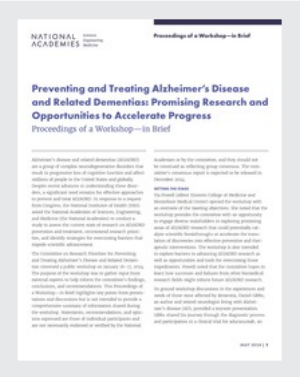

Preventing and Treating Alzheimer's Disease and Related Dementias: Promising Research and Opportunities to Accelerate Progress: Proceedings of a Workshopin Brief (2024)

DETAILS

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Proceedings of a Workshop—in Brief

Preventing and Treating Alzheimer's Disease and Related Dementias: Promising Research and Opportunities to Accelerate Progress

Proceedings of a Workshop—in Brief

Alzheimer's disease and related dementias (AD/ADRD) are a group of complex neurodegenerative disorders that result in progressive loss of cognitive function and affect millions of people in the United States and globally. Despite recent advances in understanding these disorders, a significant need remains for effective approaches to prevent and treat AD/ADRD. In response to a request from Congress, the National Institutes of Health (NIH) asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to conduct a study to assess the current state of research on AD/ADRD prevention and treatment, recommend research priorities, and identify strategies for overcoming barriers that impede scientific advancement.

The Committee on Research Priorities for Preventing and Treating Alzheimer's Disease and Related Dementias convened a public workshop on January 16–17, 2024. The purpose of the workshop was to gather input from external experts to help inform the committee's findings, conclusions, and recommendations. This Proceedings of a Workshop—in Brief highlights key points from presentations and discussions but is not intended to provide a comprehensive summary of information shared during the workshop. Statements, recommendations, and opinions expressed are those of individual participants and are not necessarily endorsed or verified by the National Academies or by the committee, and they should not be construed as reflecting group consensus. The committee's consensus report is expected to be released in December 2024.

SETTING THE STAGE

Tia Powell (Albert Einstein College of Medicine and Montefiore Medical Center) opened the workshop with an overview of the meeting objectives. She noted that the workshop provides the committee with an opportunity to engage diverse stakeholders in exploring promising areas of AD/ADRD research that could potentially catalyze scientific breakthroughs or accelerate the translation of discoveries into effective preventive and therapeutic interventions. The workshop is also intended to explore barriers to advancing AD/ADRD research as well as opportunities and tools for overcoming those impediments. Powell noted that the committee hopes to learn how successes and failures from other biomedical research fields might inform future AD/ADRD research.

To ground workshop discussions in the experiences and needs of those most affected by dementia, Daniel Gibbs, an author and retired neurologist living with Alzheimer's disease (AD), provided a keynote presentation. Gibbs shared his journey through the diagnostic process and participation in a clinical trial for aducanumab, an

anti-amyloid drug, which resulted in hospitalization for a severe adverse drug reaction known as amyloid-related imaging abnormalities (ARIA). When asked for his perspective on potential priority research areas for NIH, Gibbs cautioned against chasing the next drug and directing all resources to a single target. He emphasized that private industry will continue to pursue drug development, but what is needed from NIH is more effort into understanding the underlying and interacting factors that lead to AD/ADRD; such information might help scientists find ways to prevent and slow disease progression, enabling people to live longer with healthier brains.

ENVISIONING THE FUTURE OF AD/ADRD RESEARCH

Perspectives from Research Funders and Advocacy Organizations

A panel of representatives from nongovernmental funding and research advocacy organizations discussed their perspectives on future research priorities and opportunities to accelerate the translation of basic research discoveries into clinical research. Several panelists underscored the importance of increased, ongoing investment in research given the magnitude of the impact of AD/ADRD across society. Russ Paulsen (UsAgainstAlzheimer's) noted that while mortality from AD in the United States is similar in scale to that of cancer, scientific progress—as measured by the annual number of scientific publications on AD/ADRD—lags far behind. Ian Kremer (LEAD Coalition) added that while increased Congressional appropriations have been welcome and impactful, NIH needs consistent, predictable funding for AD/ADRD research to effectively allocate its resources.

Commenting on the role of public funders of AD/ADRD research, Meg Smith (Cure Alzheimer's Fund) emphasized the importance of addressing gaps in industry focus, such as the repurposing of generic drugs. She also noted that public funding can be used to investigate unproven strategies, which, if promising, may subsequently be pursued by the for-profit sector. Along with direct research support, public funders also have a critical role in research workforce development, Smith said. Kremer and Maria Carrillo (Alzheimer's Association) both discussed the need for continued NIH investment in research to increase understanding of the underlying biology and constellation of risks and other causal factors that contribute to AD/ADRD development and progression. Such research could better inform risk reduction strategies and help expand targets for intervention.

