2018 NIA-AA Research Framework to Investigate the Alzheimer's Disease Continuum

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Abstract

In 2011 the National Institute on Aging and Alzheimer's Association (NIA-AA) created separate diagnostic recommendations for preclinical, mild cognitive impairment, and dementia stages of Alzheimers disease. Scientific progress in the interim led to an initiative by the NIA-AA to update and unify the 2011 guidelines. This unifying update is labeled a "research framework", because its intended use is observational and interventional research studies, not routine clinical care. In the 2018 research framework Alzheimers disease is defined by its underlying pathophysiologic processes which can be documented in vivo by biomarkers or by post-mortem examination. Notably, the clinical consequences of the disease (i.e. symptoms/signs) will no longer be required for diagnosis. The framework outlined here focuses on the diagnosis of Alzheimer's disease with biomarkers in living persons. Biomarkers are grouped into those of β-amyloid deposition, tau pathology, and neurodegeneration. Three cognitive staging schemes are described with different contexts of use envisioned for each: a scheme employing 3 traditional syndromal categories, a 6 stage numeric scheme and staging using continuous cognitive measures. We envision that this framework will help establish a

research agenda for the next 5-10 years. Defining Alzheimers disease as a pathophysiological construct will enable a more precise understanding of the sequence of events that lead to cognitive impairment and the multi factorial etiology of dementia. Importantly, the validity of this construct should be determined in more diverse populations. This approach will also enable a more precise approach to therapeutic intervention trials where specific pathways can be targeted at specific points in the disease process and to the appropriate people.

Background: Rationale for updating 2011 NIA-AA guidelines for Alzheimer's disease

In 2011 the National Institute on Aging and Alzheimer's Association (NIA-AA) created separate sets of diagnostic guidelines for the symptomatic or "clinical" stages of Alzheimer's disease (AD) which were mild cognitive impairment (MCI) and dementia [1,2]. Recommendations were also created for a stage of AD in individuals without overt symptoms, called "preclinical AD" [3]. The criteria for the *symptomatic stages* were intended, in part, to aid clinicians in diagnostic decision making, and in part to provide researchers a common framework to define these clinical stages [1,2,4]. The recommendations for *preclinical AD* were not designed for routine clinical care but rather to provide researchers a common language to identify and stage research participants who were not cognitively impaired but had abnormal AD biomarkers [3,4].

Since the publication of the 2011 guidelines, data has continued to accumulate indicating that the cognitive decline in AD occurs continuously over a long period [5-7], and that progression of biomarker measures is also a continuous process that begins prior to symptoms [8-13]. Thus the disease is regarded to be a continuum rather than 3 separate clinically defined compartments [14]. This concept was already recognized but was not formalized in the 2011 NIA AA guidelines [3,4].

A common theme in the 2011 recommendations was the use of imaging and cerebrospinal fluid (CSF) biomarkers. In symptomatic individuals, biomarkers were used to increase (or decrease) confidence that AD pathophysiologic processes contributed to a person's cognitive impairments [1,2,4]. In the case of pre-clinical AD, biomarkers were used to define the

construct [3]. In the 2011 recommendations, biomarker evidence of cerebral β-amyloidosis in the absence of cognitive symptoms was proposed as sufficient to diagnose preclinical AD. While amyloid biomarkers were placed at the apex of the biomarker hierarchy preclinically [3], all AD biomarkers, including those reflecting neurodegeneration, were placed on equal footing in the MCI and dementia guidelines [1,2]. While this discrepancy was noted at the time [4], there is now a general consensus that application of biomarkers should be harmonized conceptually across the disease continuum and that biomarkers of neurodegeneration are not equivalent to those reflecting amyloid and tau deposition.

A major motivation for updating the 2011 guidelines has been the evolution in thinking about biomarkers. In the interim additional studies have shown that selected imaging and CSF biomarkers are valid proxies for pathologic changes of AD. Imaging-to-autopsy comparison studies have established that amyloid PET imaging is a valid in vivo surrogate for fibrillar β-amyloid deposits (in brain parenchyma or vessel walls) [15-20]. It is also now widely accepted that CSF Aβ42 (or preferably the Aβ42/40 ratio) is a valid indicator of the abnormal pathophysiologic state associated with brain fibrillar β-amyloid deposition [21]. An additional development has been the introduction of tau PET ligands [22-24]. By contrast, additional research has highlighted the fact that measures of neurodegeneration or neuronal injury that are commonly used in AD research - MRI, FDG PET, and CSF total tau (T-tau) - are not specific for AD but rather are nonspecific indicators of damage that may derive from a variety of etiologies [25].

Based on this background, the NIA-AA committee recommended that the 2011 guidelines be reviewed and updated.

Guiding principles for updating NIA-AA guidelines for AD

The charge to the 2018 NIA-AA work group was to unify and update the 2011 recommendations in a manner that is consistent with current understanding of the disease process. The work group approached this mandate with several guiding principles.

First, the overall objective was to create a scheme for *defining* and *staging* the disease across its entire spectrum. Experience with the 2011 NIA AA recommendations has shown that a common framework for *defining* and *staging* the disease facilitates standardized reporting of research findings across the field [26-41].

Second, we determined that that these recommendations should be cast as a "research framework to investigate the Alzheimer's disease continuum"; not as diagnostic criteria or guidelines. Unlike the 2011 NIA-AA criteria for MCI or AD dementia based on clinical criteria (i.e. without biomarkers) [1,2], the 2018 research framework is not intended for clinical practice. It is called a "research framework" because it needs to be validated and modified if needed before being adopted into general clinical practice. Moreover, we recognize that there are substantial gaps in our knowledge that need to be investigated with additional research, including the need for more biomarker and clinical data in socioeconomically and ethnically diverse cohorts, continued exploration of subjective cognitive decline and early neuropsychiatric symptoms, as well as further research on biomarker methods. There are two categories of studies that will achieve this: longitudinal cohort studies and randomized placebo controlled trials. Cohort studies, particularly community and population based cohorts, will examine how well the temporal relationships and patterns of signs, symptoms and biomarkers described in this framework fit with what is observed. These results will support convergent and divergent validity. Trials showing that an intervention modifies both biomarkers and signs and symptoms will establish criterion validity (i.e. a disease modifying effect). This approach has validated other disease definitions that use biomarkers to define pathophysiology and explain clinical outcomes. Osteoporosis and vascular disease used this approach to define, respectively, diagnosis based on bone mineral density, cardiac stress tests and carotid ultrasound Interventions on these biomarkers have been shown to reduce the likelihood of developing fractures, heart attacks, strokes and heart failure.

Third, the committee recognized the research framework must function equally well in the two major contexts of use we envision – observational cohort studies and interventional clinical trials.

The committee took a step wise approach to creating the 2018 research framework by posing a series of questions where each incremental step built on earlier conclusions.

The term "Alzheimer's disease" refers to an aggregate of pathophysiologic processes and thus is defined in vivo by biomarkers and post mortem by pathologic changes, not by clinical symptoms

We approached the definition of Alzheimer's disease with awareness of the distinction between a syndrome and a disease. Some will argue that a specific syndrome, i.e. multi domain amnestic dementia, should define AD in living people. Our position, however, is that dementia is not a "disease" but rather is a syndrome composed of signs and symptoms that can be caused by multiple diseases, one of which is AD. As discussed in the following paragraph, there are two major problems with using a syndrome – i.e. amnestic multi domain dementia - to define AD; one, it is neither sensitive nor specific, and two, it cannot be used in individuals who have the disease but do not (yet) manifest signs or symptoms [42,43].

It is now well established that the prototypical multi domain amnestic dementia phenotype historically used to define AD dementia [44] does not rule in AD pathologic change at autopsy [45-47]. From 10% to 30% of individuals clinically diagnosed as AD dementia by experts do not display AD pathologic changes at autopsy [45] and a similar proportion have normal amyloid PET or CSF Aβ42 studies [48-57]. Thus the multi domain amnestic dementia phenotype is not specific; it can be the product of other diseases as well as AD [46]. Non amnestic clinical presentations, i.e. language, visuospatial, and executive disorders, may also be due to AD [58-61]. Thus the prototypical clinical phenotype is not necessarily sensitive for AD pathologic changes. In addition, AD pathologic changes are often present without signs or symptoms, especially in older persons. Thirty to forty percent of cognitively unimpaired elderly persons have AD pathologic changes at autopsy [62,63,64] and a similar proportion have abnormal amyloid biomarkers [29,48-50,55,65-68]. The fact that an amnestic multi domain dementia is neither sensitive nor specific for AD pathologic change suggests that cognitive symptoms are not an ideal unifying principle around which to organize the definition of the disease.

