A Review of Biomarker Use for Diagnosis and Research of Early Stages of Alzheimer's Disease

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Summary. Alzheimer's disease (AD) is expected to become not only a massive health issue, but also a major social and economic problem during the next decades; therefore a thorough understanding of this disease is required. Researchers and clinicians might benefit from the use of biomarkers – quantifiable substances or traits that are observed before or during AD and might predict or detect it. Biomarkers are believed to advance clinical trials to understand better the mechanisms of AD, design disease modifying therapies, and create new clinical and research criteria for diagnosing AD in its earliest stages. The purpose of this review is to examine current guidelines concerning the use of biomarkers in research and clinical diagnostics, present assessment of cognition and olfaction in relation to AD, and discuss widely known biomarker tests involving cerebrospinal fluid (CSF) sampling, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT) as well as plasma and saliva sampling. Finally, the possibility for an AD signature and the potential future impact of biomarkers for both AD-related science and healthcare are considered.

Keywords: Alzheimer's disease, mild cognitive impairment, biomarkers, cognitive decline, cerebrospinal fluid, amyloid beta.

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INTRODUCTION

Causing 60 to 80% of all dementias, Alzheimer's disease (AD) was estimated to account for 46.8 million cases of dementia worldwide in 2015 and this figure is thought to double every 20 years [1–3]. The burden of AD is comprised of economic and social factors: this disease is both costly and requires taking great care of the patient. While mortality due to other diseases such as AIDS, cardiovascular events or common breast and prostate cancers was seen decreasing in the period between 2000 and 2014, deaths from Alzheimer's disease increased by 89% [2]. There are currently four drugs approved for treating AD: three acetylcholinesterase inhibitors (rivastigmine, donepezil, and galantamine) and an N-methyl-D-aspartate receptor inhibitor (memantine) [4]. It is noteworthy that all of these drugs ameliorate the symptoms of AD for some period, but do not prevent further decline afterward due to their nature of treating only symptoms of AD rather than any possible underlying causes [5]. In the aging society of the future, new treatments are required to preserve neurological function in older adults. The G8 dementia summit even set a goal to develop disease modifying therapy for AD by 2025 [6, 7]. The purpose of this article is to review emerging AD biomarker possibilities for the diagnosis of preclinical and early stages of AD. Early AD diagnosis could serve drug developing research groups when targeting AD several years or even decades before the onset of the first cognitive and functional symptoms; the use of biomarkers is important for the emergence of new criteria in clinical diagnostics as well.

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MECHANISMS OF ALZHEIMER'S DISEASE

Unfortunately, an explicit model of AD mechanism has not been established yet. On the macroscopic level, AD comprises three major changes in the brain: the enlargement of ventricles, widening of sulci (and narrowing of gyri) as well as a decrease in brain mass [8]. The observation of two pathologic changes dates back to the first cases of AD: amyloid plaques (APs), which are widely spread extracellularly throughout the brain, and neurofibrillary tangles accumulated intracellularly. A link between these two widely known abnormalities, however, requires further investigation [9]. Amyloid plaques are mainly composed of amyloid beta (A) peptides that vary in the number of amino acids [10]. Highly relevant to AD development are those A peptides which consist of 42 amino acids and thus are referred to as A 42. Another peptide, A 40, comprises up to 90% of A peptides; however, A 42 is described as much more toxic [11]. A 42 nucleates and forms plaques faster than A 40 in patients with

AD due to additional hydrophobic amino acids in A 42. The formation of A plaques involves the amyloid precursor protein (APP). APP is a large transmembrane glycoprotein found in neuronal bodies, dendrites, and non-neuronal cells; however, its physiological functions are not well understood. The APP is split by three enzymes: alpha-secretase, beta-secretase, and gamma-secretase. Alpha-secretase hydrolyzes APP to form a soluble APP (sAPP) and a C83 transmembrane protein. Beta-secretase hydrolyzes the APP to produce a soluble APP (sAPP) and a C99 transmembrane protein [11, 12]. Then gamma-secretase cleaves either C83 to form an APP intracellular domain (AICD) and a soluble N-terminal peptide (P3) (both AICD and P3 are non-toxic; it is the non-amyloidogenic pathway of APP hydrolysis) or C99 to form AICD and A (the amyloidogenic pathway). Depending on the action of gamma-secretase, either more of the toxic A 42 or the non-toxic A 40 is formed. Some genes (PSEN1, PSEN2, and APP on chromosomes 14, 1 and 21, respectively) are directly linked to AD and may lead to clarity when considering sporadic AD, which manifests in up to 99% of AD cases [2]. It has been found that mutations in these genes disrupt normal APP metabolism and promote the formation of amyloid plaques, therefore leading to AD with an autosomal dominant inheritance pattern [8, 13]. Amyloid plaques are thought to disrupt synaptic transmission, long term potentiation (LTP), neuronal metabolism, and induce inflammatory changes and neuronal death [12–17]. However, even when amyloid plaques are targeted and attempted to be removed from the living brain, AD does not cease to progress [18]. It is therefore critical to emphasize the complexity of AD and regard amyloid plaques as only one of the pathophysiological changes at the same time bearing in mind the lack of clear knowledge about AD mechanisms [18, 19]. Therefore, A peptides and amyloid plaques will be discussed here as markers, but not as causative factors of AD. Another important mechanism in the development of AD is the formation of neurofibrillary tangles (NFTs), which are formed due to hyperphosphorylation and accumulation of tau proteins found on microtubules of neuronal cell bodies and of proximal dendrites. Tau is a microtubule-associated protein (MAP) which accounts for the integrity and the structural support of microtubules to preserve axonal transport, and synaptic functioning [8]. Both oligomers of hyperphosphorylated tau that become detached from microtubules and NFTs are thought to disturb neuronal metabolism and integrity; problems, such as redistribution of mitochondria, interrupted vesicular (and therefore synaptic) transport, lack of cytoskeletal stability, abnormal Ca^{2+} metabolism, arise [11, 20–22]. Microtubule disruption is then said to be followed by the injury and death of neurons [23]. Many other factors related to AD, for example, brain trauma, vascular changes, hypertension or diabetes mellitus, might exist [24–26]. Symptoms of AD represent the deterioration of neuronal networks and neuronal injury processes that are thought to precede the clinical stage of the disease. Cognitive decline is observed at first: abnormal formation of new memory might be noted at the beginning (or even precede AD as mild cognitive impairment, MCI) together with disturbances in language production, problem-solving, visuospatial perception, attention, personality, and behaviour [27–29]. Afterward, problems with daily living arise, and severe cognitive and functional impairment proceeds: as T. Amemori et al. noted, the disease "finally robs the patients of their sense of self" [30]. Being a multifactorial disease, AD becomes a problematic research field with the need to analyze complex biological factors and their interactions; much of AD mechanisms are yet to be elucidated.

