In vivo Detection of Alzheimer’s Disease

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Recent revisions to the diagnostic criteria for Alzheimer’s disease (AD\(^†\)) incorporated conceptual advances in the field. Specifically, AD is now recognized to encompass a continuum, spanning from preclinical (accumulating brain pathology in the absence of symptoms) through symptomatic predementia (prodromal AD, mild cognitive impairment) and dementia phases. The role of biological markers (biomarkers) of both the underlying molecular pathologies and related neurodegenerative changes has also been acknowledged. In this abridged review, we provide an overview of fluid (cerebrospinal fluid and blood) and molecular imaging-based biomarkers used within the field and discuss the potential role of computer driven artificial intelligence approaches for both the early and accurate identification of AD and as a tool for population enrichment in clinical trials testing candidate disease modifying therapies.

INTRODUCTION

Alzheimer’s disease (AD) is the leading cause of dementia, accounting for between 50 and 70 percent of cases [1]. Clinically, AD is characterized by progressive global cognitive decline, affecting memory, language, visuospatial abilities, and executive function, leading ultimately, to dementia [2]. Neuropathologically, the two major hallmarks of AD are the deposition of insoluble amyloid-β (Aβ) plaques and the formation of neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau. It is currently believed that the dysmetabolism of Aβ triggers a cascade of secondary abnormalities that involved tau-associated neurodegeneration as well as unresolved neuroinflammation [3] (reviewed in [4]).

During the past two decades, advances in the abil-
Table 1. Performance of AD biomarkers.

| Biomarker | Sensitivity / Specificity | References |
|-----------|---------------------------|------------|
| **CSF**   |                           |            |
| Aβ<sub>1-42</sub> | 0.86/ 0.90            | [7]        |
| Aβ<sub>1-42</sub>/Aβ<sub>1-40</sub> | 0.93/ 1.0            | [8]        |
| p-tau     | 0.80/ 0.92              | [7]        |
| t-tau     | 0.81/ 0.90              | [7]        |
| **Plasma** |                           |            |
| Aβ<sub>1-42</sub> | 0.93/ 0.96              | [9]        |
| Aβ<sub>1-42</sub>/Aβ<sub>1-40</sub> | 0.90/ 0.90          | [10]       |
| APP<sub>669-711</sub>/A<sub>1-42</sub> | 0.85/ 0.95           | [10]       |
| Composite | 0.95/ 0.95              | [10]       |
| **PET**   |                           |            |
| Aβ        | 0.85/ 0.88              | [11]       |
| Tau       | 0.93-0.97/ 1.0          | [12]       |
| FDG       | 0.84/ 0.86              | [11]       |
| **MRI**   |                           |            |
|           | 0.81/ 0.75              | [11]       |

Sensitivity and specificity figures for AD biomarkers, for the comparison AD dementia versus controls. Though these are in line with recommendations by the 1998 Biomarker Working Group, stating that an ideal AD biomarker should have sensitivity and specificity > 80% [13], performance is imperfect; this relates to the use of patients possibly misdiagnosed or harbouring mixed pathologies, the use of amyloid-positive “controls” and the high overlap in pathology between AD and other dementia disorders. Composite = APP<sub>669-711</sub>/Aβ<sub>1-42</sub> to Aβ<sub>1-40</sub>/Aβ<sub>1-42</sub>.

Figure 1. Fluid and imaging biomarkers in Alzheimer’s disease. A schematic overview of established and candidate imaging and fluid-based AD biomarkers.
ity to identify AD pathology using biological markers (biomarkers) have changed the way we understand AD entirely. A biomarker, by definition, is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [5]. Currently, AD hallmarks can be assessed in vivo by analyzing biomarkers in two main categories: i) fluid biomarkers, including cerebrospinal fluid (CSF) and promising developments in blood; and ii) imaging biomarkers, such as positron emission tomography (PET) and magnetic resonance imaging (MRI) [6] (Figure 1; Table 1). These biomarkers are now providing reliable quantitative measures that can support the early and accurate diagnosis of AD and carry the potential to surpass precision levels using clinical measures [14].

In this short review, we discuss the recent revisions to the conceptualization of AD and provide an overview of fluid and imaging-based biomarkers commonly used in the assessment of AD. Further, we address the use of artificial intelligence (AI) as a strategy to help identify individuals at risk for developing AD.