The traditional approach to incorporating biomarkers into models of AD began with patients' clinical symptoms, which appear late in the disease, and worked backwards. The committee recommends a different approach which starts with the pathophysiologic changes detected by biomarkers to define the disease. Defining AD by pathophysiology independent from clinical symptoms represents a profound shift in thinking. For many years AD was conceived as a clinical-pathological construct [44]; it was assumed that if an individual had typical amnestic multi domain symptoms they would have AD pathologic changes at autopsy and if symptoms were absent they would not have AD at autopsy. Symptoms/signs defined the presence of the disease in living persons and therefore the concepts of symptoms and disease became interchangeable. AD became a clinical-biomarker construct with International Work Group (IWG) [59,69,70] and 2011 NIA-AA guidelines where biomarkers were used to support a diagnosis of AD in symptomatic individuals, but the definition of AD was not divorced from clinical symptoms (with the exceptions of the 2011 NIA AA recommendations on preclinical AD and IWG criteria in autosomal dominate mutation carriers).

AD biomarkers

Various imaging and CSF biomarkers are widely used in AD and brain aging research. In order to meet the committee's mandate of arriving at a generalizable research framework, it is helpful to reduce the complexity that results from the variety of available biomarkers. The committee addressed this by following the recommendations from a recent position paper that outlined a descriptive classification scheme for biomarkers used in AD and cognitive aging research [71]. The scheme (which is labeled ATN) recognizes three general groups of biomarkers based on the nature of the pathophysiologic process that each measures (**Table 1**) [71]. Biomarkers of β-amyloid plaques or associated pathophysiologic process (labeled "A)" are cortical amyloid PET ligand binding [72,73] or low CSF Aβ42 [74-76]. Biomarkers of aggregated pathologic tau or associated pathophysiologic processes (labeled "T") are elevated CSF phosphorylated tau (P-tau) and cortical tau PET ligand binding [75,77]. Biomarkers of neurodegeneration or neuronal injury (labeled "N") are CSF total tau (T-tau) [78], FDG PET hypometabolism and atrophy on MRI [79-85].

A limitation of the 2011 NIA-AA recommendations was grouping biomarkers into just 2 categories – amyloid and tau-related neurodegeneration. Tauopathy and neurodegeneration were placed into the same biomarker category. In persons with only AD it is reasonable to assume

that neurodegeneration is associated with tauopathy. However, it is increasingly recognized that neurodegeneration/injury, even in classic AD brain regions, also occurs in many non-AD conditions. This is particularly so in elderly individuals where co morbidities are common [86]. ATN classification s provides a solution to this problem which is to separate biomarkers that are specific for fibrillar tau deposits and its associated pathophysiologic processes from those that are nonspecific measures of neurodegeneration/neuronal injury.

The ATN system was designed with both a CSF and an imaging biomarker in each of the 3 biomarker groups (**Table 1**) [71]. Thus complete ATN biomarker characterization of research participants is possible using either imaging or CSF biomarkers alone. However, some research groups may prefer a mixture of imaging and CSF biomarkers for ATN characterization. For example when CSF and MRI are available but PET is not, investigators may choose to use CSF Aβ42 and P-tau as the A and T biomarkers and MRI as the N biomarker.

Defining AD

Once the committee agreed that AD should be defined as a pathophysiologic construct that is identified by biomarkers in living people, the next logical question was: what biomarker signature or profile(s) define AD? The committee agreed that only biomarkers that are specific for hallmark AD proteinopathies (i.e. Aβ and pathologic tau) should be considered as potential biomarker definitions of the disease. Different possible biomarker profiles were considered.

Numerous studies have shown that cognitively unimpaired individuals with abnormal amyloid biomarkers have more rapid progression of atrophy, hypometabolism or clinical/cognitive decline than individuals without biomarker evidence of β-amyloid deposition [12,29,76,87-92] The proportion of amyloid PET positive clinically normal individuals by age nearly perfectly parallels the (increasing) age specific prevalence of individuals clinically diagnosed as AD dementia 15-20 years later [48]. The first biomarkers to become abnormal in carriers of deterministic AD mutations are those of β-amyloid [8-10,13]. These data suggest a causal up-stream role for β-amyloid in the pathogenesis of AD; and while β-amyloidosis alone is insufficient to cause cognitive deterioration directly, it may be sufficient to cause downstream pathophysiologic changes (i.e. tauopathy and neurodegeneration) that ultimately lead to cognitive deterioration. These findings are supported by clinic-pathologic studies as well [93,94]. Consequently there is a

general consensus in the field that amyloid biomarkers represent the earliest evidence of AD pathophysiologic processes currently detectable in living persons. This suggests that abnormal β-amyloidosis biomarkers alone could serve as the defining signature of AD. However, both β-amyloid and paired helical filament (PHF) tau deposits are required to fulfill pathologic criteria for AD [95,96] which suggests that evidence of abnormalities in both β-amyloid and tau biomarkers should be present in order to apply the label "Alzheimer's disease" (in contrast to Alzheimer's pathophysiology) in a living person (**Fig 1**). With these considerations in mind, the committee agreed on the following definitions.

An individual with biomarker evidence of Aβ pathophysiology alone (amyloid PET or low CSF Aβ 42 or 42/40 ratio) with a normal tau biomarker would be assigned the disease label "Alzheimer's pathophysiology" (**Table 2**) (**Fig 2**). The term "Alzheimer's disease" would be applied if biomarker evidence of both Aβ and pathologic tau was present (**Fig 1**). Alzheimer's pathophysiology and Alzheimer's disease are not regarded as separate entities but earlier and later phases of the "Alzheimer's pathophysiologic continuum" (an umbrella term that includes both Alzheimer's pathophysiology and Alzheimer's disease). These definitions apply regardless of clinical symptoms. These definitions meet our specifications to function equally well across the disease spectrum: from early through late life onset, from pre symptomatic through symptomatic phases, and for typical and atypical clinical presentations.

Staging

We next developed a system for staging severity. Our guiding principles were the following. Two types of information about the patient are staged independently from each other: 1) grading disease pathophysiologic severity using biomarkers, and 2) grading the severity of cognitive impairment. Measures used to define AD must be specific for the disease while measures used to stage severity need not be. Thus different measures have different roles. Aβ biomarkers determine whether or not an individual is in the Alzheimer's pathophysiologic continuum. Tau biomarkers determine if someone with amyloidosis has AD. Neurodegenerative/

neuronal injury biomarkers and cognitive symptoms, neither of which is specific for AD, are used only to stage severity not to define the presence of AD.

Biomarker profiles and categories

In many research studies it will be most appropriate to treat biomarkers of amyloid, tau and neurodegeneration/neuronal injury as continuous measures without employing normal/abnormal cut points. However most (if not all) biomarkers used in medicine have a cut point denoting normal vs abnormal values. The need for discrete categorization of biomarker continua is most obvious for AD clinical trials where hard cutpoints are needed to serve as inclusion/exclusion criteria.

The addition of a normal/abnormal cut point for each ATN biomarker type results in 8 different ATN *"biomarker profiles"* (**Table 2**); A+T-N-, A+T+N+, etc. Based on the definitions of Alzheimer's pathophysiology and AD outlined earlier, the ATN biomarker system with cut points assigns every individual one of three *"biomarker categories"* (**Table 2**): 1) individuals with normal AD biomarkers; 2) those in the Alzheimer's pathophysiologic continuum (subdivided into Alzheimer's pathophysiology and AD); and, 3) those with a normal amyloid biomarker but with abnormal T or N, or both. This latter biomarker profile implies evidence of one or more non-AD pathologic processes and has been labeled suspected non Alzheimer's pathophysiology (SNAP) [34].

It is worthwhile to re-emphasize that, like the 2012 NIA-AA classification system for AD neuropathic change [95,96], ATN scoring of biomarkers is independent from clinical symptoms.

The rate of cognitive decline is significantly greater for cognitively unimpaired and impaired individuals who have abnormalities in *both* an amyloid biomarker and a second biomarker type which could be CSF tau (t tau or p tau), atrophy or hypo metabolism in comparison to individuals who have neither or only one of these biomarker abnormalities [26-31,35,36,38-41]. These data firmly establish that more advanced disease pathophysiology defined by biomarkers predicts more rapid cognitive decline. Thus a solid evidence base exists proving that combinations of biomarker abnormalities are useful for staging the pathophysiologic processes of AD.

