Progress and challenges in the diagnosis of dementia: a critical review

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ABSTRACT

Longer life expectancies have led to an increased number of neurodegenerative disease cases globally. Accurate diagnosis of this devastating disorder is of crucial importance but is still feasible only by a brain biopsy after death. An enormous amount of attention and research has been in place over the years towards the better understanding of the mechanisms, as well as the early diagnosis, of neurodegeneration. However, numerous studies have been contradictory from time to time, while new diagnostic methods are constantly developed in a tireless effort to tackle the disease. Nonetheless, there is not yet a conclusive report covering a broader range of techniques for the diagnosis of different types of dementia. In this article, we critically review current knowledge on the different hypotheses about the pathogenesis of distinct types of dementia, as well as risk factors and current diagnostic approaches in a clinical setting, including neuroimaging, cerebrospinal (CSF) and blood tests. Encouraging research results for the diagnosis and investigation of neurodegenerative disorders are also reported. Particular attention is given to the field of spectroscopy as an emerging tool to detect dementias, follow-up patients and potentially monitor the patients' response to a therapeutic approach. Spectroscopic techniques, such as infrared and Raman spectroscopy, have facilitated numerous disease-related studies, including neurodegenerative disorders, and are currently undergoing trials for clinical implementation. This review constitutes a comprehensive report with an in-depth focus on promising imaging, molecular biomarker and spectroscopic tests in the field of dementive diseases.

Keywords: neurodegenerative disease; dementia; biomarkers; diagnostic methods; neuroimaging; spectroscopy

INTRODUCTION

Estimates of dementia prevalence have shown that 46.8 million people live with this condition worldwide and this is expected to reach 75 million by 2030 [1]. People living with dementia are under-detected in high income countries, with only 20-50% of cases being accurately diagnosed in primary care; lack of diagnosis is even more evident in low- and middle-income countries [2-4] (Fig. 1). The number of new cases of dementia every year was estimated to be over 9.9 million, implying one new case every 3.2 seconds [5]. A definitive diagnosis is still only been given post-mortem, thus an accurate detection is essential for providing an early intervention and improving the lives of those affected.

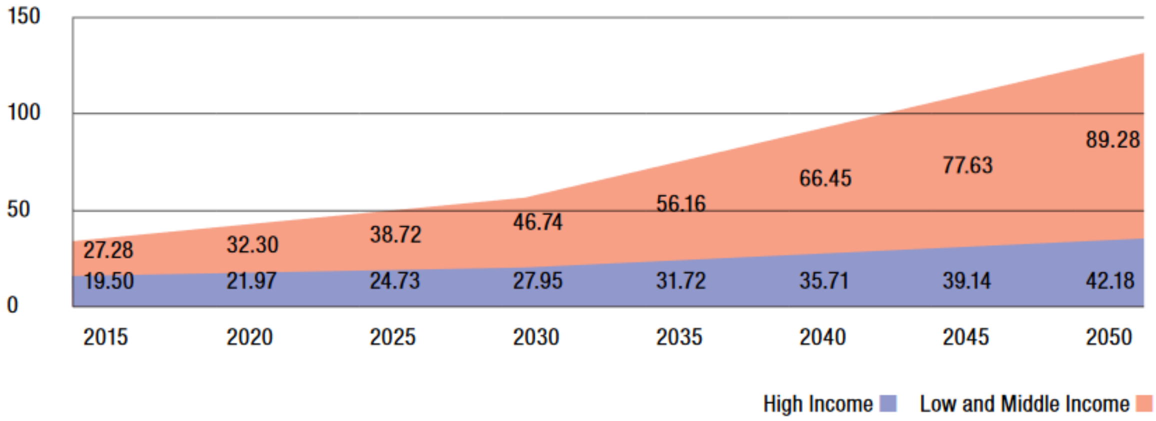

Figure 1: Estimation of people with dementia, in millions, in high- and low/middle-income countries. Adapted from [5].

Symptoms of different dementias vary depending on the type but they all share some common characteristics, such as loss of memory and other mental abilities. Under the "umbrella" term of dementia, Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) constitute the two most common types of underlying pathology [6]. Other, common types of dementia include vascular dementia (VaD), frontotemporal dementia (FTD), Parkinson's disease dementia (PDD) and mixed dementia [7-9]. The majority of the above-mentioned dementias undergo the same pathological mechanism of protein misfolding, which subsequently leads to clumps of proteins and neuronal death, with VaD being an exception as it has a distinct mechanism than the other dementias. Brain damage in VaD patients occurs due to the lack of blood supply from bleeding, clotting or narrowing of arteries which can cause nerve cell injury or death. As AD often co-exists with VaD, signs of both syndromes are most likely to be present. Furthermore, recent work by Novarino *et al*. has interestingly shown that, even though it does not fall into the spectrum of dementia, motor neuron disease (MND) has common features with other neurodegenerative disorders such as AD, PD and amyotrophic lateral sclerosis (ALS) [10]. This indicates that study of one neurodegenerative disease could possibly advance the understanding of others as well.

A number of risk factors have been associated with the development of neurodegenerative diseases and dementia. Increasing age, family history and susceptibility genes are some of the well-known unavoidable risk factors [11-13]. Numerous studies have associated neurodegeneration with a range of other risks which could be more easily managed, such as lifestyle choices (*e.g*., diet, exercise and alcohol intake) [14-16], environmental factors (*e.g*., pesticides and neurotoxic metals, such as lead, mercury, arsenic) [14, 17], education [18], gender [19, 20], Down syndrome [21, 22], head injuries [23, 24] or diabetes and cardiovascular diseases [25, 26]. Recent findings have suggested that some factors could actually reduce risk in PD patients, including smoking, caffeine, and urate [27]. These could potentially act as neuroprotective agents and thus be beneficial for patients with early neurodegeneration. A use of these methods in clinical trials, facilitated by an accurate diagnosis with the techniques described in this paper, might be more effective at an early stage prior to significant brain damage. Current ongoing trials assessing long-term treatment with nicotine (using transdermal patches for over 60 months in early PD patients), caffeine (400 mg per day for five years) and inosine for urate elevation (using early PD patients to increase serum urate concentration within 24 months) aim to conclude whether these factors could facilitate therapeutic intervention or secondary prevention.

It is most likely that the majority of neurodegenerative disorders occur as a result of complex interactions between any or all the above risk factors; this renders them complicated and difficult to study. The complexity of dementia is further demonstrated by the fact that drugs aiming to improve cognitive functions and delay the deterioration, such as cholinesterase inhibitors, still remain ineffective [28, 29]. Much effort has been put on clinical trials, over the years, to help treat people experiencing dementia but without much success [30, 31]. It is increasingly thought that drugs should be administered at an early, pre-symptomatic stage of dementia in order to provide successful treatment. However, there is yet no robust way to pre-clinically detect people who will develop dementia, which renders the need of early biomarkers crucial.

Research in the field of neurodegeneration and dementias currently undergoes fast progress. Promising results from recent studies have led to a wide consensus that dementia is a slowly progressive disease which means that a diagnosis may be feasible years before symptoms develop. An early diagnosis with biological markers would greatly facilitate and accelerate the development of effective drugs and/or allow the diagnosed individuals to make better lifestyle choices. However, different research groups have employed different diagnostic approaches and studied a range of diagnostic and/or prognostic biomarkers, thus causing controversy and debate regarding the optimal method to take forward. This review will present and evaluate current knowledge with regard to a number of different dementias, including both 'traditional' and novel diagnostic approaches.

EPIDEMIOLOGY

The types of dementia that will be studied in more detail in this critical review include AD, DLB, FTD, VaD, PDD and mixed dementia.

Alzheimer's disease (AD)

AD is the most common cause of dementia accounting for 60-80% of the cases. Previous estimates have shown that ~34 million people worldwide have AD, with the prevalence expected to triple by 2050 [32]. Determining the age of onset and defining a disease-free cohort have been two of the reasons that incidence rates for AD are difficult to calculate. After bringing together data from 24 published studies, Mayeux and Stern reported an approximate incidence of 0.5% per year for the age cohort 65-70 years which increased to 6-8% for the individuals over 85 years of age (Fig. 2) [33].

