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Biomarkers of Alzheimer's disease: Past, present and future clinical use

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disease and the leading cause of dementia worldwide. AD is associated with several neuropathologic changes including the progressive accumulation of extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tau tangles, neuroinflammation, cerebral small vessel disease and neurodegeneration, many of which are known to begin years before the onset of clinical symptoms. As such, there is a growing interest in developing biomarkers that can be used to detect these changes in the brains of at-risk individuals to facilitate earlier and more accurate diagnosis. This may allow for earlier intervention with disease-modifying therapies to slow the progression of irreversible neurodegeneration and improve quality of life. The current review seeks to provide a concise overview of the neuropathology and genetics underlying AD, and then summarize the most promising clinically available and experimental biomarkers of AD. These include structural neuroimaging, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), cerebrospinal fluid (CSF), and blood-based assays. Multiple potential clinical uses for these biomarkers are then described, including screening at-risk populations for disease, aiding in differential diagnosis of dementia and mild cognitive impairment (MCI), monitoring the impact of lifestyle intervention and disease modifying therapies, identification and treatment of neuropsychiatric symptoms of dementia, and aiding in planning for end of life care. Finally, additional areas of future research are discussed, including replication of biomarker studies in more diverse patient cohorts, characterization of real-world clinical and psychological impacts of biomarker testing, as well as novel biomarkers currently under investigation.

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease and the leading cause of dementia worldwide (World Health Organization, 2021). While the clinical diagnosis of AD is defined by marked and gradually progressive cognitive and functional decline, neuropathologic changes in the brain are known to begin long before the onset of symptoms. While the exact pathophysiology underlying disease progression remains unknown, plaques and tangles have come to biologically define AD (Jack et al., 2018). First described in 1906 by Alois Alzheimer who noted distinctive plaques and neurofibrillary tangles in the brains of affected individuals (Hippius and Neundörfer, 2003), there has since been substantial research indicating that these changes are driven by extracellular aggregation of misfolded Aβ and intracellular deposition of hyperphosphorylated tau proteins (Scheltens et al., 2016; Zetterberg and Mattsson, 2014). Ongoing research efforts seek to elucidate other biological underpinnings of the disease, such as neuroinflammation, metabolic dysfunction and cerebrovascular dysfunction (Mahaman et al., 2022).

Given the rapid advancements in positron emission tomography (PET), whole exome sequencing, label-free proteomics and multiplex immunoassays, there has been a growing movement to establish biological targets, or biomarkers, that can help to characterize AD risk, diagnose and monitor disease progression (Jack et al., 2018). An ideal biomarker is cost effective, non-invasive, reproducible, accessible, and able to identify patients at early stages of disease. Biomarker analysis aids in detecting preclinical phases of disease and developing novel targets for disease modifying therapies. Together, these features may

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allow for personalized interventions to slow disease progression prior to the development of irreversible neurodegeneration and cognitive/-functional decline (Blennow et al., 2010; Mahaman et al., 2022). To this end, the National Institute on Aging (NIA) and Alzheimer's Association (AA) created a research framework for establishing biomarkers in AD. The NIA-AA Amyloid/Tau/Neurodegeneration (ATN) Criteria classifies these biomarkers into three basic components which can be used together to stage disease in living persons: Aβ plaque deposition, pathologic tau accumulation, and neurodegeneration (Jack et. al., 2018). Biomarkers corresponding to these categories will be discussed throughout this review (*see examples* in Table 1; Fig. 1).

With quickly rising disease prevalence and corresponding economic burden, AD has been deemed a global health crisis soon to affect up to 139 million people worldwide by 2050 (World Health Organization, 2021). By aiding in early detection, biomarkers will likely play a critical role in ensuring the success of future treatments, as several clinical trials have shown limited clinical benefit when experimental treatments are used after the accumulation of several insults (Morris and Selkoe, 2011; Salloway et al., 2014; Sperling et al., 2011). Given the relentless nature of the disease and the limited potential treatment window, we must continue to research biological targets and develop reliable, low cost and accessible biomarkers to detect AD in larger numbers of people and at earlier stages of disease. The current review seeks to provide a broad overview of the landscape of AD biomarkers research, with an emphasis on biological targets of disease modifying therapies and novel, promising biomarkers.

2. Genetics

Genetic risk factors of AD have been well established and have been used for stratification of low and high-risk groups in research trials. The apolipoprotein (*APOE) ε4* allele is known to confer increased risk of AD while the *APOE ε2* allele has demonstrated protective benefit (Liu et al., 2013). While genetics can be used to identify risk of disease occurrence, and be a factor in future treatment dosing, they are not a measure of AD neuropathological change. As a result, *APOE* is not considered a true biomarker of AD, as outlined in the ATN criteria (Jack et al., 2018). *APOE* status has proved useful in stratifying results in the biomarker studies discussed in this review, and has also demonstrated utility in aiding in biomarker interpretation by identifying populations with high disease prevalence. Polygenic profiling, which leverages multiple single nucleotide polymorphisms (SNPs) from genome-wide association studies, is also useful for characterizing AD risk; however, the field still lacks consensus on how best to standardize polygenic risk score (PRS) calculation methodology (Leonenko et al., 2021).

Table 1
Examples of biomarkers of cerebral amyloidosis.

Assay	Population	Sensitivity (%)	Specificity (%)	Reference
PET Imaging				
Florbetapir	Mixed	92	91	(Camus et al., 2012; Morris et al., 2016)
Flumetamol	Mixed	93	69	(Morris et al., 2016; Vandenberghe et al., 2010)
CSF Immunoassays				
P-tau217	Dementia	91	91	(Janelidze et al., 2020a)
Aβ42/40	SCD, MCI	97	88	(Janelidze et al., 2016a)
Plasma Immunoassays				
P-tau217	SCD, MCI	62	93	(Palmqvist et al., 2020)
Aβ42/40	SCD, MCI	72	65	(Verberk et al., 2020)
GFAP	SCD, MCI	75	69	(Verberk et al., 2020)
NfL	SCD, MCI	16	83	(Palmqvist et al., 2020)

Representative studies examining diagnostic utility of PET, CSF and plasma biomarkers. SCD: Subjective cognitive decline; MCI: Mild cognitive impairment. Mixed studies included healthy individuals and individuals with dementia in addition to SCD/MCI.

