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Predicting Cognitive Decline in Alzheimer's Disease (AD): The Role of Clinical, Cognitive Characteristics and Biomarkers

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1. Introduction

Given the rapid ageing of the population worldwide, global estimates of AD - generally considered to be the commonest subtype of dementia - are expected to increase from the current estimated 25 million to 63 million in 2030, and by 2050, a staggering 114 million [1]. Over the last two decades in particular, significant but modest breakthroughs in pharmacological treatment of this devastating condition have occurred. Presently, there is increasing conviction that intervention (especially disease-modifying therapy) will have to be instituted at the earliest possible stage of the illness to confer the greatest benefit.

Prevailing clinical criteria for Mild Cognitive Impairment (MCI) have low to moderate diagnostic accuracy in identifying and predicting progression to dementia. MCI is an unstable clinical construct where some patients convert (MCI-converters) while others remain relatively stable (MCI non-converters). As observed from neuropathological and recent biomarker studies, the accumulation of AD pathology (β -amyloid plaques and neurofibrillary tangles) may precede the onset of clinical disease by as long as 20-30 years [2,3]. This suggests that functional and structural brain changes may occur prior to apparent clinical manifestations of cognitive impairment (Figure 1). However, the current definition of MCI is based primarily on clinical and neuropsychological criteria, and this may have contributed to limited demonstration of efficacy in therapeutic and disease-modifying trials thus far. Supplementing existing criteria with information about biomarkers may enrich the definition of MCI. This provided the impetus for the development of reliable biomarkers such as cerebrospinal fluid (CSF), neuroimaging and blood biomarkers to complement clinical approaches in early diagnosis and predicting progression. In support of this, the recent proposed criteria for symptomatic pre-dementia phase of AD (MCI), preclinical AD and presymptomatic AD have included biomarkers reflecting molecular pathology, downstream

measures of structural and functional/metabolic changes, and associated biochemical changes in their research diagnostic armamentarium [4].

Longitudinal studies in AD subjects have also noted variability in disease progression. In one study, 11.9% of subjects exhibit rapid cognitive decline while some remained relatively stable [5]. Other studies that utilized parameters such as the decline in Mini Mental State Examination (MMSE) scores [6, 7] (≥ 3 point decline) also reported a distinctive difference in the clinical course between the fast-progressors and slow-progressors.

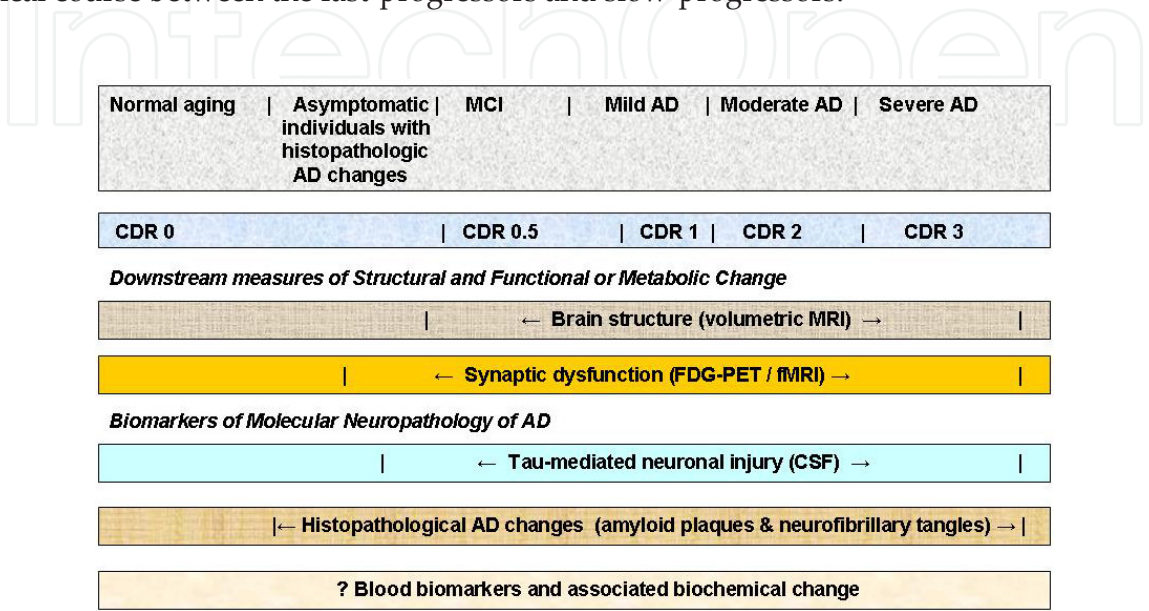


Figure 1. Clinical Continuum of Alzheimer’s disease and hypothetical biomarker model

In this chapter, we will review the body of evidence on the use of various clinical and comorbid factors, alone and/or in combination with biomarkers, on predicting rapid cognitive decline across the spectrum of cognitive impairment – defined in terms of AD progression in MCI subjects and rapid cognitive decline in AD subjects. We will also look at longitudinal biomarker measurements as well as their role (alone and/ in combination with clinical and comorbid factors) in predicting cognitive decline and disease trajectories. We will discuss the implications of current research findings to their application in clinical and therapeutic trials. The chapter is not intended to be an exhaustive review of this burgeoning literature, but instead to highlight integrative and potentially novel lines of inquiry.

2. Clinical and cognitive/ behavioural characteristics (table 1)

A number of socio-demographic factors and vascular risk factors have been found to increase risk of development of AD.

Increased risk of cognitive decline in diabetes may reflect a dual pathologic process involving both cerebrovascular damage and neurodegenerative changes. Several possible pathophysiological mechanisms may include hyperglycemia, insulin resistance [8], oxidative stress, advanced glycation end products, and inflammatory cytokines. A shared clinicopathologic

study alluded to the potential shared predisposition for developing amyloid in both the pancreas and brain [9]. This is supported by a study of intranasal insulin preventing cognitive decline, cerebral atrophy and white matter changes in mouse models [10]. Diabetes and pre-diabetes have been found to be associated with AD progression in MCI subjects, with progression from MCI to dementia accelerated by 3.18 years[11]. The stronger effect of pre-diabetes on MCI conversion may be caused by high glycemic level in pre-diabetes and increased insulin resistance [12]. Although antihypertensive therapy has been shown to be associated with reduced rate of conversion to AD in midregional proatrial natriuretic peptide-stratified subjects with MCI [13], there has been a paucity of data with regard to the individual effect of hypertension on MCI-converters[14]. A non-significant trend was found for cerebrovascular disease as a risk factor for MCI-converters[15]. Diabetes, hypertension and cerebrovascular disease have been found to be associated with faster progression rate in dementia [16-19]. Although mid-life hypercholesterolemia has been repeatedly shown to increase risk of late-life dementia, there is relatively little evidence of its influence on MCI-converters and the rate of AD decline [20].

Study variable	Population	Results	Key findings
Predicting AD conversion in MCI subjects			
Diabetes and pre-diabetes [11]	302 aMCI and 182 CIND subjects aged ≥ 75 years over 9 years	155 subjects had AD progression	HR 2.87 diabetes (95%CI 1.3-6.34) HR 4.96 pre-diabetes (95% CI 2.27-10.84) Accelerated progression by 3.18 years
Vascular risk factors [21]	837 MCI subjects followed annually over 5 years	298 converters 352 stable	HR 2.04 (95% CI 1.33-3.11) Hypertension HR 1.84 (95% CI 1.19-2.84) Diabetes HR 1.62 (95% CI 1.00 – 2.62) Hypercholesterolemia HR 1.11 (95% CI 1.04-1.18) Cerebrovascular disease HR 1.60 (95% CI 1.03 – 2.49)
Diabetes, baseline white matter severity, baseline moderate-to-severe carotid stenosis and carotid stenosis change [22]	257 MCI subjects over 3 years	MCI conversion to AD 7.05%/year	Diabetes HR 2.92 (95% CI 1.12-7.6) Baseline WMC severity (mild vs severe) HR 0.04 (95% CI 0.006-0.242) Baseline carotid stenosis (moderate vs mild) HR 8.46 (95% CI 2.1-34.14) Carotid stenosis change HR 124.1 (95% CI 0.95- 16,209.68)
Stroke [15]	121 MCI subjects over 3 years	MCI conversion to AD based on age strata rate (per 100 person-years) Total 2.3 65-69y 0 70-74y 0 75-79 3.1 80-84y 2.0	Stroke RR 4.0 (95% CI 0.92-13.87)
Metabolic syndrome [8]	49 MCI subjects with metabolic syndrome and 72 without metabolic syndrome	Progression to dementia	67.6 (95% CI 35.17 – 129.93) Rate 1000 per person-years
Age [23]	97 amnesic MCI 88 cognitively-unimpaired controls followed up mean 38.8 mths	Annual rate of progression to AD	Odds ratio = 4.5 of AD progression Older age [exp(β)=1.11, SE(β)=0.7, WALD=4.2, p=0.040] predictors of AD conversion
Empirically weighted and Combined neuropsychological battery [42]	43 MCI subjects	14 subsequently converted to AD	Multivariate combinations achieved 84% accuracy, 86% Sn, 83%Sp in predicting AD progression (using episodic memory, speeded executive function, recognition memory (false positives), recognition memory (true positives), speed in visuospatial memory, visuospatial episodic memory)
Learning measure and retention measure [43]	607 MCI and HC patients in ADNI cohort divided into 4 groups: (based on learning and retention)	Conversion to AD at 2 years	Low-learning, Low retention OR17.84, 95%CI 7.37-43.10, p<0.001; Low-learning, High retention OR 9.01, 95%CI2.98-27.21,p<0.001; High learning, low retention OR8.48, 95%CI 3.45-20.86, p<0.001 (high learning, high retention as reference group)
MISplus [44]	40MCI subjects	Conversion to AD at 18 months (n=7)	OR 0.28, 95%CI 0.099-0.79) At cut-off of 2, PPV 71.5%, NPV 91.5%, Accuracy 87%

