How early can we diagnose Alzheimer disease (and is it sufficient)?
The 2017 Wartenberg lecture

Ronald C. Petersen, PhD, MD

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Abstract

A seismic shift in our understanding of the ability to diagnose Alzheimer disease (AD) is occurring. For the last several decades, AD has been a clinical–pathologic diagnosis, and this conceptualization of the disease has served the field well. Typically, the clinician would identify a syndrome such as mild cognitive impairment or dementia, and label the condition as “probable AD” since the diagnosis of definite AD could not be made until an autopsy revealed the presence of amyloid plaques and tau-based neurofibrillary tangles. However, with the advent of biomarkers for AD including neuroimaging and CSF, the identification of AD pathology can be made in life, which greatly enhances the ability of clinicians to be precise about the underlying etiology of a clinical syndrome. Hypothetical models of the temporal relation among the pathologic elements and the clinical symptoms have been proposed and have influenced the field enormously. This has enabled clinicians to be specific about the underlying cause of a given clinical syndrome. As such, the diagnostic capability of the clinician is evolving. However, AD pathology is only a component of the puzzle describing the causes of cognitive changes in aging. Most often, there is a multitude of pathologic entities contributing to the neuropathologic explanation of cognitive changes in aging. AD changes contribute important elements to the diagnosis, but the final answer is more complex. The field of aging and dementia will have to incorporate these additional elements.
Alzheimer disease (AD) may be the most devastating disorder of the current generation due to its impact on individuals, families, societies, and health care economies. It is estimated that there are 5.7 million people with AD in the United States and approximately 46-million worldwide, keeping in mind that, in these figures, AD and dementia are often conflated.\(^1\) Nevertheless, these figures are projected to triple by 2030, and AD/dementia has become the most costly disorder in America, surpassing cancer and cardiovascular diseases.\(^2\) Therefore, diagnosing and developing therapies for AD are an absolute necessity.

In order to treat AD, the classification of the disorder must be properly characterized and its natural history understood. Current thinking suggests that by the time clinical symptoms develop, sufficient damage has taken place in the CNS that many symptoms may be irreversible.\(^3\) As such, early intervention and work toward prevention are preferred strategies. Hence, a complete understanding of the temporal course of the disease is essential, and that understanding is evolving.

**History**

In 1906, Alzheimer described a patient, Auguste Deter, who had memory loss and suspiciousness about her family and at autopsy was found to have plaques and tangles in her brain.\(^4\) In 1968, Blessed et al.\(^5\) described the association between quantitative measures of dementia and brain pathologic changes. Glenner and Wong\(^6\) identified the amyloid protein in 1984 as being the major constituent of plaques and Brion et al.\(^7\) in 1985 identified tau as the major component of neurofibrillary tangles, thus characterizing the molecular substrate of AD. These discoveries laid the groundwork for the current clinical and neuropathologic approaches to the disease.\(^8\)

**The problem**

In 1984, the National Institute on Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria were published and set the stage for the conceptualization of AD for over 30 years.\(^9\) Essentially, AD was defined as a clinical–pathologic entity, meaning that, if a person had the gradual onset of a cognitive disorder, usually involving memory, and it led to functional impairment in daily activities, the person would be labeled as having dementia. Once other potential contributing factors had been ruled out, a degenerative disorder was implicated and the label of probable AD was given. The disorder could only be labeled as definite AD when the person went on to have an autopsy and, at postmortem examination, the brain showed neuritic plaques (amyloid) and neurofibrillary tangles (tau). Hence, the clinical picture was confirmed, with pathology thus defining the disease. This conceptualization stood for over 30 years and became so well-accepted that the clinical diagnosis of possible/probable AD was typically shortened to simply AD. Thus, the clinical diagnosis has become equated to the disease process in much of the medical community and the general public. However, problems arose when numerous studies showed elderly cognitively unimpaired persons could have numerous neuritic plaques and neurofibrillary tangles at autopsy, and conversely, people with the clinical picture of probable AD did not have the defining features of AD on postmortem examination.\(^10,11\) The latter finding posed awkward problems for some recent randomized controlled trials (RCTs) showing that up to 10%–30% of APOE\(_4\) noncarriers enrolled in a clinical trial for bapineuzumab and solanezumab failed to have amyloid plaques on PET scanning.\(^12,13\) These features of the 1984 criteria posed a problem for the field, particularly as biomarkers for AD were evolving.

