

Exploring Outcomes and Value across the Spectrum of Alzheimer's Disease

1201 Pennsylvania Avenue NW, Washington, DC 20004

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Meeting Summary

Meeting Objectives

Alzheimer's disease (AD) has a considerable health impact on the US population, and it imparts significant costs on individuals and the healthcare system as a whole. While the scientific understanding of AD pathology is incomplete, advances to disease treatment and even disease modification promise improved efficacy and the potential to delay disease onset. However, serious questions remain, including how accurately promising therapies can be matched with patients, which outcomes are most promising for measuring ongoing effectiveness, and the potentially high prices of these new transformative therapies bring uncertainties regarding coverage and reimbursement under the current system.

On June 20, 2017, under a cooperative agreement with the Global CEO Initiative on Alzheimer's Disease (CEOi), the Duke-Margolis Center for Health Policy convened an expert workshop to consider the challenges and potential approaches to address Alzheimer's drug development and valuation challenges. This expert workshop involved a broad group of stakeholders, including clinicians, payers, large and small manufacturers, professional organizations, patient advocacy organizations, and regulatory officials. During the workshop, stakeholders identified treatment issues in current clinical practice, explored strategies to improve the diagnosis and screening of AD, and discussed how to leverage data and evidence to assess the value of AD therapies. This summary highlights the challenges and potential solutions discussed by the group.

Disease progression and diagnosis

Uncertain delineation of progression and diagnosis of AD leads to a number of challenges in drug development and appropriate treatment of patients. AD can be challenging to diagnose and treat because symptoms manifest differently in each patient, and progression from preclinical to mild to severe disease varies by individual. While progress has been made in understanding the pathology of AD, workshop participants emphasized that progression is still not completely understood, and highlighted that defining the clinical stages of AD can be difficult. Rather than considering each stage individually, progression of AD should be viewed as a continuum.

There are currently five drugs used to treat AD and dementia, and three of the drugs – donepezil, galantamine and rivastigmine – are cholinesterase inhibitors that aim to prevent the breakdown of acetylcholine in neurons. Acetylcholine is a neurotransmitter that is important for memory, and drugs that prevent its breakdown aim to improve thinking and memory functions. Another drug, memantine, is an NMDA (N-methyl-D-aspartate receptor) inhibitor that blocks the activities of the neurotransmitter glutamate, which also plays a role in learning and memory. The last drug, donepezil + memantine, is a combination therapy. All of these drugs treat the symptoms of disease without impacting progression. While the effects vary by individual, on the whole, use of these drugs can help maintain cognitive

function and delay nursing home placement.¹ However, they do not prevent disease progression, reverse damage, or improve survival. Many drugs currently in the clinical pipeline are designed to modify disease progression by preventing the buildup of amyloid beta (A β); however, testing these drugs in patients with moderate symptoms has not been successful. Scientists hypothesize that damage to the brain has already occurred at this stage, resulting in poor clinical trial results. As a result, many of these drugs are now being tested in patients who have very mild clinical symptoms, and if any of these drugs are approved early diagnosis of disease will be critical to their success.

Under current clinical practice, stages of AD are measured through a combination of mental status testing, brain imaging, and examination of a patient's health history. As cognitive impairment is irreversible and treatment options are limited once severe AD symptoms develop, screening of high-risk individuals, early diagnosis, and early therapeutic and behavioral interventions are needed to achieve better clinical outcomes for patients. There are several methods available for screening and diagnosing patients, but participants noted that each has limitations.² Those who are A β positive are more likely to develop AD symptoms than those who are A β negative, so the presence of excess A β is frequently used as a diagnostic marker. Screening usually occurs after the patient develops observable signs of cognitive impairment. However, A β accumulation and brain atrophy can occur as many as 15 years before symptoms emerge, and while A β is necessary for an Alzheimer's diagnosis, its presence alone is not sufficient evidence of disease. To confirm the onset of AD, a variety of secondary techniques, including PET scan or molecular imaging, are also required. Yet, the workshop participants noted that these procedures are cost-prohibitive. In recent years, genetic testing has gained increasing attention, and presence of the APOE- ϵ 4 gene has been associated with an increased risk of developing AD. However, due to the high costs and uncertainty about correlation, genetic testing is not widely implemented for preventive screening in primary care settings.