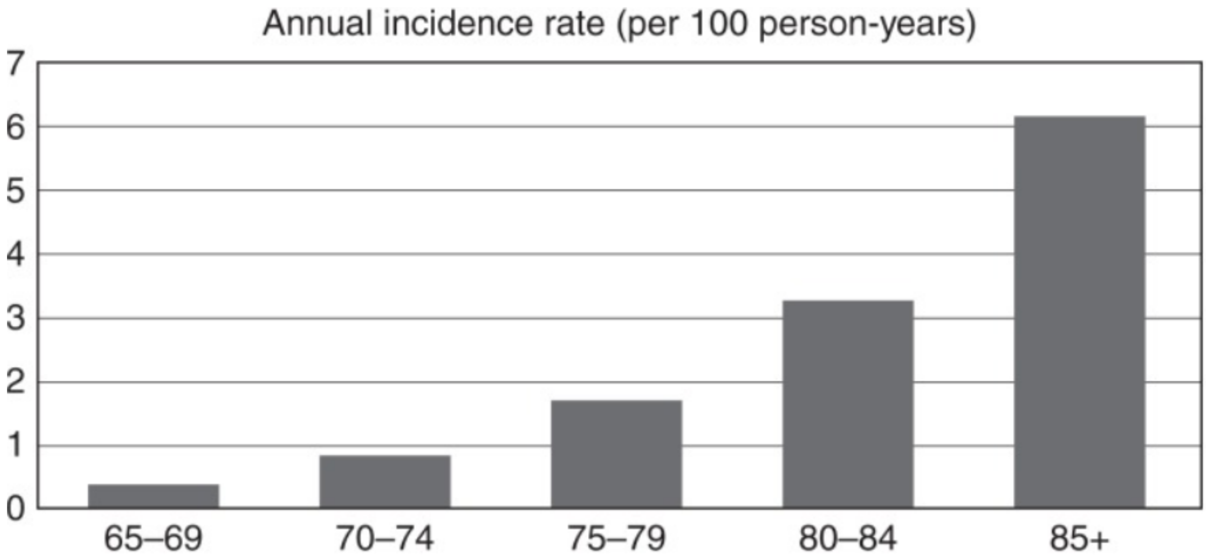

Figure 2: Annual incidence rate (per 100 person-years) for Alzheimer's disease. The graph illustrates an estimate of data from 24 published studies. Adapted from [33]. With permission from Cold Spring Harbor Laboratory Press.

The terminology of AD has been revised in the 2011 guidelines (after almost 30 years from the original criteria) to also include cases from the time point of the initial pathologic changes in the brain; in other words, before symptoms of memory loss incur [34]. Three different stages were suggested to characterise the disease according to its progression: preclinical (or pre-symptomatic) AD; mild cognitive impairment (MCI) due to AD; and dementia due to AD (Fig. 3). In a preclinical stage, the key biological changes are under way but without presenting any obvious, clinical symptoms; this primary phase is thought to begin years in advance. MCI includes some changes in memory and thinking that can be noticeable but do not affect the ability for daily tasks; more importantly, not all people with MCI develop AD dementia eventually. In a meta-analysis of 41 cohort studies, it was found that only 38% of MCI progressed to dementia during a follow-up period of 5 years [35]. Finally, the last stage of AD due to dementia includes the well-known symptoms of memory loss as well as cognitive and behavioural impairment.

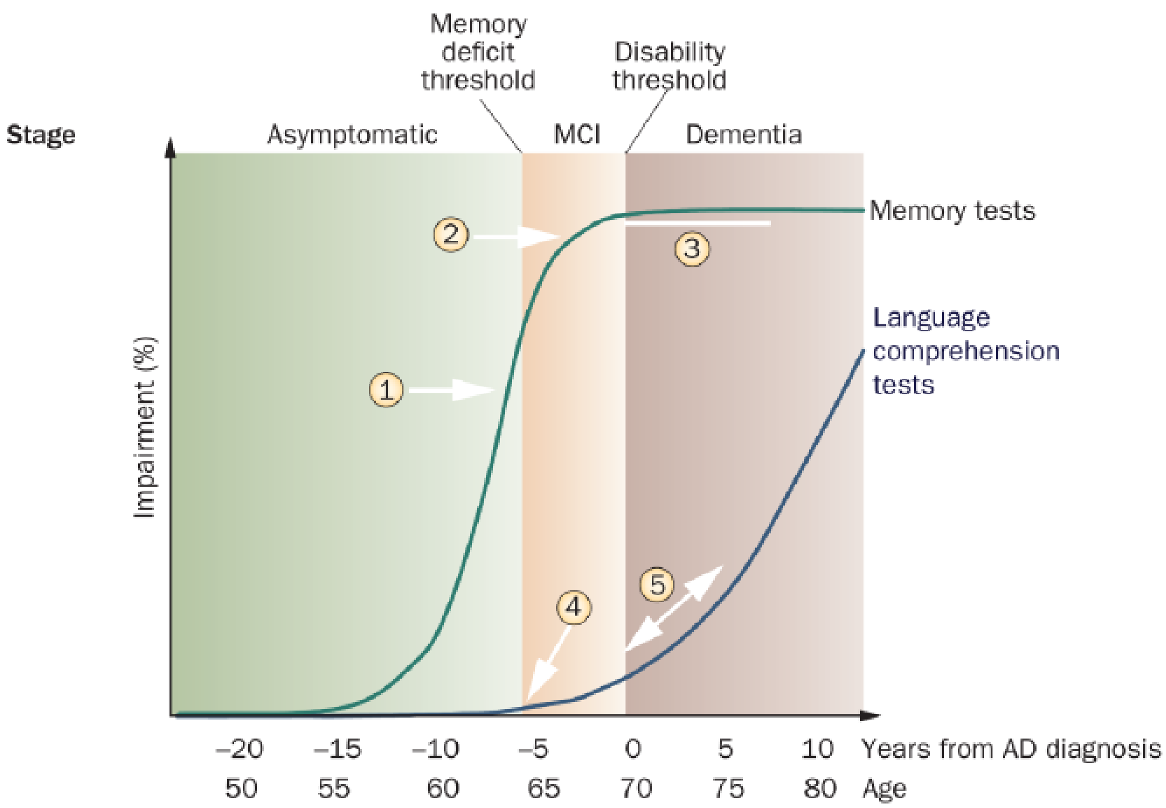

Figure 3: Known natural history of cognitive markers implies that memory tests, which change relatively early in the disease course (1) and soon reach the maximal level of impairment (2), are useful for diagnosis at the MCI stage, but are less useful for tracking later disease progression (3). Verbal comprehension tests start to change later in the disease course: during MCI they show mild or no impairment (4), and are of limited use in diagnosis. These markers become more sensitive at the dementia stage, when the slope of change steepens (5). Adapted from [36]. Reprinted by permission from: Springer Nature, Nature Reviews Neurology, The clinical use of structural MRI in Alzheimer disease, Giovanni B. Frisoni, Nick C. Fox, Clifford R. Jack Jr, Philip Scheltens, Paul M. Thompson (2010). License Number 4279300909074.

The greatest risk factor for AD is increasing age but other factors also play a significant role in developing the disease. AD can be either familial, which is inherited by a family member and is rarer, or sporadic. Family history and carrying the gene for the production of the apolipoprotein ε4 (ApoE ε4) are now well-established risk factors. ApoE is a major cholesterol carrier and has three distinct isoforms: ε2, ε3 and ε4 [37]. The human ApoE protein contains 299 amino acids and despite the fact that the three isoforms differ by only one or two amino acids, their structure and function is entirely different [38]. Individuals with two alleles of ε4 have 12-fold risk to develop the disease about 10-20 years earlier than others with no ε4 alleles, whereas one ε3 allele increases the risk 3-fold. In contrast, ε2 allele decreases the risk [37, 38]. Previous studies have reported the frequency of AD and mean age at clinical onset being 91% and 68 years of age in ε4 homozygotes; 47% and 76 years in ε4 heterozygotes; and 20% and 84 years in ε4 non-carriers (Fig. 4) [37]. Strong evidence suggests that the major mechanism by which ApoE influences AD is via its effects on Aβ metabolism [38]. The toxic events of ApoE are thought to initiate when the lipoproteins bind to several cell-surface receptors to deliver lipids and to amyloid-β (Aβ) peptide; this in turn leads to synaptic dysfunction [37]. Normally each ApoE isoform enhances the degradation of Aβ but ApoE ε4 seems to be less effective in Aβ clearance [37]. Several mechanisms have been proposed for the role of ApoE in AD, such as promoting aggregation of Aβ or phosphorylation of tau (Fig. 5).

	APOE4		
	Non-carrier	Heterozygous	Homozygous
AD frequency	20%	47%	91%
Mean age of clinical onset	84-yr	76-yr	68-yr

Figure 4: Apolipoprotein ε4 (*APOE* ε4) as a genetic risk factor for AD. Adapted from [37]. Reprinted by permission from: Springer Nature, Nature Reviews Neurology, Apolipoprotein E

and Alzheimer disease: risk, mechanisms and therapy, Chia-Chen Liu, Takahisa Kanekiyo, Huaxi Xu, Guojun Bu (2013). License Number 4279310010694.

