Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

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Abstract (175)

In 2018, the National Institute of Aging and the Alzheimer Association proposed a purely biological definition of Alzheimer's disease (AD) relying on biomarkers. While the intended use of the framework was for research purposes, it has engendered debate and challenges regarding its application in everyday clinical practice. For instance, cognitively unimpaired individuals may have biomarker evidence of both amyloid and tau pathology, but may never develop clinical manifestations in their lifetime. Furthermore, a positive AD pattern may be observed in other brain diseases where AD pathology is present as co-morbidity. In this Personal View, the international Working Group (IWG) presents what we consider to be the current limitations of biomarkers in the diagnosis of AD, and on the basis of this evidence we propose recommendations for how biomarkers should and should not be used for diagnosis of AD in a clinical setting. We recommend that AD diagnosis be restricted to the occurrence of positive biomarkers together with specific AD phenotypes, whereas biomarker positive cognitively unimpaired individuals should be considered only at-risk for progression to AD.

"Search strategy" box. Search strategy and selection criteria for this Review were identified by searches of PubMed between January 1st 2018 and July 1st 2020, and references from relevant articles. The search terms "biomarker", "amyloid", "tau", "neurodegeneration", "preclinical", "CSF", "PET", "subjective cognitive decline" in the context of "Alzheimer's disease" and "ATN classification" were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review. This Review identifies conceptual and practical limitations of its utility and appropriateness for application in clinical practice. ---------

Introduction

In 2018, the National Institute of Aging (NIA) and the Alzheimer Association (AA) proposed the amyloid, tau, neurodegeneration (ATN) research framework for the definition and diagnosis of Alzheimer's disease (AD)[1]. This framework has enabled the move from a clinical-biological diagnosis to a purely biological definition of AD that can be applied in both the asymptomatic and symptomatic stages of the disease. The increased accessibility to biomarkers and the perspective to have blood-based information on the underlying pathophysiological process in the future make it necessary to consider the limitations of biomarkers in the diagnosis of AD and to propose recommendations for how these biomarkers might and might not be used for the diagnosis of AD in a clinical setting.

I - Evolution of the diagnostic frameworks for Alzheimer's disease

Over the last 15 years, there has been a remarkable evolution in the development and availability of in-vivo AD biomarkers, in the characterization of the natural history of the disease, and in turn in the application of this new knowledge to revised diagnostic research frameworks for AD (see Table 1). The first revision to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria[2] was provided by the International Working Group (IWG) in 2007[3]. It was the first research framework to propose AD as a clinical-biological entity based on in-vivo biomarkers with specific clinical phenotypes of AD and to extend the definition to the prodromal (predementia) dementia stages. In 2010, the IWG introduced a new supporting lexicon for AD with recommendations in the classification of the preclinical stages without symptoms[4] including a) "asymptomatic at-risk" for those with biomarker evidence of Alzheimer pathology; b) "presymptomatic" for those carrying monogenic AD mutations[4]. The next important development

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occurred in 2011 with the NIA-AA criteria that defined three different preclinical stages, according to the amyloid cascade hypothesis: amyloid lesions first, then tau pathology causing neurodegeneration, and finally occurrence of subtle cognitive changes[5,6]. In 2016, an IWG and NIA-AA consensus advanced the classification scheme to include AD for research purposes diagnosed at a preclinical stage of the disease, on the presence of both in-vivo amyloid and tau positivity "where the risk of a further progression to clinical AD is high"[7], a proposal that was further developed by Jack and collaborators[1,8]. In the latest 2018 NIA-AA diagnostic framework, AD diagnosis is centred exclusively around a biomarker definition of disease according to ATN status[1]. Even in the absence of any cognitive symptoms, those subjects having both abnormal amyloid and tau biomarkers (A+T+) were defined as 'Alzheimer's disease'.

The development of 'positive' in-vivo biomarkers has moved the field from diagnosing AD at the dementia stage, towards earlier AD diagnosis at the prodromal stage, and have introduced the potential for preclinical diagnosis. These developments are particularly relevant in advancing testable therapeutic hypotheses towards secondary prevention of AD.

II - Limitations of a purely biological definition of AD

These 2016 consensus meeting and 2018 criteria[1,7] have engendered significant debate about applying a biomarker-based disease diagnosis, with clinical symptoms and phenotype being used only for staging[9,10]. Four years after their introduction, a reevaluation of a diagnostic approach based only on biological markers is warranted, both on conceptual and evidence-based practical levels.

Risk of confusion between presence of brain lesions and disease

Based on A/T/N definition, AD may be considered as a purely biological condition, dissociated from a clinical component or patient status. By dissociating AD from a clinical phenotype, the disease equates to AD neuropathologic changes, whereas in 2012, neuropathologists stated that "There is consensus to disentangle the clinicopathologic[al] term 'Alzheimer's disease' from [Alzheimer's disease] neuropathologic[al] change"[11]. As a consequence, it provides a classification, which gathers under the same label - AD - an extended continuum from cognitively normal individuals to severely demented patients.

Low predictive accuracy (Panel 1)

A major limitation of a purely biological definition of AD is the lack of predictive accuracy. Several recent studies indicate that the presence of tau and amyloid positivity is insufficient to definitively predict the invariable occurrence of symptoms (mild cognitive impairment [MCI] or dementia) in those subjects without clinical impairment (evidence is summarized in Panel 1). Another challenge to a biomarker-only diagnosis of AD is that the presence in-vivo of biomarkers of AD lesions may not certify the existence of AD as the primary diagnosis: such lesions are a frequent co-pathology in other neurodegenerative diseases, dementia with Lewy bodies (DLB) being most frequent[12]. These patients should not be considered as having a primary diagnosis of AD. These exemplars of co-pathologies will create potential confusion for those receiving a biomarker-based diagnosis in such circumstances.