Cognitive assessment tests are also useful tools to diagnose and track AD progression, but participants noted that they are often only recommended for symptomatic patients as a means to rule out other causes of cognitive impairment. Cognitive screening is a simple and low-cost method for diagnosis, but scoring is subjective and there are a large number of tests available that can give variable results. Further, these tests have low sensitivity at early stages, and they do not sufficiently capture subtle changes in cognitive impairment. As a result, clinicians have struggled to translate cognitive testing results into clinical practice.

While tests for AD have limitations, participants noted that screening for identification of potential early stage AD patients is underutilized. It is important to identify signs of AD because starting treatment early can slow functional decline, allowing the patient additional independence and alleviating caregiver burden. There are multiple issues that contribute to the lack of effective screening and diagnosis of early AD. These include lack of familiarity with the diagnostic tools available, outdated guidelines that do not

¹ Mohs, R.C., et al. "A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients." *Neurology*. 2001 Aug 14;57(3):481-8. [<https://www.ncbi.nlm.nih.gov/pubmed/11502917>]; Lopez, O.L., et al. "Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease." *J Neurol Neurosurg Psychiatry*. 2002; 72:310-314. [<http://jnnp.bmj.com/content/jnnp/72/3/310.full.pdf>]

² The Alzheimer's Association. "Policy Brief – Early Detection and Diagnosis of Alzheimer's Disease." [http://www.alz.org/alzheimers_disease_steps_to_diagnosis.asp]

include newer tests, concerns that prognosis with an Alzheimer's diagnosis would do more harm than good for patients, and uncertain coverage and reimbursement.

Additionally, physicians may not recognize or look for early AD, and they may not have the specialized knowledge needed to perform cognitive screening for dementia. Primary care clinicians treat patients in a range of ages, and in relation to the number of patients they treat, physicians may encounter few individuals with AD or dementia. Further, while there has been rapid progress in diagnostic technology, there is a lack of updated guidance for physicians on the use of diagnostic and screening tools, particularly regarding biomarker screening for AD.

Regardless of the type of screening available, participants also noted that clinicians may be reluctant to conduct formal screening due to concerns that an AD diagnosis itself may have a negative impact on patient wellbeing, in part due to perceptions that available medications will have a limited impact on patient health. As a result, it is estimated that over half of AD patients do not receive a formal diagnosis.³

The cost burden of screening is another reason for the underutilization of diagnostic tests. Participants noted that payers do not always see the value of covering diagnostic tests because there is not enough evidence that confirming disease is a cost-saving measure. This leads to clinician reluctance to adopt these tests into clinical practice because the healthcare institution or patient will be burdened with the cost.

In order to address the challenges described above, participants proposed strategies to improve screening and early diagnosis of AD. First, clinical guidelines should be updated to incorporate preventive screening. A simple step would be to incorporate cognitive testing into annual wellness visits, which would serve the dual purpose of ensuring early intervention and collecting baseline data for outcomes analysis. Educating primary care physicians about the benefits of AD screening could also help to encourage its use in regular clinical settings.

Besides efforts to increase utilization of preventive screening, it was suggested that providing training for physicians on how to treat and manage AD across different stages of disease could improve AD care and drug utilization. Participants noted that there is a perception that current AD drugs are not effective; but in fact, current drugs can slow functional decline and relieve AD symptoms. In addition to disease-targeting medications, clinicians should also incorporate behavioral interventions into treatment plans, which have been shown to have a positive impact in improving the patients' overall physical functioning and quality of life.

Given the high costs of AD screening tools and the need to identify patients early for treatment to be more effective, better diagnostic protocols are necessary. Participants suggested two methods to incorporate screening and diagnosis more broadly in a cost-effective manner. One proposal, based on ongoing research, was to develop a standard algorithm to assess a patient's disease risk based on a combination of factors such as age, genetic profile, cognitive testing, and brain imaging. This algorithm

³ The Alzheimer's Association. "2015 Alzheimer's Disease Facts and Figures." [https://www.alz.org/publichealth/downloads/policy-brief.pdf]

could guide early diagnosis and inform potential use of drugs that slow disease progression at early stages, as well as reduce the uncertainty that currently exists at this stage. Early research using EHR data and clinical notes for predictive modeling resulted in patient clusters, which may be used to better define dementia risks for individuals. The second suggested proposal was the use of a low-cost diagnostic tool, like cognitive testing, on a large scale to filter out high-risk individuals, who would then undergo more sensitive and expensive testing. In addition to these measures, participants suggested that more economic studies should be done to demonstrate the cost-effectiveness of AD screening and to inform the coverage and reimbursement decisions of payers.

