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Fluid and imaging biomarkers for Alzheimer's disease: where we stand and where to head to

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Abstract

There is increasing evidence that a number of potentially informative biomarkers for Alzheimer disease (AD) can improve the accuracy of diagnosing this form of dementia, especially when used as a panel of diagnostic assays and interpreted in the context of neuroimaging and clinical data. Moreover, by combining the power of CSF biomarkers with neuroimaging techniques to visualize A β deposits (or neurodegenerative lesions), it might be possible to better identify individuals at greatest risk for developing MCI and converting to AD. The objective of this article was to review recent progress in selected imaging and chemical biomarkers for prediction, early diagnosis and progression of AD. We present our view point of a scenario that places CSF and imaging markers on the verge of general utility based on accuracy levels that already match (or even surpass) current clinical precision.

Keywords

Alzheimer; Mild Cognitive Impairment; Biomarker; Cerebrospinal Fluid; Diagnosis; Neuroimaging

1. Introduction

Alzheimer's disease (AD) is one of the most common illnesses of later life and currently affects 35.6 million worldwide, with such number expected to increase to 65.7 million people in 2030 and to 115.4 million in 2050 (1). At present, AD cannot be diagnosed until a dementia phenotype has been clinically established (2) and there are no treatments to change the course of this progressive neurodegenerative disorder (3, 4). Growing evidence suggests that cellular and brain changes associated with the disease begin years — even decades —

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before people first show clinical symptoms of memory loss or cognitive/behavioral difficulties (5–8). Mild cognitive impairment (MCI) usually precedes the AD-related cognitive dysfunctions, despite not all MCI cases evolve into AD (7). MCI individuals display increased risk of developing AD within 3–5 years, and almost 45% of all MCI patients evolving to AD within 5 years (9, 10). Researchers are increasingly investigating biomarkers for AD — specific proteins in blood or cerebrospinal fluid (CSF) as well as imaging of brain structures and functions (11) — to identify changes which could measure the risk for AD onset, mostly in MCI context but even in symptom-free people, in pursue of strategies to effectively diagnose and treat as soon as possible, or provide the opportunity to intervene before major neuronal and synaptic losses occur. Large-scaled, controlled multicenter trials on biomarkers are currently being conducted in an attempt to develop and validate core feasible candidate elements, mostly related to structural and functional imaging and neurochemistry (12, 13).

Although the clinical symptoms of AD are frequently diagnosed at older ages, such degenerative processes start many years before the clinical onset of the disease (14). The presymptomatic detection of AD is crucial, and could facilitate implementation of early and efficient treatments (pharmacological and non-pharmacological) to modify the course of the natural history of this important, life-threatening disorder. Besides an important role in diagnostics, biomarkers can also provide insight into the AD pathogenesis.

The diagnosis of late-onset AD based solely on clinical symptoms has shortcomings, particularly in the prodromal phase (3). This difficulty is reflected in the modestly accurate clinical method for AD diagnosis existent to date which cannot rely on fairly informative and accessible biomarkers. Sensitivities of the classical clinical approach have been reported to range from 71% to 88% whereas specificities varies from 44% to 71% (15), given how different dementia with very distinct histopathological and pathophysiological properties resemble each other at first glance. It is expected that accuracy of any clinically-based diagnosis is probably even lower in the very early stages of a disease (i.e., in patients with prodromal AD), preventing the disease from being properly addressed and treated. The major pathological hallmarks of the late-onset AD are the loss of neurons, occurrence of extracellular senile plaques as well as intracellular neurofibrillary tangles (NFT) (2, 16). Core CSF biomarkers for AD are the amyloid beta peptides A β , total tau protein and phosphorylated tau (17, 18). Beyond fluid biomarkers, imaging tests to determine the likelihood of AD pathology, the staging of preclinical AD and the progression from prodromal to clinical AD (19–21) are under development by means of positron emission tomography (PET) for amyloid deposits, by magnetic resonance imaging (MRI) for mesial temporal lobe (MTL) atrophy and by 18F-fluorodeoxyglucose (FDG) – PET for tempoparietal/precuneus hypometabolism or hypoperfusion.

Based on the potential of these CSF and imaging markers in accurately estimating the risk of and/or detecting AD and MCI (18), the authors summarize their understanding on the most importantly studied biomarkers that are likely to advance the field of AD diagnosis in forthcoming years.

2. Biomarkers

2.1 Chemical Established Biomarkers

Amyloid beta peptides—One of the major pathological features of AD consists in the presence of senile plaques and a reasonable amount of evidence demonstrates that $A\beta_{42}$ levels are decreased in the CSF of AD patients (18, 22–24). About 20 studies (2,000 patients and controls) have been conducted so far showing a reduction of $A\beta_{42}$ by around 50% in AD patients compared to age-matched, nondemented controls, with diagnostic sensitivity and specificity levels ranging between 80% and 90% (25). It is not clear why $A\beta_{42}$ titers are reduced in AD, but deposition of the peptide (“amyloid sinks”) in plaques is considered the underlying basis for such phenomenon. In favor to a usefulness of this marker, studies have demonstrated an inverse correlation between $A\beta_{42}$ levels in the CSF of AD patients and the number of plaques both at autopsy (26) and *in vivo* (24). Also, it was recently shown that subjects with the greatest positive signals in amyloid positron emission tomography (PET) scans using the Pittsburgh Compound B (PIB) had the lowest $A\beta_{42}$ values in CSF of patients with MCI (27). Having that in mind, total $A\beta_{42}$ in the CSF has high potential as a biomarker for plaque burden and prognosis for neurodegeneration and may provide useful clue for preclinical AD (16, 28). A more precise AD biomarker than $A\beta_{42}$ alone appears to be the $A\beta_{42}/A\beta_{40}$ ratio, even though $A\beta_{40}$ is slightly increased or unchanged in the CSF of AD patients (23).

Total tau protein—The protein tau is an intracellular protein which maintains the stability of microtubules in neurons. Plenty of studies conducted with patients and control groups have all demonstrated an increase in the concentration of total tau (t-tau) in AD patients by approximately 300% compared to nondemented elderly subjects (4), whereas a systematic increase in the concentration with age was observed in the control groups (29). Augmented levels of tau protein predicts MCI conversion to AD with 83% sensitivity and 90% specificity (25, 30). For this reason, CSF t-tau seems a more dynamic biomarker, which reflects the intensity of both acute neuronal damage and chronic neuronal degeneration in the brain, with high levels of CSF t-tau associated with faster progression from MCI to AD, more rapid cognitive decline and higher mortality rate among AD patients (4). Both t-tau and $A\beta_{42}$ are significantly altered in MCI subjects who are at increased risk of AD over time (31).

Hyperphosphorylated tau protein—In AD patients, tau protein is present in a pathologic, hyperphosphorylated form, and several experimental studies suggest that formation of neurofibrillary tangles (NFT) constitutes a downstream phenomenon in AD pathophysiology (32). In this disorder, tau becomes hyperphosphorylated (p-tau) and gets dissociated from microtubule to subsequently polymerize into insoluble paired helical filaments (PHF) that eventually contributes to the formation of neurofibrillary tangles. NFT formation and neuronal degradation is an essential part of AD pathology (33). Several studies also assessed CSF p-tau as potential biomarkers for AD (34, 35). Experimental evidences of high CSF concentrations of p-tau in selected patients with a very typical AD phenotype have suggested that p-tau is not a simple marker of axonal damage and neuronal degeneration, as is shown for t-tau. Instead, p-tau is more closely related to an AD pathology

and, accordingly, to the formation of NFT (16). P-tau is a more specific marker for AD and has proven its value for differential dementia diagnosis (30).

