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Use of Cerebrospinal Fluid Biomarkers of Alzheimer's Disease Risk in Mild Cognitive Impairment and Subjective Cognitive Decline in Routine Clinical Care in Germany

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Abstract.
Background: The National Institute of Aging and Alzheimer's Association's diagnostic recommendations for preclinical Alzheimer's disease (AD) and mild cognitive impairment (MCI) define AD by pathological processes which can be detected by biomarkers. These criteria were established as part of a research framework intended for research purposes but progressively enter the clinical practice.
Objective: We investigated the availability, frequency of use, interpretation, and therapeutic implications of biomarkers for the etiologic diagnosis and prognosis in MCI and subjective cognitive decline (SCD) in routine clinical care.
Methods: We conducted a cross-sectional questionnaire survey among 215 expert dementia centers (hospitals and memory clinics) in Germany.

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Results: From the 98 centers (45.6% of contacted centers) included, two-thirds reported use of the cerebrospinal fluid (CSF) biomarkers $A\beta_{42}$, tau, and phospho-tau in the diagnostic workup of MCI and one third in SCD. CSF biomarker analysis was more often employed by neurological (MCI 84%; SCD 42%) compared to psychiatric institutions (MCI 61%; SCD 33%; $p \leq 0.001$). Although dementia experts disagreed on the risk of progression associated with different CSF biomarker constellations, CSF biomarker results guided therapeutic decisions: ~40% of responders reported to initiate cholinesterase inhibitor therapy in MCI and 18% in SCD ($p = 0.006$), given that all CSF biomarkers were in the pathological range.

Conclusion: Considering the vast heterogeneity among dementia expert centers in use of CSF biomarker analysis, interpretation of results, and therapeutic consequences, a standardization of biomarker-based diagnosis practice in pre-dementia stages is needed.

Keywords: Alzheimer's disease, biomarker, mild cognitive impairment, prediction, questionnaires, subjective cognitive decline, surveys

INTRODUCTION

Alzheimer's disease (AD) pathology starts many years before clinical symptoms evolve [1]. This has directed research efforts toward biomarker-based concepts to identify affected persons already in the preclinical disease stages, i.e., prior to onset of cognitive symptoms. The International Working Group (IWG) and National Institute of Aging-Alzheimer's Association (NIA-AA) criteria from 2011 and especially their 2018 update define and stage AD as a disease continuum from an asymptomatic preclinical stage, followed by a prodromal or mild cognitive impairment (MCI) stage to manifest dementia [2, 3]. The NIA-AA criteria distinguish three stages of preclinical AD where stage three is characterized by subtle cognitive decline. MCI is defined by objective memory deficits which do not fulfill the criteria of dementia.

The NIA-AA criteria allow an etiological diagnosis of AD already in the preclinical and prodromal disease stages, based on the presence of biomarkers. Amyloid biomarkers (A) include decreased cerebrospinal fluid (CSF) $A\beta_{42}$ levels or increased retention of amyloid positron emission tomography (amyloid PET) tracers in the brain. Neurodegeneration markers (N) are less disease-specific and comprise increased CSF tau levels, mediotemporal brain atrophy in cranial magnetic resonance imaging (cMRI), and temporoparietal hypometabolism in fluodeoxyglucose positron emission tomography (FDG-PET). The recent update also includes increased phospho-tau CSF levels (T) as a specific marker of AD-associated tau pathology [3]. The A/T/N classification summarizes the status of amyloid (A), tau (T) and neurodegeneration (N) biomarkers, e.g., a person with positive amyloid biomarkers, either by CSF or PET in the absence of markers for tau pathology and neurodegeneration markers would be classified as *A* + /T-/N-.

Subjective cognitive decline (SCD) describes a self-reported memory decline in the absence of objective memory deficits exceeding subtle cognitive impairment. It is associated with a higher probability of progression toward cognitive deterioration [4–6]. In the presence of AD biomarkers, SCD can be classified according to NIA-AA 2011 criteria [7] as preclinical AD stage two in the absence and as stage three in the presence of subtle cognitive impairment [8].

The probability of progression from SCD or MCI toward AD dementia is an important question for affected individuals in clinical practice. Importantly, the NIA-AA guidelines for preclinical AD were designed to provide a common framework for research purposes and their use outside of a research context, e.g., in routine clinical care, is not recommended. NIA-AA guidelines state that in MCI, a biomarker-aided diagnosis is primarily indicated to support patient stratification for clinical intervention trials. In clinical practice, biomarkers *may* contribute to an increase in the level of certainty for a diagnosis of MCI due to AD pathology [1]. However, a concern for a risk of misuse was expressed by the workgroups as well as the need for validation of the biomarker criteria in longitudinal cohorts, standardization of sample acquisition, analysis methods, cut-off values and comparison of the different individual or combined biomarkers of each category prior to their broad application in the routine clinical setting.

Despite this concern, biomarker-aided diagnosis has already been implemented into the clinical diagnostic workup of patients with MCI and SCD [9]. However, there is still a lack of empirical research on the use of biomarkers in actual clinical practice within and between different professional, institutional, and national settings. In a survey, addressed at

215 specialized hospitals and memory clinics in Germany, we aimed to investigate availability, frequency, interpretation of results, perceived uncertainty of biomarker-based prediction, and impact on therapy decisions of biomarker-aided diagnosis of AD pathology in SCD and MCI. Due to demographic aging, late-onset dementia is a prominent topic in public and political debates in Germany and the country is an important site for neuroscientific dementia research. Yet, there is no national dementia strategy in Germany nor is there an official guideline for the use of biomarkers in SCD and MCI in clinical practice.

MATERIALS AND METHODS

Questionnaire

The questionnaire for this cross-sectional survey has recently been described in detail [10] (see Supplementary Material for an English and German version). In short, it was composed using EvaSys^{TM}, a web-based, automated software, and comprises quantitative as well as qualitative items. Overall, it contains 37 predominantly closed questions (mainly nominal or ordinal scales) attributable to five topics: 1) sociodemographics and center characteristics, clinical practice of 2) diagnostic procedures for SCD and MCI, 3) patient information and consent to biomarker-based diagnostics, 4) interpretation and disclosure of biomarker results, 5) impact of biomarker results on treatment decisions, and 6) ethical implications of predictive testing. In some cases, free response sections allowed explaining opinions in more detail. The questionnaire was pre-tested by seven dementia experts from two different medical institutions. Of note, these experts were not participating in the survey later. A comprehensive evaluation of professionals' attitudes toward ethical and legal aspects of predictive testing and early detection as well as of future demands obtained in this survey was reported previously [10].

