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Perspectives

Can we prevent Alzheimer's disease? Secondary "prevention" trials in Alzheimer's disease

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Abstract Current research including the basic biology of Alzheimer's disease (AD) provides a foundation to explore whether our current state of knowledge is sufficient to initiate prevention studies and allow us to believe prevention of AD is possible. Current research and recently revised criteria for the diagnosis of AD by the National Institutes on Aging and the Alzheimer's Association suggest a continuum of disease from preclinical asymptomatic to symptomatic Alzheimer's dementia. In light of these revised criteria, the possibility of secondary prevention and even primary prevention is under discussion. The Alzheimer's Association Research Roundtable convened a meeting to discuss the rationale and feasibility of conducting secondary prevention trials in AD.

Keywords: Alzheimer's disease; Prevention; Diagnosis; Mild cognitive impairment; Preclinical Alzheimer's

1. Introduction

Advances in the treatment of heart disease and cancer are largely responsible for a true postponement of mortality and a marked change in the biodemographics of aging over the past 150 years [e1]. If the trend continues, most babies born in many highly developed countries at the beginning of the 21st century can expect to live past the age of 100 years, nearly double the average life expectancy only 1 century ago.

As the population ages, the prevalence of Alzheimer's disease (AD) and related dementias is also increasing. In the Kame project, a population-based cohort study of Japanese-Americans living in King County, Washington, the prevalence of AD increased from 1.4% among those aged 70 to 74 to 50.2% among those aged 90 to 94 [1]. Nearly three fourths of individuals over the age of 95 were found to be demented. However, neuropathological studies have shown that most individuals diagnosed with sporadic AD do not have "pure" AD and that the prevalence of comorbidity for illnesses that contribute to cognitive impairment increases with advancing age. Most persons diagnosed in late life have AD in combination with cerebrovascular pathology or other neurodegenerative pathologies such as Lewy body disease [2].

There is also increasing evidence suggesting that many risk factors that contribute to the development of late-life dementias are modifiable. Moceri et al proposed that

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because the hippocampus is the area of the brain that takes the longest to mature but is the first area affected in AD, environmental exposures during early life could influence the development of late-life AD [3]. Subsequent studies have suggested that education, complexity of occupation, and an engaged lifestyle have protective effects. Exercise has also been associated with a reduced risk of dementia [4], and many vascular risk factors, including high cholesterol, hypertension, diabetes, smoking, and atrial fibrillation have also been linked to AD and vascular dementia (VaD) [5, e2].

What does this all mean in terms of prevention? Is there a magic bullet that might prevent Alzheimer's and other dementias in late life? Up until now, studies that have targeted various potentially modifiable risk factors have been disappointing, although emerging evidence from large descriptive cohort studies has suggested that general improvements in midlife health, especially better control of vascular risk factors, may be associated with a decline in the incidence of cognitive impairment.

Barnes and Yaffe calculated the population-attributable risk for seven lifestyle risk factors that seem most promising in terms of primary prevention [6]. Worldwide, low education, smoking, physical inactivity, and depression were most strongly correlated with AD risk; in the United States, physical inactivity, depression, smoking, and midlife hypertension had the highest correlations. They concluded that up to half of AD cases may be attributable to modifiable risk factors, and that even a modest reduction of 10% in all of these risk factors combined could reduce the incidence of AD by over 1 million people worldwide.

Other potentially modifiable lifestyle risk factors that increase the risk of AD but have gotten less attention include sleep disorders and diet. Sleep-disordered breathing is common among older adults, and one study showed that older women with sleep-disordered breathing had nearly twice the risk of developing mild cognitive impairment (MCI) or dementia compared with women without sleep-disordered breathing [7].

The influence of diet is more controversial. Some studies have suggested that supplementation with omega-3 fatty acids or adherence to the "Mediterranean diet" may reduce the incidence of dementia. However, at a State-of-the-Science Conference convened by the National Institutes of Health (NIH) in 2010, insufficient evidence was found to support the association of diet or any other modifiable risk factors with AD [8].

