ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-7

Alzheimer's & Dementia

Alzheimer's disease: The next frontier—Special Report 2017

Jason Karlawish[a], Clifford R. Jack, Jr.[b] Walter A. Rocca[c,d], Heather M. Snyder[e], Maria C. Carrillo[e,*]

[a]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[b]Department of Radiology, Mayo Clinic, Rochester, MN, USA
[c]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
[d]Department of Neurology, Mayo Clinic, Rochester, MN, USA
[e]Division of Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA

Abstract In the history of medicine, one means to progress is when we make the decision that our assumptions and definitions of disease are no longer consistent with the scientific evidence, and no longer serve our health care needs. The arc of scientific progress is now requiring a change in how we diagnose Alzheimer's disease. Both the National Institute on Aging—Alzheimer's Association (NIA-AA) 2011 workgroup and the International Work Group (IWG) have proposed guidelines that use detectable measures of biological changes in the brain, commonly known as biological markers, or biomarkers, as part of the diagnosis. This Special Report examines how the development and validation of Alzheimer's disease biomarkers—including those detectable in the blood or cerebral spinal fluid, or through neuroimaging—is a top research priority, and how this has the potential to markedly change how we diagnose Alzheimer's disease and, as a result, how we count the number of people with this disease. As research advances a biomarker-based method for diagnosis and treatment at the earliest stages of Alzheimer's disease, we envision a future in which Alzheimer's disease is placed in the same category as other chronic diseases, such as cardiovascular disease or diabetes, which can be readily identified with biomarkers and treated before irrevocable disability occurs.

1. Introduction

After Dr. Alois Alzheimer's 1906 case report of the disease that came to bear his name, for much of the 20th century, Alzheimer's disease was defined as an unusual cause of dementia in adults we now consider middle-aged [1]. "Senile dementia" was the diagnosis for the more common cause of dementia in individuals 65 and older. In 1976, Robert Katzman, M.D., made the case that these definitions should change.

Arguing that an age-based distinction between dementia due to Alzheimer's disease and senile dementia was neither scientifically nor medically sensible [2], he used scientific data to conclude that the two conditions were in fact one and to call them both Alzheimer's disease. "Although further studies are clearly indicated, the fact remains that neither the clinician, the neuropathologist nor the electron microscopist can distinguish between the two disorders [Alzheimer's disease and senile dementia] except by the age of the patient" [2]. His rationale was pragmatic—dementia at any age causes substantial personal, medical and economic burden.

Dr. Katzman's contribution that Alzheimer's disease was a cause of dementia across a wide age span was incorporated into diagnostic criteria published in 1984, known as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) Criteria, or NINCDS-ADRDA Criteria [3]. These criteria did not include biomarkers for the diagnosis of Alzheimer's disease.

Since Dr. Katzman's time, Alzheimer's science has made notable discoveries. Using certain biomarkers, we can now distinguish between Alzheimer's disease and other causes of dementia. In this sense, the arc of scientific progress is

*Corresponding author. Tel.: (312) 335-5722; Fax: (866) 875-2553.
E-mail address: mcarrillo@alz.org

http://dx.doi.org/10.1016/j.jalz.2017.02.006
1552-5260/

now requiring another change in how we diagnose Alzheimer's disease. Both the National Institute on Aging—Alzheimer's Association (NIA-AA) 2011 workgroup [4–6] and the International Work Group (IWG) [7–9] have proposed guidelines that use biomarkers as part of the diagnosis. The guidelines use biomarkers (such as brain imaging of amyloid plaques, changes in brain volume, and measures of tau and amyloid in spinal fluid) and clinical symptoms to define dementia caused by Alzheimer's disease, and also preclinical Alzheimer's and mild cognitive impairment (MCI) due to Alzheimer's [10–19].

