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Using biomarkers to improve detection of Alzheimer's disease

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SUMMARY

Disease-modifying approaches for Alzheimer's disease (AD) might be most effective when initiated very early in the course, before the pathologic burden and neuronal and synaptic degeneration make it unlikely that halting disease progression would have a significant impact on patient outcomes. Biomarkers of disease may provide important avenues of research to enhance the diagnosis of individuals with early AD and could assist in the identification of those individuals at risk for developing AD. However, for such biomarkers to become clinically useful, long-term follow-up studies are necessary to evaluate the relevance of cross-sectional biomarker changes to the longitudinal course of the disease. The objective of this article is to review recent progress in AD biomarkers for the early diagnosis, classification, progression and prediction of AD and their usefulness in new treatment trials.

Alzheimer's disease (AD) is the most common cause of dementia, characterized by progressive cognitive, functional, behavioral deficits from mild, preclinical symptoms to devastating loss of independence and total disability and death [1]. AD affects 25 million people worldwide; prevalence increases exponentially with age, rising from 8% among those aged 65–74 years to almost 50% among those 85 years or older [201]. In the USA, prevalence was estimated to be 5.3 million in 2010 and, by 2050, is projected to increase to over 14 million in the USA alone [1,2]. Taking into consideration the fact that advanced age is the most significant risk factor for AD, with the increase in population as a whole and an increase in longevity, one cannot underestimate the problem this disease poses in terms of its financial and human cost; if left untreated, AD will soon become a public health crisis [2].

To date, the diagnosis of AD as outlined in the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRD) criteria is based on clinical neuropsychological examinations, identification of typical symptoms of AD and exclusion of other known causes of dementia [3,4]. However, these criteria do not take into account recent advances in knowledge regarding AD and related disorders and fail to encompass the value of biological markers (biomarkers) of disease improving the detection of those at-risk for AD. Despite the benefits of validated criteria, the clinical phenotype remains highly variable and accurate diagnosis is not always easy, particularly in its earliest symptomatic stage [5,6]. One possible explanation for the limited detection of AD may be the lack of brief screening tests

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that have been adequately validated to detect the earliest signs of impairment and that correspond to underlying AD pathology [7]. Therefore, there is a strong need to develop measurable *in vivo* AD biomarkers that could facilitate early and accurate diagnosis as well as prognostic data to assist in monitoring therapeutic efficacy.

Although biological markers such as MRI, PET scans and cerebrospinal fluid (CSF) increase the diagnostic likelihood that AD is present [8–11], obtaining biomarkers can be invasive and uncomfortable, measuring biomarkers is expensive, and thus their use may not be readily available to rural areas, underserved communities, underinsured individuals or developing countries. However, the knowledge gained from the study of biomarkers may be applied to clinical practice to increase the likelihood that clinicians will be able to detect disease at earlier stages and differentiate AD from other forms of dementia, some of which may share common pathologies (e.g., Lewy body dementias for amyloid and frontotemporal dementias for tau).

Recent reports support that dementia evaluation using the AD8, a brief informant interview [6,12], is sensitive to early cognitive change compared with a comprehensive clinical and neuropsychological evaluation with a very large effect size to discriminate healthy older adults from those with the mildest forms of impairment (Cohen's $d = 1.6$). The AD8 is also strongly correlated with CSF measurements of amyloid and tau protein and amyloid imaging using Pittsburgh compound B (PIB) [7], and superior to brief performance measurements such as the Mini-Mental State Examination [13] and Short Blessed Test [14]. Furthermore, in the absence of an informant, the AD8 may be administered directly to the patient providing a large effect size (Cohen's $d = 0.96$) to discriminate those with intact cognition from those with very mild impairments.

In this article, we focus on current areas of biomarker investigation (e.g., genetics, CSF and plasma markers, structural and functional MRI (fMRI), PET markers of metabolism and amyloid and neurofibrillary tangle burden measured by PET) and their potential clinical utility for both diagnosis and use in clinical trials. This is particularly relevant in light of recent changes in US Health Reform; mild cognitive impairment (MCI) [15,16] and AD may have limited detection in the community owing to the inability of clinicians to detect the earliest signs of impairment. However, recent health-care reform (Patient Protection and Affordable Care Act) proposes a Personalized Prevention Plan including screening for cognitive disorders, reimbursable through Medicare [202].

