ELSEVIER

Alzheimer's & Dementia ■ (2014) 1-18

Alzheimer's & Dementia

Review Article

Innovative diagnostic tools for early detection of Alzheimer's disease

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Abstract Current state-of-the-art diagnostic measures of Alzheimer's disease (AD) are invasive (cerebrospinal fluid analysis), expensive (neuroimaging) and time-consuming (neuropsychological assessment) and thus have limited accessibility as frontline screening and diagnostic tools for AD. Thus, there is an increasing need for additional noninvasive and/or cost-effective tools, allowing identification of subjects in the preclinical or early clinical stages of AD who could be suitable for further cognitive evaluation and dementia diagnostics. Implementation of such tests may facilitate early and potentially more effective therapeutic and preventative strategies for AD. Before applying them in clinical practice, these tools should be examined in ongoing large clinical trials. This review will summarize and highlight the most promising screening tools including neuropsychometric, clinical, blood, and neurophysiological tests.

Keywords: Alzheimer's disease; Diagnostic tools; Screening tests; Noninvasive tests; Early detection

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, affecting more than 35 million people worldwide [1]. Aging populations in developed countries ensure that AD will reach epidemic proportions unless therapies are developed to cure or prevent it [2]. Unfortunately, to date nearly all "disease-modifying" experimental interventions for AD have failed to demonstrate clinical benefits in individuals with symptomatic AD. The most likely explanation for these failures is that the drugs were administered too late in the course of the AD neuropathological processes [3]. It is plausible to assume that these therapies will be more effective when applied before major brain damage

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1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2014.06.004

has occurred which makes the identification of biomarkers sensitive to preclinical or early clinical stages of AD crucial [4]. Whether an earlier treatment start in the preclinical stage of AD is associated with a better outcome is still unknown and is actually examined in ongoing treatment trials [3]. These trials include the Dominantly Inherited Alzheimer Network Trial (DIAN-TU; ClinicalTrials.gov number, NCT01760005), Alzheimer's Prevention Initiative (NCT01998841), and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study (A4 Study; NCT02008357). Early-stage identification may also help to develop new treatments that are more effective at this stage as it can facilitate monitoring of the response to the intervention. In addition, a positive early diagnosis gives the patients and their family the necessary time to understand the disease, to decide on the life and financial burdens of the disease, and to arrange for the future needs and care of the patients.

The current state-of-the-art clinical diagnosis of AD requires a specialty clinic and includes a medical examination, neuropsychological testing, neuroimaging, cerebrospinal fluid (CSF) analysis and blood examination. This process is neither time nor cost-effective. Additionally, given the rapidly aging global population with an expected dramatic increase of AD cases, there are insufficient numbers of specialty clinics to meet the growing needs. While CSF and neuroimaging markers are gold standards for the *in vivo* assessment of the patients, they are invasive and expensive and, therefore, have limited utility as frontline screening and diagnostic tools. In addition, prior work has shown that nonspecialist clinicians are inaccurate at identifying early AD and mild cognitive impairment (MCI) [5], which is a major impetus to the search for clinically-useful screening and diagnostic tools.

Thus, there is an increasing need for additional noninvasive and/or cost-effective tools, allowing frontline identification of subjects in the preclinical or early clinical stages of AD. Further examination of patients with conspicuous noninvasive cognitive and noncognitive measures could be performed in a next step by established clinical, CSF and/or neuroimaging analyses in a specialty clinic. The identification of methods to predict the risk for developing AD would be of great value for healthcare systems. Identification of AD risk markers could help to identify individuals who might benefit from early intensive lifestyle consultations and pharmacological interventions. The relevance of early diagnosis of AD is supported by recent neuropathological, biochemical and neuroimaging findings showing that biomarkers of AD can be detected in the brains and CSF of approximately 20% to 30% of cognitively healthy elderly individuals [6–8].

This review will summarize and highlight the most promising novel noninvasive and/or inexpensive screening and diagnostic tools such as neuropsychometric, clinical, blood, and neurophysiological tests for early detection of AD beyond the established clinical, CSF and neuroimaging dementia diagnostics.

2. Socioeconomic aspects of dementia diagnostics

While many have argued the need for screening methods that are accessible and time- and cost-effective, few have empirically demonstrated this point. To empirically illustrate the need for noninvasive and inexpensive screening/diagnostic tools, we use the U.S. numbers of geriatrician, neurology, and psychiatry physician providers and available magnetic resonance imaging (MRI) machines below. In the United States there were an estimated 7162 physicians certified in geriatrics in 2011 [9]. This translates to 5585 patients aged 65 years old and above to be seen per specialist per year based on 2009 census estimates if all geriatrics were to receive an annual screening that included cognitive examination. This is particularly problematic when geriatric specialists are becoming less and less available [9]. Table 1 outlines the situation for the fields of neurology and psychiatry as well.

The situation is worse considering that not all geriatricians, neurologists or psychiatrists are dementia specialists. Furthermore, psychiatrists and neurologists are aging and working fewer hours than in the past [10,11], therefore this is likely a significant overestimation of capacity in that field. If one considers MRI as frontline screening tool, the situation does not improve. There are an estimated 11,000 MRI machines within the United States currently [12]. This would mean that each MRI machine should be used for 3636 US elders with current estimates and for over 6000 US elders by the year 2030, based on projected age estimates. These numbers assume that all MRI machines

Table 1
US estimates of population age 65 and above for 2009 and 2030 along with estimates of physician availability

Physicians by specialty and MRI machines in the United States	Number of physicians by specialty and of MRI machines	Population age >65 years in 2009, n = 40 million	Population age >65 years in 2030, n = 70 million
		Patients per physician	Patients per physician
Physicians certified in geriatrics [8]	7162	5585	9773
Neurologists [10]	10,154	3939	6893
Psychiatrists [9]	39,457	1014	1774
MRI machines in the United States [11]	10,000	3636	6364

Abbreviation: MRI, magnetic resonance imaging.

would be exclusively used for dementia screening. If one considers using positron emission tomography (PET) imaging machines (e.g. Amyvid©, Elli Lilly), the situation becomes even more difficult given that there are only an estimated 2000 PET/computed tomography scanners in the United States. Again, this does not take into account other indications for the use of these machines. With both clinical and imaging modalities, the above estimates do not take into account the need for repeated (i.e., annual) examinations or cost burden. The high costs of MRI and PET machines further limits their use as frontline screeners. Thus, there is need for inexpensive and/or noninvasive diagnostic tools that do not require a specialist. If, for example, a blood-based assessment was available for $200 per person (costs far above this limit the economic benefit), the cost savings would be substantial. For example, if PET amyloid beta (Aβ) imaging were made available at $1000 per examination and only 1 million elders were screened annually, the cost would be US $1 billion annually, whereas the cost of a blood test would be $200 million annually. If 15% screened positive, and went on to PET Aβ imaging, the cost savings of this screen–follow-up procedure would be $650 million dollars annually. Given that there are approximately 40 million Americans age 65 and older, then the examples listed above substantially underestimate the current need and explain why many have suggested that AD alone could bankrupt many medical systems if nothing is done immediately concerning the development of inexpensive and/or noninvasive screening tools that do not require a specialist.

