

Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup

Abstract

The National Institute on Aging (NIA) and the Alzheimer's Association (AA) convened three 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 tenets.

These include, 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 treatments that target core disease pathology 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 to inform both research and clinical care. Second, accepted biomarkers in 2018 were based on either CSF assays or imaging. Since then, plasma-based biomarkers have been developed and clinically studied; some (but not all) demonstrate excellent diagnostic performance. 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 interchangeable for many intended uses. In the present document we have updated biomarker classification criteria to accommodate nonequivalence between fluid and imaging biomarkers within a category.

Defining diseases biologically, rather than based on syndromic presentation, has become standard in many areas of medicine (e.g., cancer), and is becoming a unifying concept common to all neurodegenerative diseases, not just AD. The present document is consistent with this overarching theme. The AD field is in a period of transition as biomarkers are increasingly being used in clinical practice. Our objective is to present objective criteria for diagnosis and staging to serve as a bridge between research and clinical care as this transition occurs. Finally, we point out that these are not intended to be specific clinical practice guidelines, but rather criteria to inform diagnosis and staging of AD that reflect current science.

1) Background

In 2011, the NIA and 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 evaluation. 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 as needed in response to scientific advances.

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.

While the purpose of this document is to update the 2018 document, a set of fundamental principles emerged from prior committees. These principles, outlined in **Text box 1**, are carried forward and serve as the foundation or starting point for these revised criteria.

Three major developments prompted this update. First, treatments that target core disease pathology have for the first time received regulatory approval. The prospect of these therapies entering clinical practice makes conceptual alignment between clinicians, industry, and academia

around diagnosis and 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 diagnostic and staging criteria to inform both research and clinical care. The title of this modular update, Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup, reflects this progression in focus.

Second, the most significant advance in AD diagnostics in recent years has been the development of plasma biomarkers with some (not all) assays exhibiting excellent diagnostic performance. This now makes the biological diagnosis of AD (which previously required PET or CSF assays) generally accessible and is projected to revolutionize clinical care and research. The field is now in a transition phase during which plasma biomarkers are being integrated with traditional CSF and PET biomarkers.

Finally, an important product of recent research is the recognition that imaging, CSF, and plasma biomarkers within a pathobiological AT(N) category are not interchangeable for many intended uses. The present document is updated to reflect this.

This update occurs at a time when biomarkers of disease can be used across clinical, research and industry settings. The specific objectives of this work were to provide a common framework addressing biomarker categorization, biologically based diagnosis, and staging of AD.

2) Biomarker categorization

Categorization of biomarkers refers to grouping biomarkers into categories that reflect a common proteinopathy or pathogenic process. Categorization of biomarkers in the 2018 framework assumed equivalence of biofluid and imaging biomarkers within each AT(N) category⁷. Ample evidence has accumulated that this is often not the case, therefore in this update we break from the assumption of equivalence between imaging and biofluid biomarkers within a given biomarker category.

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 brain 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.

Throughout the document we distinguish between imaging and fluid analyte biomarkers. Imaging biomarkers measure cumulative effects, capture topographic information, map onto established neuropathologic constructs, and in the case of PET represent insoluble aggregates⁸⁻¹⁴. Fluid biomarkers reflect net of rates of production/clearance of analytes in near real time.

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 in the 2018 document as ATX(N) where X indicated a new biomarker category beyond A, T or (N). Accordingly, **Tables 1,2** include three 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).

Table 1 illustrates biomarker categories by mechanism or proteinopathy. CSF and plasma are listed together as fluid analytes in this table because the same analyte is measured in CSF or plasma. **Table 2** lists intended uses for biomarkers which fall into several categories: diagnosis; staging, prognosis, as an indicator of biological treatment effect; and identification of co-pathologies. While **Table 1** lists fluid *analytes*, **Table 2** lists *assays* and accordingly CSF and plasma are broken into separate columns because assay implementation may differ between CSF and plasma. **Table 2** also includes hybrid ratios which are assays rather than individual analytes. **Table 2** includes assays that may be in vitro diagnostics, laboratory developed tests, or research use only tests. Criteria the committee used for inclusion in **Table 2** were: the imaging, CSF, or plasma biomarker has either received regulatory approval or has played a prominent role in recent clinical research and, in the opinion of the committee, enough evidence exists to support its clinical value and the assumption that it may receive regulatory approval in the future.

Tables 1,2 categorize core and non-core biomarkers. In the remainder of section 2 of the document, we focus only on core biomarkers to create a logical progression to the follow-on topics of diagnosis and staging and which employ only core biomarkers. Non-core biomarkers (i.e., NIVS) are discussed later in section 7.

Core AD biomarkers are those in the A (β -amyloid) and T (tau) categories (**Tables 1, 2**). The A category denotes biomarkers of the β -amyloid proteinopathy pathway. Soluble A β peptides are the molecular building blocks of insoluble fibrillar β -amyloid aggregates in plaques.