CURRENT DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE

The National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) working group proposed clinical criteria for Alzheimer's disease in 1984 [31]. The diagnosis of AD dementia was divided into possible, probable and definite. Possible AD could be diagnosed with an unrecognized alternative cause of dementia. Probable AD was defined as dementia (deterioration of cognitive functions, such as memory) with gradual onset between 40 and 90 years, two or more additional cognitive symptoms, the absence of other neurological or psychiatric disorder and supported by various behavioural or associated symptoms, atrophy visualized by computed tomography (CT), and family history; definite AD required clinical criteria mentioned above and positive histopathologic evidence. Although these criteria are still used (for example, in Lithuania), the need to consider additional features for diagnostic and research criteria is inevitable as new information about biomarkers associated with AD emerge and could help diagnosing AD in earlier stages than the classic AD dementia [32, 33].

National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (2011)

Three articles published in Alzheimer's and Dementia in 2011 set to define potential stages of AD. The first, the preclinical stage, is by definition asymptomatic and encompasses only that part of the population that has an elevated risk to develop AD due to inherited risk factors or measurable changes in specific biomarkers, associated, but not apparently causing AD [18, 34]. These biomarkers mainly include low A 42 protein levels in the CSF and high tracer uptake in PET imaging of amyloid fibrils. They point to the earliest stages of a preclinical AD, when no evidence of neuronal injury is present, according to the National Institute on Aging-Alzheimer's Association (NIA-AA). The NIA-AA notes a correlation estimate from several studies between the percentage of asymptomatic subjects (but with amyloid deposition in the brain detected post-mor-

tem) and the percentage of new cases of AD about ten years later. The NIA-AA further discusses that lower metabolism measured with FDG-PET, elevation of phosphorylated tau protein in the CSF or cortical thickness loss/atrophy in specific areas on volumetric MRI could be considered as factors revealing neuronal damage and would indicate the progression of preclinical AD, which later becomes defined as mild cognitive impairment (MCI), a prodromal phase of AD, when cognitive symptoms are exposed during tests, such as the Mini-Mental State Examination (MMSE), or are reported by the patient or family members [27]. By emphasizing the continuous nature of AD, the NIA-AA states that the transition between the preclinical stages and MCI is subtle. Biomarkers in preclinical stages (A 42 levels in the CSF, for instance) could be used only by research groups, but screening healthy members of the population for AD, however, would not comply with Wilson's classic screening criteria: AD is incurable, and both the cost and the specificity/sensitivity of the mentioned tests would probably be considered inadequate as well [35, 36]. The proposal by the NIA-AA for further staging AD involves the mentioned MCI, a pre-demential stage of cognitive impairment, which is not normal for the patient's age group; however, the patient has intact functional abilities (a lack of interference with everyday life) [37, 38]. MCI might be caused by other underlying conditions (trauma, depression, stroke or others) and might not always represent a prodromal phase of AD, however [27]. Although the diagnosis of MCI might be consolidated by findings of CSF proteins and PET scans mentioned above, any clear consensus is lacking as the sensitivity of these estimates is controversial [27, 37]. According to the NIA-AA, markers of both A peptides/amyloid plaques and neuronal injury (mentioned above) signal an increased likelihood to develop AD more than any of these markers alone. It is after the first functional (daily life) symptoms that the NIA-AA proposes declaring AD rather than MCI. A patient should present with at least two cognitive symptoms from the following: impaired memory, reasoning, visuospatial cognition, language and changes in behaviour to meet criteria for AD dementia. Diagnosis of probable AD is specified by a gradual onset of symptoms, clear deterioration of function (otherwise – possible AD) and no evidence of other dementias; mutations in genes APP, PSEN1, and PSEN2, but not the presence of allele APOE- 4 increase the level of certainty, according to NIA-AA [39]. Biomarkers of amyloid beta protein and of neuronal injury are helpful in making a diagnostic decision of AD (especially when both present as "positive" according to cutoff values), but the NIA-AA discourages their routine use as clinical criteria satisfy the diagnostic needs in a clinical setting.

International Work Group (IWG) criteria (2013)

The International Work Group (IWG) set to redefine AD in a way which would oppose the NINCDS-ADRDA criteria and acknowledge both a diagnostic possibility of definite AD dementia in vivo (not only post-mortem) and the integration of biomarkers in the diagnostic process. When the NIA-AA added some information about AD biomarkers in their criteria for diagnosing AD dementia, they noted that biomarker tests add extra confidence when diagnosing probable AD dementia, but are not equivalent, in their opinion, to core clinical criteria (cognitive and functional symptoms) [39]. The IWG, however, incorporated biomarker use into their diagnostic criteria: to be diagnosed with probable typical AD dementia, the patient should have cognitive memory symptoms of gradual onset which progress further and have one or more supportive features: positive for decreased CSF A 42 concentration/increased total tau (t-tau) or hyperphosphorylated tau (p-tau) concentration, positive for decreased glucose uptake in bilateral temporoparietal regions/positive for PET amyloid imaging, have medial temporal lobe atrophy (MRI scanning) or have an autosomal-dominant AD mutation [40]. However, the IWG does not accept the notion of a preclinical AD in subjects with biomarkers; rather they note them being only at risk of developing AD. The preclinical definition of AD is preserved only for those with known autosomal-dominant mutations (PSEN1, PSEN2, APP genes) as their chances of developing AD are much greater than for those asymptomatic subjects showing AD-like changes as measured with biomarkers [40, 41]. Only when the patient starts exhibiting clinical symptoms of function and cognition, the assessment of biomarkers becomes valuable as the diagnosis of prodromal AD (daily functioning is preserved) or AD dementia (loss of normal daily functioning) is much more probable. The combination of decreased CSF A 42 and increased CSF p-tau or t-tau was endorsed by one of the members of the IWG, B. Dubois, as one of the most reliable indicators (therefore, increasing the probability of future AD dementia), but differences in measurements and cutoff values (to be evaluated as positive for amyloid/tau) across clinics should be recognized as well [41]. In a substantially different way than the NIA-AA, B. Dubois and the IWG do not distinguish between biomarkers merely associated with AD (CSF amyloid peptide and PET amyloid tracer retention) and those potentially causing or demonstrating neuronal pathology in AD (elevated CSF p-tau and t-tau values, decreased glucose metabolism in FDG-PET, brain atrophy). Instead, they propose that any biomarker associated with AD should be regarded as pointing to the pathophysiological process. Therefore, a biomarker should have high specificity (if adopted for diagnosis) as well as be used to diagnose AD dementia as a disease, not some heterogenic syndromes of MCI or potentially preclinical AD. The differences between NIA-AA and IWG criteria reveal the main problem for diagnostic measures in drug research for AD: specific and reliable biomarkers are available only in the late stages of AD and merely consolidate symptomatic diagnostics. It is therefore important to search for combinations of several biomarkers (such as the early decrease of CSF A 42 levels, increased tracer retention for amyloid fibrils measured with PET, and p-tau and t-tau elevation in the CSF) that

could lead to a statistically reliable early diagnosis of AD and help create criteria for the most initial stages of symptomatic disease. Testing for new biomarkers that could demonstrate more biological causation of the existing pathology and morbidity seen in AD could lead to the development of a targeted disease-modifying therapy as the pathophysiological importance of amyloid deposition recently began to lose validity [18].

