The Clinical Use of Alzheimer's Biomarkers in Patients With Mild Cognitive Impairment: A European Alzheimer's Disease Consortium Survey

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Research

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Abstract

Background. This study aims to investigate the clinical use of the main Alzheimer's disease (AD) biomarkers in patients with mild cognitive impairment (MCI) by examining the beliefs and preferences of clinicians and biomarker experts of the European Alzheimer's Disease Consortium (EADC).

Methods. Out of 306 contacted EADC professionals, 150 (101 clinicians, 43 biomarker experts, and 6 falling into other categories) filled in an online survey from May to September 2020. The investigated biomarkers were: medial temporal lobe atrophy score (MTA) on structural MRI, typical AD (i.e. temporoparietal and posterior cingulate) hypometabolism on FDG-PET, CSF ($A\beta_{42}$, p-tau, t-tau), amyloid-PET and tau-PET.

Results. Despite the abnormal accumulation of amyloid rather than tau was deemed by the majority of responders as the initial cause of AD, responders did not show a clear preference for amyloid-PET. The most widely used biomarker is MTA (77% of responders reported to use it at least frequently), followed by $A\beta_{42}$, p-tau, t-tau levels in CSF (45%), typical AD hypometabolism on FDG-PET (32%), amyloid-PET (8%), and tau-PET (2%). Imaging and CSF biomarkers were found to be widely used to support the etiological diagnostic process in MCI, while *APOE* genotyping was performed only in a minority of patients. CSF is considered the most valuable biomarker in terms of additional diagnostic value, followed by amyloid-PET, tau-PET, and typical AD hypometabolism on FDG-PET. The combination of amyloidosis and neuronal injury biomarkers is associated with the highest diagnostic confidence in an etiological diagnosis of AD in MCI, while MTA alone was perceived as the less reliable biomarker.

Conclusions. Biomarkers are widely used across Europe for the diagnosis of MCI. Overall, we observed that CSF is currently considered as the most useful biomarker, followed by amyloid-PET. Moreover, the use of molecular imaging (i.e. amyloid-PET and tau-PET) in the diagnostic work-up of MCI patients is increasing over time.

1. Background

The clinical understanding of Alzheimer's disease (AD) and its diagnostic implications have radically changed over time. Currently, AD is defined as a biological disease characterized by the abnormal accumulation of amyloid plaques and neurofibrillary tangles in the brain [1, 2], and is clinically considered a continuum ranging from a long preclinical phase (abnormal biomarkers in asymptomatic individuals) to mild cognitive impairment (MCI) and finally dementia. Even if this mainly represents a research framework, it points to the clinical relevance of AD biomarkers, and supports their increasing use in clinical practice. Consistently, several studies demonstrated that the use of biomarkers has different clinical implications [3–6] with MCI patients being the ones who might benefit the most from biomarker testing [7]. Indeed, an early etiological diagnosis of AD in MCI patients should initiate specific counseling [8] and allow interventions to potentially delay the progression to dementia [9]. For an etiological diagnosis of early symptomatic patients, this concept has already been picked up by most academic

memory clinics and is implemented in clinical practice. However, to date, no clinical guidelines recommend a “biomarker-based diagnosis of AD” as the state-of-the-art for the etiological diagnosis of MCI (or even dementia) patients.

The main biomarkers able to capture AD pathophysiological changes can be classified into two categories: (i) diagnostic / pathophysiological biomarkers are measures of amyloid (i.e. positive amyloid-PET, low CSF $A\beta_{42}$) and tau (i.e. positive tau-PET, high CSF p-tau) deposition, and have the necessary specificity for a diagnosis of AD [10]; (ii) progression / topographical biomarkers include measures of neurodegeneration (e.g. medio-temporal lobe atrophy (MTA) on structural MRI, hypometabolism on FDG-PET, high CSF t-tau), are not specific to AD but can be used to track the disease progression [10]. Among all these biomarkers, a major progress in the last years is the advent of amyloid-PET and tau-PET: this novel molecular imaging technique makes possible to visualize the topography of amyloid and tau deposits in the brain, previously measurable only indirectly via CSF. Specifically, given the strong association between tau pathology and symptoms, already known from neuropathological studies, and given the relative specificity of tau-PET tracers for tau deposits in AD, tau-PET could represent the most efficient imaging modality in AD: a positive tau-PET might be an indicator of both amyloid and tau pathology and thus provide a definite diagnostic answer with only one test [11, 12]. However, this interpretation might depend on the relative role attributed by the interpreting physician and clinician to amyloid and tau pathology in the physiopathology of AD [13].

A previous European survey conducted in 2012 investigated the use of biomarkers in MCI patients, and showed that physicians felt comfortable delivering a diagnosis of MCI due to AD when both amyloid and neurodegeneration biomarkers were abnormal [14]. The most frequently used biomarkers were found to be MTA (75% of responders reported to use it at least frequently), $A\beta_{42}$, p-tau, t-tau levels in CSF (22%), FDG-PET (16%), and amyloid-PET (3%). In light of the notable advances recently occurred in the field of AD biomarkers, namely clinical studies on real-word patients and introduction of newly developed techniques, an up-to-date depiction of their clinical use is needed. Thus, the aim of this study is to investigate the clinical use of the main AD biomarkers in MCI patients by examining the beliefs and preferences of clinicians (i.e. neurologists, geriatricians, psychiatrists) and biomarker experts (i.e. nuclear medicine, radiology, and laboratory physicians) within the framework of the European Alzheimer’s Disease Consortium (EADC, http://www.eadc.info), a functional network comprising 70 European memory clinics of excellence working in the field of AD (from 20 countries), providing a setting in which to increase the scientific understanding of AD.

2. Methods

2.1. The survey

A survey consisting of an online questionnaire assessing the clinical use of biomarkers in MCI patients (see the Supplementary Material for the full questionnaire) was made accessible from May 14th to September 30th, 2020. The number of items/questions depended on the respondent specialty and

answers: 26 for clinicians and 14 for biomarker experts, i.e. nuclear medicine, radiology, and laboratory physicians; the difference being due to 12 questions specific to the treating clinicians.

The questionnaire was subdivided in ten sections assessing respectively (i) respondent's details, i.e. specialty, center, city, country, role in memory clinic, years of experience in the field of neurodegenerative disorders, competence to answer to questions regarding neurodegenerative disorders; (ii) for clinicians only, the request to provide names and contacts of nuclear medicine, radiology, and laboratory physicians associated with the respondent's memory clinic; (iii) beliefs about the pathogenic role of amyloid and tau in Alzheimer's disease; (iv) respondent's clinical work, i.e. consultation with MCI, number of new MCI patients per month; (v) frequency of use of biomarkers (MRI, FDG-PET, CSF, amyloid-PET, tau-PET); (vi) use of imaging biomarkers in clinical reports (vii); use of biochemical biomarkers in clinical reports; (viii) diagnostic additional value of biomarkers; (ix) clinical vignette where respondents were asked to rate the diagnostic confidence on the basis of abnormality of the biomarkers (alone or combined); and (x) perceived clinical utility of amyloid-PET and tau-PET.