AD pathology provides a potential source of biological markers

Characteristic histological changes including hyperphosphorylated forms of the microtubule-associated protein tau and amyloid plaques (extracellular deposits composed predominantly of amyloid- β peptide [17]) remain the hallmarks of AD. Early neurofibrillary tangles and amyloid plaque pathology are estimated to start decades before the symptoms [17,18]; in the evolution, clinical symptoms closely relate to neurofibrillary tangles, neurodegeneration and synaptic loss [19,20]. However, antemortem diagnosis is obviously problematic, as *in vivo* brain biopsy is impracticable and clinical diagnosis may be delayed until a more advanced symptomatic stage of the disease [21,22]. Nevertheless, as the pathology begins decades before clinical symptoms, measurements of amyloid, tau and associated neurochemical and neurophysiological alterations provide a potential pool of biological markers of disease presence and progression.

Based on current hypotheses of pathological progression and its clinical expression, AD can be divided into three phases (Figure 1) [23]: a pre-symptomatic phase in which subjects are cognitively normal but AD pathology has started to accumulate (but is insufficient to affect cognition), a prodromal phase with MCI [16,24], and a third phase when patients show

clinical dementia with impairments in multiple cognitive domains and loss of function in activities of daily living [25,26]. Searching for the presence of biomarkers (as well as in some instances their absolute values) will be differentially helpful depending on the phase of disease under investigation.

Future disease-modifying therapies will probably be at their most effective in patients in the earliest stage of the disease before neuropathology leads to significant neuronal and synaptic loss. Therefore, patients will need to be identified in the prodromal phase or even the presymptomatic phase of the disease. For an AD drug to be labeled as disease modifying, evidence must be available that the agent affects the central disease processes and hallmark neuropathology, in addition to a beneficial effect on cognition [27].

What is a biomarker?

Criteria for an ideal biomarker of AD have been proposed by a consensus group on molecular and biochemical markers of AD; “The ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases; it should have a diagnostic sensitivity of more than 80% for detecting AD and a specificity of more than 80% for distinguishing other dementias; it should be reliable, reproducible, noninvasive, simple to perform, and inexpensive” [28]. Beyond these criteria for early and accurate diagnosis, it would be especially useful if the biomarker could capture the beneficial effect of disease-modifying therapy [29], predict conversion from MCI to AD, correspond closely to available clinical detection methods and thus provide an opportunity for early intervention or prevention. Currently, the diagnosis of AD and MCI is based on clinical data alone but calls to revise the diagnostic criteria to include biological markers have recently been advanced [26] and more formally endorsed at the most recent International Congress on Alzheimer’s Disease [203].

Despite the large number of promising results, AD biomarkers are at various stages of development and clinical evaluation, and have so far not generally been established in clinical routine. However, in the case of neurodegenerative diseases, the disease process may begin long before clinical symptoms manifest. The biologic onset of disease usually cannot be identified, but at some point the pathological evidence of disease can be obtained from biomarkers such as MRI measurements of atrophy [30] or surface deformation [31], glucose hypometabolism on FDG-PET [32], CSF measurements of amyloid and tau [33–35] or PET imaging with amyloid ligands [36]. Which of these lines of evidence occurs first has been hypothesized but not firmly established [23]. Some biological biomarkers offer the opportunity to look at specific pathological features of AD neuropathology, although they may not be sensitive to disease progression (i.e., CSF β -amyloid 42 [A β 42]). Still others (i.e., FDG-PET) strongly correlate with disease progression but may not be specific for AD. It is worth reviewing what is currently known in each area and what potential role these biomarkers play in clinical diagnosis.

Genetic biomarkers

A small fraction of AD patients (<5%) suffer from autosomal dominant familial AD with prevalent early-onset AD. Genetic studies support the view that the Mendelian forms of early-onset familial AD are caused by rare and usually highly penetrant mutations in three genes encoding the proteins: amyloid precursor protein, presenilin-1 and presenilin-2 [37].