Several panelists emphasized the importance of ensuring AD/ADRD research benefits all affected populations and of designing programs to meet the needs of those living with these diseases. While acknowledging excitement generated by recently approved anti-amyloid drugs for AD, Smith cautioned that the target population and window of timing for these drugs is narrow. "We can't leave everyone else behind," she urged. Kremer added that for those with mixed etiology disorders, clearing amyloid will have limited benefit if people are left with vascular dementia or Lewy body dementia (LBD). He then emphasized the need to improve the generalizability of research results by increasing inclusiveness in AD/ADRD research, reducing exclusion criteria for studies, and investing in recruitment science. Given the persistent health disparities in AD/ADRD, greater emphasis is needed on understanding differences across racial and ethnic groups, said Paulsen. When asked how representativeness can be improved in clinical trials and other studies, Smith said that it needs to be easier for people to find out which studies they are eligible for and that participants need to be compensated for their time. Paulsen emphasized that diversity goals for studies cannot be aspirational, and researchers should work until they reach their target demographics. According to Kremer, relationship building is key. Investing in establishing long-term reciprocal relationships between research institutions and communities is needed, as is focusing on helping to meet community needs before asking for their participation in studies, he said.

A central discussion topic included what can be done to ensure a more patient-centric future for AD/ADRD research. Kremer reiterated the importance of "nothing about us without us." He suggested that one potential mechanism is conditioning research funding on the degree to which a proposed study includes the people most affected by or at risk for AD/ADRD as partners throughout the entire study process. Paulsen then noted research efforts conducted by UsAgainstAlzheimer's to capture what matters most to individuals living with AD and care partners and caregivers across different racial and ethnic groups. Adding to that, Carrillo discussed

how Alz-Net, a voluntary health care provider-enrolled patient network, is designed to capture real-world experiences of patients and their caregivers and care partners, including changes in how they feel or what they observe in response to treatment.

Building on Successes and Lessons from Other Fields

Emelia Benjamin (Boston University) presented lessons from efforts to apply precision medicine approaches to atrial fibrillation, a cardiovascular condition affecting many people in the United States. At the individual level, these approaches entail stratifying patients by phenotype and genotype to better advise clinicians on management strategies. She also described a population-level strategy that stratifies risk of atrial fibrillation onset and complications. Recent guidelines for diagnosing and managing atrial fibrillation introduced a staging approach, which recognizes atrial fibrillation as a disease continuum and informs the application of different intervention strategies at different stages. The strategies at stage 1 (at risk for atrial fibrillation) focus on risk factor modification, whereas those at stage 4 (permanent atrial fibrillation) emphasize therapies to prevent complications, including risk factor modification. Benjamin noted that experience with high-cost therapeutics like PCSK9 inhibitors within the cardiovascular field may serve as a cautionary tale for dementia. She said there is a sizable gap between drug discovery and utility at the practice, patient, and population levels. That gap may stem from such barriers as cost impediments to drug access, complexity of use, marginal value over existing therapies, and unintended consequences, such as increasing health inequities. Benjamin acknowledged that comprehensively addressing social determinants of health requires a broader societal-level effort, but related opportunities exist at the health care system level to increase the diversity of study participants, push research into community settings, and develop innovative methods to analyze intersectional identities and cumulative disadvantage across the life course related to social determinants of health.

Laura Esserman (University of California, San Francisco) spoke about precision medicine approaches for breast cancer and detailed how platform trials can serve as engines for a continuous learning system. The problem with most clinical trials, she noted, is that the trial design often assumes the disease is the same for all participants, and the trials are designed as one offs that are not integrated with clinical care processes. As a result, knowledge is gained slowly and becomes harder to disseminate. Another issue in cancer studies, she said, is that new drugs are often tested in late disease stages, at which point progress is measured in increased lifespan in the range of months. However, a series of clinical trials called I-SPY addresses these deficiencies; I-SPY aims to improve how new breast cancer treatments are evaluated by accelerating knowledge accumulation, prospectively incorporating heterogeneity into trial design through subtyping, testing new therapies in earlier disease stages, and identifying early endpoints that may be predictive of clinical outcomes. The platform trial design with adaptive randomization eliminates the need to stop and start trials to evaluate new drugs. This allows not only changing or introducing new therapies within the trial, but also changing therapies for individual patients during the trial, enabling a more patient-centric approach. Importantly, Esserman stressed that this approach enables continuous learning in a manner more like clinical care. Esserman concluded with lessons potentially relevant to dementia, emphasizing that precision medicine relies on understanding underlying disease biology and that achieving diversity in research participants is crucial but requires concerted effort.

When asked about early screening and potential associated risks, Benjamin stated that screening can be beneficial but is not a panacea. Esserman added that a one-size-fits-all screening approach can be problematic, sometimes resulting in unintended consequences. As with treatment, a personalized approach can benefit screening. She then described a breast cancer screening trial that uses a risk-based approach and differentiates those at risk for fast- versus slow-growing cancer since prevention strategies will differ for different tumor types.

Another issue raised with the panel was data sharing and its practical implementation. Benjamin underscored the importance of data sharing, noting the potential for wasted resources when researchers conduct duplicative studies because they are unaware of results from prior investigations. Esserman stated that platform trials within an academic consortium can facilitate improved

data sharing; while private industry may put drugs into the trial, the consortium controls the data. This not only ensures access for requesters but also ensures that new insights generated from data analyses are fed back into the system for continued learning.