Presence of other pathologies

Conversely, neuropathologically-defined AD is frequently associated with other pathologies. Pure AD pathology is the exception rather than the rule in autopsy cases (~3-30% of cases according to age[12]). AD, as described years ago in its "pure" form, is a model that may not apply especially in late-life dementia where multiple proteinopathies are more frequent. Co-

pathologies, including synucleinopathy, vascular pathology, non-AD tauopathies - in particular argyrophilic grain disease and cortical aging-related tau astrogliopathy - and TAR DNA binding protein 43 (TDP-43) pathology - in particular limbic-predominant age-related TDP-43 encephalopathy [LATE] neuropathological changes – influence significantly both clinical trajectory and phenotypes of AD (~50-60% of dementia of the Alzheimer type cases are estimated to be attributable to these co-pathologies)[12–16]. Unfortunately, pathological biomarkers are currently unavailable for the non-AD proteinopathies, and disentangling AD from non-AD neurodegenerative diseases remains phenotypic or cannot be achieved in life.

Uncertainty regarding the pathogenesis model of AD

The biological model that supports the A/T/N classification opens up the possibility for research into the biological changes prior to the onset of symptoms, which is necessary to develop drugs for the earliest stage. Advocates for a biological definition of AD often refer to the cancer model where a long asymptomatic phase of the disease can exist and where all affected patients, located anywhere along this disease continuum, will benefit from the same therapeutic approach even at a preclinical stage. However, the follow-up of cognitively unimpaired biomarker positive individuals suggests that they do not all progress overtime. At the present time, the determination of whether AD fits better with the long and asymptomatic 'prostate cancer' continuum or with an at-risk model of the disease (where the asymptomatic (A+T+) would be the at-risk state, i.e. the precancerous condition, and where clinical phenotype would be the disease state, i.e. the cancer state) is not yet determined.

Finally, defining the disease by its pathological lesions only - and not by a clinical phenotype - leads to the risk of creating confusion particularly within the healthy oldest old where memory complaints and low levels of AD pathology are the rule[17,18]. Publications in the field of dementia,

which propose that the disease is a myth[19] or a decoy[20], illustrate the potential for confusion between AD and old age.

Taken together, these data indicate that amyloid and tau biomarkers are not sufficient to confidently predict the trajectory towards prodromal AD or AD dementia to define the AD continuum without clinical input. The relationships between co-occurrence of tau and amyloid pathology on the one hand, and the development of cognitive decline and neurodegeneration on the other hand remain uncertain at an individual level. Besides the dominating amyloid cascade model, additional pathogenesis models have been advanced, including the role of endosomal recycling deficiency[21], of immunity, of lipid metabolism and endocytosis deficiency[22], of vascular dysfunction[23], etc.

Difficulty in classifying cognitively unimpaired biomarker positive subjects (Panel 2)

The challenge to a purely biological definition of AD is mostly centred on the preclinical stage of the disease, i.e. in conditions where, by definition, cognitive testing does not support the presence of an AD phenotype. In case of symptomatic patients, the identification of the specific clinical phenotype (interfering or not with independence in everyday activities) is a major step for the diagnosis as it expresses the brain dysfunction that the biomarkers are signalling. Cognitively unimpaired individuals with biomarker positivity are not invariably doomed to subsequent cognitive decline: the best current estimates of lifetime dementia risk range from 5% to 42%[24]. Because of the uncertainty of their evolution over time (Panel 1), asymptomatic individuals who are biomarker positive should be classified as "at-risk for progression" - ARP - distinguishing two different subgroups for clinical and research purposes:

A) Some individuals will remain stable over long periods of time: this subgroup includes people who may never develop symptoms. These persons may compensate and maintain normal

functioning for many years even in the presence of an on-going neurodegenerative process, or some may have no accelerated neurodegeneration despite AD brain lesions.[25]

B) Other will progress: this subgroup includes individuals who demonstrate signs of accelerated neurodegeneration and whose compensatory mechanisms are overcome. They can be reliably predicted to progress to prodromal AD and AD dementia in the future.

For research purposes, both subgroups have to be separated in order to define factors of prevention and to develop algorithms to predict progression. This risk of progression depends on several modulating factors whose magnitude and interactions still remain to be determined (see Panel 2). These factors are either risk markers or risk factors and are related to brain resilience (e.g. cognitive reserve) and resistance[25], biological and genetic factors that are directly related to the amyloid, tau, and their neurodegeneration-induced pathways (genetic protection and risk factors regarding tau binding proteins and amyloid precursor protein metabolism; protection and risk factors related to immunity, endocytosis, and lipid metabolism[26–30]; newly described brain cellular senescence mechanisms[31]), and co-pathology. For instance, is a 60-year-old *APOE* ε4 carrier with a negative tau PET and an amyloid PET scan just below the threshold at less risk than an 85-year-old who is A+T+ with cerebrovascular lesions on MRI? We anticipate the emergence of age- and risk factor-adjusted individualized predictions and the ability to rank the risk by analogy with the example of cardiovascular risk factors[32]. Such modelling is in its early stages but exemplified through the example of age adjusted polygenic hazard scores[33]. However, disclosing individual patient-level risk with the current state of knowledge is premature and to be avoided as current individualized prediction models perform insufficiently well in cognitively unimpaired subjects compared to those in the prodromal stage of AD[34]. Besides conceptual issues, there are several practical aspects that may limit the use of biomarkers for the pure

biologically-based diagnosis of AD. They concern the thresholds, generalization, metric performance, accessibility, amongst others.

