

## TRANS-NIH INITIATIVES

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## NATIONAL INSTITUTES OF HEALTH

## Trans-NIH Initiatives

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## **Advisory Committee to the Director Working Groups**

### **Institutes, Centers, and Offices (ICOs) Involved:**

NIH-wide

Immediate Office of the Director (IMOD)

Office of Data Science Strategy (ODSS)

The Advisory Committee to the Director (ACD) brings together a diverse set of voices from outside NIH to provide consultation to the NIH Director on issues relevant to the NIH mission and goals for the conduct of biomedical research. The ACD meets twice yearly to make recommendations on program development, resource allocation, administrative regulations and policies, and other issues of interest to NIH. To make recommendations with the best information, the ACD forms working groups (WGs) and subcommittees to provide in-depth information and perspectives on specific topics.

Several currently active ACD WGs include the following:

- **Working Group on Diversity:** The group is a permanent WG of the ACD and has been charged with providing regular advice to the ACD and NIH Director on effective strategies to increase the representation of diverse individuals underrepresented nationally in biomedical research and to reduce disparities in research awards from diverse applicants underrepresented nationally in biomedical research. The goals of the WGD are to:
  - Enhance access and opportunities for all in order to foster a diverse scientific community
  - Enrich the educational, mentoring, and scientific experience of individuals in the biomedical research training pipeline
  - Promote personal and professional growth for biomedical researchers underrepresented nationally in biomedical research
  - Foster mutual respect and valuing of differences, as well as cross-cultural understanding and the realization of the value of diversity in science
  - Advance programs that prepare diverse individuals underrepresented nationally in biomedical research as scientific leaders.

To accomplish these goals, the group promotes professional development of underrepresented researchers, programs which prepare underrepresented researchers to be scientific leaders, and identifies ways to enrich the education and training opportunities for diverse individuals.

- **Next Generation Researchers Initiative Working Group:** NIH has taken steps over the last several years to ensure the long-term success of biomedical research by supporting early and mid-career researchers. The Next Generation Researchers Initiative was designed to offer specific funding to these scientists. This WG, using a systems-oriented, data-driven approach to analyze the impact of this Initiative on NIH's scientific portfolio and workforce, advises NIH on related activities and provides mechanisms for collecting input on the Initiative from the research community. Their work has focused on considering independent assessments of productivity, advising on ways to support early-stage investigators, identifying overlapping

needs and initiatives across NIH especially as it relates to diversity, and assessing the effectiveness of such actions. The recommendations put forth in FY 2019 centered around a few main areas. First, they identified ways to modify the original NGRI policy, such as by defining a new class of "at risk" investigators who are at risk for losing all NIH support and leaving the scientific enterprise. They encouraged NIH to foster more collaboration and engagement with scientists across career stages to inform policy decisions. Strategies were also suggested to address salary support from NIH awards and improve career development for post-doctoral fellows. The WG also promoted sustainable training opportunities that incorporate diversity and inclusion, along with establishing policies requiring discrimination and harassment-free work environments. Finally, new metrics and access to data are needed to help continually understand the dynamics of the workforce, optimize workforce stability, as well as increase transparency in decision making at NIH. NIH staff are currently evaluating all of the recommendations, assessing which have the best opportunities for success, while also addressing any potentially unintended consequences.

- **Working Group on Artificial Intelligence (AI):** In 2019, the NIH Director announced the formation of an AI working group of the ACD. Coordinated by the OD, this ACD AI WG is identifying trans-NIH opportunities in AI and machine learning (ML), determining how NIH can best collaborate with computer and data science communities, defining approaches for NIH to encourage computer scientists to engage in biomedical research, and identifying the major ethical considerations related to AI in health research and care. Recommendations include a proposal to build large, diverse programs to foster development of a new field, BioMed ML and a call for new, large-scale datasets, built by multidisciplinary teams. Ethical principles for AI use are also a focus, including considerations for how datasets and algorithms can be labeled with data sheets and model sheets to help researchers use and reuse data and models appropriately, analogous to prescription medication labels that explain to patients how to safely use medications. The ACD AI WG reported their recommendations to the ACD in December 2019, and the ACD accepted the recommendations.<sup>37</sup> Over the coming months, NIH will work toward implementation. The recommendations are to:
  - Support flagship data generation efforts to propel progress by the scientific community
  - Develop and publish criteria for ML-friendly datasets
  - Design and apply “datasheets” and “model cards” for biomedical ML
  - Develop and publish consent and data access standards for biomedical ML
  - Publish ethical principles for the use of ML in biomedicine
  - Develop curricula to attract and train ML-BioMed experts
  - Expand the pilot for ML-focused trainees and fellows
  - Convene cross-disciplinary collaborators
  
- **HeLa Genome Data Access Working Group:** The HeLa Genome Data Access WG reviews research applications requesting access to HeLa cell line genomic sequence data. Formed in response to an agreement with the family of Henrietta Lacks (from whom the cells were derived), this WG respects the wishes of family members who hope to see the HeLa genomic

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<sup>37</sup> [https://acd.od.nih.gov/documents/presentations/12132019AI\\_Report.pdf](https://acd.od.nih.gov/documents/presentations/12132019AI_Report.pdf)

sequence data used for the advancement of biomedical research but want to ensure concerns surrounding the family's consent and privacy were addressed. The WG, on which three members of the Lacks family currently serve, provides a review mechanism by which researchers can apply to NIH to access and use the data in a specific research study, and the WG reviews to ensure that specific terms of use are adhered to. This process, including the terms of use, was developed in consultation with the Lacks family and represents a novel and historic partnership between NIH and the family of Henrietta Lacks.

- **Working Group on Changing the Culture to End Sexual Harassment:** As a part of a large NIH-wide effort to end sexual harassment in biomedical research, the WG on Changing the Culture to End Sexual Harassment has assessed the current state of reporting, investigation, and remediation at NIH-funded organizations, proposed actions for the NIH to promote safe inclusive workplaces, and suggested systemic changes to mentored networks and leadership to change climate and prevent harassment. Additionally, the WG was charged with, among other things, developing strategies for encouraging research on anti-harassment policies, procedures, and training, including measures and evaluations of their effectiveness. This WG presented interim recommendations to the ACD in June 2019, including an interim recommendation to treat professional misconduct, including sexual harassment, as seriously as research misconduct. The WG presented its report and final recommendations to the ACD in December 2019. The key themes from the report accepted by the NIH Director include:
  - Increase transparency and accountability in reporting of professional misconduct, especially sexual harassment;
  - Establish mechanisms for restorative justice;
  - Ensure safe, diverse, and inclusive research and training environments; and
  - Create system-wide change to ensure safe, diverse, and inclusive research environments
  
- **Working Group on Enhancing Reproducibility and Rigor in Animal Research:** In response to growing concern about the rigor and replicability of animal research for improving health outcomes, this group has been charged with assessing and making recommendations to enhance the reproducibility and rigor of animal research by improving experimental design, optimizing translational validity, enhancing training, and increasing the transparency of research studies involving animal models. Building on the efforts already undertaken by NIH to improve rigor, reproducibility, and transparency, and taking into account work done by outside organizations, including the National Academies of Sciences, Engineering, and Medicine, the National Centre for the Replacement, Refinement, and Reduction of Animals in Research, and scientific societies (e.g., American Physiological Society, Society for Neuroscience), the WG will consider how training in animal research can be improved, assess the current state of science in alternative methods to animal models, how animal models of human disease are currently developed, and their use in translational research. This WG is expected to make its recommendations in late FY 2020.

## **Harnessing Artificial Intelligence for Health**

### **ICOs Involved:**

NIH-wide

Office of Data Science Strategy (ODSS)

Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI)

Immediate Office of the Director (IMOD)

### **The Potential of Artificial Intelligence for Health Research**

Artificial Intelligence (AI) is not new, but advances in technology and data collection in the past decade have rapidly advanced AI, and it is now being integrated into every realm in human society. AI methodologies offer the ability to make sense of complex datasets that are too large for humans to manually process, to reduce noise in the data, and to find the most relevant data relating to the question being asked. AI has the potential to accelerate biomedical and clinical research, and improve clinical care, if used with an understanding of its limitations and consideration of the ethical complications. AI could be particularly beneficial in places with limited access to health care, for example, patients and populations in middle and low resource areas. Researchers use AI in research-related activities in efforts to move toward translation to use in the clinic; clinicians use AI to continuously learn and understand their patients; patients use AI to better understand themselves; society uses AI to enable computational creativity (i.e., to complement and enhance human intelligence, rather than replace it); policymakers regulate AI to ensure its ethical and safe use. Across the NIH, AI is being applied to various areas of health research in order to fully realize this potential.

The NIH Office of the Director (OD) hosted a workshop, *Harnessing Artificial Intelligence and Machine Learning to Advance Biomedical Research*, to centralize the NIH's interest in AI and gather feedback from experts in the community. Four major needs in AI were identified – preparing data for AI use, applying AI ethically, increasing engagement with computer science communities, and improving AI methods and interpretation at NIH. As discussed in the previous section on Advisory Committee to the Director Working Groups, in 2019, the NIH Director announced the formation of an AI WG of the ACD that made eight recommendations for how NIH can best collaborate with computer and data science communities, encourage computer scientists to engage in biomedical research, and identify the major ethical considerations related to AI in health research and care.

### **Leveraging Artificial Intelligence across the NIH**

Application of AI to biomedical research is part of a larger effort at NIH to harness big data. Specifically, rapid advances in data generation, computing, networking, and algorithms, such as artificial intelligence, are intertwined in a newly evolving digital infrastructure. For example, with the rise of DNA sequencing and other technology advances, rapid and high throughput data generation drove the need for advances in information-based algorithms and memory-rich computers that made it possible to interpret these data in new ways. Today, biomedical data is measured in the petabytes and is comprised of data types ranging from DNA sequences to wearable activity sensor-generated outputs, like heart rate. This increase in pace, scale, and complexity of biomedical data, which can be used to understand and alleviate diseases, underpins the notion of 'big data' for biomedical research. These types of data are ripe for

analysis through the use of AI. NIH's Office of Data Science Strategy coordinates trans-NIH efforts to implement the NIH Strategic Plan for Data Science,<sup>38</sup> which aims to keep NIH at pace with rapid changes in biomedical data science, including seeking out new applications of AI to biomedical research.

NIH ICOs continue to pursue the application of AI approaches in their scientific domains. For example, the National Advisory Council on Aging recently approved in concept a Funding Opportunity Announcement (FOA) on Artificial Intelligence and Technology Centers for Aging Research. Each Center will facilitate the development of a pipeline of technologies representing themes such as early detection of cognitive and functional decline; protection against financial abuse and fraud; safe and comfortable aging in place; and effective management of multiple chronic conditions. NIH anticipates that these Centers will be active in FY 2021. The National Library of Medicine (NLM) has utilized AI to analyze medical images that can improve detection, diagnosis, and treatment of disease, resulting in advances such as: a screening tool for improving classification of cervical cancer and assisting in early treatment in low-resource areas; novel approaches to classify the severity of age-related macular degeneration (AMD) and predict risk of progression to late-stage AMD better than existing clinical standards; an algorithm to detect abnormalities in chest X-ray images and screen for tuberculosis in low-resource settings for populations with high incidence of HIV; and an algorithm that screens for malaria with 99 percent accuracy by detecting the presence of the malaria-causing parasite in red blood cell images. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is supporting use of a machine learning (ML) framework to predict severe maternal morbidity. Severe maternal morbidity, or life-threatening pregnancy complications at delivery, has been increasing steadily, affecting more than 50,000 women in the United States in 2014. Researchers aim to analyze population-based data, linking Maryland state databases with hospital survey data, in order to develop techniques that can predict maternal risks early. Identifying key predictors of severe maternal morbidity can help ascertain health disparities, strengths and weaknesses in obstetric care, and prevent adverse maternal and neonatal outcomes. The National Heart, Lung, and Blood Institute (NHLBI) is building a cloud-based computing infrastructure under its BioData Catalyst hosting large volume of image data and tools supporting AI computing for image data. Its beta version with data on 20,000 chest CT scans from COPDGene is scheduled to be released in late FY 2020. The National Human Genome Research Institute (NHGRI) funds projects that utilize AI/ML in genomics with aims to improve our understanding of the regulatory code, annotate genome structure and function, and elucidate the effects of genetic variation on molecular and disease phenotypes. The ENCODE Data Analysis Center uses machine learning techniques to gain novel insights about the relationship between classes of functional elements, with the goal of annotating functional elements of the genome. The National Center for Advancing Translational Sciences (NCATS) Biomedical Data Translator program is tackling a major challenge in translation, connecting highly compartmentalized data—including health records, publications, chemical biology datasets—across diseases and disciplines. Translator is not only connecting data, but it is creating software that will lead to AI-guided knowledge mapping to help inform research

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<sup>38</sup> NIH Strategic Plan for Data Science. <https://datascience.nih.gov/strategicplan>

directions. While primarily a research tool, and not intended for clinical decision support, Translator also has the potential to inform areas like undiagnosed diseases or ultra-rare diseases, where it is unlikely that clinicians have seen these types of cases. While such AI/ML algorithms can support clinical care decisions, national standards and protocols for validating such algorithms don't yet exist. The Clinical and Translational Science Awards (CTSA)-supported Center for Data to Health (CD2H) is developing best practices (i.e., Good Algorithm Practices) and aiming to establish standards for transparency, reproducibility, and understandability for use of such algorithms in clinical practice. Looking to FY 2021, the Common Fund is also exploring a potential program in AI based on the December 2019 recommendations of the ACD AI WG. Generating data that is amenable to AI, supporting research on the ethical use of AI approaches, and training a suitable workforce are likely themes for the program.