The science of Alzheimer's is the primary driver of this change. Drug interventions in people with Alzheimer's disease dementia have repeatedly reported negative results. Research shows points in the course of the disease when an intervention might effectively slow or even stop the disease. The Dominantly Inherited Alzheimer's Network (DIAN) study findings have shown brain changes starting 10 to 20 years before the onset of dementia symptoms in people genetically destined to get Alzheimer's disease [20]. Ongoing trials in this population are testing interventions at this pre-symptomatic point in an effort to delay or even prevent the onset of dementia symptoms. Other clinical trials (A4 Study, etc.) are testing interventions in people who do not have memory (cognitive) and thinking (functional) changes or these genes but do have measurable Alzheimer's biomarkers [21].

The development and validation of biomarkers—including those detectable in the blood or cerebrospinal fluid, or through neuroimaging—may significantly change how we identify Alzheimer's disease and, as a result, how we estimate the number of people with this disease. This is important because Alzheimer's disease prevalence and incidence estimates are used to calculate other statistics, which are used to describe the scope of the Alzheimer's problem in the U.S., illustrate the need to combat the disease, and identify and allocate the resources needed to address it.

2. Rethinking our assumptions about Alzheimer's disease

The U.S. has, since 2011, charted a national plan to address Alzheimer's disease. The first of the plan's five goals is to effectively treat and prevent the disease by 2025 [22]. Researchers and those who translate research into clinical practice have reached a consensus: a core strategy to achieve this goal relies on studies testing drugs in persons who have biomarker confirmation of the presence of Alzheimer's disease [23]. Studies such as the A4 Study discussed above, as well as trials in persons with Alzheimer's disease dementia, are enrolling persons who have these biomarkers [24,25].

This strategy aligns with approaches taken with other common diseases of aging, such as cardiovascular disease. Clinicians use measures of biological change, such as elevated levels of blood pressure or cholesterol, to diagnose and treat individuals. Their goal is to prevent the person from suffering another heart attack or worsening heart failure, or to prevent these problems from happening in the first place. Someday, clinicians may have a similar strategy to diagnose and treat Alzheimer's disease. They may use biological measures (biomarker-based) to diagnose and then prescribe treatments to these persons, treatments that trials have shown to either slow cognitive and functional decline or even prevent the onset of symptoms of dementia.

Alzheimer's-related brain changes—amyloid plaques and tau tangles among others—contribute to the cognitive impairment observed in dementia due to Alzheimer's [26–29]. A clinically effective intervention that targets these brain changes will help to validate the disease as a continuum that begins before cognitive decline. This confirmation will change how we identify (and therefore estimate) individuals with Alzheimer's disease. It will alter the prevalence and incidence of the disease, just as the treatment of vascular disease has altered the prevalence of dementia among individuals with primarily vascular lesions [30,31]. As these events unfold, they compel us to plan for a future when Alzheimer's disease is defined using biomarkers alone, not symptoms. (See sidebar: "Determining the incidence and prevalence of Alzheimer's disease.")

3. The evolving diagnosis of Alzheimer's disease

Current methods of diagnosis do not conform to what we know about the disease. The 1984 NINCDS-ADRDA criteria for Alzheimer's disease defined it as a clinical disease caused by underlying brain changes [3]. The assumption was that an individual with an amnestic dementia would have Alzheimer's-related brain changes, namely amyloid plaques and tau neurofibrillary tangles, if the individual came to autopsy. Conversely, individuals without amnestic dementia would not have plaques or tangles at autopsy. This definition of Alzheimer's intertwines the signs and symptoms of dementia and the underlying brain changes [3].

In the years that followed the adoption of those criteria, studies suggested that the clinical symptoms and underlying brain changes do not always align. Autopsy studies found that 10–30% of individuals who met NINCDS-ADRDA criteria for Alzheimer's disease did not have significant Alzheimer's-related brain changes (i.e., plaques and/or tangles). Instead, they had other (non-Alzheimer's) brain changes at autopsy [32]. Often Alzheimer's was mixed with non-Alzheimer's brain changes, such as cerebral infarctions or Lewy body disease, particularly in older individuals [26,27,33]. Furthermore, autopsy studies in individuals who were cognitively normal for their age found that roughly 30% had Alzheimer's-related brain changes at death [34–36].

Over the past roughly two decades, biomarkers of Alzheimer's disease-related brain changes continued to be developed. They fit into two classes: (1) brain imaging of

What are biomarkers?