In MCI subjects, high CSF p-tau concentrations correlated with a decline in cognitive performance and conversion to AD (36). An European multicenter trial on CSF p-tau among MCI subjects has shown that abnormally high p-tau levels predicts AD in this risk group, producing stable and consistent evidence throughout multiple centers. In that study, p-tau proved to be a powerful predictor of AD among MCI subjects even in short-term conditions as 1 or 2 years of follow up (37). In line, the high negative predictive value of p-tau of approximately 90% appears to be particularly significant (38), with barely no patients with normal p-tau titers evolving into an AD phenotype. This result is particularly promising regarding clinical use of p-tau to inform patients as early as possible.

Also seen in some 2-years follow up studies (39, 40), p-tau is considered to be an accurate marker of MCI conversion to AD, with 80% specificity and 80% total diagnostic accuracy. Moreover, it shows 90.2% sensitivity and 80.0% specificity in discriminating between AD and all non-AD disorders (39). Altogether, p-tau shows to be the strongest predictor of the decline from MCI to AD (33, 40).

2.2 Neuroimaging

A very important progress in human brain research was the development of imaging techniques, which allows the visualization of brain characteristics *in vivo*, providing information about chronological and spatial evolution of disease pathology (41). Functional and molecular neuroimaging provide insights into brain structure and physiology and can detect specific proteins and protein aggregates associated with AD in the brain (42). In AD, structural imaging data from computerized tomography (CT) and magnetic resonance imaging (MRI) show a progressive cerebral atrophy as a probable reflection of dendritic and neuronal loss, a neurodegenerative hallmark of the disease. Another type of information can be acquired using radioligands to detect molecules of interest using positron emission tomography (PET) imaging. In AD, the most applied imaging modalities so far are the ones measuring brain metabolism ([¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG)) and amyloid load ([¹⁸F]florbetapir and [¹¹C]Pittsburg Compound B ([¹¹C]PIB)).

Magnetic Resonance Imaging (MRI)—Blood flow and metabolism in the brain reflects brain activity. In a functional MRI (fMRI), blood flow is measured by applying a magnetic field that aligns and measures resonance frequencies produced by protons in blood, being an indirect measurement of neural activity. By fMRI, AD individuals show decreased activity in the medial prefrontal cortex and orbitofrontal gyrus in comparison to MCI patients, brain regions associated with the human default-mode network which is involved in autogenic thought. Deterioration of the default-mode network in AD patients reflects a continuous breakdown of spontaneous brain activity during disease progression.

It is also possible to distinguish early AD stage atrophy from the atrophy associated with normal aging using the structural MRI (sMRI) approach (43). In AD, atrophy usually initiates in the medial temporal lobe along with regions as entorhinal cortex, hippocampus and amygdala, and tends to spread to the temporal neocortex and associated areas (for

review see (44). Studies have suggested that atrophy starts years before diagnosis, based on findings of the reduced rate of atrophy detected in AD patients (~3–5% per year) compared to what is observed in mildly affected individuals (~15–25% per year) (for details see (44)). The rate of brain atrophy was associated with cognitive decline, indicating a potential use of volume measurements as marker for disease progression (45, 46).

The ability of MRI to distinguish AD subjects from normal controls with a reasonable sensitivity and specificity has long been established in the literature. Significant atrophy in medial temporal lobe structures, including the hippocampus can be demonstrated by MRI even in preclinical stages of AD (7, 48). MRI can also reveal disease progression from cognitive normalcy to mild cognitive impairment (MCI) and then to AD (47). Decline in hippocampal volume correlates with the clinical progression of the disease, with the literature reporting a 10–15% reduction in MCI compared with healthy subjects, and evolving to a 15–30% level of reduction in the mild dementia stage of AD and to a 15–40% reduction in its moderate to severe stages (47, 49, 50). In this scenario, sMRI alone can predict later conversion to AD with about 80% of accuracy (32). When predicting the conversion from MCI to AD, a study showed that a combination of biomarker measures presented the best predicting power (51). They achieved the best accuracy when combining a composite measure of diffusion measures (mean diffusivity x mode of anisotropy) with gray matter volume as well as with a composite measure of CSF proteins (tau/A β_{42} ratio), which enabled them to accurately classify 91% of amnesic MCI patients (based on 85% sensitivity, 96% specificity and CI= 75–97).

In summary, hippocampal volumetry is the best established structural biomarker for AD in the field of imaging, particularly for early diagnosis, and appears to be suitable for risk stratification in MCI cohorts and follow up in AD patients aiming for treatment trials, especially given the availability of practical software for measurements (52). Hippocampal volume is thus a core candidate structural progression marker for AD.

Positron Emission Tomography—To measure cerebral metabolism and synaptic activity with PET, it is possible to use a FDG labeled with Fluorine-18 to identify the brain regions with more or less FDG consumption. In the brain, the most energetically costing process is maintenance of the neuron's membrane potential (53). Based on this, researchers developed a radiolabeled glucose analog ([^{18}F]FDG) that is able to trace glucose utilization (for review see (54)). In the past decades, many studies have shown a tight link between glucose consumption and neuronal activity, demonstrating that local stimulations are coupled with higher [^{18}F]FDG signal in efferent regions and lesions have the opposite effect on [^{18}F]FDG (55, 56). In contrast, in several diseases (including dementias), metabolic reduction was observed in brain regions associated to the symptoms, probably reflecting neurodegeneration (for details see (57)).

Studies with AD patients have shown that the hypometabolic regions are mainly the precuneus, the posterior cingulate gyri, the medial temporal cortices, the inferior parietal lobule and the posterior lateral parts of the temporal lobe, suggesting that they compose the [^{18}F]FDG profile of the disease (58–60), being able to distinguish AD patients from those with no cognitive impairment (NCI) (37). MCI subjects already show — to a lesser extent —

a similar distribution of metabolic deficits that can predict conversion from MCI to AD with accuracy greater than 80% (42, 48). Additionally, hypometabolism was associated with high amyloid load in parietal regions (61, 62) and is believed to act as a mediator between preceding changes in CSF biomarkers and subsequent cognitive decline (63). Based on the exposed and on the growing number of studies comparing brain [^{18}F]FDG uptake in different stages and across different forms of dementia, researchers suggest [^{18}F]FDG as a very relevant and highly specific biomarker for the *in vivo* diagnosis of early stages of AD as well as for differential diagnosis of major neurodegenerative diseases (37, 64).

Brain amyloid load is an important AD hallmark that can also be detected with PET imaging. In a similar fashion, [^{11}C]PiB and [^{18}F]florbetapir show, with comparable efficacy, cerebral regions where amyloid accumulation is higher than background levels (65). In AD individuals, increased retention of [^{11}C]PiB shows a very specific pattern that is restricted to brain regions (frontal, parietal, temporal, occipital cortices, and striatum), typically associated with A β_{42} deposition (66), showing a good agreement between the imaging measurement and the immunohistochemical exam, and supporting the use of amyloid imaging modality for research purposes (67–69).

An important theoretical basis to support amyloid imaging for AD research came from the detection of amyloidosis in NCI older adults and MCI subjects, enabling studies to predict at-risk individuals for converting to AD, and to better understand the progression of the pathology. For example, a positive [^{11}C]PiB scan predicts conversion from MCI to AD (55% of [^{11}C]PiB-positive patients with MCI progressed to AD in 2 years, vs. 10% of [^{11}C]PiB-negative patients). In MCI converters, the higher the [^{11}C]PiB retention rate, the faster the conversion to AD (within 1 year of follow-up) (70). It was also shown that, despite the correlation found between brain amyloid and CSF-A β in AD patients, these measurements might partially reflect independent processes occurring in different stages of the disease (71).