Lastly, NIH is harnessing the power of AI for use with internal NIH data to support data-driven decision-making. The Office of Portfolio Analysis (OPA) uses AI-based approaches to support analysis of the biomedical research landscape and inform data-driven decision-making by NIH leadership. In addition, the Office of Extramural Research (OER) is currently collaborating with the National Institute on Aging to determine if machine-learning techniques can enhance the current Research, Condition, and Disease Categorization (RCDC) process for identifying aging-related research activities. The National Institute of General Medical Sciences (NIGMS) has used natural language processing and machine learning for the grant referral process. Benefits include substantial time savings, allowing experts time to work on higher value tasks, additional objectivity, standardized results, and better accuracy. OER and NIGMS are collaborating to incorporate this algorithm into NIH-wide Enterprise Systems.

#### Continued Engagement with Artificial Intelligence

NIH ICOs are also hosting workshops to engage stakeholders and identify key priorities to continue to integrate AI into their portfolios. In October 2019, NHLBI organized a workshop on imaging genomics. AI and Machine Learning is one of the major topics discussed in the workshop. A white paper is in progress. The NIH Artificial Intelligence Interest Group, Office of Intramural Research, and NIH AI WG for Autonomous Therapeutics held a joint workshop in October 2019 to convene expertise on the potential of AI. A workshop funded by the National Institute of Environmental Health Sciences (NIEHS), "Leveraging Artificial Intelligence and Machine Learning to Advance Environmental Health Research and Decisions", hosted a range of scientists to present AI applications in environmental epidemiology, chemical hazard assessment, and fields beyond environmental health sciences. The workshop was held in Washington, DC in June 2019 and sponsored by the National Academies of Sciences, Engineering, and Medicine (NASEM). The National Institute of Biomedical Imaging and Bioengineering (NIBIB) has convened two workshops on the promise and challenges of AI technologies in medical imaging to provide a roadmap to optimize the use of AI in biomedical imaging. The first workshop held in August 2018 resulted in the issuance of The Roadmap for AI in Medical Imaging. A follow-up workshop in November 2019 focused on developing the partnerships necessary to realize the tremendous potential of AI use in medical imaging. Both workshops included participation by multiple ICs, academia, and radiological societies. These events are continuing to expand application of AI approaches to all areas of NIH-supported health research.

## **All of Us Research Program**

### **ICOs Involved:**

NIH-wide

All of Us Research Program

### **Program Overview:**

Thirty years after Congress funded the Human Genome Project (HGP)<sup>39</sup> the *All of Us* Research Program,<sup>40</sup> a key component of the Precision Medicine Initiative and the 21<sup>st</sup> Century Cures Act (P.L. 114-255), continues its progress toward enrolling at least one million or more participants who reflect the rich diversity of the United States. The program is an ambitious effort to accelerate health research, medical breakthroughs, and to develop individualized care. Precision medicine would not be possible without the HGP's pivotal step towards discovery in mapping the DNA sequence of the entire human genome. Building on the knowledge gained through the HGP, *All of Us* will have the scale and scope to enable research for a wide range of diseases, both common and rare, as well as increase our understanding of health and wellness.

Additionally, a research program of this size will have the statistical power to detect associations between environmental and/or biological exposures and a wide variety of health outcomes.

*All of Us* is a participant-engaged, data-driven enterprise supporting research at the intersection of human biology, behavior, genetics, environment, data science, computation, and much more to produce new knowledge and develop more effective ways to treat and prevent disease. The program officially opened for enrollment in May 2018 and currently enrolls participants 18 years of age or older from all 50 states, D.C., and the five populated U.S. territories through a network of more than 290 enrollment sites. This network includes regional medical centers, Federal Qualified Health Organizations (FQHC), Veterans Affairs (VA) medical centers, and local laboratories as part of the direct volunteer pathway. The program collects a variety of biomedical information from participants, including questionnaires, electronic health records (EHRs), physical measurements, data from digital health technologies, and biospecimens. As of mid-December 2019, more than 305,000 people had consented to join the program as the first step in the participant journey, including more than 235,000 core participants who have completed all the initial steps of the protocol (consent, health record authorization, biospecimen donation, and survey data).

A total of 34 health care provider organizations have uploaded EHR data on more than 150,000 participants. The current recruitment rate is approximately 3,000 core participants per week.

Diversity is a key component of the *All of Us* Research Program because the program wants to ensure that all people benefit from the new biomedical advancements made with *All of Us* data. The program plans to achieve its diversity goals through partnerships with organizations that have ties to, and can assist with the long-term engagement of, participants from communities that have been historically underrepresented in biomedical research (UBR). *All of Us* considers the following populations historically underrepresented: racial and ethnic minority groups; children and seniors; sexual and gender minorities; people with disabilities; people with barriers

<sup>39</sup> [www.genome.gov/human-genome-project](http://www.genome.gov/human-genome-project)

<sup>40</sup> [www.allofus.nih.gov/](http://www.allofus.nih.gov/)

in access to care, have low economic status, or have low educational attainment; and rural residents. Of the core participants as of mid-December 2019, more than 50 percent self-identify as members of racial and ethnic minority groups and 80 percent meet the program's definition of UBR; these percentages exceed the program's original goals of 50 percent and 75 percent, respectively.

True to one of the program's core values, the program considers participants to be its partners. *All of Us* participants are integrated into the program's governance in numerous ways by serving on boards, committees, and task forces, alongside researchers and staff at the local and national levels. Participant partners in *All of Us* provide feedback on multiple elements of the program, including program design, policies, and specific participant-facing elements. Participants will also be able to identify their preferences for what information they would like returned to them. The participant relationship is supported by engagement efforts that establish and maintain the trust needed for participants to join and remain in the program.

As another key element of the *All of Us* engagement strategy, the program has established a diverse network of approximately 40 funded community partner organizations and many more unfunded grassroots community partners across the country. These entities support engagement, outreach, and dissemination of *All of Us* information to diverse communities and populations, including African Americans, Asians, Latinos/Hispanics, older and rural adults, and sexual and gender minorities. The program also has an ongoing partnership with the National Network of Libraries of Medicine (NNLM), which further extends program outreach across the country. Establishing authentic engagement with participants and providing value are key to continued recruitment and long-term retention of participants.

#### Scientific and Programmatic Roadmap:

*All of Us* continues to take advantage of innovative technological and scientific opportunities to guide amendments to the program's evolving protocol and examine the quality and utility of the data the program is collecting. The program anticipates that the data collected will help to identify risk factors and biomarkers (including biological and genetic factors, environmental exposures, lifestyle choices, habits, and social determinants) to improve health by bringing about more efficient and accurate diagnosis and screening, leading to a better understanding of disease in diverse populations, more targeted use of existing therapeutics, and the development of new treatments. In the future, the program plans to develop further iterations of its protocol, which may include additional biospecimen collection and inclusion of other new data elements. In these efforts, *All of Us* will continue to engage with NIH personnel, research communities, participants, and other stakeholders to gather their input on the best ways to shape the future data collection and scientific efforts of the program.

In August 2019, *All of Us* leadership published an article in the *New England Journal of Medicine* describing the program and its progress to date.<sup>41</sup> It details *All of Us*' unique aspects such as a focus on diversity, the nationwide scale and accessibility, and the return of data to participants. The value of the program resides in the richness of data being collected, which will provide researchers the ability to analyze intersections among biological, environmental, and behavioral influences. The program is also leveraging EHR data to provide researchers valuable

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<sup>41</sup> [www.nejm.org/doi/full/10.1056/NEJMSr1809937](http://www.nejm.org/doi/full/10.1056/NEJMSr1809937)

historical health data and piloting a direct volunteer pathway model that leverages new tools and resources to optimize the participant journey – simplifying the process for interested individuals living anywhere in the United States to join and remain enthusiastic partners. While the techniques to collect EHR data through the direct volunteer enrollment pathway are in their infancy, these revolutionary approaches may transform how medical research is collected and utilized by researchers in the future.

#### Trans-NIH Collaboration:

*All of Us* is building a research resource that may be utilized across the NIH and the entire biomedical research enterprise. The program hosts a trans-NIH committee whose members act as liaisons between the program and the NIH ICs. This committee serves as a critical connection to the ICs' strategic goals and provides input on the scientific design of *All of Us*. This includes the variables to be collected on all participants, opportunities to identify scientific partnerships and ancillary studies that may collect data within or in addition to the *All of Us* data collection protocol, and the tools and support needed for funded researchers to use the platform to ask key precision medicine questions. Additionally, the *All of Us* Director formed an Institute and Center (IC) leadership group of 13 IC Directors that provides strategic input and advice about the future of the program. Along with these trans-NIH committees, *All of Us* currently maintains a partnership with the NLM, focusing on consumer access of high-quality health information to UBR communities throughout the United States, while raising awareness of precision medicine and the importance of the program. *All of Us* is currently in the process of establishing additional partnerships across NIH, including with the National Institute of Mental Health to incorporate online modules that will capture cognitive and behavioral data from program participants and with the NICHD using PregSource<sup>42</sup> to capture information on pregnancy for participants that are or become pregnant.

Future trans-NIH collaborations that are in the early planning stages include partnerships with NHLBI to evaluate the burden of sickle cell trait across the population; NHGRI to collaborate on the responsible return of genetic information and on ethical, legal, and social implications research; the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) on precision nutrition; and the National Institute on Drug Abuse (NIDA) to develop a mechanism to link data of future *All of Us* participants dually enrolled in the Longitudinal Study of Adolescent Brain Cognitive Development (the ABCD Study). *All of Us* will continue its efforts to engage NIH ICs to leverage resources to answer a wide range of biomedical research questions and assist with targeted outreach to the research community.

#### Investment in the Future:

The *All of Us* Research Program will continue to make progress towards reaching its long-term target goal of recruitment and retention of one million or more people from diverse populations and walks of life. The program plans to achieve these goals by establishing an authentic, bi-directional, engagement experience and by working with participants and community partners to create and leverage new and innovative tools and resources to optimize the participant journey, making it as easy as possible for interested individuals living anywhere in the United States to join. The program also continues to refine and streamline the enrollment experience through piloting a self-guided participant journey, which flows as a series of steps rather than all at once,

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<sup>42</sup> [pregsource.nih.gov](https://pregsource.nih.gov)

that is scalable and allows for individuals who are not located near traditional research institutions to participate in the program. Additionally, the program also plans to support targeted regional campaigns aimed at increasing UBR enrollment.

Along with enrolling new participants, retaining current participants is a top priority for the program. The program plans to achieve these goals through enhancements to its digital and in-person participant experience, the responsible return of genetic and health information to participants, and the establishment of long-term relationships with participants who are true partners.

*All of Us* will eventually deliver the largest, richest biomedical dataset of its kind that is easy to use and accessible to the research community. Although most research programs similar to *All of Us* grant researchers access to data on a project-by-project basis, *All of Us* has developed a “passport model” through which researchers will be approved for broad data access to study any topic that meets the program’s criterion for allowable use. In May 2019, the program launched its interactive Data Browser<sup>43</sup> to provide the public a first look at aggregate participant data. This tool allows researchers to begin to generate hypotheses and assess the potential of *All of Us* data for their studies. The program plans to open additional data to researchers through the beta release of the Researcher Workbench in 2020. *All of Us* will be a national resource that will grow richer over time as more participants join; the program adds new data types, from digital health data to whole genome sequences; and participants continue their involvement over many years.

Recent *All of Us* awards have laid the foundation for the future return of individual genetic results responsibly to participants who wish to receive them. With the funding provided by Congress, *All of Us* funded three premier genome centers<sup>44</sup> and established a nationwide genetic counseling resource<sup>45</sup> that will enable the responsible return of genetic results to participants. *All of Us* anticipates beginning to return individual genetic results to participants in 2020. *All of Us* entered into a partnership with the NCATS to fund a fourth genome center to test advanced sequencing tools and explore more elusive parts of the genome. Through this additional NCATS funding, *All of Us* will be able to offer approved researchers an even greater depth of genetic information than originally planned, making the resource even more valuable for them and the diverse communities we seek to serve.

*All of Us* is continually expanding methods of enrolling participants “where they are,” including initiating a pilot program that allows participants to send in a saliva sample via the mail. The program also supports two mobile units that travel across the country to educate potential participants about the importance of precision medicine and support on-site account registration; one unit is also equipped for participants to provide physical measurements and biosamples onboard.

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<sup>43</sup> [www.researchallofus.org](http://www.researchallofus.org)

<sup>44</sup> [www.allofus.nih.gov/news-events-and-media/announcements/nih-funded-genome-centers-accelerate-precision-medicine-discoveries](http://www.allofus.nih.gov/news-events-and-media/announcements/nih-funded-genome-centers-accelerate-precision-medicine-discoveries)

<sup>45</sup> [www.allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-issues-funding-opportunity-genetic-counseling-resource](http://www.allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-issues-funding-opportunity-genetic-counseling-resource)

The enrollment of children in the *All of Us* Research Program has been and remains a priority. The program is building a team to lead the complex efforts necessary for the future enrollment of children. In order to do this responsibly there are important considerations including ensuring compliance with state legal requirements, having the appropriate consent and assent procedures required for children to join the study, enabling variable data collection methods across the childhood lifespan, considering the challenges of returning information, and managing different communications and informational needs for child participants and their guardians at each developmental stage. The program is cognizant of the need to maximize the long-term scientific utility of the pediatric data collected, ensuring that data from the pediatric protocol has the power to advance precision medicine research for participants who continue in the program as adults. *All of Us* understands the urgency and critical importance of enrolling this population into the cohort and acknowledges the excitement from the pediatric research community. The program's careful approach will enable a wide range of important precision medicine discoveries to improve children's health while also being mindful of the sensitivities and protections required to include minors.

