NIH Workshop on HIV-Associated Comorbidities, Coinfections, and Complications: Summary and Recommendation for Future Research

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Background: With potent antiretroviral therapy and simplified regimens, people living with HIV (PWH) are achieving near-normal lifespans but not necessarily a normal health span or healthy aging. PWH have a higher than expected risk of developing a number of non-AIDS comorbidities, coinfections, and complications (CCC), often against a background of stigma, poverty, and isolation.

Setting: To gain a better understanding of research needs for HIV-associated CCC, the NIH convened a 2-day workshop (HIV-associated CCC, or HIV ACTION).

Methods: A cross-institute NIH planning committee identified 6 key research areas: epidemiology and population research, pathogenesis and basic science research, clinical research, implementation science research, syndemics research and international research in low and middle income countries. Investigators were selected to lead working groups (WGs) to assess the state-of-the-art and identify 3–5 priority areas in each field before the workshop. A 2-day program at the NIH was developed which included presentations by invited experts and WG members.

Results: Over 400 participants attended the workshop. After general and individual WG discussions, the most pressing gaps, questions, or proposed action items were identified. Priority lists of pressing research issues were presented by cochairs of each WG. A detailed report is posted at the NHLBI website. This article reports the streamlined priority list and a summary of WG discussions to inform investigators of current priorities in the field.

Conclusion: Collaborative efforts of many disciplines are needed to improve the health and wellbeing of PWH. Several common themes emerged across WG representing potential priorities for investigators and recommendations for the NIH.

Key Words: HIV comorbidities, pathogenesis, epidemiology, syndemics, implementation science, international research

(*J Acquir Immune Defic Syndr* 2021;86:11–18)

Received for publication July 23, 2020; accepted September 8, 2020.

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Supported by NHLBI and OAR and cosponsoring institutes, centers, and offices: FIC, NCI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP, ORIP, and ORWH.

Presented at the HIV-associated Comorbidities, Coinfections, and Complications Workshop; September 19–20, 2019; Bethesda, MD.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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INTRODUCTION

The success of antiretroviral therapy (ART) has ushered in a new era for the HIV pandemic in which people who access modern regimens early in the disease process and adhere to these therapies can expect to achieve a normal or near-normal lifespans. Despite these advances, people living with HIV (PWH) are more likely to suffer from chronic HIV-associated comorbidities, coinfections, and complications (CCC) than their age-matched uninfected peers.[1–3] This excess disease burden contributes to a lower than normal healthspan in many affected populations.

Multiple mechanisms likely contribute to this excess risk. Nearly all organ systems are known or expected to be affected by HIV and/or its treatment. Factors associated with aging—including polypharmacy, social isolation, and stigma—are common in PWH. Immune dysfunction and inflammation persist indefinitely during ART and likely also negatively affects health.

To gain a better understanding of HIV-associated CCC and to foster cross-disciplinary collaborations in future research, the NIH assembled a diverse group of 96 experts

and community advocates to participate in a year-long process assessing the state-of-the-art. A 2-day CCC workshop (HIV-associated Comorbidities, Coinfections, and Complications, or HIV ACTION) was held in September 2019 and attended by over 400 individuals.

METHODS

In late 2018, a cross-institute panel from the NIH identified workshop cochairs and worked with them to assemble 5 working groups (WG): epidemiology and population science, pathogenesis and basic science, clinical research, implementation science, and syndemics, with a cross-cutting international WG (Table 1). These WG were charged with summarizing the state of the CCC research agenda, identifying major research gaps, key challenges, and opportunities, and developing a list of future research priorities. The WG selected the top 3–5 priority topics for presentations and discussion at the HIV ACTION workshop along with invited special talks. Details of the process, agenda, executive summary, detailed report, and outcomes were posted on the NHLBI website: https://www.nhlbi.nih.gov/events/2019/hiv-associated-comorbidites-co-infections-complications-workshop.

