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

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BD and NV contributed equally to the manuscript. All authors conceptualised this Personal View. BD and NV curated the data. BD, NV, and HHF wrote the original draft. All authors revised and edited the manuscript and approved the final version. BD had final responsibility for the decision to submit for publication.

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Abstract

In 2018, the US National Institute on Aging and the Alzheimer's Association proposed a purely biological definition of Alzheimer's disease that relies on biomarkers. Although the intended use of this framework was for research purposes, it has engendered debate and challenges regarding its use in everyday clinical practice. For instance, cognitively unimpaired individuals can have biomarker evidence of both amyloid β and tau pathology but will often not develop clinical manifestations in their lifetime. Furthermore, a positive Alzheimer's disease pattern of biomarkers can be observed in other brain diseases in which Alzheimer's disease pathology is present as a comorbidity. In this Personal View, the International Working Group presents what we consider to be the current limitations of biomarkers in the diagnosis of Alzheimer's disease and, on the basis of this evidence, we propose recommendations for how biomarkers should and should not be used for diagnosing Alzheimer's disease in a clinical setting. We recommend that Alzheimer's disease diagnosis be restricted to people who have positive biomarkers together with specific Alzheimer's disease phenotypes, whereas biomarker-positive cognitively unimpaired individuals should be considered only at-risk for progression to Alzheimer's disease.

Introduction

In 2018, the US National Institute on Aging (NIA) and the Alzheimer's Association (AA) proposed the amyloid β, tau, neurodegeneration (ATN) research framework for the definition and diagnosis of Alzheimer's disease (for a glossary of terms, see panel 1).[1] This framework enabled movement from a clinical–biological diagnosis to a purely biological definition of Alzheimer's disease that can be applied in both the asymptomatic and symptomatic stages. Increased accessibility to biomarkers, and the potential for blood biomarkers to provide information about the underlying disease processes in the future, necessitate consideration of the limitations of biomarkers in the diagnosis of Alzheimer's disease, and recommendations about how these biomarkers should and should not be used in a clinical setting.

Evolution of the diagnostic frameworks for Alzheimer's disease

Over the past 15 years, there has been remarkable progress in the development and availability of in-vivo Alzheimer's disease biomarkers, in the characterisation of the natural history of the disease, and in the application of this new knowledge to diagnostic research frameworks (table 1). The first revision to the US 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] That revision was the first research framework to propose Alzheimer's disease as a clinical–biological entity based on a combination of in-vivo biomarkers and specific clinical phenotypes and to extend the definition to the prodromal (predementia) stages. In 2010, the IWG introduced a new supporting lexicon for Alzheimer's disease, with recommended classifications of the presymptomatic stages,[4] including asymptomatic at-risk for people with biomarker evidence of Alzheimer's disease pathology, and presymptomatic for people carrying monogenic Alzheimer's disease mutations.[4] In 2011, NIA–AA criteria defined three different preclinical stages using the amyloid cascade hypothesis: first amyloid lesions, second tau pathology causing neurodegeneration, and third, occurrence of subtle cognitive changes.[9,10] In 2016, an IWG and NIA–AA consensus advanced the classification for research purposes to include Alzheimer's disease diagnosed at a preclinical stage, on the basis of both in-vivo amyloid β and tau positivity "when the risk [of a further progression to clinical Alzheimer's disease] is high",[8] a proposal that was developed further by Clifford R Jack Jr and colleagues.[1,11] In the 2018 NIA–AA diagnostic framework, Alzheimer's disease diagnosis was centred exclusively around a biomarker definition of disease according to ATN status.[1] Even in the absence of cognitive symptoms, the presence of abnormal amyloid β and tau biomarkers (amyloid-positive and tau-positive) was defined as Alzheimer's disease.

The development of in-vivo biomarkers has moved the diagnosis of Alzheimer's disease from the dementia stage towards the prodromal stage, and has introduced the potential for preclinical diagnosis (ie, before symptom onset). These developments are relevant for the testing of potential therapies for secondary prevention of Alzheimer's disease.

Limitations of a purely biological definition of Alzheimer's disease

The 2016 NIA–AA and IWG consensus meeting and 2018 NIA–AA criteria[1,8] engendered substantial debate about using biomarkers to diagnose disease and using clinical symptoms and phenotype only for staging.[12,13] 3 years after introduction of the NIA–AA criteria, a re-evaluation of a diagnostic approach based only on biological markers is warranted, for both conceptual and evidence-based practical reasons.

Risk of confusion between the presence of Alzheimer's brain lesions and Alzheimer's disease

Based on ATN status, Alzheimer's disease could be considered as a purely biological condition, dissociated from a clinical component or individual status. By dissociating Alzheimer's disease from a clinical phenotype, the disease instead equates to Alzheimer's disease neuropathological 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”.[14] As a consequence, the term Alzheimer’s disease includes a continuum that ranges from cognitively unimpaired individuals to people with severe dementia.

Low predictive accuracy

A major limitation of a purely biological definition of Alzheimer’s disease is its low predictive accuracy. Several studies (panel 2) indicate that the presence of both tau and amyloid β positivity is insufficient to definitively predict the occurrence of symptoms (mild cognitive impairment or dementia) in individuals without clinical impairment.