Through the scale, scope, and accessibility of its data, *All of Us* will be positioned to address scientific questions from across the biomedical research enterprise and be leveraged by the NIH as a whole. For example, the program's data will be able to answer questions such as:

- Can a risk profile that includes genetic and other factors better explain and predict type 2 diabetes?
- Can we develop and validate machine learning approaches to diagnosing various cancers at earlier stages?
- How do non-pharmacological interventions impact health/resilience?
- What are the genetic factors associated with maternal mortality in African American women?
- What are the factors that influence vulnerability and resilience for opioid misuse in the face of chronic pain?

Ultimately, the program aims to enable research that will increase wellness and resilience, and promote healthy living; reduce health disparities and improve health equity; develop improved risk assessment and prevention strategies to preempt disease; provide earlier and more accurate diagnosis to decrease illness burden; and improve health outcomes and reduce disease burden through improved treatment and development of precision interventions. The program's approaches to meet participants where they are, engage them as true partners, and provide broad data access will transform how medical research is conducted in the future.

## **The Brain Research through Advancing Neurotechnologies (BRAIN) Initiative**

### **ICOs Involved:**

National Eye Institute  
 National Institute on Aging  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
 National Institute on Deafness and Other Communication Disorders  
 National Institute of Mental Health  
 National Institute on Minority Health and Health Disparities  
 National Institute of Neurological Disorders and Stroke  
 National Center for Complementary and Integrative Health  
 National Institute on Drug Abuse  
 National Institute on Alcohol Abuse and Alcoholism  
 National Institute of Biomedical Imaging and Bioengineering

### **Program Overview:**

Dysfunction of brain circuits underlies all the neurological, psychiatric, sensory, and substance use disorders. Until recently, research tools have not been powerful enough to answer fundamental questions about how brain circuits work, and what goes wrong in these diseases: How many cell types make up the 170 billion cells in the brain? How are these cells connected to one another? How does the flow of information through the circuits of interconnected cells in the brain enable us to move, sense, think, communicate, and make us who we are as individuals? The BRAIN Initiative takes advantage of emerging opportunities, arising from decades of investment across many areas of science and engineering, to develop and apply technologies to answer these profound questions. Solutions for those suffering with neuro/mental/substance abuse disorders will come from seeing how malfunctions of brain circuits drive the many brain disorders.

Since NIH launched the BRAIN Initiative in 2014, Congress has expressed continuing interest and support through the 21<sup>st</sup> Century Cures Act, in yearly Appropriations report language, at hearings, in visits to the NIH, and during many other discussions with the NIH leadership.

From the Initiative's inception, the report BRAIN 2025: A Scientific Vision<sup>46</sup> has provided an overarching vision, operating principles, concrete goals, and milestones for this many faceted program. A stellar group of independent, interdisciplinary scientists, under the aegis of the NIH Advisory Committee to the Director, developed the BRAIN 2025 plan through extensive interactions with the scientific community. The Initiative builds on progress in neuroscience, optics, genetics, physics, engineering, informatics, nanoscience, chemistry, mathematics, and other disciplines to underpin a research program of unprecedented scope.

As befits the breadth of the program, the Initiative is highly collaborative within NIH, across Federal agencies, and with private organizations and the international scientific community. Scientific and engineering staff from 10 NIH Institutes and Centers manage the program through fully integrated teams. A Multi-Council Working Group (MCWG), with members from

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<sup>46</sup> <https://www.braininitiative.nih.gov/strategic-planning/brain-2025-report>

participating Institute and Center Advisory Councils, provides advice and oversight through 10 Institute and Center Advisory Councils. Representatives from the Food and Drug Administration (FDA), National Science Foundation (NSF), Defense Advanced Research Projects Agency (DARPA), and Intelligence Advanced Research Projects Activity (IARPA) bring their expertise and coordinate activities through the MCWG. Together with non-profit and academic members of the BRAIN Initiative Alliance, the Initiative has engaged talent from academia and companies across a broad spectrum of science and engineering throughout the United States.

The seven priorities of the BRAIN 2025 plan, each with detailed goals and milestones, guide the activities of the BRAIN Initiative. These priorities are:

*Discovering diversity:* Identifying all the diverse brain cell types is essential to understand how brain circuits work and to develop research tools and therapies that precisely target specific cell types. The nearly 170 billion cells in a human brain differ in location, shape, connections, activity, and in their molecular composition, presenting a formidable challenge.

*Maps at multiple scales:* To understand how brain circuits work and solve the vexing problems of brain disorders, researchers must map the brain’s anatomical and functional connections at multiple scales, from the major nerve fiber “highways” connecting areas of the brain to the trillions of microscopic synapses that connect individual cells.

*The brain in action:* To observe brain circuits in action, researchers must develop and apply tools to monitor simultaneously the activity of the thousands of brain cells, in real time, with millisecond time resolution, as they carry out their functions.

*Demonstrate causality:* By altering the activity of specific nerve cells in a brain circuit as an animal behaves, researchers can move beyond observation to demonstrating how circuits cause behaviors. Just as understanding how faulty genes cause disease has led to therapies for gene disorders, understanding how circuit malfunction underlies brain disease points the way toward reestablishing healthy circuits.

*Theory and data analysis tools:* Projects that monitor activity of thousands of nerve cells, map millions of synaptic connections, or assess activity of all genes in the myriad cell types of the brain generate immense amounts of data, which presents extraordinary opportunities and challenges. The data is of many types and scales—anatomical data from whole brain imaging to high resolution electron microscopy, physiological data from many individual cells to whole brain regions, and molecular data on genes and proteins, among others. Theories, simplifying principles, and testable models are essential to understand what this data tells us about how the brain works, what goes wrong in disease, and to predict the effects of altering brain circuits.

*Advancing human neuroscience:* Developing technologies to understand the human brain and treat its disorders presents special challenges, because of the human brain’s size, complexity, and sensitivity to intervention, and the ethical caution that must guide research on the organ that is at the core of what makes us human.

*From BRAIN Initiative to the brain:* Integrating the new technological and conceptual approaches, which range from the nanoscale to whole organism behavior, is essential to discover how dynamic patterns of brain activity are transformed into cognition, emotion, perception, and action in health and disease. This integration is the ultimate goal of the BRAIN Initiative.

#### Scientific Highlights:

The BRAIN 2025 report advised NIH to monitor progress, adapt to the rapidly changing scientific and technical landscape, and take advantage of new opportunities arising from the Initiative itself and other areas of science and engineering. Following that recommendation, the ACD formed a new external scientific working group, the ACD BRAIN Initiative WG 2.0, to assess progress and identify how the Initiative can best invest to realize its vision. After intensive investigation and outreach to the research community, the group reported to the ACD in June 2019 that the BRAIN Initiative is making significant progress on all seven major priorities of the plan, with many specific objectives and milestones already accomplished, and unanticipated progress in some areas. The ACD also engaged a separate working group, which also reported in June 2019, to ensure that the BRAIN Initiative continues to consider the ethical implications of its pioneering studies on the workings of the brain and how these will be understood and applied.

Cell diversity is one priority on which progress has been remarkable, well ahead of what was anticipated. This enabled the multi-site BRAIN Initiative Cell Census Network to scale up using high throughput methods and begin developing a comprehensive mouse brain cell atlas and to advance cell type identification into human brains. Several powerful brain mapping and activity monitoring tools that were in their infancy when the BRAIN Initiative began have also dramatically improved. Researchers throughout neuroscience are rapidly adopting these advances, which range from better anatomical and functional brain imaging, to genetic “barcodes” for mapping connections, and automated 3D reconstruction from highly magnified electron microscopy of serial brain sections. Optical monitoring methods now enable researchers to simultaneously monitor the activity of thousands of brain cells, capturing the contributions of every nerve cell in simple experimental animals as the animals carry out simple behaviors. Likewise, the BRAIN Initiative is both dramatically enhancing existing methods and developing entirely new technologies to manipulate circuits. These methods variously use electromagnetic, ultrasound, chemical, and optical techniques in laboratory animals, and may be adaptable to treat human patients in the future.

To make useful data available to the research community, the BRAIN Initiative, using the authorities in the 21<sup>st</sup> Century Cures Act, has issued a strong data sharing policy. The Initiative has also supported the development of data standards, developed data archives for the various types of data, and is developing and disseminating data analysis tools.

From its inception, the focus of the BRAIN Initiative has been on understanding the normal brain, largely in laboratory animals. This will, in due course, provide the tools and knowledge to combat human brain diseases that have proven so challenging to medical science. The extent to which advances within the Initiative itself and the use of these new capabilities throughout neuroscience programs are already stimulating new opportunities against human disease is encouraging. The progress in developing high throughput methods to study cell diversity in

laboratory animals is now enabling researchers for the first time to determine precisely which human brain cells are affected by diseases such as Alzheimer's, autism, and Zika virus infection, with the potential to direct treatment to those cells. Cell typing has also provided insights about why so many drugs that are effective in mouse models of brain diseases do not translate to humans. New methods to release circulating drugs from carriers using ultrasound have demonstrated proof in principle of a strategy to deliver active drugs precisely where they are needed in the brain. "Closed-loop" deep brain stimulation (DBS), which monitors brain activity and automatically adjusts stimulation accordingly, has shown promise for treating Parkinson's disease, and DBS is being explored for depression, epilepsy, and several other disorders. Noteworthy brain computer interface projects have, for example, decoded speech directly from brain activity and developed a feasible approach to restore vision using a visual neural prosthesis. The BRAIN Initiative has also targeted initiatives to bring new neurotechnologies to bear on developing new approaches to addiction and to non-addictive treatments for pain to address the opioid crisis. Just as the Human Genome Project had an impact far beyond medicine, the BRAIN Initiative is also inspiring private sector developments, with major private sector investments based on neuroscience progress underway in artificial intelligence, computer hardware, and human computer interface systems.

#### Next Steps:

The BRAIN 2.0 WG recommended that the NIH BRAIN Initiative stay on the productive path that is underway; that is, continuing the development of technology while increasing the emphasis on application of the new methods to understanding brain circuits, as per the original plan. The WG also suggested many "tune ups" to specific goals and new milestones, now that many objectives of the original plan have been met or exceeded.

Among the general recommendations, the group also recommended increasing attention to organization of science as the Initiative moves forward. To capitalize on the value of data from the Initiative to neuroscience, BRAIN data should be FAIR (findable, accessible, interoperable, and reusable). To accomplish this, NIH must follow through on the data sharing policy that the Initiative issued in 2019 and on development of data standardization, archiving, and analysis tools that has begun. BRAIN must also renew the focus on human capital, which has been critical to progress since the Initiative's inception. Not only is there is a continuing need to engage scientists and engineers from a broad range of fields and background, but, as the Initiative progresses, translational and clinical scientists, and experts in quantitative domains become all the more essential. Throughout its programs, the Initiative must balance individual-investigator research with team science as new opportunities emerge.

None of the above cited recommendations from the BRAIN 2.0 group represent a notable departure from the original vision of the BRAIN 2025 report. However, the group did suggest that the BRAIN Initiative, given the remarkable progress to date, could now consider investing in larger scale, transformative projects that might propel neuroscience far into the future. These include opportunities from across all BRAIN Initiative priority areas, for example, a large scale project to generate methods to precisely access, manipulate, and model hundreds of clinically relevant brain cell types, a comprehensive cell-type atlas of the human brain, complete "connectome" maps of the mouse brain, or developing a truly specific circuit intervention for a

major human psychiatric or neurological disease symptom. The BRAIN Initiative is considering the feasibility and impact of these large-scale scientific opportunities for its next five years.

## **Investigating Co-occurring conditions across the Lifespan to Understand Down syndrome (INCLUDE) Project**

### **ICOs Involved:**

National Cancer Institute  
 National Eye Institute  
 National Heart, Lung, and Blood Institute  
 National Human Genome Research Institute  
 National Institute on Aging  
 National Institute of Allergy and Infectious Diseases  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
 National Institute of Arthritis, Musculoskeletal and Skin Diseases  
 National Institute on Deafness and Other Communication Disorders  
 National Institute of Dental and Craniofacial Research  
 National Institute of Diabetes and Digestive and Kidney Diseases  
 National Institute of Environmental Health Sciences  
 National Institute of Mental Health  
 National Institute on Minority Health and Health Disparities  
 National Institute of Neurological Disorders and Stroke  
 National Institute of Nursing Research  
 National Center for Advancing Translational Sciences  
 National Center for Complementary and Integrative Health  
 Office of the Director: Office of Research Infrastructure Programs, Office of Strategic Coordination (Common Fund), Immediate Office of the Director

In the last 25 years, the expected lifespan for people with Down syndrome (DS) has doubled, leading to a pressing need to understand the medical needs and challenges faced by individuals with Down syndrome as they age. The INCLUDE Initiative, a trans-NIH effort, is engaging diverse expertise across the agency to address the complex nature of Down syndrome and the need for a comprehensive approach. This effort is attracting new investigators into the field and is continuing to grow and support Down syndrome research with new opportunities across the spectrum of basic and clinical research, building a cohort of individuals with Down syndrome across the lifespan and developing outcome measures for impactful clinical trials tailored to these individuals. INCLUDE is hosting workshops to bring together patients and patient advocates, investigators, clinicians, and NIH staff to better engage the community and garner input on these research objectives.