A LIFE COURSE APPROACH TO ADVANCING AD/ADRD RESEARCH

From Early Life to the Oldest-Old

To understand AD/ADRD risk and resilience and how those dimensions translate to prevention and treatment opportunities, research needs to focus earlier in the life course, said Sid O'Bryant (University of North Texas Health Science Center). He noted that analyses using historical data from longitudinal cardiovascular health studies reveal that even early childhood events can impact brain health trajectories. Mark Mapstone (University of California, Irvine) added that genetic contributions to AD/ADRD are set at conception. He suggested that research into factors that modify genetic vulnerabilities could focus on late childhood and adolescence, since there is no reason to wait decades to begin to understand these interactions. Acknowledging challenges in using early-life data to predict the development of late-life sporadic forms of dementia, he proposed focusing initially on more genetically predetermined models such as autosomal dominant forms or dementia in people with Down syndrome.

Findings from such models could then be applied to sporadic forms of disease. Laura Baker (Wake Forest University) proposed capturing data on early-life exposures, which are not routinely collected, as a near-term opportunity to advance a life course approach. Dawn Mechanic-Hamilton (University of Pennsylvania) added that even if exposure data were not collected prospectively, some historical data (e.g., residential records) may be available, from which it may be possible to determine likely exposures in earlier life stages. She noted that another promising opportunity for facilitating the collection of early-life cognitive data involves leveraging digital tools that capture data remotely. Goldie Byrd (Wake Forest University) returned the discussion to prevention by highlighting opportunities to enact policy changes that address early-life exposures linked to AD/ADRD risk, citing changes to educational systems as an example.

While several panelists commented on the importance of studying early life, additional discussions focused on opportunities to learn more about later life stages. Rachel Buckley (Harvard Medical School) emphasized the need for more research focused on midlife and cited the inadequate understanding of the impact of menopause transition on women's brain health as an example. Maria Corrada (University of California, Irvine) said the fastest-growing segment of the U.S. population is people aged 90 and older—referred to as the oldest-old. She noted that the oldest-old have the highest rates of dementia yet are understudied. Existing research, which is limited, has been conducted almost exclusively in predominantly white cohorts. Evidence from a longitudinal cohort study of individuals aged 90 and older suggests that dementia risk factors in this population differ from those in younger elderly groups. Dementia among the oldest-old results from multiple neuropathologic changes, with most cases exhibiting three or more of these changes. In this population, vascular neuropathological changes account for a larger proportion of dementia cases than AD neuropathologies. Unfortunately, Corrada said, the oldest-old are often excluded from research, including intervention studies, because functional disabilities, frailty, and sensory impairment make collecting data from this population difficult. Such limitations may be addressed through future technologies that enable continuous passive data collection.

Maximizing Learning from Longitudinal Cohort Studies

Longitudinal cohort studies serve as an important means of building understanding of brain health across the life course and of the development and trajectory of AD/ADRD in different populations. Several panelists discussed opportunities to maximize learning from cohort studies and addressed the need to ensure cohorts are representative of the broader population, with consideration to race and ethnicity, age groups, and social phenotypes (e.g., socioeconomic status). O'Bryant suggested that conducting community-engaged research and recruiting from communities instead of specialty clinics will increase cohort representativeness and generalizability of the research. Community engagement needs to happen early in the study process, said Mechanic-Hamilton, so that the result is a partnership instead of a one-way conversation on what researchers want to do. Byrd

added that the approach to working with communities is important, and researchers should be sensitive to communities' needs and focus on building trust and trustworthiness. Baker emphasized the need for budgeting adequate resources to effectively engage with communities to ensure not only that recruited populations are representative but also that diversity is not lost during the study due to poor retention.

One challenge with cohort studies, said Buckley, is that they represent a single snapshot, limiting generalizability. Multi-cohort analysis can be used to study questions where effect sizes may be small but contributions to understanding AD/ADRD across the life course are very meaningful. She noted that efforts are underway at the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium to harmonize different data across multiple cohorts. O'Bryant emphasized the importance of data access from individual cohort studies to enable this multi-cohort analysis and suggested a need for infrastructure to simplify retrieving and combining data from different data warehouses. An additional need, said Mapstone, is addressing the shortage of trained data scientists with the skills and biological understanding to do this kind of analysis. When large cohort studies collect data in different ways, merging and creating an integrated interpretation of data across data sets becomes difficult and labor intensive. One way to reduce challenges related to retrospective data harmonization is to gather investigators of different cohort studies early in the planning stages of the study to discuss harmonization approaches so that more consistent measures and tools are used, said Baker.

The banking of samples was discussed by several participants as another opportunity for maximizing learning from cohort studies. This is the dawn of a new era for precision medicine, AD/ADRD biomarkers, and multi-omics, said Buckley. There may be things that investigators cannot necessarily imagine for current cohorts but that could be leveraged in future research, and banked samples will be important for that, she added. Byrd noted that beyond blood and plasma, banking donated brains and samples from lumbar punctures will be valuable but acknowledged that accessing these samples is harder. This is where community engagement and understanding cultural nuances and community concerns are important, she said.