BIOMARKERS FOR ALZHEIMER'S DISEASE

Principles of biomarker use

According to Giovanni B. Frisoni et al., a biomarker is "an objectively measurable substance, characteristic, or other parameter of a biological process that enables assessment of disease risk or prognosis and provides guidance for diagnosis or monitoring of treatment." [42]. As discussed above, biomarkers could help distinguish patients with preclinical AD, since pathologic changes in the brain are known to appear well before a symptomatic cognitive decline. Whenever a disease modifying therapy is present, biomarkers would help distinguish patients requiring treatment to prevent major pathologic changes [43]. Different biomarkers present varying sensitivity and specificity, parameters that depend on the nature of the technique employed as well as other variables specific to the patient or clinical implementation of measures. The Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease stated in 1998 that both the specificity and the sensitivity of a particular biomarker should exceed 80%, so the biomarker could be considered useful (or as the report called, ideal) in the process of decision-making on the diagnosis [44]. It is critical to note that the whole potential of biomarkers as sensitive and specific AD indicators cannot be fulfilled until standard operating procedures (SOPs) or harmonized protocols (HarPs) are developed, as many inconsistencies arise because of different pathways of biochemical experimentation or imaging in research centers across the world. Knowing the complexity of AD itself and the fact that biomarkers are employed to capture varying neurobiological constructs, it is essential to come up with specific regulations to successfully employ biomarkers in clinical trials and diagnostic procedures, and make them more comparable in meta-analyses or other trials.

Cognitive tests

Although not defined as biomarkers, cognitive tests are used to evaluate mental decline in subjects selected for research or those with reported complaints. While most tests have cutoff values to determine MCI or AD dementia, subtle changes in cognitive function that are abnormal for the age group of the subject in question might be predictive of developing MCI and therefore be significant in diagnosing what might be called the boundary between preclinical AD and MCI [34, 42, 45]. Memory has been noted to change even before a noticeable MCI, but there is no clear consensus on qualitative testing of the earliest prodromal features of MCI (subjective cognitive decline, SCD), and extensive research is needed to develop cognitive tests for disturbances in otherwise presymptomatic AD, while cognitive tests remain largely appreciated for diagnoses of MCI or AD dementia [46–50]. Objective evaluation of SCD is proposed despite difficulties concerning such tests, as the potential benefits of diagnostic measures during the first cognitive changes are appreciated [49, 51]. In the earliest symptomatic stage of AD (or MCI, which precedes AD), the patient himself might complain about cognitive problems, thus collecting a thorough history (from the patient or a family member) is required [52]. The most important cognitive features (memory, language, visuospatial cognition, reasoning, executive function, and behaviour) are assessed through history or simple questioning and testing (word recall, geometric figure copying and their recall, etc.) [53, 54]. This type of testing is helpful, as differentiating among several types of dementia becomes possible (for example, dominant behaviour disturbances in frontotemporal dementia, more severe problems with visuospatial cognition in dementia with Lewy bodies can be observed) [55]. However, because of the variety of cognitive symptoms and the subjective nature of the neurologic history, the latter is hardly quantifiable and cognitive tests with a grading system are needed for trials. One widely used tool to quantify the level of cognitive impairment is a brief Mini-Mental State Examination (MMSE) with a total maximum of 30 points. The limitations of this test include the ceiling effect (28–30 points with otherwise abnormal cognition), poor sensitivity for MCI, dependence on the educational background of the subject and the fact that not all essential cognitive functions are evaluated [56–59]. However, a cutoff score of 23/30 (or higher, e.g. 27/30, for well-educated and high performing subjects) has acceptable sensitivity and specificity to be used for AD dementia assessment [60–62]. Clinicians and researchers are encouraged to use a modified variant of MMSE, the Montreal Cognitive Assessment (MoCA) to spot MCI, as this test is stated to have 90% sensitivity for MCI and 100% for mild AD [58]. Many other tests are available, but for some of them, further trials are required to demonstrate their reliability [63, 64]. Simplicity is sought in a clinical setting, while more complex testing criteria to spot even subtle changes could be dedicated to research trials [64]. It was observed that MCI is a good predictor of AD when assessed with cognitive tests [53]. However, the subjectivity of the clinician, the patient (or his informant) and the potential complexity of cognitive testing for SCD (or the most subtle and early stages of MCI) uncover the need to use additional quantifiable biological biomarkers during testing, so not only cognitive consequences, but also pathophysiological processes during the asymptomatic stages of potential future MCI and AD could be investigated.

Olfactory impairment

The olfactory deficit is supported by meta-analyses to be associated with AD risk and MCI [65–67]. Even when cognitive features are intact, loss of odor identification is found in patients later progressing to MCI [68–71]. Impaired olfaction during MCI itself was seen to increase the probability of conversion to dementia as well [70, 72–74]. Such disturbances were noted to be better at predicting cognitive decline than was episodic memory loss, but the combination of cognitive and olfactory tests might be even more valuable [75, 76]. In one study, 47% of patients with olfactory disturbances converted to AD (2-year follow-up) compared with 11% of MCI patients with normal olfaction [77]. Worsening of olfactory deficits is expected when the conversion from MCI to AD occurs as well [78]. The pathological mechanism of this link is unclear, but hypotheses include atrophy and amyloid deposits in the entorhinal, olfactory cortex, and the olfactory bulb and nerve [79–81]. There might also be a potential link between AD fibrillar pathology and olfactory deficits [82]. Association between olfactory impairment, lower scores on neuropsychological tests and other preclinical AD or MCI biomarkers (increased CSF tau protein, decreased A 42, hippocampal volume reduction, entorhinal cortical thinning, increased amyloid tracer retention during PET) was observed as well [76, 83, 84]. The University of Pennsylvania Smell Identification Test (UPSIT) is often used as a noninvasive and easily administrable test for the olfactory function: 88–89% sensitivity and 71–83% specificity for detecting AD have been noted [85, 86]. When included in diagnostics for AD trials as one of the variables, olfactory impairment might help better assess the risk for AD or the risk of MCI progression [66, 85, 87].

