NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease

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Clifford R. Jack, Jr. M.D., David A. Bennett, M.D., Kaj Blennow, M.D., Ph.D., Maria C. Carrillo, Ph.D., Billy Dunn, M.D., Samantha Budd Haeberlein, Ph.D., David M. Holtzman, M.D. William Jagust, M.D., Frank Jessen, M.D., Jason Karlawish, M.D., Enchi Liu, Ph.D., Jose Luis Molinuevo, M.D., Thomas Montine, M.D., Ph.D., Creighton Phelps, Ph.D., Katherine P. Rankin, Ph.D., Christopher Rowe, M.D., Philip Scheltens, M.D., Eric Siemers, M.D., Heather M. Snyder, Ph.D., Reisa Sperling, M.D.

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Abstract

In 2011 the National Institute on Aging and Alzheimer's Association (NIA-AA) created separate diagnostic recommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's 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 for observational and interventional research, not routine clinical care. In the NIA AA research framework Alzheimer's disease (AD) is defined by its underlying pathologic processes which can be documented by post-mortem examination or *in vivo* by biomarkers. The diagnosis is not based on the clinical consequences of the disease (i.e. symptoms/signs) in this research framework which shifts the diagnosis of AD in living people from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons. Biomarkers are grouped into those of β-amyloid deposition, pathologic tau, and neurodegeneration. Although we focus on AD as a continuum, the severity of cognitive impairment is denoted using two different categorical cognitive staging schemes: a scheme employing 3 traditional syndromal categories, and a 6 stage numeric scheme. We envision that defining AD as a biological construct will enable a more accurate characterization and understanding of the sequence of events that lead to cognitive impairment as well as the multi factorial etiology of dementia. This approach also will enable a more precise approach to interventional trials where specific pathways can be targeted in the disease process and in the appropriate people. Importantly, this construct should be examined in more diverse populations.

Finally we emphasize, that this report does *not* outline a rigid set of diagnostic criteria or guidelines. Rather, this framework is a flexible tool to generate and test hypotheses about the interactions among different pathologic processes (denoted by biomarkers) and cognitive symptoms.

1. Preamble

Alzheimer's disease (AD) was initially defined as a clinico-pathologic entity which was diagnosed definitely at autopsy and in life as possible or probable AD. Over time, however, the distinction between neuropathologic change and clinical symptoms became blurred. Consequently the term AD is often used to describe two very different entities: a prototypical clinical syndrome without neuropathologic verification, or AD neuropathologic changes. However, a syndrome is not an etiology but rather a clinical consequence of one or more diseases. A biological rather than a syndromal definition of AD is a logical step toward greater understanding of the mechanisms underlying its clinical expression. Disease modifying interventions must engage biologically defined targets and the dementia syndrome does not denote a specific biological target(s). In addition, the most rational framework with which to discover interventions that prevent or delay the initial onset of symptoms is a biologically based definition of the disease that encompasses both the clinical and the preclinical phases. This will advance the public health. Thus a framework suitable for interventional trials should be founded on a biologically based definition of AD and the framework should be harmonized between interventional and observational research.

Neuropathologic examination is the standard for defining AD and there are validated biomarkers that are proxies for AD neuropathologic changes. We propose a research framework grounded on a biomarker based definition of AD in living people. In many situations, however, biomarker characterization of research participants is not possible. Research without biomarkers has and will continue to constitute a vital part of the effort to evaluate the dementia and MCI syndromes. The presence of a biologically based research framework does not devalue research without biomarkers; the two approaches are complimentary. Also, this framework does not limit but rather enhances research into broadly defined dementia by providing a biologically based definition of one cause of dementia - AD.

The AD field is fortunate that biomarkers of important categories of neuropathologic change, i.e. β-amyloid deposition, pathologic tau, and neurodegeneration, have been and are being developed. This framework is focused on characterizing research participants with these biomarkers. AD biomarker characterization will identify some research participants who have no AD biomarker abnormalities as well as some who likely have diseases other than AD. This research framework does not ignore these individuals but rather provides a system for

characterizing them alongside individuals who are in the Alzheimer's continuum. The framework is also expandable to incorporate new biomarkers.

2. 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]. The framework described in this document has that same intention – to provide researchers a common language with which to communicate observations.

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 distinct clinically defined entities [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 refine confidence that AD pathologic changes 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

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 pathologic tau accumulation [15].

A major motivation for updating the 2011 guidelines has been the evolution in thinking about biomarkers. Studies published since 2011 have reinforced the idea that certain imaging and CSF biomarkers are valid proxies for neuropathologic changes of AD. Imaging-to-autopsy comparison studies have established that amyloid PET imaging is a valid *in vivo* surrogate for β-amyloid deposits (in brain parenchyma or vessel walls) [16-23]. It is also now widely accepted that CSF Aβ42 (or the Aβ42/40 ratio) is a valid indicator of the abnormal pathologic state associated with cerebral β-amyloid deposition [24]. An additional development has been the introduction of PET ligands for pathologic tau [25-27]. 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, for example cerebro vascular injury [28].

Based on this background, NIA-AA leadership commissioned a work group whose charge was to examine the 2011 guidelines in the context of current scientific knowledge and if appropriate update them. Members of the workgroup were selected by NIA-AA leadership with the goals of providing a range of scientific expertise, broad representation of different institutions and professional organizations involved with AD research, and gender and geographic diversity (including both within the US and international scientists).

3. 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 AD continuum. 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 [29-44].

Second, we determined that that these recommendations should be cast as a "research framework"; 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 general 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. 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 the extent to which temporal relationships and patterns of signs, symptoms and biomarkers expected by this framework align 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). Other areas of medicine have used this approach to define pathologic processes using biomarkers, for example, bone mineral density, hypertension, hyperlipidemia and diabetes are defined by biomarkers. Interventions on these biomarkers have been shown to reduce the likelihood of developing fractures, myocardial and cerebral infarctions [45,46].

Third, the committee recognized the research framework must function in two major applications – observational cohort studies and interventional 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.

4. The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined *in vivo* by biomarkers and by post mortem examination, not by clinical symptoms

We approached the definition of Alzheimer's disease with the distinction between a syndrome and a disease in mind. Some will argue that a specific syndrome, i.e. a multi domain amnestic dementia (after other potential etiologies have been excluded), 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 we elaborate in the following paragraph, there are two major problems with using a syndrome to define AD; one, it is neither sensitive nor specific for the neuropathologic changes that define

the disease, and two, it cannot identify individuals who have the disease but do not (yet) manifest signs or symptoms [47,48].