Presence of other pathologies

Another challenge with using a biomarker-only diagnosis of Alzheimer’s disease is that the in-vivo presence of biomarkers of Alzheimer’s disease lesions could certify Alzheimer’s disease as the primary diagnosis, because such lesions are commonly found in people who have other neurodegenerative diseases, most often dementia with Lewy bodies.[40] Patients who have evidence of other brain pathology in addition to Alzheimer’s disease lesions should not be considered as having a primary diagnosis of Alzheimer’s disease. Dementia with Lewy bodies exemplars of copathologies create potential confusion for individuals receiving a biomarker-based diagnosis in such circumstances. For example, physicians would know about the pathology of dementia with Lewy bodies because of clinical signs (eg, hallucination, Parkinson syndrome) or indirect biomarkers (eg, DaTscan denervation) and a diagnosis of dementia with Lewy bodies would be clear according to these data (ie, clinical data and DaTscan). However, the Alzheimer’s disease biomarkers will come back positive, which creates confusion: what is the final diagnosis—Alzheimer’s disease or dementia with Lewy bodies? According to NIA–AA 2018[1] it is Alzheimer’s disease, yet according to McKeith 2017 and colleagues,[41] it is dementia with Lewy bodies. Does the patient have both diseases and should both diagnoses be given to the patient? Could the patient be included in a disease-modifying trial designed for Alzheimer’s disease, or Lewy body dementia, or both? This example shows the confusion of using a pure biomarker diagnosis of Alzheimer’s disease in the absence of a pathology biomarker for other proteinopathies.

Conversely, even when Alzheimer’s disease has been defined neuropathologically as the primary diagnosis, it can be associated with other pathologies. Pure Alzheimer’s disease pathology is the exception rather than the rule (found in 3–30% of neuropathological series of people with dementia of the Alzheimer type, depending on age[40]) at post-mortem examination. Alzheimer’s disease in its so-called pure form is a model that is unlikely to apply to most cases of Alzheimer’s disease, especially those in people with late-life dementia, in whom multiple proteinopathies are increasingly common. Both the clinical trajectory and phenotypes of Alzheimer’s disease can be affected by copathologies, including α-synucleinopathy, vascular pathology, non-Alzheimer’s disease tauopathies (particularly argyrophilic grain disease and cortical ageing-related tau astrogliopathy), and TAR DNA-binding protein 43 (TDP-43) pathology (especially limbic-predominant age-related TDP-43 encephalopathy [LATE] neuropathological changes): 50–60% of

Alzheimer's-type dementia (dementia defined clinically as Alzheimer's disease) is estimated to be attributable to these copathologies.[40,42–45] Unfortunately, biomarkers are currently unavailable for the pathological changes that underlie the non-Alzheimer's neurodegenerative diseases often found in people with dementia, and disentangling Alzheimer's disease from other neurodegenerative diseases continues to depend on phenotype or postmortem examination.

Uncertainty about the pathogenesis model of Alzheimer's disease

The biological model that supports the ATN classification opens up the possibility for research into the biological changes before the onset of symptoms, which is necessary to develop drugs to treat the earliest disease stages. Advocates for a biological definition of Alzheimer's disease often refer to the cancer model, in which a long asymptomatic phase of the disease can exist, and all affected individuals, located anywhere along this disease continuum, will benefit from the same therapeutic approach even at a preclinical stage.[46] However, the follow-up of cognitively unimpaired biomarker-positive individuals suggests that the majority of these individuals do not progress over time (panel 2). Currently, it is not clear whether Alzheimer's disease fits better with the long and asymptomatic prostate cancer continuum model, or with an at-risk model, in which asymptomatic amyloid-positive and tau-positive people would be at-risk (analogous to the precancerous condition) and in which people with the clinical phenotype would be in the disease state (analogous to the cancer state).

Defining the disease by its pathological lesions only, and not by a clinical phenotype, risks creating diagnostic confusion, particularly regarding healthy oldest old people (ie, aged over 85 years) for whom memory complaints and low amounts of Alzheimer's disease pathology are almost constant.[17,47] Publications in the field of dementia that propose that the disease is a myth[48] or a decoy[49] show the potential for confusion between Alzheimer's disease and old age.

In summary, amyloid β and tau biomarkers are not sufficient to confidently predict progression to prodromal Alzheimer's disease or Alzheimer's disease dementia, or to define a person's position on the Alzheimer's disease continuum, without clinical input. The relationship between the coexistence of tau and amyloid β 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 dominant amyloid cascade model, additional models of pathogenesis in Alzheimer's disease include those highlighting the roles of endosomal recycling deficiency,[50] immunity, lipid metabolism, endocytosis deficiency,[51] and vascular dysfunction.[52]

Difficulty in classifying cognitively unimpaired biomarker-positive individuals

The challenge to a purely biological definition of Alzheimer's disease is mostly centred on the preclinical stage of the disease—ie, in conditions for which, by definition, cognitive testing does not support the presence of an Alzheimer's disease phenotype. In symptomatic patients, the identification of the specific clinical phenotype (interfering or not with independence in everyday activities) is a major step in diagnosis, because it expresses the

brain dysfunction that the biomarkers are signalling. Cognitively unimpaired individuals with biomarker positivity will not invariably experience subsequent cognitive decline; the best current estimates of lifetime dementia risk range from 5% to 42%.[33]

Because of the uncertainty about their progression over time (panel 2), we authors recommend that asymptomatic individuals who are biomarker positive should be classified as at-risk for progression, with a distinction between two different subgroups of individuals for clinical and research purposes. The first subgroup is likely to remain stable over long periods and includes people who might never develop symptoms. These people might compensate for the presence of an ongoing neurodegenerative process and manage to maintain normal functioning for many years, or some individuals might have no abnormal neurodegeneration despite having Alzheimer's disease brain lesions.[53] The second subgroup of people will progress, including individuals who show signs of accelerated neurodegeneration and whose compensatory mechanisms have been overwhelmed. This group will probably progress to prodromal Alzheimer's disease and Alzheimer's disease dementia in the future.