**Enter biomarkers**

Biomarkers reflecting underlying amyloid and tau have been available for 35 years, particularly in the CSF.\(^14\) Hundreds of studies have shown that, in general, A\(_\beta\)42 was decreased and total tau and phosphorylated tau were elevated relative to persons without AD.\(^15,16\) While these data have been replicated numerous times, there has been great laboratory-to-laboratory variability in the measurements, such that the results have not been standardized.\(^16\) In addition, there has been some resistance to lumbar punctures among some patients and clinicians, and consequently, the routine use of CSF for the diagnosis of AD has not been widely adopted.

In 2004, Klunk et al.\(^17\) working in Pittsburgh with colleagues from Uppsala, Sweden, demonstrated the utility of the C\(_{11}\) PET radioligand, Pittsburgh compound B (PiB), to identify amyloid plaques in living persons. This changed the landscape dramatically since clinicians no longer had to perform a lumbar puncture or wait for an autopsy to identify the presence of amyloid.\(^17,18\) While PiB is a carbon 11 compound with a 20-minute half-life, several fluorine\(^{18}\) compounds, flurbetapir, flumetamol, and florbetaben, have been developed and received approval from the US Food and Drug Administration for demonstrating the presence or absence of amyloid in living persons.\(^19\) This altered the field since the clinical profile coupled with amyloid positivity on PET scan strongly suggested the diagnosis of AD, and RCTs

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**Glossary**

AD = Alzheimer disease; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; IWG = International Work Group; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging–Alzheimer’s Association; PiB = Pittsburgh compound B; RCT = randomized controlled trial; SCD = subjective cognitive decline.
could now be designed requiring the presence of amyloid in their study design for an amyloid-targeted therapy.\textsuperscript{20}

**Theoretical modeling**

With the evolution of biomarkers for AD, Jack et al.\textsuperscript{21} posed a theoretical model of the temporal course and putative role of several pathologic entities and measures antedating the development of clinical symptoms. Figure 1 shows this model with amyloid deposition preceding the development of tau and with subsequent measures of neurodegeneration as measured by with MRI atrophy, such as hippocampal atrophy, cortical thinning, or the presence of hypometabolism in a particular pattern on fluorodeoxyglucose PET. The features of neurodegeneration tended to follow the temporal course of amyloid and tau but with a time lag. All of these events, however, preceded the development of clinical symptoms, such as in mild cognitive impairment (MCI) and dementia. This new classic model has been revised to allow for the subthreshold development of tau preceding detectable amyloid, but otherwise, the essential features of the model have proved accurate and provide the prevailing theoretical picture of AD.\textsuperscript{22}

**2011 Criteria**

The development of amyloid imaging and the ability to measure neurodegeneration incorporated in the Jack et al. model led to a proposed set of revisions of AD criteria, largely for research, in 2011.\textsuperscript{23–26} Figure 2 denotes the progression of criteria and frameworks over the years. The clinical continuum was divided into 3 phases, beginning with the preclinical state, whereby persons harbored the underlying pathologic features of amyloid deposition and neurodegeneration but were clinically unimpaired. The MCI state denoted individuals with a subtle decline in cognition with preserved function in daily activities, and the final stage constituted dementia.\textsuperscript{27} The clinical criteria for these phases of the AD clinical continuum were coupled with various combinations of biomarkers denoting the presence of amyloid and neurodegeneration to yield various degrees of likelihood that the underlying clinical syndrome, preclinical (normal cognition), MCI, or dementia, was likely due to AD pathology.\textsuperscript{28–30} For example, in MCI due to AD, the first level of certainty involved the clinical syndrome of MCI itself. Next, with various combinations of biomarkers for amyloid and neurodegeneration, the clinical syndrome coupled with these markers increased the confidence of AD being the underlying etiology. When both measures of amyloid and neurodegeneration were present in conjunction with the clinical syndrome of MCI, the diagnosis of MCI due to AD with high likelihood was made. This approach was a major advance over the clinical syndrome alone and yielded better results with respect to characterizing a person with the MCI syndrome, estimating the likelihood that person actually possessed the underlying pathophysiology of AD and predicted the likelihood of cognitive/clinical decline in the future.\textsuperscript{30–32} The design of clinical trials has been profoundly influenced by this advance, combining the clinical criteria with biomarkers.

**Other approaches**

Concurrently with the National Institute on Aging–Alzheimer’s Association (NIA-AA) 2011 criteria development, 2 other efforts have been developed. An International Work Group (IWG) proposed a new conceptualization of AD,
building on the clinical syndrome of amnestic MCI and adding amyloid or amyloid and tau biomarkers. At the MCI stage, this was characterized as prodromal AD. In many respects, this characterization of the disease at the predementia stage was similar to MCI due to AD, high likelihood. This proposal also accommodates atypical clinical presentations of AD.