Hence fluid and imaging A biomarkers represent different biochemical pools of the same proteinopathy¹⁵. Moreover although some studies suggest that that fluid A β 42/40 analytes become abnormal slightly before amyloid PET¹⁶, much evidence suggests that the two become abnormal around the same time¹⁷⁻²¹.

Timing relationships are different across the spectrum of T biomarkers. Phosphorated N terminal fragment analytes (ptau 181, 217 and 231) become abnormal around the same time as amyloid PET and well before tau PET^{17, 18, 22, 23}. This has led to the suggestion that secretion of N terminal fragments phosphorated at specific residues (181, 217, and 231) may represent a physiologic reaction to β -amyloid plaques²⁴. In contrast other tau fragment analytes (MTBR-243 and non-phosphorylated tau) become abnormal later and correlate better with tau PET than amyloid PET²⁵⁻²⁸. These observations led us to splitting the T biomarker category into 2 sub-categories: T₁ (analytes of soluble tau fragments that may reflect a reaction to amyloid plaques or to soluble A β in plaque penumbra), and T₂ (tau PET imaging or fluid analytes that signal paired helical filament tau aggregates).

We introduce the concept of Core 1 and Core 2 AD biomarkers which are differentiated by the timing of abnormality onset and intended use. Core 1 biomarkers become abnormal around the same time as amyloid PET and are those in the A, T₁, or hybrid ratio categories (**Tables 1, 2**). As discussed later in the section on biological staging, Core 1 biomarkers define the initial stage of AD that is detectable in vivo. Core 1 biomarkers are useful in identifying the presence of AD in both symptomatic and asymptomatic people. The Core 1 biomarker category addresses the difficult conceptual issue around classification of plasma ptau 217, 181 and 231. Because of the onset timing, these analytes have been proposed as biomarkers of amyloid plaques, but at the same time plasma p-tau 181, 217, and 231 are tau fragments and it is difficult to reconcile these analytes as biomarkers of the A β proteinopathy pathway.

Core 2 biomarkers are those in the T₂ category in **Tables 1, 2** and include tau PET, pT205, MTBR-423 and non-phosphorylated tau. Core 2 biomarkers become abnormal later in the evolution of AD and are more closely linked with the onset of symptoms than Core 1 biomarkers. Combination of Core 2 biomarkers with Core 1 biomarkers provides information about how likely symptoms are related to AD, disease staging, the risk of progression in people without symptoms, and the likely rate of progression in symptomatic individuals.

CSF assays and PET ligands that have received regulatory approval for clinical use are listed in **Supplementary Table 1**. Readers are referred to recent reviews for details describing specific fluid biomarker assays and PET ligands ²⁹⁻³¹.

3) Diagnosis

In this update we propose that abnormality on specific Core 1 biomarkers are sufficient to diagnose AD. Specifically, we propose that the following can be diagnostic of AD: amyloid PET; CSF A β 42/40, CSF p-tau181/A β 42, CSF t-tau/A β 42; or, “accurate” plasma assays where “accurate” is defined as equivalent accuracy to approved CSF assays in detecting abnormal amyloid PET in the intended use population (**Text box 2**). This definition of “sufficient accuracy” is consistent with recent recommendations on minimum acceptable performance criteria for blood-based biomarkers [*ref coming*].

Core 2 biomarkers have many uses (**Table 2**) but would typically not be used as standalone diagnostic tests for AD. The A-T₂+ biomarker profile is not consistent with a diagnosis of AD. First, this combination is rare ^{32, 33}. Second, when it does occur it is often due to quantitative values close to cut points that may fall on one side vs the other of a cutpoint due to measurement variation. Third, from a neuropathologic perspective A-T₂+ corresponds to PART which is not considered to represent AD ^{4, 34}.

3.1) Rationale for diagnosis of AD by specific Core 1 biomarkers

Natural history studies have unequivocally shown that biomarkers in the Core 1 category become abnormal well before overt symptoms arise (**Figure 1**) ³⁵⁻⁴¹. Our rationale for diagnosing AD by the presence of an abnormal Core 1 core biomarker, is that the disease exists when the earliest manifestation of AD pathophysiology can be detected, even though onset of symptoms may be years in the future. Our position is that the onset of β -amyloidosis defines the initially detectable stage of AD. An analogy can be drawn with adult-onset diabetes, where most individuals are diagnosed by screening HbA1C or fasting glucose testing while 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 has been status quo for years in other areas of medicine (e.g. oncology) and is becoming a unifying concept common to all neurodegenerative diseases as exemplified by recent efforts in Parkinson's disease⁴²⁻⁴⁴ **Huntington's disease**⁴⁵, and amyotrophic lateral sclerosis⁴⁶.