For research purposes, these subgroups should be separated, to identify protective factors and to develop algorithms to predict progression. The risk of progression depends on several modulating factors for which the magnitude and interactions have yet to be determined (panel 3). These factors are either risk markers or risk factors, and can be related to several mechanisms: brain resilience (eg, cognitive reserve) and resistance;[53] 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;[54–58] newly described brain cellular senescence mechanisms,[59] and copathology. For instance, is a person aged 60 years who is an *APOE* ε4 carrier, with a negative tau PET scan and an amyloid PET scan just below the threshold for being classed as amyloid positive, at less risk than a person aged 85 years who is amyloid-positive and tau-positive with cerebrovascular lesions on MRI? We anticipate the emergence of individualised predictions adjusted for age and risk factors, and the ability to rank the risk, as occurs with cardiovascular risk factors.[60] Such modelling is in its early stages, but is exemplified by age-adjusted polygenic hazard scores.[61] However, given the existing state of knowledge, disclosing individual patient-level risk would be premature and is to be avoided: current individualised prediction models do not work sufficiently well in cognitively unimpaired people compared with people who are in the prodromal stage of Alzheimer's disease.[62] Besides conceptual issues, there are several practical aspects that could limit the use of biomarkers for the purely biologically based diagnosis of Alzheimer's disease, which include thresholds, generalisation, metric performance, and accessibility.

Biomarker thresholds

A biological diagnosis of Alzheimer's disease that is linked to positive biomarkers brings the need to define with certainty thresholds of positivity: any modification of these thresholds would substantially affect both the diagnosis and the stages of the disease. The clear-cut separation between negative and positive patients in relation to a given biomarker is

somewhat artificial and differs between sites and studies. Factors contributing to this uncertainty include the specifics of the biomarker used and the threshold determination. Most of all, this binary threshold does not reflect the reality of amyloid β and tau pathology, which is continuous and present at a minimal extent in almost all people older than 70 years, [17] with important discrepancies between pathology burden and clinical symptoms at intermediate extents (panel 2). Neuropathology criteria for Alzheimer's disease provide no cutoff for establishing Alzheimer's disease diagnosis, but only define low, intermediate, or high levels of Alzheimer's disease neuropathological change.[14]

For amyloid β biomarkers, the use of binary thresholds of amyloid PET standard uptake value ratio has long restricted the measure of amyloid β deposition to intermediate and high amounts.[63] The use of different amyloid PET tracers is also a known cause of variability in measurements, although the centiloid quantification approach helps to diminish its effect.[64] Studies using the centiloid scale or longitudinal amyloid PET have opened up the possibility of identifying earlier stages of amyloid accumulation.[65,66] In CSF, a positive amyloid measure despite a negative amyloid PET or the use of novel biomarkers (eg, CSF Aβ 34/42 ratio[67]) might also prove to be reliable biomarkers of early amyloid deposition.[67,68]

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 age 70 years)17,19 and in-vivo measures of tau aggregates on PET (36% of individuals are tau positive after the age of 70 years23). The current in-vivo detection of tau positivity using ^{18}F-flortaucipir PET seems to correspond only to widespread tau pathology in the brain (ie, Braak stages ≥IV),[69] whereas CSF phosphorylated tau elevation can reflect earlier stages of tauopathy.[70] In the near future, in-vivo tau measurements might detect very early tau deposits (ie, tau Braak stages I–II), with second generation tau PET tracers or by detection of other phosphorylated species of tau such as phosphorylated tau 217 in the CSF or the plasma.[71]

In clinical practice, such an extension to earlier thresholds in amyloid or tau biomarkers might lengthen the duration of the asymptomatic stages and decrease the lifetime probability of clinical progression. Biomarker thresholds also depend on their intended use (eg, to identify the first signs of amyloid β pathology, or to predict the occurrence of clinical symptoms) and no consensus on the context of use (eg, in asymptomatic *vs* symptomatic individuals; in people who complain about subjective cognitive decline *vs* non-complainers) is currently available.[1]

Evaluating cognitive changes and determining the Alzheimer's disease stages and state (ie, objective cognitive impairment: mild cognitive impairment or dementia) also raise threshold issues. The emergence of lower thresholds in cognitive testing, to define objective subtle cognitive changes, further extends the clinical stages of neurodegenerative diseases, before the occurrence of mild cognitive impairment.[10] However, this increased sensitivity in the detection of cognitive decline comes at the expense of a reduced specificity, and numerous other causes than neurodegeneration or Alzheimer's disease can be responsible for the observed changes, such as metabolic disorders, psychiatric disorders, or sleep apnoea.[72]

