Alzheimer’s disease (AD) accounts for the majority of dementia cases within USA and worldwide and its incidence increases with age. Its prevalence is estimated to be 5.3 million of cases in the USA [1] and over 25 million cases worldwide. The disease progresses within 12-18 years from an insidious onset dominated by short-term memory deficit to severe brain dysfunction rendering subjects mute and non-ambulatory. Currently, there is no specific diagnostic test to distinguish AD from other less frequent dementing illnesses. Furthermore, there is no test to accurately predict development of AD in older patients with isolated memory dysfunction but otherwise functioning well within their social environment, a condition dubbed mild cognitive impairment (MCI).

Making a diagnosis of AD is based on clinical experience and skill of an evaluating neurologist whose diagnostic accuracy can be further improved by complex, expensive and time consuming psychometric testing. Thus, current challenges concerning the diagnostic process of AD include:

- Providing reliable diagnosis of incipient AD in patients with MCI (or even in cognitively normal) within a defined time period of 3-5 years. This process should also reliably dismiss patients with subjective memory complaints.
- Improving differential diagnosis of AD vs other forms of dementia.
- Providing clinicians who are not experts in AD with tools enabling diagnostic conclusions with similar accuracy to dementia experts.

Alzheimer’s disease (AD) is characterized by progressive cognitive deficit which clearly separates AD patients from the mild decline in cognitive functions associated with normal aging. Mild cognitive impairment is a clinical state, sometimes prodromal to fully symptomatic AD, where cognitive deficit can be delineated by psychometric testing. AD pathogenesis is associated with progressive accumulation of a toxic and hydrophobic Aβ peptide in the brain, which starts a number of years prior to the onset of clinical symptoms (yellow dotted line). This preclinical stage of the disease is dubbed the “brain AD stage”. Progressive accumulation of Aβ in the brain results in a number of secondary pathological processes including neurofibrillary degeneration, inflammation, synaptic loss, and neuronal dropout, whose severity correlates with clinical symptoms of the disease (magenta dashed line).
A number of studies based on longitudinal designs have shown progressive changes in mesial temporal lobe atrophy on structural imaging and in CSF levels of ß-amyloid peptide (Aß), tau protein, and phosphorylated tau (P-tau) as subjects advance from a state of being cognitively normal to age, to MCI, and then to AD. Although these markers show statistically significant differences between AD and control groups, but due to substantial intergroup overlap, neither marker alone attains sufficient specificity and sensitivity to clearly separate among normal, MCI and AD subjects when subjected to cross-sectional analysis.

Functional imaging in form of Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) can be used to help confirming AD diagnosis and differentiate AD from other forms of dementia based on brain hypometabolism patterns, but this remains underutilized in clinical practice.

Several studies have also indicated that FDG-PET in conjunction with structural imaging can also be helpful in predicting incipient AD in MCI patients, but these approaches are not available for clinical use. Recent advances in Aß targeted imaging ligands have made it possible to demonstrate brain Aß accumulation in living subjects by PET. The most widely used ligand is 11C labeled Pittsburgh compound B (PiB), whose use has been thus far limited to research studies. Studies utilizing PiB have demonstrated the presence of Aß in brains of AD patients and in some of MCI patients but also in brains of many cognitively normal subjects, which finding is consistent with previous autopsy data showing Aß deposition to precede neurodegeneration and cognitive decline.

Thus, Aß targeting ligands can detect accumulation of Aß in the brain, but do not provide insight into the actual temporal relationship between brain Aß deposition and onset of cognitive decline, and does not rule out co-existence of other forms of dementia pathology. In the absence of one specific disease diagnostic marker, ways to improve diagnostic accuracy can be sought through developing tools to enhance analysis of available markers and through development of the decision support system for dementia diagnosis, which would be based on concomitant analysis of several biomarkers. Such a system could derive a statistical probability of diagnosis based on built-in normative values for particular biomarkers and marker combinations. Its application would allow for accurate earlier diagnosis, and improved differential diagnosis of AD from other dementias.

