (LSP)

The LSP, led by ORWH and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and embedded within the AMP-AIM program, was launched in 2022 to train research scholars to lead interdisciplinary, cross-sectoral collaborative projects.²³⁹ The LSP is a joint initiative that aligns NIAMS' goal of supporting team science and collaboration with the ORWH vision of preparing leaders in women's health research.

Future Directions

ORWH leads the development of an NIH-wide strategic plan for research on the health of women that serves as a guide for future NIH efforts to improve the health of all women throughout their lifespan and promote advancement of women in STEMM. Development of the next iteration of the plan, the FY 2024-2028 NIH-Wide Strategic Plan for Research on the Health of Women, is currently underway. As in past years, the strategic planning process will be a collaborative effort, with involvement from members of the NIH Coordinating Committee for

²³² grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html

²³³ grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html

²³⁴ grants.nih.gov/grants/guide/rfa-files/rfa-od-21-010.html

²³⁵ orwh.od.nih.gov/career-development-education/prize-competition

²³⁶ orwh.od.nih.gov/career-development-education/nih-working-group-on-women-in-biomedical-careers

²³⁷ orwh.od.nih.gov/career-development-education/prize-competition

²³⁸ womeninscience.nih.gov/women-science/women-color-research-network-wocrn

²³⁹ niams.nih.gov/about/about-the-director/letter/new-pilot-program-will-mentor-leaders-and-advance-womens-health

Research on Women’s Health (CCRWH); the NIH Advisory Committee for Research on Women’s Health (ACRWH); staff from NIH ICOs; other federal partners; and input from the public.

In FY 2023 NIH will implement several activities to advance maternal health research, such as the IMPROVE initiative Maternal Health Research Centers of Excellence, a national network of research centers prioritizing community partnerships in maternity care deserts and underserved populations.²⁴⁰ Additionally, the Implementation Science to Advance Maternal Health and Maternal Health Equity initiative aims to disseminate and implement evidence-based findings with emphasis on strategies for populations with health disparities.²⁴¹ The IMPROVE – Community Implementation Project will establish community-engaged implementation science projects for evidence-based interventions in disproportionately impacted populations.²⁴² The Connecting the Community for Maternal Health Challenge will build a research infrastructure that helps address structural barriers for community and advocacy organizations conducting maternal health research.²⁴³ Lastly, the NIH Rapid Acceleration of Diagnostics (RADx[®]) Tech for Maternal Health Challenge aims to innovate point-of-care and home-based diagnostics that can predict and/or diagnose risk of MMM for postpartum individuals.²⁴⁴

NIH is strongly committed in engaging stakeholders to address, prevent, and treat CDCW. As such, ORWH has recently engaged the National Academies of Sciences, Engineering, and Medicine (NASEM) to generate a framework for consideration of CDCW and describe current gaps in evidence. To ensure that NIH is fully supporting scientists who have caregiving responsibilities, NASEM has also been contracted to conduct a comprehensive study to explore promising and innovative policies and practices for supporting caregivers working in STEM. Additionally, ORWH and NIH partners provide online interprofessional health educational resources and have launched a new research education program, Galvanizing Health Equity Through Novel and Diverse Educational Resources (GENDER) R25 to meet the need for sex- and gender-specific training in science, medicine, and allied health professions by supporting the development of courses, curricula, and methods for the extramural community.²⁴⁵

Together with the NIH community, federal partners and additional stakeholders, NIH strives to advance research for the health of women, ensure women are appropriately represented in biomedical studies, and support advancement of women in biomedical careers.

²⁴⁰ grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-035.html

²⁴¹ grants.nih.gov/grants/guide/notice-files/NOT-OD-22-125.html

²⁴² nhlbi.nih.gov/sites/default/files/media/docs/IMPROVE-CIP_ROA_FINAL_508C.pdf

²⁴³ nichd.nih.gov/research/supported/challenges/community-maternal-health

²⁴⁴ grants.nih.gov/grants/guide/notice-files/NOT-HD-22-035.html

²⁴⁵ grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-015.html