

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Cross-Cutting Initiatives

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INTRODUCTION

As the Nation's premier biomedical research agency, the National Institutes of Health (NIH) is entrusted with leading scientific research and development for the United States with the ultimate goal of improving understanding of fundamental human biology and enhancing human health. The pace of biomedical research and development continues to accelerate in a constantly evolving global landscape, and the forthcoming years are poised to bring forth novel scientific opportunities as well as new and persistent challenges to human health. NIH strives to address the current and developing needs of biomedical science while setting the standard for high-caliber and ethical scientific research.

The NIH's more than 27 Institutes, Centers, and Offices (ICOs), which each have a specific research agenda and budget, pursue a host of collaborative efforts to address important scientific and clinical questions in areas such as emerging technologies, pain research, and scientific and workforce capacity building. These NIH-wide efforts allow NIH ICOs to leverage expertise and combine resources strategically to tackle complex challenges in broader and more impactful ways than they would be able to alone. Building strong research collaborations and partnerships across ICOs requires both a diverse scientific workforce and participant pool to develop thoughtful and innovative approaches to answering crucial questions about human health and disease. NIH-wide efforts continue to focus on gaining understanding of human biology, developing and testing interventions, therapeutics, and tools to enhance health, and promoting targeted research on tailored public health, clinical, and community preventive services in diverse settings and contexts.

The scope, scale, and complexity of many biomedical questions and health challenges requires multi-disciplinary and collaborative teams to address the wide variety of human health needs. For example, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Allergy and Infectious Diseases (NIAID) co-lead the Researching COVID to Enhance Recovery (RECOVER) Initiative to understand, prevent, and treat the long-term effects of COVID-19, which can affect nearly all body systems. As a comprehensive, multi-faceted, and nationwide research program, RECOVER involves collaboration with several NIH ICOs and other agencies across the Department of Health and Human Services (HHS). Similarly, NIH ICOs are collaborating with other HHS agencies to address the growing maternal mortality and morbidity crisis through programs such as the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative, an NIH-wide program that aims reduce preventable causes of maternal deaths and improve health for women before, during, and after delivery. Collaborative programs like the Helping to End Addiction Long-term (HEAL)SM Initiative are also key parts of NIH's efforts to address the opioid misuse and overdose crisis by providing scientific solutions to the opioid crisis via research on prevention and treatment of opioid misuse, addiction, and overdose, as well as enhancing pain management. Nutrition impacts health in a myriad of ways, so multiple ICOs support research on how nutrition affects health and disease.

To stimulate scientific discovery and sustain progress also requires investment in innovative tools and research methodologies as well as in the next generation of scientists that can drive forward research. The NIH engages in efforts to enhance the development and use of emerging

technologies to catalyze scientific discovery; these “Novel Alternative Methods” provide a complementary approach to traditional models while offering tremendous promise for enhancing understanding of the human system and for more effectively treating human conditions. These methods, including techniques performed on cells outside the body like organoids and 3D tissue culture and methods using computing platforms or custom hardware that use various computational techniques, may transform how scientists study health and disease. Rapidly developing technologies like artificial intelligence (AI) and machine learning (ML) capabilities have become ubiquitous across biomedical and health research. NIH-wide collaborations allow for leveraging these technologies in tailored ways to meet the needs of the NIH mission and to ensure ethical and trustworthy AI development. Supported by several NIH ICOs, the Common Fund’s High Risk, High Reward initiative is designed to launch new science areas, refine our understanding of complex systems, and pioneer new therapies to produce rapid advancements in biomedicine with the potential for broad impact. The NIH Clinical Center has supported multidisciplinary, ethical, and efficient clinical research since 1953 to translate laboratory discoveries into state-of-the-art diagnostic, preventive, and therapeutic interventions to improve the nation’s health. The biomedical research enterprise also relies upon a talented, qualified, diverse group of investigators to bring new insights and translate fundamental research findings into improved health. NIH ICOs collaborate in several efforts to support the successful recruitment and retention of outstanding independent, early career researchers essential to the sustainable success of the biomedical research enterprise.

During FY 2025, NIH will continue to utilize multi-Institute, NIH-wide, and inter-agency collaborations and partnerships to leverage existing infrastructure, coalesce scientific expertise, and ultimately improve health and prevent disease through effective scientific discovery. Fostering new and existing collaborative relationships is critical to facilitate scientific and clinical research that improves human health. NIH will continue to learn and grow from these essential partnerships going forward. As the steward of medical and behavioral research for the United States, NIH will continue to rapidly respond to the American people’s urgent, evolving health needs, examine health disparities, and build upon previous discoveries and capabilities. While emphasizing diversity, equity, inclusion, and accessibility, NIH will remain a leader in biomedical research and development in FY 2025 and beyond.

ARTIFICIAL INTELLIGENCE

Program Overview

The use of artificial intelligence (AI) and machine learning (ML) capabilities is becoming ubiquitous across biomedical, behavioral, and health research. AI and ML have the potential to drive new research discoveries by finding patterns in very large datasets that are otherwise not apparent to human researchers and, through new generative AI techniques, to transform the way we capture data and create connections among data. NIH leverages and adapts these technologies to meet the unique needs of the NIH mission,¹⁹⁹ support business operations, and ensure ethical and trustworthy AI development. Bias in AI/ML models is a significant concern, particularly in applications for biomedicine, behavioral, and social sciences, and health. Potential sources of bias include under- or over-representation of racial and ethnic groups and underserved rural, low socio-economic status, or other demographic groups. NIH has made significant investments in making diverse, AI-ready datasets and analysis tools available to the research community, in supporting new collaborations among biomedical researchers and AI and ethics experts, and in developing and applying AI methods to speed discoveries and treatments, as well as improving NIH business operations. NIH has several overarching high-profile AI activities that address the agency’s priorities in diverse AI-ready data, ethical AI, and development of new capabilities to address unique challenges in biomedicine.²⁰⁰ This includes NIH-wide programs to support new training opportunities in AI, activities to bring new communities to biomedical-AI research, new research to develop social and advanced AI-technical solutions that will embed ethics across the lifecycle of AI applications, and support to make existing NIH funded data AI-ready while ensuring participant privacy protections. Furthermore, NIH initiatives in AI are aligned to the priorities by the implementation of the President’s October 2023 Executive Order, “Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence.”²⁰¹

NIH Collaboration

NIH is committed to harnessing the power of AI/ML to advance research across diverse fields, diseases, and scientific communities. NIH has launched innovative and ambitious initiatives to propel fusion of biomedicine and AI/ML.

The NIH Common Fund supports several collaboratives, NIH-wide programs related to AI/ML. The *Nutrition for Precision Health, powered by the All of Us Research Program* (NPH)²⁰² aims to develop AI algorithms that predict individual responses to food and dietary patterns. NPH will leverage advances in AI, microbiome research, and the infrastructure of the large and diverse *All of Us* participant group. NPH is designed to implement some of the goals and objectives within the first Strategic Plan for NIH Nutrition Research²⁰³ by leveraging the *All of Us* infrastructure to study how a range of factors, including genes, lifestyle, health history, the gut microbiome, and social determinants of health influence a person’s response to diet. The

¹⁹⁹ nih.gov/about-nih/what-we-do/mission-goals

²⁰⁰ datascience.nih.gov/artificial-intelligence/initiatives

²⁰¹ whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/

²⁰² commonfund.nih.gov/nutritionforprecisionhealth

²⁰³ dpcpsi.nih.gov/onr/strategic-plan

NIH Bridge to Artificial Intelligence (Bridge2AI)²⁰⁴ program will set the stage for widespread adoption of AI that addresses complex biomedical challenges beyond human intuition. The key deliverables are the generation of new “flagship” datasets and best practices for ML analysis. Bridge2AI will also produce tools, software, and standards to accelerate the creation of AI/ML-ready datasets and design training materials and activities for skills and workforce development.

NIH’s Artificial Intelligence and Machine Learning Consortium to Advance Health Equity and Research Diversity (AIM-AHEAD)²⁰⁵ supports projects that use or develop novel AI/ML algorithms to address health disparities and improve health outcomes in underrepresented and/or underserved communities and was highlighted in the Executive Order. The initiative was developed to redress the lack of diversity among AI/ML researchers and lack of representation in AI training data, including electronic health record data. These gaps contribute to harmful biases in how AI/ML is used, how algorithms are developed and trained, and how findings are interpreted, ultimately leading to continued health disparities and inequities. AIM-AHEAD initiated a range of training opportunities across the academic continuum to increase participation of underrepresented researchers and leaders in AI/ML biomedical research, like the PRIME training practicum,²⁰⁶ the Research Fellowship,²⁰⁷ and the Leadership Fellowship.²⁰⁸ AIM-AHEAD collaborates with *All of Us* and the National Center for Advancing Translation Sciences (NCATS) National Covid Cohort Collaborative (N3C)²⁰⁹ to increase researcher diversity in AI/ML by leveraging data, resources, and infrastructure.

The National Institute on Minority Health and Health Disparities’ (NIMHD) Science Collaborative for Health disparities and Artificial Intelligence bias Reduction (SchARe)²¹⁰ is a social science data repository and multidisciplinary research collaboration platform co-sponsored with the National Institute of Nursing Research. SchARe is a cloud platform with population, social determinants of health, and other social science AI-ready datasets. It is a resource to test AI bias mitigation strategies and to advance health disparities research. An integral part of the program is the Think-a-Thons,²¹¹ which prepare low resource institutions and researchers, students, and collaborators from populations with health disparities and are underrepresented in the AI field, to learn how to leverage the SchARe platform for reducing health disparities, improving health care delivery, and conducting bias mitigation research.

The National Institute of Biomedical Imaging and Bioengineering’s Medical Imaging and Data Resource Center (MIDRC)²¹² is an imaging repository to develop methods to reliably diagnose COVID-19 from medical images. MIDRC fulfills the high priority need of researchers for large, high-quality image datasets to develop reliable AI/ML methods that identify disease. MIDRC has addressed this need by ingesting over 309,000 demographically diverse imaging datasets and releasing more than 135,000 images into the open commons for research use. The need for high-

²⁰⁴ commonfund.nih.gov/bridge2ai

²⁰⁵ aim-ahead.net/

²⁰⁶ aim-ahead.net/p/prime

²⁰⁷ aim-ahead.net/research-fellowship/

²⁰⁸ aim-ahead.net/leadership-fellowship/

²⁰⁹ ncats.nih.gov/n3c

²¹⁰ nimhd.nih.gov/resources/schare/

²¹¹ nimhd.nih.gov/resources/schare/think-a-thons.html

²¹² nibib.nih.gov/medical-imaging-and-data-resource-center

quality imaging datasets in AI/ML research extends to all diseases, so MIDRC plans to expand its repository to include other organs and diseases.

AI Programs to Address Specific Opportunities to Improve Health and Treat Disease

NIH invests in AI programs to address disease-specific challenges, while advancing trustworthy AI methods and socio-technical approaches to screen for, detect, and diagnose health conditions and predict disease trajectory.

National Heart, Lung, and Blood Institute (NHLBI) investigators are engaged in AI/ML-driven research and collaborations focusing on heart, lung, blood, and sleep (HLBS) disorders. The Integrative Omics Analysis of NHLBI TOPMed Data²¹³ effort aims to apply the power of AI/ML to the institute's TOPMed²¹⁴ resource to uncover biological function and disease pathobiology. NHLBI's IDEA2Health²¹⁵ stimulates HLBS research and advancement of data science methodologies of data science. Published by RADx-rad in partnership with RECOVER, the NIH Long COVID Computational Challenge (L3C) Prize competition focused on the prognostic problem by developing AI/ML models and algorithms that serve as open-source tools for using structured medical records to identify which patients infected with SARS-CoV-2 have a high likelihood of developing PASC/Long COVID.

The Center for Alzheimer's and Related Dementias,²¹⁶ a collaboration between the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke, uses AI/ML to extract insights on disease risk and protective factors from large networks of data and supports precision medicine applications like prediction of disease risk and progression. These efforts and others at NIA support the use of AI to identify genetic variants that contribute to or protect against the development of Alzheimer's Disease (AD), leading to new strategies for treatments or prevention. AI/ML in this space helps achieve insights faster, accelerating discovery and facilitating the growth of open science and precision medicine for AD and AD-related disorders.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development supports research on Autism Spectrum Disorders (ASD) that uses AI research methods to optimize diagnosis and care for ASD patients. These techniques can expedite ASD screening in children and reach commonly overlooked individuals, thereby lowering many of the hurdles and access issues experienced by these underserved communities.

The National Institute on Drugs and Addiction²¹⁷ is developing and evaluating a machine-learning opioid prediction and risk-stratification e-platform²¹⁸ to assist healthcare providers and systems in safe opioid prescribing by identifying patients at high risk for opioid use disorder and overdose.

²¹³ grants.nih.gov/grants/guide/notice-files/NOT-HL-23-074.html

²¹⁴ topmed.nhlbi.nih.gov/

²¹⁵ grants.nih.gov/grants/guide/notice-files/NOT-HL-22-001.html

²¹⁶ card.nih.gov/

²¹⁷ The FY 2025 President's Budget proposes to rename the National Institute on Drug Abuse to the National Institute on Drugs and Addiction

²¹⁸ reporter.nih.gov/project-details/10597698

The National Cancer Institute’s interagency partnership with the U.S. Department of Energy²¹⁹ accelerates advances in precision oncology and scientific computing as part of the Cancer MoonshotSM program. The program leverages AI and advanced computing to improve drug discovery and patient outcomes. Many AI/ML resources have been openly released²²⁰ to the community, including software, datasets, and trained models.

The National Institute of Mental Health’s Explainable AI for Decoding and Modulating Neural Circuit Activity Linked to Behavior²²¹ uses new AI/ML techniques to better understand the causal links between brain activity and complex behaviors, opening new avenues for clinical therapeutics.

The National Eye Institute is advancing the use of AI and clinical imaging data to advance telemedicine, diagnosis, and treatment decisions for eye diseases and disorders. The first U.S. Food and Drug Administration-approved AI system²²² detected eye-related complications of diabetes. Another new screening tool²²³ was approved for use with multiple camera options increasing access to care while allowing clinics to use existing equipment. A patient-centric home-based system²²⁴ allows doctors to manage age-related macular degeneration (AMD) through remote monitoring, and other new AI algorithms²²⁵ predict progression to late AMD and patients with rapidly advancing disease.

The National Institute of Diabetes and Digestive and Kidney Diseases is supporting research on applications of AI/ML to advance diagnosis, treatment, and prevention of its mission diseases. This includes research using ML to identify²²⁶ panels of biological markers that can predict development of early stages of type 1 diabetes months in advance and to develop²²⁷ automated, more reliable measurement tools for kidney stone detection.

NCATS’ Biomedical Data Translator²²⁸ connects compartmentalized and disparate data across diseases and disciplines using AI-guided knowledge mapping for drug repurposing, disease classification, and identification of possible treatments for rare and difficult-to-treat diseases. NCATS’ Challenge prize competition for Minimizing Bias and Maximizing Long-Term Accuracy, Utility and Generalizability of Predictive Algorithms in Health Care Challenge²²⁹ aims to mitigate the risk of unwitting bias in algorithms used in clinical decisions. This challenge fosters “good algorithmic practices” and the creation of tools that increase the accuracy of AI/ML algorithms used in the healthcare setting.

²¹⁹ datascience.cancer.gov/collaborations/nci-department-energy-collaborations

²²⁰ datascience.cancer.gov/collaborations/nci-department-energy-collaborations/ai-ml-resources

²²¹ grants.nih.gov/grants/guide/notice-files/NOT-MH-23-110.html

²²² fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye

²²³ eyenuk.com/us-en/articles/news/eyenuk-fda-multiple-cameras/

²²⁴ notalvision.com/assets/press-releases/Feb-22-2023-Clinical-trials-results-demonstrate-value-of-home-OCT-at-international-meetings.pdf

²²⁵ nei.nih.gov/about/news-and-events/news/ai-based-systems-can-help-identify-rapidly-advancing-age-related-macular-degeneration

²²⁶ pubmed.ncbi.nlm.nih.gov/37390828/

²²⁷ pubmed.ncbi.nlm.nih.gov/35908740/

²²⁸ ncats.nih.gov/translator

²²⁹ ncats.nih.gov/funding/challenges/bias-detection-tools-in-health-care

The National Institute of General Medical Sciences supports AI/ML research in numerous areas that provide a foundation for improving diagnosis and treatment, including drug discovery, molecular modeling, -omics data analysis, image analysis, protein structure modeling and prediction, and sepsis risk prediction.