MRI scans

MRI scanning for Alzheimer's disease is based on structural changes during the progression of the disease. Hippocampal volume reduction, ventricular expansion, cortical atrophy with enlarged sulci, and white matter hyperintensities (WMH) may be observed; however, these changes are not specific for AD [88, 89]. Structural changes in the brain seen in MRI scans are suggested (by the NIA-AA, for example) to precede clinical symptoms and even be a predictor of future disease progression [34]. Atrophy seen in MRI scans was noted to have increased acceleration several years before the onset of first symptoms: about 3 to 8 years for brain, ventricular and hippocampal atrophy (with presumed gradual acceleration) in one study and 5.5 years for hippocampal volumetry in another [90, 91]. Cortical thinning correlates less with total brain volume than does hippocampal volumetry; otherwise, both tests are almost comparable to one another. For this reason, cortical thinning is more applicable for epidemiological studies, when a greater variation of brain volumes exists [92]. Those with autosomal dominant mutations or positive for amyloid deposits, but having no MCI might exhibit cortical thinning as well, once more suggesting that cortical thinning could be a potential biomarker of preclinical AD [93–95]. Furthermore, subtle cortical thinning could indicate an increased risk of AD a decade before the onset of symptoms even in patients with no indications of pathologic amyloid changes [96]. A small subject sample size makes the latter study less reliable, but also points out the difficulty in AD research to test great numbers of patients with such long follow-up periods [97]. Patients with subtle MCI or clinical AD dementia are evaluated by MRI cortical thickness as well: an estimate of 83% sensitivity and 65% specificity for MCI to progress to mild AD was found [98]. WMH volume changes, which are thought to result from small blood vessel disruption in the brain, was a predictor of rapid decline in MMSE scores (by 3 points in 6 months and by 6 points in 12 months in one study) for patients with MCI [99, 100]. H1 Magnetic resonance spectroscopy (H1-MRS) is also a useful method to identify MCI conversion to AD: sensitivity was found to be 78% and 82% and specificity 72% and 69% for posterior cingulated gyri/left occipital cortex, respectively [101]. Changes in functional imaging (activity loss in posterior cingulate, hippocampus and other regions) are noted as well when distinguishing between control subjects and AD patients [89, 102, 103]. Medial temporal lobe atrophy (MTA) seems one of the best features defining clinical AD dementia using MRI [41, 42]. Several studies mention sensitivity and specificity of MTA imaging to be about 79–85% and 82–98%, respectively, and also consider MTA imaging to be valuable for predicting the conversion from MCI to AD; however, its use in diagnosing MCI rather than AD dementia lacks accuracy [104–109]. Being a notable measure in research centers, MTA atrophy is difficult to evaluate in a clinical setting; much skill and time are required [42]. Hippocampal atrophy is said to be the most "robust" diagnostic test and may be one of the most reliable MRI tools for diagnosing clinical AD dementia with about 80–85% sensitivity and specificity, despite the heterogeneity of hippocampal atrophy, pointed out by B. Dubois [41, 107]. It also represents elevated chances of MCI progression to AD and was also seen to increase the confidence of clinicians when making a diagnosis of AD pathology [110, 111]. MRI scanning for hippocampal atrophy is also encouraged by the European Federation of the Neurological Societies (EFNS) guidelines of 2010, stating acceptable sensitivity and specificity for diagnosing AD [112]. As discussed, MRI scanning is useful to follow the integrity of brain parenchyma from the preclinical to the most severe stages of AD. MRI is not an invasive or substantially complicated procedure; however, its potential in diagnosing the earliest possible risk for AD is to be determined with more clarity as problems, such as heterogeneity of causes of structural changes, emerge.

CSF protein sampling

CSF sampling could be a promising indicator of the early stages of AD because of an altered biochemical composi-

tion of the CSF [113]. The CSF makes contact and executes molecular exchange with the brain or brain blood vessels: some CSF proteins might be absorbed into the brain through the choroid plexus, while others are secreted to the CSF from the interstitium and capillaries in a similar manner [114–117]. Therefore, CSF proteins can reveal the internal metabolism of the brain to some extent, and the main components of interest have been p-tau, t-tau, and peptides of amyloid beta (A 37 to A 43). A decrease in A 42 levels in the CSF, for instance, could signal retention of this peptide in the form of amyloid plaques in the parenchyma. Among the mentioned CSF biomarkers, Shaw et al. found CSF A 42 levels to be the most sensitive markers for AD detection, with a sensitivity of 96.4% and a specificity of 76.9% [118]. Similar values of CSF A 42 levels with sensitivities and specificities that often exceed 80% are being mentioned in other studies as well [97, 119, 120]. Hansson et al. found a significant decrease of the AB 42/AB 40 ratio in patients diagnosed with MCI that later developed AD in contrast to patients with stable MCI or developing other dementias; the study also showed superiority of the AB 42/AB 40 ratio to AB 42 concentration testing alone [121]. Furthermore, it could be inferred from the study by Hoglund et al. that simultaneous evaluation of levels of Ab1–37, Ab1–38, Ab1–39, Ab1–40, and Ab1–42 and the calculation of their ratios could yield more specific results than could separate measures. After comparing different ratios, it was demonstrated that the AB 42/Ab1-37 ratio separated AD patients from those with stable MCI better (81% sensitivity, 72% specificity) than other ratios, while various combinations of results were even more informative [122]. Values of protein tau (t-tau or p-tau) alone are increased in AD, but are not as promising as the combination of both CSF A peptides and tau values – this combination has earned its name of "AD signature" (discussed later) [123–125]. One study found decreased CSF AB 42 and increased CSF-tau levels in probable and possible AD as well as MCI (sensitivities of 94%, 88%, and 75%, respectively). When the possession of APOE- 4 allele was taken into consideration, sensitivity for discriminating AD patients was approaching 100% [126]. In another trial, the ratio of p-tau to AB 42 was found to be significantly elevated in patients with AD (against controls) with a sensitivity of 86% and a specificity of 97% [127]. Even when solely distinguishing between AD patients and controls, testing for CSF amyloid beta peptides and tau is not as accurate as one would expect, therefore, detecting MCI or preclinical stages of AD is yet more difficult [125]. However, there are efforts to predict MCI conversion to AD or even predict future AD in asymptomatic subjects with the use of CSF sampling. Considering MCI patients alone, for example, Hansson et al. showed that after a simultaneous evaluation of CSF t-tau and AB 42 levels, AD patients could be discriminated from MCI subjects with a sensitivity of 95% and a specificity of 83% [128]. Mattson et al. also conducted a multicenter study on various parameters of CSF biomarkers and found AB 42, p-tau, and t-tau to have good accuracy, when identifying MCI progression to AD, likewise do several other studies [119, 129–131]. Findings during preclinical stages are less defined, but there are studies showing correlation between CSF markers and cognitive decline after several years of follow-up, as both A 42 and tau (combined or not) are predictive [130, 132, 133]. Such longitudinal studies are difficult to accomplish, but they are of great value for understanding CSF proteins as AD biomarkers. Even though some approaches regarding CSF sampling are promising (for example, combining several marker protein values for a prognosis), their appropriateness for successfully diagnosing AD remains unclear. Some propose that the correlation of decreased amyloid peptide levels and AD is inconsistent even if widely acknowledged due to studies, which often find an association between CSF and AD [134]. For example, K. Blennow et al. state that A 42 is not specific for AD and thus cannot be used alone to predict the disease [135]. Not only there is no final proof that amyloid peptides directly cause AD, but also other parameters like the patient's age, or the presence of the APOE- 4 allele have an impact on amyloid changes: an article published in 2003 with a provoking title "Age but Not Diagnosis Is the Main Predictor of Plasma Amyloid -Protein Levels" found AB 40 and AB 42 levels to be firstly influenced by age rather than by cognitive disease [120, 136, 137]. It was also shown that diagnosing AD from CSF components in older patients was less accurate than in younger populations [138]. CSF sampling poses a particular threat to a patient as lumbar punctures might cause headaches, iatrogenic meningitis, subdural hematoma or even death, therefore the use of this test might be limited, especially when many subjects are being evaluated [139–141].