In the 2018 research framework, an A+T+ biomarker profile was required for a designation of Alzheimer's disease based on the ATN biomarker classification scheme. However, in this update biofluids and PET are no longer considered interchangeable, and the T category has been split into T₁ and T₂. So rather than defining AD as A+T+, we now define AD as abnormality on Core 1 biomarkers that meet specific diagnostic accuracy criteria which are described in the following section and in **Text box 2**.

3.2) Anchoring biomarkers for AD diagnosis to reference standards

The amyloid PET visual reading scale on which regulatory approval of florbetapir was based is highly accurate (sensitivity 96%, specificity 100%) at discriminating CERAD none/sparse vs moderate/frequent plaques in individuals who came to autopsy within 1 year of the PET scan⁴⁷. Quantification of amyloid PET is also accurate at distinguishing intermediate/high vs none/low AD neuropathological change (ADNPC) (in one example, sensitivity 84%, specificity 88%)⁹. Visual reads of other approved PET tracers demonstrated similar sensitivity/specificity with respect to a neuropathologic reference standard^{48,49}. Ideally the reference standard for validation of any biomarker would be neuropathologic examination, but this may not always be practical given the challenges with obtaining biomarker and autopsy sampling close in time in representative populations. Accordingly, regulatory approval of CSF assays (**Supplemental Table 1**) was anchored to positive/negative visual reads of amyloid PET: sensitivity/specificity (or positive % agreement/negative % agreement) of approved CSF assays ranged from 97%/84% to 91%/89% to 88%/92% against this reference standard⁵⁰⁻⁵².

Currently, no plasma assays have received regulatory approval although this is expected to change soon. Diagnostic accuracy varies substantially among various plasma p-tau and A β 42/40 assays^{53, 54, 55}. Accuracy estimates with respect to an amyloid PET or CSF reference standard using a single preselected cut point or area under the receiver operating curve (AUC, i.e., accuracy over all cut points) range from .6s (60%) to over .9 (90%)^{53, 56-58}. Thus, some

plasma assays, particularly p-tau 217, have accuracy that is equivalent to approved CSF assays^{53, 58, 59, 60, 61, 62} while others do not. Accuracy must be defined in the intended use population and presently the population in which a diagnosis of AD would provide medically actionable information is cognitively impaired individuals. Thus, our definition of plasma assays that may suffice as standalone diagnostic tests for AD are those with accuracy of approximately 90% to detect abnormal amyloid PET by visual read in the intended use population, or more simply, plasma assays that have diagnostic performance equivalent to approved CSF assays (**Text box 2**).

Core 1 fluid biomarkers become abnormal around the time amyloid PET does, thus we anchor the onset of AD in vivo to approximately the onset of abnormal amyloid PET (**Figure 1**). However, it is important to bear in mind that amyloid PET is not sensitive to low levels of ADNPC. The FDA approved amyloid PET tracers cannot, by visual reads, reliably detect sparse neuritic plaques^{8, 9, 47-49}. Also, while accurate plasma assays are effective in identifying intermediate/high ADNPC they do not reliably discriminate among Braak stages 1-IV in cognitively unimpaired subjects⁶³. Therefore, defining the onset of detectable AD by the onset of abnormalities in Core 1 biomarkers does not mean that mild levels of ADNPC with questionable clinical significance are used to define the biological onset of AD. Intermediate/high ADNPC is considered sufficient to produce dementia^{4, 5}.

In the following sections, we outline recommendations around application of biomarkers for the biologically based diagnosis of AD (**Text box 2**).

3.3) Plasma vs CSF

While we list CSF and plasma *analytes* under the common heading of fluid biomarkers in **Table 1**, CSF and plasma *assays* are separated in **Table 2** which lists assays for specific intended uses. CSF p-tau is typically not used as a standalone test, rather, diagnostic CSF assays are hybrid ratios, p-tau 181/A β 42, total tau/A β 42, or A β 42/40. In contrast plasma p-tau is used as a standalone assay^{18, 59, 64-72}.

The fold difference between individuals with vs without β -amyloid pathologic change is around 50% for CSF A β 42/40 but only 10%-15% for plasma A β 42/40^{16, 54, 73-75}. This limited diagnostic range accounts for the generally worse accuracy of plasma A β 42/40 assays compared to CSF assays or plasma p-tau 217 assays^{53, 54}.

3.4) Biofluid assay development transparency

Specific regulations are established by national and international laboratory medicine associations and regulations for the use of laboratory tests include the International Medical Device Regulations, FDA, and European In Vitro Diagnostic regulations. The common principle is that for clinical use of biomarker tests, documentation and proof needs to be made available at the level of a) scientific validity, which includes details of the reference standard i.e., autopsy, approved CSF assays, or amyloid PET; b) analytical validation, which includes criteria for test precision, bias, and linearity which are addressed by the Clinical and Laboratory Standards Institute guidelines; c) clinical validation, including validation data in the intended use population, showing clinical accuracy, positive and negative predictive value at the medical decision limit (i.e. predetermined cut-point(s)) in each intended use population, and safety (which includes the effect of incorrect test diagnosis); d) information provided should also include details of the population(s) tested, such as, demographic data (e.g., sex, age, race, etc.) and pertinent clinical data (e.g., degree of cognitive impairment).