INNOVATIVE TOOLS FOR TRACKING BRAIN HEALTH AND AD/ADRD

Realizing the Promise of Digital Technologies

One size does not fit all when it comes to digital tools and technologies, emphasized Jeffrey Kaye (Oregon Health and Sciences University). He noted a vast array of capabilities that can be realized with these technologies and mentioned that it can be helpful to map the different tools to the continuum of use cases related to AD/ADRD, including prediction, diagnosis, treatment, and management.

Yannis Paschalidis (Boston University) began by noting that current practices for diagnosing AD/ADRD, which rely on a neuropsychological exam and evaluation of a conventional biomarker (e.g., MRI and PET imaging), are not particularly scalable and can accentuate disparities given that this screening level may be available only in well-resourced settings. Digital data coupled with artificial intelligence (AI), he argued, offer a path toward a scalable diagnostic method that can be used remotely and implemented globally, independent of language or social norms, enabling frequent, cost-effective screenings. To illustrate these technologies' diagnostic capabilities, Paschalidis described his group's use of AI and digitalized data from conventional neuropsychological exams (drawings, voice recordings), combined with basic demographic data, to develop classifiers that assess participants' cognitive status (normal cognitive status, mild cognitive decline, or dementia). Using similar AI-based methods, the group also developed a tool that predicts whether individuals with mild cognitive impairment may progress to dementia within six years.

Kaye discussed how digital technologies could support and accelerate developing new AD/ADRD treatments. Such tools can enable more inclusive, culturally relevant study designs that also measure more meaningful outcomes for people living with AD/ADRD (e.g., functional outcomes). Wearables and other sensors can collect data in the environments in which people live and capture that personal context and experience, he said. Additionally, Kaye noted that the ability to collect multiple complementary data (e.g., sleep, computer use, walking

speed) on a continuous basis may reduce the necessary sample size for intervention trials, enabling more trials to be conducted with a given level of resources.

A key issue when evaluating digital technologies is determining how best to obtain ground truth, said Diane Cook (Washington State University). Ground truth data are referential data obtained by observations or measurements and are considered to be accurate or "true." Such data are often used to calibrate models and machine learning algorithms. Cook noted that while digitally recreating conventional clinical markers of cognitive health and impairment currently collected with pen and paper assessment is possible, whether this is the best way to determine the success and usefulness of digital health technologies and machine learning approaches is unclear. Rather than defining success based on how well a tool predicts existing clinical markers, she suggested looking at value related to monitoring and predicting functional ability and quality of life using a person's own baseline for comparison. Kaye proposed moving away from the concept of ground truth or gold standards and suggested that existing clinical assessments such as the clock drawing test be considered as reference standards for benchmarking.

Discussing academia's role in realizing the promise of digital technologies for AD/ADRD research, Kaye emphasized the importance of experimentation and small-scale, proof-of-concept development, to which industry may not be as well suited. Cook indicated academia's advantage in engaging learners and their creativity and innovation. A challenge, Kaye noted, is the inability of universities to compete with industry salaries. Paschalidis added that the difference in available resources—including computing power—between industry and academia increases the likeliness that universities will fall behind and suggested creating national-level computational resources to support academic researchers. When asked about potential concerns regarding privacy and confidentiality related to digital tools and data access needs, Kaye explained that procedures exist for protecting data, but determining which to use depends on how data are used and for what purpose. Paschalidis mentioned de-identification, encryption, federated learning methods, and the generation of synthetic data as possible data-protection approaches.

Advancing Fluid Biomarkers

Biomarkers are used for several purposes across the AD/ADRD clinical continuum, including diagnosis, treatment decisions, and evaluation of intervention impacts, said Charlotte Teunissen (Amsterdam University Medical Center). As disease-modifying treatments become available, blood-based biomarkers play an important role in diagnosis and in guiding treatment. For example, explained Teunissen, amyloid positivity is necessary for treatment with anti-amyloid drugs, but patients with LBD or frontotemporal dementia (FTD) may not be current candidates for amyloid-modifying treatments despite having amyloid co-pathology.

The goal, Teunissen said, is to develop a panel of diagnostic biomarkers that can provide more clinically relevant information than use of single biomarker assays. Teunissen then described efforts to develop immunoassays that could be used in subtyping patients. Biological subtypes can influence the course of disease and may guide the use of specific treatments that are most effective for selected patient populations. For example, mass spectrometry has been used to identify five subtypes within a population of AD patients, including an inflammatory subtype and a subtype related to amyloid processing. The latter may suggest a benefit from amyloid therapy while anti-inflammatory treatments may be more effective for the former. Translating mass spectrometry results to immunoassays may result in a tool that can be used for prediction and could be incorporated into clinical practice with adequate validation, said Teunissen.