It is now well established that the prototypical multi domain amnestic dementia phenotype historically used to define AD dementia [49] does not rule in AD pathologic change at autopsy [50-52]. From 10% to 30% of individuals clinically diagnosed as AD dementia by experts do not display AD neuropathologic changes at autopsy [50] and a similar proportion have normal amyloid PET or CSF Aβ42 studies [53-62]. Thus the multi domain amnestic dementia phenotype is not specific; it can be the product of other diseases as well as AD [51]. Non amnestic clinical presentations, i.e. language, visuospatial, and executive disorders, may also be due to AD [63-66]. In addition, AD neuropathologic changes are often present without signs or symptoms, especially in older persons. Thirty to forty percent of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy [67,68,69] and a similar proportion have abnormal amyloid biomarkers [32,53-55,60,70-73]. The fact that an amnestic multi domain dementia is neither sensitive nor specific for AD neuropathologic change suggests that cognitive symptoms are not an ideal way to define AD.

The traditional approach to incorporating biomarkers into models of AD began with patients' clinical symptoms, which appear late in the disease, and worked backwards to relate symptoms to biomarker findings. The committee recommends a different approach where the neuropathologic changes detected by biomarkers define the disease. Defining AD by neuropathologic change independent from clinical symptoms represents a profound shift in thinking. For many years AD was conceived as a clinical-pathological construct [49]; it was assumed that if an individual had typical amnestic multi domain symptoms they would have AD neuropathologic 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 later became a clinical-biomarker construct with International Work Group (IWG) [64,74,75] 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, and NIA AA neuropathologic guidelines).

5. AD biomarkers

Various imaging and CSF biomarkers are widely used in AD and brain aging research and an organized approach is needed for a generalizable research framework. The committee addressed this by following the recommendations from a recent position paper that outlined an unbiased descriptive classification scheme for biomarkers used in AD and brain aging research [15]. The scheme (which is labeled ATN) recognizes three general groups of biomarkers based on the nature of the pathologic process that each measures (**Table 1**) [15]. Biomarkers of β-amyloid plaques (labeled "A)" are cortical amyloid PET ligand binding [76,77] or low CSF Aβ42 [78-80]. Biomarkers of fibrillar tau (labeled "T") are elevated CSF phosphorylated tau (P-tau) and cortical tau PET ligand binding [79,81]. Biomarkers of neurodegeneration or neuronal injury (labeled "N") are CSF total tau (T-tau) [82], FDG PET hypometabolism and atrophy on MRI [83-89].

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 closely associated with pathologic tau. However, it is increasingly recognized that neurodegeneration/injury, even in classic AD brain regions, also occurs in non-AD conditions. This is particularly so in elderly individuals where co morbidities are common [90]. ATN classification provides a solution to this problem which is to separate biomarkers that are specific for pathologic tau 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**) [15]. 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 lumbar puncture and MRI are accessible 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.

6. Definition of AD

Once the committee agreed that AD should be defined as a biologic construct that is identified by biomarkers in living people, the next logical question was: what biomarker signature or profile(s) defines 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 and clinical/cognitive decline than individuals without biomarker evidence of β-amyloid deposition [12,32,80,91-97] 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 [53]. 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 pathologic changes (i.e. tauopathy and neurodegeneration) that ultimately lead to cognitive deterioration. These findings are supported by clinic-pathologic studies as well [98,99]. Consequently a widely held view is that amyloid biomarkers represent the earliest evidence of AD neuropathologic change 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 neuropathologic criteria for AD [100,101] which suggests that evidence of abnormalities in both β-amyloid and pathologic tau biomarkers should be present in order to apply the label "Alzheimer's disease" 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 deposition alone (abnormal amyloid PET scan or low CSF Aβ 42 or 42/40 ratio) with a normal pathologic tau biomarker would be assigned the label "Alzheimer's pathologic change" (**Table 2**, **Fig 2**). The term "Alzheimer's disease" would be applied if biomarker evidence of both Aβ and pathologic tau was present (**Table 2, Fig 1**). Alzheimer's pathologic change and Alzheimer's disease are not regarded as separate entities but earlier and later phases of the "Alzheimer's continuum" (an umbrella term that includes both Alzheimer's pathologic change and Alzheimer's disease). These definitions

are applied independently from 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.

7. 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 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 continuum. Pathologic tau biomarkers determine if someone who is in the Alzheimer's continuum has AD, since both Aβ and tau are required for a neuropathologic diagnosis of the disease. 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 the Alzheimer's continuum.

8. Biomarker profiles and categories

In many research studies it will be most appropriate to treat biomarkers of amyloid, pathologic tau and neurodegeneration/neuronal injury as continuous measures without employing normal/abnormal cut points. However biomarkers used in medicine often use a cut point denoting normal vs abnormal values to support management decisions for an individual patient. The need for discrete categorization of biomarker continua is also obvious for AD clinical trials where hard cutpoints serve as inclusion/exclusion criteria. We recognize from the experience of more mature biomarker defined disease such as cardiovascular disease and osteoporosis that as knowledge of biomarkers and other factors increase, the biomarker categorization may change from using cut-points of "normal" or abnormal," to multi-factorial and multidimensional scoring systems (see for example FRAX criteria for osteoporosis).

The addition of a normal/abnormal cut point for each ATN biomarker group results in 8 different ATN *"biomarker profiles"* (**Table 2**); A+T-N-, A+T+N+, etc. Based on the definitions

of Alzheimer's pathologic change and AD outlined earlier, the ATN biomarker system assigns every individual one of three *"biomarker categories"* (**Table 2**): 1) individuals with normal AD biomarkers; 2) those in the Alzheimer's continuum (subdivided into Alzheimer's pathologic change 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 neuropathologic processes other than AD [102] and has been labeled "suspected non Alzheimer's pathophysiology" (SNAP) [37].

It is worthwhile re-emphasizing that, like the 2012 NIA-AA classification system for AD neuropathic change [100,101], ATN scoring of biomarkers is independent from clinical symptoms.

The rate of cognitive decline is significantly greater for cognitively impaired and unimpaired 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 [29-34,38,39,41-44]. These data firmly establish that more advanced disease 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 Alzheimer's continuum.

