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Clinical utility and applicability of biomarker-based diagnostic criteria for Alzheimers disease : a BeDeCo survey

Clinical utility and applicability of biomarker-based diagnostic criteria for Alzheimer's disease: a BeDeCo survey.

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Abstract:

We conducted a survey regarding the medical care of patients with dementia in expert settings in Belgium. Open, unrestricted and motivated answers were centralized, blindly interpreted and structured into categories. The report of the results was then submitted to the participants in subsequent plenary meetings and through e-mail. Fourteen experts responded to the questionnaire, confirming that recent propositions to modify AD diagnostic criteria and options have stirred-up debate among well-informed and dedicated experts in the field. The opinions were not unanimous and illustrate how difficult it is to find a standardized method of diagnosing this disease. The responses to the survey suggest that application of a step-by-step pragmatic method is used in practice. Only when the combination of clinical findings and classical structural neuro-imaging is insufficient for a diagnosis or suggests an atypical presentation, additional biomarkers are considered. Interestingly, few differences, if any, were observed between the use of biomarkers in MCI and in AD.

In conclusion, the Belgian experts consulted in this survey were generally in agreement with the new diagnostic criteria for AD, although some concern was expressed about them being too "amyloidocentric". Although the clinical examination, including a full neuropsychological evaluation, is still considered as the basis for diagnosis, most experts also stated that they use biomarkers to help with diagnosis.

Background, aims and objectives: Concepts, notions and knowledge evolve as research provides new evidence. This process gradually leads to changes in our understanding of neurodegenerative diseases and how to diagnose them. Changing attitudes towards cognitive disorders have highlighted the potential stigmatization associated with some of the older diagnostic labels (e.g., "dementia") and raise questions related to appropriate semantics. Experts in the field of dementia are well placed to reflect on these changes and their implications for clinical practice. The "Belgian Dementia Council" (BeDeCo) is a non-profit association that gathers together clinicians with expertise in the care of patients suffering from dementia – mostly, but not exclusively, medical doctors (neurologists, geriatricians, old age psychiatrists and general practitioners).

In this article, we present the results of a BeDeCo survey aimed at providing an overview of the medical care available for patients with dementia in expert settings in Belgium. The survey took the form of a questionnaire inquiring about the experts' personal experiences and their opinions regarding international and national recommendations and the currently available literature ("Evidence Based Medicine").

Introduction: Alzheimer's disease (AD) is the most frequent cause of dementia, accounting for 50% to 60% of all cases [1,2]. Until recently, the diagnosis of AD required solely a thorough clinical and neuropsychological examination (NPE) and exclusion of specific underlying etiologies. However, this purely clinical approach, requiring that a threshold of functional decline compatible with the concept of dementia should be reached to allow a diagnosis of AD, needs to be reconsidered for several reasons:

1/ Pathophysiological reasons:

AD is a neurodegenerative disorder in which two proteins (amyloid-β and Tau) undergo pathological changes: brain accumulation of an insoluble form of amyloid-β, and hyperphosphorylation of the tau protein with modifications of the stereotactic configuration. Although the exact chronology and interaction between these proteins is still debated, it is generally accepted that these alterations arise years and probably decades before the appearance of any clinical symptoms [2].

2/ Therapeutic reasons:

Any disease-modifying treatment should be proposed at the earliest stage, ideally before the occurrence of cognitive decline, in order to maximize its efficacy. Indeed, the recent failure to demonstrate efficacy of anti-amyloid drugs in clinical studies in patients with mild to moderate stages of AD has been explained by some as being the result of late administration. Many authors believe these agents could have been more effective if given before the occurrence of significant neuronal damage and thus well before any clinical symptoms.

Considering there is a gradual evolution of the neurodegenerative lesions over time, an intermediate clinical syndromic category between normality and dementia has been proposed and labeled: "mild cognitive impairment" (MCI) [3]. MCI patients present with mild forms of cognitive impairment without significant loss of autonomy (i.e., criteria of dementia are not fulfilled). It has been demonstrated that MCI patients have a high risk of developing dementia in the years following a diagnosis of MCI (up to 15% conversion rate per year). However, not all MCI patients evolve towards dementia and some even regain normal cognition with time [4]. This observation is likely because MCI is a generic (syndromic) term rather than a specific diagnosis, concealing various underlying etiologies. If MCI is the result of an underlying

neurodegenerative disease, such as AD, progression to dementia will occur but this is difficult to predict on the basis of clinical and cognitive assessments alone.