Hypertension [16]	135 incident AD Patients in Cache County Dementia Progression Study	Rapid decline on CDR-sum of boxes and MMSE using linear mixed models	Systolic BP ≥ 160 versus < 160 mmHg (controlling for other vascular variables) for CDR-SB coeff X time 1.78 (95% CI 1.20-2.36) for MMSE coeff X time -2.38 (-3.23,-1.53)
Hypertension [17]	719 AD patients In multi-center Trial	ADAS-cog increase by ≥ 1 standard deviation of baseline ADAS-cog score of	OR 6.9 (95% CI 1.5-31.1, $p=0.005$)
Diabetes [18]	154 AD patients attending Dementia center	Disease progression of decrease of 5 pts or more on MMSE	Crude OR 0.38 (95% CI 0.2-0.9) Multivariate OR 0.36 (95% CI 0.1-0.9)
Cerebrovascular disease[19]	224 AD patients	Decline in MMSE, ADAS-cog and SIB difference	No difference in vascular risk factors except cerebrovascular disease (mean difference in MMSE 13.6 (-14.3—7.6); ADAS-cog 27 (-30.1-13.7); SIB 54.4 (-62.3—29.9)
Vascular risk factors including heart disease, stroke, diabetes, hypertension), smoking, pre-diagnosis blood lipid and LDL-C [20]	156 AD patients living in community mean age 83 y	AD decline using generalized estimating equation models	Only higher LDL-cholesterol was independently associated with faster cognitive decline. Stratified according to APOE ϵ 4 showed higher total cholesterol, higher LDL, stroke and heart disease associated with faster decline.
Age [24]	201 Caucasian Probable/Possible AD subjects at ADRC, Pittsburgh	Latent class mixture models of quadratic trajectories including random intercept and concomitant variables (MMSE)	Best latent trajectory model: Initial MMSE and age. Parameter estimate 0.85, $p<.001$ for MMSE, Parameter estimate 0.04, $p=0.04$ for age.
Education [27]	127 persons in Bronx Aging study developed dementia (out of 488 community dwelling subjects)	Change point models to test predictions of cognitive reserve hypothesis using Buschke Selective Reminding Test (SRT)	Prior to diagnosis, lower levels of formal education associated with poorer performance on memory and verbal fluency. Accelerated decline in SRT shown by estimated annual rates of decline for 16 years, 9.5 years and 4 years of formal education was 3.22, 2.57 and 2.03 points/year respectively.
Neuropsychiatric symptoms [30]	177 memory-clinic AD outpatients	Rapid disease progression defined as loss of ≥ 1 ability in ADL or drop of ≥ 5 points on MMSE	Affective syndrome increased risk of functional decline (HR2.0, 95%CI 1.1-3.6) AND Manic syndrome (HR 3.2, 95% CI 1.3-7.5)
Pre-progression rate-Clinician estimate of duration and baseline MMSE [28]	798 probable AD subjects from Alzheimer's Disease and Memory Disorders Centre	Random effects linear regression to calculate pre-progression categories and of change in ADAS-cog, VSAT Time, VSAT Errors, CDR Sum of boxes, PSMS and IADL scores	Slopes of ADAScog and PSMS change for slow pre-progression smaller than fast pre-progression. Rates of change on ADAScog slower for intermediate pre-progression group. Slow progressors survived longer.
Memory and executive Functioning [45]	154 newly diagnosed AD Patients	Rapid progression of ≥ 5 MMSE decrease over 2yrs	Memory moderate deficits: HR 1.3 (95%CI: 0.4-4.5); severe deficits: HR 2.3 (95%CI: 0.6-9.0). Executive functions moderate deficits: HR 3.5 (95%CI 0.9-13.7); severe deficits: HR 5.7 (95%CI 1.4-23.2)

HR = Hazards ratio; PPV = Positive predictive value
95% CI= 95% confidence interval; NPV= Negative predictive value
WMC= White matter severity; MMSE =Mini Mental State Examination
RR= Relative risk; SIB = Severe Impairment Battery
OR= Odds ratio

Table 1. Clinical and cognitive/ behavioural characteristics in predicting AD conversion in MCI patients and rapid AD progression/ decline

Vascular risk factors, as a composite entity, have been shown to be associated with MCI conversion [21]. The individual risk factors of hypertension, diabetes, cerebrovascular disease and hypercholesterolemia in the study were associated with high risk of MCI conversion. Treatment of hypertension, diabetes and hypercholesterolemia showed reduced risk of MCI conversion. In the same Chongqing study, the authors showed separately the association of

diabetes, baseline white matter changes (WMC), baseline moderate-to-severe carotid stenosis and carotid stenosis change during follow-up to be predictors of MCI conversion [22]. A separate longitudinal community study (ILSA- Italian Longitudinal Study on Aging) showed MCI progression to AD of 2.3 per 100 person-years with stroke as the only vascular risk factor associated with progression [15].

The heterogeneity of AD syndrome is likely related to, other than amyloid and tau pathology, a number of other factors, such as impaired energy metabolism, oxidative stress, neuro-inflammation, insulin and insulin growth factor (IGF) resistance, and insulin/ IGF-deficiency. These factors are often included as variables of interest in studies attempting to develop diagnostic and therapeutic targets for this disease. Brain insulin resistance promotes oxidative stress, reactive oxygen species (ROS) generation, DNA damage and mitochondrial dysfunction, all of which drive pro-apoptosis, pro-inflammatory and pro-A β PP-A β cascades. Also, hyperinsulinaemia increases A β PP-A β and inflammatory indices in the brain, also promoting formation of advanced glycation end-products which lead to increased generation of ROS. Tau gene expression and phosphorylation are also regulated by insulin and IGF stimulation, where brain insulin and IGF resistance may result in decreased signaling through phosphoinositol-3-kinase (PI3K), Akt and Wnt/ β -catenin and increased activation of GSK-3 β – which is partly responsible for tau hyperphosphorylation. Hence, the focus on vascular factors in AD is justified based on chronic hyperglycemia, hyperinsulinemia, oxidative stress, advanced glycation end-products and inflammation promoting vascular disease [8].

The metabolic syndrome defined by the Third Adults Treatment Panel of the National Cholesterol Education Program as a combination of three or more of the following components: abdominal obesity (waist circumference >102cm for men and >88 cm for women; elevated plasma triglycerides (≥ 150 mg/dl); low HDL cholesterol (<40mg/dl for men and <50mg/dl for women); high blood pressure ($\geq 130/ \geq 85$ mmHg) or being in hypertensive treatment; and high fasting plasma glucose (≥ 110 mg/dl). This represents a clustering of vascular risk factors for morbidity and mortality. In addition, these factors may interact synergistically to influence cognition in a negative manner. Among MCI patients the presence of metabolic syndrome independently predicted an increased risk of progression to dementia over 3.5 years of follow-up. [23]

Older age has been shown to predict MCI-converters [24]. Latent class modeling methods and disease system analysis approach to characterize trajectories of cognitive decline in AD cohorts have also shown initial MMSE and age to best predict decline [25,26]. However, separate studies using AD clinical trial data with subjects on Donepezil have shown younger age to predict faster decline in placebo-treated patients [27]. Low education is a risk factor for AD. The cognitive reserve hypothesis predicts that persons with higher education delay the onset of accelerated cognitive decline; however, once AD disease process begins, it takes a more rapid course due to increased disease burden [28]. Pre-progression rate (calculated using clinician's standardized assessment of symptom duration in years and baseline MMSE) has also been shown to predict cognitive decline trajectory [29]. Neuropsychiatric symptoms have also been shown to predict faster cognitive and functional decline [25,30,31].