On the other hand, more than 95% of AD patients suffer from the sporadic type of the disorder and develop, in the majority, late-onset AD (LOAD); more than 200 genes have been suggested to be involved in the establishment and progression of LOAD [38,39]. In LOAD, twin studies have shown an estimated concordance of between 20 and 80% for AD,

suggesting that LOAD is a complex non-Mendelian disease [40,41]. The best-established risk gene for LOAD is the *e4* variant of *APOE* (*APOE e4*) on chromosome 19. Biochemical studies demonstrated the critical role of *APOE e4* at several levels of the disease: in neuronal repair [42], A β fibrillization, plaque formation [43] and by decreasing brain–blood clearance [44]. All these *APOE e4* effects presumably accumulate and tend to lower the age at disease onset [45,46] and increase the risk of developing AD by approximately 15-fold for *e4* homozygotes, and threefold for heterozygotes; risk is reduced for *e2* heterozygotes [46,47]. However, the presence of the *APOE e4* genotype is neither necessary nor sufficient for the development of the disorder. Finally, CSF and PIB studies show evidence for higher levels of amyloid deposition in *e4* carriers compared with controls [48].

Although the contribution of other candidate genes for LOAD is probably minor [49], the prominence of *APOE e4* has now been nuanced by the observation of an FDG-endophenotype of AD [50,51] in offspring of affected mothers controlled for *APOE e4*. These preliminary FDG-PET observations are complemented and extended by an MRI study [52] that demonstrated significantly reduced gray matter volumes in AD-vulnerable regions (e.g., the frontal cortex, precuneus and lingual gyrus) in individuals with a positive maternal family history of LOAD compared with individuals with positive paternal family history and control groups. Additionally, a recent PIB-PET study showed that cognitively normal subjects with a positive maternal family history have more severe and widespread fibrillar A β deposits than demographically matched subjects with a positive paternal family history and controls [53]. These findings remained significant while controlling for the *APOE* genotype. While specific genes remain to be identified, there is a growing body of evidence for a prevailing maternal transmission [49,54,55] in LOAD families.

Genome-wide association studies in LOAD identified several genes as potentially important susceptibility genes [39,56]. The results of genome-wide association studies are now adding to an already vast and complicated body of data; to facilitate the evaluation and interpretation of these findings a database was recently created for genetic association studies in AD ('AlzGene'; [204]).

Recommendation

At present, there is little reason clinically to genotype individuals in the absence of an autosomal-dominant inheritance pattern, since knowing the *APOE* genotype will not enhance clinical diagnosis nor alter treatment recommendations.

Structural MRI

Atrophy of the medial temporal lobe, including the hippocampus and entorhinal cortex, is an early feature of AD neuropathology and has been shown to be associated with increased risk of developing AD [57]. In early-onset AD the MRI atrophy pattern has been described to affect posterior brain regions compared with LOAD; predominantly the precuneus and posterior cingulate gyrus [58]. Structural MRI biomarkers provide measures of brain atrophy that correlate with Braak neurofibrillary tangle stage, neurofibrillary tangle load, neuropathological progression [59,60] and the degree of cognitive impairment [61]. Atrophy on structural MRI represents the most proximate histological correlate of loss of neurons and synapses [62]. In AD patients atrophy rates of 3–7% per annum were demonstrated [63,64], whereas healthy controls showed a maximum atrophy rate of 0.9% in old age [65]. Hippocampal volume is thus a core candidate for a structural progression marker of AD. The hippocampus volumetry method is already being used as a secondary end point in several pharmacologic trials [66]. However, these changes are not specific to AD [60,67].

Measuring individual structures or regions of the medial temporal lobe using manual techniques, such as linear or volumetric tracing, visual ratings or automatic segmentation techniques, are time-consuming and expert-dependent, thus making clinic use unlikely. By contrast, voxel- or tensor-based morphometry can assess global atrophy in a fully automated manner. Such methods are typically used for calculating group differences rather than to classify individual patients. Recently, support vector machines, trained on a specific algorithm, have been used to automatically classify individual scans with a feature reduction step to select the voxel locations or pattern that best differentiates AD from control participants [68]. A combination of volumetric results and neuropsychological tests generated accuracy rates of 94% for AD (n = 120) versus controls (n = 111), 83% for MCI (n = 120) versus controls and 82% for AD versus MCI [69].

Recommendation

In clinical practice, structural MRI can help to support clinical diagnosis with medial temporal lobe atrophy being the most consistent finding, but it is not sufficient for establishing a definitive diagnosis [69].

Functional MRI

Functional MRI allows for the measurement of brain activation during rest, or more commonly, in association with a cognitive task or stimulus that requires the involvement of related brain areas and networks [70]. It has a relative high level of temporal and spatial resolution, does not require the injection of a contrast agent or any radiation exposure and can be repeated many times over the course of a longitudinal study.