3. Neuroimaging

In the past, a post mortem neuropathological examination was required for a definitive diagnosis of AD using the Montine Scoring Criteria, which encapsulates Aβ burden, the Braak Staging Scheme for neurofibrillary degeneration and The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scoring for neuritic plaques (Braak et al., 2006; Mirra et al., 1991; Montine et al., 2012). While neuropathology remains the gold standard for a definitive diagnosis of AD, with the advancement of neuroimaging, we can begin to assess cases in vivo. Several modalities have been researched, including Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), which are reviewed below.

3.1. Structural MRI

AD is associated with a number of structural changes in the brain which are able to be visualized using standard MRI techniques and have been relatively well documented in the literature. Neurodegeneration, and thus cerebral atrophy, is most prominent in the hippocampus and entorhinal cortex, which are often the first brain regions affected in AD and thought to be responsible for the characteristic impairments in short-term and working memory observed in early-stage disease (Basaia et al., 2019; Blumenfeld, 2021; Devanand et al., 2007). The degree of atrophy in the medial temporal lobe is highly correlated with patient scores on cognitive testing, such as the Mini-Mental State Examination (MMSE), and thus thought to be associated with disease progression (Scheltens et al., 1992; Wei et al., 2019). Medial temporal atrophy has also been used to help predict the conversion of mild cognitive impairment (MCI) to dementia (Visser et al., 2002), and may be more specific to AD than other neuroimaging changes such as lateral ventricle volume (Scheltens et al., 1992, 2020). As neurodegeneration progresses to include other cortical structures, enlargement of the lateral ventricles can be seen in later stages of disease (Nestor et al., 2008). Structural MRI can also be used to help differentiate AD from other etiologies, including vascular dementia, based on the typical pattern of brain atrophy, including medial temporal lobe atrophy (Burton et al., 2009; Frisoni et al., 2010). For example, AD has more pronounced atrophy in the medial temporal lobe compared to dementia with lewy bodies (DLB) (Tam et al., 2005). A deep learning algorithm using convolutional neuronal networks has also been used to both diagnose AD and predict conversion of MCI to AD (Basaia et al., 2019).

While structural imaging can be used to aid in diagnosis when taking clinical presentation into account, one limitation is that it requires there to be structural evidence of neurodegeneration at the time of diagnosis. This somewhat limits its clinical utility in the initial work-up of MCI, since atrophy may not be present during these earlier/prodromal stages. Since treatment efforts for AD aim to target earlier prodromal stages of disease to prevent these irreversible changes, alternate biomarkers should also be considered for early intervention with disease-modifying treatments.

3.2. Diffusion Tensor Imaging (DTI)

DTI is an MRI technique used to measure white matter tracts via water molecule diffusion. The directionality of diffusion allows for better understanding of tracts and specific fiber bundles affected by neurodegeneration. Mean diffusivity (MD) and fractional anisotropy

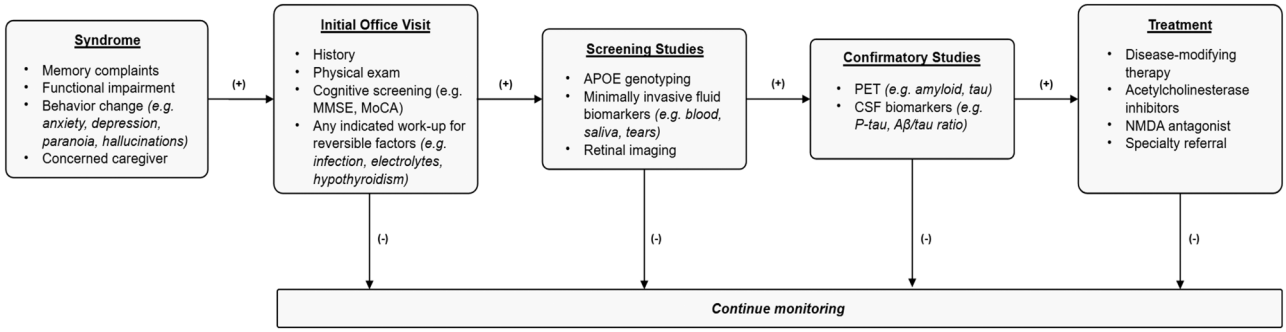

Fig. 1. Example of biomarker-informed diagnosis and treatment of AD. Biomarkers may soon be available in clinical practice to work-up patients in the primary care setting. Following the initial office visit, the treating physician could order a low-burden screening test (or panel of tests), which, if positive, may lead to additional confirmatory testing and treatment of AD. Patients with negative results should continue to be monitored for any change in clinical condition, with potential need for repeat testing at a later time.

(FA) are major measures of DTI. Increased MD has been consistently found within the literature in areas of known neurodegenerative changes in AD, including the hippocampus, the entorhinal cortex, parahippocampal gyrus, temporo-parietal association cortex, and posterior cingulate gyrus (Fellgiebel et al., 2004, 2005; Firbank et al., 2007; Kantarci et al., 2010; Medina et al., 2006; Oishi et al., 2011; Rose et al., 2008; Magalhães et al., 2023). Use of DTI has enabled better understanding of patterns of white matter and gray matter changes in AD, and a more in-depth review of studies utilizing DTI to help better understand MCI to AD progression and changes in the brain was done by Talwar et al. (2021).