While the term stage is more familiar, we use 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 that 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+ [103]. It is not certain though where the A+T-N+ profile would fit in a sequential staging scheme. A likely possibility is that A+T-N+ represents evidence of comorbidity – i.e. A+T- represents Alzheimer's pathologic change while N+ represents evidence of non-AD neurodegeneration/neuronal injury [104] (see **Fig 3**). Biomarker-autopsy studies are needed to clarify this. We can, however, be confident that A+T-N- represents an early neuropathologic stage while A+T+N+ represents the most advanced. Staging disease severity is thus accomplished by combining binary information from each of the 3 biomarker groups; the more biomarker groups that are abnormal, the more advanced the pathologic stage [103].

8.1 Alternatives to binary biomarker groups: Given that Alzheimer's pathologic change and AD are defined by biomarkers, a single cut point is needed in many situations. However, as pointed out in the ATN position paper [15] , 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 [105,106].

Situations can be also envisioned where a three range (2 cut points) approach might be useful [15,107]. 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.

8.2 *Personalized medicine:* The ATN system moves AD research in the direction of personalized medicine by coding pathologic change in three categories for each research participant and allows for future flexibility by adding other biomarkers as they are discovered and validated. This level of granularity in biomarker classification, combined with genetic and clinical information, will presumably be useful in tailoring treatment to the individual when various treatments become available.

9. Characteristics and limitations of biomarkers

9.1 *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 from the lumbar sac 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 [108,109]. Imaging measures, on the other hand, represent the magnitude of the neuropathologic load or damage accumulated over time. Low CSF Aβ42 is therefore best considered a biomarker of a *pathologic state* that is *associated with* amyloid plaque formation and not a measure of amyloid plaque load as amyloid PET is. Similarly, CSF P-tau is best considered a biomarker of a *pathologic state* that is *associated with* PHF tau formation and not a measure of pathologic tau deposits as tau PET is.

Discordances between imaging and CSF biomarkers may occur [35,40,110-113]. In some situations discordance in normal/abnormal labels between an imaging and CSF biomarker within a study is simply a product of how cut points were established that can be rectified by adjusting cut points. The continuous relationship between CSF Aβ42 and amyloid PET, however, is "L-shaped" rather than linear [110,111,114]. This may be due to a temporal off set between these 2 measures [115-117]. In the limited data currently available, tau PET ligand binding is linearly correlated with elevated CSF P tau [109,118,119], however, the correlation is imperfect. Given these observations one might ask how could a CSF and an imaging measure be used as biomarkers of a common pathologic process – e.g. amyloidosis, pathologic tau or neurodegeneration/neuronal injury? The answer lies in the chronic nature of AD which spans years- to-decades. Thus an ongoing active pathologic state, denoted by CSF, and the accumulation of neuropathologic load, denoted by imaging, will agree over the long term.

9.2 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 [27]. 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 [120-122]. *In vivo* imaging to autopsy comparisons also indicate specific binding of AV1451 to PHF tangles [22] and correlation with Braak NFT stage [123]. 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 [119,124-135]. New tau PET ligands are in the early stages of development [136] 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.

9.3 CSF T tau and P tau: The most thoroughly examined P-tau epitope as a CSF biomarker for AD is Threonine 181 (P-tau181) [137], but other assays for the concentration of P-tau231 and P-tau199 correlate tightly with P-tau181 and show very similar diagnostic accuracy [138]. CSF levels of T-tau and P-tau are tightly correlated within cohorts of AD patients and controls [139], and the

correlation between CSF T tau and P tau is typically much higher than between CSF T tau and MRI or FDG PET [35,109]. Therefore it is reasonable to ask why not place both CSF T tau and P tau in the pathologic tau biomarker group? The answer lies in the divergent behavior of these two measures in other diseases. There is a marked temporary increase in T-tau, with no change in P tau, in traumatic brain injury and stroke that correlates with the severity of neuronal damage [140,141]. It is difficult to rationalize 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 [142,143]. The only disorder that consistently shows an increase in CSF P-tau is AD [137], 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 [81,144]. Taken together these data indicate that CSF T-tau reflects the intensity of neuronal damage at a specific point [108] while elevated CSF P-tau reflects an abnormal pathologic state associated with PHF tau formation.

9.4 Biomarkers of neurodegeneration or neuronal injury: Biomarkers in the N group (**Table 1**) are indicators of neurodegeneration or neuronal injury from many causes; they are not specific for neurodegeneration 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. In addition, unlike A and T, the N biomarkers do not map onto neuropathologic findings used to diagnose AD. For purposes of simplification, it might therefore be tempting to eliminate the N biomarker group from the research framework. 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 [29-34,38,39,41-44] than an abnormal amyloid study alone. This is logical given that neurodegeneration particularly synapse loss is the aspect of AD neuropathologic change that correlates most closely with symptoms [145]. Thus the neurodegeneration/ neuronal injury biomarker group provides important pathologic staging information and for this reason it seems inadvisable to eliminate this class of biomarkers from the AD research framework. Also, without the N category, the A+T-N+ would

not be formally captured and this will likely be a biomarker category of significant academic interest (see **Fig 3**).

It is important to note some differences among biomarkers in the N group. [108]Atrophy on MR likely reflects cumulative loss and shrinkage of the neuropil [146-148]. CSF T tau likely indicates the intensity of neuronal injury at a given point in time [105,108,149,150]. FDG PET likely indicates both cumulative loss of the neuropil and functional impairment of neurons. These differences may result in discordances [35,42,109,113,151].

9.5 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 [152]. 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 [17,21]. 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 [20]. Thus, a negative amyloid PET should not be equated with the complete absence of β-amyloid in the brain or even with absent sparse neuritic plaques. Clinico-pathologic studies suggest that low levels of pathologic changes are associated with subtle cognitive deficits among cognitively unimpaired persons [7,153]. The amount of pathologic 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 pathologic change 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 neuropathologic 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 neuropathologic changes in the brain.

