CROSS-CUTTING INITIATIVES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Cross-Cutting Initiatives

INTRODUCTION

The National Institutes of Health (NIH), the Nation's premiere biomedical research agency, is tasked with guiding U.S. scientific research and development in an ever-changing world. The pace of research and development is moving faster than it ever has before, and the coming years are certain to offer both new scientific opportunities and pose continued serious challenges for human health. The 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's mission is to seek fundamental knowledge about the nature and behavior of living systems and apply that knowledge to enhance health, lengthen life, and reduce illness and disability. To achieve its mission, the NIH supports research on the causes, prevention, and treatment of human diseases and disorders; processes in healthy development and aging; and methods for collecting and disseminating data and health information. In addition, the NIH Institutes, Centers, and Offices (ICOs) leverage existing strengths and resources by collaborating in innovative, creative and multidisciplinary ways to answer complex and crucial questions about human health and disease.

To tackle some of the biggest questions facing biomedical science today, the NIH relies on crosscutting, multi-ICO initiatives and research programs which bring together diverse experts and leaders from across the agency. For example, 10 NIH Institutes and Centers (ICs) collaborate on the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, a public-private partnership (PPP), focused on innovative technologies which allow researchers to gain a new understanding of the brain to ultimately lead to discoveries in treatments, cures, and preventions for brain disorders. The NIH Common Fund brings together over 20 ICOs to support high-risk, innovative endeavors with the potential for extraordinary impact. This includes programs such as the Single Cell Analysis efforts, which developed novel tools to overcome major technological hurdles and developed a catalogue of phenotypic and transcriptomic data. These initiatives and others like them are designed to tackle multifaceted questions about human health and disease that are best served by inter-Institute, interdisciplinary collaborative efforts that fully capture the complexities of the research need.

The coronavirus disease 2019 (COVID-19) pandemic required more engaged and creative collaborations across NIH than ever before. The NIH ICOs came together to address emerging scientific and clinical questions and are now building on those partnerships to lead rapid innovations in research practices. For example, the Researching COVID to Enhance Recovery (RECOVER) Initiative, led by the National Heart, Lung, and Blood Institute (NHLBI), seeks to understand, prevent, and treat post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including Long COVID, to mitigate the long-term public health effects of the COVID-19 pandemic. RECOVER utilizes coordinating centers, digital health platforms, and master protocols to enhance our basic knowledge of viral infections in general and is likely to improve understanding of other chronic post-viral syndromes and autoimmune diseases in the future.

Building strong research collaborations and partnerships requires both a diverse scientific workforce and the recruitment of diverse research participants to ensure thoughtful methodology

can capture the wide variety of human health needs. NIH-wide efforts will 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. The NIH UNITE Initiative, comprised of representatives from across all 27 NIH ICs, was launched with the goal of identifying and addressing structural racism within the NIH community and the greater biomedical research community. The NIH Data Science Initiative also works to address goals relevant to diversity in health. For example, NIH's Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) program, a key facet of the NIH Data Science Initiative, will broaden the benefits of AI across demographic groups and improve health equity. In considering diverse research participation, the *All of Us* Research Program has been designed to reflect the diversity of the United States, with a special focus on including participants from groups that have previously been underrepresented in health research. Efforts in Tribal health research coordination, led by the Tribal Health Research Office (THRO), support the development of culturally relevant health research vital to improving the health of American Indian and Alaska Native communities.

During FY 2023, NIH will continue to facilitate partnerships across ICOs to leverage infrastructure and scientific expertise to effectively turn scientific discovery into improved human health. Building partnerships and leveraging existing relationships are critical to supporting and facilitating scientific and clinical research to prevent illness and disease. The NIH will learn from advances made during the COVID-19 pandemic to build on these collaborations going forward. By responding to urgent and evolving health needs, addressing health disparities, and building on previous discoveries, NIH will remain a leader in biomedical research and development into the future.

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES® (BRAIN) INITIATIVE

Program Overview

The NIH *Brain Research Through Advancing Innovative Neurotechnologies®* (BRAIN) Initiative is an ambitious program to develop and apply new technologies to answer fundamental questions about the brain and ultimately to inspire new treatments for brain diseases. Launched in 2014, The BRAIN® Initiative leverages a timely convergence of public health needs and scientific opportunity. The need: similar to electrical networks, the brain operates through circuits of cells to perform complex functions. Dysfunction of brain circuits underlies neurologic, psychiatric, and substance use disorders that impose an immense public health burden, yet the complexity and inaccessibility of the brain exceed the limits of research tools currently available to answer fundamental questions about brain function in health and disease. The opportunity: research advances in science and engineering now offer the potential for researchers to overcome these limitations, enabling them to monitor the activity of thousands of brain cells in real time, map connections between cells, and precisely modulate brain circuits. Solutions for those suffering with Alzheimer's and Parkinson's disease, for example, will come from seeing how malfunctions of brain circuits drive disease, and learning how to rewire errant circuits into healthy function. The work of the BRAIN Initiative will help lay the groundwork for understanding the mechanisms underlying a variety of conditions and diseases that impact brain function, including the neurological symptoms of COVID-19.

Collaboration Within and Beyond NIH

The BRAIN Initiative is highly collaborative within NIH, across Federal agencies, and with private organizations and the international scientific community. Under the leadership of the BRAIN Initiative Director, fully integrated teams from 10 NIH Institutes and Centers (ICs) manage the program. The BRAIN Multi-Council Working Group (MCWG) provides critical input to the IC Advisory Councils and to NIH leadership on how best to achieve the BRAIN Initiative goals. NIH also works in close collaboration with scientists and engineers from other government agencies, including the Food and Drug Administration (FDA), National Science Foundation (NSF), Defense Advanced Research Projects Agency (DARPA), Intelligence Advanced Research Projects Activity (IARPA), and Department of Energy (DoE), and representatives from FDA, NSF, DARPA, and IARPA regularly contribute their expertise through *ex officio* memberships on the MCWG. The BRAIN Initiative Alliance,[69] comprising federal, non-profit, industry, and academic members of the BRAIN Initiative, coordinates and facilitates communications to the public and the scientific community about BRAIN Initiative successes and opportunities for further discovery. This extensive collaboration has allowed the NIH to engage talent from across a broad spectrum of science and engineering experts at institutions and companies throughout the United States and internationally.

Exciting Research Findings

The BRAIN Initiative has enabled scientific advances that provide opportunities to understand the structure and function of the brain at an unprecedented level of detail. Researchers throughout neuroscience are rapidly adopting these advances, and the BRAIN Initiative is both

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[69] www.braininitiative.org

dramatically enhancing existing methods and developing entirely new technologies to study and manipulate brain circuits.

BRAIN Initiative Cell Census Network (BICCN)[70]
The human brain, with its nearly 100 billion neurons, a roughly equal number of non-neuronal cells, and nearly 100 trillion connections, is arguably the most complex biological machine known to humankind. A critical step toward unraveling this complexity is to catalogue how many and what types of cells make up the brain. The BICCN is a collaboration of over 250 NIH-supported scientists at nearly 50 institutions across 3 continents, focused on exactly this challenge. Recently the BICCN published a landmark series of articles that describe a comprehensive atlas of the cell types comprising the motor cortex of mice, monkeys, and humans. The data collected through this effort are available to all scientists through the BICCN Data Inventory. Already, these results are enabling significant advances in our understanding of the locations and functions of these cell types, the differences and similarities in cell types between species, and the accuracy of the technologies used to acquire the data. The single cell analysis techniques used by the BICCN reveal the unique genetic fingerprints of different cell types, offering a powerful new tool for studying brain disorders. For example, researchers have used these approaches to define specific human brain cell types that are particularly vulnerable in Alzheimer's disease. Together these studies herald a comprehensive cell atlas of the entire mouse brain and set the stage for extending these efforts to the human brain.

Progress in human brain diseases and beyond
From its inception, the BRAIN Initiative had as its goal to understand the human brain by developing and testing new technologies in animal models, with the expectation that this will, in due course, provide tools and knowledge applicable to the human brain and brain diseases. Ultimately, the Initiative aims to inspire new approaches to reduce the enormous burden of neurological diseases, psychiatric disorders, and disabilities resulting from developmental disorders and brain and spinal cord injuries. The extent to which the Initiative is already opening new avenues for progress is encouraging. Among the advances showing promise are, for example, methods to identify the brain cell types affected by specific diseases, which is revolutionizing the field of investigative neuropathology; visual neuroprostheses for vision restoration in those with blindness; Brain Computer Interfaces (BCI) that decode intelligible speech and written text directly from brain activity for those unable to speak due to paralysis; and technologies for self-adjusting or "closed-loop" Deep Brain Stimulation (DBS) therapies for persons with Parkinson's disease and essential tremor. The latter not only minimize unwanted effects but also allow continuous and direct feedback while people with movement disorders are going about their daily lives in their natural environments. While information obtained from such technology has immense benefits for the patient and society at large, data and patient privacy are safeguarded by rigorous ethical considerations. Beyond medical science, private sector investments inspired by the BRAIN Initiative are also already underway in artificial intelligence, human computer interfaces, and "neuromorphic" computer hardware engineered to mimic the architecture of the nervous system.

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[70] braininitiative.nih.gov/brain-programs/cell-census-network-biccn

Setting Priorities and Assessing Progress
From the Initiative's launch, the report BRAIN 2025: A Scientific Vision[71] has provided an overarching vision and plan for this multi-faceted program. An independent group of interdisciplinary scientists developed the BRAIN 2025 plan through extensive deliberation with the scientific community. BRAIN 2025 recommended that the BRAIN Initiative focus on technology development in the first five years followed by a shift in future years to integrating and disseminating these technologies for broad, effective use by the wider scientific community. Because of the fast pace and unpredictable path of science and technology development, in 2019, a new external scientific working group reviewed progress towards the BRAIN 2025 goals. In the report, The BRAIN Initiative 2.0: From Cells to Circuits, Towards Cures,[72] they concluded the Initiative was advancing on all major priorities with new opportunities emerging and that given the remarkable progress to date, the BRAIN Initiative should invest in larger scale, transformative projects that could propel neuroscience far into the future.

Neuroethics as an integral part of BRAIN Initiative research
The BRAIN Initiative has committed at the outset to consider in a serious and sustained manner the ethical implications of emerging neuroscience research technologies. The BRAIN 2025 report recognized that neuroethics is an essential partner to neuroscience that can play a key role in guiding neuroscience research and the application of its findings toward addressing human health. Similarly, the BRAIN 2.0 report The BRAIN Initiative and Neuroethics: Enabling and Enhancing Neuroscience Advances for Society[73] anticipated ethical considerations in the context of rapidly evolving science. The external Neuroethics Working Group (NEWG), alongside the MCWG, provides expert input on neuroethics to the BRAIN Initiative. The BRAIN Initiative funds neuroethics research projects, facilitates collaborations to integrate neuroethics into neuroscience research, scans the BRAIN Initiative research portfolio to identify ethical questions, organizes workshops on neuroethics topics that are important for the BRAIN Initiative, and disseminates NEWG findings through high profile publications.