Characteristic changes in areas can assist in differentiating AD from other dementias including DLB and frontotemporal dementia (FTD) using DTI (Firbank et al., 2016; Oishi et al., 2011; Zhang et al., 2009). A recent study has explored if the degree of white matter integrity measured by DTI correlates with executive function (Mayo et al., 2019). While there was an association, there was not a significant linear relationship between cognitive functioning as measured by select neuropsychological testing and degree of white matter disruption (Mayo et al., 2019). More work is needed to establish its use as a diagnostic biomarker to discriminate AD from other neurodegenerative processes.

Applications in clinical practice using DTI to diagnose AD have yet to be demonstrated, and in larger scale biomarker studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), they have chosen not to incorporate DTI (Oishi et al., 2011). A recent smaller scale study using DTI explored associations between CSF biomarkers and hippocampal volume in hopes of better understanding the underlying pathology of AD dementia (Magalhães et al., 2023). The study found significant correlation between white matter tracts and p-tau and t-tau. The higher MD in the right cingulum hippocampus and the lower FA in right fornix are both associated with increasing levels of t-tau; however, not with $A\beta_{42/40}$ (Magalhães et al., 2023). While promising, there are still limitations on use of DTI alone to serve as biomarker. DTI also is not clinically accessible, as it is not reimbursable, and thus limited to use in research settings. Other limitations include longer scan times than other modalities, which can both decrease accessibility to patients and increase chance for movement during the scan leading to artifact.

3.3. Functional MRI (fMRI)

In contrast to structural MRI, fMRI measures changes in blood flow in different areas of the brain, which can be used as a proxy for neuronal activity. In research studies, measurements like blood-oxygen-level dependent (BOLD) signal can be taken at rest (imaging of the default mode network [DMN]), and while participants are doing a cognitive task to detect changes in neuronal activity across groups. Relative to healthy controls, patients with both AD and MCI demonstrate decreased connectivity in the DMN, which is associated with memory and processing (Damoiseaux et al., 2012; Mahaman et al., 2022; Zhu et al., 2013). In earlier stages of disease, there are fewer changes in connectivity among DMN structures (Das et al., 2013; Mahaman et al., 2022; Yu et al., 2017). The utilization of machine learning to help detect earlier phases of disease has had conflicting results within the literature (Nicholas et al., 2022; Odusami et al., 2021). However, use of structural MRI in combination with resting-state fMRI has shown promise for being able to detect MCI that is more likely to convert to dementia (Khatri and Kwon, 2022). Further utilization of multiple functional neuroimaging biomarkers of disease may be the most promising approach moving forward. Overall, fMRI is a noninvasive and relatively safe technique, yet still may present a barrier for patients, due to lack of accessibility to imaging centers and time required for testing while in the scanner.

3.4. PET

PET is an imaging modality that allows for in vivo measurement of disease pathology using ligands to identify compounds of interest, such as neurofibrillary tangles and Aβ plaques. While PET imaging shows much promise, there is a high barrier to care at this time. Imaging is very costly and is typically an out-of-pocket cost to patients, however this hopefully will change with advancements in novel treatments. There is also the downside of radiation exposure and potential for toxicity with injection of radioligands, which may further limit their usefulness as a broad screening modality for AD, or for cases where serial monitoring may be preferable for surveillance of disease progression. PET scanners are also not readily available or accessible, particularly in rural areas or developing countries.

3.4.1. FDG-PET

The use of ^{18}F-fluorodeoxyglucose (FDG-PET) allows researchers to estimate glucose metabolism in different areas of the brain and identify which areas may have higher or lower metabolic activity. FDG-PET shows a characteristic pattern of temporoparietal hypometabolism in patients with AD (Nestor et al., 2003). Additionally, in both patients with dementia due to probable AD and amnestic MCI, there was an observed reduction of metabolism in the posterior cingulate cortex and precuneus (Minoshima et al., 1997). This deficit is thought to be related to observed episodic memory deficits. FDG-PET has been utilized to help differentiate AD dementia from healthy controls (AUC 0.93) with improved accuracy when use in combination with DTI measures (AUD 0.96) (Li et al., 2022a). In addition, FDG-PET findings also allow AD to be differentiated from similar disease states like DLB and FTD (Mahaman et al., 2022; Mosconi et al., 2008) and TDP-43 proteinopathy (Grothe et al., 2022).

3.4.2. Amyloid and tau ligands

In AD, there is increased amyloid tracer binding in areas known to be

affected by the disease (temporal parietal and frontal regions) (Jack et al., 2018; Mahaman et al., 2022). Multiple tracers have been developed to help assess amyloid burden (see examples in Table 1). Pittsburgh Compound B (PiB) was one of the first PET radiotracers shown to bind to misfolded amyloid plaques and help to map the distribution of amyloid and quantify amyloid burden (Jack et al., 2018; Mahaman et al., 2022). Limitations of PiB include challenges in producing the tracer and its short half-life. Numerous other amyloid PET tracers have since been developed, including some that may have greater sensitivity to preclinical disease (Rowe et al., 2016). Florbetapir is a FDA approved compound that binds to amyloid aggregates in the brain. Research of this compound has shown that a negative scan can reliably rule out disease at that time and a positive scan (Yang et al., 2012). Other FDA approved Aβ tracers include ^{18}F-labeled flutemetamol, and ^{18}F-labeled florbetaben. Amyloid PET has been instrumental to screening for secondary prevention drug trials, as well as a key tool for characterizing and monitoring treatment effects in trials for disease modifying therapies (ten Kate et al., 2018; Salloway et al., 2014). While useful for confirmatory diagnosis, use of amyloid PET in clinical settings is limited by cost as well as low positive predictive value (PPV) (Mahaman et al., 2022; Pearson et al., 2014). The Imaging Dementia - Evidence for Amyloid Scanning (IDEAS) study enrolled Medicare beneficiaries with MCI or dementia of uncertain etiology to investigate the impact of the scan results on diagnosis and treatment. The study found that use of this imaging modality was associated with changes in clinical management, yet it remains unclear if the scan led to improved clinical outcomes (Rabinovici et al., 2019). A New IDEAS study is now underway to further investigate the diagnostic utility of amyloid PET scans in diverse populations with MCI and dementia. Currently, aducanumab and lecanemab are the only FDA-approved compounds for which use of amyloid PET scans could impact treatment course. Imaging or other biomarker testing to accurately identify elevated cerebral amyloid will be a critical step in determining whether there is sufficient precedent for the use of these new therapies. More research is needed along with development of more treatments that impact other aspects of AD etiology.