DEFINING AD: THREE DECADES OF ADVANCES

When the first diagnostic criteria for AD were published in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [15], the typical amnestic syndrome that defines AD clinically and AD neuropathological changes were considered interchangeable. AD has since become a clinical-biomarker construct with the introduction of the International Working Group (IWG) [16-18] and National Institute on Aging and the Alzheimer’s Association (NIA-AA) guidelines [2,19,20]. Incorporating biomarkers for Aβ, tau, and neurodegeneration, these guidelines highlighted how AD pathology and resulting symptoms are not related in a one-to-one fashion, and delineated a continuum spanning preclinical (AD neuropathology begins to accumulate in the brain, yet in the absence of overt symptoms) and clinical stages (encompassing both a prodromal or mild cognitive impairment (MCI) phase, characterized by objective cognitive impairment, no dementia, and a dementia phase, each supported by biomarker evidence of AD pathology) (Figure 2). This separation of AD neuropathology from the signs/symptoms of the disease was further refined in recent revisions to the NIA-AA guidelines, with AD now an entity defined entirely on the basis of biomarkers for amyloid, tau, and neurodegeneration [21]. Though the IWG and 2011 NIA-AA guidelines incorporated criteria intended, in part, to assist in clinical decision-making, these guidelines overall are largely intended to provide a common framework for defining and staging AD.

FLUID BIOMARKERS

Cerebrospinal Fluid Biomarkers

The core CSF biomarkers used in the diagnostic work-up of and research in AD are residues from the enzymatic cleavage of the amyloid precursor protein (APP) at different lengths (Aβ1-38, Aβ1-40, and Aβ1-42), total tau
(t-tau), and phosphorylated tau (p-tau, mainly phosphorylated at threonine 181 or serine 199) [22].

Of the different cleavage residues of APP, Aβ 1-42 is the main constituent of Aβ plaques. Multiple studies have demonstrated a marked decrease in CSF Aβ 1-42 levels in AD, possibly due to the deposition of the peptide in Aβ plaques. Levels of Aβ 1-38 and Aβ 1-40, however, are not affected in AD [23] and may be useful for the normalization of interindividual differences in Aβ-production [24] in the form of ratios (Aβ 1-42/Aβ 1-38 and Aβ 1-42/Aβ 1-40), though some studies have failed to show increased diagnostic accuracy using these [23,25].

In contrast to Aβ, cognitive decline in AD better relates to tau and neurodegeneration, processes that are reflected in the CSF as elevated t-tau and p-tau. Measurement of t-tau is considered to reflect the intensity of neurodegeneration at a given point while p-tau is thought to reflect a pathologic state of hyperphosphorylation leading to the formation of NFTs [22]. Both have been shown to be of value in the separation of AD from cognitively unimpaired (CU) controls and non-AD disorders, as well as prognostic abilities in predicting the conversion from MCI to AD [26]; here, ratios with Aβ 1-42 have been shown to provide increased sensitivity and specificity [25,26]. Interestingly, the axonal neuron-specific protein neurofilament light (NFL), which has been shown to correlate with low Aβ 1-42 and elevated tau levels [27], may serve as a useful marker of progression in AD.

**Blood Biomarkers**

The invasiveness of lumbar puncture as a procedure for collecting CSF stands as a drawback when considering its widespread use in the clinical work up of patients presenting with cognitive complaints, and for participant selection in therapeutic trials. A blood-based measure for AD pathology would therefore have significant practical advantages.

Establishing robust blood biomarkers for Aβ and tau species has proven troublesome. Aβ peptides are readily measured in plasma but historically the correlation with brain Aβ levels (measured by Aβ PET or CSF) has been weak, with levels being confounded by platelet production and other extra-cerebral tissues [28]. However, this generalized opinion is beginning to change with recent mass spectrometric and ultrasensitive immunoassay (single-molecule array, Simoa) evidence suggesting that Aβ peptide ratios (Aβ 1-42/Aβ 1-40, APP 669-711/Aβ 1-42 and a composite APP 669-711/Aβ 1-42 to Aβ 1-40/Aβ 1-42) identify Aβ-positive individuals with high sensitivity and specificity [10,29,30]. There are currently no robust immunoassays for p-tau in plasma whereas the Simoa platform allows for femtomolar measures of t-tau. Nominal group differences between AD and CU individuals are consistently observed [31], however the lack of correlation of plasma t-tau with CSF suggests that these two body fluids are differentially regulated [32]. The half-life of tau appears to be much shorter in plasma (hours) than in CSF (weeks) [33,34]. In contrast, plasma and CSF NFL tightly correlate [35,36], with plasma levels shown to have a marked elevation in AD compared to MCI and healthy controls [37], comparable to differences seen with core CSF biomarkers [38]. However, it is likely that increased plasma NFL lacks disease specificity as it is found to be a feature in many conditions [36,39,40].

