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The National Institute on Aging and the Alzheimer's Association Research Framework for Alzheimer's disease: Perspectives from the Research Roundtable

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Abstract

The Alzheimer's Association's Research Roundtable met in November 2017 to explore the new National Institute on Aging and the Alzheimer's Association Research Framework for Alzheimer's disease. The meeting allowed experts in the field from academia, industry, and government to provide perspectives on the new National Institute on Aging and the Alzheimer's Association Research Framework. This review will summarize the "A, T, N System" (Amyloid, Tau, and Neurodegeneration) using biomarkers and how this may be applied to clinical research and drug development. In addition, challenges and barriers to the potential adoption of this new framework will be discussed. Finally, future directions for research will be proposed.

Keywords

Alzheimer's disease; Amyloid; Tau; Neurodegeneration; Clinical trials; Biomarkers

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1. Introduction

The identification of Alzheimer's disease (AD) biomarkers and their ability to measure pathology antemortem has led to a fundamental reconsideration of the pathogenesis of AD. The importance of biomarkers was already reflected in revised diagnostic criteria proposed by the National Institute on Aging and the Alzheimer's Association in 2011 [1–4] and the International Working Group in 2007 [5]. The International Working Group criteria were subsequently updated in 2010 [6] and 2014 [7]. With each of these iterations, the field has achieved greater sensitivity and specificity of AD diagnoses, which in turn has better enabled our ability in clinical trials to test hypotheses of treatment and ultimately prevention of AD.

Beginning in 2016, the NIA and AA convened a new workgroup to develop a research framework for AD that embodied the paradigm shift occurring in the field. Rather than conceptualizing AD primarily as a clinicopathological entity, biomarkers have demonstrated that AD pathology exists over the continuum of the disease–from a stage preceding overt symptomatology (the "preclinical state") to the progressively more impaired symptomatic states of mild cognitive impairment (MCI) and dementia. The same biomarkers have also shown in greater resolution how dementia may occur in people with both AD and non-AD pathology.

The National Institute on Aging and the Alzheimer's Association Workgroup's Research Framework uses a biomarker classification scheme proposed by Jack et al [8], which divides the current major AD biomarkers into three categories, based on the type of pathologic change each measures: β-amyloid (A), pathological tau (T), and neurodegeneration (N). The framework is intended to provide the research field with a common language for diagnostic purposes. Its scope is therefore focused on those aspects of research involving humans where specificity of the diagnosis of AD is important. Although the framework contains certain assumptions about diagnostic relevance to AD, it should not be conceived as a mechanistic hypothesis about the pathogenesis of AD. An important goal of this effort is to speed up and improve the development of disease-modifying treatments for AD.

A draft of the framework was presented at the Alzheimer's Association International Conference in July 2017, and an updated draft was posted online in November 2017 [9], with the intent of collecting comments from the research community. Given the importance of this issue, the Alzheimer's Association's Research Roundtable convened scientists from academia, industry, and government in the of Fall 2017 to discuss the framework.

2. The ATN system

The ATN nomenclature represents a conceptual framework that is based on the past decade's empiric observations of relationships between markers of amyloid, tau, and neurodegeneration. "A" refers to amyloid β (Aβ) as measured either by amyloid positron emission tomography (PET) imaging of amyloid plaques or in the cerebrospinal fluid (CSF) as $A\beta_{42}$ or the $A\beta_{42}$ to $A\beta_{40}$ ratio. "T" refers to tau pathology as measured by CSF phosphorylated tau or tau PET imaging of parenchymal neurofibrillary tangles. "N" refers to

neurodegeneration or neuronal injury and dysfunction, as measured for example by hippocampal volume or cortical volume or thickness. While “A” and “T” are considered to have diagnostic specificity for AD, “N” is not specific for AD diagnoses because it can reflect any number of etiologies in addition to AD. The roundtable discussion devoted several sessions to understand the details of each category of biomarkers, which is summarized below.

2.1. Classification and staging with ATN

The ATN biomarkers may reflect the presence (state) or progression (stage) of a disease. State biomarkers indicate the presence or absence of pathology and by extrapolation, the presence or absence of a disease. In AD, the $A\beta_{42}$ peptide, deposited in a β-pleated sheet conformation in cored or neuritic plaques, is the principal state biomarker defined neuropathologically [10]. Biomarkers of amyloid pathology are the first to change in dominantly inherited AD [11]. In persons without dominantly inherited mutations, elevations of PET amyloid can also appear in some cognitively normal 50- and 60-year-olds anticipating incident dementia by roughly 15 years [12]. The neuropathological definition [10] of AD drives the ATN definition of AD and requires the presence of amyloid plaques (as evidenced by PET or CSF) for diagnosis.