As several clinical trials with treatments focused on amyloid pathology have failed, many sought to develop treatments targeting neurofibrillary tangles (NFTs), another hallmark of AD. NFTs are composed of hyperphosphorylated tau proteins. Several tracers have demonstrated the ability to view this pathology in vivo to help assess disease progression (Mahaman et al., 2022; Okamura et al., 2014). Use of these tracers also can assist in determining efficacy of novel medication under investigation that target tau pathology of AD. In a comparative study, tau radiotracers had higher sensitivity for earlier detection of disease in comparison to amyloid PET radiotracers (Mahaman et al., 2022; Ossenkoppele et al., 2019). Other studies have shown tracking progression of disease is improved when both tau and amyloid tracers are utilized (Firouzian et al., 2018; Koychev et al., 2017; Mahaman et al., 2022).

3.4.3. *Neuroinflammatory ligands*

Neuroinflammatory cascades leading to increased microglial activation occur as part of underlying pathophysiology of AD (Dupont et al., 2017; Heneka et al., 2015; Mahaman et al., 2022) and are thought to occur at earlier stages of disease (Hamelin et al., 2016; Mahaman et al., 2022; Yasuno et al., 2012). Establishing biomarkers of these cascades has potential to aid early diagnosis of AD. Radiotracers that bind to translocator protein-18 kDa (TSPO) have been used as a biomarker of the neuroinflammatory cascades seen in AD (Mahaman et al., 2022). TSPO is a peripheral benzodiazepine receptor on the mitochondrial membrane. Increased expression of TSPO is used as an estimate for increased inflammation, as expression is upregulated by activated microglial cells (Dupont et al., 2017; Mahaman et al., 2022; Papadopoulos et al., 2006). Studies in AD patients have found TSPO expression increased relative to healthy controls (Dupont et al., 2017). In addition, the data on correlation between TSPO and CSF biomarkers of neuroinflammation are mixed, with one study finding a significant association (Melah et al., 2016), but this was not replicated (Dupont et al., 2017). This may be in part explained by the lack of specificity of TSPO for brain-derived microglia; reactive astrocytes and infiltrating macrophages also have increased expression and may not be able to distinguish between this and microglial TSPO expression (Wilms et al., 2003, Winkeler et al., 2010). Further studies looking to modify TSPO ligands and develop new radiotracers may help to improve specificity of TSPO for microglial activity, although it is unclear whether this will translate to better performance for detecting AD-related inflammation (Mahaman et al., 2022; Narayanaswami et al., 2018).

4. Cerebrospinal fluid (CSF)

CSF analysis can be utilized to aid in the diagnosis, monitoring, and clinical treatment of AD (Table 1; Bouwman et al., 2022; Jack et al., 2018; Mahaman et al., 2022). Unlike imaging biomarkers described in the previous section which help assess accumulation in the brain, CSF biomarkers give information on protein production and clearance (Jack et al., 2018). Core proteins used in analysis are total tau (t-tau), phosphorylated tau (P-tau), and Aβ_{42} (Bouwman et al., 2022; Jack et al., 2018; Mahaman et al., 2022). Many of these biomarkers have been studied against imaging modalities described in the previous section (Bouwman et al., 2022; Jack et al., 2018). CSF biomarker changes may be appreciated earlier than PET-tracer markers however (Bouwman et al., 2022; Meyer et al., 2020). CSF also allows for analysis of multiple markers of CNS disease simultaneously, which is a benefit over imaging studies. Other biomarkers are under investigation that focus on neuroinflammation, synaptic dysfunction and glial activation, including neurofilament light chain (NfL) and glial fibiliary acid protein (GFAP) (Jack et al., 2018; Mahaman et al., 2022; Ott et al., 2018). Other promising biomarkers include neurogranin, SNAP-25 and YKL-40 are further described elsewhere (Jack et al., 2018; Mahaman et al., 2022; Ott et al., 2018).

Use of CSF analysis is not without potential downsides. While relatively safe, lumbar puncture (LP) is perceived by many patients as an invasive procedure, which may deter some. Most common side effects of LP include headache and back pain (Bouwman et al., 2022). Rarely, more severe side-effects can occur, which include infection, spinal and subdural cerebral hematoma and cerebral venous thrombosis (Blazel et al., 2020; Bouwman et al., 2022; Cognat et al., 2021; Engelborghs et al., 2017; Monserrate et al., 2015). Use of PET imaging in conjunction with CSF analysis may be useful in some cases, particularly as CSF findings can be similar across different pathologies (Bouwman et al., 2022).

Aβ_{42} and Aβ_{40}*:* In AD, Aβ is sequestered in the brain in plaques. As a result, there is less soluble protein in the extracellular fluid, and thus lower levels detected in CSF (Andreasen et al., 1999; Mahaman et al., 2022). Research has demonstrated a correlation between higher plaque burden in the brain and lower CSF Aβ_{42} and Aβ_{40} levels (Mahaman et al., 2022; Strozyk et al., 2003). This finding can also be seen in other neurodegenerative processes, including amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease (CJD), and multiple system atrophy (Holmberg et al., 2003; Mahaman et al., 2022). The A$\beta_{42/40}$ ratio can be used to aid in differentiation between AD and other forms of dementia, including vascular dementia and DLB (Bouwman et al., 2022; Mahaman et al., 2022; Nutu et al., 2013; Struyfs et al., 2015). In addition, the ratio has an increased predictive value for MCI conversion to AD than just Aβ_{42} alone (Baldeiras et al., 2018; Mahaman et al., 2022). This ratio may also correct for the normal variance between individuals in Aβ levels (thought to be related to systemic clearance of protein) (Bouwman et al., 2022; Hansson et al., 2018).