Biomarker thresholds

A biological diagnosis of AD that is linked to positive biomarkers brings the invariable need to define and be certain about thresholds and cut-off points of positivity, as any modification of these thresholds would significantly impact both the diagnosis and the stages of the disease. The clear-cut separation between negative and positive subjects in relation to a given biomarker is somewhat artificial and different from one site or one study to another. Factors contributing to this uncertainty include the specifics of the biomarker used as well as the threshold determination. Most of all, this binary threshold does not reflect the reality of amyloid and tau pathology which is continuous and present at a minimal level in almost all the aging population[18], with important discrepancies between pathology burden and clinical symptoms at intermediate levels (Panel 1). It is noteworthy that neuropathology criteria of AD provide no cut-off for establishing AD but only define 'low, intermediate or high' levels of AD neuropathologic change[11].

For amyloid biomarkers, the use of binary thresholds of amyloid PET standard uptake value ratio (SUVR) has long restricted the measure of amyloid to intermediate and high levels of amyloid deposition [35].The use of different amyloid PET tracers is also a known factor of variability in measurements, though the centiloid quantification approach helps at diminishing its impact[36]. Recent works (using the centiloid scale or longitudinal amyloid PET) open the possibility to identify earlier stages of amyloid accumulation[37,38]. In CSF, a positive amyloid measure despite a negative amyloid PET or the use of novel biomarkers (for instance, CSF Aβ34/42 ratio[39]) might also prove to be reliable biomarkers of early amyloid deposition stages[39,40].

For tau biomarkers, there is also a strong discrepancy between neuropathological identification (in post-mortem studies, the presence of tau Braak stages I-II is almost universal after the age 70)[18,41] and in-vivo measures of tau aggregates on PET (~36% of (T+) detected after the age of 70[42]). The current in-vivo definition ability of tau PET to detect 'tau positivity' using flortaucipir PET seems to correspond only to widespread tau pathology in the brain (i.e. Braak stages $\geq$IV)[43], while CSF phospho-tau (p-tau) elevation may reflect earlier stages of tauopathy[44]. In the near future it might become possible to have in-vivo tau measurements that detect very early tau deposits, i.e. tau Braak stages I-II with 2^d generation tau PET tracers or by detecting other phosphorylated species of tau such as p-tau 217 in the CSF or the plasma[45].

In clinical practice, such an extension to "earlier" thresholds in amyloid or tau biomarkers may lengthen the duration of the asymptomatic stages and decrease the lifetime clinical progression probability. Biomarkers thresholds also depend on the intended use and no consensus on the context of use is currently available[1].

On the other hand, evaluating cognitive changes and determining the stages in patients with AD (i.e. identification of objective cognitive impairment, MCI or dementia) also raise threshold issues. The emergence of lower thresholds in cognitive testing to define the 'objective subtle cognitive changes' entity further extends the clinical stages of neurodegenerative diseases, before the occurrence of MCI[6]. However, this increased sensitivity in the detection of cognitive decline comes at the expense of a reduced specificity, and numerous other etiologies can be responsible for the observed changes, such as personality traits, psychiatric disorders, and sleep apnea amongst others[46].

Generalization and accessibility in clinical practice

Considering general medical practice and standard of care, the six currently available Cochrane reviews regarding the use of CSF or amyloid PET biomarkers have consistently led to the same

conclusion: "we cannot recommend the routine use of [these biomarkers] in clinical practice"[47–52]. These reviews considered the ability of-biomarkers to predict the future occurrence of clinical AD dementia in patients with MCI. Their recommendation answers the pragmatic question in clinical practice: "will my patient decline?". As underscored by the Cochrane reviews, the prognostic value of biomarker diagnosis remains limited by the fact that 1) there is a high variability of decline rate amongst biomarker-positive AD patients[53] and 2) non-AD neurodegenerative diseases contribute to cognitive decline. The Cochrane reviews further point out the "the heterogeneity in the conduct and interpretation of the biomarkers and the lack of defined thresholds for determination of test positivity". The choice of lower or higher biomarker thresholds correspond to earlier or later pathological burden and may change the duration of the asymptomatic stages and decrease the lifetime clinical progression probability. Finally, the Cochrane reviews underline the high financial cost of PET exams and the invasiveness of CSF measurements, which limit their interest and applicability in clinical practice, especially in low-income countries.

While these limitations were highlighted for patients with MCI, but data are even more sparce for cognitively unimpaired individuals as available currently models are lacking in the clinical setting, especially in cognitively unimpaired subjects. As seen in Panel 1, the magnitude effect of biomarker positivity on clinical progression remains weak to moderate and was established on selected volunteers from research cohorts. The generalization of these cohort findings to clinical practice also faces several obstacles: the risk of attrition bias from these data is strong, especially in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort with many individuals lost to follow-up[54], and the risk of selection bias is even stronger since individuals included in these longitudinal cohorts were usually selected by advertisement and do not represent the variety of individuals in clinical practice to whom the biomarker investigations will be applied.

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An increasing number of persons now seek consultation in memory clinics complaining of subjective memory problems or cognitive decline (SCD) while scoring normally on formal cognitive testing. SCD may be a risk factor of clinical progression[55] but the magnitude of prediction ability of SCD regarding cognitive decline remains low (OR ~1.5-3[56]). SCD may result from many factors besides aging: anxiety, depression, fatigue, sleep disorders, attention deficits, and drug side effects amongst others[57]. In this regard, it is noteworthy that the frequency of CSF AD profiles between those with normal cognition and SMC is similar[58]. The heterogeneity of this population is important according to the nature of complaint (self-report versus report by an informant) and to the cognitive status (normal cognition versus subtle cognitive changes)[17].