To avoid future large, expensive, and unsuccessful prevention trials, enrichment of study cohorts through risk stratification may be the key. In addition, cognitive outcomes, biomarkers, and imaging should be added to other prevention trials in which cognition is not the primary outcome. Multidomain approaches that combine lifestyle modification with pharmaceutical intervention are also needed.

2. Prevention of disease—lessons learned

2.1. Prevention of heart disease and cancer

Prevention trials in other areas provide important lessons that may be instructive for future AD prevention trials in regard to sample size, duration, use of biomarkers, and intermediate outcomes. Although heart disease remains the leading cause of death worldwide, the number of deaths from cardiovascular disease has decreased significantly in the past few decades [9]. The reduction in deaths is attributable to treatment improvements, including revascularization, and secondary prevention after a myocardial infarction, as well as changes in risk factors, particularly a reduction in cholesterol levels and blood pressure, a decrease in smoking, increased exercise, and a general change in the U.S. diet away from animal fats [e3,e4]. These successes in lowering mortality from heart disease were built on a strong basic science foundation, experimental models that reflected key pathogenic elements of disease in humans for preclinical development, strong consensus from the scientific community regarding the importance of lowering cholesterol, and large cohort hypertension and smoking studies. Large, successful, and informative drug trials followed. More than 12 trials have investigated the ability of statins to lower cholesterol. Three of these trials looked specifically at simvastatin: the West of Scotland Coronary Prevention Study (WOSCOPS), the Heart Protection Study, and the Scandinavian Simvastatin Survival Study (4S). These trials concluded that statins reduced the risk of recurrent heart disease by between 25% and 35% in different high-risk populations. Each of these trials lasted for 5 years and enrolled between 4400 and over 20,000 subjects. Other prevention trials, such as the Women's Health Initiative, which tested the effects of postmenopausal hormone therapy and other dietary changes on heart disease and cancer, and the Breast Cancer Prevention Trial, which tested whether tamoxifen could prevent breast cancer in women at high risk, also enrolled large numbers of subjects and lasted for many years. In contrast, an Alzheimer's Disease Cooperative Study (ADCS) trial of statins in a population of mild to moderate AD, which did not find an effect on cognitive function, enrolled only 406 subjects and lasted only 18 months [10].

These trials raise many questions relevant to AD prevention trials but few clear answers. Have AD prevention trials been too short, too late, too small, or too narrow? The heart disease trials suggest that long duration of follow-up is critical for prevention trials. In AD, there are few clinical data regarding how long treatment with disease-modifying therapy might be needed before an effect is seen, and it may be that short trials lead to incorrect conclusions (i.e., that a preventive approach is ineffective although it might have shown efficacy in a longer trial). In addition, little is known about the appropriate biomarkers that are indicators of disease progression, especially in the asymptomatic phase of

the disease. Additionally, we are at the early stages of understanding the number of individuals required to adequately power a prevention trial.

At what point in the disease process a preventive treatment needs to be started is another critical question. Although overt symptoms of AD typically begin after age 65, the pathological cascade almost certainly begins decades earlier, and risk factors for AD may begin early in life. Moreover, AD is a heterogeneous disorder with multiple important therapeutic targets, about which we know relatively little. These include not only the amyloid pathway, but tau, ApoE4, and inflammation. However, in contrast to heart disease, in which there is no lower limit beyond which cholesterol level is thought to be dangerous, the functions of β-amyloid (Aβ) and the upper and lower safe limits are not fully known in AD. High levels of Aβ have been shown to impair long-term potentiation (LTP) and memory [11,e5] whereas some more recent studies suggest that very low levels may also impair LTP and memory as well as synaptic plasticity [12, e6].

2.2. Screening for disease or elevated risk

Screening to identify individuals at elevated risk could be helpful in selecting subjects for clinical trials and for targeting public health prevention messages. Screening for individuals with latent disease would, in theory, be essential to identifying individuals with presymptomatic disease, allowing for intervention and medical management at the earliest stages. However, screening campaigns may carry with them risks of their own, as seen in cancer screening efforts. In 1968, the World Health Organization published screening guidelines [e7], which stated among other points that the disease must be an important cause of morbidity and mortality with a well-understood natural history; screening tests should be accurate; treatments should be efficacious, cost-effective, and more effective early than late; the risks of screening should be low; and the appropriate follow-up should be ensured.