Alzheimer’s disease is classified either as familial or sporadic. The familial form accounts for about 1% of all cases and is characterized by the onset before age of 60–65 years. Disease pathogenesis in the familial form is triggered by a mutation in one of the AD specific genes. The sporadic form, which accounts for prevailing majority of cases, starts after age of 60–65, and its incidence closely correlates with advancing age. Insidious onset and slow progression of short-term memory and learning dysfunction, followed by deficits in other cognitive domains makes a pattern of clinical presentation, which is classical for early stage of AD. The full clinical course of the disease from early signs of memory disturbances until its end-stage when patients become mute and non-ambulatory, and eventually succumb to a systemic infection may take 12 to 18 years.

The principles of clinical diagnosis of AD are based on demonstrating evidence of dementia during an interview with deficits involving memory and at least one other area of cognition [2]. The magnitude of cognitive deficit should be documented by a Mini-Mental State Examination (MMSE) or Alzheimer’s Disease Assessment Scale – Cognitive part (ADAS-Cog). Further diagnostic requirements include evidence of a progressive nature of decline involving memory and other cognitive functions, no disturbances of consciousness, onset between age of 40 and 90 years, and absence of systemic disorders or other brain diseases that could account for the deficits and progression [2,3]. There is no diagnostic test allowing for screening or confirming diagnosis of AD. Fulfilling the aforementioned criteria permits diagnosis of probable AD, which is the highest level of confidences clinically attainable. An atypical pattern of cognitive deficit and/or the presence of other atypical symptoms or diagnostic findings (e.g. vascular lesions) reduce the diagnostic confidence to the level of possible AD.

Definitive diagnosis of AD can be made only by demonstration of AD pathology upon autopsy in the absence of other significant brain pathologies. A caveat in making a postmortem AD diagnosis lies in the requirement of documenting a history of progressive dementia as it has been well established that some patients may carry a substantial burden of AD pathology in the brain without signs of cognitive deficits [4,5].

Diagnostic dilemmas concerning AD are even more challenging during the incipient stage of the disease when a clinical picture of the disease has not yet fully emerged. A clinical term, mild cognitive impairment (MCI), has been coined
The pathogenesis of AD is initiated by an accumulation of a toxic and insoluble Aβ peptide in the brain. Critical challenges include an ability to correctly differentiate AD from other dementias. The pathogenesis of AD is initiated by an accumulation of a toxic and insoluble Aβ peptide in the brain which predates other lesions, neuronal loss and symptoms of dementia [7,8]. Aβ is a hydrophobic 39-43 amino acid peptide derived from cleavage of a larger, synaptic transmembrane protein, the amyloid precursor protein (APP) [9]. Accumulation of Aβ in the brain is an effect of a mismatch between its rate of production and brain clearance and is exacerbated by its inherently low solubility and its natural propensity to self-aggregate into toxic oligomers and insoluble fibrils [10]. Rare cases of familial AD, with onset before age 60-65 years, are related to mutations in the APP sequence which, depending on the location, can cause one of the following: an increase in total Aβ production, an Aβ mutant which is highly toxic and more prone to self-aggregation, or an increased production of more toxic and aggregation prone Aβ1-42 at the expense of less fibrillogenic Aβ1-40. Mutations in presenilins (PS) 1 and 2 genes also result in increased Aβ1-42 to Aβ1-40 ratio. The causes of Aβ accumulation in the more prevalent sporadic AD cases are less well understood. It is believed that a combination of inherited predispositions and acquired factors plays a role in developing a mismatch between Aβ production and its clearance.

