Original Research

The Journal of Prevention of Alzheimer's Disease - JPAD
Volume 6, Number 1, 2019

Designing Trials of Disease Modifying Agents for Early and Preclinical Alzheimer's Disease Intervention: What Evidence is Meaningful to Patients, Providers, and Payers?

D.A. Messner[1], P. Rabins[2], A.C. Downing[3], M. Irizarry[3], N.L. Foster[4], J. Al Naber[1], O. Dabbous[5], H. Fillit[6], S. Gabler[4], R. Krakauer[7], D. Lotz[8], E. Payzant[9], L. Schneider[10], J. Tyrone[11], D. Van Amerongen[12], D. Wuest[13]

1. Center for Medical Technology Policy; 2. Johns Hopkins University (retired); 3. Eli Lilly; 4. University of Utah; 5. AveXis, Inc.; 6. Alzheimer's Drug Discovery Foundation; 7. Aetna (Retired); 8. New Hampshire Department of Health and Human Services; 9. Patient Advocate / University of Utah Health Care; 10. Keck School of Medicine; 11. Patient advocate / Beating Alzheimer's by Embracing Science (BABES); 12. Humana; 13. GNS Healthcare

Corresponding Author: Donna A. Messner, PhD, Center for Medical Technology Policy, 401 E. Pratt Street, Suite 631, Baltimore, MD 21202, Tel: 410.547.2686 x101, Fax: 410.547.5088, Email: donna.messner@cmtpnet.org

J Prev Alz Dis 2019;1(6):20-26
Published online October 19, 2018, http://dx.doi.org/10.14283/jpad.2018.42

Abstract

BACKGROUND: Drug development for disease modifying agents in Alzheimer's disease (AD) is focused increasingly on targeting underlying pathology in very early stages of AD or in cognitively normal patients at elevated risk of developing dementia due to Alzheimer's. Very early interventional studies of this type have many uncertainties, including whether they can provide the clinical results that payers, providers, and patients will wish to see for decisions. This paper describes an initiative to create greater transparency for researchers to anticipate these decision needs.

OBJECTIVE: To create multi-stakeholder–vetted recommendations for the design of studies in later phases of drug development to evaluate the ability of disease modifying agents to delay or prevent the onset of dementia due to Alzheimer's disease (AD).

DESIGN: A multi-stakeholder expert workgroup and overseeing steering group were convened to discuss current advances in early interventional clinical trial design and the evidence needs of patients, providers, and payers. Eight teleconferences and one in-person all-day meeting were held. Meetings were recorded and summary notes prepared between sessions. Final conclusions were consolidated by the project team with the workgroup Chair based on these discussions and were reviewed by group members.

SETTING: The in-person meeting was held in Baltimore, MD.

PARTICIPANTS: In total, 36 stakeholders representing life sciences industry, payers or health technology assessors, patient advocates and research advocacy organizations, regulators, clinical experts and academic or NIH researchers.

INTERVENTION: N/A.

MEASUREMENTS: N/A.

RESULTS: Certain aspects of clinical trial design were deemed important to address stakeholder decision needs for future Alzheimer's prevention drugs even as the field rapidly progresses. These include the need for more robust behavioral and psychological outcome data in early symptomatic disease and the need to update activities of daily living measures to include "digital independence."

CONCLUSIONS: Amyloid, tau, and biomarkers of neurodegeneration should be included in trials and studied in relation to other early measures of change meaningful to individuals with AD, their families, and health plans. These measures include early sensitive changes in behavioral and psychological measures and ability to navigate the contemporary digital landscape. Additional work is needed to generate more robust behavioral and psychological outcome data in early symptomatic disease, and to generate multi-stakeholder consensus on early measures of change and magnitudes of change that will be meaningful to patients, providers, and payers.

Key words: Alzheimer's disease, drug development, disease modifying agents, disease interception, coverage and reimbursement.

Introduction

Between 2002 and 2012, candidate drugs to treat Alzheimer's disease had a 99.6 percent failure rate (1). Several lines of evidence support the hypothesis that these trials may have failed because disease modifying therapies for mild cognitive impairment (MCI) due to Alzheimer's and dementia due to AD will need to be administered years before the onset of symptoms (rather than after onset of symptoms, the approach which has traditionally dominated Alzheimer's therapeutics). Evidence supporting this hypothesis is that the amyloid neuropathology that defines the disease is present for 15-20 years before disease onset (2–5); that individuals with Down syndrome who all develop neuropathology by their fifth decade do not develop dementia for many years thereafter (6); and the failure of anti-amyloid and anti-tau drugs to modify disease course when administered after the onset of clinically diagnosed MCI (or prodromal disease (7) or clinically identified dementia due to AD. Some evidence also suggests a need to address several features of neuropathology, not only amyloid beta (8).