### **Past: Launch of the INCLUDE Initiative**

Beginning in FY 2018, the existing NIH Down Syndrome WG expanded to the 21 ICOs listed above, adding expertise to inform the development of the INCLUDE initiative. This broad representation across NIH captures the trans-NIH effort and appropriately reflects the complex nature of Down syndrome and the need for full engagement of NIH's collective scientific expertise. A research plan for the INCLUDE initiative was developed through the NIH Down Syndrome WG and posted on the NIH website to inform the Down syndrome community about its priorities and encourage the scientific community to apply for research funding.<sup>47</sup>

<sup>47</sup> [www.nih.gov/include-project/include-project-research-plan](http://www.nih.gov/include-project/include-project-research-plan)

The INCLUDE effort is centered on the need for scientific discoveries aimed at improving the health of individuals with Down syndrome as well as the health of those without Down syndrome who share common co-occurring conditions including Alzheimer's disease, cancer, cardiovascular disease, immune system dysregulation, and autism, among others. This research opportunity has a unique “double benefit” in that chromosome 21 provides a genetic foothold and a starting point for a molecular understanding of these co-occurring conditions. Therefore, it has the potential not only to improve the health of those with Down syndrome, but also that of many others through a greater understanding of common conditions present, or absent, in individuals with Down syndrome.

The three primary components of the INCLUDE initiative are:

- Component 1: Conduct targeted, high-risk, high-reward basic science studies on chromosome 21.
- Component 2: Assemble a study population of individuals with Down syndrome.
- Component 3: Include individuals with Down syndrome in existing and future clinical trials.

In the first year of INCLUDE, NIH supported 49 administrative supplements to existing grants, either to expand existing efforts on Down syndrome, or add a Down syndrome-related component to other grants. Thirteen ICs participated, and all three major components of the INCLUDE initiative were addressed, covering the waterfront of INCLUDE’s research plan. The goal of these FY 2018 investments were to lay the critical groundwork needed for building this initiative and to further engage with the Down syndrome community and other stakeholders, informing further development of INCLUDE. Strategic use of administrative supplements in this first year also drew investigators into the field, leveraging ongoing work across the participating ICs and enabling individuals with Down syndrome to be pulled into existing cohorts and clinical trials quickly, a major concern in the DS community. The first scientific meeting of the INCLUDE project took place in November 2018 at NIH and gathered together clinical researchers to discuss optimal ways of conducting clinical trials in adults with Down syndrome who are at high risk to develop Alzheimer’s disease, a major health challenge for adults with Down syndrome and their families.

#### Building INCLUDE into a full-fledged Trans-NIH Program

In FY 2019, this program continued to grow, shifting support towards new awards and Request for Applications (RFAs) developed following community engagement. Five FY 2019 Funding Opportunities covered a broad range of research areas related to Down syndrome, from basic to clinical research and focusing on transformative opportunities, preparation and initiation of clinical trials, and building the pipeline of Down syndrome researchers. Through these funding opportunities, 43 awards were made including support for four early-stage or new investigators and five training grants, expanding the pipeline of investigators in Down syndrome research.

#### Into the future of INCLUDE: An integral part of the NIH Down syndrome research agenda

Looking to FY 2020 and beyond, INCLUDE has released 12 FOAs (detailed below) in FY 2020 to further expand the INCLUDE Project. These funding opportunities will continue to invest in the three components of INCLUDE, with additional emphasis on component 2 (assembling a

study population of individuals with Down syndrome) following input from a scientific workshop “Planning a Virtual Down Syndrome Cohort Across the Lifespan,” on September 23-24, 2019, which provided input on how to create a large cohort for natural history and biomarker studies -- to include current, smaller cohorts -- all critical aspects of the cohort development component 2 of the INCLUDE research plan.

The three RFAs developed in FY 2019 were re-issued in FY 2020 to further capitalize on those efforts, specifically continuing the R01 Transformative Research Award, the R21 Clinical Trial Readiness Research Award and the R61/R33 Phased Awards for Clinical Trials for Co-Occurring Conditions in Individuals with Down syndrome.

Two new RFAs were developed in FY 2020 that further address component 2. One solicitation will support the development of a center to coordinate the collection, storage, quality control, and harmonization of data and biospecimens related to the creation of a large clinical cohort of individuals with DS across the lifespan. This center will also provide an integrated data portal for investigators. The goal is to advance the diagnosis, management, and treatment of Down syndrome and its co-occurring conditions through the collection of pan-‘omics datasets from existing and prospective DS clinical cohorts. A second opportunity will encourage applicants that propose to conduct primary data analysis or interpretation of DS data from existing cohorts or secondary analysis of publicly available NIH-funded datasets to enhance an understanding of DS across the lifespan. Expanded use of existing datasets and biorepositories will allow researchers to address research questions within the scientific scope of the INCLUDE project at relatively low cost and effort and enhance the value of INCLUDE investments in research.

In addition, three Notices of Special Interest released in FY 2020 specifically target fellowship and career development awards to continue to build the pipeline of Down syndrome researchers. Another new Notice of Special Interest aims at developing research models of Down syndrome to provide novel tools for understanding Down syndrome and assessing potential interventions. The remaining funding opportunities are Notices of Special Interest for administrative supplements and competitive revisions to continue to leverage ongoing work across NIH where needed, and new grants applications (R01) focused on Down syndrome across a range of scientific approaches.

Through this constellation of funding opportunities, all three components of INCLUDE continue to be further developed, with establishment of the data coordinating center a major step in development of a Down syndrome cohort. Two additional workshops are planned for Spring and Fall 2020 to address the state of the science for clinical trials in Down syndrome, and promising areas in basic research, respectively. NICHD will provide additional impetus for clinical trial development through INCLUDE by working with its national Pediatric Trials Network to incorporate cohorts of people with Down syndrome into their pediatric drug testing trials. In addition, NICHD will create a training program for these clinical researchers, using the expertise of currently funded researchers who study Down syndrome, on how to work best with individuals and families of people with Down syndrome in conducting clinical trials. This program could be applicable to including individuals with other intellectual and developmental disabilities in clinical research.

Lastly, NIH is revisiting its research plan on Down syndrome, last updated in 2014.<sup>48</sup> This plan will include an update on the INCLUDE research plan released in FY 2018 at the launch of the program. NIH will begin this strategic planning exercise by utilizing Requests for Information to garner input from the Down syndrome community, including the public-private Down Syndrome Consortium led by the NIH. This effort will provide a critical opportunity to re-assess program priorities as INCLUDE continues to mature as it enters its third year and will ensure continued strategic alignment between INCLUDE and the overarching goals of Down syndrome research across the NIH.

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<sup>48</sup>[www.nichd.nih.gov/sites/default/files/publications/pubs/Documents/DSResearchPlan\\_2014.pdf](http://www.nichd.nih.gov/sites/default/files/publications/pubs/Documents/DSResearchPlan_2014.pdf)

## **NIH Pediatric Research Consortium (N-PeRC)**

### **ICOs Involved:**

NIH-wide

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding for pediatric research across NIH has increased steadily since 2013, reaching \$4.5 billion in FY 2018. Nearly all of the NIH ICOs support some pediatric research. The NIH Pediatric Research Consortium (N-PeRC) is a trans-NIH initiative established in June 2018 to provide a venue for NIH ICs to harmonize activities related to pediatric research, explore gaps in the overall NIH portfolio, and share best practices to advance science across ICs. Initial efforts concentrated on surveying the global landscape of pediatric research and training at NIH to identify and articulate areas in which N-PeRC can work collaboratively to fill gaps or augment ongoing initiatives.

*Making pediatric data resources more accessible* – Currently, there are many pediatric datasets available to researchers but there is no central location that lists these resources and provides information on how to access them. One of N-PeRC’s initial endeavors is to identify databases supported by NIH to explore development of a central location to list and link these databases. This would provide a single reference point for pediatric researchers to identify data that may be available for hypothesis testing and secondary analyses.

*Expanding the pediatric research workforce* – Pediatric training and career development efforts are currently supported by multiple NIH ICs, and N-PeRC members are discussing ways to coordinate and communicate these efforts to the child health research community. An initial analysis showed that support for pediatric training is broadly distributed across NIH ICs, just as support for pediatric research itself is broadly distributed across ICs.

*Supporting pediatric reviewers* – Development and maturation of the brain and other organs, ongoing changes in physiology and growth, and specific processes such as puberty are important considerations for research on diseases and conditions that affect children. N-PeRC has added representation from the Center for Scientific Review to help facilitate appropriate review, including identifying potential pediatric experts to serve on review panels for grant applications that require pediatric expertise.

*Transition from pediatric to adult healthcare* – Although many typically developing adolescents may find it challenging to transition to adulthood, individuals with chronic conditions (such as congenital heart disease) or intellectual or physical disabilities face increased challenges during the transition from pediatric to adult healthcare. Ensuring continuity of care for these individuals is vital for their health and wellbeing. N-PeRC members formed a working group to examine NIH’s investment in this area and are now generating ideas for collaborative activities to begin to address gap areas.

*Prioritize drug and device testing for pediatric labeling through the Best Pharmaceuticals in Children Act (BPCA) and other activities* – Each of the ICs was asked to provide a list of the highest priority drugs relevant to each IC’s focus on organ or disease. These suggestions will be

discussed and then considered for incorporation into the BPCA priority list.<sup>49</sup> N-PeRC is also reviewing NIH's research on pediatric devices to identify opportunities to work together across the agency.

In the future, N-PeRC will catalyze greater trans-NIH collaborations across pediatric research, especially in areas of common interest such as the transition of adolescent to adult healthcare and pediatric drug and device development. Expert meetings or workshops to assess the state of the science and/or gather input from external stakeholders could inform future efforts, including NIH funding opportunities and notices. N-PeRC will further analyze the available opportunities for training the next generation of pediatric researchers. N-PeRC anticipates a series of efforts to inform the pediatric community about little-known or overlooked training and career development opportunities in pediatric research. N-PeRC leadership will maintain strong links and regular communication with the domestic and global pediatric research communities to harmonize study designs if possible and to increase general awareness of funding opportunities and the availability of publicly shared resources such as the NICHD's Data and Specimen Hub. Finally, N-PeRC plans to promote further engagement with other federal partners that have substantial investments in child health.

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<sup>49</sup> [www.nichd.nih.gov/sites/default/files/inline-files/2018PriorityList-Feb19.pdf](http://www.nichd.nih.gov/sites/default/files/inline-files/2018PriorityList-Feb19.pdf)

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

### **ICOs Involved:**

National Heart, Lung, and Blood Institute  
 National Institute of Allergy and Infectious Diseases  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
 National Institute of Arthritis, Musculoskeletal and Skin Diseases  
 National Institute of Mental Health  
 National Institute of Neurological Disorders and Stroke  
 National Center for Complementary and Integrative Health  
 National Institute on Drug Abuse  
 National Center for Advancing Translation Sciences  
 National Institute for Biomedical Imaging and Bioengineering

### **Program Overview:**

The national crisis of opioid misuse, addiction, and overdose, one of the largest and most complex public health crises that our nation has faced, continues to affect communities across America. The crisis has many contributors, including the need for pain management among the 100 million Americans with chronic pain at risk for opioid misuse, the limited number of effective options for the prevention and treatment of opioid use disorder, and the failure to implement the successful interventions that we have.

To advance scientific breakthroughs aimed at tackling the crisis, the HEAL Initiative, a major coordinated effort through the NIH Office of the Director, was launched in April 2018. This trans-NIH effort builds on well-established NIH research to accelerate scientific solutions to stem the national opioid public health crisis and offer new hope for individuals, families, and communities affected by the devastating crisis.

Since its inception, the NIH HEAL Initiative Research Plan<sup>50</sup> has provided an overarching vision, concrete goals, and milestones that are built around two overarching priorities: 1) enhancing pain management, and 2) improving the prevention and treatment for opioid misuse and addiction. The HEAL Initiative leverages expertise from almost every NIH Institute and Center to approach the crisis from all angles and disciplines, and across the full spectrum of research from basic research to implementation science. In consultation with a broad range of stakeholders, NIH identified six research focus areas that fall within the Initiative's two overarching priorities. Each focus area, as well as their aims, are briefly summarized below:

### **Enhancing Pain Management with Non-Addictive Therapies**

*Preclinical and translational research in pain management:* More effective, non-addictive, therapies for pain are needed, but limitations in current animal models, changes in biopharmaceutical industry business focus, and perceived regulatory and reimbursement concerns have posed obstacles to research. Through a suite of targeted research efforts, the HEAL Initiative will accelerate the discovery and preclinical and translational development of new medications and devices to treat pain.

<sup>50</sup> <https://heal.nih.gov/about/research-plan>

*Clinical research in pain management:* The HEAL Initiative supports research to evaluate the safety and efficacy of innovative, non-addictive, therapies for pain management in a number of different pain conditions. These clinical trials will help inform evidence-based guidelines for the treatment of pain with non-opioid therapies and reduce the risk of prescription opioid medications.

### **Improving Prevention and Treatment for Opioid Misuse and Addiction:**

*New strategies to prevent and treat opioid addiction:* The HEAL Initiative supports research focused on preventing individuals with low-severity opioid use disorder (OUD) from developing a more severe OUD, building strategies to keep people in medication treatment for opioid addiction for long enough to support long-term recovery, understanding the role of sleep dysfunction in OUD and recovery, preventing at-risk adolescents from developing OUD, and exploring collaborative care for people with OUD and mental health conditions.

*Translation of research to practice for the treatment of opioid addiction:* There are multiple effective evidence-based treatments and programs for OUD, but most Americans at risk for or with OUD do not receive appropriate treatment for their disorder. To better understand how promising evidence-based strategies and treatments might help more people with OUD, the HEAL Initiative will deploy a suite of implementation science efforts to test the integration of evidence-based interventions in a multitude of settings.

*Novel medication options for opioid use disorder and overdose:* Expanded treatment options for OUD are needed to promote long-term recovery in more patients. The HEAL Initiative will accelerate the development of novel medications and devices to treat all aspects of the opioid addiction cycle, including progression to chronic use, withdrawal symptoms, craving, relapse, and overdose.