Promoting a Shift in Research Culture in Neuroscience
Given the ambitious goals of the BRAIN Initiative, success will require the engaged participation of a diverse collection of individuals from a variety of disciplines as well as widespread availability and use of research data and tools. The BRAIN Initiative is working to build a more inclusive and diverse research community and foster productive collaboration across research teams and disciplines, including through new requirements to the research it will support.

Building a more diverse research community
NIH recognizes that diverse teams working together to capitalize on innovative ideas and distinct perspectives outperform homogeneous teams. Accordingly, the BRAIN Initiative now requires that most applicants include a Plan for Enhancing Diverse Perspectives (PEDP) as part of the application. The PEDP will outline the strategies that applicants will use to advance the scientific and technical merit of the proposed project through the inclusion of diverse

[71] braininitiative.nih.gov/strategic-planning/brain-2025-report
[72] braininitiative.nih.gov/strategic-planning/acd-working-groups/brain-initiative%C2%AE-20-cells-circuits-toward-cures
[73] braininitiative.nih.gov/strategic-planning/acd-working-groups/brain-initiative%C2%AE-and-neuroethics-enabling-and-enhancing

perspectives. Examples of potential strategies investigators can use to compose teams richly diverse in perspectives, backgrounds, and academic disciplines can include inclusion and mentoring of personnel from groups historically underrepresented in the research workforce and inclusion of community advisory boards to inform research project design and/or dissemination of results. In addition to this new effort towards inclusivity, the Initiative also funds grant supplements that allow investigators to support a new trainee or early career researcher from an underrepresented group and further their career development. Further, the Blueprint/BRAIN Diversity Specialized Predoctoral to Postdoctoral Advancement (DSPAN) and BRAIN Initiative Transition to Independence Award programs support talented researchers from diverse backgrounds as they transition to the postdoctoral and the independent investigator career stages, respectively.

Recognizing the value of data sharing
The BRAIN Initiative projects are generating vast amounts of data. It is essential that these data are widely available to the research community for further analyses and to take into account any potential ethical considerations when neuroscience data are used to investigate human brain function. The BRAIN Initiative places a high priority on ensuring that the increasingly valuable data that it generates are FAIR (Findable, Accessible, Interoperable, and Reusable). To that end, and in line with NIH-wide efforts,[74] in 2019 the Initiative established a robust data sharing policy[75] which requires current awardees and new grantees to submit data from BRAIN supported research to one of the BRAIN data archives. This policy is supported by the authorities in the 21st Century Cures Act. The BRAIN Initiative has also substantially increased support for the development of data standards, archives, and analysis tools, and has funded multiple projects focused explicitly on the dissemination of research tools and results. These efforts to ensure that BRAIN Initiative data are FAIR will maximize their utility and promote a cultural shift towards data sharing and collaboration across different sub-fields of neuroscience research.

Next Steps: New Transformative Projects at the Frontiers of Science and Technology
Building on the success of the BICCN and following recommendations from the BRAIN 2.0 reports, the BRAIN Initiative is investing in three new projects that will accelerate the development of tools and techniques that will transform neuroscience research and our ability to treat human brain disorders. Two of these projects, the Human Brain Cell Atlas and the Armamentarium for Brain Cell Access, were jump-started by FY 2021 Congressionally directed funds and are already underway, while the third on Next Generation Technologies for Brain Micro-Connectivity Analysis is currently under development, with funding opportunity announcements (FOAs) potentially planned for FY 2022 and first awards to be issued in FY 2023, pending the availability of appropriations. Together these projects mark an unprecedented new phase for neuroscience research and the BRAIN Initiative, with an eye toward understanding the highly complex human brain.

The Human Brain Cell Atlas
Building on the successes of the BICCN, the Human Brain Cell Atlas project will provide a critically-needed inventory of all cell classes in the human brain, including detailed analyses of

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[74] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html
[75] braininitiative.nih.gov/brain-programs/informatics

their genetic fingerprints. Representing an acceleration and expansion of the goals of the BICCN, The Human Brain Cell Atlas project will build directly on the remarkable technical progress and research infrastructure that is now in place to generate comprehensive brain cell atlases in humans and other species and establish annotated digital repositories for brain cell types available to the neuroscience research community. The tools, discoveries and resources that emerge from this project have the potential to transform our understanding of the human brain in health and disease in much the same way sequencing the human genome heralded the revolution in gene-based precision medicine.

Armamentarium for Brain Cell Access
In parallel with the Human Brain Cell Atlas, the Armamentarium for Brain Cell Access will support the development of technologies that can precisely target specific cells and circuits in the brain to probe their functions and roles in disease. An expanded toolkit for accurately targeting brain cells will enable precision treatments for human disorders. Research in the Human Brain Cell Atlas in conjunction with the Armamentarium for Brain Cell Access will accelerate the translation of discoveries toward exquisite precision for molecular and genetic human brain circuit therapies.

Next Generation Technologies for Brain Micro-Connectivity Analysis
The third transformative project will aim to usher in a new era of brain research and therapies where detailed wiring diagrams or "connectomes" of the brain will provide new vistas of how cells in the brain talk to each other and how brain circuits work. The first goal of this project will be to complete a nanometer-level wiring diagram of an entire mouse brain, which represents an orders of magnitude leap from the connectomes of significantly smaller brains of worms and flies. This project will also support research to map the long-distance projections or "projectomes" in humans and non-human primates. Projectomes are akin to mapping the major highways in the brain as opposed to the "street-level" connectome view that will be mapped in the mouse brain. These initiatives will also generate data at an unprecedented scale—a whole mouse brain connectome would take up 1 exabyte (1,000 petabytes) of data, whereas a whole human brain connectome would comprise 1 zettabyte, which is roughly equivalent to the world's annual internet traffic. Managing and processing data at this scale will require collaborations across biology, engineering, computer science, physics, and chemistry. In spring 2021, NIH partnered with the DOE Office of Science to host a series of workshops to foster these collaborations and consider challenges and opportunities presented by state-of-the-art technologies for mapping brain circuits.

Conclusion
The BRAIN Initiative funds cross-cutting research and facilitate fundamental discoveries in neuroscience that will inspire new therapies to alleviate the burden of diseases of the brain. The BRAIN Initiative has also taken major steps in shifting the research culture within neuroscience through its emphasis on neuroethics, diversity and inclusion in the research community, and FAIR data sharing practices to enable and enhance the scientific and technological advances from the BRAIN Initiative. The new BRAIN transformative projects represent an ambitious new era in neuroscience. The discoveries on the horizon promise to reshape our understanding of the brain as well as the approaches to improving human health and treating the many neurologic and neuropsychiatric diseases afflicting humankind.

COMMON FUND SINGLE CELL ANALYSIS RESEARCH

Program Overview
The adult human body contains an estimated 37 trillion cells, carefully organized in tissues to carry out the daily processes to keep us alive and healthy. Many biomedical research studies are performed using groups of cells, which can obscure important differences between individual cells within the same population. In these studies, rare cell types and differences in cellular states may go undetected, normal variation between cells is often not appreciated, and the function and context of individual cells as part of the whole can be impossible to identify. Understanding the organization, specialization, and cooperation of different cells within tissues may lead to a paradigm shift in our understanding of development, health, aging, and disease. However, despite recent technological advances, novel tools and approaches to study cellular heterogeneity in complex environments are still greatly needed and understanding high-resolution features of cells within tissues remains a major challenge in biomedical research.

Single cell research is of relevance to many National Institutes of Health (NIH) Institutes, Centers, and Offices (ICOs), and is supported through a variety of ICO-specific activities across the agency. In addition, the NIH Common Fund (CF),[76] a dedicated source of support for cross-cutting NIH priorities, has been advancing single cell research in partnership with ICOs for approximately 10 years through a series of complementary programs. Launched in 2012, the CF's Single Cell Analysis[77] program aimed to examine signatures of individual human cells to measure, analyze, and manipulate cellular heterogeneity and to define specific cell types or states in a population. This program also developed innovative tools and technologies to enable single cell analysis and examine biological processes at the single cell level. Led in partnership with the National Institute of Mental Health (NIMH) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), 19 ICOs across NIH participated in scientific oversight and management for the Single Cell Analysis program.

By the end of the Single Cell Analysis program in 2017, the program had developed a publicly available portal containing phenotypic and transcriptomic data from over 600 cells across over 50 subjects. It also developed novel tools that overcame major technological hurdles in single cell analysis research, including new tools that enabled high-throughput detection of gene transcripts in single cells, improvements in imaging techniques to enhance spatial resolution, and barcoding techniques to detect cell-type-specific gene expression. Harnessing the creative energy of the research community, the Single Cell Analysis program supported a "Follow that Cell" Grand Challenge to develop new approaches for analyzing dynamic states of individual cells that could serve as the basis for predicting cell behavior and function over time. This Challenge yielded multiple innovative solutions, with the winning project demonstrating a novel nanopipette technology to monitor the properties of single cells over time, allowing repeated measurements without destroying cells. Evaluation of the Single Cell Analysis program demonstrated that it had an important impact on advancing single cell research, with over 200 highly cited papers published before the program's end. Additionally, there was a substantial increase in NIH-funded projects in single cell analysis during this time, as well as an increase in
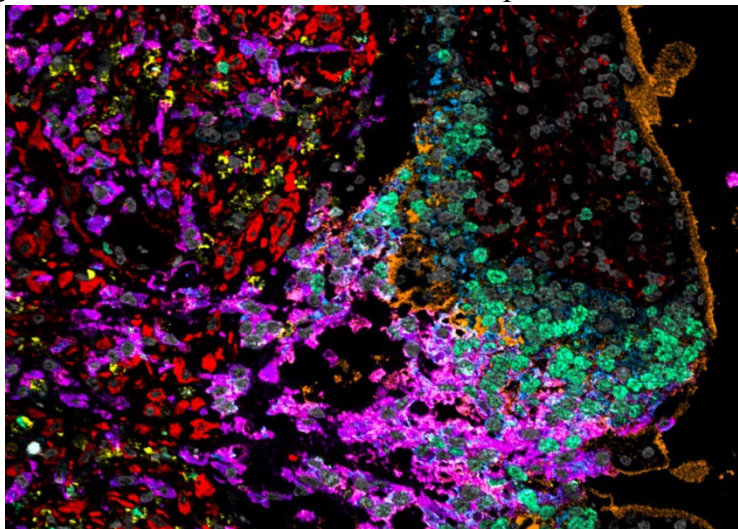
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[76] commonfund.nih.gov/
[77] commonfund.nih.gov/singlecell

publications in this area, suggesting that the Single Cell Analysis program contributed to a rapid growth in this research field.[78]

Thanks in part to the success of the Single Cell Analysis program and other related technological advances, it is now within the realm of possibility to map the entire human body at single cell resolution. However, given the enormity of this task, this remains a significant challenge. To address this challenge, CF launched the Human BioMolecular Atlas Program (HuBMAP)[79] in 2018. Co-led by the National Heart, Lung, and Blood Institute (NHLBI), NIBIB, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), along with an additional 12 participating NIH ICOs, HuBMAP is developing an open, global framework for mapping the human body at single cell resolution. These efforts will lay the groundwork for researchers across the world to contribute to mapping efforts using a standardized, coordinated approach, sharing data and tools with the entire biomedical research community.