For these reasons, researchers are increasingly focused on early intervention, particularly intervention before a diagnosis of dementia has been made, when the

Received July 17, 2018
Accepted for publication August 1, 2018

individual is still considered cognitively normal or mildly symptomatic. This interventional strategy, sometimes called "disease interception," (9) has been employed in other disease areas, most notably cardiovascular disease. In Alzheimer's disease, this early intervention strategy hypothesizes that drugs will be effective prior to widespread neuronal loss and onset of symptoms. There are persistent questions about how early is early enough, and whether amyloid targeting will prove to be an effective strategy (8). Nevertheless, this approach raises a number of design challenges for clinical trials. Key among these challenges are:

- Identifying appropriate asymptomatic candidates for study. A disease interception study for Alzheimer disease must identify cognitively normal people more likely than an unselected population to progress to MCI or dementia due to AD and target them for inclusion in the study.
- Reliably detecting early signs of change or progression. Since following cognitively normal people to a clinical diagnosis of Alzheimer's-type dementia will take years, studies relying on clinical endpoints requiring long follow-up are expensive and difficult to sustain, although potentially highly informative. Predictive biomarkers of progression and treatment response are lacking, and current measures of cognition and function lack sensitivity for detection of very early change. Endpoints detectable at an earlier stage of disease development are needed for disease interception to be a viable clinical development strategy.

This move towards preclinical trials of AD, and the challenges of doing so, are reflected in recent Guidance for Industry issued by the U.S. Food and Drug Administration (FDA) on drug development for early Alzheimer's disease (10). The new draft guidance creates four categories to characterize individuals who may participate in AD clinical trials. Stage 1 covers patients with characteristic pathophysiologic changes of AD but no evidence of impact on everyday function or clinical symptomatology. Stage 2 encompasses patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment. Stage 3 describes patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment. Finally, Stage 4 is patients with overt dementia.

For studies of Stage 2 patients progressing into stage 3, the FDA will consider "strongly justified arguments" of a persuasive effect on neuropsychological performance (preferably demonstrated across multiple individual tests). However, in Stage 1 patients, a clinically meaningful benefit cannot be measured (in a trial of reasonable duration) because there is no clinical impairment to assess. In this case, the FDA advised that an effect on characteristic pathophysiologic changes of AD, as demonstrated by an effect on a biomarker, may be the basis for an accelerated approval with post-approval study requirements to confirm predicted clinical benefit. A pattern of treatment effects seen across multiple individual biomarker measures would strengthen the persuasiveness of the result. At present, insufficient evidence exists that an effect on any biomarker is reasonably likely to predict clinical benefit, but the FDA urges the research community to continue work towards this goal. Biomarkers related to brain physiology and signs of abnormal protein accumulation are seen as increasingly important tools to address these challenges.

A similar move to accommodate preclinical study of AD can also be seen in a new NIA/Alzheimer's Association (AA) workgroup proposal for an updated AD research framework (11). Whereas previous NIA (2011) guidelines characterize Alzheimer's disease mainly through its symptomatology, the 2017 proposal classifies cognitively unimpaired populations according to whether they are "normal" or "abnormal" across three biomarker-based characteristics: amyloid deposition (A), tauopathy (T), and neurodegeneration or neuronal injury (N). In this framework, "Alzheimer's disease" refers to the presence of plaque and tangle pathophysiologic processes as evidenced by "abnormal" findings for both amyloid and tau in vivo. Combinations of these biomarker test results are mapped onto the previously used cognition-based staging terminology of "unimpaired," "MCI," and "dementia."

While intended for research use, not current clinical practice, the NIA/AA proposal provides a window on a likely framework for future clinical trials for the delay or prevention of Alzheimer's dementia. It is thus also a view of where clinical practice is likely to go if predictive biomarkers are successfully developed in conjunction with disease modifying agents having an effect on the development and progression of AD. The idea of "preclinical" disease reflects not only a change in drug development strategy, but a transformation in the underlying understanding and characterization of Alzheimer's disease. AD has gone from being synonymous with dementia to being located on a continuum that encompassing cognitively normal people with changing neuropathology (characterized by biomarkers) with the traditionally recognized stages of dementia.