*Enhanced outcomes for infants and children exposed to opioids:* The best approaches to address the medical and social needs of children with neonatal abstinence syndrome and neonatal opioid withdrawal syndrome, which increased fivefold among infants covered by Medicaid in 46 states, is critical for the future health of the country.

The HEAL Initiative has established extensive collaborations across NIH. Staff from nearly every NIH Institute and Center manage the program through fully integrated teams of research program experts. A Multi-Disciplinary WG, made up of research experts from the private sector, patient and academic research community, and multiple NIH advisory councils, provides input to the HEAL and NIH leadership to help ensure research meets the bold, trans-NIH goals set for the initiative.

### Scientific Highlights:

NIH intends to maximize the availability of publications and the sharing of underlying data generated through the HEAL Initiative research projects. By making publications and the

primary data behind them available as rapidly as possible, the HEAL Initiative promotes dissemination of new knowledge, enhances reproducibility, and accelerates the ability of researchers to build upon the Initiative’s research to make new discoveries. In 2019, over 350 research projects were awarded under the HEAL Initiative within the six research focus areas. Twelve NIH ICOs lead 25 research programs that support a diverse community of researchers working across the research spectrum. Below is a summary of the research programs that fall within each of the six research focus areas and the challenges that they seek to address.

#### *Preclinical and translational research in pain management*

The overreliance on prescription opioids for the management of chronic pain conditions, despite limited effectiveness among some patients, has contributed to the recent epidemic of deaths due to opioid overdose. To address this challenge, the National Institute of Neurological Disorders and Stroke (NINDS) leads efforts to accelerate the scientific discovery and validation of novel treatment targets for acute and chronic pain conditions.<sup>51</sup> The newly created Preclinical Screening Platform for Pain aims to further identify and profile non-addictive therapeutics for pain conditions,<sup>52</sup> while the NCATS has established a complementary in vitro screening platform for testing of therapeutic candidates for pain in non-animal models.<sup>53</sup> Translating these discoveries requires more accurate research models to help understand how potential new drugs will affect humans. To this end, research led through NCATS facilitates novel human cell-based screening platforms, pharmacological probes, and pre-clinical drug development.<sup>54</sup> Further efforts aim to advance optimization and early development of promising small molecules and biologic agents to advance low-risk treatment options for chronic pain toward clinical development.<sup>55</sup> NINDS, NIBIB, and the Common Fund foster the development of next-generation medical devices to diagnose and treat pain,<sup>56</sup> including implanted devices, such as electrodes, and noninvasive targeted stimulation of nerve cells and regions of the brain associated with pain perception.

#### *Clinical research in pain management*

Advancing clinical research on pain management is a core goal of the HEAL Initiative. The Early Phase Pain Investigation Clinical Network (EPPIC-Net), led by NINDS, provides proof-of-concept clinical testing of potential biomarkers and new treatments to help identify specific pathways or mechanisms that hold promise for future therapeutic development.<sup>57</sup> EPPIC-Net also interfaces with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) led Back Pain Consortium, which studies how people with different types of back pain respond to specific interventions.<sup>58</sup> The Pain Management Effectiveness Research Network clinical trials, which leverage the infrastructure of NCATS Trial Innovation Network, are designed to evaluate the effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of acute and chronic pain conditions. This program is closely aligned with the high-priority recommendations of the Federal Pain Research Strategy and supports implementation of

<sup>51</sup> <https://heal.nih.gov/research/preclinical-translational/novel-targets>

<sup>52</sup> <https://heal.nih.gov/research/preclinical-translational/screening-platform>

<sup>53</sup> <https://ncats.nih.gov/heal>

<sup>54</sup> <https://heal.nih.gov/research/preclinical-translational/novel-drugs-screening-platforms>

<sup>55</sup> <https://heal.nih.gov/research/preclinical-translational/optimization-non-addictive-therapies>

<sup>56</sup> <https://heal.nih.gov/research/preclinical-translational/discoveries-into-devices>

<sup>57</sup> <https://heal.nih.gov/research/clinical-research/eppic-net>

<sup>58</sup> <https://heal.nih.gov/research/clinical-research/back-pain>

the recommendations of the Pain Management Best Practices Inter-Agency Task Force.<sup>59</sup> It will be of particular importance to determine which evidence-based strategies are most effectively implemented in health systems. Pragmatic trials led by the National Center for Complementary and Integrative Health (NCCIH) will help determine the effectiveness of multiple non-opioid interventions for treating pain and assess the impact of implementing interventions or guidelines.<sup>60</sup> Similarly, NIDDK coordinates an integrated approach to pain and opioid use in hemodialysis patients to identify novel risk factors in this population, which has the potential to reduce the rate of opioid prescription and opioid use and address related issues, such as depression, anxiety, and pain.<sup>61</sup>

#### *New strategies to prevent and treat opioid addiction*

Expanding the evidence of what treatments work in the real world is a priority of the HEAL Initiative, which requires prevention measures that incorporate the specific challenges of opioids. For example, there is an urgent need to identify effective approaches to treat people who have an opioid use disorder and co-occurring mental health conditions, especially in primary care settings. HEAL-supported research led by National Institute of Mental Health (NIMH) utilizes the collaborative care model to determine its usefulness in treating this population.<sup>62</sup> Studies led by NIDA focus on other high-risk populations, including older adolescents and young adults, that require strategies and settings that can identify and reach those at risk, such as health care, justice, school, and child welfare systems.<sup>63</sup> Understanding whether sleep deficiency contributes to the overuse of opioids and addiction could open avenues for novel prevention and treatment approaches. As a result, the NHLBI leads basic and clinical research to identify the behavioral and molecular mechanisms that directly connect sleep to the biological underpinnings of OUD.<sup>64</sup> Additional prevention research carried out through the National Drug Abuse Treatment Clinical Trials Network brings together medical and specialty treatment providers, researchers, and patients to test interventions aimed at stopping the progression from risky opioid use to more severe OUD,<sup>65</sup> and supports research to define the optimal length of medication treatments for OUD approved by the FDA.<sup>66</sup>

#### *Translation of research to practice for the treatment of opioid addiction*

The integration of evidence-based intervention into routine clinical usage requires focused efforts. The HEAL Initiative utilizes implementation studies to test the systematic uptake of research findings into routine practice. For example, NIH and the Substance Abuse and Mental Health Services Administration (SAMHSA) launched the HEALing Communities Study to investigate how tools for preventing and treating opioid misuse and OUD are most effective at the local level.<sup>67</sup> The goal of the study is to reduce opioid-related overdose deaths by 40 percent over the course of 3 years. NCCIH-led projects will also be carried out in the context of treatment services that SAMHSA provides for OUD and will layer additional research into state

<sup>59</sup> <https://heal.nih.gov/research/clinical-research/pain-management-research>

<sup>60</sup> <https://heal.nih.gov/research/clinical-research/prism>

<sup>61</sup> <https://heal.nih.gov/research/clinical-research/hemodialysis>

<sup>62</sup> <https://heal.nih.gov/research/new-strategies/optimizing-collaborative-care>

<sup>63</sup> <https://heal.nih.gov/research/new-strategies/at-risk-adolescents>

<sup>64</sup> <https://heal.nih.gov/research/new-strategies/sleep-dysfunction>

<sup>65</sup> <https://heal.nih.gov/research/new-strategies/prevent-progression>

<sup>66</sup> <https://heal.nih.gov/research/new-strategies/duration-retention-discontinuation>

<sup>67</sup> <https://heal.nih.gov/research/research-to-practice/healing-communities>

efforts to expand access to evidence-based treatment and recovery support services, including evidence-based behavioral interventions.<sup>68</sup> Additional NIDA-led efforts expand effective treatment and care in partnership with local and state justice systems and community-based treatment providers for people with opioid use disorder who pass through the criminal justice system.<sup>69</sup>

#### *Novel medication options for opioid use disorder and overdose*

To comprehensively address opioid addiction, the HEAL Initiative supports the development of new medications to treat all aspects of the opioid addiction cycle. Existing medications effectively reduce illicit opioid use when they are provided at a sufficient dose and patients adhere to their treatment plan, but not all patients respond to these medications. Growing knowledge of the neurobiology of opioid addiction has helped researchers to identify novel molecular targets and new ways of modifying brain circuits that may produce more effective and safer treatments for opioid use disorders.<sup>70</sup> NIDA and National Institute of Allergy and Infectious Disease (NIAID) lead novel approaches in development, including vaccines that recruit the body's immune system to prevent opioids from entering the brain. This approach has already shown great promise in animal studies.<sup>71</sup>

#### *Enhanced outcomes for infants and children exposed to opioids*

To best inform clinical care for infants born with opioid withdrawal syndrome, the HEAL Initiative supports an expansion of the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome program, led by the NICHD, to assess both drug-free treatment approaches and currently used medications. The effects of early exposure to opioids on infant and child development are unknown, and therefore complementary efforts through NIDA-supported research are critical to help predict and prevent risk for future substance use, mental disorders, and other behavioral and developmental problems.<sup>72</sup>

#### Next Steps:

The HEAL Initiative's comprehensive approach to addressing the opioid epidemic includes concrete steps toward reducing the impact of opioid abuse on communities. Research supported through the Initiative is working to discover new, safer treatment options for pain management in order to improve quality of life and reduce the number of people exposed to the risks of opioids. Additionally, a series of highly focused studies will expedite the development of therapies to treat OUD and reverse overdose, including promising prevention strategies and evidence-based treatment in multiple settings, including primary and emergency care, the criminal justice system, and other community settings, and in communities highly affected by the opioid crisis.

In the short term (within three to five years), a few of the HEAL research investments are expected to deliver:

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<sup>68</sup> <https://heal.nih.gov/research/research-to-practice/brim>

<sup>69</sup> <https://heal.nih.gov/research/research-to-practice/jcoin>

<sup>70</sup> <https://heal.nih.gov/research/medication-options/focusing-development>

<sup>71</sup> <https://heal.nih.gov/research/medication-options/immunotherapies>

<sup>72</sup> <https://heal.nih.gov/research/infants-and-children/healthy-brain>

- Implementation strategies demonstrated to significantly increase initiation of medication assisted treatment and retention in treatment beyond six months, and decrease rates of opioid addiction and overdose death;
- A clinical trials network poised for the rapid testing of new, non-addictive, pain therapies;
- New evidence-based approaches to inform previous practice-based approaches and improve care for infants with neonatal opioid withdrawal syndrome;
- Evidence for the non-pharmacological management of multiple acute and chronic pain conditions.

In the longer-term (over five years), HEAL will deliver:

- Pharmaceutical programs leading to 15 Investigational New Drugs (INDs) and Investigational Device Exemptions (IDEs), with the goal of 5 New Drug Applications (NDAs) or 510(k) premarket approvals for devices submitted to the FDA for novel medications to treat withdrawal, craving, and relapse;
- A pipeline of novel non-opioid therapies that can be further developed and tested for the treatment of acute and chronic pain;
- Understanding of the lasting effects of early exposure to opioids on children and young adults.

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

The NIH has long recognized that the most critical assets in the biomedical research enterprise are the scientists who comprise its workforce. The biomedical research enterprise relies upon a pipeline of highly trained investigators to convey new insights, develop innovative ideas, and advance the translation of scientific research into improved health for all.

In September 2017, with support from the 21<sup>st</sup> Century Cures Act (P.L. 114-255), the NIH launched the Next Generation Researchers Initiative (NGRI).<sup>73</sup> This initiative aims to bolster opportunities for early-stage investigators (ESIs), those within 10 years of completing postgraduate clinical training or their highest advanced research degree. Applications from ESIs, like those from all new investigators, are given special consideration during peer review as well as at the time of funding consideration.

Through this initiative, NIH ICOs prioritize funding for ESIs<sup>74</sup> and track the impact of funding decisions for ESIs to ensure that this new strategy is effectively implemented. As a result of this initiative, NIH has substantially increased support for ESIs – from less than 600 ESIs in FY 2013, to 1,287 in FY 2018, and 1,316 in FY 2019. As part of NGRI, NIH is also developing methods to identify and support meritorious investigators (new or established) who are at risk for losing all NIH funding and who do not have significant research support from other sources.

NIH will continue to incorporate guidance from the ACD NGRI WG, coordinated by the OD, and the National Academies of Sciences, Engineering, and Medicine (NASEM) report “The Next Generation of Biomedical and Behavioral Sciences Researchers: Breaking Through”<sup>75</sup> in the future design, testing, implementation, and evaluation of policies and programs to enhance the success of the next generation of talented biomedical researchers. To address concerns raised in the NASEM report, NIH will continue to collect and analyze workforce related data to assess workforce trends. To this end, NIH published a report on trends in early stage, new, and established investigator demographics from 2009 and 2016.<sup>76</sup>

NIH currently has several successful programs to support ESIs and will continue to expand upon them, including the:

- NIH Director's New Innovator Award Program (DP2)
- Maximizing Investigators' Research Award (R35)
- NIH Pathway to Independence Awards (K99/R00)
- Director's Early Independence award (DP5)
- High Priority, Short-Term Project/Bridge Awards (R56)

In response to the ACD NGRI Workgroup Report recommendation, “2.1: Expand Pathways for funding ESIs through programs that do not require preliminary data,” NIH plans to issue an

<sup>73</sup> <https://grants.nih.gov/ngri.htm>

<sup>74</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html>

<sup>75</sup> <https://www.nap.edu/catalog/25008/the-next-generation-of-biomedical-and-behavioral-sciences-researchers-breaking>

<sup>76</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29920223>

award in honor of the late Stephen I. Katz, M.D., Ph.D, Director of NIAMS from 1995-2018, who exhibited a profound dedication to mentoring the next generation of scientists. As described in a recent update to the ACD,<sup>77</sup> this new ESI award will be for investigator-initiated R01s; will not allow preliminary data; will support a change in research direction for the PI; and will provide for five years of funding.

