The second of 10 listening sessions to gather feedback on the proposed Advanced Research Projects Agency for Health (ARPA-H) program was held virtually on July 23, 2021, with about 140 attendees. Advocates for research on aging, arthritis, and musculoskeletal and skin disorders 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)
Tara A. Schwetz, Ph.D., Assistant Director for Biomedical Science Initiatives

National Institutes of Health (NIH)
Francis S. Collins, M.D., Ph.D., Director
Robert H. Carter, M.D., Deputy Director, National Institute of Arthritis and
Musculoskeletal and Skin Diseases (NIAMS)
Richard J. Hodes, M.D., Director, National Institute on Aging (NIA)

Stakeholders
James C. Appleby, M.P.H., Sc.D. (Hon), Chief Executive Officer, Gerontological Society of America (GSA), Washington, DC
S. Louis Bridges, Jr., M.D., Ph.D., President, Board of Directors, Rheumatology Research Foundation, Atlanta, GA; Physician-in-Chief and Chair, Department of Medicine, Hospital for Special Surgery; Chief, Division of Rheumatology, Hospital for Special Surgery and NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY
Maria C. Carrillo, Ph.D., Chief Science Officer, Medical and Scientific Relations, Alzheimer’s Association, Chicago, IL
Suzanne M. Jan De Beur, M.D., President, American Society for Bone and Mineral Research (ASBMR), Washington, DC; Associate Director, Johns Hopkins Bayview Clinical Research Unit Network (Institute for Clinical and Translational Research [ICTR]), and Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
Rebecca Minnillo, D.M., M.P.A., Chief Program and Development Officer, Society for Investigative Dermatology (SID), Cleveland, OH
Alison A. Moore, M.D., M.P.H., AGSF, Member, Board of Directors, American Geriatrics Society (AGS), New York, NY; Larry L. Hillblom Chair in Geriatric Medicine and Chief, Division of Geriatrics, Gerontology, and Palliative Care, University of California, San Diego, CA
Meeting Summary

Welcome and Opening Remarks
Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health (NIH)
Tara A. Schwetz, Ph.D., Assistant Director for Biomedical Science Initiatives,
White House Office of Science and Technology Policy (OSTP)
Richard J. Hodes, M.D., Director, National Institute on Aging (NIA)
Robert H. Carter, M.D., Deputy Director, National Institute of Arthritis and
Musculoskeletal and Skin Diseases (NIAMS)

Dr. Collins welcomed participants and attendees to the second of 10 listening sessions to
gather feedback on the proposed Advanced Research Projects Agency for Health (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 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. OSTP and NIH
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.

Dr. Schwetz said that ARPA-H will be transformative for biomedical research. The
United States has a strong biomedical research ecosystem that is supported by NIH-
funded research. Results from these research studies have informed the pharmaceutical
industry in its development of treatments for a range of conditions. However, the current
system has some gaps between traditional fundamental research and industry. ARPA-H
will help provide a new lens and a mechanism through which to support exciting
biomedical research that can improve human health. Such ambitious and cutting-edge
research requires a novel funding approach, and such approaches have been used in other
areas of science. In ARPA-H, OSTP and NIH aim to create a distinct entity whose
leadership will have the autonomy and resources to tackle some of the biggest challenges
facing human health.

Dr. Hodes expressed enthusiasm for the ARPA-H vision, which proposes to advance
science from the molecular to the societal level. This vision encourages us to imagine the
possibility of using small blood samples to track all of a person’s proteins and
metabolites for risk of disease across their lifespan and analyzing the data with machine
learning. At the other extreme, ARPA-H presents opportunities for integrating detailed
digital data about people’s cognitive and physical function with information about their
environments that is developed with geospatial methodologies.