4.1. *Tau*

T-tau is generally considered a biomarker of neuronal injury and

neurodegeneration, as it is a normal component of the intracellular neuronal architecture that is released into the extracellular fluid during the process of cell death (Jack et al. 2018). CSF levels of t-tau and P-tau are increased in AD, with the abnormally phosphorylated P-tau perhaps being a more specific marker for AD than t-tau (Bouwman et al., 2022; Mahaman et al., 2022). As neurodegeneration and neuronal injury occur prior to clinical symptoms of AD (Bouwman et al., 2022; Luo et al., 2020), they may be used for earlier diagnosis of disease. Tauopathy is also seen in other pathologies, such as stroke and CJD (Mahaman et al., 2022; Mattsson, 2011), as a result, its use as a stand-alone biomarker in diagnosis is limited. Measurement alongside other AD-specific biomarkers can help differentiate AD from FTD and DLB (Hampel et al., 2004; Mahaman et al., 2022). Furthermore, continued research is being conducted for more precise tau biomarkers focused on specific patterns of phosphorylation (reviewed further in the Blood Biomarkers section).

4.2. Amyloid and tau ratios

Both the sensitivity and specificity of AD diagnosis is higher when tau and amyloid markers are used in combination (Blennow & Hampel, 2003; Bouwman et al., 2022; Mahaman et al., 2022). Studied CSF biomarker ratios include P-tau/Aβ_{42}, t-tau/Aβ_{42} as well as A$\beta_{42/40}$ (Bouwman et al., 2022). Ratios are more specific to AD and can help differentiate from other pathologies (Mahaman et al., 2022; Bouwman et al., 2022). In particular, the P-tau181/Aβ_{42} ratio better differentiates AD from FTD as well as other non-AD dementias than either measurement alone (Bouwman et al., 2022; Ortner et al., 2022; Santangelo et al., 2019). CSF ratios may also be used to predict conversion of MCI to AD (Blennow et al., 2019; Bouwman et al., 2022; Buchhave et al., 2012; Mahaman et al., 2022; Struyfs et al., 2015).

4.3. NfL

NfL is an axonal scaffolding protein which is widely distributed in the CNS and may prove useful as a biomarker of AD (Gafson et al., 2020). NfL has been studied as a potential dynamic, cross-disease biomarker of increased neuronal turnover that is observed in acute brain injury as well as primary neurodegeneration, as it is released into the extracellular fluid during cell death (Bridel et al., 2021; Khalil et al., 2018). Clinically, NfL can be readily detected in CSF using immunoassays (Norgren et al., 2002), and while levels do increase with aging, further elevations have been observed in a variety of neurodegenerative diseases including multiple sclerosis, ALS and AD (Rosengren et al., 1996; Lycke et al., 1998; Bridel et al., 2019). This lack of specificity limits its utility as a definitive diagnostic test for AD, it can provide important information about the rate of neurodegeneration in affected individuals (Zetterberg et al., 2016; Bridel et al., 2019). This notion is supported by the finding that elevated CSF NfL concentrations are observed in early-onset AD and correlates with cortical volume loss (Contador et al., 2021). Furthermore, NfL positively correlates with MCI to AD progression and faster brain atrophy over time, suggesting that it may be a useful measure to monitor disease progression in affected individuals (Zetterberg et al., 2016).

4.4. GFAP

Reactive astrogliosis has been thought to be part of the pathogenesis of AD, and is associated with neuroinflammation as well as extracellular fibrotic changes, both of which may occur in response to brain aging and neurovascular injury in AD (Garwood et al., 2017). GFAP, a major cytoskeletal constituent of astrocytes which increases in response to inflammation, has been studied as a potential biomarker of AD, with a recent meta-analysis finding that CSF GFAP concentrations were higher in both early-onset and late-onset AD patients compared to healthy controls (Bellaver et al., 2021). A subsequent longitudinal study found that GFAP levels were elevated across the symptomatic continuum of AD, including preclinical, MCI and dementia phases compared to Aβ-negative controls (Benedet et al., 2021). However, like with NfL, reactive astrocytosis is not specific to AD and is implicated in pathogenesis of other disease states, including other forms of dementia like FTD, DLB, and Parkinson's disease (Oeckl et al., 2019; Benussi et al., 2020b; Heller et al., 2020).

5. Blood-based biomarkers

Blood based biomarkers for AD are perhaps the most promising for widespread clinical use, as they present a relatively accessible and minimally invasive approach to assessing disease state in both tertiary and non-tertiary care settings. Relative to other approaches like CSF analysis and imaging, they are lower in cost and less time intensive. With advancement in biochemical analysis technologies, like ELISA, Electrochemiluminescence immunoassays (Mesoscale Discovery), single molecule array (Simoa), and mass spectrometry, research findings have been more promising (Teunissen et al., 2022). While there have been numerous blood-based biomarkers tested, the main biomarkers of current interest are Aβ, tau, neurofilament light chain (NFL) and glial fibrillary acid protein (GFAP) (Table 1; Teunissen et al., 2022).