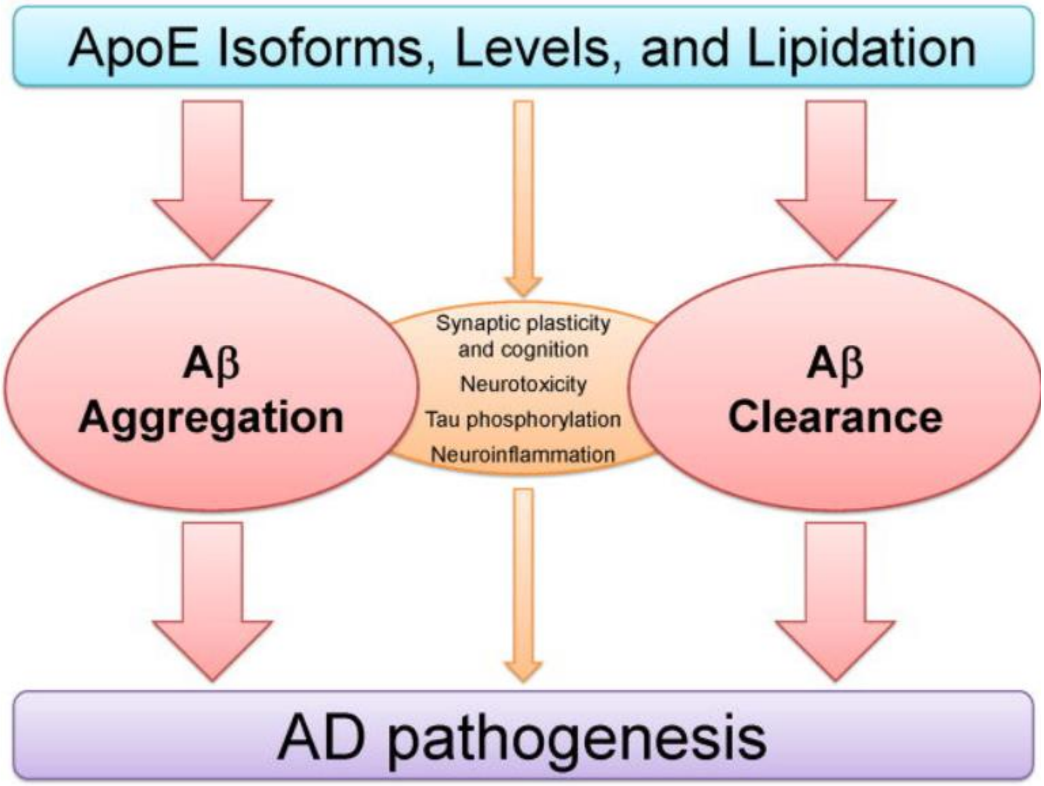

Figure 5: Proposed mechanisms for the role of apolipoprotein (ApoE) in AD pathogenesis. The major effect of ApoE isoforms on AD development is via its effect on Aβ aggregation and clearance. Other mechanisms, including the effects of ApoE isoforms on synaptic function, neurotoxicity, tau phosphorylation, and neuroinflammation, may also contribute. Independent of *ApoE* genotype, differences in the ApoE levels and lipidation state may also mediate processes involved in AD pathogenesis. Adapted from [38] (doi: 10.1038/nrneurol.2012.263). No changes have been made to the figure; License Number 4278980016081.

Other genetic factors that increase the risk of early-onset AD (*i.e.*, below 65 years of age) include mutations in *Amyloid Precursor Protein* (*APP*), *Presenilin 1* (*PSEN1*) and *Presenilin 2* (*PSEN2*). APP is cleaved into fragments by α-, β- and γ-secretases; proteolysis by α- and γ-secretases results in non-pathogenic fragments whereas proteolysis by β- and γ-secretases produces a mixture of Aβ peptides: $A\beta_{1-40}$ (90%) and $A\beta_{1-42}$ (10%). $A\beta_{1-42}$ peptides are more likely to aggregate and form amyloid plaques in AD patients [39]. PSEN1 and PSEN2 proteins are essential components of the γ-secretase; thus, mutations of *PSEN1* and *PSEN2* result in an increased ratio $A\beta_{1-42}$ / $A\beta_{1-40,}$ either through an increased $A\beta_{1-42}$ production or decreased $A\beta_{1-40}$ production, or a combination of both. However, other studies have demonstrated contradictory results showing decreased or unchanged levels of the proteins [40, 41]. Another study has suggested that even though they found no differences in the CSF $A\beta_{1-42}$ or $A\beta_{1-40}$ production rate, there was an impairment of the clearance rate which subsequently led to higher levels of the protein [42].

Over the years, different mechanisms have been proposed for the pathogenesis of AD and many more are suggested as our knowledge of the disease continues to evolve [43, 44]. The two main hypotheses that have prevailed though include the amyloid cascade hypothesis which leads to the aggregation of toxic Aβ oligomers, subsequently creating the extracellular Aβ plaques in the brain, and the tau hypothesis which involves hyperphosphorylation of protein tau causing aggregation and deposits in the brain as intracellular neurofibrillary tangles (NFTs) [45]. In a healthy brain, tau protein binds to microtubules to stabilise them with neuron cells and facilitate effective transport within the cell [46]; in AD, however, tau protein becomes hyper-phosphorylated which causes its detachment from the microtubules and subsequently the formation of oligomers and tangles. The theory of tau hyperphosphorylation is not universally accepted with some suggesting that post-translational modifications, other than phosphorylation, could promote the aggregation of tau; acetylation of tau, for instance, has been previously proposed to play a significant role in this [47]. The initial sites and spread of neurofibrillary tangles within the brain are entirely predictable; they start in the allocortex of the medial temporal lobe (entorhinal cortex and hippocampus), then spread to the associative isocortex, sparing the primary sensory, motor and visual areas until the very end stages [48, 49]. Similarly, Aβ deposition is also predictable [50], starting in the isocortical areas of the brain, then spreading to allocortical brain regions and in the later stages to subcortical structures, including the basal ganglia and the cerebellar cortex [48].

Dementia with Lewy bodies (DLB)

DLB is the second most common type of dementia after AD, sharing clinical and pathological characteristics with both AD and PD. The incidence of DLB had been estimated ~0.1% a year for the general population and accounts for 3.8% of new dementia cases [51, 52]. The pathological hallmark of this type of dementia is the formation of characteristic clumps of proteins, called Lewy bodies (LBs). The main structural component of LBs is α-synuclein which is also found in patients with PD and multiple system atrophy (MSA), all of which are defined as synucleinopathies [53]. However, LBs have also been associated with neurofibrillary tangles and Aβ plaques which are mostly present in AD. Alpha-synuclein consists of 140 amino acids and is encoded by the *SNCA* gene [54]. Nevertheless, due to the constant and abundant $A\beta_{42}$ in DLB cases, it has been suggested that synucleinopathy is also promoted by *APP* dysfunction [55].

DLB and AD have many symptoms in common leading to frequent misdiagnosis. Differential diagnosis of the two subtypes of dementia is crucial to provide a more accurate prognosis, administration of the appropriate treatment and/or inclusion to a suitable clinical trial. For instance, even though DLB cases respond well to drugs prescribed to AD patients, such as cholinesterase inhibitors, they also have severe neuroleptic sensitivity reactions, which are associated with significantly increased morbidity and mortality [56]. Previous work studying the survival and mortality differences between AD and DLB showed that DLB patients had increased risk of mortality with a median survival time of 78 years, which in AD was 84.6 years [57].

In an effort to improve the management of this disorder, new international guidelines were very recently established [6]. Clinically, DLB presents with symptoms of dementia and delirium-like alterations in cognition, attention and arousal. Other clinical symptoms, less frequent in AD, include visual hallucinations, rapid eye movement (REM) sleep behaviour disorder and Parkinsonism. Other, supportive symptoms indicating the disease are hypersomnia, presenting as excessive daytime sleepiness and hyposmia, which occurs earlier in DLB than AD cases. Imaging, genetic and fluid biomarkers have also been established for the diagnosis of DLB [6]. It has also been suggested that accumulation of LB pathology starts in the brainstem, then spreads progressively to limbic regions and finally cerebral neocortex [58].

Frontotemporal dementia (FTD)

Frontotemporal lobar degeneration (FTLD) is a broader term to describe three syndromes that affect the frontal and temporal lobes of the brain: frontotemporal dementia (FTD) mainly causing behavioural changes, semantic dementia (SD) mainly causing impaired word comprehension and semantic memory, and progressive non-fluent aphasia (PNFA) mainly causing impaired speech production [59, 60]. Of those, FTD, or else Pick's disease, is the most common clinical phenotype; it is thought to be third after AD and DLB, with a prevalence ranging from 3% to 26% in people with early onset dementia (*i.e.*, <65 years of age) [61]. This subtype is particular common in younger patients (i.e., <45 years: 10% prevalence; 45-64 years: 60% prevalence; >64 years: 30% prevalence). As the disease progresses with duration, patients develop global cognitive impairment and motor deficits which inevitably lead to death. Death usually occurs after eight years after symptom onset and is frequently due to pneumonia or secondary infections [61].