Prospective studies of amnesic MCI (a-MCI) subjects have shown that episodic memory (such as delayed recall of word lists [32-34], spatial short term memory and visual recognition memory [35], and paired-associates learning [36,37]), semantic memory [37,38], attentional processing [39] and mental speed consistently predicted MCI converters. Within a very mild cognitive impairment group, higher CDR-sum of boxes and lower executive function predicted AD conversion [40]. Similarly, in a retrospective study of MCI-converters, verbal and visual memory, associative learning, vocabulary, executive functioning and other verbal tests of general intelligence were impaired at baseline [41]. An empirically weighted and combined set of neuropsychological tests involving domains of episodic memory, speeded executive functioning, recognition memory (false and true positives), visuospatial memory processing speed, and visual episodic memory together were strong predictors of MCI conversion to AD [42]. A recent study demonstrated that MCI individuals with learning deficits on the Rey Auditory Verbal Learning test showed widespread pattern of gray matter loss at baseline, as compared to retention deficits which was associated with more focal gray matter loss. However, impaired learning had modestly better predictive power than impaired retention, highlighting the importance of including learning measures in addition to retention measures when predicting outcomes in MCI subjects [43]. Verbal cued recall measured using the Memory Impairment Screen plus (MISplus) has also been shown to predict MCI conversion [44].

In subjects with AD, rapid disease progression was noted more frequently in subjects with higher education and those with moderate severity of global impairment. More severe memory impairment and executive dysfunctioning were associated with higher probabilities of progression at 2 years [45].

Longitudinally, follow-up of those who developed AD versus those who were non-demented prior to AD diagnosis, showed no evidence for accelerated decline of episodic memory from 6 to 3 years prior to incident dementia diagnosis [46]. Working memory (using digit span backward and forward as well as digit ordering) also did not show temporal change as a potentially useful marker of progression [47].

2.1. Summary

Age, vascular risk factors and metabolic syndrome affect AD conversion in MCI subjects. However, there is currently a lack of data on the effect of intensive vascular risk factor treatment in delaying/ halting the rate of progression in MCI subjects. Educational attainment plays an interesting role in AD. In support of the cognitive reserve hypothesis, higher educational attainment predicts delay of the onset of accelerated cognitive decline; however, once AD disease process begins, it takes a more rapid course due to increased disease burden.

Neuropsychological tests, especially episodic memory and executive functioning tests, seem to predict MCI-converters. When assessing MCI subjects, the inclusion of impaired learning in addition to retention measures may improve predictive power of AD progression from MCI. More severe cognitive impairment is associated with rapid AD progression.

3. Cerebrospinal fluid biomarkers (tables 2)

The most widely studied candidate CSF biomarkers include CSF total tau (t-tau), 42 amino acid form of A β (A β_{1-42}) and phosphorylated tau protein (p-tau) [48]. They reflect respectively the corresponding central pathogenetic process of neuronal degeneration, amyloid- β peptide deposition in plaques, and hyperphosphorylation of tau with subsequent tangle formation. Fagan et al has also recently demonstrated that CSF A β and tau protein measurements, performed using INNOTEST enzyme-linked immunosorbent assay (ELISA) and INNO-BIA AlzBio3, were highly correlated with brain amyloid load, as assessed by PET and Pittsburgh compound B amyloid-imaging (r value from 0.77 to 0.94)[49]. This was further suggested, by a study of antemortem CSF concentrations of A β_{1-42} and t-tau/ A β_{1-42} ratio in an autopsy-confirmed AD cohort, that the standardization of biomarker techniques could potentially replace autopsy-confirmed AD for future diagnosis of definite AD [50].

3.1. Established CSF biomarkers

CSF biomarkers of elevated t-tau [51-56], high p-tau [52,53,57,58], low A β_{1-42} [52,53], and combinations of high t-tau/ p-tau and low A β_{1-42} concentrations [59-64], have been shown to be predictive of MCI-conversion to AD. The consistent feature in all of these studies is that increased CSF t-tau and p-tau concentrations are highly sensitive while low A β_{1-42} concentration is more specific. A recent longitudinal study showed that subjects with the lowest baseline A β_{42} , highest tau and p-tau concentration exhibited the most rapid MMSE decline. In addition, while there was little difference in the levels of these CSF biomarkers between stable MCI and cognitively healthy subjects, MCI-AD converters had the highest total tau concentrations [65].

High CSF t-tau and p-tau concentration (but not A β_{42}) was associated with more rapid MMSE decline in a 3-year prospective longitudinal study. This suggests that increased t-tau levels reflect intensity of disease and hence rapidity of AD progression, while A β_{42} is more a diagnostic state marker, not associated with rate or stage of AD [65,66]. Another study showed p-tau to poorly differentiate between AD and vascular dementia, but to correlate with MMSE progression [67]. In contrast, another recent report showed lower A β_{42} levels to be associated with rapid-progressors compared with slow-progressors [68]. Wallin et al showed that AD subjects with a combination of low A β_{42} and very high CSF t-tau and p-tau levels performed worse on baseline cognitive tests, with faster deterioration, poorer outcome to cholinesterase inhibitor treatment and increased mortality [69].

With respect to serial biomarker measurements with disease progression, we found studies showing increasing p-tau 231 levels with disease progression in MCI subjects [70, 71] compared to controls over a period of 12-24 months. No definite trends were observed with A β_{40} and A β_{42} in the same studies [70,71]. A recent longitudinal study showed that nonspecific CSF biomarkers, in particular isoprostane, demonstrated an increase over time, which was correlated with AD conversion in MCI subjects and cognitive decline (as assessed by MMSE) [72].

Study variable	Population	Results	Key findings
Predicting AD conversion in MCI subjects Combination CSF biomarkers [64]	137 MCI subjects compared to 39 healthy controls	42% converted to AD	- t-tau >350ng/L & Aβ42 <530 ng/L: Sn: 95%, Sp 83% of AD conversion HR 30, 95% CI 9.32-96.8, p<0.001 - p-tau >60ng/L & Aβ42 <530 ng/L: Sn 95%, Sp 81% of AD conversion HR 26.3, 95% CI 8.16-83.4, p<0.001 - t-tau/ Aβ42 ratio < 6.5 (t-tau>350ng/L) Sn 95%, Sp 87% of AD conversion HR 32.8 (10.2-105.6,p<0.001)
Predicting rapid AD progression/ decline CSF biomarker concentration [66]	142 AD subjects followed-up over 5 years	35 subjects had t-tau>800ng/L	- High levels of t-tau correlated with lower baseline MMSE scores. More rapid decline in MMSE score correlated with higher baseline t-tau (r _s =-0.23,p=008). - p-tau>110ng/L showed lower baseline MMSE scores but no difference in progression. - Aβ42 showed no difference in baseline scores or progression.
CSF p-tau concentration [67]	70 AD and VD subjects with 36 age-matched healthy controls	Cognitive decline assessed 12 mth (MMSE ≥ 5 point decline after 1yr)	58% of probable AD patients showed p-tau concentration higher than 36.08ng/L. Cognitive decline correlated with p-tau concentration (x ² =12.442, p=0.001).
CSF Aβ42 concentration [68]	74 AD subjects	Rapid progressors defined at MMSE decline >4/years	Lower Aβ42 CSF concentration (mean 292 pg/ml) in fast-progressors compared to slow-progressors (mean 453 pg/ml) (p=0.042)
Low CSF Aβ42 and high CSF t-tau and p-tau levels [69]	151 AD subjects	k-means cluster analysis done. Cluster 1 low Aβ42 and low t-tau, p-tau and intermediate t-tau, p-tau Cluster 2 low Aβ42 and high t-tau, p-tau	Cluster 3 performed poorer on baseline cognitive tests. They exhibited poorer outcome of cholinesterase inhibitor treatment. Cognition deteriorated faster over time with substantially increased mortality rate.