Dr. Carter encouraged listeners to consider new technologies and paradigms that could
close research gaps. Examples might include skin sensors that could detect systemic
inflammation on the skin and in joints and an implanted chip to monitor repair processes
and improve wound repair or healing after fractures or joint replacement. ARPA-H is uniquely positioned to advance health equity by supporting the development of technologies that could eradicate the health effects of racism and discrimination, such as by developing diagnostic and treatment algorithms relevant to populations affected by health inequities or the integration of patient decision making in planning for joint replacement surgery. Gene therapy could benefit from revolutionary new approaches, such as comparative testing of viral, exosome, and nanoparticle delivery vehicles; DNA, mRNA, and RNAi cargos; and tissue-specific CRISPR approaches. ARPA-H is also positioned to catalyze data science by accelerating the interoperability of datasets and enabling artificial intelligence and machine learning. There is a need for tools to compare omics across diseases. With such targets, big data science could generate a new paradigm for medicine that is based on mechanisms instead of manifestations.

Dr. Collins introduced brief statements from the invited stakeholders. Each was given a series of questions to consider, including the opportunities ARPA-H could catalyze, what systemic gaps in the research and development (R&D) enterprise are impeding progress, challenges in advancing research based on an ARPA model, and partnership strategies that should be incorporated in the ARPA-H design.

Comments from Invited Stakeholders
Alison A. Moore, M.D., M.P.H., AGSF, Member, Board of Directors, American Geriatrics Society (AGS), New York, NY; Larry L. Hillblom Chair in Geriatric Medicine and Chief, Division of Geriatrics, Gerontology, and Palliative Care, University of California, San Diego, CA
James C. Appleby, M.P.H., Sc.D. (Hon), Chief Executive Officer, Gerontological Society of America (GSA), Washington, DC
S. Louis Bridges, Jr., M.D., Ph.D., President, Board of Directors, Rheumatology Research Foundation, Atlanta, GA; Physician-in-Chief and Chair, Department of Medicine, Hospital for Special Surgery; Chief, Division of Rheumatology, Hospital for Special Surgery and NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY
Suzanne M. Jan De Beur, M.D., President, American Society for Bone and Mineral Research (ASBMR), Washington, DC; Associate Director, Johns Hopkins Bayview Clinical Research Unit Network (ICTR), Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
Rebecca Minnillo, D.M., M.P.A., Chief Program and Development Officer, Society for Investigative Dermatology (SID), Cleveland, OH
Maria C. Carrillo, Ph.D., Chief Science Officer, Medical and Scientific Relations, Alzheimer’s Association, Chicago, IL

Speaking on behalf of AGS, Dr. Moore expressed support for the President’s ARPA-H proposal. She said that the new agency must address age as a common risk factor in many diseases. Key principles that deserve ARPA-H’s attention include the contribution of biological mechanisms of aging to diseases that drive illness, death, and health care costs in the United States and the impact of these mechanisms across the lifespan, including their role in disabling conditions in children. Other priorities for funded research include
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the study of patients with more than one illness, removal of upper age limits for participants, and aligning research aims with patient priorities and concerns. In partnership with NIA, ARPA-H could accelerate geroscience and gerotechnology research. Geroscience, the study of biological mechanisms that drive aging and disease, holds promise for interventions such as senolytic drugs that could delay the onset of chronic disease. Gerotechnology seeks to optimize older adults’ independence, using wearables, robots, and other devices. These technologies could also be used to identify digital phenotypes of disability and illness. AGS also recommends that ARPA-H invest in building network capacity so that universities can collaborate using common data and in training the next generation of researchers in aging.

Speaking for the GSA, Dr. Appleby applauded the administration for creating ARPA-H and commended statements in support of maintaining robust funding for NIH. To “accelerate the pace of breakthroughs to transform medicine and health,” he recommended that ARPA-H embrace a geroscience approach, targeting the intersection of aging and chronic disease, instead of a disease-specific approach. ARPA-H should also exploit opportunities in the social and behavioral sciences, along with biomedicine, that could provide rapidly scalable innovations while also advancing health equity. Collaboration with other federal agencies and with private-sector partners should also be commended.