Concerning tau-PET, the following disclaimer was added to the survey: *"Please note that some of the following questions concern tau-PET. We are aware that while amyloid-PET tracers are well established and show similar performances, tau-PET tracers have been more recently developed and are less established. e.g., Flortaucipir is the most used tracer and has been validated against neuropathology and second-generation tracers are promising for an increased diagnostic accuracy. For this reason, we chose not to specify further which tau-PET tracer, and we would ask you to consider in answering a "theoretical" tau-PET tracer with a diagnostic accuracy deemed adequate for clinical use in AD."*

The survey took place in two steps: first, we contacted the clinicians working in the EADC memory clinics asking them to fill in the online questionnaire and to provide names and contacts of nuclear medicine, radiology, and laboratory physicians associated with their memory clinics; second, we contacted the nuclear medicine, radiology, and laboratory physicians recommended by the clinicians during the first step.

2.2. Outcomes of interest

In the present study we assessed the i) responders' belief about the pathogenic role of amyloid and tau in Alzheimer's disease pathology and symptoms (Sect. 2.2.1), ii) frequency of use of AD biomarkers in MCI patients (Sect. 2.2.2), iii) use of AD biomarkers to support etiological diagnosis in MCI (Sect. 2.2.3), iv) additional value of FDG-PET, CSF, amyloid-PET and tau-PET over neuropsychological testing and structural MRI in an MCI patient (Sect. 2.2.4), v) responders' confidence in making a diagnosis of MCI due to AD in a typical MCI patient based on different AD biomarkers (Sect. 2.2.5), vi) responders' opinion on the perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia patients (Sect. 2.2.6).

2.2.1. Belief on the pathogenic role of amyloid and tau in AD

The following question was posed to all responders: "*What is your belief/opinion about the pathogenic role of amyloid and tau in Alzheimer's disease pathology and symptoms?*". Possible answers went from 0 to 10 (11-point Likert scale): *0*, *the abnormal accumulation of amyloid is the initial cause of AD*; *5*, *amyloid and tau have the same relevance in causing AD*, or *neither amyloid nor tau are the initial cause of AD*; *10*, *the abnormal accumulation of tau is the initial cause of AD*. Answers were grouped into three categories: 0–4, favoring amyloid; 5, neutral; 6–10, favoring tau.

2.2.2. Frequency of use of AD biomarkers in MCI patients

The following question was posed: "*In MCI, in your clinical practice, please state frequency of use for medial temporal lobe atrophy (MRI), FDG-PET, CSF (e.g. $A\beta_{42}$, p-tau, t-tau), amyloid-PET, tau-PET*". Possible answers were: *not used* (0%), *rarely* (< 10%), *regularly* (20–60%), *frequently* (60–80%), *always* (> 80%). Answers were grouped into three categories: no use, rare-to-regular use (rarely or regularly), frequent-to-constant use (frequently or always). This item was applicable only to clinicians. Since the frequency of use of biomarkers is strongly dependent on the center expertise, policies, guidelines and facilities, we included only the answers of the head of the memory clinic or, if not possible, the answers of the most experienced (years of expertise in the field of neurodegenerative disorders) clinician of that memory clinic.

2.2.3. Use of AD biomarkers to support etiological diagnosis in MCI

The following question was posed: "*Do you use imaging biomarkers / CSF collection (e.g. $A\beta_{42}$, p-tau, t-tau) / APOE genotyping to support your etiological diagnosis in MCI?*". Possible answers were *yes* or *no*. Concerning imaging biomarkers, an additional question was posed: *"Do you use any quantitative reading tool (e.g. SPM) or scale (e.g. MTA scale; Scheltens et al., 1992) for your clinical reports?"*. Possible answers were *yes* or *no*. In case of affirmative answer, a further question was posed: "*In MCI please state what kind of quantitative reading tool (e.g. SPM) or scale (e.g. MTA scale; Scheltens et al., 1992) you use for your clinical reports for the answers indicated in previous question".* These items were applicable only to clinicians.

2.2.4. Additional value over neuropsychological testing and structural MRI in MCI

The following question was posed to all responders: "*Assuming that clinical examination with neuropsychological testing and brain structural MRI are the most feasible procedures in most memory clinics, please rate the additional diagnostic value (i.e. the ability to provide diagnostic information in excess of that already provided by neuropsychological testing and brain structural MRI) in an MCI patient of FDG-PET, CSF markers (e.g. $A\beta_{42}$, p-tau, t-tau), amyloid-PET, tau-PET*". Possible answers were: *none*, *little*, *moderately significant*, *greatly significant*, *decisive*. Answers were grouped into three categories: none-to-little (none or little), moderate (moderately significant), great-to-decisive (greatly significant or decisive).

2.2.5. Confidence in an etiological diagnosis of AD in MCI

The following case vignette was proposed to all responders: "*A 75 years old person comes into your office complaining of memory deterioration in the past 6–12 months, he/she is in good physical health, has no problems in his/her daily chores, but is clearly worried. Routine labs are normal, but he/she performs 1.5 SD below the age-and education-adjusted mean on a test of verbal or non-verbal recall. How confident would you be with a diagnosis of MCI due to AD (or prodromal AD) on the basis of i) evidence of clear-cut medial temporal lobe atrophy alone, ii) clear-cut temporoparietal and posterior cingulate hypometabolism on FDG-PET alone, iii) clearly abnormal CSF levels of Aβ and tau alone, iv) clearly positive amyloid-PET, v) clearly positive tau-PET, vi) at least one clearly positive amyloid marker and at least one clearly positive neuronal injury marker.*". Possible answers were: *not at all comfortable*, *moderately comfortable*, *comfortable*, *very comfortable*, *extremely comfortable*. Answers were grouped into three categories: not comfortable, sufficiently comfortable (moderately comfortable or comfortable), very-to-extremely comfortable (very comfortable or extremely comfortable).

2.2.6. Perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia

The following question was posed to all responders: "*Independent of any specific patient's feature and based on your clinical experience with patients usually seen in your memory clinic, what is, in your opinion, the most clinically useful exam for etiological diagnosis of MCI and mild dementia?*". Possible answers went from 0 to 10 (11-point Likert scale): *0*, *amyloid-PET is in general the most useful exam*; *5*, *amyloid-PET and tau-PET are equally useful*, or *neither amyloid-PET nor tau-PET are the most useful exam*; *10*, *tau-PET is in general the most useful exam*. Answers were grouped into three categories: 0–4, favoring amyloid-PET; 5, neutral; 6–10, favoring tau-PET.

2.3. Statistical methods

The outcomes of interest were assessed using proportion test (χ^2). Significance was set at $p < 0.05$ and post-hoc pairwise comparisons were adjusted using Bonferroni correction.

All statistical analyses were performed with R, version 3.4.2 (R Foundation for statistical computing, https://www.r-project.org/).

3. Results

3.1. Responders' features

First, 168 clinicians working in the EADC memory clinics were contacted, and 51% of them (86/168) filled in the survey questionnaire recommending 138 additional professionals (20 clinicians, 42 biomarker experts, 1 neuroscientist and 1 psychologist) related to their memory clinics, 46% (64/138) of whom filled in the survey. In total, 150 professionals filled in the survey questionnaire, with an overall answer rate of

49% (150/306). Among them, 6 did not fall into the pre-defined categories of interest (i.e. physicians and biomarker experts), being research staff (n = 4) or general practitioner (n = 2), and were therefore excluded from the analyses. Among the remaining responders, 5% (7/144) declared that they were not competent enough in the field of neurodegenerative disorders to fulfill the questionnaires, and therefore did not proceed with the questionnaire. The final sample consisted of 100 clinicians and 37 biomarker experts (9 radiologists, 18 nuclear medicine physicians, and 10 laboratory physicians). Among clinicians, 45% (45/100) were head of their memory clinics, while the remaining ones were memory clinic staff or collaborators. Clinicians had more years of experience in the field of neurodegenerative disorder than biomarker experts (clinicians: 19 ± 9, biomarker experts: 13 ± 8; $p < 0.001$). On average, clinicians consulted 17 ± 13 new patients with MCI in a typical month. Detailed respondent's characteristics are reported in Table 1, while Fig. 1 shows the geographic distribution of responders.