This changing conceptualization creates a roadway to the future upon which payer expectations of effectiveness and value for diagnostics and therapeutics may be seen as barriers to progress by innovators and also patients seeking access to new medical technologies for AD. A current example can be seen in the lack of reimbursement pathway for amyloid PET scans, considered by many to be a diagnostic aid having proven concordance with autopsy for the demonstration of the presence of amyloid

pathology; conversely a negative scan rules out AD as a cause of dementia. Given the future course of drug development and significant reliance on biomarkers, the example of amyloid PET is potentially one of many reimbursement challenges to come in AD diagnostics and therapeutics. The FDA guidance cited above also makes clear that clinical trials for preclinical AD may result in accelerated approval decisions based on biomarkers for which confirmation of predicted clinical benefit takes place in the post-market phase of development. Broad uncertainty exists as to how payers will view the evidence supporting these early entrants to the market.

For these reasons, engaging payers and patients to understand their concerns and priorities while products are still in development is a challenge of utmost importance. We therefore assembled an expert working group and engaged patient advocates and caregivers, payers, drug developers, regulators, clinicians, and others to discuss current challenges in clinical trial methods and the trial design features of special concern especially to payers and patients. Our discussions resulted in a set of recommendations summarized below. These recommendations will likely need to be updated in the future, as biomarker development and research on AD are moving rapidly. Hence, there will be a continuing need for adjudication between current and future advances in the understanding of how to diagnose, treat, or prevent progression of this disease, including the outcomes most relevant for coverage and reimbursement decision-making and assessment of value.

Methods

A 20-person multi-stakeholder expert working group was formed to discuss specific methodological questions on study design for the purposes of this project. The group was composed of methods and clinical experts (7 clinical drug developers from sponsoring organizations and 6 clinical experts from academia and the NIH, which included neuroscientists and psychiatrists), 4 payers (2 from Medicare, 1 from a state Medicaid program, and 1 from a major national private health insurance carrier), 1 regulator and 3 patient advocates (1 private caregiver, 1 foundation advocate, and 1 hospital-based advocate for patients in research). The group was chaired by Dr. Peter Rabins. A project steering group was composed of 14 clinical and policy experts: 6 life sciences industry, 2 AD research advocacy foundation, 1 U.S. FDA, 4 payer or health technology assessor (representing a large U.S. commercial health plan, the Canadian Agency for Drugs and Technologies in Health, the European Network for Health Technology Assessment, U.S. state Medicaid program); and 1 patient advocate.

In coordination with the workgroup Chair, the project team scanned recent developments related to Alzheimer's drug development, AD disease modification and interception, diagnostic criteria and disease definitions, AD biomarker development, and other topics, to prepare background materials to inform workgroup discussions. A joint steering/workgroup kickoff webinar was held on Feb 28, 2017. A total of 8 workgroup teleconferences, including 2 teleconferences held jointly with the steering group, was held between then and September 2017. An in-person stakeholder meeting with these two groups and additional stakeholders (including an additional private patient advocate) was held on September 28, 2017 in Baltimore, MD. Teleconferences and meetings were transcribed and key conclusions were summarized from each meeting by the project team. These summaries were provided to participants in a shared electronic folder and points of consensus from previous calls were reviewed in subsequent calls.

Due to schedule conflicts and a change in employment, key health plan representatives were not able to participate in the later teleconference or in-person meeting (only 2 payers participated in the in-person meeting, one of whom dialed in remotely for part of the meeting). To assure robust payer input into the project recommendations, the project team reached out to additional external payers (2 commercial payers from companies with covered lives across the U.S. and one of whom was a director for the Medicare advantage plan) who reviewed draft materials, provided written comments, and participated in teleconferences with the project team to discuss their comments and concerns in more detail. These payers did not wish to talk "on the record" because they did not want their views to be taken as formal positions or future policies of their companies. In providing them this anonymity, they felt free to speak freely about the rapidly changing field and concerns of health plans to serve the needs of patients (both of these payers have had personal family experiences with AD and are sympathetic to the needs of patients and families) while also guarding against unanticipated or unmanageable budget impacts. For this reason, these payers are not formally acknowledged or included in the counts of workgroup members above, but their input was taken into consideration.