Dr. Bridges discussed the transformative potential of ARPA-H for arthritis and rheumatic diseases. For example, ARPA-H could play an important role in quantifying the effects of environmental exposures. Technologies to characterize exposure to foreign substances through the lungs, skin, and gastrointestinal tract would be game-changing. With genetics and predictive biomarkers, detailed exposure data could help advance prevention and mitigation strategies, lowering disease incidence. Those data could also make it possible to employ screening to identify at-risk individuals or those with subclinical disease, with particular benefit for poorer communities. He proposed predictive analytics as another ARPA-H priority. Integrating diverse datasets could help ensure patients get the most effective medicines with the fewest risks. There is also a need for rapid, accurate, and inexpensive analysis of blood, fluid, and tissue samples to improve diagnoses and tailor treatments. African American, Hispanic, and Native American communities disproportionately affected by rheumatic diseases would benefit from ARPA-H support for Research Centers in Minority Institutions and Native American Research Centers for Health that have existing relationships with rheumatologists. Practice-based research networks could be used to disseminate findings to communities with no rheumatology specialists. ARPA-H is also well positioned to fund clinical trials for treatments for osteoarthritis. Resources available to support the transformative goals of ARPA-H include the American College of Rheumatology’s Rheumatology Informatics System for Effectiveness (RISE), a clinical data registry.

Dr. Jan De Beur, speaking on behalf of ASBMR members, argued that the advanced R&D approaches supported through initiatives like ARPA-H rely on the fundamental science at the core of NIH’s mission. As a result, investment in ARPA-H should be balanced with robust investment in NIH. ARPA-H should not compromise the excellent ongoing research in intramural and extramural programs. It is important that the targets of
ARPA-H support not overlap excessively with currently supported areas of research and that Institutes and Centers (ICs) not be required to commit their resources to ARPA-H. She also warned that administrative oversight and reporting expectations from the DARPA model could create burdens for ARPA-H–funded researchers or limit the pool of potential candidates. More flexible compliance schemes and funding support for administrative requirements should be considered for ARPA-H. In addition, ARPA-H should engage academic institutions on these matters and on ways to recognize ARPA-H projects in tenure decisions.

Drawing on suggestions from SID stakeholders, Dr. Minnillo offered concrete targets for advancing research in the field of skin science. Images of manifestations of skin and systemic conditions on skin of color are a priority for accurate diagnosis and reducing health disparities; imaging tools also need to be refined to eliminate bias. In addition, there is a gap in data describing disease severity, such as that of melanoma, in Black patients. Opportunities for new technologies include microbiopsy, transdermal delivery of RNA- and DNA-based vaccines, nanoparticulate drugs that can be applied to the skin, photodynamic therapy, CAR T-cell therapies for autoimmune diseases, manufacturing of vector and cellular therapies and GMP plasmids, using CRISPR to create topical applications to correct genetic diseases (e.g., sickle cell disease and cystic fibrosis), consistent dosing through slow-release media, and repurposing existing medicines for rare skin diseases. Additional opportunities exist in data integration and advancing methods development to facilitate data integration; advancing personalized medicine through the collection of genomic, diet, and microbiome data; and incorporating data priorities for aging, arthritis, musculoskeletal and skin research in the National Health and Nutrition Examination Survey and other national surveys. In the area of peer review, a Special Emphasis Panel supporting a skin of color initiative could inspire the research community, and including patient representatives in clinical research study sections could help better define needs and acceptable solutions. An NIH-funded database providing guidance on commercialization could be adapted by individual institutions and would benefit the research community as a whole. There is also a need for incentives for industry to research rare diseases. A national biobank for skin biopsy tissue was suggested as a resource that could help promote partnership. In addition, fostering collaboration between clinical and engineering departments and funding multi-institute data analysis centers could break down silos.