3. Neuropsychometric tests

A previous retrospective cohort study examining descendants of carriers of the PSEN1 E280 A mutation identified three predementia clinical stages according to neuropsychological assessment: (1) asymptomatic pre-MCI, (2) symptomatic pre-MCI, and (3) MCI [13]. The first identifiable clinical stage, called asymptomatic pre-MCI, was detected 11 to 15 years before onset of dementia and was characterized by neuropsychological test scores two SD or more away from the mean normal value score for noncarriers in at least one test on any cognitive domain and the absence of memory complaints and no effect on activities of daily living. The second clinical stage, called symptomatic pre-MCI, was timed 5-11 years before dementia and was characterized by additional subjective memory complaints. The third clinical stage, called MCI, was timed 1 to 5 years before reaching dementia and was characterized by higher scores in subjective memory complaints without or with minimal impairment in complex instrumental functions. Thus, subtle cognitive changes could be detected in these subjects even 15 years before clinical manifestation of dementia. However, this staging has been reported in PSEN1 E280 A mutation carriers. The situation in familial AD may be different from that in sporadic AD where other, age-related factors may contribute to the preclinical and clinical outcome. Therefore, results from this study may not be directly transferable to those in sporadic AD.

3.1. Episodic memory tests

Episodic memory is the first and most severely affected cognitive domain in AD and in prodromal stages including amnestic MCI (aMCI) [14]. Several tests can be used to assess episodic memory such as the Logical Memory subtest from the Wechsler Memory Scale [15], the California Verbal Learning Test, now in its second revision (CVLT-II) [16], and the Free and Cued Selective Reminding Test (FCSRT) [17]. A comparison of CVLT and Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery has shown that CVLT is more sensitive to preclinical changes in the episodic memory [18]. The FCSRT free recall was more predictive than the Wechsler Logical Memory immediate recall for identifying individuals with memory complaints who developed incident AD over 2 to 4 years [19]. Among a standardized neuropsychological battery, the FCSRT was also the most sensitive and specific test for diagnosis of prodromal AD in another study [20]. In addition, the FCSRT better predicted the likelihood of an AD-like CSF profile among MCI subjects than the Wechsler Logical Memory delayed recall [21].

A large study examining members of families with dominantly inherited AD was called the DIAN study. In this study, significant differences between mutation carriers and noncarriers were detected in the Mini-Mental State Examination [22] and the Clinical Dementia Rating-Sum of Boxes [23] scores at assessments performed five years before expected symptom onset and thus in the preclinical stage [24]. In the delayed-recall portion of the Logical Memory test [25], however, significant cognitive impairment was found in mutation carriers, as compared with noncarriers, even ten years before expected symptom onset. The Logical Memory test has also been used in prospective studies for sporadic AD and has predicted AD 10 years before its clinical diagnosis [26]. Thus, use of an episodic memory test such as the Wechsler Logical Memory test or the FCSRT allows early detection of subtle cognitive deficits in both, familial AD and sporadic AD, favoring inclusion of one of these tests in a screening battery for detection of preclinical and early symptomatic AD.

4. Clinical tests

4.1. Assessment of subjective memory complaints

With regard to cognitive decline, objective deficits as measurable with specific neuropsychological tests need to be distinguished from subjective memory complaints (SMC) as reported by the individual or an informant (family members, care-givers, or clinician). Currently, there is increasing interest in SMC and a debate as to whether they

are meaningful or not with respect to the diagnosis of preclinical AD. Recent studies have demonstrated that SMCs are associated with pathological brain amyloid burden in cognitively normal older individuals and with increased risk for development of late-onset AD even before any measurable cognitive decline [27,28]. In addition, a study with carriers of the PSEN1 E280 A mutation identified a pre-MCI stage with already existing SMC [13]. A recent study demonstrated that one-third of the adults aged ≥50 years attending primary care centers with SMC were already affected by MCI [29]. Cognitive impairment as reported by informants (family members) was associated with an even higher prevalence of MCI. Thus, SMC may serve as an indicator of preclinical and early symptomatic AD and information concerning cognitive impairment in screening for AD and other dementias should be obtained from both, the individuals and informants (family members or caregivers). Apart from the effects of depression and personality factors, SMC report could be potentially a very good time point to start any preventive trial. Diagnostic tools to assess SMC such as the Subjective Cognitive Failures Questionnaire [30,31] or simple questions concerning the presence of memory impairment and about their concerns [27,28] are noninvasive and inexpensive and might therefore be suitable as additional parameters for a broader screening of putative amyloid positive but still cognitively healthy individuals. The definition of SMC continues to be a work in process, especially given the current lack of a single standardized test.

4.2. Assessment of late-onset depression

Depression is common across the lifespan with one in five individuals experiencing a depressive episode during their lifetime [32]. Dementia is also very common in late life with the risk doubling every 5 years after age 65, increasing up to 50% among those greater than 90 years old [33]. Although studies have shown that depression and late onset dementia frequently coexist [34], causality remains controversial. Depression has been reported in women carrying presenilin-1 mutation at preclinical phase of familial AD, supporting the hypothesis that AD neuropathology may be involved in depression occurrence at least in this group of females [35]. Depression or depressive symptoms may reflect (1) a risk factor for dementia, (2) a prodromal phase of dementia or (3) a consequence of the dementia neurodegenerative processes.

A personal history of depression seems to be a risk factor for later development of dementia [36–41]. The type of dementia seems to depend on the time point when depression occurs during life. In a longitudinal study, Barnes and colleagues [42] compared the risk of AD or vascular dementia (VaD) in those with depressive symptoms at mid- and late-life and found that subjects with late-life depressive symptoms had a twofold increase in AD risk, whereas subjects with midlife and late-life symptoms had more than a threefold increase in VaD risk.

Depression that presents for the first time in late life may also reflect an early symptom of dementia, particularly of AD. It is assumed that the combination of late-onset depression with currently elevated depressive symptoms may represent an active neurodegenerative process (i.e., a prodromal state of dementia), whereas an association between a late-onset depression that remitted and currently shows no elevation of depressive symptoms and subsequent dementia may represent an indirect effect (i.e., a risk factor for subsequent dementia) [43]. In line with this, the vast majority of longitudinal and cross-sectional studies proposed that late-life depression seems to be a prodromal stage of AD [34,43–47]. Further studies demonstrated that the number [36] and severity [37] of depressive symptoms or even a clinical diagnosis of depression at baseline in close temporal proximity to dementia [40,44,48] or together with apolipoprotein E (*APOE*) ε4 status [39] predicted development of dementia during follow-up with increased risk of AD.

In a recent longitudinal study, Heser and colleagues [43] investigated whether late-onset depression is a risk factor for a prodrome of AD or for dementia of other etiologies in a cohort of elderly patients (n = 2,663, mean age = 81.2 years). The authors showed that depression parameters and subjective memory impairment predicted AD independently of objective cognition [43]. The authors concluded that late-onset depression with currently elevated depressive symptoms accompanied by worrisome subjective memory impairment in the elderly best suggested an AD pathology requiring close neuropsychological monitoring. Thus, an assessment for depressive symptoms should be included in a screening battery for the early diagnosis of AD.