AD clearly meets the importance criteria, although there is no consensus on whether screening an asymptomatic population for risk or early disease is warranted. Moreover, uncertainty about the natural history of the disease and the lack of effective treatment raises questions about screening.

One of the most widely used screening tests in the cancer field is the prostate-specific antigen (PSA) test, a tumor marker measured by a simple blood test. Like other screens, the PSA test is not diagnostic and must be followed up with a true diagnostic test (in this case a biopsy) to detect cancer. The problem is that as many as 75% of men over the age of 85 would be diagnosed with the histological prostate cancer if biopsied [13], but most of those cases are not of clinical significance and the treatments for prostate cancer have serious side effects. The PSA test itself has poor specificity and will not differentiate aggressive versus nonaggressive cancers [14, e8].

Screening accuracy is a critical issue in AD as in cancer, with tradeoffs between sensitivity and specificity. Although true negatives have few adverse consequences, false negatives could delay treatment (if a treatment were available); and false positives could have major detrimental effects on a person who falsely believes he has a neurodegenerative disease. Even true positives carry risks because a positive test initiates a cascade of events fundamentally changing the decision-making process.

2.3. Preventing Parkinson's disease through early detection

The effort to prevent and treat Parkinson's disease (PD) is more closely allied to AD efforts than those in heart disease or cancer and is similarly not as developed. Thus, although PD is the second most common neurodegenerative disease [e9], there have been no prevention trials in PD at this time. However, like AD, the pathologic processes underlying PD begin well ahead of symptoms and the potential for disease modification most likely requires early detection and treatment. Also similar to the AD field, there is an expanding prediagnostic toolbox available to PD clinicians and researchers, including biomarkers, imaging, genetic testing, and evidence of early clinical signs.

A collaborative study called the Parkinson's Associated Risk Study (PARS; www.parsinfosource.com) has developed a paradigm for early identification of PD through a sequential screening approach, starting with primary biomarkers that have high sensitivity but low specificity and are easy to administer and inexpensive, and following that with high-specificity, quantitative biomarkers that are responsive to change and reliable [15, e10]. In the first phase of the study, eligible subjects (PD relatives and nonrelatives over the age of 60) are mailed the University of Pennsylvania Smell Identification Test (UPSIT) [16]. Loss of smell has been shown to be one of the earliest signs of PD, often predating motor symptoms by many years, although loss of smell also occurs normally with aging. Subjects who score in the lowest 15 percentile of those who return the screening test are evaluated by a clinician and then may be invited to take part in dopamine transporter imaging, a test that has been shown to identify PD in individuals 1 or 2 years before developing symptoms. Early follow-up data from a few subjects in the PARS study showed that 4 of 12 individuals with abnormal dopamine transporter imaging scans had developed PD in a 2-year period, suggesting that this approach indeed effectively identifies PD in its earliest stages.

3. Biology of AD

Since the time of Alois Alzheimer, neuropathologists have identified amyloid plaques and neurofibrillary tangles (NFTs) in the autopsied brains of people with AD, suggesting that these pathologies cause the disease [e11]. Aβ and

phosphorylated tau (p-tau), the proteins that structurally makes up plaques and NFTs, respectively, are being intensely studied as possible biomarkers [e12]. Recent results from the Dominantly Inherited Alzheimer's Network (DIAN) observational trial indicated that these possible surrogate disease markers change decades before people show signs of cognitive impairment [17]. Changes in Aβ and tau in the cerebral spinal fluid (CSF) or deposition of Aβ in the brain as measured by neuroimaging studies, along with memory studies, fluorodeoxyglucose positron emission tomography (FDG-PET), and hippocampal volume, suggest that there may be a temporal order to these markers [18]. The importance of understanding where and when these markers change is critical for understanding which targets are appropriate in the early stages of disease to halt or reverse the neurodegenerative process [19]. Because we do not know the etiology(ies) of Alzheimer's, which is probably due to the interaction of environmental and genetic factors, there are still many other unanswered questions regarding the biological basis of AD [e13].