In view of these diagnostic difficulties, but also in acknowledgement of progress in medical knowledge and technology, Dubois and coworkers proposed, in 2007, a revision of the diagnostic research criteria for AD that incorporated some biological markers in addition to clinical assessment, which was also better defined [5]. These criteria were updated in 2014[6]. First, these authors stressed the importance of disclosing a memory deficit that preferentially involves encoding and consolidation capacities, similar to those observed in typical AD, albeit at a milder degree [5]. Second, when such mild cognitive deficit is observed, it was recommended that some technical diagnostic tools that have been shown to have validity, considered as "biological markers" of AD, can have additional diagnostic value. Such markers may be anatomical, functional or molecular and include positron emission tomography (PET) with either fluorodeoxyglucose (FDG) or with an amyloid tracers, cerebrospinal fluid (CSF) analysis for amyloid-β_{1-42}, total-Tau and phospho-Tau, focal medial temporal atrophy measured on magnetic resonance imaging (MRI), or DNA sequencing in families known to have autosomal dominant AD – in the rare case of dominant mutations known to cause autosomal dominant AD in a close relative [5].

In 2011, similar considerations from a National Institute on Aging–Alzheimer's Association workgroup led to the proposal that AD should be reconsidered as a continuum with different disease stages ranging from preclinical, asymptomatic individuals who have positive biological markers suggestive of AD through an MCI clinical picture to full-blown dementia [2,7,8,9]. The proposal of being able to make a

diagnosis of Alzheimer pathology in asymptomatic individuals raises important ethical questions, especially because there is currently no curative treatment available [10]. Moreover, there is no agreement on the positive and negative predictive values of these markers, which vary depending on the study and the stage of the disease at which they were identified [7,11,12].

Before issuing any recommendation based on these new criteria, BeDeCo initiated a survey among its members to investigate their opinions on the current semantic and lexical nature of pathophysiological concepts and diagnostic criteria for AD. These concepts have not been unanimously accepted by specialists in this field and therefore need to be discussed before any other considerations.

Method: Initial meetings were organized between September 2009 and March 2012 to update our knowledge and allow discussions. During these sessions, many questions were raised, such as the clinical validity of the amyloid theory, the practical usefulness of biomarkers, etc. We prepared a list of the 40 key unanswered questions (Q1 to Q19, Table 1) and sent them to the whole expert group in the form of a questionnaire in June 2012. The participants were asked to provide open, unrestricted and motivated answers to each question. The answers were centralized during the subsequent year and two members of the group (JCB & AI) blindly interpreted and structured them into the following categories – see Appendix for a detailed overview:

- agrees completely (A), rather agrees (RA), rather disagrees (RD), disagrees completely (D) for questions 1-3, 5, 15, 18 and 28.
- YES routinely, YES in selected cases, Exceptional and Never for questions 6-

12, 19-25, 29-35.

- More, Less, No comparison for questions 4 and 17.

For questions 13, 14, 16, 26, 27, 36-40 the two raters extracted the information from the unstructured answers separately and blindly. To assess their inter-observer variability we calculated Cohen's kappa coefficient, which showed strong agreement (kappa = 0.838, standard error: 0.0206, 95% CI: 0.797 to 0.878) using the MedCalc software (*MedCalc, MedCalc Software, http://www.medcalc.org/index.php*). Thereafter, a third evaluator (JV), who is not a physician and did not participate in our discussions, blindly rated the discordant classifications. When no agreement could be reached, consensus was used to resolve any remaining disagreement.

The results were shown to the group during subsequent plenary meetings and by email. Each participant was given the opportunity to provide feedback on the results and the written report on several occasions.

Results: Fourteen BeDeCo members answered the questionnaire: four of them work in Flanders, five in Brussels and five in Wallonia. One expert is a geriatrician, one a psychiatrist and all the others are neurologists (86%). Seven of the neurologists work in academic institutions (50%), the others in non-academic practice (50%).

1) *Pertinence of the amyloid theory as a basis for the preclinical diagnosis of AD (Q1)*

   (Figure 1): Three respondents (21%, 1 academic) considered the amyloid theory to be sufficiently robust to be used to elaborate preclinical diagnostic criteria. Overall, five (36%, 3 academic) had a positive opinion of this theory (A + RA). Three (21%, 1 academic) participants completely disagreed with the use of the amyloid hypothesis to elaborate preclinical criteria (Table1).

2) *The pertinence of a diagnosis of AD at the stage of MCI (Q2):* Six respondents (36%, 3 academic) considered that dementia is not necessary for a diagnosis of

AD to be made at the MCI stage; overall, nine participants (64%) were in favor of this possibility (A+RA). Three participants (21%, 1 academic) were completely against this possibility.

3) *Cognitive evaluation vs. biomarker assessment in AD and MCI (Q3, 4, 8, 9, 16 and 17) (Figure 2 & 3):* Eight (57%, 2 academic) considered that a cognitive evaluation is needed to establish a diagnosis of AD dementia. Overall eleven respondents (79%) had a positive opinion of this possibility (A + RA) but one completely disagreed with it**.** Eleven participants (79%, 5 academic) replied that cognitive evaluation is more important than "biological markers" to diagnose AD dementia. None of the respondents considered cognitive evaluation as less important than biological evaluation. It is noteworthy that three respondents considered it impossible to compare cognitive evaluation with biomarker assessment in terms of "more" or "less" because the two methods give different and mutually complementary information.