4.3. Speech testing

Verbal communication is a complex process, which draws on a wide range of cognitive abilities including short term memory, knowledge of phonological structure and grammatical convention, and word meaning. Language is produced spontaneously in large quantities by all humans on a more or less daily basis, and its recordability (in spoken or written format) makes it one of the easiest biological samples to collect. In addition, the multitude of dimensions available for analysis means that recorded speech is potentially one of the most informative biological samples to assay. The deterioration of spoken language immediately affects the patient's ability to interact naturally with his or her social environment, and is usually also accompanied by alterations in emotional responses. Both of these changes appear early in the progress of AD and both can be measured using automatic speech analysis techniques. These diagnostic procedures can (after proper training) be performed by anyone in the patient's habitual environment, without altering or blocking the patient's abilities [49,50]. These methodologies also help to estimate the severity of AD in

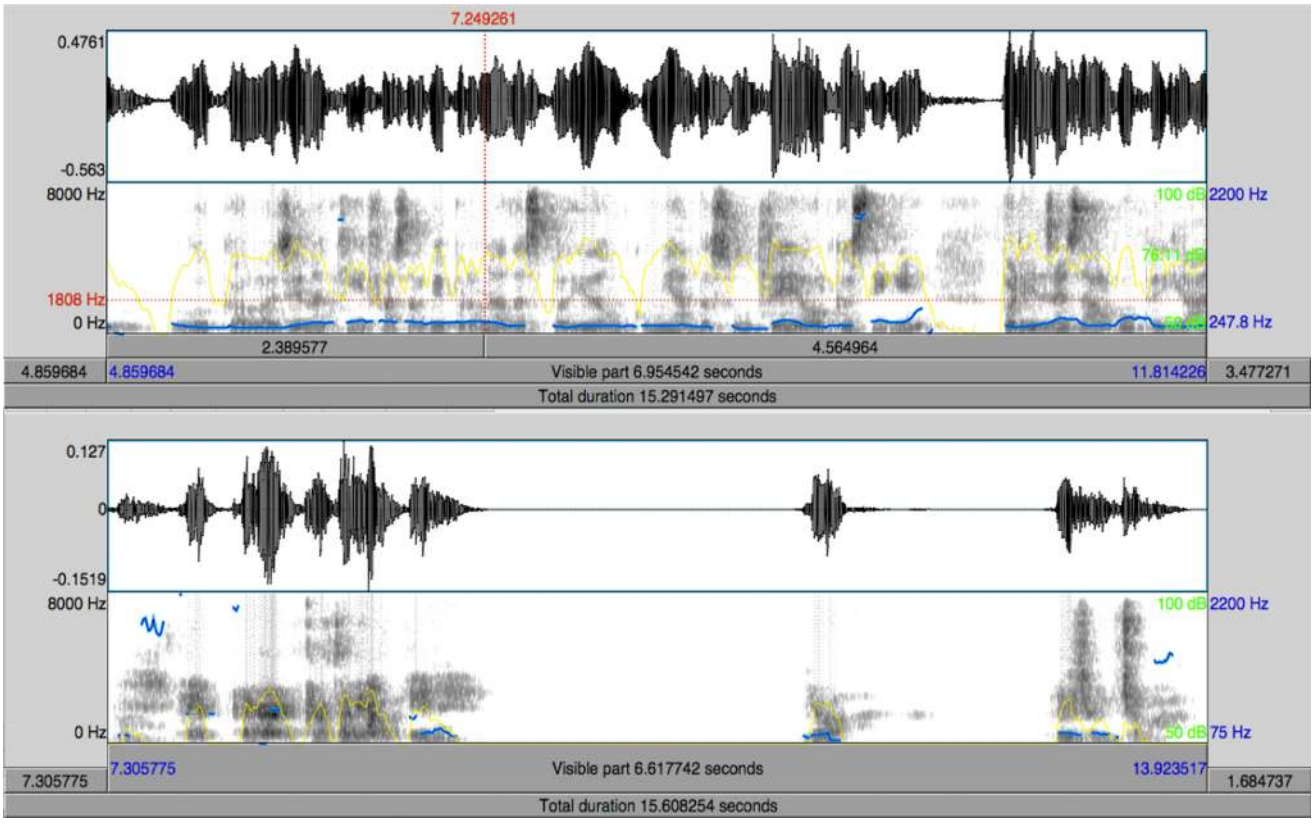

Fig. 1. Signal and spectrogram of a control subject (top) and a subject with Alzheimer's disease (AD) (bottom) during spontaneous speech (pitch in blue, intensity in yellow) [194].

the patient. AD produces a variety of communication deficits in spoken language, including aphasia (difficulty speaking and understanding) and anomia (difficulty recognizing and naming things) [51,52]. The specific communication problems a patient encounters depend on the stage of the disease. A common symptom of incipient cognitive problems (e.g., in MCI stage, which may indicate future AD) is that the patient has trouble finding the right word during spontaneous speech. Although this affects verbal fluency, it often remains undetected. Another area that is affected early is emotional responsiveness; one often observes social and behavioral changes in the early stages of the disease [53]. Altered perception and communication skills may magnify some emotional responses; on the other hand, memory loss may also reduce the ability to feel emotions, which may in turn induce the appearance of apathy and depression.

Automatic Speech Analysis and Recognition (ASR) provide powerful tools to analyze fluency and semantic relations and emotional responses. None of these speech analysis based techniques require extensive infrastructure or the availability of medical equipment; gathering information using these techniques is easy, quick, and inexpensive [49,54,55]. Moreover, the analysis of spontaneous speech or task-restricted speech is not perceived as a stressful test by the patients [55,56]. Indeed, the diagnosis and characterization of MCI using these techniques only requires verbal tests and interviews with the patient.

With regard to testing language abilities, a common test used in AD detection is the test of Verbal Fluency by categories (VFc). This VFc test explores two underlying components of verbal fluency tasks: clustering (the ability to generate successive words within a subcategory) and switching (the ability to shift from one subcategory to another). This test is also useful for AD detection in the early clinical stage [57,58]. Traditionally, medical specialists have administered these tests manually, but in recent years ASR based tools have been gaining ground in clinical practice as well. For semantic measurements or indexes on language features that measure VF quality, the new automatic systems obtain results faster and with less effort than their manual counterparts [59,60].

Beyond automating the analysis of specific tests, current research has also made important advances in analyzing spontaneous speech. Automatic Spontaneous Speech Analysis and Emotional Response Analysis [50,55] examine such features as utterance duration, filler typology, and analysis of voiced and voiceless segments, among others. Figure 1 shows an example of signal and spectrogram of a

control subject and a subject with AD during spontaneous speech. Use of spontaneous speech fluency test integrated with a fractal dimension set allowed discrimination between AD patients and healthy controls with a clinically relevant accuracy of >80% [50]. The analysis of emotional responses includes classical features like pitch, intensity, and variation of frequency components, and, most recently, of Emotional Temperature. This last feature is based on the analysis of a number of prosodic and paralinguistic features [50]. Emotional response test including emotional temperature allowed discrimination between AD patients and healthy controls with a high accuracy of >97.7% [50]. In a similar vein, some researchers have recently proposed that slight cognitive changes in the early and preclinical stages could be detected using nonlinear speech parameters such as fractals [50].