NIH will continue to analyze the impact of NGRI policies on women and individuals from nationally underrepresented backgrounds in the NIH portfolio. Several sources of data show modest improvements in the representation of women in the biomedical research pipeline, but underrepresentation of women at faculty career levels remains a persistent issue. For example, an investigation of the gender makeup of the NIH funded research workforce found that female scientists are more likely than their male counterparts to be in the trainee/fellow postdoctoral and career development (K)-awardee pools and are less likely to be in the RPG and R01-equivalent awardee groups.<sup>78</sup> Although ESIs and new investigators (NIs) include a higher proportion of underrepresented minorities, Hispanics, and women than experienced investigators, the share of funding awarded to ESIs and NIs declined between 2009-2016, suggesting these populations may not be well supported.<sup>79</sup> NIH has developed and implemented a range of approaches to address these challenges:

- In FY 2018, NIH implemented automatic extensions of ESI status for childbirth for one year within the ESI period.<sup>80</sup>
- In FY 2018, NIH strengthened and clarified the NRSA parental leave policy to continue stipends during parental leave.<sup>81</sup>
- For many years, NIH has offered support for investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.<sup>82</sup>
- In FY 2018, NIH issued a Guide Notice describing its interest in diversity, stating that “NIH encourages institutions to diversify their student and faculty populations to enhance the participation of individuals from groups that are underrepresented in the biomedical, clinical, behavioral and social sciences.”
- In FY 2020 NIH updated its interest-in-diversity Guide Notice by expanding the definition of socio-economic disadvantage to be more inclusive and diverse.<sup>83</sup>
- Many ICs are piloting new programs to enhance workforce diversity.<sup>84 85</sup>
- In FY 2020, NIH will approve an automatic extension of one year for childbirth within the 4-year K99 eligibility window.<sup>86</sup>

<sup>77</sup> <https://acd.od.nih.gov/documents/presentations/12122019NextGen.pdf>

<sup>78</sup> Acad Med. 2016 August; 91(8): 1164–1172. doi:10.1097/ACM.0000000000001209

<sup>79</sup> FASEB J. 2018; 32:6410–6422. doi: 10.1096/fj.201800639

<sup>80</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html>

<sup>81</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-154.html>

<sup>82</sup> <https://grants.nih.gov/grants/guide/pa-files/pa-18-592.html>

<sup>83</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html>

<sup>84</sup> <https://grants.nih.gov/grants/guide/pa-files/PAR-18-813.html>

<sup>85</sup> <https://grants.nih.gov/grants/guide/pa-files/PAR-18-814.html>

<sup>86</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-011.html>

NIH remains strongly committed to the goals of NGRI to fund more early-career investigators, protect and retain meritorious at-risk scientists, and enhance the diversity of the biomedical research workforce.

## **Diversity and Inclusion Initiatives at NIH**

### **ICOs Involved:**

NIH-wide

Office of Extramural Research (OER)

Office of Research on Women's Health (ORWH)

National Institute on Minority Health and Health Disparities (NIMHD)

Office of Scientific Workforce Diversity (OSWD)

Office of Equity, Diversity and Inclusion (EDI)

Office of Human Resources (OHR)

### **Growing and Maintaining a Diverse Biomedical Workforce**

Through a comprehensive approach, NIH is working to develop a diverse, skilled biomedical workforce for the future. Increasing representation and diversity in both the NIH intramural and extramural communities is a key goal of training, career development, and workforce-related programs. The Diversity Program Consortium is a trans-NIH program funded by the NIH Common Fund and coordinated by the NIGMS to bring together institutions to engage a more diverse field of individuals at the student, faculty, and institutional levels. This program is developing, implementing, assessing, and disseminating innovative, effective approaches to training and mentoring, with the ultimate goal of engaging a more diverse field of individuals in biomedical research careers. The NIH Distinguished Scholars Program works to build an inclusive community within the NIH Intramural Research Program by providing mentoring and professional development training to yearly cohorts of investigators with diverse backgrounds. The Future Leaders Research conference offers career development opportunities for diverse early-career researchers to share their scientific work and learn from NIH leaders and investigators. Additionally, OD, through the work of the Chief Officer for OSWD, is enhancing transparency and accountability in scientific workforce diversity metrics through a trans-NIH results-based accountability network, online data and reporting tool, and formalization of a trans-NIH committee devoted to this initiative.

In addition, the NIH Working Group on Women in Biomedical Careers (WgWBC) is a trans-NIH group composed of senior leadership of NIH ICOs. This trans-NIH effort considers and addresses barriers for women in science by developing innovative strategies including policies and funding initiatives. The strength of the group lies in its trans-NIH approach, which provides a framework for influence, collaboration, and action across the agency. Specifically, the WgWBC is chartering innovative strategies to promote recruitment, entry, retention, and sustained advancement of women in biomedical research careers. Current efforts underway include the development of a portfolio of initiatives to address the underrepresentation of women in biomedical careers. Together, these programs complement ongoing or other nascent programs at the NIH to enhance diversity and comprise a comprehensive approach that targets both individual investigators and institutional change. These initiatives are expected to be released in FYs 2020 and 2021. In addition, the Women of Color (WOC) committee<sup>87</sup> of the WgWBC created a Women of Color Research Network (WoCRN) on the LinkedIn platform to provide women of color and supporters of their advancement in the biomedical sciences with information about the NIH grants process, advice on career development, and a

<sup>87</sup> <https://womeninscience.nih.gov/about/committees.asp#womenofcolor>

venue or forum for networking and sharing information. With the addition of two regional chapters in of WoCRN recent years, the ORWH and the WgWBC continue to improve upon the content and grow the network. Moving forward, the WgWBC will periodically review policies and progress related to NIH childcare, the NIH intramural workforce concerning gender, and work-life integration issues.

The WgWBC continues to convene thought leaders to consider these issues and propose plausible solutions, thus serving as a strong framework by which change can occur. Relatedly, the ORWH is co-sponsoring a National Academies consensus study on this topic that will be concluded and published in early 2020. The report will provide recommendations for funding agencies, institutions, and other stakeholders to drive progress for women in Science, Technology, Engineering, Mathematics, and Medicine (STEMM) careers. This report will inform future directions for the ORWH and for the NIH WgWBC to propose systemic approaches including policy, institutional transformation programs, and interagency and private-public partnerships.

The ORWH within the OD, the NIH WgWBC, the OD OER, and other NIH ICO leadership and staff have developed and implemented a constellation of initiatives and programs to enhance work-life integration for the scientific workforce on behalf of the agency as a means to maintain a diverse biomedical workforce. Approaches in the NIH extramural community include targeted support for investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. The NIH has also strengthened the parental leave policy on National Research Service Awards (NRSAs). The revised policy allows for the recipients, who are predoctoral and postdoctoral fellows, to continue to receive their stipends from their awards for up to eight weeks during their parental leave. Another key action has been the automatic extension of Early-Stage Investigator status for childbirth, which extends the period during which R01 applications from these investigators are given appropriate consideration for the investigator's less extensive research experience compared to senior investigators. An update to the NIH Support for Conferences and Scientific Meetings requires that applicants "describe plans to identify resources for childcare and other types of family care at the conference site to allow individuals with family care responsibilities to attend."

NIH has also implemented a multitude of policies and programs to address these challenges for those working at NIH. To ensure effective communication about the programs available, the Office of Research Services supports a publicly accessible website that describes the on-site childcare facilities and other resources available to NIH employees, intramural trainees, and contractors. The NIH Office of Human Resources has implemented a range of support tools, including a leave bank program for NIH employees to have access to paid medical leave if they or a family member become sick or for the birth of a child. Specific policies and programs for the NIH intramural community developed by the Office of Intramural Research within the OD include paid parental leave extension for NIH intramural trainees from six to eight weeks. In addition, the OD provides for tenure-clock modification for NIH intramural scientists that automatically incorporates an additional year to accommodate family leave, and the "Keep the Thread" program, an accommodation program for intramural postdoctoral fellows that offers flexible schedule options and part-time work options. Through all of these approaches, both

within and outside the agency, NIH is investigating ways to continue to develop work-life integration policies that will ensure a competitive and diverse workforce for the biomedical research enterprise now and in the future.

The NIH Intramural Loan Repayment and Undergraduate Scholarship Programs offer financial incentives along with other benefits to attract highly qualified physicians, nurses, and scientists into careers in biomedical, behavioral, and clinical research as employees of NIH. The Intramural Loan Repayment Program (ILRP), housed in the Office of Intramural Research, repays outstanding eligible educational debt for NIH employee postgraduates. In return, participants enter into a contractual agreement to conduct qualified research in one of several areas as identified by the ILRP and coinciding with the NIH mission. The Undergraduate Scholarship Program (UGSP), also housed in the Office of Intramural Research, offers competitive scholarships to exceptional undergraduate students from financially disadvantaged backgrounds. Awardees must be committed to biomedical, social science, or behavioral health-related research career paths. In exchange for each year or partial year of scholarship funding, UGSP award recipients are contractually obligated to participate in a 10-week summer internship and 1 year as a full-time paid employee of the NIH Intramural Research Program. The goal of these programs is to continue to build and maintain a diverse biomedical workforce.

#### NIH Efforts to End Harassment and Cultivate A Culture of Respect

NIH does not tolerate harassment of any kind, including sexual harassment, whether it is within the agency, at research organizations that receive NIH funding, or anywhere else NIH-funded activities are conducted. The OD is bolstering policies and practices to foster a culture of respect wherever NIH research activities are conducted, and ensure sexual harassment is not tolerated or ignored. Over the last year, NIH leadership has been heavily focused on this issue, with guidance from the NIH Anti-Harassment Steering Committee, coordinated by the OD, and recommendations developed by the ACD Working Group on Changing the Culture to End Sexual Harassment. (See discussion of the Working Group's recommendations earlier in this narrative.) These actions aim to create a paradigm shift in the scientific culture wherever NIH research activities take place to eliminate sexual harassment and enhance contributions by women and others to scientific advancements.

Through a multi-faceted campaign, NIH has taken actions to address harassment for all NIH staff, including the launch of a new, central website on all NIH anti-sexual harassment activities that comprehensively outlines NIH policies, practices, and initiatives. NIH has also issued two new policies that apply to the entire NIH community, including contractors and trainees/fellows, and focus on preventing harassment and inappropriate conduct and addressing personal relationships in the workplace. NIH has also developed a new training module to inform the NIH community of the anti-harassment policy and expanded the existing NIH Civil Program to establish a centralized, independent office to consistently address allegations of harassment, manage related administrative inquiries, and track and report data regularly to the Anti-Harassment Steering Committee and annually to the NIH community. NIH also established a new centralized process for managing reports of harassment and subsequent administrative inquiries for both NIH staff and the extramural community. In early 2019, a survey was disseminated to all NIH staff, including contractors and fellows, to assess NIH workplace climate and harassment, with the goal of implementing programs to address sexual harassment in

the workplace and set a baseline to evaluate their effectiveness to ensure effective policies and successful implementation.

NIH efforts on harassment at recipient institutions include the launch of a new, central website on its anti-harassment activities that comprehensively outlines NIH policies, practices, and initiatives as a funding agency. NIH has reminded applicants of the requirements for applicant and recipient research institutions to ensure safe and healthful working conditions for their employees and foster work environments conducive to high-quality research. NIH continues to require that institutions notify the NIH if the institution takes an administrative or disciplinary action against its employee(s) that affects the ability of the employee(s) to continue as principal investigator (PI) or other senior key personnel on an NIH award. NIH can take a variety of actions including suspension or termination of the grant if the proposed alternative arrangements are not acceptable. Several different means of communication have been used to publicize these efforts and ensure that NIH expectations are understood and met.

NIH will continue working with stakeholders to develop best practices for establishing safe, diverse, and inclusive research environments. NIH is a member of the subcommittee of the National Science and Technology Council (NSTC) Joint Committee on Research Environments. Safe Inclusive Research Environments (SIRE) has representation from a number of Federal departments and agencies and builds upon previous and current interagency or agency-specific efforts. One goal of the committee is to coordinate and facilitate sharing of best practices.

## **Foreign Influence on Research Integrity**

NIH research is built on the bedrock principles of scientific excellence, unassailable integrity, and fair competition. The U.S. biomedical enterprise sets the standard for discovery and innovation excellence for the world. This is made possible because the overwhelming majority of researchers participating on NIH grants, whether U.S. or foreign-born, are honest contributors to the advancement of knowledge that benefits us all. NIH recognizes the importance of scientific collaborations, including those involving international institutions, to advance its mission. Yet, there are threats to the integrity of the biomedical research enterprise, including the failure by some researchers at NIH-funded institutions to disclose contributions of resources from other organizations; diversion of intellectual property produced by NIH-supported biomedical research to other entities, and sharing of confidential information by peer reviewers with others or otherwise attempting to influence funding decisions.

### **NIH's Overall Approach**

NIH's commitment to tackling these important challenges is reflected in a variety of recent actions, including the convening of an NIH ACD WG for Foreign Influences on Research Integrity.<sup>88</sup> Acting on ACD recommendations, NIH is increasing awareness with institutions on their need to disclose all affiliations and other support, mitigate and prevent risks, and work with federal partners on issues of research security and integrity. Moreover, NIH is clarifying long-standing policies that require disclosure of all other support (including support from foreign entities), foreign components, and financial conflicts of interest.

