NIA-AA Revised Clinical Criteria for Alzheimer's Disease

Abstract

The National Institute on Aging and the Alzheimer's Association (NIA-AA) convened 3 separate work groups in 2011 and a single work group in 2018 to create recommendations for the diagnosis and characterization of Alzheimer's disease (AD). The NIA-AA also convened a workgroup that published a consensus document on the neuropathologic diagnosis of AD in 2012. Several core principles emerged from these efforts which we regard as fundamental tenants. These include, Alzheimer's disease (AD) should be defined biologically, not based on a clinical syndrome(s). The disease is a continuum that is first evident with the appearance of brain pathologic changes in asymptomatic individuals and progresses through stages of increasing pathologic burden eventually leading to the appearance and progression of clinical symptoms. Pathophysiologic mechanisms involved with aggregation and clearance of protein fragments may be involved very early in the disease process, but these are not yet well understood. The disease is diagnosed in vivo by abnormalities on core biomarkers. In the 2018 document, biomarkers were categorized based on the pathogenic processes measured using a classification scheme labeled AT(N). Eight different AT(N) profiles were identified, and individuals were staged based on integrating biomarker profile and the severity of the clinical impairment.

This document updates the 2018 research framework document in response to several recent developments. First, no disease targeted therapies had received regulatory approval in 2018 but since then several have. In response, the present document has progressed from a framework for research, to criteria for diagnosis and staging that are intended for clinical use as well as research. Second, validated biomarkers in 2018 were based on either CSF assays or imaging. Since then, plasma-based biomarkers with excellent diagnostic performance have been developed and clinically validated. The present document has correspondingly incorporated plasma biomarkers into updated criteria for biomarker categorization, disease diagnosis and staging. Third, research studies have demonstrated that imaging and fluid biomarkers within a category are not equivalent for many use cases. In the present document we have updated biomarker classification criteria to accommodate nonequivalence between fluid and imaging biomarkers within a category.

Defining neurodegenerative diseases biologically, rather than based on syndromic presentation, has become a unifying concept common to all neurodegenerative diseases, not just AD, and the present document is consistent with this overarching theme.

1) Background

In 2011 the National Institute on Aging and the Alzheimer's Association (NIA-AA) convened three workgroups that published separate recommendations for the diagnosis and evaluation of Alzheimer's disease in its preclinical, mild cognitive impairment, and dementia phases [1-3]. In 2012 an NIA-AA workgroup published a consensus document on the neuropathologic diagnosis of AD [4,5]. Several years later, the NIA-AA convened a single workgroup to update 2011 recommendations for diagnosis and staging. The product of that workgroup, published in 2018, was labeled a research framework [6]. The 2018 publication stated that the framework should be updated in the future but did not specify a rigid schedule; rather, updates should occur as needed in response to scientific advances. Major developments have occurred since 2018 which now warrant an update.

The convening organization for this update is the Alzheimer's Association. The Alzheimer's Association identified a 4-person core leadership group for this effort (i.e., a steering committee) as well as a larger full workgroup. Members of the full workgroup were selected to provide a range of relevant scientific expertise, to achieve a representative sample of professional stakeholders, a balance of academic and industry representation, sex/ethnicity, and geographic location. The steering committee also engaged expert advisors to provide reviews of the project.

1.1) Modular updates

We designate this work as a modular update to the 2011 and 2018 versions of the NIA AA documents. The term modular update reflects the idea that periodic publications updating those aspects of the NIA AA criteria that are no longer current due to advances in the field are needed; but we leave intact core principles developed in the earlier documents that remain valid

(**text box 1)**. The advantage of modular updates is that those aspects that need to be updated will be addressed without having to recapitulate the entire AD criteria every few years.

1.2) Motivation for the modules that are updated

Developments that prompted this update include the following (**text box 2**). Disease targeted treatments for AD have for the first time received regulatory approval. The prospect of targeted therapies entering clinical practice makes conceptual alignment between industry, academia and clinicians around biomarker classification, AD diagnosis, and biologically based staging of AD highly relevant. A major new direction therefore is to expand the 2018 framework from a research-only focus to one that provides recommendations that are applicable for both research and clinical care. The title of this modular update, NIA-AA Revised Clinical Criteria for Alzheimer's Disease, reflects this progression in focus.

The most significant advance in AD diagnostics in recent years has been the development of plasma biomarkers with excellent diagnostic performance. This now makes biological diagnosis of AD (which previously required PET or CSF assays) generally accessible and is projected to revolutionize research and clinical care.

An important product of recent research is the recognition that imaging and fluid biomarkers within a pathobiological AT(N) category are not interchangeable for many use cases. The present document is updated to reflect this.

This updated criteria document was constructed with the intent that it would be useful for academia, industry, and clinical practice. The specific objectives of this work were to provide updates addressing the categorization of biomarkers, the biologically-based diagnosis of AD, the biological staging of AD, integrated biological and clinical staging, and multimodality biomarker profile characterization to identify co- pathologies.

2) Biomarker categorization

Categorization of biomarkers as defined here refers to grouping biomarkers into categories that reflect a common proteinopathy or pathogenic process. In contrast, disease

staging, which is addressed later, is based on the timing/onset of biomarker abnormalities in the natural history of the disease. Categorization of biomarkers in the 2018 framework assumed equivalence of fluid and imaging biomarkers within each AT(N) category. Ample evidence has accumulated that this is often not the case, therefore in this update we explicitly break away from the assumption of equivalence between imaging and fluid biomarkers within a given category. Imaging biomarkers measure cumulative effects and map onto established neuropathologic constructs [7-13]. Fluid biomarkers represent net of rates of production/clearance of analytes in near real time.

We group biomarkers into 3 broad categories: core AD biomarkers, non-specific biomarkers that are important in AD pathogenesis but are also involved in other neurodegenerative diseases, and biomarkers of common non-AD co-pathologies (**Table 1)**. Within each of these 3 broad categories we further subcategorize biomarkers by the specific proteinopathy or pathogenic process that each measures. Within each biomarker subcategory we list fluid and imaging biomarkers in separate columns to highlight the distinction. The 2018 framework recognized the need to modify the AT(N) biomarker classification scheme to incorporate newly developed biomarkers within an existing AT(N) category which we have done by including recently developed plasma biomarkers of A, T and (N) in this update. The 2018 framework also called for incorporating new biomarker categories beyond AT(N) as appropriate. This was denoted as ATX(N) where X indicated a new biomarker category beyond A, T or (N). Accordingly, **Tables 1-3** have 3 new biomarker categories: I for inflammatory/immune mechanisms, along with categories for two common non-AD co-pathologies - vascular brain injury (V) and synucleinopathy (S).

Use cases for biomarkers fall into several categories: diagnosis; staging and prognosis; multi modal biomarker characterization of individuals to aid in identification of co-pathologies; and, indicators of biological treatment effects. These topics are addressed in subsequent sections but use cases for specific biomarker categories are outlined in **Table 2**. **Tables 1** and **2** are limited to biomarkers currently suitable for clinical use. Biomarkers that are currently suitable for research use appear in **Table 3**. Biomarkers were placed into **Tables 1,2** vs **Table 3** based on the committee's assessment of the strength of available evidence of high diagnostic accuracy (sensitivity, specificity) compared to a valid gold standard, high reproducibility, and diagnostic utility based on clinical studies in real world settings [14,15].

