White House Office of Science and Technology Policy
U.S. Department of Health and Human Services National Institutes of Health
ARPA-H Listening Sessions

Listening Session 10: Advocates for Research on Neurology and Mental Health August 16, 2021

The last of 10 listening sessions to gather feedback on the proposed Advanced Research Projects Agency for Health (ARPA-H) was held virtually on August 16, 2021. Advocates for research on neurology and mental health shared their opinions. The National Institutes of Health (NIH) is working closely with the White House Office of Science and Technology Policy (OSTP) to establish ARPA-H to focus on ambitious and innovative projects that will shape the future of health and medicine for all Americans.

Participants

White House Office of Science and Technology Policy (OSTP)

Max G. Bronstein, M.P.P., Assistant Director for Health Innovation
Tara A. Schwetz, Ph.D., Assistant Director for Biomedical Science Initiatives

National Institutes of Health (NIH)

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director
Joshua A. Gordon, M.D., Ph.D., Director, National Institute of Mental Health (NIMH)
Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS)

Stakeholders

Jonathan E. Alpert, M.D., Ph.D., Chair, Department of Psychiatry and Behavioral Sciences; Professor, Psychiatry, Neuroscience and Pediatrics, Albert Einstein College of Medicine, New York, NY; Distinguished Fellow, American Psychiatric Association (APA), Washington, D.C.

Juliane Baron, MPAff, Executive Director, Federation of Associations in Behavioral and Brain Sciences, Washington, D.C.; Executive Committee Member, Friends of NIMH

Judith N. Ford, Ph.D., Professor, Psychiatry, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA; President, Society of Biological Psychiatry, Brentwood, TN

Robert A. Hummer, Ph.D., Howard W. Odum Distinguished Professor of Sociology, University of North Carolina, Chapel Hill; President, Population Association of America, Alexandria, VA

Mary A. Pittman, DrPH, President and Chief Executive Officer, Public Health Institute, Oakland, CA

Margaret E. Ross, M.D., Ph.D., Professor of Neurology and Neuroscience, Weill Cornell Medicine, New York, NY; Vice President, American Neurological Association, Mount Laurel, NJ

Hongkui Zeng, Ph.D., Executive Vice President and Director, Allen Institute for Brain Science, Seattle, WA

Meeting Summary

Welcome and Opening Remarks

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, National Institutes of Health (NIH)
Max G. Bronstein, M.P.P., Assistant Director for Health Innovation, White House Office of Science and Technology Policy (OSTP)
Joshua A. Gordon, M.D., Ph.D., Director, National Institute of Mental Health (NIMH)
Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS)

Dr. Tabak welcomed attendees and provided logistical information for the Q&A session that would occur at the end of the session. If approved, the Advanced Research Projects Agency for Health (ARPA-H) will be a new division within NIH, with a radically different culture and organization. The new agency will be designed to foster bold ideas that are largely use-driven and to conduct research that solves practical problems. The resulting platforms, capabilities, and resources will apply across many diseases and conditions. ARPA-H will also have a distinct focus on equity to ensure diversity in funding recipients and in the patient populations that will benefit from its breakthroughs.

Dr. Collins welcomed participants and attendees to the last of 10 listening sessions to gather feedback on the proposed ARPA-H. NIH is working closely with OSTP on ARPA-H, which is a high priority for the Biden administration. ARPA-H is designed to catalyze ambitious ideas and approaches that will shape the future of health and medicine for all Americans. The new agency, which will follow the Defense Advanced Research Projects Agency (DARPA) model, will focus on high-risk, high-reward projects and will be guided by visionary project managers. ARPA-H will recruit researchers who might otherwise not apply to NIH for support, and its projects will be driven by clearly defined milestones. NIH and OSTP wish to gather opinions from stakeholders, who will play a critical role in the establishment and success of ARPA-H. The 10 listening sessions will focus on specific research areas and will involve NIH Institute and Center (IC) directors who represent those areas.

Mr. Bronstein said that ARPA-H aims to fill gaps in the biomedical research ecosystem to which NIH supplies vital infrastructure. Advancing new ideas to improve human health and biomedical science will require a novel approach. The ARPA model has taken shape as the Advanced Research Projects Agency–Energy (ARPA-E), the Intelligence Advanced Research Projects Agency (IARPA), and DARPA; these examples show that the model works. It is now time to deploy the model for innovation in health.

Dr. Koroshetz emphasized that our current understanding of the brain and nervous system is rudimentary, with the unfortunate result that therapies for neurological disorders have a high failure rate. New tools that match the complexity of the brain hold promise for the future, and ARPA-H should consider itself a toolmaker. The greatest need is in the delivery of genomic therapies for neurogenetic disorders—tools that, if successful, could also be used for common nongenetic disorders. Discovery research is a strength of NIH,

but tool building, which requires input outside biomedical science, is not. The challenge for ARPA-H is to create a tool-driven revolution, with an offramp for testing, validation, and distribution. Delivery tools are a particular need. ARPA-H can help capture the opportunity to jump-start the development of a pharmacopoeia of genomic therapies and precise genomic tools to influence brain cell activity and neural networks.