Partnerships with other federal agencies, professional organizations, and institutions have led to extensive discovery about the nature of the threats, actions by the relevant institutions against certain investigators, referrals to the HHS Office of Inspector General (OIG), and institutional implementation of additional internal systems control measures. NIH's efforts to raise awareness have prompted several institutions to perform internal reviews that revealed undisclosed conflicts of interest, which the institutions self-report to NIH.<sup>89</sup>

NIH will continue to actively partner with other federal departments and agencies to address concerns related to undue foreign influence on the biomedical research enterprise. These federal partners include the Central Intelligence Agency, Federal Bureau of Investigation, OIG, Department of Defense, Department of State, Department of Energy, and the National Science Foundation (NSF). Notably, the NSF recently released report by the independent science advisory group JASON titled "Fundamental Research Security."<sup>90</sup> Research agencies across the federal government are coordinating to address the challenges outlined in the report. NIH will also continue engaging the HHS' Office of National Security and the NIH Counterintelligence and Insider Threat program to address security issues appropriately for the protection of all NIH-funded assets, including data.

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<sup>88</sup> <https://www.acd.od.nih.gov/working-groups/foreign-influences.html>

<sup>89</sup> [https://cancerletter.com/articles/20191220\\_2/](https://cancerletter.com/articles/20191220_2/)

<sup>90</sup> [https://www.nsf.gov/news/special\\_reports/jasonsecurity/JSR-19-2IFundamentalResearchSecurity\\_12062019FINAL.pdf](https://www.nsf.gov/news/special_reports/jasonsecurity/JSR-19-2IFundamentalResearchSecurity_12062019FINAL.pdf)

NIH participates in the White House Office of Science and Technology Policy (OSTP) Joint Committee on the Research Environment (JCORE), with several subcommittees co-chaired by NIH. The Rigor and Integrity subcommittee will focus on areas to promote baseline policies across Federal agencies and work with external stakeholders to share recommendations and best practices. The Research Security subcommittee will focus on coordinating Federal efforts to effectively communicate and provide outreach to academic and research institutions, develop guidance and best practices for academic and research institutions, and standardize financial conflict of interest and commitment disclosure requirements and enforcement behaviors that affect the safety and inclusivity of our research environments.

NIH has also been working to bolster its own internal controls and increasing awareness among NIH staff. The NIH Office of Intramural Research added guidance to the Intramural Source Book to help PIs navigate international interactions and avoid inappropriate foreign influences on their research. The goal is to enable continuing and future interactions among NIH scientific staff and foreign scientists under circumstances where the NIH PI and the NIH as an institution are satisfied that the circumstances of such interactions do not allow undue foreign influence on NIH-supported research.

#### Extramural Institutions and Grantee Compliance

NIH continues to strongly encourage universities to look closely at their organizations to mitigate unscrupulous practices by individuals and entities that aim to capitalize on the collaborative nature of the U.S. biomedical enterprise. Regular communications to the extramural community over the last several years have focused on protecting the integrity of U.S. biomedical research and the imperative to inform NIH of any foreign support. These communications have included several notices and statements to the community (most recent notice on other support and foreign components<sup>91</sup>), including the unprecedented step of the NIH Director issuing a letter to officials at approximately 10,000 recipient institutions.<sup>92</sup> This letter informed the research community that the agency is aware that some foreign entities have mounted systematic programs to influence NIH-supported researchers and peer reviewers, as well as to take advantage of the long tradition of trust, fairness, and excellence of NIH-supported research activities.

NIH has contacted more than 75 institutions regarding specific scientists who may have failed to disclose substantial foreign research support or financial conflicts of interest or who may have engaged in substantial breaches of peer review integrity. This outreach has led to referrals to the OIG, communications with FBI, disciplinary actions by the relevant institutions (including terminations or resignations), revisions of grant terms, and new efforts on the part of institutions to enhance oversight and security of their research operations.

Furthermore, NIH regularly communicates with grantees to provide training and compliance support for issues involving financial conflict of interest requirements at NIH-led conferences such as the NIH Regional Seminars. NIH also communicates this information through professional organizations such as the Society for Research

<sup>91</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-114.html>

<sup>92</sup> <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-protecting-integrity-us-biomedical-research>

Administrators, and the National Council of University Research Administrators. There have been a number of special meetings involving these groups and others to address the recent concerns on foreign influence. In addition, NIH has recently updated an online training module<sup>93</sup> on Financial Conflict of Interest as a resource for both NIH staff and the extramural community. NIH's outreach and engagement have facilitated extensive faculty outreach at research organizations as well as led to developing and sharing best practices.

One indication that these communication strategies are proving to be successful is a report on *Actions Taken by Universities to Address Growing Concerns about Security Threats and Undue Foreign Influence on Campus*,<sup>94</sup> issued by the American Association of Universities and the Association of Public and Land-Grant Universities, and updated in April 2019. This report shares practices that universities are employing to “ensure the security of research, protect against intellectual property theft and academic espionage, and prevent actions or activities by foreign governments and/or other entities that seek to exert undue foreign influence or that infringe on core academic values.”

NIH's collaborations with other federal agencies and outreach to the research community have led to several research institutions terminating or accepting the resignations of scientists due to conflicts of interest with foreign institutions.<sup>95,96,97</sup> One case led to an outside institution paying \$5.5 million to resolve allegations that it violated the False Claims Act by submitting federal grant applications and progress reports to the NIH in which it failed to disclose foreign government grants that funded two researchers.<sup>98</sup>

### Protecting Peer Review Integrity

In recent years, NIH has taken numerous steps to protect the integrity of the peer review process. All participants in the NIH peer review system are responsible for promoting integrity. Maintaining integrity in the peer review process – including keeping application data confidential and secure – is essential for ensuring robust exchange of scientific opinions and evaluations without fear of reprisal; protecting trade secrets and other proprietary, sensitive and/or confidential information; providing reliable input to NIH about which research projects it should support; and maintaining public trust in science.

In addition to issuing several Guide Notices<sup>99</sup> and blogs<sup>100</sup> on the confidentiality and integrity of peer review, NIH has referred several cases to the HHS OIG for consideration of debarment or suspension and has removed the violating individuals from peer review service. Also, in 2018, reviewer conflict-of-interest certifications were converted to a completely electronic format,

<sup>93</sup> <https://nexus.od.nih.gov/all/2018/12/03/new-financial-conflict-of-interest-training-module-available/>

<sup>94</sup> <https://www.aplu.org/members/councils/governmental-affairs/Effective-Sci-Sec-Practices-What-Campuses-are-Doing.pdf>

<sup>95</sup> <https://www.sciencemag.org/news/2019/04/exclusive-major-us-cancer-center-ousts-asian-researchers-after-nih-flags-their-foreign>

<sup>96</sup> <https://www.sciencemag.org/news/2019/05/emory-ousts-two-chinese-american-researchers-after-investigation-foreign-ties>

<sup>97</sup> [https://cancerletter.com/articles/20191220\\_2/](https://cancerletter.com/articles/20191220_2/)

<sup>98</sup> [https://www.justice.gov/usao-wdmi/pr/2019\\_1219\\_VARI](https://www.justice.gov/usao-wdmi/pr/2019_1219_VARI)

<sup>99</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-115.html>

<sup>100</sup> <https://nexus.od.nih.gov/all/2019/06/25/breaches-of-peer-review-integrity/>

enabling a more thorough assessment of compliance across the agency and in cases of individual breaches.

The NIH OER has expanded its internal training for NIH Scientific Review Officers (SROs) to raise their awareness of integrity concerns. OER held three well-attended, interactive training sessions on peer review integrity in the last year. These events covered case studies largely based on actual events and stimulated lively discussion of the best course of action in each scenario. NIH is also working to implement recommendations from the NIH Advisory Committee to the Director on Foreign Influences on Research Integrity that focus on peer review integrity.

NIH continues to explore new technologies and ideas to protect the integrity and security of the peer review process. For example, a new electronic forensics dashboard is being developed to assist the Office of the Director in identifying data needed to investigate possible peer review integrity violations. Other electronic systems are being enhanced, including those that investigators use to submit applications and peer reviewers use to access applications for evaluation. Finally, policies for permissions to access certain information such as the preliminary score matrix are being re-assessed, and a new application is being developed to more efficiently implement those rules. Taken together, these efforts to communicate internally and externally, as well as modernize controls, are raising the profile on peer review integrity concerns and reducing risks.

## **Big Data and the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative**

Rapid advances in data generation, computing, networking, and algorithms, such as artificial intelligence (AI), are intertwined in a newly evolving digital infrastructure. High throughput data generation is driving the need for advances in information-based algorithms and memory-rich computers to interpret data in new ways. Today, biomedical data is measured in petabytes and comprises data types ranging from DNA sequences to wearable sensor-generated outputs, like heartrate. This increase in pace, scale, and complexity of data, which can be used to understand and alleviate diseases, underpins the notion of “big data” for biomedical research. Researchers working with “big data” envision a biomedical research enterprise in which data and information generated in the field, laboratory, and clinic are processed and analyzed quickly in real-time and readily shared. In addition to data generation, tools, and technologies like AI are creating opportunities to maximize the use of these data. Making these data findable, accessible, interoperable, and reusable (FAIR) is a major goal for NIH, and the STRIDES Initiative is enabling through storage of rich datasets, advanced computational infrastructure, tools, and professional services. The Office of Data Science Strategy (ODSS)<sup>101</sup> is leading a cross-agency effort with NIH institutes, centers, and offices to address complex challenges and build solutions in a unified, economic, and sustainable way. A subset of those efforts, and programmatic examples from specific Institutes, Centers, and Offices, are included in this narrative.

In June 2018, NIH provided Congress a new roadmap to modernize the NIH-funded biomedical data ecosystem, the NIH Strategic Plan for Data Science.<sup>102</sup> The ODSS, created in October 2018 after a request in the Senate appropriations language, now leads and coordinates the NIH-wide efforts to implement the plan in consultation with the Scientific Data Council. Over 30 teams across NIH work on specific goals with visible outcomes, exemplified below.

### **Piloting FAIR**

#### **Common Fund New Models of Data Stewardship (NMDS) Initiative**

Before ODSS was formed, NIH invested in the NMDS to learn how to harness and use big data to its fullest capacity. From FY 2017 to FY 2018, the Common Fund supported the NMDS program, an integrated set of activities that piloted new digital data management strategies. One initiative under NMDS was the NIH Data Commons Pilot Phase,<sup>103</sup> which explored new ways to store, access, and share biomedical data and associated tools in the cloud, so they were FAIR. The Data Commons Pilot Phase iteratively experimented with a set of key capabilities needed for datasets to operate and meet FAIR standards. Three different test case datasets from across NIH helped in setting policies, processes, and architecture for the Commons. The tools and best practices from the Data Commons Pilot Phase informed a broader trans-NIH data ecosystem strategy that is being planned through ODSS. The Common Fund will continue to test, evaluate, and refine a subset of deliverables from the Data Commons Pilot Phase in the development of the Common Fund Data Ecosystem (described below).

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<sup>101</sup> [datascience.nih.gov/](https://datascience.nih.gov/)

<sup>102</sup> [datascience.nih.gov/sites/default/files/NIH\\_Strategic\\_Plan\\_for\\_Data\\_Science\\_Final\\_508.pdf](https://datascience.nih.gov/sites/default/files/NIH_Strategic_Plan_for_Data_Science_Final_508.pdf)

<sup>103</sup> [commonfund.nih.gov/commons](https://commonfund.nih.gov/commons)

### **Bringing Cloud Environments to Biomedical Research**

The NIH STRIDES Initiative<sup>104</sup> is an ongoing effort that enables NIH to provide researchers cost-effective access to industry-leading cloud service providers (CSPs) for the storage of rich datasets, advanced computational infrastructure, tools, and professional services. ODSS, in close partnership with the NIH Center for Information Technology (CIT), is supporting and managing the STRIDES Initiative. The initiative reduces economic and technological barriers to accessing and computing on large biomedical datasets and aims to accelerate biomedical advances by providing discounts on STRIDES Initiative partner and professional services, training, and potential collaborative engagements. In the past year, NIH has co-located over 25 petabytes of high-value datasets and data resources to STRIDES CSPs. ODSS anticipates that by the summer of 2020, the amount of NIH-supported data in the cloud will be more than 50 petabytes. Data resources across NIH are supporting biomedical data in the cloud under STRIDES, including:

#### **Common Fund Data Ecosystem (CFDE)**

The Common Fund is supporting a coordinated effort among several data-generating programs to develop the CFDE,<sup>105</sup> where Common Fund datasets will be accessible and interoperable in a digital cloud environment. The CFDE will provide a framework for researchers to analyze data simultaneously from different and diverse datasets. During its initial development, the CFDE will work with four Common Fund datasets from the Gabriella Miller Kids First Pediatric Research (Kids First<sup>106</sup>), Genotype-Tissue Expression (GTEx<sup>107</sup>), Library of Integrated Network-based Cellular Signatures (LINCS<sup>108</sup>), and Human Microbiome Project (HMP<sup>109</sup>) programs. Starting this effort with four unique and complex datasets will allow for a deeper understanding of the issues around using and integrating diverse datatypes, identify specific needs for individual programs, and help with collaboration across programs to enhance data searching. Since Common Fund datasets are highly relevant to datasets supported by institutes and centers, the Common Fund is working with NHLBI, NHGRI, and the National Cancer Institute (NCI) to work toward broader interoperability. Working with STRIDES will enable proper data versioning and upkeep, as well as favorable pricing for cloud data storage and use. As CDFE learns best practices and new lessons, they will be applied to additional datasets from Common Fund programs.