2.1) Core AD biomarkers

Core AD biomarkers are those in the A and T categories. A and T biomarkers map onto the two proteinopathies that define AD and can therefore be used to diagnose the disease. While fluid and imaging biomarkers within an A or T subcategory represent distinct biochemical pools of a given protein, they reflect the same pathogenic process of protein accumulation [16]. For example, the A category denotes biomarkers of the β-amyloid proteinopathy pathway. Nevertheless, abnormal fluid A biomarkers specifically indicate dysregulated Aβ metabolism and processing, while imaging (amyloid PET) denotes aggregated Aβ in β-amyloid plaques. Fluid biomarkers detect soluble Aβ peptides which are the molecular building blocks of what can become insoluble β-amyloid aggregates in plaques. Similarly, the T category denotes biomarkers of AD tau proteinopathy. Abnormal fluid T biomarkers denote dysregulated tau metabolism and processing, while imaging (tau PET) denotes aggregated pathologic tau deposits. While soluble phosphorylated N terminal tau fragments may not aggregate into neuritic threads and neurofibrillary tangles themselves, mid-region fragments that contain the micro tubule binding domain do. And, all fragments are derived from the same parent tau protein.

Fluid ptau becomes abnormal well before tau PET and the two T measures thus are often discordant in the early or mid-portions of disease evolution [17-20]. In contrast, while fluid Aβ42/40 may become abnormal slightly before amyloid PET, the discrepancy in timing is not as apparent as between fluid ptau and tau PET [18,19,21-23]. The discordance in timing of fluid ptau vs tau PET has invited much speculation. Tau phosphorylation (and other post translational modifications) and secretion may represent a neuronal response to β-amyloid plaques [24].

Plasma and CSF Aβ42/40 both correlate with amyloid PET and predict clinical progression: however, the fold difference between individuals with vs without β-amyloid pathologic change is around 50% for CSF Aβ42/40 but 10%-15% for plasma Aβ42/40 [25-28]. Plasma and CSF assays for ptau at several different phosphorylation sites discriminate AD from non-AD clinical phenotypes, predict future clinical change and correlate with amyloid PET, tau PET and post-mortem measures of AD neuropathologic change [19,29-38]. Head-to-head comparisons of various plasma assay platforms for both Aβ42/40 and ptau show considerable variation in diagnostic performance [39-42]. Similarly, a variety of ligands exist for amyloid PET

and tau PET, and several have been approved by the FDA. Readers are referred to recent reviews for details describing specific fluid biomarker assays and PET ligands [14,39,43].

Two CSF assays for β-amyloid have FDA and IVDR-CE approval for clinical use. Many current plasma assays for both Aβ and tau are listed as suitable for research use (**Table 3**). Some of these may advance to general clinical use, but at this point that is difficult to determine and will ultimately depend on utility assessments by users. Under the category of "A" fluid assays in **Table 3** we list Aβ oligomers with the intent to include assays to detect both globular oligomers and linear protofibrils. Both are soluble but have different quaternary structures and characteristics and for that reason the term oligomers is not consistently applied to both.

2.2) Biomarkers that are non-specific but important in AD pathogenesis

In this update we identify two categories of biomarkers that are not specific to AD but are important in the AD pathogenic pathway. These are N and I biomarkers.

In the 2018 research framework we placed (N) in parenthesis to emphasize that, in contrast to A and T, (N) biomarkers were not specific for AD. From this point forward we no longer employ this notation because it should be clear from the construction of the present document that N biomarkers do not belong in the same group as core biomarkers. N biomarkers denote evidence of past or active neuronal injury or neurodegeneration. While neurodegeneration and neuronal injury are obviously important steps in AD pathogenesis, abnormalities in N biomarkers occur in many other conditions including non-AD neurodegenerative diseases, traumatic brain injury, and ischemic injury. Fluid N biomarkers denote active neuronal injury or more subtle neuronal dysfunction. Neurogranin is a marker of post-synaptic injury and degeneration while SNAP- 25 and GAP-43 are markers of pre-synaptic degeneration and dysfunction [14,39,43]. NfL is a marker of large caliber axonal injury that can be measured in CSF or plasma and is used clinically in various disorders including MS, ALS, and traumatic brain injury [14,43-52]. The absence of total tau from the fluid biomarker N category in **Tables 1-3** is a departure from the 2018 research framework. CSF and plasma total tau begin to increase early in the disease course in autosomal dominant AD [18] and closely correlate with fluid ptau in autosomal dominant and sporadic AD [53]. This could be taken as evidence that total tau should be considered a T biomarker. However, CSF and plasma total tau also increase dramatically in Creutzfeldt Jacob disease, head trauma, anoxia, cerebral infarction, as well as peripheral

neuropathies which has been taken as evidence that this belongs in the N category [53,54]. When all evidence is considered, it is unclear how best to categorize this measure.

Imaging N biomarkers represent the net result of cumulative insults to the neuropil. Neurodegenerative loss of neurons and synapses results in volume loss (or decreased cortical thickness) on MR [55,56] and FDG hypometabolism. Like their fluid counterparts, imaging N biomarkers are not specific to AD and may result from a variety of prior or ongoing brain insults [57,58]. Diffusion and perfusion MR are complicated and are discussed in the V section below. PET imaging of synapses has recently entered the research arena based on ligands that bind to the synaptic vesicle glycoprotein 2A, a presynaptic component that may be lost with neurodegeneration [59]. Initial studies employed the [^{11}C]-labeled compound UCB-J that demonstrated reduced synaptic density in cortex of AD patients [60,61]; subsequent studies have indicated the feasibility of this approach using an [^{18}F]-labeled ligand, SynVesT-1 [62]. How this family of radiopharmaceuticals will be used in research and whether they will be useful in clinical application is unknown at this time.

In the paragraphs above we list both fluid and imaging biomarkers of synaptic function in the N biomarker category. Synaptic loss and dysfunction are an important feature of neurodegenerative diseases, most notably AD. A future direction for the field could be to identify more specific roles that various synaptic biomarkers could play in defined contexts of use. It could be beneficial to break out synaptic biomarkers from the broader N category in the future. EEG may be one of the synaptic measures since it provides insight into synaptic connectivity. Functional connectivity measures have shown to be related both to cognitive performance and to AD pathophysiology[63].

Biomarkers of inflammatory/immune processes (I) are divided into 2 subcategories, activation of astrocytes and microglia. A substantial body of evidence from genetics, animal models, and neuropathology indicates that immune/inflammatory mechanisms are important in AD pathogenesis [64-66]. And a growing list of interventional strategies targets immune/inflammatory pathways [67]. Glial fibrillary acidic protein (GFAP) can be measured in plasma or CSF and is a marker of astrocytic activation. It is not specific to AD but is associated with higher risk of incident dementia and faster rates of cognitive decline [14,39,50,52,68-72]. Soluble TREM2 is a biomarker of microglial activation that can be measured in CSF. Longitudinal studies indicate that sTREM2 begins to increase in the preclinical phase of the disease process

around the time of A biomarkers but decreases at later AD stages [73,74]. Cytokines and complement factors may be CSF biomarkers of both astrocytic and microglial activation. PET ligands exist for microglia and astrocytic activation. This is an active area of research but none of these ligands are thought to be suitable for clinical use currently.