4) *Current use of biomarkers for the early diagnosis of AD:*

 a) Biomarker assessment at different stages: AD with dementia, MCI, preclinical AD (Q5, 11, 14) (Figure 4):

- For AD with dementia: 100% of the participants classified the cognitive evaluation as the most important assessment. The assessments considered as second in importance were MRI and CSF biomarkers (33% of participants), amyloid PET (25% of participants) and FDG-PET (17%). The third criterion most often cited was FDG-PET and CSF results (42%) followed by amyloid PET (17%) and MRI (8%). No respondents classified genetic testing among the first three most important biomarkers.

- For MCI: in first position came cognitive evaluation (85%), amyloid PET (15%) and MRI and CSF (both 8%): no respondents placed FDG–PET or genetic testing in first position. In second position were MRI and CSF (both 38%), followed by FDG-PET and amyloid PET (both 23%) and cognition (8%); in third position came CSF (46%), FDG–PET (38%) and MRI and amyloid PET (both 15%).

b) *Types of biomarkers used in AD and their classification in order of importance (Q3 to Q7) (Figure 5):* six respondents (43%, 4 academic) stated that they use "biological markers" to diagnose AD in patients with dementia. Twelve participants (86%) had a positive opinion regarding this approach (A + RA); one participant disagreed completely with it. The use of these biomarkers depends critically on their accessibility (amyloid PET, volumetric analyses, ...), the respondent's background (e.g., the rare use of genetic markers in geriatric cases), and personal views. Ten respondents (71%) were positive or rather positive regarding the use of FDG-PET and eight (57%) use CSF analysis (either routinely or in selected cases). Thirteen respondents (93%) use amyloid PET only exceptionally or never (but this method is currently not available outside a few centers and a research environment). Eight respondents (57%, 1 academic) rarely or never use DNA analysis of genes that cause autosomal dominant AD in cases of AD dementia. Eleven (79%) respondents never use analysis of genetic risk factors (like *APOE*).

c) *Types of biomarkers used in MCI and their classification in order of importance (Q8 to Q13) (Figure 6):* all participants indicated that, in terms of clinical importance, NPE is the first marker of AD. Nine respondents (64%) use CSF analysis and 10 (71%) FDG-PET (routinely + selected cases); 13 (93%) rarely

or never use amyloid PET. Eight participants (57%) did not use DNA analysis of causal genes for autosomal dominant AD and 12 (86%) do not use analysis of genetic risk factors (like *APOE*) but two (14%) use them routinely. Two respondents (1 academic) considered that, in terms of clinical importance, NPE is less important than other markers of AD in patients with MCI; eight (57%) considered it to be more important.

d) *The potential use of currently unavailable biomarkers in AD and MCI (Q6 and 12):* in cases of suspected AD, seven respondents (50%, 5 academic), and in cases of suspected MCI, eight (57%, 4 academic), would use "biological markers" if they had access to them. The most cited biomarkers were amyloid-PET (n=9), volumetric MRI (n=2) and CSF markers (n=1) for diagnosis of AD and amyloid PET (n=8), volumetric MRI (n=2) and CSF (n=1) for diagnosis of MCI. Eleven respondents (79%) had a positive opinion of this issue and none had a negative one. Only one respondent had access to all of these biomarkers.

e) *Other biomarkers in AD and MCI (Q5 and Q11):* in addition to the five biomarkers we considered in the questionnaire, some participants also indicated other methods they use for the diagnosis or differential diagnosis of AD, including DAT-scan (n=2), brain perfusion SPECT-scan (n=1), sleep monitoring (n=1), electroencephalography (EEG) (n=1). For the diagnosis of MCI they also indicated using DAT (n=1) and EEG (n= 1).

f) *The specific problem of preclinical diagnosis (Q14 and Q16):* three respondents (21%, 2 academic) stated that they use "biological markers" in cases of preclinical AD; eight (57%) never use this approach.

5) *The new pathological criteria for AD (Q17 and Q18) were not included in this more clinically-oriented study* [13].

6) *The Alzheimer's "lexicon" (Q19):* the stated classifications varied among participants probably, at least partially, because of varying understanding of its finality.

Discussion: Our study shows that recent propositions to modify AD diagnostic criteria have stirred up debate among well-informed and experienced experts in the field. These differences in opinions illustrate how difficult it is to find a uniform means of diagnosing this disease. Of note, different points of view were not related to regional, linguistic or academic differences.