Elevated numbers of amyloid plaques have long been considered necessary but not sufficient for the diagnosis of AD neuropathologically. The debate over the centrality of elevated Aβ peptide in AD pathogenesis is a separate matter; to be sure, there is much controversy regarding Aβ peptide’s role in causing AD. But diagnostically, this is a settled issue as far as a necessity for the majority of the field: a minimum burden of amyloid plaques (composed of the $A\beta_{42}$ peptide) is necessary for the diagnosis of AD. In 2012, the NIA and AA published consensus guidelines on the neuropathological diagnosis of AD to more precisely describe the meaning of neuropathological findings [10]. They developed a scoring system to assess the level of AD neuropathological change, concluding that parenchymal Aβ plaques are sufficient for a diagnosis of low-level AD neuropathological change; and necessary, but not sufficient for a diagnosis of intermediate- or high-level neuropathological change, which also requires the presence of neurofibrillary degeneration. ATN assumes that biomarkers for amyloid plaques are necessary for assignment of an individual to the Alzheimer’s continuum.

Stage indicates the level of disease progression and can be described either categorically or as a continuous measure. A stage biomarker need not be abnormal throughout the spectrum of the disease. Neuropathological studies link the level of neurofibrillary tangle-related tau to the clinical severity of disease, suggesting that in AD, tau is the principal stage biomarker [13]. However, how tau is measured is important: CSF tau and tau as measured by PET imaging appear to reflect different things. Although tau PET levels continue to rise in persons with dementia, CSF tau levels, while abnormal, do not keep rising with worsening dementia [14]. Thus, PET imaging provides superior accuracy for the staging of AD dementia and additionally provides information on state, whereas CSF tau levels act mainly as state biomarkers only. The combination of Aβ and tau biomarkers also provides stage information, for example, in people who have amyloid plaques but low tau. CSF Aβ appears

to be more sensitive than PET to detect amyloid plaques in early disease [14] but subsequently reaches a plateau [15]. Conversely, while both CSF $A\beta_{42}$ and Aβ PET standard uptake value ratio approach a plateau, amyloid PET does so later in the disease [16].

Thus, while "A" is heavily weighted to state biomarkers (CSF Aβ and amyloid PET), "T" biomarkers share both state and stage characteristics. "N" is heavily weighted to stage (18F-fluorodeoxyglucose [FDG]-PET and magnetic resonance imaging [MRI]) but also includes a component of state because it likewise assesses the presence of neurodegeneration which, while not a diagnostic feature of AD, is directly related to cognitive impairment. "N" is closely linked to clinical symptoms. It is predictive of decline in cognitively normal individuals [17] although it has limited specificity for AD versus other neurodegenerative diseases, and its specificity is modulated by age and clinical status [18]. There are also regional differences with N-imaging biomarkers, which can provide clues about pathoetiology and thus contribute to specificity.

Interpreting radiotracer PET evidence of amyloid plaques or CSF levels of $A\beta_{42}$ as binary constructs for disease state requires the establishment of cut points, which vary by the method of quantification [19]. Typically, the goal of establishing cut points is to dichotomize results into "positive" and "negative" groups. This can be relatively easy to do if results show a clear bimodal distribution. However, when results occur along a continuum, setting a cut-point can be more difficult although it is done in every disease for which a biomarker is available—for example, diabetes, hypertension, and so forth. In the Baltimore Longitudinal Study of Aging, for example, amyloid PET scans were conducted longitudinally on 190 participants over several years. Radiotracer uptake was assessed as the mean cortical distribution volume ratio for each scan, enabling the investigators to plot within-individual amyloid accumulation by age over time. These longitudinal data showed that while the cortical distribution volume ratio for some people stayed low, once they reach a threshold of low but detectable Aβ deposition, they transition to an upward trajectory. Based on the Baltimore Longitudinal Study of Aging analysis pipeline and a 2-class Gaussian mixture model, a mean cortical distribution volume ratio of approximately 1.06 was chosen as the cut point. The Mayo Clinic did a similar study and found a reliable Pittsburgh compound B cut point to be standard uptake value ratio 1.42. Setting the cut point higher would miss many people on the upward trajectory.