The National Library of Medicine (NLM) conducts and funds research to advance AI methods and approaches to enable discovery and improve health. NLM intramural researchers leverage AI techniques to develop computational tools to improve screening and diagnosis of conditions, like cervical cancer, and facilitate health and biomedical information retrieval by researchers, patients, and the public. NLM-funded extramural researchers across the United States are reimagining health care delivery with AI and are advancing AI methods and approaches and developing tools that support care across the care continuum. NLM-funded researchers have applied AI/ML to predict treatment effectiveness and inform personalized medicine approaches and have developed new AI methods for image and biomedical data analysis. The FY 2025 Budget includes \$30.0 million within NLM to support a new Clinical Data Initiative to develop the tools, computational resources, and datasets necessary to extend NIH clinical capabilities, including supporting AI research and development.

The National Human Genome Research Institute is planning to solicit grant applications to spur the development of novel adaptive AI/ML tools within an Ethical, Legal, and Social Implications framework to explore their potential applicability and feasibility in using multi-modal data to help uncover novel relationships between genotypes and phenotypes.²³⁰

AI/ML to Support NIH Decision Making and Operations

NIH also leverages AI/ML to enhance data-driven decision making and ensure good stewardship – including using AI tools to inform research investments, improve business processes, and improve access to and retrieval of biomedical data. The Office of Portfolio Analysis has developed AI/ML approaches and tools to implement data-driven decision making across the NIH research community. NLM has developed and applied AI to provide PubMed® end users with new functionality that helps them efficiently find the most relevant and high-quality information they need across its biomedical literature services. NLM also continues to build on its automated indexing of medical literature by refining its indexing algorithm to incorporate new terms in the biomedical literature. Importantly, AI tools are also used to create and track standardized metrics to measure the productivity and impact of NIH research investments.

Next Steps and Goals

NIH will support activities aligned with the Executive Order on AI and will continue to support collaborations among biomedical, behavioral, and AI and ethics experts for research and the development of new AI tools. Human-derived data will be essential to these efforts. NIH will invest in privacy-preserving methods and opportunities to use synthetic data to advance these fields. In addition, federated or distributed learning capabilities will also be essential for implementing AI research with diverse and/or disparate data. NIH will continue to lead the development of ethical AI for biomedical and behavioral research. NIH has unique needs and

²³⁰ [genome.gov/sites/default/files/media/files/2023-09/ML_AI_Tools_to_Advance_Genomic_Translational_Research.pdf](https://www.genome.gov/sites/default/files/media/files/2023-09/ML_AI_Tools_to_Advance_Genomic_Translational_Research.pdf)

responsibilities for ethical AI that require renewed attention to data governance, diversity, and equity of AI outcomes. NIH will focus on the development of social and technical solutions to ensure transparency across the data and AI model life cycle, participatory approaches to tool development for more equitable AI outcomes, explainable AI, and new methods for assessing AI performance. NIH will continue to play a critical role in interagency collaborations like the National Science Foundation's National AI Research Resource²³¹ by providing AI-ready high-impact data and secure analysis platforms, with expertise in data and system interoperability. NIH will invest in research and community engagements in support of responsible, safe, and effective use of important new technologies, such as generative AI, including Large Language Models.

²³¹ [nsf.gov/cise/national-ai.jsp](https://www.nsf.gov/cise/national-ai.jsp)

CATALYZING THE USE AND DEVELOPMENT OF NOVEL ALTERNATIVE METHODS (NAMS)

Program Overview

From its foundation to the present day, NIH has funded research into the development and application of novel technologies and approaches. These efforts converge with NIH's commitment to the continual development of non-animal model alternative methods and to support efforts to replace, reduce, and refine the use of animals in studies (also referred to as the 3Rs).²³² In different contexts, methods that incorporate the 3Rs have been referred to as "Novel Alternative Methods," non-animal models, or New Approach Methodologies (NAMs). These experiments *in chemico* (cell-free models), *in vitro* (cultured cells), and *in silico* (computational modeling and simulation) can complement and sometimes replace and refine the use of animal studies. The development of effective NAMs may both increase the tools available to achieve the NIH mission and reduce and refine the future use of animals in some areas of research. However, for the foreseeable future, both approaches are necessary to establish rigorous evidence for translating research into clinical intervention.

The promise of the use of NAMs in research is recognized by researchers, Congress, and the public. In 2022, Congress directed the NIH to assess its current portfolio of NAMs. Accordingly, NIH established an internal working group to articulate how NAMs are currently advancing NIH-supported research, including the value and limitations of these approaches in biomedical research. Following from this assessment, in January 2023, the NIH Acting Director charged a new Advisory Committee to the Director (ACD) Working Group on *Catalyzing the Use and Development of Novel Alternative Methods* (Working Group) to identify how NAMs are currently being used and to make recommendations on where NAMs are positioned to be most applicable or beneficial, especially in terms of advancing our understanding of human health.²³³ This Working Group included members with expertise in a wide range of technologies, scientific fields, and backgrounds including members from academia, industry, and federal partners with *ex officio* members from the U.S. Food and Drug Administration (FDA) and Environmental Protection Agency (EPA).

To inform these efforts, the NIH sought public input via a Request for Information (RFI) from June 12 through September 5, 2023, on challenges and opportunities for the further development and use of NAMs in biomedical research.²³⁴ Additionally, the NIH held a public virtual workshop on August 21, 2023, on approaches, challenges, and opportunities relating to the development of NAMs.²³⁵ The output from this workshop, along with the information received from the RFI, was used to inform the development of the ACD Working Group's recommendations on high-priority areas for future investment in NAMs. These recommendations hinge upon the importance of putting together diverse, multi-disciplinary teams with the right complementary knowledge. To break down silos between researchers in various disciplines, it is critical to set up collaborations between groups (e.g., disciplines, sectors), train scientists in a multi-disciplinary fashion, create standardized language to

²³² caat.jhsph.edu/principles/the-principles-of-humane-experimental-technique

²³³ acd.od.nih.gov/working-groups/novel-alternatives.html

²³⁴ grants.nih.gov/grants/guide/notice-files/NOT-OD-23-140.html

²³⁵ osp.od.nih.gov/events/nih-workshop-on-catalyzing-the-development-of-novel-alternatives-methods/

communicate across specialties and sectors, and build and maintain an infrastructure to foster data interoperability and integrated models.

NIH's Longstanding Leadership in the Development and Use of NAMs

The recent activity to catalyze the development and use of NAMs builds on NIH's longstanding commitment to leadership in the field over the past two decades through programs like the National Toxicology Program (NTP) run out of the National Institute on Environmental Health Sciences (NIEHS) and the Tissue Chips for Drug Screening program run out of the National Center for Advancing Translational Science (NCATS).

Toxicology research and testing have been particular areas of focus and critique for the use of animal studies but have also been the focus of significant effort and progress in the development and adoption of alternative methods. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM),²³⁶ an office within NIH/NTP, evaluates alternatives to animal use for chemical safety testing with a focus on scientific publishing. Additionally, NICEATM runs the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM),²³⁷ formally established in 2000 by the ICCVAM Authorization Act (42 U.S.C. 2851-3). NICEATM has multiple initiatives to address diversity, equity, inclusion, and accessibility (DEIA) and environmental justice public health concerns by optimally leveraging and further developing NAMs to better represent the full variability of the U.S. population.

NIH has also been a leader in the development of tissue chips (also called organ-on chips), which are *in vitro* 3-D platforms engineered to support living human tissues and cells. In 2012, NIH partnered with the Defense Advanced Research Projects Agency (DARPA) and the FDA to lead the development of these tools to test safety and efficacy in drug development. Today, the Tissue Chip for Drug Screening program partners with 11 Institutes, Centers, and Offices (ICOs) and 3 federal agencies, including a partnership with the International Space Station U.S. National Laboratory on the Tissue Chips in Space program,²³⁸ a research program to better understand the role of microgravity on human health and diseases and translate those findings to improve human health on Earth.

These and other efforts have led to a four-fold increase in use of NAMs in the past two decades. Researchers are adapting and building upon these tools to increase their use beyond toxicological testing and drug screening into broader biomedical research use.

Current NIH Investments in NAMs

The NAMs field itself has seen tremendous growth over the past 15 years alongside NIH's ever-expanding technological capabilities. NAMs are used in research by every ICO at NIH that funds and/or conducts research. Often, NIH-funded researchers use these methods to help guide animal studies and bolster evidence for their conclusions by going from simpler to more complex models. In many cases, NAMs allow scientists to control variables and establish clearer roles for the building blocks of biological systems, while research in animal models is critical to

²³⁶ ntp.niehs.nih.gov/whatwestudy/niceatm/index.html

²³⁷ ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/index.html

²³⁸ ncats.nih.gov/research/research-activities/tissue-chip/projects/space

understanding just how these fundamental pieces interact in a living organism as it behaves over time in its environment. Researchers continue to apply and develop NAMs in a wide range of areas of basic and clinical research, including cancer, diabetes, cardiovascular disease, Alzheimer’s disease, mental illness, infectious disease, and rare and genetic diseases.

In vitro models

NIH supports efforts to create and characterize *in vitro* models for research, which involves growing and using cells outside of the body. These models traditionally include two types of *in vitro* systems: 1) cell lines (i.e., cells established in culture that can continue to replicate indefinitely), and 2) primary cells from biopsies, which are grown as 2-D monolayer cell cultures and tissue explants. Advances in cell culture techniques and bioengineering have led to the advent of 3-D cell culture technologies that can better replicate the physiological complexity of tissues and organs than can traditional 2-D cell culture. 3-D cell culture systems, also called Microphysiological Systems (MPS), are rapidly increasing the ability to model complex biology and disease and should continue to serve as a valuable tool in reducing and refining the number of animals required for basic and preclinical research in the future. One type of MPS, bioprinted tissue constructs and tissue- and organs-on-chips called organoids, has become common in research. A subset of select programs and discoveries are outlined here to illustrate the wide-ranging applications of *in vitro* methods in NIH-supported research.

The Engineering Next-Generation Human Nervous System Microphysiological Systems program, supported by the National Eye Institute (NEI), National Institute on Mental Health (NIMH), National Institute on Aging (NIA), National Institute on Alcohol Effects and Alcohol-Associated Disorders (NIAAA),²³⁹ and National Institute on Deafness and Other Communication Disorders (NIDCD), aims to develop 3-D human cell-based assays that replicate complex nervous system architectures and physiology with improved fidelity over current capabilities. Addressing this complex technical challenge requires the collaboration of experts from diverse fields, including developmental and stem cell biology, circuit and systems level neuroscience, materials science, engineering, and bioethics. The resulting assays are expected to have a multi-lineage, complex architecture representing the normal characteristics and functions of the relevant nervous system structure (e.g., sensory input systems, brain or spinal integrative systems, motor output systems). It is anticipated that they will substantially exceed the state of the art in cellular maturation and integration, allowing reproducible measurement of human-relevant circuit-level activity under physiological conditions over a long period. A similar program was also launched by the Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative.²⁴⁰ These improved assays may enable complex studies of the development, function, and aging of nervous systems in healthy and disease states.

Investments in *in vitro* technologies led to an influx of exciting and influential findings in the past year. In a new study published in 2023, NIH-funded researchers used a chip to simulate repeated overdoses and treatments to study the effects on the chip’s organs. The project was part of the Helping to End Addiction Long-term® Initiative (NIH HEAL Initiative®) in partnership with NCATS. In another study, NEI and NCATS co-developed 3-D bioprinted vascularized eye

²³⁹ The FY 2025 President’s Budget proposes to rename the National Institute on Alcohol Abuse and Alcoholism to the National Institute on Alcohol Effects and Alcohol-Associated Disorders.

²⁴⁰ RFA-MH-20-140: grants.nih.gov/grants/guide/rfa-files/rfa-mh-20-140.html

tissue with native tissue-like properties and used it for drug testing.²⁴¹ NEI and NCATS performed drug screening using similar models, leading to the discovery of drug candidates to treat ciliopathy and macular degeneration.²⁴² NEI and the National Heart, Lung, and Blood Institute (NHLBI) used patient-specific human adult cell-derived induced pluripotent stem cells (iPSCs) to discover disease causing mechanisms in a 3-D bioprinted vascularized eye tissue that reproduced macular degeneration in a dish.

In silico models

NIH also supports the development and use of *in silico* models to advance biomedical research. In recent years, the increased use of computational models using artificial intelligence (AI), including machine learning (ML) and deep learning (DL), has been enabled by greater computer performance and the ability to collect, store, and process vast amounts of data. NIH has prioritized the development of transformative AI/ML-based systems, emerging tools, and modern technologies for diagnosing and recommending treatments for a broad range of human diseases. The section on Artificial Intelligence within this chapter on cross-cutting initiatives goes into greater detail about the many initiatives that NIH has launched to tackle complex biomedical challenges, including Bridge2AI²⁴³ and AIM-Ahead²⁴⁴ (Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity).

These programs and initiatives further leverage existing data and discoveries by using *in silico* models in a broad array of applications and fields. For example, researchers funded by NIDCD are developing a machine learning model to diagnose inner ear conductive pathologies to improve surgical specificity, minimize unnecessary exploratory surgery and imaging, and provide an objective clinical means of postoperative monitoring. Meanwhile, researchers funded by the National Institute for Allergy and Infectious Disease (NIAID) are using *in silico* models to predict the activity of new antibiotic combinations to fight antimicrobial resistance. As the need for combinatorial antibiotic approaches grows, these methods allow researchers to optimize therapies for patients in the clinic.

In chemico models

NIH continues to support efforts to use and develop *in chemico* NAMs, or cell-free experiments in which biological molecules can be studied in isolation or in complexes separate from their native environment. These highly controlled experiments allow detailed observation of biochemical interactions such as the structure and function of DNA, RNA, or proteins in isolation or in combination, and how potential drugs interact with these biological molecules, including to help establish therapies. As one example, researchers funded by the National Center for Complementary and Integrative Health (NCCIH) are using high-throughput methods to help better understand the basic mechanisms of action of botanical natural products, which can in turn accelerate the process to advance natural product drug discovery.

²⁴¹ pubmed.ncbi.nlm.nih.gov/36550275/

²⁴² pubmed.ncbi.nlm.nih.gov/34911940/; pubmed.ncbi.nlm.nih.gov/36975211/

²⁴³ bridge2ai.org/

²⁴⁴ aim-ahead.net

Resources and Education to Support the Use of NAMs

To move these technologies into widespread use, there must be targeted efforts to broaden their reach. To this effect, NIH is working to develop and disseminate resources to researchers across the biomedical research enterprise. As one example, NIH is creating large scale resources of iPSCs and related data that will be shared broadly with the biomedical community. Human adult cell-derived iPSCs represent a significant improvement in reliable and reproducible use of human-derived biological material to model human biology. Their remarkable developmental potential and unlimited self-renewal capacity *in vitro* enables the generation of many cell types of the human body from a single individual in large quantities. The iPSC Neurodegenerative Disease Initiative²⁴⁵ is the largest iPSC genome engineering project to date and will model more than 100 mutations associated with Alzheimer's disease and related dementias (ADRD) in isogenic iPSC lines. Similarly, the Molecular Phenotypes of Null Alleles in Cells (MorPhiC) program²⁴⁶ aims to create a catalogue characterizing the impact on *in vitro* multicellular systems when genes do not produce functioning proteins. NIH supports the Scalable and Systematic Neurobiology of Psychiatric and Neurodevelopmental Disorder Risk Genes (SSPsyGene) program^{247,248} that aims to functionally characterize phenotypes for more than a hundred risk genes for neurodevelopmental and psychiatric disorders.

In January 2023, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) launched the intramural Center for Biomedical Engineering and Technology Acceleration (BETA Center), a multi-institute NIH resource that accelerates the development, validation, and dissemination of high-impact biomedical technologies to address urgent national and global health needs.