One of the important unanswered questions involves the mechanism of neuronal death caused by changes in tau. There is also much debate about whether tangle formation and aggregation are necessary or sufficient for neuronal death. Indeed, there is good evidence that there are two modes of tau-mediated cell death at work: one related to NFT toxicity (e.g., biochemical changes in tau resulting from phosphorylation, oxidation, etc.) and another related to conformational and morphological abnormalities in tangles [20]. Recent evidence suggests that tau pathology is a spreading process that begins in the entorhinal cortex and extends early on to adjacent areas into the hippocampus, with small foci in the temporal neocortex, impairing neuronal function and ultimately killing cells [e14]. Moreover, there is new evidence that abnormal tau in one cell can catalyze formation of abnormal tau in other cells, perhaps by a prion-like mechanism [21]. It is important to note that it is not until around Braak stage III, IV, or V that cognition commonly is impaired [22], suggesting that blocking the development of tau pathology (e.g., with passive immunotherapy) could prevent the progression of disease. Studies in mouse models have already demonstrated that antibodies directed against pathological forms of tau can reduce pathology and delay onset of functional decline [23].

The evidence for Aβ playing a major role in AD pathogenesis is also strong. Dominantly inherited forms of AD are characterized by missense mutations in the amyloid precursor protein (APP) or presenilin1 or 2 genes, which lead to increased $A\beta_{42}$ production throughout life. Late-onset AD is thought to be related to a failure of Aβ clearance mechanisms [24] (including those involving ApoE4, which accounts for about half of the genetic risk [e15]) leading to gradually rising $A\beta_{42}$ levels in the brain. In both cases, increased levels of $A\beta_{42}$ result in oligomerization and aggregation, subtle effects on synaptic efficiency, deposition of Aβ as diffuse plaques, and a cascade of other injurious processes in the brain eventually leading to dementia. Moreover, Aβ dimers isolated from the brains of AD patients induce tau phosphorylation and neuritic degeneration, and passive immunotherapy mitigates this pathophysiology [25]. In addition, when tau is knocked out, neurons are protected against the effects of soluble Aβ oligomers, suggesting that Aβ and tau work together in causing AD [26].

Evidence further suggests that diffusible soluble species of Aβ oligomers are responsible for cytotoxicity and synaptotoxicity [27, e16]. Amyloid plaques may serve as reservoirs to sequester these soluble oligomers. Thus, the plaque burden may stay relatively stable once patients are symptomatic (as has been shown in amyloid imaging studies) whereas free oligomers are nonetheless causing damage. These findings may suggest that future trials targeting Aβ may be successful, particularly if drugs are given in the mild stages of AD or earlier during asymptomatic stages.

Amyloid may also help explain why dementia is common after an ischemic stroke. In the Canadian Study of Health and Aging, individuals with cognitive impairment but no dementia were at a greater risk for stroke [28]. Additionally, individuals that had a stroke were at a significantly greater risk of cognitive impairment, suggesting there is a reciprocal relationship between stroke and cognitive impairment [28]. Moreover, subcortical infarcts increase the negative effect of Alzheimer's pathology, raising the odds of dementia some 4-fold, and had a significant effect on lowering memory [29]. Now investigators are trying to determine the mechanism for this apparent interaction and have shown that when strokes are induced in rats, intracerebroventricular injection of Aβ results in learning and memory deficits, larger infarcts, and increased neuroinflammation [30]. Furthermore, Alzheimer's mouse models undergoing experimental stroke increased amyloid deposition [31]. These studies and the high prevalence of AD in stroke patients suggest that stroke patients may be a reasonable group in which to test new anti-amyloid or anti-inflammatory agents for their effect on the development of AD. Conversely, antistroke prevention and therapy may benefit individuals at risk for developing Alzheimer's [28].

4. Planned prevention trials for AD

Several prevention trials are currently in the planning stages or have begun enrolling subjects. As described below, these trials focus on different populations—asymptomatic individuals with biomarker evidence of AD pathology (i.e., late onset) and presymptomatic individuals with dominant mutations or other genetic risk factors for Alzheimer's (i.e., early onset). Thus, the differences in these trials raise questions about generalizability because it may be that early-onset and late-onset AD represent different pathological processes that would respond differently to a given treatment. Nonetheless, these trials should provide important information for moving forward.