At present, it is not clear whether the diagnostic accuracy of amyloid PET can prevail over [^{18}F]FDG in terms of accuracy. However, despite the drawback side of the high cost of performing PET, it is conceivable that coupled usage of these imaging techniques will, in a near future, contribute in determining pathological profiles that better suit prevention or disease-modifying therapy studies and in assisting clinical diagnosis. Some longitudinal studies suggested that amyloid PET may be more sensitive than CSF A β_{42} in identifying subjects with MCI who will convert to AD (7).

2.3 Chemical novel approaches

Neurogranin—Biomarkers that reflect synaptic integrity could therefore be useful for both an accurate, early diagnosis and disease prognosis. Scientists have been searching for more biomarkers in CSF to identify synaptic degeneration, an Alzheimer's-related brain change. Studies have identified a promising marker in neurogranin (Ng), a protein found in dendritic spines which is involved in long-term potentiation and memory consolidation (72). Longitudinal studies with CSF samples showed that Ng has potential as a novel biomarker for synaptic dysfunction in AD (73), and it could be a link to both cognitive symptoms and therapeutic response (74). CSF Ng is increased in AD compared to other dementias already

in early clinical stages (75) and is also associated with brain atrophy and reduced brain glucose uptake (76). Thus, the CSF neurogranin level appears to have a prognostic as well as a diagnostic value (77).

Isoprostanes—It is suggested that oxidative stress and lipid peroxidation have a role in neurodegenerative diseases (78). It is hypothesized that oxidative stress plays an important role in the pathogenesis of neuron degeneration in AD (22), rendering isoprostanes as a possible marker to monitor progression of AD-related neurodegenerative changes (79). Specific isoprostanes (for example, 8,12-iso-iPF₂α-VI) have shown to be a sensitive and specific marker of *in vivo* lipid peroxidation, found elevated either in urine, blood or CSF of AD patients (9). Isoprostanes are also found in increased levels in MCI and asymptomatic carriers of familial AD mutations (16, 80). Interestingly, baseline measurements of CSF F₂-isoprostanes could distinguish AD-converting MCI patients from healthy controls with high accuracy (81). And apart from showing a correlation to the cognitive impairment of these patients (22), CSF 8,12-iso-iPF₂α-VI levels correlated with other known biomarkers of the disease such as CSF tau and the percentage of CSF Aβ₄₂ and the number of APOε4 alleles (9). A combined analysis of CSF Aβ₄₂, tau, and F₂-isoprostanes was able to diagnose AD with a sensitivity of 84% and specificity of 89% (16), reassuring 8,12-iso-iPF₂α-VI as another potential AD biomarker to be pursued.

2.4 Imaging novel approaches

Imaging tracers targeting microglial activation, synaptic density, gene expression and phosphorylated tau are under development, and hopefully they will improve our knowledge about the mechanisms underlying AD pathology. Regarding AD, one of the most eagerly anticipated PET modality is the tau imaging, due to the notable participation of tau protein in the disease pathophysiology. However, developing a tau tracer has been challenging as there are several isoforms of the protein in the brain and because of the spatial characteristics of tau aggregates (82). Several radioligands have presented high “off-target” retention (83) that hinders their use for research or clinical purposes. Despite that, the tracers currently being tested have shown reasonable uptake patterns akin to those described in Braak staging (84), and a significant difference in tracer accumulation is detectable between AD, MCI and normal subjects (85), reassuring the potential of establishing tau radioligands to track disease progression (possibly another diagnostic tool as well).

Two new radioligands being tested are [¹¹C]Martinostat and [¹¹C]UCB-J, indexing gene expression and synaptic density, respectively. [¹¹C]Martinostat is a PET tracer which binds to histone deacetylases (HDACs), enzymes known to silence expression of genes associated with neuroplasticity (86, 87). This PET compound is currently being tested in AD patients, who are expected to present less uptake as compared to cognitively preserved subjects. If this holds true, this tracer could become a biomarker of gene expression, determining genetic and/or epigenetic signatures in such complex scenario (88) and helping pharmaceutical companies to identify the best individuals to undergo clinical trials of HDAC inhibitors—which have been proposed as treatment for degenerative diseases (89).

Moreover, it would be useful to quantify neurodegeneration by measuring synaptic density. This is the purpose of [^{11}C]UCB-J PET, a tracer that targets synaptic vesicle glycoprotein 2A (SV2A) (90). As it is homogeneously located in presynaptic vesicle membranes across the brain (91), SV2A may be a good proxy of synaptic activity. Cognitive impairment has already been associated with synaptic loss in AD (92–94), but being able to quantify this in clinical trial settings would probably boost the understanding of disease onset and progression.

3 Combined Approaches

Driven by the escalating prevalence of the disease and by consistent advances in drug discovery research, AD is at the forefront of biomarker development for neurodegenerative diseases, and many current concepts about ideal biomarkers for these disorders have come from AD research. There is also growing interest in identifying markers of prodromal AD (including MCI), as well as assays that are predictive of AD years before its onset. AD biomarkers could therefore have multiple uses, such as identifying those at greatest risk, confirming a diagnosis, monitoring disease progression and response to treatment, and being of explicit importance in enriching clinical trials with specific subsets of patients or at-risk individuals.

Approaches for development of biomarkers so far complied with premises initially proposed by the Working Group on Biological Markers of Alzheimer's Disease (95), concerning ideal aspects for AD biomarkers, as follows: linked to fundamental features of AD neuropathology, validated in neuropathologically confirmed cases of AD, able to detect AD early in its course and to distinguish from other dementias. Nonetheless, aspects as being non-invasive, simple to use and inexpensive are challenges to be addressed and still hinder broad clinical usage.

It has also being considered that, for a biomarker to be useful in the diagnosis of AD, it should have a sensitivity and specificity of $> 85\%$, and a positive predictive value of $> 80\%$ (9), given the accuracy already in place for the core clinically-based diagnosis criteria. To the authors of the present view point, the scenario above tells a tale that places biochemical and imaging testing on the verge of real-world utility since their accuracy already match (or even surpass) current clinical precision in AD diagnosis regardless of the quite varied range of accuracy levels shown by different long-term clinical trials. This scenario (considering costs associated with the biochemical and imaging testing) discourages widespread dissemination of laboratory assessments when it comes to symptomatic AD patients.

On the other hand, core CSF biomarkers have proven to provide good prognostic accuracy to identify prodromal Alzheimer's disease conversion from mild cognitive impairment (5, 8, 80, 96), and are the ones which have been validated in post mortem studies (11, 70). This predictive value is markedly boosted when CSF markers are combined (rather than considered independently as discussed above) since t-tau titers coupled to measures of species of p-tau in addition to $\text{A}\beta_{42}$ correlates best with an AD symptomatic stage (9, 16, 17). As observed in different follow up studies, the combination of $\text{A}\beta_{42}$ /p-tau ratio with t-tau in MCI patients display a sensitivity of 83% and a specificity of 72% to distinguish

patients who converted into AD after 7 years of prospective follow up (97). Also, combination of the t-tau, p-tau, and $A\beta_{42}$ in the CSF was informative to detect incipient AD among patients who fulfill the criteria for MCI with a sensitivity of 68% (95% CI 45–86%) and a specificity of 97% (95% CI 83–100%) (7). In a longitudinal study that followed patients for 4–6 years, the combination of CSF p-tau and $A\beta_{42}$ at baseline yielded a sensitivity of 95% and a specificity of 83% for the detection of incipient AD in patients with MCI, and revealed an increased in relative risk (hazard ratio 17.7, $p < 0.0001$) for progression to AD from MCI cases taking pathologic tau and diminished $A\beta$ levels at baseline (98). A more recent analysis of CSF samples from patients in the Amsterdam Dementia Cohort showed that the t-tau/ $A\beta_{42}$ ratio was the most robust combination for predicting AD in subjects with MCI (8). Given the examples above, it is likely that a combination of biomarkers will provide greater diagnostic accuracy than any single analyte alone (4, 39).