The National Cancer Institute (NCI) is advancing resources for researchers to use patient-derived and next generation cancer models to understand unique characteristics of individual cancers, identify possible treatments, and test those treatments for efficacy. The Human Cancers Model Initiative is an international collaboration that has generated over 250 models from 27 different cancer types available to researchers through an online catalogue.²⁴⁹ Similarly, NCI's Patient-Derived Models Repository has created over 1,800 various patient-derived models to date that it distributes to the cancer research community upon request.²⁵⁰

Likewise, computational models are an increasingly used tool in research, including the cancer field. NCI supports the development and use of computational models to understand how cancer develops, progresses, and may or may not respond to treatment. NCI-funded researchers recently used both mouse and computational models to understand the evolution of pancreatic cancers, including inflammatory events that can lead to tumor development in certain subpopulations of cells with a specific mutation. Having this roadmap for cancer development

²⁴⁵ card.nih.gov/research-programs/ipsc-neurodegenerative-disease-initiative

²⁴⁶ genome.gov/research-funding/Funded-Programs-Projects/Molecular-Phenotypes-of-Null-Alleles-in-Cells

²⁴⁷ grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-110.html

²⁴⁸ grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-111.html

²⁴⁹ cancer.gov/ccg/research/functional-genomics/hcmi

²⁵⁰ pdmr.cancer.gov/

can help with strategies to detect or even prevent pancreatic tumors before they reach an advanced stage.

The Office of Resource Infrastructure Programs (ORIP) supports research infrastructure and research-related resource programs. One such resource is BioGRID: Biological General Repository for Interaction Datasets,²⁵¹ a public database that archives and disseminates genetic and protein interaction data from model organisms and humans. BioGRID currently holds over 1,400,000 interactions curated from both high-throughput datasets and individual focused studies, as derived from over 57,000 publications in the primary literature.

NIH also collaborates with partners in the private and public sectors, including DARPA and FDA, on advancements for NAMs. Recently, the Validation Workgroup of ICCVAM, co-chaired by the National Institute of Science and Technology (NIST), FDA, and Consumer Product Safety Commission (CPSC), put out a draft report on Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies and is now reviewing and incorporating public comment it received in September 2023.²⁵² The report has been reviewed by the Scientific Advisory Committee on Alternative Test Methods and will be finalized by early 2024.

As part of the commitment to promote the use of the most appropriate models, NIH provides numerous trainings, programs, and resources to researchers to promote animal care and appropriate use of NAMs. NIH works directly with the research community to advance their understanding of the science underlying alternative methodologies, through podcasts (See NIH All About Grants Podcast on Alternatives to Animals)²⁵³ and webinars.

Many educational programs are run by specific ICOs to focus on a disease- or system-specific use of NAMs. As one example, the National Institute on Diabetes and Digestive and Kidney Disease (NIDDK) held a workshop entitled “Microphysiological Systems for Studying Type 2 Diabetes, Obesity, and Their Complications” in September 2023.²⁵⁴ Other educational programs are held to discuss overarching methods for catalyzing the development and use of NAMs across the biomedical research enterprise, such as the Office of Laboratory Welfare’s (OLAW) annual support of the 3Rs Symposium in partnership with John Hopkins University and the U.S. Department of Agriculture (USDA). In May of 2023, the symposium celebrated its 10th anniversary, with the theme “The 3Rs in Action!”²⁵⁵

An Ambitious Path Forward: Spurring Scientific Advances with NAMs

In its final report, the ACD Working Group on NAMs identified seven bold, ambitious, and equitable high priority areas for future investment in NAMs: 1) combinatorial NAMs; 2) interoperable, reliable datasets; 3) effective technology dissemination and interconnection; 4) comprehensive training; 5) multidisciplinary teams; 6) socially responsible technologies; and 7)

²⁵¹ orip.nih.gov/resource-directory/biogrid-biological-general-repository-interaction-datasets-0; thebiogrid.org/

²⁵² ntp.niehs.nih.gov/sites/default/files/2023-08/VWG%20Report%20Draft_for%20public%20comment_08Aug2023.pdf

²⁵³ nexus.od.nih.gov/all/2020/11/18/all-about-grants-podcast-alternatives-to-animals/

²⁵⁴ nidk.nih.gov/news/meetings-workshops/2023/microphysiological-systems-for-studying-t2d-obesity-and-complications?agenda

²⁵⁵ olaw.nih.gov/news/registration-open-10th-annual-3rs-symposium-3rs-action.html

coordinated infrastructure.²⁵⁶ These areas highlight the power and opportunity of integrated work that brings together different disciplines, sectors, technologies, and data. The ACD Working Group's final report, which was accepted by the ACD and shared for consideration of the NIH Director in December 2023, provides a roadmap forward to catalyze the development and use of NAMs at NIH and beyond.

The implementation of these recommendations will be an NIH-wide effort that builds upon the ongoing projects described here. For example, the Common Fund, a funding entity within NIH that supports bold scientific programs that catalyze discovery across all biomedical and behavioral research, is planning a potential new program called Complement Animal Research in Experimentation (Complement-ARIE) that would bring together multiple ICOs to catalyze the development, standardization, validation, and use of human-based NAMs.²⁵⁷ The NIH looks forward to using this collaborative and innovative funding model, along with other programs outlined above and new, nascent ideas inspired by the new ACD Working Group recommendations to expand the researcher toolkit and catalyze scientific advances using NAMs.

²⁵⁶ acd.od.nih.gov/documents/presentations/12142023_NAMs_Working_Group_Report.pdf

²⁵⁷ commonfund.nih.gov/complementarie/strategicplanning

CHRONIC PAIN AND SUBSTANCE USE DISORDER

Program Overview

NIH launched the Helping to End Addiction Long-term (HEAL)[®] Initiative to provide scientific solutions to the opioid crisis by accelerating research on prevention and treatment of opioid misuse, addiction, overdose, and non-addictive treatments for pain conditions. NIH has a crucial role in reducing overdose deaths through research aligned with the HHS overdose prevention strategy (primary prevention, evidence-based treatment, harm reduction, recovery support). Extensive overprescribing of opioid analgesics contributed to the opioid crisis, highlighting an urgent need for evidence-based, effective, and safe pain management to alleviate pain and mitigate need for opioids. Moreover, addressing the intersection of chronic pain and opioid use disorder (OUD) is an important part of HEAL research, as chronic pain often co-occurs in people with OUD, and people with chronic pain on long-term opioid therapy can be at risk for OUD.

The HEAL Initiative is led by the National Institute on Drugs and Addiction (NIDA)²⁵⁸ and the National Institute of Neurological Disorders and Stroke (NINDS) in collaboration with other NIH Institutes, Centers, and Offices (ICOs), including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute of Mental Health (NIMH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Center for Complementary and Integrative Health (NCCIH), National Institute of Allergy and Infectious Diseases (NIAID), National Center for Advancing Translational Sciences (NCATS), National Cancer Institute (NCI), National Institute of Nursing Research (NINR), National Institute on Minority Health and Health Disparities (NIMHD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of General Medical Sciences (NIGMS), National Institute on Alcohol Effects and Alcohol-Associated Disorders (NIAAA),²⁵⁹ National Heart, Lung, and Blood Institute (NHLBI), National Institute on Aging (NIA), National Institute of Biomedical Imaging and Bioengineering (NIBIB), NIH Clinical Center (CC), and the NIH Tribal Health Research Office. Appropriated funds for HEAL are split between NIDA for substance use disorder (SUD) research and NINDS for pain management research. ICO partners coordinate overarching research and related initiatives at the intersection of pain and addiction; diversity, equity, inclusion, and accessibility; health disparities; community engagement; data sharing; and dissemination of research results. HEAL research on SUD extends beyond the intersection of pain and OUD discussed in this chapter. (See the CJ chapters for NIDA and NINDS for more about other HEAL programs.) NINDS and other ICOs also support research on understanding, treating, and preventing chronic pain beyond the HEAL programs highlighted here.

HEAL Programs at the Intersection of Treatment for Pain and Opioid Use Disorder

Chronic pain often co-occurs in people with OUD, yet for these individuals, a lack of evidence-based guidelines for concurrent treatment of both conditions can lead to poor health outcomes.

²⁵⁸ The FY 2025 President's Budget proposes to rename the National Institute on Drug Abuse to the National Institute on Drugs and Addiction.

²⁵⁹ The FY 2025 President's Budget proposes to rename the National Institute on Alcohol Abuse and Alcoholism to the National Institute on Alcohol Effects and Alcohol-Associated Disorders.

HEAL addresses this problem with two related programs. The Integrative Management of chronic Pain and OUD for Whole Recovery (IMPOWR) network will develop and test patient-centered interventions for co-occurring chronic pain and OUD in healthcare settings including primary care, opioid treatment programs, and hospitals. IMPOWR research focuses on treatment of the whole person, recognizing the influence of stigma, health inequities, and co-occurring mental health disorders. Challenges and solutions related to treatment barriers are addressed through partnerships with patient and community partners to maximize benefits of interventions and embed effective practices into health care systems. IMPOWR is generating a comprehensive dataset on chronic pain and OUD that includes measures on co-occurring psychiatric conditions, social determinants of health, cost-effectiveness evaluations, and intervention implementation. Researchers also have run several pilot studies to understand how stigma toward these populations affects health service provision and outcomes.

The second program is the Multilevel Interventions to Reduce Harm and Improve Quality of Life for Patients on Long Term Opioid Therapy (MIRHIQL). This program enhances IMPOWR through research to develop and evaluate interventions to prevent SUD in people who are on long-term opioid therapy without access to safer, high-quality care for chronic pain and may be at risk for OUD. Harms of long-term opioid therapy can include tolerance development with reduced analgesic relief and increased risk for concurrent benzodiazepine or alcohol use. MIRHIQL supports effective, patient-centered protocols for decreasing opioid doses (tapering) for patients on long-term opioid therapy and is creating a risk-benefit assessment tool to assist providers in deciding when opioids should be continued as prescribed, tapered, or discontinued.

Health Disparities in OUD and Pain

Quality care for all people with OUD, pain, and other co-occurring conditions often is difficult to access, but this challenge is especially great for populations who experience health disparities, including racial/ethnic minorities, socioeconomically disadvantaged populations, underserved rural populations, and members of the LGBTQ+ minority community. The HEAL Advancing Health Equity in Management of Pain and Co-occurring Conditions program supports research on evidence-based interventions tailored to these populations, with a goal to improve health outcomes via culturally appropriate approaches. ICOs with interests in many pain conditions manage the program, including NCI, NCCIH, NIA, NICHD, NINR, and NIMHD. The research explores multi-level interventions—from single providers to communities to health care systems—that are scalable, sustainable, and can be implemented rapidly into health care. For example, one project is developing an interactive simulation to assess effects of a care provider's biases on treatment decisions for patients prescribed opioids for pain. The simulation allows the research team to evaluate the influence of race or income on the doctor's decision about continuing opioid therapy. Their data will help to design solutions to reduce treatment biases.

Quality Data Collection and Sharing

Data harmonization and sharing across all pain and OUD studies are needed to ensure that data can be compared and used to answer broader research questions. The HEAL Data Ecosystem provides a platform for scientists to securely share data so they can be reused and reanalyzed by the broad OUD and pain research community, providing a foundation for future research. HEAL Connections translates data to put results into practice, building a bridge between the research setting and patients, caregivers, care providers, and others who can benefit from the findings.

The Initiative also includes a suite of other programs to enhance data collection and examination. The HEAL Data2Action (HD2A) program is a network of research projects and resource centers to accelerate use and enhance quality of data on the epidemiology of the opioid crisis and guide health service improvements for OUD and pain management. HD2A projects link data systems and create dashboards to track care quality and treatment strategies that improve patient outcomes. Researchers work with health care partners to improve data infrastructure to identify and fill service delivery gaps. The HD2A Data Infrastructure Support Center developed the HEAL Initiative HD2A Addiction and Chronic Pain Template,²⁶⁰ an open-source online application to help researchers create Data Management and Sharing plans that comply with data sharing policies. The tool helps in navigating sharing requirements and provides policy guidance to support overall HEAL goals to make data more FAIR (Findable, Accessible, Interoperable, and Reusable) and amplify use of research findings on pain and addiction. Another innovative program, the HEAL Data and Methods to Address Urgent Needs to Stem the Opioid Epidemic program,²⁶¹ is developing approaches to provide insights into patterns of opioid and other prescription drug use and misuse from data streams such as electronic health records, epidemiological surveillance, health claims data, pharmacy dispensing, and mortality records. These projects will facilitate rapid monitoring of the opioid crisis to advance prevention and treatment efforts and inform decision making and resource allocation in local jurisdictions.

Enhancing the Research Workforce

A collective effort across all HEAL ICOs aims to improve the quality of research on pain and OUD through training, mentoring, and networking experiences for early-stage career scientists. This includes programs to support diverse populations at different career stages and innovative strategies for learning and career development. One approach couples a nationwide networking and training platform for pain scientists with a national network of mentors to train scholars in clinical pain research. The PURPOSE Network—for Positively Uniting Researchers of Pain to Opine, Synthesize, & Engage—is the first online platform for connecting pain researchers, serving as a central facilitator to enhance career development, integrate training, and connect with mentors. The National K12 Clinical Pain Career Development Program is a nationwide network of mentors and scholars to provide research training for early-stage career clinicians. It works with PURPOSE to offer training tools and resources for both scholars and mentors. The program enrolled its first wave of scholars and developed guidelines for mentoring and career development to promote their successful transition into independent research careers. HEAL also provides early- and mid-career scientists pursuing pain or opioid misuse research with hands-on training in translational research aimed at therapeutics development in industry, academia, or government research laboratories. Trainees receive broad exposure to therapeutics development while institutions benefit from trainees' pain or addiction expertise.

Other HEAL Research on Non-Opioid Pain Management

HEAL pain research spans early discovery of therapeutic targets and implementation of evidence-based care. HEAL preclinical and translational research in pain management supports efforts to discover new medications and devices to treat pain. HEAL clinical pain research

²⁶⁰ hd2arasc.org/resources/

²⁶¹ grants.nih.gov/grants/guide/rfa-files/RFA-DA-22-044.html

includes networks to run trials to test effectiveness of pharmacologic and non-pharmacologic treatments and studies approaches to embed quality pain care into health care systems. Examples described below show progress toward effective, non-opioid approaches to treating pain.

Finding New Targets for Non-Addictive Pain Treatments

A long sought-after goal has been to understand changes in brain activity related to pain. A recent HEAL study reported new findings on brain activity associated with pain that offer opportunities to modulate brain circuits to reduce chronic pain. For the first time researchers recorded pain-related data over several months from inside the brain of individuals with chronic pain disorders and analyzed the data with machine learning tools. They identified a brain area associated with chronic pain and objective biomarkers of chronic pain in individual patients.²⁶²

Another HEAL team set out to find brain regions in preclinical models that might be targets for non-opioid pain interventions. Their novel approach was to find a pain-relief center in the brain by exploring regions that are activated by surgical anesthetics that block pain. Through optogenetic technology they identified neurons in the amygdala that were activated when mice were exposed to anesthetics. This brain region did not previously have a known role in pain relief. Further studies showed that activating these neurons suppressed pain by inhibiting a network of pain-activating neurons in other regions of the brain.²⁶³ These two sets of findings are important steps towards developing novel methods for assessing and treating chronic pain.

The Program to Reveal and Evaluate Cells-to-gene Information that Specify Intricacies, Origins, and the Nature of Human Pain (PRECISION Human Pain) network focuses on identifying mechanisms underlying the pain experience. It coordinates, harmonizes, and integrates comprehensive datasets generated from human tissue-based research by capitalizing on recent technological advances to study human tissues and cells involved in pain processing. It seeks to identify molecular signatures and cell types that underlie pain pathways, to enable future translational research leading to development of non-addictive pain therapies.

To address the shortage of promising treatments in the drug development pipeline, the Pain Therapeutics Development Program is providing funding that is propelling potential pain drugs closer to testing in human participants and helping small companies attract venture capital to support late-stage clinical trials. Eight potential new pain treatments have received the green-light from the Food and Drug Administration to proceed with Phase 1 clinical trials.