3.5) Conservative treatment of values near a cutpoint; the indeterminant zone

The definition of an abnormal test value requires creating a cut point in the continuous range of values for a biomarker. Cutpoints denoting normal vs abnormal values may be selected by various means⁷⁶ and will vary with the fluid assay, and for PET will depend on the specific ligand and details of the analytic pipeline for quantitative analyses. Furthermore, criteria for cutpoint selection depends on intended use. Sensitivity and specificity are obviously inversely related and optimizing one vs the other will depend on the intended use as well as the prior probability of AD in the relevant population.

Regardless of assay or modality, however, a level of diagnostic uncertainty exists for values at or near any cutpoint. When using a CSF, plasma, or PET biomarker quantitatively for diagnosis, a useful approach would be 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 based on 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. The width of the indeterminant zone would depend on assay precision⁷⁷. Higher precision would allow a narrower indeterminant zone and vice versa. We recognize that regulatory approval for assays are usually based on a single validated cutpoint; however, the package insert for one approved CSF assay does include a range described as “likely consistent with a positive amyloid PET scan result” which conveys the notion of an indeterminate zone⁵¹.

For imaging, visual reads would usually provide a normal/abnormal output, but 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. Visual and quantitative approaches each have their own strengths. While regulatory approval of amyloid and tau PET ligands was based on visual reads, the field is moving toward greater use of quantitative methods⁷⁸⁻⁸⁰. When PET is assessed quantitatively, however, images should still be inspected visually by a qualified expert to assure adequate image quality.

3.6) Clinical judgment

Important considerations in diagnosing AD biologically include the limitations of currently available biomarkers. These are outlined in **Text box 3**, but the limitations of biomarkers lead directly to the importance of clinical judgement in their clinical application.

When using a biomarker for clinical care, clinical judgement is always required to address the question, is AD a cause of (or a dominant component of) a patient’s symptomatic presentation? The nature of the syndromic presentation may indicate the likelihood that AD is or is not a dominant contributor to symptoms. For example, in someone with clinical features of

Lewy Body disease but who also has a positive Core 1 biomarker, the judgement of the clinician is needed to assess the degree to which cognitive symptoms are likely attributable to AD vs Lewy Body disease. In such a situation, additional testing may be clinically indicated. An

abnormal Core 2 biomarker would suggest that AD is, while a normal Core 2 biomarker would suggest that AD is not likely to be a significant contributor to symptomatic presentation.

Another area where clinical judgment is essential is when a Core 1 biomarker is discordant with the clinical impression, for example a negative test result in a patient in whom the clinical presentation suggests a high probability of AD. In such a situation, additional testing

is logical. And the committee strongly recommends that clinicians should not be restricted by payers in pursuing further testing when this is indicated by clinical judgement.

Clinical judgement is also required to assess potential effects of confounding conditions on biomarker results. For example, head trauma or cardiorespiratory arrest may acutely and transiently increase p-tau values⁸¹. Some MAPT mutation carriers with a 3R+4R tauopathy may have elevated p-tau 217 in the absence of amyloid pathologic change⁸². Elevated p-tau 181 has been reported in autopsy verified ALS cases with little to no AD copathology⁸³. Certain medications and impaired renal function can elevate, while obesity may depress, some plasma biomarker values^{84, 85}. Recent results indicate that plasma testing may have to be performed under fasting conditions and at a standardized time of day⁸⁶. All these potentially confounding situations should be obvious clinically. Knowledge of patient history is necessary to avoid interpretation errors.

For all the reasons above, we recommend that biomarkers testing should only be performed under the supervision of a physician. This is particularly pertinent for plasma testing given its much wider projected accessibility.

3.7) Intended uses

Intended uses for a biological diagnosis of AD in clinical care include counseling, tailoring medications for symptomatic (i.e., non-disease modifying) treatment, and determining eligibility for treatments targeting core disease pathology based on drug registration criteria^{87 88}.

We do not see a clear role in clinical care for plasma biomarkers that do not have sufficient accuracy to be used for diagnosis (**Text box 2**). Use of less accurate plasma biomarkers for screening or triaging purposes (with PET or CSF required for confirmatory diagnosis) seems to make little sense when plasma biomarkers exist with equivalent accuracy to CSF.

The major intended use for the biological diagnosis of AD in clinical trials is as an inclusion criterion. While a purely symptomatic therapy may not require documentation of AD biology, therapy directed toward a biological target requires confirmation of that biology.