Other individuals do not report cognitive problems and may be just worried about future cognitive decline due to family history, results from commercial direct-to-consumer genetic testing or *APOE* status, or simply concerned about preserving their memory and general cognitive abilities (sometimes referred to as "worried well" patients). Such individuals are seeking to understand their risk and their future. They represent up to 20-30% of new patients in some specialty memory clinics[59–61] and in some of these cases, biomarker investigations may have been performed. In these situations, reliance on a biomarker-only diagnosis would require a very secure and tightly elaborated natural history connecting the positivity of biomarkers with an invariable - or at least extremely high probability of - subsequent expression of clinical symptoms. This is not the case today. Recent experience with the Sokrates study underscores some of the uncertainties (e.g. inability to make an accurate short- or medium-term prediction about cognitive decline for an individual), which are inherent in revealing amyloid PET results alone to cognitively unimpaired individuals[62]. This issue also applies for patients who may

undergo a work-up for other medical conditions where AD biomarkers are included in the absence of any clinical context, and are positive[63].

As a whole, evidence for the use of biomarkers in clinical practice remains highly disputed and suffers from a lack of evidence-based data to recommend biomarker assessments for those with subjective memory complaints (SMC).

Ethical concerns

Diagnostic disclosure is ethically challenging when physicians inform cognitively unimpaired individuals that they have an irreversible disease based on biomarkers when the clinical trajectory towards prodromal AD or AD dementia is uncertain and where there is no way to significantly prevent the development of symptoms in the absence of modifiable risk factors or specific therapies[64]. Disclosing biomarker results and the related risk profile should be seen as different from disease diagnosis disclosure. Within the lay community, AD is amongst the most feared diseases given its outcomes including profound disability and loss of personal dignity[65]. A discourse by physicians where AD equates AD neuropathological changes is profoundly discrepant with patients' narratives where AD equates dementia, dependency, and death, and this can adversely impact the therapeutic alliance[9]. In the future, being said to be 'at-risk for progression' instead of 'in the preclinical stage of AD' may help in the discussion of the 'Risk-Benefit balance' regarding a putative treatment and its side effects.

III- The IWG recommendations for the clinical setting

Based on this evidence, the IWG proposes the following recommendations:

1. The diagnosis of AD is **clinical-biological**. It requires the presence of both a specific clinical phenotype of AD (P+) and biomarker evidence of AD pathology (A+T+).

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2. Specific clinical phenotype commonly associated with AD pathology (common AD phenotypes) are: the amnestic syndrome of the hippocampal type[66](typical), the posterior cortical atrophy variant[67], and the logopenic variant primary progressive aphasia[68,69] (Supplementary Figure 1). Other phenotypes, including the behavioural/dysexecutive variant[70,71], the cortico-basal variant[72,73], and the other variants of primary progressive aphasia [69,74] (Supplementary Figure 1), are less commonly related to AD pathology (uncommon AD phenotypes). These phenotypes may or may not interfere with independence in everyday activities.

3. With these common phenotypes, amyloid, and tau biomarkers positivity establishes an AD diagnosis (Table 2). The positivity of **both** amyloid and tau biomarkers is required because an amnestic phenotype with only amyloid positivity is not specific to AD, being observed in other neurodegenerative diseases with amyloid co-pathology, including LATE, DLB, etc[1,12,75] or in patients with cerebral amyloid angiopathy and amnestic vascular cognitive impairment[76] (Supplementary Figure 1). On the other hand, an isolated amnestic syndrome of the hippocampal type with only tau biomarker positivity can be encountered in primary age-related tauopathy (PART)[77,78] or in atypical presentations of mixed 3R/4R frontotemporal lobar degeneration (FTLD) tau[75,79] (Supplementary Figure 1). Finally, uncommon phenotypes with positive AD biomarkers should not be a priori classified as an established AD (Table 2): in such cases the clinician may deem that AD is not the dominant pathology driving the clinical phenotype but only a copathology.

4. Recommended biomarker measures for amyloid pathology are low CSF Aβ42, increased CSF Aβ40/42 ratio (which is, if possible, preferred to low CSF Aβ42), or increased tracer retention in amyloid PET; for tau pathology, we recommend high CSF p-tau (not total tau

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[t-tau] due to its lack of specificity[80]) or increased ligand retention in tau PET. Amyloid

and tau PET recommendation for use in clinical practice is conditional on regulatory

approval and reimbursement by payers in different countries.

5. Diagnosis conclusion requires clinician expertise in both the critically assessment of

    clinical and biomarker results. The different situations encountered in clinical practice are

    summarized in Table 2. In the case of cognitive testing and/or biomarkers in the 'grey

    zone', it may be useful to complete the workup with another investigation (repeated

    measure of pathophysiological biomarker, clinical follow-up, use of neurodegeneration

    biomarkers such as FDG-PET, etc).

6. CSF investigation is prioritized as it provides simultaneous information on the 2 types of

    biomarkers (amyloid and tau) and is less expensive than amyloid-PET and/or tau-PET.

    Where lumbar puncture is contraindicated, PET investigations are an alternative

    consideration.

7. In clinical practice, plasma biomarkers for amyloid and tau pathology are not currently

    recommended. Although promising, they require further standardization and validation

    before they can be broadly regarded as secure biomarker evidence of AD pathology

    $(A+T+)$[45,81].