HEAL Pain Clinical Research

HEAL established clinical research networks for various stages of clinical trials. The Back Pain Consortium (BACPAC) is exploring biological, psychological, and social factors that contribute to chronic low back pain and has developed diagnostic tools and a data analysis platform for its various trials to leverage. One of those trials is studying the link between such factors and whether they influence the effectiveness of four different treatments. The evidence generated could help doctors and patients determine the best personal course of action for their back pain treatment. Through the Effectiveness Research Network, clinical trials are evaluating best

²⁶² [nature.com/articles/s41593-023-01338-z](https://www.nature.com/articles/s41593-023-01338-z)

²⁶³ pubmed.ncbi.nlm.nih.gov/32424286/

approaches for acute pain management to prevent onset of chronic pain, including one trial showing that shared treatment decision strategies and education about post operative pain care reduced post-operative prescription opioid use after cesarean section.

A trial supported through the Small Business Innovation Research Program showed that effective perioperative pain management improved post-surgical pain outcomes, including reduced use of opioids. This research team questioned the trend toward reducing opioids during surgery, a practice intended to reduce opioid prescribing that may actually lead to increased postoperative pain and subsequent increased need for postoperative opioid prescribing. The team showed that increasing fentanyl administration during surgery led to less uncontrolled pain, lower risk of chronic pain after surgery, and fewer opioid prescriptions up to six months after surgery.²⁶⁴ Their findings suggest that optimizing opioid use during surgery may prevent chronic pain.

Future Directions for HEAL Research

As HEAL looks to the future, the newest funding opportunities will ensure that research being generated will reach all of those in need of quality care for chronic pain and OUD, particularly in populations where access or evidence is lacking, such as American Indian/Alaska Native communities, pediatric populations, and those requiring integrated care from multiple providers.

NIH held Tribal consultations on research needs to address opioid misuse and pain management in Native communities. These highlighted the importance of Indigenous knowledge and local expertise and the need to invest in community-prioritized research led by Tribes and Native American Serving Organizations (T/NASOs). In response, HEAL established the Native Collective Research Effort to Enhance Wellness (N CREW) as a partnership with American Indian/Alaska Native and Native Hawaiian communities. N CREW is a collaboration between NIDA, NINDS, and NCATS with other ICOs participating. It will support T/NASOs in leading community research projects with a focus on integrating Indigenous knowledge and culture. N CREW will enhance research capacity within T/NASOs through accessible, culturally grounded technical assistance and resources, as well as improved access to quality data on substance use, pain, and related health and well-being factors for use in local decision-making.

Children represent another population in urgent need of better pain management. Care for children is often challenging in part because of lack of evidenced-based pain treatment guidelines. They also are often at risk for OUD because they are opioid naïve and may be exposed to opioids without proper risk assessment. HEAL KIDS is a program led by NICHD and NIAMS that supports innovative clinical trials to test safe effective therapies and at the same time advance the understanding, assessment, measurement, and treatment of pain in infants, children, and adolescents, including those with disabilities and/or experiencing health disparities.

Future activities also will focus on integrated care models for chronic pain. The Coordinated Approaches to Pain Care in Health Care Systems program, led by NINDS with other ICO support, will support research projects to embed effective coordinated pain care into health care systems. The goal will be to improve pain and health outcomes through delivery of integrated

²⁶⁴ jamanetwork.com/journals/jamasurgery/fullarticle/2806264

multidisciplinary care that includes appropriate medication, behavioral therapy, physical rehabilitation, and pain self-management. The coordinated care delivery will be centered in primary care settings with referrals to specialty care or delivered through specialty care settings in coordination with primary care.

CUTTING-EDGE CLINICAL RESEARCH AND INFRASTRUCTURE AT THE NIH CLINICAL CENTER

Program Overview

At the NIH Clinical Center, clinical research participants—more than 500,000 since the hospital opened in 1953—are active partners in medical discovery, a partnership that has resulted in a long list of medical milestones, including development of chemotherapy for cancer; the first use of an immunotoxin to treat a malignancy (hairy cell leukemia); identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer; the demonstration that lithium helps depression; the first gene therapy; the first treatment of Acquired Immunodeficiency Syndrome (AIDS) (with azidothymidine [AZT]); and the development of tests to detect AIDS/HIV and hepatitis viruses in blood, which led to a safer blood supply. Patients come from all 50 states and from around the world.

Currently, there are about 1,600 clinical research studies in progress at the Clinical Center. About half are studies of the natural history of disease, especially rare diseases, which often are not studied anywhere else. What researchers learn by studying rare diseases often adds to the basic understanding of common diseases. Most other studies are clinical trials, which often are the first tests of new drugs and therapies in people. The clinical trials at the Clinical Center are predominantly Phase I and Phase II, often first-in-human to test safety and efficacy.

The Clinical Center has been a leader in “bench-to-bedside” medicine. Its specialized hospital design places patient care units in close proximity to research laboratories, facilitating interaction and collaboration among clinical researchers. The Clinical Center also offers world-class training in clinical research for physicians, nurses, medical students, dentists, and other members of the medical research community. This environment, offering access to the most advanced techniques, equipment, and ideas, attracts a global network of top scientists.

The hospital has 200 inpatient beds, 11 operating rooms, 93 day-hospital stations, critical care services and research labs, an ambulatory care research facility for outpatient visits, two onsite pharmacies, a blood bank, and a complex array of imaging and diagnostic services. The Clinical Center’s infrastructure allows for isolation capabilities for infection control while patients participate in clinical research studies.

The Clinical Center serves as a valuable resource to researchers, its patients, and biomedical research, and as such conducts a wide array of clinical research in conjunction with other Institutes and Centers at NIH. Due to its unique environment as a government research hospital, the Clinical Center also participates in a number of additional accrediting programs to ensure it is a world-class facility. For example, Clinical Center graduate medical education (GME) programs are accredited by the Accreditation Council for Graduate Medical Education (ACGME), and the Department of Laboratory Medicine (DLM) is accredited by the College of American Pathologists (CAP).

Furthermore, the Clinical Center is accredited as a whole by the Joint Commission, an independent, not-for-profit organization that accredits and certifies more than 20,500 health care organizations and programs in the United States. Joint Commission accreditation and

certification is recognized nationwide as a symbol of quality that reflects an organization's commitment to meeting certain performance standards. To maintain and earn accreditation, organizations must have an extensive onsite review by a team of Joint Commission healthcare professionals at least once every three years. The review's purpose is to evaluate the organization's performance in areas that affect patient care. The Clinical Center received full accreditation status in 2021.

Diversity, Equity, Inclusion and Accessibility Efforts

The Clinical Center is dependent on a diverse workforce with a culture of teamwork and collaboration. The hospital has developed a comprehensive DEIA program to combat racism and reduce disparities across its workforce. Efforts are focused on promoting diversity and inclusion by reducing disparities, promoting inclusivity and equity, and lifelong learning.

Importantly, one of the many benefits of this program is that it also supports the Clinical Center's emphasis on providing culturally sensitive care for its patients. The Clinical Center provided a video²⁶⁵ to staff announcing the launch of the program.

The Clinical Center is committed to transparency in addressing Diversity, Equity, Inclusion and Accessibility (DEIA). Workforce demographics specifically of Clinical Center government employees are available on the NIH Office of Equity, Diversity, and Inclusion's Workforce Demographics webpage.²⁶⁶

The Clinical Center has made many strides in the last year in support of its DEIA program, including the hiring of a new Scientific Diversity Officer and implementation of multiple additional programs born out of its Racial and Ethnic Equity Plan, some of which are outlined below.

In striving to support more diverse representation in recognition, retention, and development programs, the Office of Workforce Management and Development (OWMD) works closely with the Clinical Center Executive Leadership team to apply the Racial and Ethnic Equity Lens (REEL) to all decisions relating to these programs. Additionally, the Clinical Center has created a written policy for hiring and advancement, initially focused on the Nursing Department. This policy is being implemented now, with nursing leadership engaging departmental Nurse Educators to train staff on the use of the policy, and the Nursing Diversity, Equity, and Inclusion Council assisting with communication and implementation of the policy and related recommendations. As potential candidates for promotion and/or hire are identified, this new policy will be utilized to help ensure equitable decision making in the selection process. As is standard practice, the policy will be reviewed regularly to assess the need for any changes or additions after implementation, and will be expanded to the entire hospital.

While the Clinical Center is a relatively diverse²⁶⁷ organization overall, there is less representation at the senior levels of the organization. In order to communicate its commitment

²⁶⁵ [youtube.com/watch?v=HGL4ROH0NHw](https://www.youtube.com/watch?v=HGL4ROH0NHw)

²⁶⁶ edi.nih.gov/data/demographics/ic-workforce-demographics#cc

²⁶⁷ edi.nih.gov/data/demographics/ic-workforce-demographics#cc

to DEIA, the Clinical Center inserted additional language into USAJobs announcements for senior positions that underlines the importance of experience with racial and ethnic equity. The Clinical Center also, when related to the duties of Clinical Center positions, inserted a specific question about experience working on DEIA initiatives in the hiring questionnaire applicants must answer to be considered for vacancies.

Further, the Clinical Center has robust programs in place when assessing existing or designing new space or facilities, reviewing hiring practices, and developing technical solutions. However, there is still always opportunity for advancement and improvement. The Clinical Center will work to eliminate barriers related to the employment, promotion, and advancement of people with disabilities as well as any physical or structural barriers. The FY 2024 focus on enhancing accessibility within the Building 10 Complex and Clinical Center operations consists of two primary components: Education and Practical Measures.

NIH Collaboration

The Clinical Center serves as the physical location for almost all the clinical research performed as a component of the NIH Intramural Program. This includes providing essential infrastructure that is responsive to the needs of the other NIH Institutes and Centers, such as the newly upgraded pharmacy and enhanced pediatrics program.

In addition to providing essential support to the rest of the organization, the Clinical Center also has its own research program, which has produced many exciting developments in the last few years. This research program is also informed by the priorities of the other NIH Institutes and Centers, and thus reflects the overall focus of NIH. Below are a few examples of advances that have recently occurred at the Clinical Center.

Sickle Cell Disease Treatment Trial

In models of sickle cell disease, a Clinical Center team conducted a pre-clinical trial of mitapivat, a drug that activates a key enzyme in the pathway to break down glucose in red blood cells. They showed that mitapivat increases adenosine triphosphate (ATP), which provides energy to power red blood cells and decreases the ineffective production of red blood cells in the model. These findings provided preclinical support for the testing of the drug in clinical trials to treat sickle cell disease in humans, which are now ongoing. If successful, the use of glycolysis activators might bring about a paradigm shift for the treatment of sickle cell disease.

Neurorehabilitation and Biomechanics Research Advance

A Clinical Center laboratory designed and implemented a real-time Electroencephalography (EEG)-based neurofeedback system to train motor skills in children with cerebral palsy who have brain injuries early in development that impair their motor abilities. Traditional therapies fail to restore some lost motor skills. The developed neurofeedback system uses brain-computer interface and deep learning methodologies to detect the child's own brain signals to activate enhanced sensory feedback during active motor training that strengthens neural and motor pathways. In the first 3 children enrolled, the team has already observed positive changes in

function and brain activation from only 10 training sessions, highlighting the potential of this novel approach.

Fungal Infection Diagnosis

Fungal infection, an often-deadly complication in transplant patients, is very difficult to identify early enough to allow successful treatment. The Clinical Center has modified a naturally occurring sugar that can be used as an imaging marker of fungal infection. This development has the potential to significantly improve the prognosis and survival of this vulnerable patient population.

Interventions for Early Puberty

Children who experience early puberty are at risk for adult short stature. Medication that blocks and delays puberty can result in decreased bone strength with risk of bone fracture later in life. An Clinical Center team evaluated children with a genetic endocrine disorder (congenital adrenal hyperplasia, CAH) at risk for early puberty and found that pubertal blockade for an average of 4.5 years did not compromise bone health in adulthood and did result in improved adult height. This finding will likely improve the treatment of children with CAH who experience early puberty.

Cutting-Edge Ventilators and Pain Management

Patients with advanced cancer frequently have pain that responds poorly to medication and greatly impacts their quality of life. In an ongoing human clinical trial at the Clinical Center, researchers are treating cancer patients with a non-opioid, non-addictive small molecule, RTX, a natural plant product. The ongoing clinical trial has shown that a single dose of this drug provides long-term pain relief, decreases the need for other pain medications, and enables the patient to resume greater activity.

The COVID-19 pandemic highlighted the need for emergency ventilators to support the respiratory care of patients during a crisis. An international collaboration including the NIH Clinical Center was assembled, and their efforts resulted in the development of a miniature (size of a memory stick), inexpensive, easy to use, no-maintenance ventilator that can be rapidly produced with a 3D printer. The Clinical Center has demonstrated proof of principle in a large animal model and is preparing for a first-in-human trial at the NIH.

Next Steps and Goals

The Clinical Center endeavors to maintain a cutting-edge facility with world class medical staff to ensure the best possible clinical care and research support. A primary focus moving forward is to mindfully construct and renovate space to meet the future needs of the NIH clinical research program. For example, in May 2023, construction began on the Surgery, Radiology, and Laboratory Medicine wing that will provide cutting-edge space for many of the necessary functions of the Clinical Center that are currently housed in 1980s-era space with outdated mechanical, electrical, and plumbing infrastructure. The construction work will add 547,290

square feet to the Clinical Center and renovate approximately 82,000 square feet of existing space. Work is anticipated to last until 2029. NIH and the Department of Health and Human Services leaders support these changes to modernize hospital facilities to ensure that the Clinical Center can continue to provide high-quality patient care alongside cutting-edge biomedical research.

THE FUTURE OF THE BIOMEDICAL WORKFORCE

Program Overview

The biomedical research enterprise relies upon a talented, qualified, diverse group of investigators to bring new insights and translate fundamental research findings into improved health. The National Institutes of Health (NIH) has long recognized that the most critical components of the biomedical research enterprise are the scientists who comprise its workforce.

The pathway to a career in biomedical research is long and challenging but ultimately rewarding. While NIH supports programs at the earliest stages of career development, including K-12, undergraduate, and graduate school training,^{268,269} a working group of the Advisory Committee to the Director recently highlighted the unique challenges faced by postdoctoral research scholars,²⁷⁰ and approaches to re-envision the NIH-supported postdoctoral experience.²⁷¹ Concerns about the decreasing numbers of NIH-supported postdocs in recent years were also considered.²⁷² As part of this effort, a 2023 Request for Information²⁷³ was issued and it received over 3,000 public comments on the role of the academic postdoc, fundamental factors influencing postdoctoral training, and possible solutions. The recommendations from this report²⁷⁴ include increasing pay and benefits for all NIH-supported postdoctoral scholars, which aligns with its goal to better support the full and varied talent pool of scholars; improving training and professional development of postdoctoral scholars and facilitating the transition of scholars into their next career stages; and supporting safe and diverse perspectives and environments across research programs. These recommendations are currently being considered by the NIH Director for possible implementation.

NIH continues to make support of early-stage investigators (ESIs) a very high priority. This includes those within 10 years of completing postgraduate clinical training or their highest research degree who have not yet competed successfully for a substantial NIH independent research award. While age to first R01 has been continuously increasing for ESIs, the rate of increase has slowed over the last 10 years.²⁷⁵ In 2023, the mean age was 42.6 for PhDs, 46 for MDs, and 45.7 for MD/PhDs, consistent with recent years.

NIH Institutes, Centers, and Offices (ICOs) oversee a variety of innovative cross-cutting initiatives aimed at supporting the next generation of the NIH-funded biomedical workforce. The following are some of these initiatives.