We emphasize that, in the absence of approved interventions in asymptomatic individuals, we do not advocate routine diagnostic testing in this population currently. This may change in the future pending results of ongoing secondary prevention trials (e.g., AHEAD 3-45

NCT04468659, and TRAILBLAZER-ALZ 3 NCT05026866), however at present we do not see how results of AD diagnostic testing in asymptomatic individuals would produce medically actionable information.

Finally, we do not advocate initiating treatments targeting core AD pathology in all symptomatic persons with biologically confirmed AD without regard to clinical context. Rather we emphasize that treatment in symptomatic individuals with biologically proven AD should be based on clinical assessment of risk/benefit at the individual patient level (**Text box 4**).

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.

Staging of AD applies only to individuals in whom the disease has been diagnosed by an abnormal Core 1 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 scheme overview

We recommend a biological staging scheme that employs only core biomarkers. N biomarkers certainly add prognostic information⁸⁹⁻⁹¹; however, the temporal relationships between core AD biomarkers, 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 β -amyloidosis alone, who by our 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 and therefore we have also not included I biomarkers in the staging scheme.

We propose 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 (**Figure 1**). Staging by amyloid and tau PET or with a combination of T₁ fluid markers and tau PET is clinically viable at the present time and is our focus for biological staging (**Table 3**). We also describe a conceptual staging scheme based on fluid biomarkers alone (**Table 4**), which at this point is not ready for clinical use but could be in the future. We do not attempt to link PET and fluid biomarker stages but rather employ the same naming convention within each modality.

4.3) Biological staging with amyloid PET and tau PET

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^{23, 92-99} or cutpoints in the continuous distribution of values from a defined region of interest (ROI)^{76, 99-101}. 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 exist between amyloid PET, tau PET and clinical symptoms. These can be summarized as follows. Abnormal amyloid PET often exists as an isolated finding in elderly individuals who are cognitively unimpaired and without neocortical tau PET uptake or neurodegeneration^{35-37, 40, 41}. In contrast, high levels of neocortical tau are rarely seen in the absence of β -amyloidosis and are usually accompanied by neurodegeneration and clinical symptoms⁴⁰. Clinical symptoms and neurodegeneration are closely related both in time and topographically with tau PET but not amyloid PET¹⁰²⁻¹⁰⁴. This set of findings is consistent with a stereotypical sequence of unidirectional biomarker events that can be summarized as: β -amyloidosis precedes neocortical tauopathy which in turn leads to neurodegeneration and clinical symptoms, **A to T to N to C**^{38, 39, 41, 105-107}. β -amyloidosis appears to facilitate topographic spread of tauopathy, with the latter most commonly, but not always, beginning in medial temporal areas^{23, 96}.

Therefore, for biological staging with amyloid and tau PET we propose the following staging scheme (**Tables 3a, 3b**): stage A (*initial*) – abnormal amyloid PET with no uptake on tau PET (A+T-). 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}+). The distinction between stage C and D could be operationalized as the midpoint of the neocortical tau PET curve in **Figure 1**.

This PET staging scheme incorporates 5 elements. Both amyloid PET and tau PET are included to capture the 2 defining proteinopathies. Within tau PET the scheme incorporates both topography (by distinguishing between MTL and neocortical uptake), and uptake magnitude in the neocortical meta-ROI. Finally, the neocortical meta-ROI will capture staging for both typical and atypical/hippocampal sparing AD presentations¹⁰⁸. 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 outcomes¹⁰⁹⁻¹¹¹. 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 uptake will be captured by progressively worse tau PET stages^{111, 112}.

Finally, we point out that continuous measures of uptake in the neocortical tau PET ROI, while not a staging method, can provide a standardized anatomic target for quantification.

4.4) Biological staging with Core 1 fluid biomarkers and tau PET

Currently approved treatments targeting A β require documentation of A β pathology for treatment eligibility. It is anticipated that many patients will undergo testing with Core 1 biomarkers to assess eligibility and that much of this testing will be with fluid biomarkers. Individuals in whom β -amyloidosis has been established by fluid Core 1 biomarkers, could then undergo tau PET and the combination of Core 1 fluid plus tau PET can be used for biological staging – i.e., a single fluid assay plus a single (tau) PET study rather than amyloid and tau PET. Core 1 fluid biomarkers can establish that an individual is stage A or higher, but cannot discriminate among stages B-D, while tau PET would discriminate among stages B-D.