Considerations for Real-World Implementation

During a panel discussion on moving from discovery to strategic and equitable implementation of novel tools across global populations and diverse settings, Niranjan Bose (Gates Ventures) said that implementation science can guide methods and strategies used to facilitate tool uptake. In this process, he emphasized, it will be important to document not only successes but also failures and lessons learned. The Davos Alzheimer's Collaborative is doing such work to understand barriers and facilitators to adopting and implementing novel tools, said Tim

MacLeod (Davos Alzheimer's Collaborative). MacLeod described a three-year study that examined integrating blood-based biomarkers and digital cognitive assessments into primary care settings in 12 different countries. While evidence on the feasibility of health systems adopting novel tools was encouraging, barriers to the scalability of these tools also existed and, in aggregate, resulted in significant impediments to realizing the benefits of novel diagnostics. Some problems included integrating tools into existing workflows and issues with current incentive structures, such as the granularity of billing codes. Workforce training was another barrier. Key takeaways from this work include the need to invest in implementation research; mitigate time and resource constraints in clinical practice settings by making knowledge more useable through such strategies as blueprints and toolkits; and build communities of practice to facilitate the sharing of learning and experience, said MacLeod. David Cutler (Harvard University) then shared insights on real-world implementation from a health economics perspective: Uptake will be lower for more complex technologies, for situations when specialization is required for use, or in instances when technology use causes inconvenience. Monetary incentives are another significant determinant of adoption, he said.

Agustín Ibáñez (BrainLat at Universidad Adolfo Ibáñez and Global Brain Health Institute) highlighted issues related to diversity and disparities when considering implementation. He cautioned against aiming for universal computational models that can be applied to every population, proposing instead a need for local data, local reference standards, and locally tailored models.

When asked about incorporating lessons from implementation experiences into early research and development processes, Debby Tsuang (University of Washington) underscored the importance of investing in understanding study communities and their nuances and cultural elements. Understanding peoples' comfort levels with different processes and technologies is important, she said. For example, a study conducted among older individuals during the COVID-19 pandemic unexpectedly found that some participants considered online assessments challenging. Talking with people about how they might use a tool is not enough, said Cutler; efforts to pilot how people actually use tools in real life are needed because tools are unlikely to be adopted if they do not fit seamlessly into people's lives.

UNDERSTANDING AD/ADRD RISK, RESILIENCE, AND ETIOLOGY

The Exposome and its Contribution to AD/ADRD Risk

The concept of the exposome has continued to evolve over the last couple of decades, said Gary Miller (Columbia University); however, it generally denotes capturing as much information as possible on the factors that influence human health (e.g., chemical, biological, physical, and psychosocial factors). Data on the exposome can come from many different sources, including self-reporting, wearables, and satellites. Exposures may also be inferred from residential histories, for example, by overlaying air pollution and pesticide maps on residential information, said Miller. Jennifer Weuve (Boston University) added that environmental lead exposures similarly require consideration of historical residential information. Given the wealth of research on such exposures, Weuve suggested improving collaboration between dementia researchers and environmental health scientists to better understand interactions between the exposome and AD/ADRD.

Exposures can also be assessed by measuring internal signatures within the body. Miller said his laboratory uses high-resolution mass spectrometry to measure exogenous (e.g., chemicals) and endogenous (e.g., metabolites) features within blood samples. Using network science, exposures identified with mass spectrometry (e.g., markers of poor diet, air pollution, and pharmaceuticals) can be connected to underlying biological systems and AD/ADRD biomarkers, such as pTau181. Analyzing samples from different cohorts featuring diverse populations enables the identification of distinctions in molecular signatures across different racial and ethnic groups, which may translate to differences in vulnerabilities.

Lisa Barnes (Rush University) spoke in depth about exposome research and links to AD/ADRD risk in diverse populations. She noted that there is a growing literature on factors within the exposome that are associated with aging outcomes among African Americans, many of which are modifiable by individuals. Contextual neighborhood factors may not be modifiable by individuals but

are often influenced by housing and other social policies. Using a social vulnerability index developed by the Centers for Disease Control and Prevention, Barnes' research showed an association between higher neighborhood-level social vulnerability and lower baseline-level global cognition, including episodic memory, among African Americans. Barnes concluded by highlighting areas of promising research that need to be expanded on in diverse populations. These include understanding how social determinants of health modify cognition and AD/ADRD risk and how this information can be used to address disparities; improving tools for measuring cognition and underlying biological features linked to cognition and disease risk; identifying resilience markers that may be targets for intervention; and assessing heterogeneity across intersections of social identities, such as race and education.

Several workshop participants echoed the need to examine the intersections of social determinants with AD/ADRD biology and risk. O'Bryant said researchers need to stop studying biology in the absence of sociocultural and environmental influences and proposed layering a health disparities framework on a systems biology approach. Amy Kind (University of Wisconsin) stressed the importance of integrating deep social phenotyping with deep biological phenotyping. She highlighted her group's efforts to link social factors—collected through archival tracings such as residential histories, military records, and birth and death certificates—to biological features using samples from biorepositories (e.g., brain banks) to elucidate interactions among different factors. She also noted that social exposome measures are being used to inform social policies at national and local levels, providing opportunities to study these natural experiments to understand their impact on brain health.