PET scans for neuronal degeneration

Positron-emission tomography (PET) has been largely investigated as a tool for diagnosing dementias and AD in particular. This technique is costly and not easy to employ: some radioactive tracers cannot be bought due to their short half-lives and have to be made in the testing center using particle accelerators. PET scans can target various components of the brain with high specificity and provide valuable information. One probe that is amyloid plaque specific is the Pittsburgh compound B (PIB), whose synthesis requires having a cyclotron. Many studies have shown this technique's ability to discriminate patients with AD, and therefore to be suitable for an early diagnosis. A significant twofold increase in amyloid load was shown with [11C]PIB-PET in AD patients in contrast to healthy individuals, while, interestingly, a significant 20–35% increase in microglial activation was detected with [11C](R)PK11195-PET [142]. One study found a prominent increase of PIB retention in frontal (1.94-fold), parietal (1.71-fold), temporal (1.52-fold), and occipital (1.54-fold) cortexes and in the striatum (1.76-fold) in AD patients in contrast to healthy controls (HC). There was no significant PIB retention difference in healthy controls of

varying age, suggesting that age would not normally confound the diagnosis. Also, an inverse correlation between PIB retention and cerebral glucose metabolism (as measured with 18F-fluorodeoxyglucose, a probe that will be discussed later) was determined, mostly in the parietal cortex [143]. Another study found no correlation of AD severity with PIB binding; however, cortical PIB binding was absent in frontotemporal dementia (FTD), higher in dementia with Lewy bodies (DLB), and markedly elevated in AD, while the pattern of MCI individuals was either as that of AD patients (60%) or presented a normal pattern [144]. PIB binding in MCI patients was observed to be significantly increased and to predict conversion to AD: higher retention meant faster conversion as well [145–147]. PIB retention during MCI is stated to resemble an intermediate state between control subjects and those with AD [148]. As with CSF sampling of beta amyloid peptides, tracer retention due to amyloid fibrils measured with PET is thought to precede any clinical symptoms of AD by a decade or more; CSF A levels and amyloid fibril tracer retention in PET correlate inversely [113, 149–152]. Therefore, the use of PIB PET might accompany CSF testing for a preclinical evaluation of asymptomatic subjects in trials [113, 153]. [11C]PIB was one of the first PET probes to be used, while newer ones, targeting amyloid plaques, include fluorine-18-labeled probes such as florbetapir (AV-45), florbetaben (18F-BAY94-9172), flutemetamol, and 18F-AZD4694. Probes radiolabeled with fluorine have similar binding profiles to PIB (binding to fibrillar protein in amyloid plaques), but their longer half-lives (110 minutes versus 20 minutes of radioactive carbon-11) is what they might be advantageous for, as their acquisition becomes simpler. After performing cerebral amyloid-beta PET using florbetaben as a radiolabeled tracer, Barthel et al. calculated a sensitivity of 80% (95% confidence interval (CI)=71–89) and a specificity of 91% (95% CI=84–98) of this technique for discriminating AD patients from HCs [154]. Tracer binding changes in the posterior cingulate were the best discriminator; however, the ratios of standardized uptake value (SUVRs) were significantly higher in all neocortical grey-matter regions of AD patients in contrast to HCs, while further SUVRs' linear discriminant analysis gave a higher sensitivity of 85% and the same specificity of 91%. Villemagne et al. also showed significantly higher SUVRs of 18F-florbetaben in neocortical areas in AD patients. Diffuse cortical retention of florbetaben was observed in 96% AD patients, 60% of MCI patients, while cortical binding in the frontotemporal lobar degeneration (FTLD), vascular dementia (VaD), DLB, Parkinson's disease (PD), and controls was only 9%, 25%, 29%, 0%, and 16%, respectively [155]. When using florbetapir (18F-AV-45) for discriminating individuals with AD from HCs, Camus et al. found a sensitivity of 84.6%, but a low specificity of 38.1%; further quantitative global cortex SUVR assessment yielded both a high sensitivity of 92.3% and a high specificity of 90.5% [156]. Another study with florbetapir (18F-AV-45) radioligand PET has demonstrated the accumulation of florbetapir in cortical regions that are thought to show high amyloid beta deposition in AD patients, while scans of healthy controls have shown only minimal accumulation of florbetapir in those regions [157]. A significant discrimination of AD patients was shown by both the spatially normalized parametric reference region methods (DVRs) and SUVRs, suggesting that florbetapir is a novel and also a well-tolerated tracer to use in AD diagnosis. In one study by Alzheimer's Disease Neuroimaging Initiative (ADNI), florbetapir binding profiles correlated with CSF amyloid values in 86% of the subjects (HCs, MCI and AD patients) [158]. In another ANDI trial, florbetapir was shown to be useful for selecting subjects with MCI for studies [159]. Vandenberghe et al. investigated 18F-flutemetamol as a potential tracer and showed a sensitivity to be 93.1% and specificity to be 93.3% for distinguishing AD from controls [160]. Also, high test-retest replicability with 1–4% variability was observed, demonstrating a similar performance of 18F-Flutemetamol to [11C]PIB, with correlation coefficients in the range of 0.89–0.92, when SUVRs of both tracers were compared. Cselényi Z et al. found significantly lower SUVRs (obtained with 18F-AZD4694 PET) and lower distribution volume ratios in grey matter (using the reference Logan approach) of control individuals with ratios of 1.08 (11%) and 1.01 (6%), respectively, in contrast to AD subjects, presenting ratios of 2.15 (24%) and 1.62 (18%), respectively [161]. Another fluorine-18-labeled probe known as FDDNP has to be mentioned separately as it binds not only to amyloid plaques but also to neurofibrillary tangles, so distinct NFT binding patterns could be investigated during differentiation of AD changes in the brain from normal aging, MCI, or other types of dementia [162]. Small et al. showed significantly different mean values (HC significantly lower than MCI and MCI significantly less than AD) for regional FDDNP binding among AD, MCI, and HC subjects [163]. FDDNP PET showed a significantly slower clearance of FDDNP in AP- and NFT-dense areas of the brain of AD patients [164]. Shin et al. used FDDNP PET and found that tangles comprise the dominant pathology seen in the medial posterior cortex of AD patients rather than amyloid plaques, also showing a significant binding of FDDNP in neocortical areas of AD individuals [165]. It was demonstrated that FDDNP tracer could be used in a different approach to investigating patient's brain to visualize neurofibrillary tangles rather than solely amyloid plaques and could provide additional information about brain tissue changes during AD. The importance of neurofibrillary tangles in the diagnosis of AD could be supported by other studies, one of which even declared that "tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease" in their title and stated that amyloid plaque burden could be of low value [166]. Other PET probes that are used for tau imaging are currently under investigation and their potential advantages are still unclear. However, [F-18]-T807 imaging presented a consistently higher SUVRs (in temporal, parietal, frontal lobes and hippocampal area) in patients with AD (1.30–1.80) than in those with MCI (1.02–1.38),