Differences in aspects of language production and comprehension embody the distinctive neurodegenerative syndromes of primary progressive aphasia (PPA), which are normally underpinned by degenerative pathologies other than AD. Three broad subtypes of PPA are recognized: patients with the fluent subtype (also referred to as semantic dementia) produce well-formed speech dominated by generic words such as "thing" or "bit", resulting in minimal informational content, and have difficulty understanding the meanings of single words [61]; in the nonfluent variety (progressive nonfluent aphasia) there is phonologically and/or grammatically distorted speech output and preserved single-word comprehension [62]; the third variant (logopenic progressive aphasia) is marked by a slow rate of speech production, marked word-finding pauses, occasional phonological errors and difficulty with sentence (but not single word) repetition [63].

Wilson et al. (2010) [64] have shown that the connected speech of these three subtypes are associated with distinct profiles using the quantitative production analysis (QPA) scoring protocol [65]. Scoring of speech samples using QPA relies on manual scoring and is therefore both laborious and subject to variation between raters. Garrard et al. (2013) [66] and Fraser et al. (2012) [67] have described more rapid and reproducible automated approaches, applying them to distinctions between individual syndromes, and between patients and controls. A comparative study of spontaneous speech in PPA and AD, however, remains to be conducted.

4.4. Olfactory testing

A number of studies have reported olfactory impairments in AD [68–70], MCI [71], and individuals positive for *APOE* ε4 allele, the main genetic risk factor for AD [72]. Interestingly, olfactory dysfunction in MCI patients may confer poorer prognosis and greater risk of conversion to AD [73]. Additionally, olfactory deficits have been reported in subjective memory complaints [74] and presymptomatic AD [75]. Olfactory impairment is a significant clinical predictor of memory decline [76]. In a previous study, a 100% classification rate of AD patients was achieved using an olfactory identification score combined with olfactory event-related potentials [77].

The neuropathological hallmarks of AD, i.e. neurofibrillary tangles (NFTs) and amyloid plaques (APs), can be seen in the neocortex and associated brain regions such as entorhinal and transentorhinal areas that are also closely involved in olfactory processing. In fact, the olfactory system has direct projections to the piriform lobe and hippocampal formation that are associated with a number of cognitive and behavioral functions including emotions, perception, and memory [78,79]. Furthermore, NFTs and APs have been found in olfactory epithelium, olfactory bulb, and olfactory cortex of AD patients [80,81]. It is widely accepted that these neuropathological features provide a specific and sensitive set of criteria for AD diagnosis. For example, in one study, a 93% diagnostic accuracy was achieved using the NFT counts per section in the olfactory bulb of AD and control brains [82]. In a transgenic mouse model, olfactory dysfunction was significantly associated with increased Aβ load in the olfactory bulb, which preceded all other brain regions [83].

There are various psychophysical, psycho-physiological, and electrophysiological methods available to measure odor memory, threshold, identification, and discrimination [84,85]. Currently, the University of Pennsylvania Smell Identification Test, a scratch-and-sniff test using cards containing odors to be identified, and Sniffin' Sticks-containing pen-like odor dispensing sticks measuring threshold, identification and discrimination of odors are well established olfactory tests available. Olfactory memory refers to both the ability of memorizing odors, and the memories that are evoked by a specific odor [86].

Recently, the olfactory stress test was introduced as a new way of assessing olfaction to detect individuals at higher risk for AD [87]. In this line of research, intranasal atropine is administered and the olfactory function is assessed. Test results have been significantly associated with memory performance. This method still in its early stages may provide an inexpensive way of screening those in the preclinical phase of AD. However, Schofield et al. [87] findings should be examined in longitudinal and cross-sectional studies to be validated for further applications.

In spite of the high sensitivity for AD, olfactory assessment has a disappointingly low specificity and is seen in other neurological and psychiatric disorders [88–91]. Olfactory imperviousness to time [92,93] may dilute its diagnostic utility in late onset AD diagnosis. However, in early onset or familial AD cases (where the symptoms can be detected at an earlier age and usually do not present with age-related, comorbid conditions) olfactory tests may become a useful screening measure. A better understanding of olfactory impairment in AD will help to elucidate the underlying mechanisms and the pathogenesis of the disease and its progression and prognosis [94–96].

4.5. Eye testing

Ocular imaging may provide a noninvasive method for early detection and monitoring of neurodegenerative diseases including AD. The retina is an extension of the brain that is more accessible for imaging. Additionally, the response of the pupil to light is largely driven by the cholinergic system, which is impaired in the AD brain [97]. Furthermore, visual disturbance is often an early complaint of AD patients [98,99] and studies have reported reduced visual performance on tests of visual field [100], color vision [101], contrast sensitivity [102], backward masking [103], visual attention, motion perception, shape-from motion, visuospatial construction, and also visual memory [104]. Both retinal morphology [105–107] and a suppressed pupil light response [108–110] have previously been reported in AD.

Retinal morphology reported in AD involves changes to the vasculature [105] and optic nerve head [111], retinal cell loss [112,113] and thinning of the retinal nerve fiber layer (RNFL) [106]. A key study by Berisha et al. [105] found that AD participants had a specific pattern of RNFL thinning, narrower retinal blood column diameter and decreased retinal blood flow. While this study was limited by its small size, other studies have supported and expanded on the existence of retinal vascular abnormalities in AD [106,107,111]. The retinal vascular changes can be summarized as vascular narrowing, reduced complexity of the branching pattern, reduced optimality of the branching geometry, and less tortuous venules [107]. A suppressed pupil light response has also previously been reported in AD, with the pupil responding to a bright flash of light with slower velocity and acceleration and a reduced amplitude of response [108,110,114].

Importantly, some retinal vascular and pupil response changes were also found to be present in cognitively healthy individuals with high brain amyloid plaque burden, suggesting that eye testing may facilitate early detection of AD neuropathology while in the prodromal stage [107,110]. The retinal changes also opposed those previously reported in vascular dementia [115], indicating that these measures have the potential to reduce the misdiagnosis rate for these most common forms of dementia.

A recent study investigated both the retina and pupil in familial AD, demonstrating that cognitively healthy carriers of the APPGlu693Gln mutation exhibit slower recovery from pupil flash response, with 100% separation between mutation carriers and noncarriers [116]. Despite the known cerebral vascular effects of the APPGlu693Gln mutation, no retinal vascular abnormalities were observed in the mutation carriers.

Amyloid plaques have also been reported in the postmortem retinas of AD patients at early stages [117], and in the ocular lens as an unusual form of cataract [118]. Studies in animal AD models have also found Amyloid plaque burden in retina and brain correlate [117].

4.6. Gait testing

Cognitive impairment due to AD is characterized not only by memory loss, but also by functional impairment [119]. Gait impairments are often associated with cognitive impairments. Both slow and irregular gait during normal, self-paced walking are risk factors for cognitive impairment and dementia [120,121]. Verghese et al. [122] have introduced the motor cognitive risk syndrome, proposing that the presence of both MCI and slow gait in an individual is a better predictor of developing dementia than either MCI or slow gait alone [122,123].

There was a previously held view that gait difficulties only occurred in advanced AD and that gait disturbances early in the disease were considered an exclusion criterion [124]. Yet quantitative gait analysis studies have shown that many gait changes are present in the early stages of AD [124,125]. Some gait changes may even appear before AD is clinically symptomatic and before cognitive decline can be detected by neuropsychological assessments [119].