Results

Based on discussions in the working group, steering group, and in-person meeting, including supplemental feedback from external payers and project participants, the group recommends the following practices. These should be employed in clinical trials of disease modifying agents to assess the delay or prevention of progression to dementia of Alzheimer's disease.

Population

1. Criteria for inclusion in disease interception studies should include the presence of an AD-associated marker. At a minimum, this could include evidence of amyloid

β deposition or tauopathy. CSF phosphorylated tau or increased signal on tau PET may provide further information on AD specific pathological staging.

2. Consider enrichment strategies to enroll patients at an increased risk of progressing to Alzheimer's-type dementia. Enrichment (recruiting people more likely than the general population to progress to dementia) is widely used in preclinical studies of Alzheimer's-type dementia and MCI because the phenomenon researchers are attempting to observe (relatively younger, cognitively normal people developing early signs of dementia within a few years of study initiation) is rare. Enrichment strategies could include the biomarkers noted in Recommendation 1 above, but could also include family history, the presence of genetic markers associated with increased risk of developing AD, or other strategies.

3. Individuals with varied educational backgrounds, ethnic status, and occupational background should be recruited for studies of disease modifying agents to prevent or delay progression to dementia due to AD. To the extent possible, patients having typical comorbidities for the population studied should also be included. Older African Americans are approximately twice as likely to have Alzheimer's (or other dementias) as older whites in the U.S., and Hispanics are approximately 1.5 times as likely to have dementia as older whites (12). Higher risk for Alzheimer's is also associated with fewer years of formal education. These and other associations point to complex and mutually implicating risk factors for Alzheimer's, some of which are modifiable.

Outcomes

4. Phase 3 trials should be designed so that variables that would be included in a Phase 4 follow-on study will be available for analysis. Direct and indirect cost of care, measures of behavioral and neuropsychiatric symptoms, and measures of adverse effects on caregivers are especially important for studies of at-risk, cognitively normal people who progress on a biomarker or to a clinical endpoint of MCI. When patients are to be followed to a diagnosis of Alzheimer's type dementia, measures of daily function in addition to cognitive measures should be included. Variables such as the incidence and severity of behavioral and neuropsychiatric symptoms, caregiver distress, participant quality of life, health care utilization and patient healthcare costs might be used to demonstrate benefit or impacts of therapy in phase 4 trials in addition to delay of cognitive and functional decline. Evidence suggests that both direct medical costs and indirect costs (e.g., need for more supervision by family members and others) are higher for people at the MCI stage of diagnosis, and some costs are measurably elevated even for people who are still testing as cognitively normal a year before a diagnosis of MCI occurs (see Discussion below) (13-15). This increase is also correlated with a reduction in paid and volunteer work for these individuals (16).

5. Consider collecting behavioral and psychological outcome data in early symptomatic disease. There is a dearth of behavioral and psychological outcome data in early symptomatic disease, even though behavioral disturbances, increased anxiety and irritability are prevalent in Alzheimer's-type dementia (17). Recent data suggests that these behaviors are seen in earlier stages of disease development, and may represent an important domain for capturing earlier changes (18). Subtle behavioral changes may be an especially useful early indicator of emergent disease since individuals can consciously practice some cognitive and functional test skills for better evaluation results; these behavioral and psychological test measures are less modifiable through practice.

6. Consider using an adjudication panel that is unaware of participant treatment status (active or control) to ascertain the presence or absence of conversion to dementia or MCI. The validity of the earliest evidence of symptomatic dementia across individual patients is unclear. Use of a panel of experts having information on the participant's baseline condition can allow individualization in the ascertainment of functional decline (for an adjudication of dementia) or memory, executive function or other cognitive domain impairments as an indicator of MCI or AD. Study partners (spouses or family members) are often helpful in detecting early change and providing baseline information. Earliest signs of change may be noted (but not be acknowledged) by the subject themselves or coworkers. As noted below, some currently used functional measures may benefit from updates.