Blood oxygen level-dependent fMRI is the most common functional imaging method and measures alterations in blood flow associated with neuronal activity, which indirectly reflects brain activity. There have been many studies that have examined brain activation changes in AD subjects, compared with normal cognition subject, and individuals with AD showed lowered brain activity in parietal and hippocampal regions and higher activity in primary cortices unaffected by the disease [71–73]. Furthermore, some studies found differential fMRI activation responses between MCI and healthy controls [72,74].

Currently, the high inter- and intra-individual variability of the signals and its inherent dependency on hemodynamics have precluded the use of this technique for differential diagnostic of dementias. However, fMRI has helped to define intrinsic functional networks in the human brain [75] and it is possible that function-critical neural networks could be affected differentially by variant neurodegenerative diseases [76].

Recommendation

Since most fMRI studies have analyzed data at a group level, the discriminative utility at the individual level has not been adequately addressed. Therefore, these findings cannot be used in their present state as a diagnostic marker and fMRI remains largely a research tool.

Biomarkers in CSF

Cerebrospinal fluid biomarker research has focused on A β 42, total tau (t-tau) and phosphorylated tau (p-tau) because of the direct link with pathologic hallmarks. The combination of low CSF A β 42, and high CSF tau have been associated with pathological features of post-mortem AD with high accuracy [77].

A β peptide

Several studies have demonstrated a CSF reduction of A β 42 by approximately 50% in AD patients compared with nondemented controls of the same age; the diagnostic sensitivity and specificity levels ranged from 80 to 90% [78,79]. Compared with other types of dementia, the specificity level was only approximately 55% for A β 42 alone but with tau, specificity of the combined test was 86% [80]. Low CSF A β 1–42 is a strong indicator of fibrillary amyloid deposition in plaques. An autopsy study demonstrated an inverse correlation between A β 42 levels in the CSF and the number of plaques [81]; furthermore, nearly complete concordance is present between individuals with positive PIB PET scans and those with low CSF A β 42 [82].

Total tau protein

Approximately 50 studies have been conducted to date and have all demonstrated an increase in the concentration of t-tau in AD patients by approximately 300% compared with nondemented elderly subjects, and a systematic increase in the concentration over an individual lifespan [83]. The sensitivity and specificity levels were between 80 and 90% for t-tau [78]. Data from various studies suggest that CSF t-tau levels reflect the intensity of neuronal and axonal degeneration and damage in the brain [84,85]. High CSF t-tau has also been associated with fast progression from MCI to AD [86] and both t-tau and A β 42 were significantly altered in subjects with MCI who are an increased risk of AD over time [87]. Additionally, the CSF tau:A β 42 ratio predicts cognitive decline in cognitively intact older adults and in individuals with MCI [34].

Hyperphosphorylated tau protein

An increase in p-tau has consistently been found in the CSF of AD patients compared with controls. Approximately 20 studies have been conducted with sensitivity and specificity levels of between 80 and 90% [79,80]. p-tau231P and p-tau181P have shown good results in distinguishing AD from control groups and even from other types of dementia [87]. The high negative predictive value of p-tau of approximately 90% appears to be particularly significant. CSF levels of p-tau seem to reflect both the phosphorylation state of tau and the formation of neurofibrillary tangles in the brain. In some studies that involved measuring p-tau in CSF samples taken both ante- and post-mortem, correlations were reported for CSF p-tau phosphorylated at thr181 (p-tau181) or thr231 (p-tau231) with neocortical neurofibrillary tangle pathology, as well as with the rate of hippocampal atrophy in the brain [77]. High CSF p-tau181 has also been associated with a fast progression from MCI to AD [86].

