

# Proceedings of a Workshop

August 2021

IN BRIEF

## Implications for Behavioral and Social Research of Preclinical Markers of Alzheimer's Disease and Related Dementias Proceedings of a Workshop—in Brief

On June 28–29, 2021, the National Academies of Sciences, Engineering, and Medicine held a virtual workshop, “Behavioral and Social Research and Clinical Practice Implications of Biomarkers and Other Preclinical Diagnostics of Alzheimer's Disease (AD) and AD-Related Dementias” (AD/ADRD). The workshop was sponsored by the National Institute on Aging (NIA) with the primary objective to engage in meaningful discussions about the implications of biomarkers and other preclinical diagnostics of AD and ADRD and to generate ideas for future research that might be of interest to the NIA. Lis Nielsen (NIA) explained to workshop participants that developing tools to measure preclinical changes on the path to dementia can help identify people early enough for them to benefit from eventual cures, route them to appropriate care, help them avoid potential harms due to functional impairments, and help them take steps to plan for their futures.

### OVERVIEW AND CONTEXT OF BIOMARKERS AND OTHER PRECLINICAL DIAGNOSTICS: PANEL PRESENTATIONS

Alzheimer's disease has a huge impact on the nation's public health, said Howard Fillitt (Alzheimer's Drug Discovery Foundation): more than 6 million Americans have clinical AD, and nearly 47 million Americans are estimated to have preclinical AD. Moreover, it is estimated that the number of people with preclinical AD will increase to 76 million by 2060. Given these numbers, said David Bennett (Rush University), “we cannot treat our way out; instead, we can focus on prevention to reduce the human and economic toll of dementia on individuals, families, and society.”

The good news, said Reisa Sperling (Harvard Medical School), is that we can now detect and monitor AD even before clinical symptoms are apparent. During the preclinical stage of AD, there are changes in the brain and in cognition that can be detected with very sensitive markers. For example, PET imaging can reveal evidence of amyloid and tau pathology, and these markers can predict the risk of cognitive decline, she said. However, there is a great deal of heterogeneity, with both sex and age influencing the relationship between preclinical pathology and the risk of decline. The data on race and ethnicity are scarce, said Sperling, but the findings thus far suggest that biomarker associations with genetic factors and risk of future cognitive decline may also be heterogeneous with respect to race. She stressed that once people become symptomatic with mild cognitive impairment or AD dementia, tauPET imaging reveals rapid change, and it may be too late to intervene. Sperling said that during the preclinical phase of AD, there are also measurable effects on learning capacity, depression, and anxiety.

There is a great deal of heterogeneity in the rate of cognitive decline in late life for all persons, said Bennett. Research seeks to examine this heterogeneity and to understand the degree to which late-life cognitive decline is driven by age-related neuropathologies. This is a complex area, he said, with a huge number of

neuropathologies contributing to cognitive decline and many individuals having a combination of pathologies. Moreover, more than one-half of cognitive decline is not explained by age-related neuropathologies. The effect of any given pathology varies widely, depending on what other pathologies are present, and there are multiple pathways to ADRD. Given this complexity, said Bennett, how do we identify appropriate targets for preventing, delaying, or reversing cognitive decline? Eliminating any individual pathology (e.g., AD) will only prevent a small proportion of decline, so it may not be practical or wise to develop biomarkers and therapeutics for each pathology. Instead, he said, it might be more prudent to consider targets that cut across the range of pathologies and lead to dysfunction and degeneration.

The majority of the estimated 47 million people who are in the preclinical phase of AD are under the age of 70, said Fillitt. This is a robust group of people to target for intervention. There are three prevention intervention strategies: primary prevention to lower the risk of amyloidosis (the buildup of amyloid in the brain), secondary prevention to lower the risk of mild cognitive impairment due to AD, and tertiary prevention to lower the risk of progression from mild cognitive impairment to AD. The short- and long-term effects of these strategies differ due to the lag time between amyloidosis and clinical AD. For example, modeling suggests that focusing on primary prevention instead of secondary or tertiary prevention would result in the lowest prevalence of AD by the year 2060, but it would also result in the highest prevalence of AD in the 15 years immediately after implementing such an approach. In addition, Fillitt said, it is worth considering whether prevention is a cost-effective approach. The current biomarker tests and treatments are expensive, and unless less expensive alternatives are developed (e.g., tests similar to cholesterol screening), the costs of screening and treatment to individuals and society (Medicare and commercial insurers) may be prohibitive. It is not clear at this point, said Fillitt, whether there is societal or individual willingness to pay for prevention of AD.

Given the capability of detecting AD early, Sperling listed several of the potential reasons to disclose increased risk to individuals with preclinical markers: there are a number of therapeutics in the pipeline that may delay or prevent AD; there are ongoing trials studying primary and secondary prevention of AD; and lifestyle and other health interventions (e.g., physical activity) may be protective against cognitive decline though they may have differential effects depending on biomarker status.