Gait difficulties at such early stages of cognitive impairment are often neither subjectively present nor visible to the naked eye (even that of a trained specialist) yet can be measured by quantitative gait analysis [126]. Compared with the gait of healthy seniors, the gait of older individuals with cognitive decline is slower with a shorter stride length, lower cadence and an increased stride-to-stride variability [124,125].

Gait has long been considered an automatic motor activity. It is, however, a complex activity, controlled by cortical processes [126,127]. It is currently thought that the neurodegenerative changes in AD affect common pathways needed for both cognition and the neuromotor control of walking [128–130]. Particularly affected are executive functions, which are needed for planning and allocating attention to simultaneously performed tasks [124,126,130,131].

Gait analysis with dual task paradigms—walking while simultaneously performing a second task (either cognitive or motor)—challenge available attention reserves and executive functions. Dual task test paradigms assess the effects of divided attention on motor performance and gait control. Dual tasking permits detection of gait deficits, which, under the single-task condition of walking alone, may otherwise remain undetected [126,132]. Increased stride variability, particularly under dual task conditions, is currently one of the most sensitive markers for underlying gait deficits and is associated with not only an increased fall risk but also with cognitive deficits. Recent evidence from quantitative gait analyses using dual task paradigms shows that gait worsens (becomes slower and more variable from stride to stride) as cognitive decline progresses [119] (Figure 2).

Quantitative gait analysis, particularly when dual task paradigms are used, may be able to aid diagnosis of those in the earliest stages of cognitive impairment. Early detection allows the timely implementation of interventions

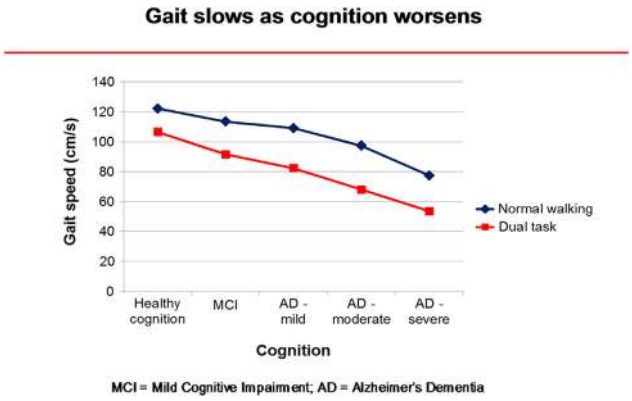

Fig. 2. Task-related gait speed: The greater the cognitive impairment, the slower the gait speed. For all cognitive groups, gait was slower during dual tasks than during the single task of normal walking [119].

with the ultimate goal of improving or maintaining mobility and functional independence for as long as possible. Early detection of gait and cognitive impairments may also provide a better understanding of the pathophysiology and progression of dementia.

5. Blood tests

The molecular changes underlying the neurodegenerative pathology in AD may take place up to 20 years before its clinical appearance. In this context, the discovery of biomarkers in biological fluids enabling an early diagnosis of AD in the pre-clinical stage is eagerly awaited. Blood is a potential source of biomarkers for neurodegenerative changes in the brain, because ~500 ml of CSF is absorbed into the blood every day. Moreover, the common finding of blood-brain barrier damage in AD may facilitate movement of proteins from brain to blood [133,134].

Blood-based biomarkers may have utility in predicting risk for AD, which is an area requiring more investigation. For example, Kivipelto and colleagues created a 20-year dementia risk score that included total cholesterol, *APOE* ε4 genotype, blood pressure readings, smoking status, gender, education, age, and physical activity level that was a significant predictor of future risk [135]. Graff-Radford et al. followed 563 cognitively normal elders over an average of 3.7 years. Baseline plasma Aβ42/Aβ40 ratios in the lower quartile indicated a greater risk of developing MCI or AD over time [136]. More recently, Yaffe and colleagues found that a low Aβ42/Aβ40 ratio significantly increased risk of cognitive decline over nine years in individuals who were dementia free at baseline [137]. When looking at C-reactive protein (CRP), data from the Honolulu-Aging Study suggests that midlife elevations are a significant risk for AD in late life [138]. Van Oijen et al. [139] found increasing levels of fibrinogen among cognitively normal elders to be a significant risk for later development of dementia (AD and Vascular dementia) in the Rotterdam Study. Tan et al. (2007) [140] analyzed data from the Framingham Study and found that increased expression of inflammatory cytokines from peripheral blood mononuclear cells increased risk for incident AD over a seven-year period. Van Exel et al. [141] studied offspring with and without family histories of AD to examine patterns of vascular factors and inflammation. These authors found that offspring with parental history of AD were more likely to carry the *APOE* ε4 genotype, have higher systolic and diastolic blood pressure, and express higher levels of proinflammatory cytokines IL-1β, IL-1β/IL-1ra ratio, TNF-α, IL-6, and IFN-γ. Mielke et al. demonstrated in their population-based prospective study a strong relationship between increased serum levels of particular ceramide species at baseline and the subsequent risk of developing all-cause dementia and AD over a 9-year period [141]. In a recent study, a plasma panel of ten phospholipids showed a high accuracy in predicting development of memory impairment (aMCI or AD) within a 2- to 3-year timeframe in older adults [142]. However, the analysis was performed with mass spectrometry not widely available in many labs and this biomarker panel needs external validation in independent cohorts before further development for clinical use. Taken together, the above results suggest that those subjects at greatest risk for AD show already in the preclinical stage characteristic alterations of several biomarkers in blood. Thus, blood-based biomarkers could play a key role in predicting future AD risk. Additional work is now needed to determine if blood markers can be combined with clinically-relevant information, to create risk profiles for later development of AD similar to the work that has been done with cardiovascular risk scores (e.g., Framingham scores).

Several recent studies have demonstrated that blood-based biomarker panels could be a useful diagnostic tool for identification of AD patients. Ray and colleagues (2007) [143] assessed 120 plasma proteins in an effort to identify a profile of multiple biomarkers indicative of AD. They identified a panel of 18 proteins that were effective to distinguish AD patients from healthy controls with an overall classification accuracy of 89%. The algorithm also accurately identified 81% of MCI patients who progressed to AD within a 2- to 6-year follow-up period. In the following years, several research groups identified different blood-based biomarker panels in serum and plasma able to discriminate AD patients from healthy controls or MCI patients progressing to AD from stable MCI individuals with a clinically relevant accuracy [144–148]. Table 2 gives an overview of recent blood-based biomarker panels for diagnostic use in AD.

Taken together, these studies suggest that a blood-based screening tool for AD is on the horizon. Although great progress is being made in this research field, blood-based biomarkers are not yet ready for clinical implementation due to a lack of standardization concerning preanalytical, analytical and postanalytical methods, which would be necessary to foster cross-validation across cohorts and laboratories.