We first inquired about the members' opinions regarding the amyloid theory of AD. In its strongest form, this theory postulates that amyloid deposition is not only the first event in the AD brain but also that amyloid plays a pathogenic role and initiates or at least accelerates other changes, therefore appearing as a potential target for disease modifying therapies [14]. A small majority of our respondents (67%) is skeptical about the amyloid theory being the sole basis for a preclinical diagnosis. Indeed, although converging evidence from basic experimental, genetic and biomarker studies suggests that deposition of toxic Aβ oligomers is the first and crucial event in the pathophysiological cascade process in AD, other possible early pathophysiological events (inflammation, synaptic loss, tau-hyperphosphorylation, microglia activation, etc) may play an equally important role but are currently not widely measured or measurable by biomarkers, precluding their use in current preclinical diagnostic criteria. Moreover, as amyloid deposition is present in 10 to 30% of the elderly without any cognitive impairment, the specificity of this method for diagnosing AD is

low [15]. Nevertheless, demonstrating the presence of excess Aβ in the brain may be helpful, and this is currently the best way to demonstrate, in vivo, the presence of a lesion that is universally accepted as being the hallmark of AD, even if it is not specific for AD or responsible for all the pathogenic alterations. Consistent with this view, the advantages and potential clinical applications of using PET amyloid tracers have recently received positive reviews [16]. Accordingly, amyloid-PET was at the top of the list of methods that the specialists consulted in this study would like to use, if available. However, the experts also felt that they need additional factors to predict progression to the clinical stage of the disease, to assess the temporal characteristics of this process, and to make treatment decisions if new therapies become available. Noteworthy, we considered here biomarkers only as diagnosis tools. In fact, a biomarker could be defined as "a charateristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention" [17]. However, their use as markers of a therapeutical response was limited to the therapeutical trials so far. In order to stay as closer as possible to the clinical practice we considered here only their diagnostic indications.

Despite the availability of at least some biomarkers, most participants (80%) still considered extensive NPE as more important than biological markers for a diagnosis of AD in cases of dementia; the proportion was (unexpectedly) less (60%) in cases of MCI. The finding concerning NPE importance is not surprising because, in accordance with the new criteria, a thorough cognitive evaluation is still required to diagnose both AD dementia and MCI. As the authors of the new neuropathological criteria for AD proposed, only lesions of AD type can be diagnosed biologically, whereas AD as a disease remains a clinical concept [6]. The same approach should

apply to the clinical use of biomarkers, which are seen as techniques to help the clinician to achieve a more accurate diagnosis, not to replace the clinical workup. Most respondents agreed with this view, at least for the diagnosis of MCI (100%); for the diagnosis of AD a minority (20%) expressed some doubts about the need for NPE, probably because in more advanced cases clinical examination alone would be sufficient. These respondents argued that, in these stages, NPE may only be needed when the usual cognitive screening tests (MMSE or Addenbrooke's) are equivocal and/or clinical or MRI findings suggest possible other contributing pathologies (dementia with Lewy bodies, vascular disease). The responses to the survey suggested that a step-by-step pragmatic approach should be used in practice. Generally, a clinical neurological examination and (if necessary detailed) NPE are the first steps in the diagnosis of AD. MRI with axial, sagittal and coronal T1, axial T2 and FLAIR and gradient echo images is used to exclude other structural brain lesions and, if available, to demonstrate hippocampal or (in younger patients) parietal/precuneus regional atrophy. Only when the combination of clinical findings and classical structural neuro-imaging is insufficient for a diagnosis of AD dementia or suggests an atypical presentation of AD, would biomarkers be considered. FDG-PET and CSF biomarkers are proposed for this purpose, especially in younger patients or when other diagnoses, such as frontotemporal dementia, cannot be ruled out. Opinions about the use of biomarkers varied depending on the stage of disease, from 87% in agreement with the use of biomarkers for the diagnosis of MCI and AD dementia to only 20% for use in preclinical stages. Of note, the recent diagnostic criteria warn against a clinical diagnosis of AD at the preclinical stage (used only in research settings) but the participants in this study considered the possibility of applying these diagnostic procedures in specific cases, such as those with a known

mutation in the family and in the context of genetic counseling (Figure 4). The rate of use of different biomarkers in Belgium is dependent on their availability and their reimbursement by the Social Security system. So far, none of the five biomarkers proposed by the recent criteria (CSF amyloid and total-tau & phospho-tau, PET-FDG, PET-amyloid and volumetric MRI) are reimbursed in Belgium and their availability is often restricted to highly specialized centers. The data shown in Figure 5 should, therefore, not be interpreted as a preference of the experts for one marker over another but rather as their choice in a relatively constrained situation. Since their introduction at the end of the 1990s, CSF assays can be performed in some specialized centers in Belgium. About 53% of experts now use CSF markers when diagnosing AD and 60% in MCI patients. The observation of frequent use of FDG-PET scans (about 73% in AD and MCI) is certainly due to its unusually high availability in Belgium; in addition, it is an older, well-standardized method. MRI is widely available in Belgium but usually is only used to exclude other conditions, such as vascular disease. The pattern of atrophy is often appreciated visually by the clinician and the radiologist. Physicians seldom use dedicated atrophy scales, such as Scheltens scale [18]. Although, in expert hands, visual rating scales provide good sensitivity/specificity of about 80–85% in distinguishing AD patients from controls, they seem less useful in MCI patients in whom the mean loss of hippocampal volume is only about 10-15% [19]. Automated or semi-automated rating methods also exist (FreeSurfer, Martinos Center for Biomedical Imaging, Boston, MA, USA, http://surfer.nmr.mgh.harvard.edu/) but they require highly trained technical staff and take too long for routine use. In this study, only about 47% of experts said they use MRI biomarkers. PET using amyloid tracers is the most recent method to be introduced [20, 21] and it is only available in some research settings, so its scarce use in