5.1. Aβ isoforms

Early research using amyloid markers had variable findings (Blennow et al., 2010; Mahaman et al., 2022; Mayeux and Schupf, 2011) and a 2016 meta-analysis showed no difference in plasma Aβ_{42} and Aβ_{40} relative to healthy controls (Olsson et al., 2016; Teunissen et al., 2022). Variability has been attributed to the fact that Aβ peptides exist in the peripheral tissues and that it may bind to plasma proteins, interfering with measurements (Kuo et al., 1999; Mahaman et al., 2022; Teunissen et al., 2022). More recent studies that utilize more sensitive technology, including mass spectrometry and automated ultrasensitive immunoassays, have demonstrated more consistent results (Teunissen et al., 2022). Keshavan et al. (2021) used population-based British 1946 (age 70) cohorts to compare liquid chromatography-mass spectrometry measure of plasma *Aβ,* Simoa measure of *Aβ* and Simoa measure of P-tau181 as predictors of *Aβ*-PET status. They found that mass spectrometry *Aβ$_{42/40}$* outperformed the base model (which includes prediction based on age, *APOE* genotype, and sex alone) while the other modalities did not. Studies have used CSF *Aβ* and *Aβ* PET measures to validate findings of decreased levels of plasma *Aβ* as a diagnostic marker for AD (Olsson et al., 2016; Ovod et al., 2017; Nakamura et al., 2018; Teunissen et al., 2022). Like with CSF analysis, the A*β$_{42/40}$* ratio has been used as a measure and has suggested that higher ratios have an 82–97% accuracy of diagnosing AD (Ovod et al., 2017; Nakamura et al., 2018; Schindler et al., 2019; Kehavan et al., 2021; West et al., 2021; Teunissen et al., 2022). Studies have also utilized *APOE* status to stratify patients and found use of stratification has improved accuracy (Chatterjee et al., 2021; De Meyer et al., 2020; de Rojas et al., 2018; Janelidze et al., 2016b; Keshavan et al., 2021; Verberk et al., 2018; Vergallo et al., 2019; Li et al., 2019; Verberk et al., 2020; Palmqvist et al., 2019; Risacher et al., 2019; West et al., 2021; Teunissen et al., 2022). A recent 2022 study by Li et al. utilized high precision immunoprecipitation mass spectrometry (IPMS) to assess the Aβ42/40 ratio. The AUC of plasma Aβ42/40 to predict CSF amyloid status was 0.85 (95% CI 0.78–0.91) and improved to 0.93 (95% CI 0.89–0.97) when stratified by APOE ε4 status (Li et al., 2022b). There are now also commercially available tests that use a combination of A*β$_{42/40}$* ratio and *APOE* genotype to create an amyloid probability score to aid in diagnosis (West et al., 2021). The score is predictive for whether a patient will test positive on *Aβ*-PET, with AUC 0.9 and a diagnostic accuracy of 86% for amyloid status (West et al., 2021). While the test is available, the assay requires costly mass spectrometry analysis and is not yet covered by insurance, with a list price of $1250, which is limiting. Furthermore, the ability of such testing to differentiate AD from non-AD dementia needs to be further

investigated (Teunissen et al., 2022).

5.2. Tau

Like *Aβ,* early studies showed that tau markers have low diagnostic value with variable findings across studies (Mahaman et al., 2022; Teunissen et al., 2022). Tau is perhaps a more challenging target as there are more than 70 post translational modification sites and over 40 distinct phosphorylation sites, in addition to truncated forms of the protein (Teunissen et al., 2022; Wesseling et al., 2020). More specific phosphorylated isoforms of the protein, including P-tau181, P-tau217 and P-tau231, have shown promise for predicting and measuring disease severity, as all are significantly elevated in AD patients compared to controls (Ashton et al., 2021a; Barthélemy et al., 2020; Brickman et al., 2021; Palmqvist et al., 2020; Teunissen et al., 2022). Furthermore, unlike the $A\beta_{42/40}$ ratio, levels increase with disease progression (Mattsson-Carlgren et al., 2020). As with *Aβ,* levels have been validated against tau-PET and *Aβ*-PET studies (Barthélemy et al., 2020a; Barthélemy et al., 2020b; Brickman et al., 2021; Janelidze et al., 2020b; Mielke et al., 2018; Teunissen et al., 2022; Thijssen et al., 2021). In addition, more specific isoforms have shown promise in differentiating between non-AD dementia and AD (Ashton et al., 2021a; Barthélemy et al., 2020; Benussi et al., 2020a; Brickman et al., 2021; Janelidze et al., 2020a; Karikari et al., 2020; Mielke et al., 2018; O'Connor et al., 2021; Palmqvist et al., 2020; Simren et al., 2020; Teunissen et al., 2022; Thijssen et al., 2020).

As the research has evolved, focus has shifted to finding an isoform target that is most specific to AD and can aid in earlier diagnosis. Both P-tau217 and P-tau181 perform well against other modalities, including neuropathological examination, as well as tau-PET and *Aβ*-PET (Barthélemy et al., 2020a; Barthélemy et al., 2020b; Brickman et al., 2021; Thijssen et al., 2021; Janelidze et al., 2020a; Teunissen et al., 2022). Relative to P-tau181, P-tau217 may be better able to predict positivity when using mass spectrometry approaches and has a strong association with tau-PET (Janelidze et al., 2020a). In studies of autosomal dominant forms of the disease, P-tau217 levels have been detected 20 years prior to symptom onset and prior to changes seen using tau-PET (Janelidze et al., 2021; Teunissen et al., 2022). Relative to P-tau181, P-tau231 performs similarly in differentiating AD from non-AD pathology (Ashton et al., 2021a; Teunissen et al., 2022). However, P-tau231 changes may occur earlier relative to P-tau181 based on both *Aβ*-PET and tau Braak stages (Ashton et al., 2021a), but this finding was not replicated in another study (Mielke et al., 2021; Teunissen et al., 2022).