The strongest and thus far the only identified genetic factor modulating the risk for late-onset sporadic AD is the inheritance of an apolipoprotein E (apoE) type, which in humans occurs in three isoforms E2, E3, and E4. A great wealth of scientific evidence exists that apoE in an isoform-specific manner interacts with Aβ, as an Aβ binding protein, what promotes Aβ sequestration in the brain and self-aggregation [11]. Multiple studies carried out in ethnically various populations, have repeatedly concluded that inheritance of the apoE4 allele increases the risk of developing AD and lowers its age of presentation in an allele-dose dependent manner. ApoE4 heterozygotes have 2-4 times increased disease risk and 5-7 years earlier age of onset, whereas homozygotes have 8-12 times increased risk and age of onset on average 10-12 year earlier, than non apoE4 carriers [12,13]. It has also been shown that E4 in allele-dose dependent manner correlated with the burden of Aβ deposits both in AD patients and in older cognitively intact subjects [14]. Since inheritance of apoE isoforms only modulates disease predisposition, apoE genotyping has no prognostic value in diagnostic assessment. Furthermore, the apoE genotype does not influence the rate of cognitive decline in already established AD [15].

The increased Aβ level in the brain and its accumulation in form of oligomers, plaques, and vascular deposits takes place for a number of years prior to the occurrence of the first
memory. At present diagnostic accuracy relies mainly on the experience of the examining physician who has to dissect whether the severity of symptoms classifies the patient as AD, MCI, or the memory performance appropriate to age i.e. the patient is healthy. Depression and excessive somatization of memory problems frequently make it difficult to separate MCI from normal aging. The diagnostic process of AD requires differentiating AD from other forms of dementia, which in the absence of disease-specific tests relies again on the expertise of the evaluating neurologist. A diagnosis scheme derived from the chief complaint of memory loss is shown in Figure 2.

Clinical assessment of patients with memory complaints and dementia is focused on exploring episodic memory function. Episodic memory refers to acquisition of new data and facts in a context of an environment in which the acquisition took place (an episode). A significant amount of time spent by a dementia expert during evaluation of a patient with amnestic memory.

A limited number of neuropathological data characterizing the MCI stage are available. Reports confirm the presence of widespread plaques in the neocortex [5] and indicate development of neurofibrillary pathology in the mesial temporal lobe structures [22] (Braak and Braak, 1991) with associated neuronal dropout exceeding 30% in the entorhinal cortex [23].

Evaluation of memory dysfunction and psychometric testing

Complaints about memory are among the most frequent problems reported to a neurologist by patients who uses it as a synonym for a broad spectrum of cognitive problems rather than specifically for a dysfunction of an episodic memory. At present diagnostic accuracy relies mainly on the experience of the examining physician who has to dissect whether the severity of symptoms classifies the patient as AD, MCI, or the memory performance appropriate to age i.e. the patient is healthy. Depression and excessive somatization of memory problems frequently make it difficult to separate MCI from normal aging. The diagnostic process of AD requires differentiating AD from other forms of dementia, which in the absence of disease-specific tests relies again on the expertise of the evaluating neurologist.
MCI is concentrated on retrieving episodic data from a range of several days to several years preceding the date of evaluation. Questions regarding details of activities of the previous day, recent family or political events, names of medications, and names of local or state public figures and how a patient performs in the real word setting are asked. The verdict of the evaluation is based on the expert’s experience and has to include the educational background of a patient; therefore it is to some extent subjective. In a number of highly educated and highly performing patients, making an accurate diagnostic determination based on interview alone is often impossible.

Office-based evaluation usually includes brief cognitive screening tasks. The brief standardized test most frequently used in clinical practice is the Mini-Mental State Examination (MMSE), which is a crude assessment of various areas of cognition. The same applies to the “clock drawing task” which is another brief test, frequently applied for dementia screening purposes, and provides crude measures of combined executive and visuospatial functions. Both tests are useful in documenting dementia and the MMSE is also used to follow the clinical progression of the disease during its early through moderate stages. Both tests have no value in the assessment of MCI, and may yield normal results even in early stages of AD, especially in subjects with high pre-morbid intelligence and education level [6]. The cognitive part of the Alzheimer’s Disease Assessment Scale (ADAS-Cog) is another well-established instrument specifically developed for assessment of AD. Although it is more complex and sensitive than the MMSE, it is rarely used in clinical practice due to the extended time required for its administration. ADAS-Cog is one of the most common metrics used in clinical trials of new AD therapeutics. Cognitive deficit in MCI and dementia can be objectively demonstrated and precisely measured with the help of a standardized psychometric test battery. Psychometric testing is most frequently used in scenarios concerning patients with MCI and early dementia and in patients with atypical presentations. In the first scenario help from neuropsychological testing is sought to differentiate among normal-to-age performance, amnestic MCI, MCI due to depression, and early AD. In the latter situation, neuropsychological testing provides a characterization of the dementia profile that allows for example to determine the co-existence of AD and vascular dementia. Psychometric testing is based on a comparison of the subject’s performance against norms for a given test adjusted for age and education of the subject. This is done by converting subjects’ test scores into “Z scores” corresponding to the number of standard deviations from a mean performance of an age and education matched control group in either a negative (below average) or positive (above average) direction. Hence, the Z score value range from -2 to 2 corresponds to 95% of the area under the normal distribution curve (i.e. mean ±2 standard deviations). The psychometric testing is standardized both in the way the test should be administered and in providing validated values for the control groups, which are used for conversion of raw test scores into Z scores.