Generalisability and accessibility in clinical practice

Considering general medical practice and standard of care, the six currently available Cochrane reviews on the use of CSF or amyloid PET biomarkers have consistently led to the same conclusion: that the routine use of these biomarkers in clinical practice cannot be recommended.[73–78] These reviews considered the ability of biomarkers to predict the future occurrence of clinical Alzheimer's disease dementia in patients with mild cognitive impairment, with the aim of answering the question "will my patient decline?". As underscored by the Cochrane reviews, the prognostic value of a diagnosis based on biomarkers remains limited, first because there is a high variability of decline rate among individuals with biomarker-positive Alzheimer's disease,[79] and second because non-Alzheimer's disease 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".[73] The choice of lower or higher biomarker thresholds corresponds to earlier or later pathological burden and can change the duration of the asymptomatic stages and decrease the lifetime probability of clinical progression. Finally, the high financial cost of PET examinations and the invasiveness of CSF measurements limit their interest to and applicability in clinical practice, especially in low-income countries.[73–78]

Although these limitations were highlighted for patients with mild cognitive impairment, [73–78] data are even more sparse for cognitively unimpaired individuals, because available current models are inadequate in the clinical setting. As shown in panel 2, the effect of biomarker positivity on clinical progression remains weak to moderate and was established using selected volunteers from research cohorts. The generalisation of these cohort findings to clinical practice also faces several obstacles. For example, the risk of attrition bias from these data is strong, especially in the Alzheimer's Disease Neuroimaging Initiative, in which many individuals are lost to follow-up;[80] individuals included in such longitudinal cohorts are usually recruited by advertisement and do not represent the variety of individuals to whom the biomarker investigations would be applied in clinical practice.

An increasing number of people now seek consultation in memory clinics complaining of subjective memory problems or cognitive decline despite scoring normally on formal cognitive testing. Subjective cognitive decline might be a risk factor of clinical progression, [24] but the ability of subjective cognitive decline to predict progression to objective cognitive decline (ie, mild cognitive decline, or dementia, or both) remains low (OR 1·5–3·0[81]). Subjective cognitive decline can result from many factors besides ageing, including anxiety, depression, fatigue, sleep disorders, attention deficits, and drug side-effects.[82] Among individuals who were cognitively unimpaired on objective cognitive testing, there was no difference in frequency of CSF Alzheimer's disease profiles between people with and people without subjective cognitive decline.[83] The heterogeneity of the subjective cognitive decline population is important; for example, prediction of subjective cognitive decline can be strong if it is reported by an informant, is associated with subtle cognitive changes (not normal cognition), and there are no comorbid psychiatric symptoms, but otherwise prediction can be very low and unspecific.[47]

Other individuals do not report cognitive problems and might be just worried about future cognitive decline because of their family history, results from commercial direct-to-consumer genetic testing, or *APOE* status, or might simply be concerned about preserving their memory and general cognitive abilities. Such individuals are seeking to understand their risk and their future, represent up to 20–30% of new patients in some specialty memory clinics,[84–86] and might have undergone bio-marker investigations. With such patients, reliance on a biomarker-only diagnosis would require dependable evidence of a connection between the positivity of biomarkers and an extremely high probability of subsequent expression of clinical symptoms. Experience with the Sokrates study[87] underscores some of the uncertainties (eg, inability to make an accurate short-term or medium-term prediction about cognitive decline for an individual) inherent in revealing amyloid PET results alone to cognitively unimpaired individuals. This issue also applies for patients who undergo an investigation for other medical conditions in which Alzheimer's disease biomarkers are included in the absence of clinical context, and are positive.[88]

Overall, evidence for the use of biomarkers in clinical practice remains highly disputed and suffers from a dearth of evidence-based data to recommend biomarker assessments for cognitively unimpaired individuals.

Ethical concerns

Informing cognitively unimpaired individuals that they have an irreversible disease on the basis of biomarkers is ethically challenging, given that the clinical trajectory towards prodromal Alzheimer's disease or Alzheimer's disease dementia is uncertain, and that there is no way to prevent the development of symptoms in the absence of modifiable risk factors or specific therapies.[89] Disclosing biomarker results and the related risk profile to patients should be seen as different from disclosure of disease diagnosis. Within the lay community, Alzheimer's disease is among the most feared diseases, given its outcomes including profound disability and loss of personal dignity.[90] For physicians, Alzheimer's disease equates with Alzheimer's disease neuropathological changes, whereas for patients, Alzheimer's disease equates with dementia, dependency, and death. This deep difference in use and understanding of the term can adversely affect the therapeutic alliance.[12] In the future, being said to be at-risk for progression, instead of in the preclinical stage of Alzheimer's disease, might help in discussions with patients of the risk–benefit balance regarding a putative treatment and its side-effects.

IWG recommendations for clinical diagnosis of Alzheimer's disease

On the basis of the evidence included in this Personal View, the IWG proposes the following recommendations:

1. The diagnosis of Alzheimer's disease is clinical–biological. It requires the presence of both a specific clinical phenotype of Alzheimer's disease (phenotype positive) and biomarker evidence of Alzheimer's disease pathology (amyloid-positive and tau positive).
2. Specific clinical phenotype commonly associated with Alzheimer's disease pathology (common Alzheimer's disease phenotypes) are: the amnestic

syndrome of the hippocampal type[91] (typical), the posterior cortical atrophy variant,[92] and the logopenic variant primary progressive aphasia[93,94] (appendix p 2). Other phenotypes, including the behavioural variant or dysexecutive variant,[95,96] the corticobasal variant,[97,98] and the other variants of primary progressive aphasia[94,99] (appendix p 2), are less commonly related to Alzheimer's disease pathology (uncommon Alzheimer's disease phenotypes). These phenotypes might or might not interfere with independence in everyday activities.