While the term stage is more familiar, we prefer the term "biomarker profile" (**Table 2**) because the term stage implies a sequence – i.e. stage 1 always precedes stage 2, etc. Many in the

field are convinced that amyloidosis induces or facilitates the spread of pathologic tau, and tauopathy in turn is a proximate cause of neurodegeneration. If so then the logical biomarker sequence of AD would be: A+T-N- then A+T+N- then A+T+N+ [97]. It is not certain though where the A+T-N+ profile would fit in a sequential staging scheme. One possibility is that A+T-N+ represents evidence of comorbidity – i.e. A+T- represents early AD pathophysiology while N+ represents evidence of non-AD neurodegeneration/neuronal injury [98] (see **Fig 3**). However until autopsy confirmation becomes available this is speculative. We can, however, be confident that A+T-N- represents an early pathophysiologic stage while A+T+N+ represents the most advanced. Staging pathophysiologic severity is thus accomplished by combining information from each of the 3 biomarker groups; the more biomarker groups that are abnormal, the more advanced the pathophysiologic stage [97].

Alternatives to binarizing biomarker groups: Given that Alzheimer's pathophysiology and AD are defined by biomarkers, a single cut point is needed in many situations. However, as pointed out in the ATN position paper other options are possible. In many research situations biomarkers are best treated as continuous variables. For example, the risk of short term cognitive decline increases continuously with worsening N biomarkers and this may be true of T biomarkers as well [99,100].

Situations can be also envisioned where a 2 cut point approach might be useful [71,101]. Two cut points define 3 ranges. If these 3 ranges were labeled, clearly normal (0), intermediate range (1), clearly abnormal (2), then a 2 cut point biomarker profile might look like $A^2T^1N^0$, etc. Designating an intermediate range using 2 cut points has evolved in other diseases for clinical care, for example, pre hypertension and pre-diabetes have proved to be useful constructs in medicine.

Characteristics and limitations of biomarkers

CSF vs imaging biomarkers: While we place imaging and CSF biomarkers into common groups a fundamental difference between the two should be recognized. CSF biomarkers are measures of the concentrations of proteins in CSF that reflect the rates of both production

(protein expression or release/secretion from neurons or other brain cells) and clearance (degradation or removal) at a given point in time [102,103]. Imaging measures, on the other hand, represent the magnitude of the pathological load or damage accumulated over time. Low CSF Aβ42 is therefore best considered a biomarker of a *pathophysiological state* that is *associated with* amyloid plaque formation and not a measure of amyloid plaque load as amyloid PET is. Similarly, CSF Ptau is best considered a biomarker of a *pathophysiological state* that is *associated with* PHF tangle formation not a measure of pathologic tau deposits as tau PET is.

Discordances between imaging and CSF biomarkers may occur [32,37,104-107]. In some situations discordance in normal/abnormal labels between an imaging and CSF biomarker within a group is simply a product of how cut points were established and can be rectified by adjusting cut points. The continuous relationship between CSF Aβ42 and amyloid PET, however, is "L-shaped" rather than linear [104,105,108]. This may be due to a temporal off set between these 2 measures [109-111]. In the limited data currently available, tau PET ligand binding is linearly correlated with elevated CSF P tau [103,112,113], however, the correlation is not perfect. Given these observations one might ask how could a CSF and an imaging measure be used as biomarkers of a common pathophysiologic process – e.g. amyloidosis or PHF tauopathy or neurodegeneration/neuronal injury? The answer lies in the chronic nature of AD which spans years/decades. Thus an ongoing active pathophysiologic state, denoted by CSF, and the accumulation of pathologic changes, denoted by imaging, will agree over the long term.

Tau PET: Tau PET is a new modality and the ligands that have been evaluated to date are considered first generation compounds. These compounds suffer from some limitation, the most common being off target binding. However, at least one first generation ligand has emerged as a legitimate biomarker of 3R/4R PHF tau deposits [24]. Autoradiographic studies have shown that the most widely studied ligand, Flortaucipir (formerly T807 and AV1451), does not bind to amyloid plaques, TDP43, argyrophillic grains or alpha synuclein. AV1451 binds weakly or not at all to sole 4R or sole 3R tau deposits in primary tauopathies [114,115]. *In vivo* imaging to autopsy comparisons also indicate specific binding of AV1451 to PHF tangles [116]. Elevated tau PET binding in both medial temporal structures and neocortex is strongly associated with positive amyloid PET scans and with clinical impairment across the normal aging to dementia clinical spectrum [113,117-123]. High binding predicts future clinical worsening [124,125]. Longitudinal accumulation correlates with concurrent clinical decline [125]. New tau PET ligands are in the

early stages of development and there is optimism that some of the limitations of the first generation compounds will be addressed in the next generation of tau PET ligands.

CSF T tau and P tau: CSF levels of T-tau and P-tau are tightly correlated within cohorts of AD patients and controls [126], and the correlation between CSF T tau and P tau is typically much higher than between CSF T tau and MRI or FDG PET [32,103]. Therefore it is reasonable to ask why not place both CSF T tau and P tau in the tau biomarker group There is a marked temporary increase in T-tau in traumatic brain injury and stroke that correlates with the severity of neuronal damage [127,128]. It is difficult to see how changes in T tau in such patients can be attributed to brain PHF tau deposition. Further, in Creutzfeldt-Jakob disease, a disorder characterized by very rapid neurodegeneration but not PHF tau accumulation, there is a very marked increase in CSF T-tau (10-20 times more than in AD), while P-tau shows no or minor change [129,130]. The only disorder that consistently shows an increase in CSF P-tau is AD [131], while this biomarker is normal in other neurodegenerative disorders. The level of CSF Ptau also does correlate with severity of PHF tau accumulation post-mortem [77,132]. Taken together these data indicate that CSF T-tau reflects the intensity of neuronal damage at a specific point [102] while elevated CSF P-tau reflects an abnormal pathophysiologic state associated with PHF tau formation.

Biomarkers of neurodegeneration or neuronal injury: Biomarkers in the N category (**Table 1**) are indicators of neurodegeneration or neuronal injury from many causes; they are not specific for neuronal damage due to AD. In any individual the proportion of observed neurodegeneration/injury that can be attributed to AD vs other possible co morbid conditions (most of which have no extant biomarker) is unknown. This is a recognized limitation of this category of biomarkers. However, the combination of an abnormal MRI, CSF T tau, or FDG PET study with an abnormal amyloid biomarker provides much more powerful prediction of future cognitive decline [26-31,35,36,38-41] than an abnormal amyloid study alone. Thus the neurodegeneration / neuronal injury biomarker group provides important pathophysiologic staging information and for this reason it seems inadvisable to eliminate this class of biomarkers from the AD research framework.

It is important to note some differences among biomarkers in the N group. [102]Atrophy on MR likely reflects cumulative loss and shrinkage of the neuropil [133-135]. CSF T tau indicates the

intensity of neuronal injury (a pathophysiologic state) at a given point in time [99,102,136,137]. FDG PET likely indicates both cumulative loss of the neuropil and functional impairment of neurons. These differences may result in discordances [32,39,103,107,138].

Limitations: None of the biomarkers are as sensitive as direct examination of tissue at autopsy. Absolute sensitivity of amyloid PET relative to an autopsy gold standard has been assessed [139]. Typical cut points used for ^{18}F amyloid PET ligands roughly label individuals with none to sparse neuritic plaques normal and individuals with moderate to high neuritic plaque load and Thal phase 4-5 abnormal [16,20]. A typical cut point used for ^{11}C PIB approximately labels individuals with Thal phase 0-1 normal and individuals with Thal phase 2 -5 abnormal [19]. Thus, a negative amyloid PET should not be equated with the absence of β-amyloid in the brain or even with sparse neuritic plaques. Clinico-pathologic studies suggest that low levels of pathologic changes are associated with subtle cognitive deficits among cognitively unimpaired persons [7,140]. The amount of fibrillar tau that can be present in the brain below the in vivo tau PET detectable threshold is unknown at this time. This limitation is important to bear in mind when considering the distinction between Alzheimer's pathophysiology and AD which hinges on in vivo detection of pathologic tau deposits; however, neither CSF P tau nor tau PET are expected to identify minimal neurofibrillary changes that are detectable by neuropathological examination. Similarly, the number of neurons or neuronal processes that must be lost in order to detect atrophy on MRI or hypometabolism on FDG PET is not known. For every biomarker there must be an in vivo limit of detection. For this reason we use the terms normal/abnormal for biomarkers rather than positive/negative. Normal/abnormal implies that the test detects what it is capable of within acknowledged limits, and is not an absolute measure of pathologic changes in the brain.