Sperling noted that we do not wait until symptoms appear for diseases such as cancer, HIV, or osteoporosis. Why would we wait for cognitive impairment to intervene for AD? However, she cautioned, there are some thorny issues that need to be resolved to realize the full potential of AD biomarkers. Currently, there are inadequate data for individual prediction of dementia risk: most of the data were acquired in nonrepresentative populations (e.g., highly educated people with concern about AD), and there is no legal protection against discrimination related to biomarkers. Moving forward, said Sperling, more research is warranted on a number of issues, including heterogeneity and the resilience of some individuals, the relationship among multiple biomarkers, the application of these biomarkers to broader populations, and the impact of disclosure on individuals, families, and health care systems.

## **ADDRESSING HEALTH EQUITY ISSUES IN STUDIES OF PRESYMPTOMATIC INDIVIDUALS: PANEL PRESENTATIONS**

“Brain health equity,” said Jennifer Manly (Columbia University), is the idea that all people have a fair and just opportunity to have as much brain and cognitive health as possible. To achieve this vision, medical professionals could identify disparities, focus on those with worse outcomes and few resources, and create environments in which people have access to information, diagnosis, and care. The diagnosis of ADRD is more likely to be missed and delayed in Black and Latino populations, said Manly. At the same time, said Lisa Barnes (Rush University), these populations are at increased risk of ADRD, and they are underrepresented in research efforts. Barnes stated that funding researchers with proven experience in underrepresented groups, as well as studying heterogeneity within racial groups individually would provide a more holistic understanding of how ADRD affects different races and ethnicities. Hector González (University of California, San Diego), noted that the number of Latino elders is set to quadruple by 2060 and will account for the largest increase in individuals with dementia.

Communities of color have unique risk factors, such as discrimination and stress, that increase the risk of cognitive decline and other health issues and can also contribute to underrepresentation in research, said Barnes. In addition, said González, Black and Latino populations have a higher prevalence of diabetes and hypertension, both of which increase the risk of cognitive decline. He added that there is growing but

incomplete evidence that there may be racial differences in the significance of biomarkers, and there is notable heterogeneity in genetics, pathology, and cognitive decline both between and within racial groups. For example, said González, the prevalence of the APOE4<sup>1</sup> allele is lower among Latino populations, but evidence suggests that the allele is actually protective against cognitive decline in Native American populations.

Barnes said that the overrepresentation of White participants in research samples threatens the overall generalizability of findings and limits the evidence base for translating findings into clinical care. She identified several barriers to increasing the participation of underrepresented populations in AD research: lower levels of awareness of dementia, variable perceptions and beliefs about dementia, and a legacy of distrust and poor linkages between communities of color and researchers. To address these barriers, Barnes said, there is a push to raise awareness and remove the stigma of AD, to work with trusted partners from the community, to recruit and train a diverse research workforce, and to ensure that research is culturally relevant to diverse populations.

Manly outlined additional approaches for making research more inclusive and equitable: research should be a community-based process from the beginning, with research questions and goals defined by and specific to the community; researchers should listen and learn long before recruiting participants; and researchers should repair and invest in the community by providing resources for unmet needs and acknowledging mistakes of past researchers. She emphasized the importance of representative sampling and said that oversampling of some groups is often necessary to have sufficient power to detect differences across groups.

Manly identified recruitment approaches that she considers ineffective for inclusive research, including recruiting through clinics or patient registries, ads or fliers, talks in churches by White researchers, cognitive screens in primary care, relying on diverse trainees to create a diverse cohort, and using inclusion/exclusion criteria that differentially exclude diverse populations (e.g., hypertension, English speaking). These approaches are problematic for many reasons, she said. For example, findings from clinic-based cohorts may not generalize to the community, and enrollment factors can lead to biased results. She pointed out that the current knowledge about biomarkers assumes a patient who is White, English speaking, well educated, insured, and has transportation and other resources.

There is a need, said Barnes, to expand research on biomarkers to identify and understand racial differences—to include other pathways that may be relevant to cognitive decline (e.g., immune function) and to assess any association between biomarkers and social determinants of health—to identify potential prevention approaches. González added that research should be focused on cognitive and clinical endpoints that are relevant to patients, rather than, for example, measurements of amyloid and tau. Outcomes such as significant cognitive decline “are why patients come to us in the first place,” he said. There is a demand to identify accessible, cost-effective, and scalable surrogate markers of dementia, said González. Manly noted that moving forward, it is critical that research efforts are centered on equity and that we are “honest about what we know and we do not know.”

## DISCUSSANTS' PERSPECTIVES

In response to the presentations, four designated discussants shared their key observations and take-home messages: Yakeel Quiroz (Harvard University), Keith Whitfield (University of Nevada, Las Vegas), Lauren Parker (Johns Hopkins University), and Crystal Glover (Rush University).

- Clear, culturally appropriate communication between researchers and communities is essential to ensure that patients and families can make informed decisions. (Quiroz)
- There is a need to acknowledge the heterogeneity both between and among underrepresented groups. Unique strategies may be necessary to facilitate participation of underrepresented groups. (Quiroz)
- Broad eligibility criteria to enable broader access to studies. Consider performing data collection, especially cognitive testing, in non-English languages to make studies more inclusive. (Quiroz)
- Researchers cannot be “part-time visitors” in the community, they must take the time and effort necessary to connect and develop trust before research begins. (Whitfield and Parker)

<sup>1</sup>APOE4 is the gene that encodes Apolipoprotein E, a type of lipoprotein that is implicated in the development of AD.

