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Symptoms of early Alzheimer's disease and new treatment options

The ‚Interdisciplinary Discussion Forum on Ethical, Economic and Medical Challenges Prior to the Onset of Dementia' was established at the beginning of 2020 in order to establish public discussion on fundamental issues regarding the diagnosis, therapy and care of dementia patients and to identify a concrete need for action. Current developments in the therapeutic field are discussed as well as ethical problems, gaps in care and special topics such as the use of biomarkers for risk stratification of patients in the early diagnosis of Alzheimer's disease. Interdisciplinary expertise is provided by different actors and experts in the health care system from the fields of science, ethics, medical care or care providers, politics as well as institutions of self-administration and research-based pharmaceutical manufacturers. Against the background of current developments in the diagnostic field and in anticipation of the possible approval of disease-modifying therapies, this first publication focuses specifically on the diagnosis of early symptoms of Alzheimer's disease and their requirements for the assessment of therapeutic effectiveness.

Summary

Due to the demographic development of the world population, a significant increase in the number of people with Alzheimer's disease is expected in the future. Biological changes are already present in this disease before clinical manifestation - this offers an opportunity in at-risk populations and for primary prevention of clinical symptoms. In the early stages of the disease, patients are autonomous in their daily lives, sometimes even still working. This is an opportunity for secondary prevention and disease-modifying therapies.

The introduction of blood biomarkers in diagnostics and the approval of disease-modifying therapies could fundamentally change the approach to dementia in the future. In this context, the early detection of early stages of Alzheimer's disease will be of particular importance. Early detection of Alzheimer's disease, education and counselling of those affected as well as prevention and early therapy are the future of age-appropriate medicine.

Medical progress in the field of Alzheimer's disease therefore requires a different overall societal and medical emphasis with rethinking towards the redesign of diagnosis and therapy in the early stages of the disease.

Schlüsselwörter

Alzheimer's disease, dementia, diagnostics, biomarkers, imaging, cognitive testing, disease-modifying therapies, DMT

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Background

>> At the end of 2021, almost 1.8 million people with dementia were living in Germany, of whom almost 1.2 million were women and 0.6 million were men (1, 2). According to estimates by the World Health Organisation (WHO), approximately 55.2 million people worldwide were already affected by dementia in 2019, with Europe in second place with 14.1 million dementia patients. The disease is strongly age-associated, with data from Europe showing an increase in prevalence from 1.9% in those aged 65-69 to over 36% in those aged 90 and over (3).

Alzheimer's disease is the most common cause of dementia, accounting for up to 80% (4). As a chronic progressive degenerative disease of the central nervous system, it is understood as a continuum in which different symptom clusters define the stages of the disease (5). The clinical manifestation and the test-psychological evidence, recorded with the cognitive test procedures and methods for recording daily living skills available to date, are preceded by a preclinical phase of many years (6). The phase of transition from the phase of continuum without clinical symptoms to a detectable clinical symptomatology can be accompanied not only by memory disorders but also by non-specific psychiatric symptoms, e.g. reduced drive or depressed mood. For methodological reasons, the nature and extent of these symptoms can only be inadequately recorded in this transitional phase. At the onset of a clear clinically manifest AD, specific impairments in the consolidation of episodic memory occur (amnestic MCI). The more global mild neurocognitive disorder is diagnosed when at least one domain of cognitive performance domains is impaired with essentially preserved daily living skills. Mild cognitive impairment and mild neurocognitive disorder are thus syndromes in the intermediate range between normal performance and dementia (7). If the disease continues to progress, dementia develops, i.e. such a marked impairment of cognitive performance areas that everyday competence is impaired (Fig. 1).

The earliest symptom of clinical Alzheimer's disease is impaired consolidation of episodic memory, sometimes accompanied by an uncharacteristic, partly reactive, partly biologically justifiable non-specific neuropsychiatric symptomatology. In the case of mild neurocognitive disorder (ICD-11) or mild neurocognitive disorder (DSM-5), deficits may be present in one or more areas - if specific biomarkers are detected (see below), this is Alzheimer-related mild cognitive disorder. Characteristic amyloid deposits or amyloid peptides are detectable in the brain or cerebrospinal fluid (CSF) (8). Finally, Alzheimer's dementia represents the advanced stage of Alzheimer's disease in the late phase of the disease with increasing loss of cognitive abilities and loss of independence in old age due to impaired everyday functions based on irreversible structural damage to the brain.