TABLE 1. NIH Workshop on HIV-Associated Comorbidities, Coinfections and Complications (HIV ACTION)

Workshop organizers: Shimian Zou (NHLBI), Natalie Tomitch (OAR), Leia Novak (NAID), and NIH Planning Committee
Workshop cochairs: Dr. Steven Deeks and Dr. Savita Pahwa
Working groups and chairs
Epidemiologic and population research: Dr. Amy Justice and Dr. Ned Sacktor
Pathogenesis research: Dr. Dana Gabuzda and Dr. Peter Hunt
Syndemics: Dr. Ken Mayer and Dr. Emily Mendenhall
Clinical research: Dr. Todd Brown and Dr. Ann Kurth
Implementation science research: Dr. Stefan Baral and Dr. Michael Mugavero
International research: Dr. Roger Detels and Dr. Eugene Mutimura

RESULTS

The top priority topics of the WG are listed in Table 2. After discussions at the workshop, the most pressing gaps, questions, or proposed action items were identified and are listed below.

Epidemiologic and Population Research Working Group

Aging with HIV

- What are the most accurate and generalizable risk indices for mortality, hospitalization, and common comorbid diseases for aging PWH?
- What are the most valid and reproducible measures to study aging with HIV?
- Is frailty a useful independent concept in the study of aging with HIV?[4]
- Do appropriate measures of frailty in PWH differ from those aging without HIV?
- How can useful indices of prognosis, quality of life, and frailty be integrated into routine clinical care and research?

Neurobehavioral Complications of HIV in the Modern Treatment Era

- What is the incidence and prevalence of neurobehavioral impairment in PWH on ART with and without viral suppression?
- What is the impact of demographic factors such as age, sex, education, race or ethnicity, and socioeconomic status on the epidemiology of cognitive impairment and mental health conditions in PWH?
- What impact do specific comorbidities, such as mood disorders, drug addiction, and coinfections, have on cognitive and mental health in PWH? Does treatment of such comorbidities improve cognitive function?

TABLE 2. Priority Topics of Working Groups of the HIV ACTION Workshop

Epidemiologic and Population Research
Aging with HIV
Neurobehavioral complications of HIV in the modern treatment era
Aging syndromes, particularly falls, frailty, and polypharmacy and the influence of HIV, risk behaviors, and ART
Pathogenesis and basic science research
Immunopathogenesis
Microbiome and virome
Aging and senescence
Clinical research
Clinical and translational studies to prevent comorbidities
Comorbidity management in HIV
Patient-reported outcomes and biomarkers
Implementation science research
Synthesizing priority implementation science HIV comorbidity research questions
Novel observational and experimental implementation science research designs
Syndemics research
Syndemic methods
HIV-infectious disease syndemics
Panel on international research
Challenges and barriers to identifying and treating comorbidities
Research needs targeting HIV/AIDS comorbidities
Curricula for training in HIV/AIDS comorbidities

- How can we systematically differentiate between cognitive impairment that is due to HIV or immune suppression and cognitive impairment that is due to age-related conditions such as cerebrovascular disease or age-related neurodegenerative conditions?
- How can we delineate phenotypes of HIV-associated cognitive impairment that have value in predicting outcomes and relate to developing specific prevention and intervention strategies?
- What are the factors that promote neurocognitive health and resiliency among PWH?
- What are the optimal methods to screen for and confirm cognitive impairment and mental health complications in research and clinical settings for both the United States and resource-limited countries?
- How does cognitive and mental health affect the behavior of PWH, including medical adherence, self-efficacy, and risk behavior?
- How can we improve our ability to assess, monitor, and intervene on neurocognitive impairment and mental health "in the field" (ie, outside of clinical and research settings)?
- What are the opportunities using mobile technology?

Aging Syndromes, Particularly Falls, Frailty, and Polypharmacy and the Influence of HIV, Risk Behaviors, and ART

- Develop and validate frailty instruments in PWH.
- Examine the effects of nondrug interventions, such as exercise, on frailty in HIV.
- Determine how ART modifies falls risk among PWH.
- Examine how alcohol, analgesics, and medication-assisted treatment affect falls risk.
- Evaluate how HIV necessitates modification to interventions for falls and fractures.
- Identify mechanisms of antiretroviral (ARV)/non-ARV drug–drug interactions.
- Evaluate polypharmacy's effects on comorbidities in people living with HIV.
- Determine the impact of deprescribing non-ART medications among people living with HIV.

Pathogenesis and Basic Science Research Working Group

This WG has recently published their topics and discussion[5] summarized here.