The 2018 research framework is designed around biomarker technology that is presently available rather than what would be desirable in an ideal world. ATN biomarkers are available in many research settings at the present time. Other proteintopathies, e.g. α-synuclein and TDP43, are intimately involved with AD pathogenesis or frequently co-occur with AD pathologic changes [141,142]; however, validated biomarkers are not presently available for these. Likewise, micro infarcts, hippocampal sclerosis and agyrophillic grains are commonly observed pathologic changes in the brains of the elderly but no reliable markers exist for these either. The ATN biomarker scheme is expandable to incorporate new biomarkers. For example, a vascular biomarker group could be added, i.e. ATNV, and when biomarkers for TDP and α--synuclein are

developed ATN can be expanded to incorporate these as well. CSF neurogranin is presumed to measure synaptic degeneration and loss [143,144] and neurofilament light chain [145] to measure axonal injury. When they have been more thoroughly studied, these measures should serve as biomarkers of damage to the neuropil in the "N" group of biomarkers.

Neurocognitive staging

Like biomarkers, cognitive performance exists on a continuum. An obvious approach to cognitive staging therefore is to use continuous instruments. While this approach may be preferable in certain circumstances, the committee felt it was also appropriate to outline categorical cognitive staging schemes. In the 2011 NIA-AA guidelines cognitive staging was implicit rather than explicit. Three different documents were published describing preclinical AD, MCI, and dementia; however, these categories have at times been interpreted to indicate three distinct entities. In 2018 we avoid the notion of separate entities, and instead use the terminology staging the continuum.

One of the specifications of the 2018 research framework was that it be applicable in two distinct contexts – interventional clinical trials and clinical-biomarker observational research. In many if not most modern AD clinical trials that address mechanisms of underlying disease pathophysiology, individuals are selected for inclusion with the aid of biomarkers. The studies are only concerned with a defined portion of the population – those in the Alzheimer's pathophysiologic continuum. For clinical-biomarker observational research on the other hand the research questions often require that all members of a recruited sample are included (those with non-AD pathophysiology, normal AD biomarkers, and those in the Alzheimer's pathophysiologic continuum). In these studies research questions often hinge on the presence of heterogeneity within the cohort –which is screened out of AD trial cohorts. We therefore outline 2 types of categorical clinical staging schemes. The first is *syndromal categorical cognitive staging* which employs traditional syndromal categories and is applicable to all members of a recruited cohort (i.e. includes all biomarker profiles). The second was a *numeric neurocognitive staging* scheme that was applicable only to those in the Alzheimer's pathophysiologic continuum.

The committee also recognized that clinical staging had to function both when prior longitudinal clinical or cognitive testing evaluations were available for participants, or when prior information is unavailable and the participant is being evaluated for the first time.

Syndromal categorical cognitive staging

The *syndromal cognitive staging* scheme divides the cognitive continuum into 3 traditional categories – Cognitively Unimpaired (CU), MCI, and dementia with dementia further subdivided into mild, moderate and severe (**table 3**). This 3-category division serves as the basis for cognitive categorization in the Alzheimer's disease Neuroimaging Initiative [146], Australian Imaging, Biomarkers and Lifestyle study of aging [48], Atherosclerosis Risk in Communities [147], and other studies [148] . Many in the research community feel that it has been and continues to be effective for clinical research and that abandoning it would unnecessarily disrupt ongoing studies. Dividing the cognitive continuum into these 3 syndromal categories also has been adopted by many medical practitioners [149]. It has also been codified for clinical practice in the DSM 5 criteria [150] by the mild cognitive disorder (essentially MCI) and major cognitive disorder (essentially dementia) labels. Thus this approach seems suited to observational clinical-biomarker research.

While the definitions of CU, MCI and dementia (**Table 3**) are largely the same as in the 2011 NIA AA guidelines there are differences. For example the 2011 guidelines included only those cognitively unimpaired individuals who had an abnormal amyloid biomarker study (i.e. preclinical AD). In contrast in the 2018 research framework the definition of CU is independent from biomarker findings. In the 2011 guidelines for MCI, the diagnosis was based on clinical judgment when all available information about the patient was considered. In the 2018 framework the diagnosis can be based on clinical judgment and/ or on cognitive test performance. In the 2011 guidelines an amnestic multi domain dementia was labeled "probable or possible AD by clinical criteria" without requiring biomarker documentation of AD. In the 2018 research framework the labels CU, MCI and dementia denote only severity of cognitive impairment and are not used to infer its underlying pathology.

Nomenclature: Every individual will have both a biomarker profile and a cognitive stage. Many researchers in the field indicated a preference to retain traditional terms from 2011 that combined these two independent sources of information. In **Table 4** we illustrate an approach to combination terminology which retains nomenclature from 2011 but does depart from 2011 naming in some ways. For example the label "Alzheimer's disease contributing to MCI (2018)" is used rather than "MCI due to Alzheimer's disease (2011)". By this we indicate that although the person has an AD biomarker profile, we cannot know if their cognitive deficit is attributable to AD alone or in addition to other potential comorbidities. In addition, the 2018 naming convention places the biomarker category in the lead position.

An alternative approach to naming is to simply combine ATN biomarker profile with cognitive stage without using descriptive phrases; that is, combine the row and column names from **table 4** without the descriptive phrases in the body of the table. For example, "A+T-N-MCI" instead of "Alzheimer's pathophysiology contributing to MCI" or "A+T+N+ dementia" instead of "Alzheimer's disease contributing to dementia". Some groups will prefer this "row and column" naming approach.

Table 4 illustrates the principle that biomarker profile and cognitive staging represent independent sources of information. For a given cognitive stage (i.e. a given column in **Table 4)** every biomarker profile will be present in the population. Likewise different cognitive stages will be present in the population among people with the same biomarker profile (i.e. a given row in **Table 4)**. Many effects can blur the relationship between pathophysiologic severity and cognitive symptoms at the individual level. These include protective factors, such as cognitive reserve [151-153], as well as risk factors, such as co morbid pathologies. Mixed forms of brain pathology are the most common findings at autopsy in both unimpaired and impaired elderly individuals. [154,155,156] . The presence of co morbid pathologies presumably lowers the threshold for cognitive symptoms for a given level of AD pathologic change.

Table 5 illustrates the principle that biomarker profiles within the Alzheimer's pathophysiologic continuum raise or lower the risk of short term cognitive decline; and that cognitive stage provides additional independent information about the risk of future cognitive decline.

Numeric neurocognitive staging

The committee also created a "numeric neurocognitive staging scheme" (**Table 6)** that avoided traditional syndromal labels and is specific for only those in the Alzheimer's pathophysiologic continuum. This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of neurocognitive symptoms culminating in dementia. A common use case for this numeric neurocognitive staging scheme would be clinical trials since it is applicable only to members of the population who are determined to be in the Alzheimer's pathophysiologic continuum by biomarker evidence of at least amyloid accumulation.

It is apparent that numeric stages 1-6 (**Table 6)** bear a close resemblance to the global deterioration scale [157] with the important distinction that the global deterioration scale was created in the pre biomarker era. Stage 1 (**Table 6**) is defined by biomarker evidence of Alzheimer's pathophysiology in asymptomatic individuals. Stage 2 describes the earliest detectable neurocognitive consequence of Alzheimer's pathophysiology and is similar to "stage 3 preclinical AD" in the 2011 NIA AA guidelines [3]. Stage 3 describes neurocognitive impairment that is not severe enough to result in significant functional loss. Stages 4-6 describe progressively worse functional loss. The nature of decline or impairment in stages 2 -6 respectively may involve any cognitive domain(s) – not only memory.

The syndromal categories in **Table 3** and numeric stages in **table 6** obviously point to similar constructs. A cognitively unimpaired individual who also has no subjective or objective evidence of subtle decline (**Table 3**) and Stage 1 (**Table 6**) both describe an asymptomatic state. A cognitively unimpaired individual who has subjective or objective evidence of subtle decline (**Table 3**) is similar to Stage 2 (**Table 6**). MCI (**Table 3**) and Stage 3 (**Table 6**) both describe cognitive impairment short of dementia. Mild, moderate and severe dementia (**Table 3**) are identical to stages 4-6 (**Table 6**)**.**

However, since the two staging systems address different needs there are important differences between them. First, numeric staging is only applicable to those in the Alzheimers pathophysiologic continuum while syndromal categorical staging includes all biomarker profiles.