4.5) Biological staging with fluids

The onset of abnormal fluid Core 1 biomarkers occurs around the time of amyloid PET and much earlier than neocortical tau PET abnormalities^{17, 27}. In contrast more recently developed CSF tau assays (MTBR-243, and non-phosphorylated tau species) are more closely linked with the onset of abnormal tau PET and correlate better with tau PET than amyloid PET, while pT205 correlates with both amyloid PET and tau PET²⁵⁻²⁷. From these data, a sequence of events has been proposed with pathologic tau species appearing in the following order: plasma or CSF ptau 181, 217 or 231; then pT205; then MTBR-243; then non phosphorylated tau²⁶⁻²⁸. Based on these data, a fluid only staging scheme (illustrated in **Table 4**) can be envisioned that mirrors the A-D scheme described earlier. Measurement of ptau-T205 in plasma has recently been reported²⁷. MTBR-243 and relevant non-phosphorylated species have only been measured in CSF, however, plasma assays may become possible. An important caveat is that this fluid only staging scheme is regarded as conceptual at present and would require extensive validation testing for clinical implementation. Also, this conceptual scheme is likely to change given the rapidly changing nature of the fluid biomarker field.

4.6) Caveats

We do not specify specific proprietary fluid assays, PET ligands or numeric cut points for staging purposes in this document. Our position is that clinicians and researchers will make those determinations empirically. Fluid assay development and standardization of tau PET quantification are currently in flux and cutoffs for various fluid biomarkers, especially plasma, have not yet been established.

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. Second, we recognize that medial temporal tauopathy does not always precede neocortical tauopathy particularly in atypical presentations¹¹³. However, medial temporal to neocortical spread is by far the most common pattern. 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 at least some of these areas should be included in a neocortical tau PET meta ROI^{89, 91, 97, 114}. Similarly, the medial temporal ROI could include hippocampus (for some ligands), entorhinal cortex, and amygdala. Efforts are underway to standardize quantification of tau PET for all tracers (for example, the CenTauR scale¹¹⁵) in the same way that the Centiloid scale¹¹⁶ is the standardized method for quantifying amyloid PET.

The Centiloid scale is the accepted method for quantifying amyloid PET in academia; however, this is based on the anatomic distribution of ligand uptake in sporadic AD¹¹⁶. 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^{117, 118}. Therefore, the approach to determining A+ vs A- may need special consideration in ADAD and DSAD.

4.7) *Intended uses*

Disease staging is well established in cancer where staging has for decades been used for prognosis, for selecting optimum treatment, and for creating homogeneous groups for interventional trials. As with other diseases, more advanced biological AD stage predicts worse prognosis (**Figure 1**)^{89-91, 110, 119, 120}. In individuals in the AD spectrum, the more advanced the

biological stage, the greater the degree of confidence that AD is meaningfully contributing to symptoms and the greater the risk of and the likely rate of future progression.

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. 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 designation¹²¹. 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^{122, 123}.

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 Scale¹²⁴, 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 AD¹²⁵.

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 guidelines¹. 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)¹²⁶ 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: amnesic or “typical”, language variant, visuospatial variant, behavioral variant and dysexecutive variant which are reviewed in^{127, 128}. 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**).

5.2) Stage 0

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))¹²⁹ 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 1 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 disease⁴²⁻⁴⁵.

5.3) Risk alleles

We have not included AD risk alleles in the staging scheme because the presence of risk alleles, does not indicate with certainty the presence or severity of AD pathology in an individual at a given point in time. This contrasts with Core biomarkers which do. We therefore regard risk alleles as a risk factor for AD, not a diagnosis of or stage of AD.

Knowledge of APOE genotype has, however, assumed heightened clinical importance in the context of anti A β immunotherapy. The risk of ARIA is substantially greater in APOE ϵ 4 homozygotes vs heterozygotes and non-carriers¹³⁰. Consequently, screening for APOE is recommended in the FDA label for lecanemab and counseling around risk is recommended for homozygotes¹³¹.

5.4) Syndromic staging

The 2018 document also included a syndromic staging scheme that is commonly used in clinical practice^{132, 133} 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)^{134, 135}. 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** where 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 comorbid pathologic change. Individuals who lie below the diagonal (i.e., better clinical stage than expected for biological stage) may have exceptional resilience or cognitive reserve¹³⁶.

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.

7) NIVS biomarker categories

Tables 1,2 categorize core and non-core biomarkers. We describe the latter here.

7.1) 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. In this revision we no longer employ this notation because it should be clear that N biomarkers do not belong in the same category as core biomarkers. 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, ischemic injury, and others.

Fluid N biomarkers denote active neuronal injury or more subtle neuronal dysfunction. For example, NfL is a marker of large caliber axonal injury that can be measured in CSF or plasma and becomes abnormal in various disorders including MS, ALS, and traumatic brain

injury^{29, 31, 137-145}. The absence of total tau from the fluid biomarker N category in **Tables 1,2** is a departure from the 2018 research framework. CSF and plasma total tau begin to increase early in the disease course in autosomal dominant AD¹⁷ and closely correlate with fluid ptau in autosomal dominant and sporadic AD⁸¹. 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^{81, 146}. 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^{147, 148} 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^{149, 150}.