Table 1
Respondent's characteristics.

Respondent's characteristics	**Clinicians** **n = 100**	**Biomarker experts** **n = 37**
Specialty	Neurologist 72%	Radiologist 24%
	Geriatrician 14%	Nuclear medicine physicians 49%
	Psychiatrist 18%	Laboratory physicians 27%
Role	Head of memory clinic 45%	Head of memory clinic 0%
	Staff 39%	Staff 0%
	Collaborator 7%	Collaborator 92%
	Other 9%	Other 8%
Years of experience in the field of neurodegenerative disorders	19 ± 9	13 ± 8
Providing clinical consultation for MCI	92%	NA
New MCI patients consulted in a typical month	17 ± 13	NA

3.2. Pathogenic role of amyloid and tau in AD

Figure 2A shows the beliefs on the pathogenic role of amyloid and tau in AD reported by clinicians and biomarker experts, while figure S1A shows the beliefs on the pathogenic role of amyloid and tau in AD reported by different biomarker experts groups, i.e. radiologists, nuclear medicine physicians and laboratory physicians. Clinicians deemed the abnormal accumulation of amyloid (answers from 0 to 4, 42% of cases) rather than tau (answers from 6 to 10, 20% of cases, $p < 0.005$; Fig. 2A) as the initial cause

of AD. A similar, although not significant possibly due to the smaller sample size, pattern was observed among biomarker experts (amyloid: 43%, tau: 27%, $p = 0.223$; Fig. 2A). When comparing the proportion of clinicians and biomarker experts favoring amyloid, no significant difference emerges. The same result was observed for tau.

3.3. Frequency of use of AD biomarkers in MCI patients

Figure 3 shows the detailed frequency of use of each biomarker. Among clinicians, 8% (8/100) did not provide clinical consultation for patients with MCI, and were therefore excluded from the analyses on the frequency of use of AD biomarkers in MCI. Moreover, due to the above-explained reasons, we included only the answers of the head of the memory clinic or, if not possible, the answers of the most experienced (as measured by years of expertise in the field of neurodegenerative disorders) clinician of that memory clinic.

The frequency of clinicians reporting a frequent-to-constant use of MTA (77%, 41/53) is higher than that of those reporting a frequent-to-constant use of CSF (45%, 24/53; $p = 0.014$), FDG-PET (32%, 17/53, $p < 0.001$), amyloid-PET (8%, 4/53; $p < 0.001$) and tau-PET (2%, 1/53; $p < 0.001$). Moreover, the frequency of clinicians reporting a frequent-to-constant use of CSF and FDG-PET is higher than that of those reporting a frequent-to-constant use of amyloid-PET ($p < 0.001$ and $p = 0.035$) and tau-PET ($p < 0.001$ and $p = 0.001$).

3.4. Use of AD biomarkers to support etiological diagnosis in MCI

Figure 4 shows the use of AD biomarkers to support etiological diagnosis in MCI. Among clinicians, 8% (8/100) did not provide clinical consultation for patients with MCI, and were therefore excluded from the analyses on use of AD biomarkers to support etiological diagnosis in MCI. Clinicians providing clinical consultation for patients with MCI used imaging (90%, 83/92) and CSF (87%, 80/92) biomarkers to support etiological diagnosis in MCI more frequently than *APOE* genotyping (27%, 25/92; $p < 0.001$).

As for imaging biomarker, 67% of clinicians (62/92) used quantitative reading tools and scales for reporting imaging biomarkers data in clinical reports. Specific results on quantitative tools or scales are presented in Table 2.

Table 2
Quantitative reading tools and scales for reporting imaging biomarkers data in clinical reports.

Imaging biomarker	Quantitative tool	n
MRI		59
	Medial Temporal lobe Atrophy score [28]	54
	Fazekas [29]	20
	Koedam [30]	13
	Global Cortical Atrophy scale [31]	11
	Age-Related White Matter Changes [32]	4
	Morpho Tool Box [33]	2
	Hippocampal Volumetry [34]	1
	Icometrix [35]	1
FDG-PET		27
	Peripheral Module interface [36]	2
	Statistical Parametric Mapping [37]	4
	Alzheimer's disease score [38]	3
	Hypometabolism pattern	3
	Z-scores	2
	BRASS medical imaging software [39]	1
	Syngo.via [40]	1
	Statistical maps	1
Amyloid-PET		27
	Visual reading	9
	Standardized Uptake Value ratio	6
	Centiloid [41]	2
	BRASS medical imaging software [39]	1
	Syngo.via [40]	1
	Statistical maps	1

For each imaging biomarker, the number of clinicians using any quantitative reading tool or scale for that biomarker in clinical reports is reported in the first row. Number of clinicians using each specific quantitative tool are reported in subsequent rows.

Imaging biomarker	Quantitative tool	n
Tau-PET		14
	Visual reading	5
	Statistical maps	1
	BRASS medical imaging software [39]	1
	Early Volume-Of-Interest	1

For each imaging biomarker, the number of clinicians using any quantitative reading tool or scale for that biomarker in clinical reports is reported in the first row. Number of clinicians using each specific quantitative tool are reported in subsequent rows.

3.5. Additional value over neuropsychological testing and structural MRI in MCI

Figure 5 shows the detailed reported additional value over neuropsychological testing and structural MRI in MCI, while figure S2 shows the detailed reported additional value over neuropsychological testing and structural MRI in MCI by different biomarker experts groups, i.e. radiologists, nuclear medicine physicians and laboratory physicians. Clinicians report more frequently a great-to-decisive additional value of $A\beta_{42}$, p-tau, t-tau levels in CSF (85%, 85/100) with respect to amyloid-PET (72%, 72/100; $p < 0.05$), tau-PET (54%, 54/100; $p < 0.001$) and FDG-PET (35%, 35/100; $p < 0.001$). Amyloid-PET, instead, has been reported as having a great-to-decisive additional value more frequently than FDG-PET only ($p < 0.001$). No significant differences emerged between amyloid-PET and tau-PET (p = 0.077), and between FDG-PET and tau-PET ($p = 0.063$).

Among biomarker experts, we observed no significant differences (p = 0.083), with the frequency of a great-to-decisive additional value being 76% (28/37) for $A\beta_{42}$, p-tau, t-tau levels in CSF, 70% (26/37) for amyloid-PET, 62% (23/37) for tau-PET, and 49% (18/37) for FDG-PET.

No significant differences were observed when comparing the frequency of clinicians and biomarker experts reporting a great-to-decisive additional value for each technique.