9.6 Flexibility to incorporate new biomarkers: The NIA AA research framework is designed around biomarker technology that is presently available. TDP43 and α-synuclein

proteinopathies, micro infarcts, hippocampal sclerosis and agyrophillic grains frequently co-occur with AD pathologic changes in elderly individuals [154,155]; however, validated biomarkers are not presently available for these. The ATN biomarker scheme is expandable to incorporate new biomarkers. For example, a vascular biomarker group could be added, i.e. ATNV, when a notion of what constitutes V+ is developed. And, when biomarkers for TDP43 and α-synuclein are developed, ATN can be expanded to incorporate these as well. An important pathologic process in AD is activation of the innate immune system with both astrocytosis and microgliosis [156]. There are not yet reliable markers of these changes though some are emerging [157,158] and when developed could likewise be added to the biomarker scheme. CSF neurogranin is presumed to measure synaptic degeneration and loss [159,160] and neurofilament light chain [161] 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. In fact these may ultimately be preferable to T tau as a CSF based N biomarker because CSF P tau and T tau are so highly correlated in AD they may not seem to provide independent information in AD.

9.7 *Biomarkers other than ATN:* While we focus on biomarkers of AD we emphasize that other currently available biomarkers have a valuable role to play. MRI provides useful information about cerebro vascular disease. Although a biomarker for alpha-synuclein does not yet exist, decreased striatal dopamine transporter uptake of ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) single photon emission computed tomography (DAT scan) is thought to reflect nigrostriatal degeneration in Lewy body disease [162]. Likewise, the FDG PET cingulate island sign is often present in Lewy body disease [163] . These tests may provide useful information about non AD pathologic processes and may be used alone or concordantly with ATN biomarkers to provide a more complete picture of the heterogeneous etiologic nature of dementia. For example, in an individual with an A+T-N+ biomarker profile and cerebral infarction(s), atrophy is attributable at least in part to vascular brain injury.

The fact that most dementia is multi factorial presents a challenge both for diagnosis and treatment. It is highly likely that in individuals with multiple brain neuropathologic processes each makes some contribution to the individual's cognitive impairment. However, the fact that biomarkers of all causes of dementia do not exist at present should not prevent investigators from

studying the disease for which a useful suite of biomarkers does exist – AD. In an individual with multiple neuropathologic processes, treating one of them (i.e. AD) should have a beneficial effect. Therefore using biomarkers to aid in discovery of treatments for AD should not be delayed until biomarkers of all possible etiologies for dementia have been developed.

10. Cognitive staging

Like biomarkers, cognitive performance exists on a continuum. An obvious approach to cognitive staging therefore is to use continuous instruments. Continuous cognitive measures may be the preferred outcome measure in many modern clinical trials [164]. While recognizing that cognition does exist on a continuum, 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 the research framework we avoid the notion of separate entities, and instead use the terminology staging the cognitive continuum.

One of the specifications of the NIA AA research framework was that it be applicable in two distinct research contexts – interventional trials and observational research. In many if not most modern AD interventional trials, individuals are selected for inclusion with the aid of biomarkers. The studies are concerned only with a defined portion of the population – those in the Alzheimer's continuum. For observational research on the other hand the research questions often require that all members of a recruited sample are included (those with non-AD pathologic changes, normal AD biomarkers, and those in the Alzheimer's 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 is a *numeric clinical staging* scheme that is applicable only to those in the Alzheimer's continuum, which the committee felt might be particularly useful in clinical trials.

The committee also recognized that cognitive 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.

10.1 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 many large ongoing studies [53,165-167]. 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 [168]. It has also been codified for clinical practice in the DSM 5 criteria [169] by the mild cognitive disorder (essentially MCI) and major cognitive disorder (essentially dementia) labels.

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 NIA AA 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 NIA AA research framework the diagnosis can be based on clinical judgment or on cognitive test performance alone. 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 NIA AA research framework the labels CU, MCI and dementia denote only severity of cognitive impairment and are not used to infer its etiology.

Nomenclature: Every individual will have both a biomarker profile and a cognitive stage. Many researchers indicated a preference to retain traditional descriptive terms from 2011 that combined these two sources of information. In **Table 4** we illustrate descriptive terminology combining biomarker profile and a cognitive stage which retains nomenclature from 2011 but

does depart from 2011 naming in some ways. For example in the research framework the label "Alzheimer's disease *with* MCI" 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 **Table 4** we further recognize contributions of co morbidities for individuals with an A+T-N+ biomarker profile with the descriptive phrase "Alzheimer's and concomitant suspected non Alzheimer's pathologic change". By this we imply that in an A+T-N+ MCI individual both Alzheimer's and non-Alzheimer's pathologic change may be contributing to the individual's impairment. In addition to carrying forward NIA AA 2011 terminology we also incorporate the term "prodromal AD" from the IWG which many investigators find useful (**Table 4)**. **Fig 4** is a Venn diagram illustrating a simplified schema of **table 4**.

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)** different biomarker profiles will be present in the population. Likewise different cognitive stages may be present in the population among people with the same biomarker profile (i.e. along a given row in **Table 4)**. Many effects can blur the relationship between neuropathologic severity and cognitive symptoms at the individual level. These include protective factors, such as cognitive reserve [170-172], as well as risk factors, such as co morbid pathologic processes [173,174,175].

Table 5 illustrates the principle that biomarker profiles within the Alzheimer's 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.

10.2 *Alternative naming, avoiding the term Alzheimer's disease:* While many investigators prefer the descriptive terms in the cells of **Table 4**, others indicated a preference to entirely avoid using terms that have any reference to Alzheimer's disease because of historic controversies associated with these terms. The NIA AA research framework provides an alternative to descriptive names in the cells of **table 4** which is to simply combine ATN biomarker profile and cognitive stage without using descriptive phrases. That is, combine the row and column names from **table 4** without the descriptive phrases in the cells of the table; for example, "A+T+N+ dementia"

instead of “Alzheimer’s disease with dementia”. Some groups may prefer this “row and column” naming approach.

10.3 Numeric clinical staging: The committee also created a “numeric clinical staging scheme” (**Table 6)** that avoided traditional syndromal labels and is applicable for only those in the Alzheimer’s 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 cognitive symptoms culminating in dementia. A common application for this numeric cognitive staging scheme would be interventional trials.

It is apparent that numeric stages 1-6 (**Table 6)** bear a close resemblance to the global deterioration scale [176] 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 the Alzheimer’s continuum in asymptomatic individuals. Stage 2 describes the earliest detectable clinical consequence of the Alzheimer’s continuum and is similar to “stage 3 preclinical AD” in the 2011 NIA AA guidelines [3]. Stage 3 describes cognitive 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 may involve any cognitive domain(s) – not only memory. We suspect that finding individuals in stages 3-6 with an A+T-N- profile will be uncommon, as clinical symptoms are typically associated with evidence of neuronal injury. We also suspect that A+T-N+ biomarker profiles in symptomatic individuals may be due to the combination of Alzheimer’s and non Alzheimer’s pathologic change. However, both of these biomarker profiles are included in all 6 numeric stages for sake of completeness.