2.3) Biomarkers of common non-AD co-pathologies

We list biomarkers of α-synuclein (S) and vascular brain injury (V) in **Tables 1-3** under the heading of biomarkers of common non-AD co-pathologies. α-synuclein seed amplification assays (αSyn-SAA) in CSF have gained attention as diagnostic biomarkers in patients with Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB), recently relabeled as Neuronal Synuclein Diseases [75,76]. αSyn-SAA are sensitive and specific for antemortem identification of limbic/neocortical α-synuclein pathologic change (but not for amygdala predominate Lewy body disease (LBD)) in patients with limbic/neocortical α-synuclein as a primary or as a co-pathology [77]. These assays are less sensitive to α-synuclein inclusions in multi system atrophy where the cellular location and conformation of inclusions differ from DLB and PD [78,79]. αSyn-SAA currently yield a binary positive/negative (or inconclusive) output that is not quantitative [80]. Utility of these assays in peripheral tissue biopsy samples is being studied and is listed in **Table 3** for research use [81,82]. Development of PET ligands for α synuclein is an active area of research but at present, no ligands are currently available for the detection of a-synuclein co-pathology in patients with AD [83,84]. DAT SPECT is a dopamine transporter imaging method that is used clinically to assess loss of striatal dopaminergic neurons in the evaluation of patients with movement disorders or suspected LBD [85,86]. DAT scan is not listed in **Tables 1-3** because it is not a direct measure of α synuclein pathologic change but rather is an indicator of striato-nigral degeneration.

Cerebro vascular disease is an umbrella term that encompasses different forms of vascular brain injury (V). Several different modalities or imaging findings are listed in the V category in **Tables 1-3**. At this point, however, a single summary measure composed of different imaging findings has not been widely accepted. Macroscopic cerebral infarctions, including both large cortical and subcortical (lacunar) infarctions, on anatomic MR are the most definitive biomarker of ischemic vascular brain injury and are widely employed for this purpose in clinical care (**Tables 1,2**). Microinfarctions are an important neuropathologic substrate of cognitive

impairment [87-89]. Most lie beneath the spatial resolution of clinical MRI [90]; however, a subset of cortical microinfarctions may be detected even on clinical grade MRI with modern methods [91]. MR methods that may be useful indicators of small vessel disease include CO2 reactivity [92]and the presence of abundant dilated perivascular spaces [93]. State of the art methods in neuroimaging of small vessel disease are reviewed in the recent STRIVE-2 guidelines [94]. Diffusion weighted imaging is used routinely in clinical practise to identify cytotoxic edema due to acute cerebral infarction. Quantitative diffusion MR has gained traction as a method to detect loss of microscopic tissue integrity due to small vessel disease [95-98]. But, diffusion MR (a broad field that encompasses many different approaches) is also abnormal in neurodegenerative diseases, traumatic brain injury etc. The same reasoning applies to perfusion MR (arterial spin labeling or variants). Because quantitative diffusion MR and perfusion MR both reflect physiological responses to brain injury that may result from multiple etiologies they are listed in **Table 3** as indicators of both V and N. White matter hyperintensities on MR have long been interpreted to indicate microvascular ischemic injury [58] and are commonly used in clinical practise for this purpose. However, WMH may also be attributed to Wallerian degeneration, autoimmune demyelination, loss of blood brain barrier integrity from cerebral amyloid angiopathy, etc. Collection of PET data immediately following injection contains information about cerebral perfusion that may also be useful as a measure of vascular physiology or neurodegeneration [99,100]. There are no specific fluid vascular injury biomarkers that are suitable for clinical use but we list CSF sPDGFRβ (an indicator of pericyte injury) as a fluid V biomarker for research use [101].

The vascular markers described above are linked with traditional systemic vascular risk factors and cerebral ischemia. Cerebral amyloid angiopathy (CAA) merits special menton because while the disorder is one of cerebral vessels, the etiology is disordered processing of Aβ rather than traditional systemic vascular risk factors and CAA is commonly observed in association with Aβ plaques in AD. CAA represents the aggregation of Aβ in cerebral vessel walls, replacing or damaging the media, leading to vessel fragility [102]. This in turn can lead to spontaneous leakage or exudate of intravascular contents, including heme products, into brain parenchyma or the sulcal space. The result is seen on MR as superficial siderosis or cerebral micro bleeds, typically in a lobar distribution which may distinguish CAA-related microbleeds from those associated with chronic hypertension more often found in the sub-cortical regions and

brainstem [103]. Rarely, spontaneous vasogenic edema can be seen. A serious potential complication is lobar hemorrhage.

TDP-43 or LATE is a clinically important and common late life co-pathology but is not listed in **Tables 1-3** because no confirmed biomarkers exist at this time [104]. Biomarkers of 4R tauopathy would also be useful. While some PET ligands may bind to 4R tau aggregates, none have gained wide use clinically or in research because they are unable to identify individual patients with 4R tauopathy [105-107]. CSF dynamics disorders may also contribute to impairment and can be detected by MRI [108].

3) Diagnosis

In this update we propose that AD can be diagnosed by the presence of any abnormal core AD biomarker – i.e., fluid Aβ42/40, ptau, amyloid PET, or neocortical tau PET (**text box 3**). Medial temporal lobe tau PET uptake without amyloidosis is considered primary age related tauopathy (PART) [109]. PART has been controversial and is not considered to represent AD in the NIA AA guidelines for neuropathologic assessment of AD [4,5]. Natural history studies have unequivocally shown that AD biomarkers become abnormal long before symptoms arise. Our rational for diagnosing AD by the presence of any abnormal core biomarker is that the disease exists when the earliest manifestation of AD pathophysiology can be detected by biomarkers, even though onset of symptoms may be years in the future. An analogy can be drawn with adult-onset diabetes, where most individuals are diagnosed by screening HbA1C or fasting glucose testing while they are asymptomatic. Symptoms from adult-onset diabetes may not appear for years after initial diagnosis, but the disease exists at this initial stage and is routinely diagnosed while patients are asymptomatic. This biological definition of AD is consistent with the distinction between a disease vs illness. A disease is a pathobiological condition that will ultimately manifest with symptoms if an affected individual survives long enough. In contrast the term illness denotes signs and symptoms that result from the disease. Importantly, defining a disease by its biology rather than syndromic description is becoming a unifying concept common to all neurodegenerative diseases as exemplified by recent efforts in Parkinson's disease [110-112] Huntington's disease [113], and amyotrophic lateral sclerosis [114].