There are no specific guidelines defining which battery of psychometric tests should be used for evaluation of MCI, AD or other dementias. Examples of tests most commonly used for evaluation of memory performance include: Wechsler Logical Memory Immediate and Delayed Verbal Recall (derived from Wechsler Adult Intelligence Scale (WAIS), Hopkins Verbal Learning Test-Revised (HVLT-R) or Rey’s Auditory Verbal Learning Test Delayed recall. The general principle for all these tests is based on providing auditory information followed by verbatim response in both immediate and delayed recall fashion. Memory based on visual acquisition of information can be tested using Rey-Osterrieth Complex Figure recall. Attention and executive functions are tested using the Digit Span Test from WAIS, the Trail Making Test, or the Symbol Digit Modalities Test. Language skills are tested using Controlled Oral Word Association (COWA-FAS), animal fluency, Boston Naming Test (BNT), or American National Adult Reading Test.

Information about visuospatial processing can be derived from copying Rey-Osterrieth Complex Figure. Consistent scores of Z values less than –1 in several tests examining the same domain raise clinical suspicion whereas scores consistently below -1.5 or -2 in the same domain are considered abnormal. Tests focusing on memory performance play a pivotal role in the evaluation of amnestic MCI. Typical patients with amnestic MCI score below –1.5 to –2 on memory tests with normal or mildly abnormal performance on tests assessing other cognitive domains. When amnestic MCI progresses to fully symptomatic AD, scores on memory tests become worse and the performance on language and executive function tests become strikingly abnormal. Down sides of psychometric testing, include the long-testing time and substantial effort both on a side of the tester and the patient. Testing is expensive requiring a trained psychometrician as well as expertise from the referring clinician to validate the results.
A number of computerized test batteries have been developed to facilitate cognitive testing. Benefits of computerized testing include inherent standardization of test administration and stimulus presentation, accurate measures of response latencies, automated comparison against individuals prior performance, as well as against age and education related norms. Two approaches to computerized test batteries for cognitive testing in the aging are pursued: adaptation of already existing tests together with their validated norms to computerized versions or development of batteries using novel interfaces and subtests. Some computerized test batteries have been already validated for application in research on aging [24]. Further development of computerized neuropsychological testing can prove beneficial in improving diagnostic accuracy and accessibility in assessment of memory disorders. Development of web based batteries would also allow for wider access to affordable testing and contribute to generating universally accessible data bases of performance. A computerized environment can also enable development of novel interfaces and subtests including application of virtual reality environments for tests investigating spontaneous memory. This would allow for validated testing of spontaneously recorded facts that appears to be more natural than forced learning and retrieval of data involved in standard format of psychometric testing.