A biomarker, or biological marker, is a measurable indicator of some biological state or condition in the human body. Clinicians use biomarkers to diagnose the presence or absence of disease, assess the risk of developing a disease, or understand how a patient has responded to a treatment. For example, a high blood glucose level (blood sugar) may be diagnostic of diabetes, and lowering that level can indicate the success of a prescribed diet or medication.

Researchers are investigating several promising biomarkers for Alzheimer's disease. These include, but are not limited to, the amount of accumulation of the proteins beta-amyloid and tau in the brain. These proteins can be measured using brain imaging or the levels in cerebrospinal fluid and blood. Another kind of biomarker is changes in brain size and activity.

Identifying and then validating biomarkers for Alzheimer's is critical. They will facilitate early diagnosis and treatment. Many researchers believe that early intervention—either at the mild cognitive impairment (MCI) stage or even before symptoms appear—offers the best chance of slowing or stopping the progression of Alzheimer's disease and therefore the best chance of preserving brain function.

Biomarkers also have an important role in the discovery of treatments. They enable researchers to identify which individuals to enroll in clinical trials to test new therapies. Biomarkers allow researchers to enroll those individuals with the brain changes that treatments target. (It's important to note that the most effective biomarker test or combination of tests may differ depending on the stage of the disease and other factors.) Biomarkers also allow researchers to monitor the effects of these treatments. The more a change in a biomarker maps onto the health of the patient, the better that biomarker is to assess whether a treatment is effective.

Research on new strategies for earlier diagnosis, including ongoing efforts to identify and validate biomarkers for Alzheimer's disease, is among the most active areas in Alzheimer's science.

amyloid and tau buildup, and of brain volume and brain metabolism changes, and (2) measures of relevant proteins in spinal fluid [10–19]. These biomarkers illustrate or represent the presence of amyloid plaques, tau tangles and brain cell death or injury [37]. Studies have validated that biomarkers are indeed reliable measures of the relevant disease-related changes in the living brain [38–44]. These studies, like autopsy studies, also demonstrated that roughly one-third of individuals who meet NINCDS–ADRDA criteria for Alzheimer's disease do not have the required brain changes (and thus do not have Alzheimer's disease) [43–46]. In addition, studies showed that roughly one-third of clinically normal older individuals do have Alzheimer's-related brain changes without the clinical symptoms [43–45,47,48].

Recognizing the potential for biomarkers, both the NIA-AA and the IWG have proposed that, when used alongside clinical criteria, biomarkers can increase the confidence that a diagnosis of dementia is or is not due to Alzheimer's disease [4–9,49]. Importantly, the NIA-AA also proposed that biomarkers could identify MCI as due either to Alzheimer's (called MCI due to Alzheimer's disease) or to other diseases [5]. The equivalent term for biomarker-positive individuals with MCI is prodromal Alzheimer's disease in the IWG criteria.

Further, the NIA-AA proposed that cognitively normal individuals with abnormal Alzheimer's biomarkers have preclinical Alzheimer's disease. If this is validated, then individuals who have no cognitive impairment but have Alzheimer's biomarkers have Alzheimer's disease [4].

A biomarker-based diagnosis of Alzheimer's disease—one based on brain changes, not cognitive or functional changes—will change the incidence and prevalence of Alzheimer's.

4. The prevalence and incidence of Alzheimer's disease in a new era of research

Today, we understand that Alzheimer's disease exists as a continuum beginning with a phase that may only be detectable through biomarkers, moving through the dementia stage. In the future, a biomarker-based diagnosis of Alzheimer's disease will impact the estimates of incidence and prevalence of Alzheimer's. It will add a population of individuals who are currently not included in estimates (people with Alzheimer's biomarkers but no dementia) and remove a population that currently is included (people with dementia but no Alzheimer's biomarkers).

The Alzheimer's Association *2017 Alzheimer's Disease Facts and Figures* (DOI: 10.1016/j.jalz.2017.02.001) reports the prevalence and incidence of Alzheimer's in the U.S. Among individuals age 65 and older, the prevalence in 2017 is estimated to be 5.3 million (one in 10 people age 65 and older or 10 percent have Alzheimer's dementia), and 480,000 people age 65 or older will develop Alzheimer's dementia in the U.S. in 2017.