In line with the assumption above, combination of neurochemical, fluid biomarkers (t-tau, p-tau, $A\beta_{42}$) with imaging markers as MRI-based tests (hippocampal and whole brain volumetry) are currently undergoing multicenter evaluation in controlled diagnostic phase IIb studies to determine the sensitivity and specificity of the markers and to make an initial assessment of their positive and negative predictive values (32). Though, underlying evidence suggests that the combination of several markers—ie, hippocampal volumetry, FDG PET, amyloid PET, CSF $A\beta_{42}$, t-tau, and p-tau, as suggested in the NIA-AA criteria—add good positive and negative predictive values to differentiate Alzheimer's disease from normal ageing in patients with MCI (5).

To date, we conclude that amyloid-pathology markers (low CSF $A\beta_{42}$ and high $A\beta_{42}$ deposition), followed by tauopathic scores, can predict abnormalities in typical high-risk individuals, whereas FDG PET and MRI volumetric measures tend to show more informativeness closer to or within the prodromal stage (99). It will be critical to identify the earliest changes in amyloid deposition that present clinical significance for downstream neurodegenerative processes. Even so, the latest revised National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (known as NINCDS-ADRDA) criteria for AD advocates that the confidence in diagnosing cognitive decline is raised with the application of imaging biomarkers (100), probably driven by the notion that such tests, added to core clinical criteria and fluid markers, will increase the sensitivity and specificity of a testing strategy. Recent findings from the Alzheimer's Disease Neuroimaging Initiative (ADNI) suggest an MRI-based global grading biomarker with accuracy in the range of 79 to 81% to predict MCI-to-AD conversion within three years, and which is enhanced when corrected by age and cognitive measures (101). In agreement with this view, current literature already states that the combined fluid measurements of the CSF t-tau, $A\beta_{42}$, and p-tau duly interpreted along with imaging assessments of regional cerebral blood flow or of medial temporal lobe atrophy provide higher predictive power than the classic diagnostic approach alone, when applied for MCI subjects (9, 11, 37). Conversely, the lack of these biomarkers lowers the diagnostic certainty of MCI due to AD or provides indeterminate, conflicting or negative results. Nonetheless, it is crucial that these markers are confirmed for diagnostic accuracy

before broad adoption as routine tests in clinical practice. Longitudinal and periodic assessments could improve diagnostic accuracy (70).

Having considered the usefulness of these markers for the diagnosis of AD, we should now comment that several studies evaluated whether these markers could be of use to monitor disease progression. To the authors, $A\beta_{42}$, t-tau and p-tau seem less suitable as biomarkers for monitoring of disease progression. Researchers at the Mayo Clinic, for instance, used PET images to identify a window of several years (over an average of 15 years) during which cerebral $A\beta$ accumulation builds up slowly until reaching a plateau which then hardly recedes, even with clinical intervention (6). On the other hand, isoprostane was the only biomarker that showed longitudinal effects when compared with the other core biomarkers (40, 79). It remains to be investigated whether this marker could be of restricted use to identify AD patients in whom brain lipid peroxidation is an early pathophysiological component.

A limitation of the trials conducted so far, despite several AD-prediction studies are published, is that reports usually undertake a follow up that seeks for the onset of (or conversion to) the disease without much thought on its considerable heterogeneity, not examining covariance for APO $\epsilon 4$ carriers status or for the possibility of $A\beta_{42}$ deposits-free forms of the condition, for instance. Studies that follow patients longitudinally to autopsy are needed to correlate biomarker findings with the ultimate neuropathological findings and reveal their actual (general or context-sensitive) value. FDG PET, for instance, should still prove itself valuable for AD diagnosis to a fair proportion of elderly individuals without detectable amyloid deposition that display non-Alzheimer patterns of hypometabolism (102). Moreover, although the good sensitivity achieved by the markers included in our review is promising, some heterogeneity in the conduction and interpretation of the tests along with a lack of defined thresholds to state positivity and high cost for their investigation still prevent their routine use in clinical practice. Besides, there's no evidence that these biomarkers are informative and sufficient for use in normal aging without any cognitive changes.

4. Concluding remarks

Therefore, there is still much room for studies to shed some light into the informativeness of fluid and imaging biomarker for early and differential diagnosis of the complex and challenging Alzheimer's disease. Nonetheless, and in due time, it is our understanding that it will lay irrefutable that such tests orderly and judiciously added on to core clinical criteria will likely be a critical, necessary advance towards increasing the sensitivity and specificity of the procedures for its diagnosis as well as for identification of "at-risk" individuals.

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References

1. Organization WH. Internacional AD. Dementia: a public health priority. Switzerland: 2012.
2. American Psychiatric Association APA. Diagnostic and statistical manual of mental disorders: DSM-5. 5. Vol. 2013. Washington, D.C: American Psychiatric Association; 2013.
3. Services USDoHaH. 2014–2015 Alzheimer's Disease Progress Report: Advancing Research Toward a Cure. National Institute on Aging; 2015.
4. Blennow K, Dubois B, Fagan AM, Lewczuk P, de Leon MJ, Hampel H. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. *Alzheimers Dement*. 2015; 11(1):58–69. [PubMed: 24795085]
5. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. *Lancet*. 2016; 388(10043):505–17. [PubMed: 26921134]
6. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013; 12(2):207–16. [PubMed: 23332364]
7. Lewczuk P, Mroczko B, Fagan A, Kornhuber J. Biomarkers of Alzheimer's disease and mild cognitive impairment: a current perspective. *Adv Med Sci*. 2015; 60(1):76–82. [PubMed: 25579841]
8. Counts SE, Ikonomic MD, Mercado N, Vega IE, Mufson EJ. Biomarkers for the Early Detection and Progression of Alzheimer's Disease. *Neurotherapeutics*. 2017; 14(1):35–53. [PubMed: 27738903]
9. Shaw LM, Korecka M, Clark CM, Lee VM, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov*. 2007; 6(4):295–303. [PubMed: 17347655]
10. Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. *Annu Rev Pathol*. 2006; 1:151–70. [PubMed: 18039111]
11. Zafari S, Backes C, Meese E, Keller A. Circulating Biomarker Panels in Alzheimer's Disease. *Gerontology*. 2015; 61(6):497–503. [PubMed: 25720553]
12. Ashton NJ, Kiddle SJ, Graf J, Ward M, Baird AL, Hye A, et al. Blood protein predictors of brain amyloid for enrichment in clinical trials? *Alzheimers Dement (Amst)*. 2015; 1(1):48–60. [PubMed: 27239491]
13. Prestia A, Caroli A, Wade SK, van der Flier WM, Ossenkoppele R, Van Berckel B, et al. Prediction of AD dementia by biomarkers following the NIA-AA and IWG diagnostic criteria in MCI patients from three European memory clinics. *Alzheimers Dement*. 2015; 11(10):1191–201. [PubMed: 25646957]
14. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9(1):119–28. [PubMed: 20083042]
15. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J Neuropathol Exp Neurol*. 2012; 71(4):266–73. [PubMed: 22437338]
16. Anoop A, Singh PK, Jacob RS, Maji SK. CSF Biomarkers for Alzheimer's Disease Diagnosis. *Int J Alzheimers Dis*. 2010; 2010
17. Sutphen CL, Jasielec MS, Shah AR, Macy EM, Xiong C, Vlassenko AG, et al. Longitudinal Cerebrospinal Fluid Biomarker Changes in Preclinical Alzheimer Disease During Middle Age. *JAMA Neurol*. 2015; 72(9):1029–42. [PubMed: 26147946]
18. Babic M, Svob Strac D, Muck-Seler D, Pivac N, Stanic G, Hof PR, et al. Update on the core and developing cerebrospinal fluid biomarkers for Alzheimer disease. *Croat Med J*. 2014; 55(4):347–65. [PubMed: 25165049]
19. Alexopoulos P, Roesler J, Thierjung N, Werle L, Buck D, Yakushev I, et al. Mapping CSF biomarker profiles onto NIA-AA guidelines for Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci*. 2016; 266(7):587–97. [PubMed: 26253588]