Clinical trials

In addition to improving outcomes for patients, early screening for AD can help identify individuals who might qualify for clinical trials, particularly as new drugs designed for use in earlier disease stages move through the pipeline. The lack of disease modifying treatments for AD is a clear unmet medical need, and there are a number of companies working to develop viable drug candidates. Despite ongoing clinical trials, due to inefficacy or toxicity, the failure rate for AD drug candidates has been as high as 99 percent.⁴ Scientists hypothesize that targeting the disease at too advanced a stage contributes to these results. As a result, developers have shifted their testing to patients in earlier stages, and many are focusing on preventing buildup of A β before symptoms are apparent.

For drugs that target preclinical and early stages of AD, one major challenge is to identify the right patients to participate in clinical trials. Since preclinical and early-stage patients are largely asymptomatic and the AD screening and diagnostics are underutilized, it takes more time and resources to identify and recruit patients for studies. Uncertainty and inconsistency in the diagnostic process, as discussed above, contribute to lengthy and expensive recruitment during clinical trials, in part because if patients are unaware that they are in the early stages of disease, they will not be informed of trial options. Once patients are recruited into trials, the lack of baseline data and predictable disease progression can make the efficacy of a drug difficult to assess. Additionally, the functional changes during early stages are difficult to capture, and clinical trials for drugs that treat early-stage AD do not have the necessary sensitive composite scales to assess clinical outcomes.

A further complication is that the endpoints used by developers during randomized controlled trials do not necessarily reflect what patients and payers would use to measure real-world effectiveness. AD progresses over a number of years, and significant changes may not be seen year to year or month to month, particularly in the early stages of disease. Clinical trials collect data over a relatively short period of time, usually between six months to two years, and any significant changes in the trial data may not translate to impactful benefit for the patient. In many cases, manufacturers must use proxy measurements, which would not be the same as those physicians would use to assess patients. As a result, it may be unclear how improvements in certain biological or cognitive markers will translate into

⁴ Cummings, J.L., Morstorf, T., Zhong, K. "Alzheimer's disease drug-development pipeline: few candidates, frequent failure." *Alzheimer's Research and Therapy*. 2014 6:37. [<https://doi.org/10.1186/alzrt269>]

clinical benefits. Therefore, one major difficulty for developers is how to demonstrate a meaningful connection between clinical trial biomarkers and improvement in patient cognitive function.

Participants proposed several potential approaches to address these development challenges. One way would be through improvements to the current clinical trial infrastructure through better coordination between developers and primary care physicians using a large study network. A national clinical trials network would streamline the recruitment of patients and collection of data. Additionally, it was suggested that more efforts are needed to develop guidelines and standards to improve the quality of patient screening and diagnosis in primary care settings. These efforts to build a strong infrastructure could lead to improved patient selection and outcomes tracking.

Second, participants noted the need for standardization and validation of biomarkers that are currently used for AD clinical trials, including more robust evidence to demonstrate the connection between biomarker changes and improvement in patient outcomes, such as life expectancy and quality of life. Additional evidence of clinically meaningful changes would help to predict the effect of early AD interventions.

Finally, since changes in cognitive function are difficult to capture during very early stages of disease, participants suggested that more precise and sensitive screening techniques need to be developed to detect a drug's impact on disease progression. It would be beneficial to have a tool that could capture the comprehensive effects of AD interventions on patient conditions based on a variety of indicators and perspectives.

New payment approaches for Alzheimer's care

Participants recognized that AD-associated costs have a large impact on the US healthcare system; the estimated aggregate annual cost of care for those with AD or dementia is \$259 billion and more than \$46,000 annually per capita.⁵ AD patients have a greater risk of co-morbidities, accidents, and hospitalization. Further, treatment is less effective in the later stages of AD, leading to greater care and treatment costs. The pipeline of new drug candidates promises to be significantly more effective at delaying the onset and progression of disease, leading to a decrease in associated symptoms and the reduction of a number of costs. However, these new drugs will likely have a high price and will be needed over a long period of time.