The American Psychiatric Association published the DSM-5 in 2013, and this classification system used “neurocognitive disorder” as the broad descriptive term, with mild neurocognitive disorder corresponding to MCI and major neurocognitive disorder resembling dementia. This approach proposed a 2-step process: fulfillment of the clinical syndrome of mild or major neurocognitive disorder followed by the delineation of the etiology. The latter can be fulfilled by using biomarkers, if available, and in the case of AD, the biomarkers discussed above would be applied when validated. In other disorders, clinical information such as the presence of, e.g., Parkinson disease, Huntington disease, HIV/AIDS, or traumatic brain injury would constitute evidence for etiology of the syndrome. This classification system is meant to encompass many forms of neurocognitive disorders, not just AD. In many respects, both the IWG criteria and DSM-5 are thematically similar to the NIA-AA criteria for AD with some subtle, but important, differences, as depicted in figure 3.

**New AD framework**

More recently, the NIA-AA empaneled a committee to review the state of the characterization of AD considering the evolving biomarker data. Since the 2011 NIA-AA criteria were developed, tau PET imaging has become available, and this, coupled with amyloid imaging, has afforded clinicians the opportunity to detect the presence of the defining neuro-pathologic features of AD, amyloid and tau, in a living person using imaging. As mentioned above, CSF markers have existed for years but the lack of interlaboratory assay agreement and clinical reluctance to perform lumbar punctures have limited its application in the United States. The development of imaging tools to identify amyloid and tau will likely lead to substantial changes in the manner in which AD is diagnosed, followed, and treated.

The new AD framework posits that the term AD be restricted to persons who have the demonstrated presence of neuritic plaques by either amyloid PET or low CSF Aβ and neurofibrillary tangles by tau PET or elevated phospho-tau protein in the CSF. This means that the disease label can only be given if the person has demonstrated positive biomarkers for amyloid and tau. If the person has only amyloid pathology, then the label of Alzheimer pathologic change should be used. Both of these descriptions, AD and Alzheimer pathologic change, are independent of the clinical status of the person. That is, a person could be clinically unimpaired, have MCI, or have dementia, since the AD description is no longer a clinical–pathologic diagnosis. The rationale for this change is partly derived from the parallel with other medical disorders such as cancer and cardiovascular disease. A person can have breast or prostate cancer based on a positive biopsy regardless of the clinical status of the person. Hence, a person will be labeled as having AD if that person has the biological defining

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**Figure 3** Interrelations of various criteria for mild cognitive impairment using a combination of clinical features and biomarkers for Alzheimer disease

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NIA-AA = National Institute on Aging-Alzheimer’s Association; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association. Reproduced with permission from Wiley. Copyright © 2014 The Association for the Publication of the Journal of Internal Medicine.
features of the disease, neuritic plaques and neurofibrillary tangles, irrespective of the clinical condition.

It is anticipated that this framework will substantially improve the design of RCTs for AD. Many of the current therapies under development and in current RCTs are targeting amyloid or tau, and this framework will enhance their ability to enroll appropriate participants and follow biologically relevant biomarkers during the course of treatment. This will be a major advancement for the field.

Concerns may arise, however, from the clinician’s perspective. The NIA-AA committee recognized the entrenched nature of the term AD and recommended that when biomarkers are not available, individuals who historically would be labeled possible or probable AD instead be labeled Alzheimer clinical syndrome. This nomenclature preserves the term AD in nonbiomarker environments but also recognizes the distinction between a disease and a clinical syndrome that is not specific for any specific disease. Nevertheless, this pathology-based label may more accurately reflect the underlying nature and pathophysiology when someone is labeled as having AD.

Implications for RCTs

Since much of the focus of developing treatments that will affect AD currently have been oriented toward early detection of the disease, this new AD research framework should be useful. Clearly, identifying persons at the early stages of the disease process, prior to the development of symptoms, would be an advantage at preventing subsequent symptom development.\textsuperscript{39–41} Identifying the disease at this stage should allow for early intervention and influence product labeling. Clinical criteria for participant selection would be adjusted accordingly and clinical as well as biomarker outcomes would need to be delineated, but research is underway addressing these issues. Recently, attention has been given to the construct of subjective cognitive decline (SCD).\textsuperscript{42,43} Formerly, it was believed that SCD was simply a manifestation of underlying depression and had little implication for the development of a neurodegenerative process.\textsuperscript{44} However, more recently, several studies have indicated that, after controlling for relevant variables such as age, sex, education, \textit{APOE}4 carrier status, depression, anxiety, and cognitive function, SCD still predicts progression from cognitively unimpaired to MCI.\textsuperscript{45} In addition, some studies have shown that SCD correlates with underlying biomarker status such as the presence of amyloid on PET imaging in asymptomatic persons.\textsuperscript{46}