3.6. Confidence in an etiological diagnosis of AD in MCI

Figure 6 shows the detailed level of confidence in an etiological diagnosis of AD in MCI, while figure S3 shows the detailed level of confidence in an etiological diagnosis of AD in MCI by different biomarker experts groups, i.e. radiologists, nuclear medicine physicians and laboratory physicians. Clinicians reported to be more frequently very-to-extremely comfortable with an etiological diagnosis of AD on the basis of at least one clearly positive amyloid marker and at least one clearly positive neuronal injury marker (86%, 86/100) with respect to abnormal CSF levels of $A\beta_{42}$, p-tau and t-tau (64%, 64/100; $p =$

0.009), positive amyloid-PET (52%, 52/100; $p < 0.001$), positive tau-PET (41%, 41/100; $p < 0.001$), typical AD (i.e. temporoparietal and posterior cingulate) hypometabolism on FDG-PET (22% 22/100; $p < 0.001$), and evidence of MTA on structural MRI (14%, 14/100; $p < 0.001$). Moreover, clinicians reported to be more frequently very-to-extremely comfortable with an etiological diagnosis of AD on the basis of abnormal CSF levels of Aβ and tau or of a positive amyloid-PET than typical AD hypometabolism on FDG-PET ($p < 0.001$ and $p < 0.001$ respectively) and evidence of MTA ($p < 0.001$ and $p < 0.001$ respectively). Additionally, they reported to be more frequently very-to-extremely comfortable with an etiological diagnosis of AD on the basis of abnormal CSF levels of Aβ and tau rather than of positive tau-PET ($p = 0.028$). Finally, clinicians reported to be more frequently very-to-extremely comfortable with an etiological diagnosis of AD on the basis of positive tau-PET than evidence of MTA ($p < 0.001$).

Biomarker experts stated to be more frequently very-to-extremely comfortable with an etiological diagnosis of AD on the basis of at least one clearly positive amyloid marker and at least one clearly positive neuronal injury marker (68%, 25/37) rather than on the evidence of MTA (14%, 5/37; $p < 0.001$). Among biomarker experts we observed no other significant differences, possibly due to the smaller sample size, with the frequency of those stating to be very-to-extremely comfortable with an etiological diagnosis of AD being 46% (17/37) for positive amyloid-PET, 43% (16/37) for typical AD hypometabolism on FDG-PET, 41% (15/37) for positive tau-PET and 38% (14/37) for abnormal CSF levels of Aβ and tau.

No significant differences were observed when comparing the frequency of clinicians and biomarker experts reporting to be very-to-extremely comfortable with an etiological diagnosis of AD on the basis of MTA, amyloid-PET, and tau-PET. Biomarker experts reported to be very-to-extremely comfortable with an etiological diagnosis of AD on the basis of typical AD hypometabolism on FDG-PET more frequently than clinicians ($p = 0.024$). Conversely, clinicians reported to be very-to-extremely comfortable with an etiological diagnosis of AD on the basis abnormal CSF levels ($p = 0.010$), or of at least one clearly positive amyloid marker and at least one clearly positive neuronal injury marker ($p = 0.028$) more frequently than biomarker experts.

3.7. Perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia

Figure 2B shows the perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia reported by clinicians and biomarker experts, while figure S1B shows the perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia reported by different biomarker experts groups, i.e. radiologists, nuclear medicine physicians and laboratory physicians. Clinicians considered amyloid-PET and tau-PET equally useful to support an etiological diagnosis in MCI and mild dementia patients (amyloid-PET: 35% vs tau-PET: 24%, $p = 0.121$; Fig. 2B). A non-significant trend towards an amyloid-PET preference was observed among biomarker experts (amyloid-PET: 46% vs tau-PET: 24%, $p = 0.088$). When comparing the proportion of clinicians and biomarker experts favoring amyloid-PET or tau-PET, no significant difference emerged.

4. Discussion

This study reports the results of the largest multidisciplinary survey on the use and the perceived utility of Alzheimer's biomarkers in clinical practice in MCI patients.

The investigation on the professionals' beliefs on the initial cause of AD revealed that a prevalent pathogenic role was attributed to amyloid (42% clinicians, 43% biomarker experts) rather than tau (20% clinicians, 27% biomarker experts). However, when the focus switched from the theoretical belief to the perceived clinical utility of PET scans assessing amyloid and tau, responders did not show a clear preference for amyloid-PET. Consistently, a recent work assessing the diagnostic value of amyloid-PET and tau-PET in a memory clinic population, showed that the two exams significantly impacted diagnosis and diagnostic confidence in a similar way [4]. Notably, clinicians and biomarker experts proved to be perfectly aligned both with regard to beliefs on the pathogenic role of amyloid and tau and to the perceived clinical utility of amyloid-PET and tau-PET.

In the clinical assessment of MCI patients, the most widely used biomarker is MTA on structural MRI (78% frequent-to-constant use), followed by $A\beta_{42}$, p-tau, t-tau levels in CSF (45%), typical AD hypometabolism on FDG-PET (32%), amyloid-PET (8%) and tau-PET (2%). These results highlight an overall increase in the use of all biomarkers, as compared with a previous survey launched in 2012 [14], and with another one launched in 2014 among members of European Academy of Neurology (EAN) and EADC [15]. In a period of less than 10 years, amyloid-PET went from being frequently or constantly used in 3% of cases to 8% (and from being used at least regularly in 16% of cases to 31%), thus highlighting a remarkable spread of this biomarker in the clinical practice. Moreover, tau-PET, which has been recently introduced [16] and was not even included in the previous survey, now appears to be used frequently or constantly used in 2% of cases and at least regularly in 6%. The use of these advanced techniques might be limited by the absence of disease modifying therapies. Their use will probably increase as new effective therapies will become available. It must be remarked that the frequency of use of each biomarker is clearly influenced by its local availability, which varies significantly from center to center with MRI being already widely available and tau-PET being available only in research contexts, despite the promising preliminary results exhibited since its recent introduction [4, 17]. Of note, the limited frequency of use detected for amyloid-PET and tau-PET might be influenced by the lack of reimbursement for this examination. As for CSF markers, their frequency of use might be further influenced not only by their availability but also by the attitude toward lumbar puncture among clinicians and patients. Performing lumbar puncture, indeed, requires specific training and evaluation of potential contraindications; however, the overall risk of complications is relatively low [18].

Imaging and CSF biomarkers were found to be widely used to support the etiological diagnostic process in MCI (i.e. ≃90%), while *APOE* genotyping was used only in 27% of cases, denoting a slight decrease from previous survey (38% in 2012). This result seems at odds with non-invasivity and affordability of *APOE* genotyping and with the crucial information that this exam might reveal. Indeed, even though the estimated risk conferred by an ε4 allele varies between studies, odd ratios ranging between 1.8 and 9.9

have been reported [19]. Moreover, it has been recently shown that *APOE* ε4 carriers have an increased rate of progression from preclinical AD to MCI, and from MCI to mild AD dementia [20]. *APOE* ε4 allele, however, is neither necessary nor sufficient to cause AD. Thus, *APOE* genotyping should not be used alone for a diagnosis of MCI due to AD in a single case [21]. Indeed, current guidelines do not do not recommend *APOE* genotyping in the workup of dementia and MCI either in isolation or as part of the diagnostic process [22, 23].