- Researchers should learn and address the health concerns of the target community itself, rather than imposing the priorities of the researcher. (Whitfield)
- There is a need to understand and incorporate diverse participant perspectives into research, including self-perceptions, behaviors, decision making, and lived experiences. This requires expanding methodological approaches via mixed-methods research, both qualitative and quantitative, to understand the life course and exposures of individuals, and drawing on several fields of research. (Glover)
- People in the community should be included and engaged throughout the entire research process. (Glover)

## IMPLICATIONS OF DECISIONS ABOUT HOW AND WHEN TO DISCLOSE A DETECTION OR DIAGNOSIS: PANEL PRESENTATIONS

### FACTORS TO CONSIDER

There are many factors to consider when deciding to screen for or disclose preclinical diagnoses of AD, said Ron Brookmeyer (University of California, Los Angeles). These factors include whether the information is clinically significant, whether there are effective interventions, whether the information is actionable, and whether the person wants to know. One important consideration, he said, is the likelihood that a person with a preclinical diagnosis will progress to “full-blown” clinical AD within their lifetime.

To calculate the likelihood—called the “lifetime risk of AD dementia”—Brookmeyer uses a multistate model that includes data on the preclinical state, progression rates, death rates from other causes, age, and gender. For example, the model shows that a 90-year-old male with amyloid plaques has only a 5.4 percent chance of developing AD within his lifetime, while a 65-year-old male in the same preclinical state has a 22 percent chance. The model also provides information about the risk of progression in the shorter term; for example, a 65-year-old White female with amyloidosis and neurodegeneration has a 40.8 percent lifetime risk of developing AD, but only a 10.7 percent risk within the next 10 years. Brookmeyer used this model to determine how many people in the United States will progress to AD within their lifetimes. As Fillet had noted earlier in the workshop, an estimated 46.7 million Americans are currently living with preclinical AD, and Brookmeyer said that 12.6 million (27%) of them will progress to clinical AD.

Using the model, said Brookmeyer, can help clinicians, researchers, and patients interpret biomarker screening tests and their prognostic value for predicting clinical disease. Brookmeyer cautioned, however, that this model uses some data from nondiverse cohorts, and it does not account for other factors such as presence of the APOE4 allele, or vascular risk factors. Improving and refining the model could allow for more individualized risk projections.

### RISK OF OVERDIAGNOSIS

The goal of using preclinical biomarkers is to identify individuals with pathology but normal cognitive function to better target effective therapies to delay or prevent the onset of dementia, said Ken Langa (University of Michigan). However, as Brookmeyer pointed out, most individuals (nearly 75 %) with preclinical disease will not progress to clinical AD in their lifetimes. The paradigm shift from treating those with clinical disease to treating those with preclinical disease raises large risks of overdiagnosis, which exposes patients to the risks and costs of treatment, without the benefit of dementia prevention. In addition, there are multiple pathways to dementia, and a large percentage of cognitive decline is not attributable to AD pathologies, he said.

Given the complexities, Langa raised the question of whether screening for and treating preclinical AD will be worth it. The costs of dementia in the United States are huge, with about \$200 billion spent per year; almost three-quarters of which is related to long-term care. However, the costs of screening and treating preclinical AD would also be enormous, he said, particularly given the fact that the majority of people will not progress to clinical AD. A back-of-the-envelope calculation reveals that treating one-half of the 38 million people who have amyloidosis with chemotherapies or other standard therapies at \$6,000/year treatment would cost \$115 billion; treating them with newly approved Aduhelm at \$56,000/year would bring the price to over \$1 trillion. In addition to the financial costs, assessing the population risks and benefits of screening and treatment would depend on factors such as treatment efficacy, treatment side effects and harms, the rate of false positives, and the rate of patient discontinuation of treatment. To mitigate the risks

and costs of overdiagnosis, said Langa, there is a need to create a tighter link between the preclinical diagnosis and lifetime risk, to do a better job of risk stratification, to ensure that the data used are generalizable to all populations, and to identify lower-cost interventions than those currently available.

### IMPACT OF DISCLOSURE

One of the goals of screening and disclosure, said Vincent Mor (Brown University), is to give patients and families more information to make decisions and prepare for the future. Mor reported on the results of the CARE (Caregivers' Reactions and Experience) study, which is a supplemental study to the IDEAS (Imaging Dementia—Evidence for Amyloid Scanning) study. IDEAS uses amyloid PET scans to gather more information on patients with an unclear diagnosis, and CARE uses surveys and interviews to examine why these patients and their care partners sought a definitive diagnosis of cognitive defects, how they reacted to the results, and what impact the results had on their future plans. The qualitative data, said Mor, showed that when PET scan results were in line with the care partner's perceptions of the patient's cognition (e.g., a positive scan for a patient with cognitive impairment), care partners reported a lack of surprise and a feeling of relief, rather than shock or frustration. When a patient with only mild cognitive impairment received a positive scan result, care partners expressed anxiety.