Clinical syndromes and staging

While the focus of the new AD framework has been on biomarkers, the clinical spectrum has been addressed as well, albeit not as part of the definition of AD. The Work Group has recognized 2 approaches to the clinical continuum. An initial description of the classical syndromes is retained—cognitively unimpaired, MCI, and dementia—using standard published criteria.\textsuperscript{27,36} In addition, a numerical staging system has been proposed to enhance the development of RCTs. Stages 1 and 2 refer to degrees of unimpaired cognitive function, with stage 1 being cognitively normal and stage 2 referring to overall normal cognition but subtle signs of early impairment including SCD, slight cognitive changes while still in the normative range, the onset of new neurobehavioral symptoms, or combinations of these features. The specificity of these entities is left purposefully vague to allow research to further delineate these clinical features. Stage 3 approximates MCI and stages 4, 5, and 6 correspond to mild, moderate, and severe dementia. It should be noted that these stages only refer to people who have the demonstrated presence of amyloid and are thus on the AD continuum. Figure 4 characterizes the correspondences between the clinical syndromes and the proposed staging scheme.

With this background, SCD has become a component in the NIA-AA theoretical depiction of the progression of stages in amyloid-positive persons designed to be used in RCTs. In the clinical staging system proposed for RCTs, stage 2 represents a transitional phase that is used to characterize persons who are cognitively unimpaired but are exhibiting slight changes in cognition, behavior, or subjective concerns. There are several ways to characterize these persons in stage 2, but SCD alone constitutes one of the qualifying features. This presents new challenges for the field in terms of defining the earliest stages of impairment due to underlying AD. Nevertheless, it moves the threshold for initiating therapies further back toward asymptomatic states.

Reality

Ultimately, aging and cognitive impairment are much more complex than just involving the pathology of AD. While AD defined by neuritic plaques and neurofibrillary tangles is an...
From this perspective, AD is an important component but only one component in the complex contribution to cognitive function in aging. Figure 5 outlines the AD component, and one wonders if this component may lose some of its significance as biomarkers are developed for the other pathologic entities. However, for now AD is a useful construct for political and advocacy purposes and allows communication among physicians, patients, families, and scientists. In the future, it may be just a fraction of the total pathologic picture in cognition and aging, and may best be referred to as the Alzheimer component.

Returning to the question: How early can we diagnose AD?

With all of these accomplishments in the field, the answer to the primary question of “How early can we diagnose AD?” is complex. From a clinical perspective, we have made large advancements in our ability to detect the earliest clinical features of the disease, for example, through the recognition of the construct MCI. A recent practice guideline from the American Academy of Neurology has characterized the prevalence of MCI, its likely trajectory, and the current state of interventions. This has enabled clinicians to counsel patients appropriately, encouraging them to engage in lifestyle modifications, and suggest enrollment in RCTs. The construct of MCI, not without its challenges, has moved the diagnostic threshold earlier in the disease continuum, opening opportunities for research on early intervention in symptomatic disease. However, as outlined above, if the new AD research framework proposes that the disease be defined by the presence of AD biomarkers, then the diagnostic process will change. A person would need to have imaging or CSF biomarkers performed to receive the diagnosis of AD irrespective of clinical state.

From a practical perspective of the clinician, and since the AD framework is strictly for research at this point, it seems that the utilization of current clinical syndromic criteria for unimpaired cognition, MCI, and dementia will persist, and biomarkers including measurement techniques, thresholds for normality, interactions, and other unrecognized contributing factors such as inflammation. Nevertheless, one could envision a scenario whereby a cognitively impaired person would have an array of biomarker tests performed to characterize the underlying pathologic profile contributing to the degree of cognitive impairment. Finally, as therapies are developed for each of these pathologic components, a treatment regimen comprising combination therapies will be tailored for each person. This type of an approach is already being used in disorders such as hypertension, cancer, and HIV/AIDS.
many alterations during that timeframe. Ultimately, our goal is to identify the disease processes as early as possible and intervene with appropriate therapies to eliminate or reduce subsequent damage to the CNS and corresponding symptoms.

Author contributions
RCP: design and conceptualization of the study, analysis and interpretation of the data, and drafting and revising the manuscript for intellectual content.

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