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**) is 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 Alzheimer's 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 continuum, then it is reasonable to label subjective complaints or evidence of subtle cognitive decline as a transitional stage attributable to the pathologic process. However, in the syndromal categorical scheme (**table 3)** where abnormal biomarkers are not required, it is not reasonable to assume that subjective complaints (which are very common in aging) represent a symptom of any specific disease(s). 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 [177]. 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 "clinical staging" rather than cognitive staging to recognize that early clinical manifestations of AD may be either cognitive or neurobehavioral. Individuals must have cognitive impairment to be placed into numeric stages 3 - 6 [178]. We recognize though 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 limited to individuals in the Alzheimer's 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 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 clinical stage and biomarker profile- i.e. stage 1a, stage 2c, etc.

11. Implementation

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 cognitive testing batteries 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 should be sensitive to location [179]. 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 [63,180]. Cut points must be determined and 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 [181], EADC-ADNI Harmonized Protocol for hippocampal segmentation [182], Alzheimer's Association Global Biomarkers Standardization Consortium [183] and International Federation of Clinical Chemistry Working Group for CSF proteins [184]. These efforts are the subject of ongoing research but universal standards have not yet been established [185]. 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 neuropathologic standards [20,21,186]. 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 methodologic issues with the assumption that this was best left to expert work groups and individual research centers.

12. Genetics

Genetics is not formally included in the research framework because our concept of disease rests on neuropathologic change (that can be detected by biomarkers). In contrast genetic variants do not measure pathologic change but rather indicate an individual's risk for developing pathologic change. For example, inheritance of an *APOE* ε4 allele neither defines the presence of Alzheimer's pathologic change or AD, nor does it indicate any particular stage of the disease.

The penetrance of the classic autosomal dominate mutations in *APP*, *PSEN1*, or *PSEN2*, is essentially 100% and for this reason it could be argued that these mutations confer a pathologic state that exists from conception. However, our definitions of AD pathologic change and AD are based on biomarker evidence of disease.

13. 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 who are reluctant to participate in research studies, or low and middle income countries without adequate financial resources to support biomarker research. In other cases, a study may simply not be able to justify the cost and participant burden, such as large, longitudinal, community-based 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 non-specific cognitive decline or dementia. Clinical research without biomarkers therefore remains a valuable component of the research landscape.

Investigators involved in studies without biomarkers may wish to employ the traditional terms possible or probable AD dementia for research participants who display a prototypical syndrome (although these terms are not employed in the NIA AA research framework). Such studies provide valuable information on the burden of disability. In both the 1984 [49] and in the

2011 NIA AA [1] criteria for AD dementia a probabilistic assumption about AD pathologic changes was inferred from the clinical presentation alone. AD neuropathologic change is documented in 80%, or more of cases with a traditional clinical diagnosis of "AD dementia" [50-52,154,174,187-189]. However, 40% or more of cognitively unimpaired individuals over age 80 have AD neuropathologic changes at autopsy or by biomarkers [60,190,191]. Thus multi domain amnestic dementia is reasonably good at identifying the presence of AD neuropathologic changes (see **Fig 5** though for an example of clinical misdiagnosis of "AD dementia"), but is incapable of identifying the absence of AD neuropathologic 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 [192-194]. 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 continuum", A-N- is normal biomarkers and A-N+ is suspected non-AD pathologic change (**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 the Alzheimer's continuum, they can be highly useful as measures of neurodegeneration which in turn is a powerful predictor of future clinical course.

14. Comparison to IWG

In addition to the NIA AA, the other group that has established diagnostic guidelines for AD that incorporate biomarkers is the international work group (IWG) [64,74,75]. In the most recent formal IWG document, published in 2014 [75], the diagnosis of AD required the presence of cognitive symptoms plus an AD biomarker signature. This could be either an abnormal amyloid PET study or both abnormal CSF Aβ and tau. The NIA-AA research framework aligns with

these criteria in recognizing that neither hypometabolism nor 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 Aβ 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 those with 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 the NIA AA research framework 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 biological construct.

In a paper on preclinical AD (published in 2016 [14] that may be considered part of the IWG series), the diagnosis of AD was extended to include asymptomatic individuals with biomarker evidence of both Aβ and tau. In contrast to IWG 2014, symptoms were no longer required to reach a diagnosis of AD. Some differences with the NIA AA research framework remain however. Preclinical AD 2016 defines a cognitively unimpaired individual with an abnormal Aβ 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 Alzheimer's pathologic change and the latter suspected non Alzheimer's pathologic change (in keeping with the NIA AA pathologic definition of primary age related tauopathy as not Alzheimer's disease [100,101]). Importantly, the NIA AA research framework uses "at risk" in a much different connotation, referring to asymptomatic individuals with biomarker evidence of 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 the NIA research framework 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 biologically defined entity throughout its continuum. This is an important step toward harmonization.

15. Future directions

We emphasize, that this framework is *not* a rigid set of diagnostic criteria or guidelines. Rather, this research framework is a flexible tool to generate and test hypotheses concerning the interactions among different pathologic processes (denoted by biomarkers) and cognitive symptoms.

For conceptual completeness, we have outlined what undoubtedly seems like a complex system, but it is important to note that the design of this frame work poses many questions that are readily testable using sub sets of individuals in the population. Many research questions may employ only a few of the cells in **Table 4** and thus large research cohorts are not necessary to evaluate many aspects of this framework. For example, are rates of cognitive decline different for different manifestations of Transitional Cognitive Decline (subjective report, subtle decline on testing, or neurobehavioral symptoms)? How do cognitive outcomes differ among various biomarker profiles? Is the prevalence of cerebrovascular disease different among the three suspected non-AD pathologic change biomarker profiles (A-T+N-, A-T-N+, A-T+N+)? Etc.

Most of the biomarker data to date has been largely been generated from 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 [195]. 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.

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 [196]. Some candidate blood biomarkers such as neurofilament light protein show promise as non-disease specific tools to identify neurodegeneration [197]. Plasma β-amyloid measures now show promise as a screening test [198]. In the future, less invasive/expensive blood-based biomarker tests along with genetics, clinical and demographic information will likely play an important screening role in selecting individuals for more expensive/invasive biomarker testing. This has been the history in other biologically defined diseases such as cardiovascular disease (see for example the 2013

ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults) [199].