Epidemiologists, demographers and biostatisticians will use these prevalence and incidence estimates to calculate other statistics, such as the numbers of people providing care and support for someone with the disease, the costs of care, and mortality. Clinicians, policy makers and organizations use these statistics to describe the size of the Alzheimer's problem in the U.S., to demonstrate the need to combat the disease, and to identify the resources needed to address it.

Determining the incidence and prevalence of Alzheimer's disease

Counting the incidence or prevalence of Alzheimer's disease or dementia due to Alzheimer's is complex. In the absence of registries akin to cancer registries or routine disease monitoring systems used to track infectious diseases, investigators must make a series of assumptions. These assumptions mean we are not so much counting as we are estimating the prevalence and incidence of Alzheimer's disease. Below, we review these assumptions, and why studies have arrived at different estimates.

The process begins with identifying a study population, usually a cohort of individuals in a given region. It could also be a representative sample in various regions. Next, investigators select a strategy to identify the cases of dementia due to Alzheimer's disease in that given population. Some studies have used a two-phase strategy that starts with a brief cognitive test administered to the total group of participants to identify potential cases (known as the screening phase of the survey), who are then more fully evaluated using the Alzheimer's disease diagnostic criteria [52–56]. Other studies fully evaluate a random sub-group from the total participants; still others fully evaluate the entire participating group.

A crucial methodological step to identify the individuals with Alzheimer's disease is the choice of diagnostic criteria that will be used in the study. Historically, studies have used a clinical diagnosis of the disease—that is, they counted people who had signs and symptoms of dementia. They have not included biomarkers as part of the criteria for the disease, nor have they excluded people with signs and symptoms of dementia but no biomarkers for Alzheimer's disease.

In most cases, the onset of dementia or dementia caused by Alzheimer's disease is gradual. It is therefore difficult in the early stages of the disease to assign a diagnosis of dementia. Consequently, investigators using brief cognitive tests face the error of mistakenly diagnosing someone as cognitively normal, and therefore without the disease, when in fact, the person is not normal; in other words, the error of false negatives, which can lead to an underestimate of prevalence and incidence. More recent studies, therefore, have abandoned brief screening tests. Instead, they either fully examine all participants in the sample or they fully examine a random sample of the study population [54–56]. Each of the design choices described above creates variability in who is selected for evaluation and, hence, as studies differ in these choices, there is variability in their respective prevalence estimates.

The Alzheimer's Association uses estimates for the prevalence and incidence of Alzheimer's disease modeled by the Chicago Health and Aging Project at Rush University Medical Center, called CHAP [57,58]. CHAP is a longitudinal, population-based study in a geographically defined area of Chicago with significant population diversity. It began in 1993 with a census of individuals age 65 or older using in-home interviews and random sampling of participants for clinical evaluation for dementia due to Alzheimer's [57].

CHAP researchers identify an individual living with Alzheimer's disease by detecting cognitive decline that then triggers a clinical assessment. The clinician uses the 1984 NINCDS-ADRDA criteria for the clinical diagnosis of Alzheimer's disease to determine if the dementia is caused by Alzheimer's disease [3]. These criteria focus on dementia assessed by an interview with the participant and an informant, usually their partner or child (if available), and cognitive testing [3].

CHAP uses newly diagnosed cases of Alzheimer's—incidence—to determine the prevalence. This is a notable feature. It minimizes missing cases of the disease whose symptoms are mild or even very mild [57–59]. Evaluation is repeated in 3-year cycles. Calculations of national and state-by-state prevalence figures as well as estimates of future prevalence are extrapolated from the CHAP data and incorporate age, sex and race: (1) risk of developing dementia due to Alzheimer's, (2) increased risk of mortality among those with dementia due to Alzheimer's, (3) U.S. mortality rates, (4) U.S. education levels, and (5) U.S. current and projected total population [30]. Since their first publication in 2003, CHAP produced updated estimates of prevalence in 2013 utilizing 2010 U.S. Census Bureau population information [58]. The Association's *2017 Alzheimer's Disease Facts and Figures* prevalence estimates are reported from these data for U.S. residents age 65 and older.