4.1. Anti-amyloid treatment for asymptomatic AD trial

The Anti-Amyloid Treatment for Asymptomatic AD Trial (A4 trial), to be conducted by the National Institute on Aging (NIA)-funded ADCS, has been proposed as a secondary prevention trial to begin in early 2013 in clinically normal, Aβ-positive individuals who will receive an anti-amyloid therapy for a 3-year period. Subjects will be selected through a stepwise process, beginning with a telephone screen and followed by a clinical screen and imaging studies that would identify those who are Aβ-positive but cognitively normal. To maximize the efficiency of the trial, it would be helpful to enrich the study population with individuals who are most likely to decline, or "tip," toward MCI during the study period; however, a complication of that strategy is that this group would likely include those with subtle cognitive symptoms who may have already experienced significant neurodegeneration and thus be less likely to respond, or to have a diminished response, to anti-amyloid treatment.

The selection of the therapeutic agent for this trial was recently announced, solanezumab and has clear evidence of target engagement in humans and adequate safety data to support a 3-year trial. Solanezumab is a monoclonal antibody given passively that targets the amyloid β protein. The primary outcome measure will be rate of cognitive decline on a cognitive measure, supported by biomarker evidence of a decrease in amyloid burden. Power calculations indicate that to detect a 25% effect on the cognitive endpoint over 3 years, 400 to 500 subjects per arm will be needed.

Ethical issues have also been considered, and an ethics project is embedded in this planned trial. Subjects enrolled in the trial will be informed of their amyloid status, although it is still unclear what amyloid positivity means at an individual level with regard to progression to MCI or AD. There are also potential risks of exposure to a biologically active anti-amyloid agent [32], but these subjects are cognitively intact and should be able to make a fully informed decision about participation.

4.2. Alzheimer's prevention initiative

The Banner Alzheimer's Institute in Phoenix, Arizona, has developed a strategy to rapidly evaluate presymptomatic treatments by enrolling subjects at high risk of developing symptoms on the basis of their age and genetic background [e17]. The Alzheimer's Prevention Initiative (API) will establish two registries, one in Antioquia, Columbia, and the other in the United States [33]. Antioquia, Columbia, is home to the world's largest early-onset AD (EOAD) kindred. Approximately one third of the members of this kindred carry a rare autosomal-dominant mutation in the presenilin 1 (*PSEN1*) gene [e18], which confers certainty of developing AD symptoms by approximately age 45. The second registry will include North Americans over the age of 50 who are homozygous for the *APOE* ε4 allele, which confers increased risk for developing late-onset AD (LOAD) [34]. Using these registries, API will enroll persons close to their estimated age of onset in prevention trials using amyloid-modifying treatments. The primary outcome will be a change in cognition, assessed by a cognitive test battery still under development. Subjects will also be assessed by a magnetic resonance imaging (MRI) battery, plasma and CSF biomarkers, amyloid positron emission tomography (PET) imaging, and FDG-PET. This study design, in addition to assessing treatment efficacy and giving those at highest imminent risk access to investigational treatments, should help qualify biomarkers for use as reasonably likely surrogate endpoints and provide a test of the amyloid hypothesis.

Crenezumab, a monoclonal antibody therapy that targets the amyloid β protein, will be used in this study. Crenezumab (MABT5102A) has gone through Phase I trials and is currently being evaluated in a clinical trial of patients with mild to moderate Alzheimer's (NCT01343966, clinicaltrails.gov). The first EOAD and LOAD trials are either underway or will be launched in the early part of 2013.