Researchers also asked patients and their caregivers to answer a hypothetical question: if there were a new treatment that could return your memory to normal but had a risk of death, what is the highest risk of death you would be willing to accept? While 36 percent of patients said they would accept no risk of death, 43 percent said they would accept up to 50 percent, and 21 percent said they would accept a risk of more than 50 percent. A positive PET scan was associated with a willingness to accept a greater risk. Care partners were generally in concordance with patients on risk tolerance. These results, he said, beg the question of whether early diagnosis will translate into more patients who are willing to take unproven or unsafe remedies. There is a need for more research in this area, he said.

### PUBLIC HEALTH PERSPECTIVE

"From a public health perspective," said Carol Brayne (University of Cambridge), "we need to start with people in their communities, in their societies, in their familial groupings." While there is an echo chamber and a special status around dementia, there are many other conditions that affect the elderly, she said. It is critical to balance the attention given to disease areas and age groups and not to allow one area to have "complete dominance." She noted that there are massive disparities in wealth both within the United States and across the world, and an approach that relies on biomarker screening and potential treatment for pre-clinical AD would require a huge amount of energy, materials, and societal resources. We need to consider the impact of exporting this "highly biomedicalized" approach across the globe, said Brayne.

Dementia is a complex syndrome, not an individual disease that has broad implications for individuals, families, and society as a whole. There is a need for research and contemplation about what, specifically, we are trying to address, she noted. Cognitive decline is extremely common in the elderly, and it is on a continuum and entangled with functional and physical decline. Brayne argued that the dementia syndrome is well beyond biomarker reductionism, and to detect all potential changes in the brain that are linked to dementia would require an enormous investment in testing of the general population. She noted that the U.S. Preventative Screening Task Force and the U.K. National Screening Committee have both determined that there is currently inadequate evidence for screening for dementia, and she cautioned that biomarkers and surrogate endpoints are not the same as lived lives for individuals. It is essential that we think about the implications of the "biomarker revolution" and look at the evidence base at both the individual and collective levels.

### DISCUSSANTS' PERSPECTIVES

In response to the presentations, two designated discussants shared their key observations and take-home messages: Lauren Nicholas (University of Colorado), and Jason Karlawish (University of Pennsylvania).

- There may be alternative approaches to biomarkers to identify individuals who would benefit from screening; for example, financial errors have been associated with early cognitive decline. Early identification of such errors could lead to avoidance of financial catastrophe for individuals. (Nicholas)

- Five key points were shared with attendees: (1) there is a need to change the nomenclature surrounding dementia and AD to reflect the enormous heterogeneity and multiple pathways to dementia; (2) studies should better integrate biology, social, and economic measures, and share data; (3) a public body that views and creates algorithms that measure risk could be developed as a part of the National Alzheimer's plan; (4) laws could be developed that foster interdependence based on the risk of living with dementia or becoming a caregiver; and (5) Clinical practices need to foster clinician's ability to integrate trusted others into the care of a patient, these are persons such as friends and family who might serve in future caregiving role. (Karlawish)

## PERSPECTIVES OF INDIVIDUALS WHO HAVE RECEIVED DISCLOSURES

Sam Gandy (Mount Sinai) is a researcher who studies cognitive health; he underwent an amyloid scan 5 years ago as a screening for a clinical trial for AD prevention. Gandy had no symptoms at the time of the scan, but he does have a strong family history of AD. He noted that although the results of the scan were negative, as many as one-third of patients with clinical AD have negative scans. The results, he said, were an “absence of confirmation not confirmation of absence.”

Gandy said that had the scan been positive, it would have changed his life forever: “I will wake up every morning and wonder whether . . . this is the day I am going to forget something.” Gandy reported that he told his wife the results immediately, and she was “relieved” although they also know that the negative scan does not exclude anything completely and could change in 2 years. The challenge for patients undergoing screening, and their providers, is the “drinking from a fire hose syndrome.” There is a flood of information and constant revision, said Gandy, and discussing this information with patients on a practical level while considering privacy and confidentiality is important. Gandy believes it is his obligation to explain why things are not so black and white: that is, that a positive test does not mean that the person will inevitably develop clinical disease, and that a negative test is not all good news. He concluded that it is a “whole lot to tell people . . . in a single session all we think we know about Alzheimer's disease.”

Renee Saxon (music teacher and English tutor, Tucson, AZ) learned that she has two APOE4 alleles when she participated in a study at the Banner Alzheimer's Institute. She shared this information with two of her brothers, knowing that her result meant that they also have at least one copy of the gene. She explained her result to them as meaning that she has the “highest probability of the APOE4 gene combinations for Alzheimer's.” The result has raised her awareness of memory issues that she sees in one of her brothers, and she said that the day will come where we will have a conversation with him about getting tested. She did not tell another of her brothers because she did not want to worry him.

Saxon said that after the result, she focused on the 45–70 percent chance that she would not develop AD and continued to use the strategies of good mental health, good brain health, good physical health, exercising, staying mentally engaged, reading, doing puzzles, and teaching. She said her husband was “surprised” at the result and understood that her first feeling would be that she did not want to burden him. Her daughter knows the result, but Saxon believes she does not truly understand the ramifications of it. As an only child, the burden will fall on her daughter to care for Saxon and her husband, who suffers from ataxia.

Saxon noted that sharing her story at the workshop was made easier by the fact that she is semiretired and on Medicare; she said she may have not chosen to share if there could have been employment and insurance consequences. In addition, Saxon said that she believes that some people may be reluctant to share a positive genetic or biomarker result because it would make other people think differently about any cognitive slip-ups they might have.