HR = Hazards ratio

CRP = C-reactive protein

MMSE =Mini Mental State Examination

OR = Odds ratio

Sn = Sensitivity

Sp= Specific

LR+ = positive Likelihood ratio

LR - = negative Likelihood ratio

HR = Hazards ratio

95% CI= 95% confidence interval

Table 2. Cerebrospinal fluid biomarkers in predicting AD conversion in MCI patients and rapid AD progression/ decline

Faster progression of brain atrophy (in terms of regional cortical thinning) has been found in the presence of lower A β 1-42 levels and higher p-tau in Alzheimer's Disease Neuroimaging Initiative (ADNI) data [73].

3.2. Novel CSF approaches

In a study in which novel CSF biomarkers were identified through mass spectrometry and re-evaluated by ELISA, it was found that NrCAM, YKL-40, chromogranin A and Carnosinase I were potentially able to improve the diagnostic accuracy of existing A β 42 and tau CSF biomarkers. This could potentially improve characterization of clinic-pathological stages of the cognitive continuum from cognitive normalcy to mild dementia, with the promise of potential utility in clinical trials and monitoring disease progression [74]. Other potential CSF biomarkers include nanoparticle-based amyloid- β -derived diffusible ligands (ADDLs)[75], as well as a multiplexed immunoassay panel of a combination of a subset of markers, in particular, calbindin, which showed significant prognostic potential [76]. Preliminary data have also shown that soluble A β oligomers might inhibit long-term potentiation and hence, play an important role in AD pathogenesis. The increasing appreciation of A β oligomers (as compared to its native forms) in the pathogenesis of AD may suggest novel pathways to biomarkers, such as anti-oligomer antibodies that are specific for the soluble oligomeric state (as opposed to the fibrillar states). By quantifying A β oligomer formation, anti-oligomer antibodies may provide a promising strategy for monitoring disease progression [77,78].

Concerns with CSF biomarkers include measurement variability occurring through lack of standardization of CSF assays [79], high inter-laboratory and between-assay variance, sampling-handling factors, post lumbar-puncture headache, and poor acceptability to patients, especially if repeated measurements are involved. In an attempt to overcome these, the Alzheimer's Association has launched a global quality-control program for AD CSF biomarkers, which will be administrated from the Clinical Neurochemistry Laboratory in Molndal, Sweden. This includes reference samples for use in studies, allowing normalization of biomarker levels and meta-analyses of published papers [80].

3.3. Summary

Elevated CSF total tau, p-tau, low A β and high tau: A β concentrations have been consistently shown to highly predict MCI-converters and AD progression. CSF A β and tau may reach a plateau at a relatively early stage of disease and remain fairly constant thereafter, limiting its utility for longitudinal measurement and in monitoring therapeutic response at the more advanced/ established stage of AD. However, it remains an important biomarker during the preclinical and prodromal stages of AD, reflecting the central pathogenic neurodegenerative process. Novel CSF biomarkers hold promise of circumventing this current limitation, especially A β oligomers and their potential use in documenting disease progression as well as being a potential therapeutic target. The invasive nature of lumbar puncture and standardization issues preclude its current routine clinical use.

4. Blood markers (table 3)

Peripheral blood is one of the most convenient sources of biomarkers. While the quest for a marker with high sensitivity and specificity has been ongoing for decades, no single blood-derived biomarker has been particularly outstanding in the diagnosis of AD, in predicting conversion from MCI to AD and in predicting slow and fast progression. The following are some of the most studied biomarkers. One should note that negative studies are usually not published and hence publication bias is possible.

<u>Study variable</u>	<u>Population</u>	<u>Results</u>	<u>Key findings</u>
Predicting AD conversion in MCI subjects			
Abeta Hansson [82]	Cohort 1: 117 MCI subjects followed up for 4 -7 years; Cohort 2: 110 followed up for 2 – 4 years	48 (41%) subjects of cohort 1 developed AD; 15 (14%) subjects of cohort 2 developed AD	No difference in plasma Abeta levels between MCI subjects that subsequently developed AD and HC or stable MCI subjects. HR (per SD decrease adjusted for age, sex): A β 40 1.08 (0.78-1.51), A β 42 0.95 (0.71-1.27), A β 42/42 ratio 0.83 (0.64-1.08)
Koyama [84]	Meta-analysis with 10,303 subjects	Summary risk ratio of 1.60 and 1.67 for AD and dementia respectively	Association of low plasma Abeta42/Abeta40 ratio with AD and dementia.
C Reactive Protein [86]	168 MCI subjects followed up over 2 years	58 subjects developed dementia	Association of high plasma CRP level with accelerated cognitive deterioration and increased risk of AD. MMSE score was significantly lower for patients with high CRP levels than those with low CRP levels (-4.9 \pm 5.4 vs -3.2 \pm 4.2, p < 0.05)
APOE [90]	35 prospective cohort studies of MCI subjects, including 6095 subjects over 2.9 years of follow-up	1236 developed AD.	APOE- ϵ 4 allele is associated with a moderately increased risk for progression from MCI to AD-type dementia. OR for MCI subjects with APOE ϵ 4 progression to AD 2.29 (95% CI 1.88 to 2.80). Sn 0.53 (95% CI 0.4 to 0.61), Sp 0.67 (95% CI 0.62 to 0.71), PPV 0.57 (95% CI 0.48 to 0.66), NPV 0.75 (95% CI 0.70 to 0.80). LR+ 1.60 (95% CI 1.48 to 1.72), and LR- 0.75 (95% CI 0.67 to 0.82). Meta-regression showed that Sn, Sp and NPV were dependent on age, APOE- ϵ 4 allele background prevalence or follow-up length
Predicting rapid AD progression/ decline			
APP isoforms in platelets [85]	48 AD subjects followed up over 1 year	Progression of AD	Association of low APPr at baseline in predicting cognitive decline in AD. APPr <0.40, Δ MMSE = -2.8 \pm 3.0, p < 0.05 APPr \geq 0.40, Δ MMSE = -0.9 \pm 2.3, p < 0.05

Combination of A β and CRP [87]	122 AD subjects	Followed up 4.2 years	Low plasma levels of Abeta40, Abeta42, and high-sensitivity CRP were associated with a significantly more rapid cognitive decline. Plasma biomarkers contributed to 5-12% variance on Blessed Dementia Scale and Activities of Daily Living.
Ceramides [89]	120 probable AD subjects	Follow-up 2.3y	Highest tertiles of DHSM/DHCer and SM/ceramide ratios declined 1.35 points (p=0.001) and 1.19 (p=0.004) less per year on the MMSE and increased 3.18 points (p=0.001) and 2.42 (p=0.016) less per year on ADAS-Cog.
APOE ϵ 4 Martins [91]	218 AD subjects	In the non-linear model, possession of an APOE ϵ 4 allele was related to earlier and faster cognitive decline. APOE ϵ 2 allele related to slower decline.	APOE genotype strongly predicts the rate of cognitive decline in AD. APOE ϵ 4 homozygotes showed faster cognitive decline than heterozygotes.
Cosentino [92]	199 population-based incident AD subjects, 215 population-based prevalent AD subjects, 156 clinic-based AD subjects followed up for an average of 4 years	Presence of at least one ϵ 4 allele associated with faster cognitive decline in the population-based incident AD group (p = 0.01). However, this association is absent in prevalent AD subjects in population or clinic based group.	APOE ϵ 4 influences cognitive decline most significantly in the earliest stages of AD.

HC = Healthy controls

SD = Standard deviation

OR = Odds ratio

95% CI= 95% confidence interval

Sn = Sensitivity

Sp= Specificity

OR = Odds ratio

PPV = Positive predictive value

NPV= Negative predictive value

LR+ = positive Likelihood Ratio

LR- = negative Likelihood Ratio

Table 3. Blood biomarkers in predicting AD conversion in MCI patients and rapid AD progression/ decline

4.1. Plasma proteins/ peptides

Teleologically the most logical candidate is plasma Amyloid-beta (A β) and its derivatives, A β 40 and A β 42. They are the most studied of blood markers.

As A β accumulation is an early step in AD pathogenesis, such a biomarker would be potentially suitable for identifying patients in the earliest stage of disease process when intervention might be more effective.