#### **Trans-Omics for Precision Medicine (TOPMed)**

NHLBI's TOPMed program is designed to improve understanding of the fundamental biological processes that underlie heart, lung, blood, and sleep disorders. It includes whole genome sequences and other clinical and imaging data from a diverse population of more than 149,000 individuals participating in more than 80 studies, including the Framingham Heart Study and Jackson Heart Study. NHLBI data scientists are developing ways to make these data available to more researchers. Genomic data from the TOPMed program were made available to researchers through the NIH Data

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<sup>104</sup> [datascience.nih.gov/strides](https://datascience.nih.gov/strides)

<sup>105</sup> [commonfund.nih.gov/dataecosystem](https://commonfund.nih.gov/dataecosystem)

<sup>106</sup> [commonfund.nih.gov/KidsFirst](https://commonfund.nih.gov/KidsFirst)

<sup>107</sup> [commonfund.nih.gov/GTEx](https://commonfund.nih.gov/GTEx)

<sup>108</sup> [commonfund.nih.gov/LINCS](https://commonfund.nih.gov/LINCS)

<sup>109</sup> [commonfund.nih.gov/hmp](https://commonfund.nih.gov/hmp)

Commons Pilot Phase, which helped guide the development of broader trans-NIH cloud computing strategies that are part of the NIH STRIDES initiative and in line with the NIH Strategic Plan for Data Science.

### **Sequence Data Delivery Project (NLM)**

The National Library of Medicine’s (NLM) Sequence Read Archive<sup>110</sup> (SRA) is the largest publicly available repository of next-generation genomic sequence data. Each month, more than 9 million records and more than 100,000 users access more than two petabytes of data. To improve access to these data and enable large-scale computational analysis for novel scientific discovery, NLM has uploaded all non-human publicly available SRA data to two commercial cloud platforms, Google Cloud and Amazon Web Services, as part of the STRIDES Initiative. Freed from the limitations of local storage and compute resources, any user is empowered to compute across the entire five-petabyte data corpus of public SRA data and metadata, which significantly expands the discovery potential and makes it possible to develop customized compute tools and methods. The public SRA data include genomes of viruses, bacteria, and nonhuman higher organisms, as well as gene expression data, metagenomes, and a small amount of human genome data that is consented to be publicly available (e.g., data from the 1000 Genomes Project<sup>111</sup>). The second phase of this effort will be to make all of SRA’s controlled-access human genomic data available on both cloud platforms, with a higher level of security and oversight to ensure the protection of data from human samples or specimens, and the authorization and authentication of users of these data.

The STRIDES Initiative also supports other data resources, including components of NCI’s Research Data Commons, parts of NHGRI’s Analysis, Visualization, and Informatics Lab-space (AnVIL<sup>112</sup>), and some other NLM data resources in addition to the SRA. These large data resources present new opportunities and challenges in the development of algorithms, such as AI, that can work on petabyte-scale datasets. By leveraging the STRIDES Initiative, NIH and NIH-funded institutions can begin to create a robust, interconnected ecosystem that breaks down silos related to generating, analyzing, and sharing research data.

In addition to making accessible large data resources, such as those typically developed by research consortiums or broader NIH initiatives, NIH is equally committed to making heterogeneous datasets resulting from NIH investigator-initiated research more discoverable. For example, researchers may find themselves with a need to share data but unable to identify an appropriate data repository to do so. NIH is evaluating how “generalist” repositories might fill this gap through the pilot development of NIH Figshare,<sup>113</sup> an instance of the commercial Figshare generalist repository platform. The NIH Figshare instance will provide NIH with information to evaluate cost, usage patterns of data deposit, and data re-use to inform future implementation activities in enabling FAIR-data sharing.

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<sup>110</sup> [ncbi.nlm.nih.gov/sra](https://ncbi.nlm.nih.gov/sra)

<sup>111</sup> [internationalgenome.org/about/](https://internationalgenome.org/about/)

<sup>112</sup> [genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL](https://genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL)

<sup>113</sup> Figshare is a generalist repository where users can make their research outputs available and citable in a searchable framework. Figshare is a part of the Digital Science, a for-profit company.

### **Unifying Authorization and Authentication**

Many institutes, centers, and high-impact programs at NIH are developing data platforms for their research communities. One major current limitation is that data platforms are not using a unified authentication and authorization system, making trans-NIH data science discoveries difficult. Having an identity and access management (IAM) system will foster a connected data platform infrastructure (e.g., an “ecosystem”), improve cost, performance, accuracy, resolution, throughput, flexibility, and usability. ODSS is working closely with the CIT and NLM to build a single, unified, efficient, and secure authentication and authorization service that will provide researchers with access to data resources that the STRIDES Initiative CSPs host. To enable data-focused research, this year, NIH will develop a minimum viable product to provide authentication, authorization, auditing, and logging support for a common, federated experience for biomedical researchers to access NIH-funded data resources.

### **Data Archive (NIMH)**

One of the many projects that will benefit from the new IAM system is the NIMH Data Archive (NDA).<sup>114</sup> The NDA houses human participant data from multiple repositories in a single database infrastructure. NDA makes data from different research projects as consistent as possible and allows other researchers access to those data for secondary analysis, methodology development, and tool development. NDA data include clinical/phenotypic, imaging, genomic, and other data from hundreds of thousands of research participants. Initially established to support autism research, NDA has grown into an informatics platform that contains several NIMH data repositories, including the National Database for Autism Research, the National Database for Clinical Trials related to Mental Illness, the Research Domain Criteria Database, and the NIH Pediatric MRI Data Repository. Additionally, this informatics platform supports other trans-NIH data repositories, such as the Adolescent Brain Cognitive Development Study, the Connectome Coordination Facility (CCF), the Osteoarthritis Initiative, and the National Institute on Alcohol Abuse and Alcoholism Data Archive. The NDA platform securely shares data, tools, methods, and provides a platform for secure analyses.

As NIH introduces these new platforms to the biomedical research communities, ODSS, the STRIDES team, and many others across NIH will work together to communicate processes and provide training and assistance to enable researchers, programs, and institutions with access to data storage and compute.

### **Advancing Clinical Research**

As data generation and access to technologies increase, NIH researchers will have increased access to clinical data from EHR systems for research, making clinical research data collected for one study useful for other research endeavors. NIBIB has supported the development of one such resource:

#### **A freely available multi-center database for critical care research (NIBIB)**

Critical care patients undergo constant monitoring for the duration of their hospital stay that typically gets stored in a hospital’s telehealth system. NIBIB-supported scientists

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<sup>114</sup> [nda.nih.gov/](http://nda.nih.gov/)

have developed a publicly available intensive care unit (ICU) database (eICU Collaborative Research Database) that contains deidentified vital signs and lab measurements, their caretakers' notes, treatment plans, official diagnoses, and other data. The free database has been accessed and used in about 500 research papers. A recent impactful study utilized the database to develop an algorithm that could be used to predict whether patients would return to the ICU within a month.

### **Enhancing Connectivity of Clinical Research Resources**

NIH is promoting the use of a specific health data standard, the HL7® Fast Healthcare Interoperability Resources® (FHIR®)<sup>115</sup> standard. To create a bridge between important EHRs and clinical research data, ODSS and NLM are supporting FHIR-enabled tools and technology applications. FHIR is a global industry standard for exchanging healthcare data electronically between information systems (such as EHR or clinical trial records systems) through an application programming interface (API). It's free, open, and designed to be quick to implement. NIH issued a Guide Notice on FHIR<sup>116</sup> to encourage NIH-funded investigators to explore the use of FHIR to capture, integrate, and exchange clinical data for research purposes and to enhance capabilities to share research data. NIH also published a Notice of Special Interest<sup>117</sup> to inform the small business community of NIH's interest in supporting FHIR applications. Existing NIH programs, including the NHGRI Electronic Medical Records and Genomics Network<sup>118</sup> are already applying FHIR to their clinical studies.

### **A Workforce to Build a New Computational Community in Biomedicine**

ODSS is leading workforce development efforts and bringing disparate research communities together through new training programs. This summer, ODSS matched 21 data-savvy students with computational and technology backgrounds with NIH mentors across 14 institutes, centers, and offices. Student were brought on as Civic Digital Fellows<sup>119</sup> through Coding it Forward, a non-profit focused on developing the next generation of technology leaders or through the Office of Intramural Training and Education's Graduate Data Science Summer Program (GDSSP)<sup>120</sup>. Civic Digital Fellows were placed primarily in administrative or extramural facing offices, while GDSSP fellows spent their summers in intramural research labs. The fellows spent 10 weeks at NIH applying their expertise to challenges in AI and data analysis, improving and automating difficult processes, and developing new algorithms for classification. NIH plans to grow these programs in the future. In spring 2020, NIH, under ODSS leadership, plans to open an announcement for the Data and Technology Advancement (DATA) National Service Sabbatical Scholar Program to recruit a cohort of experienced professionals in computer science or tech-related fields and embed them in high-impact NIH programs for one to two years.

### **Data Science to Discover New Targets and Therapies**

Data science will transform the way researchers approach target discovery, validation, and novel therapeutic identification. NIH programs are leading efforts to advance platforms and tools that

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<sup>115</sup> [hl7.org/fhir/](http://hl7.org/fhir/)

<sup>116</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-19-122.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-122.html)

<sup>117</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-19-127.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-127.html)

<sup>118</sup> [genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE](https://genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE)

<sup>119</sup> [datascience.nih.gov/meet-coding-it-forward-civic-digital-fellows](https://datascience.nih.gov/meet-coding-it-forward-civic-digital-fellows)

<sup>120</sup> [datascience.nih.gov/meet-graduate-data-science-summer-program-interns](https://datascience.nih.gov/meet-graduate-data-science-summer-program-interns)

will make these discoveries accessible to researchers and enhance the data science approaches applied to these challenges:

### **Accelerating Medicines Partnership-Alzheimer’s Disease (NIA)**

The Accelerating Medicines Partnership-Alzheimer’s Disease<sup>121</sup> (AMP-AD) is transforming the way new therapeutic targets and biomarkers are discovered using powerful molecular profiling and advanced information technologies. This public-private partnership also provides an infrastructure for rapid and broad sharing of valuable and robust datasets. The Target Discovery component of the AMP-AD Program applies a systems biology approach to the discovery and validation of new therapeutic targets in an open science research model. Since its inception in 2014, the research teams within the AMP-AD Target Discovery Consortium have established a centralized data resource/infrastructure, the AMP-AD Knowledge Portal<sup>122</sup>, for rapid and broad data sharing; generated human data from over 2000 brains and over 1000 plasma samples (across all stages of AD) and made them widely available to researchers; developed network models of disease pathways/targets; and nominated over 100 novel candidate targets. Also, the newly nominated targets and associated data and analyses have been made broadly available through the Agora<sup>123</sup> web-based interactive platform. NIA renewed this ground-breaking program in 2018.

### **High-Content Screening (HCS) Informatics (NCATS)**

At NCATS, automated instrumentation generates high-resolution digital micrographs from many thousands of cellular samples per day, following cell treatment with large pharmaceutical compound libraries. The resulting digital image files that capture cellular phenotypes are produced at a rate of several terabytes per day. Because of the rapidly growing HCS datasets, NCATS has an immediate requirement for expandable data storage and data management systems that are linked with high-speed computer resources for automated image analysis. Investigators are developing a flexible, open-source platform at NCATS to meet these critical needs. The platform is optimized for scalable deployment using both on premise compute resources and cloud-based resources. The plugin-based architecture of the platform allows new customized informatics functions to be added as they are required by individual researchers and is designed to be accessed by both experimental biologists and informaticists.

### **Platform Technologies**

The activities highlighted here enhance and increase access to platform technologies across NIH. Using Other Transaction Authority<sup>124</sup> the STRIDES Initiative is leveraging the commercial cloud

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<sup>121</sup> [www.nia.nih.gov/research/amp-ad](http://www.nia.nih.gov/research/amp-ad)

<sup>122</sup> [adknowledgeportal.synapse.org/#/](http://adknowledgeportal.synapse.org/#/)

<sup>123</sup> [agora.ampadportal.org/genes](http://agora.ampadportal.org/genes)

<sup>124</sup> Other Transaction Authority is limited to those government agencies and operational divisions with appropriated authority and is a funding mechanism which targets non-traditional sources and allows a high degree of flexibility in how the agreement is awarded. Typical government procurement and grant laws, regulations and policies do not apply to OT awards.

space and will continue to increase access to industry expertise by engaging current partners and additional platform and software analytics partners in the coming year. IAM and the STRIDES Initiative lay a foundation for researchers to search across research datasets on various disease types, minimizing the silo effect created by having unique disease-specific platforms. FHIR will achieve similar goals by implementing standards for clinical research data. NIH workforce development efforts are recruiting experts from computational, mathematical, and related backgrounds and are also opening more opportunities to partner with those communities and engage them in our research. Through workshops on emerging technologies such as artificial intelligence, NIH will continue to engage technical experts and bring them together with the biomedical research community to foster new ideas and adopt emerging technologies. As NIH increases its capacity for platform technologies, a major challenge will be bringing the tools and software needed for usability to the platforms. As part of the strategic plan, NIH has a team working on multi-pronged approaches to address this issue, including potential new funding opportunities and industry partnerships. These and other activities will push NIH and the researchers it supports to continue to leverage advancing platform technologies.

### **Shaping Current Efforts into Future Results**

NIH will continue to build trans-NIH infrastructure to support growing datasets. Ongoing efforts will move NIH toward enhanced abilities to integrate and connect data ecosystems and increase open data sharing and access while maintaining best practices in security and privacy. NIH will build a workforce with computational expertise to work alongside its biomedical experts and ultimately broaden access to data, tools, and resources across diverse scientific communities to advance biomedical and clinical research.