Table 2
Recent blood-based biomarker panels for diagnostic use in AD

Working groups	Sample mediums	Number of biomarkers in the panels	Diagnostic accuracy training set/test set
Ray et al. [143]	Plasma	18	Biomarkers alone: accuracy = 89%/89%
O'Bryant et al. [144]	Serum	108	Biomarkers alone: AUC = 0.91 Biomarkers + clinical[x] + demographic parameters[y]: AUC = 0.95
Laske et al. [145]	Serum	3 (cortisol, vWF, OLAB)	Biomarkers alone: accuracy = 82%/87%
Soares et al. [146]	Plasma	7	Test set: Sensitivity = 80% to 90% Specificity = 70% to 80%
Doecke et al. [147]	Plasma	18	AIBL cohort: AUC = 0.87 ADNI cohort: AUC = 0.85%
Hu et al. [148]	Plasma	4 (*APOE*, B-type natriuretic peptide, C-reactive protein, pancreatic polypeptide)	No data provided

Abbreviations: AUC = area under the receiver operating characteristic curve; [x] = i.e. cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, lipoprotein-associated phospholipase, homocysteine, and C-peptide; [y] = i.e. age, gender, education, and *APOE* status; *APOE*, apolipoprotein; ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing.

6. Neurophysiological tests

6.1. Novel EEG biomarkers

Recent MRI studies have demonstrated that amyloid pathology is linked to neural dysfunction including altered resting state connectivity in a distributed network of brain regions supporting memory function in subjects with preclinical AD [149,150]. It is widely accepted that the cerebral EEG rhythms reflect underlying brain network activity [151]. As a consequence, modifications in EEG rhythms could be an early sign of AD.

EEG biomarkers would provide a noninvasive and relatively inexpensive screening tool for early diagnosis of AD and could be automatically analyzed in just a few minutes. However, traditional EEG biomarkers have not been considered accurate enough to be useful in clinical practice [152,153]. The capability to extract useful information from a rough EEG track, using only mathematical algorithms, is a challenging but promising task. Novel EEG biomarkers and their combination into a diagnostic classification index may be able to discriminate AD patients in different clinical stages from normal subjects with an even higher accuracy.

In the last twenty years, many powerful learning machines and algorithms were proposed to face this hard problem with different and interesting results [154]. Computerized EEG analysis in aged people has been enriched by a number of modern techniques capable of exploiting the large amount of information on time-frequency processes in single recording channels and on spatial localization of these processes [155–158]. Recent studies have convincingly demonstrated that several novel measures of EEG analysis could be useful for predicting MCI conversion to AD and for identification of early AD with a clinically useful accuracy. These novel measures include the use of high EEG upper/low alpha frequency power ratio [159], the combination of multiple EEG biomarkers mainly related to activity in the beta-frequency range (14–30 Hz) into a diagnostic index in the eyes-closed resting state [160], optimized EEG frequency bands [161] and the alpha (8–13.9 Hz)/theta (4–7.9 Hz) ratio [162].

An alternative and promising attempt to make the EEG analysis suitable for clinical applications in aging has been accomplished through the use of neural networks, capable of extracting specific and smooth characteristics from enormous amounts of data. Some authors [163] developed a system based on recurring neural nets processing spectral data in EEG. They succeeded in classifying AD and non-AD patients with a sensitivity of 80% and a specificity of 100% in a small study cohort. In other studies, classifiers based on artificial neural networks, wavelets, and blind source separation achieved promising results [164–168]. In recent years, a completely new approach to EEG analysis has emerged, called I-FAST (Implicit Function as Squashing Time) [169]. I-FAST is composed of three steps (see Figure 3): (1) The transformation of the N EEG channels of each subject into a vector of features (Squashing Phase). (2) The dynamic elimination of the noisy features from the vector representing each subject (Noise Elimination Phase). (3) The intelligent classification, with the support of Machine Learning, of the features of each subject (classification phase). I-FAST approach has shown to be able to distinguish elderly AD, MCI, and control elderly subjects in a blind manner with an accuracy of over 94% [169,170]. Recently, I-FAST methodology was also applied to a consistent sample of MCI subjects (n = 143), where a subsample (n = 51) converted to AD within three to five years [171]. I-FAST succeed in predicting which subjects were MCI stable and which ones were MCI converted with an accuracy of over 92%, using only data coming from EEG signal.

The next milestone of the EEG analysis using complex artificial adaptive systems aims to be able to extract from

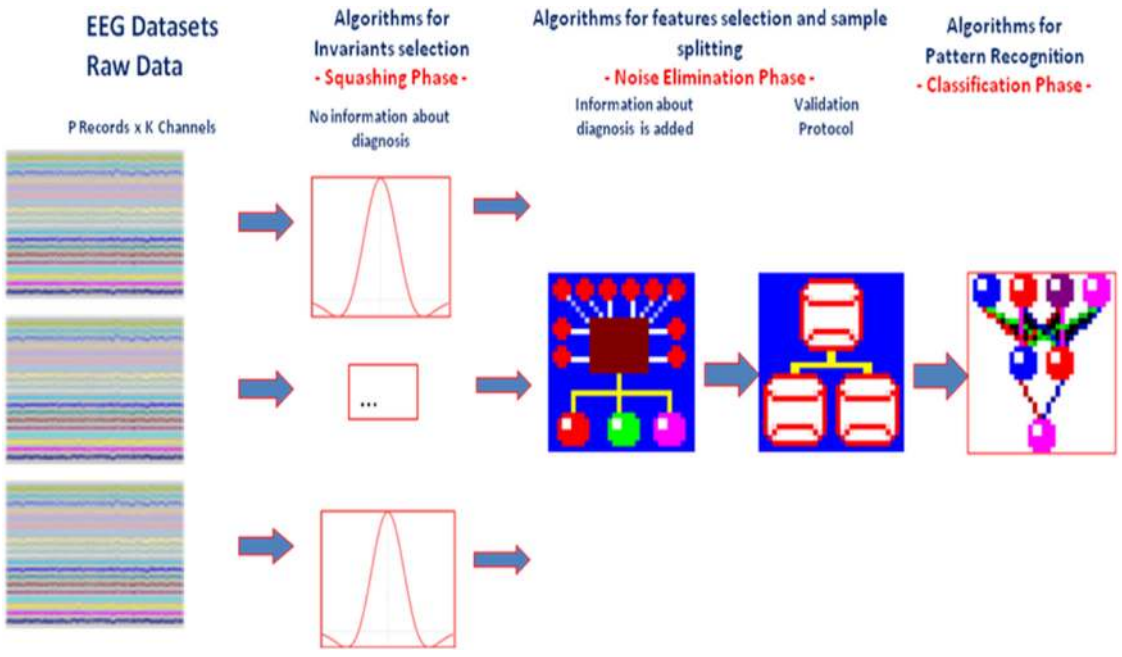

Fig. 3. I-FAST (Implicit Function as Squashing Time)structure: squashing phase, noise elimination phase, classification phase [169].

the EEG signal specific clinical information about single subjects. In this way, EEG analysis could become an important component of a more global analysis of the specific brain of each single patient.