²⁶⁸ researchtraining.nih.gov/career-path

²⁶⁹ nigms.nih.gov/research-training/programs/high-school-and-undergraduate

²⁷⁰ acd.od.nih.gov/documents/presentations/12152023_Postdoc_Working_Group_Report.pdf

²⁷¹ nexus.od.nih.gov/all/2023/02/14/share-your-thoughts-on-how-to-re-envision-nih-supported-postdoctoral-training/

²⁷² nexus.od.nih.gov/all/2023/03/02/number-of-postdoctoral-researchers-supported-by-nih-grant-awards-fy-2017-fy-2022/

²⁷³ nexus.od.nih.gov/all/2023/02/14/share-your-thoughts-on-how-to-re-envision-nih-supported-postdoctoral-training/

²⁷⁴ acd.od.nih.gov/documents/presentations/12152023_Postdoc_Working_Group_Report.pdf

²⁷⁵ nexus.od.nih.gov/all/2021/11/18/long-term-trends-in-the-age-of-principal-investigators-supported-for-the-first-time-on-nih-r01-awards/

Program Descriptions and Accomplishments

Next Generation Researchers Initiative (NGRI) Focusing on Early-Stage Investigators

NIH has long been committed to expanding opportunities that support and prioritize researchers early in their career. The 21st Century Cures Act (P.L. 114-255) directed NIH to establish the NGRI in an effort to further cultivate and support talent entering the biomedical and behavioral research workforce.²⁷⁶ NGRI promotes opportunities for new researchers and earlier research independence through policies that increase opportunities for new researchers to receive funding, enhance training and mentorship programs, and enhance workforce diversity. As an example, ESI applications are given special consideration during peer review as well as at the time of funding consideration. NIH also tracks the impact of ESI funding prioritization, including subsequent grant submission and success. As a result of this initiative, the number of NIH-funded ESIs has increased from 978 in FY 2016 (before NGRI was started) to 1,513 in FY 2021²⁷⁷ and 1,609 in FY 2022, and 1,587 in FY 2023.^{278,279}

The Stephen I. Katz ESI Research Project Grant Program

The Katz ESI Research Project Grant Program is an initiative with multiple participating NIH ICOs. This program encourages ESIs' innovative ideas by supporting their proposed research that is a change in direction from their past work and experience, and for which they have no preliminary data. All applications received are clustered and reviewed together in appropriate standing NIH study sections, in alignment with NGRI efforts.

The NIH Director's Early Independence Award

The NIH Director's Early Independence Award is a Common Fund initiative coordinated with multiple NIH ICOs. This award supports outstanding junior scientists with the intellect, scientific creativity, drive, and maturity to bypass the traditional postdoctoral training period to accelerate the launch of their independent research careers. The Early Independence Award supported 13 investigators in FY 2023.²⁸⁰

The NIH Director's New Innovator Award

The NIH Director's New Innovator Award, a component of the High-Risk, High-Reward Program of the Common Fund, is coordinated with multiple NIH ICOs. The award supports exceptionally creative ESIs who propose innovative, high-impact projects in the biomedical, behavioral, or social sciences within the NIH mission. This award is different from traditional NIH grants as it specifically supports unusually creative investigators with highly innovative research ideas at an early stage of their career when they may lack the preliminary data required for a conventional R01 grant application. The New Innovator Award supported 58 investigators in FY 2023.²⁸¹

²⁷⁶ grants.nih.gov/ngri.htm

²⁷⁷ nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nih-next-generation-researchers-initiative/

²⁷⁸ report.nih.gov/nihdatabook/category/15

²⁷⁹ report.nih.gov/nihdatabook/report/304

²⁸⁰ commonfund.nih.gov/earlyindependence/fundedresearch

²⁸¹ commonfund.nih.gov/newinnovator/fundedresearch

The NIH Pathway to Independence Award

The Pathway to Independence Award offers an opportunity for highly promising postdoctoral scientists to receive both mentored and independent research support from the same award. The award is intended to foster the development of a creative, independent research program that will be competitive for subsequent independent funding and that will help advance the NIH mission.

Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC)

The MOSAIC program supports talented investigators from diverse backgrounds as they transition from postdoctoral scholars to independent early-stage faculty. The National Institute of General Medical Sciences (NIGMS) leads MOSAIC in coordination with multiple NIH ICOs. The program innovates on the design of individual postdoctoral career transition awards via a cohort-based program that not only builds a community of talented early-career researchers, but also engages scientific professional societies and academic institutions to provide the necessary mentorship, networking, and professional development activities required to successfully achieve this career transition. As of FY 2023, 17 NIH Institutes and Centers have funded a diverse pool of 137 MOSAIC scholars.²⁸² Forty-two scholars have already found faculty positions, with more expected to transition as they progress through the program.

The Medical Scientist Training Program (MSTP)

The NIGMS-led MSTP supports eligible domestic institutions that implement effective and evidence-based approaches for dual degree (e.g., MD-PhD, DO-PhD, DDS-PhD) training leading to the award of both a clinical degree and a research doctorate degree. In FY 2022, the MSTP supported over 1,100 trainees. In FY 2023, NIGMS, in coordination with the National Institute of Mental Health, launched the Leading Equity and Diversity MSTP, a second branch of the program. This program seeks to broaden the institutional and regional diversity of dual-degree clinician scientist training by supporting programs at Historically Black Colleges and Universities, Tribal Colleges and Universities, and institutions in Institutional Development Award (IDeA) states.

Other Efforts to Support Early-Career Researchers

The following initiatives provide additional opportunities to enhance training, retention, and diversification of the broader research community.

The Early-Career Reviewer (ECR) program

The Center for Scientific Review created the ECR program to enrich NIH review panels and develop well-trained peer reviewers. The ECR program provides first-hand experience at grant review to early-career scientists who tend to be more diverse than the applicant pool and reviewers on the whole.²⁸³ As of 2023, 8,032 researchers have served as ECRs and 1,061 ECRs have been or are now members of standing study sections.

Biomedical Informatics and Data Science Training programs

Through this program, the National Library of Medicine supports PhD-level research training in biomedical informatics and data science at 18 universities across the United States, enrolling

²⁸² nigms.nih.gov/training/careerdev/Pages/mosaic-scholars.aspx

²⁸³ public.csr.nih.gov/AboutCSR/Evaluations#reviewer_demographics

approximately 200 trainees per year.²⁸⁴ It offers graduate and postdoctoral training and research experiences in a wide range of areas focused on biomedical data science concepts and methods, helping trainees to develop skills needed to lead independent future research.

The NIH Loan Repayment Program (LRP)

The LRP aims to recruit and retain highly qualified health professionals to careers in biomedical or biobehavioral research. LRPs can repay up to \$100,000 of qualified educational debt over two years for those who are eligible and agree to perform NIH mission-relevant research. A total of 1,323 LRP awards totaling \$92.5 million were made in FY 2023.²⁸⁵

Childcare Supplements for Ruth L. Kirschstein National Research Service Awards (NRSAs)

Recognizing the high cost of childcare, in 2021 NIH began allowing full-time NRSA fellows and trainees to request support for childcare costs. NIH issued fellows 224 childcare cost awards in FY 2021, 313 awards in FY 2022, and 328 awards in FY 2023.²⁸⁶

ESI Extensions

NIH recognizes that some researchers may have lapses in their research or research training or have experienced periods of less than full-time effort. Therefore, NIH offers support for ESIs with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. Reasons such extension requests may be granted include: childbirth, medical concerns, disability, family care responsibilities, natural disasters, and active duty military service.

Administrative Supplements

- **Research Supplements to Promote Diversity in Health-Related Research** have supported eligible individuals from diverse backgrounds, including those from groups that have been shown to be underrepresented in health-related research and researchers with disabilities. NIH renewed its support of these administrative supplements in June 2023 and expanded eligibility to three new grant types.
- The **Research Continuity and Retention Supplements** program assists early-career investigators experiencing crucial life events. Applicants who are mentored career development awardees or first-time recipients of research project grants are eligible for this continuity and retention supplement program. The supplemental funds may be used for additional personnel, computational services, supplies and equipment, or other resources needed to sustain the investigator's research. Critical life events that qualify for consideration include high-risk pregnancy; childbirth; adoption; serious personal health issues such as illnesses and/or debilitating conditions; and primary caregiving responsibilities for an ailing spouse, child, partner, parent, or other member of the

²⁸⁴ nml.nih.gov/ep/GrantTrainInstitute.html

²⁸⁵ report.nih.gov/nihdatabook/category/29

²⁸⁶ nexus.od.nih.gov/all/2022/08/10/preliminary-data-on-childcare-cost-support-for-national-research-service-award-nrsa-individual-fellows/

immediate family. During the first two fiscal years of the program (2020–2021) the most cited reason for requesting a supplement was childbirth (77 percent).²⁸⁷

- The **Research Supplements to Promote Re-entry and Re-integration into, and Retraining in Health-Related Research Careers** set of programs provide provides administrative supplements to existing NIH research grants to support full- or part-time research by researchers returning to the scientific workforce or those wishing to expand their skill set. The Re-entry Supplements Program provides mentored research training opportunities for a minimum of one year to scientists who have had at least six months of interruption in their careers for family responsibilities or other qualifying circumstances. The Reintegration program addresses the critical need to enable researchers, including predoctoral students, who are adversely affected by unsafe or discriminatory environments resulting from unlawful harassment, to rapidly transition into new safer, and more supportive research environments. The Retraining/Retooling program provides support and protected time for a mentored research experience that allows an early or mid-career candidate to obtain new skills and permits the candidate to move to a new research environment while augmenting the parent grant. The supplements are designed to enhance existing research skills and knowledge to prepare applicants to apply for independent research support.²⁸⁸

Diversity, Equity, Inclusion, and Accessibility (DEIA)-Focused Initiatives and Awards

The one-time NIH DEIA Prize Competition coordinated by the Chief Officer for Scientific Workforce Diversity rewards effective strategies for enhancing DEIA in research environments. It aims to recognize transformative cultures, systems, projects, and processes developed by academic institutions to promote inclusive excellence and create environments that foster and value a culture of DEIA. NIH awards up to 10 prizes of \$100,000 each through the competition with up to half of the prizes set aside for consideration of limited-resource institutions. Awardees will be announced in 2024.

Advisory Committee to the Director (ACD) Working Group (WG) on Diversity, Subgroup on Individuals with Disabilities

The ACD WG on Diversity subgroup on Individuals with Disabilities released a report in 2022²⁸⁹ proposing detailed and actionable suggestions to support the inclusion of individuals with disabilities in the scientific workforce.²⁹⁰ Some key changes the WG suggested include expanding efforts to include the perspectives of disability communities including researchers with disabilities in NIH initiatives. In response, an ad hoc group was formed to re-examine the NIH mission statement in response to a recommendation that it be made more inclusive of people with disabilities. Furthermore, the DEIA working group of the NIH Steering Committee established a Disabilities Subgroup to address recommendations without a clear owner, such as changing culture, addressing ableism, and examining research gaps.

²⁸⁷ orwh.od.nih.gov/career-development-education/research-continuity-retention-supplements

²⁸⁸ grants.nih.gov/grants/guide/notice-files/NOT-OD-23-170.html

²⁸⁹ acd.od.nih.gov/documents/presentations/12092022_WGD_Disabilities_Subgroup_Report.pdf

²⁹⁰ nexus.od.nih.gov/all/2023/06/05/more-early-stage-investigators-supported-in-fy-2022/

Simplified Peer Review Framework for Research Project Grants

NIH is implementing a simplified peer review framework for research project grants across the agency for grant receipt deadlines of January 2025 and beyond.²⁹¹ Amongst other things, the new framework changes the evaluation of investigator and environment from scored criteria to a binary assessment of sufficiency. This will focus reviewers on expertise and resources in the context of the proposed work, thus mitigating the undue influence of the reputation of the institution or investigator. These changes will help to better focus reviewers on the scientific merit of proposed research and deemphasize the career stage and institutional record of the investigator. This change is intended to give less established investigators a better chance of securing NIH funding.

Faculty Institutional Recruitment for Sustainable Transformation (FIRST)

The Common Fund's FIRST program aims to enhance and maintain cultures of inclusive excellence in the biomedical research community. "Inclusive excellence" refers to cultures that establish and sustain scientific environments that cultivate and benefit from a full range of talent. NIH aims to facilitate institutions in their building a self-reinforcing community of scientists, through recruitment of a critical mass of early-career faculty who have a demonstrated commitment to inclusive excellence. The program also seeks to have a positive impact on faculty development, retention, progression, and eventual promotion, as well as to develop inclusive environments that are sustainable.²⁹² The program supports a total of 15 cohorts.²⁹³

Implementing UNITE Efforts to Address Structural Issues Impacting Career Progression for Investigators from Diverse Backgrounds

The UNITE program acts as a think tank to promote equity, generate bold ideas, and catalyze new actions. UNITE is committed to identifying and addressing any racial and ethnic inequities in the greater scientific community via strategic, short- and long-term actions and funding initiatives that will result in significant, lasting change. UNITE focuses on health disparities and minority health research, the internal NIH workforce, and the external research workforce—topics that intersect and enable greater transparency, accountability, and communication across NIH and the biomedical and behavioral research community. UNITE released a progress report on data-driven efforts and developing initiatives in 2022.²⁹⁴ To support the overall diversity in the biomedical workforce, UNITE has released a funding opportunity called the **Research With Activities Related to Diversity** program. The program's overarching goal is to enhance the breadth and geographical location of research and research-related activities supported by NIH by providing support for the health-related research of scientists who are making a significant contribution to DEIA and who have no current NIH research project grant funding.²⁹⁵

Conclusion

NIH recognizes that researchers are the foundation of the biomedical research enterprise. To ensure a sustainable, diverse workforce of the future, NIH is supporting many efforts to support

²⁹¹ nexus.od.nih.gov/all/2023/10/19/announcing-a-simplified-review-framework-for-nih-research-project-grant-applications/

²⁹² commonfund.nih.gov/FIRST

²⁹³ commonfund.nih.gov/first/fundedresearch

²⁹⁴ nih.gov/sites/default/files/research-training/initiatives/ending-structural-racism/UNITE-progress-report-2022.pdf

²⁹⁵ grants.nih.gov/grants/guide/pa-files/PAR-23-122.html

individuals throughout the research career continuum. Moving forward, NIH is committed to the continued support of early career researchers through these and other targeted initiatives.

HIGH-RISK, HIGH-REWARD RESEARCH

Program Overview

Scientific progress often advances in modest steps, building on a strong foundation of previous research and preliminary data. In contrast, more rapid advances in science can be stimulated by approaches that foster innovation and risk taking, and/or allow investigators flexibility to pursue surprising and fortuitous discoveries. Such research is often referred to as “high-risk, high-reward” research.²⁹⁶ Awards designed to support high-risk research may emphasize different criteria during peer review compared to more traditional grant mechanisms, weighting innovation and potential impact more heavily than feasibility and preliminary data. Thus, these awards provide an opportunity for investigators and projects that might not fare well in typical peer review due to a lack of preliminary data and/or ideas that appear scientifically risky.

High-risk, high-reward research is often categorized as “person-based” or “project-based.” In person-based awards, the emphasis of the award is on supporting individuals who have demonstrated high levels of creativity, innovation, and scientific ability. These awards may allow researchers to flexibly pursue new lines of inquiry or launch independent research careers. Project-based awards emphasize the innovative nature and potential for impact of the proposed research project.

The Common Fund provides an avenue for NIH to experiment with funding processes that explore new ways to better achieve agency R&D missions. A major source of support for high-risk, high-reward research at NIH is the Common Fund’s High-Risk, High-Reward (HRHR) program.²⁹⁷ The HRHR program supports exceptionally creative scientists pursuing highly innovative research with the potential for broad impact in biomedical, behavioral, or social sciences within the NIH mission. The HRHR program consists of four complementary initiatives that provide opportunities across various career stages:

Person-based:

- NIH Director’s Pioneer Award: supports individual scientists with outstanding records of creatively pursuing pioneering approaches to major research challenges
- NIH Director’s New Innovator Award: supports exceptionally creative early career scientists proposing innovative, high-impact projects
- NIH Director’s Early Independence Award: supports exceptional junior scientists bypassing postdoctoral training to launch independent research careers as quickly as possible

Project-based:

- NIH Director’s Transformative Research Award: supports individual investigators or teams proposing groundbreaking, unconventional research with the potential to create new scientific paradigms

²⁹⁶ “High risk” in this context refers to the type of science supported, which is often more innovative and paradigm-shifting than traditional research studies. “High risk” does not refer to risks posed to research participants. As with all NIH-funded studies involving people, any risks posed to participants are carefully evaluated by institutional or tribal review boards and explained to participants so that their consent is fully informed.