Clinicians deemed $A\beta_{42}$, p-tau, t-tau levels in CSF as the most valuable biomarker in terms of additional diagnostic value over neuropsychological testing and structural MRI (85% great-to-decisive additional value), followed by amyloid-PET (72%), tau-PET (54%) and lastly typical AD hypometabolism on FDG-PET (35%). Notably, clinicians perceived the diagnostic value of CSF and amyloid-PET dramatically increased from previous survey (60% and 43% in 2012), whilst that of FDG-PET (46% in 2012) decreased. Similarly, biomarker experts attributed more value to CSF (76%), amyloid-PET (70%), tau-PET (63%) and lastly FDG-PET (49%). The remarkable level of perceived utility attributed to $A\beta_{42}$, p-tau, t-tau levels in CSF can be easily explained in light of the different pathophysiological process which is able to capture (i.e. amyloid load, brain tauopathy, neurodegeneration). However, Ramusino and colleagues recently compared the relative incremental diagnostic value of amyloid-PET and CSF (Aβ42, p-tau, t-tau), showing that amyloid-PET induces greater changes in the diagnosis of AD patients as compared to CSF [3]. A recent survey further confirmed the value of amyloid pathology markers, highlighting that these biomarkers are perceived by clinicians as the most valuable to predict progression and rate of progression in MCI patient [8].

As for tau-PET, both clinicians and biomarker experts appear to already rely on this exam in clinical practice. This might be due to its ability to differentiate between amyloid-positive and negative neurodegenerative diseases with high accuracy [11] and to the evidence that the accumulation of pathologic tau is closely related to functional and structural deterioration in the AD spectrum [24]. The relatively low additional value attributed to FDG-PET might be due its nature of nonspecific measure of neurodegeneration, detecting damage that may derive not only from AD but from a variety of etiologies, for example cerebrovascular injury [2].

Concerning diagnostic confidence in an etiological diagnosis of AD in MCI, both clinician and biomarker experts quite predictably deemed the combination of amyloidosis and neuronal injury biomarkers as the most convincing in vivo signature of AD, while MTA alone was perceived as the less reliable biomarker. As for other biomarkers, different considerations emerged between clinicians and biomarker experts. Typical AD hypometabolism on FDG-PET, indeed, was perceived as of great-to-decisive additional value by 44% of biomarker expert but only 22% of clinicians. Conversely, CSF collection was perceived as more useful by clinicians (64%) than biomarker experts (38%). A more balanced pattern emerged for amyloid-PET (52% vs 46%) and tau-PET (41% vs 40%). Notably, among experts in the field of neurodegenerative disorders, newly developed biomarkers mainly used in research and still not clinically validated, i.e. amyloid-PET and tau-PET, have already reached (and in some cases exceeded) the level of reliability of

well-established and validated biomarkers, in agreement with their level of clinical validity, namely for Flortaucipir as tau-PET tracer, as recently assessed [25, 26].

Limitations

The here-reported results allow an up-to-date depiction of the clinical use of Alzheimer's biomarkers in patients with MCI in European countries and of their perceived utility among a multidisciplinary group of experts in the field of neurodegenerative disorders. Nevertheless, this study has some limitations. Firstly, the participation of EADC centers was only partial (51% response rate). Secondly, the nature of the responding centers, i.e. memory clinics with a clinical research background, might prevent to generalize our results to ordinary memory clinics. Thirdly, since tau-PET tracers have been developed only recently and are less established, we had to ask responders to consider a "theoretical" tau-PET tracer with a diagnostic accuracy deemed adequate for clinical use in AD, maybe affecting their answers concerning this technique. Fourthly, plasma biomarkers were not included in the present survey. However, since they are emerging as potentially scalable and valuable biomarkers [27], their inclusion in future survey is needed. Lastly, the results of the survey might be influenced by the local indications for prescription, reimbursement policies, and costs of biomarkers, which are not always consistent across Europe [7]. Indeed, the same biomarker might be indicated without restrictions and reimbursed in some countries (e.g. CSF in France), and indicated only in specific cases (e.g. CSF in UK) or not reimbursed (e.g. CSF in Spain) in others [7]. As a consequence, in some cases, wealthy patients might pay out of pocket to have access to advanced diagnostic exams that would otherwise be inaccessible. In other words, the European heterogeneity in indications for prescription and reimbursement policies and other financial aspects might have influenced the results of the survey.

Conclusions

Altogether, the results of this ample and multidisciplinary survey suggest that both traditional and newly-developed (e.g. amyloid-PET and tau-PET) biomarkers are widely adopted across European memory clinics in patients with MCI, not only for research purposes but also in clinical practice. Overall, we observed that CSF is currently considered as the most useful biomarker by clinicians and biomarker experts, followed by amyloid-PET. Moreover, the use of molecular imaging in the diagnostic work-up of MCI patients is increasing over time.

List Of Abbreviations

Alzheimer's disease (AD)

Mild cognitive impairment (MCI)

European Alzheimer's Disease Consortium (EADC)

Medial temporal lobe atrophy score (MTA)

European Academy of Neurology (EAN)

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

Data can be shared upon request.

Competing interests

Valentina Garibotto received financial support for research and fees through her institution from Siemens Healthineers, GE Healthcare, Life Molecular Imaging, Cerveau Technologies, Roche, Merck.

Frank Jessen reports fees for advice and presentation from Roche, Biogen, Eisai, Eli Lilly, Janssen, Abbvie, Vifor Pharma. Lutz Frölich received research funding or consultancy fees by Abbott, Allergan, Axon Neuroscience, Biogen, Eisai, InfectoPharm, MerckSharpe & Dohme, Novo Nordisk, Roche, Schwabe Pharma; he is also part of Data and Safety Monitoring boards or endpoint committees with: Avanir, Pharmatropix, Forschungszentrum Jülich, Neuroscios, Novartis.

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The other coauthors declare that they have no competing interests.

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Authors' contribution

Daniele Altomare and Camilla Caprioglio conceptualized this Paper, drafted the manuscript for intellectual content, and approved the manuscript. Valentina Garibotto, Frank Jessen, Lutz Frölich, Gilles Allali, Frédéric Assal, and Giovanni B. Frisoni revised the manuscript for intellectual content, and approved the manuscript.

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Figures

Figure 1

Geographical distribution of the responders. Responders were distributed as follows: University of Antwerp, Antwerp, Belgium (2 responders); Radiology Department, Universitair Ziekenhuis Brussel, Brussel, Belgium (1 responder); Vrije Universiteit Brussel, Brussel, Belgium (3 responders); University