8. In clinical practice, the investigation of pathophysiological biomarkers in cognitively

    unimpaired individuals is not recommended, given their current inability to predict

    reliable clinical trajectories of those who are asymptomatic with biomarker positive status

    $(A+T+)$. In the future, if therapies or prevention programs show significant efficacy in

    delaying onset of disease it will probably change the need for biomarker investigations in

these individuals, although the problem of the prediction of clinical trajectories in cognitively unimpaired biomarker positive individuals will still remain.

9. In cases where a biomarker investigation is performed in cognitively unimpaired individuals (for any specific situations: will to know, brain health services, expert centres, research project, cohort study, diagnostic workup for other conditions…), a risk stratification of biomarkers is proposed (Panel 3) distinguishing an absolute risk group (carriers of autosomal dominant monogenic mutations for AD)[82], a high-risk group[42], and an undefined risk group, to be further clarified in the future as additional evidence accrues[55,83,84]. The proposed stratification is a starting point for research purposes. Validation studies on large cohorts with long periods of follow-up are needed. The challenge for the future is to reliably and predictably define the level of risk for further progression.

    In these situations, subjects should be counselled before AD biomarker investigation so that they can be informed of the ins and outs of the test results and can decide whether or not the result will be disclosed. If they decide to receive the results and they return positive, subjects should be counselled that they are at-risk for subsequent clinical progression (ARP) to prodromal AD or AD dementia and not clinically diagnosed as having AD.

10. SMC and SCD, when isolated and not supported by objective cognitive impairment, are not specific enough to be considered as part of the AD phenotype[85]. In cognitively unimpaired individuals, self-reported complaints and complaints reported by an informant should be clearly distinguished as the latter are more at-risk of progression[86] and merit a closer follow-up with regular clinical and neuropsychological evaluations.

11. Alzheimer's <u>disease</u> can be associated with other brain pathologies, including synucleinopathy[28], vascular pathology, non-AD tauopathies, and TDP-43 pathology[12–15]. Alternatively, <u>lesions</u> of the Alzheimer type are frequently observed as co-pathology in post-mortem examination of other neurodegenerative diseases[12,69,71]. In both situations, pathophysiological AD biomarkers can be positive[87]. This is particularly ambiguous in the case of behavioural variant frontotemporal dementia (bvFTD), cortico-basal syndrome (CBS), semantic or non-fluent variants of primary progressive aphasia where the presence of positive AD biomarkers can be considered either as AD co-pathology or atypical forms of AD[69,71,73,74] (Supplementary Figure 1). In all these situations, it is recommended that the physician relies more on the phenotype and follow-up to determine the final diagnosis (AD or co-pathology) (Table 2). In some complex cases, only post-mortem evaluation will provide definitive information.

12. It is recommended that the physician objectively evaluates the added-value of biomarker investigation for each symptomatic patient according to the clinical situation (age, risk of comorbidity, complexity of the phenotype), the life context, the wishes of the patient to know the most likely diagnosis, the possibility to participate in a disease-modifying trial, and more globally the appreciation of how exactly this information will change the management of the patient. Biomarker investigations may also be limited by the availability, cost, and health care payment coverage of biomarkers across countries and centres as well as clinical situations.

13. When pathophysiological biomarkers are not available, patients should have a clinical syndromic diagnosis: 'amnestic AD phenotype' or 'logopenic variant primary progressive aphasia' etc (P+ with A and T unknown), where staging (MCI or dementia) may still be applied. In these situations, more attention should be given to rule out non-degenerative

causes[75]. If a positive neurodegeneration biomarker (FDG-PET hypometabolism, T1-MRI

atrophy, CSF NFL, etc) is associated with a common AD phenotype, the term

'neurodegenerative disease of Alzheimer type' can be used (Table 2).

Conclusion

While the definition of AD based exclusively on biological markers has gained significant

traction in research settings, emerging studies suggest that the biomarker definition is not ready

for application in clinical settings and for diagnosis of individuals without cognitive impairment.

The evidence of the natural history of those asymptomatic at-risk with positive biological

markers is insufficient to predict subsequent cognitive decline and dementia. In light of these

findings, we provide recommendations for diagnosis and disclosure in the clinical setting which

avoid labelling AD in individuals who are biomarker positive and cognitively unimpaired and

who are at-risk for progression to prodromal AD or AD dementia. We recommend that the

diagnosis of AD in the clinical setting remains tied to the clinical phenotypic presentation.

There are several critical requirements to achieve the utility of biomarkers to predict progression

to clinical stages of AD. The first is the relationship between pathological burden, biomarker

thresholds, and the respective impact and weight of modulating factors in relation to future risk of

clinical progression. The second concerns the pathogenesis of AD itself. As detailed above, data

suggest that AD may result not only from tau and amyloid pathologies but from synergy and

interactions among these pathologies which lead to the highest stages of protein accumulation,

the highest rates of cognitive decline. Investigating such synergies and understanding protective

factors in those who are asymptomatic with biomarkers of AD pathology represent both a

direction to better define the disease and to prevent it in the future.

Glossary of terms

Alzheimer's disease: a clinico-biological entity defined by a specific clinical phenotype (either typical or atypical) associated with in-vivo evidence of Alzheimer's pathology

Alzheimer's pathology: can be approached today in-vivo by biomarkers of amyloid pathology (decreased Aβ42 or elevation of Aβ 1-40/Aβ 1-42 ratio in CSF; increased tracer retention in amyloid PET) and of tau pathology (increased P-tau in CSF; increased tracer retention in tau PET).

Prodromal Alzheimer: refers to the early symptomatic and pre-dementia phase of AD.