HuBMAP is composed of several integrated initiatives. These include development of novel transformative technologies to map the human body, rapid integration of promising technologies into the HuBMAP research consortium so that HuBMAP funded researchers have access to the most cutting-edge approaches, tissue mapping centers to produce 3D tissue maps from various organs at high-resolution, and demonstration projects to showcase how HuBMAP data, in combination with other data sets as needed, can be used to build improved tools and models of cellular organization and communication in tissues. Additionally, HuBMAP also supports the HuBMAP Integration, Visualization, and Engagement (HIVE) Collaboratory, charged with managing data; coordinating across

Cell atlas of the maternal-fetal interface in the uterus during early pregnancy. Image produced by HuBMAP researcher Dr. Mike Angelo, Stanford University.

the HuBMAP consortium; developing tools for visualizing, searching, and modeling data; and building an atlas of tissue maps. To ensure that HuBMAP's efforts complement and do not duplicate other ongoing single cell atlas programs, HuBMAP is coordinating with related NIH programs, such as The Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) initiative, the National Cancer Institute's (NCI) Human Tumor Atlas Network, the NIDDK Precision Medicine Program and GenitoUrinary Development Molecular Anatomy Project (GUDMAP), and NHLBI's LungMAP. HuBMAP is also coordinating with international

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[78] Roy et al. *Accelerating a paradigm shift: The Common Fund Single Cell Analysis Program.* science.org/doi/10.1126/sciadv.aat8573
[79] commonfund.nih.gov/HuBMAP

mapping efforts, such as the Human Cell Atlas and the Human Protein Atlas, to make data interoperable across different programs and initiatives.

HuBMAP has begun releasing foundational data sets that can be used by the entire biomedical research community. The HuBMAP data portal[80] provides access to almost 600 data sets, consisting of over 500 samples from over 60 donors. These data sets include single cell information from human kidney, spleen, lymph node, large and small intestine, thymus, lung, heart, liver, and pancreas. HuBMAP has also developed a number of innovative tools and resources to facilitate single cell analysis research, including technologies to map proteins to distinct cell types within tissue samples, processes for "anchoring" different types of data to link multiple data sets across the same type of cell, molecular profiles of proteins specific to different types of cells that can be used to predict where cells are in relation to each other in healthy and diseased tissues, and a web application that allows researchers to map their own data onto reference maps of eight organs.
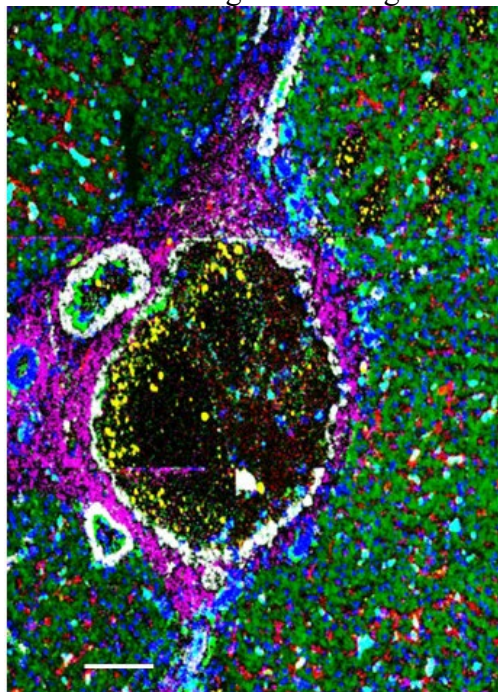

Image of portal triad in the human kidney, where three blood vessels meet to carry blood and nutrients to the liver. Image from HuBMAP researchers Drs. Hua Tian (Pennsylvania State University) and Brent Stockwell (Columbia).

In 2021, the CF launched an exciting new chapter in single cell research, the Cellular Senescence Network (SenNet).[81] Co-led by the National Institute on Aging (NIA) and NCI, with participation from an additional 19 NIH ICOs, SenNet is leveraging single cell approaches to comprehensively identify and characterize the differences in rare senescent cells across different tissues, various stages of human health, and the lifespan. Senescent cells are specialized cells within the body that no longer divide. Under certain circumstances, such as aging, senescent cells accumulate and release a collection of molecules that can cause damage to nearby tissue. Under other conditions, such as cancer or wound healing, senescent cells can protect health by preventing tumor growth or releasing molecules that promote the growth of new tissue. Biomedical researchers still have many unanswered questions about how, when, why, and where senescent cells form, but their rarity and diversity make them difficult to identify and characterize in the body. Despite this, senescence is an attractive target for new therapeutics, with some already in development. A deeper understanding of cellular senescence will help researchers to develop therapies that encourage beneficial effects of senescent cells while suppressing their tissue-damaging effects.

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[80] portal.hubmapconsortium.org/
[81] commonfund.nih.gov/senescence

SenNet will provide publicly accessible atlases of senescent cells, the differences among them, and the molecules they secrete, using data collected from multiple human and model organism tissues. To identify and characterize these rare cells, SenNet will develop innovative tools and technologies that build upon previous advances in single cell analysis, such as those from the Single Cell Analysis program and HuBMAP. Lastly, SenNet aims to unite cellular senescence researchers by developing common terms and classifications for senescent cells.

Next Steps

HuBMAP and SenNet are ongoing, with HuBMAP and the first stage of SenNet both continuing through 2025. At that time, it is anticipated that these programs will have achieved the ambitious goals defined at the beginning of each program, propelling single cell research forward in different ways. At the end of the first stage of SenNet, CF will consider whether there are additional, high-impact goals that may best be achieved through support of a second stage of the program. Additionally, the Common Fund Data Ecosystem (CFDE), [82] a trans-CF effort to enable researchers to query across multiple disparate data sets, is working closely with HuBMAP and SenNet to ensure the single cell data from both programs is interoperable for maximum utility for the biomedical research community.

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[82] commonfund.nih.gov/dataecosystem

RESEARCHING COVID TO ENHANCE RECOVERY (RECOVER) INITIATIVE

Program Overview

In the summer of 2020, as the National Institutes of Health (NIH) and its industry partners worked rapidly to complete critical safety and efficacy trials of COVID-19 vaccines and therapeutics, reports began to emerge that some people who had already struggled with COVID-19 were still fraught with symptoms months later. By December 2020, SARS-CoV-2 had spread to more than 20 million Americans, and researchers had published the first case studies of people who experienced long-term effects.[83] That same month, NIH brought together researchers, clinicians, and patients for a workshop to summarize emerging knowledge about post-acute sequelae of SARS-CoV-2 infection (PASC, or Long-COVID) and to identify key scientific questions that would drive future studies.[84] That workshop helped set the stage for NIH's Researching COVID to Enhance Recovery (RECOVER) Initiative, which is working to improve our understanding of Long-COVID, and ultimately to inform how to prevent and treat it.[85]

An evolving body of research shows that recovery from infection with SARS-CoV-2 varies from person to person. Most patients seem to recover quickly and completely, while for other individuals there are significant post-acute sequelae. Reported symptoms among people who have been infected with SARS-CoV-2 range from mild to incapacitating, may persist after recovery from acute disease, may involve multiple organs and systems, and can adversely affect overall quality of life. Persistent symptoms sometimes called Long COVID, have been reported to include fatigue, shortness of breath, "brain fog," sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression. However, in some cases, new symptoms arise after acute infection or evolve over time, even among people who initially had no symptoms.

Recognizing the importance of this public health challenge, in December 2020, Congress appropriated $1.15 billion in NIH funding, available for obligation over four years, to support research into the long-term effects of SARS-CoV-2. Buoyed by this funding, NIH launched RECOVER in February 2021.

Among the questions that RECOVER hopes to answer are:
- What is the clinical spectrum of Long-COVID and how can we help physicians diagnose it?
- What fraction of people develop Long-COVID after acute SARS-CoV-2 infection?
- What is the biology underlying Long-COVID and recovery from SARS-CoV-2 infection over time?
- Does SARS-CoV-2 infection trigger changes in the body that increase the risk of other conditions, such as chronic heart or brain disorders?
- Does Long-COVID share mechanisms with or offer insights into other post-viral syndromes, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)?

At the heart of RECOVER is a longitudinal cohort study of children and adults, including pregnant women, at various stages of recovery from SARS-CoV-2 infection. The study will also

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[83] pubmed.ncbi.nlm.nih.gov/32644129/
[84] pubmed.ncbi.nlm.nih.gov/33780290/
[85] recovercovid.org/

enroll participants without SARS-CoV-2 infection to serve as a comparison group. NIH envisioned that to quickly assemble a nationally representative cohort, RECOVER would include participants enrolled from Long COVID clinics as well as from existing NIH-funded studies of population health. Many of these existing studies include high representation of people from minority and underserved groups that have been disproportionately affected by COVID-19, including African Americans, Hispanic Americans, American Indian/Alaska Natives, and people in rural communities. A Clinical Science Core (CSC) would coordinate the study and establish a collaborative network for investigators, with additional cores to facilitate appropriate analysis and sharing of data and biospecimens.

In June 2021, an award was made to New York University Langone Health to serve as the CSC. The CSC convened researchers, people affected by Long COVID, and representatives from advocacy organizations to develop a harmonized set of master study protocols—agreed-upon methods, measures, and terminology that will be used to monitor people recovering from Long COVID and generate data that will underpin critical studies of Long COVID. With those master protocols now in hand, researchers from different sites
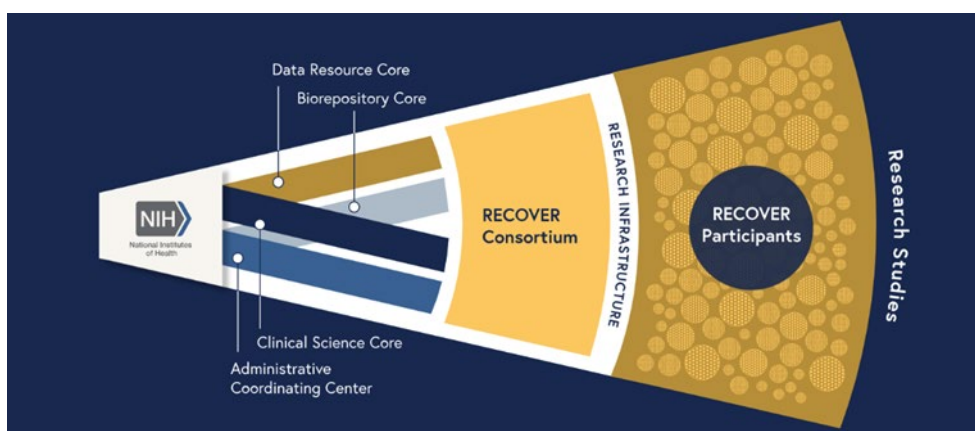
across the country will all be speaking the same language and using the same tools as they collect, analyze, share, and compare data on Long COVID.