As a result, payers will likely look for ways to lower their costs as well as to reduce treatment uncertainty, particularly for high cost drugs that may have variability in effectiveness across different stages of AD. In other disease areas, payers and manufacturers are exploring new value-based payment models, including outcomes-based contracts that tie drug payment to actual observed outcomes. In parallel, the Center for Medicare and Medicaid Innovation (CMMI) is actively considering ways to incorporate medical products into alternative payment models (APMs) to move away from fee-for-service payments. Ideally, the payment models should encourage utilization of high-value AD therapies, which would improve patient outcomes and reduce total costs of care. Reforms focused on outcomes

⁵ "2017 Alzheimer's disease facts and figures." 2017. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 13 (4): 325-373. [https://www.alz.org/documents_custom/2017-facts-and-figures.pdf]

and patient quality of life could also potentially apply to models of supportive and other care, reducing costs and improving outcomes.

Participants discussed factors that would be needed to make a value-based payment approach feasible. New payment models should tie payments to the value that the drug provides, and a value assessment framework could help to distinguish higher-value from lower-value therapies. Participants agreed that any type of payment approach based on value would require communication and flexibility between stakeholders to come to consensus on benefit and outcome measures.

Given the high costs of AD care, stakeholders have different perspectives on what kinds of benefits AD therapies should be able to deliver. From a patient perspective, a central goal of AD treatment is to slow the progression of the disease and prolong their independence to manage daily activities. From a caregiver's perspective, an effective treatment can reduce the burden of caregiving, which includes lower costs and fewer hours spent caring for patients. Since payers, providers, drug manufacturers, patients, and caregivers all have different perspectives, they can have difficulty in reaching an agreement on the selection of outcome measures. Additionally, since the underlying disease mechanism for AD is still incompletely understood, it is difficult to select clinically meaningful measures that accurately reflect the pathological changes in disease progression in a given patient. There are also long-term and indirect impacts from appropriate and effective AD treatment that may be harder to quantify, such as workplace productivity and reduced burden on the healthcare system.

In addition, effective tracking and collection of data limits the assessment of outcomes. Measuring the effectiveness of AD drugs requires tracking individuals over a long period. However, patients often move between insurance providers, which can disrupt data tracking. Further, the lack of standard baseline data makes it difficult to measure an AD drug's effectiveness, even over a shorter period. Adding to these issues is the lack of interoperability between different databases. The electronic medical record (EMR)/electronic health record (EHR) databases used by different health systems are often not compatible with each other, which limits data sharing, exchange, and analysis.⁶ Ownership of data and privacy regulations further restrict access to health data.

Outcomes assessment is closely tied to the ability to diagnose and track the progression of disease. Therefore, improvements in these areas will positively impact measurement of outcomes. In addition, improving infrastructure, such as through a clinical trials network, could serve as the foundation for improved data collection and sharing, even in the post-market setting. This type of infrastructure would allow input from all stakeholders, including nursing care facilities, patients, and caregivers, to be leveraged. Another step would be to improve care coordination so that existing data can be used to help determine appropriate outcomes.

Participants suggested that a patient registry could also provide the infrastructure needed to address data tracking and sharing issues. Such a registry could help identify target populations and accelerate enrollment for clinical trials. It could also improve standardization and interoperability of different data

⁶ Kellerman, A.L. and Jones, S.S. "What will it take to achieve the as yet-unfulfilled promises of health information technology?" *Health Affairs*. October 2015, vol. 36; 10. [<http://content.healthaffairs.org/content/32/1/63.short>]

sources. However, establishing a national registry has its own challenges. The cost for establishing and maintaining such as database can be expensive. If the registry were to be maintained by the government, it would possibly require new legislation from the Congress and a change of existing CMS rules on disease reporting. Additionally, since a registry would contain sensitive patient data, using data from the registry may require complex IRB reviews and may raise legal and patient privacy issues. Participants suggested that further discussion is needed to provide strategies to overcome these challenges.

Role of the Caregiver in Clinical Practice and Data Collection

As described above, accurate evidence and outcomes reporting will be critical to judging the effectiveness of Alzheimer's drugs, both for clinical trials and for supporting new alternative payment approaches. Participants agreed that caregivers can be an important source of this data, but that they are currently underutilized, and that several challenges will need to be overcome to effectively utilize caregiver input.