Study procedure

The local ethics committee was informed about the survey. Due to its nature (survey on professional/institutional practice without individual patient data), an ethical approval was not required.

Potential participants were identified in a web-based databank search, using among others databases provided by the German Alzheimer Society and the German Federal Ministry of Family Affairs. 215 expert dementia centers from all 16 German federal states were identified and the questionnaire was sent to all 215 centers by letter. The centers were distributed across Germany and included urban and rural areas, university and non-university centers, psychiatric, neurological, and geriatric institutions, and out- and in-patient clinics. These center characteristics were asked for in the questionnaire to analyze their potential impact on clinical routines.

All specialized dementia centers were localized in hospitals. No resident physicians or private practices were included in the survey since patients with SCD and MCI are usually referred to specialized dementia centers for further testing as recommended by the S3 dementia guidelines in Germany [11]. The survey was specifically addressed to the head of the center or memory clinic who was asked to answer the survey with regard to the common practice conventions in their institution. No monetary or other incentives were offered. Response and return of the questionnaire were anonymous except for postal code. Data collection took place between February and October 2015.

Statistical analysis

Data processing was performed semi-automatically (manual correction of non-recorded or incorrectly recorded data by EvaSys^{TM}, manual input of free response sections). Items were nominally or ordinally scaled in most cases and presented descriptively in terms of frequency or percentage distribution. For comparisons of variables/frequencies between different types of institutions or between the categories SCD and MCI, χ^2-tests for categorical variables were performed, whenever applicable. In the case that analyses were based on specific diagnostic procedures, only centers were considered which had access to or provided these procedures. All statistical analyses were two-sided with significance levels set to $p = 0.05$ and carried out using SPSS Statistics 24.0.

RESULTS

Sample

Of the 215 centers contacted, 108 returned the completed questionnaire (response rate of 50.2%), 8 (3.7%) explicitly refused participation, and 99 (46.0%) did not respond (see Supplementary Figure 1 for geographic distribution of contacted centers

Table 1
Descriptive data of respondents and participating centers ($N = 98$)

Respondents characteristics		Center characteristics	
Gender		Type of institution	
Male:female:n/a	67:28:03 (68.4:28.6:3.1%)	Psychiatric departments	79 (80.6%)
		Neurological departments	19 (19.4%)
Age			
25–29 y	02 (02.0%)		
30–39 y	16 (16.3%)		
40–49 y	44 (44.9%)	University centers	36 (36.7%)
50–59 y	27 (27.6%)	Specialized hospitals	62 (63.3%)
≥60 y	07 (07.1%)		
n/a	02 (02.0%)		
Position			
Head of department	30 (30.6%)	Dementia research centers	43 (43.9%)
Senior physician	44 (44.9%)	**Type of research:***	
Assistant physician	11 (11.2%)	Clinical studies	28 (65.1%)
Others	11 (11.2%)	Biomarkers	28 (65.1%)
n/a	02 (02.0%)	Neuropsychology	26 (60.5%)
Practice years		Imaging	25 (58.1%)
0–5 y	08 (08.2%)	Health services	22 (51.2%)
6–10 y	18 (18.4%)	Genetic	12 (27.9%)
11–15 y	27 (27.6%)	Basic	07 (16.3%)
16–20 y	20 (20.4%)	Sociology	01 (02.3%)
>20 y	17 (17.3%)	Medical ethics	01 (02.3%)
n/a	08 (08.2%)	No dementia research	55 (56.1%)

n/a, not available. *adds up to $n > 98$ (>100%) due to multiple choice options.

(Supplementary Figure 1A) and response rates (Supplementary Figure 1B) in the different federal states). All of the 108 questionnaires were filled out completely (no missing data) with the exception of two centers for which no information on specialization was provided.

The majority of responding centers was specialized in psychiatry (73.1%) followed by neurology (17.6%) and geriatric/internal medicine (7.4%). The latter group ($n = 8$) as well as centers without information on specialization ($n = 2$) were excluded from further analyses due to the sample size which was too small for between-center comparisons. Therefore, only the questionnaires of 98 centers (45.6% of all contacted centers) were included in the analysis. Sociodemographic information of the final study sample and center characteristics are presented in Table 1. Of the participating centers, 63.3% belonged to non-academic institutions ($n = 63$) and 36.7% to university hospitals ($n = 36$). Dementia research was pursued in 43.9% of all centers with a research focus on clinical (65.1%), biomarker (65.1%), neuropsychology (60.5%), imaging (58.1%), and health care research (51.2%).

Availability of diagnostic methods

Participating centers had access to the following diagnostic methods either in-house or by referral to specialists (Supplementary Figure 2): analysis of blood parameters (100%), neuropsychological assessments (screening tests, e.g., Mini-Mental State Examination (MMSE): 100%, cognitive testing with the Consortium to Establish a Registry for Alzheimer's Disease [CERAD]–plus: 98%, in-depth neuropsychological assessment: 93.9%), cranial computer tomography (cCT: 99%), cranial MRI (cMRI: 96.9%), FDG PET scan (82.7%), MRI volumetry (70.4%), amyloid PET scan (64.3%), lumbar puncture/biomarker analysis (100%).

Diagnostic procedures for MCI and SCD in memory clinics and specialized dementia centers

Assessment of patients with MCI and SCD (in those centers where the method was available or accessible; Fig. 1) included analysis of blood parameters (MCI 92.9%, SCD 85.7%), cognitive scales (screening tests: MCI 89.8%, SCD 89.8%; CERAD test battery: MCI 87.5%, SCD 68.8%; in-depth neuropsychological assessment: MCI 88%, SCD 89.1%), cMRI (MCI 88.4%, SCD 78.9%), cCT (MCI 45.4%, SCD 29.9%), MR volumetry (MCI 8.7%, SCD 5.8%), FDG PET (MCI 7.4%, SCD 4.9%), and lumbar puncture with subsequent CSF biomarker analysis (65.3% in MCI versus 34.7% in SCD).