Alzheimer dementia: refers to the phase of AD where cognitive symptoms are sufficiently severe to interfere with social functioning and instrumental activities of daily living.

Typical AD: refers to the most frequent clinical phenotype of AD that is characterized by an initial progressive and predominant episodic memory deficit (not normalized by retrieval facilitation) and is followed by or associated with other cognitive impairments (executive dysfunction, language, praxis and complex visual processing impairments) and neuropsychiatric changes.

Atypical AD: refers to the less frequent clinical phenotypes of AD. These clinical syndromes include logopenic variant primary progressive aphasia, posterior cortical atrophy, behavioural/dysexecutive variant, cortico-basal syndrome, and the other variants of primary progressive aphasia.

Common AD phenotype: refers to the phenotypes where AD pathology is the most common underlying primary pathology. These phenotypes include amnestic AD, logopenic variant primary progressive aphasia, and posterior cortical atrophy.

Uncommon AD phenotype: refers to the phenotypes where AD pathology can be uncommonly the underlying primary pathology (common underlying primary pathology include FTLD-Tau, FTLD-TDP, etc). These phenotypes include behavioural/dysexecutive variant, cortico-basal syndrome, and other variants of primary progressive aphasia.

Neurodegenerative disease of Alzheimer type: refers to cases where pathophysiological biomarkers are missing and common AD phenotypes are observed together with neurodegeneration biomarkers (FDG-PET hypometabolism, T1-MRI atrophy, CSF NFL, etc).

Asymptomatic at-risk (ARP): refers to cognitively unimpaired individuals who have in-vivo evidence of Alzheimer's pathology. Some can remain stable over long period of time. Other will progress.

Pathophysiological biomarkers: refer to in-vivo biological changes that reflect the underlying Alzheimer's pathology. They are markers of diagnosis, more targeted at identifying AD.

Markers of neurodegeneration: refer to topographical biomarkers or downstream markers. They can be structural (atrophy/MRI) or metabolic (hypometabolism/FDG-PET). They are more targeted at assessing changes over time and predicting outcomes.

Clinical-biological diagnosis: refers to a diagnosis based on both clinical and biomarker findings.

Biological diagnosis: refers to a diagnosis only based on biomarker evidence

Co-pathology: co-morbid pathological changes superimposed to a primary pathological diagnosis.

Prevention of AD: becomes a major challenge. Discovery of pathophysiological biomarkers makes possible to distinguish:
- Primary prevention based on interventions before the presence of positive AD biomarkers
- Secondary prevention based on interventions performed when positive biomarkers are present.

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Author's contribution

BD and NV equally contributed to the Manuscript.

BD and NV conceptualised, performed data curation, wrote the original draft, and performed revision and editing of the Manuscript.

HHF conceptualised, wrote the original draft, and performed revision and editing of the Manuscript.

GBF, GDR, MS, SC, AB, SB, SE, MT, MOH, AN, KB, DG, YS, CCR, SS, LSS, JLC conceptualised and performed revision and editing of the Manuscript.

Each of the authors has approved the final version. The corresponding author had final responsibility for the decision to submit for publication.

Panel 1 - Evidence limiting the predictive accuracy of amyloid and tau lesions for a further cognitive decline in cognitively unimpaired subjects

A - Cross-sectional data
There is an overlap between AD pathological changes in cognitively normal subjects and in patients with AD dementia.
Post-mortem
➢ Numerous cognitively normal and impaired individuals have comparable burden of AD brain lesions, confirmed with large post-mortem cohorts using quantification and digital neuropathological methods[88,89]
➢ All stages AD brain lesions (including both amyloid and tau lesions) are found in 2/3 of subjects aged of 70 years in systematic post-mortem examination regardless of clinical status[18], well beyond the expected prevalence of having cognitive impairment (30%)[90].
➢ Neurofibrillary tangles in the medial temporal regions are found in almost all cognitively unimpaired individual over 70 years old[18,41]*
Molecular neuro-imaging cohorts
➢ Numerous cognitively normal and impaired individuals have comparable amyloid and tau PET burden[91,92].
➢ Both amyloid and diffuse tau (i.e. outside the medial temporal lobe) pathologies are found in 19% of 576 cognitively unimpaired elderly subjects (mean age 71 years)[93] **.

B - Longitudinal molecular neuro-imaging data
They are insufficient to predict an invariable occurrence of symptoms:
➢ Amyloid positivity is associated to an overall cognitive decline although a majority of (A+) subjects remain cognitively stable over time even after several years[42,55,83,84,94-99]***:
  - INSIGHT Study: 83% (73/88) of A (+) subjects (77 years at entry) had no changes in any cognitive, behavioural and neuro-imaging parameters compared to baseline or to A (-) individuals after a 5-year follow-up[96];
  - AIBL Study: 81% (111/137) of amyloid positive subjects (75 years old at entry) remains cognitively unimpaired after a 6-year follow-up (Hazard Ratio = 2·27)[94] in the AIBL study;
  - Lifetime risk of AD dementia for cognitively unimpaired A (+) individuals ranged between 5 and 42% according to age and sex, from pooled data of 13 cohorts in US and Europe[24].
➢ Both amyloid and tau pathologies in cognitively unimpaired (A+T+) individuals increases the risk for middle-term progression to prodromal AD or AD dementia****
  - 35% (6/17) of A(+) cognitive unimpaired elderly progressed to MCI or AD dementia after 7 years of follow-up of a longitudinal amyloid and tau PET study[100]*****;
  - (A+T+) status significantly increases the 5-year risk of clinical progression to a prodromal stage (44·4% vs. 10·7%; HR = 2·8)[83,84], even more in case of (SCD)[55];
  - Longitudinal tau PET studies showed no or only minimal acceleration of tau tracer uptake in the following 1 or 2 years in A(+) versus A(-) cognitive unimpaired elderly [101] *****.