**Role of neuroimaging**

**Structural neuroimaging**

Although structural imaging, in the form of either brain CT or MRI, is recommended for every patient undergoing evaluation for memory loss or dementia [4], these modalities play only a supportive role in the diagnosis of MCI, AD, and other dementias with neurodegenerative pathogenesis. They also detect possible co-morbidities including stroke, chronic ischemic white matter changes, areas of encephalomalacia resulting from remote brain contusions, or space occupying lesions (e.g. brain tumor or abscess), whose anatomical location could account for the cognitive deficit. A typical MRI scan for an AD patient reveals generalized cortical atrophy, enlargement of the ventricular system which is secondary to the brain atrophy, and prominent shrinkage of the mesial temporal lobe structures, which can be frequently out of proportion to the degree of generalized atrophy. Since the mesial temporal lobe structures appear to be affected the earliest and to much greater extent than other brain areas, a number of studies have investigated the presence of atrophy of the hippocampus and/or the entorhinal cortex (two prominent mesial temporal lobe structures) with raw values normalized to skull volume as potential diagnostic markers of AD.

Despite widespread application of structural imaging during the initial dementia evaluation quantification of the mesial temporal lobe structures have not been standardized or validated sufficiently to warrant routine clinical use. Visual inspection of the mesial temporal lobe atrophy is still the only technique used in clinical practice to provide more information about the possible cause of memory loss. Development of validated software allowing for automated, region-specific analysis of brain atrophy could be helpful in improving diagnostic accuracy especially when analyzed together with other data (e.g. performance on neuropsychological testing) by a decision support system.

**Metabolic imaging**

Single photon emission CT (SPECT) and Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) have been used to evaluate the presence and anatomical pattern of hypometabolic areas in the brain with the aim of confirming dementia diagnosis and in differential diagnosis support. A pattern of brain hypometabolism, which is classical for fully symptomatic AD, includes symmetrical reduction in metabolism in parietal and temporal lobes,
and to a lesser extent in the frontal lobes with characteristic sparing of primary motor and sensory cortical strips and the visual cortex [31]. In fronto-temporal dementia (FTD) abnormalities primarily involve frontal and temporal lobes and tend to be asymmetric, whereas temporal-parietal-occipital pattern of abnormalities are typical for dementia with Lewy bodies (DLB). In vascular dementia (VAD), areas of hypometabolism correlate with structural vascular lesions revealed by structural imaging. Although validation of these methods generally has shown high sensitivity, relatively low specificity poses the risk of false-positive diagnoses. FDG-PET scans are routinely subjected to visual interpretation, hence a factor of inter-rater reliability is included in the overall sensitivity and specificity.

Development and wider introduction of standardized software could enable automatic detection of hypometabolic areas and their pattern of distribution that may improve diagnostic accuracy even among radiologists who are trained as brain imaging experts. An example of this approach is the Philips System CAD4D [32] which automatically detects areas of hypometabolism based on an automatic adjustment for global glucose metabolism and supports the clinical diagnostic process by providing automated analysis of the hypometabolism pattern, comparing it against encoded patterns characteristic for various dementias. Although FDG-PET serves well as a confirmatory and differential tool for AD, it shows some limitations in the MCI stage where the disease process is primarily limited to the mesial temporal lobe, where basic metabolism is lower than in other areas of the brain. Several studies have shown that reduced hippocampal metabolism can be considered a predictor of cognitive decline and conversion from normal to MCI and then to AD, but these data come exclusively from FDG-PET studies that used a manual region-of-interest sampling method guided by co-registered MRI [33]. Recently, some attempts have been made to automate the method of delineating hippocampal region-of-interests on PET and measuring hippocampal metabolism [34]. This method allows for cross-sectional differentiation of cognitively normal subjects from MCI with overall 78% accuracy.

**Aβ imaging**

Recently, blood-brain-barrier-permeable compounds, with high binding specificity to Aβ deposits and labeled with PET compatible isotopes have been developed. These enable imaging of the Aβ burden in living patients. The first such compound was a non-toxic derivative of a thioflavin, an amyloid binding histological dye, which was dubbed Pittsburgh Compound B (PIB) and labeled with 11C for PET imaging [35]. 11C-PIB shows the greatest binding to the cortex of frontal and parietal lobes that is consistent with the burden and distribution of Aβ deposits usually seen on autopsy of AD subjects. 11C-PIB shows no signal in the mesial temporal lobe as this area, despite a prominent level of neural destruction, is characterized by relatively low burden of Aβ deposits.