3. In people who have these common phenotypes, amyloid and tau biomarker positivity establishes an Alzheimer's disease 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 Alzheimer's disease and is seen in other neurodegenerative diseases with amyloid copathology (including LATE and dementia with Lewy bodies[1,40,41,100]) or in patients with cerebral amyloid angiopathy and amnestic vascular cognitive impairment[101] (appendix p 2). However, an isolated amnestic syndrome of the hippocampal type with only tau biomarker positivity can occur in primary age-related tauopathy[37,38] or in atypical presentations of mixed 3 repeat or 4 repeat tau frontotemporal lobar degeneration[100,102] (appendix p 2). Finally, uncommon phenotypes with positive Alzheimer's disease biomarkers should not be a-priori classified as an established Alzheimer's disease (table 2); in such cases the clinician could deem that Alzheimer's disease is not the dominant pathology driving the clinical phenotype but only a copathology.

4. Recommended biomarker measures for amyloid β pathology are low CSF Aβ42, increased CSF Aβ40–Aβ42 ratio (which is, if possible, preferred to low CSF Aβ42[103]) or high tracer retention in amyloid PET. For tau pathology, we recommend high CSF phosphorylated tau (not total tau because of low specificity[104]) or increased ligand retention in tau PET. Recommendation of amyloid PET and tau PET for use in clinical practice is conditional on regulatory approval and reimbursement by payers in different countries.

5. Conclusion of diagnosis requires clinician expertise in the assessment of both clinical and biomarker results. The different situations encountered in clinical practice are summarised in table 2. If the results of cognitive testing, or biomarkers, or both, are close to the cutoff points, it would be useful to complete the work-up with another investigation (eg, repeated measure of pathophysiological biomarkers, clinical follow-up, or use of neurodegeneration biomarkers such as ^{18}F-fluorodeoxyglucose-PET).

6. CSF investigation is prioritised because it provides simultaneous information on the two types of biomarkers (amyloid β and tau) and is less expensive than amyloid PET, tau PET, or both. If lumbar puncture is contraindicated, PET investigations are an alternative.

7. In clinical practice, plasma biomarkers for amyloid β and tau pathology are not currently recommended. Although promising, plasma biomarkers require further standardisation and validation before they can be broadly regarded as secure

evidence of Alzheimer's disease pathology (amyloid-positive and tau-positive).[71,105]

8. In clinical practice, the investigation of pathophysiological biomarkers in cognitively unimpaired individuals is not recommended, given the current inability to predict reliable clinical trajectories of people who are asymptomatic with biomarker positive status (amyloid-positive and tau-positive). In the future, if therapies or prevention programmes show substantial efficacy in delaying onset of disease, that 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. If a biomarker investigation is done in a cognitively unimpaired individual (eg, because of the will to know, referral by brain health services or an expert centre referral to a disease-modifier trial that requires biomarker investigations, as part of a cohort study, or in diagnostic workup for other conditions), a risk stratification of biomarkers is proposed (panel 4). Stratification would distinguish an absolute risk group (ie, carriers of autosomal dominant monogenic mutations for Alzheimer's disease),[106] a high-risk group,[42] and an undefined risk group, to be further clarified in the future as additional evidence accrues.[24–26] 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 define the risk of further progression reliably and predictably. Such individuals should be counselled before Alzheimer's disease biomarker investigation about the potential implications of the test results, and should be able to decide whether or not to have the result disclosed to them. If a person decides to receive the results and the results are positive, they should be counselled that they are at risk for subsequent clinical progression to prodromal Alzheimer's disease or Alzheimer's disease dementia, but are not clinically diagnosed as having Alzheimer's disease.

10. Subjective memory complaints and subjective cognitive decline, if isolated and not supported by objective cognitive impairment, are not specific enough to be considered part of the Alzheimer's disease phenotype.[109] In cognitively unimpaired individuals, self-reported complaints and complaints reported by an informant should be clearly distinguished, because informant complaints indicate that these individuals are at increased risk of progression[110] and merit a closer follow-up with regular clinical and neuropsychological evaluations.

11. Alzheimer's disease can be associated with other brain pathologies, including α-synucleinopathy,[56] vascular pathology, non-Alzheimer's disease tauopathies, and TDP-43 pathology.[40,42–44] Alternatively, lesions of the Alzheimer type are frequently observed as copathology in post-mortem examination of people who had other neurodegenerative diseases.[40,41,94,96] In both situations, pathophysiological Alzheimer's disease biomarkers can be positive.[111] This biomarker positivity is particularly ambiguous in the case of behavioural or

dysexecutive variants, corticobasal syndrome, and semantic or non-fluent variants of primary progressive aphasia, in which the presence of positive Alzheimer's disease biomarkers can be considered either as Alzheimer's disease copathology or atypical forms of Alzheimer's disease[94,96,98,99] (appendix p 2). In all of these situations, it is recommended that the physician relies on the phenotype and follow-up to determine the final diagnosis (ie, whether Alzheimer's disease is the primary pathology or a copathology; table 2). In some complex cases, only post-mortem evaluation will provide definitive information.

12. Physicians are recommended to evaluate the added-value of biomarker investigation for each symptomatic patient objectively, 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 of participation in a disease-modifying trial, and the appreciation of how this information will change the management of the patient. Biomarker investigations can also be limited by the availability, cost, and health-care payment coverage of biomarkers across countries, centres, and clinical situations.