Immunopathogenesis

- Do all "root drivers" contribute equally to inflammation and immune activation?
- Do some inflammatory pathways ("branches" of the "tree") drive some diseases more than others and are they different in PWH from HIV uninfected?
- Do inflammation, immune activation, and immune dysfunction in HIV differ across the lifespan?
- Will intervening on some inflammatory pathways have adverse consequences (eg, infections and cancer)?
- Can systems biology approaches help us prioritize interventions?
- Can we improve our understanding of systems biology from clinical trials and animal models?
- Can we use novel inflammatory indices and imaging to stratify risk and monitor treatment response?
- Is there need for a tailored approach to decrease inflammation?

Microbiome and Virome

- What are the mechanisms of host–HIV–microbiome interactions and do they differ based on age of the host?
- Does the microbiome play a causal or contributory role in HIV comorbidities?
- How do other cofactors interact with HIV infection to affect the microbiome and downstream comorbidities?
- If the microbiome is causal or contributory to HIV-related comorbidities, rather than just a consequence or association, can it be manipulated to modify these pathways?

Aging and Senescence

- Have we overlooked important drivers or mechanisms?
- How do markers and drivers of senescence, including immune senescence, change with advancing age?
- Which are the most critical drivers or mechanisms to target, and how do we target them?
- Can we identify overlapping or intercepting pathways to disrupt or are we doomed to address each driver or mechanism separately?
- Which are the best models to use to perform both mechanistic and treatment studies of aging with HIV infection?

Clinical Research Working Group

Clinical and Translational Studies to Prevent Comorbidities

- What are the best ways to screen for, identify, and prevent comorbidities, in research and clinical settings for both the United States and resource-limited countries?
- What are the high-priority screening and prevention guidelines (across the age spectrum) that need to incorporate HIV as an additional risk factor, and do screening tools for age-related comorbidities underperform in the HIV/AIDS population?
- Are there high-priority prevention strategies that need to be used or targeted in PWH across the age spectrum?
- Are standard prevention strategies, such as diet and exercise, as effective in HIV+ individuals?
- Are there modeling strategies that can assist in delineating the risk, benefit, and cost savings of implementing

screening and prevention strategies among people with HIV?

Comorbidity Management in HIV

- How should clinical practice guidelines and standards of care for different comorbidities be tailored to older PWH, including those with multimorbidity?
- How do interventions aimed at decreasing inflammation and immune activation in older PWH affect risk and progression of individual comorbidities as well as multimorbidity?
- How should treatment of comorbidities be prioritized among older PWH who have multimorbidity? Should frailty and measures of physical function be used to prioritize and tailor therapies?

Patient-Reported Outcomes and Biomarkers

- How do comorbidities affect different understudied patient populations, including older PWH (eg, age 65 years or older), gender (male, female, and transgender/nonbinary), racial and ethnic minorities in the United States, and people in low-resource settings?
- What patient-reported outcomes and biomarkers are most useful for prevention, early detection, and management of common comorbidities in PWH?
- What are mechanisms by which HIV may accelerate aging processes and increase the risk for comorbidities, and how can patient-reported outcomes and biomarkers help explicate these?
- How can patient-reported outcomes and biomarker studies in comorbidity clinical trials be used to optimize HIV care across the lifespan?
- How can new technologies facilitate efficient assessment of patient-reported outcomes and biomarkers?

Implementation Science Research Working Group

Synthesizing Priority Implementation Science HIV Comorbidity Research Questions

- Given limited resources in our jurisdiction, what implementation strategies will be most effective when implementing interventions for HIV-related comorbidities at the lowest cost?
- How can we learn from our successes and challenges as we roll out interventions for HIV-related comorbidities over time to more expediently achieve implementation?
- Can the cost and resources involved in a successful multicomponent implementation strategy package be reduced while maintaining its impact?
- How can the field begin to optimize implementation during the development and testing of new interventions for HIV-related comorbidities?

Novel Observational and Experimental Implementation Science Research Designs

- How do we define program or implementation equipoise, versus clinical equipoise, and how does it influence experimental methods?
- How can we define and measure counterfactuals in implementation science research methods?
- How do we attribute changes in incidence of comorbidities and health outcomes to a complex system of interventions that have been adopted or implemented and adapted over time?
- How can we characterize the context and the mechanisms by which context influences the impact of interventions?
- How can we evaluate and assign effect size to the adaptive decision-making that health service providers make for patients?
- How can we leverage multiple layers of routinely collected programmatic data to rapidly adapt the implementation of services to incoming data?