In the 2018 research framework, an A+T+ biomarker profile was required for a designation of Alzheimer's disease based on the AT(N) biomarker classification scheme. A+T- individuals were described as having Alzheimer's pathologic change. A+T+ corresponds to what neuropathologically would be intermediate/severe AD neuropathologic change and thus the in vivo definition of AD aligned with the established neuropathological definition [4,5]. By defining AD as any abnormal core AD biomarker, as we have done in this update, the link between the pathologic gold standard and the in vivo definition will not always be consistent. Many individuals with only an abnormal amyloid PET, fluid Aβ 42/40 or ptau may not be at Braak NFT stage 3 or higher neuropathologically and thus would not qualify for a pathological diagnosis of intermediate/high AD neuropathologic change.

3.1) Limitations of currently available biomarkers

Important considerations in diagnosing AD biologically are the limitations of currently available biomarkers (**text box 4**). First, PET and fluid biomarkers are less sensitive than neuropathology. The FDA-approved PET amyloid and tau agents are incapable of accurately identifying low densities and/or distributions of AD pathologic change restricted to medial temporal structures. The FDA approved amyloid PET tracers cannot, by visual reads, reliably detect sparse neuritic plaques [7-9,115,116] and tau PET cannot reliably differentiate between neuropathologically defined Braak stages I-III [12,13,117]. Newer plasma ptau assays are effective in identifying neuropathologically defined Alzheimer's disease at intermediate and high pathologic change levels but do not reliably discriminate among Braak stages I-IV in cognitively unimpaired subjects [118].

Second, there has been insufficient validation of biomarkers against a rigorous neuropathologic standard in some areas. Generally, only the FDA-approved PET amyloid and tau ligands have had sufficient validation against autopsy [9,13,115,116]. Biofluid assays do not require FDA approval; the much-less rigorous CLIA or CAP (in the US) certifications do not require autopsy validation.

Third, biomarkers are not available for all relevant neuropathologies, therefore it cannot be known with certainty in vivo what neuropathologies in addition to AD are present in any individual, or what the proportional neuropathologic burden is among various pathologies.

Finally, the proportion of the observed cognitive deficit in any individual that is attributable to AD vs other neuropathologies cannot be known with certainty given the present state of technology (**text box 4**).

3.2) Thresholds

The limitations of biomarkers discussed above are all relevant; however, diagnostic performance of a biomarker and its relationship to a neuropathologic standard will always depend on the normal/abnormal cutpoints selected. Sensitivity and specificity are obviously inversely related and optimizing one vs the other will depend on the desired context of use. Selecting cutpoints is an active research area and changes to what now might be considered appropriate are likely to occur. For example, what might be considered an appropriate amyloid PET cutpoint of Centiloid 20-25 [8] could be too conservative for use cases that require early detection [119-121]. Lowering the cutpoint would obviously increase sensitivity but at the expense of specificity.

3.3) Protections from misdiagnosis

Diagnosing AD by an abnormal core biomarker demands a high level of fidelity when applied clinically. However, any diagnostic test value, fluid or imaging, has a degree of uncertainty associated with it. We therefore recommend 3 protections against misdiagnoses (**text box 3**). First, we recommend using only fluid assays or PET ligands for clinical diagnosis and staging/prognosis that have met rigorous validation standards. Second, we recommend conservative interpretation of values near cutpoints and we recommend employing an indeterminant zone around a normal/abnormal biomarker cutpoint. Third, biomarker results should always be interpreted in the context of an individual patient's history.

3.3.1) Rigorous validation

We recommend using only assays/tests for clinical diagnosis and staging/prognosis that have met rigorous validation standards. For both PET and fluid assays this would include validation against an accepted gold standard. Ideally the standard would be large biomarker to autopsy correlation studies, but this may not always be possible given the challenges with obtaining biomarker and autopsy sampling close in time in representative samples. We avoid

prescribing specific performance metrics; however, fluid or PET biomarkers used for diagnosis should meet high standards for sensitivity, specificity, and precision. An important feature of validation is evidence of diagnostic utility from prospective clinical studies in real world settings as opposed to assessment limited to highly selected cohorts [14,15,122-125]. Plasma AD biomarker assays have only recently reached sufficient accuracy for clinical use and this field is still in a period of active development. Head-to-head comparisons of different plasma Ab [41] and ptau [40] assays have shown wide variability in diagnostic performance. Clinical use of plasma biomarkers should therefore be undertaken with particular attention to rigorous performance validation.

3.3.2) Conservative interpretation of values near a cutpoint; the intermediate zone

Except for αSyn-SAA, all biomarkers we discuss exist on a continuous scale and the definition of an abnormal test value requires creating a cut point in that continuous range. Cutpoints denoting normal vs abnormal values may be selected by various means [126] and will vary with the assay platform, and for PET will depend on the specific ligand and details of the analytic pipeline. However, regardless of assay or modality, a level of diagnostic uncertainty exists for values at or near any cutpoint. When using a fluid or PET biomarker quantitatively for *diagnosis*, our recommendation therefore is to report study results with 3 elements: first, what is the value on a continuous scale (with an appropriate reference scale); second, is the value normal or abnormal on the basis of an established cut point; third, where does this value fall with respect to a zone of uncertainty on either side of the normal/abnormal cut point. The zone of uncertainty thus divides the continuous range of values into confidently normal, confidently abnormal, and indeterminant. In addition, incorporating a zone of uncertainty may lessen fluid/ PET discordances, particularly for A biomarkers.

For imaging, visual reads would provide a normal/abnormal output. In addition, the approach of labeling some exams indeterminate is common in clinical radiology and serves the same function as the zone of uncertainty in quantitative analyses. However, quantitative analysis of PET is more sensitive than visual interpretation and, for example, can detect nominally negative but increasing levels of Aβ pathologic change that are likely to be clinically meaningful [120,127,128]. For this reason, the committee recommends greater incorporation of quantitative analysis in both research and clinical use.

3.3.3) Clinical context

No biomarker test should be ordered or interpreted in the absence of clinical context. For example, head trauma or cardiorespiratory arrest may acutely and transiently increase ptau values [53]. Some MAPT mutation carriers with a 3R+4R tauopathy may have elevated ptau 217 in the absence of amyloid pathologic change [129]. Elevated ptau 181 has been reported in autopsy verified ALS cases with little to no AD copathology [130]. Certain medications and impaired renal function can elevate, while obesity may depress, some plasma biomarker values [131,132]. All these potentially confounding situations should be obvious clinically. Knowledge of patient history is necessary to avoid interpretation errors.

3.4) Use cases

While a purely symptomatic therapy may not require documentation of AD biology, therapy directed toward a biological target requires confirmation of that biology. The major use case for the biological diagnosis of AD in clinical trials is as an inclusion criterion. Use cases for biological diagnosis of AD in clinical care include counseling, tailoring medications for symptomatic (i.e., non-disease modifying) treatment, and determining eligibility for disease targeted treatment based on drug registration criteria [133]. Specific use cases will determine how biomarkers are employed. In many instances a single biomarker will be sufficient for clinical diagnosis and trial inclusion, for example a single biomarker documenting the presence of β-amyloid plaques is sufficient for inclusion in trials or for instituting clinical treatment directed against fibrillar β-amyloid. In the next section we discuss staging which would require multiple biomarkers.