4.3. DIAN

DIAN is an international research partnership established to study the adult children of parents with dominantly inherited AD [17]. These offspring are at 50% risk of themselves inheriting the gene, which makes them an ideal cohort in which to evaluate preventive therapies [e19]. Not only can investigators determine with 100% certainty whether they will get the disease, but also approximately when they will begin to show symptoms. In addition, because most disease-modifying treatments were developed with animal models on the basis of human disease-causing mutations, individuals with these mutations are more likely to respond to those treatments. Because biomarker studies show marked similarities between dominantly inherited AD and sporadic AD, results of these studies are likely to inform treatment studies for sporadic AD. However, one difference between these two populations that needs to be considered is that because most dominantly inherited forms of AD occur before age 60, DIAN participants are more likely to have "pure" AD whereas most elderly people with AD have mixed types and several comorbidities [35]. This is an important distinction from a clinical trials and public health perspective. It is noteworthy that early trials demonstrating the value of antihypertensive treatment were conducted in individuals with extremely high blood pressure; however, the public health benefit of antihypertensive treatment probably results from treating a much larger fraction of the population, including those less severely affected.

The DIAN registry of participants at risk for autosomal-dominant AD had enrolled 301 participants as of September 2012 and hopes to reach 400 participants. Participants undergo a battery of assessments including cognitive and other neuropsychological tests, MRI, amyloid imaging with

Pittsburgh compound B positron emission tomography (PET-PiB), FDG-PET, and lumbar puncture for CSF biochemical analysis. Estimated age of onset for those with a mutation is based on the parent's age of onset, and interim analysis of data from 128 participants shows changes in clinical, cognitive, imaging, and biochemical markers long before onset. A decline in CSF Aβ was apparent 25 years before expected onset; increased amyloid deposition, CSF tau, and brain atrophy 15 years before expected onset; cerebral hypometabolism and impaired episodic memory 10 years before expected onset; and global cognitive impairment 5 years before expected onset [17]. DIAN expects to launch proof-of-concept studies followed by three parallel clinical studies of efficacy in 2013. The primary outcome of the initial phase of the trial will be rate of change for amyloid deposition and other biomarkers as secondary outcomes. In the second phase of the trial, cognitive endpoints will be the primary outcome with biomarkers as secondary outcomes.

4.4. Canadian prevention trial

The Centre for Studies on Prevention of AD (StoP-AD) at the Douglas Institute in Montreal, Canada, has established a PREVENT-Alzheimer program (www.douglas.qc.ca/page/prevent-alzheimer) aimed at testing several preventive interventions in people over age 60 with a family history of AD. Interventions that may be tested include naproxen, an ApoE inducer, and nasal insulin, all of which have some data to support their use in presymptomatic individuals. Lifestyle modifications such as aerobic exercise and dietary modifications may also be tested. Over a 2-year period, participants will undergo structural and functional MRI scans and contribute CSF and plasma for biomarker studies. The goals are to find and document optimal biomarker endpoints, including patterns and inter-relationships among different biomarkers; identify interventions that move biomarkers or mitigate their progression; and establish optimal intervention strategies that will inform pivotal Phase III trials. The project was launched in September 2011, and by mid-October it had already enrolled 100 volunteers.

4.5. Australian imaging biomarkers and lifestyle flagship study of aging intervention

The Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging (AIBL) is a study designed to investigate the possibility of delaying AD by reducing vascular risks through physical activity [36] (www.adni-info.org/scientists/Pdfs/AIBL2011FINAL.pdf). This randomized controlled trial will examine the interaction between vascular and Alzheimer's pathologies in 150 community-dwelling individuals over the age of 60 recruited from the Melbourne AIBL cohort. Participants must have a subjective memory complaint (SMC) or diagnosis of MCI and at least one cardiovascular risk factor. The primary outcome measure will be change in white matter hyperintensities (WMH) over the 24-month study period. The study should help answer questions regarding the clinical relevance of WMH and whether treatment of cardiovascular risk factors can alter WMH and produce clinically relevant outcomes. Results are expected in June 2014.