In September 2021, the NIH announced a nearly $470 million award to the CSC, which will disseminate funds to more than 30 institutions. Those institutions will partner with hundreds of sites across the country to enroll tens of thousands of volunteers and follow their health over the next several years.

In addition to clinical exams and laboratory tests, RECOVER will collect data through electronic health records and mobile health technologies, such as smartphone apps and wearable devices; this will help reduce the burden on participants and enable the analysis of real-world data from participants in their daily life. An autopsy component will analyze multiple organs and tissues, including the brain, to identify tissue injury due to SARS-CoV-2 infection and/or its sequelae.

In summary, the comprehensive and inclusive composition of the Recovery Cohort, the harmonized master protocols—developed with input from patients—and the broad array of expertise represented in the investigator consortium will support a robust multi-disciplinary assessment of Long COVID that will help determine what causes it and find much needed answers to prevent and treat this often-debilitating condition.

NIH Collaboration

Given the clear involvement of cardiovascular-pulmonary, neurologic, and immune systems in Long COVID, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Neurological Disorders and Stroke (NINDS) are co-leading RECOVER. Critical expertise is also provided by the National Cancer Institute (NCI), National Center for Advancing Translational Sciences (NCATS), National Center for Complementary and Integrative Health (NCCIH), National Institute on Aging (NIA), *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute for Mental Health (NIMH), and National Library of Medicine (NLM), as well as the *All of Us* Research Program and the Office of Data Science Strategy within the NIH Office of the Director.

Next Steps/Goals

The RECOVER infrastructure is in place to support more than 30 funded cohorts in enrolling racially and ethnically diverse children and adults, including pregnant women, across the country. The participants may be followed for up to four years. This will increase understanding about the biological basis of Long COVID and help inform researchers and clinicians investigating potential therapies. Additional efforts related to RECOVER may include developing approaches and technologies to help identify individuals susceptible to developing Long COVID.[86] RECOVER also has the potential to enhance our basic knowledge of how humans recover from viral infections in general and is likely to improve understanding of other chronic post-viral syndromes and autoimmune diseases. Such knowledge could help inform future pandemic response preparedness.

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[86]grants.nih.gov/grants/guide/notice-files/NOT-HL-21-018.html

UNITE INITIATIVE

Program Overview:
The National Institutes of Health (NIH) launched the UNITE Initiative[87] at a special meeting of the Advisory Committee to the Director[88] on February 26, 2021, with the goal of identifying and advancing racial and ethnic equity at the NIH and within the greater biomedical ecosystem. UNITE is comprised of five workstreams with separate but coordinated objectives to tackle the problem of racism and discrimination in science while developing methods to promote diversity and inclusion across the biomedical enterprise. These workstreams include:

- U - Understanding stakeholder experiences through listening and learning
- N - New research on health disparities, minority health, and health equity (HD/MH/HE)
- I - Improving the NIH culture and structure for equity, inclusion, and excellence
- T - Transparency, communication, and accountability with NIH's internal and external stakeholders
- E - Extramural research ecosystem: changing policy, culture, and structure to promote workforce diversity

UNITE is an idea generator that establishes proposals for review and consideration by the NIH Steering Committee. Through this NIH-wide, collaborative effort, UNITE will work to address challenging issues stemming from structural racism. These challenges specifically include but are not limited to:

- Attracting and Retaining Scientists from Underrepresented Groups
- Addressing Disparities in the Success Rates for Grants Supporting Black Scientists
- Improving Transparency of Race-Based Demographic Data
- Increasing Funding of Research for Minority Health, Health Disparities, and Health Equity[89]

Attracting and Retaining Scientists from Underrepresented Groups: The NIH is instituting several efforts to attract and retain scientists from underrepresented groups and is implementing UNITE recommendations that enhance end expand those efforts. For example, NIH is expanding the Distinguished Scholars Program,[90] a cohort model for enhancing diversity and inclusion of Principal Investigators in the NIH Intramural Research Program, to Senior Investigators hired with tenure and enhancing recruitment of researchers from underrepresented groups as candidates for open tenure-track investigator positions. This program is led through a collaboration between the Chief Officer for Scientific Workforce Diversity (COSWD) Office and the Intramural Research Program (IRP).

NIH is working to expand the NIH Science Education Partnership Award (SEPA) program.[91] SEPA funds innovative pre-kindergarten to grade 12 science, technology, engineering and

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[87] www.nih.gov/ending-structural-racism/unite
[88] acd.od.nih.gov/meetings.html
[89] www.cell.com/cell/fulltext/S0092-8674(21)00631-0
[90] diversity.nih.gov/programs-partnerships/dsp
[91] nihsepa.org/

Addressing Disparities in the Success Rates for Grants Supporting Black Scientists: In 2011, Ginther et al. reported a significant racial gap apparent in NIH Research Project Grants (R01) funding.[92] The funding rate for R01 applications from African American/Black (AA/B) scientists was 10 percentage points lower than for all other groups. This spurred NIH and the biomedical community to look closely at individual and systemwide potential contributors and solutions, codified in 13 recommendations by the NIH Advisory Committee to the Director (ACD).[93] Today, there are still far too few Black applicants and applicants from other groups underrepresented in the biomedical workforce (Figure 1). While success rates for receipt of R01 equivalent grants from Black applicants have increased slightly,[94] further work remains to eliminate the well-documented funding gap.
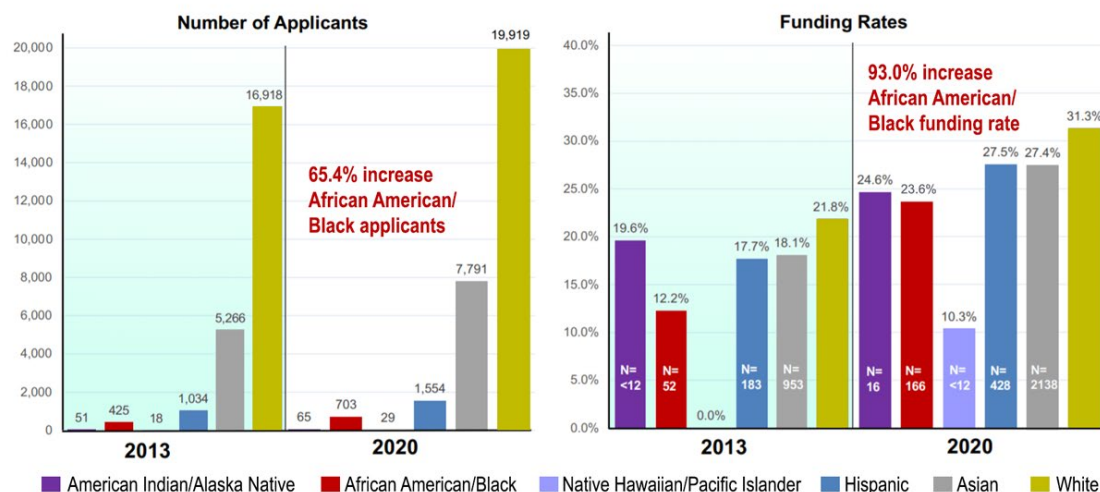

Fig. 1. Disparities in NIH R01 Grant Application and Funding Rates. Disparities in number of applicants and funding rates between NIH R01 grants that support non-white investigators and NIH R01 grants that support white investigators. From 2013 to 2020, both application and funding rates for grants that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

To better understand funding differences, NIH analyzed data from 2011-2015 (Figure 2) and found that 10 percent of 148 topics account for 50 percent of applications submitted by AA/B Principal Investigators (PIs). Applications on "AA/B Preferred" topics were funded at lower

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[92] www.ncbi.nlm.nih.gov/pmc/articles/PMC3412416/
[93] acd.od.nih.gov/documents/reports/DiversityBiomedicalResearchWorkforceReport.pdf
[94] diversity.nih.gov/sites/coswd/files/images/docs/SWD_Progress_2021_Infographic.pdf

rates despite peer review outcomes being similar. The lower rate of funding was primarily due to their assignment to ICs with lower award rates.[95, 96]

In summary, differential award rates were critical drivers of differences, with ICs that had lower award rates receiving a greater proportion of applications in topics to which AA/B PIs disproportionately apply. These data present a new potential target for intervention that the NIH will be exploring. The President's FY 2023 budget proposal may help address this gap, as it proposes increased funding for the National Institute on Minority Health and Health Disparities (NIMHD), the National Institute of Nursing Research (NINR), the National Heart Lung and Blood Institute (NHLBI), and the Fogarty International Center (FIC) -- ICs that have disproportionate numbers of institutional applications whose scientists are from underrepresented groups, but lower than average R01 success rates.
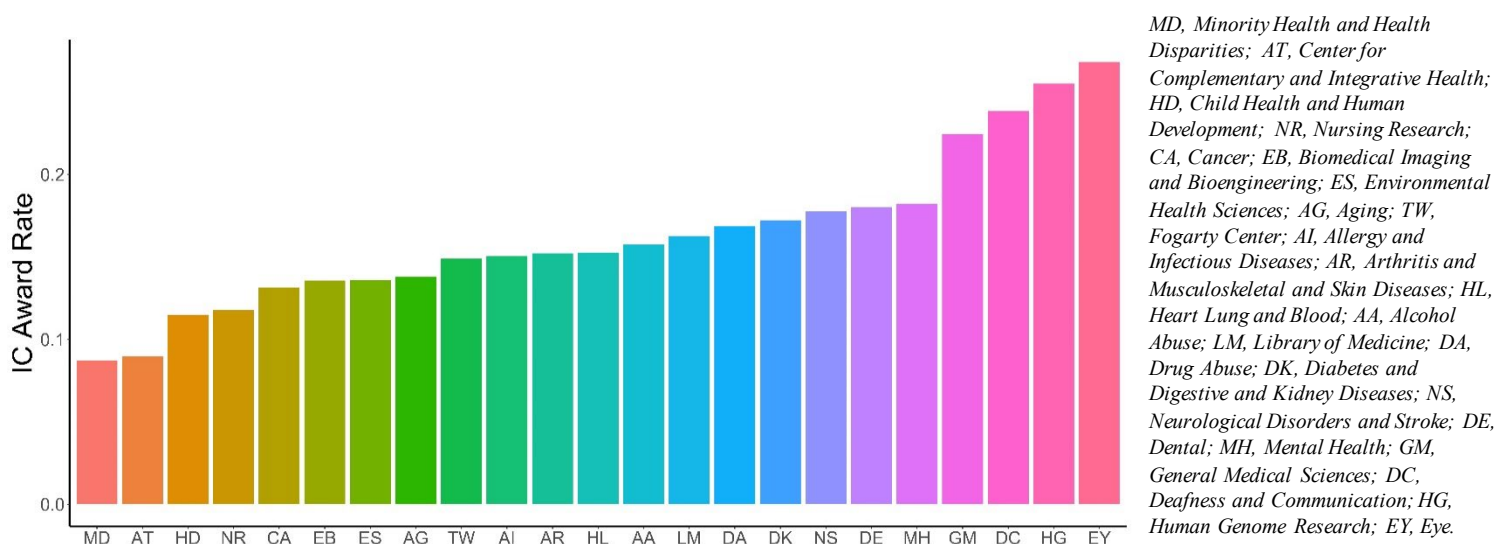