Circulating A β is composed of A β produced by brain and peripheral tissue, and can be transported across the blood-brain barrier. They are derived from the amyloid precursor protein (APP). APP is catabolized via 2 pathways, one of which is amyloidogenic, and involves 3 enzyme systems, alpha, beta and gamma secretases. In the amyloidogenic pathway, APP is first cleaved by beta secretase to generate a secreted form of APP (sAPPbeta) and a C99 fragment. The C99 is then cleaved by gamma secretase to yield A β . Different cleavage sites on the C99 fragment produces two forms of A β – A β 40 and A β 42. While A β 40 is the more common product, A β 42 aggregates into amyloid fibrils more rapidly and is contained in both early diffuse plaques and fully formed neuritic plaques. In the non-amyloidogenic pathway, alpha secretase is involved and does not lead to A β formation [81].

Since elevation appears to be before or just at the onset of the clinically diagnosed disease, it has been hypothesized that high plasma A β 42 is an antecedent risk indicator for AD, and its plasma levels declines with onset and progression. There have been many studies involving A β 40 and A β 42, though results have been inconclusive and at times contradictory refer to Table 1 [82, 83]. These inconsistent results may reflect variability due to technical reasons, such as timing of sample collection with reference to AD onset, the assay methods, and differential affinities of the antibodies used for different A β species. Koyama [84], in a large systematic review, concluded that plasma levels of A β 40 and A β 42 individually were not associated with development of AD and dementia. However the *ratio of A β 42:A β 40* could predict development of AD and dementia, although the evidence is limited in MCI conversion and AD progression.

APP isoforms in platelets have been suggested to predict cognitive decline. APP metabolism has been found to be altered in the platelets of AD patients, specifically a reduced ratio of the upper (130kDa) to the lower (110-106 kDa) immunoreactivity band (APPr) [85].

The level of plasma C-reactive protein (CRP) rises in response to inflammation. Its role is primarily to activate the complement system. CRP by itself has been reported to be associated with accelerated cognitive deterioration and increased risk of conversion in MCI patients [86]. A combination of raised CRP with low A β has been associated with a significantly more rapid cognitive decline [87].

Homocysteine has been reported to be associated with human disease states, notably cardiovascular disease. Deficiencies of the B vitamins – B6(pyridoxine), B9(folic acid) and B12(cobalamin) are associated with high homocysteine levels. However, there is no data on homocysteine with MCI conversion and AD progression.

Clusterin, also called apolipoprotein J and coded by gene CLU, has been reported in genome-wide association studies (GWAS) to be associated with AD [83]. Clusterin is functionally associated with apoptosis and the clearance of cellular debris, including amyloid. Thambiesetty [88] found that higher clusterin levels were associated with slower brain atrophy in normal subjects who developed MCI during a 6-year follow-up. However, there is no current data with MCI conversion and AD progression.

Ceramides are a family of lipid molecules that are made up of sphingosine and a fatty acid. They are also constituent of sphingomyelin (SM). In addition to their structural function, they play a role as signaling molecules in regulating cell differentiation, proliferation, and programmed cell death. Mielke [89] found that high plasma levels of dihydroceramides (DHCer) and ceramide were associated with AD progression, though results did not reach significance. Nevertheless, higher plasma levels of SM, dihydrosphingomyelin (DHSM), SM/ceramide, and DHSM/DHCer ratios were associated with less progression on the MMSE and ADAS-Cog with the ratios being the strongest predictors of clinical progression. There is no current data on MCI progression.

4.2. Genetic and transcriptomic markers

APOE ϵ 4 is the best-established genetic risk factor for AD. APOE genotyping is not recommended for the routine diagnosis of AD. However many studies have investigated whether APOE ϵ 4 has a predictive value for progression from MCI to AD.

In a large meta-analysis, Elias-Sonnenschein [90] and co-workers found that APOE ϵ 4 is associated with a moderately increased risk of progression from MCI to AD.

Martins [91] found that the APOE ϵ 4 genotype predicts the age of onset of AD and neuropathic progression in a non-linear fashion. In their non-linear model, possession of an APOE ϵ 4 allele was related to earlier and faster cognitive decline, while possession of an APOE ϵ 4 was associated with slower decline. Homozygous APOE ϵ 4 showed faster cognitive decline than APOE ϵ 4 heterozygotes. The linear model was less sensitive and did not detect differences between APOE ϵ 4 homo- and heterozygotes.

Cosentino [92] also showed that the presence of at least one allele of APOE ϵ 4 was associated with faster decline in the incident population-based AD group. However the findings could not be extrapolated to prevalent AD in population or clinic-based samples. Hence APOE ϵ 4 influence may be more stage-dependent, with its effect on cognitive decline most evident in the earliest stages of disease and less so in moderate to severe stages.

Other genetic markers that have been identified in genome-wide association studies (GWAS) have not yet been shown to aid in diagnosis of AD or predict progression of disease in MCI or AD.

Unlike the static genome, the transcriptome comprises the dynamic expression of the genome over the course of the disease. Transcriptomic, or genome-wide gene expression studies, have been used to distinguish AD from healthy controls. One of the genes identified from transcriptomic studies is TOMM40, which has also been identified in GWAS studies [93]. We found that TOMM40 remained significantly downregulated over three time points in a longitudinal study (manuscript submitted for review). Transcriptomic products would ideally be used to track the progression of disease, identify markers that predict conversion of MCI to AD, and distinguish between fast and slow progressors. Hence this is a potential area of biomarker development in predicting MCI conversion and rapid AD progression.

4.3. Multiple marker arrays

Given the disappointing results achieved by single markers despite tremendous efforts, the field has now moved towards multiple markers that are obtained through high throughput technologies, sophisticated statistical analysis and bioinformatics. Ray [94] published a blood plasma-based proteomic screening tool to identify patients with AD and also to identify those likely to progress from MCI to AD. Biological analysis of the 18 proteins points to systemic dysregulation of hematopoiesis, immune responses, apoptosis and neuronal support. However efforts at independent validation of Ray's findings have been discouraging [95].

Based on current literature, no single marker has been found to be significant in all the multiple marker arrays. Moreover one can expect that utilizing high throughput array technology, more multiple marker arrays will appear and dominate the blood biomarker landscape. To sound a note of caution, however, some panels may be derived from 'over-fitting' the dataset and may not survive generalization and independent validation. To date, multiple marker arrays have not been employed to study the conversion of MCI to AD and to differentiate between fast and slow progressors. This would be a logical next step for investigation.

4.4. Summary

Plasma A β is an appealing biomarker since many AD interventions under investigation are directed against A β . Thus an A β -based biomarker is attractive for those who will benefit from such treatments. However, many studies involving various blood biomarkers have conflicting and/or inconclusive results.

APOE ϵ 4 influence may be more stage-dependent, with its effect on disease trajectory most evident in the earliest stages of disease and less so in moderate to severe stages. Hence it should be included as a covariate in various clinical progression and therapeutic trials. A major challenge is that the literature thus far has focused on the use of blood biomarkers for diagnosis (requiring the identification of dichotomous - disease versus normal- states), which may not be applicable to the use of such biomarkers for tracking disease progression (for which an effective biomarker must show continuous change rather than merely being present or absent). Nevertheless blood biomarkers should be employed in combination with clinical assessment and neuroimaging to improve diagnostic and prognostic accuracy, especially given the peripheral nature and ease of blood sampling.

5. Neuroimaging (Table 4)

5.1. Structural imaging

Neuroimaging is now one of the most common tools used to aid the diagnosis of AD. It is a huge and burgeoning field and only select modalities and important studies on longitudinal imaging are discussed here.