Dr. Carrillo, speaking for the Alzheimer’s Association, urged the administration not to duplicate or supplant current Alzheimer’s disease research conducted through NIH and pointed instead to unfunded targets outlined in the NIH Professional Judgment Budget for Alzheimer’s Disease and Related Dementias for Fiscal Year 2023. Examples of such projects include the acceleration of advances toward using brain and eye imaging and blood and fluid biomarkers to measure neuronal health. The innovative preclinical Accelerating Medicines Partnership is a good model for collaboration for partnerships that should be included in the ARPA-H design. Taking this model to the next level could include developing a funnel for validated targets that would bring together nontraditional partners, promote earlier collaboration, offer guidance from regulatory agencies, and include Small Business Innovation Research and Small Business Technology Transfer program mechanisms. The level of resources necessary to bring all these elements
together is now out of reach for many stakeholders. Including community advisory boards at the early planning stages could provide more local and culturally sensitive guidance and help advance health equity in creative new ways. Digital technologies for diagnosis, assessment, and disease monitoring present another opportunity and could be used to measure cognition or function (e.g., with passive measurement of changes in the brain through voice recognition). There are other opportunities for investment in developing complex models that chart risks that contribute to cognitive decline with age and validated algorithms for disease risk using big data. Finally, Dr. Carrillo urged administrators to ensure that ARPA-H does not operate in isolation, is transparent in its activities, and shares data openly.

Discussion
Dr. Schwetz and Dr. Collins fielded questions submitted through the meeting platform.

- **When will ARPA-H funding start and at what level?** Dr. Collins explained that ARPA-H was allocated $6.5 billion in the President’s fiscal year (FY) 2022 budget. In response to this proposal, the House Appropriations Committee issued a budget with $3 billion allocated to ARPA-H. The House also increased its proposed support for the rest of NIH by $3.5 billion, giving NIH a $6.5 billion FY 2022 increase in total. There is no proposal yet from the Senate. In addition to funding, Congress will need to provide for new authorities for ARPA-H, including specific authority to hire the director and program managers and to issue contracts. Ultimately, ARPA-H cannot get off the ground until it is funded. Based on recent experience, it seems the FY 2022 budget is unlikely to pass before the start of the fiscal year, October 1. More likely, NIH will be funded through a continuing resolution, possibly until November or December 2021. Current planning activities will help ensure that there is no delay in starting the new agency once funding is ready.

- **How will project ideas be reviewed and selected?** Dr. Schwetz explained the general ARPA approach that will be the backbone of the review process at ARPA-H. At DARPA, program manager candidates are asked to pitch ideas during their interview. Also, experts across the federal government review project ideas. The reviewers do not rank ideas; rather, a yes-or-no decision is made based on whether an idea meets the agency’s goals. For ARPA-H, it will be important to have many mechanisms for input and feedback, yet program managers will be expected to bring forward project ideas. Other project ideas may bubble up naturally or will be suggested by the agency director. Further, ICs will have the opportunity to put forward good ideas from the research community; industry, patient advocacy organizations, professional societies, and academia will also generate ideas. Ideas may also come from investigator-initiated proposals. Following a review that will be similar to the DARPA process, program managers then put together a portfolio of projects that address the challenge at hand, which the director then approves. Dr. Collins added that in this light, it is clear how important it is to get the right mix of entrepreneurial experience, commitment, and ability to share excitement in the possibilities of ARPA-H in the skill set of the person hired as director.
• **How will ARPA-H ensure that projects address health equity and that the agency’s staff are diverse?** Dr. Collins said ARPA-H needs to be inclusive in everything it does. Acknowledging the agency’s role in the history of structural racism, he said that NIH must rectify the lack of diversity in its workforce and in the way it addresses problems. Dr. Collins pointed to the Science article he authored with Dr. Lander, Dr. Schwetz, and NIH Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., highlighting health equity as a priority and offering examples of projects that could be supported by ARPA-H, including the development of a nationwide community health worker (promotores de salud) model to advance the prevention of illness and management of chronic disease.