Recent prevalence estimates based on recent literature searches and a model that included the biomarker-confirmed pathology of Alzheimer's disease highlight the previously undetected proportion of individuals who are in the early stages of the disease (9). For example, the number of people with preclinical AD is estimated to be approximately 315 million worldwide, representing 17% of all people aged ≥50 years (52% of whom are women); the number of people with prodromal AD is estimated to be approximately 69 million worldwide, representing 3.7% of all people aged ≥50 years (57% of whom are women). These data can be interpreted to mean that

the majority of people with AD pathology do not have dementia but are in the early stages of the disease. Against this background, early detection, education and counselling as well as early treatment and prevention of dementia gain in importance insofar as they are accompanied by specific counselling or treatment options. In particular, these figures highlight the optimal time window for dementia prevention (9).

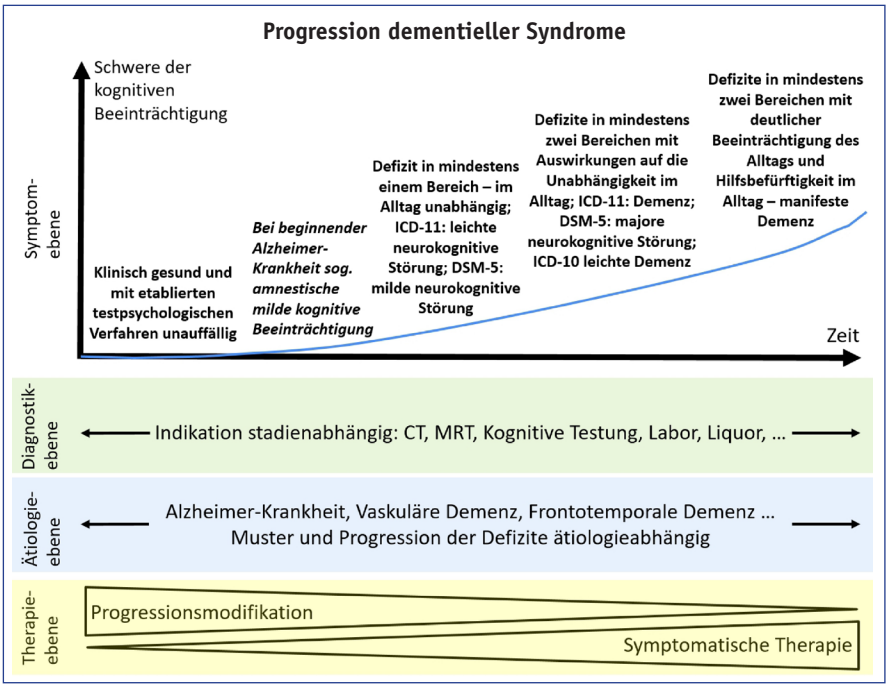


Fig 1: Progression of dementia syndromes. The cognitive deficits do not initially impair independence in everyday life. The ICD-11 classification system calls this stage mild cognitive disorder, the American Psychiatric Society system, DSM-5, mild neurocognitive disorder. At the stage of impaired independence in everyday life, the syndrome is called dementia in the ICD-11 classification system, and majore cognitive disorder in the DSM-5 classification system. In the predecessor system ICD-10, the term dementia means marked impairment of independence in everyday life. In the progression of symptoms of Alzheimer's disease, there is a stage where there is only an impairment in the consolidation of episodic memory - amnestic mild cognitive impairment. Although the symptomatology is a continuum, it should be noted in the early diagnosis of Alzheimer's disease that the early clinical symptomatology requires extensive testing of memory performance (source: Riepe; own presentation). 1 1: In Germany, all physicians in SHI-accredited care and in facilities managed by physicians are obliged to code diagnoses according to the ICD (International Statistical Classification of Diseases and Related Health Problems) in the respective German version (6). The current version of ICD-10 has been revised and is currently available as a draft version of ICD-11 on the Internet as the first version of a German translation(https://www.bfarm.de ICD/ICD-11). The revision of ICD-10 was unavoidable, especially for dementias and their precursor syndromes, due to medical advances in the field of early and differential diagnosis of neurodegenerative diseases and the latest findings.