Methods

7. Measures of Activities of Daily Life (ADLs) for early stage detection of change should be updated to reflect declines in function at work and "digital independence," i.e., decline in ability to use common electronic devices for everyday tasks. While most of the basic skills questions posed to caregivers or a study partner on these assessments continue to be relevant and valid ("ate without physical help and used a knife"), most IADL questions were developed prior to the rapid expansion of smartphones, tablets, email, and the Internet. Yet for detection of early changes in function, these devices may provide opportunities for more fine-grained assessment. For example, an individual may be able to use a smartphone for calling people already listed as a contact, but may have lost the ability to add new contacts. Additionally, many contemporary IADLs, such as shopping, money management, and leisure activities, are commonly done with electronic devices. Hence, these heretofore separately assessed activities require electronic literacy and skills not currently taken into account. Measurement of ability to use electronic devices in these

contexts may allow for earlier detection and possibly greater sensitivity to early changes. In addition, these types of functional deficits may be perceived by affected individuals and family members as more relevant than, e.g., the ability to write a check.

Supplemental recommendations

The following recommendations, while not specifically methodological, were strongly voiced by members of the group, thus are included here as 'supplemental' recommendations related to ethical and sensitive conduct of research in this area.

S1. When APOE or other genetic testing for Alzheimer's predisposition is planned to be conducted with trial participants, patients should receive genetic counseling BOTH prior to and after genetic testing, and be well-informed of their right to withdraw from the study without receiving a disclosure of genotype.

S2. When amyloid status is to be conveyed to cognitively normal individuals in preclinical trials for AD, best practices for participant education, preparation, and counseling should be followed.

S3. All clinical researchers of dementia should be sensitive to ethical issues underlying dementia research, including guidelines articulated in the Nuffield Council on Bioethics' report on ethical issues in dementia (21, 22).

S4. Extra care should be taken in clinical trials for AD to assure that patients and their families recognize the possibility of early trial termination.

Discussion

Drug Development Strategies

As noted, the use of genetic testing and family history is an appropriate strategy for population enrichment and drug studies of preclinical AD. The pathological similarity between autosomal dominant and sporadic forms of AD has led to the hypothesis that autosomal dominant cases are likely to benefit from therapies demonstrated to have benefit in late-onset cases. At least one group has therefore suggested that drug efficacy studies conducted in people having heritable, early-onset AD should be considered generalizable to populations of patients having sporadic, late-onset AD (23). This hypothesis is beyond the scope of this report and the workgroup takes no position on it.

Candidate predictive biomarkers should be (and usually are) included in clinical trials of disease modifying agents for disease interception. Developing a greater understanding of the predictive utility of biomarkers and their relationship to clinical endpoints is critical to reducing clinical trial size, making coverage decisions and individual treatment recommendations. It should be recognized, however, that while the focus of this document has been primarily on phase 3 drug trials, outcome and epidemiologic researchers in settings outside of commercial drug development also have a role to play. Clinical drug trials alone are necessary but not sufficient to solve the riddle of preventing Alzheimer's disease.

Coverage, Reimbursement and "Meaningful" therapies

Our health plan informants on this project offered personal opinions that a new agent demonstrated to delay progression to dementia and approved by the FDA would have to be a covered benefit in a health plan. However, a concern is that the first successful trials of disease modifying agents will be initially approved in the U.S. via accelerated approval, which (as noted) may provide health plans with little information on clinical benefits.

Accordingly, a 2015 report called for agreement of a set of "reimbursement endpoints," presumably meaning measures needed by payers for decision-making (24). The report noted the challenge of modeling long-term outcomes on the basis of short-term data; they affirmed that stakeholders need to agree on endpoints that, taken together, could provide a composite picture of long-term effectiveness; it stressed that study designs must reflect varying priorities of stakeholders (clinically and economically relevant to payers, realistic to developers, and important to patients and caregivers); and it noted that longer term follow-up for endpoint validation must be supported through broad-scale registries, analysis of electronic medical records, and other databases. The group indicated that in their forum, "HTAs and payers demonstrated a clear preference for objective end points such as functional measures or resource consumption measures, whereas patient advocates placed greater emphasis on quality-of-life metrics." The group recommended a series of clinical effectiveness endpoints for collection less than 2 years post-launch and 2 to 5 years post-launch of a disease modifying therapy. However, for prevention trials enrolling cognitively normal individuals, some of the recommended measures may not produce measurable change in the time horizons suggested. For example, in asymptomatic populations or those with only mild cognitive impairment, there may be no discernable change in quality of life, independence or autonomy, or frequency of adverse events during a two-year span. Similarly, for these populations, significant differences in mortality may not be seen within the 2 to 5-year timeframe. Hence, overall, these recommendations and timeline may be more applicable to products targeting early symptomatic disease, rather than products developed for disease interception.