²⁹⁷ commonfund.nih.gov/highrisk

HRHR awards often break new ground, providing foundations on which future research can build and supporting significant technological breakthroughs that enable a wide range of research questions to be explored. For example, HRHR support contributed to the development of revolutionary techniques that allow researchers to precisely control the activity of neurons with light (optogenetics) and expand the contents of tissue samples to allow detailed viewing of fine subcellular structures (expansion microscopy).^{298,299} HRHR awardees are also addressing pressing public health issues, such as identifying racial/ethnic disparities in exposure to harmful contaminants in public drinking water.³⁰⁰ The flexible nature of HRHR awards and the creativity of awardees enable rapid pivots to address emerging challenges that profoundly affect human health, such as defining the origin and genetic evolution of the 2014 Ebola outbreak in West Africa and exploring novel therapeutic approaches to treat and reduce transmission of SARS-CoV-2, the virus that causes COVID-19.^{301,302}

The Common Fund has supported objective evaluations of several HRHR award initiatives.³⁰³ Independent evaluations of the Pioneer, New Innovator, and Early Independence Awards concluded that these awards support research that is more innovative and impactful compared to traditional NIH research awards, based on expert assessment and bibliometric analyses. Additionally, evaluations of the New Innovator and Early Independence Awards demonstrated that these non-traditional awards for scientifically risky projects do not negatively impact early-career professional advancement.

NIH Collaboration

The Common Fund's HRHR program is a NIH-wide endeavor, managed by a Working Group that includes members from 28 Institutes, Centers, and Offices (ICOs) across NIH. These Working Group members work collaboratively to coordinate and oversee the program. ICOs may also support HRHR awards that address exciting scientific projects relevant to their missions. In FY 2023, 18 New Innovator awards were funded by ICOs. Additionally, one Pioneer Award, one Transformative Research Award, and two Early Independence Awards were co-funded by the Common Fund and ICOs.

In addition to participating in the Common Fund's HRHR program, several Institutes and Centers (ICs) support awards that target exceptionally creative and innovative researchers and high-risk projects within the IC's mission.

NIH IC Person-Based Awards

The National Institute of Dental and Craniofacial Research (NIDCR) Award for Sustaining Outstanding Achievement in Research (SOAR) provides support to mid-career NIDCR-funded investigators who have outstanding records of research productivity, mentorship, and professional service to the research community.³⁰⁴ This award provides longer-term grant

²⁹⁸ eurekaalert.org/news-releases/878709

²⁹⁹ directorsblog.nih.gov/2015/03/26/diaper-compound-brings-change-to-cell-microscopy/

³⁰⁰ pubmed.ncbi.nlm.nih.gov/36460659/

³⁰¹ nih.gov/news-events/news-releases/single-animal-human-transmission-event-responsible-2014-ebola-outbreak

³⁰² pubmed.ncbi.nlm.nih.gov/36074824/

³⁰³ commonfund.nih.gov/assessment/reports

³⁰⁴ nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/nidcr-award-soar-r35

support, allowing researchers to have freedom to perform high-risk, high-reward research that has the potential to break new ground or expand previous discoveries in new directions. One SOAR awardee is creating new tools and strategies to unravel the molecular pathways underlying craniofacial birth defects, including a novel platform for rapid detection of key signaling pathway changes in fluorescent zebrafish embryos exposed to environmental toxins.³⁰⁵ They also designed a way to test the effects of nicotine exposure during embryonic zebrafish development, which not only disrupted formation of the craniofacial skeleton, but also modified social behavior and caused hyperactivity in adults. This will be a useful new model for the study of nicotine-related craniofacial and behavioral outcomes.³⁰⁶ Another SOAR awardee is leading a research team to help develop novel approaches to reverse salivary gland damage caused by aging, autoimmune disease, or cancer treatments. Through sustained local delivery of a hydrogel loaded with a nerve-boosting drug (cevimeline) to damaged salivary glands in a mouse model, the research team has shown that it is possible to restore and maintain salivary gland structure and function for months after radiation treatment.³⁰⁷ This novel approach could help inform new treatment strategies for patients living with salivary gland dysfunction.

The National Institute of Mental Health (NIMH) Biobehavioral Research Awards for Innovative New Scientists (BRAINS) award is intended to support the research and career advancement of outstanding, exceptionally productive scientists in the early, formative stages of their careers who plan to make a long-term career commitment to research in specific mission areas of the Institute.³⁰⁸ This award seeks to assist these individuals in launching an innovative basic, translational, clinical, or services research program that holds the potential to profoundly transform the understanding, diagnosis, treatment, or prevention of mental illness. The BRAINS initiative can be distinguished from most other research grants in that these projects emphasize career goals relevant to the Institute's mission, active participation of an external advisory committee, and a commitment from the institution to actively support research program development. Research projects proposed in response to this initiative are expected to directly address the goals and objectives of the NIMH Strategic Plan for Research and to have a defined impact on the understanding of the pathophysiology, trajectories, effective treatment, and/or prevention of mental illnesses.³⁰⁹

The National Institute of General Medical Sciences (NIGMS) Maximizing Investigators' Research Award (MIRA) encourages innovative research by supporting a cohesive scientific program of study within an investigator's laboratory rather than a series of individual projects.³¹⁰ MIRA provides investigators with flexibility to change research directions to pursue novel scientific insights, along with enhanced stability of support to allow researchers to take on more ambitious and creative scientific questions and studies.

MIRA has two separate components: one for early-stage investigators (ESIs) and one for more established investigators (EIs). The ESI-focused program shares certain characteristics with

³⁰⁵ pubmed.ncbi.nlm.nih.gov/36369674/

³⁰⁶ pubmed.ncbi.nlm.nih.gov/36287892/

³⁰⁷ pubmed.ncbi.nlm.nih.gov/36542703/

³⁰⁸ nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2021/nimh-biobehavioral-research-awards-for-innovative-new-scientists-nimh-brains

³⁰⁹ nimh.nih.gov/about/strategic-planning-reports

³¹⁰ nigms.nih.gov/Research/mechanisms/MIRA

high-risk, high-reward programs in that ESIs applying for MIRA awards are neither expected nor required to include preliminary data in their applications. Applications from ESIs are also reviewed independently from those submitted by more established investigators, focusing on evaluating an ESI's scientific potential. Together, these unique characteristics of MIRA have catalyzed the ESI community to pursue ambitious research programs at an earlier stage in their scientific careers, as evidenced by both the tripling of the number of ESIs supported by NIGMS over the last decade and the lower average age at which ESIs obtain their first MIRA award relative to ESIs getting R01 awards. In FY 2023, several ESI MIRA awardees have taken advantage of the program's flexibilities to take their research in unexpected and innovative directions. For example, a researcher originally studying the molecular mechanisms of how bacterial growth responds to environmental stress was able to shift research directions into the metabolism and behavior of an infectious pathogen commonly contracted by hospitalized patients, which could inform future development of antibiotic treatments.³¹¹

NIH IC Project-Based Awards

The National Institute on Drugs and Addiction (NIDA)³¹² supports two awards focused on high-risk, high-reward research. The NIDA Avant-Garde Award Program for HIV and Substance Use Disorder Research supports individual scientists of exceptional creativity at all career levels who propose high-impact research that will open new areas of HIV research and/or lead to new avenues for prevention and treatment of HIV among people who use drugs.³¹³ A recent Avant-Garde project identified genes that are down-regulated during HIV-related brain inflammation, suggesting a potential early step in HIV-associated neurocognitive disorder, which affects up to 50 percent of people with HIV.³¹⁴

NIDA's Avenir Awards provide grants to ESIs who propose highly innovative studies. These awards represent NIDA's commitment to supporting researchers who represent the future of addiction science. NIDA has two Avenir award programs, one for HIV/AIDS and another on the genetics and epigenetics of substance use.^{315,316} Examples of innovative research conducted by Avenir awardees include: leveraging machine learning to elucidate multiple social and spatial drivers of HIV transmission among people who inject drugs, determining that injection venue was most associated with HIV incidence and therefore a prime target for intervention; and identification of a previously undiscovered X-linked gene X-chromosome inactivation (XCI) escaper that will aid future research aimed at understanding the contribution of XCI escape to known sex disparities in rapid substance use escalation and negative withdrawal symptoms that disproportionately affect females.^{317,318}

³¹¹ pubmed.ncbi.nlm.nih.gov/36321838/

³¹² The FY 2024 President's Budget proposes to rename the National Institute on Drug Abuse to the National Institute on Drugs and Addiction.

³¹³ nida.nih.gov/about-nida/organization/offices/hiv-research-program-hrp/avant-garde-award-hiv-aids-research

³¹⁴ pubmed.ncbi.nlm.nih.gov/36525955/

³¹⁵ nida.nih.gov/about-nida/organization/offices/hiv-research-program-hrp/avenir-awards-hiv-aids-research

³¹⁶ nida.nih.gov/about-nida/organization/divisions/division-neuroscience-behavior-dnb/genetics-molecular-neurobiology-research-branch-gmnr/avenir-award-winners

³¹⁷ pubmed.ncbi.nlm.nih.gov/36260674/

³¹⁸ pubmed.ncbi.nlm.nih.gov/37207894/

Next Steps

High-risk, high-reward projects are a fundamental component of the NIH portfolio of investments designed to launch new scientific areas, refine our understanding of complex biological systems, and pioneer new therapies. NIH is committed to supporting high-risk research with the potential for exceptionally large impact, balanced with support for more traditional, yet extremely important, research that also advances our understanding of human health and disease.

The most recent cohort of Common Fund HRHR awardees is just beginning to undertake exciting and innovative research projects. These include: investigating novel approaches to unlock the potential of chemotherapy-induced immune system modulation to treat the most aggressive form of breast cancer; exploring how odors may be used to diagnose a variety of diseases; leveraging advances in artificial intelligence technology to automate documentation from doctor-patient interactions; and harnessing naturally occurring electromagnetic sensing mechanisms to precisely tune metabolism to treat diseases such as diabetes.^{319,320,321,322}

Advances made possible by these awards, as well as other NIH high-risk, high-reward research investments, are expected to transform our understanding of biological processes and lead to breakthroughs in the treatment of a broad range of diseases and health conditions.

Enhancing Diversity, Equity, Inclusion, and Accessibility

The Common Fund's HRHR program is undertaking R&D and applying technology advances to ameliorate inequities and create opportunity in ways that strengthen the program's values. To ensure that diverse perspectives contribute to scientific discoveries that benefit all groups, the HRHR program encourages applications from researchers from diverse backgrounds (including individuals underrepresented in the biomedical research workforce), from the full range of eligible institutions (including emerging research institutions and historically underserved communities), and from all research areas broadly relevant to NIH's mission. Based on recommendations from the Advisory Committee to the Director Working Group on High-Risk, High-Reward Programs and input from the scientific community, the HRHR program is applying a four-pronged approach to enhance applicant diversity: (1) increasing outreach to meet underrepresented researchers where they are and ensuring these efforts are strategic and effective, (2) bolstering language in funding opportunities and on public websites to encourage applicants from the full range of backgrounds, institutions, and research areas, (3) taking steps to mitigate potential bias against some scientific topics, and (4) piloting anonymized review within the Transformative Research Award initiative to reduce inappropriate influence of investigator or institutional reputation.^{323,324} NIH is evaluating these efforts and will continue to modify them as needed to support diversity across the HRHR program.

³¹⁹ reporter.nih.gov/project-details/10695288

³²⁰ reporter.nih.gov/project-details/10695420

³²¹ reporter.nih.gov/project-details/10701364

³²² reporter.nih.gov/project-details/10687635

³²³ acd.od.nih.gov/working-groups/hrhr.html

³²⁴ grants.nih.gov/grants/guide/notice-files/NOT-RM-20-002.html

MATERNAL MORTALITY

Program Overview

The United States has the highest rate of maternal mortality among high-resource countries, and the number and rate of pregnancy-related deaths has risen over the past several years.³²⁵ In 2021, as many as 1,200 women died from a pregnancy-related health issue or an existing condition exacerbated by pregnancy, either during pregnancy or in the first 42 days after giving birth.³²⁶ The maternal mortality rate increases from 2020 to 2021 for all race and Hispanic-origin groups were significant.² Some populations are disproportionately affected by maternal morbidity and mortality (MMM). Maternal mortality rates for African American/Black women are 2.6 times higher than mortality rates for White women, and American Indian/Alaska Native women are about two times more likely to die from pregnancy-related complications compared to White women, according to the most recent data for each group.³²⁷ Risk of death during pregnancy and up to one year postpartum is also significantly elevated among women residing in maternity care deserts, which are counties that lack hospitals with obstetric care or midwives.³²⁸ Leading causes of pregnancy-related deaths up to one year after pregnancy include mental health conditions (including deaths due to suicide and overdose/poisoning related to substance use), excessive bleeding (hemorrhage), cardiac and coronary conditions, infection, blood clots, and hypertensive disorders of pregnancy.³²⁹ Additional research showed that in 2020, pregnant or postpartum women had a 35 percent higher risk of homicide compared to their nonpregnant peers.³³⁰ Black women were the most likely to die by pregnancy-associated homicide. Overall, more than 80 percent of pregnancy-related deaths may be preventable,³³¹ confirming the need for the ongoing NIH-wide research response to develop solutions for this crisis.

NIH coordinates maternal health research across all its Institutes, Centers, and Offices (ICOs) as well as with other HHS and government agencies. For example, NIH is part of the HHS Action Plan to Improve Maternal Health in America³³² and the White House Blueprint for Addressing the Maternal Health Crisis.³³³ NIH's Office of Research on Women's Health (ORWH) maintains the NIH Maternal Morbidity and Mortality Web Portal, a central information hub for funding opportunities and research efforts at NIH and other HHS agencies.³³⁴ The NIH Office of Disease Prevention (ODP) addressed maternal health through its **Pathways to Prevention (P2P) Program**, holding a workshop that brought together participants from across NIH and other federal agencies, researchers, and community members to understand the current state of the science, identify gaps, and suggest a research agenda and action plan to move the field

³²⁵ [cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm](https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm)

³²⁶ [cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm](https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm)

³ [cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm](https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm)

³²⁸ [marchofdimes.org/maternity-care-deserts-report](https://www.marchofdimes.org/maternity-care-deserts-report)

³²⁹ [cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html](https://www.cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html)

³³⁰ [nichd.nih.gov/newsroom/news/091622-pregnancy-associated-homicide#:~:text=Results,deaths%20per%20100%2C000%20live%20births.](https://www.nichd.nih.gov/newsroom/news/091622-pregnancy-associated-homicide#:~:text=Results,deaths%20per%20100%2C000%20live%20births.)

³³¹ [cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html](https://www.cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html)

³³² aspe.hhs.gov/sites/default/files/private/aspe-files/264076/healthy-women-healthy-pregnancies-healthy-future-action-plan_0.pdf

³³³ [whitehouse.gov/wp-content/uploads/2022/06/Maternal-Health-Blueprint.pdf](https://www.whitehouse.gov/wp-content/uploads/2022/06/Maternal-Health-Blueprint.pdf)

³³⁴ orwh.od.nih.gov/mmm-portal

forward.³³⁵ The NIH-wide **Implementing a Maternal health and PRenancy Outcomes Vision for Everyone (IMPROVE) Initiative**³³⁶ is led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Nursing Research (NINR), and ORWH. Launched in 2019, IMPROVE’s goals are to reduce preventable causes of maternal deaths and improve health for women before, during, and after delivery. In FY 2023, \$43.4 million in IMPROVE funds (\$30 million in NICHD appropriations and \$13.4 million in other ICO funding) contributed to a robust NIH maternal health research portfolio.

The IMPROVE Initiative weaves together basic, clinical, social, training, and technological program components to address the leading causes of pregnancy-related MMM with an emphasis on incorporating community perspectives and inclusion of disproportionately affected populations (e.g., racial and ethnic minorities, very young women and women of advanced maternal age, and people with disabilities), as well as those who experience health disparities or limits in access to care (e.g., residents of maternity care deserts). Established in FY 2023, the **IMPROVE Maternal Health Research Centers of Excellence (COEs)** will develop, implement, and evaluate community-tailored interventions to address health disparities in maternal health and risk factors and mechanisms of the leading causes of MMM. The ten COEs are geographically diverse and include projects that will work with Tribal populations, rural populations, and Historically Black Colleges and Universities, among others. COEs will also support training and professional development of maternal health researchers, including those from backgrounds underrepresented in the biomedical research workforce, and work with a data innovation and coordination hub and an implementation science hub. The COEs received \$24.4 million in first-year funding and are expected to operate for seven years and total an estimated \$168 million, pending the availability of funds.