Synaptic loss and dysfunction are an important feature of neurodegenerative diseases, most notably AD. Various synaptic CSF markers have been used for research purposes²⁹⁻³¹. PET imaging of synapses has also entered the research arena based on ligands that bind to the synaptic vesicle glycoprotein 2A, a presynaptic component that may be lost with neurodegeneration¹⁵¹⁻¹⁵³. 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 pathophysiology¹⁵⁴.

Biomarkers of inflammatory/immune processes (I) are divided into 2 subcategories, reactivity of astrocytes and microglia. A substantial body of evidence from genetics, animal models, and neuropathology indicates that immune/inflammatory mechanisms are important in AD pathogenesis¹⁵⁵⁻¹⁵⁷. And a growing list of interventional strategies targets immune/inflammatory pathways¹⁵⁸. Despite the importance of these mechanisms, there is presently a dearth of available I biomarkers. An I marker that may gain clinical use is glial fibrillary acidic protein (GFAP). This can be measured in plasma or CSF and is a marker of astrocytic reactivity. While not specific to AD it is associated with higher risk of incident dementia and faster rates of cognitive decline^{29, 30, 145, 159-164}. Plasma GFAP seems to perform

better than CSF measures for reasons that are not well understood. Another I biomarker that has received recent attention in research is soluble TREM2 which reflects microglial reactivity and can be measured in CSF^{165, 166}. CSF cytokines and complement factors may be useful biomarkers of both astrocytic and microglial reactivity. PET ligands exist for microglial and astrocytic reactivity in research settings.

7.2) Biomarkers of common non-AD co-pathologies

We list biomarkers of α -synuclein (S) and vascular brain injury (V) in **Tables 1,2** under the heading of biomarkers of common non-AD co-pathologies. A-synuclein seed amplification assays (α Syn-SAA) in CSF have gained attention in Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB), recently relabeled as Neuronal Synuclein Diseases^{167, 168}. Although no α Syn-SAA assay has yet received regulatory approval, one has received Breakthrough Device Designation from the FDA and is commercially available. α Syn-SAA are sensitive and specific for antemortem identification of limbic/neocortical α -synuclein pathologic change in patients with limbic/neocortical α -synuclein as a primary or as a co-pathology¹⁶⁹. 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^{170, 171}. α Syn-SAA currently yield a positive, negative, or inconclusive output that is not quantitative¹⁷². 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^{173, 174}. 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^{175, 176}. DAT scanning plays a prominent role in recent staging criteria for Parkinson/Neuronal Synuclein Disease⁴²⁻⁴⁴.

Cerebro vascular disease is an umbrella term that encompasses different forms of vascular brain injury (V). Various modalities or imaging findings for vascular brain injury exist; however, at this point a single summary measure composed of different imaging findings has not been widely accepted. Macroscopic cerebral infarctions, including both large cortical and subcortical infarctions and lacunes, on anatomic MR or CT are the most definitive biomarker of ischemic vascular brain injury and are widely employed for this purpose in clinical care (**Tables 1,2**). State of the art methods in neuroimaging of small vessel disease (reviewed in the recent STRIVE-2 guidelines¹⁷⁷) include microinfarctions¹⁷⁸, CO2 reactivity¹⁷⁹ and the presence of

abundant dilated perivascular spaces¹⁸⁰. 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 in research¹⁸¹⁻¹⁸⁴. 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). Thus, these modalities are not disease-specific. White matter hyperintensities (WMH) on MR have long been interpreted to indicate microvascular ischemic injury¹⁵⁰ 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^{185, 186}.

The vascular markers described above are linked with traditional systemic vascular risk factors and cerebral ischemia. Cerebral amyloid angiopathy (CAA) merits special mention because while the disorder is one of cerebral vessels, the etiology is disordered processing of A β rather than traditional systemic vascular risk factors and CAA is commonly observed in association with A β plaques in AD. CAA represents the aggregation of A β in cerebral vessel walls leading to vessel fragility¹⁸⁷. 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 brainstem¹⁸⁸. Rarely, spontaneous vasogenic edema can be seen. A serious potential complication is lobar hemorrhage¹⁸⁹. MR evidence of CAA (microbleeds or siderosis) increases the risk of Amyloid Related Imaging Abnormalities (ARIA) in patients undergoing anti A β immunotherapy, and thus detection will play an important role in clinical care¹⁹⁰.

8) 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

neuropathophysiological 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 1,2**, a full multimodal biomarker profile would appear as ATN/ISV with results indicated (+/- dichotomized, or a continuous quantitative scale) 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 practice to characterize individuals.