13. If pathophysiological biomarkers are not available, patients should have a clinical syndromic diagnosis—eg, amnestic Alzheimer's disease phenotype or logo-penic variant primary progressive aphasia (ie, phenotype positive with unknown amyloid β and tau status), and staging (mild cognitive impairment or dementia) can still be applied. In these situations, attention should be given to ruling out non-degenerative causes.[100] If a positive neurodegeneration biomarker (eg, ^{18}F-fluorodeoxyglucose-PET hypometabolism, T1-weighted MRI atrophy, elevated CSF neurofilament light chain) is associated with a common Alzheimer's disease phenotype, the term neurodegenerative disease of Alzheimer type can be used (table 2).

Conclusion

Although the definition of Alzheimer's disease based exclusively on biological markers has gained substantial 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. Current evidence about the natural history of people who are 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 that avoid labelling Alzheimer's disease in individuals who are biomarker positive and cognitively unimpaired and who are at risk for progression to prodromal Alzheimer's disease or Alzheimer's disease dementia. We recommend that the diagnosis of Alzheimer's disease in the clinical setting remains tied to the clinical phenotypic presentation.

There are several crucial requirements for using biomarkers to predict progression to clinical stages of Alzheimer's disease. The first requirement is the relationship between pathological burden, biomarker thresholds, and the respective effect and weight of modulating factors in relation to future risk of clinical progression. The second concerns the pathogenesis of

Alzheimer's disease itself. Data suggest that Alzheimer's disease can result not only from tau and amyloid β pathologies but from synergy and interactions among these pathologies that lead to the highest stages of protein accumulation (tau Braak 5 or 6), and the highest rates of cognitive decline. Investigating such synergies and understanding protective factors in people who are asymptomatic with biomarkers of Alzheimer's disease pathology offers opportunities both to define the disease better and to prevent it in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Panel 1: Glossary of terms

Alzheimer's dementia
Refers to the phase of Alzheimer's disease in which cognitive symptoms are sufficiently severe to interfere with social functioning and instrumental activities of daily living.

Alzheimer's disease
A clinical–biological entity defined by a specific clinical phenotype associated with in-vivo evidence of Alzheimer's pathology.

Alzheimer's pathology
Can be assessed and defined in vivo by biomarkers of amyloid β pathology (low CSF Aβ42 or increased CSF Aβ40–Aβ42 ratio; increased tracer retention in amyloid PET) and biomarkers of tau pathology (increased phosphorylated tau in CSF; increased tracer retention in tau PET).

Asymptomatic at risk
Cognitively unimpaired individuals who have in-vivo evidence of Alzheimer's disease pathology. Some individuals can remain stable over a long period of time, whereas others will progress.

Biological diagnosis
A diagnosis based on only biomarker evidence.

Clinical–biological diagnosis
A diagnosis based on both clinical and biomarker findings.

Common Alzheimer's disease phenotype
The phenotypes in which Alzheimer's disease pathology is the most common underlying primary pathology. These phenotypes include amnestic Alzheimer's disease, logopenic variant primary progressive aphasia, and posterior cortical atrophy.

Copathology
Pathological changes found in patients who have a different primary pathology.

Neurodegenerative disease of Alzheimer type

A proposed diagnosis for people whose pathophysiological biomarkers are either not present or not assessed and common Alzheimer's disease phenotypes are observed together with neurodegeneration biomarkers (eg, ^{18}F-FDG-PET hypometabolism, atrophy on T1-weighted MRI, or elevated CSF neurofilament light chain).

Prevention of Alzheimer's disease

Prevention of Alzheimer's disease is a major challenge. The discovery of pathophysiological biomarkers makes it possible to distinguish between primary prevention, based on interventions before the presence of positive Alzheimer's disease biomarkers, and secondary prevention, based on interventions when positive biomarkers are present.

Prodromal Alzheimer's disease

The early symptomatic and predementia phase of Alzheimer's disease.

Uncommon Alzheimer's disease phenotypes

The phenotypes in which Alzheimer's disease pathology is less commonly the underlying primary pathology (the most common underlying primary pathology includes frontotemporal lobar degeneration–tau, frontotemporal lobar degeneration–transactive response DNA-binding protein). These phenotypes include behavioural or dysexecutive variants, corticobasal syndrome, and the non-fluent and semantic variants of primary progressive aphasia.

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Panel 2:

Evidence limiting the accuracy of amyloid and tau lesions for predicting subsequent cognitive decline in cognitively unimpaired individuals

Cross-sectional data

There is an important overlap between Alzheimer's disease pathological changes in cognitively unimpaired individuals and in patients with Alzheimer's disease dementia.

Post-mortem

- Numerous cognitively unimpaired and impaired individuals have a similar burden of Alzheimer's disease brain lesions, confirmed with large post-mortem cohorts using quantification and digital neuropathological methods[15,16]
- All stages of Alzheimer's disease brain lesions (including amyloid β and tau lesions) are found in two-thirds of individuals aged at least 70 years in systematic post-mortem examination, regardless of clinical status,[17] which far exceeds the expected prevalence (30%)[18] of cognitive impairment
- Neurofibrillary tangles in the medial temporal regions are found in almost all cognitively unimpaired people aged 70 years or older17,19*

Molecular neuroimaging cohorts

- Numerous cognitively healthy and cognitively impaired individuals have similar amyloid and tau PET burden[20,21]
- Both amyloid and diffuse (ie, outside the medial temporal lobe) tau pathologies were found in 140 (24%) of 576 cognitively unimpaired older individuals (mean age 71 years)[22]†

Longitudinal molecular neuroimaging data

Such data are insufficient to predict an invariable occurrence of symptoms.