Nevertheless, consistent with the cited report, our external informants indicated that, for them, "meaningful" outcomes would demonstrate long-term

differences that can be perceived by patients, families, and providers. Chief among these would be maintaining the ability for individuals with dementia to remain at home in a safe, reasonably well-functioning manner, rather than being institutionalized. While they also acknowledged that payers are concerned about resource use, our informants underscored that use of medical resources can serve as an effective proxy for patient quality of life. Our payer informants recognized that these outcomes are far in the future from disease interception studies. Nevertheless, they continued to emphasize "real" change, regardless of the stage of disease. Hence, the importance of connecting changes in biomarkers to subtle cognitive, psychological, or behavioral changes, especially if these portend changes in function, such as an ability to keep working, and other delays in progression that patients, providers, and families can perceive.

Consistency and Relevance of Outcomes Used in Prevention Trials

Recent reviews of early symptomatic and prevention trials of AD have shown broad inconsistency in the clinical outcome measures used to measure cognitive and functional declines associated with AD, which complicate comparisons between drug trials. The National Academies of Medicine called for greater consistency in the selection of outcomes in AD studies and a 2012 Institute for Clinical and Economic Review (ICER) report called for a common core set of outcomes for development of diagnostic tests for Alzheimer's (25). Similarly, the 2016 Alzheimer's Disease-Related Dementias Summit recommended harmonizing test batteries (but avoided mandating a specific test) (26). Also of note: a recent AHRQ systematic review suggested that the use of the Alzheimer's disease Assessment Scale – Cognitive Subscale (ADAS-Cog) has improved consistency of methodology across studies in symptomatic patients (27).

As these reports imply, continued inconsistency as trials multiply will make it more difficult for patients, caregivers, clinicians, and payers to make informed decisions on covered benefits and appropriate treatment options. However, the composite cognitive outcome measures developed for use in preclinical AD are similar in that they all include scales capturing domains of episodic memory, executive function/processing speed, and language/semantic processing (28). So in preclinical studies, there may be more consistency at least across composite cognitive outcomes. Nevertheless, as biomarker-based surrogate outcomes are developed measurement heterogeneity is likely to proliferate. One possible solution is the development of a core outcome set: a minimum set of outcomes recommended to be collected in all clinical trials for a given condition (29). One group has recently published recommendations for a core outcome set for assessment of interventions in mild to moderate dementia due to Alzheimer's (30). However, these recommendations apply to mild to moderate dementia, not disease interception, hence early stage markers of change have yet to be addressed. Given that, measurement tools for detecting changes in biomarkers, cognition, or function that are predictive of dementia are imperfect, the expert working group on this project recommended against developing a core set for studies of preclinical or pre-dementia stages of AD at this time.

Even so, the project team's consultation with external payers pointed to the need for a better understanding of patient and caregiver priorities and concerns for research, care, and resource use across the disease spectrum. Specifically, they called for a patient-centered, patient-informed framework for defining drug effects (the character and magnitude of effects) that should be considered in the context of value assessment. This would be an important preparatory step for then defining core outcomes of importance to patients and caregivers across the disease spectrum. If informed also by the needs of regulators, payers, and other stakeholders, the resulting core outcomes could form the heart of a value assessment framework for therapies intended to treat this condition.

Concluding Remarks

While any new disease modifying therapies entering the market will require a longer-term development strategy, several measures of direct and indirect costs of care, early subtle cognitive change (possibly very early functional changes with respect to use of electronic devices), and behavioral and neuropsychiatric symptoms would be useful data to collect throughout phase 3 and 4 studies. (Note that these potentially important psychosocial endpoints are missing from the Tapestry Networks list cited above. From the point of view of some of our workgroup members, this is a serious omission.) These may be very early signs of changes predictive of progression and may thus serve as early data points for long-term models. If these early clinical measures are carefully correlated with physiological (biomarker) changes and later progression, they may also reduce the number of scans, lumbar punctures, and other techniques required for patient assessment.