Some of the clinical symptoms of FTD include progressive deterioration of behaviour and/or cognition as well as behavioural disinhibition (*e.g.*, socially inappropriate behaviour or loss of manners), apathy or inertia, loss of sympathy and empathy (*e.g.*, diminished response to others' needs and feelings), stereotyped or compulsive/ritualistic behaviour (*e.g.*, repetitive movements) or hyperorality and dietary changes (*e.g.*, consumption of inedible objects, altered food preferences) [62]. Due to the similarity of behavioural changes with those seen in psychiatric disorders, such as compulsive behaviours, delusions and euphoria, diagnosing FTD can be challenging [61]. Also, overlap of symptoms with other neurodegenerative disorders such as AD, DLB, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), renders the differential diagnosis even more difficult [60].

Vascular dementia (VaD)

VaD, also known as a single- or multi-infarct dementia, causes around 10% of dementia cases and develops in around 15-30% of individuals three months after a stroke. [63]. Risk factors for VaD can be divided into four categories: demographic (*e.g.*, age, gender, educational level), genetic (*e.g.*, ApoE4, familial vascular encephalopathies), atherosclerotic (*e.g.*, hypertension, smoking, myocardial infarction, diabetes mellitus) and stroke-related (*e.g.*, volume of cerebral tissue lost, bilateral cerebral infarction, white matter disease) [64]. Having one or two *ApoE4* alleles has been found to elevate the risk but not to the same extent as in AD [65].

VaD patients can present with different extents of impaired memory and, in contrast to AD, this criterion of memory disturbance cannot provide an accurate diagnosis. Cognitive changes also vary significantly, and thus it is thought that the classical mini-mental state examination (MMSE) may be less efficient for VaD. Another difference from AD is that the brain pathology is not developing in a predictable pattern and there is still no agreed pathological scheme to facilitate diagnosis and staging. Trials that have utilised drugs originally destined for AD have shown that these may not be appropriate for VaD as well [63]. The rationale for trial of cholinesterase inhibitors and memantine (both established for AD) in VaD patients was based on evidence of their common features and specifically the cholinergic deficit seen in VaD. However, it was later suggested that the cholinergic system might not be affected in VaD alone, but be affected to the same extent as in AD in cases of mixed dementia (*i.e.*, VaD and AD). Even though there has been substantial progress, VaD is yet under-investigated and further research is necessary to elucidate the pathologic mechanisms and facilitate treatment strategies.

Parkinson's disease dementia (PDD)

As patients with Parkinson's disease (PD) progress with time, they often develop a progressive dementia which is similar to AD and DLB. For PDD, a preceding diagnosis of PD, before any symptoms of dementia, is necessary; in contrast, when both parkinsonism and dementia arise in early stages, then DLB is the most likely cause of degeneration [66]. The prevalence of PDD has been estimated to almost 0.2-0.5% in individuals older than 65 years [67], while the incidence rate was found 2.5 per 100,000 person/year for all ages (0-99 years), which increased to 23 per 100,000 person/year for older individuals (>65 years) [68].

The major pathological feature of PDD is the aggregation of α-synuclein mainly in the substantia nigra of the brain; these clumps impair dopaminerging nerve cells thus leading to the characteristic motor and non-motor symptoms of PD [69, 70]. Previous work on the clinical symptoms of PDD has shown that decline in attention, executive functions and visuo-spatial construction is greater than in AD, whereas verbal and visual memory as well as language function are less impaired than in AD [71]. Also, delusions have been reported to be less common than AD and DLB, prevalence of depression is thought to be higher than AD, anger and aggressive behaviour was found more common in AD and sleep quality in PDD and DLB was poorer than AD and normal controls [71].

Mixed dementia

Current studies demonstrate that mixed dementia is more common than previously thought, with pathology resulting from more than one causes. Brain changes result from the combination of pathological hallmarks of different dementive diseases such as AD, DLB and VaD [72, 73].

The coexistence of AD and VaD is a very common type of mixed dementia; according to an autopsy study, 45% AD patients also had cerebrovascular pathology [74]. A recent paper also indicated that in people over 80 years, mixed dementia is the norm, not the exception [63]. It has, thus, been proposed that assessing symptoms by investigating only one pathology may not apply to older patients who are at-risk from both AD and cerebrovascular disease [9]. Similarly, the majority of DLB cases also have co-existing AD pathology [57, 75]. A previous study has shown that combining different pathologies from AD and LBs (*i.e.*, Aβ, tau and α-synuclein) was a better predictor of PDD than assessing any single pathology [76].

CORRELATION OF DEMENTIA & HEAD INJURY

Emerging evidence demonstrates that traumatic brain injury (TBI), occurring after repeated head injuries, is one of the risk factors for the development of dementia. Chronic traumatic encephalopathy (CTE), previously known as dementia pugilistica, is caused by TBI. The abnormal accumulation of hyperphosphorylated tau protein, along with Aβ plaques, are the key components in the brains of CTE patients [77] which are also common to other dementia subtypes, rendering an accurate diagnosis challenging.

It is only after many years of repeated concussive or subconcussive injuries to the head that an individual eventually goes on to develop CTE [23]. This could serve as a time window and allow for a preclinical, early-phase diagnosis which may subsequently lead to the development of preventative and therapeutic strategies. Clinical symptoms accompanying CTE include memory impairment, behavioural and personality changes, Parkinsonism, and abnormalities in speech and gait [78].

Previous neuropathological studies have detected CTE in brains of athletes who played box, rugby, soccer, baseball and ice hockey, as well as in subjects who had experienced a brain trauma from physical abuse, head-banging or even an explosion in a military combat [77]. A very recent study on 202 deceased football players revealed that 177 of them (87%) had CTE at biopsy, suggesting that it may be related with their prior participation in football [24]. However, at present, a definitive diagnosis for CTE is only given after neuropathological examination and therefore, further research is needed for the further understanding and characterisation of the pathology [77]. Investigation is also necessary for the development of neuroimaging and other biomarkers such as CSF and blood biomarkers.

CURRENT DETECTION METHODS

A definitive diagnosis of dementia can only be given post-mortem after histopathological examination of the brain tissue. However, a working diagnosis can be provided clinically after a combination of different neuropsychological tests, brain imaging techniques as well as CSF and blood testing. Newly discovered biomarkers and techniques have been proposed to improve the diagnostic accuracy and characterization of dementive diseases (Table 1).

The Mini-Mental State Examination (MMSE) is the most widely used cognitive screening tool to provide an initial assessment of cognitive impairment, as well as to monitor the progression of the disease with time [79]. The MMSE is in the form of a 30-point questionnaire with a score less or equal to 24 denoting dementia; it assesses temporal and spatial orientation, memory as well as language and visuospatial functions. However, it requires the presence of symptoms and therefore it is not effective with preclinical, asymptomatic cases. Recent studies have shown that more tests, other than MMSE, should be used as its utility is decreased when individuals with MCI and psychiatric conditions are assessed [80, 81]. Aside from MMSE, neurological assessment should be conducted in patients with possible cognitive impairment to evaluate ataxia, anosmia, involuntary movements, reflexes, visual acuity and other signs [82]. For instance, as AD progresses the patients may develop akinesia, rigidity and myoclonus due to the extended impairment of cortical and subcortical structures; patients with PDD will present with bradykinesia, akinetic-rigid symptoms, depression, early visual hallucinations due to subcortical dysfunctions in the areas of executive function and memory; the initial presentations of FTD patients include personality change, emotional problems and behavioural disturbance; in VaD some of the common clinical symptoms include dysarthria, dysphagia, rigidity, visuospatial deficits, ataxia and pyramidal or extrapyramidal signs; DLB often involves visual hallucinations, parkinsonism and fluctuating attention and alertness with intervals of clarity [82]. Predisposing family history is also important for a complete assessment. Even though having a first-degree relative with dementia increases the risk, it does not necessarily lead to dementia. Other environmental and lifestyle factors have been suggested to play a significant role as well [83].

Brain imaging techniques, such as magnetic resonance imaging (MRI) and positron electron tomography (PET), are also widely used in the diagnosis and monitoring of dementias. Structural MRI can indicate the presence of neurodegeneration by showing the tissue damage and loss in characteristic regions of the brain such as the hippocampus and other temporal lobe structures [36]. PET imaging techniques can either use ^{18}F-fluorodeoxyglucose (^{18}F-FDG) to measure the glucose hypometabolism and neurodegeneration, or ^{11}C Pittsburgh compound B (^{11}C-PiB) to visualise the Aβ plaques [84, 85]. Tau PET has been developed to visualise the regional distribution of tau pathology in vivo using suitable tau-specific tracers. The ability to investigate the patterns of tau deposition holds great promise for the future as it would facilitate the segregation between different neurodegenerative diseases, including tauopathies. It has also been demonstrated that tau imaging, in contrast to Aβ imaging, is strongly associated with patterns of neurodegeneration and clinical presentation of AD. It is, however, still in early stages of development and further research needs to be conducted to validate the sensitivity of tau PET for age-related tau accumulation [86, 87].