which were higher than in healthy individuals (1.03–1.16), in addition to little non-specific binding in healthy individuals [167]. Similar [F18]-T808 tracer requires further investigation [168]. Probes that bind to other structures in the brain are also being tested and include, for example, one 11C-(R)-PK11195 probe that binds to a benzodiazepine receptor known as 18 kDA translocator protein (TSPO); it could reflect neuroinflammatory processes that might be related to cognitive decline [169]. Even though PET scanning is not widely used for routine clinical trials and its spread is limited, emerging evidence of the usefulness of PET for diagnosing AD is predicted to foster PET use routinely. ADNI has published potential guidelines for further standardizing PET use in trials, while the importance of imaging NFTs in addition to amyloid fibrils was emphasized as well [170]. Likewise, The Society of Nuclear Medicine and Molecular Imaging and Alzheimer's Association issued a report on the criteria of amyloid-PET use in 2013 [171]. These recommendations are an important step for PET use on a clinical basis and provide information for further considerations of when amyloid-PET should be an appropriate choice as part of diagnosis. However, guidelines clearly state that amyloid-PET should not be used without an objective confirmation of cognitive decline (in asymptomatic patients, for instance). Therefore, for clinicians amyloid-PET could become a way to provide a more accurate diagnosis, to inform the patient and his family about the course of the disease and to prepare for required expenses or social needs. Otherwise, during research, PET should be considered as one of the most useful biomarkers for preclinical or early detection of subjects with future AD dementia, even when symptoms are lacking.

FDG-PET

18F-fluorodeoxyglucose (FDG) is a PET tracer with a radioactive fluorine-18 and is used to observe cerebral glucose metabolism. There are many studies showing that PET probe FDG could provide substantial quantitative data of glucose metabolism in the brain and specific changes in AD patients, as it has been noticed that FDG uptake decreases over time if AD is present. Such changes could be explained by the loss and injury of neurons in areas, such as frontal, parietotemporal, and posterior cingulate cortices. A longitudinal multi-center study demonstrated that the cerebral metabolic rate for glucose (CMRgl) in patients with probable AD and those with MCI was significantly lower, mainly in the precuneus, posterior cingulate, parietotemporal regions, and occipital cortex compared to HCs [172]. There was also a significant relationship between lower CMRgl observed in brain regions and lower MMSE scores. Silverman et al. detected AD by FDG-PET with a sensitivity of 94% and a specificity of 73% [173]. Panegyres et al. found a sensitivity of FDG-PET of 78% (95% CI=66–90%) and a specificity of 81% (95% CI=68–86%) for AD patients, while FDG-PET specificity for discriminating other dementias was more than 95% [174]. Mosconi et al. declared that CMRgl reductions in parietotemporal, frontal and posterior cingulate cortices using fluoro-2-deoxy-D-glucose PET could be predictive of AD, as sensitivity averaged at 90% with a lower and more variable specificity [175]. Furthermore, FDG-PET has been shown to predict whether patients with MCI would progress to AD, as MCI patients presenting abnormal FDG-PET and abnormal episodic memory results had an 11.7 higher chance of developing AD than had controls normal in regard to both measures [176]. Overall, FDG-PET is a useful tool for the observation of physiological brain changes from the early stages of MCI throughout AD and provides additional insight into the possible mechanism of AD development.

SPECT

Single-photon emission computed tomography is another promising technique for diagnosing AD before advanced clinical stages. Various SPECT tracers include those targeting the acetylcholine pathway: 123I-quinuclidinyl benzilate (123I-QNB) is used to target muscarinic acetylcholine (ACh) receptors, 123I-IBVM targets vesicular ACh transporters, while 123I-5IA-85380 is known to target nicotinic acetylcholine receptors. The uptake of three former tracers is reduced in AD patients in contrast to controls of the same age. Targeting muscarinic acetylcholine (ACh) receptors is a promising diagnostic test for Alzheimer's as the decline in cholinergic neurotransmission and changes in acetylcholine receptors is a common AD characteristic. Colloby et al. have shown a voxel spatial covariance pattern (SCP) obtained from 123I-QNB SPECT to significantly differentiate patients with AD from controls, while Mazère et al. has found a significant decrease of 47–62% in 123I-IBVM binding in patients with AD in parahippocampal–amygdaloid complex and cingulate cortex [177, 178]. O'Brien et al. have demonstrated the sensitivity of 123I-5IA-85380 SPECT in identifying AD patients to be 73% and a specificity to be 88%, while a sensitivity of 80% and specificity of 81% has been estimated for 99mTc-HMPAO SPECT imaging [179]. Furthermore, SPECT could be used for discriminating MCI progression to AD: one study used SPECT to show its potential in predicting MCI development to a more progressive MCI and questioned the use of SPECT for detecting preclinical stages [180]. Another study showed a significant decrease in regional cerebral blood flow (rCBF) in the left posterior cingulate cortex in patients who later progressed to AD in contrast to MCI individuals who remained stable [181]. Relative blood flow is observed to be significantly reduced in various areas of the brain, but left prefrontal, left frontal and left parietal areas had both sensitivities and specificities >75% for discriminating patients who later developed AD from those who remained stable MCIs [182]. Likewise, Habert et al. showed a significantly reduced right parietal and hippocampal perfusion in MCI patients who later developed AD in contrast to stable MCIs [183]. Uptake patterns in vivo and kinetics of molecular probes allow to evaluate (both qualitatively and quantita-

tively) the activity of various biochemical processes and specific changes, including those of different enzymes, transporters, and receptors. While both PET and SPECT are carried out using radiolabeled probes, PET has higher temporal and spatial resolution than SPECT and is also easier to quantify. However, it has to be noted that both PET and SPECT have spatial resolution limitations and could lead to incorrect qualitative and quantitative results, therefore MRI, for example, could be used for structural imaging to take brain atrophy into account before evaluation with PET or SPECT.