Interactions Between Genetics and the Exposome

Margaret Pericak-Vance (University of Miami) spoke about current efforts to study interactions between the exposome and genetics. Through initiatives like the Alzheimer's Disease Sequencing Project, more than 80 regions of the genome have been identified as containing risk factor genes for late-onset AD. Additional genetic variants have been shown to have protective effects. Key AD-related pathways identified based on genetic findings include inflammation, lipid metabolism, and endocytosis, she said. Genetic analysis also confirmed the critical role of ancestral background in AD risk and protection, evidenced by risk-effect variation for the APOE4 allele across diverse populations. APOE4 is a known risk factor for late-onset AD, but initial studies primarily involved individuals with European ancestry; subsequent findings revealed lower APOE4-related risk among African Americans. These findings underscore the importance of including diverse populations in studies, said Pericak-Vance. She ended by stressing the need to identify interactions between genes and exposures that jointly affect AD/ADRD risk and progression. Such information would guide prevention strategies focused on exposure modification, particularly for individuals at greatest risk. However, accessing data sets that include both genetic and exposome data has been a barrier to such analyses, she said.

AD/ADRD Neuropathology and the Link to Dementia

One perplexing problem in dementia research is the inconsistent, nonlinear relationship between the biology of the disease and the clinical phenotype, said Zaven Khachaturian, founding editor-in-chief of *Alzheimer's & Dementia*. No single etiologic factor is responsible for this heterogeneous, polygenic condition, and the pathology is often mixed. Clinical symptoms can be viewed as emergent behaviors, which are often context dependent. Understanding the complex relationship between neurobiology and clinical features will require a multi-scale modeling system and a unifying conceptual framework, said Khachaturian.

Delving deeper into the neuropathology of dementia, Virginia Lee (University of Pennsylvania) noted overlap in pathologic features found in neurodegenerative diseases. Tau-mediated neurofibrillary tangles—a hallmark of AD—can also be found in FTD. Similarly, she said, Lewy bodies comprising alpha-synuclein protein aggregates are features of LBD and Parkinson's disease with dementia. A critical question her group has tried to address is whether such shared pathologic features are the same in different neurodegenerative diseases. The answer has important implications for treatment strategies. For example, if a drug was found to be effective in removing neurofibrillary tangles in AD, a reasonable question is

whether it would also be effective in removing tangles in FTD. Preliminary evidence suggests that there are differences that distinguish pathologic features like Lewy bodies and neurofibrillary tangles in different neurodegenerative diseases, said Lee.

Bart de Strooper (UK Dementia Research Institute) suggested a need for more precision in how AD is defined, focusing specifically on the presence of plaques and tangles. In cases of mixed pathology, which, he reiterated, is the predominant form in older patients with neurodegenerative disease, it is important to specify which forms of disease are present rather than calling them all AD. This will have implications when considering therapies, since personalized approaches should be based on the pathologies present, he said. Khachaturian agreed with the need for more precise characterization of the disease and suggested the name "Dementia Alzheimer Syndrome."

Several workshop participants commented on needing to better understand why some people with neuropathology do not develop dementia. Gill Livingston (University College London) emphasized that many people with amyloid or other neuropathologies will never develop dementia; understanding this is important, as people care more about how they function than about what is happening in their brains. Jürgen Götz (University of Queensland) said that mechanisms for cognitive reserve are understudied, and more research on these mechanisms is needed. David Bennett (Rush University) underscored the complexity involved in understanding cognitive decline, noting that in addition to pathologies, there are resilience indices and interactions that need to be considered.

Molecular and Cellular Mechanisms Contributing to AD/ADRD Neuropathology

The mechanistic interactions among the many etiologic factors, risks, and susceptibility genes for AD/ADRD are not well understood, said Khachaturian, but the disorder's complexity indicates multiple upstream variables. He emphasized a need to understand what each contributes and how they interact. Götz proposed that recently published aging hallmarks could provide a framework for analyzing the manifestation of AD-associated pathology and highlighted opportunities to better integrate aging and AD/ADRD research.

To kickstart discussing specific molecular and cellular mechanisms contributing to neurodegenerative diseases, de Strooper described a cascade that begins with a biochemical phase and culminates in AD clinical phenotypes. Acknowledging upstream triggers (e.g., environmental exposures, defective clearance mechanisms), he proposed that disease begins with the aggregation of the amyloid-beta peptide. This biochemical phase is followed by a cellular phase during which cells in the brain react to the aggregation of amyloid-beta. A major factor in the cascade is the generation of an innate inflammatory reaction mediated by microglia, which triggers reactions from other cells, including abnormal tau accumulation and neuronal cell death. Resulting brain damage, some potentially irreversible, leads to the clinical phase and dementia. This scheme can inform the development of treatments, he said. A challenge with current anti-amyloid treatment is that the effectiveness of a drug targeting the biochemical phase is not being measured until the clinical phase. This contrasts with the cancer field, where there is agreement that treatment should ideally occur before symptoms emerge. For antibody-based therapeutics, de Strooper suggested moving toward prevention earlier in the cascade but added that targeting other aspects of the biochemical and cellular phases is also important.