Belgium should not be interpreted as a lack of interest. As expected, genetic testing is used in selected cases and about 87% of the experts said they never used APOE genotyping as a diagnostic tool. Interestingly, few differences, if any, were observed between the use of biomarkers in MCI and in AD. This is understandable, however, as the requirement for biomarkers is not only driven by the need to reveal early brain changes but also by other reasons, mainly related to the differential diagnosis or to situations that impede the use of a proper cognitive evaluation.

Conclusion: the Belgian experts consulted in this survey were largely in agreement with the new diagnostic criteria for AD, although some concern was expressed about the criteria being too "amyloidocentric". Although clinical examination, including a full NPE, is still considered as the basis for diagnosis, most experts also stated that they use biomarkers to help with diagnosis. This finding is of some concern, because the biomarkers are neither widely available nor reimbursed in Belgium, meaning that only a few patients who attend highly specialized centers can benefit. In the future, the authorities should weigh the cost of these methods against the potential benefit in terms of a correct diagnosis, especially if disease-modifying therapeutic agents become available. The use of biomarkers may be even more helpful in general practice, where the expertise required to make a good clinical and cognitive assessment is less available. In addition, biomarkers are useful not only for early diagnosis but also to differentiate AD from other types of dementia, especially when the presentation is atypical. Finally, in cases where a full cognitive assessment is not possible because of the presence of unrelated pre-existing cognitive deficits, sensory or motor impairment, or different cultural background and/or maternal language, the use of biomarkers is practically unavoidable.

An obvious limitation of this study should be emphasized. Our 14 member sample is

small, but it nevertheless comprised clinical experts representative of all relevant disciplines in the country. That being said, the high levels of expertise of the participants in this survey do not allow an extrapolation to the general practice. In any case, NPS and functional assessments should remain the basis of the diagnosis of AD. A larger overview of the methods used to diagnosis AD in clinical practice in Belgium would be of interest in order to make recommendations about the implementation of the new diagnostic criteria and to establish the place of biomarkers within the diagnostic workup.

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Table 1:
Questions collected from meeting:

Agree or Routinely	Rather agree or Selected	Rather disagree or Exceptional	Disagree or Never	
Q1/ Do you think that the amyloid theory is sufficiently robust to be used to elaborate pre-clinical diagnosis criteria?	3 (21%)	2 (14%)	6 (43%)	3 (21%)
Q2/ Do you think that current knowledge is sufficient to allow a diagnosis of AD to be made before any dementia at an MCI stage?	6 (43%)	3 (21%)	2 (14%)	3 (21%)
Q3/ Do you think that an NPE is needed when diagnosing AD?	8 (57%)	3 (21%)	2 (14%)	1 (7%)
Q4/ Is an NPE more or less important than "biologic markers" in the diagnosis of AD?	**More** **11 (79%)**	**No comparison** **3 (21%)**		**Less** **0**
Q5/ Do you use "biologic markers" in the presence of dementia to diagnose AD?	6 (43%)	6 (43%)	1 (7%)	1 (7%)
CSF analysis	5 (36%)	3 (21%)	3 (21%)	3 (21%)
Amyloid PET-scan:	1 (7%)	0	1 (7%)	12 (86%)
FDG-Pet scan:	7 (50%)	3 (21%)	1 (7%)	3 (21%)
Volumetric MRI:	6 (43%)	1 (7%)	1 (7%)	6 (43%)
Genetic analysis (PS1&2-APP):	2 (14%)	4 (29%)	3 (21%)	5 (36%)
Genetic analysis (ApoE, ...):	1 (7%)	0	2 (14%)	11 (79%)
Other:	**6 (43%) rather (2 agree – 4 disagree)** (2 DATscan, 1 SPECT, 1 EEG, 1 AD Sleep monitoring)			**4 (29%)**
Q6/ Would you use one of these biologic markers (that you don't currently use) if you had access to it?	7 (50%)	4 (29%)	0	0
Q7/ Classify the markers (including cognitive evaluation) in order of clinical importance for diagnosis of AD.	**When done, Neuropsychological evaluation (NPE) is first for all**			
Q8/ Do you think that anNPE is needed when assessing for MCI?	14 (100%)	0	0	0
Q9/ Which cognitive profiles are the most accurate for the diagnosis?	2 (14%) any	2 (14%) amnesic + atypical		10 (71%) amn
Q10/ Is an NPE more or less important than "biologic markers" for diagnosis.	8 (57%)	**No comparison** **5 (36%)**		1 (7%)
Q11/ Do you use "biological markers" in the presence of MCI to diagnose AD?	9 (64%)	3 (21%)	0	2 (14%)
CSF analysis	5 (36%)	4 (29%)	1 (7%)	4 (29%)
Amyloid PET-scan:	1 (7%)	0	1 (7%)	12 (86%)
FDG-Pet scan:	8 (57%)	2 (14%)	1 (7%)	3 (21%)
Volumetric MRI:	7 (50%)	0	0	7 (50%)
Genetic analysis (PS1&2-APP):	2 (14%)	4 (29%)	0	8 (57%)
Genetic analysis (ApoE, ...):	2 (14%)	0	0	12 (86%)
Other:	**3 (2 rather) (21%) Agree** (1 DATscan, 1 EEG, 1 Sleep monitoring)			**4 (29%)**
Q12/ Would you use one of these "biological markers" (that you don't currently use) if you had easy access to it?	8 (57%)	3 (21%)	1 (7%)	1 (7%)
Q13/ Classify the markers (including NPE) in order of clinical importance for assessing for a diagnosis of AD.	**When done, NPE is first for 8 but not for 2**			
Q14/ Do you use "biological markers" to assess for a diagnosis of AD at a preclinical stage?	3 (21%)	0	3 (21%)	8 (57%)
CSF analysis	2 (14%)	0	1 (7%)	11 (79%)
Amyloid PET-scan:	0	0	0	14 (100%)
FDG-Pet scan:	2 (14%)	0	1 (7%)	11 (79%)
Volumetric MRI:	1 (7%)	0	0	13 (94%)
Genetic analysis (PS1&2-APP):	1 (7%)	0	3 (21%)	10 (71%)
Genetic analysis (ApoE, ...):	0	0	0	14 (100%)
Other:	**2 (1 rather) agree** (Amyloid PET)			**4 (29%)**
Q15/ Would you use one of these "biological markers" (that you don't currently use) if you had easy access to it?	4 (29%) (Amyloid PET)	0	0	5 (36%)
Q16/ Classify the markers (including NPE) in order of clinical importance when assessing for a diagnosis of AD at a preclinical stage.	**Not unambiguous**			
Q17/ What is your opinion regarding the new anatomopathological classification of AD?	**Not unambiguous**			
Q18/ What reflection does this suggest to you?	**Not unambiguous**			
Q19/ State which Alzheimer's "lexicon" seems most accurate	**Not unambiguous**			