Helene DeCoste (Somerset, MA) learned she had a positive amyloid scan as a participant in a study at Brigham and Women's Hospital. On the first day she was onsite, she had a “huge TV camera” in her face, and a news reporter asked her “How does it feel to have a death sentence?” DeCoste said that she does not feel like she has a death sentence: “Having one part of the disease does not mean that I have the whole disease and does not mean that I will have it.”

DeCoste was motivated to join the study because her mother died from AD, and her sister was “on the path” from mild cognitive impairment to full-blown Alzheimer's. Receiving the positive result was not a negative thing for DeCoste, she said, because it meant that she was eligible for the study and this was her

primary goal. Participating in the study gave her a chance to make a difference, she said, after witnessing the toll that the disease took on her mother and is taking on her sister. She does not think of herself as someone with AD, she said, because she does not have cognitive issues or trouble in her daily life. She added that the positive result did not affect the way she thinks about her memory or cognitive abilities and that she has not made any changes to her life or plans for her future based on the result—other than doing jigsaw puzzles with her twin granddaughters. Her focus, DeCoste said, is on educating people about what it is like to have family members with AD and what it is like to participate in a study and receive a positive result.

## ETHICAL CONSIDERATIONS RELATED TO PRECLINICAL DIAGNOSTICS

Currently, preclinical AD is not used as a clinical diagnosis, said Joshua Grill (University of California Irvine). This should not change, he said, until and unless a few basic questions are answered: What exactly should be disclosed to patients? Is a preclinical diagnosis meaningful and actionable? Can anyone predict which patients with preclinical AD will advance to symptomatic disease?

Grill said that there are several ethical concerns with disclosing genetic or biomarker status to patients, which include the risks of clinical depression, anxiety, and suicide. Given the ethical challenges of studying the reactions to disclosure, said Grill, the evidence has come almost exclusively from interventional trials in which participants receive biomarker results prior to randomization as a function of learning eligibility. One such study is the A4 study (Anti-Amyloid treatment in Asymptomatic Alzheimer's Disease), which tested a monoclonal antibody for preclinical AD. In addition to studying the drug, the A4 study also tested the model for an eventual practice in which older, cognitively unimpaired adults are screened and started on therapy if indicated. Participants in the A4 study who were given an elevated result were no more likely than those with a nonelevated result to experience suicidality, depression, or anxiety, said Grill. However, an elevated result was associated with intrusive thoughts and mild distress; individuals also adjusted their perceived risk for developing AD based on their results.

Although these results may suggest that clinicians can safely disclose a diagnosis of preclinical AD, he said, it is important to acknowledge the limitations of the data. A4—and essentially all preclinical AD trials—suffer from “extreme sample bias.” Most participants expected to have an elevated result and to be eligible to participate, and the participants were almost exclusively non-Hispanic, White, and highly educated. These characteristics are not representative of a general clinical population. Understanding the relationship between genetics and biomarkers for AD and race, ethnicity, and social determinants of health is poor, said Grill, and this needs to be strengthened before using preclinical AD diagnoses in clinical practice.

In addition, Grill noted, there is a need for research on the safety and implications of preclinical AD diagnosis in diverse communities; there may be important differences in terms of cultural perceptions of disease, attitudes toward disclosure, experience with discrimination, trust in the health care system, and health priorities. If and when preclinical diagnostics moves into clinical practice, it will be essential to balance the risks of disclosure against the potential benefits, such as treatment, accessing supportive services, and being able to plan for the long term. Grill emphasized the lack of studies to instruct methods to ensure optimal health and planning outcomes for all individuals screened for preclinical AD, not just those who are indicated for drug treatment.

A diagnosis of Alzheimer's disease before the onset of cognitive impairment is going to change the lived experience of Alzheimer's disease for millions of adults, said Emily Largent (University of Pennsylvania). Although not all of these people will progress to experiencing cognitive impairment, the diagnosis itself is a “clinical experience” and can change people's perceptions of themselves as patients. Families are also affected, both because of what it may mean for their own risk, in addition to the risk of becoming a caregiver to their loved one.

Largent presented findings from her research, which used qualitative methods to look at the disclosure of AD biomarker results. Largent said that participants saw biomarker results as qualitatively different than other medical test results for four reasons: (1) their brains and minds are seen as uniquely part of who they are as a person; (2) other people may perceive the participants to have cognitive impairment based on test results; (3) even with a positive result, cognitive impairment may be many years away or may never happen at all; and (4) a positive result may not be medically actionable.

Participants' reactions to receiving a positive test result were extremely varied, said Largent. Some were sad or disappointed, others expected the result and expressed resignation, while still others viewed it as a posi-

tive and empowering experience. Participants with a positive result reported that they adopted new health behaviors, such as exercise, playing brain games, and changing their diet. In addition, she said, people made changes to future plans, including purchasing long-term care insurance, revising their wills, writing advanced directives, and communicating end-of-life wishes to family members. Interestingly, said Largent, about 1 in 5 participants expressed an interest in medical aid in dying; she noted, however, that Alzheimer's patients would be unlikely to satisfy the usual requirements of having the cognitive capacity to make the choice while also having less than 6 months to live. Study participants also voiced significant concerns about stigma and discrimination in interpersonal relationships, employment, insurance, and housing. Due to these concerns, people may choose to selectively share information about their biomarker result, and participants reported it was an emotionally fraught experience.