Amyloid positivity associated with an overall cognitive decline, although a majority of amyloid-positive individuals remain cognitively stable over time, even after several years: [23–32]‡

- INSIGHT study: 73 (83%) of 88 amyloid-positive people (aged 77 years at trial entry) had no changes in any cognitive, behavioural, or neuroimaging parameters compared with baseline or compared with amyloid-negative individuals after a 5-year follow-up[29]

*Primary age-related tauopathy has emerged as an age-related normal occurrence of tauopathy in the absence, or with a low extent, of amyloid β pathology (Thal phase ≤2[36]). The cognitive decline of these patients (who could be considered tau positive and amyloid positive or negative according to sensitive in-vivo detection methods of biomarkers[37]) is significantly slower than that of patients with Alzheimer's disease,[38] a noteworthy finding indicating that a small amount of amyloid β pathology (ie, Thal phase ≤2) (amyloid positive—ie, Thal phase ≤2) associated with tau positivity does not necessarily lead to an accelerated cognitive decline and dementia.

†Probable intermediate or high amounts of Alzheimer's disease pathology according to neuropathological criteria.[14]

‡This finding at the group level might result from the admixture of a proportion of progressors with the (amyloid positive) non-progressors.

- AIBL study: 111 (81%) of 137 amyloid-positive participants (aged 75 years at entry) remained cognitively unimpaired after a 6-year follow-up (hazard ratio 2·27, 95% CI 1·17–4·35; p=0·0145 for clinical progression to mild cognitive impairment or dementia in amyloid positive participants *vs* amyloid-negative participants)[27]
- Lifetime risk of Alzheimer's disease dementia for cognitively unimpaired amyloid-positive individuals ranged between 5% and 42% according to age and sex, from pooled data of 13 cohorts in the USA and Europe[33]

Both amyloid and tau pathologies in cognitively unimpaired (amyloid-positive and tau-positive) individuals moderately increase the risk for middle-term progression to prodromal Alzheimer's disease or Alzheimer's disease dementia compared with cognitively unimpaired biomarker negative (amyloid and tau) individuals:§

- 6 (35%) of 17 amyloid-positive and tau-positive cognitively unimpaired people (mean age 74·4 years) progressed to mild cognitive impairment or Alzheimer's disease dementia after 7 years of follow-up in a longitudinal amyloid and tau PET study[34]¶
- Amyloid-positive and tau-positive status moderately increases the 5-year risk of clinical progression to a prodromal stage (44·4% *vs* 10·7%, HR=2·79, 95% CI 1·14–6·9; p=0·03),[25,26] even more so in individuals with subjective cognitive decline.[24]
- Longitudinal tau PET studies showed no or only minimal acceleration of tau tracer uptake in the following 1 or 2 years in cognitively unimpaired older people who were amyloid-positive (median age 80 years) versus amyloid-negative (median age 66 years).[35]‖

§A substantial proportion of people remain 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 degree of tau PET tracer retention between the amyloid-positive converters and non-converters, indicating that baseline tau deposition was not a strong predictor of clinical progression.

‖In apparent contradiction of the widely accepted disease model in which the accumulation of brain amyloid β lesions triggers the fast spreading of tau lesions outside the medial temporal lobes.[39]

Panel 3:

Towards a personalised Alzheimer's disease risk profile in asymptomatic at-risk people

Factors that can increase the risk of progression to Alzheimer's disease

- Increased age
- Frailty
- Female sex
- Low education level
- Heterozygous *APOE* ε4 status
- Polygenic risk factors beyond *APOE*
- Family history of Alzheimer's disease
- Memory complaint or subjective cognitive decline
- Magnitude of brain lesions, inferred from pathophysiological biomarker results especially if searched with PET
- Presence of markers of neurodegeneration (ie, isolated hippocampal atrophy on MRI, ^{18}F-fluorodeoxyglucose-PET hypometabolism, or elevated CSF neurofilament light chain)
- Copathology

Factors that could decrease the risk of progression to Alzheimer's disease

- Protective genes, such as the presence of the *APOE* ε2 allele, the *APOE* ε3 Christchurch mutation, or the *A673T APP* Icelandic mutation
- Higher cognitive reserve

Factors that need further confirmation

- Pattern of neuroinflammation
- Functional brain marker of cognitive reserve (eg, connectivity on functional MRI)
- Lifestyle factors (eg, physical activity, sleep, social activity)
- Psychiatric diseases (eg, depression)

For references see appendix pp 5–6.

Panel 4:

Proposed stratification of risk of asymptomatic people according to biomarker results

People with absolute risk

Carriers of autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*, or trisomy 21)[106]

People with high risk

Cognitively unimpaired individuals with:

- CSF or PET that is amyloid-positive and tau positive[24–26]
- PET that is tau positive outside the limbic cortex (Braak stage 5 or higher)[107]
- *APOE* ε4 homozygosity[108]

People with undefined risk*

Cognitively unimpaired individuals with an incomplete biomarker pattern:

- Amyloid positive; tau negative or unknown[33]
- Amyloid negative; tau positive[51]

For further details, see IWG recommendations for clinical diagnosis of Alzheimer's disease.

*Risk to be worked out depending on the presence of modulating factors.