One study conducted by Palmquist et al. (2021) investigated plasma tau using participants enrolled in either The Swedish BioFINDER-2 Study (BioFINDER-2) or ADNI. The study found that P-tau217 predicted future conversion to AD dementia within four years (AUC 0.83), and furthermore, when plasma P-tau217, select cognitive tests results, and *APOE* genotype status were used in combination, the accuracy was further increased (AUC 0.91) (Palmquist et al., 2021). Use of more invasive CSF P-tau, CSF $A\beta_{42/40}$, and plasma NfL was not shown to increase accuracy significantly compared to accessible biomarkers alone (Palmquist et al., 2021). Similarly, Karikari et al. (2021) also used a cohort from the ADNI study to investigate another tau isoform, P-tau181. They found that P-tau181 was increased in preclinical stages of AD and subsequently increased throughout the course of disease (Karikari et al., 2021). In participants with subjective cognitive decline, higher baseline P-tau181 accurately predicted future conversion to AD and had a high diagnostic accuracy for AD (AUC 0.85) (Karikari et al., 2021). Both of these studies suggest that plasma P-tau isoforms may identify AD prior to symptom onset and may be promising for evaluation of subjects for future clinical trials, or for use in the clinical setting.

5.3. NfL

In AD studies, increased concentrations in both plasma and CSF have been associated with neurodegeneration on MRI, as well as tau and amyloid PET positivity (Mattsson et al., 2019; Zetterberg et al., 2016). However, NfL changes are not specific to AD, as elevations are also seen in FTD, vascular dementia, Human Immunodeficiency (HIV) associated dementia, amyotrophic lateral sclerosis, and atypical Parkinson's disease (Bridel et al., 2019). Despite these limitations, there could be utility in further research using this biomarker as part of a panel of more specific biomarkers to improve the sensitivity of AD screening.

5.4. GFAP

Plasma GFAP levels are elevated in clinical AD (Verberk et al., 2020; Chatterjee et al. 2021; Simrén et al., 2021; Oeckl et al., 2019; Teunissen et al., 2022) and higher concentrations have been associated with cognitive impairment and atrophy on MRI (Verberk et al., 2020, Chatterjee et al. 2021; Elahi et al., 2020; Oeckl et al., 2019; Teunissen et al., 2022). In one study, elevated GFAP levels predicted MCI conversion to AD dementia (Cicognola et al., 2021). Utilization of GFAP alongside other markers in a panel does show some potential (Verberk et al., 2020). A recent study by Verberk et al. (2020) utilized GFAP and $A\beta_{42/40}$ to predict A*β*-PET status with success. Furthermore, the study showed promise for utilization of both GFAP and NfL for disease monitoring (Verberk et al., 2020). Further studies should be done to assess the utility of multiple plasma biomarkers to diagnose and monitor disease progression.

6. Under investigation

There are several other approaches that are promising as we look to develop accessible and accurate biomarkers in AD. Several are described in brief below, including retinal imaging, peripheral body fluid analysis (saliva, tears, nasal discharge), and small non-coding RNA (scnRNAs) (Mahaman et al., 2022).

6.1. Retinal imaging

Research on the use of retinal imaging techniques to identify markers of AD in the human retina has advanced rapidly during the past decade. Retinal imaging methods, such as ocular coherence tomography (OCT), are non-invasive, and more accessible and affordable relative to advanced neuroimaging techniques. As such, this research is a highly promising and potentially impactful area of biomarker development.

Structural, vascular, and neuropathological changes in the retina have been found in both mouse models of AD and older adults with amnestic MCI and AD (Alber et al., 2020; Chidlow et al., 2017; Koronyo et al., 2017; Mirzaei et al., 2020). While retinal A*β* is well documented in transgenic mouse models of AD, research identifying retinal A*β* in humans has been more limited and inconsistent (Jiang et al., 2016). Multiple intracellular and extracellular A*β* deposits in retinal tissue from AD patients were first reported by Koronyo and colleagues (2011) using histological methods in whole mount retinas. This team later developed an in vivo technique to successfully detect A*β* in human AD patients (Koronyo et al., 2017); however, several subsequent efforts have failed to replicate their findings (Ho et al., 2014; Williams et al., 2017).

Similar to research on retinal A*β,* the literature thus far on the identification of tau pathology in the retina is limited, with some early efforts failing to find P-tau in retinal tissue samples from AD patients (Ho et al., 2014). More recently, den Haan and colleagues (2018) reported finding an increased immunoreactive signal for P-tau in the inner and outer plexiform layers of the retina in post-mortem tissue from six AD cases compared to controls (den Haan et al., 2018).

Potential structural retinal AD biomarkers include thinning of the retinal nerve fiber layer (RNFL), captured via OCT, which is consistently seen in older adults with MCI and AD relative to healthy controls (Alber et al., 2020; Chan et al., 2019). How RNFL thinning progresses over the disease course, particularly during the preclinical and prodromal stages,

is less clear and more longitudinal studies are needed in this area. Recently, RNFL thickness has been associated with levels of CSF Aβ and tau in older adults with preclinical AD (Asanad et al., 2020), as well as with hippocampal volume in older adults with normal cognition (Shi et al., 2020, Shi et al., 2014), suggesting that RNFL thinning may begin early in the disease course and may be a useful biomarker for AD screening.

Finally, a number of vascular changes in the human retina may provide potential markers of neurodegeneration and AD (Czakó et al., 2020; Frost et al., 2013). In the first study to report retinal vascular abnormalities in association with AD, Frost and colleagues (2013) found reduced vascular widths and branching in asymptomatic older adults with elevated cerebral Aβ relative to healthy controls. More recently, in an OCT-angiography study, increased area of the foveal avascular zone (FAZ) was found to be associated with elevated cerebral Aβ in cognitively normal older adults (O'Bryhim et al., 2018). Using ROC analysis, the authors found that the FAZ area distinguished between the A$\beta-$ from A$\beta+$ groups with an area under the curve of 0.8, suggesting that this vascular metric could be effective for identifying preclinical AD. In sum, retinal imaging biomarker research is still in its early stages, but has produced a number of potential structural, vascular, and neuropathological markers of AD that are continuing to be investigated. Some significant limitations that will need to be addressed prior to clinical implementation of retinal biomarkers include the need to reconcile variability across different types of OCT devices and imaging software from different manufacturers that can impact results, as well as the need for more longitudinal within-subjects studies to better understand how retinal biomarkers interact with other AD biomarkers and cognition over the course of the disease (Alber et al., 2020).