Pathogenetic process of Alzheimer's disease

During the pathogenetic process, cerebral autoaggregation of amyloid peptides into amyloid plaques, aggregation of tau fibrils and neuroinflammation occur, leading to neurodegeneration at the cellular level and cognitive decline clinically (10, 11). According to the amyloid cascade hypothesis, the occurrence of cerebral amyloid deposits precedes tau pathology and is considered a necessary condition for the progression of Alzheimer's disease (12). Furthermore, the changes in the immune system triggered by protein aggregates are an important pathogenetic factor as a motor of neurodegeneration (13). The two neuropathological markers (altered amounts of amyloid-beta peptide and tau protein in the brain or the CSF) are detectable long before the first clinical symptoms appear.

Turning point in the treatment of Alzheimer's disease: disease-modifying therapies

In Europe, only therapies for the symptomatic treatment of Alzheimer's disease in the dementia stage have been approved so far. These medications aim to improve or at least stabilise cognitive deficits and daily living skills, and to reduce the behavioural disturbances associated with dementia.

In the past 10-15 years, intensive research has been conducted into the development of drugs that target the pathophysiology of the neurodegenerative processes in Alzheimer's disease. These so-called disease-modifying therapies (DMT) specifically target neuropathological molecular processes that are at the beginning of the cascade of pathological events, such as amyloid aggregation (14). Therefore, the concept of DMT for the treatment of Alzheimer's disease specifically targets the early stages with biomarkers as a diagnostic basis. Confirming the diagnosis in early stages requires the investigation of biomarkers, as the phenotype alone, e.g. in differentiation from cognitive deficits in depressive disorders, is not sufficient (15).

Early detection of Alzheimer's disease: biomarker candidates

In 2010, Jack et al. developed a model for the chronology of pathophysiological changes in the course of Alzheimer's disease, which was supported by many findings, was realigned several times in the following years and was groundbreaking for the basis of new pharmacological interventions (5, 16, 17). In this model, a distinction is made between biomarkers for amyloid pathology, tau pathology and neurodegeneration (ATN classification).

For the detection of amyloid pathology, the pathologically relevant fragment amyloid beta1-42(Aß 1-42) and the Aß 42/40 ratio can be determined by means of lumbar puncture in the cerebrospinal fluid. The Aß 42/40 ratio canimprove the sensitivity and specificity of the detection of Alzheimer's disease compared toAß1-42 (18). Another possibility is to measure the cerebral amyloid level by positron emission tomography (PET). Various studies have shown a correlation between cerebral amyloid tracer binding and a reduced Aß 1-42 concentration or Aß 42/40 ratio inthe cerebrospinal fluid (19, 20).

The detection of total tau (tTau) protein in the CSF indicates nerve cell loss and neurodegeneration and correlates with the concentration of phosphorylated tau protein (pTau) in the CSF in Alzheimer's disease (18, 21). The detection and quantification of tau pathology in Alzheimer's disease is based on the measurement of pTau in the CSF. To date, only tau PET tracers in development are in scientific use to detect cerebral tau deposition. Studies have shown a positive correlation between cerebral tau deposition measured by tau PET and concentrations of pTau and tTau protein in the CSF as well as histopathological evidence of tau (22-24). When appropriate cognitive testing procedures are used, there are correlations between biomarkers and memory performance (25, 26).