CSF biomarker combinations

The combination of tau and A β measurements in CSF enhance the accuracy of the diagnostic power. In a meta-analysis of five studies, low CSF A β 42 levels along with high t-tau and p-tau predicted conversion from MCI to AD [88]; this information will be invaluable in the selection of patients to undergo clinical trials with disease-modifying drugs [89], since high-risk patients would benefit more from these therapies. CSF parameters may also be useful to monitor response to treatment and indicate the effectiveness of disease modification. A recent report used the US Alzheimer's Disease Neuroimaging Initiative data set, and developed a combination model composed of A β 42 and p-tau181 [10]. This model identified CSF 'signatures' for healthy controls and AD, with the AD pattern found in 90, 72 and 36% of patients in the AD, MCI and cognitively normal groups, respectively. The most interesting finding was that up to a third of cognitively intact older adults had biomarker changes, suggesting that the use of biomarkers may indeed assist in the identification of individuals at risk for AD. An alternative conclusion is that in well-characterized samples the use of CSF biomarkers may accurately classify cases versus controls [10,35]; however, it

remains to be seen if these signatures translate to patient populations where co-morbid disorders are more rampant and likely to lead to increased frequencies of mixed dementias.

Recommendation

Lumbar puncture is a routine procedure, but may not be readily acceptable to all patients. Despite being associated with side effects such as headache, it is generally well tolerated. CSF studies perhaps afford the most promising use of biomarkers for prediction, diagnosis and disease progression. CSF studies are particularly useful clinically in diagnostically challenging cases, but probably do not add significantly to diagnostic certainty when the patient meets current clinical criteria for probable AD. CSF studies may provide confirmation whether the underlying cause of MCI is likely owing to AD and may guide the choice of whether to offer 'off-label' use of AD medications.

Plasma markers

Effective plasma biomarkers would provide a truly minimally invasive test. So far, efforts to use plasma A β as a marker for AD have not been successful [90]. However, novel molecular approaches have identified plasma proteins (e.g., IL-1 α , IL-3 and TNF- α), which can distinguish AD from control subjects with nearly 90% accuracy, and can identify patients with MCI who progress to AD [91]. Unbiased approaches have been pursued to evaluate a broad range of proteins (proteomics), small molecule metabolites (metabolomics) or transcripts (transcriptomics) in blood [92].

Recommendation

The complexity of serum and plasma, and difficulties in assay standardization make these approaches challenging, but the rapid evolution in technological and computational facilities should allow greater diagnostic accuracy and broader applicability of these methods [93]. At the present time, however, plasma markers remain relegated to research platforms.

PET imaging of A β

In addition to measuring A β levels in the CSF, more recently A β deposits have become measurable using PET and radiotracer ligands that bind to the aggregated fibrillar form of A β . Radiotracers with a high affinity for amyloid (in extracellular A β plaques) have been developed for use in humans [94,95]. The three most common ligands in use to image A β deposition with PET are the ¹¹C-labeled PET tracer 6-OHBTa (also known as PIB [94]), the ¹⁸F-labeled tracer FDDNP [95] and florpiramine F18 (also known as ¹⁸F-AV-45) [96].

The most researched of these is PIB. PIB binds to amyloid plaques in AD [94]. PIB may serve as an antecedent biomarker of AD in nondemented older adults [36] with higher mean cortical binding potential values for PIB (hazard ratio: 4.85; 95% CI: 1.22–19.01) and age (hazard ratio: 1.14; 95% CI: 1.02–1.28) predicting progression to AD and disrupting resting state default mode network connectivity in cognitively normal elderly [97]. Furthermore, PIB may serve as an endophenotype of AD with 61% heritability [98]. AV-45 has a similar amyloid binding pattern to PIB [99,100], but using ¹⁸F as its radiolabel compared with ¹¹C for PIB makes it a more desirable clinical tool. The ¹⁸F-labeled tracer FDDNP binds to both A β plaques and neurofibrillary tangles *in vitro* and predicts progression from MCI to AD [101]. However, the change in signal between asymptomatic controls and patients is small (e.g., 10%). The most robust binding in patients is consistently seen in the medial temporal cortex, which correlates with a high burden of neurofibrillary tangles in the same region relatively early in the disease process.

Several groups have achieved sensitivities approaching 100% for AD in small studies comparing healthy controls with patients [102], but a high proportion of controls (21%) and approximately half of patients with MCI show an AD-like pattern of PIB binding. In MCI, this pattern appears to predict progression to AD over the subsequent 2 years in MCI [103], however, there appears to be little change in PIB binding longitudinally in either MCI or AD [104].

Amyloid imaging is attractive for evaluation of anti-amyloid therapy. Several therapeutic strategies for preventing or diminishing insoluble A β accumulation, such as secretase inhibitors or modulators, A β vaccines, tau kinase inhibitors, cholesterol-lowering statins and anti-inflammatory drugs, are being evaluated as interventions for delaying onset or slowing the progression of AD [105]. Combining these neuro-imaging with other biological markers improves diagnostic accuracy, reduces the number of individuals needed for a clinical trial of a new treatment and could be a measure *in vivo* of reduction in A β plaques.