• **Some stakeholders mentioned concerns about the burden of project oversight in the ARPA model. Are there ways to make oversight more efficient?** Dr. Schwetz noted that active project management is an element of the ARPA model. ARPA program managers typically check in with their funded researchers biweekly or monthly to track progress against project milestones. In the ARPA model, the program managers also have the autonomy to make adjustments, such as changing timelines or combining teams, based on project developments. Dr. Collins added that because they are milestone-driven, ARPA-H projects will require more frequent interactions with program staff than typical NIH grants, which track progress with annual reports. The parallel at NIH is the cooperative agreement.

• **How will ARPA-H interact with the existing infrastructure at NIH?** Dr. Collins said that NIH wants to be sure that ARPA-H’s autonomy is clearly defined; it is not intended to function like another NIH IC. The ARPA-H director will have the ultimate authority to decide which projects to fund, with money from a line in the Congressional budget. NIH hopes to foster clear, porous interactions about exciting scientific ideas between ARPA-H and the ICs, but no IC can demand funding for a particular project. Funded projects should be use-driven rather than curiosity-driven and show clear potential for clinical benefit. Being situated within the NIH scientific environment is a benefit, but administrators will have to make sure that ARPA-H’s decision making process is appropriately insulated and given independent authority. The aim is to build on the success of DARPA.

• **How is the development of partnerships being envisioned?** It will be important for ARPA-H to catalyze partnerships with many different stakeholders, such as by incentivizing industry to partner on moving outputs to market or working with federal government agencies such as the Centers for Medicare & Medicaid Services and the U.S. Food and Drug Administration to decrease regulatory and reimbursement hurdles. Other federal agencies could also be customers for ARPA-H outputs.

• **What is the Heilmeier Catechism?** Dr. Collins explained that George Heilmeier, DARPA’s director in the 1970s, formalized his “catechism,” a list of 8 questions to use when evaluating project ideas. Stakeholders can expect that ARPA-H will adopt some version of the list to determine which projects are worth the investment.
• What are you trying to do? Articulate your objectives using absolutely no jargon.
• How is it done today, and what are the limits of current practice?
• What is new in your approach, and why do you think it will be successful?
• Who cares? If you are successful, what difference will it make?
• What are the risks?
• How much will it cost?
• How long will it take?
• What are the midterm and final “exams” to check for success?

• How will the director and program managers be selected, and what characteristics will NIH be seeking for people in those roles? Dr. Collins said that the director will be selected at a high level, probably by appointment of the President or the Secretary of Health and Human Services. The director can be expected to play a major role in hiring program managers, who will be invited for a 3-year appointment with a possible extension to 5 years. Due to the short turnaround, it may be that these positions will be more appealing to people in the private sector, who change jobs more frequently than people who have committed to a tenure-track position. Program managers have broad latitude to define and manage projects, which makes the role an exciting opportunity.

• What scientific focus areas are priorities for ARPA-H? Dr. Collins posed an example from the audience: the study of fibrosis. Dr. Carter said that that would be a ripe topic for research and added that there is an upcoming roundtable on methods for resolution of inflammation as a way to prevent fibrosis. Dr. Collins concurred that mechanisms of fibrosis could be a viable platform applicable to multiple disorders. Dr. Schwetz added that this idea touches on a key tenet of ARPA-H: that it be used to build capacity in platforms that can be applied across many conditions. ARPA-H should be an enabler and a catalyst.

• How will the research community learn about new projects and find out how to take part? Dr. Schwetz explained that, particularly at first, ARPA-H will probably issue open announcements for applications based on investigator-initiated ideas. Community engagement will also be an important element of program development. In addition, program managers will need to conduct market research to understand the landscape to answer the Heilmeier questions, gathering information from the community in that process. That process will also signal what the agency is interested in exploring. Following the public announcement of an approved program, ARPA-H will offer program days so that potential applicants can ask staff questions.

Closing
Francis S. Collins, M.D., Ph.D., Director, NIH

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