The pattern of brain atrophy can be assessed by structural ma-

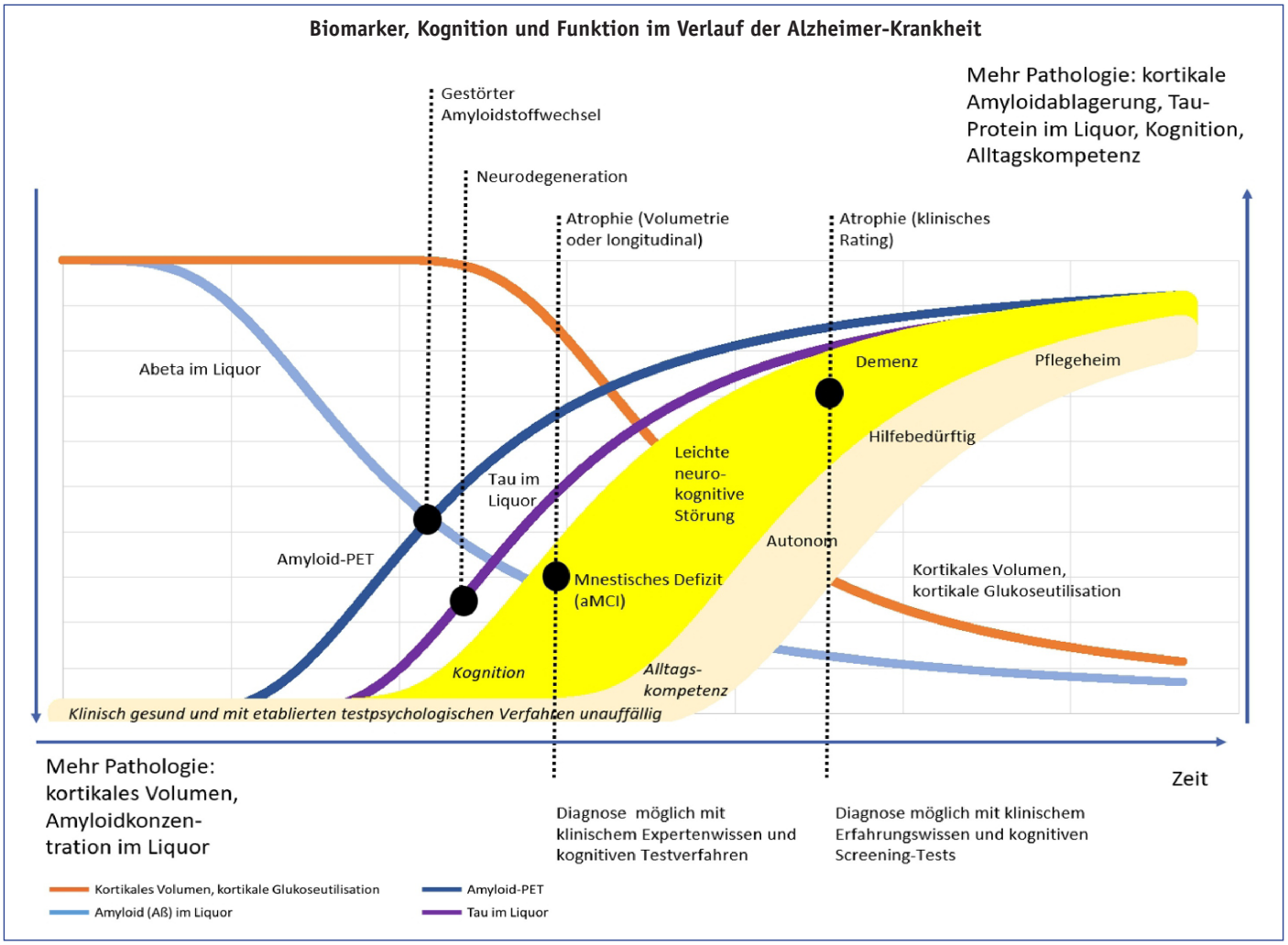


Abb. 2: Adaptiertes Modell zum zeitlichen Verlauf von Biomarker-Auffälligkeiten und erster kognitiver Symptome im Alzheimer-Kontinuum, vgl. auch Abb. 1 (Quelle: Riepe; eigene Darstellung).

gnetic resonance imaging (MRI). In particular, medial temporal lobe atrophy is considered typical of neurodegeneration in the presence of Alzheimer's disease. Fluorodeoxyglucose (FDG)-PET can be used to visualise cerebral glucose metabolism, which indicates synaptic dysfunction and the extent of neurodegeneration. Hypometabolism in the medial parietal lobe (praecuneus) and in the temporoparietal and frontal brain areas is typical for Alzheimer's disease (27).

Based on the model of Jack et al., the current understanding is that the disease begins long before symptom onset with amyloid deposits that can first be detected by CSF or PET examinations in the preclinical stage. The tau pathology subsequently spreads across the medial temporal lobes and both the concentrations of tTau and pTau in the CSF become conspicuous in the course of this spread to other brain regions; in vivo , the spread can be visualised using tau PET. This is followed by neurodegeneration, the consequence of which - cerebral atrophy - can be detected by MRI and the neuronal dysfunction by FDG-PET.