Significant differences in the diagnostic work-up of MCI and SCD were detected for the frequency of

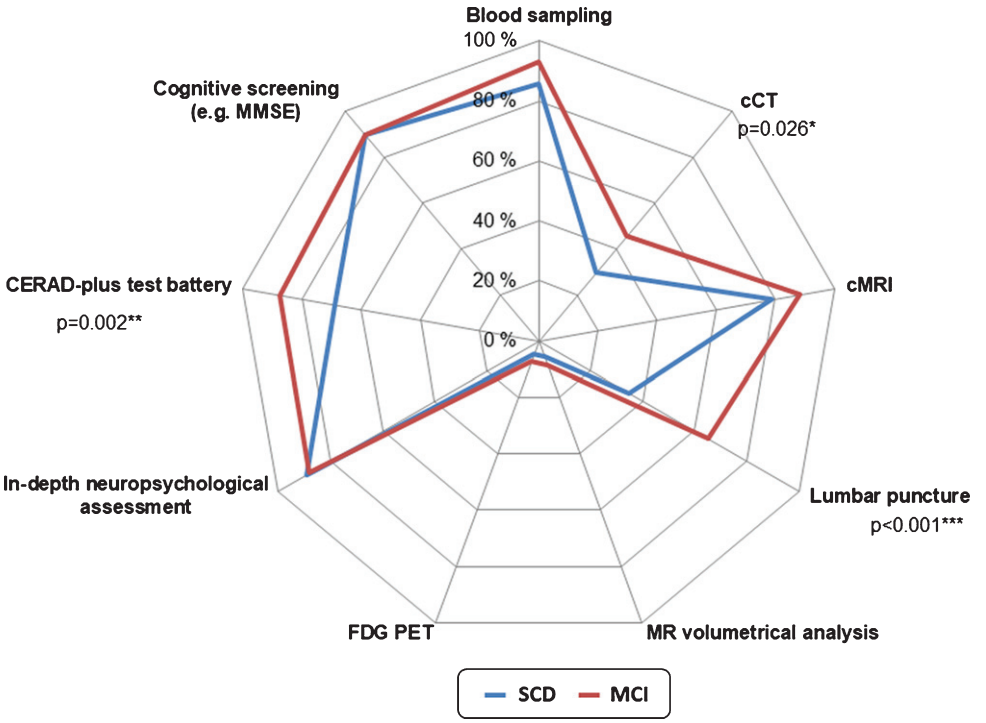


Fig. 1. Differences in the diagnostic workup of MCI versus SCD. Centers more often perform lumbar puncture ($p < 0.001$), the CERAD-plus test battery ($p = 0.002$), and cCT ($p = 0.026$) during the diagnostic workup of MCI compared to SCD. cCT, cranial computer tomography; cMRI, cranial magnetic resonance imaging; FDG PET, fluodeoxyglucose positron emission tomography; MMSE, Mini-Mental Status Examination, CERAD, Consortium to Establish a Registry for Alzheimer's Disease

cCT ($p = 0.026$), the CERAD test battery ($p = 0.002$), and lumbar puncture ($p < 0.001$; Fig. 1; Table 2).

In general, lumbar puncture was more frequently performed for the diagnostic work-up of MCI compared to SCD regardless of the type of institution (Table 2). Neurological centers more often performed diagnostic lumbar puncture compared to psychiatric centers (84.2% versus 60.8%; $p = 0.054$; Table 3).

Criteria for offering lumbar puncture and CSF biomarker assessment

We next asked which criteria usually guide the decision to offer lumbar puncture and CSF biomarker analysis in MCI and SCD (Fig. 2a). CSF biomarker analysis is currently the only broadly available test for amyloid positivity because amyloid PET is not covered by the public German health care system, including differential diagnostic purposes. In most cases, lumbar puncture was considered important for differential diagnosis in the case of abnormal MRI findings (MCI 71.4%, SCD 69.4% of all centers) or to exclude neuroinflammatory or paraneoplastic diseases (MCI 79.6%, SCD 72.4% of all centers). Centers also offer CSF biomarker analysis on patients' or relatives' request (MCI 65.3%, SCD 54.1% of all centers) or in the case of a family history of dementia (MCI 51.0%, SCD 42.9% of all centers). Given the diagnosis of MCI, 54.1% of the participating centers offer CSF biomarker analysis for detection of AD pathology and 33.7% in the case of SCD ($p = 0.004$).

Criteria not to offer CSF biomarker analysis (Fig. 2b) included the notion that neither negative nor positive AD biomarkers would allow a reliable prognosis on subsequent progression of SCD or MCI to AD dementia (MCI 27.6% versus SCD 45.9%; $p = 0.008$), the lack of therapeutic consequences if biomarkers would be positive (MCI 44.9%; SCD 60.2%; $p = 0.032$) and potential complications of lumbar puncture (MCI 27.6% versus SCD 30.6%; n.s.). The uncertainty of CSF AD biomarker-based prognosis as a reason not to offer lumbar puncture was given significantly less often for the diagnostic work-up of MCI compared to SCD in neurological centers (MCI 10.5% versus SCD 47.4%; $p = 0.012$), university centers (MCI 16.7% versus SCD 50.0%; $p = 0.003$), and dementia research centers (MCI 20.9% versus SCD 51.2%, $p = 0.004$).

Table 2
Rate of diagnostic lumbar puncture for MCI versus SCD within centers ($N = 98$)

	MCI	SCD	p
All centers ($N = 98$)	64 (65.3%)	34 (34.7%)	*<0.001***
Neurological centers ($n = 19$)	16 (84.2%)	8 (42.1%)	*0.007***
Psychiatric centers ($n = 79$)	48 (60.8%)	26 (32.9%)	*<0.001***
Academic centers ($n = 36$)	27 (75.0%)	13 (36.1%)	*0.001****
Non-academic centers ($n = 62$)	37 (59.7%)	21 (33.9%)	*0.004***
Centers with dementia research c ($n = 43$)	31 (72.1%)	15 (34.9%)	*0.001****
Centers without dementia research ($n = 55$)	33 (60.0%)	19 (34.5%)	*0.008***

Frequency presented as absolute numbers and percentages (%). *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

Table 3
Rate of diagnostic lumbar puncture for MCI and SCD: Between-centers comparisons ($N = 98$)

		Frequency of diagnostic lumbar puncture	p
MCI	Neurological versus psychiatric centers	84.2% versus 60.8%	*0.054*
	Academic versus non-academic centers	75.0% versus 59.7%	*0.124*
	Centers with versus centers without dementia research	72.1% versus 60.0%	*0.212*
SCD	Neurological versus psychiatric centers	42.1% versus 32.9%	*0.450*
	Academic versus non-academic centers	36.1% versus 33.9%	*0.822*
	Centers with versus centers without dementia research	34.9% versus 34.5%	*0.972*