Establishing cut-points and interpreting amyloid radiotracer uptake at low levels is particularly challenging because adjusting Aβ cut-points may give high sensitivity for early stage AD but possibly at the cost of specificity. Imposing stage cutoffs may also lead to artificial categorization and loss of important information. An alternative to be explored further is to allow for several levels of each ATN category, for example, by using both lenient and conservative cut-points for each biomarker category [8].

3. Barriers to adopt ATN for clinical trials

There are numerous challenges to implement the ATN framework in clinical trials. Obtaining biomarkers by either CSF or by imaging adds expense and burden to any study and involves invasive procedures and/or exposure to radiation. PET imaging technology is

often not readily available outside of major medical or research centers. Multiple procedures are generally needed to inform each of the three legs of the ATN framework. In addition to these operational and economic barriers, there are also numerous conceptual and scientific hurdles presented by available biomarker tests, creating interpretational challenges that will require further research for clarification. Scientific hurdles include the fact that most fluid biomarker assays use CSF, yet blood-based biomarkers would be cheaper and more accessible for both research and clinical use. Challenges for some fluid biomarker assays include their limited technical and clinical validation, the use of heterogeneous preanalytical methodologies, and inter-batch and cross-site variability. Research use only assays that need to be performed at a central laboratory, and performance was carefully monitored.

3.1. Amyloidosis biomarkers

Many studies show good, but not perfect, concordance between CSF $A\beta_{42}$ and amyloid PET [20–24]. The reasons for discordance include both technical issues such as between-run and between-laboratory variability and biological differences because these methods measure different aspects of amyloid, fibrillar amyloid in PET studies but soluble $A\beta_{42}$ in CSF [25]. As mentioned previously, it may be that CSF $A\beta_{42}$ becomes abnormal first. The question that naturally arises is whether CSF and PET amyloid measurements could be used within the same clinical trial. While such flexibility is laudable in large phase III trials, allowing a mix of biomarkers may lead to differences between treatment groups. Further complicating the interpretation of CSF data, there is no clear alignment across the field when it comes to using $A\beta_{42}$ levels alone or in combination with other analyte(s) to make a determination of amyloid positivity; for instance, some groups advocate for use of the CSF $A\beta_{42}$:$A\beta_{40}$ ratio or the $A\beta_{42}$:tau ratio to improve concordance with amyloid PET.

Multidisciplinary studies generally reveal a high level of agreement between neuroimaging biomarkers and neuropathological measures. For example, studies using florbetapir as the PET radioligand correspond to amyloid burden documented at autopsy [26], and subsequent studies using the radioligand flutemetamol also demonstrated similar neuritic plaque burden in 90% of cases [27]. Furthermore, studies using Pittsburgh compound B as the amyloid radioligand demonstrated stereotypic progression of Pittsburgh compound B binding across antemortem amyloid plaque stages but did not correlate with neuropathologic findings of neurofibrillary tangles or neuritic plaques or the severity of cerebral amyloid angiopathy. These findings suggest that amyloid imaging reflects neuropathologic measures of plaque amyloid [28].

3.2. Tau biomarkers

Several studies have assessed the relationship between CSF total-tau (t-tau) and phosphorylated tau and tau PET [29]. As with amyloid, there are biological differences between tau species assessed using these two techniques. In numerous studies, CSF tau measures correlate only modestly with tau PET, suggesting that the two metrics may reflect distinct pathophysiologies and that the poor correlation seen was among cognitively normal individuals, who do not have significant isocortical tau burden [30]. There is also low agreement between CSF t-tau and neurodegeneration imaging biomarkers [15,20,31–33]; one explanation for this discrepancy is that they have a very different temporal evolution,

another is that like tau, studies have been done in cognitively normal individuals where little neurodegeneration exists and therefore the range of the variables is artificially restricted. Therefore, CSF t-tau and imaging biomarkers of neurodegeneration cannot be used interchangeably.