Dr. Gordon noted that the need for novel approaches to the delivery of molecular therapies will be equally important in psychiatry, particularly for neurodevelopmental disorders, and for common diseases. ARPA-H cannot succeed if it does not devote significant time and attention to the brain. Neuropsychiatric disorders exact the greatest burden and have the greatest need for biomedical research and innovation. In particular, ARPA-H could make significant contributions in two areas: an enhanced understanding of the biological underpinnings of neuropsychiatric disorders using high-throughput genomic interrogation and common platforms for the digital delivery of psychotherapy and other nonpharmaceutical treatments and monitoring patients. A high-throughput genomic approach to discovery demands better tools. The way to tackle this priority is with an organized, milestone-driven effort, not with a cottage industry of labs studying one gene at a time. A common platform for digital delivery of evidence-based treatments would provide researchers, patients, and caregivers with a common language to study, evaluate, and select from the army of apps currently available. Finally, ARPA-H should ensure that its efforts apply to all who need them; its emphasis on underserved and underrepresented populations is particularly welcome.

Comments from Invited Stakeholders

Margaret E. Ross, M.D., Ph.D., Professor of Neurology and Neuroscience, Weill Cornell Medicine, New York, NY; Vice President, American Neurological Association, Mount Laurel, NJ

Hongkui Zeng, Ph.D., Executive Vice President and Director, Allen Institute for Brain Science, Seattle, WA

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Mary A. Pittman, DrPH, President and Chief Executive Officer, Public Health Institute, Oakland, CA.

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Dr. Ross argued that ARPA-H's greatest contribution could be in creating new tools for understanding the underlying mechanisms of neuropsychiatric diseases and accelerating

the translation of insights into therapeutics. Computational tools to assess genome variation, including intergenic non–protein-coding regions; protein quantitative trait loci; and new platforms for gene therapies have exciting potential. In addition, the application of mRNA vaccines may hold promise for other, noninfectious diseases, including neurodegenerative conditions that promote neuroinflammation. There is a significant need for new vehicles to deliver therapeutics. Further development of brain–machine interfaces for prosthetics for neurological injury and neurodevelopmental disorders is an exciting area with potential for ARPA-H. Finally, the gut–brain axis is an understudied topic, and research in this area—investigating how to manipulate peristalsis, for example—could have an enormous impact on patients with spinal cord injury (SCI) or spina bifida and on understanding the microbiome and its impact on neurological function.

Dr. Zeng advocated for translational research based on cell type. In the last decade, high-throughput, single-cell technologies have revolutionized biology. Looking at millions of cells from different stages of the lifespan, different conditions, or different species allows for insights of unprecedented breadth and depth. Single-cell technologies present enormous opportunities to understand systematically how the brain works and how it goes awry in disease. Not only do cell-type investigations offer a different level of understanding than before, but the scale of data to be collected and analyzed is beyond the scope of current activities. ARPA-H offers a unique opportunity to organize a large-scale single-cell research effort to collect and manage data at this scale, develop the tools needed to share and understand the data, and accelerate advances toward therapies for many diseases.

Ms. Baron, speaking on behalf of the Friends of NIMH, urged ARPA-H leaders to integrate mental health into the priority research portfolio, both through dedicated research on standalone mental health issues such as suicide and by weaving a mental health focus through all aspects of physical health research. Specifically, ARPA-H could help accelerate progress in implementation science, early intervention, and data collection from wearable devices. ARPA-H should support implementation incubators to develop processes for translating findings to the public; models for working directly with patients would accelerate the impact of NIH research and increase its return on investment. It can be especially difficult to compete for funding to research early interventions, but they can have an outsized impact and deserve ARPA-H's attention. Conditions such as schizophrenia, for which many institutes have funded advances, are areas of focus where the coordinating efforts of an entity such as ARPA-H hold promise. Finally, tools for remote monitoring might advance understanding of health and disease and make time-sensitive interventions possible.

Dr. Alpert outlined four areas of psychiatric research that the APA's Council on Research proposed as particularly deserving of ARPA-H's attention: behavioral dimensions of neuropsychiatric conditions, including autism, traumatic brain injury (TBI), and dementia; disability associated with psychiatric conditions; suicide prediction and prevention, especially among marginalized groups, veterans, law enforcement officers, health care workers, and people with a history of trauma; and health disparities due to mental illness. Examples of specific approaches where ARPA-H could accelerate

progress include national psychiatry clinical registries and biorepositories; technology, including machine learning and natural language processing to detect early treatment responses, relapses, and suicide risk and improve adherence; neuromodulation; rapidly acting treatments that can engage novel targets; and studies of drugs in combination with psychotherapy.