Frequency presented as percentages (%). *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

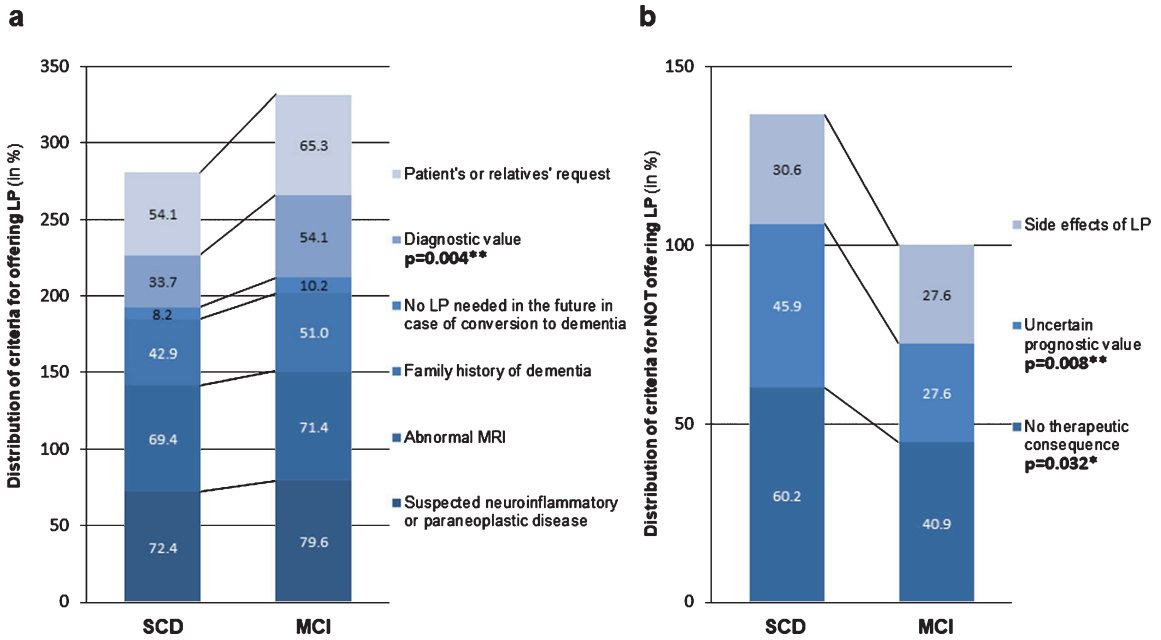


Fig. 2. a) Reasons to offer lumbar puncture during the diagnostic evaluation of MCI and SCD. Participating centers offer lumbar puncture to detect AD pathology ("diagnostic value") more often in MCI compared to SCD ($p = 0.004$). b) Criteria for not offering lumbar puncture for etiological diagnosis of MCI and SCD. Percentage of centers that do not offer lumbar puncture due to its "uncertain diagnostic value" (MCI versus SCD, $p = 0.008$), and the "absence of therapeutic consequences" (MCI versus SCD, $p = 0.032$). MRI, magnetic resonance imaging; LP, lumbar puncture.

In MCI, the lack of therapeutic consequences guided the decision not to offer lumbar puncture more often in non-university (53.2%) compared to university centers (30.6%; $p = 0.03$). For SCD, the different institutional types did not differ regarding their criteria not to offer CSF biomarker analysis (all between-center comparisons n.s.).

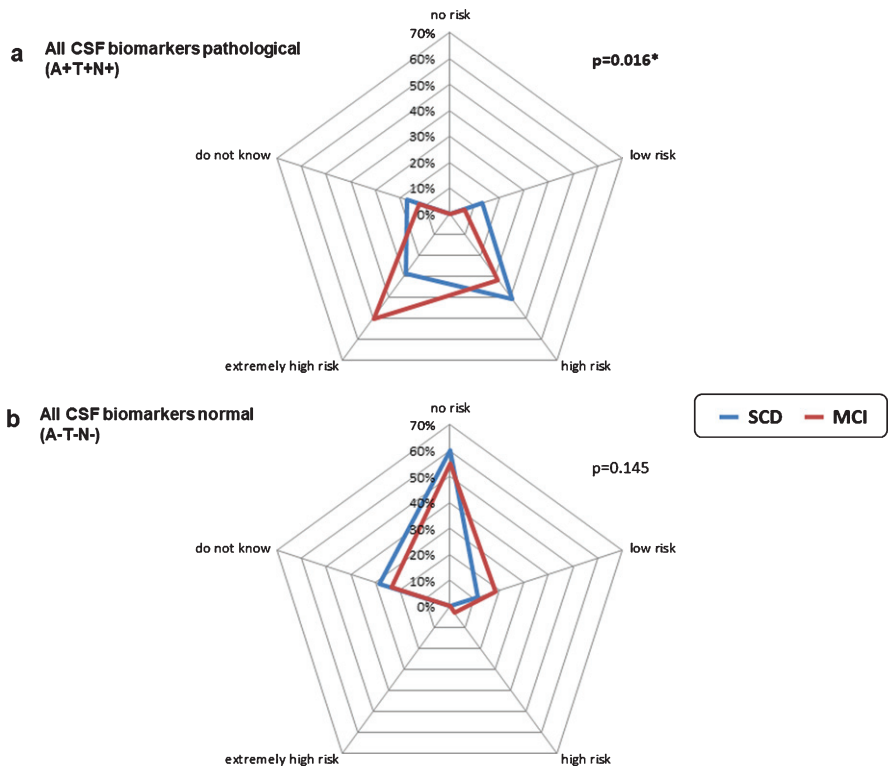


Fig. 3. Interpretation of CSF biomarker results. Estimated risk of progression from MCI or SCD to AD dementia (a) when all CSF biomarkers were in the pathological range ($A+T+N+$; $p=0.016$) (b) when all CSF biomarkers were within the normal range (A-T-N-; n.s.). CSF, cerebrospinal fluid.

Interpretation of CSF biomarker results

We next wanted to explore to what extent CSF biomarkers contribute to the experts' confidence regarding prognosis in MCI and SCD. Participating centers were first asked for their etiologic interpretation of different CSF biomarker constellations, including 1) $A\beta_{42}$, phospho-tau and tau within the normal range (A-T-N-), 2) $A\beta_{42}$ in the pathological range, phospho-tau and tau normal ($A+$T-N-), 3) $A\beta_{42}$ normal, pathological values for phospho-tau and tau (A-T+N+), and 4) $A\beta_{42}$, phospho-tau and tau all in the pathological range ($A+T+N+$; Fig. 3). For each of the four different biomarker constellations, centers were asked for their estimation of the five-year progression risk from either SCD or MCI to AD dementia.