Three panelists subsequently elaborated specific molecular and cellular mechanisms related to AD/ADRD. Ralph Nixon (New York University) described pathobiological processes early in the biochemical phase, which precede the development of hallmark neuropathologies (e.g., plaques, tangles), that relate to endosomal-lysosomal system dysfunction. This intracellular system plays a key role in the sorting and degradation of proteins and other macromolecules. Causative genes associated with AD and other neurodegenerative diseases have been linked to the endosomal-lysosomal system, he said. Dysfunction in this system, such as disturbed or insufficient acidification of lysosomes, interferes with degradation of beta-amyloid, leading to pathological accumulation of beta-amyloid aggregates within select neurons. When these neurons die, amyloid plaque remains in the brain tissue. Nixon indicated that the accumulation of other proteins in other neurodegenerative diseases may also relate to failure to clear these proteins through the

lysosomal system, suggesting that more attention to this early-stage intracellular dysfunction is needed when considering potential targets for intervention.

Bruce Lamb (Indiana University) spoke about immune pathways and the role of microglia. Genetic studies have shown that many genes associated with late-onset AD are related to the innate immune system. Animal models have shown that following the deposition of amyloid, microglia—innate immune cells in the brain—transform from a homeostatic state to a disease-associated phenotype and accumulate around plaques. Downstream signaling after microglial activation can lead to tau pathology. Evidence of roles for the adaptive immune system and cellular immune responses is also increasing, but these, like the innate immune response, need to be better understood, said Lamb.

Ameer Taha (University of California, Davis) described his research on lipidomics and its relation to inflammation. He suggested an alternative to preventing proteinopathy in AD/ADRD: resolving subsequent inflammation. This happens in the brain through pro-resolving lipid mediators made from the enzymatic oxygenation of polyunsaturated fatty acids. A deficit in the free form of these pro-resolving lipid mediators occurs in AD—a situation his laboratory has shown arises from a depletion in the pool of bound or esterified lipid mediators, the predominant form of these lipid mediators in the brain. Interestingly, he said, air pollution also reduces esterified pro-resolving lipid mediators, suggesting some convergent pathways. Taha said more research is needed to understand the biology of pro-resolving lipid mediators (e.g., the regulation of esterification and release) and to explore how dementia risk factors like environmental exposures modify this system and impair inflammation resolution.

Khachaturian expanded on the presentations by emphasizing the importance of each described pathway and the benefit of linking event cascades to form a broader picture and better understand the sequencing of various elements. He noted that other pathways and changes (e.g., vascular, metabolic, energetic) take place prior to the appearance of hallmark proteinopathies and also need to be better understood. Integrating these ideas will require a conceptual modeling approach, he said. Götz added that such modeling needs to account for feedback mechanisms, noting that the sequence of events may be nonlinear and that some pathways may converge while others may act independently.

Bennett described efforts to use deep multi-omics profiling of donor brains to create pseudotime trajectories, which represent the molecular distance from no cognitive impairment to Alzheimer's dementia. By integrating layers of different omics data, his group identified three different molecular paths leading to dementia. Going forward, Bennett said, these data need to be integrated with other data collected from living individuals (e.g., clinical phenotype data, imaging and fluid biomarker data). Computational tools will be needed to link these data in a meaningful and actionable way, he said.

ADVANCING PREVENTION AND TREATMENT STRATEGIES FOR AD/ADRD

Pharmacologic and Nonpharmacologic Interventions

Describing the current AD/ADRD drug-development landscape, Jeffrey Cummings (University of Nevada, Las Vegas) said that at present there are 171 clinical trials assessing 134 drugs for AD and noted the number of evaluated therapeutics is an order of magnitude less than what would be expected for cancer. Importantly, said Cummings, many of the drugs being evaluated target mechanisms and pathways that are not specific to AD, such as inflammation and synaptic plasticity, and are therefore applicable to other neurodegenerative diseases (e.g., Parkinson's disease, LBD, and FTD).

Michael Irizarry (Eisai) spoke on opportunities for industry–academic collaborations to help advance drug discovery and development for AD/ADRD. Regarding discovery, he highlighted an example: a partnership between Eisai and University College London to create a portfolio of new therapeutics for neurodegenerative diseases, which resulted in seven projects covering a range of targets (e.g., tau, microglia, lysosomes). One advanced and is currently in Phase II clinical trials. In the clinical development space, Irizarry noted Eisai's engagement with academic clinical trial consortiums, including the Alzheimer's Clinical Trials Consortium and the Dominantly Inherited Alzheimer Network Trials Unit. Considering industry participation in such clinical trials, having trials fit into the drug candidate's overall development program

and timeline is important, as is understanding whether studies will support regulatory submission and approval.