This is an area, said Largent, where “the science is far outstripping the ability of the legal system to handle discrimination.” As people learn more about their risk of Alzheimer's, society will have to have interesting ethical debates about this issue. She noted that additional research in this area, and consideration of the ethical, social, and legal challenges, could be beneficial for those debates. Following Largent's discussion, attendees discussed the disagreement among scientists about whether there is an ethical obligation to disclose results to a patient.

## DISCUSSANTS' PERSPECTIVES

In response to the presentations, three designated discussants shared key observations and take-home messages: Winston Chiong (University of California, San Francisco), Gary Marchant (Arizona State University), and Richard Milne (University of Cambridge).

- The 21st Century Cures Act has created a situation in which patients may view biomarker results long before their providers can help them with interpretation; this can cause confusion and distress among patients. (Chiong)
- Preclinical biomarker results could eventually play a role in determining a person's state of mind, for example, whether a person was competent to enter legal agreements. (Marchant)
- The experience of living with a disclosure of Alzheimer's risk differs from knowledge of other types of risks because AD is not an “abrupt” event that is clearly delineated. (Milne)

## ECONOMIC IMPACT OF PRECLINICAL DIAGNOSTICS

The economic implications of preclinical biomarkers are massive, said Julie Zissimopoulos (University of Southern California). The economic effects of biomarkers could arise through several different pathways: treatment could prevent or delay onset of disease, the health care system could be incentivized to deliver better care, patients could have more quality-adjusted life years, and direct and indirect costs could be reduced (e.g., medical care, employment productivity losses, long-term care).

Zissimopoulos described the Future Elderly Model for Alzheimer's disease, which quantifies the economic and social impacts of AD in order to evaluate the value of interventions and innovations for individuals, caregivers, families, and societies. The model uses data from a variety of longitudinal, population representative sources, and with these data, models how people age; that is, the demographic, health, and economic risk factors associated with AD-onset and the onset of other diseases and conditions, their use of health care services, and the formal and informal caregiving they receive. This model, she said, allows for quantifying the “what-if” scenarios: for example, if the use of biomarkers and therapy could delay onset of AD by 3–5 years, what would be the effect on the prevalence of AD and on costs? Based on the scenario, the model computes potential costs and benefits to society and individuals. The model can also be used with clinical trial data: for example, individual-level outcomes from a trial on the impact of a new treatment could be aggregated to population-level estimates for costs and benefits to society. Zissimopoulos identified two limitations of the model and said more information is needed in these areas to make accurate estimates. First, the model assumes equal access, uptake, and effectiveness across races and ethnicities, despite evidence that there are disparities and heterogeneity. Second, there are other economic characteristics that need to be built into the model, including loss of future wages, the effects of AD on the labor supply, the macrolevel impact on economic growth, and the disparities in economic effects depending on insurance type and geography.



There are three major policy questions surrounding preclinical diagnostics, said Amitabh Chandra (Harvard University). How will these diagnostics affect the sustainability of health care spending? How will they affect society's well-being? How will they affect the pricing of medicines? Chandra emphasized that an intervention or innovation that results in a large increase in health care costs is not necessarily unsustainable; what matters, he said, is the increase in value. The value of a preclinical diagnostic depends in large part on positive predictive value, that is, how well a diagnostic identifies those who will get the disease. If the predictive value is high, it allows a patient to make plans and select appropriate caregivers, as well as to optimize choices in employment, consumption, and bequest plans. A good preclinical diagnostic could also allow researchers to identify ways to prevent AD by examining behaviors and other characteristics that affect risk. Chandra noted that while there are many good cancer drugs available, nothing has saved as many lives as primary prevention efforts (e.g., antismoking campaigns). If the predictive value of diagnostics is high and there is a good therapeutic, said Chandra, the therapeutic could be used earlier and potentially extend and improve patients' lives. He explained that in oncology the diagnostics used to detect cancer are "60 years behind the treatment," and that we should not let that happen with AD. Instead of looking "under the street light," we should aim to detect AD early so that it could potentially be treated more effectively.

If a patient were told of indicators of cognitive decline many years in advance, what would be the value of that information to the individual and family?," asked Michael Hurd (RAND). He identified some of the potential benefits of a preclinical diagnosis, noting that this scenario assumes that there is no effective treatment available. The value, he said, lies in the types of actions the individual and family can take: they can create a living will, involve other family members in financial decisions and responsibility, downsize housing or move closer to other family, plan for informal or formal caregiving, make decisions about driving, modify spending decisions, and change employment or lifestyle. In short, Hurd said, the information would be of value if it led to welfare-improving practical actions.