One potential use of multimodal biomarker profiles is to provide simple conceptual organization and practical shorthand notation to characterize persons with comorbid pathologies. With advancing age, co-pathologies are the rule and isolated AD is the exception. Common age-related brain pathologies that underlie cognitive impairment or dementia in elderly persons are AD, cerebrovascular disease, Lewy Body disease, and Limbic associated TDP-43 encephalopathy (LATE)^{191-196 197, 198 199}. CSF dynamics disorders may also contribute to impairment and can be detected by MRI²⁰⁰. LATE merits special mention because while it is a common and clinically important contributing pathology to late life cognitive impairment, no confirmed disease-specific biomarkers exist currently²⁰¹. 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, 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 profile²⁰²⁻²⁰⁵. Neurodegeneration in AD is closely related in time and topography to tau deposition. A T-N+ biomarker profile (i.e., TN mismatch) therefore indicates 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 amnesic presentation 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 T-N+)²⁰¹.

8.1) Intended uses

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 not respond to anti A β 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 in phase 2 trials in which a biologically homogeneous cohort with purer AD is desirable to maximize statistical power. Individuals with indicators of co-pathology could be included in Phase 3 AD trials, with preplanned subset analyses, to establish efficacy in a broader population.

9) Treatment effects

The focus of this document is on criteria for diagnosis and staging of AD; detailed discussion of the roles of biomarkers as outcome measures or indicators of target engagement in clinical trials is beyond the scope of this work. Nonetheless, the recent regulatory approval of treatments targeting core AD pathology promises to be transformative. Anti A β immunotherapy can dramatically reduce the load of amyloid plaque in a time and dose dependent manner and also change downstream biomarkers in the direction of normalization, including fluid ptau and total tau (CSF and plasma)^{130, 206-208}, plasma GFAP^{130, 207}, and also reduce the level of or slow accumulation on tau PET^{130, 206}. Most importantly, recent trials have demonstrated that anti A β immunotherapy that substantially reduces fibrillar amyloid levels measured on PET, can slow the rate of cognitive decline in early symptomatic AD^{121, 130, 155, 206, 208}. 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^{155, 209}. These findings linking biology to clinical manifestations, which have been replicated across independent therapeutic programs^{121, 130, 206, 208}, 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 pathology of the disease has been eradicated. Individuals followed after cessation of A β immunotherapy have shown decreasing plasma A β 42/40, small recurrent accumulation of amyloid on PET, and clinical progression similar to patients receiving placebo²¹⁰. The underlying AD pathophysiologic process is therefore still active in an individual who has had fibrillar amyloid removed to below detection levels based on PET scanning alone. The biological diagnosis and staging schemes outlined earlier are based on observations of the natural history of

the disease. Successful disease modifying therapies 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 A β monoclonal antibody may change from A+T_{MOD}+ at baseline to A-T_{MOD}+ following treatment, but the disease process is still present. 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 A β immuno therapy often results in higher rates of whole brain volume loss or ventricular enlargement in treated vs placebo individuals^{121, 206, 211}. Interestingly the hippocampus seems to be spared from this effect^{130, 208}. Explanations for the pseudo-atrophy effect include therapy induced fluid shifts or reduction in volume of amyloid plaque and peri-plaque inflammation. It has become apparent that slowing of the rate of whole brain 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 whole brain atrophy rates may occur over much longer time scales with successful therapy, but this remains to be shown. Whole brain volume measures can only be considered a measure of neurodegeneration in conditions of physiologic steady state – i.e., in the absence of abrupt changes in plaque volume or brain edema – which seems not to be the case during active anti A β 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^{190, 212}.

10) 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^{72, 213-215}. 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)^{85, 216, 217}. SDOH may also modify the predictive effect of biomarkers for cognitive decline. The interaction between biomarkers and genetic markers may differ by race^{218, 219}. The prevalence of APOE e4 is lower in Black and Asian than in White populations²²⁰. 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 socioeconomic status are universal barriers to inclusion in research studies that are present in all countries.

11) Future directions

The series of 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 alone to the priorities required for both research and clinical practice. Future directions to consider for updating these criteria for diagnosis and staging could include the following. 1) Identify specific quantitative criteria for cutpoints to define diagnosis and stages. Like biomarker and imaging standards in other diseases, such as HgbA1c for diabetes or imaging for cancer staging, the exact thresholds for abnormality may evolve over time as additional data inform prognostic value. 2) Improved understanding of various post translational modifications of tau may enable clinically applicable fluid based biological staging. 3) With improved understanding of the role of inflammatory processes and astrocyte biology in AD pathogenesis¹⁵⁵⁻¹⁵⁷, we envision a more prominent role for I biomarkers in biological characterization and prognosis. 4) As clinical trials targeting mechanisms other than anti A β immunotherapy are performed, the effects of these interventions on biomarkers and clinical outcomes should be included in future criteria. 5) 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. 6) However, all these goals will depend first on standardization of biofluid assays, standardized quantification of tau PET, and standardization of cutpoints for all fluid and PET biomarkers.

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