Research has also focused upon the detection of other circulating blood proteins which may serve as peripheral indicators for clinical AD (reviewed in [41]). Increasingly, promising “endophenotype” studies that utilize imaging surrogates of brain atrophy [42] and amyloid-β PET [43] have pointed to peripheral biomarker panels indicative of on-going disease pathophysiology. However, these pilot data should be interpreted with some caution as they are derived from multi-marker panels and as a mechanistic understanding of the associations is currently lacking.

**MOLECULAR IMAGING**

**Aβ and tau PET**

Since the first application of the PET ligand 11C-Pittsburgh Compound B (11C-PIB) to the in vivo study of Aβ plaques in AD, numerous studies using 11C-PIB have shown that the global amount of Aβ in AD dementia patients is typically 50 to 70 percent above levels seen in CU older individuals [44]. Similar studies in CU individuals and MCI patients have shown Aβ positivity in a high proportion (30 percent and 60 percent, respectively) [45,46], consistent with autopsy data in both groups showing comparable percentages meeting neuropathological criteria for AD [47,48]. Aβ positivity among patients diagnosed clinically as AD dementia lies around 90 percent, with Aβ-negative cases assumed to represent clinical misdiagnosis [49]. Driven by the success of 11C-PIB and limitations tied to its short half-life (~20 min, making it impractical for clinical use), several Aβ labelling 18F compounds have been developed (half-life ~110 min), including 18F-florbetapir, 18F-flutemetamol, 18F-florbetaben, and 18F-NAV4694 (previously 18F-AZD4694) [50]. Using these tracers, findings similar to those for 11C-PIB have been reported [49] (Figure 3). Importantly, 18F-florbetapir (Amyvid), 18F-flutemetamol (Vizamyl), and 18F-florbetaben (Neuraceq) are now approved for clinical use. Interestingly, preliminary findings suggest that retinal levels of Aβ plaques, measured in vivo, may provide an index of overall Aβ brain levels [51]. Other autofluorescence based techniques have also shown potential for future in vivo use [52,53].
Since approved by the Food and Drug Administration (FDA) in 2004 for use in the diagnostic work up of dementia disorders, 18F-FDG PET has come to play an important role in the evaluation of patients with suspected AD. A marker of neurodegeneration, decreased uptake of 18F-FDG is interpreted as largely reflecting synaptic depletion [62]. In AD, a characteristic pattern of glucose hypometabolism is observed, involving the precuneus/posterior cingulate, inferior parietal lobule as well as posterolateral and medial aspects of the temporal lobe, including the hippocampus and entorhinal cortex [63,64]. In patients with MCI, the presence of this metabolic signature has been shown to predict progression to AD dementia [65,66]. Further, 18F-FDG has shown high sensitivity and specificity in identifying AD and related neurodegenerative diseases using neuropathologic diagnosis as the standard of truth [67] and has been shown to be a helpful adjunct in clinical practice [68]. Moreover, 18F-FDG hypometabolism has been shown to relate closely to cognitive decline, predicting progression from normal cognition through MCI and AD dementia [69,70].

11C-UCB-J, a marker of the synaptic vesicle glycoprotein 2A [71], also shows promise as a marker of synaptic loss; building on the success of Aβ imaging, PET ligands selective for AD-related paired-helical filament (PHF) tau have recently made their entry into the field. Using “first generation” tracers, including 18F-THK5317, 18F-THK5351, and 18F-flortaucipir (also known as 18F-AV-1451, 18F-T807) (reviewed in [54]), robust differences in uptake have been reported between CU elderly controls and patients with AD have been observed, as well as elevated uptake in subjects with MCI [55,56] (Figure 3). Further, several tau imaging studies have shown good correspondence between ligand retention and Braak staging of post mortem tau pathology [56,57], and tight associations with neurodegenerative markers such as cortical atrophy measurements and 18F-fluorodeoxyglucose (18F-FDG) PET [58,59]. Comparative studies between tau ligands suggest varying sensitivity/specificity toward AD type tau [60,61], highlighting the complexity of tau pathology and the likely need for multiple tracers to properly address the full range of tauopathies. Importantly, first generation tracers have been shown to exhibit “off-target” binding, notably to monoamine oxidase B. Early findings from “second generation” tracers, including 18F-MK-6240 and 18F-PI-2620, appear promising; presented data, however, has so far mostly been limited to international conferences.