Appendix

Category definition:

Agrees (A): the expert agrees fully and without reserve with the assertion and he/she applies/advises it

Rather agrees (RA): the expert agrees partially and with some reserve with the assertion and he/she applies/or advises it in a majority of cases in his/her practice

Rather disagrees (RD): the expert agrees only with some aspects of the assertion and he/she only applies/or advises it in a minority of cases in his/her practice

Disagrees (D): the expert disagrees totally with the assertion and he/she does not apply/or advice it in practice

Figure 1

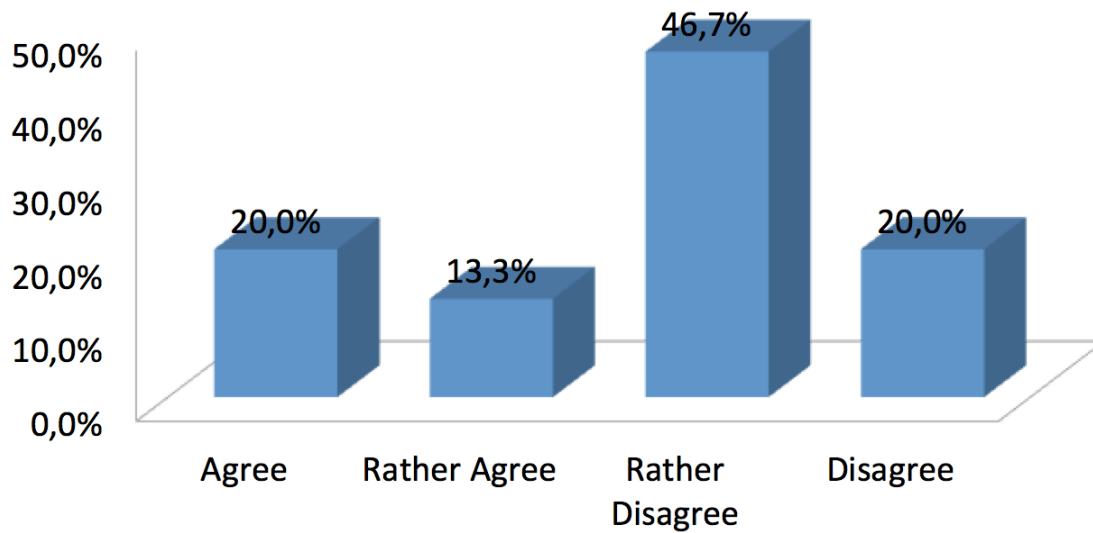## Q1 : Amyloid theory as a basis for the preclinical diagnosis