Other U.S.-based studies have measured either the prevalence or incidence of dementia. Two of note are the Health and Retirement Study-Alzheimer's Disease and Memory Study (HRS-ADAMS)—a nationally representative sample [30,60]—and the Framingham Heart Study (FHS)—a study of all-cause dementia over time in Framingham, Massachusetts [61]. HRS-ADAMS and FHS have consistently reported estimates that are lower than CHAP estimates [30,60–62].

At a 2009 conference convened by the NIA and the Alzheimer's Association, researchers concluded that these discrepancies were mainly due to differences in diagnostic criteria, differences that reflect the study's different goals [59]. HRS-ADAMS defines a case using the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria for dementia, incorporating impairments in both cognition and function [59,63]. In addition, people exhibiting the symptoms of Alzheimer's disease are not counted as having Alzheimer's if they are determined to have vascular dementia. HRS-ADAMS focuses on the severity of disability, not the precision of the diagnosis of Alzheimer's disease, which is the goal of CHAP [57,60,62]. The Framingham Heart Study uses *DSM* criteria for dementia and the NINCDS-ADRDA criteria, an approach that achieves the goal of determining if a case of dementia is caused by Alzheimer's [61].

The estimates from each of these studies are often discussed as different numbers measuring the same thing, a conclusion that destabilizes confidence that we can talk coherently about the prevalence of Alzheimer's disease. They are in fact different numbers because they are measuring different things in different populations using different means of identifying individuals with all-cause dementia and/or dementia due to Alzheimer's [59]. None of the studies referenced above used biomarkers in their estimates; inclusion of biomarkers would markedly alter estimates of the prevalence and incidence of Alzheimer's disease.

As research advances a biomarker-based strategy for detection and treatment at the earliest stages of Alzheimer's disease, ever more accurate estimates of the number of persons affected will be needed to understand the full extent of that burden. These estimates will very likely be greater than current estimates and will require appropriate, modernized research and public health strategies.

Validated Alzheimer's disease biomarkers will transform how study results are interpreted and change the messages and terms professionals and society use to talk about who has Alzheimer's disease and how big of a problem the disease poses.

To accurately answer the question, "What is the true prevalence and incidence of Alzheimer's disease?" we have to identify Alzheimer's disease in a way that is grounded in current science and makes sense to individuals, families, clinicians, researchers and healthcare policy makers. Looking ahead, a biologically-based Alzheimer's disease diagnosis will yield different prevalence and incidence figures than a diagnosis that uses only the severity of cognitive or functional impairment (either using *DSM* or NINCDS-ADRDA criteria). It will exclude individuals who have dementia but do not have the Alzheimer's biomarkers and thus do not have Alzheimer's disease. On the other hand, it will include individuals with MCI who have Alzheimer's biomarkers and therefore have Alzheimer's disease, a proportion that may, according to existing studies, be as high as 56% of persons with a diagnosis of MCI [50,51]. Even further in the future and with more research, it will also include people who do not have cognitive impairment but have Alzheimer's disease biomarkers.

Epidemiologic and related natural history studies that measure cognition in older adults and that want to estimate the prevalence and incidence of Alzheimer's disease will need to gather biomarker data from their participants. We should expect that these study results will further disrupt our understanding of the causes and trajectories of cognitive impairment. Studies that do not use these measures will not be able to accurately report the prevalence and incidence of Alzheimer's disease. (They can report on the clinical severity of cognitive impairment in a population using constructs such as dementia or mild cognitive impairment.)

It is possible that these biomarker measures will add to the burdens and risks encountered by research participants. This, in turn, may hinder study recruitment, retention and accessibility. Studies to assess why individuals might refuse to undergo biomarker measures, test interventions to change that decision, and discover messaging that motivates the intention to undergo biomarker testing will be essential to address this problem. Studies will likely benefit from collaborations among epidemiologists, bioethicists, clinicians, biomarker scientists and decision-scientists who interpret data and help make public health recommendations.