Biological fluids, such as cerebrospinal fluid (CSF) and blood, are increasingly utilised for the diagnosis, prognosis and monitoring of dementias [88]. Three of the main proteins that have been studied extensively are total tau (T-tau), phosphorylated tau (P-tau) and $A\beta_{42}$ [36], but a number of other biomarkers have been recently reported to be moderately associated with AD as well, such as neurofilament light chain (NfL), vinisin-like protein 1 (VLP-1), neuron-specific enolase (NSE), heart fatty acid binding protein (HFABP) and glial activation (YKL-40) [88]. T-tau and P-tau have been repeatedly found elevated in patients with AD and are indicative of neuronal degeneration and accumulation of tau, respectively [85]. P-tau is more specific for AD whereas T-tau can be increased in other brain disorders as well, such as stroke and brain trauma non-AD dementias [89]. As previously mentioned, results have been controversial among different research groups [90]; for instance, $A\beta_{42}$ level in CSF has been reported to decrease [85, 88] or increase [91], in comparison to healthy subjects, but was found unchanged in blood plasma samples [88]. Other studies have reported a reduction in plasma $A\beta_{42}$ in MCI and AD subjects [92] while serum $A\beta_{42}$ was found unchanged in AD and healthy normals [93]. The inconsistent results may occur due to changes in age and timing relative to incident AD [94]. A more detailed summary of these biomarkers is given in Table 1.

BIOSPECTROSCOPY AS AN EMERGING DIAGNOSTIC MEANS

Vibrational spectroscopy has been increasingly used in biomedical research to discriminate and classify normal and pathology. Interrogation of samples with spectroscopic techniques, and more specifically infrared (IR) and Raman spectroscopy, allows for the generation of a “spectral fingerprint” which subsequently facilitates the discrimination of different populations and identification of potential biomarkers. As previously described, mixed dementias are now recognised as a highly common phenomenon; with this in mind, we believe that targeting specific molecules and investigating separate pathological pathways may not provide a complete picture. On the contrary, with spectroscopy it is feasible to simultaneously study a range of different biomolecules. Unlike immunological methods, which detect only one molecule at a time, the spectra obtained from a clinical sample represent a range of biomolecules such as proteins, lipids and carbohydrates (Figure 6).

Briefly, spectroscopic methods explore the interaction between matter and light; the biological sample in question (*e.g.*, tissue, CSF, blood) is shone with light of specific electromagnetic radiation which causes the samples’ molecules to vibrate. These characteristic, generated movements are then detected and depicted in the form of a spectrum. Spectral peaks correspond to specific biomolecules and can be used as potential biomarkers for disease. Further spectral analysis can also allow classification of the diseased and healthy population and diagnostic values (*i.e.*, sensitivity and specificity) can be determined.

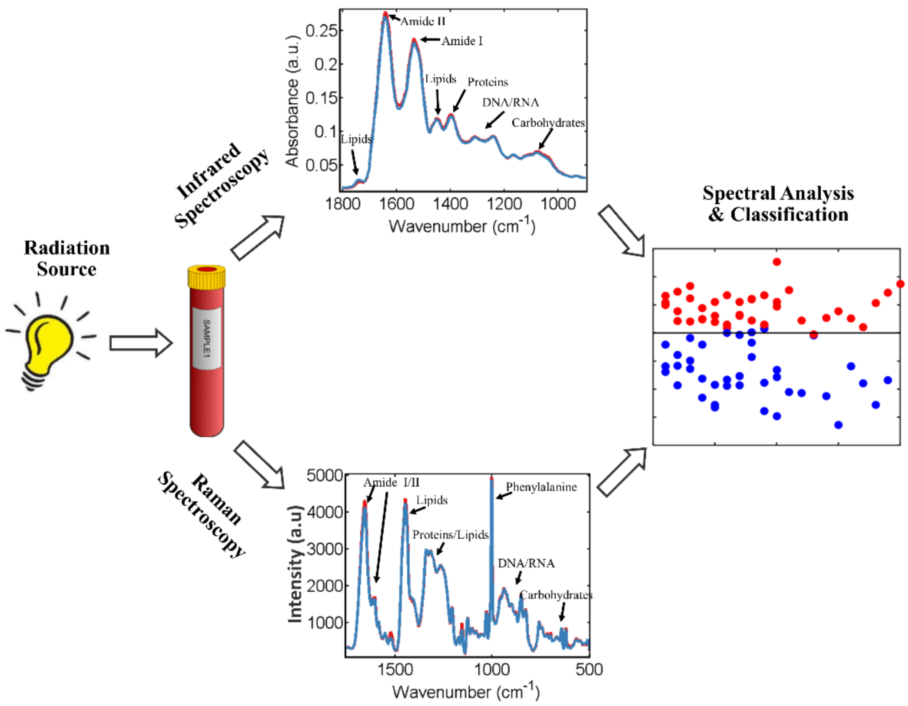

Figure 6: The basic principle of biospectroscopy: a source is used to direct radiation to the clinical sample and cause vibrations to its molecules – spectral information is generated – spectral analysis allows for classification and biomarker extraction.

At present, a number of spectroscopic studies have achieved promising results in diagnosing dementia subtypes and some examples will be presented in this section. Two decades ago, the first evidence of the structure of Aβ plaques was revealed by IR microspectroscopy methods after in situ analysis of a section of AD brain [95]. This showed that the plaques in the brain consisted of β-sheet in contrast to the surrounding areas which gave signal of α-helical and/or unordered conformation.

Low levels of unsaturated lipids have been suggested to increase the risk or severity of AD. Using IR imaging, Leskovjan *et al*., visualised the unsaturated lipid levels in the axonal, dendritic and somatic layers of the hippocampus of an AD mouse model as a function of plaque formation [96]. As the disease progressed, the lipid unsaturation in the axonal layer was found significantly lower when compared to normal aging subjects, suggesting that maintenance the level of unsaturated lipid content may be critical in slowing down the disease.

A following paper tested 50 AD cases against 14 healthy subjects with both IR and Raman spectroscopy to account for potential changes in peripheral blood [97]. An increased spectral peak found in AD patients, denoted β-sheet enrichment and was attributed to Aβ peptide formation. Diagnostic approaches were used to distinguish the patients from the healthy individuals and achieved an accuracy of ~94%.

Another study analysed both CSF and blood plasma using an immune-IR-sensor to measure the Aβ peptide secondary distribution [98]. The IR-sensor detected a significant downshift of the Amide I spectral region in patients with AD. The authors concluded that the shift signalled the transition from a healthy to a dementive status which was depicted in the spectra from a transition from α-helical (1652 cm^{-1}) to β-sheet (1627 cm^{-1}) spectral region. The achieved diagnostic accuracy was 90% for CSF and 84% for blood samples.

Recently, Paraskevaidi *et al*. published the results of a large-cohort study showing IR spectroscopy's ability to discriminate different types of dementia in blood [99]. The study incorporated AD, DLB and FTD as well as other neurodegenerative disorders, such as PD, and achieved exceptionally high diagnostic accuracy. Distinctive patterns were seen between the dementia subtypes representing different pathological changes, mostly attributed to proteins and lipids. The high sensitivity and specificity achieved for distinguishing AD from DLB were outstanding (90%) and would potentially provide an excellent diagnostic test. A small number of early-stage AD cases was also included and showed 80% sensitivity and 74% specificity. A following study by the same group employed Raman spectroscopy achieving equal, and in some cases even higher, diagnostic accuracies, thus establishing the effectiveness of bio-spectroscopy as a diagnostic tool [100]. An additional advantage of Raman spectroscopy over IR is its ability to analyse aqueous samples which would allow the analysis of fresh samples without the need of prior dehydration; this would be particularly beneficial for use in a clinic.

The inherently weak signal of spontaneous Raman spectroscopy can be addressed by employing signal enhancement techniques, such as surface enhanced Raman spectroscopy (SERS) or coherent anti-Stokes Raman scattering (CARS). A recent review by Devitt *et al.*, has explored the promise of Raman spectroscopic techniques as an emerging tool to study and diagnose neurodegenerative disorders [101]. A number of diseases have been reviewed in this paper, namely AD, PD, prion diseases and Huntington's disease. The cost-effectiveness of spectroscopy over other expensive and laborious techniques has also been demonstrated, suggesting its potential for translation into clinic. More studies that have employed spectroscopy to study different types of dementias and their mechanisms are given in Table 1.