4.6. Zinfandel-Takeda pharmaceuticals alliance

A Phase III primary prevention study is planned in cognitively normal elderly subjects, stratified by applying an algorithm of their TOMM40-523 genotype, presence of *APOE* ε4, and age at entry to high or low risk for developing cognitive impairment, within the next 5 to 7 years. This 5-year study will enroll approximately 5000 subjects. High-risk subjects will be randomized to receive either placebo or pioglitazone, an antidiabetes drug. The primary outcome measure will be the change in the development of cognitive impairment as measured by a battery of neuropsychological tests. Variants in the *TOMM40* gene, which codes for a mitochondrial membrane channel through which proteins and peptides are transported into the mitochondria, have been linked to an increased risk of AD and may be predictive of age at onset. Prospective qualification of the algorithm will be performed, and low-risk subjects who receive placebo will be followed as well to allow positive and negative predictive value to be assessed. *TOMM40* and *ApoEAPOE* variants together are estimated to account for 85% to 90% of age-dependent genetic risk [37].

5. Biomarkers in prevention trials: Biofluids and imaging

A hypothetical biomarker model of AD, developed with data collected from the Mayo Clinic Study of Aging and the Alzheimer's Disease Neuroimaging Initiative (ADNI) [19], continues to gain credence as additional supporting data become available. Moreover, the temporal ordering of these biomarkers defines their roles in upcoming prevention trials: amyloid imaging and CSF Aβ measurements to select individuals on the AD pathway, and neurodegenerative biomarkers (FDG-PET, CSF total tau [t-tau] and p-tau, and structural MRI) to determine how close in time an individual is to relevant cognitive events. A recent study concluded that a reduction in CSF $A\beta_{42}$ is the earliest identified upstream marker of AD [38] and that t-tau and hippocampal volume denote disease progression immediately preceding and through symptomatic phases [e12].

In terms of operationalizing biomarker data according to the NIA-AA criteria for preclinical AD [39], an analysis of nondemented elderly subjects in the Mayo Clinic Study of Aging found that, using clinically derived cutpoints, 96% of nondemented subjects could be classified into five categories—the three stages previously defined plus two additional categories: stage 0 in which there are no abnormal biomarkers, and a new category called SNAP (suspected

nonamyloid pathology) in which biomarkers for amyloid are normal but biomarkers of neurodegeneration are abnormal [e12].

As these criteria get further refined, they should prove useful in selecting subjects for preventive trials, although many issues remain with regard to standardization, intersite variability, and quality control of biomarkers. ADNI has made substantial progress in standardizing imaging protocols and continues to expand the network to worldwide sites. In terms of CSF biomarkers, the Alzheimer's Association (AA) initiated a global quality control program for AD CSF biomarkers, which now includes over 70 participating laboratories [40]. Blood-based biomarkers are also highly desirable, but at this point their potential has yet to be realized.

Imaging and biofluid markers are useful not only to select patients for prevention trials, but also to provide more detailed assessment of pathological processes to track progression of disease, select optimal windows for intervention, and assess and exclude other pathologies. For example, structural and functional imaging modalities, including diffusion tensor imaging, magnetic resonance spectroscopy, structural magnetic resonance imaging to assess cortical thinning and hippocampal atrophy, magnetization transfer imaging, functional MRI (fMRI), and FDG-PET all detect changes presymptomatically but with wide ranges in variability and with different dynamic ranges over the course of disease. Further study is needed to develop more precise evidence-based predictors of progression and correlate pathological markers with clinical changes.

6. Cognition and noncognitive measures in prevention trials

The Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), two longitudinal cohort studies in elderly populations, have accumulated large amounts of data correlating cognitive measures with neuropathology and investigating risk factors for cognitive decline [e20]. ROS began in 1993 and MAP in 1997 with 1150 and 1500 nondemented subjects, respectively. Nineteen neuropsychological tests that assessed five cognitive domains were given each year. Large numbers of subjects in both studies developed AD or dementia, and a total of over 900 autopsies have been completed. Among those subjects without cognitive impairment at death, using the NIA-Reagan pathological criteria, over one third had an intermediate likelihood of AD, and these individuals also scored lower on tests of episodic memory [41]. Further studies using stereology indicated that most older people have some AD pathology.

Data from these two studies were also analyzed to assess cognitive decline in prodromal AD and MCI. Among the subjects who developed AD, global cognitive decline accelerated 5 to 6 years before diagnosis of AD, with even earlier signs of cognitive decline evident in tests of semantic and working memory [42]. Declines in cognition were also seen in individuals before the development of MCI but not in those who do not develop AD or MCI. However, there was a great deal of variability and heterogeneity of slopes. Assessments over a long period of time (e.g., 5 years or more) are thus needed to capture these declines. Composite scores can also maximize the power of a trial, particularly when the individual items measure different domains.