There also remain unanswered questions about quantification of tau PET. Some laboratories [34,35] have favored adopting the Braak and Braak staging system from neuropathology whereas others favor creating a tau PET staging system grounded in observed imaging changes [36]. The ATN framework, however, requires a dichotomized tau PET metric. In Lilly's Expedition3 trial, a subgroup of participants who had baseline florbetapir PET scans also had baseline tau scans with flortaucipir (aka [^{18}F]T807, [^{18}F]AV-1451). Those with higher levels of flortaucipir uptake at baseline had about threefold greater reduction in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog$_{14}$) scores by the end of the study, indicating a link between worse cognitive decline and higher tau burden, using a dichotomous measure.

Tau PET imaging using the radioligand flortaucipir corresponds to the presence of neurofibrillary tangles at autopsy but not to neuritic amyloid plaques or less mature forms of tau [37]. The close relationship between fibrillar tau deposition and neurodegeneration implies that the anatomic distribution of tau pathology corresponds to the particular cognitive symptoms present in patients with focal cortical subtypes of AD. Similarly, abnormalities on FDG-PET images also overlap with areas showing tau on AV-1451 images, although the biological mechanisms that cause the metabolic changes observed with FDG-PET remain unclear [38]. Anatomic MRI studies also suggest neurodegeneration that corresponds to that seen neuropathologically, including relative sparing of the hippocampus in about 10%–15% of neuropathologically diagnosed AD cases [39].

Plasma markers for tau protein would be particularly worthwhile for enabling AD research outside of major medical centers that do not have access to research-level lumbar punctures, research magnetic resonance, or PET scans. There has been progress in the development of plasma tau assays.

3.3. "N" biomarkers

While "A" and "T" have specific neuropathological correlates and they each refer to a specific AD-related protein, the candidate biomarkers that represent "N" comprise diverse physiological processes. Markers of neurodegeneration are conceptualized as reflecting the downstream effects of the molecular pathology of AD and are believed to be closely linked to the cognitive and behavioral manifestations of disease. As such, markers of neurodegeneration predict cognitive decline in both preclinical and prodromal populations with greater temporal precision than molecular markers alone. This attributes position "N" biomarkers as important outcome measures in clinical trials or for enrichment of individuals expected to progress within a particular time frame.

A challenge for neurodegenerative markers is that they have limited specificity for underlying AD-related pathology. These measures are affected by normal aging and strict cutoffs, leading to greater prevalence in those with evidence of neurodegeneration, both

within and outside of the AD continuum. There remains uncertainty in whether to adjust cutoffs for age, which appear to enhance the specificity of these measures but may not capture the totality of neurodegeneration, potentially reducing its link to cognitive stage. Similarly, other neurodegenerative and non-neurodegenerative conditions, including cerebrovascular disease, also contribute to both “N” markers and cognitive decline further limiting specificity. Another potential source of nonspecificity is the fact that measures are often applied in a cross-sectional manner and therefore reflect the sum total of developmental differences and other biological changes throughout the lifespan. Conceptually, neurodegeneration is a dynamic process, and longitudinal measures of neurodegeneration may better capture more proximal brain changes associated with AD.

Strategies that capture the spatial patterns of neurodegeneration with MRI or FDG-PET enhance the linkage of these measures to AD-related changes versus other neurodegenerative conditions but still often with considerable overlap. Advances in methodologies may allow for greater specificity, particularly in early stages in which relatively stereotyped brain changes associated with AD may be discriminated from other conditions. For example, measurements of subregions with the medial temporal lobe may provide greater precision in staging of AD effects than the commonly used whole hippocampal volume which is affected in multiple disease processes, as well as normal aging. However, heterogeneity in the topographic manifestations within the AD continuum (e.g., posterior cortical atrophy vs. amnestic AD) produce additional challenges for deriving a measure that can be dichotomized as normal or abnormal across a wide age range. Because a given level of neurodegeneration may have multiple drivers, it remains unclear the degree to which a given level of, for example, hippocampal atrophy is linked to the same degree of cognitive impairment depending on the underlying pathology.

There is a risk of confusion and poor comparability of findings across studies, when one study uses one metric to make an “N+/−” determination and another study uses a different metric; Roundtable presenters agreed that researchers should always endeavor to be very specific about the assays underlying an “N+/−” determination. Clearly, more research is required to clarify the inter-relationships between each candidate’s neurodegeneration biomarker and the particular aspects of the disease that each predicts. In the future, with the building of this clarity, there could be a data-driven rationale to divide the “N” category into meaningful component parts.