Several thousand patients have thus far been imaged using 11C-PIB and the experience with this new biomarker is growing. A positive 11C-PIB scan in the presence of clinical dementia can confirms the contribution of AD pathology to cognitive decline, but cannot rule out other forms of dementia, which may co-exist with AD. Evaluation of patients clinically diagnosed as MCI have shown diversity in PIB binding which might help to predict their clinical course and risk of conversion to AD [36]. Most studies have found that the MCI group includes subjects with no PIB binding (these are thought not to convert to AD), subjects whose intensity of PIB binding falls between negative controls and AD, (uncertain whether they will convert to AD or not) and subjects with 11C-PIB signal comparable to that of AD patients (who are believed to convert to AD relatively soon).

Whether these concepts correlating 11C-PIB binding and likelihood of developing AD are correct is being tested in a number of ongoing longitudinal studies. Evaluations of cognitively normal patients have also confirmed various degrees of 11C-PIB in about 10-20% [37,36]. These asymptomatic subjects can be identified with levels of PIB retention that are intermediate between those typically observed in normal controls and clinically diagnosed AD patients [37]. This finding is consistent with a fact previously recognized on autopsy material that cognitively normal individuals may harbor a significant amount of Aβ deposits [4,5,14]. Taken together these data underscore the notion of a slow buildup of Aβ in the brain preceding the onset of clinical AD. However, since longitudinal Down syndrome subject data indicate the presence of Aβ deposits for longer than a decade before the onset of cognitive decline [17,18,19], other metrics beyond merely a finding of positive PIB binding have to be developed to help effectively predict incipient disease with diagnostic accuracy. These markers may include defining a specific cut off value for the PIB binding signal and/or combining positive PIB binding with other metrics.
The former approach is justified by the fact that the burden of Aβ deposition increases exponentially in preclinical disease and plateaus during the clinical phase of the disease [38,39], thus a cut-off value indicating full saturation of PIB binding can be established. The latter approach suggests combining the positive PIB binding with FDG-PET, CSF biomarkers (see below), or cognitive deficit to demonstrate when Aβ presence starts taking its damaging toll. A longitudinal study combining PIB and FDG PET in AD patients has revealed stable PIB retention after 2 years of follow-up in patients with mild Alzheimer’s disease but progressive reduction in glucose metabolism in Aβ laden cortical areas by 20% during the period of follow-up. It was also found that cortical PIB binding intensity significantly correlates with hippocampal atrophy and episodic memory dysfunction in MCI patients [40,36]. This suggests that combining biomarkers in the setting of positive PIB binding can provide a disease predictor with enhanced accuracy, although validation studies assessing the conversion rate from MCI to AD for various biomarker scenarios are needed.

Besides [11C]-PIB a number of other PET ligands are being evaluated for utility in AD diagnosis. Recently, promising results of phase two clinical trials evaluating toxicity and diagnostic efficacy of [18F] labeled PIB derivative dubbed GE007 (GE Health Care) [41] and another [18F] labeled Aβ binding ligand AV-45 (Florpiramine, AVID Radiopharmaceuticals) [42] were reported, heralding the possible introduction of [18F] labeled Aβ PET imaging to clinical practice within next couple of years. A compound called FDDNP was shown not only to bind to Aβ but also to bind to neurofibrillary tangles [43]. Although FDDNP also nonspecifically binds to the white matter it is investigated as a ligand useful for quantifying mesial temporal lobe pathology which primarily includes neurofibrillary tangles with limited presence of Aβ deposits. Therefore, it may be useful in the diagnosis of MCI.