The NIA-AA research framework defines the presence and severity of AD 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 neuropathologic changes; and, by equating the absence of the prototypical dementia syndrome with the absence of AD neuropathologic changes.

Text Box 1 - Glossary

Alzheimer disease (AD) – refers to β-amyloid plaques and pathologic tau deposits, defined in vivo by abnormal biomarkers of β-amyloid and pathologic tau (both are required)

Alzheimer's pathologic change – early stage of Alzheimer's continuum, defined in vivo by an abnormal β-amyloid biomarker with normal pathologic tau biomarker

Alzheimer's continuum – refers to individuals with biomarker designation of either AD or Alzheimer's pathologic change

Biomarker group – refers to three different pathologic processes of AD that a biomarker can measure: β-amyloid (A), pathologic 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 continuum, any A+ combination; non Alzheimer's pathologic change (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

Transitional cognitive decline –cognitive performance in the non-impaired range but with a subjective complaint of cognitive decline, or a subtle decline measured on longitudinal cognitive testing, or neurobehavioral symptoms, or combinations of these.

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806 **Text Box 2 – ATNC measures have different roles for definition and staging**

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Definition
A: Aβ biomarkers determine whether or not an individual is in the Alzheimer's continuum.
T: Pathologic tau biomarkers determine if someone who is in the Alzheimer's continuum has AD.

Staging severity
N: Neurodegenerative/ neuronal injury biomarkers
C: cognitive symptoms

Text Box 3 – Flexibility of the ATN system

The ATN system is designed to incorporate new biomarkers within existing ATN groups. For example, CSF neurogranin or NFL will likely be added to N group.

The ATN system is also designed to incorporate new biomarkers in categories beyond ATN. For example when a standard measure of cerebro vascular disease has been developed ATN will be expanded to ATNV. When a biomarker for synuclein has been developed ATNV will be expanded to ATNVS, etc.

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813 **Text Box 4 – Alternative naming, avoiding the term Alzheimer's disease**

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Some investigators may prefer to avoid using descriptive names in the cells of Table 4, including the term Alzheimer's disease. An alternative is to combine the row and column names from table 4 without the descriptive phrases in the cells of the table; for example, "A+T+N+ with dementia" instead of "Alzheimer's disease with dementia".

Text Box 5 – changes from NIA AA 2011

The NIA AA research framework builds on but implements a number of changes from the 2011 NIA AA guidelines. In the research framework the term AD refers to pathologic processes and therefore in living persons is defined by biomarkers. AD is defined as a continuous process in both cognitive and biomarker domains in the research framework rather than as three separate clinical entities in the 2011 guidelines. Characterization of pathologic processes by biomarkers is harmonized across the disease continuum in the research framework. Biomarkers are grouped into those of β-amyloid, pathologic tau, and neurodegeneration or neuronal injury; unlike 2011 where tau and neurodegeneration/neuronal injury biomarkers were placed into the same category. Unlike 2011, biomarker staging includes all members of the population - i.e. individuals in the Alzheimer's continuum, with non-AD pathologic changes and with normal biomarker profiles. The research framework outlines 2 different systems for staging the severity of cognitive symptoms. A *syndromal categorical* scheme which largely preserves the three clinical categories from 2011 – cognitively unimpaired, MCI and dementia. This is applicable to all members of the population regardless of biomarker profile. A *numeric clinical* staging scheme that is defined only for individuals in the Alzheimer's continuum.

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Table 1 - ATN biomarker grouping

(A) Aggregated β-amyloid or associated pathologic state

CSF Ab 42, or 42/40 ratio

Amyloid PET

(T) Aggregated tau (neurofibrillary tangles) or associated pathologic state

CSF phosphorylated tau

Tau PET

(N) Neurodegeneration or 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-	Alzheimer's pathologic change	Alzheimer's continuum*
A+T-N+	Alzheimers pathologic change	
A+T+N-	Alzheimers disease	
A+T+N+	Alzheimers disease	
A-T+N-	Non- AD pathologic change	
A-T-N+	Non- AD pathologic change	
A-T+N+	Non- AD pathologic change	

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 pathologic change (dark grey), and those who are in the Alzheimer's continuum (light grey). The term "Alzheimer's continuum" is an umbrella term that denotes either Alzheimer's pathologic change 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 continuum"

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. Descriptive 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 pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ N^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ N^+$			
	$A^+ T^- N^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementi
	$A^- T^+ N^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic cha with dementia
	$A^- T^- N^+$			
	$A^- T^+ N^+$			

Shading denotes 3 general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathologic change (dark grey), and those who are in the Alzheimer's continuum (light grey).

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 pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^- N^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^+ T^+ N^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ N^+$			

Non-Alzheimer's continuum 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 clinical staging - applicable only to individuals in the Alzheimer's 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. Neurobehavioral symptoms should have a clearly defined recent onset which persists and cannot be explained by life events. **

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.