20. Guo LH, Alexopoulos P, Eisele T, Wagenpfeil S, Kurz A, Perneczky R. The National Institute on Aging-Alzheimer's Association research criteria for mild cognitive impairment due to Alzheimer's disease: predicting the outcome. *Eur Arch Psychiatry Clin Neurosci*. 2013; 263(4):325–33. [PubMed: 22932720]
21. 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(3):280–92. [PubMed: 21514248]
22. Frank RA, Galasko D, Hampel H, Hardy J, de Leon MJ, Mehta PD, et al. Biological markers for therapeutic trials in Alzheimer's disease. Proceedings of the biological markers working group; NIA initiative on neuroimaging in Alzheimer's disease. *Neurobiol Aging*. 2003; 24(4):521–36. [PubMed: 12714109]
23. Pannee J, Portelius E, Minthon L, Gobom J, Andreasson U, Zetterberg H, et al. Reference measurement procedure for CSF amyloid beta (A β)1-42 and the CSF A β 1-42 /A β 1-40 ratio - a cross-validation study against amyloid PET. *J Neurochem*. 2016; 139(4):651–8. [PubMed: 27579672]
24. Grimmer T, Riemenschneider M, Forstl H, Henriksen G, Klunk WE, Mathis CA, et al. Beta amyloid in Alzheimer's disease: increased deposition in brain is reflected in reduced concentration in cerebrospinal fluid. *Biol Psychiatry*. 2009; 65(11):927–34. [PubMed: 19268916]
25. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *Lancet neurology*. 2003; 2(10):605–13. [PubMed: 14505582]
26. Strozzyk D, Blennow K, White LR, Launer LJ. CSF A β 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology*. 2003; 60(4):652–6. [PubMed: 12601108]
27. Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging*. 2008; 29(10):1456–65. [PubMed: 17499392]
28. Mo JA, Lim JH, Sul AR, Lee M, Youn YC, Kim HJ. Cerebrospinal fluid beta-amyloid1-42 levels in the differential diagnosis of Alzheimer's disease--systematic review and meta-analysis. *PLoS One*. 2015; 10(2):e0116802. [PubMed: 25710596]
29. Burger nee Buch K, Padberg F, Nolde T, Teipel SJ, Stubner S, Haslinger A, et al. Cerebrospinal fluid tau protein shows a better discrimination in young old (<70 years) than in old old patients with Alzheimer's disease compared with controls. *Neurosci Lett*. 1999; 277(1):21–4. [PubMed: 10643888]
30. Struyfs H, Molinuevo JL, Martin JJ, De Deyn PP, Engelborghs S. Validation of the AD-CSF-index in autopsy-confirmed Alzheimer's disease patients and healthy controls. *J Alzheimers Dis*. 2014; 41(3):903–9. [PubMed: 24705548]
31. Hampel H, Teipel SJ, Fuchsberger T, Andreasen N, Wiltfang J, Otto M, et al. Value of CSF beta-amyloid1-42 and tau as predictors of Alzheimer's disease in patients with mild cognitive impairment. *Mol Psychiatry*. 2004; 9(7):705–10. [PubMed: 14699432]
32. Ritchie C, Smailagic N, Noel-Storr AH, Takwoingi Y, Flicker L, Mason SE, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*. 2014; (6):CD008782. [PubMed: 24913723]
33. Tang W, Huang Q, Yao YY, Wang Y, Wu YL, Wang ZY. Does CSF p-tau181 help to discriminate Alzheimer's disease from other dementias and mild cognitive impairment? A meta-analysis of the literature. *J Neural Transm (Vienna)*. 2014; 121(12):1541–53. [PubMed: 24817210]
34. Pascoal TA, Mathotaarachchi S, Mohades S, Benedet AL, Chung CO, Shin M, et al. Amyloid-beta and hyperphosphorylated tau synergy drives metabolic decline in preclinical Alzheimer's disease. *Mol Psychiatry*. 2016
35. Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*. 2016; 15(7):673–84. [PubMed: 27068280]

36. Smailagic N, Vacante M, Hyde C, Martin S, Ukoumunne O, Sachpekidis C. (1)(8)F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2015; 1:CD010632. [PubMed: 25629415]
37. Hampel H, Burger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimers Dement.* 2008; 4(1): 38–48. [PubMed: 18631949]
38. Mitchell A, Brindle N. CSF phosphorylated tau--does it constitute an accurate biological test for Alzheimer's disease? *Int J Geriatr Psychiatry.* 2003; 18(5):407–11. [PubMed: 12766916]
39. Papaliagkas VT. The role of cerebrospinal fluid biomarkers for Alzheimer's disease diagnosis where are we now? *Recent Pat CNS Drug Discov.* 2013; 8(1):70–8. [PubMed: 23489287]
40. Brys M, Pirraglia E, Rich K, Rolstad S, Mosconi L, Switalski R, et al. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. *Neurobiol Aging.* 2009; 30(5):682–90. [PubMed: 17889968]
41. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. *Alzheimer's & Dementia.* 2013; 9(5):e111–e94.
42. Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, et al. (11)C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2014; (7):CD010386. [PubMed: 25052054]
43. Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet neurology.* 2002; 1(1):13–21. [PubMed: 12849541]
44. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2012; 2(4):a006213. [PubMed: 22474610]
45. Cardenas VA, Chao LL, Studholme C, Yaffe K, Miller BL, Madison C, et al. Brain atrophy associated with baseline and longitudinal measures of cognition. *Neurobiology of aging.* 2011; 32(4):572–80. [PubMed: 19446370]
46. Hua X, Leow AD, Parikshak N, Lee S, Chiang MC, Toga AW, et al. Tensor-based morphometry as a neuroimaging biomarker for Alzheimer's disease: an MRI study of 676 AD, MCI, and normal subjects. *Neuroimage.* 2008; 43(3):458–69. [PubMed: 18691658]
47. Del Sole A, Malaspina S, Magenta Biasina A. Magnetic resonance imaging and positron emission tomography in the diagnosis of neurodegenerative dementias. *Funct Neurol.* 2016; 31(4):205–15. [PubMed: 28072381]
48. McConathy J, Sheline YI. Imaging biomarkers associated with cognitive decline: a review. *Biol Psychiatry.* 2015; 77(8):685–92. [PubMed: 25442005]
49. Shi F, Liu B, Zhou Y, Yu C, Jiang T. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus.* 2009; 19(11): 1055–64. [PubMed: 19309039]
50. van der Flier WM, van Straaten EC, Barkhof F, Ferro JM, Pantoni L, Basile AM, et al. Medial temporal lobe atrophy and white matter hyperintensities are associated with mild cognitive deficits in non-disabled elderly people: the LADIS study. *J Neurol Neurosurg Psychiatry.* 2005; 76(11): 1497–500. [PubMed: 16227537]
51. Douaud G, Menke RA, Gass A, Monsch AU, Rao A, Whitcher B, et al. Brain microstructure reveals early abnormalities more than two years prior to clinical progression from mild cognitive impairment to Alzheimer's disease. *J Neurosci.* 2013; 33(5):2147–55. [PubMed: 23365250]
52. Louzada LL, Morato TN, Almeida REF, Camargos EF, Nobrega OT, Farage L. OSIRIX as a feasible tool for in office manual hippocampal volumetry in the elderly: a technical note. *Geriatr Gerontol Aging.* 2016; 10(1):34–40.
53. Shulman RG, Rothman DL, Behar KL, Hyder F. Energetic basis of brain activity: implications for neuroimaging. *Trends in neurosciences.* 2004; 27(8):489–95. [PubMed: 15271497]
54. Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. *Journal of neurochemistry.* 1977; 29(1):13–26. [PubMed: 407330]