Possible answers were (i) no increased risk, (ii) low, (iii) high, (iv) extremely high risk and (v) "do not know". In MCI (Fig. 3), 23.5% selected "do not know" if all CSF biomarkers were negative (A-T-N-) and 12.2% if all biomarkers were positive ($A+T+N+$). 50% rated the risk of progression from MCI to AD dementia as extremely high, 31.6% as high, and 6.1% as low if all CSF biomarkers were pathological ($A+T+N+$; Fig. 3a). When all CSF biomarkers were in the normal range (A-T-N-), MCI progression to AD was estimated to be high by 3.1% of participating centers, to be low by 18.4%, and to constitute no increased risk in 55.1% (Fig. 3b). Centers attributed an extremely high (6.1%) or high risk (42.9%) to normal CSF $A\beta_{42}$ with pathological tau and phospho-tau (A-T+N+), whereas 45.9% associated a low risk of progression to abnormal $A\beta_{42}$ in the absence of pathological tau or phospho-tau markers ($A+$T-N-).

Centers were additionally asked for their risk estimation for SCD progression to AD dementia (Fig. 3). In the case that all CSF biomarkers were in the pathological range ($A+T+N+$), 17.3% of centers chose "do not know" the risk, whereas 28.6% estimated the risk of progression from SCD to AD dementia as extremely high, 40.8% as high and 13.3% as low (Fig. 3a). With all CSF biomarkers in the normal range (A-T-N-), 28.6% of centers chose "do not know" the risk of progression to AD demen-

tia, 11.2% estimated the risk as low and 60.2% as not increased (Fig. 3b). Pathological CSF tau and phospho-tau together with normal $A\beta_{42}$ levels (A-T + N+) was linked with an extremely high risk of progression to AD dementia by 4.1% and with a high risk by 27.6% of responders. In contrast, none of the participating centers estimated the risk of pathological CSF $A\beta_{42}$ only (*A* + T-N-) as extremely high and 16.3% of the centers interpreted the risk of progression to AD dementia as high.

Risk attribution was significantly different between *A* + T+N+SCD and *A* + T + N + MCI in all centers ($p = 0.016$) and MCI was associated with a higher risk for progression to AD dementia than SCD. However, risk estimates for ambiguous biomarker constellations (*A* + T-N- or A-T + N+) or in the absence of pathological biomarkers (A-T-N-) did not differ between MCI and SCD (n.s.).

Criteria for offering amyloid PET imaging

The German public health care system does not refund the costs for PET imaging in neurodegenerative diseases. Thus, we asked for criteria which would guide the decision to employ amyloid PET imaging (either alone or in combination with MR volumetry) if it were available. In the case of MCI, 16.3% of the centers would not use amyloid PET imaging, whereas 30.6% would not offer amyloid PET imaging in SCD ($p = 0.018$). Of the participating centers, 54.1% would suggest amyloid PET to patients with pathological CSF markers and MCI, 49% to patients with SCD and pathological CSF markers (n.s.). In the case of MCI, 48% of the centers would supply amyloid PET in MCI and 41.8% in SCD on the patient's request (n.s.). MCI or SCD plus a positive family history of AD was given as another reason to offer amyloid PET (MCI: 56.1%, SCD: 51%; n.s.). Several centers would implement amyloid PET as part of their diagnostic routine in MCI (18.4%) and SCD (8.2%; $p = 0.038$).

Therapeutic implications of CSF biomarker results

We next inquired whether CSF biomarker results would guide therapeutic decisions. In MCI with pathological CSF biomarkers (*A* + T + N+), 39.8% of the participating centers stated that they would start treatment with cholinesterase inhibitors (CEI), 7.1% would prescribe memantine, and 13.3% would initiate non-pharmacological therapy, e.g., occupational therapy (Fig. 4). In *A* + T + N + SCD, 18.4% of the participating centers would prescribe CEIs, 4.1% would treat with memantine, and 20.4% would initiate non-pharmacological therapies (Fig. 4). These treatment regimens differed significantly between MCI and SCD ($p = 0.006$).

Therapeutic consequences were less frequent in the case of pathological CSF $A\beta_{42}$ but normal tau and phospho-tau values (*A* + T-N-; MCI: 19.4% CEI treatment, 1% memantine, 14.3% non-pharmacological treatment; SCD: 5.1% CEI, 0% memantine, 19.4% non-pharmacological treatment, MCI versus SCD: $p = 0.031$).