5. Conclusion

Even with scientific progress, a common question from the public has been, "What's the difference between Alzheimer's disease and dementia?" The NINCDS-ADRDA diagnostic criteria of 1984 aimed to help answer that question [3]. Alzheimer's disease is the most frequent cause of the dementia syndrome.

As dementia science has progressed, biomarker-based data have advanced our understanding of who has Alzheimer's disease as well as contributed to a more accurate clinical diagnosis of who has dementia due to Alzheimer's. Biomarker-based clinical criteria and future clinical trial data will continue to change our understanding of who has Alzheimer's disease, as improved diagnostic techniques will provide earlier identification of cognitive impairment, and of the brain changes that lead to it.

As with cardiovascular disease, we must care not just about those who have had a disease-manifesting event, such as a heart attack, but everyone who has cardiovascular disease-related biological changes that precede the heart attack. All of these individuals represent the societal burden of cardiovascular disease. Similarly, although we have known for years about the occurrence of dementia due to Alzheimer's, as a result of the recent use of biomarkers in studies, we have learned that a proportion of people previously thought to have cognitive impairment caused by Alzheimer's disease lack those biomarkers. The diagnosis of Alzheimer's disease will come to include the full spectrum of persons with Alzheimer's biomarkers, those who are symptomatic—with either dementia or MCI—and those who are still asymptomatic but have preclinical Alzheimer's disease. All individuals with biomarkers of Alzheimer's disease, including those with and without dementia symptoms, will represent the full disease burden.

Additional research and development of guidelines for the future use of biomarkers is urgently needed to optimize therapeutic strategies for this potentially much larger population of people with Alzheimer's disease. Successful validation of biomarkers will bring our definition of Alzheimer's disease in line with the remarkable advances we have seen in

Alzheimer's research over the past decade. This latest research is now allowing us to envision a future in which Alzheimer's is no longer a disease leading to irrevocable cognitive and functional decline and death, but rather a chronic condition like cardiovascular disease, AIDS or some cancers that can often be managed with early intervention.

Acknowledgments

The Alzheimer's Association wishes to provide a special thank you to Dr. Lenore Launer, Senior Investigator and Chief, Neuroepidemiology Section, at the National Institute on Aging of the National Institutes of Health, and Dr. David Knopman, Professor of Neurology at the Mayo Clinic in Rochester, MN, and chair of the Alzheimer's Association Medical & Scientific Advisory Council, for their review and comments during the preparation of this manuscript.

References

[1] Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". Clin Anat 1995;8:429–31.

[2] Lijtmaer H, Fuld PA, Katzman R. Letter: Prevalence and malignancy of Alzheimer disease. Arch Neurol 1976;33:304.

[3] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

[4] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–92.

[5] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association Workgroup. Alzheimers Dement 2011;7:270–9.

[6] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup. Alzheimers Dement 2011;7:263–9.

[7] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118–27.

[8] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–46.

[9] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–29.

[10] Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx 2004;1:213–25.

[11] Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol 2003;2:605–13.

[12] Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol Chem Neuropathol 1995;26:231–45.

[13] Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 2006;59:512–9.

[14] Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol 2007;64:343–9.

[15] van Harten AC, Smits LL, Teunissen CE, Visser PJ, Koene T, Blankenstein MA, et al. Preclinical AD predicts decline in memory and executive functions in subjective complaints. Neurology 2013;81:1409–16.

[16] Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 2009;66:382–9.

[17] Tapiola T, Overmyer M, Lehtovirta M, Helisalmi S, Ramberg J, Alafuzoff I, et al. The level of cerebrospinal fluid tau correlates with neurofibrillary tangles in Alzheimer's disease. NeuroReport 1997;8:3961–3.

[18] Visser PJ, Verhey F, Knol DL, Scheltens P, Wahlund LO, Freund-Levi Y, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. Lancet Neurol 2009;8:619–27.

[19] Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009;302:385–93.

[20] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.

[21] Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. The A4 study: stopping AD before symptoms begin? Sci Transl Med 2014;6:228fs13.

[22] U.S. Department of Health and Human Services. National Plan to Address Alzheimer's Disease 2012. Available at: https://aspe.hhs.gov/national-plan-address-alzheimers-disease-and-other-napa-documents. Accessed January 18, 2017.