<u>Study variable</u>	<u>Population Results</u>	<u>Key findings</u>
<u>Predicting AD conversion in MCI subjects</u>		
<u>Structural Imaging</u>		
Jack et al. [96]	55 NC, 41 MCI, 64 AD subjects; 1-5 years follow-up	Atrophy rates of four structures (hippocampus, entorhinal cortex, whole brain, and ventricle) progression in AD. Atrophy rates greater among MCI converters. Atrophy rates greater among AD fast progressors
Jack et al. [97]	133 MCI subjects	52 subjects MRI brain atrophy rate measures can be used as indicators of disease progression in a multi-site therapeutic MCI setting. APC was greater in converters than non-converters. APCs greater in APOE ϵ 4 non-carriers. APCs and changes in cognitive test performance uniformly correlated in expected direction ($p < 0.000$)
Jack et al. [98]	72 aMCI subjects, 91 HC; 1-2 years follow-up.	13 HC developed MCI or AD; 39 MCI subjects developed AD Larger ventricular APC (HR for a 1-SD increase 1.4, $p = 0.007$) increased risk of AD conversion. Both ventricular APC (HR for a 1-SD increase 1.59, $p = 0.001$) and whole brain APC (HR for 1-SD increase 1.32, $p = 0.009$) provided additional predictive information to covariate-adjusted sectional HC volume at baseline about risk of AD conversion. However, overlap present among those converters and non-converters indicate that these measures are unlikely to provide absolute prognosis for MCI-converters.
Apostolova et al. [99]	20 MCI subjects followed up over 3 years	6 subjects developed AD (MCI-c), 7 remained stable (MCI-nc), and 7 improved (MCI-i). Smaller hippocampi and specifically CA1 and subicular subfields are associated with increased risk for conversion from MCI to AD. Larger hippocampal volumes and relative preservation of both the subiculum and CA1 are associated with cognitive stability or improvement.
Risascher et al. [101]	339 MCI (277 MCI-stable, 62 MCI-converters) subjects, 206 HC, 148 AD subjects	62 MCI developed AD Degree of neurodegeneration of MTL structures is the best antecedent MRI marker of imminent conversion, with decreased hippocampal volume (left > right) being the most robust structural MRI feature. Effect sizes of hippocampus (0.6) and MTL structures (0.53) comparing MCI-stable and converters.
Querbes et al. [103]	122 aMCI (50 stable MCI, 72 progressive MCI), 130 HC, 130 AD followed up over 24 months.	72 aMCI developed AD. Normalised cortical thickness can predict AD conversion with 76% cross-validated accuracy.
<u>Molecular Imaging</u>		
Lo et al. [105]	229 normal, 397 MCI and 193 AD subjects followed up 3 years	Rates of change in CSF A β 42, glucose metabolism and hippocampal volume Amyloid deposition is an early event before hypometabolism or hippocampal atrophy, suggesting that biomarker prediction for cognitive change is stage dependent. Positive APOE4 status accelerated hippocampal atrophy changes in MCI and AD.
Okello et al. [106]	31 aMCI subjects, 26 HC followed up over 3 years	17 out of 31 MCI (55%) had increased [11C]PIB retention at baseline (PIB-positive). 14 of these 17 PIB-positive MCI (82%) developed AD. Half (47%) converted to AD within 1 year. Fast converters have higher PIB retention levels at baseline than slower converters in anterior cingulate, ($p = 0.027$) and frontal cortex ($p = 0.031$). Only 1 out of 14 PIB-negative subjects develop AD. 7 of 17 PIB-positive MCI, APOE ϵ 4 carriers associated with faster conversion rates ($p = 0.035$)
Koivunen et al. [107]	29 MCI, 13 HC followed up over 2 years	17 MCI developed AD Hippocampal atrophy increases and amyloid deposition changes modestly during conversion to AD, suggesting dissociation between the two during evolution of MCI. AD converters had greater [11C]PIB retention at baseline in posterior cingulate ($p = 0.022$), putamen ($p = 0.041$), caudate nucleus ($p = 0.025$). Greater hippocampal atrophy in MCI converters at baseline.

Small et al. [108]	22 HC and 21 MCI followed up over 2 years	Increases in frontal, posterior cingulate, and global binding at follow-up correlated with progression of memory decline ($r = -0.32$ to -0.37 , $P = 0.03$ to 0.01). MCI A β + and HC A β + associated with greater clinical worsening on ADAS-Cog and CDR-SB. MCI A β + associated With greater decline in memory, DSS and MMSE ($p < 0.05$). Global cortical [11C]PIB BPND is significantly increased in MCI subjects, but no changes was observed in AD subjects or HC. Increase most prominent in lateral temporal lobe ($p < 0.05$). No changes in global [18F] FDDNP.	[18F]FDDNP PET scanning may be useful in identifying people at risk for future cognitive decline. Higher [18F]FDDNP binding at baseline is associated with future decline in most cognitive domains ($r = -0.31$ to -0.56 , $P = 0.05$ to 0.002). Frontal and parietal [18F]FDDNP binding yielded highest diagnostic accuracy. ROC 0.88 (95% CI 0.72-1.00) compared with 0.68 (95% CI 0.45-0.91) for medial temporal binding. Florbetapir PET, which detects A β pathology, may be helpful in identifying individuals at increased risk for progression to AD. Higher SUVR in MCI associated with greater decline on ADAS-Cog, CDR-SB, memory measure (DSS) and MMSE (all $p < 0.05$). MCI A β + had higher risk of developing AD.
Doraiswamy et al. [109]	51 MCI, 69 HC, and 31 AD followed up over 18 months.		
Ossenkoppele et al. [110]	11 HC, 12 MCI, and 8 AD followed up over 2.5 years.		[11C]PIB and [18F] FDG track molecular changes in different stages of AD. MCI subjects were found to have an increased amyloid load while AD subjects had increased progressive metabolic impairment. [18F]FDDNP is less useful for examining disease progression. Reduction in [18F]FDG uptake at follow-up observed in AD subjects only (esp frontal, parietal, temporal lobes (all $p < 0.01$). Changes in global [11C]PIB binding ($p = -0.42$, $p < 0.05$) and cingulate [18F]FDG uptake ($p = 0.43$, $p < 0.01$) correlated with changes in MMSE score over time across groups but not for [18F] FDDNP binding ($p = -0.18$, $p = 0.35$).
Zhang et al. [111]	Meta-analysis of 13 research studies (7 FDG-PET)	FDG-PET pooled estimates: 78.7% Sn (95% CI 68.7-86.6%) 74% Sp (95%CI 67.0-80.3%) PIB-PET pooled estimates: 93.5% Sn (95% CI 71.3-99.9%) 56.2% Sp (95% CI 47.2-64.8%)	Both FDG-PET and PIB-PET are valuable techniques for prediction of AD progression in MCI subjects.
Predicting rapid AD progression/ decline			
Thompson et al. [100]	12 AD subjects, 14 HC	Followed up 3 years	Cortical atrophy occurred in a well defined sequence (temporal- frontal- sensorimotor) as the disease progressed. Mirroring the sequence of neurofibrillary tangle accumulation observed in cross sections at autopsy. Left hemisphere degenerates faster ($5.3 \pm 2.3\%$ per year in AD v.s. $0.9 \pm 0.9\%$ per year in controls; $p < 0.029$) than the right Fast decliners had a more extensive cortical atrophy than slow decliners, especially in the medial occipitoparietal areas (specifically precuneus, Lingual gyrus and cuneus which was not yet detected by clinical and neuropsychological assessment.
Kinkingnéhun et al.[103]	23 mild AD subjects and 18 HC followed up	Followed up 3 years	
Functional Imaging Silverman et al. [107]	284 patients presenting symptoms of dementia	Progressive dementia in 59%	In patients presenting symptoms of dementia, regional brain metabolism was a sensitive indicator of AD. A negative PET scan indicated that pathologic progression of cognitive impairment during the mean 3-year follow-up was unlikely to occur. Sn 93%, Sp 76%. -LR 0.1 (95% CI 0.06-0.16) experiencing progressive course after a single negative PET scan.

NC = Normal Controls
MRI = Magnetic Resonance Imaging
APC = Annual percent change

HC = Healthy Controls

SD = Standard deviation

MTL = Medial Temporal Lobe

aMCI = amnesic MCI

PIB = Pittsburgh Compound B

FDDNP = Fluoroethyl(methylamino]-2-naphthyl)ethylidene) malononitrile

PET = Positron Emission Tomography

MMSE =Mini Mental State Examination

Sn = Sensitivity

Sp= Specific

-LR = negative Likelihood ratio

Table 4. Neuroimaging methods in predicting AD conversion in MCI patients and rapid AD progression/ decline

With technological advances over the past three decades, MRI is now readily available and relatively economical. Currently it is widely used as a diagnostic tool, to complement clinical assessment and neuropsychological testing. Moreover, MRI has also been considered for longitudinal tracking of the disease progression and to predict whether a MCI patient may go on to develop AD, or whether an AD patient will have an indolent or rapid course. Advances in technology have led to automated data-driven methods, such as automated measurement of whole brain volume over time, voxel-based morphometry (VBM), deformation-based morphometry (DBM) and analysis of cortical thickness. These technologies ameliorate the previous problems associated with manual measurement, inter-rater reliability and difficulties in cross-study comparisons.