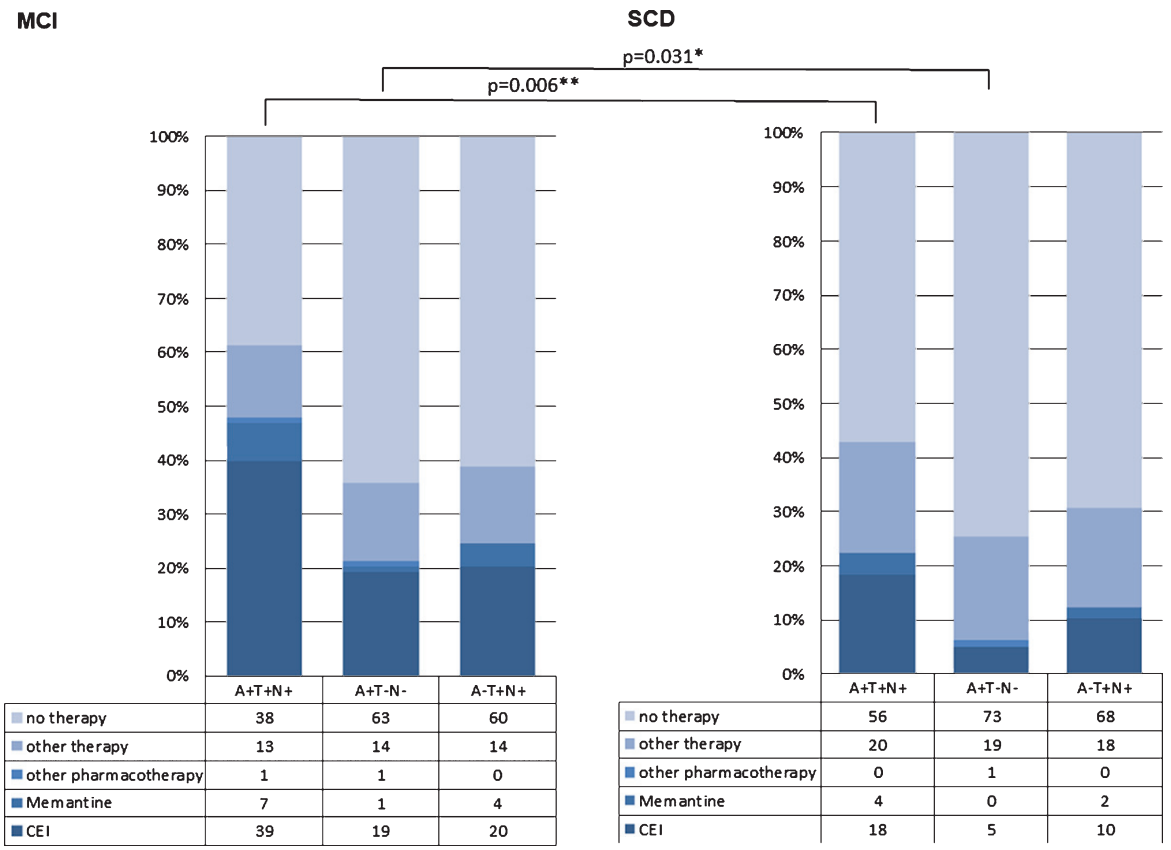
In the presence of MCI and normal CSF $A\beta_{42}$ but pathological tau and phospho-tau values (A-T + N+), 20.4% of the centers would initiate CEI treatment, 4.1% memantine, and 14.3% other non-pharmacological therapy. In A-T + N + SCD, 10.2% would prescribe CEIs, 2% memantine, and 18.4% would start other non-pharmacological therapies (MCI versus SCD: n.s.).

In neither of the different biomarker constellations, between-center differences could be observed with the exception of *A* + T-N- MCI, where CEI and also memantine prescription rates were higher in neurological compared to psychiatric centers (CEI: 31.6% versus 16.5%; memantine: 5.3% versus 0%; $p = 0.048$).

DISCUSSION

In light of the new biomarker-based criteria which allow the detection of AD pathology already in preclinical and prodromal disease stages several questions arise regarding their use outside a research context in the routine clinical setting: How early should these tests be used, based on which criteria should biomarker testing be offered, how should the results be interpreted and communicated to the patient, how to address the uncertainty of test results and what are the prognostic and therapeutic implications. This survey aimed to investigate the use and interpretation of AD biomarkers in SCD and MCI and the therapeutic consequences arising from different biomarker constellations in clinical practice at different institutional types of expert dementia centers throughout Germany.

Although the NIA-AA criteria state that their application in prodromal and especially preclinical disease stages should be restricted to research purposes [2, 7], our survey shows that approximately one third of individuals with SCD and two thirds of patients with



MCI	A+T+N+	A+T-N-	A-T+N+
no therapy	38	63	60
other therapy	13	14	14
other pharmacotherapy	1	1	0
Memantine	7	1	4
CEI	39	19	20

SCD	A+T+N+	A+T-N-	A-T+N+
no therapy	56	73	68
other therapy	20	19	18
other pharmacotherapy	0	1	0
Memantine	4	0	2
CEI	18	5	10

Fig. 4. Therapeutic implications of $A+$T+N+CSF results in MCI and SCD. Centers were asked which, if any, therapeutic implications would follow the three different CSF biomarker constellations in patients with MCI (left) and SCD (right). Centers would initiate different treatment regimes in MCI compared to SCD when all CSF biomarkers are in the pathological range ($A+$T+N+; $p=0.006$), or in case of isolated $A\beta_{42}$ abnormalities ($A+$T-N-; $p=0.031$). CEI, cholinesterase inhibitor.

MCI are offered CSF biomarker analysis routinely in clinical practice. Interestingly, these numbers were significantly lower for amyloid PET imaging even if it would be available and refunded by the public health insurance (SCD 8.2% and MCI 18.4%; $p=0.038$). This difference may be caused by the lack of experience with amyloid PET and the possibility of additional information on tau pathology which can be obtained from CSF analysis.

CSF biomarkers can help with the etiologic diagnosis, prognosis and guide therapeutic decisions. However, our survey demonstrates heterogenous interpretations among expert physicians in respect to etiological diagnosis [10] and prognosis. The vast majority of dementia experts regarded CSF-based evidence of $A+$T+N+ pathology as indicative of an extremely high or at least high risk of MCI (81.6%) progression toward AD dementia over the following five years. An extremely high or high risk of progression of $A+$T+N+SCD to AD dementia was less often estimated as in MCI.

With other CSF biomarker constellations, experts' opinions differed considerably. A-T+N+ associated risk was estimated as extremely high by 30% in SCD and 50% in MCI, whereas 42% (SCD) and 35% (MCI) deemed the risk as not or only slightly increased. Also, the absence of any pathological CSF markers (A-T-N-) in SCD and MCI was attributed to an unknown risk of conversion to AD dementia by ~30% of the clinical centers in SCD and by ~25% in MCI.

The uncertainty of dementia experts regarding a biomarker-based clinical prognosis is particularly problematic given the frequency with which CSF biomarker tests are offered as well as the therapeutic decisions which are made based on the results. Uncertainty may be caused by conflicting data from different observational studies which all state an

increased progression risk associated with SCD and MCI, but which differ markedly in respect to the exact level of risk. In addition, longitudinal data from large prospective SCD cohorts are missing, and observation times mostly cover short periods of two to three years (for review, see [12]). Clearly, observational studies with longer follow-up times and multimodal individualized risk scores would improve confidence in the predictive values of CSF biomarkers in SCD [13].

A number of studies have evaluated longitudinal outcomes and rates of MCI conversion to AD dementia. However, a recent Cochrane review on the prognostic value of CSF biomarkers in MCI states a risk of mis- and overdiagnosis due to the markers' better sensitivity than specificity [14] which is further supported by a recent study that retrospectively analyzed 628 memory clinic patients and found only a low correlation between CSF biomarker-based etiology and clinical syndromes [15]. Therefore, it was suggested to employ CSF biomarkers for ruling out AD etiology in MCI rather than for diagnostic or prognostic purposes [14]. Recommendations have also been issued for amyloid PET imaging in MCI as appropriate use criteria by the Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging [16]. The group recommends amyloid PET imaging in MCI only in those cases where a higher diagnostic certainty is needed, e.g., in the case of atypical clinical presentation or comorbidities which could also be responsible for the cognitive impairment or if a higher certainty of diagnosis would impact treatment or future plans of the patient.