The question arises not only what are meaningful therapeutic effects, but also what are meaningful effect magnitudes or durations. Some observers perceive the payer emphasis on "real" change as representing expectations that may be difficult to meet in the near term, leading possibly to lack of coverage for promising newly approved agents. On the other hand, some payer informants expressed concern that health plans would be compelled to pay for new drugs having a modest effect on a biomarker and unknown value in terms of lived patient experience. Both of these concerns point to the

continuing need for multi-stakeholder deliberation and agreement on the minimal clinical differences and early measures of change that will be meaningful.

Disclosure: Dr. Messner reports grants from Eli Lilly and Co., Roche, Pfizer, and Johnson and Johnson in support of the submitted work. The Center for Medical Technology Policy also received grants from Eli Lilly and Co. in the previous 18 months unrelated to the submitted work.. Dr. Rabins reports personal fees from The Center for Medical Technology Policy during the conduct of the study. Full-time employee of Eli Lilly and Company and minor shareholder. Dr. Irizarry reports other from Eli Lilly and Company outside the submitted work. Dr. Foster reports receiving research grants from the June Morris Trust, the Rodney and Carolyn Brady Fund, the National Institutes of Health, and contracts to perform clinical trials from Biogen, Lilly Pharmaceuticals, AbbVie and GE Healthcare. He is a consultant to AbbVie, Inc. and CEO and co-owner of Proactive Memory Services, Inc. Ms. Al Naber reports grants from Eli Lilly and Co., grants from Roche, grants from Pfizer, grants from Johnson & Johnson during the conduct of the study; grants from Eli Lilly & Co. outside the submitted work. Dr. Dabbous has nothing to disclose. Dr. Fillit reports personal fees from Axovant, personal fees from Eli Lilly, personal fees from Roche, personal fees from Samus Therapeutics, personal fees from vTv Therapeutics, personal fees from Otsuka, personal fees from Lundbeck outside the submitted work. Ms. Gabler has nothing to disclose. Dr. Krakauer has nothing to disclose. Dr. Lotz has nothing to disclose.

Acknowledgments: We wish to express gratitude for the thoughtful input and participation of all the experts and stakeholders who contributed to this work.

Funding sources: This project was funded by a precompetitive consortium of life sciences companies. The Center for Medical Technology Policy, an independent 503(c)(3) non-profit, and its multistakeholder platform for clinical evidence standards, the Green Park Collaborative, gratefully acknowledge support from: Eli Lilly & Co., Roche, Pfizer, and Johnson & Johnson.

Conflict of interest: All potential conflicts of interest have been reported in the disclosures above.

Ethical standards: All applicable ethical standards were observed in the conduct and reporting of this work.