**Blood tests and spinal fluid markers**

The Aβ level can be quantified by sandwich ELISA in plasma and in the cerebrospinal fluid (CSF) in normal subjects. The CSF of normal subjects also contains some level of tau and phosphorylated tau (P-tau) proteins. Serum Aβ levels can be markedly increased in subjects with early onset familial AD, but show no difference between sporadic AD patients and normal subjects [44]. Significant reduction in the CSF Aβ1-42 level and significant increase in the total tau and in P-tau levels (detected using antibodies against tau phosphorylated at serine in position 181 or threonin in position 231, therefore dubbed P-tau181, or P-tau231, respectively) are seen in AD subjects compared to age-matched controls. The decreased Aβ1-42 CSF level is explained by entrapment of the aggregation-prone Aβ1-42 in plaques and vascular Aβ deposits and inversely correlates with intensity of the [11C]-PIB binding on PET scan [45]. Increase in the CSF tau and P-tau levels reflect development of brain neurofibrillary pathology. Multiple longitudinal studies have shown that these changes are progressive and the CSF level of Aβ1-42 decreases while levels of tau and P-tau raise as cognitively normal subjects start displaying memory complaints (normal to MCI converters). Then the changes becomes more pronounced when patients progress to fully developed dementia (MCI to AD) [46]. The differences in CSF Aβ1-42, tau and P-tau levels between AD and older, cognitively normal subjects remain unfortunately, statistical phenomena related to differences in the mean values between groups.

A large dispersion and substantial overlap of particular subjects between AD and control groups makes it impossible to establish norms allowing for clear cut separation of AD subjects from normals. For the same reasons generating a separate category for MCI subjects is also impossible. A solution to dispersion of the marker values in particular subjects is sought by combining particular metrics to create markers with increased sensitivity and specificity. Combining levels of decreasing Aβ1-42 and increasing tau in the CSF (tau/ Aβ1-42 ratio) can attain sensitivity and specificity above 85% when distinguishing AD from controls [47,48].

Measurement of P-tau in combination with Aβ1-42 appears to be even more sensitive and specific than measurement of the total tau [49]. It has also been demonstrated that reduced tau/ Aβ1-42 and P-tau/Aβ1-42 ratios may predict conversion from normal to MCI or AD, and thus help to diagnose preclinical disease. Fagan et al. [45] demonstrated that using a ratio of CSF tau to Aβ1-42 ≥1.15 or a ratio of P-tau/Aβ1 to Aβ1-42 ≥ 0.214 as cutoff values, identified 60% of cognitively normal subjects who convert to MCI or AD within less than three years. However, the remaining patients meeting the same tau/Aβ ratio criteria continued cognitively normal over the 8 year period of study follow-up, which disqualify this approach as a clinical diagnostic tool. Nevertheless, predicting onset of AD symptoms based on tau/Aβ ratio might
be utilized in design of clinical trials testing anti-β compounds targeting preclinical disease with rationale to prevent or delay onset of dementia symptoms.

**Differential diagnosis of AD**

AD is routinely differentiated from other dementing illnesses based on the pattern of cognitive deficit documented during office evaluation, structural imaging and frequently with help from psychometric testing. While dementia with insidious onset, dominated by progressive short-term memory deficit and structural imaging findings limited to atrophy are classical for AD, stepwise cognitive deterioration in multiple cognitive domains associated with clinical strokes documented by structural imaging indicates multiinfarct dementia. Progressive cognitive decline, especially data retrieval, but with relatively preserved short-term episodic memory, associated with extensive white matter disease (on structural imaging) in the setting of diabetes, hypertension, and hypercholesterolemia is indicative of another form of vascular dementia called leukoariosis orBinswanger disease, which primarily affects small arteries supplying subcortical white matter.