Shifting the discussion from pharmacologic to nonpharmacologic interventions, Kristine Yaffe (University of California, San Francisco) described a recent clinical trial focused on personalized interventions designed to reduce dementia risk factors. Recognizing diversity in the risk factors people have, including across racial and ethnic groups, Yaffe noted that a one-size-fits-all approach will be ineffective. The Systematic Multi-Domain Alzheimer's Risk Reduction Trial (SMARRT) took a personalized approach by identifying relevant risk factors (e.g., physical inactivity, hypertension, poor sleep) for each participant and asking participants which they would want to work on and how. The hope was that this participant-driven approach might improve adherence, a common problem in behavioral interventions. Over the two-year intervention period, both groups improved in cognition from baseline, but the statistically significant improvement in the intervention group was 75 percent greater than that in the health education control group. Changes in the risk factor composite score showed that the intervention resulted in behavior changes. Given their general low risk and low cost, such risk reduction strategies are already being recommended to the public, but more work is needed to expand prevention efforts earlier in the life course and to evaluate these efforts in more diverse populations, said Yaffe. She noted additional important actions: partnering with the pharmaceutical industry to examine how risk factors may modify the effects of different pharmacologic agents and advancing combination therapies that include both pharmacologic agents and nonpharmacologic risk reduction strategies. Kirk Erickson (University of Pittsburgh) agreed, cautioning against siloing pharmacologic and nonpharmacologic approaches.

Livingston emphasized the importance of targeting risk reduction interventions to those most likely to develop dementia, including people in minority ethnic and lower socioeconomic groups. With a five-year grant cycle, the ability to observe an intervention's impact on cognitive outcomes is much higher when targeting people at high risk, she said. As an example, she described a project involving the engagement of people at food banks in designing an intervention to which they would be likelier to adhere, noting that the clinical trial results are not yet available. Kind urged considering opportunities for policy-level interventions that can modify the exposome, such as environmental lead mitigation. This will require partnering with multiple levels of government and using a multidisciplinary approach, she said.

Improving Clinical Trials

Cummings noted that drug development for AD takes about 13 years to move from the laboratory to the Food and Drug Administration. By the time a drug reaches patients, it is using decade-old technology and information. He said bridging this gap will require transformational, not incremental, change.

Recruitment is a major bottleneck for testing drugs. To address this challenge, Cummings proposed a large initiative that he called "America's Brain Health Initiative." One approach to public engagement could feature outreach during sign-up for Medicare or other retirement benefits. Using multiple approaches to screening (e.g., online, face-to-face) would maximize the ways in which people could engage with the initiative, he said. Depending on results of blood-based biomarker tests, follow-up with at-risk individuals, education about risk reduction strategies, and presentation of options for participating in clinical trials would occur. Those wishing to participate would then be matched with a clinical trial and referred to a trial site.

Cummings suggested several opportunities for improving clinical trial efficiency for AD/ADRD, including operational (administration), scientific (trial designs and methods), and workforce development (diversity and training). Instead of building infrastructure for each new clinical trial, he encouraged expanding platform trials for AD/ADRD, referencing the successful I-SPY platform trial series discussed earlier. Each trial could test multiple drugs using a shared placebo group and biomarkers (including digital biomarkers) to evaluate effect. A hub-and-spoke design could centralize much of the needed trial infrastructure (e.g., biobanks, informatics) while running trials at multiple sites embedded in communities, including those for underserved groups.

Rema Raman (University of Southern California) also addressed facilitating greater diversity in study populations, noting its critical role in achieving external validity—namely, the extent to which trial settings and participants represent target populations and contexts in real-world settings. Clinical trials, including those for AD/ADRD, are often not representative of the intervention's target population across demographic, cultural, social, and geographic characteristics. To address this gap, Raman highlighted several ways to increase trial inclusivity and access, including moving trial screening procedures into communities; making prescreening methods site and study agnostic, enabling participants to choose which trial they want to join; creating partnerships between trial sites and community organizations (e.g., hospitals, community centers); and establishing international clinical trial networks. Irizarry noted the value of not only embedding trial sites in communities but also bringing trial activities directly to participants' homes. Bennett agreed, suggesting this may improve retention and follow-up rates and population representation.

Several panelists commented on the need to improve sharing of clinical trial data to advance prevention and treatment interventions for AD/ADRD. Raman emphasized that a single trial may lack adequate power to detect intervention effects in the many subpopulations of interest; also, open data and image- and sample-sharing are needed to conduct rigorous meta-analyses. A lot of data are already available, she said, but they are distributed across different systems rather than integrated within a single framework. Cummings underscored the costs associated with data sharing and emphasized the need to account for this in budgets, both in industry and academia. Irizarry then noted that there have been examples of successful collaboration between academia and industry to integrate data from multiple clinical trials, which could offer a model to build upon. Finally, Bennett suggested that data sharing could be required for all clinical trials, including those within industry, and NIH could support a repository to host the data.

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REVIEWERS To ensure that it meets institutional standards for quality and objectivity, this Proceedings of a Workshop—in Brief was reviewed by **Jeffrey L. Cummings,** M.D., Sc.D., University of Nevada, Las Vegas. **Leslie Sim,** National Academies of Sciences, Engineering, and Medicine served as the review coordinator.

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