18F-FDG PET

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the cause of AD [79], the predominant view is that dyshomeostasis of Aβ is the initiating event [80,81]. According to this hypothesis, aggregation of Aβ1-42 leads to tau pathology, neurodegeneration, and clinical symptoms. Accordingly, the first biomarkers to become abnormal are CSF Aβ1-42 followed by Aβ PET; Aβ then induces tau pathology in the medial temporal lobe (an alternative model stipulates that medial temporal tau in fact precedes Aβ [82]) and fosters its spread into neocortical areas; this process is reflected by abnormal CSF p-tau, and later, tau PET. This tauopathy would then lead to abnormalities in biomarkers of neurodegeneration, namely t-tau, structural MRI and 18F-FDG PET, with clinical symptoms following these markers [83-85]. Though Aβ biomarkers, and, possibly, CSF tau [86,87] are thought to reach a plateau during the early symptomatic phase of the disease (i.e. prodromal AD) [88], tau PET and neurodegenerative biomarkers are believed to remain dynamic though the dementia phase [6,89]. Importantly, the relationship between a given individual’s cognitive status and biomarker profile is thought to be influenced by genetic risk factors, comorbid pathologies, and cognitive reserve [90].

**COMPUTER-ASSISTED BIOMARKER DRIVEN APPROACHES**

One of the most pressing challenges facing the field currently is the failure of clinical trials testing candidate disease modifying treatments. Given the recognition that

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Figure 4. Representative artificial intelligence workflow for predicting patients at-risk for developing Alzheimer’s disease. Large-scale multicentric studies in heterogeneous populations (a) collecting a wide range of biomarkers (imaging and fluid), genetics and neuropsychological data (b) can provide enormous quantity of valuable data, which can be promptly analyzed and shared. Using these big databases as input variables in highly refined machine learning and deep machine learning algorithms (c) it is expected that in the near future we will be able to identify and predict patients at-risk to develop Alzheimer’s disease (d).
therapies may prove ineffective in those already exhibiting dementia, focus has shifted toward the inclusion of minimally symptomatic and asymptomatic CU elderly individuals with biomarker evidence of AD pathology [91]. In order to facilitate reductions in required sample size, and to better assess treatment outcomes, identifying individuals who will show disease progression within a reasonable time frame is critical. Given the likely need to move beyond single variable approaches [92], instead accounting for high number of variables, as well as complex interactions between them, computer aided approaches, including AI, are emerging as a useful strategy for population enrichment (Figure 4). Findings derived using machine learning or deep learning, which involve computer algorithms extracting patterns from a dataset, and then learning to predict an outcome of interest [93], indeed suggest that the risk to develop AD can be detected prior to symptomatic onset [94].

CONCLUSIONS AND OUTLOOK

While further studies are required to more fully assess the utility of fluid and imaging biomarkers, particularly for tau PET given its recent introduction, findings are thus far promising and suggest that the informed and appropriate use of biomarkers can be of help in the early and accurate identification of AD. The complexity of many findings, aggravating the definition of thresholds for biomarker "positivity," and the high cost of these investigations, however, remain as obstacles to their routine use in clinical settings. Further, additional markers for targets such as α-synuclein and transactive response DNA binding protein 43 kDa (TDP-43) are likely needed to increase capabilities with respect to characterizing the full range of proteinopathies that can underlie dementia disorders. Given the recognition that potential disease modifying treatments are most likely to succeed if administered during the preclinical phase of AD, biomarker driven strategies for population enrichment are critical. In this respect, AI driven approaches may help optimize selection algorithms in order to increase study power and decrease observational periods.

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Leuzy et al.: Detection of Alzheimer’s disease
Leuzy et al.: Detection of Alzheimer’s disease

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