One major obstacle to adequate CSF biomarker-based diagnosis in the routine clinical application is the lack of common standard operating procedures (SOPs) regarding preanalytical processing and employed techniques (e.g., ELISA, MSD, SIMOA, fully-automated versus non-automated) which can result in high variability of CSF biomarker values [17, 18]. In addition, cut-off values differ between laboratories [19, 20] and so far, there is no global cut-off value available, which impedes the comparison to cohort findings. Partially, this problem may be solved by the introduction of correction factors [21], and recently, certified reference materials have been developed to allow the calibration of assays. However, these improvements have not yet been implemented in the routine clinical application and only few studies have been undertaken to test predictive values of CSF markers in the routine clinical setting [22, 23]. This is important as, e.g., progression rates of SCD were shown to be significantly lower in the general population compared to memory clinic patients [24].

CSF biomarkers influenced therapy decisions in both SCD and MCI. Although the majority of centers would not initiate CEI treatment in $A + T + N + SCD$, 18% reported that they would start CEI therapy. More than 50% of expert centers would not initiate any therapy, including non-pharmacological therapies. In CSF biomarker positive ($A + T + N+$) MCI patients, a significantly higher proportion of centers would prescribe CEIs (39%), whereas 38% would not initiate any treatment. Previous intervention studies do not support CEI therapy in MCI and no data are available that would suggest a beneficial effect in SCD [25]. In line with this, practice guidelines from the American Academy of Neurology state that there is "no high quality evidence to support pharmacological treatment for MCI" [26]. These guidelines also recommend not to offer biomarker diagnosis in MCI. The German S3 guidelines suggest that in case a patient with MCI asks for risk assessment, information about different biomarkers, predictive values, consequences and the diagnostic procedures should be provided/initiated by a dementia expert (S3 Leitlinie [11]).

However, our survey shows that there is no broad consensus among German dementia experts regarding indication for CSF biomarker assessment in SCD or MCI nor in respect to the therapeutic implications. Non-academic centers were less likely to offer CSF biomarker analysis due to the lack of therapeutic consequences compared to academic centers. Interestingly, when asked for therapeutic implications in patients with CSF AD biomarker positive MCI, academic and non-academic centers did not differ significantly in the rate of CEI or memantine treatment initiation. It is feasible to assume that academic centers more often engage in early intervention trials and may therefore consider participation in experimental drug trials as a potential therapeutic option for patients with MCI. In light of the increasing number of persons seeking prognostic advice already at very early disease stages, clearly a guideline on appropriate use of CSF biomarkers, similar to the recommendations by the amyloid imaging task force (AIT) [16, 27] or the disclosure guidelines of the A4 trial for amyloid status [28], would also be helpful. Guidelines should address constellations which justify CSF biomarker analysis and should contain the need for harmonization of analysis protocols, stan-

dardized informed consent, assessment of motivation to undergo biomarker analysis, education on risk and prognostic uncertainty.

One strength of our survey is the inclusion of a large number of dementia expert centers in Germany that also encompasses non-academic institutions. Thus, our study is likely to reflect "real-life" use of biomarkers since in contrast to other studies, it was not restricted to highly specialized research centers [29]. However, the majority of respondents in our study were specialized in psychiatry. To address this potential bias, we analyzed all data separately for psychiatric, neurologic and additionally for academic and non-academic institutions. Not unexpectedly, centers specialized in neurology were more likely to offer CSF biomarker diagnosis compared to centers with a psychiatric background and were also more prone to pharmacological treatment in SCD and MCI.

It would be worthwhile to extend our survey to enable multi-country comparison of CSF biomarker use in SCD and MCI, especially in countries which have already established more detailed guidelines, such as the American Academy of Neurology guidelines.

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Jack CR, Jr., Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 257-262.

[2] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.

[3] Jack CR Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Contributors (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* **14**, 535-562.

[4] Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, Rabin L, Rentz DM, Rodriguez-Gomez O, Saykin AJ, Sikkes SAM, Smart CM, Wolfsgruber S, Wagner M (2020) The characterisation of subjective cognitive decline. *Lancet Neurol* **19**, 271-278.

[5] van Harten AC, Smits LL, Teunissen CE, Visser PJ, Koene T, Blankenstein MA, Scheltens P, van der Flier WM (2013) Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology* **81**, 1409-1416.

[6] Wolfsgruber S, Polcher A, Koppara A, Kleineidam L, Frolich L, Peters O, Hull M, Ruther E, Wiltfang J, Maier W, Kornhuber J, Lewczuk P, Jessen F, Wagner M (2017) Cerebrospinal fluid biomarkers and clinical progression in patients with subjective cognitive decline and mild cognitive impairment. *J Alzheimers Dis* **58**, 939-950.

[7] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Jr., Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[8] Colijn MA, Grossberg GT (2015) Amyloid and tau biomarkers in subjective cognitive impairment. *J Alzheimers Dis* **47**, 1-8.

[9] Eckerstrom M, Gothlin M, Rolstad S, Hessen E, Eckerstrom C, Nordlund A, Johansson B, Svensson J, Jonsson M, Sacuiu S, Wallin A (2017) Longitudinal evaluation of criteria for subjective cognitive decline and preclinical Alzheimer's disease in a memory clinic sample. *Alzheimers Dement (Amst)* **8**, 96-107.

[10] Schweda M, Kogel A, Bartels C, Wiltfang J, Schneider A, Schicktanz S (2018) Prediction and early detection of Alzheimer's dementia: Professional disclosure practices and ethical attitudes. *J Alzheimers Dis* **62**, 145-155.

[11] Deuschl G, Maier W (2016) Deutsche Gesellschaft für Psychiatrie und Psychotherapie PuND, Deutsche Gesellschaft für Neurologie (DGN).

[12] Hong YJ, Lee JH (2017) Subjective cognitive decline and Alzheimer's disease spectrum disorder. *Dement Neurocogn Disord* **16**, 40-47.