Finally, in the AD continuum, tau is conceptualized as being strongly linked to neurodegeneration. Discordance between biomarkers of tau and neurodegeneration may then provide important clues to disease stage and the underlying drivers of disease state. T+N- may represent an earlier point in the AD continuum, whereas T-N+ strongly supports the notion that a non-Alzheimer’s pathology may be the primary driver of neurodegeneration and symptoms. Nonetheless, even in the case of T+N+, it is certainly possible that there are additional contributors to neurodegeneration beyond the neurofibrillary tangles of AD. Indeed, relative burden of “T” and “N” may suggest the degree to which additional processes are driving neurodegeneration. Understanding the expected degree of neurodegeneration for a given level of tau burden is a potentially important area for future investigation.

Additional fluid biomarkers of neurodegeneration are needed to broaden the reach of clinical research studies beyond academic medical centers that have access to state-of-the-art imaging technologies. Challenges for fluid biomarker assays are their limited technical and clinical validation, especially blood-based ones. “N” markers that could be more accessible in research contexts outside of major medical centers are at earlier stages of development. Among the most promising biomarkers are CSF and plasma neurofilament light chain [40,41], and CSF neurogranin [42], visinin-like protein-1 [43], YKL-40 (an inflammatory marker) [44], and fatty acid–binding protein 3 [45].

4. Challenges to the biological definition of AD

A major motivation for the development of the ATN system was the recognition that biomarkers reflect the key diagnostic markers of AD. Whereas previously, clinical diagnoses were the sole basis for inclusion in clinical trials, the use of amyloid imaging in several recent large clinical trials of anti-amyloid agents showed that 20%–30% of participants did not have elevated amyloid biomarkers and therefore did not have the target required by many of the therapies. Because clinical trials are a multinational effort in the 21st century, developing a common language for biomarker designations in the AD spectrum is critical for harmonization across the international roster of clinical trial sites and investigators. Thus, even before there was a formal international consensus document, leaders in the AD clinical trial field have recognized that an abnormal amyloid imaging study or abnormal CSF $A\beta_{42}$ is a necessary inclusion criterion for any clinical trial purporting to target AD pathology specifically. Much more work needs to be done to determine the proper diagnostic role in clinical trials for “T” and “N” biomarkers. However, to the extent that those who are A+, T+, and N+ appear to have a worse prognosis than those who lack abnormalities in all three categories, selecting participants for AD dementia or MCI trials based on the ATN scheme would enrich the trial with persons with the greatest likelihood of decline in the time frame of a clinical trial. Whether those individuals would have the greatest response to a treatment targeting the Aβ peptide or amyloid plaques is a testable hypothesis.

4.1. Correlation of cognition with biomarkers

Many studies have shown that cognitively normal people with elevated amyloid biomarkers show subtle longitudinal cognitive decline across multiple domains (e.g., [46]). Furthermore, the combination of elevated amyloid and neurodegeneration biomarkers (stage 2 according to the National Institute on Aging and the Alzheimer’s Association 2011 preclinical AD stages [4]) correlates better with accelerated cognitive decline than either elevated amyloid or elevated neurodegeneration alone and substantially better than those who lack elevations of either [17,47]. In cognitively normal individuals with elevated amyloid plaques, elevated levels of tau are seen on PET scans in the medial temporal lobe, entorhinal cortex, and lateral inferior temporal cortex; and amyloid-positive individuals with high tau show the most decline in memory. Thus, the ATN framework represents a common language for diagnostic criteria that potentially increase etiological homogeneity and increase likelihood for identifying persons likely to progress.

4.2. Multi-etiology pathology and AD mimics

There are a number of conditions that co-occur or mimic AD spectrum of cognitive disorders; for some, there are existing biomarkers, but for others, biomarker characterization is not as developed as for AD. The ATN framework has enhanced the antemortem diagnoses of non-AD conditions such as Lewy body disease, hippocampal sclerosis (HS), cerebrovascular disease, and frontotemporal degenerations by identifying those cases that are A-T-. However, how well the ATN framework does when there are multiple etiologies including AD (A + T+) remains to be seen. AD pathology is commonly mixed with other pathologic conditions. Although AD biomarkers can identify the pathologic diagnosis of AD with good sensitivity and specificity, they do not give an indication of whether there are other coexisting conditions and whether it is the AD or other pathology that is primarily driving the clinical syndrome. Similarly, it cannot be currently determined whether the A and T are driving the N because other pathologies can also be related to neurodegeneration. Nonetheless, when there are coexisting conditions, amyloid PET has been shown to continue to work well in identifying amyloid positivity [48]. The most common mixed pathologies include TAR DNA-binding protein 43 (some with HS), vascular, and Lewy body pathologies. Neuropathologic studies have also shown that these pathologies can cause dementia syndromes that mimic AD in the absence of AD pathology.