References

1. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy. 2014;6(4):37. doi:10.1186/alzrt269
2. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. The Lancet Neurology. 2013;12(4):357-367. doi:10.1016/S1474-4422(13)70044-9
3. Reiman EM, Quiroz YT, Fleisher AS, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. The Lancet Neurology. 2012;11(12):1048-1056. doi:10.1016/S1474-4422(12)70228-4
4. Jack CR, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain. 2009;132(5):1355-1365. doi:10.1093/brain/awp062
5. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. New England Journal of Medicine. 2012;367(9):795-804. doi:10.1056/NEJMoa1202753
6. Head E, Powell D, Gold BT, Schmitt FA. Alzheimer's Disease in Down Syndrome. Eur J Neurodegener Dis. 2012;1(3):353-364.
7. Cummings JL, Dubois B, Molinuevo JL, Scheltens P. International Work Group Criteria for the Diagnosis of Alzheimer Disease. Medical Clinics of North America. 2013;97(3):363-368. doi:10.1016/j.mcna.2013.01.001
8. Murphy MP. Amyloid-Beta Solubility in the Treatment of Alzheimer's Disease. New England Journal of Medicine. 2018;378(4):391-392. doi:10.1056/NEJMe1714638
9. Walsh C, Drinkenburg WHIM, Ahnaou A. Neurophysiological assessment of neural network plasticity and connectivity: Progress towards early functional biomarkers for disease interception therapies in Alzheimer's disease. Neurosci Biobehav Rev. 2017;73:340-358. doi:10.1016/j.neubiorev.2016.12.020
10. US Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment, Guidance for Industry (Draft Guidance). February 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf. Accessed February 23, 2018.
11. Jack CR, Bennett DA, Blennow K, et al. 2018 NIA-AA Research Framework to Investigate the Alzheiemr's Disease Continuum (DRAFT). September 2017. https://alz.org/aaic/_downloads/draft-nia-aa-7-18-17.pdf. Accessed February 6, 2018.
12. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2017;13(4):325-373. doi:10.1016/j.jalz.2017.02.001
13. Zhu CW, Sano M, Ferris SH, Whitehouse PJ, Patterson MB, Aisen PS. Health-Related Resource Use and Costs in Elderly Adults with and without Mild Cognitive Impairment. Journal of the American Geriatrics Society. 2013;61(3):396-402. doi:10.1111/jgs.12132
14. Leibson CL, Long KH, Ransom JE, et al. Direct medical costs and source of cost differences across the spectrum of cognitive decline: A population-based study. Alzheimer's & Dementia. 2015;11(8):917-932. doi:10.1016/j.jalz.2015.01.007
15. Lin P-J, Zhong Y, Fillit HM, Chen E, Neumann PJ. Medicare Expenditures of Individuals with Alzheimer's Disease and Related Dementias or Mild Cognitive Impairment Before and After Diagnosis. Journal of the American Geriatrics Society. 2016;64(8):1549-1557. doi:10.1111/jgs.14227
16. Sano M, Zhu CW, Whitehouse PJ, et al. ADCS Prevention Instrument Project: pharmacoeconomics: assessing health-related resource use among healthy elderly. Alzheimer Disease & Associated Disorders. 2006;20(Supplement 3):S191-S202.
17. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. International Journal of Geriatric Psychiatry. 2008;23(2):170-177. doi:10.1002/gps.1858
18. Geda YE, Roberts RO, Mielke MM, et al. Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study. American Journal of Psychiatry. 2014;171(5):572-581. doi:10.1176/appi.ajp.2014.13060821
19. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE Genotype for Risk of Alzheimer's Disease. New England Journal of Medicine. 2009;361(3):245-254. doi:10.1056/NEJMoa0809578
20. Messner DA. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society. 2011;30(1):59-72. doi:10.1080/14636778.2011.552300
21. Nuffield Council on Bioethics. Dementia: Ethical Issues. London: Nuffield Council on Bioethics; 2009.
22. Black BS, Taylor HA, Rabins PV, Karlawish J. Study partners perform essential tasks in dementia research and can experience burdens and benefits in this role. Dementia. May 2016:147130121664879. doi:10.1177/1471301216648796
23. Progress and Challenges in Alzheimer's Disease Drug Development: An Update on Scientific, Clinical, and Regulatory Considerations from an Industry Perspective | Global CEO Initiative on Alzheimer's Disease. http://www.ceoalzheimersinitiative.org/node/90. Accessed February 2, 2018.
24. Bradley P, Akehurst R, Ballard C, et al. Taking stock: A multistakeholder perspective on improving the delivery of care and the development of treatments for Alzheimer's disease. Alzheimer's & Dementia. 2015;11(4):455-461. doi:10.1016/j.jalz.2014.01.007
25. Pearson SD, Ollendorf DA, Colby JA. Diagnostic Tests for Alzheimer 's Disease : Generating and Evaluating Evidence to Inform Insurance Coverage Policy. December 2012. https://pdfs.semanticscholar.org/2750/577ecc59b14aaaaa8d0bffb02aebba8c8498.pdf. Accessed January 5, 2018.
26. Holtzman DM, Corriveau RA. 2016 Alzheimer's Disease-Related Dementias Summit: Report to the National Advisory Neurological Disorders and Stroke Council. https://www.ninds.nih.gov/sites/default/files/ADRD2016_summit_council_rpt_508Cpdf.pdf. Published September 15, 2016. Accessed November 16, 2017.
27. Agency for Healthcare Research and Quality. Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/cognitive-decline_research-2017.pdf. Published Maarch 2017. Accessed November 16, 2017.
28. P. Aisen, J. Touchon, R. Amariglio, et al. EU/US/CTAD Task Force: Lessons Learned from Recent and Current Alzheimer's Prevention Trials. 2017. doi:10.14283/jpad.2017.13
29. Home :: Core Outcome Measures in Effectiveness Trials Initiative (COMET). http://www.comet-initiative.org/. Accessed November 16, 2017.
30. Webster L, Groskreutz D, Grinbergs-Saull A, et al. Core outcome measures for interventions to prevent or slow the progress of dementia for people living with mild to moderate dementia: Systematic review and consensus recommendations. PlosOne. June 2017. doi:doi.org/10.1371/journal.pone.0179521