Second, stage 2 is called out as a distinct transitional stage between asymptomatic (stage 1) and mildly impaired (stage 3) in the numeric scheme (**table 6)** but there is no separate category between clinically unimpaired and MCI in the syndromal categorical scheme. Our reasoning was that if an individual is in the Alzheimer's pathophysiologic continuum, then it is reasonable to label subjective complaints or evidence of subtle cognitive decline as a transitional stage. However, in the syndromal categorical scheme (**table 3)** where abnormal biomarkers are not required, it is not reasonable to assume that subjective complaints represent a symptom of any specific disease process. Third, neurobehavioral symptoms are treated differently between the two staging systems. While cognitive symptoms represent the core clinical feature of AD, in some individuals the initial presentation may be neurobehavioral (e.g. depression, anxiety, apathy) rather than cognitive [158]. Therefore in the numeric scheme an individual may be placed into stage 2 on the basis of neurobehavioral symptoms alone – i.e. without evident cognitive decline. To reflect this we use the term "neurocognitive" to describe staging in the numeric scheme. Neurobehavioral symptoms should have a clearly defined recent onset which persists and cannot be explained by life events. Individuals must have cognitive impairment to be placed into numeric stages 3 -6 [159]. We recognize that neurobehavioral symptoms often do not have a neurodegenerative etiology. Thus, our position is that without biomarker abnormalities indicating the presence of a neurodegenerative disease, it is not reasonable to classify patients with isolated neurobehavioral symptoms as having MCI or dementia. Consequently, cognitive symptoms are required for inclusion in these categories in the syndromal staging scheme which is not specific limited to individuals in the Alzheimer's pathophysiologic continuum.

Because only 4 biomarker profiles are eligible for numeric staging, the committee saw an opportunity to streamline nomenclature. In this shorthand naming scheme the four Alzheimer's pathophysiologic continuum biomarker profiles are labeled a-d:

a) A+T-N-
b) A+T-N+
c) A+T+N-
d) A+T+N+

Thus, individuals can be fully described by a single number/letter combination denoting numeric neurocognitive stage and biomarker profile- i.e. stage 1a, or stage 2c, etc.

Cognitive staging using continuous measures

A third option for cognitive staging is to use continuous measures – e.g. MMSE [160], CAMCOG, ADAS, CDR-SB [161] - and eliminate categories entirely. Cognitively homogenous cohorts for therapeutic trials or observational research can be created by selecting a narrow range on test batteries for inclusion.

Implementation and methods

The committee avoided making specific recommendations for many implementation details. Our objective was to outline a general research framework that could be adapted by individual research groups to their own research goals and environment. For example, different research groups will employ the cognitive testing battery and cut points that best fit their own research samples.

Evaluation of images may be by visual interpretation or by quantitative methods. Methods of image quantification vary among research groups and are constantly being refined. For tau PET, FDG and MRI the locations of the abnormalities are closely related to symptoms and thus quantification methods must be sensitive to location [162]. This is not the case for amyloid PET, however, where ligand uptake appears diffusely throughout the cortex and its topography is not directly related to symptoms [58]. If quantification is used then cut points must be determined that label individual scans normal or abnormal. Age norming biomarker cut points is controversial. Arguments have been made that neurodegenerative biomarkers should be age normed because loss of neuropil is closely tied with ageing. By contrast a strong argument can be made that any amyloid or pathologic tau detected by a biomarker is abnormal regardless of age and thus age norming biomarker cutpoints is inappropriate. The distinction between normal aging and age related disease has been debated for decades and we do not presume to settle this here.

Initiatives to standardize imaging and CSF biomarker measures exist , e.g., the Centiloid Project [163], t EADC-ADNI Harmonized Protocol for hippocampal segmentation [164], Alzheimer's Association Global Biomarkers Standardization Consortium [165] and International Federation of Clinical Chemistry Working Group for CSF proteins. These efforts are the subject of ongoing research but universal standards have not yet been established [166]. For amyloid imaging, where over a decade of data are available, different ligands, methods of image acquisition, and image

processing can result in different thresholds when compared to pathological standards [19,20,167]. These issues are currently less understood for pathologic tau imaging, but the questions are equally tractable. The committee avoided taking a proscriptive approach to these methodological issues with the assumption that this was best left to expert work groups and individual research centers.

Clinical research without biomarkers or with incomplete biomarker information

Although incorporation of biomarkers into clinical research is already widespread and growing, we recognize that in some settings it may not be feasible to obtain biomarkers, such as areas without access to the necessary laboratories and imaging facilities, persons less trusting of the health care system that are reluctant to participate in studies with a spinal tap or injection, or low and middle income countries without adequate financial resources. In other cases, a study may simply not be able to justify the cost and participant burden, such as large, longitudinal, community-based analytic cohort studies that can tolerate the loss of diagnostic precision more than it can tolerate the bias that will be introduced by modest participation rates in biomarker data collections. Finally, there may be research studies that do not require biomarker evidence of AD to achieve the specific goals of the research program such as studies of cognitive decline, or all cause cognitive impairment or dementia.

Investigators involved in studies without biomarkers may elect to label research participants by the appropriate clinical syndrome without inferring etiology For example, someone with the prototypical syndrome would be labeled multi domain amnestic dementia rather than probable AD dementia - i.e. not go beyond what is know with certainty which is the presence or absence of the syndrome. However, some investigators in this situation may wish to employ the terms possible or probable AD dementia for research participants who display a prototypical syndrome. In both the 1984 [44]and the 2011 NIA AA [1] criteria for AD dementia a probabilistic assumption about AD pathologic changes was inferred from the clinical presentation alone. Pathologic AD is documented in 80%, or more of cases with a clinical diagnosis of AD dementia [45-47,141,155,168-170]. However, 40% or more of cognitively unimpaired individuals over age 80 have AD pathologic changes at autopsy or by biomarkers [55,171,172]. Thus multi domain amnestic dementia has reasonably good sensitivity for the presence of AD

pathologic changes but poor specificity for the absence of AD pathologic changes. This situation is analogous to inferring cerebral infarction from a clinical diagnosis of stroke which can be made, albeit with less diagnostic fidelity, in the absence of MRI based solely on a history and neurologic examination. What cannot be done without MRI is make a diagnosis of subclinical or silent stroke which is present in about 25% -30% of older persons [173-175]. Similarly, without biomarkers one has no information on preclinical AD.

A related issue is that many studies will not have biomarker data for complete ATN characterization of study participants. Because tau PET is relatively new, incomplete biomarker information will occur in studies that use *imaging* for amyloid and neurodegenerative biomarker characterization but lack tau PET. Participants in these studies may be categorized on the basis of information that is available i.e. A+ places the participant in the "Alzheimer's pathophysiologic continuum", A-N- is normal biomarkers and A-N+ is suspected non-AD pathophysiology (**Table 2**). A second common situation where biomarker data will be incomplete is studies with MRI or FDG PET, but without either PET or CSF molecular biomarkers for amyloid and tau. In this situation, while MRI or FDG PET cannot be used to indicate Alzheimer's pathophysiologic processes, they can be highly useful as measures of the severity of neurodegeneration which in turn is a powerful predictor of future clinical course.

Comparison to IWG

In addition to NIA AA, the other group that has established diagnostic guidelines for AD that incorporate biomarkers is the international work group (IWG) [59,69,70]. In the most recent formal IWG document, published in 2014 [70], the diagnosis of AD required the presence of cognitive symptoms plus biomarker evidence of AD pathophysiologic processes. This could be either an abnormal amyloid PET study or both abnormal CSF Ab and tau. The 2018 NIA-AA framework aligns with these criteria in recognizing that neither FDG PET nor MRI atrophy are specific for AD and thus cannot be used to support a diagnosis of AD. One difference though is that we regard CSF T tau as a nonspecific marker of neuronal injury while the IWG 2014 treats the combination of elevated T tau and low Ab 42 as a biomarker signature that is specific for AD. In addition, tau PET was not available in 2014 and thus was not included in the 2014 IWG criteria. In addition to an AD biomarker signature, cognitive symptoms (specifically either a typical or a known atypical AD phenotype) were also required to diagnose AD in IWG 2014.

Individuals with symptoms that fell short of dementia were labeled prodromal AD. Asymptomatic individuals with deterministic autosomal dominant mutations and Down's syndrome were an exception and were labeled presymptomatic AD. Cognitively unimpaired individuals with an abnormal amyloid PET study or a CSF study demonstrating both abnormal Ab and tau were labeled "asymptomatic at risk for AD". The most significant difference between 2014 IWG and 2018 NIA AA is that, with the exception of genetically determined AD, the 2014 IWG diagnosis of AD in living persons required both biomarker and clinical findings and therefore was not purely a pathophysiological based construct.