Figure 2

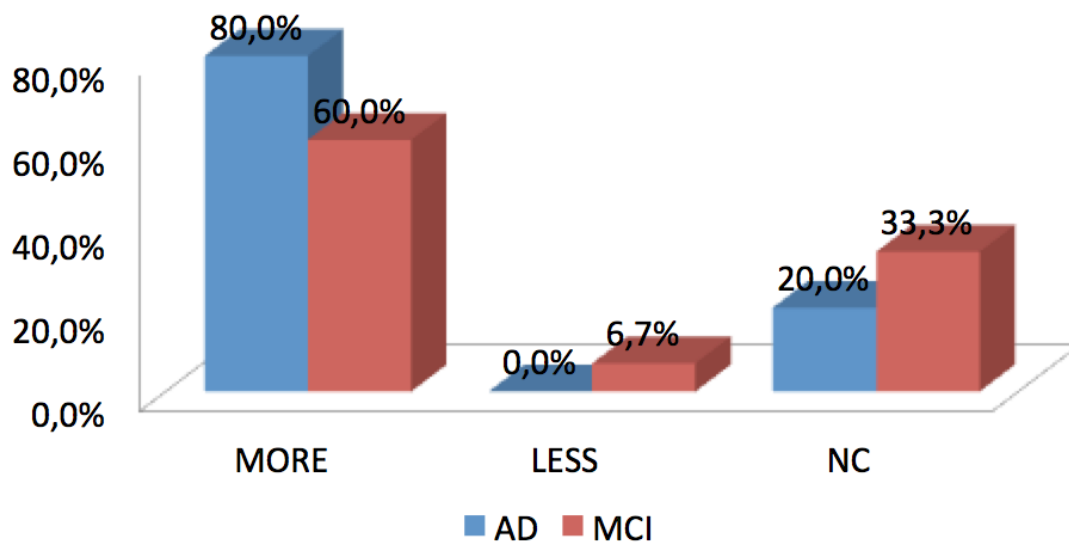## Q4 & 10 : Is cognitive evaluation more important than biomarker ?