CONCLUSIONS AND FUTURE PERSPECTIVE

Improvement of health care and scientific breakthroughs have resulted in increased life expectancy. Data from the World Health Organization (WHO) have indicated that global average life expectancy increased by 5 years between 2000-2015, making it the fastest increase since 1960s; this is estimated to increase by 4 more years by 2030 [102]. Due to their common appearance at an older age, neurodegenerative diseases have become a major challenge for scientific and medical communities. It is now thought that future treatments aiming to delay or even stop/reverse the disease would be effective if administered at an early stage. Therefore, it is crucial to develop new techniques and biomarker tests that would allow the detection of presymptomatic individuals. An on-time diagnosis of patients who are destined to develop the disease would allow them to enroll in clinical trials with the hope that this would prevent the disease.

Another important consideration is that the affected persons and their families need to be adequately informed about the disease characteristics, symptoms, prognosis, available treatments and ongoing clinical trials so that they can plan their future, develop strategies and seek healthcare assistance if necessary.

A more reliable, affordable and less-invasive test is an unmet need in the field of neurodegeneration. Despite the significant advancement in deciphering the underlying pathology and mechanisms, these diseases remain incurable. Much effort has been put into alternative methodologies such as spectroscopic methods, which provide a panel of different biomolecules, rather than focusing on specific molecules, such as Aβ and tau proteins. Biospectroscopy can be a label-free, non-destructive and inexpensive method and it has shown potential as a means for diagnosing and/or monitoring disease progression. Surely, as with every novel method or biomarker, additional research is needed for the repetition and validation of current studies in larger cohorts and from different research groups. The new knowledge acquired could then be incorporated into the diagnostic criteria and guidelines. Minimally invasive sampling, such as in blood plasma and serum, are gaining increasing attention as biomarkers in neurodegenerative diseases. Changes in the blood are often subtle and may reflect a range of peripheral and central processes; however, with increasing age the blood-brain barrier is disrupted and it has also been found that 500 ml of CSF is daily discharged into the bloodstream which renders it an information-rich sample [103, 104].

To summarise, there has been a great advancement in the understanding of the complex neurodegenerative processes. World-leading experts are now confident that we are approaching a major breakthrough in the field of dementia which could potentially improve patients' lives by alleviating or even curing the devastating symptoms of the condition. There is also a strong consensus that a definitive and early diagnosis would more likely be given after a combination of different biomarkers and analytical methods, rather than a focus on traditional approaches; perhaps an unconventional and "fresh" look on the problem is the key for a turning point in dementia research. Increasing research funding is also a very important factor that has to be secured in order to accelerate the pace of progress and continuous efforts should be made to maintain this.

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AUTHOR CONTRIBUTIONS

MP conducted the literature search and assessed the studies that were included in this review; MP wrote the manuscript; PLMH and FLM provided constructive feedback during manuscript preparation. All authors have contributed with critical revisions to manuscript.

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Table 1: Biomarkers for the diagnosis of dementia subtypes.

Study	Technique	Type of Dementia	Sample	Outcome/Accuracy
		Imaging Tests		
Frisoni, 2017 [85]	MRI	AD	In vivo imaging	Decreased volume of hippocampus & temporal lobe structures due to tissue loss & neurodegeneration
	^{18}FDG-PET	AD	In vivo imaging	Decreased uptake due to glucose hypometabolism & neurodegeneration
	Amyloid PET	AD	In vivo imaging	Increased binding due to Aβ in the cortex
Saint-Aubert, 2017 [105]	Tau PET	AD, FTLD, DLB	In vivo imaging	In contrast to Aβ plaques, tau protein aggregates primarily intracellularly rendering it difficult to access in vivo. Novel (~5 yrs) tau PET tracers show promise for the discrimination between neurodegenerative diseases and monitoring of disease progression; more research is required as, despite promising, it has been suggested that the tracer might not bind substantially to the tau burden
McKeith, 2017 [6]	SPECT/PET	AD, DLB	In vivo imaging	Reduced DAT uptake in basal ganglia provided 78% sensitivity and 90% specificity
	^{123}Iodine-MIBG scintigraphy	AD, DLB	In vivo imaging	Reduced uptake on MIBG myocardial scintigraphy was reported in LB disease; sens (69%) and specif (87%) values that discriminated between probable DLB and AD, increased to 77% and 94% in milder cases
	CT/MRI	AD, DLB	In vivo imaging	Relative preservation of medial temporal lobe (MTL) structures on CT/MRI scan; in contrast to AD, DLB patients do not show a great atrophy of MTL; 64% sens and 68% specif were the values for separating AD from DLB
	Amyloid PET	AD, DLB	In vivo imaging	Increased Aβ deposition in >50% DLB patients; limited value in differentiating from AD; combining biomarkers could improve differential diagnosis

	Tau PET	AD, DLB	In vivo imaging	Tau PET imaging, along with MTL atrophy, may indicate coexisting AD pathology in DLB
Ossenkoppele, 2016 [87]	Tau, Aβ and ^{18}FDG PET	AD	In vivo imaging	Tau imaging, in contrast to Aβ, showed a strong regional association with clinical and anatomical heterogeneity in AD; results from a novel PET tracer were promising but still preliminary, requiring further research
Beach, 2014 [106]	Amyloid PET	AD	In vivo imaging	The diagnostic accuracy of a positive Aβ scan was estimated at between 69%-95% sens and 83%-89% specif.
Richard, 2013 [107]	MRI	MCI	In vivo imaging	After administration of a short memory test, the added improvement in classification, coming from an MRI, was only +1.1%, showing it does not substantially affect the diagnostic accuracy for predicting progression in MCI patients; the study highlights the importance of the order of different tests when assessing cognitive complaints
Frisoni, 2010 [36]	MRI	AD	In vivo imaging	Atrophy of medial temporal structures is a valid biomarker of AD and its progression; MRI is also a partially validated candidate marker for MCI and non-AD dementias
McKeith, 2005 [58]	MRI	DLB	In vivo imaging	Preserved medial temporal lobes (relative to AD)
Neary, 1998 [108]	MRI	FTLD	In vivo imaging	Focal frontal or temporal atrophy
Roman, 1993 [109]	MRI	VaD	In vivo imaging	Strategic infarct or extensive white matter changes
		Biomarker Tests		
Frisoni, 2017 [85]	Proteomics	AD	CSF	Decreased $A\beta_{42}$ or $A\beta_{42}$:$A\beta_{40}$ ratio due to abnormal Aβ metabolism; increased T-tau and P-tau due to neuronal damage and accumulation of tau
Mattsson, 2017 [110]	Proteomics	AD, MCI	CSF & Blood Plasma	Plasma NFL was correlated with CSF NFL and was increased in MCI and AD when compared to HC; high

				NFL levels were correlated with poor cognition and AD-related atrophy; diagnostic accuracy was 87%; however, plasma NFL levels are increased in other neurological disorders too and thus, could not be used for differential diagnosis of AD
McKeith, 2017 [6]	Proteomics	DLB	CSF, blood, peripheral tissue	Biomarkers for DLB are elusive and the understanding of the core biomarkers remains limited; CSF α-synuclein is not yet proven as a biomarker, while Aβ and tau may be more useful in detecting coexisting AD
Tatebe, 2017 [111]	Proteomics	AD, VaD	Blood Plasma	Plasma levels of P-tau181 were significantly higher in AD than in HC, providing 60% sens and 86% specif; P-tau181 levels in AD and VaD were significantly correlated with those in CSF; further study was suggested to validate the preliminary results
Olsson, 2016 [88]	Proteomics	AD	CSF & Blood serum/plasma	The core CSF biomarkers for neurodegeneration (T-tau, P-tau and Aβ42), CSF NFL and plasma T-tau were associated with AD; the core biomarkers were strongly associated with MCI due to AD; promising CSF biomarkers also included NSE, VLP-1, HFBP and YKL-40; plasma $A\beta_{42}$ and $A\beta_{40}$ were not strongly associated with AD
Wolters, 2016 [112]	Proteomics	AD	Blood Serum	APOE associated with long-term risk of AD in general population; additional value was limited
Forlenza, 2015 [113]	Proteomics	AD	CSF	$A\beta_{42}$ levels showed 89% sens and 70% specif; T-tau levels showed 82% sens and 67% specif; P-tau levels showed 83% sens and 49% specif; $A\beta_{42}$:P-tau ratio showed 88% sens and 78% specif; $A\beta_{42}$:T-tau ratio showed 80% sens and 80% specif; combining $A\beta_{42}$ and $A\beta_{42}$:P-tau ratio was able to predict the conversion in 2 yrs
González-Domínguez, 2015 [114]	Metabolomics	AD	Blood Serum	Alterations in the levels of 23 metabolites were detected in AD patients; metabolic pathway analysis showed different impairments such