Hospital Gasthuisberg, Leuven, Belgium (5 responders); University of Liège, Liège, Belgium (1 responder); Université catholique de Louvain (UCL) & Cliniques Universitaires Saint-Luc, Louvain, Belgium (4 responders); University Hospital Center Zagreb & University of Zagreb School of Medicine, Zagreb, Croatia (4 responders); Charles University & Motol University Hospital, Prague, Czech Republic (3 responders); Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (4 responders); Kuopio University Hospital, Kuopio, Finland (3 responders); Centre Hospitalier Universitaire (CHU), Bordeaux, France (2 responders); CHU Inserm, Lille, France (2 responders); CHU Timone, Marseille, France (3 responders); Montpellier University Hospital, Montpellier, France (1 responder); Hôpital Salpétrière, Paris, France (3 responders); University of Paris Diderot, (1 responder); CHU La Grave-Casselardit, Toulouse, France (1 responder); Clinique Universitaire CHRU & Université François Rabelais, Tours, France (2 responders); Charité – Universitätsmedizin, Berlin, Germany (3 responders); Clinical Dementia Center, Department of Neurology, University Medical Center, Georg August University, Göttingen, Germany (1 responder); Uniklinik, Cologne, Germany (2 responders); Zentralinstitut für Seelische Gesundheit, Mannheim, Germany (2 responders); Technische Universität, Munich, Germany (1 responder); National and Kapodistrian University of Athens, Medical School, Aiginition Hospital, Athens, Greece (4 responders); Mercer's Institute for Research on Ageing, St James' Hospital, Dublin, Ireland (1 responder); University of Genoa, Genoa, Italy (6 responders); School of Medicine, University of Milano-Bicocca, Milan, Italy (1 responder); Geriatric Department, University of Perugia, Perugia, Italy (3 responders); Università Cattolica del Sacro Cuore, Rome, Italy (3 responders); Vrije University Medical Centre, Amsterdam, The Netherlands (3 responders); Radboud University Medical Center, Nijmegen, The Netherlands (3 responders); Polish Academy of Sciences, Medical Research Center, Warsaw, Poland (1 responder); Faculdade de Medicina de Lisboa, Lisbon, Portugal (2 responders); University Hospital of Coimbra, Coimbra, Portugal (5 responders); Elias University Hospital, Bucharest, Romania (1 responder); Institute of Neurobiology, Belgrade, Serbia (4 responders); Fundació ACE Institut Català de Neurociències Aplicades – Universitat Internacional de Catalunya (UIC), Barcelona, Spain (6 responders); Hôpital Sant Pau, Barcelona, Spain (4 responders); Hospital Clinic IDIBAPS, Barcelona, Spain (7 responders); Hospital Universitario Reina Sofía, Cordoba, Spain (1 responder); Hospital Universitario Santa Maria, Lleida, Spain (1 responder); Hospital Universitario Ramón y Cajal, Madrid, Spain (2 responders); Clinica Universidad de Navarra, Pamplona, Spain (5 responders); Skåne University Hospital & Lund University, Malmö, Sweden (5 responders); Karolinska Institutet, Stockholm, Sweden (3 responders); University of Bern, Bern, Switzerland (1 responder); Geneva University Hospital, Geneva, Switzerland (7 responders); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (4 responders); Dokuz Eylul University, Izmir, Turkey (2 responders); RICE (The Research Institute for the Care of Older People), Bath, UK (1 responder); Centre for Public Health, Belfast, UK (3 responders); Bristol Medical School, University of Bristol, Bristol, UK (2 responders); University College London, London, UK (1 responder); Imperial College, London, UK (1 responder); National Health Service, Perth, United Kingdom (1 responder). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

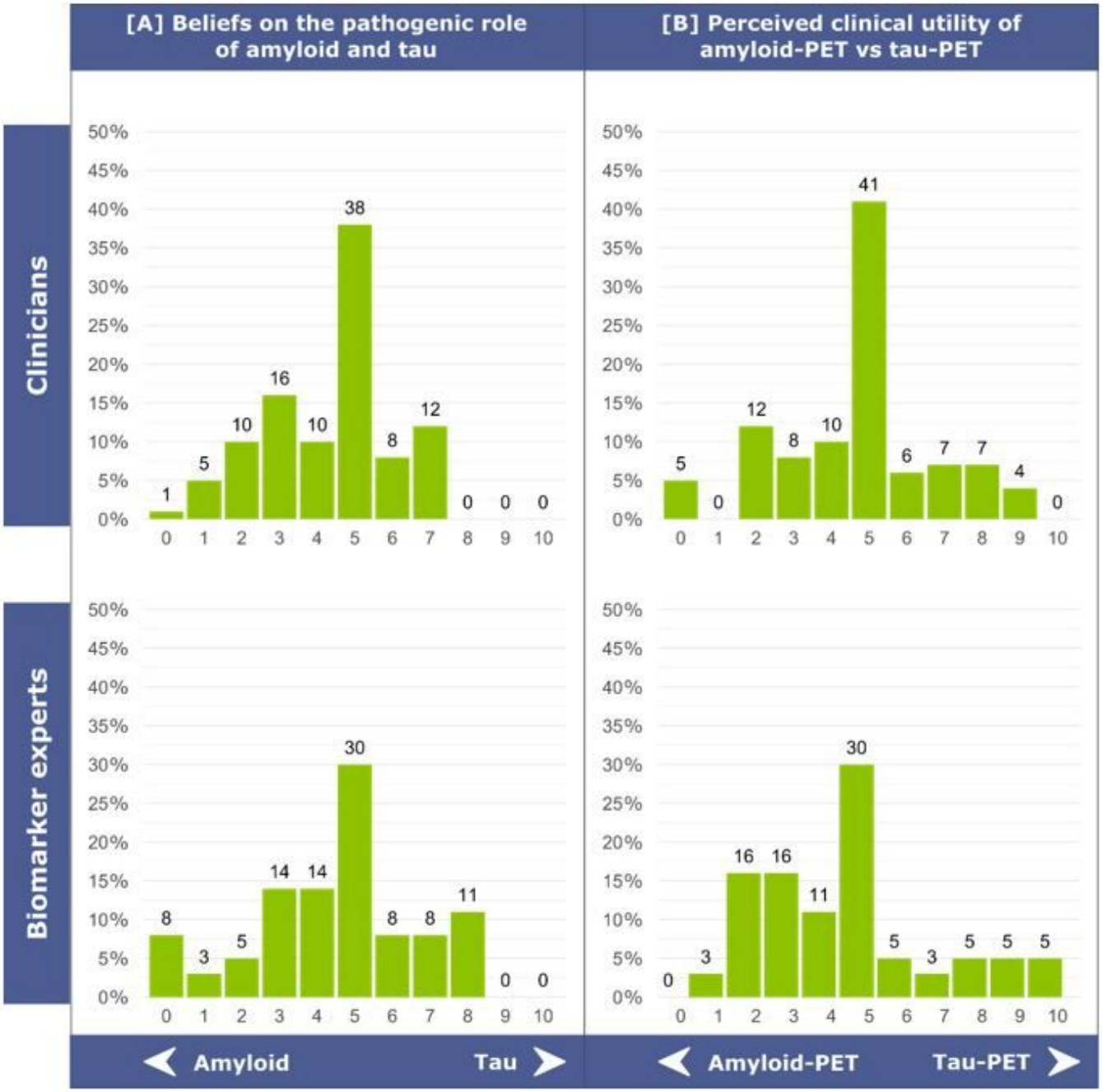

Figure 2

Beliefs on the pathogenic role of amyloid and tau in AD [A] and perceived clinical utility of amyloid-PET vs tau-PET in MCI and mild dementia [B]. (A) The question asked to responders was: “What is your belief/opinion about the pathogenic role of amyloid and tau in Alzheimer’s disease pathology and symptoms?”. Answers were grouped into three categories: 0-4, favoring the abnormal accumulation of amyloid as the initial cause of AD; 5, amyloid and tau have the same relevance in causing AD, or neither amyloid nor tau are the initial cause of AD; 6-10, favoring the abnormal accumulation of tau as the initial cause of AD. (B) The question posed to responders was: “Independent of any specific patient’s feature and based on your clinical experience with patients usually seen in your memory clinic, what is, in your

opinion, the most clinically useful exam for etiological diagnosis of MCI and mild dementia?". Answers were grouped into three categories: 0-4, favoring amyloid-PET; 5, neutral; 6-10, favoring tau-PET.