Hurd outlined the steps for a research study that could address this in a systematic manner; the goal would be to examine whether and how people know about their cognitive status, what actions they took with this information, and how much gain in welfare they achieved by those actions. He noted that there is extreme heterogeneity in people's understanding of and response to risk, so any research study should closely look at heterogeneity. He has used data from the Health and Retirement Study (HRS) to explore these issues, noting that it is particularly relevant for AD studies because it includes cognitive data, information about activities of daily living, and biomarkers. He noted that awareness of memory can be measured within HRS with some observation error. These data reveal that when people are aware of cognitive problems, they act on this information. For example, people who are aware of an issue are more likely to have a living will, move in with a family member, and include children in financial decisions. The next steps, said Hurd, would be to undertake a more thorough study of knowledge acquisition and to develop a better understanding of what is exogenous. Ultimately, it would be beneficial to study the value of these types of actions as well as other measures that may influence people's understanding of their cognitive status and actions that stem from that knowledge.

## DISCUSSANTS' PERSPECTIVES

In response to the presentations, two designated discussants shared their key observations and take-home messages: Gary Mottola (FINRA Foundation), and Norma Coe (University of Pennsylvania).

- There could be major personal financial implications of a preclinical diagnosis of AD, and there are questions that need to be addressed about privacy, the role of financial professionals, communication, and financial disclosures. (Mottola)
- A preclinical diagnosis can affect the decision making of spouses, children, and other family members; as diagnoses are received earlier in life, this could affect decisions about employment, insurance, family size, and financial planning across generations. (Coe)

## DESIGN AND CONDUCT OF TRIALS OF PRECLINICAL DIAGNOSTICS AND EARLY DETECTION

Oskar Hansson (Lund University) told workshop participants about the BioFINDER (Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably) study, which was aimed at developing methods for diagnosing AD that could be accessed and implemented in primary care settings. Hansson said that

researchers developed an algorithm using measures of phospho-tau, APOE4, and memory and executive function; the algorithm had a predictive ability of 0.91.<sup>2</sup> In comparison, dementia experts who had met with the patients and had their cognitive test and structural imaging information had a predictive ability of 0.72, which was “clearly inferior to this very simple algorithm,” he said. Furthermore, Hansson noted, the algorithm performed just as well as algorithms based on cerebral spinal fluid biomarkers, which are much more difficult to access in a primary care setting.

Hansson predicted that this algorithm could be used in the future as part of an online app: clinicians could input age, phosphor-tau levels, APOE4 status, and cognitive test results and could obtain the quantified risk of the patient developing ADRD in the next 4 years. If this kind of information becomes available, he said, it will be imperative to consider how to best disclose the risk to the patient and to consider how screening and communication may differ depending on age or cognitive status. In addition, an appropriate cut-off point must be determined in order to identify patients at risk while not overwhelming memory clinics with many patients who will not progress to AD.

Randy Bateman (Washington University St. Louis) told participants about the SEABIRD (Study to Evaluate Amyloid in Blood and Imaging Related to Dementia) program, which uses a community-based population to ensure better diversity along multiple dimensions. The bar to get into the study is purposefully low in order to encourage diversity, he said: participants are recruited from general clinics or the community, rather than from specialty clinics. Participants provide a blood sample and take two brief phone assessments (MoCA and AD8<sup>3</sup>). After the initial assessments, about one-quarter of participants will be offered a confirmatory PET scan and a larger blood collection. The exclusionary criteria, said Bateman, are also designed to encourage a diverse study population: people with cancer, heart conditions, or diabetes are all welcome to participate. In addition, he said, researchers are actively searching for participants with certain comorbidities and for participants who are from certain socioeconomic classes and racial/ethnic groups. The study was interrupted by the COVID-19 pandemic, he said, but is now resuming.

There is a big opportunity right now to leverage new study methodologies to advance dementia prevention, said Jeff Burns (University of Kansas). The pandemic—and the associated increased ability to connect and collaborate—have made pragmatic, practice-based trials more feasible. Trials that are integrated into practice settings allow researchers to leverage electronic health records to identify potential study participants, study real-world patients and primary care providers, and reach a more diverse and generalizable population. “The time is right for these efforts,” said Burns; primary care practitioners “need answers to the questions that they’re getting all the time as our population ages.”

Burns explained that his research focuses on the impact of exercise on cognitive decline, and he noted that previous studies suffered from nonrepresentative participants, high burden interventions, and long duration. Now he has discovered what he called the power of pragmatic trials, with around 50 doctors prescribing a lifestyle medicine approach that is delivered in community fitness centers. An algorithm identifies patients who are near fitness centers, and doctors can prescribe with the click of a button on the electronic health record. This is a way, said Burns, of packaging exercise better and scaling up an intervention in the real world. Another pragmatic study uses those records to identify patients with uncontrolled hypertension and automatically expands the care team to include a pharmacist and home blood pressure monitoring. These pragmatic trials create an opportunity to move into populations and communities that are usually not accessible to academic medical centers. For example, Kansas is a large state, and many residents outside of Kansas City may not view the University of Kansas as serving their needs. The university is working with its health system to build a network of primary care providers across the state to further community engagement and research. Burns said that conducting pragmatic trials in the community is an important way to scale up to a larger and broader population with a higher sample size, lower cost, and true impact.

## DISCUSSANTS’ PERSPECTIVES

In response to the presentations, three designated discussants shared key observations and take-home messages: Rhoda Au (Boston University), Jeffrey Kaye (Oregon Health and Science University), and Paul Aisen (University of Southern California).