Risk factors for AD, including *APOE* ε4 positivity [e21], physical frailty [43], depression, olfactory identification [44], and memory complaints [45] have also been shown to track with AD pathology. These studies suggest that any of these risk factors, as well as brief measures of working memory, semantic memory, and perceptual speed, might be used for enrichment of prevention trials. Indeed, using imaging or CSF biomarkers for enrichment could limit the recruitment of old and frail subjects, the very subjects who are most likely to decline. Because of regression toward the mean, subject selection that is based on baseline clinical scores is not recommended.

The GuidAge study suggested that in the early stages of cognitive decline, SMC by self-report may be an accurate indicator of impairment [46]. A study conducted as part of the Mayo Clinic Study of Aging determined that SMC, assessed and scored using a 10-point scale adapted from the Blessed dementia rating scale, was associated with a 30% increased hazard for developing MCI. The investigators went on to evaluate ECog, which can be used as an informant- or self-rated instrument to assess everyday cognition [47]. They concluded that self- and informant-rated ECog scores differ across the spectrum of cognitive impairment. Subjects with dementia under-report cognitive problems whereas normal subjects tend to over-report. ADNI has also used ECog, but reported different results than those reported by Mayo. Thus, if this instrument is to be included in trials, careful attention must be paid to the stage of the disease process and the population being tested. Longitudinal data are also need to determine whether ECog or other SMC assessments are predictive of future decline.

The Multidomain Alzheimer Preventive Trial (MAPT), a 3-year trial in France, has already implemented noncognitive tests in its recruitment design [48]. MAPT will test the protective effects of a multidomain intervention, consisting of nutritional advice and cognitive and physical activity, along with omega-3 treatment. The trial has randomized 1680 frail or pre-frail nondemented subjects, age 70 or older and living in the community, with SMC and a limitation in at least one instrumental activity of daily living. These selection criteria were selected based on evidence linking frailty to cognitive decline. At baseline, 58.3% of subjects were assessed as frail or pre-frail by the Fried criteria [49]. In comparison to normal subjects in ADNI, subjects in MAPT at baseline are more likely to have bilateral temporal hypometabolism and positive amyloid imaging. Thus, these subjects are more likely to convert to dementia during the trial, which makes them a good target population for prevention.

7. Regulatory issues for prevention trials

The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have both been grappling with issues regarding prevention trials for some time and will continue to adapt their requirements as the science progresses. Both agencies meet regularly with sponsors to review data and consider specific aspects of trial designs. The FDA continues to be concerned about using biomarkers alone as inclusion criteria, although genetic markers would probably be acceptable. In terms of outcome measures, a functional measure is preferable although a cognitive measure plus biomarker might be acceptable. If the biomarker or cognitive measure had previously been shown to be clinically meaningful, this would increase confidence and might be considered as a measure of very early disease. In terms of safety, a drug with a very large treatment effect might be approved despite significant toxicity.

The EMA's Committee for Human Medicinal Products (CHMP) issued a qualification opinion regarding CSF biomarkers that reflect amyloid burden, accepting the CSF biomarker signature of low $A\beta_{42}$ and high total tau as a means of identifying MCI or prodromal patients at risk to evolve into AD. Another qualification opinion by the EMA accepted hippocampal volume as measured by MRI for enrichment of participants in trials aimed at slowing the progression of AD.

8. Conclusions

The move toward preventive trials for AD faces numerous hurdles, but evidence from previous prevention studies in various fields can provide guidance about subject recruitment, study design, the use of biomarkers, and the need to better understand the biological basis of disease to identify appropriate targets. Although prior studies suggest the need for prolonged and very large clinical trials, maximizing efficiency through the use of various enrichment strategies may yield study designs with achievable sample sizes and sufficient power to detect evidence of disease modification. These enrichment strategies in combination with adaptive study designs (e.g., I-Spy 2) can help us maximize our results in a minimal amount of time [50].

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