Search strategy and selection criteria

We searched PubMed on July 1, 2020, for articles published in English between Jan 1, 2018, and July 1, 2020, using the search terms “biomarker” OR “amyloid” OR “tau” OR “neurodegeneration” OR “preclinical” OR “CSF” OR “PET” OR “subjective cognitive decline” AND “Alzheimer’s disease” OR “ATN classification”. We also searched the references of relevant articles. The final reference list was generated on the basis of relevance to the topics covered in this Personal View.

Table 1:

Details of successive proposed criteria for Alzheimer's disease diagnosis

	NINCDS–ADRDA (1984)[2]	IWG (2007)[3]	IWG (2010)[4]	NIA–AA (2011)[5,6]	IWG (2014)[7]	IWG–AA (2016)[8]	NIA–AA (2018)[1]	IWG (2021)
Applicable settings	Research and clinical	Research	Research	Research and clinical	Research	Research	Research	Research and clinical
Clinical requirements	Dementia (memory changes and another cognitive impairment)	Amnestic syndrome of a hippocampal type	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	Mild cognitive impairment (amnestic or non-amnestic) or dementia	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	None	None	Amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia, behavioural or dysexecutive frontal variant, corticobasal syndrome, semantic and nonfluent variants of primary progressive aphasias *
Biological requirements	None	CSF biomarkers, MRI atrophy, ^{18}F-fluorodeoxyglucose PET hypometabolism, amyloid PET positive, or Alzheimer's disease autosomal dominant mutation	Pathophysiological markers: CSF changes (low CSF Aβ42, high phosphorylated tau, or high total tau) or amyloid PET positive	Amyloid β marker (CSF or PET) or marker of degeneration (CSF tau, phosphorylated tau, ^{18}F-fluorodeoxyglucose-PET, and T1-weighted MRI)	CSF amyloid β and tau or amyloid PET positive	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)

ADRDA=Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) Work Group. IWG=International Working Group criteria. IWG–AA=International Working Group and Alzheimer's Association joint criteria. NIA–AA=US National Institute on Aging and Alzheimer's Association joint criteria. NINCDS=US National Institute of Neurological and Communicative Disorders and Stroke criteria.

*Cognitively unimpaired individuals are considered at-risk for Alzheimer's Disease.

Table 2:

Alzheimer's disease diagnosis in a clinical setting

	Likelihood of Alzheimer's disease as a primary diagnosis	Further investigation
Common Alzheimer's disease phenotypes (amnestic variant, logopenic variant of primary progressive aphasia, and posterior cortical atrophy)		
Amyloid positive, tau positive	Highly probable–established	None required
Amyloid positive, tau unknown	Probable	Consider a tau measure (PET, CSF)
Amyloid positive, tau negative	Probable	Consider an additional tau measure (PET, CSF)
Tau positive, amyloid unknown	Possible	Consider an amyloid measure (PET, CSF)
Tau positive, amyloid negative	Possible	Consider an additional amyloid measure (PET, CSF)
Amyloid negative, tau unknown	Unlikely	Full investigation of cause and consider a tau measure (PET, CSF) *
Amyloid unknown, tau negative	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF) *
Amyloid negative, tau negative	Highly unlikely–excluded	Full investigation of cause *†
Amyloid unknown, tau unknown	Non-assessable	Consider tau and amyloid measures (PET, CSF)
Uncommon Alzheimer's disease phenotypes (behavioural or dysexecutive variant, corticobasal syndrome, non-fluent variant of primary progressive aphasia, and semantic variant of primary progressive aphasia)		
Amyloid positive, tau positive	Probable	None required; careful follow-up needed: an incongruent clinical phenotype and neurodegeneration pattern should trigger a new investigation *
Amyloid positive, tau unknown	Possible	Consider a tau measure (PET, CSF)
Amyloid positive, tau negative	Possible	Consider an additional tau measure (PET, CSF)
Tau positive, amyloid unknown	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)
Tau positive, amyloid negative	Unlikely	Full investigation of cause *
Amyloid negative, tau unknown	Highly unlikely–excluded	Full investigation of cause *†
Amyloid negative, tau negative	Highly unlikely–excluded	Full investigation of cause *†
Amyloid unknown, tau negative	Highly unlikely–excluded	Full investigation of cause *†
Amyloid unknown, tau unknown	Non-assessable	Full investigation of cause and consider tau and amyloid measures (PET, CSF) *
Other phenotypes (eg, dementia with Lewy bodies, Richardson syndrome, Huntington's disease, and amyotrophic lateral sclerosis)		
Amyloid positive, or tau positive, or both	Unlikely	Full investigation of cause *
Amyloid negative, tau unknown	Highly unlikely–excluded	Full investigation of cause *
Amyloid unknown, tau negative	Highly unlikely–excluded	Full investigation of cause *
Amyloid negative, tau negative	Highly unlikely–excluded	Full investigation of cause *
Amyloid unknown, tau unknown	Highly unlikely–excluded	Full investigation of cause *

Note that biomarker positivity status relies on local laboratory standards (see Biomarker thresholds section).

*Full investigation of cause depends on the specific clinical phenotype and can imply, for example, ^{18}F-fluorodeoxyglucose PET, dopamine imaging, progranulin serum dosage, genetic analysis, oculomotor recordings, or electromyoneurography.

†Consider a new Alzheimer's disease biomarker investigation only if there is a reasonable doubt about the validity of the biomarker results.