6.2. Novel MEG biomarkers

MEG, the assessment of the brain's magnetic fields, is a relatively new technique first introduced by David Cohen in the late 1960s [172]. As dynamic electrochemical processes in the brain result in changing magnetic fields that pass conductive boundaries (e.g., the skull) undistorted [173], placement of superconducting quantum interference devices (SQUID) [174] in close proximity to the human head allows for reliable assessment of these processes with high temporal (millisecond) and, depending on the number of SQUIDs used, spatial (millimeter) resolution [175,176]. Current state-of-the-art systems use up to 300 sensors that, if combined with appropriate algorithms, provide an unprecedented information depth of task-free and task-related neuromagnetic brain activity. After Berendsen et al. showed for the first time that individuals with AD exhibit a general slowing of task-free brain oscillatory activity [177], subsequent MEG studies identified delta (2–4 Hz) and beta (16–28 Hz) oscillations as most significantly changed in AD [178,179]. Further analysis indicated an increase of frontal, central delta and theta signal power, while posterior temporal and occipital areas exhibited a decrease of signal power in higher frequencies [177]. In line with a previously described association between the level of cholinergic activity and increased delta power [180], a correlation between cognitive decline and an increase in magnetic dipole density (MDD) of temporoparietal delta and theta activity in AD was found [181]. MEG allowed discrimination of individuals with AD from healthy controls with accuracies above 80% using, for instance, spectral mean frequency [182]. Quantification of MDD during a memory task resulted in sensitivity of 90% and specificity of 100% when combined with MRI (myoinositol/N-acetyl aspartate) spectroscopy [183]. To investigate the value of whole-head MEG recordings to assess *in vivo* biomarkers for AD, a recent study evaluated delta current density (DCD) across the posterior parietal, occipital, prerolandic, and precuneus cortices of individuals with MCI, AD with different severity scores, and healthy controls [184]. The transition from MCI to mild dementia and from mild to more severe dementia could be reliably indexed by an increase in the right parietal cortex and precuneus DCD. Besides these promising results, introducing other linear and nonlinear measures to assess large-scale brain network activity (e.g. spectral entropy measures [182]), or measures to quantify functional connectivity (e.g. coherence analysis [185], phase lag index (PLI) [186] or synchronization likelihood [187]) might further improve the reliability and robustness of detecting and identify individuals who are at risk to develop neurodegenerative disorders and progressive cognitive decline at an early stage. Once identified, these neurophysiological measures could be used as a specific target for neurofeedback training, using, for instance, brain–machine interfaces and brain stimulation aimed at normalizing disturbed neural network activity [188].

The combination of MEG with MRI spectroscopy is associated with costs of a few hundred US dollars per examination and requires the availability of a MEG and MRI facility, thus favoring their use not as a primary dementia screening

instrument but rather as a promising alternative diagnostic option to already established diagnostic measures. Recent technical advances, e.g. development of ultra low-field microtesla MRI during MEG recordings [189] and atomic magnetometers [190] operating at room temperature, suggest that associated costs will significantly decrease and availability of such combined MEG/MRI recordings improve in near future.

7. Conclusions

Current state-of-the-art diagnostic measures of AD are invasive (CSF analysis), expensive (neuroimaging), and time-consuming (neuropsychological assessment). Furthermore, these measures are limited to specialty clinics and thus have limited accessibility as high-throughput, or frontline, screening and diagnostic tools for AD. More importantly, nonspecialists are often inaccurate at identifying early AD and MCI [5]. Thus, there is an increasing need for additional noninvasive and/or cost-effective tools, allowing frontline identification of subjects in the preclinical or early clinical stages of AD who could be suitable for monitoring in specialty clinics and for early treatment. Implementation of effective screening instruments will allow diagnosis earlier in the course of dementia, even at the point when memory function is still essentially within the normal range. This strategy would enable an earlier, and potentially more effective, prevention and treatment of AD with a special focus to preserve cognitive functions.

Early AD development is clinically characterized not only by progressive memory loss presented in subjective cognitive complaints [27,28] and objective psychometric testing [14], but also by noncognitive symptoms such as late-onset depression [43] and progressive functional impairment of speech (language use and emotional responses) [50,55], olfaction [75], pupil light response [108,110], retinal vasculature [105–107], and gait [124,125] with a gradual increase along the continuum of AD from preclinical via MCI to the dementia stage. The recognition that several noncognitive symptoms, such as olfactory dysfunction [75] and gait impairment [191,192], occur very early in the disease course and can predict the subsequent development of AD suggests that noncognitive functions may serve as phenotypic markers of preclinical AD. Increasing knowledge of affected systems in AD development furthers our understanding of the pathophysiology of AD and allows us to identify novel candidate biomarkers for diagnosis of AD.

Assessment of subjective cognitive complaints, late-onset depression, speech (language use and emotional responses), olfactory function, pupil light response, retinal vasculature, and gait may have potential utility as clinical tools for detection of preclinical and early clinical AD. These measures are noninvasive and inexpensive and thus suitable for a broader screening of individuals with preclinical or early clinical AD. In addition, use of measures such as EEG and MEG and use of blood-based biomarkers may enlarge the spectrum of AD diagnostics. Several measures (e.g., speech, gait, EEG, and MEG) can be automatically analyzed, allowing a multidimensional, objective and reliable diagnostic procedure. These novel measures will not replace a comprehensive clinical and neuropsychological assessment and standard tests with CSF analysis and neuroimaging, but rather will enhance these modalities by offering primary care providers a means for determining who needs referrals for comprehensive assessment for diagnostic confirmation.

Given the complex nature of AD pathophysiology [1], it is likely that the optimal prediction models for future development of MCI and/or AD, and risk for progression from MCI to AD, will come from algorithmic approaches that combine multiple diagnostic methods. Actually, we do not know which of the described tests in the present review manuscript work best for screening of preclinical and early symptomatic AD. As an example, one potential Screening Approach could include a quick but reliable measure of subjective cognitive complaints (either patient, informant or both), a brief cognitive assessment (e.g., episodic memory) and an assessment for depressive symptoms plus one or more of the following measures chosen for their availability including olfactory, speech, eye test, gait, blood biomarkers (e.g. *APOE*, serum Aβ load, etc.) and EEG (Figure 4). As the average time spent in primary care settings with geriatric patients is usually less than 20 minutes, it seems reasonable to allocate these tests on two or more consecutive visits (Figure 4). Inclusion of cognitive and noncognitive approaches may aid in discrimination across neurodegenerative disease states to aid in appropriate referrals. A potential diagnostic approach may utilize a comprehensive battery, adding neuropsychological assessment plus brain imaging, MEG or CSF analysis to the screening approach battery (Figure 4). Future research may indicate the utility of these two approaches or the need for revisions. Large prospective cohort studies of patient performance and correlation with brain imaging modalities and/or biochemical markers of AD will, however, be required before the best combination of selected biomarkers to optimize diagnostic sensitivity and specificity is identified. Thus, before applying them in clinical practice, these tools should be further examined, as some are now, in ongoing large clinical trials such as ADNI (Alzheimer's Disease Neuroimaging Initiative), AIBL (Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing) or DIAN. Despite the difference in underlying cause and age of onset, familial AD and the more common sporadic AD have similar neuropathological hallmarks and clinical features [193]. Further investigation of the reported novel candidate biomarkers in familial AD, and utilization of familial AD cohorts in future biomarker studies, provides a powerful opportunity to investigate the temporal sequence of different AD biomarker changes during disease progression. Studying pre-symptomatic individuals with autosomal dominant inheritance alleviates many problems inherent in studies of pre-symptomatic sporadic AD, including uncertainty about