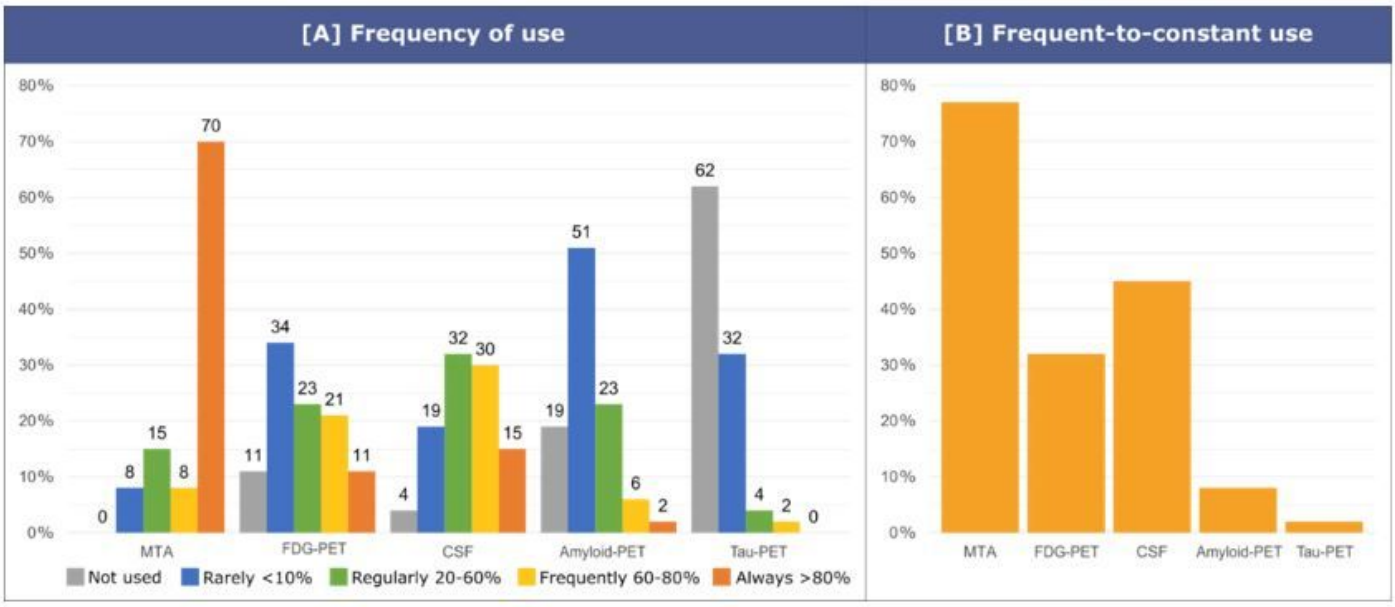

Figure 3

Frequency of use of AD biomarkers in MCI patients. The question asked to clinicians was: "In MCI, in your clinical practice, please state frequency of use for medial temporal lobe atrophy (MRI), FDG-PET, CSF (e.g. Aβ42, p-tau, t-tau), amyloid-PET, tau-PET". Possible answers were: not used (0%), rarely (<10%), regularly (20-60%), frequently (60-80%), always (>80%). Answers were grouped into three categories: no use, rare-to-regular use (rarely or regularly), frequent-to-constant use (frequently or always).

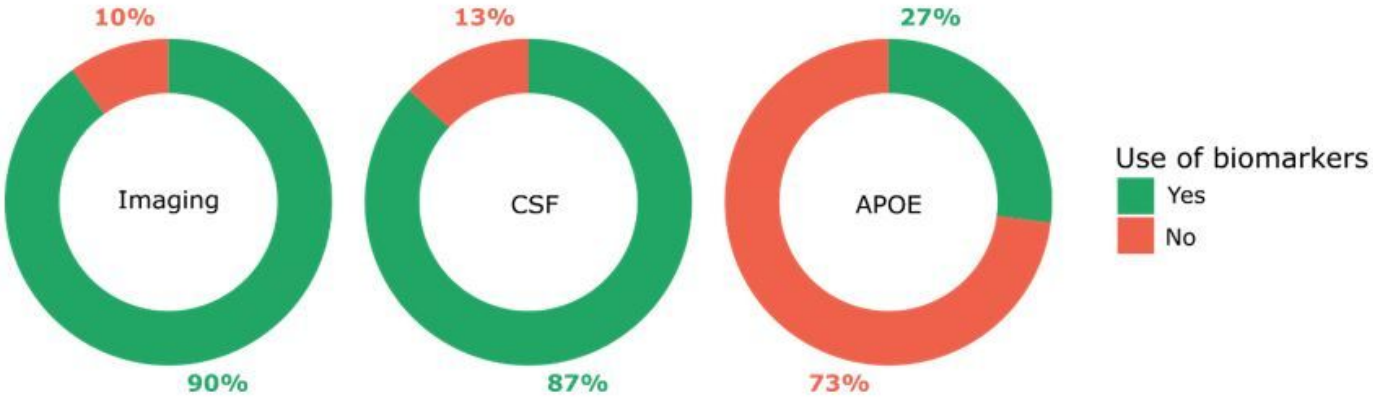

Figure 4

Use of AD biomarkers to support etiological diagnosis in MCI. The question asked to clinicians was: "Do you use imaging biomarkers / CSF collection (e.g. Aβ42, p-tau, t-tau) / APOE genotyping to support your etiological diagnosis in MCI?". Possible answers were yes or no. Clinicians reported to use imaging to

support their etiological diagnosis in MCI in 90% of cases, CSF in 87% of cases and APOE in 27% of cases.