In a paper on preclinical AD (published in 2016 [14] may be considered part of the IWG series), the diagnosis of AD was extended to include asymptomatic individuals with biomarker evidence of both Ab and tau. In contrast to IWG 2014, symptoms were no longer required to reach a diagnosis of AD. Some differences with NIA AA 2018 remain however. IWG 2016 defines a cognitively unimpaired individual with an abnormal Ab biomarker and normal tau (A+T-) as "at risk for AD, asymptomatic A+" and one with A-T+ as "at risk for AD, asymptomatic T+". We label the former Alzheimers pathophysiology and the latter suspected non Alzheimer's pathophysiology (in keeping with the NIA AA pathologic definition of primary age related tauopathy as not Alzheimer's disease [95,96]). Importantly, the NIA AA 2018 criteria use "at risk" in a different connotation, referring to asymptomatic individuals with biomarker evidence of preclinical AD as having AD but being "at risk" of subsequent cognitive decline (as opposed to "at risk" for AD). While differences remain, IWG 2016 and NIA 2018 are aligned on the key issue that the combination of an abnormal Ab and tau biomarker constitutes AD regardless of cognitive symptoms and thus AD is a pathophysiologically defined entity throughout its continuum. This is an important step toward harmonization.

Future directions

The degree to which this framework adds value to the AD research field will be determined empirically by investigators in coming years. The design of this frame work poses many obvious and readily testable questions. For example, does the ATN biomarker scheme enable more refined prediction of future cognitive course than the four-class AN biomarker construct formed from 2011 NIA AA staging plus SNAP? Does the ATN biomarker scheme function equivalently when CSF vs. imaging are used for biomarker categorization? Does the

framework with numeric staging offer advantages for design of clinical trials over the traditional syndromal approach? Most of the biomarker data to date has been generated from largely highly educated people of European ancestry and it will be necessary to evaluate this framework in diverse cohorts across a range of ethnic and socio-economic groups. Similarly, much of the biomarker data to date has been generated from highly selected clinic samples and evaluation of the framework in population based samples is needed.

PET biomarkers of amyloid [15-20]or tau [114,115] deposition or MRI measures of neurodegeneration/neuronal injury [133,134] have been convincingly validated using tissue to tissue or image to tissue comparisons. However, CSF biomarkers reflect a complex interaction among many different physiologic rates and validation is more difficult than with imaging. Development of physiologically based methods to validate CSF biomarkers would be extremely helpful.

The framework we outline defines the presence and severity of Alzheimer's pathophysiologic processes by biomarkers and treats cognitive impairment as a symptom/sign of the disease rather than the definition of the disease. This approach should enhance efforts to understand both the biology of AD and the multi factorial etiology of dementia which has been obscured to some extent in the past by equating amnestic multi domain dementia with the presence of AD pathologic changes; and, by equating the absence of the prototypical dementia syndrome with the absence of AD pathologic changes. This approach can be adopted for other neurodegenerative disorders when specific biomarkers of other proteinopathies (α-synuclein, TDP43 and 3R or 4R tauopathies) become available.

We recognize that current biomarkers used in AD research are either expensive or invasive. The current generation of biomarkers is invaluable for discovery; however, widespread, routine clinical use will be facilitated by the development of less expensive and invasive biomarkers. For example, new ultrasensitive immunoassay techniques may enable measurement of minute amounts of brain specific proteins in blood samples [176]. Some candidate blood biomarkers such as neurofilament light protein show promise as non-disease specific tools to identify neurodegeneration [177]. An additional important significant scientific gap is the absence of biomarkers for common comorbidities in brain of older individuals. Both of these areas are in need of development.

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714 **Text Box #1 - Glossary**

Alzheimer disease (AD) – refers to plaque and tangle pathophysiologic processes, defined in vivo by abnormal amyloid and tau biomarkers (both are required)

Alzheimer's pathophysiology – early stage of Alzheimer's pathophysiological continuum, defined in vivo by an abnormal Ab biomarker alone

Alzheimer's pathophysiologic continuum – refers to individuals with biomarker designation of either AD or Alzheimer's pathophysiology

Biomarker group – refers to three categories of pathophysiologic processes a biomarker can measure: b-amyloid (A), paired helical filament tau (T) and neurodegeneration/neuronal injury (N)

Biomarker profile – binarizing each of the 3 biomarker groups into normal/abnormal (+/-) results in 8 possible biomarker profiles – e.g. A+T-N-, A+T+N-, etc.

Biomarker category – biomarker profiles are grouped into three possible biomarker categories: normal AD biomarkers, A-T-N-; Alzheimer's pathophysiologic continuum, any A+ combination; non Alzheimer's pathophysiology (i.e. SNAP), A-T+N-, A-T-N+, or A-T+N+.

Cognitively Unimpaired (CU) – cognitive performance in the non-impaired range for that individual – defined as not MCI or demented

Neurobehavioral symptoms – symptoms attributable to mood or behavioral disorders – e.g. anxiety, depression, apathy

Neurocognitive symptoms – umbrella term referring to either cognitive or neurobehavioral symptoms

Transitional neurocognitive decline –cognitive performance in the non-impaired range but with a subjective complaint of cognitive decline, a subtle decline measured on longitudinal cognitive testing, or both. May also be due to neurobehavioral symptoms alone.

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Text Box #2 – changes from NIA AA 2011

The 2018 NIA AA research framework builds on but implements a number of changes from the 2011 NIA AA guidelines. In 2018 the term AD refers to pathologic changes and therefore in living persons is defined solely by biomarker evidence of Alzheimer's pathophysiologic processes. Thus, the terms probable and possible AD based on clinical presentation alone are not used. AD is defined as a continuous process in both cognitive and biomarker domains (2018) rather than as three separate clinical entities (2011). Characterization of pathophysiologic processes by biomarkers is harmonized across the disease continuum in 2018. Biomarkers are grouped into those of b-amyloid, pathologic tau, and neurodegeneration or neuronal injury; unlike 2011 where tau and neurodegeneration/neuronal injury biomarkers were placed into the same category. While AD is defined by biomarkers, severity is staged by both biomarkers and cognitive symptoms. The 2018 NIA AA research framework outlines 3 different systems for staging the severity of cognitive symptoms. A *syndromal categorical* scheme which largely preserves the 3 clinical categories from 2011 – cognitively unimpaired, MCI and dementia. This is applicable to all members of the population (i.e. individuals with AD, non-AD and normal biomarker profiles are all included). A *numeric neurocognitive* staging scheme that is applicable only to individuals in the Alzheimer's pathophysiologic continuum. Finally, staging may be accomplished using continuous cognitive tests without defining discrete categories.

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Table 1 - ATN biomarker grouping

(A) Aggregated b-amyloid or associated pathophysiology
- CSF Ab 42, or 42/40 ratio
- Amyloid PET

(T) Aggregated tau (neurofibrillary tangles) or associated pathophysiology
- CSF phosphorylated tau
- Tau PET

(N) Neurodegeneration/ neuronal injury
- Anatomic MRI
- FDG PET
- CSF total tau

Table 2 – Biomarker profiles and categories

ATN profiles	Biomarker category	
A-T-N-	Normal AD biomarkers	
A+T-N-	Alzheimers pathophysiology	Alzheimer's pathophysiologic continuum*
A+T-N+	Alzheimers pathophysiology	
A+T+N-	Alzheimers disease	
A+T+N+	Alzheimers disease	
A-T+N-	Non- AD pathophysiology	
A-T-N+	Non- AD pathophysiology	
A-T+N+	Non- AD pathophysiology	

Binarizing the 3 ATN biomarker types leads to 8 different biomarker "profiles". Every individual can be placed into one of 3 general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathophysiology (dark grey), and those who are in the Alzheimer's pathophysiologic continuum (light grey). The term "Alzheimer's pathophysiologic continuum" is an umbrella term that denotes either Alzheimer's pathophysiology or AD.

*If an individual has an abnormal amyloid biomarker study, but a biomarker for tau is not available, then the individual is placed into the "Alzheimer's pathophysiologic continuum" category

Table 3 – Syndromal staging of cognitive continuum: applicable to all members of a research cohort independent from biomarker profiles

Cognitively Unimpaired

Cognitive performance within expected range for that individual based on all available information. This may be based on clinical judgment and/ or on cognitive test performance (which may or may not be based on comparison to normative data with or without adjustments for age, education, occupation, sex, etc.).

Cognitive performance may be in the impaired/abnormal range based on population norms but performance is within the range expected for that individual

A sub set of cognitively unimpaired individuals may report subjective cognitive decline and/or demonstrate subtle decline on serial cognitive testing.

Mild cognitive Impairment

Cognitive performance below expected range for that individual based on all available information. This may be based on clinical judgment and/ or on cognitive test performance (which may or may not be based on comparison to -normative data with or without adjustments for age, education, occupation, sex, etc.).