Training Opportunities and Resources to Expand the Implementation Science Research Workforce

- Investigators cannot just "do" implementation science research without training.
- What can be easily layered onto current implementation science generalist training?
- What can be easily layered into HIV-related research consortia and activities?
- Almost all NIH-sponsored trainings are targeted to a specific content area; there is nothing specific to HIV.
- There is high demand for, but a low supply of, implementation science training programs.
- Except for larger NIH-funded training programs to a specific institution, most NIH-funded trainings target only clinician investigators.

Syndemics Research Working Group

Syndemic Methods

- On a theoretical level, what does it mean when we assert that epidemics are "interacting" within populations or when we assert that diseases are "interacting" within individuals?
- Do the competing theoretical models yield differing programmatic, clinical, and/or policy recommendations?
- Are there settings in which co-occurring epidemics do not need to be characterized as a syndemic, when a more parsimonious appeal to social determinants of health would suffice?

- On an empirical level, how do epidemics interact at the level of populations?
- Which co-occurring epidemics warrant being characterized as a syndemic?
- How does the syndemic label improve the public health response?

HIV–Infectious Disease Syndemics

- What are the optimal prophylactic regimens to decrease sexually transmitted infections, viral hepatitis, and/or tuberculosis acquisition in PWH and those at greatest risk?
- To what extent does early diagnosis and treatment of copathogens result in improved health?
- What insights into mucosal biology can lead to better prophylactic approaches in the prevention of HIV and copathogen acquisition?
- Which structural interventions (eg, economic empowerment and enabling legal environments) are most effective in decreasing the spread of HIV and synergistic copathogens?

HIV–Chronic Disease Syndemics

- Which chronic diseases should be considered as syndemic with HIV?
- Which drivers of HIV acquisition and progression affect the prevalence and expression of chronic diseases in PWH?
- What are the optimal models of chronic disease prevention and management in PWH that address syndemic factors?
- Which structural and clinical interventions are most effective in decreasing the development of synergistic chronic conditions in PWH?

Panel on International Research in Low-Income and Middle-Income Countries

Challenges and Barriers to Identifying and Treating Comorbidities

- What instruments will improve data collection on comorbidities for reliable estimates of the global burden of disease in PWH?
- How can HIV services be decentralized to mobile clinics, community drug distribution sites, and other settings for improving care delivery.

Research Needs Targeting HIV/AIDS Comorbidities

- Strategies to expand care for noncommunicable diseases (NCDs) at HIV clinics
- Behavioral and social science programs to understand stigma and health-seeking behaviors
- Engagement of basic science and translational research scientists coupled with implementation research.

Need for Training in HIV/AIDS Comorbidities

- Develop curricula to build the community of HIV researchers.
- Use training opportunities from the Fogarty International Center.

DISCUSSION

This NIH-sponsored initiative involved multiple experts and stakeholders in an effort that was sustained for over 12 months, culminating in a highly interactive 2-day conference. During this process, it became apparent that cross-disciplinary (and hence at the NIH, cross-institute) collaboration will be necessary to accelerate progress in studies aiming to improve the quality and quantity of life for PWH in the era of ART and for bridging the gap between chronologic age (lifespan) and complex biologic processes that affect it (healthspan). With the momentum of the President's initiative to end the HIV epidemic (EHE), greater numbers of PWH will enter into care under the "diagnose" and "treat" pillars and the people aging with HIV will continue to grow. From the community perspective, the need for new models of research providing real time data about clinical needs, care, and implementation of services for people aging with HIV was emphasized. The impact of social, cultural, economic, political, and other factors on the susceptibility for HIV and coconditions has major implications for a disease that is increasingly concentrated in vulnerable populations, yet how these societal factors affect health in PWH is largely undefined. Several common themes emerged that highlight priority areas for investigators and recommendations for the NIH. Salient discussion points, research priorities, and recommendations emerged from the various working groups, underscoring the importance of community engagement in decision making.