Genetic risk factors as biomarkers

Genetic risk factors for early onset Alzheimer's disease (EOAD) are quite clearly understood, and the genetic material itself can be considered as a biomarker. PSEN1, PSEN2, and APP genes, all encoding APP breakdown pathway proteins, are associated with a Mendelian pattern of inheritance. Mutations that are linked to AD are highly penetrant (>85%) and with certainty lead to an early-onset disease. Despite that, EOAD comprises only 1–5% of AD cases, and it is clear that biomarkers are not suitable for the majority of AD cases. However, genes possibly linked to the late onset Alzheimer's disease (LOAD) are not associated with a Mendelian pattern of inheritance, and it is harder to investigate their relation to AD. The main allele that has been associated with LOAD is the APOE- 4, which is situated on chromosome 19q13, while the APOE protein has three isoforms, APOE- 2, APOE- 3, and APOE- 4. Kuusito et al. have found a strong association of the APOE- 4 allele and AD: the frequency of APOE- 4 allele was double in AD patients than in non-AD subjects (0.359 versus 0.165) [184]. Also, it has been shown that possession of one APOE- 4 allele increased the risk of AD 2.7-fold, while the presence of two APOE- 4 alleles increased the risk of AD 9.3-fold. Another study has found APOE- 4 alleles to lower the age-at-onset of Alzheimer's as the age-specific prevalence of Alzheimer's disease in participants lacking APOE- 4 alleles peaked at the age of 95, while in those possessing one APOE- 4 allele (heterozygotes) the peak was noted at the age of 87 and in homozygotes the prevalence of AD reached the maximum at the age of 73 [185]. According to Corder et al., the proportion of AD-affected subjects increased with a highly significant additive trend from 20% of individuals with APOE- 2/APOE- 3 or APOE- 3/APOE- 3 genotypes to 47% with APOE- 2/APOE- 4 or APOE- 3/APOE- 4 genotypes to 91% with APOE- 4/APOE- 4 genotype. For each additional APOE- 4 allele risk of Alzheimer's increased by a factor of 2.84 (95% CI=2.03–3.96) [186]. The researchers have also found that each APOE- 4 allele lowered the age-at-onset: from mean onset of 84.3 years in individuals possessing no APOE- 4 alleles to 75.5 years in individuals possessing a single APOE- 4 allele to 68.4 years in individuals possessing two APOE- 4 alleles. However, another study has gathered results indicating that although APOE- 4 alleles are a risk factor for amnestic MCI, they do not predict the conversion to AD [136]. Likewise, Tyas et al. has shown that although age, education, and APOE- 4 gene were significantly predictive of MCIs, only age seems to be associated with the development of dementia [187]. Finally, it is worth mentioning that the APOE- 4 allele alone is not sufficient as a biomarker because its presence does not indicate that AD will definitely develop. On the other hand, AD could develop even without a single copy of APOE- 4 allele in the genome. Other genetic biomarkers include polymorphisms of CHRNA7 and ACT genes and have been investigated as potential AD indicators. Barabash et al. have found a T allele of -86 C/T CHRNA7 polymorphism to be associated with a 50% reduction in the probability to develop AD in 5 years. However, at least a single copy of the T allele of the ACT polymorphism seems to increase the risk of progressing to AD rapidly [136]. Genetic information is easy to obtain and very often collected during clinical trials; however, more extensive research is required for the evidence of genetic AD (especially, LOAD) causation to be acquired and for genetic biomarkers to be considered as clearly characteristic features of potential AD.

Plasma sampling

One group of biomarkers that has drawn attention over the years is that of plasma components. Tests requiring patient's blood are cost and time effective, as well as barely invasive and safe. Blood sampling could be used even for population screening; such metabolomic diagnostic approach would be very effective if these biomarkers presented high sensitivity, specificity, and other parameters. While measuring one single metabolite might not yield such high accuracy, the combination of several or tenths of metabolites could be a promising diagnostic approach. One study investigated ten lipids of peripheral blood and calculated a 90% accuracy of diagnosing cognitively normal subjects that would convert to amnestic MCI or AD in 2–3 years of time [188]. However, a substantially larger study failed to replicate these results [189]. Hye et al. investigated a combination of proteins rather than lipids and found ten proteins which measurements predicted a progression to AD from MCI with a sensitivity of 85%, a specificity of 88%, and an accuracy of 87% [190]. Similarly, another study found ten autoantibody biomarkers that would differentiate AD patients from healthy individuals with 96.0% sensitivity and 92.5% specificity [191]. Ray et al. found 18 signaling plasma proteins that could discriminate AD patients from healthy controls with an accuracy of up to 90% [192]. One longitudinal study found plasma biomarkers that were either significantly decreased or significantly increased in AD patients in contrast to healthy individuals, providing >80% accuracy of diagnosis [193]. In a study with a remarkable approach, DeMarshall et al. used a panel of 50 most differentially expressed autoantibodies from sera of patients with amnestic MCI and presented their autoantibody biomarker test to

have a sensitivity, a specificity and an accuracy of 100% for discriminating MCI patients from controls, providing potential insight into development of novel immunological tools to combine various biomarkers and to detect MCI [194]. Another group of studies investigated individual plasma biomarkers: one study showed that the concentration of apolipoprotein J (ApoJ, an extracellular chaperone protein) was significantly higher in MCI and AD patients than in healthy individuals. Also, plasma ApoJ was a predictor for AD (in contrast to healthy individuals) with >80% accuracy and for MCI with >75% accuracy [195]. Winston et al. found CD81-normalized neuron-derived exosome (NDE) concentrations of A 42 to be significantly higher in MCI patients converting to AD than in healthy controls; similar results were presented for p-tau [196]. Concentrations of these plasma components were also significantly higher in AD patients in contrast to those in healthy individuals and AD patients in comparison to stable MCI individuals. Other biomarkers including neurogranin (NRGN) and repressor element 1-silencing transcription factor (REST) were also shown to significantly discriminate AD and MCI patients who would convert to AD from those with stable MCI or healthy individuals. Combining all proteins together, a sensitivity of 99.2% for discriminating AD patients from healthy individuals was found, as well as a sensitivity of 78.3% for discriminating healthy controls from stable MCI, a sensitivity of 93.1% for discriminating those with stable MCI from the ones who would convert to AD, and a sensitivity of 93.2% for discriminating patients with stable MCI from AD patients [196]. Even though plasma biomarkers might seem highly predictive, it is worth mentioning a meta-analysis and a systematic review published in The Lancet in 2016, where plasma A 42 was not shown to significantly differentiate patients having AD, nor did A 40 concentration, only t-tau in plasma or serum showed a large effect size (average ratio 1.95, 95% CI=1.12–3.38, p=0.02) [197]. Unfortunately, other plasma components were either under-investigated or showed no significant differentiation of AD patients, signaling that further studies of large scale are required.

Saliva sampling

Another group of biomarkers includes components of saliva. Even though there are very few studies and a limited amount of data regarding salivary biomarkers, salivary examinations were suggested as not invasive, cheap and easy to perform. Such testing would be very convenient if screening of population is required. Carro et al. have shown that abnormally reduced lactoferrin levels (<7.43 g/mL) could be indicative of the conversion of amnestic MCI to AD with a sensitivity of 100%, and a specificity of 98.6% [198]. However, only 14 individuals later diagnosed with AD were tested, so more numerous studies are required to validate lactoferrin as a potential biomarker of AD. Lee et al. found A 42 levels secreted in saliva to be more than double for AD patients than for patients with non-AD cases, but merely 7 AD patients were examined [199]. Other trials have also been carried, but studies of greater impact and size are required to further investigate this diagnostic approach [200–202].