Cognitive performance is usually in the impaired/abnormal range based on population norms but this is not required as long as is performance is below the range expected for that individual

In addition to evidence of cognitive impairment, evidence of decline in cognitive performance from baseline must also be present. This may be reported by the individual or by an observer (e.g. study partner) or observed by change on longitudinal cognitive testing/behavioral assessments or by a combination of these.

May be characterized by cognitive presentations that are not primarily amnestic*

Although cognitive impairment is the core clinical criteria, neurobehavioral disturbance may be a prominent feature of the clinical presentation**

Performs daily life activities independently but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, either self-reported or corroborated by study partner.

Dementia

Substantial progressive cognitive impairment that affects several domains and/or neurobehavioral symptoms. May be reported by the individual or by an observer (e.g. study partner) or observed by change on longitudinal cognitive testing

Cognitive impairment and/or neurobehavioral symptoms result in clearly evident functional impact on daily life. No longer fully independent/requires assistance with daily life activities. This is the primary feature differentiating dementia from MCI.

May be subdivided into mild, moderate and severe

* For MCI and dementia: Cognitive impairment may be characterized by presentations that are not primarily amnestic

**For MCI and dementia: Although cognition is the core feature, neurobehavioral changes - e.g. changes in mood, anxiety, or motivation – commonly co-exist and may be a prominent part of the presentation.

Table 4. Nomenclature: syndromal cognitive staging combined with biomarkers

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	**A-T-N-**	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	A+T-N-	Preclinical Alzheimer's pathophysiology	Alzheimer's pathophysiology contributing to MCI	Alzheimer's pathophysiology contributing to dementia
	A+T-N+			
	A+T+N-	Preclinical Alzheimer's disease	Alzheimer's disease contributing to MCI	Alzheimer's disease contributi to dementia
	A+T+N+			
	A-T+N-	non-Alzheimer's pathophysiology, cognitively unimpaired	non-Alzheimer's pathophysiology contributing to MCI	non-Alzheimer's pathophysiolo contributing to dementia
	A-T-N+			
	A-T+N+			

Table 5. Risk of short term cognitive decline based on biomarker profile and cognitive stage*

		Syndromal Cognitive Stage		
		Cognitively unimpaired	**MCI**	**dementia**
Biomarker Profile	**A-T-N-**	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^- N^-$	Preclinical Alzheimer's pathophysiology	Alzheimer's pathophysiology contributing to MCI	Alzheimer's pathophysiology contributing to dementia
	$A^+ T^- N^+$	Preclinical Alzheimer's pathophysiology	Alzheimer's pathophysiology contributing to MCI	Alzheimer's pathophysiology contributing to dementia
	$A^+ T^+ N^-$	Preclinical Alzheimer's disease	Alzheimer's disease contributing to MCI	Alzheimer's disease contributing to dementia
	$A^+ T^+ N^+$	Preclinical Alzheimer's disease	Alzheimer's disease contributing to MCI	Alzheimer's disease contributing to dementia

*Non-Alzheimer's pathophysiology profiles are not included in table because the risk associated with different combinations of T+N-, T+N+, T-N+ among A- individuals has not been established

☐ rate of short term clinical progression expected to be low

■ rate of short term clinical progression expected to be high

Table 6: Numeric neurocognitive staging - applicable only to individuals in the Alzheimer's pathophysiological continuum

Stage 1

Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (again the choice of the investigators) for age, sex, education, etc.*

Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern

No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g. study partner) or by longitudinal cognitive testing if available

Stage 2

Normal performance within expected range on objective cognitive tests.

Transitional cognitive decline: decline in previous level of cognitive function which may involve any cognitive domain(s) (i.e. not exclusively memory).

May be documented through subjective report of cognitive decline that is of concern to the participant

Represents a change from individual baseline within past 1-3 years, and persistent for at least 6 months

May be corroborated by informant but not required

OR may be documented by evidence of subtle decline on longitudinal cognitive testing but not required

Or may be documented by both subjective report of decline as well as objective evidence on longitudinal testing

Although cognition is the core feature, mild neurobehavioral changes - e.g. changes in mood, anxiety, or motivation – may co-exist. In some individuals the primary compliant may be neurobehavioral rather than cognitive. **

No functional impact on daily life activities

Stage 3

Performance in the impaired/abnormal range on objective cognitive tests.

Evidence of decline from baseline, documented by the individual's report or by observer (e.g. study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments.

May be characterized by cognitive presentations that are not primarily amnestic***

Performs daily life activities independently but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, i.e., may take more time or be less efficient but still can complete, either self-reported or corroborated by study partner.

Stage 4

Mild dementia
Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g. study partner) report or by change on longitudinal cognitive testing.
Clearly evident functional impact on daily life, affecting mainly instrumental activities.
No longer fully independent/requires occasional assistance with daily life activities.

Stage 5

Moderate dementia
Progressive cognitive impairment or neurobehavioral changes Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.

Stage 6

Severe dementia
Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible.
Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

* For stages 1-6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
**For stages 2-6: Although cognition is the core feature, neurobehavioral changes - e.g. changes in mood, anxiety, or motivation – may co-exist. In some individuals the primary compliant may be neurobehavioral rather than cognitive.
***For stages 3-6: Cognitive impairment may be characterized by presentations that are not primarily amnestic

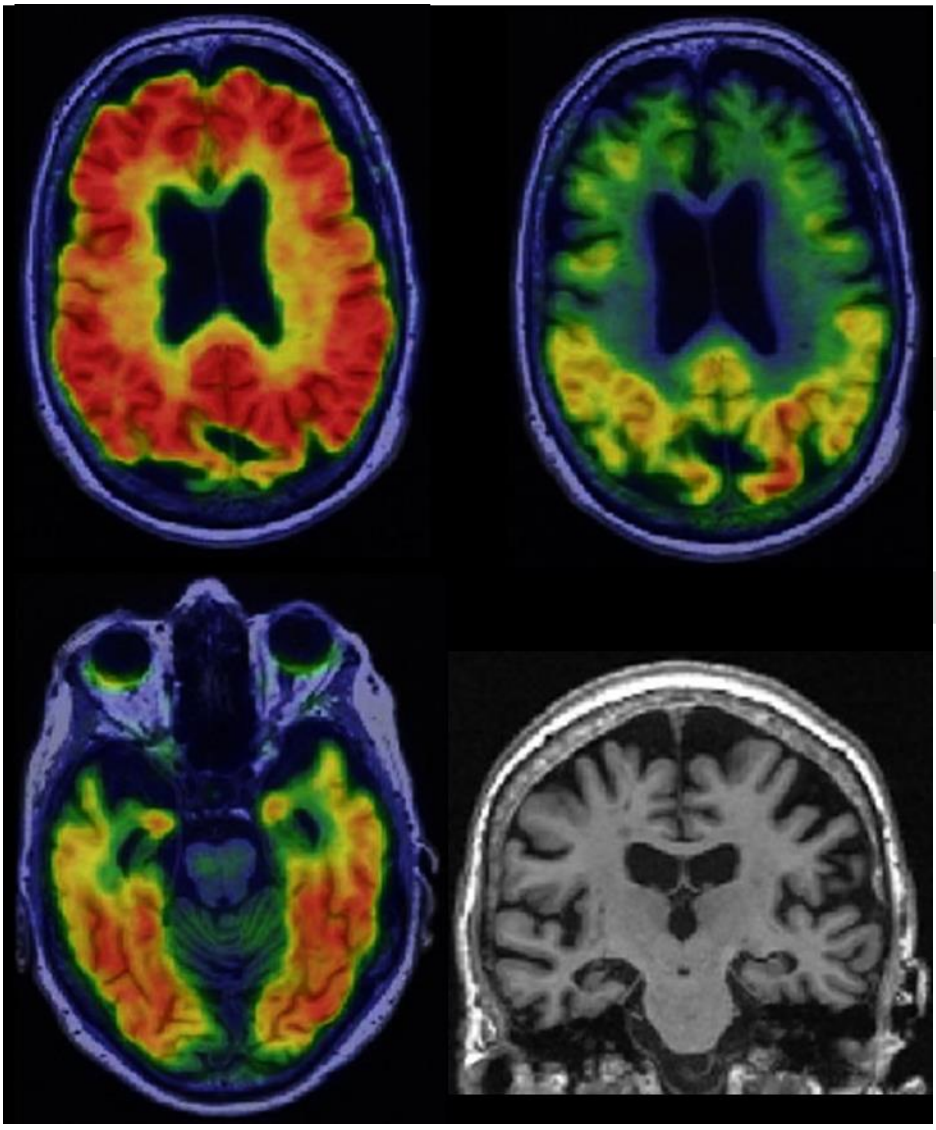

Fig 1 amnestic multi domain dementia. 75 yo woman, abnormal amyloid PET (a), tau PET (b,c) and atrophy on MRI (d). Biomarker profile, A+T+N+.