MD, Minority Health and Health Disparities; AT, Center for Complementary and Integrative Health; HD, Child Health and Human Development; NR, Nursing Research; CA, Cancer; EB, Biomedical Imaging and Bioengineering; ES, Environmental Health Sciences; AG, Aging; TW, Fogarty Center; AI, Allergy and Infectious Diseases; AR, Arthritis and Musculoskeletal and Skin Diseases; HL, Heart Lung and Blood; AA, Alcohol Abuse; LM, Library of Medicine; DA, Drug Abuse; DK, Diabetes and Digestive and Kidney Diseases; NS, Neurological Disorders and Stroke; DE, Dental; MH, Mental Health; GM, General Medical Sciences; DC, Deafness and Communication; HG, Human Genome Research; EY, Eye.

Fig. 2. Institute and Center Award Rates for 157,405 R01 Applications 2011-2015. ICs have widely varying award rates (the ratio of funded applications to all applications). These marked variations (from 9.1% to 26.9%) may explain funding differences for different topics.[97]

UNITE is listening to and learning from internal and external stakeholders through many mechanisms and engaging all of the NIH for change and then noting examples of bidirectional communication which impacts institutional and cultural transformation. One example of this process can be seen in NIH's Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative funding opportunity announcement (FOA), which was posted April 8, 2021. The NIH BRAIN FOA is the first to use a Plan to Enhance Diverse Perspectives (PEDP) as consideration for scoring.[98] The term diverse perspectives is broadly defined (e.g., diversity of discipline, geography, etc.), including consideration of diversity as

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[95] pubmed.ncbi.nlm.nih.gov/31633016/
[96] elifesciences.org/articles/67173
[97] doi.org/10.1016/j.neuron.2021.10.021
[98] grants.nih.gov/grants/guide/notice-files/NOT-MH-21-310.html

defined in NIH's notice of interest in diversity.[99] This innovative approach is expected to foster the UNITE goal of racial and ethnic equity.

Improving Transparency of Race-Based Demographic Data: Another critical aspect of the UNITE Initiative is to develop a sustainable process to systematically gather and make public the demographics of NIH's internal and external workforce. The NIH has made several efforts to ensure transparency of these data:

- Published NIH internal federal workforce data[100] that describe the demographic composition of the NIH workforce. Data will be used to investigate potential disparities which may present barriers to equity in the scientific workforce.

- Published NIH's Intramural Research Program data dashboard[101] to capture 2019/2020 data on employee demographics and allow cross-tabulations of sex, race/ethnicity, and career stage.

- Enhanced reporting of NIH grantee demographics in the NIH Databook,[102] which provides basic summary statistics on extramural grants and contract awards, grant applications, the organizations that NIH supports, the trainees and fellows supported through NIH programs, and the national biomedical workforce.

To facilitate public access of these data and more, UNITE has developed a data dashboard on the NIH Ending Structural Racism Webpage. This one-stop shop for high-level NIH data related to Diversity, Equity, Inclusion, and Accessibility links to more granular data across the NIH website and will be regularly updated towards UNITE's mission of transparency and accountability.[103]

Increasing Funding of Research for MH/HD/HE: As COVID-19 has made painfully clear, health disparities and inequities continue to contribute to morbidity and mortality in our nation, making it essential to redress the fundamental causes of these disparities/inequities and identify research programs that could identify effective interventions. All NIH ICs, led by the NIMHD, will seek to expand and enhance research on health disparities and health equity. NIH has implemented several strategies that seek to expand and enhance research on health disparities and health equity:

- The NIH Common Fund, led by the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), has published two FOAs, RFA-RM-21-021[104] and RFA-RM-21-022,[105] to support innovative investigator-initiated projects aimed at reducing health disparities and inequalities and advance health equity, totaling $58 million over five years. Emphasis was placed on projects aimed at developing effective interventions,

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[99] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html
[100] www.edi.nih.gov/data/demographics
[101] oir.nih.gov/sourcebook/personnel/irp-demographics
[102] report.nih.gov/nihdatabook/
[103] www.nih.gov/ending-structural-racism/data-dashboard
[104] grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-021.html
[105] grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-022.html

and institutions that serve minority populations. Eleven awards were issued, with five focused on supporting researchers at MSIs.

- The NIH published the RFA-MD-21-004[106] that supports observational research to understand the role of structural racism and discrimination (SRD) in causing and sustaining health disparities, and intervention research that addresses SRD in order to improve minority health or reduce health disparities; and up to $30.8 million committed from 25 NIH Institutes, Centers, and Offices (ICOs).

- Republishing RFA-RM-21-022: Transformative Research to Address Health Disparities and Advance Health Equity at Minority Serving Institutions (U01 Clinical Trial Allowed)[107] in FY 2022.

Addressing Racism in the NIH Workplace: The NIH has identified accounts of racism in the workplace reported by people of color throughout the biomedical research enterprise both through personal accounts and through Notification and Federal Employee Antidiscrimination and Retaliation (NoFEAR) Act data collected and shared by the Office of Equity, Diversity, and Inclusion (EDI). [108] To address racism in the NIH workplace, NIH will publicly identify and correct any NIH policies or practices that may have helped to perpetuate structural racism and discrimination. Efforts NIH has made to date to identify and correct any disparities include:

- Developing FY 2022 performance plan element for IC Directors to be held accountable for diversity, equity, inclusion, and accessibility.

- Updating internal NIH policy[109] to acknowledge the full range of protected categories for reporting harassment and discrimination.

- Developing Racial and Ethnic Equity Plans that set expectations for each IC as a component of the FY 2022 performance plan element.

- Updating eRA Commons to include racial discrimination as a specific concern that NIH grantee institutions can report to the NIH. [110]

NIH-wide 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 for Management, and the Principal Deputy Director. The five interrelated, but distinct, workstreams of UNITE have nearly 80 members from across the NIH workforce with representation from each of NIH's 27 ICs as well as the Office of the Director. Members of UNITE were nominated by NIH ICO Leadership. UNITE works in collaboration with several NIH key stakeholders including EDI, COSWD, the Office of Human Resources (OHR), OHR/Civil Program, the Office of Communications and Public Liaison, DPCPSI, and others. The UNITE Initiative

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[106] grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-004.html
[107] grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-022.html
[108] www.edi.nih.gov/no-fear-act
[109] policymanual.nih.gov/1311
[110] public.era.nih.gov/shape/public/notificationForm.era

reports to the NIH Steering Committee and to the NIH ACD. The infrastructure described here allows UNITE to receive input from across NIH and external stakeholders at all levels and encourages the community to general proposals and concepts that includes an NIH-wide support system.

Next Steps/Goals: While NIH understands that ending structural racism and achieving racial and ethnic equity in the biomedical research enterprise will take time, NIH believes doing so will propel our work in biomedical research and discovery. Recommendations put forward by UNITE for next steps include:

- Continue to listen and learn from a wide variety of stakeholders, both internal and external, including those who are not frequently engaged

- Develop actionable data dashboards that track and provide visualizations of the intramural workforce and NIH HD/MH/HE research investments with key performance indicators and metrics

- Encourage additional FOAs that focus on IC-specific disease/topic areas related to HD/MH/HE

- Develop programs to spur institutional culture change in support of inclusivity and equity

- Examine NIH staff (e.g., program officer, scientific review officer) interactions with applicants (e.g., underrepresented group applicants) to address bias or inequities that may impact funding opportunities

- Develop programs to expand NIH interactions with and support of HBCUs, TCUs, and other MSIs

- Change the physical and virtual representations at NIH to more accurately reflect the diversity of our society

DATA SCIENCE AT NIH

Overview

Immense amounts of data are generated throughout the biomedical research enterprise and in health care settings, from fundamental experiments using cells and research organisms to clinical studies and community-level epidemiological research. These data have value to the original studies in which they are generated as well as benefit for future investigations. Thus, careful acquisition, management, storage, and analysis of these data quickly and accurately are priority interests for the NIH. Investing in data science is critical to draw meaning from these data. In addition, NIH must support the wide range of research and advanced data analysis needs, both those arising in response to the NIH COVID-19 response as well as future challenges and opportunities. Guided by its Strategic Plan for Data Science,[111] NIH supports efforts to build the infrastructure and capabilities needed to discover, access, analyze, and combine data in innovative ways that respect the conditions under which the original data were collected. In addition, NIH must develop a diverse and talented data science workforce that will address critical priorities in research, clinical care, and human health.

The Office of Data Science Strategy (ODSS) within the NIH Office of the Director (OD) Division of Program Coordination, Planning, and Strategic Initiatives supports catalytic efforts to advance data science as well as efforts to integrate NIH resources into a modern data ecosystem built on principles of Findability, Accessibility, Interoperability and Reusability (FAIR). ODSS leads the implementation of the NIH Strategic Plan for Data Science through partnerships and collaborations with NIH Institutes, Centers, and Offices (ICOs), other federal government agencies, and the private sector.