As neurodegeneration progresses, cognitive deficits and cerebral atrophy become measurable in addition to the markers of amyloid metabolism and neurodegeneration (Fig. 2). The impairment begins as a disorder with a mnestic deficit, in which everyday functions are still undisturbed. Affected persons are unable to classify the unspecific impairment that is often present at this time; neither is the currently prevailing routine clinical care.

Diagnostics by means of amyloid PET is currently only used to a very limited extent outside the context of research. For example, cost coverage is only granted by the G-BA within the framework of the ENABLE study in the trial phase (28). The subject of the trial study is the question of whether patients with a confirmed diagnosis of dementia, but with an unclear cause, benefit from an additional examination by means of amyloid PET.

The use of blood-based tests could potentially complement screening in GP care settings and bring a higher proportion of people to qualified screening in memory outpatient clinics. The use of plasma-based biomarkers for screening is less risky for patients, less costly to use (even outside specialist centres) and less expensive than, for example, PET, MRI or invasive CSF puncture, but has not yet been validated (29, 30). Blood-based biomarkers have so far only played a role in research contexts, but this could change in a few years with the approval of adequate biomarker tests for routine diagnostics and care.

Both the introduction of blood biomarkers into care and the approval of disease-modifying therapies will fundamentally change the therapeutic situation and the diagnostic approach to dementia. The coordination of possible therapies with the then necessary diagnostic procedures will ultimately require institutional and precise clarification.

Need to adapt the diagnostic procedure

In the 1980s, according to the common definition of dementia, the presence of deficits relevant to everyday life in patients was required to a considerable extent for both the diagnosis and the therapeutic approach. During this time, neuropsychological tests were used in the form of composite scales that mapped the severity of individual clinical deficits in multiple cognitive domains - such as episodic memory, attention and language - by summing the deficits in these areas.

Currently, drugs are in development that target the pathophysiology of Alzheimer's disease. Drugs are being tested in symptomatic patients with mild cognitive impairment or mild dementia in phase III trials (12). However, only the most recent study with a drug targeting the pathophysiological process of Alzheimer's disease provided clinical proof of efficacy. These study results (as of Dec. 2022) show for the first time significant clinical results and a connection between an antibody-mediated reduction of amyloid deposits in the brain and a simultaneous slowing of the decline in mental abilities in Alzheimer's patients in early stages. The clinical relevance of the currently published study results is still the subject of discussion.

One possible explanation for the lack of quantitative proof of efficacy in earlier studies is that the drugs were used too late - namely at a stage when deficits were already present in multiple areas. This is associated with two problems associated with this: The progression of the disease is recorded differently in clinical scales depending on time and severity and thus escapes detection due to a lack of sensitivity (31), and secondly, the tissue damage may already have led to such pronounced cell death that the clinical symptoms resulting from the tissue damage can no longer be influenced in a relevant way.

If evidence is available, the development of therapeutic strategies for early disease stages requires a change in the diagnostic procedure and the recording of the therapeutic effect. Instead of global scales, specific and sensitive cognitive testing procedures must be used. In the case of Alzheimer's disease, the earliest symptoms are impairment of episodic memory and spatial orientation in unfamiliar environments. Other symptoms, such as apraxia and language disorders, only appear later in the course of the disease (32). Cognitive testing for the early diagnosis of Alzheimer's disease must therefore include detailed tests of episodic memory and spatial orientation. These cognitive tests must be supplemented by biomarker tests (15).

At the same time - but independent of diagnostic procedures and measurement of therapeutic efficacy - there is a need, for health policy reasons and for reasons of acceptance in the broad medical profession, to demonstrate the prognostic significance of early symptoms and the importance of biomarker diagnostics in clinical symptoms.

The clinical judgement of GPs regarding the presence of dementia is more specific than sensitive (33). Hypothetically - although not yet investigated - the clinical judgement of physicians with years of experience in dementia diagnostics is also very specific with regard to the recognition of the onset of dementia - however, less sensitive than with the accompanying application of a standardised procedure oriented towards early diagnostics. So far, these findings have not been incorporated into the staged diagnosis of Alzheimer's disease.