4) Biological disease staging

We distinguish staging the severity of AD biology with biomarkers from staging the severity of clinical symptoms. This section addresses the former. Disease staging is a measure of biological severity which can be used to identify groups of individuals who have similar

expected natural history outcomes and should require similar treatment. While diagnosis of AD is based on an abnormal core biomarker study, the prognosis associated with an abnormal test result will not be the same for different biomarkers. The short to medium term prognosis of an individual with abnormality only on an early changing core biomarker will be different from someone with an abnormal later changing core biomarker, yet both individuals will be diagnosed with AD. Biological staging of the disease is therefore an important element of this update.

An important principle is that biological staging of AD applies only to individuals in whom the disease has been diagnosed by an abnormal core biomarker. AD staging does not apply to individuals who are not in the AD pathway, and many such individuals exist in observational research cohorts and in the population at large. We have structured this document to reflect this – i.e., diagnosis is the first step and only then does staging of AD become relevant.

4.1) Approaches to biological staging

In the 2018 framework, the "plus/minus" combinations of ATN were used as an informal staging scheme; individuals in the AD continuum were expected to progress from A+T-N- to A+T+N- to A+T+N+. However, in 2018 the term biomarker "profile" was used rather than "staging" to avoid confusion with clinical staging. In this update, however, we recommend an explicit scheme for staging the biological severity of AD that is distinct from staging the severity of clinical impairment.

Two general approaches may be taken for biological disease staging. Staging may be based on the order of biomarker events in the natural history of the disease where each event is categorized as present/abnormal (+) or absent/normal (-). This approach assumes that an archetypical order of biomarker events can be established through natural history studies; this sequence of biomarker events is then the de facto staging scheme. Alternatively, biological staging may be based on the magnitude of a continuous biomarker denoting progressively more severe disease. This latter approach is widely used for some diseases (e.g., HgbA1c for diabetes or eGFR for chronic kidney disease) but presents complexity for AD where two defining proteinopathies exist rather than a single physiologic read out.

4.2) Biological staging

We recommend a biological staging scheme that employs only core biomarkers. N biomarkers certainly add prognostic information; an A+T+N+ individual by PET has a worse short-term clinical prognosis that someone who is A+T+N- [134-136]. However, the temporal relationships among core biomarkers (A, T) and both N biomarkers and cognitive symptoms are inconsistent between people. Biological staging implies that a person should progress from initial to advanced stages in sequence and N biomarkers do not always follow a stereotypical A+ to T+ to N+ sequence. People with amyloidosis, who by definition have AD, may develop significant neurodegeneration prior to tauopathy due to co-pathologies (**Figures 1,2**). The same reasoning is applicable to I biomarkers. Although inflammation, like neurodegeneration, is obviously an important component of the AD pathological process, we have also not included I biomarkers in the staging scheme. Although, astrocytic activation denoted by elevated GFAP has been proposed as link between β -amyloidosis and tau phosphorylation [137], it has not been unequivocally established where I biomarkers fit into the disease sequence. In addition, like N biomarkers, I biomarkers are involved in non-AD disease processes and therefore the temporal relationships among core biomarkers, I biomarkers and cognitive symptoms will be inconsistent between people with varying types and degrees of non-AD copathology.

In keeping with recognition of nonequivalence between imaging and fluid biomarkers we propose separate staging schemes for imaging and fluid but with a common overarching concept. For both imaging and fluid, we describe a 4-stage scheme based on the sequence of events observed in natural history studies: stage a, *initial* changing biomarkers; stage b, *early* changing; stage c, *intermediate* changing; stage d, *advanced* changing (**Table 4, Figure 1**). We do not attempt to link PET and fluid biomarker stages but rather describe biological staging separately within each modality.

Unlike fluid biomarkers, imaging captures both topographic and magnitude information. Separate staging schemes for amyloid and tau PET have been proposed using either topographic distribution [20,138-145] or cutpoints in the continuous distribution of values from a defined region of interest (ROI) [126,145-147]. However, PET staging that integrates both amyloid and tau PET has not been described and a comprehensive disease staging scheme for AD should include both biomarker categories.

Highly replicable temporal interrelationships between amyloid PET, tau PET and clinical symptoms exist. This can be summarized as follows. Abnormal amyloid PET often exists as an

isolated finding in elderly individuals who are cognitively normal and without neocortical tau PET uptake or neurodegeneration [148-152]. In contrast, high levels of neocortical tau are rarely seen in the absence of amyloidosis, are usually accompanied by neurodegeneration and are usually incompatible with normal cognition [151]. Clinical symptoms and neurodegeneration are closely related both in time and topographically with tau PET but not amyloid PET [153-155]. This set of findings is consistent with a stereotypical sequence of unidirectional biomarker events that can be summarized as: amyloidosis precedes neocortical tauopathy which in turn leads to neurodegeneration and clinical symptoms [152,156-160]. Amyloidosis appears to facilitate topographic spread of tauopathy, with the latter most commonly, but not always, beginning in medial temporal areas [20,142].

Therefore, for biological staging with PET we propose the following staging scheme (**Table 4, Supplementary Table 1**): stage a (*initial*) – abnormal amyloid PET with no uptake on tau PET (A+T-) [127]. Stage b (*early*) – abnormal amyloid PET plus tau PET uptake that is restricted to medial temporal areas (A+T_{MTL}+). Stage c (*intermediate*) - abnormal amyloid PET plus tau PET uptake in the moderate SUVR range on a neocortical ROI (A+T_{MOD}+). Stage d (*advanced*) - abnormal amyloid PET plus tau PET uptake in the high SUVR range in the same neocortical ROI (A+T_{HIGH}+). Note that this PET staging scheme incorporates 5 elements. Both amyloid PET and tau PET are included to capture the 2 diagnostic proteinopathies. Within tau PET it incorporates staging by both topography (by distinguishing between MTL and neocortical uptake), and by uptake magnitude in the same neocortical meta-ROI. Finally, the neocortical ROI will capture staging for typical but also atypical/hippocampal sparing AD presentations [161]. We recognize that amyloid PET, like tau PET, also exists on a continuous scale and that higher amyloid PET SUVR or Centiloid values are associated with more advanced disease and worse outcomes [162-164]. However rather than incorporating a separate continuous amyloid PET scale into the PET staging scheme, amyloid PET is denoted in a binary manner with the recognition that increasing amyloid PET Centiloid values do not have widely varying spatial locations and will be captured by progressively worse tau PET stages [164,165].

The onset of abnormal ptau 181, 217 and 231 seems to occur around the time of amyloid PET and much earlier than neocortical tau PET abnormalities [18,166]. In contrast several more recently developed CSF tau assays (ptau-T205, MTBR-243, and non-phosphorylated tau species) seem more closely linked with the onset of abnormal tau PET and correlate better with tau PET

than amyloid PET [166-168]. Moreover, a sequence of events has been proposed with these pathologic tau species appearing in the following order: ptau 181, 217 or 231, then ptau- T205, then MTBR-243, then non phosphorylated tau species [166,168]. We therefore recommend a staging scheme with fluid biomarkers that follows the same 4-stage approach as described for PET. Stage a (*initial*) – abnormal Ab 42/40, ptau 217, 231 or 181, and normal ptau-T205, MTBR-243 and non-phosphorylated species. Stage b (*early*) – abnormal Ab 42/40, ptau 217, 231 or 181 and ptau-T205, with normal MTBR-243 and non-phosphorylated species. Stage c (*intermediate*) – abnormal Ab 42/40, ptau 217, 231 or 181, ptau-T205, and MTBR-243 and normal non-phosphorylated species. Stage d (*advanced*) – all abnormal (**Table 4, Supplementary Table 2**). Measurement of ptau-T205 in plasma has recently been reported [166]. MTBR-243 and relevant non-phosphorylated species have only been measured in CSF so this staging scheme could not be fully implemented with plasma alone, however plasma assays may become possible for these analytes. Furthermore, the fluid biomarker field is in a period of rapid change and our recommendations for fluid staging should be regarded as conceptual, not as fixed guidelines.