6.2. sncRNAs

sncRNAs, such as micro-RNA (miRNAs), are involved in oligonucleotide regulation and control genetic programing of cells. miRNA is thought to have a role in the pathogenesis of AD along with other neurodegenerative diseases (Zendjabil, 2018; Zhang et al., 2020; Mahaman et al., 2022). Prior research has suggested that miRNA is dysregulated in brain-derived extracellular vesicles passed into blood and CSF in AD patients relative to controls (Müller et al., 2016; Cha et al., 2019). A more recent study has also identified one miRNA, hsa-mir-567, that is significantly upregulated in serum from individuals with amnestic MCI relative to controls, and could therefore prove useful as a non-invasive early biomarker of disease progression (De Felice et al., 2020). For a more detailed review, sncRNA and AD research is further discussed in Zhang et al. (2020).

6.3. Biomarkers in peripheral bodily fluids

Analysis of nasal discharge, saliva, and tears show promise as non-invasive approaches for AD biomarker investigation (Jung et al., 2022; Mahaman et al., 2022). Currently, non-invasive methods for acquiring and analyzing AD biomarkers in nasal discharge using swabs are being explored (Liu et al., 2018). Using protein analysis of swab samples taken from different regions of the nasal cavity and passages, P-tau/t-tau ratios in certain regions were shown to be significantly higher in AD cases relative to healthy controls (Liu et al., 2018). Several studies have also characterized AD biomarkers using metabolomic analysis of saliva samples (Huan et al., 2018; Mahaman et al., 2022; Sapkota et al., 2018; Yilmaz et al., 2017). Panels of two and three metabolites have been shown to successfully distinguish AD from MCI and healthy controls in both discovery and validation stages (Huan et al., 2018). Analysis of tear samples, which have proven to be useful for biomarker analysis in other diseases, may also have potential in AD (Gijs et al., 2019; Jung et al., 2022). Results in one small study suggest that there is a correlation between the amount of total tau and Aβ_{42} within the ocular tears of AD patients in comparison to controls (Gijs et al., 2019). Other bodily fluids, such as urine, also hold promise for further investigation (Jung et al., 2022).

7. Discussion

The past decade has seen exponential progress in identifying, testing and implementing biomarker-based diagnostic strategies for AD in research settings (Ashton et al., 2021b). Ongoing progress in this area has already revolutionized AD drug development by allowing for biomarker-informed study endpoints in clinical trials, as recently seen in the case of several disease modifying therapies (Mintun et al., 2021; Sevigny et al., 2016; Tolar et al., 2020). Now, our ability to translate these and future treatments to a wider and more diverse clinical population may hinge upon the development of low cost, minimally invasive and widely accessible diagnostic biomarkers in the general clinical setting. Improvements in our ability to detect these changes and use them to diagnose earlier stages of AD may allow for an earlier and more personalized approach to diagnosis and treatment via more precise disease staging as well as identification of co-pathologies earlier in the clinical work-up (Fig. 1).

Biomarker-driven detection, treatment and monitoring may soon provide a potent combination in the fight against the rising tide of AD. In particular, fluid biomarkers (plasma, CSF, saliva, and other body fluids) may prove particularly useful in simultaneously screening for multiple biomarkers of neurodegenerative diseases in the primary care setting, guiding specialty referrals and additional work-up needed to differentiate between AD variants and other related dementias, such as FTD, LBD and vascular cognitive impairment. While more studies are needed to develop this type of comprehensive biomarker panel, routine screening for AD, analogous to screening for hyperlipidemia or diabetes at an annual physical, appears promising and could have several potential applications, including:

(1) To guide additional work-up, risk assessment and patient-centered counseling regarding a cognitive complaint that is grounded in the underlying biology.

(2) To provide motivation for an at-risk individual to engage in lifestyle modification to reduce one's risk of progression, and possibly in monitoring for response to these interventions.

(3) To enable a personalized approach to disease-modifying treatment that stratifies patients by risk/benefit ratio, and to monitor for treatment response or predict adverse events.

(4) To assist with differentiating (and treating) behavioral symptoms of dementia versus *primary psychiatric illnesses.*

(5) To allow for affected individuals and their families to take a more proactive role in medical decision-making prior to the onset of significant cognitive impairment.

This future may seem far removed from our current standard of care, yet there are already clinically available biomarker assays that are now being used in specialty memory care settings including amyloid PET scans, CSF Aβ/tau ratios, APOE genotyping, and most recently plasma $A\beta_{42/40}$ quantification which is now available in most US states (Servick, 2021). While access is limited and most assays are rarely covered by insurance, the rising prevalence of AD, limited specialty care resources and new disease-modifying agents may together help to justify routine use outside of clinical trials. Combining accessible biomarkers into multimodal diagnostic algorithms is a viable path towards developing the next test for AD (Karikari et al., 2020; Palmqvist et al., 2020; Verberk et al., 2020). One notable study found that a machine learning algorithm using accessible measures, including rapid cognitive screening, structural MRI and a blood draw, could predict progression to AD more accurately than the experts (Palmqvist et al., 2021).

Despite these reasons for optimism coming from scientific progress, the problem of translating them into clinical practice is not just a technical one, but also a matter of individual preferences, healthcare economics and cultural attitudes around the aging process. The availability of disease-modifying treatments may soon provide sufficient motivation

to undergo such testing in the near future (Cummings, 2021; Servick, 2021). More studies are needed to understand how these biomarkers may best be used by doctors, patients and families in guiding their treatment, particularly in diverse cohorts which are traditionally underrepresented in research. Future studies should seek to not just develop more accurate biomarkers, but also to better understand how the information these biomarkers provide will impact patient's medical decision-making, clinical outcomes and overall quality of life in the real world.

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Declaration of Competing Interest

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