In a seminal paper, Jack [96] studied annualized changes in volume of four structures in serial MRI studies: hippocampus, entorhinal cortex, whole brain and ventricles of normal, MCI and AD subjects. All four atrophy rates were greater among MCI-converters compared to non-converters and fast-progressors versus slow progressors. Although the differences in atrophy rates have been replicated consistently in several follow-up studies [97,98], given the overlap among those who did and did not convert, the authors cautioned that these measures were unlikely to provide absolute prognostic information for individual patients.

Using hippocampal volumetry, a prospective longitudinal cohort study found that greater atrophy in the CA1 hippocampal and subicular subfields predicted MCI conversion, whereas larger hippocampal volumes predicted cognitive stability and/or improvement [99].

Employing a 3-dimensional cortical mapping approach, Thompson [100], demonstrated a temporal-frontal-sensorimotor sequence of cortical atrophy with AD progression in a longitudinal series of 12 AD subjects, where left brain was found to degenerate faster than right.

Employing VBM technique, Risacher [101] found that AD and MCI converters demonstrated high atrophy across regions as compared to HC in global and hippocampal grey matter (GM)

density, hippocampal and amygdalar volumes, and cortical thickness values from entorhinal cortex and other temporal and parietal lobe regions. MCI-stable showed intermediate atrophy. Degree of atrophy of medial temporal structures, especially the hippocampi, was found to be the best antecedent MRI marker of imminent conversion.

A separate study also showed that occipitoparietal (specifically precuneus, lingual gyrus and cuneus) atrophy at baseline better anticipated the rate of progression (fast decliners from slow decliners) over 3 years compared to clinical and neuropsychological assessment [102].

Cortical thickness is another measure of interest in structural neuroimaging where a normalized thickness index was computed using a subset of these regions, namely the right medial temporal, left lateral temporal and right posterior cingulate. Normalized thickness index at baseline differed significantly among all the four diagnosis groups (HC, stable MCI, progressive MCI and AD). Furthermore, normalized thickness index also correctly predicted evolution to AD for 76% of aMCI subjects after cross-validation [103].

5.2. Functional and molecular imaging

There are many functional imaging studies for AD though only a few specifically investigate longitudinal progression of MCI and AD using Fluorodeoxyglucose (18F) (FDG)-Positron Emission Tomography (PET) [104].

Lo [105] found that the rate of change of glucose metabolism and hippocampal volume accelerated as cognitive function deteriorated. Moreover, glucose metabolic decline and hippocampal atrophy were significantly slower in subjects with normal cognition compared to those with MCI or AD. Positive APOE4 status was also associated with accelerated hippocampal atrophy.

Molecular imaging utilizes small molecule ligands that bind with nanomolar affinity to amyloid and enters the brain for imaging with PET. It is a measure to detect and quantify cerebral beta-amyloidosis. It should be noted that besides AD, there are other disease conditions that may have cerebral A β . The most commonly used ligand is the carbon-11(11C)-based Pittsburgh compound B (PIB), which binds specifically to fibrillar A β but exhibits no demonstrable binding to neurofibrillary tangles. However, fluorine-18 (18F)-based tracers, e.g. 2-(1-{6-[(2-fluorine 18-labeled fluoroethyl)methylamino]-2-naphthyl}ethylidene) malononitrile ([18F]FDDNP) have a considerably longer half-life compared to [11(C)]PIB and some types have been shown to also bind to neurofibrillary tangles.

Okello [106] showed that PIB-positive subjects with MCI are significantly more likely to convert to AD than PIB-negative ones. A separate longitudinal study showed that hippocampal atrophy and amyloid deposition (in posterior cingulate, lateral frontal cortex, temporal cortex, putamen and caudate nucleus) seem to dissociate during the evolution of MCI, the atrophy increasing clearly and [(11C)] PIB retention changing modestly when conversion to AD occurs [107]. Using [(18F)]FDDNP PET, higher baseline binding was associated with future decline in most cognitive domains. Specifically, frontal and parietal [(18F)]FDDNP binding yielded the greatest diagnostic accuracy in identifying MCI-converters versus non-converters [108]. With 18F florbetapir (18F-AV-45) tracer, baseline A β + scans were associated with greater

clinical worsening on the AD Assessment Scale-Cognitive subscale (ADAS-Cog) and Clinical Dementia Rating-sum of boxes (CDR-SB). In MCI, $A\beta$ + scans were also associated with greater decline in memory, Digit Symbol Substitution (DSS) and MMSE. $A\beta$ + MCI subjects again tended to convert to AD at a higher rate than $A\beta$ - subjects [109].

In a seminal comparison study of three modalities [110], using [(11)C]PIB, [(18)F]FDDNP and [18F]FDG, there was a significant increase in global cortical [(11)C]PIB binding (most prominent in the lateral temporal lobe) in MCI patients, but no changes in AD patients or controls. Interestingly, [(18)F]FDDNP did not show any changes in global binding potential. Moreover, changes in global [(11)C]PIB binding and posterior cingulate [(18)F]FDG uptake were correlated with changes in MMSE score over time across groups, but not with [(18)F]FDDNP binding. Hence it was postulated that [(11)C]PIB and [(18)F]FDDNP track molecular changes in different stages of AD. There was an increased amyloid load in MCI patients and progressive metabolic impairment in AD patients. The authors opined that [(18)F]FDDNP was less useful for examining disease progression.

To estimate the diagnostic accuracy of FDG-PET and PIB-PET for prediction of short-term conversion to AD in patients with MCI, Zhang [111] and co-workers performed a meta-analysis undertaken with a random-effects model. Overall diagnostic accuracy determined for both FDG-PET and PIB-PET suggests that they are potentially valuable techniques for prediction of progression in patients with MCI. Both have their advantages and their combined use is a promising option.

Villain et al recently published a longitudinal PIB study (testing conducted 18 months apart), showing a significant increase in amyloid- β accumulation in both PIB-positive and negative subjects (significantly higher in PIB-positive individuals) with a bimodal distribution of individual rates of neocortical amyloid- β accumulation [112].

5.3. Summary

MRI volumetry and brain atrophy rates have fairly good diagnostic and predictive value in MCI subjects. Longitudinal data on brain atrophy rates with disease progression are available and hence, can be used for monitoring disease progression in clinical trials. The limitations of structural neuroimaging as a biomarker include problems with the accurate delineation of regions of interest and lack of standardization of imaging and measurement techniques, making it difficult to compare data across the different institutions out of Europe, North America and Australia (all of which have their unified imaging consortiums). The advent of automated data-driven innovations for structural imaging holds promise. FDG-PET appears to be the leading candidate among the functional neuroimaging modalities, with available evidence for MCI diagnosis, prediction of MCI-converters and longitudinal data in monitoring serial progression. To date, [(11)C] PIB is the most extensively studied PET amyloid tracer, although 18F florbetapir proves to be an attractive alternative given the longer half-life. There is emerging evidence for amyloid imaging in the diagnosis of preclinical AD. From the standpoint of clinical trials of anti-amyloid therapy, in-vivo amyloid imaging pre-treatment allows selection of patients with demonstrable cerebral $A\beta$ loads; repeated imaging during ongoing treatment allows detection of decrease in insoluble $A\beta$ load in response to amyloid-

clearing drugs such as immunotherapy. Amyloid imaging needs to be more practically accessible and affordable before it can be transferable to the clinical diagnostic routine.

6. Combinational biomarkers

Many of the aforementioned biomarker modalities are not separate discrete entities but have an effect on each other. For example, the association of hypertension with CSF tau and ptau-181, was found to be modified by APOE ϵ 4 phenotype, where hypertension is directly related to tau pathology (and not A β 42) in APOE ϵ 4 homozygous carriers [113]. Elevated CSF t-tau and p-tau in presence of APOE ϵ 4/ ϵ 4 genotype has also been shown to influence faster AD progression in MCI subjects [114].

For the identification of MCI-converters, various literature showing combination biomarkers have been published. They include looking at clinical measures (such as cognitive or neuropsychological tests) in combination with CSF biomarkers [115], neuroimaging measures [116, 117], or in combination with both CSF and neuroimaging measures [118-119].

A combination of CSF and neuroimaging biomarkers [120-4] has found improved predictive accuracy of MCI-converters, supported by slope analyses of annual cognitive decline [120]. Okamura showed that a high ratio between cerebrospinal fluid (CSF) tau and posterior cingulate perfusion on SPECT is useful in identifying MCI converters [125]. Using a machine-learning approach (support vector machines), Furney et al examined the utility of adding cytokine and neuroimaging biomarkers to conventional measures, and found that the combination of cytokine and neuroimaging with clinical and APOE ϵ 4 genotype improved accuracy [126]. Recent studies have also looked at multimodal neuroimaging techniques to predict MCI progression [127-129].