Progress

The importance of data science to the NIH mission continues to increase, partly driven by the volume, velocity, and complexity of health and life science data, as well as the potential for these rich data to inform our understanding of human health and disease. Supporting innovative workflows that integrate disparate data resources continues to be a grand challenge for the research community and an NIH focus. In response, several NIH-wide programs include efforts to enhance data interoperability and cross-data workflows, including the NIH Helping to End Addiction Long-term (HEAL) Initiative,[112] the Common Fund Data Ecosystem,[113] and the *All of Us* Research Program.[114] In addition, other NIH-wide programs aim to advance data science more broadly including the new Harnessing Data Science for Health Discovery and Innovation in Africa program.[115]

1. Data Infrastructure & Interoperability

As a first step to connecting the data across NIH, ODSS has partnered with the Center for Information Technology (CIT) in an NIH-wide effort to develop a Research Authentication Service (RAS). RAS will streamline access to NIH's controlled access data by creating common

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[111] datascience.nih.gov/nih-strategic-plan-data-science

[112] heal.nih.gov/

[113] commonfund.nih.gov/dataecosystem

[114] www.researchallofus.org/

[115] commonfund.nih.gov/AfricaData

authentication and authorization protocols for identity and access management across NIH systems. Reducing researcher burden for data access through RAS is a foundational component of NIH's data ecosystem. Eight NIH platforms are participating in RAS: National Cancer Institute's (NCI) Cancer Research Data Commons;[116] Common Fund's (CF) Common Fund Data Ecosystem;[117] National Human Genome Research Institute's (NHGRI) Genomic Data Science Analysis, Visualization, and Informatics Lab-space (AnVIL);[118] National Heart, Lung, and Blood Institute's (NHLBI) BioData Catalyst;[119] National Institute of Mental Health's (NIMH) NIMH Data Archive;[120] NIH *All of Us* Research Program's Research Hub;[121] National Library of Medicine's (NLM) National Center for Biotechnology Information's (NCBI) database of Genotypes and Phenotypes (dbGaP);[122] and CF/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD) Kids First Data Resource Center.[123] An important milestone was reached in FY 2021, with researchers now able to use RAS to seamlessly log in once across participating platforms steps to access relevant data.

A second effort to support data interoperability across NIH is the NIH Cloud Platform Interoperability (NCPI) program, which is a partnership between ODSS and five NIH Institutes and their platforms: NCI's Cancer Research Data Commons, CF's Kids First Data Resource Center, NHGRI's AnVIL, NHLBI's BioData Catalyst, and NLM/NCBI's dbGaP. NCPI uses a federated model to simplify research access to genomic data and serves as a test ground for new interoperability approaches to large scale data analysis. As of FY 2021, researchers can access and analyze genomic data across these five important NCPI platforms.

Finally, commercial cloud companies provide a foundational computational infrastructure for interoperability. Cloud services are ideally suited to geographically distributed collaborations and big data analysis. The NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative is a collaboration between ODSS and CIT promoting commercial cloud access. With ODSS funding support, STRIDES is harnessing the power of the cloud to help advance biomedical research by providing cost-effective access to industry-leading partners. These partnerships enable researchers' access to rich datasets and advanced computational infrastructure, tools, and services. In FY 2021, NIH added Microsoft Azure as an industry partner joining Google and Amazon Web Services to advance the STRIDES Initiative's aim to accelerate biomedical research in the cloud.

2. Modernized Data Ecosystem

To modernize its data-resources ecosystem, NIH supports efforts to store and share datasets and to leverage ongoing initiatives to better integrate clinical and observational data into data science. Accessible, well-organized, secure, and efficiently operated data resources are critical to modern scientific inquiry.

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[116] datascience.cancer.gov/data-commons

[117] commonfund.nih.gov/dataecosystem

[118] www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL

[119] biodatacatalyst.nhlbi.nih.gov/

[120] nda.nih.gov/

[121] www.researchallofus.org/

[122] www.ncbi.nlm.nih.gov/gap/

[123] kidsfirstdrc.org/

To support a seamless repository ecosystem, ODSS has collaborated across the NIH ICOs to support existing data repositories of all sizes and all stages in their life cycle and to increase their FAIR-ness and Transparency, Responsibility, User focus, Sustainability and Technology (TRUST)-worthiness. These efforts improve NIH-supported data repositories' usage, utility, and impact. ODSS also supports new collaborations to make data from NIH-funded research efforts FAIR and artificial intelligence and machine learning (AI/ML)-ready. In FY 2021, ODSS supported 14 repositories and 36 collaborative projects in these efforts, and 1 ICO supported an additional 5 projects.

Challenges remain in utilizing the advances in data science to address questions of health disparities in underrepresented populations. For example, American Indian and Alaska Native (AI/AN) communities across the Nation have been among the hardest hit by the COVID-19 pandemic. In response to the May 20, 2020 Tribal Consultation for COVID-19 Research,[124] NIH solicited Tribal input for the design of the data management efforts under the Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) initiative.

Recognizing and respecting Tribal sovereignty, ODSS and the National Institute on Minority Health and Health Disparities (NIMHD) conducted a Tribal Consultation to establish a RADx Tribal Data Repository (TDR).[125] Designed to be an independent, Tribally managed and governed research data repository resource, the TDR will house data collected from RADx projects conducted in AI/AN communities. Specifically, the TDR will facilitate, manage, and oversee responsible data access and sharing of de-identified AI/AN RADx research data.

In addition, for more than a decade, NIH has encouraged the use and development of common data elements (CDEs), which are standardized, precisely defined questions paired with a set of specific allowable responses representing important research concept that must be captured in a systematic manner across different sites, studies, or clinical trials. Given the urgent need to develop new vaccines and therapeutics, design tools for rapid diagnosis, and understand the health impacts of COVID-19, CDEs are an important tool for collecting data in consistent ways to facilitate their use and reuse. NIH convened a COVID-19 CDE Coordinating Committee to help ensure consistent use of CDEs across the thousands of COVID-19 studies.

These projects together are intended to provide for the changing research landscape and develop an ecosystem comprising of both domain-specific and generalists repositories better suited to allow researchers to efficiently comply with the data management and sharing expectations per NIH's new Policy for Data Management and Sharing[126] (effective January 25, 2023), and most importantly, to prepare the research community to better maximize the value of data generated through NIH-funded efforts and accelerate the pace of biomedical discoveries and medical breakthroughs for better health outcomes.

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[124] dpcpsi.nih.gov/thro/tribal-consultations/covid-19
[125] dpcpsi.nih.gov/thro/tribal-consultations
[126] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html

3. Data Management, Analytics, and Tools

For the development and dissemination of advanced data management, analytics, and visualization tools, NIH supports the creation and dissemination of useful, generalizable, and accessible tools and workflows, to broaden the utility, usability, and accessibility of specialized tools, and to improve discovery and cataloging resources.

One important program is the Smart and Connected Health interagency program, which supports innovative, high-risk/high-reward research with the promise of disruptive transformations in biomedical research. This initiative is a partnership among the National Science Foundation (NSF), ODSS, and 22 NIH ICOs and was recently expanded to focus on the use of AI/ML and advanced data science in biomedical research.

Additionally, new partnerships with the U.S. Department of Energy (DOE) to advance petabyte-scale genomic search will bring new computational techniques to address critical challenges in large-scale biomedical data science.

Finally, in FY 2021, NIH continued its efforts to advance the use of the Health Level Seven International® (HL7®) Fast Healthcare Interoperability Resources (FHIR®) standard for transmitting research data. The FHIR application programming interface, already widely used to exchange clinical care data, is critical to enabling standardized timely extraction of COVID-19 patient data from electronic health record systems for research on the epidemiology, disease pathology, and immune response to the virus. Furthermore, NIH is supporting the use of FHIR for biomedical research through multiple other initiatives. ODSS has developed a training program for NIH staff on FHIR broadly and analyzing data with personal identifiable information and ways to protect the confidentiality of such information specifically.

4. Supporting Workforce and Diversity in Data Science

NIH is leading efforts to increase and diversify the data science workforce through code-a-thons, data science training, and fellowship and scholar programs. ODSS supported enhancing the data science capacity in minority-serving institutions, in collaboration with NIMHD; Institutional Development Award (IDeA) state institutions, in collaboration with National Institute of General Medical Sciences (NIGMS); and Tribal Colleges and Universities (TCU) by funding the devolpment of data science curriculum and hands-on training programs. These programs aim to develop data scientists who are not only proficient in the computational arena but also in applying such skills to address research on health equity.

The Data and Technology Advancement (DATA) National Service Scholar Program, coordinated by ODSS, offers one- to two-year positions to skilled data scientists to directly work with NIH leadership on high-profile projects that leverage large datasets to impact biomedical research and policy across fields of study.[127] Currently, 13 data scholars are working across the NIH to address important areas of science including childhood cancer, rare diseases, environmental and public health, and cardiovascular research.

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[127] datascience.nih.gov/data-and-technology-advancement-data-national-service-scholar-program-data-scientists-advancing

The Promise of Artificial Intelligence and Machine Learning

In addition to the coordinated NIH efforts to build an ecosystem of FAIR data, FY 2021 appropriations provided funds to accelerate progress in AI/ML with a focus on preparing NIH data and enhancing understanding of ethics transparency in the use of AI/ML. AI/ML are a collection of data-driven analytical technologies with the potential to significantly advance biomedical research. With this support, NIH has launched two new flagship AI initiatives: The Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) Program[128] which is also focused on health equity; and the CF's Bridge to Artificial Intelligence (Bridge2AI) program,[129] which will change the way biomedical researchers address data-driven grand challenges in biomedicine.

While NIH is committed to ensuring that its clinical research reflects the Nation's diversity, many existing biomedical studies and datasets lack diverse representation, leading to inadequate understanding of continued health disparities and inequities. Furthermore, a lack of diversity in both data and researchers contributes to a risk that AI/ML applications perpetuate harmful biases. Launched in 2021, and led by ODSS, the NIH AIM-AHEAD program will establish mutually beneficial and coordinated partnerships to increase the participation and representation of researchers and communities currently underrepresented in the development of AI/ML and enhance the capabilities of this emerging technology.

The Bridge2AI program will propel biomedical research forward by setting the stage for widespread adoption of AI that tackles complex biomedical challenges beyond human intuition. A key step in this process is generating new flagship data sets and best practices for machine learning analysis. A new partnership between the DOE and the Bridge to AI program will develop AI/ML algorithms for privacy-sensitive datasets such as biomedical or personal healthcare information.

NIH makes a wealth of biomedical data available and reusable to research communities; however, not all these data can be used efficiently and effectively by AI/ML applications. In 2021, ODSS issued a new funding opportunity to support collaborations between NIH-funded researchers and AI/ML experts to improve the AI/ML-readiness of biomedical and behavioral research data. Another new funding opportunity was issued in FY 2021 to support the development of curricula and training activities for researchers to learn the skills needed to make biomedical and behavioral research data AI/ML-ready. Competitive opportunities for supplemental funding in the areas of AI/ML-readiness of biomedical data, and workforce development for AI/ML-ready data resulted in co-funded efforts between ODSS and 15 other ICOs.