***For stages 3-6: Cognitive impairment may be characterized by presentations that are not primarily amnestic

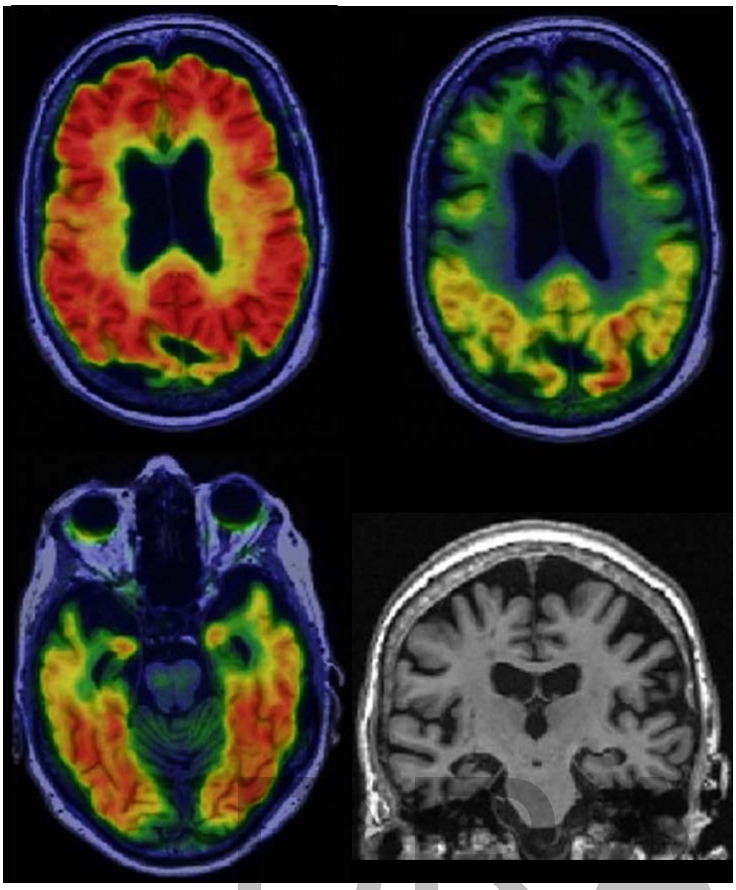

Fig 1. Alzheimer's disease with dementia. 75 yo woman with amnestic multi domain dementia. Participant in the Mayo Alzheimers Disease Research Center. Abnormal amyloid PET (a), tau PET (b,c) and atrophy on MRI (d). Biomarker profile A+T+N+.

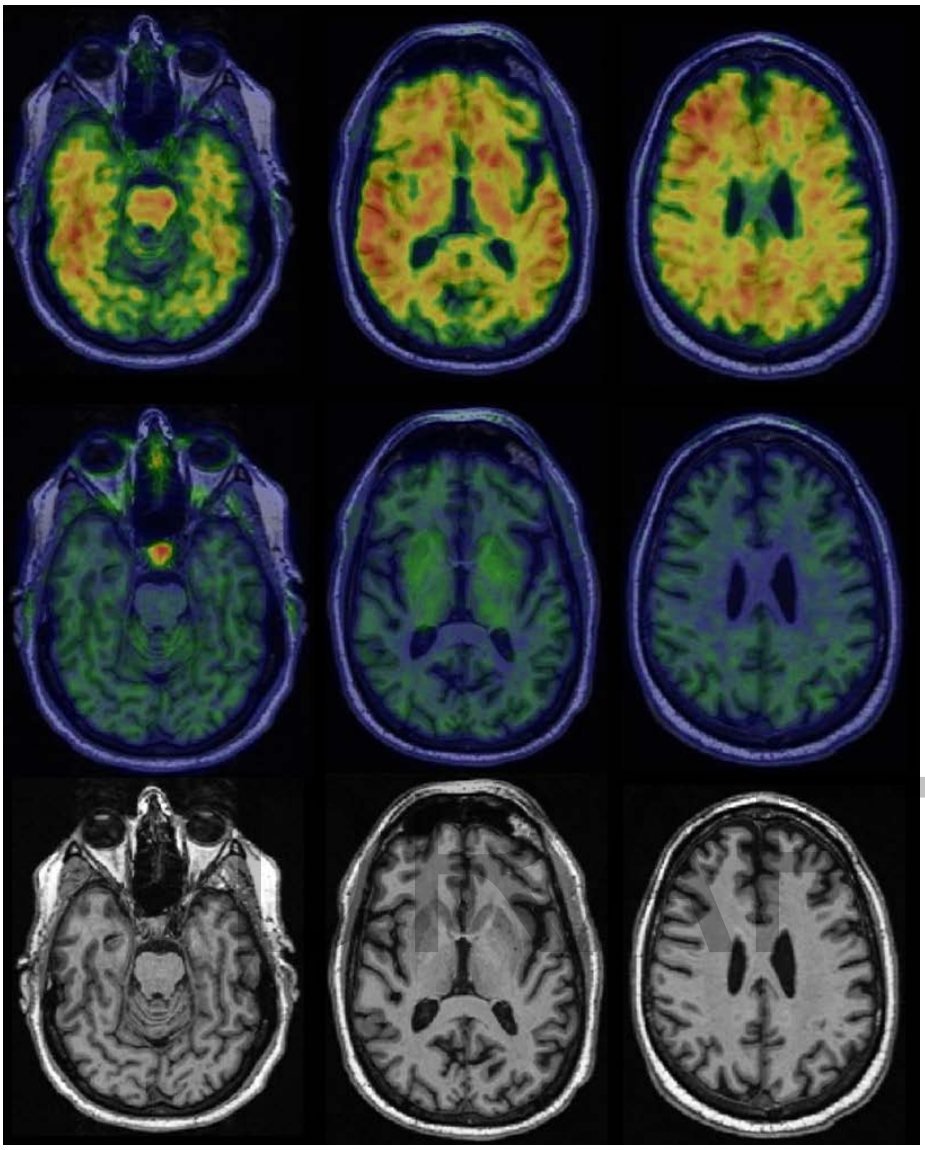

Fig 2. Preclinical Alzheimer's pathologic change. Cognitively unimpaired 67 yo man. Participant in the Mayo Clinic Study of Aging. Abnormal amyloid PET (top row), no uptake on tau PET (middle row), no atrophy on MR (bottom row). Biomarker profile A+T-N- .