Other recent studies have used endophenotype-based approach and found single nucleotide polymorphism (SNP) such as rs1868402 to have strong, replicable association with CSF ptau₁₈₁ association with rate of AD progression [130].

7. Conclusion and future directions

Clinical criteria alone, often subjective and dependent on clinical judgment, are insufficient to identify the pre-clinical stages of AD accurately. This has prompted the past decade-long intensive research into the use of more objective neuroimaging and biochemical markers to either replace, or complement, clinical approaches to facilitate an early and accurate diagnosis of the illness [131,132]. The chapter thus far details the rationale (most evident from Table 1) for the combined approach of clinical measures with other biomarkers in predicting AD progression; but in the earlier stages (prodromal and especially preclinical AD stages), biomarkers would play an increasingly important role. Combination biomarker approaches appear to be superior to a single biomarker approach, with the recent focus of researchers being

Subjects	Follow-up (years)	Biomarker	Results
MCI (n=8) NC (n=10) [70]	1	CSF p-tau231 CSF A β 40 CSF A β 42	MCI: 5.0; NC: 3.0 * MCI: 4.0; NC: 8.0 MCI: 4.0; NC: 2.0
MCI (n=7) NC (n=9) [71]	2	CSF p-tau231 CSF A β 40 CSFA β 42	MCI: 2.0; NC: 20.0 * MCI: 0.5; NC: 3.5 MCI: 0.35; NC: 1.5
MCI (n=62) AD (n=68) NC (n=24) [72]	2	CSF isoprostane CSF neurofilaments light CSF A β 40 No change in A β 42 or p-tau 181.	NC:-1.9; MCI:-0.4; AD: 5.0 ** NC:-0.18; MCI:-0.79; AD: -0.96 NC: 0.61; MCI:0.28; AD:0.43
MCI (n=57) AD (n=56) [65] NC (n=8)	3	CSF A β ₄₂ CSF tau CSFp-tau CSFA β 42/tau CSFA β 42/ptau	MCI(stable): 3.42, MCI (converters):0.78, AD:-11.9** MCI(stable):19.7, MCI(converters):17.4, AD: 0.55 MCI(stable):1.24, MCI(converters):-0.21, AD: -2.2 MCI(stable):-0.54.MCI(converters):-0.4,AD: -0.008 MCI(stable):-0.19, MCI(converters):-0.07,AD:0.18
NC (n=55) MCI (n=41) AD (n=64) [99]	1.2-2.4	Hippocampus* Entorhinal cortex Whole brain Ventricle	MCI (stable):-4.4,MCI(converters):-7.8, AD slow -9.4, AD fast -15.4 MCI(stable):-15.9, MCI(converters):-16.0, AD slow-20.5, AD fast -22.7 MCI (stable):-0.8, MCI (converters):-2.5, AD slow -2.4, AD fast -3.6 MCI (stable):0.8, MCI(converters):1.8, AD slow -6.5, AD fast 1.9
MCI (n=131) [101]	3	Hippocampus * Entorhinal cortex Whole brain Ventricle	MCI (converters) -6.78; MCI (non-converters) -3.86 MCI (converters) -15.08 ; MCI (non-converters) -8.32 MCI (converters) -0.88 ; MCI (non-converters) -0.36 MCI (converters) 5.66 ; MCI (non-converters) 3.33
MCI (n=72) [104]	1-2	Hippocampus * Entorhinal cortex Whole brain Ventricle	-3.3 (2.7) -7.0 (4.3) -0.7 (1.0) 3.3 (2.3)
AD (n=32) MCI (n=49) NC (n=103) [116]	1.5	PiB-PET (neocortical PiB rate of change) (SuVR _{pons} /year) *	AD: PiB-(acc) +0.06; PiB+(acc) +0.05; PiB (non-acc) -0.01 MCI: PiB-(acc) +0.04; PiB-(non-acc) -0.001; PiB+ (acc) +0.04; PiB (non-acc) -0.01 HC: PiB-(acc)+0.03; PiB- (non-acc) -0.01; PiB+(acc) +0.04; PiB+ (non-acc) -0.004
NC (n=210) MCI (n=357) AD (n=162) [135]	2	CSF A β ₄₂ CSF tau PiB FDG-PET Hippocampus Ventricles ADAS-Cog total MMSE CDR-SB RAVLT (5 trial total)	NC: -0.94; MCI: -1.4; AD: -0.1 * NC: 3.45; MCI: 2.34; AD: 1.24 NC: 0.098; MCI: -0.008; AD: -0.004 NC: -177; MCI: 752; AD: 2993 NC: -40; MCI: -80; AD: -116 NC: 848; MCI: 1551; AD: 2540 NC: -0.54; MCI: 1.05; AD: 4.37 NC: 0.0095; MCI:-0.64; AD: -2.4 NC: 0.07; MCI 0.63; AD: 1.62 NC: 0.29; MCI: -1.37; AD: -3.62

* expressed as % change per year compared to baseline values

** expressed as annual change β

MCI = Mild Cognitive Impairment

NC = Normal Controls

AD = Alzheimer's Disease

CSF = Cerebrospinal fluid

PiB = Pittsburgh Compound B

FDG-PET = Fluorodeoxyglucose (18F)-Positron Emission Tomography

MMSE = Mini Mental State Examination

CDR-SB = Clinical Dementia Rating – Sum of Boxes

RAVLT = Rey Auditory Verbal Learning Tes

Table 5. Longitudinal biomarker studies

on multimodal approach using various systems biology and multivariate modeling methods. Additionally, multi-site prospective studies, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), allow for global summary of results and patterns of change observed in clinical measures and candidate biomarkers [133] (Table 5). It must also be highlighted that some of the heterogeneity of biomarker findings thus far is related to the different periods of follow-up and hence AD conversion rates in MCI subjects.

The dynamic biomarker model, in the AD pathological cascade first proposed by Jack in 2010 [134], has been an area of intense interest. However, this inverse relationship between fibrillar amyloid plaque burden (on PIB imaging) and corresponding decrease in CSF A β 42 and elevated tau, has led to the simplistic interpretation that the AD pathological cascade is purely driven by the amyloid cascade (Figure 1). This is partly due to extrapolation from cross-sectional studies, where in fact, longitudinal studies are required to determine the temporal order of the appearance of various pathogenic processes involved in this complex disease. Storandt et al [135] has recently demonstrated in a community cohort that CSF A β 42 and tau were minimally correlated, suggesting that they represent independent processes. Additionally, they accounted for only 60% of variance on PIB imaging, suggesting that a third process may be related to brain atrophy or plaque formation [136].

In addition, understanding longitudinal biomarker change allows its potential inclusion in clinical trials, with recent studies advocating the use of neuroimaging biomarkers [137,138], CSF biomarkers [139] and/or combination biomarkers [137,140] to boost the power of clinical trials and decrease sample size in MCI trials. An integrated analyses approach using patient (age) severity- and disease-related (severe baseline cognitive, global or behavioural status) factors in established AD has been shown, with the potential of symptomatic AD therapy, to decrease likelihood of faster decline [141].

Further work on biomarkers is important because of their multiple potential roles. Biomarkers have the potential to be used as a prognostic tool for the prediction of AD conversion in MCI subjects and rapid AD progression, with translation into clinical practice by using a most practical algorithm, and as a diagnostic tool in prodromal/ preclinical stages of AD. Biomarkers may also lead to a deeper understanding of the complex pathogenesis of AD disease – including stage-specific and stage-independent processes. There is also currently an unfulfilled potential in biomarker-enriched clinical trials and the use of biomarkers in preclinical AD, especially in the advent of newer therapeutic targets. Finally there is also potential to extrapolate biomarker findings 'backwards' into the earliest stages of disease so that we may be able to identify those at risk and consider instituting interventions. This would enable earliest therapeutic intervention for at-risk subjects most amenable to disease-modifying treatments, and exclude those for whom the possible risks from investigational treatment would be more difficult to justify. At the very least, it would identify those who might benefit most from intensive monitoring and management of clinical factors, e.g. blood pressure, diabetes and lipids, and also non-invasive interventions, e.g. cognitive training. This vital work can only be done through multi-center studies and standardized evaluation techniques using various systems biology and statistical modeling approaches.

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