Recommendation

Amyloid imaging is an exciting potential tool to ascertain that cognitive difficulties are likely due to AD pathology and identify presymptomatic individuals at risk for future AD with minimal invasiveness. The advent of ^{18}F compounds (as opposed to ^{11}C -PIB) increases the potential for clinical utility. At the present time, amyloid imaging remains a research tool, although once approved would serve as antemortem confirmation of AD pathology.

[^{18}F] FDG-PET in AD

FDG-PET provides qualitative and quantitative estimates of regional cerebral metabolic rates of glucose, considered as an index of synaptic activity [106] and density [107]. In AD, the most prominent and consistent cerebral metabolic rates of glucose findings are decreased metabolism starting in the entorhinal cortex [108] and hippocampus [109,110] and spreading to the posterior cingulate cortex, temporoparietal areas, precuneus and prefrontal cortex in more advanced stages [111–113]. This pattern of regional hypometabolism appears to be strongly associated with AD, yielding sensitivity and specificity as high as 93% [114]. It also appears to have a higher accuracy than PIB-PET (85 and 75%, respectively [115]) in the distinction of normal versus MCI subjects. MCI is a prodromal stage of dementia characterized by milder abnormalities in the same areas except for frontal cortex [116–122]. Last, in MCI and AD it has been demonstrated that metabolism reductions exceed volume losses [109]. FDG-PET has been used as an end point in single center studies [123] and automatic diagnostic expert systems using FDG-PET are being developed [120]. Lower scanner costs and greater availability of PET tracers is expected to lead to wider use of PET for dementia diagnosis.

A recent and interesting finding from FDG-PET studies is the identification of maternal inheritance patterns for AD [49]. After advanced age, having a parent affected with AD appears to be the most significant risk factor for developing LOAD. The authors found that although many LOAD cases were sporadic, a substantial number demonstrate familial aggregation. Using FDG-PET, individuals with a maternal history of LOAD, but not with a paternal family history, express a pattern of glucose hypometabolism that is phenotypic of AD [51].

Recommendation

FDG-PET is already available as a clinical diagnostic tool, reimbursable through Medicare for the differentiation of AD from frontotemporal dementia. However, other third party payers may not approve FDG-PET for dementia diagnosis. In the proper clinical setting, FDG-PET may increase diagnostic certainty that cognitive impairment is most likely due to

AD, and FDG-PET is sensitive to disease progression showing decreased glucose metabolism.

Future perspective

Clinical diagnosis & disease-modifying clinical trials

One of the most discussed topics at the 2010 International Congress on Alzheimer's Disease (ICAD) was the call to improve clinical–cognitive diagnostic and staging criteria based on new research on the temporal ordering of AD biomarkers. Jack and colleagues proposed that biomarkers of amyloid deposition (i.e., CSF A β 42 and PET-PIB) become abnormal early, before neurodegeneration and clinical symptoms become apparent (preclinical AD) [23]. Furthermore, morphometric changes on MRI and metabolic deficits identified by FDG-PET precede the development of clinical cognitive symptoms and correlates with future cognitive decline. Cognitive symptoms are directly related to biomarkers of neurodegeneration (brain atrophy) rather than biomarkers of A β deposition [23].

There are several limitations to this model. The most important is that it is hypothetical, and is not based on actual data. This stems, in part, because of the lack of extensive longitudinal data that includes longitudinal collection of all biomarkers in a well-characterized cohort. While multicenter studies often offer a larger sample for analysis, a significant limitation is the presence of intercenter and interlaboratory variations in biomarker measurements [124]. However, this model affords an opportunity to consider how biomarkers may be used in the context of clinical diagnoses (Figure 1).

Biomarkers might also be valuable in drug development, as such biomarkers could be used as diagnostic markers for enriching the number of AD cases, for patient stratification, as safety markers, and to detect and monitor the biochemical effects of drugs. Enrichment schemes may also incorporate brief tests, such as the AD8, since individuals with abnormal scores are likely to have abnormal AD biomarkers. Several clinical trials of disease-modifying drug candidates that include biomarkers as end points are currently ongoing. These trials will provide further evidence to indicate whether biomarkers can be used to assess disease modification, and as surrogate markers for predicting clinical outcomes [125].