Dr. Ford underscored the game-changing nature of optogenetics, which can turn neurons on and off, and the emerging technology of low-frequency ultrasound, which can be used to release drugs to specific areas of the brain. Another opportunity worth developing for clinical use is closed-loop neurostimulation, which can build on research that has delivered valuable information about neural circuit disfunction. Advancing such promising areas of research will require support for partnerships among commercial, technology, and academic organizations. Barriers to accelerating promising innovations include U.S. Food and Drug Administration (FDA) requirements that drugs target a diagnosis, rather than a system or circuit that might cut across many diagnoses. Regulatory constraints on the use of Schedule 1 psychoactive drugs in research also limit progress; developing less addictive versions of these drugs could be another promising area of research. Since innovations are fueled by clinical needs, engaging clinicians in ARPA-H research efforts should be prioritized. Finally, communicating results to the field and society through social media should not be overlooked.

Dr. Pittman, speaking on behalf of the Public Health Institute, underscored the importance of emphasizing equity, justice, and the impact of trauma when setting an agenda for mental health research and the health of communities. Neurological and mental health research must include a trauma-informed lens, embed trauma-informed practice, and encompass a public health approach. ARPA-H should mobilize community-driven research to the same degree as research guided by clinical needs. The agency should foster international collaboration for a better understanding of shared issues and work to balance biomedical research with social and public health research. Because even proven treatments are not accepted by all populations, higher-quality data that addresses all populations is a priority, as is communicating findings broadly.

Dr. Hummer expressed the population science community's excitement at the potential of ARPA-H to find breakthrough solutions to society's most pressing problems. Examples of population science research projects that fit the spirit of ARPA-H include structural racism and understanding how its facets can shorten the lifespan. Advancing tools to measure and understand structural racism could lead to important breakthroughs. Because existing data can be sparse or poor quality, and given gaps where data do not exist, ARPA-H could help the scientific community improve collection of population-representative data to inform breakthrough solutions for the most significant health disparities. Population scientists have unique expertise to contribute to ARPA-H and would make good candidates for the agency's staff. Finally, funding dedicated to ARPA-H should supplement rather than supplant existing funding for NIH.

Discussion

- *What are the most exciting tools and platforms that ARPA-H could pursue that would be game-changers for neurodegenerative disorders?* Dr. Koroshetz

marveled at the long list of genomic approaches to therapies that could be derived with a little time. One example is a protein in the brains of people with amyotrophic lateral sclerosis (ALS) that, when deactivated, could offer a cure. Leaving industry to develop this cure could take a decade, but ARPA-H would be in a position to accelerate the translation of previous findings about this protein. In addition, therapies that focus on delivery to certain cell types offer promise for treatments with high potency that are also targeted where they can be most effective. Dr. Gordon added that he is particularly excited about the potential for neurodevelopmental disorders with single-gene disruptions, which could be amenable to genetic therapies. Many of these disorders are so rare that there is no pathway to commercial development of interventions. ARPA-H can augment the basic science that has been advanced through the IC approach and provide a more corporate, milestone-driven approach to interrogating the genome.

- *When will ARPA-H funds be appropriated?* Dr. Schwetz said that the process of establishing ARPA-H is still ongoing. The President's budget request totaled $6.5 billion, and draft House appropriations allocated $3 billion. In tandem, ARPA-H will need specific authorizations to ensure it has the authority to achieve its mission.

- *What type of research will ARPA-H fund?* Dr. Schwetz said that ARPA-H funding is best suited for tackling those biomedical problems that represent high-risk, high-reward, use-driven research. Such research could span the spectrum of basic, translational, or clinical research. It is often described by saying that ARPA-H will focus on research from the molecular to the societal level and everything in between.

- *Will ARPA-H review entail peer review and study sections?* Dr. Schwetz explained that the review process will follow the ARPA model, which is based on a set of core questions known as the Heilmeier Catechism. ARPA-H is expected to follow them in essence, although it may be necessary to tweak some questions to be more applicable to biomedical research. Dr. Tabak added that the ARPA review model is quite distinct from the traditional two-level NIH review system. For one thing, proposals will be evaluated by federal employees. In addition, reviewers do not deal with averages of study section scores. The DARPA model, which has been used successfully for many years, allows for rapid turnaround and robust risk taking.

- *How will ARPA-H collaborate with other government agencies, especially to ensure cooperation rather than competition with other mental health agencies?* Dr. Tabak noted that the operation of ARPA-H has to be a team sport. Due to the complexity of the issues ARPA-H will tackle, it will be essential for many separate entities to work together. HHS is well-represented on an interagency federal committee that has been meeting on the topic of ARPA-H, and the desire for collaboration expressed at these meetings bodes well for ARPA-H's success. Dr. Schwetz added that beyond the federal space, ARPA-H will want to cooperate

with industry, nonprofits, philanthropic funding agencies, patient groups, and stakeholders in academia to refine approaches to ARPA-H programs. An important element of developing new program ideas will be a "market research" phase to collect input from patients, providers, researchers, the literature, Requests for Information (RFIs), webinars, meetings, and workshops.

Closing

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

Dr. Tabak thanked participants and attendees for their interest in ARPA-H. ARPA-H is a work in progress, and that OSTP and NIH will be hosting additional listening sessions to continue gathering information to help guide its establishment. Dr. Tabak invited attendees to send comments and questions to the ARPA-H comment box (ARPAHcomments@nih.gov) and to visit the ARPA-H webpage.