The epidemiologic and population research working group discussed comorbidities[6] and raised questions about the differences in aging with and without HIV infection. Multiple factors likely contribute to health in aging HIV-infected adults, including the direct impact of HIV infection on multiple organ systems, toxicity of ART, polypharmacy, social isolation, stigma, and others as yet poorly defined risk factors. Notably, most of these factors are known to affect aging in the general population but are overrepresented or more pronounced in PWH. Frailty, for example, is often discussed in the context of HIV disease and aging, but how this should be defined and measured in HIV populations is not known. The importance of studying neurocognition, the roles of polypharmacy, and substance use in neurocognitive compromise in people aging with HIV was highlighted. Tools are needed to help identify common pathways for multimorbidity, for clinical phenotype definitions and practical guidance for clinical management. The group's recommendations included cataloging and developing tools to assess exercise, frailty and fall risk, brain health and

cognitive decline, and to capture social factors with qualitative research, machine learning approaches on large data sets and polypharmacy research.

The pathogenesis and basic science research working group proposed that underlying pathogenesis and mechanisms of HIV-associated CCC that involve multiple systems and manifest as concurrent conditions in PWH may be fundamentally different from the same "diagnosis" in persons without HIV along the lifespan.[5] The appropriate phenotypes, indicators, and indices/biomarkers for research on HIV-associated CCC will likely prove to be unique among those with and without HIV.[7–9] Factors that drive chronic immune activation and dysfunction in treated HIV infection, shared immune pathways and microbiome/virome contributions toward inflammation/chronic immune activation and immune dysfunction, and mechanisms that drive accentuated aging are among the overlapping etiologies and pathogenesis mechanisms.[10–12] New research methods or technologies, including appropriate animal models[13] are needed for research of HIV-associated CCC across the lifespan. Ultimately, there is a need to move toward interventional studies using knowledge gained from basic research. As PWH on ART inch closer to the healthy non-HIV aging population in longevity, a proposal for inclusion rather than exclusion of PWH from clinical trials investigating new therapeutic modalities in emerging fields such as geroscience was recommended.[14]

The clinical research working group discussed different comorbidities associated with HIV and prioritized prevention, management, patient-reported outcomes, and biomarkers.[15] Discussions included the need for research to design better screening tools for the early detection of age-related comorbidities including cardiovascular and musculoskeletal diseases in PWH and whether more aggressive management of blood pressure or cholesterol would alleviate the difference in outcomes of treatment in PWH and general populations.

As research moves forward, patient-reported outcomes will need to be measured more carefully. There is also a need for clinical trials that are not limited to specific diseases. It will be important to think more broadly and more holistically. The working group's discussions highlighted several principles, including the importance of addressing a life course perspective, disparities (including African Americans and other vulnerable populations), and age, sex, gender, and sexual orientation issues, given the disproportionate burden of several age-related comorbidities in women living with HIV. It was also recommended that funding calls should solicit applications from both international and domestic perspectives.

The syndemics research working group discussions focused largely on definitions. Members emphasized how local context matters and how strong the impact of social determinants of disease is.[16–19] Several overall priority questions were addressed. When is something syndemic and when is it not? How does the syndemic approach advance our understanding of mitigating upstream or clinically to make the biggest impact? Why does syndemic thinking matter for HIV? The discussions highlighted the importance of syndemics research for characterizing and integrating various comorbid diseases/disorders and their synergistic effects in PWH, while taking into account social, political, and ecological factors. The group discussed how to intervene upstream to mediate the emergence and interaction of multiple conditions that cluster with HIV. Focusing on nonmedical contributors and interventions at the policy and clinical level was emphasized. Such research can help us gain a deeper understanding of the interplay between these factors and their role in promoting disease clustering at the population level, and the impact they have on disease pathologies at the individual level; findings of such research will encourage more holistic approaches in the clinical management of PWH.

The implementation science research working group introduced a theoretical and foundational discussion of methods. Implementation science is an emerging area for HIV-related research,[20] and hence, coordinated support is needed for development of new observational and experimental implementation research designs and for training, including leverage of existing training opportunities and resources. What combination of implementation strategies would be necessary and sufficient to increase the impact of interventions for HIV-related comorbidities was a discussion theme. Recommendations included bringing implementation scientists to the table early to help determine which approaches have the most impact for HIV-associated comorbidity and optimal designs for evaluation, and to learn from implementation science research that has been conducted outside the HIV setting. Moreover, how can we better use nonexperimental designs including quasiexperimental and natural experiments to provide insight into outstanding research priorities for HIV-related comorbidity research. In resource-limited settings, we can learn about screening, diagnosis, and management of HIV-related comorbidities that will be relevant to the care of PWH. Implementation science methods and strategies will be essential to address barriers that impede the scale-up and application of scientifically proven interventions in community and clinical settings for the prevention, control, and treatment of HIV-associated CCC in PWH.