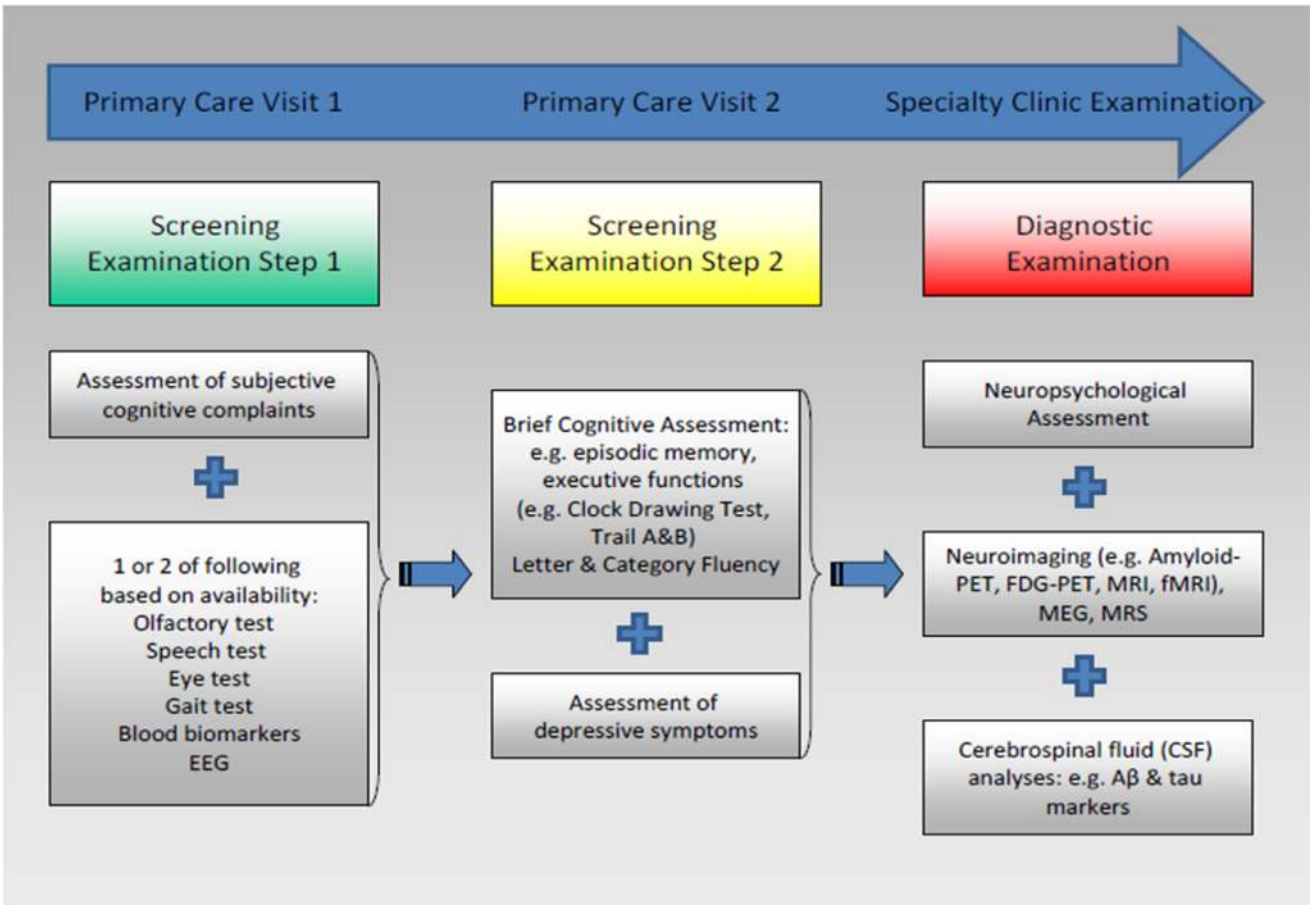

Fig. 4. Algorithm of a potential Screening Approach (two steps) and Diagnostic Approach (third step) for early detection of Alzheimer's disease. The first two screening steps can take place in the primary care setting and the third diagnostic step can take place in a specialty clinic. The Screening Approach is splitted in two steps for economic reasons and limited available time per one visit in the primary care setting. The second step could be used to even tailor where the third step (i.e. Diagnostic Approach) is best managed (i.e. if clinical depression then psychiatry/psychology needs to be included). Future research may indicate the utility of this algorithm or the need for revisions. Thus, before applying them in clinical practice, these tools should be further examined, as some are now, in ongoing large clinical trials.

the age of onset and age-related co-morbidities such as hypertension and cardiovascular disease and age-related decline in cognition, olfaction, and motor abilities. However, it is not clear if the results of studies in familial AD can be directly extrapolated to sporadic AD.

A key need in the field is the inclusion of AD and non-AD neurodegenerative dementias into studies of screening tools and biomarkers. Some of the diagnostic tests presented in this review are specific and sensitive for AD (e.g., amyloid detection during retinal examination), while others are nonspecific for AD but sensitive for cognitive disorders including AD (e.g., subjective cognitive complaints, late-onset mood disorders, gait changes and blood markers such as CRP). To date, most of the studies presented in this review were obtained comparing AD patients vs. normal controls, but not AD patients vs. other neurodegenerative diseases. Thus, while the available case-control studies comparing AD patients vs. normal controls have yielded extensive information, it remains still unclear, how these methods and markers will function across different neurodegenerative diseases. Given the pathological overlap and comorbidities, this is an important area for future studies and it is likely that the inclusion of biomarkers will greatly aid in the differential diagnostic process.

To date, research has significantly contributed to our understanding of the AD neuropathology, its course and the related dementia development. However, our progress in terms of screening individuals at higher risk, diagnosing those with the disease, and developing preventive and ameliorative interventions has been modest and far from clinical applicability. It should be noted that the measures derived from studies on genetic mutation carriers should be cautiously examined when their findings are going to be utilized in sporadic and late onset research. However, the time seems right to incorporate new measures and to examine unexplored avenues that may shed further light into what is going to be a catastrophic epidemic disease in near future affecting not only the elderly, but also the younger generations as care-givers, family members, or familial AD mutation carriers.

Acknowledgments

This work was supported by the German Federal Ministry of Education and Research (BMBF, 01GQ0831, 16SV5840), the Deutsche Forschungsgemeinschaft (DFG SO932-2) and the European Union (FP7-ICT-2011-288551). RNM is the founder and owns stock in Alzhyme. HRS is working as a Site Lead neuropsychologist or Neuropsychological rater for Takeda, Wyeth, and Pfizer. None of the authors of this manuscript have any biomedical financial interests or potential conflicts of interest.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature on noninvasive and inexpensive cognitive and noncognitive diagnostic measures for early detection of Alzheimer's disease (AD) beyond established dementia diagnostics with cerebrospinal fluid analysis, neuroimaging and neuropsychometric testing.
2. Interpretation: Assessment of subjective cognitive complaints, late-onset depression, speech, olfactory function, pupil light response, retinal vasculature and gait may have potential utility as noninvasive and inexpensive clinical tools for detection of preclinical and early clinical AD. In addition, use of measures such as electroencephalography and magnetoencephalography and use of blood-based biomarkers may enlarge the spectrum of AD diagnostics.
3. Future directions: Before applying the presented tests in clinical practice, these tools should be examined now in ongoing large clinical trials.

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