More detailed guidelines are needed on how biomarkers can be implemented in the diagnostic procedure for early AD in the clinic. Such guidelines should provide details of the scales to be used in measuring memory impairment, the assays and cutoffs to be employed for CSF biomarkers, the brain regions (e.g., whole brain, hippocampus or entorhinal cortex) to be evaluated by MRI for atrophy, and the amyloid ligands to be used and brain regions to be evaluated by PET. In particular, the challenge may not lie in developing guidelines but how to standardize assays and methods across laboratories. Such programs are already beginning with the Alzheimer Association Quality Control Program.

New research criteria for AD have been constructed to allow a diagnosis of AD to be made in the early stages of the disease. These criteria are centered on the clinical identification of episodic memory impairment alongside the detection of one or more abnormal biomarkers, including MRI, PET and CSF biomarkers [26]. Brief dementia screening methods such as the AD8 ($\pm$ a performance task) parallel changes in biomarkers of AD, suggesting that the use of these screening measures to first identify someone with a high likelihood of AD followed by a confirmation evaluation using either a detailed clinical/cognitive evaluation (costly in terms of time and effort) or a biomarker evaluation (costly in terms of expense) may provide a robust and evidence-based method for detection of MCI and AD.

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Practice Points

- The diagnosis of Alzheimer's disease (AD) and related disorders remains a clinical one, based on the principle of intraindividual change in cognitive abilities that interfere with social and/or occupational functioning. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for AD were written in 1984, well before knowledge of the potential of biomarkers were considered. Recent recommendations have proposed incorporating the evaluations of biomarkers in the diagnostic criteria for mild cognitive impairment and AD.
- Clinical trials testing potential disease-modifying medications are incorporating biomarkers both as inclusion criteria and as secondary outcomes. These trials may provide evidence for the use of biomarkers in clinical practice.
- AD biomarkers may come in three varieties: biomarkers that are sensitive to disease presence but not necessarily progression (e.g., cerebrospinal fluid β -amyloid 42 and Pittsburgh compound B imaging); biomarkers that are sensitive to disease progression but not necessarily presence (e.g., MRI atrophy); and biomarkers that mark disease presence and are characterized by change over the course of disease progression (e.g., FDG-PET).
- Current hypothetical models of AD progression suggest that biomarkers of amyloid deposition are the primary initiating event, followed by changes in tau, brain structure and function, cognitive domains and finally activities of daily living.
- AD biomarkers, alone or in combination, may assist in earlier recognition of AD, aid in differentiation of AD from other dementias, and may detect the presence of disease in asymptomatic individuals.
- The use of a brief test such as the AD8 ($\pm$ a brief performance measure) may improve strategies for detecting dementia in clinical practice and enrich clinical trial recruitment by increasing the likelihood that participants have underlying biomarker abnormalities.

Figure 1. Conceptual model of phases of Alzheimer's disease and the appearance of biomarkers

AD can be conceptualized as three phases: a 'presymptomatic' phase in which subjects are cognitively normal but have AD pathology (insufficiently severe to affect cognition), a 'prodromal' MCI phase in which cognition is impaired but patients' daily functioning is minimally impaired and a third 'symptomatic' phase (clinical AD) when patients show dementia with impairments in multiple domains and loss of function in activities of daily living. At each phase, biomarkers supporting detection of AD appear and once present generally persist. Here, we depict the likelihood of success in using each biomarker for prediction, diagnosis and prognosis. The first group of biomarkers reflecting pathology (CSF β -amyloid 42, tau and amyloid imaging) appear in the presymptomatic phase of the disease and can be detected in cognitively normal individuals. The second group of biomarkers reflecting neuronal structure and function (structural and functional MRI and FDG-PET) appear in the late presymptomatic–early prodromal phase. Finally, clinically detectable markers of disease (e.g., cognition, function and behavior) appear in the prodromal phase and continue throughout the symptomatic phase. Temporal appearance of biomarkers suggests that clinical diagnosis can be assisted by knowing which biomarker to look for depending on the phase of the disease being investigated.

AD: Alzheimer's disease; CSF: Cerebrospinal fluid; MCI: Mild cognitive impairment; PIB: Pittsburgh compound B.