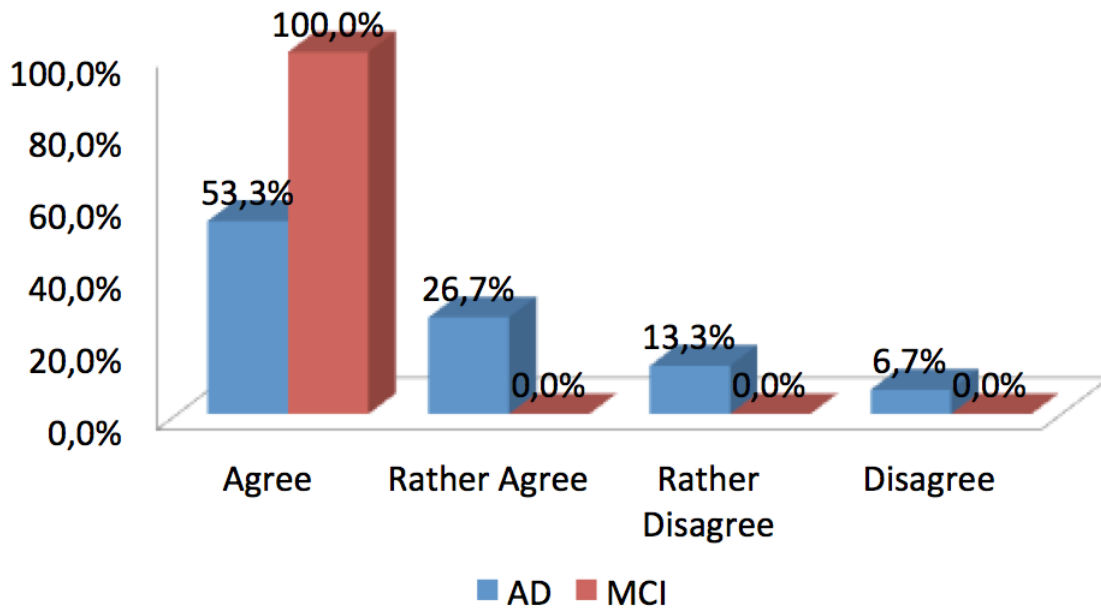Figure 3

Q3 & 8 : The necessity of a cognitive evaluation

Figure 4
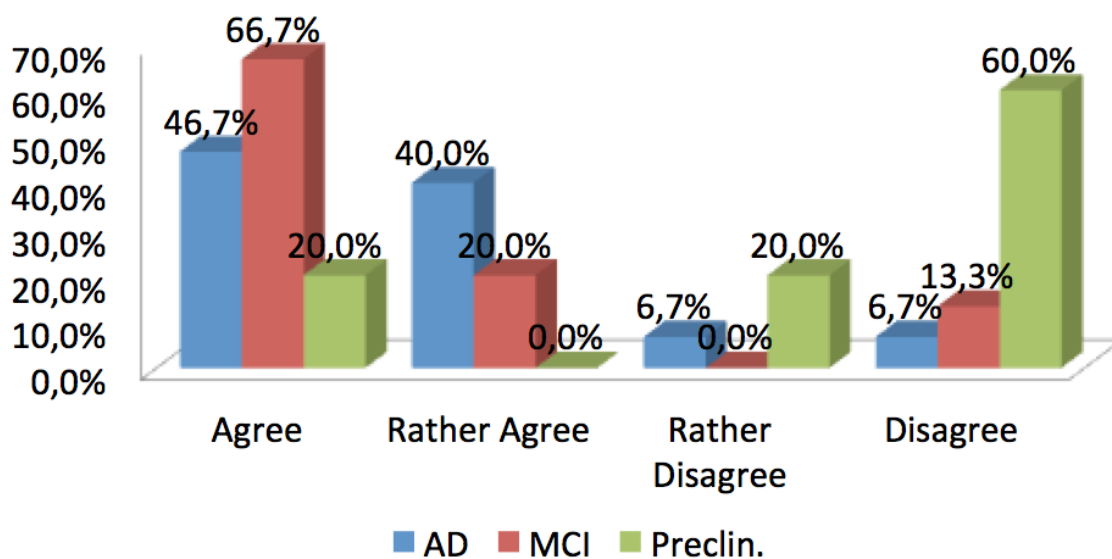
Q5,11&14 : Biomarker assessment at different stages

Figure 5

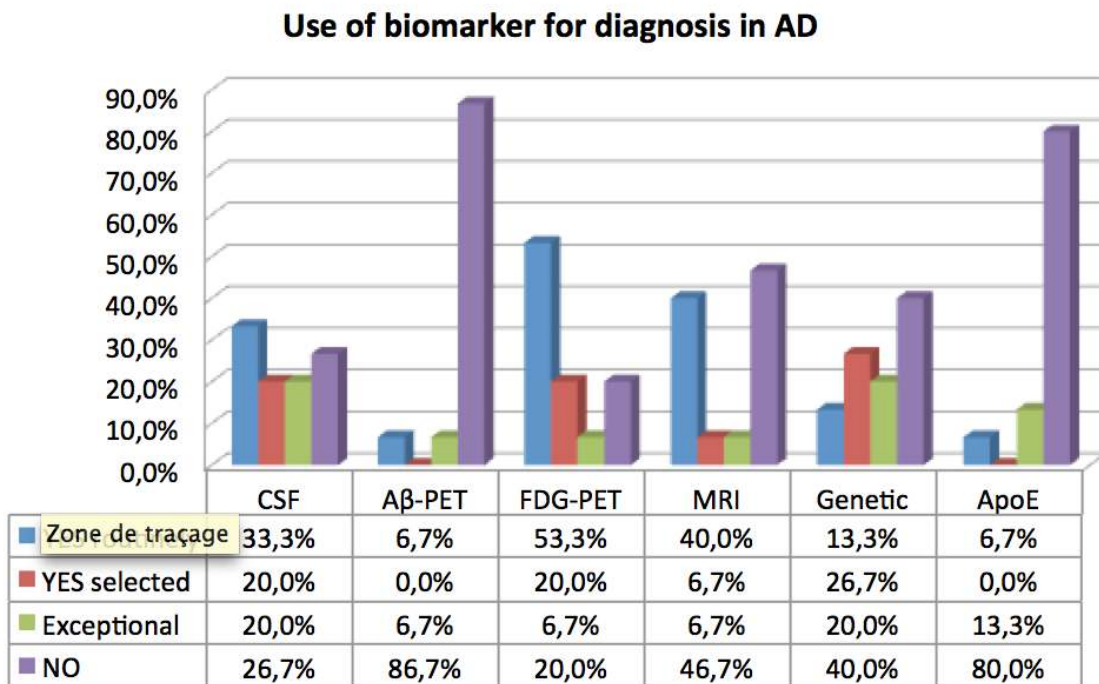## Use of biomarker for diagnosis in AD

	CSF	Aβ-PET	FDG-PET	MRI	Genetic	ApoE
Zone de traçage	33,3%	6,7%	53,3%	40,0%	13,3%	6,7%
YES selected	20,0%	0,0%	20,0%	6,7%	26,7%	0,0%
Exceptional	20,0%	6,7%	6,7%	6,7%	20,0%	13,3%
NO	26,7%	86,7%	20,0%	46,7%	40,0%	80,0%

Figure 6

Use of biomarker for diagnosis in MCI

	CSF	Aβ-PET	FDG-PET	MRI	Genetic	ApoE
YES routinely	33,3%	6,7%	60,0%	46,7%	13,3%	13,3%
YES selected	26,7%	0,0%	13,3%	0,0%	26,7%	0,0%
Exceptional	6,7%	6,7%	6,7%	0,0%	6,7%	0,0%
NO	33,3%	86,7%	20,0%	53,3%	53,3%	86,7%