4.3) Caveats

Various assays are available for fluid biomarkers within a category (**Table 1-3**). Also, a variety of PET ligands exist for both amyloid and tau. We do not specify specific assays, PET ligands or numeric cut points for staging purposes in this document. Nor do we outline a specific triage paradigm for use of different biomarkers in clinical workup or clinical trials. Our position is that researchers and clinicians will make those determinations empirically. Both the quantification of tau PET and fluid biomarker development are in a state of flux and we believe rigid recommendations would not be helpful at this point.

We describe separate within-modality staging schemes for imaging and fluid biomarkers but with a common 4-stage framework. It would ideally be possible to link imaging and fluid biomarkers in a single staging scheme that included both; however, this does not seem feasible at present. Standardization of fluid assays and tau PET quantification are currently in flux and cutoffs for various fluid biomarkers, especially plasma, have not yet been established. However, when the field has stabilized, then we envision that quantitative anchors between PET and fluid stages could be operationalized. At present, if both fluid and PET biomarkers are available in an individual, we recommend assigning stage by the method with the most advanced stage.

Several caveats are specific to tau PET. First, care must be taken to identify off-target tau ligand binding, which is not relevant to AD staging. For example, uptake may occur in areas of severe neurodegeneration in patients who are in the FTLD spectrum as well as in areas of infarction, but this should be easily recognized as off target based on clinical context. Second, we recognize that medial temporal tauopathy does not always precede neocortical tauopathy [169]. However, medial temporal to neocortical spread is by far the most common pattern, and the magnitude of ligand uptake in the neocortical meta-ROI will stage atypical presentations. Third, we employ topographic location of ligand uptake as one element of staging (medial temporal vs neocortical), but we do not specify a rigid set of anatomic ROIs to define the medial temporal or the neocortical meta-ROIs for tau quantitation. Neocortical areas that reflect intermediate and advanced staging by virtue of association with amyloid positivity, diagnostic utility, and prediction of cognitive decline include inferior and lateral temporal and inferior parietal lobes and sampling of these areas should be included in a neocortical tau PET meta ROI [134,136,143,170]. Similarly, the medial temporal ROI could include entorhinal cortex, amygdala, and hippocampus. However, off target uptake and binding properties differ among available tau PET ligands and therefore the anatomic extent of medial temporal and neocortical ROIs may need to be tailored to the properties of specific tau PET ligands. Efforts are underway to standardize quantification of tau PET for all tracers (for example, the CenTauR scale [171]) in the same way that the Centiloid scale [172] is the standardized method for quantifying amyloid PET. This is an evolving area that will likely undergo changes, and rigid specification of methods at this time seems unwise.

The Centiloid scale is the accepted method for quantifying amyloid PET; however, this is based on the anatomic distribution of ligand uptake in sporadic AD [172]. Florid striatal amyloid PET uptake often occurs early in individuals with autosomal dominant AD and DSAD which is usually not the case in sporadic AD [173,174]. Therefore, the approach to determining A+ vs A- may need special consideration in ADAD and DSAD.

We have identified specific fluid biomarkers to denote the early, intermediate, and advanced fluid stages. However, these fluid biomarkers have not yet been widely tested. And, unlike PET where worse biological stage predicts worse clinical prognosis [20,134-136,163,175,176], the prognosis associated with fluid biomarker staging has not been thoroughly established. For this reason, T205, MTBR-243 and other tau species are listed in **Table 3** (research use) and not in

Tables 1, 2 (clinical use). It is also highly likely that new fluid core biomarkers will be developed.

Cut points are obviously needed to operationalize biological staging with biomarkers. In the section on diagnosis, we recommend that all quantitative biomarker reports include an indeterminate zone around a cutpoint – i.e., functionally 3 cutpoints. However, 3 cutpoints around the division between each successive stage is obviously not tenable for staging. Therefore, our recommendation for an indeterminate zone around a diagnostic normal/abnormal cutpoint is applicable to diagnosis but not for staging.

4.4) Use Cases

Disease staging is well established in cancer where staging is used for prognosis, for selecting an optimum treatment, and for creating homogeneous groups for interventional trials. As with other diseases, more advanced biological AD stage predicts worse prognosis (**Figure 1**) [134-136,163,175,176].

Biological staging in clinical trials would sharpen inclusion or stratification criteria by identifying individuals that should respond to treatment in a similar fashion thus decreasing biological heterogeneity and increasing trial efficiency. Inclusion in the Trailblazer-Alz and Trailblazer-Alz 2 studies was based on an abnormal amyloid PET but also on tau PET stage, not a binary normal/abnormal tau PET designation [177]. In the A4 and AHEAD studies, while inclusion was based on an abnormal amyloid PET study, study assignment within the trial was based on amyloid PET severity/stage [178,179]. In the DIAN-TU NexGen combination (amyloid and tau immunotherapies), the ordering of tau monotherapy followed by the addition of amyloid immunotherapy or amyloid monotherapy followed by the addition of tau immunotherapy is determined by the presence of neocortical tau on PET.

5) **Clinical staging**

5.1) Numeric clinical staging

In the 2018 research framework we described a 6-stage numeric clinical staging scheme which is brought forward largely unchanged into this update and readers are referred to the

earlier document for additional details. Numeric clinical staging applies only to individuals who are in the AD pathophysiologic continuum and includes the following 6 clinically defined stages (**Table 5**): 1- biomarker evidence of AD in asymptomatic individuals; 2- transitional decline. These are the earliest detectable clinical symptoms that might be due to AD in individuals who are cognitively unimpaired; 3- objective cognitive impairment but of insufficient severity to result in significant functional loss – i.e., inefficient activities of daily living (ADLs) but still independent; 4- 6 - loss of independence with progressively worse functional loss. Stages 4-6 map onto mild, moderate and severe dementia respectively.

Numeric clinical stages 1-6 (**Table 5)** bear a close resemblance to the Global Deterioration Scale [180], with the important distinction that the latter was created before the development of disease specific AD biomarkers. The 6-stage numeric scheme also closely resembles staging in the FDA guidance for conduct of clinical trials in early AD [181].