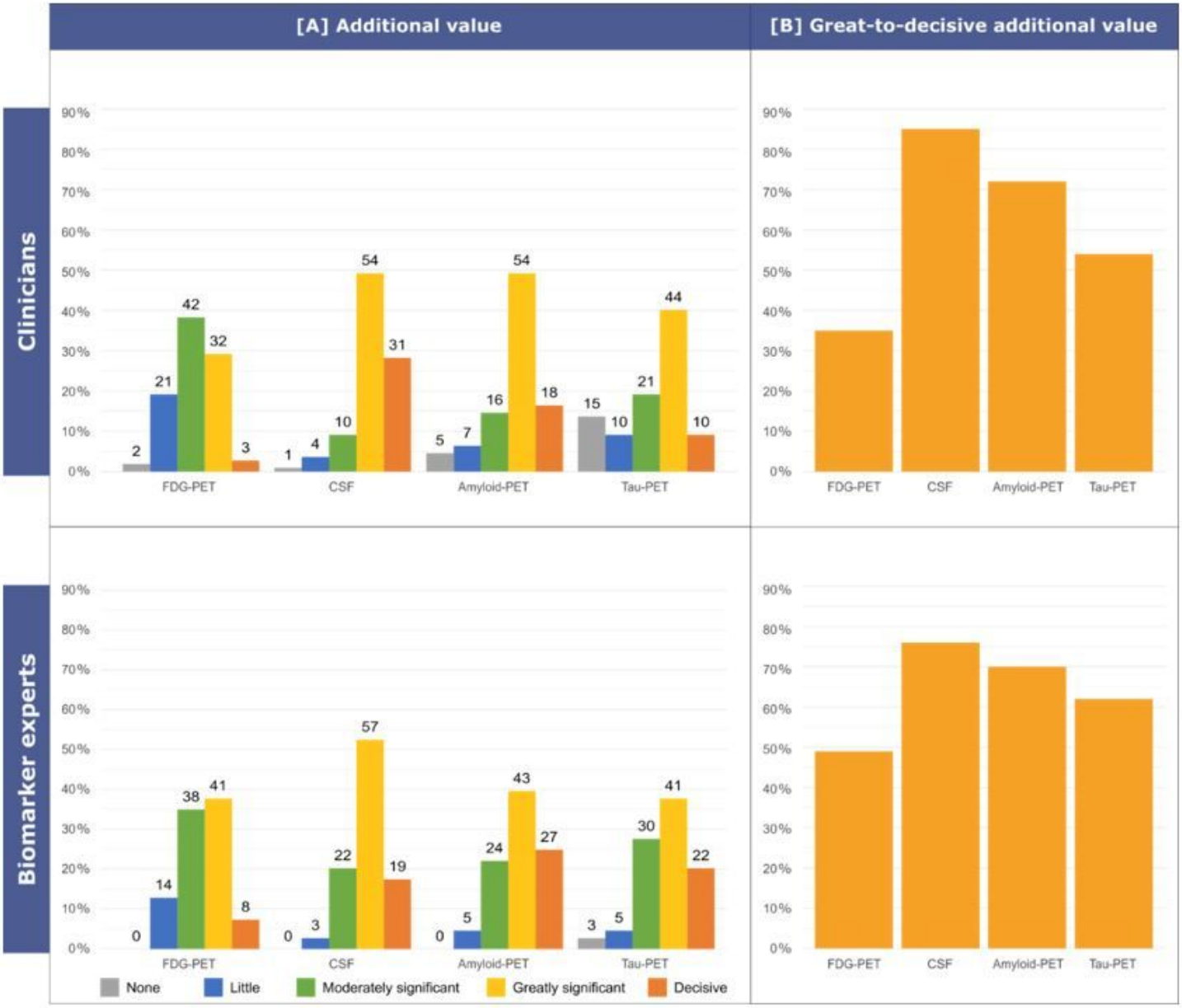

Figure 5

Additional value over neuropsychological testing and structural MRI in MCI. The question asked to responders was: “Assuming that clinical examination with neuropsychological testing and brain structural MRI are the most feasible procedures in most memory clinics, please rate the additional diagnostic value (i.e. the ability to provide diagnostic information in excess of that already provided by neuropsychological testing and brain structural MRI) in an MCI patient of FDG-PET, CSF markers (e.g. Aβ42, p-tau, t-tau), amyloid-PET, tau-PET”. Possible answers were: none, little, moderately significant, greatly significant, decisive. Answers were grouped into three categories: none-to-little (none or little), moderate (moderately significant), great-to-decisive (greatly significant or decisive).

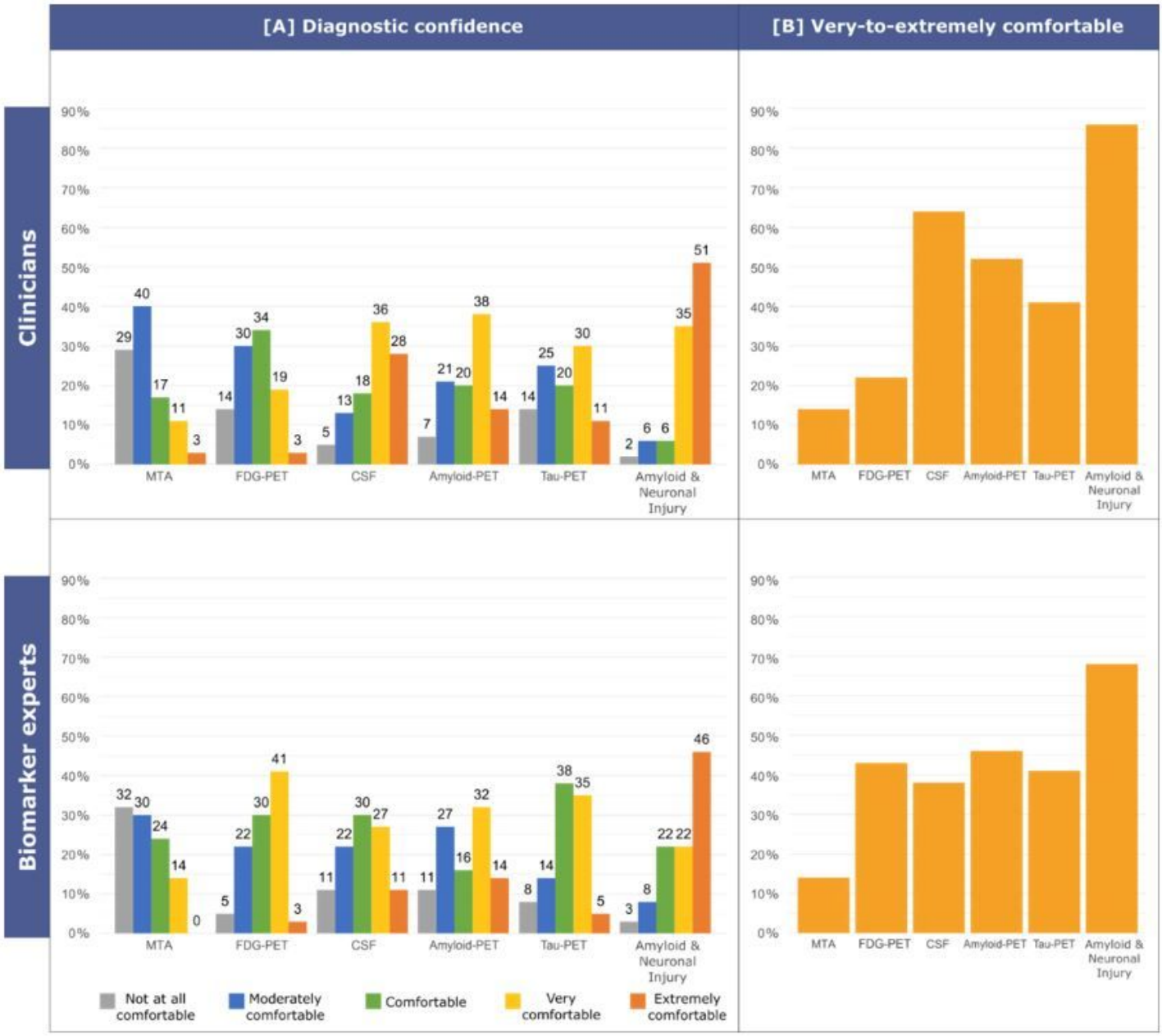

Figure 6

Confidence in an etiological diagnosis of AD in MCI. The following case vignette was proposed to responders: “A 75 years old person comes into your office complaining of memory deterioration in the past 6-12 months, he/she is in good physical health, has no problems in his/her daily chores, but is clearly worried. Routine labs are normal, but he/she performs 1.5 SD below the age-and education-adjusted mean on a test of verbal or non-verbal recall. How confident would you be with a diagnosis of MCI due to AD (or prodromal AD) on the basis of i) evidence of clear-cut medial temporal lobe atrophy alone, ii) clear-cut temporoparietal and posterior cingulate hypometabolism on FDG-PET alone, iii) clearly abnormal CSF levels of Aβ and tau alone, iv) clearly positive amyloid-PET, v) clearly positive tau-PET, vi) at least one clearly positive amyloid marker and at least one clearly positive neuronal injury marker.”. Possible answers were: not at all comfortable, moderately comfortable, comfortable, very comfortable,

extremely comfortable. Answers were grouped into three categories: not comfortable, sufficiently comfortable (moderately comfortable or comfortable), very-to-extremely comfortable (very comfortable or extremely comfortable).

Supplementary Files

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- ARTUseBiomarkersCaprioglio07SupplementaryMaterial.docx