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* Primary Age Related Tauopathy (PART) has emerged in the lexicon as an age-related normal occurrence of tauopathy in the absence or with a low extent of amyloid pathology (Thal ABeta Phase ≤ 2 [102]). The cognitive decline of these patients (who could be considered (T+A±) according to sensitive in vivo detection methods of biomarkers[78]) is significantly slower than that of patients with AD[77], a noteworthy finding indicating that low (A+) (i.e. Thal ABeta Phase ≤ 2) associated with (T+) does not necessarily lead to an accelerated cognitive decline and dementia.
**Probable intermediate or high level of AD pathology according to neuropathological criteria[11]

*** This finding at the group-level may result from the admixture of a proportion of progressors with the (A+) non-progressors.

**** A significant proportion remains cognitively stable for some years limiting any prediction of when or whether such progression will take place in a given individual.

***** In this study there was no significant difference at baseline in term of the degree of tau PET tracer retention between the amyloid positive converters and non-converters, indicating that baseline tau levels were not a strong predictor of clinical evolution.

***** In apparent contradiction of the widely accepted disease model where the accumulation of brain amyloid lesions triggers the fast spreading of tau lesions outside the medial temporal lobes[103].

Panel 2: Toward a personalized risk profile in Asymptomatic at-risk

1- Factors that may increase the risk of progression to AD
- Increased Age
- Frailty
- Female sex
- Low education level
- Heterozygous *APOE* ε4 status
- Polygenic risk factors beyond *APOE*
- Familial history of AD
- Memory complaint/SCD
- Magnitude of brain lesions, inferred from pathophysiological biomarker results especially if searched with PET
- Presence of markers of neurodegeneration (isolated hippocampal atrophy on MRI, FDG-PET hypometabolism or elevated CSF NFL…)
- Co-pathology

2- Factors that may decrease the risk
- Protective genes, such as the presence of the *APOE* ε2 allele and homozygous, *APOE* ε3 Christchurch, A673T APP Icelandic mutation
- High cognitive reserve

3- Factors that need to be further confirmed
- Pattern of neuroinflammation
- Functional brain marker of Cognitive Reserve (e.g. using fMRI connectivity)
- Lifestyle factors: physical activity, sleep, social activities…
- Psychiatric diseases (depression…)

Table 2 - AD diagnosis in clinical setting

CLINICAL PHENOTYPE	BIOMARKER	Likelihood of AD as a primary diagnosis	Further investigations
Common AD phenotypes (amnestic variant, lvPPA, and PCA)	A(+) T(+)	Highly probable - Established	None required
	A(+) T(unknown)	Probable	Consider tau measure (PET, CSF)
	A(+) T(-)	Probable	Consider additional tau measure (PET, CSF)
	T(+) A(unknown)	Possible	Consider amyloid measure (PET, CSF)
	T(+) A(-)	Possible	Consider additional amyloid measure (PET, CSF)
	A(-) T(unknown)	Unlikely	Full etiology work-up* and consider tau measure (PET, CSF)
	A(unknown) T(-)	Unlikely	Full etiology work-up* and consider amyloid measure (PET, CSF)
	A(-) T(-)	Highly unlikely - Excluded	Full etiology work-up*#
	A(unknown) T(unknown)	Unassessable	Consider tau and amyloid measures (PET, CSF)
Uncommon AD phenotypes (behavioural-dysexecutive variant, CBS, nfvPPA, and svPPA)	A(+) T(+)	Probable	None required Careful follow-up needed: an incongruent phenotype and neurodegeneration pattern should trigger a new etiology work-up*
	A(+) T(unknown)	Possible	Consider tau measure (PET, CSF)
	A(+) T(-)	Possible	Consider additional tau measure (PET, CSF)
	T(+) A(unknown)	Unlikely	Full etiology work-up* and consider amyloid measure (PET, CSF)
	T(+) A(-)	Unlikely	Full etiology work-up*
	A(-) T(unknown)	Highly unlikely -	Full etiology work-up*#

			Excluded
	A(unknown) T(-)	Highly unlikely - Excluded	Full etiology work-up*#
	A(-) T(-)	Highly unlikely - Excluded	Full etiology work-up*#
	A(unknown) T(unknown)	Unassessable	Consider tau and amyloid measures (PET, CSF)
Other phenotypes (eg DLB, Richardson syndrome, Huntington's disease, ALS, etc)	A(+) or/and T(+)	Unlikely	Full etiology work-up*
	A(-) T(unknown) or A(unknown) T(-) or A(-) T(-)	Highly unlikely - Excluded	Full etiology work-up*

Note that positivity status must rely on local laboratory standards (see text for details).

A = amyloid; T = tau; AD = Alzheimer's disease; lvPPA = logopenic variant of primary progressive aphasia; PCA = posterior cortical atrophy; bvFTD = behavioural variant of fronto-temporal dementia; CBS = cortico-basal syndrome; nfvPPA = non-fluent variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; DLB = dementia with Lewy body; ALS = amyotrophic lateral sclerosis; PET = positron emission tomography; CSF = cerebrospinal fluid.