Future Directions

In the coming years, NIH will continue to invest in foundational and strategic capabilities to support a data science ecosystem, accelerate the development and use of AI/ML, enhance the availability of biomedical data for research, and continue to prioritize the development of a diverse data science workforce. Greater data science capabilities are required to build an NIH-wide FAIR data ecosystem. While the NIH RAS single-sign on service facilitates streamlined

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[128] datascience.nih.gov/artificial-intelligence/aim-ahead
[129] commonfund.nih.gov/bridge2ai

data access, new NIH-wide search capabilities are needed to enable dataset findability, build cohorts for clinical studies, and to bring together knowledge and data for greater understandings. ODSS is engaging the community to identify challenges and opportunities in data discovery and will support the development of new tools and services in data discovery in FY 2023. Consistent and seamless discovery of data across NIH repositories as well as third-party, generalist repositories will better connect researchers with the relevant data that meet their specific needs and use cases. Continued support for the NCPI program will test some of these potential strategies including the use of FHIR to enhance cohort discovery.

NIH will continue to work across the federal government and industrial sector to ensure that the agency both leverages emerging advances and ensures consideration of the special nature of health phenomena in enveloping in data science, data security and analytics.

NIH expects the increasing interest in and rapid adoption of AI/ML capabilities to expand to new areas and more complex challenges. The AIM-AHEAD program will develop diverse leadership in AI/ML to address health disparities research. The Bridge2AI program will attract new AI/ML expertise to AI/ML-ready, flagship datasets. In addition, in collaboration with NIH ICOs, ODSS will increase the focus on ethics in AI/ML, will pursue external collaborations to address open research questions regarding the preservation of privacy and redressing representational biases in data and models and will explore systems approaches to embedding ethics across the AI/ML workflow. Taken together, these efforts in FAIR data sharing, interoperable data platforms, and advances in AI/ML will help meet the critical needs of the 21st Century biomedical research enterprise.

ALL OF US RESEARCH PROGRAM

Program Overview
In FY 2021, the *All of Us* Research Program continued its mission to accelerate health research and medical breakthroughs to enable individualized prevention, treatment, and care for all of us. The program expanded data and access to the Researcher Workbench, the online destination where registered users can explore the *All of Us* data, including COVID-19 related data; witnessed the first publications of peer-reviewed studies using *All of Us* data; expanded the program's trusted network of community engagement partners; released the next steps of the program's enhanced tribal engagement; and through its collaboration with the NIH ICs, launched its first ancillary study and continues to build additional partnerships.[130] *All of Us* is on its way to enrolling one million or more participants, and as of February 2022, nearly 466,000 participants have consented to join the program and more than 321,000 participants had completed all steps in the initial protocol. The program also continues to explore more enrollment options and in July 2020, began a pilot to mail saliva collection kits to participants. The pilot has collected biosamples from more than 11,130 additional participants, and anticipates rolling out the program nationwide in 2022.

The data available on the Researcher Workbench platform continues to expand and currently includes physical measurements, surveys, electronic health records (EHRs), data from wearable devices, such as Fitbits, and results from the COVID-19 Participant Experience (COPE) survey, the first repeated survey within *All of Us*. The Researcher Workbench is broadly available to any U.S.-based academic, nonprofit, or health care organization researcher. Once their institution has signed-off for any researchers and entered into the program's Data Use and Registration Agreement (DURA), users will be asked to go through a process to verify their identity and ensure they understand their responsibilities.[131] Diversity and inclusion are core principles of the *All of Us* Research Program -- a priority in both the program's researcher and participant base. As of February 2022, more than 1,480 researchers have gained access, over 1,100 research projects have been launched, and more than 293 institutions, including 29 Historically Black Colleges and Universities and Hispanic-Serving Institutions, have signed a DURA with the program.[132] The program envisions the Researcher Workbench supporting thousands of studies across different research domains with the data available, and anticipates data updates and expansion at least twice a year.

Over the last year, the program saw the publication of the first peer-reviewed study that used *All of U*s data by researchers outside of the program. The researchers used the data platform to study health care access and utilization among adult cancer survivors.[133] The results of this study indicated that a majority of cancer survivors who are participants in *All of Us* saw a doctor or a specialist in the past 12 months, but that a significant number of participants delayed care due to out-of-pocket health care expenses, such as deductibles or copayments. *All of Us* developed a strategy to engage with researchers to enhance their awareness of its resource and expand future

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[130] www.researchallofus.org/data-tools/workbench/
[131] www.researchallofus.org/data-tools/data-snapshots/
[132] www.researchallofus.org/institutional-agreements/
[133] onlinelibrary.wiley.com/doi/full/10.1002/cam4.3924

use of the platform. Another publication built artificial intelligence/machine learning models to predict patients with glaucoma who would need surgery, and demonstrated that use of *All of Us* data provided a much more predictive model than use of single site data. More than 20 publications have now used *All of Us* data.

All of Us remains dedicated and committed to the program's core value of engaging participants as partners. This core value is driven by guiding principles of privacy and trust and a mission to empower participants, and intends to promote transparency, reciprocity, and involvement of communities in the governance, oversight, design, implementation, and evaluation of the program. The program is applying lessons learned and charting a new, positive path for engagement through active strategies and providing value to them. *All of Us* remains committed to community engagement as a key way of building trust and community among participants. In 2021, the program funded the next iteration of engagement work, which includes adding three additional partners to the program's robust network of engagement partners.[134] These three new community partners are the American Association on Health and Disability, National Baptist Convention USA Inc., and Baylor College of Medicine. These partners will fortify the program's existing network of trusted community organizations, provide a vital sounding board to shape program activities and direction, lend their expertise to help engage with researchers from underrepresented groups, motivate diverse communities to enroll, and advance the science of engagement.

Additionally, in March 2021, NIH and *All of Us* released the program's Tribal Consultation report, highlighting the agency's commitments to expand and strengthen the respectful engagement of American Indian and Alaska Native (AI/AN) people and support their inclusion in the program.[135] *All of Us'* consultation was one of the most extensive Tribal Consultations that NIH has held to date, encompassing multiple events across the country, a formal request for information, and comment periods for tribal leaders to weigh in on draft proposals. In response to tribal leader input gathered from a nearly two-year consultation process, *All of Us* will initiate specialized education efforts for researchers, take steps to ensure the diverse perspectives and needs of AI/AN communities are integrated into the program, and support ongoing engagement activities with Tribal Nations to pave the way for collaborations in the future. *All of Us* has an opportunity to help address underrepresentation in research and uncover factors that contribute to health disparities, but that can only be accomplished if the program goes about engagement in the right way, in partnership with communities. The program's Tribal Consultation is a critical element in fostering the ongoing dialogue needed to achieve those goals.

NIH Collaboration

COVID-19 Research
At the start of the pandemic, *All of Us* was positioned to aid researchers around the country who were interested in discovering when and where COVID-19 began to spread in the United States and its impact on individuals. The program's COVID-19 research initiatives included antibody

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[134]allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-awards-funding-seven-community-partners

[135]allofus.nih.gov/news-events-and-media/announcements/nih-enhance-tribal-engagement-efforts-precision-medicine-research

serology testing participant samples, the ongoing collection and expansion of EHR data available to researchers, and the results of the COPE survey in which more than 100,000 participants completed at least one survey.

All of Us antibody testing started with participant blood samples from those who enrolled in March 2020 and the program worked backwards until January 2, 2020.[136] Altogether, more than 24,000 samples from participants across all 50 states were tested.[137] The study found evidence of SARS-CoV-2 infections in five states earlier than had initially been reported. These participants were from outside the major urban hotspots of Seattle and New York City, believed to be key points of entry of the virus in the United States. The positive samples were from participants in Illinois, Massachusetts, Mississippi, Pennsylvania, and Wisconsin. The program discovered that most positive samples were collected by *All of Us* prior to the first reported cases in those states and providing evidence that the virus that causes COVID-19 was present in the United States as far back as December 2019. This study provides valuable information about the beginning of the U.S. epidemic and highlights the real-world value of longitudinal research in understanding dynamics of emerging diseases like COVID-19.

All of Us is also rapidly collecting relevant information from participants' EHR data. As of October 2021, researchers have accessed EHR data from over 214,200 participants, producing basic descriptive statistics within the Data Browser and utilizing the Researcher Workbench for in depth analysis. Through the use of EHR data, researchers can better understand patterns in symptoms and severity of COVID-19. The program continues to work diligently with health care provider organizations to make COVID-19 EHR data available to researchers in a timely manner while ensuring privacy and security safeguards are maintained. The program's initial COVID-19 data are now all available to NIH and approved researchers through the *All of Us* Researcher Workbench.

Nutrition for Precision Health, powered by the *All of Us* Research Program
Nutrition for Precision Health (NPH) is the program's first ancillary partnership with the NIH Common Fund. The study will focus on developing algorithms that predict individual responses to food and dietary patterns.[138] NPH will build on recent advances in biomedical science including artificial intelligence, microbiome research, as well as the infrastructure and large, diverse participant group of *All of Us*. During this first phase, NPH will leverage *All of Us* by recruiting a subset of 10,000 participants, which will be the largest precision nutrition study to date. Subsets of these individuals will be asked to undergo more detailed dietary regimens and analyses. The first awards to support phase one of NPH are anticipated to be made in 2022. The diverse study population in *All of Us* will illuminate important insights into diet-related health disparities. Building on phase one, a second phase of the initiative is envisioned to support studies to validate those algorithms that predict responses to diet. NPH is a great example of how NIH may leverage *All of Us* to support additional ancillary studies.

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[136] allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-launches-covid-19-research-initiatives

[137] academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab519/6294073

[138] commonfund.nih.gov/nutritionforprecisionhealth

Promoting Biomedical Workforce Diversity
NIH recognizes the need to diversify the scientific workforce by enhancing the participation of individuals from diverse backgrounds in the biomedical, clinical, behavioral and social sciences research workforce. As a result, *All of Us* has partnered with the National Human Genome Research Institute and the National Institute of Biomedical Imaging and Bioengineering to solicit R01 grant applications that propose independent research projects intended to support Early Stage Investigators from diverse backgrounds, including those from groups underrepresented in the health-related sciences, with plans to make the first awards in FY 2022.[139] Through this initiative, *All of Us* hopes to foster diversity in the workforce and provide opportunities for researchers from diverse backgrounds, including those from groups nationally underrepresented in the genomics and bioinformatics workforce.