Stage 2 is called out as a distinct transitional stage between asymptomatic (stage 1) and mildly impaired (stage 3) and resembles "stage 3 preclinical AD" in the 2011 NIA AA guidelines [1]. This stage is defined by one or more of 3 components: objective cognitive decline, subjective cognitive decline, or subtle neurobehavioral difficulties. All 3 of these components can be attributable to AD but also to factors other than AD, particularly neurobehavioral symptoms (e.g., depression, anxiety, apathy) [182] which are often not associated with neurodegenerative disease. An individual may be placed into stage 2 based on neurobehavioral symptoms alone – i.e., without objective or subjective cognitive decline – but individuals must have cognitive impairment to be placed into numeric stages 3 – 6. Advances in unsupervised, digital cognitive testing may improve the ability to reliably detect the subtle cognitive alterations characteristic of stage 2 through repeated testing, but this remains to be determined.

The nature of cognitive decline or impairment in stages 2 - 6 may involve any cognitive domain(s) – not only memory. Clinical staging is based on severity of cognitive/functional impairment rather than on phenotype, but different phenotypic presentations of AD are well known. Five characteristic AD phenotypes are recognized: amnestic or "typical", language variant, visuospatial variant, behavioral variant and dysexecutive variant which are reviewed in [183,184]. Different phenotypes often overlap within an individual and severity of impairment within each domain is variable.

Although we describe clinical AD stages, it is important to bear in mind that the severity of clinical impairment is the product of all neuropathological insults an individual has experienced, not only AD. The presence and severity of symptoms in an individual with abnormal AD biomarkers cannot be ascribed solely to AD with confidence particularly in elderly persons because of the likely presence of comorbid pathologic change (**Text Box 3 and 5**).

5.2) Stage 0 and genetics

The change we propose in clinical staging from 2018 is addition of stage 0. Stage 0 represents part of the AD continuum and is defined as an individual with genetically determined AD (which includes autosomal dominant AD (ADAD) or Down Syndrome AD (DSAD, Trisomy 21)) [185] who are biomarker negative and clinically asymptomatic (**Table 5)**. The rationale is that an individual with DSAD or ADAD has the disease from birth, prior to onset of brain pathologic change or symptoms. A person with DSAD or ADAD would move from stage 0 into stage 1 when a core biomarker became positive. The idea of stage 0 as genetically determined disease which has not yet manifest clinically or with biomarkers is conceptually consistent with recent staging proposals for Huntington's and Parkinson's disease [110-113].

We have not included AD risk alleles in the staging scheme. Unlike autosomal dominate mutations which have 100% penetrance (barring premature death from other causes), carriers of risk alleles including some APOE e4/4 individuals, may survive to late life without developing fully manifest AD pathologic change or symptoms. We therefore regard risk alleles as just that, and not a stage of AD.

5.3) Syndromic staging

The 2018 document also included a syndromic staging scheme that is commonly used in clinical practice [186,187] and consists of 3 clinically defined stages: cognitively unimpaired (CU); mild cognitive impairment (MCI); and dementia. Numeric clinical stages 1 and 2 correspond to CU; numeric stage 3 roughly corresponds to MCI although the MCI syndrome would apply to some individuals in stage 2 as well; numeric stages 4, 5 and 6 correspond to mild, moderate, and severe dementia respectively. Unlike numeric clinical staging, syndromic staging is not conditioned on a biological AD diagnosis and is applicable to individuals who are and who are not in the AD continuum.

6) Integrated biological and clinical staging

As in the 2018 framework we distinguish between clinical staging and biological disease staging. These are regarded as quasi-independent variables. The symptomatic consequence of biological AD is modified by interindividual differences in co-pathologies, resistance, and reserve (i.e., education other social determinants of health) [188,189]. Consequently, the degree of cognitive/functional impairment does not follow in lock step with biological AD severity - i.e., a range of possible relationships between biological AD stage and clinical stage will be found across the population (**Figure 1**). While clinical staging and biological staging must be performed independently, these two types of staging information can be integrated while still preserving independence of content.

We propose an integrated biological and clinical staging scheme outlined in **Table 6**. As with biological staging, the integrated staging scheme is only applicable to individuals diagnosed with AD by core biomarkers. In **Table 6**, clinical stages are denoted in the columns using the numeric 6-stage scheme plus stage 0. Biological stages are denoted in the rows. Integrated stages appear in the cells. This display format is intended to convey the concept that biological AD stage and clinical severity are related, but do not travel in lockstep. The typical or average relationship between biology and symptoms can be envisioned as moving along an upper left to lower right diagonal (the shaded cells) in **Table 6**, but considerable variation will occur in the population. Individuals who lie above the diagonal (i.e., worse clinical stage than expected for biological stage) are expected to have greater co morbid pathologic change. Individuals who lie below the diagonal (i.e., better clinical stage than expected for biological stage) may have exceptional resistance or cognitive reserve.

To avoid confusion when integrating numeric clinical staging with biological staging, we use numbers for clinical staging and letters for biological staging (**Table 6**). For example, clinical stage 2 and biological stage a is integrated stage 2a. If the biological stage was ascertained with PET this would appear as integrated stage 2Pa and if by fluid as stage 2Fa.

7) Multi-modal biomarker profiles and identification of comorbid pathologic change

We distinguish multi-modal biomarker "profiles" from AD biological staging. Biomarker profiles may employ core and non-core biomarkers to characterize the general pathophysiologic state of an individual beyond or in addition to the presence of AD. Biological staging of AD applies only to individuals in whom AD has been detected by core biomarkers, in contrast biomarker profiles are applicable to all individuals in the population.

Using biomarkers outlined in **Tables 1-3**, a full multimodal biomarker profile would appear as ATNISV with +/- indicated as appropriate to each category. Full profiles require extensive biomarker phenotyping; however, partial profiles are more likely to be available and may be useful conceptually and in clinical practise to characterize individuals.

One potential use of multimodal biomarker profiles is to provide simple conceptual organization and practical shorthand notation to characterize persons with multiple coexistent pathologies. With advancing age, co-pathologies are the rule and isolated AD is the exception. The four most common age-related brain pathologies that underlie cognitive impairment or dementia in elderly persons are AD, cerebrovascular disease (CVD), limbic associated TDP-43 encephalopathy (LATE), and Lewy Body disease [89,190-192]. Direct indicators of co-pathology would be a positive SAA assay (A+T+S+) or multiple infarctions (A+T+V+) in someone who also had biomarker evidence of AD. There are, however, several useful indirect indicators that one or more non-AD co-pathologies likely is present.

To this point we have not emphasized N biomarkers, but a useful indirect indicator of copathology is a "TN" mismatch in an ATN profile [193-196]. Neurodegeneration in AD is closely related in time and topography to tau deposition. T-N+ biomarker profiles (i.e., TN mismatch) therefore indicate the presence of neurodegeneration or neuronal injury due to a disease(s) other than AD. An archetypical example of this is an older person presenting with a progressive memory problem and an A+T-N+ biomarker profile (where N+ is represented by severe medial temporal lobe atrophy on MR or hypometabolism on PET) (**Figure 1, 2**). Such a person has AD biological stage a (denoted by A+T-), but in addition likely also has LATE disease (denoted by N+) with the latter likely responsible for current symptoms [104]. TN mismatches in the opposite direction (i.e., less N than expected for the degree of T) may be an indicator of an individual with exceptional resistance to the effects of AD tauopathy. Similar logic could be applied to T-I+

mismatches in individuals who are A+, although much less experience is currently available with I biomarkers compared with the N category.