* Full etiology work-up depends on the specific phenotype and can imply for example FDG-PET, dopamine imaging, progranulin serum dosage, genetic analysis, oculomotor recordings, electromyoneurography, etc
# Consider a new AD biomarker investigation only in cases where you have a reasonable doubt regarding the validity of biomarkers' results

Table 1: AD diagnosis according to the successive criteria proposals

	NINCDS 1984[2]	IWG 2007[3]	IWG 2010[4]	NIA-AA 2011[105,106]	IWG 2014[107]	IWG/AA 2016[7]	NIA-AA 2018[1]
Criteria mainly for	Clinical setting	Research		Research and clinical setting	Research	Research	Research
Clinical requirements	Dementia, (memory changes, another cognitive impairment)	Amnestic Syndr. of hippocampal type	- Amnestic Syndr. of hippocampal type - Posterior cortical V - Logopenic V - Behav.-frontal V	- MCI (amnestic; non amnestic) - Dementia	- Amnestic Syndr. of hippocampal type - Posterior corticalV - Logopenic V - Behav.-frontal V	NONE	NONE
Biological requirements	NONE	- CSF biomarkers - MRI atrophy - hypometabolism FDG -amyloid PET +	- pathophysiological markers: . CSF changes . Amyloid PET +	- amyloid markers: CSF, PET - marker of degeneration: CSF tau/p-tau FDG-PET, MRI	- CSF Aβ and tau OR - amyloid PET +	- amyloid marker (CSF, PET) AND -tau markers (CSF, PET)	- amyloid marker (CSF, PET) AND -tau markers (CSF, PET)

Supplementary Material

Amnestic AD	Posterior Cortical Atrophy	Logopenic variant PPA	Behavioural-dysexecutive variant	Cortico-basal Syndrome	Other variants of PPA
Phenotype[1]	**Phenotype[2]**	**Phenotype[3]**	**Phenotype[4]**	**Phenotype[5]**	**Phenotype[3]**
Progressive amnestic syndrome of the 'hippocampal type'	Progressive disturbance of visual ± other posterior cognitive functions	Progressive impairment in single-word retrieval and in repetition of sentences	- Progressive apathy or behavioural disinhibition and stereotyped behaviours - or progressive predominant executive dysfunction	Progressive asymmetric clinical presentation including limb rigidity or akinesia, limb dystonia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit, alien limb phenomena	Semantic or non fluent variants PPA
Main neurodegenerative differential diagnoses (rare)[6]	**Main neurodegenerative differential diagnoses (rare)[6]**	**Main neurodegenerative differential diagnoses (rare)[6]**	**Main neurodegenerative differential diagnoses (frequent)[6]**	**Main neurodegenerative differential diagnoses (frequent)[6]**	**Main neurodegenerative differential diagnoses (frequent)[6]**
• LATE • PART • FTLD-Tau (AGD) • Atypical FTLD-Tau or TDP (17q21.31, MAPT, GRN, C9ORF72 mutations or GGT) • Atypical LBD • Atypical CTE • Prion-associated diseases	• LBD • FTLD-Tau (CBD) • Prion-associated diseases	• FTLD-Tau (CBD) or TDP • Atypical LBD • Prion-associated diseases	• Behavioural AD: FTLD-Tau, TDP or FUS • Dysexecutive AD: FTLD, LBD, Parkinson's disease, PSP, CBD, Huntington's disease…	• FTLD-Tau (CBD, PSP) • FTLD-TDP • Atypical LBD	• FTLD-Tau or TDP or FUS • Atypical LBD • Prion-associated diseases

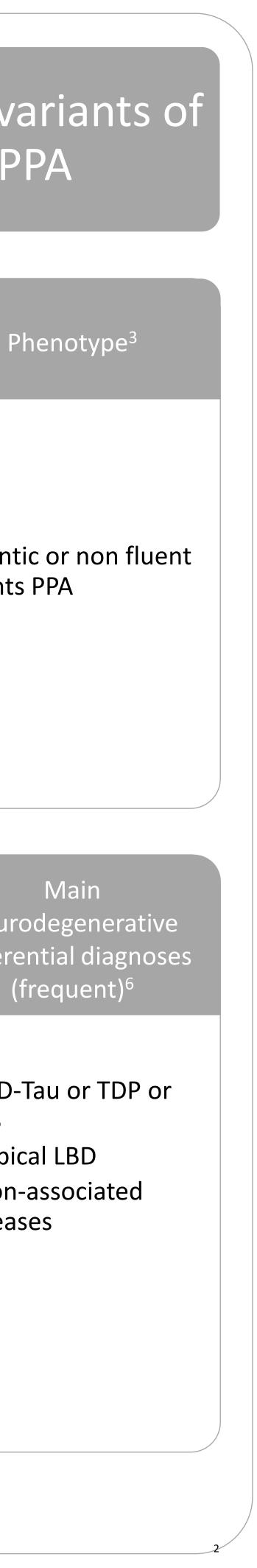**Common AD phenotypes**

Uncommon AD phenotypes

Figure caption

Supplementary Figure. Common and uncommon clinical phenotypes of Alzheimer's disease (AD) and the relative frequency of differential diagnoses for each phenotype (including only neurodegenerative diseases). Common phenotypes are phenotypes where AD is a common underlying pathology, while uncommon phenotypes are phenotypes where AD is not the most frequent underlying pathology. LATE = limbic-predominant age-related TDP-43 encephalopathy; PART = primary age-related tauopathy; AGD = argyrophilic grain disease; FTLD = frontotemporal lobar degeneration; LBD = Lewy body disease; CTE = chronic traumatic encephalopathy; PRNP = PRioN protein; CBD = cortico-basal degeneration; TDP = TAR DNA-binding protein; FUS = fused in sarcoma; PSP = progressive supranuclear palsy; PPA = primary progressive aphasia'

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