Community involvement and empowerment in addressing the factors affecting women in the communities where they live is one of the cornerstones of the IMPROVE initiative. The **IMPROVE Connecting the Community for Maternal Health Challenge**³³⁷ (CCMH) encourages and rewards non-profit community-based or advocacy organizations to develop sustainable research capabilities and infrastructure to pursue research projects in maternal health, inclusive of MMM. In addition to \$3 million in cash prize awards planned to be awarded in 2024, CCMH provides expert guidance and consultation on maternal health research project design, implementation, and evaluation. Organizations that advanced to the final phase of the competition are testing programs that include doula services, nutrition to reduce gestational diabetes, and maternal mental health care (e.g., depression, post-traumatic stress), among others. Another community-engaged effort, the **IMPROVE Community Implementation Program (CIP)**, supports three coalitions that will build strategies to adopt and integrate evidence-based interventions into community settings to improve maternal health outcomes before, during, and after pregnancy, particularly among populations experiencing health disparities and in maternity care deserts. The program will include community partners engaged in every level of the project, including shared leadership. The IMPROVE-CIP program complements the **Maternal**

³³⁵ prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/identifying-risks-and-interventions-optimize-postpartum-health

³³⁶ nichd.nih.gov/research/supported/IMPROVE

³³⁷ nichd.nih.gov/research/supported/challenges/community-maternal-health

Health-CIP³³⁸ supported by the National Heart, Lung, and Blood Institute (NHLBI), which has established four coalitions to engage communities and pilot test the implementation of proven interventions in at-risk populations.

Improving maternal health in the communities that need it most requires technologies and tools that increase access to care and enable earlier diagnosis and intervention. The IMPROVE-funded **Rapid Acceleration of Diagnostics Technology (RADx Tech) for Maternal Health Challenge**³³⁹ aims to accelerate development and commercialization of home-based or point-of-care diagnostic devices, wearables, or other remote-sensing technologies to extend postpartum care to improve maternal health outcomes in maternity care deserts. Prototype devices have the potential to identify women at risk and enable timely intervention. The initiative plans to award up to \$8 million in FY 2024. Expanding on the need for technology-based solutions, in FY 2023, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) led the **NIH Technology Accelerator Challenge for Maternal Health** to award prizes for innovative diagnostic technologies integrated with a digital platform to identify maternal health conditions during and after pregnancy and to guide clinical decision-making, improve patient outcomes, and ultimately prevent MMM. Winning technologies included a mobile health monitoring tool for community health workers to detect postpartum surgical-site infections and anemia, as well as devices and wearables to detect fetal distress during labor, preeclampsia, maternal sepsis, and hemorrhage.³⁴⁰

Beyond the work of IMPROVE and the other programs already mentioned, NIH ICOs support a broad research portfolio to promote maternal health and address causes of and risk factors for MMM. For instance, 23 percent of pregnancy-related deaths in 2022 were due to mental health conditions.³⁴¹ Recognizing the ongoing struggle with these issues, the National Institute of Mental Health (NIMH) funded awards supporting research to improve intervention delivery to at-risk individuals to **prevent perinatal depression**,³⁴² and the National Institute on Drugs and Addiction (NIDA)³⁴³ launched a funding opportunity to support research to identify barriers to opioid use disorder (OUD) treatment among pregnant and postpartum people and models for recovery-oriented, family-centered care.³⁴⁴ NIDA also supports research to optimize the efficacy and safety of OUD medications for pregnant people through the **Medication Treatment for Opioid-dependent Expecting Mothers (MOMs)** study.³⁴⁵

Preexisting diabetes can cause pregnancy complications, maternal morbidity, and health consequences in the child. The development of gestational diabetes can also lead to short- and long-term health risks for mother and child. The National Institute of Diabetes and Digestive and Kidney Diseases launched the **Glycemic Observation and Metabolic Outcomes in**

³³⁸ maternalhealthcip.org/

³³⁹ nichd.nih.gov/research/supported/challenges/radx-tech-maternal-health

³⁴⁰ nibib.nih.gov/news-events/newsroom/nih-announces-prize-winners-maternal-health-diagnostics-challenge

³⁴¹ cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html

³⁴² grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-240.html

³⁴³ The FY 2025 President's Budget proposes to rename the National Institute on Drug Abuse to the National Institute on Drugs and Addiction.

³⁴⁴ grants.nih.gov/grants/guide/notice-files/NOT-DA-24-008.html

³⁴⁵ nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/medication-treatment-opioid-dependent-expecting-mothers-moms-pragmatic-randomized-trial-comparing

Mothers and Offspring (GO MOMS) study³⁴⁶ to better understand what happens to a mother's metabolism during pregnancy. Researchers at nine clinical sites are enrolling participants without preexisting diabetes to monitor glucose changes during pregnancy with the hope to develop a better way to detect gestational diabetes and enable earlier intervention and better health outcomes.

Cardiac and coronary conditions are other leading underlying causes of pregnancy-related complications and deaths, particularly among non-Hispanic Black people.³⁴⁷ Building on NICHD's Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2B), NHLBI supported the **nuMoM2b Heart Health Study**,³⁴⁸ which found that certain pregnancy complications are associated with increased long-term risks for heart disease, such as developing high blood pressure, years after pregnancy. Additional NHLBI research showed that treatment of mild chronic hypertension during pregnancy was associated with better pregnancy outcomes than reserving treatment only for severe hypertension.³⁴⁹ These findings impacted treatment guidelines from the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine. Further research supported by NHLBI indicated that early pregnancy blood pressure patterns can predict preeclampsia and gestational hypertension.³⁵⁰

Placental complications can also lead to maternal morbidity. The NICHD-supported Human Placenta Project³⁵¹ stimulated a robust research effort directed at safe, non-invasive, real-time assessment of placenta development and function across pregnancy. These efforts have led to new imaging approaches, both magnetic resonance imaging (MRI) and ultrasound, that show promise for early prediction of placenta-mediated pregnancy complications such as preeclampsia.³⁵² The National Institute of Allergy and Infectious Diseases (NIAID) supports research to investigate the factors and mechanisms that control interactions between the maternal immune system and the developing fetus as well as immune cells that support pregnancy and enable optimal placental development and function.³⁵³ The importance of the interaction between the maternal immune system and the developing fetus was highlighted during the COVID-19 pandemic. NICHD-supported research showed that COVID-19 vaccination was safe and effective for pregnant people,³⁵⁴ and NIAID-supported research showed that pregnant people who received a COVID-19 vaccine produced antibodies in their own blood and the umbilical cord blood, indicating protection for both mother and fetus.³⁵⁵ The NICHD-supported **Maternal-Fetal Medicine Units (MFMU) Network**, consisting of 14 research centers focused on improving obstetric care, pregnancy health, and outcomes for lactating people and their babies, also pivoted to address unanswered questions for these populations during the COVID-19 pandemic. The MFMU conducted a clinical trial to assess the impact of COVID-19 infection during pregnancy and found that SARS-CoV-2 infection was associated with an increased risk

³⁴⁶ gomomsstudy.org/

³⁴⁷ [cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html](https://www.cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html)

³⁴⁸ [nhlbi.nih.gov/news/2023/moms-helping-moms-through-research](https://www.nhlbi.nih.gov/news/2023/moms-helping-moms-through-research)

³⁴⁹ [nejm.org/doi/full/10.1056/NEJMoa2201295](https://www.nejm.org/doi/full/10.1056/NEJMoa2201295)

³⁵⁰ [ahajournals.org/doi/full/10.1161/JAHA.123.029617](https://www.ahajournals.org/doi/full/10.1161/JAHA.123.029617)

³⁵¹ [nichd.nih.gov/research/supported/human-placenta-project/default](https://www.nichd.nih.gov/research/supported/human-placenta-project/default)

³⁵² [ncbi.nlm.nih.gov/pmc/articles/PMC9295947/](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC9295947/)

³⁵³ [grants.nih.gov/grants/guide/rfa-files/RFA-AI-23-027.html](https://www.grants.nih.gov/grants/guide/rfa-files/RFA-AI-23-027.html)

³⁵⁴ [nichd.nih.gov/newsroom/news/032921-COVID-vaccine-pregnancy](https://www.nichd.nih.gov/newsroom/news/032921-COVID-vaccine-pregnancy)

³⁵⁵ [covid19.nih.gov/news-and-stories/covid-19-vaccination-pregnancy-likely-benefits-moms-babies](https://www.covid19.nih.gov/news-and-stories/covid-19-vaccination-pregnancy-likely-benefits-moms-babies)

for MMM.³⁵⁶ Other ongoing studies through the MFMU are addressing the long-term impacts of COVID-19 on women, children, and families.³⁵⁷

Other infectious diseases and bacterial infections can increase the risk for MMM. Nine percent of maternal deaths in 2022 were associated with infections that can be prevented or treated with timely intervention.³⁵⁸ For example, the NICHD-supported **Global Network (Global Network) for Women’s and Children’s Health**, co-funded by the Bill and Melinda Gates Foundation, found that a single oral dose of the antibiotic azithromycin during labor can reduce the risk of postpartum sepsis and death by one-third among women who deliver vaginally.³⁵⁹ This result will likely change clinical practice and help prevent MMM worldwide. Pregnant people with HIV have a higher risk of dying during pregnancy and the postpartum period than nonpregnant people. NIAID (along with NICHD and NIMH) supports the **International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network**,³⁶⁰ a global collaboration to advance the prevention and treatment of HIV and its complications for pediatric and pregnant/postpartum populations. The IMPAACT Network is prioritizing research to evaluate safety and dosing of antiretroviral therapies in pregnant people, which have not been thoroughly studied in that population despite 30 years of use.

Although 9 in 10 pregnant people take medication during pregnancy and about 70 percent take at least 1 prescription medication, little is known about the effects of taking most medicines during pregnancy because pregnant people are often not included in studies that determine the safety of the medication.³⁶¹ In 2016, Congress established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the HHS Secretary regarding gaps in knowledge and research on safe and effective therapies for pregnant and lactating people.³⁶² To address some of the recommendations put forward by this group, NICHD established the **Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub**, which serves as a national resource to collect and expand the knowledge and expertise in this area. MPRINT also supports Centers of Excellence in Therapeutics (CETs). Current CETs are evaluating the effectiveness of maternal pharmacotherapy for opioid use disorder on “real world” outcomes for pregnant women and infants³⁶³ and investigating how maternal antibiotics alter breast milk composition and impact infant outcomes.³⁶⁴

NIH also plans to fund new studies in FY 2024 on **Translational Research in Maternal and Pediatric Pharmacology and Therapeutics**,³⁶⁵ focusing on improving precision medicine in pregnant and lactating people, neonates, and children through advancements in tools, methodology and technology development; understanding drug action in these populations; and developing novel therapeutics or enhancing the use of existing therapeutics. Precision medicine

³⁵⁶ pubmed.ncbi.nlm.nih.gov/35129581/

³⁵⁷ mfmunetwork.bsc.gwu.edu/web/mfmunetwork/research-projects

³⁵⁸ cdc.gov/media/releases/2022/p0919-pregnancy-related-deaths.html

³⁵⁹ nichd.nih.gov/newsroom/news/020923-azithromycin-postpartum-sepsis

³⁶⁰ impaactnetwork.org/

³⁶¹ cdc.gov/pregnancy/meds/treatingfortwo/facts.html

³⁶² nichd.nih.gov/about/advisory/PRGLAC

³⁶³ mprint.org/research/centers/vanderbilt-cet.html

³⁶⁴ mprint.org/research/centers/ucsd-cet.html

³⁶⁵ grants.nih.gov/grants/guide/pa-files/PAR-23-130.html

aims to provide disease treatments tailored to an individual's unique genes and environment. The **Trans-Omics for Precision Medicine (TOPMed)** program, sponsored by NHLBI, for example, integrates whole-genome sequencing (WGS) and other omics data (e.g., metabolic profiles, epigenomics, protein and RNA expression patterns) with molecular, behavioral, imaging, environmental, and clinical data.³⁶⁶ Multiple studies/cohorts included in TOPMed include pregnant people, facilitating opportunities for future insights into conditions that co-occur with and contribute to pregnancy complications.

NIH-supported research has highlighted many facets of health disparities in MMM. For example, NHLBI-supported research showed that Black women with sickle cell disease (SCD) have worse maternal health outcomes than those without SCD.³⁶⁷ NINR-supported researchers found that historical redlining, a tool of structural racism that influenced the trajectory of neighborhood social and material conditions, is associated with increased risk of experiencing severe maternal morbidity among Black and Hispanic birthing people in California.³⁶⁸ NIH ICOs are supporting a range of research to address these disparities, including the IMPROVE initiative noted above. NINR's **Advancing Integrated Models (AIM) of Care** projects intend to stimulate research to develop or evaluate supportive care models that address healthcare access or healthcare quality, together with structural or social inequities, in efforts to prevent adverse pregnancy outcomes among racial and ethnic minority women.³⁶⁹ The National Institute on Minority Health and Health Disparities (NIMHD) is supporting studies to address racial disparities in MMM, testing the efficacy and/or effectiveness of interventions or research strategies to deliver proven-effective prevention and treatment interventions to reduce these disparities.³⁷⁰ The National Institute of Environmental Health Sciences, NICHD, and NIMHD support the Centers of Excellence on Environmental Health Disparities Research.³⁷¹ Two of these Centers conduct research with pregnant women. One assesses factors that contribute to environmental health disparities and the other explores the relationship among prenatal exposures, maternal social stressors, and maternal depression and cardiovascular health in the years after childbirth. The Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH) program supported by NHLBI aims to test the effectiveness of an implementation-ready intervention, delivered in the context of early childhood home visiting, to promote and address disparities in maternal and early childhood cardiovascular health.³⁷²

NIH will continue to invest in research and technology to prevent MMM and improve maternal health outcomes. The IMPROVE COEs and IMPROVE-CIP coalitions will conduct research through 2029, and NIH will encourage collaboration among investigators to explore potential new or augmented research projects, pending availability of funds. Innovators in the RADx Tech for Maternal Health and CCMH Challenges may be able to connect and collaborate with IMPROVE COE and IMPROVE-CIP investigators to further test and implement their technologies or community-based interventions. NIH will continually seek opportunities for IMPROVE components to collaborate with other maternal health research efforts throughout

³⁶⁶ topmed.nih.gov/

³⁶⁷ onlinelibrary.wiley.com/doi/10.1002/ajh.26818

³⁶⁸ pubmed.ncbi.nlm.nih.gov/36420897/

³⁶⁹ grants.nih.gov/grants/guide/rfa-files/RFA-NR-23-002.html

³⁷⁰ grants.nih.gov/grants/guide/rfa-files/RFA-MD-20-008.html

³⁷¹ niehs.nih.gov/research/supported/centers/ehd/index.cfm

³⁷² hvenrich.org/ENRICH_about.asp

NIH and across HHS. The IMPROVE Initiative also plans to support new awards in FY 2024 for an initiative developed by NIH's Office of Behavioral and Social Sciences Research to address the interrelation of intimate partner violence and MMM.^{373,374} Across NIH, ICOs will remain agile and work with Federal partners and other collaborators to respond to the crisis and reduce MMM.

³⁷³ grants.nih.gov/grants/guide/rfa-files/RFA-OD-24-001.html

³⁷⁴ grants.nih.gov/grants/guide/rfa-files/RFA-OD-24-002.html

PRECISION NUTRITION

Good nutrition is essential for healthy development and basic survival, but it is also integral to well-being and disease prevention. Health conditions linked to poor diet constitute the most frequent and preventable causes of death in the United States and are major drivers of health care costs, estimated in the hundreds of billions of dollars annually.³⁷⁵ What should we eat to stay healthy? The answer to this question is not as simple as one might expect and there is no such thing as a perfect, one-size-fits-all diet. Precision nutrition aims to predict and account for differences in the way people respond to food based on a combination of genetic, environmental, and social factors to optimize their diets. Given the promise of precision nutrition to promote health and address diet-related chronic diseases, NIH has been bolstering the coordination of nutrition research and has placed a high priority on precision nutrition initiatives to accelerate its development.