<sup>2</sup>Predictive ability is expressed as AUC: area under the ROC (receiver operating characteristic) curve.

<sup>3</sup>MoCA, the Montreal Cognitive Assessment, is a rapid screening instrument for mild cognitive dysfunction. AD8 (Adenovirus Type 8) is a brief screening tool that may discriminate healthy older adults from those with very mild dementia.

- Digital biomarkers differ from traditional biomarkers in several important ways, and these differences must be accounted for when validating biomarkers, seeking regulatory approval, and implementing them into practice. (Au)
- Digital biomarkers have several benefits compared to other biomarkers: they are “markers of real change” that capture a person’s cognitive abilities; their use can reduce the sample size necessary for studies; and they can be used to track intra-individual change. (Kaye)
- Primary prevention trials for AD will need to target a young population (to age 45) and select high-risk individuals using plasma biomarkers and genetic markers of risk. The impact of therapies will be assessed using sensitive plasma measures of metabolic perturbations that precede AD neuropathology. (Aisen)

## CLOSING COMMENTS: ISSUES AND NEXT STEPS

Sperling led a closing discussion to capture workshop participants’ concrete thoughts on the big issues and next steps for the field of biomarkers and AD and to identify priority areas for research. Many participants noted that there is a critical lack of information on diverse populations, both in terms of biomarkers and disease progression and in terms of how diverse communities may perceive issues around risk, health, cognitive decline, and disclosure. Glover said that the best place to start is by asking, noting that this must be not just a conversation, but a systematic, mixed-methods approach to understand diverse perspectives. Bennett pointed out that the patient perspectives presented at the workshop were all of people who opted to know about their AD risk, and emphasized the importance of also understanding the perspectives of those who would opt not to know. Barnes noted that one way to expand understanding is through strengthening partnerships with community leaders and nontraditional stakeholders, for example, barbers or pharmacists. Au added that there are many existing digital tools (e.g., precision marketing and social engagement technologies) that could be repurposed to reach some populations of interest.

Chiong brought up the ethical challenges in the design of research on disclosure, noting that researchers may not be on firm ethical ground if they randomly assign some people to receive the information on their status and some people not to receive that information. He also cautioned that while it would be valuable to have data about differences in how groups perceive risk and differences in wanting to receive information, ultimately each individual patient is in the best position to decide. Nicholas added that in addition to patients, family members are also affected by preclinical diagnoses and may have very heterogeneous opinions about disclosure. Glover echoed this observation and emphasized the importance of including family members in research.

Burns said that in all of this work, it is critical to focus on patient-defined outcomes, with the potential value to individuals driving the work on biomarkers, disclosure, and interventions. Largent noted that one potential value of disclosure is allowing patients to begin to plan and build a support network for the future. She said that research has shown that advanced directives are not well-suited to dementia care and that preclinical disclosure presents an opportunity to think about alternative support structures for patients and families that promote autonomy while also protecting the vulnerable.

Sperling and other committee members noted that the workshop discussion was very valuable in highlighting the need for additional data collection and analyses, particularly in more diverse populations, to inform plans for disclosure in both ongoing studies and eventually in clinical care.

## PLANNING COMMITTEE HOW BIOMARKERS AND OTHER PRECLINICAL DIAGNOSTICS MAY CHANGE ALZHEIMER'S DISEASE AND AD-RELATED DEMENTIAS RESEARCH AND CLINICAL CARE

**Resia A. Sperling** (*Chair*), Harvard Medical School; **David A. Bennett**, Rush University Medical College; **Nathaniel A. Chin**, University of Wisconsin School of Medicine; **Jessica Langbaum**, University of Arizona; **Molly Checksfield Dorries**, Study Director; **Ashton Bullock**, Senior Program Assistant.

---

**DISCLAIMER:** This Proceedings of a Workshop—in Brief was prepared by Erin Hammers Forstag, rapporteur, as a factual summary of what occurred at the workshop. The statements made are those of the rapporteur or individual meeting participants and do not necessarily represent the views of all meeting participants; the planning committee; the Board on Behavioral, Cognitive, and Sensory Sciences; the sponsors; or the National Academies of Sciences, Engineering, and Medicine. The planning committee was responsible only for organizing the public session, identifying the topics, and choosing speakers.

**REVIEWERS:** To ensure that it meets institutional standards for quality and objectivity, this Proceedings of a Workshop—in Brief was reviewed by Nathaniel Ark Chin, University of Wisconsin School of Medicine and Public Health. We also thank staff member Tracy Lustig for reading and providing helpful comments. Kirsten Sampson Snyder, National Academies of Sciences, Engineering, and Medicine, served as review coordinator.

**SPONSORS:** The workshop was supported by the National Institutes of Health.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. (2021). *Implications for Behavioral and Social Research of Preclinical Markers of Alzheimer's Disease and Related Dementias: Proceedings of a Workshop—in-Brief*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/26295>.

Division of Behavioral and Social Sciences and Education

*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE

The nation turns to the National Academies of Sciences, Engineering, and Medicine for independent, objective advice on issues that affect people's lives worldwide.

[www.nationalacademies.org](http://www.nationalacademies.org)

Copyright 2021 by the National Academy of Sciences. All rights reserved.

Copyright National Academy of Sciences. All rights reserved.