55. Meguro K, Blaizot X, Kondoh Y, Le Mestric C, Baron JC, Chavoix C. Neocortical and hippocampal glucose hypometabolism following neurotoxic lesions of the entorhinal and perirhinal cortices in the non-human primate as shown by PET. Implications for Alzheimer's disease. *Brain*. 1999; 122(Pt 8):1519–31. [PubMed: 10430835]
56. Millien I, Blaizot X, Giffard C, Mezenge F, Insausti R, Baron JC, et al. Brain glucose hypometabolism after perirhinal lesions in baboons: implications for Alzheimer disease and aging. *J Cereb Blood Flow Metab*. 2002; 22(10):1248–61. [PubMed: 12368664]
57. Kiyosawa M, Pappata S, Duverger D, Riche D, Cambon H, Mazoyer B, et al. Cortical hypometabolism and its recovery following nucleus basalis lesions in baboons: a PET study. *J Cereb Blood Flow Metab*. 1987; 7(6):812–7. [PubMed: 3500958]
58. Foster NL, Chase TN, Fedio P, Patronas NJ, Brooks RA, Di Chiro G. Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology*. 1983; 33(8):961–5. [PubMed: 6603596]
59. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol*. 1997; 42(1):85–94. [PubMed: 9225689]
60. De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiology of aging*. 2001; 22(4):529–39. [PubMed: 11445252]
61. Edison P, Archer HA, Hinz R, Hammers A, Pavese N, Tai YF, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [¹¹C]PIB and [¹⁸F]FDG PET study. *Neurology*. 2007; 68(7):501–8. [PubMed: 17065593]
62. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004; 55(3):306–19. [PubMed: 14991808]
63. Dowling NM, Johnson SC, Gleason CE, Jagust WJ. Alzheimer's Disease Neuroimaging I. The mediational effects of FDG hypometabolism on the association between cerebrospinal fluid biomarkers and neurocognitive function. *Neuroimage*. 2015; 105:357–68. [PubMed: 25450107]
64. Mosconi L, Berti V, Glodzik L, Pupi A, De Santi S, de Leon MJ. Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. *J Alzheimers Dis*. 2010; 20(3):843–54. [PubMed: 20182025]
65. Landau SM, Thomas BA, Thurfjell L, Schmidt M, Margolin R, Mintun M, et al. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *Eur J Nucl Med Mol Imaging*. 2014; 41(7):1398–407. [PubMed: 24647577]
66. Leuzy A, Chiotis K, Hasselbalch SG, Rinne JO, de Mendonca A, Otto M, et al. Pittsburgh compound B imaging and cerebrospinal fluid amyloid-beta in a multicentre European memory clinic study. *Brain*. 2016; 139(Pt 9):2540–53. [PubMed: 27401520]
67. Clark CM, Pontecorvo MJ, Beach TG, Bedell BJ, Coleman RE, Doraiswamy PM, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. *The Lancet Neurology*. 2012; 11(8):669–78. [PubMed: 22749065]
68. 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. *Archives of neurology*. 2011; 68(2):232–40. [PubMed: 21320990]
69. Wolk DA, Grachev ID, Buckley C, Kazi H, Grady MS, Trojanowski JQ, et al. Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. *Archives of neurology*. 2011; 68(11):1398–403. [PubMed: 21747004]
70. Forlenza OV, Diniz BS, Teixeira AL, Stella F, Gattaz W. Mild cognitive impairment. Part 2: Biological markers for diagnosis and prediction of dementia in Alzheimer's disease. *Rev Bras Psiquiatr*. 2013; 35(3):284–94. [PubMed: 24142092]
71. Mattsson N, Insel PS, Donohue M, Landau S, Jagust WJ, Shaw LM, et al. Independent information from cerebrospinal fluid amyloid-beta and florbetapir imaging in Alzheimer's disease. *Brain*. 2015; 138(Pt 3):772–83. [PubMed: 25541191]

72. Diez-Guerra FJ. Neurogranin, a link between calcium/calmodulin and protein kinase C signaling in synaptic plasticity. *IUBMB life*. 2010; 62(8):597–606. [PubMed: 20665622]
73. Mattsson N, Portelius E, Insel PS, Palmqvist S, Zetterberg H, Weiner M, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. *EMBO Mol Med*. 2016; 8(10): 1184–96. [PubMed: 27534871]
74. Kester MI, Teunissen CE, Crimmins DL, Herries EM, Ladenson JH, Scheltens P, et al. Neurogranin as a Cerebrospinal Fluid Biomarker for Synaptic Loss in Symptomatic Alzheimer Disease. *JAMA Neurol*. 2015; 72(11):1275–80. [PubMed: 26366630]
75. Kvartsberg H, Duits FH, Ingelsson M, Andreassen N, Ohrfelt A, Andersson K, et al. Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. *Alzheimers Dement*. 2015; 11(10):1180–90. [PubMed: 25533203]
76. Portelius E, Zetterberg H, Skillback T, Tornqvist U, Andreasson U, Trojanowski JQ, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. *Brain*. 2015; 138(Pt 11):3373–85. [PubMed: 26373605]
77. Services USDoHaH. Health NIO. STOPPING ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: Advancing Our Nation's Research Agenda. 2015.
78. Schneider P, Hampel H, Buerger K. Biological marker candidates of Alzheimer's disease in blood, plasma, and serum. *CNS Neurosci Ther*. 2009; 15(4):358–74. [PubMed: 19840034]
79. Kester MI, Scheffer PG, Koel-Simmelink MJ, Twaalfhoven H, Verwey NA, Veerhuis R, et al. Serial CSF sampling in Alzheimer's disease: specific versus non-specific markers. *Neurobiology of Aging*. 2012; 33(8):1591–8. [PubMed: 21741127]
80. Lista S, Zetterberg H, Dubois B, Blennow K, Hampel H. Cerebrospinal fluid analysis in Alzheimer's disease: technical issues and future developments. *J Neurol*. 2014; 261(6):1234–43. [PubMed: 24807087]
81. de Leon MJ, Mosconi L, Li J, De Santi S, Yao Y, Tsui WH, et al. Longitudinal CSF isoprostane and MRI atrophy in the progression to AD. *J Neurol*. 2007; 254(12):1666–75. [PubMed: 17994313]
82. Harada R, Okamura N, Furumoto S, Tago T, Yanai K, Arai H, et al. Characteristics of Tau and Its Ligands in PET Imaging. *Biomolecules*. 2016; 6(1):7. [PubMed: 26751494]
83. Lowe VJ, Curran G, Fang P, Liesinger AM, Josephs KA, Parisi JE, et al. An autoradiographic evaluation of AV-1451 Tau PET in dementia. *Acta Neuropathol Commun*. 2016; 4(1):58. [PubMed: 27296779]
84. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991; 82(4):239–59. [PubMed: 1759558]
85. Saint-Aubert L, Lemoine L, Chiotis K, Leuzy A, Rodriguez-Vieitez E, Nordberg A. Tau PET imaging: present and future directions. *Mol Neurodegener*. 2017; 12(1):19. [PubMed: 28219440]
86. Wang C, Schroeder FA, Wey HY, Borra R, Wagner FF, Reis S, et al. In vivo imaging of histone deacetylases (HDACs) in the central nervous system and major peripheral organs. *J Med Chem*. 2014; 57(19):7999–8009. [PubMed: 25203558]
87. Schroeder FA, Wang C, Van de Bittner GC, Neelamegam R, Takakura WR, Karunakaran A, et al. PET imaging demonstrates histone deacetylase target engagement and clarifies brain penetrance of known and novel small molecule inhibitors in rat. *ACS Chem Neurosci*. 2014; 5(10):1055–62. [PubMed: 25188794]
88. Moraes CF, Lins TC, Carmargos EF, Naves JO, Pereira RW, Nobrega OT. Lessons from genome-wide association studies findings in Alzheimer's disease. *Psychogeriatrics*. 2012; 12(1):62–73. [PubMed: 22416831]
89. Wey HY, Gilbert TM, Zurcher NR, She A, Bhanot A, Taillon BD, et al. Insights into neuroepigenetics through human histone deacetylase PET imaging. *Sci Transl Med*. 2016; 8(351): 351ra106.
90. Nabulsi NB, Mercier J, Holden D, Carre S, Najafzadeh S, Vandergeten MC, et al. Synthesis and Preclinical Evaluation of 11C-UCB-J as a PET Tracer for Imaging the Synaptic Vesicle Glycoprotein 2A in the Brain. *J Nucl Med*. 2016; 57(5):777–84. [PubMed: 26848175]
91. Bao W, Jia H, Finnema S, Cai Z, Carson RE, Huang YH. PET Imaging for Early Detection of Alzheimer's Disease. *PET Clinics*.

92. Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science*. 2002; 298(5594):789–91. [PubMed: 12399581]
93. Raskin J, Cummings J, Hardy J, Schuh K, Dean RA. Neurobiology of Alzheimer's Disease: Integrated Molecular, Physiological, Anatomical, Biomarker, and Cognitive Dimensions. *Curr Alzheimer Res*. 2015; 12(8):712–22. [PubMed: 26412218]
94. Pooler AM, Noble W, Hanger DP. A role for tau at the synapse in Alzheimer's disease pathogenesis. *Neuropharmacology*. 2014; 76(Pt A):1–8. [PubMed: 24076336]
95. Group CW. Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. *Neurobiol Aging*. 1998; 19(2): 109–16. [PubMed: 9558143]
96. Blennow K, Zetterberg H. The application of cerebrospinal fluid biomarkers in early diagnosis of Alzheimer disease. *Med Clin North Am*. 2013; 97(3):369–76. [PubMed: 23642576]
97. Mattsson N, Zetterberg H, Hansson O, Andreassen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*. 2009; 302(4): 385–93. [PubMed: 19622817]
98. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol*. 2006; 5(3):228–34. [PubMed: 16488378]
99. Beckett LA, Donohue MC, Wang C, Aisen P, Harvey DJ, Saito N, et al. The Alzheimer's Disease Neuroimaging Initiative phase 2: Increasing the length, breadth, and depth of our understanding. *Alzheimers Dement*. 2015; 11(7):823–31. [PubMed: 26194315]
100. 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-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):270–9. [PubMed: 21514249]
101. Tong T, Gao Q, Guerrero R, Ledig C, Chen L, Rueckert D, et al. A Novel Grading Biomarker for the Prediction of Conversion From Mild Cognitive Impairment to Alzheimer's Disease. *IEEE Trans Biomed Eng*. 2017; 64(1):155–65. [PubMed: 27046891]
102. Cohen AD, Klunk WE. Early detection of Alzheimer's disease using PiB and FDG PET. *Neurobiology of disease*. 2014; 72(Pt A):117–22. [PubMed: 24825318]
103. Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. *NeuroRx*. 2004; 1(2):213–25. [PubMed: 15717022]
104. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol*. 2009; 65(4):403–13. [PubMed: 19296504]
105. Palmqvist S, Zetterberg H, Mattsson N, Johansson P, Minthon L, et al. Alzheimer's Disease Neuroimaging I. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology*. 2015; 85(14):1240–9. [PubMed: 26354982]
106. Vos SJB, Gordon BA, Su Y, Visser PJ, Holtzman DM, Morris JC, et al. NIA-AA staging of preclinical Alzheimer disease: discordance and concordance of CSF and imaging biomarkers. *Neurobiol Aging*. 2016; 44:1–8. [PubMed: 27318129]
107. Moradi E, Pepe A, Gaser C, Huttunen H, Tohka J. Alzheimer's Disease Neuroimaging I. Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. *Neuroimage*. 2015; 104:398–412. [PubMed: 25312773]
108. Cheng B, Zhang D, Shen D. Domain transfer learning for MCI conversion prediction. *Med Image Comput Comput Assist Interv*. 2012; 15(Pt 1):82–90.
109. Casanova R, Hsu FC, Sink KM, Rapp SR, Williamson JD, Resnick SM, et al. Alzheimer's disease risk assessment using large-scale machine learning methods. *PLoS One*. 2013; 8(11):e77949. [PubMed: 24250789]
110. Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Alzheimer's Disease Neuroimaging I. Multimodal classification of Alzheimer's disease and mild cognitive impairment. *Neuroimage*. 2011; 55(3): 856–67. [PubMed: 21236349]

111. Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frolich L, et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage*. 2002; 17(1):302–16. [PubMed: 12482085]
112. Zetterberg H, Wahlund LO, Blennow K. Cerebrospinal fluid markers for prediction of Alzheimer's disease. *Neurosci Lett*. 2003; 352(1):67–9. [PubMed: 14615052]
113. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B, Jung HH, Hegi T, Nitsch RM, et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. *Arch Neurol*. 2003; 60(9):1202–6. [PubMed: 12975284]
114. Duits FH, Teunissen CE, Bouwman FH, Visser PJ, Mattsson N, Zetterberg H, et al. The cerebrospinal fluid “Alzheimer profile”: easily said, but what does it mean? *Alzheimers Dement*. 2014; 10(6):713–23. e2. [PubMed: 24721526]
115. Fagan AM, Shaw LM, Xiong C, Vanderstichele H, Mintun MA, Trojanowski JQ, et al. Comparison of analytical platforms for cerebrospinal fluid measures of beta-amyloid 1-42, total tau, and p-tau181 for identifying Alzheimer disease amyloid plaque pathology. *Arch Neurol*. 2011; 68(9):1137–44. [PubMed: 21555603]
116. Kapaki E, Paraskevas GP, Zalonis I, Zournas C. CSF tau protein and beta-amyloid (1-42) in Alzheimer's disease diagnosis: discrimination from normal ageing and other dementias in the Greek population. *Eur J Neurol*. 2003; 10(2):119–28. [PubMed: 12603286]
117. Hinrichs C, Singh V, Xu G, Johnson SC. Alzheimers Disease Neuroimaging I. Predictive markers for AD in a multi-modality framework: an analysis of MCI progression in the ADNI population. *Neuroimage*. 2011; 55(2):574–89. [PubMed: 21146621]
118. Westman E, Muehlboeck JS, Simmons A. Combining MRI and CSF measures for classification of Alzheimer's disease and prediction of mild cognitive impairment conversion. *Neuroimage*. 2012; 62(1):229–38. [PubMed: 22580170]

Highlights

- Amyloid-pathology CSF markers can indicate high-risk individuals for AD earlier.
- Imaging tends to be more informative only closer to or within the prodromal stage.
- A β_{42} , t-tau and p-tau seem less suitable as markers of disease progression.
- Combination of markers present best predicting power of conversion to AD.
- Biomarkers are on the verge of surpassing current clinical precision in AD diagnosis.