				as hypometabolism, oxidative stress, hyperammonemia and others
Hye, 2014 [115]	Proteomics	AD, MCI	Blood Plasma	Sixteen proteins correlated with disease severity and cognitive decline; strongest associations were in the MCI group with a panel of 10 proteins predicting progression to AD with 85% sens and 88% specif
Mapstone, 2014 [116]	Lipidomics	AD	Blood Plasma	In a 5-yr observational study, a panel of ten lipids was shown to predict phenoconversion to either amnestic MCI or AD within a 2-3 yr. timeframe; accuracy was found 90%
Chiu, 2013 [117]	Proteomics	AD, MCI	Blood Plasma	$A\beta_{42}$ and tau protein are significantly lower in the HC group; differentiation of MCI from AD was achieved with ~90% accuracy; combined biomarkers differentiate HC from MCI and AD
Trushina, 2013 [118]	Metabolomics	AD, MCI	CSF & Blood Plasma	Researchers found 23 altered pathways in plasma and 20 in CSF after the comparison of MCI *versus* HC; the number of affected pathways increased with disease severity; affected pathways included energy metabolism, mitochondrial function, lipid biosynthesis and others; data from this study suggested that metabolomics could reveal early disease mechanisms shared in progression from HC to MCI and AD
Richard, 2013 [107]	Proteomics	MCI	CSF	After administration of a short memory test, the added improvement in classification, coming from a CSF test (P-tau:Aβ ratio), was -2.2%, showing it does not improve the diagnostic accuracy for predicting progression in MCI patients; the study highlights the importance of the order of different tests when assessing cognitive complaints
Zetterberg, 2013 [119]	Proteomics	AD, MCI	CSF & Blood Plasma	Tau levels in AD plasma were increased when compared to MCI and HC but with overlapping ranges across the groups which diminishes its utility as a diagnostic test; there was also no correlation between plasma tau and CSF tau which may

				be due to its clearance from the bloodstream (within 24 hrs)
Blennow, 2010 [120]	Proteomics	AD	CSF & Blood Plasma	CSF $A\beta_{42}$ level is reduced in AD and prodromal AD; CSF P-tau and T-tau levels are increased in AD and prodromal AD and are indicative of tau phosphorylation and neuronal degeneration, respectively; a panel of 18 plasma proteins has been reported to diagnose & predict AD in MCI; contradictory results in plasma $A\beta_{42}$ or $A\beta_{40}$ may reflect that peripheral plasma does not reflect Aβ metabolism; plasma levels of complement factor H (CFH) and alpha-2-macroglobulin (A2M) were increased in AD
Cedazo-Minguez, 2010 [40]	Proteomics	AD	Blood Plasma	Plasma total Aβ or $A\beta_{42}$ levels were found increased in familial AD but the results were not consistent in sporadic AD; elevated $A\beta_{42}$ levels, low levels of $A\beta_{42}$ or a reduced $A\beta_{42}$/ $A\beta_{40}$ ratio may indicate the conversion from HC to MCI or AD
Lui, 2010 [92]	Proteomics	AD	Blood Plasma	Lower $A\beta_{42}$:$A\beta_{40}$ ratio in AD; $A\beta_{42}$ reduction in MCI and AD
Brys, 2009 [121]	Proteomics	AD, MCI	CSF	P-tau_{231} was the strongest predictor of the decline from MCI to AD; isoprostane levels showed longitudinal progression effects
Lambert, 2009 [122]	Genomics	AD	DNA samples	Markers with suggestive evidence of association with AD, apart from APOE, were examined; two loci gave replicated evidence: one within CLU (or else APOJ) on chromosome 8 and the other within CR1 on chromosome 1; CLU and CR1 are involved in the clearance of Aβ
Lopez, 2009 [123]	Proteomics	AD	Blood Plasma	Plasma levels of $A\beta_{40}$ and $A\beta_{42}$ were not associated with incident AD after adjustment for age and vascular risk factors; Aβ not useful as a biomarker
Roher, 2009 [124]	Proteomics	AD	Blood Plasma, Platelets & Peripheral Tissues	Plasma Aβ fluctuated over time and among individuals, failing as a biomarker; substantially higher Aβ was found in liver tissue from AD; brain & skeletal muscle has elevated Aβ

Bian, 2008 [125]	Proteomics	AD, FTLD	CSF	T-tau and T-tau:Aβ_{42} levels were significantly lower in FTLD than in AD; T-tau:Aβ_{42} ratio was a sensitive biomarker distinguishing FTLD from AD with 79% sens and 97% specif
Blasko, 2008 [126]	Proteomics	AD, MCI	Blood Plasma	Plasma levels of Aβ_{42} alone is not a suitable biomarker for predicting AD; Aβ_{42} increase seems to be an initial event in AD and changes in the levels may reflect a transition from HC/MCI to AD. HC to MCI converters were found with ~60% sens/specif, while HC to AD converters with ~50% sens and 63% specif
Schupf, 2008 [127]	Proteomics	AD	Blood Plasma	Higher Aβ_{42} levels at the onset of this 4.6 yr follow-up study, were associated with a threefold increased risk of AD; conversion to AD was accompanied by a decline in Aβ_{42} and Aβ_{42}:Aβ_{40} ratio which may indicate compartmentalization of Aβ in the brain
Sundelof, 2008 [94]	Proteomic	AD, VaD, FTD, PDD	Blood Plasma	Low Aβ_{40} levels predicted incident AD in elderly men (77 yrs); Aβ_{42} was not significantly associated with AD; high ratio of Aβ_{42}:Aβ_{40} was associated with VaD risk
Abdullah, 2007 [93]	Proteomics	AD	Blood Serum & Plasma	AD patients had significantly higher Aβ_{40} but no difference in Aβ_{42} levels; serum Aβ_{42}:Aβ_{40} ratio was lower in AD
Ewers, 2007 [128]	Proteomics	AD, MCI	CSF	Levels of Aβ_{42} are decreased in AD and MCI, while levels of T-tau and P-tau are increased; P-tau levels were a significant predictor of conversion from MCI to AD, independent of age, gender, MMSE and *APOE* genotype
Graff-Radford, 2007 [129]	Proteomics	AD, MCI	Blood Plasma	Aβ_{42}:Aβ_{40} ratio may be a useful premorbid biomarker for cognitive normal individuals who are at risk of MCI or AD; subject with lower Aβ_{42}:Aβ_{40} levels showed significantly higher risk for MCI or AD and had greater cognitive decline
Hansson, 2006 [130]	Proteomics	AD, MCI	CSF	CSF concentrations of T-tau, P-tau$_{181}$ and Aβ_{42} were strongly associated with future development of AD in MCI patients; combination of T-tau

				and $A\beta_{42}$ yielded 95% sens and 83% specif for detection of incipient AD in MCI; combination of T-tau and $A\beta_{42}$/P-tau_{181} yielded 95% sens and 87% specif
Pesaresi, 2006 [131]	Proteomics	AD, MCI	Blood Plasma	Reduction of plasma $A\beta_{42}$ as marker for AD, specifically a transition from HC/MCI to AD
van Oijen, 2006 [132]	Proteomics	AD, VaD	Blood Plasma	High concentrations of $A\beta_{40}$ along with low concentrations of $A\beta_{42}$ showed increased risk of dementia; increased $A\beta_{42}$:$A\beta_{40}$ ratio showed reduced risk of dementia; associations were similar for AD and VaD
Rüetschi, 2005 [133]	Proteomics	FTD	CSF	Forty-two protein peaks were differentially expressed in FTD in comparison to non-demented controls; ten peaks were selected, five of which were increased and five decreased, allowing sens of 94% and specif of 83%
Sobow, 2005 [134]	Proteomics	AD, MCI	Blood Plasma	Plasma levels of $A\beta_{42}$ were higher in MCI in comparison to HC and AD; $A\beta_{40}$ did not differ between the groups; Aβ would not allow an accurate differential diagnosis of AD but might be useful for MCI patients (~95% sens and ~75% specif)
Assini, 2004 [135]	Proteomics	MCI	Blood Plasma	Levels of $A\beta_{42}$ were slightly higher in MCI than in HC but did not reach significance; when grouped for sex, women with MCI had increased $A\beta_{42}$; no significant sex-related were found for $A\beta_{40}$
Hampel, 2004 [136]	Proteomics	AD, MCI, VaD, FTD, DLB	CSF	P-tau_{181} differentiated AD and DLB, whereas P-tau_{231} differentiated AD and FTD; P-$tau_{396/404}$ was a promising biomarker to differentiate AD and VaD; high P-tau_{231} levels may indicate progressive cognitive decline in MCI subjects
Fukumoto, 2003 [137]	Proteomics	AD	Blood Plasma	Plasma Aβ levels increased significantly with age but were correlated to age rather than diagnosis, medication or *APOE* genotype, thus Aβ is not sensitive or specific biomarker of AD or MCI
Zetterberg, 2003 [138]	Proteomics	AD, MCI	CSF	Combination of three CSF biomarkers (T-tau, P-tau, $A\beta_{42}$) can