Health policy consequences

A considerable increase in the number of patients with Alzheimer's disease can be expected in the coming years. Due to demographic developments, it is estimated that up to 2.8 million people aged 65 and over will be affected by dementia in Germany by 2050, assuming that prevalence rates remain the same (1). According to the organisation Alzheimer Europe , the numbers in Western Europe will probably double by 2040 (34), and according to WHO projections, 139 million people worldwide will be living with dementia in 2050 (35). These figures illustrate the explosive nature of the development of this widespread disease, which as a global epidemic burden has immense social, economic and health policy consequences. According to cost analyses, the social costs of dementia in Europe alone are estimated at 105.6 billion euros in 2010 (36).

Although progress has been made in the right direction by the legislator in Germany in recent years, there is a particular need to catch up in early detection. For example, the National Dementia Strategy promotes many measures to improve care, but with little focus on early intervention. The increasing development of biomarkers for early detection and prediction of dementia also requires early reflection including a discourse on ethical, social and legal aspects. Therefore, the development of new ways of cooperation between physicians in private practice and expert centres as well as for infrastructure and logistics is urgently required according to the consensus of the experts of the Interdisciplinary Dementia Forum.

As early as 2020, the G-BA issued a guideline for the testing of amyloid PET in dementia (37). This was followed in February 2022 by the commissioning of study monitoring for the trial of amyloid PET in dementia in order to ensure quality and close the gap between clinical research and health services research. The German Centre for Neurodegenerative Diseases e. V. (DZNE) accompanies the trial study on behalf of the G-BA and will evaluate it (28). The results of the trial study should enable the G-BA to make a reliable decision on the medical benefit of amyloid PET in the presence of dementia of unclear etiology. This was a first step towards a decision by the legislator as to whether this examination method may be provided as a service by SHI-accredited physicians and will be paid for by the SHI funds in the future. For the implementation of early diagnosis of Alzheimer's disease for a usable therapy, further reforms are thus necessary to standardise and strengthen diagnostic pathways so that incentives for access, service providers and health care providers are aligned. Demands for an ethically correct dementia prediction have already been formulated in the joint statement of German associations and professional societies (38). This includes new impulses for a participation-oriented understanding, research into the effects of prediction as well as guidelines for laboratories and counselling as well as agreements on authorised test providers.

Within the framework of a suitable catalogue of measures, it is primarily also indispensable to destigmatise Alzheimer's disease. For patients and doctors, ‚Alzheimer's' is still directly associated with the final stage of dementia. However, the course of Alzheimer's disease clearly shows its correlated character with increasing age, which extends over a relatively long period of time, with dementia

ultimately characterising the final stage. However, this is often mistakenly considered to be the characteristic of the entire duration of the disease. Social stigma and lack of information often prevent patients from seeking help on their own, which often results in patients presenting late to their doctor.

The view of Alzheimer's disease thus requires a different overall social and medical emphasis. The choice of adequate measuring instruments for testing cognitive deficits and the use of biomarkers would allow the early and accurate identification and diagnosis of patients with Alzheimer's disease. Germany should face the opportunities both in the development and the financial feasibility of test procedures with high test quality for the prediction of Alzheimer's dementia using biomarkers.

Conclusion

The importance and task of diagnostics with regard to the detection of dementia has changed. Whereas in the past the task was to diagnose and characterise a dementia syndrome at an early stage, today the task and challenge is to diagnose diseases that lead to a dementia syndrome in the course of their progression already in the predementia stage. For this purpose, specific cognitive test procedures related to the early symptoms of Alzheimer's disease as well as biomarkers have to be applied.

Both diagnostic tools for measuring therapeutic efficacy in the predementia stage, including the selection of endpoints in clinical trials, need to be sensitive to this stage - otherwise the potential efficacy of pathophysiology-oriented drugs could be underestimated, leading to a health economic misjudgement.

Diagnostic instruments for measuring therapeutic effectiveness in the predementia stage should directly reflect performance relevant to everyday life (‚ecological validity' of the test procedure) - in this way, cognitive testing is identical to the recording of a patient-relevant endpoint. <<

Author statement

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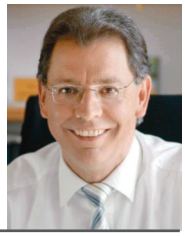
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