[13] van Maurik IS, Slot RER, Verfaillie SCJ, Zwan MD, Bouwman FH, Prins ND, Teunissen CE, Scheltens P, Barkhof F, Wattjes MP, Molinuevo JL, Rami L, Wolfsgruber S, Peters O, Jessen F, Berkhof J, van der Flier WM, Alzheimer's Disease Neuroimaging Initiative (2019) Personalized risk for clinical progression in cognitively normal subjects-the ABIDE project. *Alzheimers Res Ther* **11**, 33.

[14] Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S (2017) CSF tau and the CSF tau/ABeta

ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev* **3**, CD010803.

[15] Carandini T, Arighi A, Sacchi L, Fumagalli GG, Pietroboni AM, Ghezzi L, Colombi A, Scarioni M, Fenoglio C, De Riz MA, Marotta G, Scarpini E, Galimberti D (2019) Testing the 2018 NIA-AA research framework in a retrospective large cohort of patients with cognitive impairment: From biological biomarkers to clinical syndromes. *Alzheimers Res Ther* **11**, 84.

[16] Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Carrillo MC, Hartley DM, Hedrick S, Pappas V, Thies WH, Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce (2013) Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement* **9**, e-1-16.

[17] Blennow K, Zetterberg H (2018) Biomarkers for Alzheimer's disease: Current status and prospects for the future. *J Intern Med* **284**, 643-663.

[18] Vos SJ, Visser PJ, Verhey F, Aalten P, Knol D, Ramakers I, Scheltens P, Rikkert MG, Verbeek MM, Teunissen CE (2014) Variability of CSF Alzheimer's disease biomarkers: Implications for clinical practice. *PLoS One* **9**, e100784.

[19] Kuhlmann J, Andreasson U, Pannee J, Bjerke M, Portelius E, Leinenbach A, Bittner T, Korecka M, Jenkins RG, Vanderstichele H, Stoops E, Lewczuk P, Shaw LM, Zegers I, Schimmel H, Zetterberg H, Blennow K, proteins IWGoSoC (2017) CSF Abeta1-42 - an excellent but complicated Alzheimer's biomarker - a route to standardisation. *Clin Chim Acta* **467**, 27-33.

[20] Mattsson N, Andreasson U, Persson S, Carrillo MC, Collins S, Chalbot S, Cutler N, Dufour-Rainfray D, Fagan AM, Heegaard NH, Robin Hsiung GY, Hyman B, Iqbal K, Kaeser SA, Lachno DR, Lleo A, Lewczuk P, Molinuevo JL, Parchi P, Regeniter A, Rissman RA, Rosenmann H, Sancesario G, Schroder J, Shaw LM, Teunissen CE, Trojanowski JQ, Vanderstichele H, Vandijck M, Verbeek MM, Zetterberg H, Blennow K, Alzheimer's Association QC Program Work Group (2013) CSF biomarker variability in the Alzheimer's Association quality control program. *Alzheimers Dement* **9**, 251-261.

[21] Stewart T, Shi M, Mehrotra A, Aro P, Soltys D, Kerr KF, Zabetian CP, Peskind ER, Taylor P, Shaw LM, Trojanowski JQ, Zhang J, and from the Alzheimer's Disease Neuroimaging Initiative (2019) Impact of pre-analytical differences on biomarkers in the ADNI and PPMI studies: Implications in the era of classifying disease based on biomarkers. *J Alzheimers Dis* **69**, 263-276.

[22] van Maurik IS, Zwan MD, Tijms BM, Bouwman FH, Teunissen CE, Scheltens P, Wattjes MP, Barkhof F, Berkhof J, van der Flier WM, Alzheimer's Disease Neuroimaging Initiative (2017) Interpreting biomarker results in individual patients with mild cognitive impairment in the Alzheimer's Biomarkers in Daily Practice (ABIDE) Project. *JAMA Neurol* **74**, 1481-1491.

[23] van Maurik IS, Vos SJ, Bos I, Bouwman FH, Teunissen CE, Scheltens P, Barkhof F, Frolich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Ruther E, Nobili F, Frisoni GB, Spiru L, Freund-Levi Y, Wallin AK, Hampel H, Soininen H, Tsolaki M, Verhey F, Kloszewska I, Mecocci P, Vellas B, Lovestone S, Galluzzi S, Herukka SK, Santana I, Baldeiras I, de Mendonca A, Silva D, Chetelat G, Egret S, Palmqvist S, Hansson O, Visser PJ, Berkhof J, van der Flier WM, Alzheimer's Disease Neuroimaging Initiative (2019) Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): A modelling study. *Lancet Neurol* **18**, 1034-1044.

[24] Snitz BE, Wang T, Cloonan YK, Jacobsen E, Chang CH, Hughes TF, Kamboh MI, Ganguli M (2018) Risk of progression from subjective cognitive decline to mild cognitive impairment: The role of study setting. *Alzheimers Dement* **14**, 734-742.

[25] Raschetti R, Albanese E, Vanacore N, Maggini M (2007) Cholinesterase inhibitors in mild cognitive impairment: A systematic review of randomised trials. *PLoS Med* **4**, e338.

[26] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A (2018) Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* **90**, 126-135.

[27] Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Hedrick S, Pappas V, Carrillo MC, Hartley DM, Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging (2013) Update on appropriate use criteria for amyloid PET imaging: Dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. *Alzheimers Dement* **9**, e106-109.

[28] Harkins K, Sankar P, Sperling R, Grill JD, Green RC, Johnson KA, Healy M, Karlawish J (2015) Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimers Res Ther* **7**, 26.

[29] Bocchetta M, Galluzzi S, Kehoe PG, Aguera E, Bernabei R, Bullock R, Ceccaldi M, Dartigues JF, de Mendonca A, Didic M, Eriksdotter M, Felician O, Frolich L, Gertz HJ, Hallikainen M, Hasselbalch SG, Hausner L, Heuser I, Jessen F, Jones RW, Kurz A, Lawlor B, Lleo A, Martinez-Lage P, Mecocci P, Mehrabian S, Monsch A, Nobili F, Nordberg A, Rikkert MO, Orgogozo JM, Pasquier F, Peters O, Salmon E, Sanchez-Castellano C, Santana I, Sarazin M, Traykov L, Tsolaki M, Visser PJ, Wallin AK, Wilcock G, Wilkinson D, Wolf H, Yener G, Zekry D, Frisoni GB (2015) The use of biomarkers for the etiologic diagnosis of MCI in Europe: An EADC survey. *Alzheimers Dement* **11**, 195-206 e191.