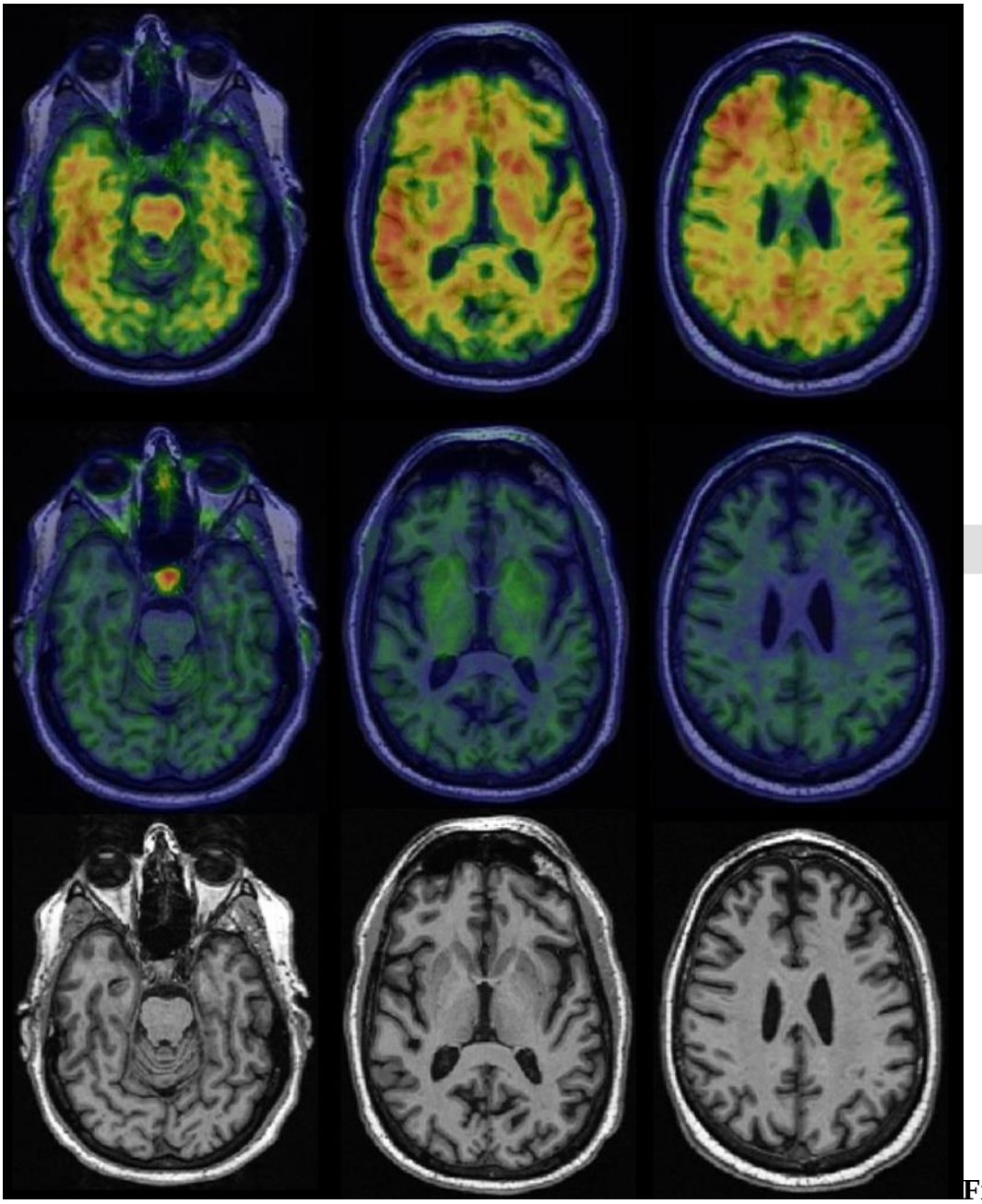

Fig 2. **Alzheimer's pathophysiology**. Cognitively unimpaired 67 yo man. Abnormal amyloid PET (top row), no uptake on tau PET (middle row), no atrophy on MR (bottom row). Biomarker profile A+T-N- .

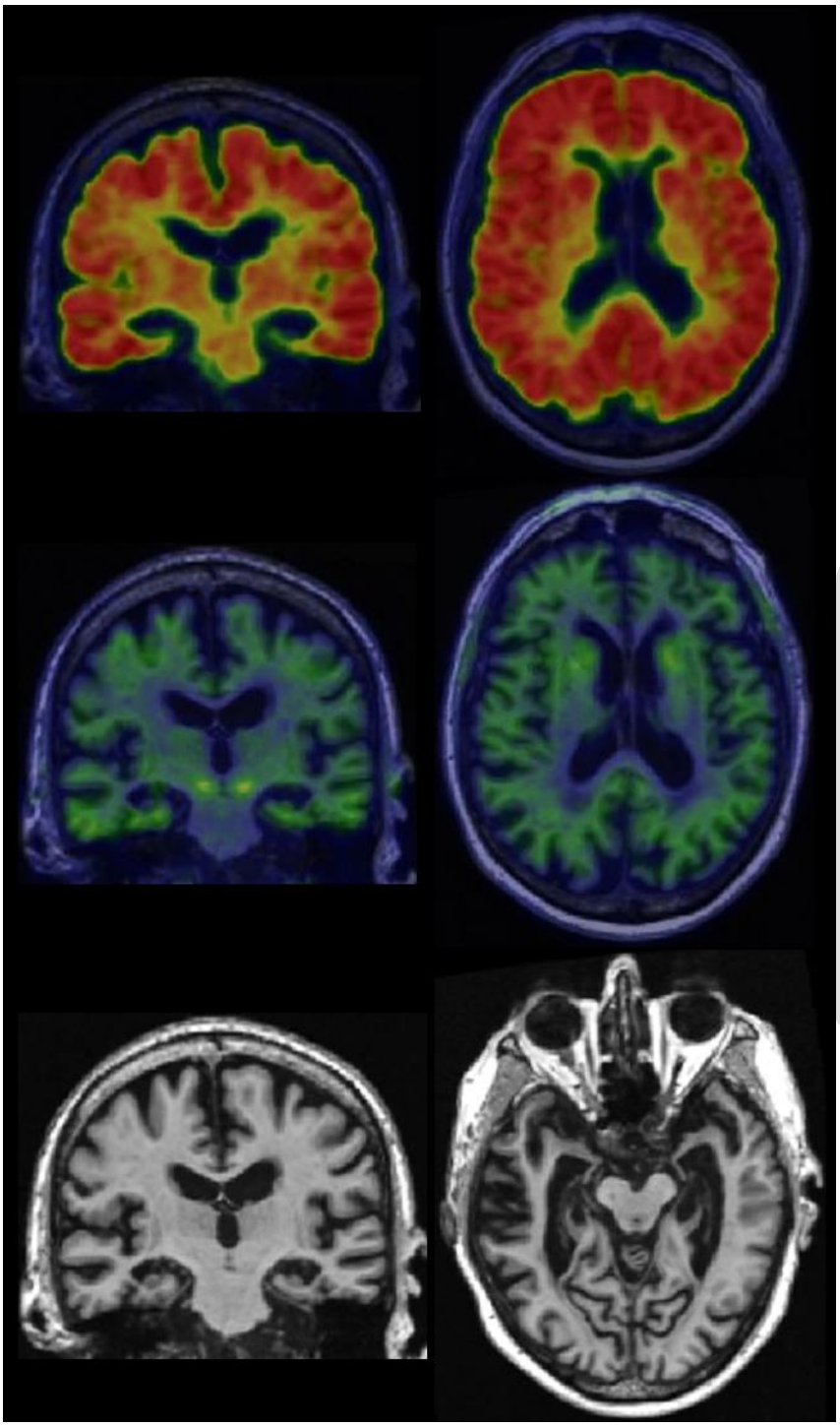

Fig 3. Amyloidosis and neurodegeneration without tauopathy

91 yo, M, severe amnestic dementia, abnormal amyloid PET (a,b), normal tau PET 9 (c,d) and severe medial temporal atrophy on MRI (e,f). The biomarker profile (A+ T- N+) suggests the patient has Alzheimer's pathophysiology (amyloidosis) plus an additional degenerative condition, possibly hippocampal sclerosis. However this assumption is speculative without autopsy confirmation.