The NIH initiatives described below aim to advance precision nutrition through diverse interdisciplinary teams of nutrition scientists and data scientists collecting and analyzing multi-dimensional datasets with the goal of creating predictive nutrition algorithms to support healthy living for individuals from every walk of life. Some of the research projects supported by these initiatives will utilize artificial intelligence (AI) and machine learning (ML) to untangle the various roles of whole foods, individual nutrients, sociocultural impacts on eating and lifestyle, and societal infrastructure on the health of individuals and populations.

One important component of NIH's precision nutrition efforts is the *Nutrition for Precision Health (NPH)*, powered by the *All of Us Research Program*.³⁷⁶ The goal of NPH is to describe and better understand variations in how different people respond to diet, with the aim of developing algorithms that predict individual responses to food and dietary patterns. NPH is building on recent advances in biomedical science, including AI and microbiome research, as well as the infrastructure and large, diverse groups of participants from the *All of Us Research Program*. These advances provide unprecedented opportunities to generate new data to provide insight into precision nutrition, and the scale and diversity of the participant population sets NPH apart from other nutrition studies. NPH launched in FY 2022, with awards to support clinical centers, data modeling and bioinformatics, multiple biological assays, and coordination efforts. The study began enrolling participants in 2023 from 14 sites across the United States, with the goal of engaging 10,000 participants from diverse backgrounds. NPH aims to develop and validate algorithms that predict individual responses to food and dietary patterns. The study's findings may allow health care providers to offer more customized nutrition guidance to improve individuals' overall health. Recruitment for clinical studies is ongoing. Over the next several years, NPH will conduct nutrition studies involving large numbers of diverse participants, perform analyses on biological specimens collected from individuals in response to various foods and dietary patterns, develop computational modeling and algorithms, and share data with the research community. NIH anticipates that these efforts will lead to more personalized nutrition guidance and improved health. NPH is supported by the NIH Common Fund and managed as a partnership with the *All of Us Research Program*, Office of Nutrition Research (ONR), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), *Eunice Kennedy Shriver*

³⁷⁵ cdc.gov/chronicdisease/about/costs/index.htm

³⁷⁶ commonfund.nih.gov/nutritionforprecisionhealth

National Institute of Child Health and Human Development (NICHD), National Heart, Lung, and Blood Institute (NHLBI), and National Cancer Institute (NCI). Multiple NIH institutes, centers, and offices (ICOs) participate in the NIH-wide Working Group that provides oversight of the program.

Another important precision nutrition initiative is the Advanced Training in Artificial Intelligence for Precision Nutrition (AIPrN) Science Research—Institutional Research Training Programs. These programs aim to diversify and expand the nutrition science workforce by equipping it to apply AL/ML to analyze large and complex datasets, such as those within the *All of Us* Researcher Workbench.³⁷⁷ The ultimate goal is to tackle challenges in biomedical science to reduce diet-related diseases and health disparities. These training programs provide graduate students and postdoctoral fellows interdisciplinary research training in AI and precision nutrition that includes ML, systems biology, systems science, big data, and computational analytics. These programs support and emphasize NIH diversity, equity, inclusion, and accessibility (DEIA) goals and interest in diversity by emphasizing the importance of inclusive research environments, diverse backgrounds of trainees and mentors, and the research topics being pursued by trainees. Four AIPrN awards were made in FY 2023 to four different universities, supported by NIDDK, NICHD, Office of Dietary Supplements (ODS), Office of Data Science Strategy (ODSS), and ONR.

One of the main challenges in nutrition research is the ability to verify dietary adherence in clinical studies to establish dietary intake with high accuracy. This is in part due to a lack of valid biomarkers that would allow for independent verification of the dietary adherence during a clinical study. The Dietary Biomarkers Development Consortium (DBDC) will explore, identify, and validate metabolomics-based dietary intake biomarkers by comparing them with existing dietary assessment methodologies. The goal is to develop a database of validated biomarkers that are readily available to the research community. The consortium sites include representative study populations from underserved and underrepresented groups to develop the biomarkers that provide objective measures to inform individualized healthy dietary patterns. The dietary biomarkers identified through the DBDC will enable advancement of precision nutrition research by allowing accurate measurement of dietary intake in clinical studies with higher accuracy. The DBDC is supported by NIDDK and the U.S. Department of Agriculture’s National Institute of Food and Agriculture. Seven awards were made in FY 2023 to establish the consortium and the clinical studies are currently recruiting research participants.

Obesity affects approximately 20 percent of children and 42 percent of adults in the U.S., putting them at risk of chronic diseases such as type 2 diabetes, heart disease, and some cancers. Obesity costs the U.S. health care system nearly \$173 billion a year.³⁷⁸ Precision nutrition studies can help us better understand the causes and risks for obesity in children. An NIDDK-supported initiative “Pediatric Obesity Discovery Science Research to Improve Understanding of Risk and Causal Mechanisms for Obesity in Early Life” will support innovative, longitudinal, and discovery-based research studies to better characterize early-life risk factors for obesity development during infancy and early childhood, as well as to elucidate underlying causal mechanisms, including those that mediate behavioral and/or metabolic risk and how risk can be

³⁷⁷ researchallofus.org/data-tools/workbench/

³⁷⁸ ncbi.nlm.nih.gov/pmc/articles/PMC7990296/

modified by psychosocial, contextual, and/or environmental contributors. One study is testing the association of the “emotion-attachment-nutritive intake-system” in infancy with maternal feeding behavior, child eating behavior, child dietary intake, and child percent body fat at age 3 years. A total of three awards were made in FY 2023 to support clinical studies which are currently recruiting research participants.

These four initiatives will advance precision nutrition science by leveraging AI/ML and other technological advances, large diverse participant datasets, and an expanded scientific workforce to better inform dietary guidance for a healthier America.

RESEARCHING COVID TO ENHANCE RECOVERY (RECOVER)

Program Overview

The NIH Researching COVID to Enhance Recovery (RECOVER) Initiative, launched in 2021 with a \$1.15 billion supplemental appropriation in the Consolidated Appropriations Act of 2021,³⁷⁹ is a nationwide research program designed to understand, treat, and prevent Long COVID. Long COVID describes long-term symptoms following infection by SARS-CoV-2, the virus that causes COVID-19. More than 200 symptoms are associated with Long COVID, and the condition can cause problems throughout the body, affecting nearly all body systems including the nervous, cardiovascular, gastrointestinal, pulmonary, autonomic, and immune systems. RECOVER is a comprehensive and multi-faceted research initiative that includes longitudinal observational studies, electronic health record (EHR) studies, pathobiology and tissue pathology studies, a mobile health platform, and clinical trials.³⁸⁰ Importantly, RECOVER is designed to be an inclusive, diverse, and patient-centered study of Long COVID across the lifespan. Clinical hubs and networks are selected for their capacity to reach disproportionately affected communities across the country. Patients have, since day one, been integral to the RECOVER initiative. Patient and community representatives serve alongside researchers in RECOVER and their input has been invaluable to the design of the various studies.

RECOVER is answering a number of important questions about Long COVID, including:³⁸¹

- What are the various forms of Long COVID?
- How long do symptoms of Long COVID last? Can there be effects later in life?
- What effect(s) does Long COVID have on other diseases or health problems?
- What are the risk factors for developing Long COVID?
- What effects do different COVID-19 virus variants, SARS-CoV-2 re-infections, or COVID vaccination have on Long COVID?
- What happens inside the body that leads to Long COVID?
- What happens inside the body that protects some people from Long COVID?
- What treatments are effective for treating or preventing Long COVID?

NIH RECOVER has partnered with government entities, industry, and the investigator community to rapidly launch studies of Long COVID. While RECOVER is an NIH initiative, other agencies and Offices within the Department of Health and Human Services (HHS) also play key roles through participation on governance committees, consultations, and collaborations, including the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and the Center for Medicaid and Medicare Services (CMS). Additionally, RECOVER funds hundreds of investigators across the country, including working with teams at New York University Langone Health, Duke Clinical Research Institute, Massachusetts General Hospital, Mayo Clinic, and RTI International to provide core functions for RECOVER investigators and studies.

³⁷⁹ www.congress.gov/116/plaws/publ260/PLAW-116publ260.pdf

³⁸⁰ recovercovid.org/research-components

³⁸¹ recovercovid.org/research#researchQuestions

NIH Collaboration

Within NIH, RECOVER is co-led by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Allergy and Infectious Diseases (NIAID). RECOVER is truly a trans-NIH effort. Many NIH Institutes and Centers contribute substantively to scientific programmatic oversight of key RECOVER components such as the observational studies, clinical trials, and mobile health platform. For instance, Institutes and Centers whose expertise and missions are highly relevant to RECOVER provide programmatic subject matter experts who consult on RECOVER projects and lead expert working groups, including, for example: NHLBI, NIAID, NINDS, the NIH Office of the Director, the *All of Us* Research Program, the National Center for Advancing Translational Sciences (NCATS), the National Institute on Drugs and Addiction (NIDA),³⁸² the National Cancer Institute (NCI), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Center for Complementary and Integrative Health (NCCIH).

Recent Findings/Key Progress

RECOVER's comprehensive research framework has provided the critical foundation for understanding and treating Long COVID and is already providing valuable insights into the condition. RECOVER studies have, for example, developed computable phenotypes (definitions based on computer analysis of electronic health record data) of Long COVID in adults and children,^{383,384,385,386,387} determined that pre-COVID vaccination reduces risk of Long COVID,^{388,389} determined prevalence of Long COVID in children (3.7 percent of children with SARS-CoV-2 develop Long COVID),^{390,391,392} identified risk factors for Long COVID in adults^{393,394,395} (severity of acute COVID, comorbidities,^{396,397} female sex,³⁹⁸ racial/ethnic minority^{399,400}) and children^{401,402} (< 5 years old, Intensive Care Unit (ICU) admission for acute infection, complex chronic conditions⁴⁰³); found that COVID-19 vaccination is safe for children

³⁸² The FY 2025 President's Budget proposes to rename the National Institute on Drug Abuse to the National Institute on Drugs and Addiction

³⁸³ www.nature.com/articles/s41591-022-02116-3

³⁸⁴ jamanetwork.com/journals/jamanetworkopen/fullarticle/2788641

³⁸⁵ www.medrxiv.org/content/10.1101/2022.04.18.22273968v2

³⁸⁶ www.medrxiv.org/content/10.1101/2022.12.18.22283646v1

³⁸⁷ www.sciencedirect.com/science/article/pii/S2589750022000486?via%3Dihub

³⁸⁸ www.medrxiv.org/content/10.1101/2022.10.06.22280795v1

³⁸⁹ www.cdc.gov/mmwr/volumes/71/wr/mm7114e1.htm

³⁹⁰ jamanetwork.com/journals/jamapediatrics/fullarticle/2795569

³⁹¹ jamanetwork.com/journals/jamanetworkopen/fullarticle/2788641

³⁹² www.medrxiv.org/content/10.1101/2022.09.26.22280364v1

³⁹³ www.medrxiv.org/content/10.1101/2022.08.15.22278603v1

³⁹⁴ pubmed.ncbi.nlm.nih.gov/36785842/

³⁹⁵ ieeexplore.ieee.org/document/9994851

³⁹⁶ www.medrxiv.org/content/10.1101/2022.08.15.22278603v1

³⁹⁷ elifesciences.org/articles/86002

³⁹⁸ www.medrxiv.org/content/10.1101/2022.04.18.22273968v2

³⁹⁹ link.springer.com/article/10.1007/s11606-022-07997-1

⁴⁰⁰ www.medrxiv.org/content/10.1101/2022.12.02.22282944v1

⁴⁰¹ academic.oup.com/jamiaopen/article/6/1/ooad016/7071577

⁴⁰² www.medrxiv.org/content/10.1101/2022.12.22.22283791v1

⁴⁰³ www.medrxiv.org/content/10.1101/2022.07.08.22276768v1

who have had MIS-C;⁴⁰⁴ and identified an increased risk of new-onset conditions in Long COVID patients (type 2 diabetes,^{405,406} anxiety, ataxia, myoneural disorders⁴⁰⁷). In addition, the first manuscript highlighting analyses of data from the RECOVER enrolling adult clinical cohort was recently published,⁴⁰⁸ identifying sub-phenotypes and specific symptom criteria of Long COVID; characterizing impacts of different variants and vaccination; and defining Long COVID prevalence in adults. Researchers also recently found that severe COVID-19 may lead to long-term innate immune system changes; this may explain why COVID-19 damages so many organs and why some people with Long COVID have high levels of inflammation throughout the body.⁴⁰⁹ As of December 4, 2023, 63 scientific papers have been published, posted as preprints, or submitted to journals and more than 60 others are in preparation.

Next Steps

In late July 2023, RECOVER launched and opened enrollment for Phase 2 clinical trials that will evaluate at least four potential treatments for Long COVID, with additional clinical trials to test at least seven more treatments expected in the coming months. This portfolio of clinical trials will explore treatments to address some of the proposed underlying causes of Long COVID as well as some of the major symptom clusters that have the greatest impact on patients' quality of life. Treatments will include drugs, biologics, medical devices, and other therapies. These trials are designed using platform protocols, which can evaluate multiple treatments simultaneously to identify more swiftly those that are effective. The trials are also adaptive, which allows potential therapies to be added or dropped quickly based on emerging findings and without the need to develop and implement entirely new protocols, which is a time-consuming process. Testing is performed at various key locations across the country and each site in a clinical trial will follow the same protocols and use common data elements, so data can be combined from many different locations to generate conclusive results. RECOVER researchers developed the portfolio of RECOVER trials with extensive input from patient representatives as well as experts in the symptom areas, proposed interventions, and clinical trial design. These platform trials are complex undertakings that require significant planning and effective coordination between multiple locations but are well-suited to studying the complexities of Long COVID.

- The first two clinical protocols launched were:
 - **RECOVER-VITAL** studies whether viral persistence, which could occur if SARS-CoV-2 stays in the body and causes the immune system to not function properly and/or causes damage to organs, is a cause of some Long COVID symptoms.
 - **RECOVER-NEURO** examines interventions for cognitive dysfunction related to Long COVID, including brain fog, memory problems, as well as difficulty with attention, thinking clearly, and problem solving.
- The following additional protocols will launch in the coming months:
 - **RECOVER-SLEEP** will test interventions for changes in sleep patterns or ability to sleep after having COVID-19.

⁴⁰⁴ www.nih.gov/news-events/news-releases/covid-19-vaccine-children-after-mis-c-appears-safe#:~:text=The%20researchers%20have%20routinely%20treated,is%20safe%20to%20do%20so.

⁴⁰⁵ www.medrxiv.org/content/10.1101/2022.12.02.22283029v1

⁴⁰⁶ www.medrxiv.org/content/10.1101/2022.11.03.22281916v1

⁴⁰⁷ www.medrxiv.org/content/10.1101/2022.07.08.22277388v2

⁴⁰⁸ jamanetwork.com/journals/jama/fullarticle/2805540

⁴⁰⁹ pubmed.ncbi.nlm.nih.gov/37597510/

- **RECOVER-AUTONOMIC** will examine interventions to help treat symptoms associated with problems in the autonomic nervous system, which controls a range of critical bodily functions without our awareness including heart rate, breathing, and digestive system activity.
- **RECOVER-ENERGIZE** will focus on exercise intolerance and fatigue as well as post-exertional malaise.

Trials will continue to launch and enroll participants on a rolling basis. Enrollment will take place at clinical research sites located throughout the United States. A track record for enrolling diverse participants was a key criterion for site selection.

Continuation of ongoing RECOVER studies and the launch of new studies are necessary to capitalize on current momentum, build an evidence base for treating Long COVID, and significantly enhance the return on Congress' original investment. Given the very broad range of symptoms seen in Long COVID and the importance of developing treatments for children, additional clinical trials are needed. RECOVER studies of the pathobiology of Long COVID are aimed at elucidating the underlying mechanisms of disease and the associated therapeutic targets and biomarkers. Such findings will inform the selection of new interventions to be tested based on their ability to more precisely target underlying causes of specific symptoms and/or the root causes of Long COVID. In addition, given the development of new onset disorders and exacerbation of pre-existing conditions seen in patients with Long COVID, longer-term follow-up of patients is needed to understand and address longer-term health outcomes.