				detect early AD among patients with MCI with 68% sens and 97% specif
Mehta, 2000 [139]	Proteomics	AD	CSF & Blood Plasma	Plasma $A\beta_{40}$ elevated in AD but not useful to support the clinical diagnosis due to considerable overlap; plasma $A\beta_{42}$ similar between AD and HC; CSF $A\beta_{40}$ similar between AD and HC; CSF $A\beta_{42}$ lower in AD
Vanderstichele, 2000 [140]	Proteomics	AD, DLB	CSF, Urine, Blood Serum & Plasma	$A\beta_{42}$ in serum and urine were below detection limit; in plasma no $A\beta_{42}$ differences were seen between HC and patients; CSF $A\beta_{42}$ was lower in AD and DLB suggesting it as a useful biomarker
Andreasen, 1999 [141]	Proteomics	AD	CSF	Decreased $A\beta_{42}$ levels were could serve as diagnostic biomarker in AD (92% sens); no significant correlations between CSF $A\beta_{42}$ level and duration or severity
Kanai, 1998 [142]	Proteomics	AD	CSF	Significant elevation of tau levels and $A\beta_{40}$:$A\beta_{42}$ ratio, as well as decrease of $A\beta_{42}$ levels, were observed in AD patients; the assays provided ~70% sens. and 83% specif.
Motter, 1995 [143]	Proteomics	AD	CSF	$A\beta_{42}$ levels were found significantly lower in AD while total Aβ levels were not, suggesting that diminished $A\beta_{42}$ clearance may account for its reduction in CSF; tau levels were increased in AD
		Spectroscopic Tests		
Huang, 2017 [144]	Raman spectroscopy	AD	Brain Tissue, Blood Serum & Plasma	Biomarkers of AD, such as Aβ and tau proteins or the neurotransmitters involved in AD (*e.g.*, glutamate and γ-aminobutyric acid), have been identified to distinguish patients from HC individuals
Michael, 2017 [145]	Raman Spectroscopy	AD	Brain Tissue	Tissue imaging identified plaques and tangles in unstained, label-free brain tissue; two times more proteins and five times more β-sheets were found inside the plaque- and tangle-like features, as compared to the surrounding tissue
Paraskevaidi, 2017 [99]	ATR-FTIR Raman Spectroscopy	AD, DLB, FTD	Blood Plasma	AD patients were detected with 86% sens and specif when individuals had

				one or two alleles of APOE ε4, while in individuals with no ε4 alleles diagnostic accuracy was lower at 72% sens and 77 specif; early AD cases were distinguished with 80% sens and 74% specif; differences coming with AD duration were also noted; AD was also distinguished from DLB with 90% sens and specif; FTD was also segregated from HC
Paraskevaidi, 2017	Raman Spectroscopy	AD, DLB	Blood Plasma	Early-stage AD was detected with 84% sens and 86% specif; late-stage AD was detected with 84% sens and 77% specific; DLB was detected with 83% sens and 87% specif; late-stage AD was distinguished from DLB with 90% sens and 93% specif; wavenumbers assigned to specific biomolecules were also suggested as a panel of biomarkers
Mordechai, 2017 [146]	FTIR Spectroscopy	AD	Blood Plasma & White Blood Cells	Mild, moderate and severe cases of AD were distinguished from HC individuals with 85% accuracy when using white blood cells and ~77% when using blood plasma
Nabers, 2016 [98]	FTIR Spectroscopy	AD	CSF & Blood Plasma	Employing an immune-IR-sensor, there was a discrimination between AD and HC with a 90% accuracy in CSF and 84% in blood plasma; a significant downshift, indicative of the overall β-sheet structure, was noted in the AD patients
Kiskis, 2015 [147]	CARS	AD	Brain Tissue	Enhanced Raman imaging of tissue sections from the prefrontal cortex showed evidence of lipid deposits co-localizing with Aβ plaques
Demeritte, 2015 [148]	SERS	AD	Whole Blood	Antibody-coated nanoparticles were used to enhance the Raman signal; Aβ and tau proteins were both detected in concentrations as low as 100 fg/mL level; the spectroscopic technique showed advantages over ELISA detecting Aβ (0.312 ng/mL) and tau (0.15 ng/mL)
Ryzhikova, 2015 [149]	Raman Spectroscopy	AD, DLB, FTD	Blood Serum	Patients with AD were differentiated from HC and other dementias with ~95% sens and specif
Carmona, 2015 [97]	Raman and IR Spectroscopy	AD	Blood Plasma	Patients with AD and age-matched healthy controls were distinguished with a diagnostic accuracy of ~94%

Magierski, 2014 [150]	Magnetic Resonance Spectroscopy	AD, DLB	In vivo Brain Tissue Imaging	Proton magnetic resonance spectroscopy has been demonstrated as a noninvasive method to assess the biochemistry of brain tissue in vivo
Carmona, 2013 [151]	Raman and IR Spectroscopy	AD	Blood Plasma	Spectral biomarkers were identified in the Raman and IR region and were indicative of protein secondary structure, protein α-helices, protein tertiary structure and oxidative stress; the diagnostic accuracy achieved 89% sens and 92% specif
Luo, 2013 [152]	Raman Spectroscopy	AD	Platelets	Early and differential (from PD) diagnosis of AD was demonstrated; 80% sens. for 12-month AD, 75% sens. for 4-month AD and 100% specif. were achieved
Chen, 2011 [153]	Raman Spectroscopy	AD, VaD	Platelets	Early and differential diagnosis of AD from VaD; two peaks (740 cm^{-1}: protein side chain vibration and 1654 cm^{-1}: Amide I of the protein α-helix structure [154]) were mostly responsible for the segregation between HC and AD
Leskovjan, 2010 [96]	FTIR Spectroscopy	AD	Brain Tissue	FTIR imaging was used to visualize the unsaturated lipid content in specific regions of the hippocampus in an AD mouse model as a function of plaque formation; the unsaturated lipid content was reduced in the hippocampal white matter during Aβ pathogenesis
Burns, 2009 [155]	NIR Spectroscopy	AD	Blood Plasma	Five spectral bands corresponding to heme, R-CH, R-OH, H_2O and R-NH were used to distinguish between AD and HC with 80% sens and 77% specif; spectra were not influenced by age, gender, exposure to cholinesterase inhibitors or sample storage time
Chen, 2009 [156]	Raman Spectroscopy	AD	Brain Hippocampus Tissue	In situ Raman analysis distinguished AD from normal tissue; biochemical changes that were observed included the increase of Aβ protein, cholesterols and hyperphosphorylated tau
Peuchant, 2008 [157]	FTIR Spectroscopy	AD	Blood Plasma	A clear separation was achieved between AD and HC by using a restricted spectral range; changes were related to modified lipid and

				nucleic acid structures involved in oxidative stress processes of AD; the diagnostic accuracy was ~98%
Kantarci, 2004 [158]	Magnetic Resonance Spectroscopy	AD, VaD, DLB, FTLD	In vivo Brain Tissue Imaging	Metabolite ratio changes were evaluated and shown as useful imaging markers in common dementias; N-Acetylaspartate/creatine levels were decreased in dementias that undergo neuron loss such as AD, FTLD and VaD; myoinositol/creatine were elevated in dementias pathologically characterized by gliosis such as AD and FTLD; choline/creatine was increased in dementias with a profound cholinergic deficit such as AD and DLB
Choo, 1996 [95]	FTIR Spectroscopy	AD	Brain tissue	The structure of Aβ protein within a slice of human AD brain tissue was reported for the first time; protein in grey matter existed predominantly in an α-helical and/or unordered conformation, whereas within amyloid deposits a beta-sheet structure predominated

Abbreviations: Aβ: amyloid beta; AD: Alzheimer's disease; APOE: apolipoprotein; APOJ: apolipoprotein J; ATR: attenuated total reflection; CSF: cerebrospinal fluid; CLU: clusterin; CR1: complement component (3b/4b) receptor 1; CT: computed tomography; CARS: Coherent anti-Stokes Raman Scattering; DAT: dopamine transporter; ELISA: enzyme linked immunosorbent assay; fg: femtogram; ^{18}FDG: ^{18}fluorodeoxyglucose; FTIR: Fourier transform infrared spectroscopy; FTD: frontotemporal dementia; FTLD: frontotemporal lobe degeneration; YKL-40: glial activation; HC: healthy controls; HFABP: heart fatty acid binding protein; hrs: hours; MRI: magnetic resonance imaging; MTL: medial temporal lobe; MIBG: metaiodobenzylguanidine; MCI: mild cognitive impairment; MMSE: mini mental state examination; NIR: near-infrared; NFL: neurofilament light chain; NSE: neuron-specific enolase; PD: Parkinson's disease; PDD: Parkinson's disease dementia; P-tau: phosphorylated tau; PET: positron emission tomography; sens: sensitivity; SPECT: single-photon emission computed tomography; specif: specificity; SERS: surface enhanced Raman spectroscopy; T-tau: total tau; VaD: vascular dementia; VLP-1: vinisin-like protein 1; yrs: years;