Unlike AD, both types of vascular dementia, multiinfarct dementia and leukoariosis, are associated with symptoms other than cognitive neurological (e.g. hemiparesis, gait dysfunction) which may occur early in the course of the disease. Fronto-temporal dementia is characterized by a distinct clinical pattern with prominent dysfunction of executive functions and language contrasting with relatively spared short-term memory. To confirm this pattern, a complex neurobehavioral evaluation and/or additional psychometric testing are required. Structural imaging may show asymmetric frontal and/or temporal lobe atrophy but since these are not routinely quantified, the role of structural imaging in fronto-temporal dementia akin to its role in AD diagnosis, remains mainly focused on ruling out space occupying lesions and assessment of a burden of vascular pathology. FDG-PET can be diagnostic for fronto-temporal dementia if it shows a pattern of hypometabolism predominant to frontal and/or temporal lobes which is often asymmetric. Fronto-temporal dementia appears to affect individuals younger than those with sporadic AD which is another discriminating factor, but is within a range of patients with familial AD, hence in cases of atypical presentation genetic testing for familial AD or/and CSF Aβ1-42, tau and P-tau testing are performed [50]. Unlike AD, in fronto-temporal dementia an increase in tau and P-tau level is not associated with lowering of Aβ1-42. Hence the tau/Aβ1-42 ratio is relatively less affected. Another relatively frequently observed form of dementia is dementia with Lewy bodies where the leading clinical symptom is a deficit in visuospatial function with relatively preserved short-term memory and episodic memory. Visual hallucination, symptoms of Parkinsonism, and sensitivity to neuroleptics (both in terms of rapid cognitive decline and worsening of Parkinsonism symptoms) are additional characteristic features. FDG-PET can be helpful in differential diagnosis by showing hypometabolism in parietal and occipital lobes.

**Summary and discussion**

Although no specific test for AD exists, the diagnosis and differentiation from other dementing illnesses can be made with high accuracy and confidence by a trained neurologist. The level of confidence can be further confirmed by psychometric testing, which is time and effort consuming. However, lack of readily available accurate tests limits diagnostic effectiveness made by non-specialists. Furthermore, readily available tests are needed to separate patients with subjective memory complaints from those with true MCI (currently done by psychometric testing) and to distinguish subjects who are unlikely to develop AD from those with incipient AD.

A number of studies based on longitudinal designs showed progressive changes in structural metabolic imaging and CSF biomarkers as patients progressed from a state of being cognitively normal to age to MCI and then to AD. However, none of these biomarkers alone attains sufficient specificity and sensitivity to clearly separate normals from MCI and AD when subjected to cross-sectional analysis. Furthermore, it appears that accuracy of clinical decisions derived from particular biomarkers is higher in research studies than in clinical practice. In addition certain metrics e.g. mesial temporal lobe atrophy are not available for clinical interpretation due to lack of appropriate tools like software for automated analysis of anatomical structure volume. Therefore, two major strategic directions toward improved diagnostic accuracy appear to be logical to pursue. One is to enhance quality of the data derived from currently available markers whereas the second is to develop a clinical decision support system for dementia evaluation, which would combine the diagnostic power of particular biomarkers toward improved diagnostic precision.

A successful example of a strategy augmenting the accuracy of routinely available clinical data
is the development and validation of Philips software CAD4D [32] that allows for accurate classification of an FDG-PET pattern of glucose hypometabolism enhancing diagnostic accuracy for various types of dementia. Other examples would be developing software for the assessment of mesial temporal lobe atrophy and computerizing psychometric testing. The computerized psychometric testing could provide new diagnostic capacity in dementia by exploring novel testing interfaces and virtual reality environments. The development of a decision support system for dementia diagnosis that would combine several biomarkers can be justified by a number of studies demonstrating that joint analysis of two or more biomarkers significantly improves diagnostic accuracy [51,52,53]. Therefore, development of decision support designed to process multidimensional data including psychometric scores, degree of brain atrophy, pattern of glucose metabolism and CSF concentration of Aβ, tau and P-tau would greatly enhance the accuracy of early AD diagnosis and differential diagnosis of dementia. Such a system would derive statistical probabilities of diagnosis based on built-in normative values for particular biomarkers, could be operational in case not all possible biomarkers data are provided (e.g. Aβ and tau CSF level are not provided), and would seek a solution in case conflicting data are present. If properly validated, such a decision support system would allow a physician who is not an expert in dementia to arrive at correct diagnosis with the accuracy demonstrated by experts. Furthermore, the system could be further developed allowing for longitudinally tracking progression of the natural course of disease. Such additional functions would allow monitoring the efficacy of prescribed treatments, and justify their modification.

References


37. Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, and Morris JC. 