The international working group was comprised of representatives from each of the other 5 WG and covered areas discussed by other WG in the context of low-income and middle-income countries. Establishment of behavioral and social science research priorities that include the roles of stigma pervading all aspects of HIV, unique aspects of sex and gender in developing strategies to expand care for NCDs at HIV clinics. Engagement of translational and basic scientists and implementation perspectives in international settings is critical. Adequate funding streams are needed to deliver effective primary care, and improved data collection on comorbidities for reliable estimates of the global burden of NCD that differs from country to country and will be essential for large-scale system changes in delivering health care, utilization of tools such as The World Health Organization's STEPwise approach to Surveillance (STEPS) methodology. The IeDEA network, spanning 42 countries,

the PEPFAR Population HIV Impact Assessment surveys and Demographic and Health Survey Program tools for HIV+ populations were discussed. The group underscored the commitment of the Fogarty International Center to supporting training in developing countries.

A sentiment echoed by various experts was that in addition to efforts targeting specific research priorities within the mission of each Institute and Centers (IC), a coordinated NIH-wide research strategy would go a long way in addressing the complexities of CCC. For example, intervention research for prevention and management of HIV-associated CCC and their attendant polypharmacy is challenging.[21] For addressing comorbidities, whether an intervention should be targeted for a specific condition or be directed at generalized chronic immune activation and inflammation is not known. Understanding basic mechanisms as well as safety and effectiveness of interventions to control inflammation and immune activation in PWH should be of interest to many NIH ICs but would be costly and better served by coordinated research efforts. Multidisciplinary strategies fostering innovative research funding models and a nonsiloed approach could best address the common research themes that emerged from the workshop. In particular, funding mechanisms that promote multimorbidity research and collaboration would be beneficial, for example, multiomics approaches and large cohorts requiring collaboration across institutes, centers, and offices of NIH. Having NIH-wide discussion on how to facilitate and fund such collaboration was recommended as a priority. The authors recognize limitations of the prescriptions offered by the workshop summary, as viewpoints of all the diverse stakeholders affected by HIV comorbidities are not represented.

ACKNOWLEDGMENTS

The authors are grateful to members including NIH representatives of all five working groups and the international panel (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B548) for their effective work on identifying research gaps and priorities before the workshop and contributing to the discussion and deliberation during the workshop. Ms. Sara Harris from Synergy Enterprise Inc. (SEI) served as the science writer for the workshop and summarized the discussions. The authors thank invited speakers of special talks for their contribution to the program: Dr. Anthony Fauci, Director, NIAID, NIH; Dr. Keri N Althoff, Associate Professor, Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, Dr. Jamie Justice, Assistant Professor, Department of Gerontology and Geriatric Medicine at the Wake Forest School of Medicine, and Mr. Jules Levin, Executive Director and founder NATAP, National AIDS Treatment Advocacy Project.

The authors acknowledge the support from many people at NHLBI and OAR for their effort in preparing and executing this workshop

NHLBI: (1) Logistics Team: Della Claiborne, Demetria Pace, Terrie Squadere, Naomi Clarke, and Alex Dillon; (2) Conference Management: Wendy Massias-Burnett, Silvia Dossmann, and Kay Valeda; (3) OSPEEC (Office of Science Policy, Engagement, Education, and Communications): Lauren Hochman; (4) Leadership: Keith Hoots, Simone Glynn, David Goff, Nakela Cook, and Gary Gibbons.

OAR: (1) Leadership (Director's Office): Dr. Maureen Goodenow; (2) Program: Amber Wilson; (3) Communications: Alessandro Gravina.

OAR support: Dami Kim and Akary Nyan Win.

The authors gratefully acknowledge the support that this workshop received from 21 NIH ICOs, in the form of scientific input from staff representatives and financial contribution toward travel for invited experts to the workshop.

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