Mental Health
All of Us is actively collaborating with the National Institute of Mental Health (NIMH) on the Research Domain Criteria (RDoC), a research framework for investigating mental disorders.[140] RDoC integrates many levels of information, from genomics and circuits to behavior and self-reporting, to explore basic dimensions of functioning that span the full range of human behavior from normal to abnormal. This collaborative partnership will support research data collection from validated tasks from the RDoC framework. In 2022, *All of Us* will focus on the integration and pilot testing of NIMH recommended tasks for data collection among the program's diverse participant sample. By leveraging the program's diverse participants, *All of Us* aims to be a critical partner in NIMH's goal of using RDoC to provide information about the basic biological and cognitive processes that lead to mental health and illness, broadly conceived. The information gained from using RDoC through this cross-cutting NIH partnership may help inform the creation of mental health screening tools, diagnostic systems, and treatments. The FY 2023 President's Budget includes a $107.1 million increase for NIMH, including $25.0 million to increase research on the impact of the COVID-19 pandemic on mental health.

Future Direction
As a result of a strategic planning process undertaken in 2021, *All of Us* set five goals to accomplish by the end of 2026: (1) enroll one million participants that reflect the diversity of the United States, over the lifespan of the program, and have participants share all baseline physical measurements and biosamples; (2) expand the data available to include surveys, health data streams, a whole genome sequence, environmental data, and physical measures; (3) launch ancillary studies as a core and scalable capability; (4) establish a global community of researchers; and (5) incorporate return of value that includes participants receiving health related genomics and EHR.

The first and most important of these goals is *All of Us'* commitment and dedication to continue the program's progress towards enrolling at least one million participants. *All of Us* also intends to expand the cohort to include pediatric participants as the first special population priority. Expansion of the cohort to include children will be led by a dedicated pediatric team that will focus on the development of approved protocols and policies, evaluation of existing capacity for pediatric participation, and addition of pediatric expertise to *All of Us'* engagement efforts

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[139] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html
[140] www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc

including partners and participant ambassador boards. This dedicated team will be headed by the new Director of Special Populations, whom the program anticipates bringing onboard in 2022. The program has already made significant progress in the ability to contribute to pediatric research as a subset of 19,729 adult participants have contributed EHR data dating back to their childhoods.

The expansion of data available to researchers will improve overall health and early detection, treatment, and prevention for a broad variety of diseases. Data will be derived from surveys, digital health technologies, data linkages, clinical or other health record data (e.g., EHRs, patient portals, health information exchanges), or bioassays. In 2021, *All of Us* reached a major milestone in this effort when the program started to analyze whole genome sequences. The program anticipates making genetic data available to researchers by 2022, with strict privacy and security safeguards in place to protect participants' information.

All of Us sees ancillary studies as partnerships that expand the program's dataset by adding participants outside of the program's target audience and/or adding opportunities for participants to donate new data. Over the next five years *All of U*s plans to launch ancillary studies as a core and scalable capability that expands the cohort and delivers phenotypic, lifestyle, environmental, and biologic data. Through the use of ancillary studies, *All of Us* will deliver on the promise to accelerate health research and medical breakthroughs by helping researchers achieve their goals more efficiently than would be possible on their own, multiplying the value of the program by expanding datatype diversity and potentially boosting participant enrollment.

Over the next five years, *All of Us* aims to establish a diverse global community of 10,000 researchers that productively use the program's dataset. The program will work to achieve this goal by working to enable data interoperability with other international cohorts to increase impact and addressing existing historical barriers that are faced by traditionally underrepresented researchers. *All of Us* anticipates measuring the utility of data from the program's different classes of researchers by including proximate impacts such as number of publications. By expanding the talent of researchers contributing to the biomedical research enterprise, the program aims to advance public health and encourage broad scientific discovery.

All of Us' strategic vision aims to integrate return of value to participants, and the evaluation of its impact, into operations and expectations. The systems and process will be designed so that when a participant makes a contribution, they know when and what to expect in return. *All of Us* will continually evaluate participants' perceptions of the program; their satisfaction with the return of information; their trust and willingness to participate; and how efforts to return value affects our mission and enrollment and retention goals. At the end of 2020, the program began delivering non-health related genetic results to participants. The choices for genetic information participants can choose to receive will also expand in 2022 such that participants will have the choice to learn new information on hereditary disease risk and pharmacogenetics from their genomes. In the future, *All of Us* anticipates the return of additional health related information to participants such as EHR records.

In *All of Us'* early years, the program focused on building the systems and processes necessary to engage a diverse cohort. In the next five years, the program will focus on a return-of-value

strategy, aiming to increase enrollment and active engagement through the return of genetic health related information to participants. Therefore, these strategic goals are designed not only to build datasets that meet researchers' interests, but also to return health information that is of value to participants. *All of Us* will continually evaluate participants' and researchers' perceptions of these efforts and remain dedicated to the program's mission.

TRIBAL HEALTH RESEARCH OFFICE (THRO)

Program Overview

The National Institutes of Health (NIH) supports a broad and expanding portfolio of American Indian and Alaska Native (AI/AN) health research, training, and research-related activities. In 2015, NIH established the Tribal Health Research Office (THRO)[141] to ensure sovereign Tribal Nations have the opportunity to participate in research leading to the development of critical health interventions and to benefit from research in addressing their health priorities. Located in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the Office of the Director (OD), THRO is NIH's point-of-contact for all federally recognized Tribal Nations. In addition to coordinating Tribal health research and activities across NIH Institutes, Centers, and Offices (ICOs), THRO ensures NIH programs, policies, and activities significantly affecting sovereign Tribes are developed with input from Tribal Nations. The first NIH *Strategic Plan for Tribal Health Research FY 2019 – FY 2023*[142] (Strategic Plan) was developed with significant input from Tribal Nations. The Strategic Plan was implemented across all NIH ICOs to increase the impact of NIH-funded research and improve NIH's relationship with Tribal Nations by accomplishing four strategic goals: 1. enhancing communication and collaboration; 2. building research capacity; 3. expanding research; and 4. enhancing cultural competency and community engagement.

NIH's successful biomedical research partnerships with Tribal Nations are built on respect for Tribal Sovereignty. This important partnership formed the foundation for AI/AN participation in clinical trials of coronavirus disease 2019 (COVID-19) vaccine candidates and investigational therapeutics. THRO and the National Institute of Allergy and Infectious Diseases (NIAID) worked together to facilitate discussions with a vaccine sponsor and Tribal Nations that resulted in a data, material, and biological specimen use agreement. As a result, Tribes in the Pacific Northwest and in the Great Plains were significant contributors to the COVID-19 phase III vaccine clinical trial process. THRO played an important role in leading the NIH Tribal Consultation on COVID-19 Research[143] in May 2020 with the NIH Immediate Office of the Director (IMOD), and partners, including the National Institute of Environmental Health Sciences (NIEHS) and the National Institute on Minority Health and Health Disparities (NIMHD). Input from Tribal Nations provided vital information to help develop effective health research programs and initiatives focused on the response to the COVID-19 pandemic in Tribal communities. The Rapid Acceleration of Diagnostics Underserved Populations (RADx®-UP) research program was shaped by comments received from Tribal Consultation and subsequently 10 awards were made to researchers who worked in partnership with Tribal communities.

NIH continues to partner with several U.S. Department of Health and Human Services (HHS) agencies including the Indian Health Service (IHS), Centers for Disease Control and Prevention (CDC), and U.S. Food and Drug Administration (FDA) to develop culturally appropriate information on COVID-19 research, therapeutics, and vaccines. This was essential to ensure sovereign Tribal Nations receive clear, accurate and timely information to support informed decisions to protect the safety of their Tribal citizens. Due to the critical need for

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[141] dpcpsi.nih.gov/thro

[142] dpcpsi.nih.gov/sites/default/files/2019_THRO_StrategicPlan_508.pdf

[143] dpcpsi.nih.gov/thro/tribal-consultations/covid-19

communication during the COVID-19 pandemic, NIH also continues to convene numerous virtual engagements with Tribal Nations across the United States.

Supporting scientific workforce development in sovereign Tribal Nations is a critical component of NIH support for Tribal health research. In 2021, THRO and the NIH Office of Data Science Strategy (ODSS) partnered with several Tribal Colleges and Universities (TCUs) to develop a data science curriculum to increase their capacity to train the next generation of AI/AN data scientists.

NIH-Wide Collaborations
The Strategic Plan includes processes and metrics for evaluating progress toward achieving the strategic goals and their supporting objectives. THRO partnered with the NIH Office of Evaluation, Performance, and Reporting to implement an NIH-wide strategic tracking process to measure NIH's progress in meeting each of the Plan's four Strategic Goals.

To ensure the opportunity for Tribal Nations to provide meaningful and timely input on NIH policies, programs, and activities with significant potential Tribal impact, NIH holds annual Tribal Consultations led by THRO. THRO also partners with NIH ICOs to hold Tribal Consultations on focused topics such as the 2021 Tribal Consultation on the Native American Research Centers for Health program evaluation with the National Institute of General Medical Sciences (NIGMS) and the 2021 Tribal Consultation on the RADx® Tribal Data Repository with NIMHD and ODSS.[144]

Next Steps/Goals
In 2021, THRO led the annual NIH Tribal Consultation focusing on the NIH Draft Tribal Consultation Policy. The NIH 2021 Tribal Consultation included engagement with Tribes in all 10 HHS Regions. This Policy is intended to complement the HHS Tribal Consultation Policy by focusing on NIH-specific issues. When the Policy is finalized in early 2022, it will replace the 2014 NIH Guidance on the Implementation of the HHS Tribal Consultation Policy. The draft Policy was developed with extensive input from the NIH Tribal Advisory Committee (TAC) and the NIH Office of Science Policy (OSP) to enhance transparency in the Tribal Consultation process and to reflect NIH's commitment to consistent engagement with Tribal Nations.

NIH will continue to provide culturally appropriate information to support the decisions of AI/AN communities to participate in COVID-19 research and clinical trials, including studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and post-acute sequelae of SARS-CoV-2 infection. Recognizing the unprecedented potential mental health effects of the COVID-19 pandemic in Tribal communities, THRO convened a virtual discussion between the THRO Director and the Director of the National Institute on Mental Health (NIMH) addressing this important public health topic.[145]

Culturally appropriate data sharing practices respecting Tribal Sovereignty are critical for successful biomedical research partnerships. NIH is developing guidance with input from Tribal Nations and the NIH TAC on appropriate data sharing and management practices for health

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[144] dpcpsi.nih.gov/thro/tribal-consultations
[145] www.nimh.nih.gov/news/media/2021/mental-health-in-american-indian-and-alaska-native-communities

research with Tribal Nations. The 2019 NIH Tribal Consultation on the NIH Draft Policy for Data Management and Sharing was essential in receiving Tribal input that helped shape the guidance.

Increasing the AI/AN biomedical research workforce is an NIH priority. NIH supports regional training hubs in partnership with Tribal Nations and TCUs to increase Tribe Nation's capacity to conduct biomedical research. Regional training hubs introduce high school students to different fields of biomedical research with the goal of encouraging them to complete internships at the NIH and ultimately to pursue biomedical research careers.