CREATING A BIOMARKER SIGNATURE FOR ALZHEIMER'S DISEASE

One of the most useful achievements, when considering AD biomarker use for research trials and even daily clinical diagnostics, could be a combination of biomarker evaluations to create what might be called a signature of AD, a prognostic score of whether a normal elderly subject would develop MCI or whether the MCI patient would progress to AD. The earliest detectable changes in preclinical AD were discussed to be CSF values of both A 42 (or various A ratios) and tau, PET imaging of tau protein and amyloid fibrils [17, 18, 34]. Decreased CSF A 42 and increased tau protein findings were first defined as an AD signature and both included in the IWG criteria (discussed earlier) [40, 124, 203]. Their prognostic potential is widely acknowledged for both MCI progression to AD and AD detection: combined values of CSF markers yield an even higher accuracy [17, 118, 124, 204]. CSF A , but not tau, however, received more approval for preclinical stages of AD [17]. The CSF signature of A and tau is especially useful when PET or MRI imaging (alone or combined as well) is included [17, 205, 206]. For instance, combined with CSF biomarkers, MRI might increase the likelihood of detecting MCI or AD and of determining MCI progression to AD (up to four times more than one of the markers alone, with 85% sensitivity, 96% specificity for progression to AD), thus the combination of these findings has much potential for early AD diagnosis, bearing in mind that specific changes of both biomarkers emerge during the preclinical stages of AD [113, 207–211]. PET is also noteworthy due to the selective binding of its tracers to amyloid fibrils (11C-PIB and others) or visual insight into brain metabolism (with FDG); PET is found to be associated with decreased A levels in the CSF, good, but not perfect agreement between these tests is found, they are useful to discriminate patients with MCI or AD and could serve in preclinical stages of AD as the biomarker values of these tests are found to be elevated even before changes on MRI or a noticeable cognitive decline [113, 149–152, 212–215]. Genetic testing alone is rarely useful, but might accompany the tests mentioned above: cognitive testing to predict MCI progression or cerebral metabolism studies for MCI or AD evaluation. The latter are, like most of the biomarkers, more reliable with cognitive testing (an increase from 65% (neuropsychological testing alone) and 75% (glucose metabolism alone) to 90% accuracy, when neuropsychological and brain glucose metabolism were measured together) [172, 216–218]. Genetic markers (allele APOE- 4, for instance) are observed to be ubiquitously used with CSF markers in research trials [219, 220].

Novel proposals for creating criteria of a preclinical or early AD diagnosis arise. Jack et al. described a system with 3 binary criteria each with either a positive or a negative score that is assigned after choosing an appropriate cutoff value: A (A 42 decreased in CSF or increased amyloid tracer retention in PET), T (p-tau, either in CSF or PET) and N (neurodegeneration, either t-tau in CSF, reduced metabolism in FDG-PET, or structural MRI, avoiding the use of more than one of these markers due to lower correlation) [221]. As a new classification scheme ("ATN"), it correlates poorly with IWG or NIA-AA criteria. On the other hand, it represents a way to determine likely MCI or AD without cognitive evaluation, thus helping researchers work with subjects in potentially preclinical stages of AD [221, 222]. Such combinations of biomarkers should become valuable in the future if more of their statistical relations were revealed and some tests reached next phases of approval (FDG PET, for example, which could be expected to move to phase 4 after sufficient phase 2 and 3 completion) [42].

FUTURE DIRECTIONS

As discussed above, new information about biomarkers for MCI and AD emerge continuously. From our overview, it becomes apparent that rarely does a single biomarker show extensively promising results in diagnosing MCI and AD in their earliest stages, and a combination of several tests is required as well as SOPs for standardized biomarker use, and HarPs for imaging studies. The Alzheimer's Disease Neuroimaging Initiative (ADNI), a long-term study initiative with investments of over $134 million between 2004–2016, shows promising harmonization of various imaging procedures (for example, in hippocampal volumetry) [223, 224]. ADNI has also included a potential scheme for drug development: they propose CSF A measures in phase I trials, CSF tau or A measures, amyloid imaging, FDG PET and MRI in phase II trials, and MRI (highly encouraged), CSF tau or A , PET imaging for phase III trials [225]. Biomarkers, therefore, are being employed in clinical research, but as no disease modifying therapy is currently available, the use of biomarkers in a clinical setting is quite limited due to risk and cost factors; non-invasive procedures and cognitive evaluations should be broadly used in our opinion, but CSF testing should be regarded with care, especially until SOPs are universally applicable and serve research as well as clinical diagnostics. Due to difficulties finding an exact number of well-defined etiological factors, H. Hampel et al. suggest regarding Alzheimer's disease from the viewpoint of systems biology, where interactions causing the disease are considered as one complex mechanism [226]. Being such a multi-step process, Alzheimer's disease could be detected at different stages of its progression, so contexts of use for biomarkers should also be considered. For example, blood biomarkers or those of other metabolites could be employed in the first steps of a diagnostic approach, while more invasive or expensive methods could be employed subsequently. By using metabolomic databases and computer learning systems, one could create a signature with many combinations of phenotypic markers, defining MCI or AD and then use these profiles to predict these disorders in research subjects or patients [226]. During creation of such MCI or AD signatures, imaging studies, CSF and blood analyses, discussed in this article, could be included.

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BIOMARKERIŲ NAUDOJIMO ANKSTYVŲ ALZHEIMERIO LIGOS STADIJŲ DIAGNOZEI IR TYRIMAMS APŽVALGA

Santrauka

Per kelis ateinančius dešimtmečius Alzheimerio liga (AL), tikėtina, taps ne tik masiška sveikatos, bet ir didžiule ekonomine bei socialine problema, todėl reikalingas nuoseklus šios ligos suvokimas. Mokslininkai ir medicinos specialistai šiam tikslui galėtų pasitelkti biomarkerius – kiekybiškai įvertinamas medžiagas arba ligai būdingus bruožus, kuriuos naudojant būtų galima prognozuoti būsimą arba diagnozuoti esamą AL. Tikimasi, kad, remiantis biomarkerių rodikliais, bus galima plėtoti tyrimus, siekiant geriau suprasti AL mechanizmą, sukurti ligą modifikuojantį gydymą, modeliuoti naujus klinikinius ir mokslinius AL diagnozės kriterijus ankstyviausioms ligos stadijoms. Šios apžvalgos tikslas – aptarti esamas gaires klinikiniam ir moksliniam biomarkerių naudojimui, pristatyti kognityvinius ir uoslės testus, susijusius su AL, plačiai žinomus AL biomarkerių testus: smegenų skysčio (SS) ėminius, magnetinio rezonanso tomografiją (MRT), pozitronų emisijos tomografiją (PET), vieno fotono emisijos kompiuterinę tomografiją (SPECT), kraujo plazmos, seilių ėminius. Galiausiai, apsvarstoma potenciali biomarkerių įtaka mokslo ir sveikatos apsaugos sritims, susijusioms su AL, ateityje ir AL profilio kūrimo galimybė.

Raktažodžiai: Alzheimerio liga, lengvas kognityvinis sutrikimas, kognityvinių funkcijų prastėjimas, biomarkeriai, smegenų skystis, beta amiloidas.

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