If an individual with abnormal AD biomarkers also presents with classic signs and symptoms of a common non-AD disease, for example Parkinsonism, then it is likely that person has synucleinopathy in addition to AD. It is likely that AD is not the sole explanation for cognitive deficits in such a person, but without a quantitative biomarker of synucleinopathy, assigning a "proportion of cognitive deficit" attributable to AD vs synucleinopathy is not realistic.

Newer image data analysis methods may be useful in identifying likely copathologies [197].

7.1) Use cases

Indicators of co-pathology may be useful in clinical diagnosis, prognosis, and treatment decisions. For example, a cognitively impaired individual with an A+T- N+ biomarker profile may track more like LATE disease than AD clinically and may not respond to anti Aβ immunotherapy in the same manner as someone who has an A+T+N- or A+T-N- biomarker profile.

In clinical trials, indicators of co pathology could be used as exclusionary criteria, particularly phase 2 trials which are often not fully powered to see clinical benefit and where a biologically homogeneous cohort with purer AD is desirable. Alternately individuals with indicators of co-pathology could be included in AD trials and analyzed in preplanned subset analyses, particularly phase 3 trials, with the goal of creating registration trial populations that are more generalizable. Identification of co-pathologies to subset AD in research cohorts may also lead to a better understanding of the genetic underpinnings of the disease.

8) Treatment effects

The focus of this document is on criteria for diagnosis and staging of AD; detailed discussion of the roles of biomarkers as a outcome measures or indicators of target engagement in clinical trials is beyond the scope of this work. Nonetheless, the recent regulatory approval of

disease targeted therapies promises to be transformative. Anti Aβ immunotherapy can dramatically reduce the load of amyloid plaque in a time and dose dependent manner and also may move downstream biomarkers in the direction of normalization, including fluid ptau and total tau (CSF, plasma or both) [198-200], plasma GFAP [198,200], and may also slow the rate of accumulation on tau PET [198] [*add donan when published*]. Most importantly, recent trials have demonstrated that anti Aβ immunotherapy, that reduces fibrillar amyloid levels measured on PET imaging, can slow the rate of cognitive decline in early symptomatic AD [64,177,198,199]. There is consistency across both successful and failed immunotherapy agents that the amount of amyloid PET reduction is associated with the degree of clinical benefit [64,201]. These findings linking biology to clinical manifestations, which have been replicated across independent therapeutic programs [177,198,199], provide solid empiric support for a biological definition of AD.

While β-amyloid may be reduced to sub detection threshold levels on PET, this does not mean that the disease has been eradicated, or that fibrillar amyloid forms are solely responsible for cognitive impairment. Individuals followed after cessation of Aβ immunotherapy have shown reversal of CSF Aβ 42/40 normalization, some clinical progression, and eventual recurrent accumulation of amyloid on PET [202]. The underlying AD pathophysiologic process is therefore still active in an individual who has had fibrillar amyloid removed to below detection levels. The biological diagnosis and staging schemes outlined earlier are based on the order of biomarker events observed in the natural history of the disease. Disease targeted therapies may alter the relationships among biomarkers that are present in the natural evolution of the disease. For example, an individual who has been treated with an anti Aβ monoclonal antibody may change from A+T+ at baseline to A-T+ following treatment. The staging schemes we outlined earlier therefore should be regarded as tools for diagnosis, staging/prognosis, and treatment assignment pretreatment but not as indicators of the stage of the natural history of the disease post treatment.

Anti Aβ immuno therapy often results in higher rates of whole brain volume loss or ventricular enlargement in treated vs placebo individuals [177,199,203]. Explanations for this include therapy induced fluid shifts, reduction in volume of amyloid plaque, or reduction in peri-plaque inflammation. It has become apparent that slowing of the rate of volume loss by successful amyloid removal, which was anticipated based on natural history studies, is not seen in the relatively short duration of most clinical trials. Slowing of atrophy rates may occur over much longer time scales with successful therapy, but this remains to be shown. MRI can only be

considered a measure of neurodegeneration in conditions of physiologic steady state – i.e., in the absence of abrupt changes in tissue water concentration or edema – which seems not to be the case during active anti Aβ immuno therapy. MR does have an important role in anti-amyloid therapy in trials and in clinical use as means of identifying amyloid imaging related abnormalities (ARIA) for safety purposes [204]. ARIA E (edema) is identified best with FLAIR images while ARIA H (hemorrhage) is best identified with some variant of gradient recalled echo imaging [205].

9) **Diversity and need for more representative cohorts**

The need for more representative cohorts for observational studies and clinical trials has been pointed out repeatedly and the committee endorses this position [38,206-208]. The biomarkers described in this document have not yet been extensively tested in broadly representative populations and further analysis in these groups is needed. Representative research cohorts are needed to assess if treatments are effective across a range of social determinants of health (SDOH) [132,209,210]. SDOH may also modify the predictive effect of biomarkers for cognitive decline. The interaction between biomarkers and genetic markers may differ by race. For example, the effect of APOE e4 on amyloid deposition repeatedly observed in White populations, may not be as strong in Black populations [211], and Asian populations have lower prevalence of APOE e4. Representativeness encompasses many factors, including race and ethnicity, but also socio-economic status, education, geographic location, lifestyle, and other SDOH. Notions of racial/ethnic representativeness are country specific. In contrast, lower education and socio-economic status are universal barriers to inclusion in research studies that are present in all countries.

10) Future Directions

The series of NIA AA documents from 2011 to the present have focused on diagnosis and characterization of AD. Over the past several decades the field has moved from diagnosing and

characterizing the disease based on clinical presentation, to diagnosing the disease biologically like most other major diseases. Biologically based diagnosis and staging is now transitioning from priorities dominated by research to the priorities required for clinical practice. Biological diagnosis and staging of AD in clinical practice will require substantial efforts around standardization and wider availability of fluid and PET biomarkers. Future directions to consider for updating these NIA AA clinical criteria could include the following. Identify more specific criteria for fluid assay and PET technical and clinical validation performance. Select specific quantitative criteria for cutpoints to define stages for fluid and PET. Link imaging and fluid biological staging of AD. Like biomarker and imaging standards in other diseases, such as cholesterol markers for vascular risk, glucose and HgbA1c for diabetes, and imaging for cancer staging, the exact thresholds for abnormality may evolve over time, as additional data inform the prognostic value of these cutpoints beginning at even earlier stage of disease. Improved understanding of various post translational modifications of tau will likely lead to modifications in fluid based biological staging. With improved understanding of the role of inflammatory processes in AD pathogenesis [64-66], we envision a more prominent role for I biomarkers in biological characterization and prognosis. Observational studies and clinical trials should be conducted with more diverse and representative cohorts. We envision creating a comprehensive system to stratify risk of progression by incorporating all biomarkers (core AD, non-core, and biomarkers of non-AD copathology) along with demographics and genetics. However, all these goals will depend first on standardization/harmonization of biofluid assays, standardized quantification of tau PET, and standardization of cutpoints for all fluid and PET biomarkers.

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