Table 1

Core biomarkers to Alzheimer's Disease

Biomarker	Specificity %	Sensitivity %	Accuracy /AUC	Cut off	Diagnostic /Prognostic	References
<i>Aβ₄₂</i>	42 to 88	72 to 100			AD x Control	(22)
	88	94	90 (AUC 0.941)	< 539 pg/mL	AD x Control	(30)
	89	86			AD x Control	(103)
	77	96	87 (AUC 0.913)	< 192 pg/mL	AD x Control	(104)
	75	85	AUC 0.90	< 500 pg/mL	MCI-AD x Control	(105)
	65	79	AUC 0.78	< 482 ng/L	AD x MCI	(97)
<i>T-tau</i>	85	75		21 – 50 years > 300 pg/ml;	AD x Control	(22)
	94	69	85 (AUC 0.868)	51 – 70 years old > 450 pg/ml;	AD x Control	(30)
	91	81		70 – 93 years old > 500 pg/ml	AD x Control	(103)
	92	70	80.6 (AUC 0.831)	> 93 pg/mL	AD x Control	(104)
	56	86	AUC 0.79	> 320 ng/L	AD x MCI	(97)
					Diagnostic + Prognostic ++	
<i>P-tau</i>	80	90			AD x Control	(22)
	79	75	77 (AUC 0.807)	> 50 pg/mL	AD x Control	(30)
	91	81			AD x Control	(103)
	73	68	70.4 (AUC 0.753)	> 23 pg/mL	AD x Control	(104)
	47	84	AUC 0.76	> 52pg/mL	AD x MCI	(97)
					Diagnostic ++ Prognostic ++	
<i>MRI</i>	72	85	79–81 (AUC 0.838)	HCV < -0.3023	AD x Control	(106)
	72	64	AUC 0.75	+ age and cognitive measures	pMCI x sMCI	(107)
	74	87	92 (AUC 0.9)		AD x Control	(107)
	66	60	AUC 0.7		AD x Control	(108)
	89	84	87	Gray matter	MCI-AD x Control	(109)
	83	77	80	White matter	MCI-AD x Control	(109)

Biomarker	Specificity %	Sensitivity %	Accuracy /AUC	Cut off	Diagnostic /Prognostic	References
	86	86	86		AD x Control	(110)
	60	78	72		MCI x Control Diagnostic ++ Prognostic +++	(110)
<i>PET</i>	87	86	86		AD x Control	(110)
	60	78	72		MCI x Control	(110)
	93	84				(111)
	84	88	AUC 0.93	> 1.62 PET posterior cingulate/precuneus	MCI-AD x Control	(105)
	86	88	AUC 0.91	> 1.48 PET prefrontal	MCI-AD x Control Diagnostic ++ Prognostic +++	(105)
<i>Aβ₄₂ P-tau and T-tau</i>	82	82	82.1		AD x Control	(110)
	59	78	71		AD x Control	(110)
	97	68		> 530 pg/mL for T-tau, > 80 pg/mL for P-tau and < 400 pg/mL for A β ₄₂		(112)
	83	95		T-tau > 350 ng/L, P-tau > 60 ng/L and A β ₄₂ < 530 ng/L	AD x MCI	(7), (98)
	87	84			AD x Control	(8)
	78	86			AD x Other dementias pMCI x sMC Diagnostic ++	(8) (8) (8)
<i>Aβ₄₂/T-tau</i>	92	98	97 (AUC 0.964)	1.25	AD x Control	(30)
	83	97	AUC 0.87	1.25	MCI-AD x Control Diagnostic +	(105)
<i>Aβ₄₂/P-tau</i>	92	96	93 (AUC 0.964)	7.24	AD x Control	(30)
	85	94	AUC 0.93	7.24	MCI-AD x Control	(105)
	87	95		< 6.25 (97) + T-tau > 350 ng/L	AD x MCI	(98)
	72	83		+ T-tau	AD x MCI	(97)
	88	83		+ T-tau	MCI-AD x Control Diagnostic ++	(97)

Biomarker	Specificity %	Sensitivity %	Accuracy /AUC	Cut off	Diagnostic /Prognostic	References
P-tau/ $A\beta_{42}$	71	91	81	> 0.10	AD x Control	(104)
	97	86	AUC 0.934		AD x Control	(113)
	89	80	AUC 0.906		AD x other neurological disorders	(113)
	88	85	AUC 0.92	> 0.11	AD x Control	(114)
	80	94	AUC 0.95	INNOTEST®	AD x Control	(115)
	80	98	AUC 0.97	INNO-BIA®	AD x Control	(115)
T-tau/ $A\beta_{42}$	86	96	AUC 0.96		AD x Control	(116)
	90	85	AUC 0.93	> 0.71	AD x Control	(114)
	85	86	70 (AUC 0.917)	> 0.39	AD x Control	(104)
	80	95	AUC 0.96	INNOTEST®	AD x Control	(115)
	80	92	AUC 0.94	INNO-BIA®	AD x Control	(115)
					Diagnostic ++	
$PET + A\beta_{42}$	81	82	AUC 0.85	CSF $A\beta_{42} < 1059$ pg/mL using Mass spectrometry	AD x Control	(23)
	91	96	AUC 0.95	$A\beta_{42}/A\beta_{40} 0.085$ PET > 1.42	AD x Control	(23)
					Diagnostic ++	
					Prognostic ++	
$PET + MRI$	91	90	90.6		AD x Control	(110)
	94	79	87.6		AD x Control	(117)
					Diagnostic ++	
					Prognostic ++	
$MRI + tau / A\beta_{42}$	96	85	91		sMCI x pMCI	(51)
$MRI + CSF (A\beta_{42}, T-tau, P-tau)$	95	88	92 (AUC 0.96)		AD x Control	(118)
	85	73	78		MCI x Control	(118)
					Diagnostic +++	
					Prognostic ++	
$PET + MRI + CSF (A\beta_{42}, T-tau, P-tau)$	93	93	93		AD x Control	(110)

Biomarker	Specificity %	Sensitivity %	Accuracy /AUC	Cut off	Diagnostic /Prognostic	References
	66	82	76	+ Cognitive scores and ApoE	MCI x Control	(110)
	74	65	70 (AUC 0.74)		MCI-AD x Control	(108)
	97	87	92		Diagnostic +++	(117)
					Prognostic ++	

Abbreviations: *Aβ42* – amyloid β peptide 42; *AUC* – area under curve; *CSF* – cerebrospinal fluid; *HCV* - Hippocampal volume; *MCBP* - Mean cortical binding potentials; *MCI* – mild cognitive impairment; *MRI* - Magnetic Resonance Imaging; *pMCI* - progressing MCI; *P-tau* - Phospho tau; *PET* - Positron Emission Tomography; *sMCI* – stable MCI; *T-tau* - Total tau; (+) Minimum; (++) Moderate; (+++) Maximum.