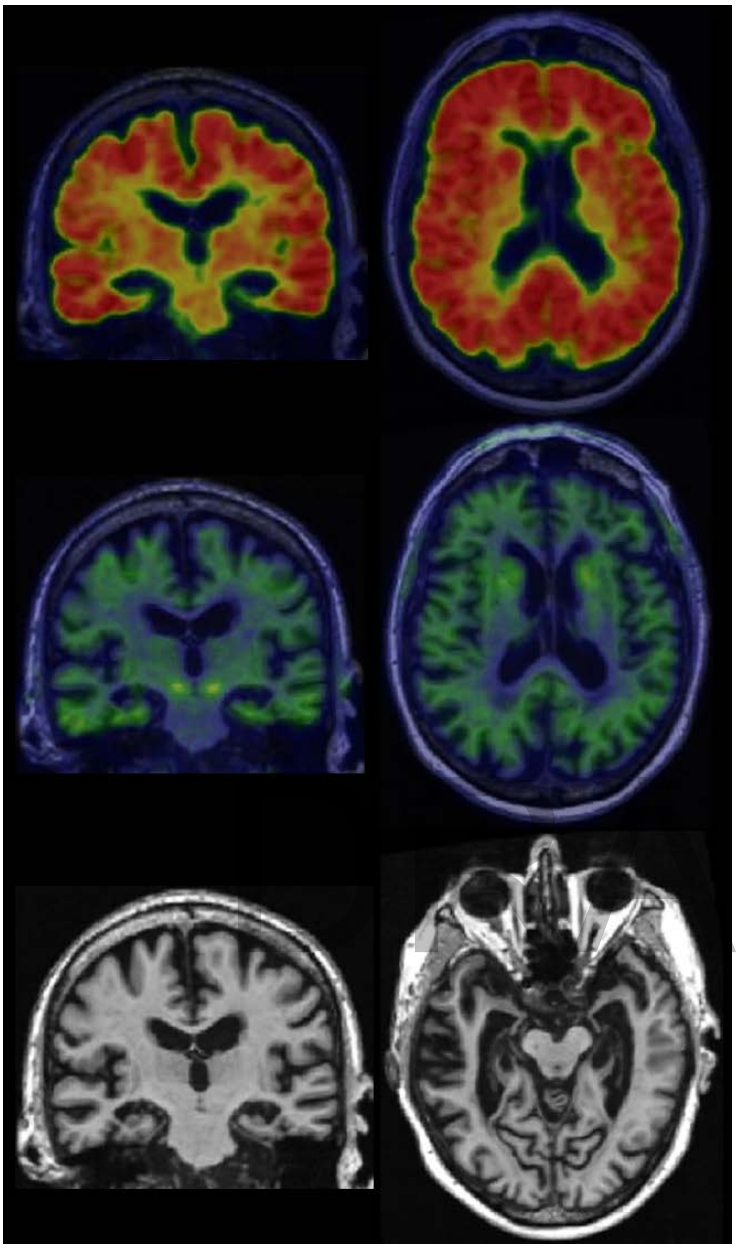

Fig 3. Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia. 91 yo, M, severe amnestic dementia. Participant in the Mayo Alzheimers Disease Research Center. Abnormal amyloid PET (a,b), normal tau PET 9 (c,d) and severe medial temporal atrophy on MRI (e,f). The biomarker profile (A+ T- N+) suggests the patient has Alzheimer's pathologic change (A+T-) plus an additional degenerative condition (N+), likely hippocampal sclerosis.

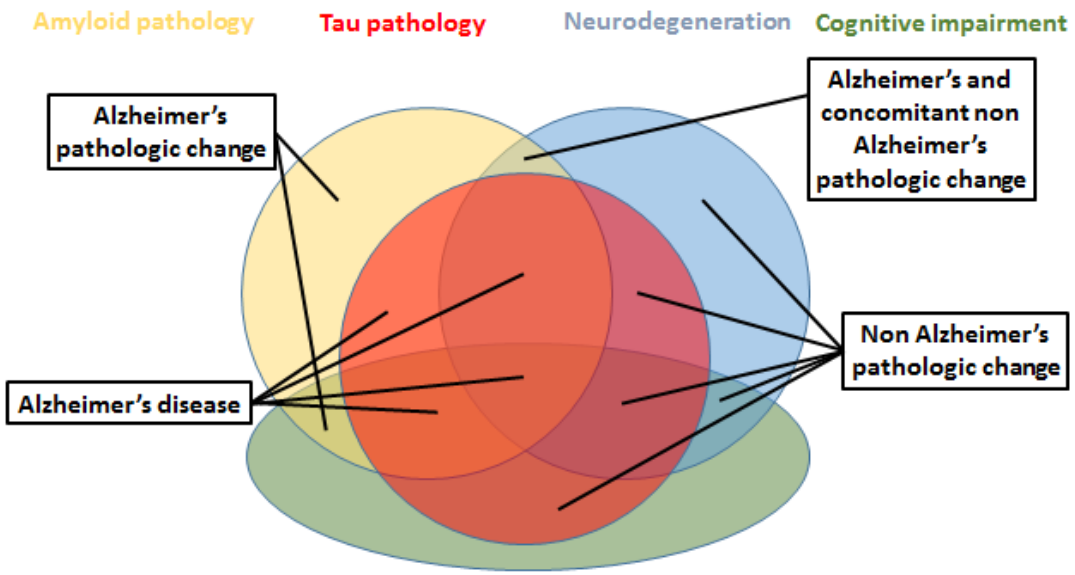

Fig 4 Descriptive nomenclature Venn diagram. As an adjunct to Table 4 we illustrate how A,T,N biomarker grouping and cognitive status interact for classification of research participants in this Venn diagram. For simplicity, MCI and dementia are combined into a single (cognitively impaired) category and the A-T-N- groups are not shown. Also "Alzheimers and concomitant non Alzheimer's pathologic change" (A+T-N+) in cognitively impaired is not shown in this figure.

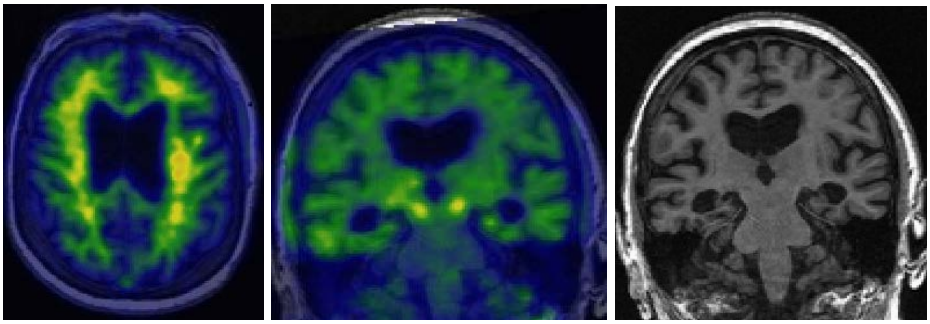

Fig 5 non Alzheimer's pathologic change with dementia. 86 yo, F, progressive amnestic dementia. The patient had been diagnosed clinically (i.e. without biomarkers) as "Alzheimer's disease dementia" by several physicians prior to enrolling in the Mayo Alzheimers Disease Research Center. Imaging performed for research purposes revealed a normal amyloid PET (left), normal tau PET 9 (middle) and severe medial temporal atrophy on MRI (right). The biomarker profile (A- T- N+) suggests the patient has non Alzheimer's pathologic change. Based on her biomarker profile, hippocampal sclerosis was suspected antemortem and hippocampal sclerosis with TDP43 (and without Alzheimer's disease) was later confirmed at autopsy.