The majority of caregivers provide care for a family member.⁷ The majority caregivers are unpaid, and providing full-time care for their loved ones often requires reduction in paid employment. However, caregivers also face a number of health burdens resulting from caregiving, including higher incidences of dementia and higher rates of depression compared to the rest of population. Caregivers are often overworked and stressed, which can in turn affect the wellbeing of the person receiving their care; nursing home admissions of AD patients are closely linked to caregiver health.⁸

While caregivers are an important part of the care equation for AD patients and physicians, they are not formally incorporated into medical assessments. Currently, caregivers are not included on the medical records of patients, which creates a missed opportunity for physicians to gather additional data on the condition of their patients. Further, when patients are no longer able to report outcomes for themselves, there is not a standard way to transition to caregiver-reported outcomes. Incorporating the perspectives of and input from caregivers could help to build a more complete picture of the AD patient and potentially improve care.

Participants proposed numerous strategies for engaging clinicians and payers with caregivers to achieve better clinical and economic outcomes. One proposal was to keep records for the household rather than for the patient alone, or to consider the caregiver and the patient as a dyad, which would enable medical records to accommodate the transition from patient-reported to caregiver-reported outcomes. Current clinical guidelines should put more emphasis on the role of the caregiver and propose strategies to improve the coordination between caregivers and clinicians, including team-based care, remote monitoring, and integration of social services. Participants suggested that meaningful lessons about data collection and reporting could be learned from mother-child cohort studies. Caregivers could also be leveraged for clinical studies by serving as asymptomatic controls. Participants suggested that caregivers

⁷ AARP. "Caregiving in the U.S." June 2015. [<http://www.aarp.org/content/dam/aarp/ppi/2015/caregiving-in-the-united-states-2015-report-revised.pdf>]

⁸ Brodaty, H., et al. "Time until institutionalization and death in patients with dementia." *JAMA Neurology*. June 1993. [<http://jamanetwork.com/journals/jamaneurology/fullarticle/592396>]

are willing and able to collect patient data and evidence to support clinical trials and outcomes studies, including through the use of mHealth technology.

High Priority Next Steps

Over the course of the workshop's discussion, there were a number of priority needs that participants felt were particularly important for advancing the care and treatment of Alzheimer's patients. In many cases, information is the foundation of these needs, and will require improvements in infrastructure, standards, data collection, and stakeholder collaboration. Each of these high priority items represents an opportunity to further innovations in Alzheimer's care and to deliver more value to patients and the healthcare system.

Improve tools for efficient treatment development

Improving standards and validating biomarkers. The need for standardization of assessments and treatment and validation of biomarkers was a consistent theme throughout the discussion. Participants noted that while there is still an incomplete understanding of AD, research advances in diagnosis and care should be utilized whenever possible to continue progress in disease treatment. As noted above, improved and widespread use of screening tools has the potential to enable earlier treatment of AD. To facilitate implementation of measurement standards, participants called for updates to clinical guidelines to incorporate cognitive testing into annual wellness visits and behavioral interventions into treatment plans. They emphasized a need for standardized training for primary care physicians regarding the benefits and administration of AD screening as well as AD treatment and management across the different stages of AD. They proposed the development of a standard algorithm to guide early diagnosis and the increased use of low-cost diagnostic tools to identify high-risk individuals. They also emphasized the importance of validation of biomarkers currently used for AD clinical trials, as well as the need for greater incorporation of biomarkers into diagnosis and treatment protocols, which could be facilitated by more robust evidence linking them to meaningful outcomes.

Improve predictive modeling to identify patients who are candidates for treatment. Participants also prioritized a more accurate predictive model that could reduce the time needed for clinical trials and provide more certainty for clinicians and payers about which patients are most likely to benefit from a treatment. A more precise and sensitive model should capture the impact of AD interventions from a variety of indicators and perspective. For example, patient data, including medical records, genetic profile, presence of biomarkers, and family history, could be entered into an algorithm to develop a risk profile for the patient. This algorithm could evolve as the knowledge of AD expands to provide a more refined picture of an individual's disease risk. Individuals with a higher risk of disease development could then be flagged for further screening, follow-up monitoring, or enrollment in clinical trials. This type of predictive modeling would require willingness to share data between stakeholders, support from physicians, and privacy protections for patients.