[23] Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. N Engl J Med 2013;368:1169–71.

[24] Honig LS, Aisen PS, Carrillo MC, Vellas B, Seimers ER. Expedition 3: A Phase 3 Trial of Solanezumab in Mild Dementia Due to Alzheimer's Disease. Available at: http://www.ctad-alzheimer.com/live-expedition-3-webcast. Accessed December 22, 2016.

[25] Sevigny J, Suhy J, Chiao P, Chen T, Klein G, Purcell D, et al. Amyloid PET screening for enrichment of early-stage Alzheimer disease clinical trials: experience in a phase 1b clinical trial. Alzheimer Dis Assoc Disord 2016;30:1–7.

[26] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204.

[27] Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol 2009;66:200–8.

[28] Mormino EC, Betensky RA, Hedden T, Schultz AP, Amariglio RE, Rentz DM, et al. Synergistic effect of beta-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. JAMA Neurol 2014;71:1379–85.

[29] Sperling RA, Johnson KA, Doraiswamy PM, Reiman EM, Fleisher AS, Sabbagh MN, et al. Amyloid deposition detected with florbetapir F 18 ((18)F-AV-45) is related to lower episodic memory performance in clinically normal older individuals. Neurobiol Aging 2013;34:822–31.

[30] Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Intern Med 2017;177:51–8.

[31] Sposato LA, Kapral MK, Fang J, Gill SS, Hackam DG, Cipriano LE, et al. Declining Incidence of Stroke and Dementia: Coincidence or Prevention Opportunity? JAMA Neurol 2015;72:1529–31.
[32] Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2011; 121:571–87.
[33] Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, et al. Ecology of the aging human brain. Arch Neurol 2011;68:1049–56.
[34] Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 2006; 66:1837–44.
[35] Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 1991;12:295–312.
[36] Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–95.
[37] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016; 87:539–47.
[38] Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008; 131:1630–45.
[39] Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA, et al. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. Brain 2015;138:1370–81.
[40] Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, et al. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol 2011;68:1404–11.
[41] Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of Florbetapir-PET for Imaging B-Amyloid Pathology. JAMA 2011;305:275–83.
[42] Sojkova J, Driscoll I, Iacono D, Zhou Y, Codispoti KE, Kraut MA, et al. In vivo fibrillar beta-amyloid detected using [11C]PiB positron emission tomography and neuropathologic assessment in older adults. Arch Neurol 2011;68:232–40.
[43] Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010; 31:1275–83.
[44] Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al. Imaging beta-amyloid burden in aging and dementia. Neurology 2007; 68:1718–25.
[45] Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 2008;131:665–80.
[46] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33.
[47] Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, et al. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 2006;67:446–52.
[48] Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008; 65:1509–17.
[49] Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257–62.
[50] Petersen RC, Aisen P, Boeve BF, Geda YE, Ivnik RJ, Knopman DS, et al. Criteria for mild cognitive impairment due to alzheimer's disease in the community. Ann Neurol 2013;74:199–208.
[51] Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010;75:889–97.
[52] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 2013;382:1405–12.
[53] Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nat Commun 2016;7:11398.
[54] Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 2013;80:1888–94.
[55] Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MM, Skoog I, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol 2016;15:116–24.
[56] Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. Neurology 1997;48:132–8.
[57] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–22.
[58] Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80:1778–83.
[59] Wilson RS, Weir DR, Leurgans SE, Evans DA, Hebert LE, Langa KM, et al. Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States. Alzheimers Dement 2011; 7:74–9.
[60] Brookmeyer R, Evans DA, Hebert L, Langa KM, Heeringa SG, Plassman BL, et al. National estimates of the prevalence of Alzheimer's disease in the United States. Alzheimers Dement 2011;7:61–73.
[61] Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med 2016;374:523–32.
[62] Launer LJ. Counting dementia: There is no one "best" way. Alzheimers Dement 2011;7:10–4.
[63] Arnold SE, Louneva N, Cao K, Wang LS, Han LY, Wolk DA, et al. Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease. Neurobiol Aging 2013;34:157–68.