Refine systems to capture real-world evidence for diagnosis and development of treatments

Establish the infrastructure for data collection and sharing. Expanding the AD knowledge base will require the development of an infrastructure that enables data collection and sharing between developers and physicians. Participants especially focused on the need to better explore the potential

value of a national clinical trials network that could streamline the recruitment of patients, as well as integrate data from multiple sources, including patients, caregivers, and nursing care facilities. Infrastructure for data collection and sharing would have benefits beyond clinical trials; it could also be leveraged for improved post-market data collection, which would be the foundation for outcomes reporting and measurement. These systems will be particularly important for tracking long-term patient measures in a disease that takes years to progress, and will provide confirmatory evidence on the effectiveness of the treatment. Further, data infrastructure that supports analyses of care improvements as well as further evaluations of long term outcomes could create a learning healthcare system instead of being focused on long-term evaluation of disease modifying therapies alone. A possible next step on this front would be to identify how existing and evolving national data systems, such as the FDA's Sentinel System⁹, PCORNet¹⁰, or new AD patient registries, could provide a national data platform for recruiting and enrolling participants into trials as well as collect high priority real-world data elements.

Collaborating with patients and caregivers. AD affects more than just the patient; it can also negatively impact the health of caregivers and family members. Reducing these burdens through better treatment of AD will result in significant savings to the healthcare system, which can boost the value of the given treatment. In order to assess these potential benefits, better utilization of patient and caregiver data will need to occur, and will require the development of data collection protocols, possibly through the use of real-world evidence systems. Additionally, there are further opportunities to collect data on care outcomes outside of the clinic, including remote monitoring of patients, integration of social services, and team-based care for patients. Leveraging data from these sources could provide information on outcomes that could not be collected in clinical settings.

Develop value-based payment models to support efficient, patient-centered AD care delivery

Explore value-based payment approaches for AD care. Under the current payment system, AD medical products are paid for on a fee-for-service (FFS) basis, without regard to patient outcomes. The current system is potentially problematic as FFS payments are not designed to support innovation in diagnosis and treatment, and may not support the emergence of future transformative therapies that have the potential to significantly alter the course of disease, but that may have high upfront costs and uncertain long-term outcomes. Participants indicated an interest in further exploring the potential of value-based payment approaches to AD medical products that would link pricing and payments to the observed or expected value in a population. Outcomes-based contracts, in particular, link payment to the product's real-world performance, and would encourage the development of high-value treatments.

Implementation of these new payment models would not only have the potential to improve quality in care, but they could also reduce the overall cost burden of AD on the healthcare system.

Accountability for results could be based on a multitude of measurements, such as clinical or patient-reported outcomes, utilization outcomes, measures of spending, and/or quality of care measures. A shift

⁹ FDA's Sentinel Initiative [<https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm>]; Ball, R., et al. "The FDA's sentinel initiative-A comprehensive approach to medical product surveillance." *Clin Pharmacol Ther.* 2016 Mar;99(3):265-8. [<http://onlinelibrary.wiley.com/doi/10.1002/cpt.320/full>]

¹⁰ The National Patient-Centered Clinical Research Network [<http://www.pcornet.org>]

to value-based payment approaches for AD medical products would require considerable effort to identify meaningful outcomes that are prioritized by multiple stakeholders and are also measurable in the post-market setting. Despite the challenges, participants prioritized the importance of exploring new value-based payment models that would emphasize efficient, patient-centered care to bring down costs and reduce uncertainty in treatment. While efforts are underway to identify ways to overcome legal, regulatory, and operational barriers of these payment models, next steps for AD could include consensus building on meaningful definitions of value for emerging treatments and translating to standardized measurable outcomes for treatment success. Further steps could include development of partnerships among payers, manufacturers, and providers that could create meaningful data sharing agreements to enable tracking such outcomes and testing new value-based payment models, where uncertainty in treatment outcomes is reduced through shared accountability.

Conclusion

Continuing to advance the knowledge of AD and support innovations in diagnosis and medical products is of utmost importance for reducing the toll of the disease on patients and their families. For AD in particular, new high-priced innovations may come with high degrees of uncertainty as to which patients should receive them and durability of effectiveness. These uncertainties may serve as high priority opportunities for exploring value-based payment arrangements, giving rise to questions about how to define and measure value and outcomes across the stages of AD. To address these high priority issues, a concerted effort among stakeholders is needed to capitalize on emerging opportunities for collaboration and development; the approaches presented in this white paper represent areas for the highest potential impact.