Although neuropathological studies have long shown that a clinical diagnosis of AD dementia has only moderate diagnostic specificity, the advent of biomarker studies in observational studies and clinical trials has demonstrated the limitations of clinical diagnoses for attribution of etiology to AD. While many in the field had come to regard the clinical diagnosis of AD dementia (designated as probable AD in the 1984 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [now known as the Alzheimer's Association] criteria) as sufficiently specific, the findings from two recent clinical trials were sobering [49,50].

Biomarker studies in cognitively normal individuals have provided a novel perspective on neurodegenerative changes that are independent of amyloidosis. Although the neuropathological literature clearly recognized the existence of such circumstances [51], the idea was largely unappreciated. Suspected non-Alzheimer disease pathophysiology [52] characterized as neurodegenerative changes without elevated amyloid plaques has been identified in as many as one-third of cognitively normal individuals aged over 65 years [47,53,54]. The most non-AD neuropathological conditions that underlie a biomarker-defined suspected non-Alzheimer disease pathophysiology case are primary age-related tauopathy, HS, cerebrovascular disease and vascular brain injury, and dementia with Lewy bodies.

Primary age-related tauopathy is characterized neuropathologically by the presence of neurofibrillary tangles but no amyloid plaques in the brain [55]. Among the oldest old, about 20% of brains examined at autopsy show this pathology [56], although many of these individuals displayed subtle or no cognitive impairment. Primary age-related tauopathy is thought to be a pathological substrate for subjective memory complaint, which is common in cognitively unimpaired elderly [57] and MCI [58] patients.

Another common disorder with an imaging neurodegeneration pattern similar to AD is HS of aging, characterized by cell loss and gliosis in the hippocampus. HS of aging is strongly associated with cognitive impairment [59]. In the National Alzheimer's Coordinating Center data set, about 20% of cases have been diagnosed with HS. Almost everyone with HS also has TAR DNA-binding protein 43 pathology, which dramatically increases the likelihood of dementia [60]. Patients with HS are commonly misdiagnosed as having possible or probable AD [59,61]. In addition to HS/TAR DNA-binding protein 43, vascular disease, Lewy body disease, and other neurodegenerative diseases can also be misdiagnosed as AD, but as noted previously, these pathologies also commonly coexist with AD pathology.

Cerebrovascular disease (and vascular risk factors) also contributes to the misdiagnosis of AD in the elderly. As yet, there is no accepted or validated diagnostic rubric for the contribution of cerebrovascular disease to cognition, and this has created confusion. For example, although epidemiological studies have associated diabetes with AD [62], autopsy studies have shown that diabetes is associated with increased cerebrovascular disease pathology but not Alzheimer's pathology [63]. Hypothyroidism has also been associated with cerebrovascular disease [64]. A large autopsy study also demonstrated cerebrovascular disease among individuals diagnosed with stable MCI [65]. Cerebrovascular pathologies commonly seen at autopsy among older adults include macroinfarcts, lacunar infarcts, microinfarcts, cerebral amyloid angiopathy, atherosclerosis (large vessel disease), and arteriolosclerosis (small vessel disease) [66]. Using MRI, cerebrovascular pathologies are detectable in patients as white matter hyperintensities, lacunar infarcts, larger regional infarcts, microbleeds, and perivascular spaces [67]. The presence of cerebrovascular disease along with AD pathologies is associated with earlier onset of cognitive impairment and greater cognitive decline compared with the presence of AD pathologies or cerebrovascular pathologies alone. However, the interactions between cerebrovascular disease and AD pathologies are highly debated in the literature. Because both processes are impacted by age, gender, and apolipoprotein E effects and may be synergistic [68], a better understanding of the mechanism of this interaction could provide insight into how reduction of vascular risk factors could reduce the incidence of AD. The application of the ATN framework to the study of cognitively impaired persons with cerebrovascular disease offers the prospect of disentangling the contributions of vascular and AD pathologies.

Lewy bodies are also commonly seen in the brains of older individuals, often in combination with AD and vascular pathology [69]. Biomarker characterization of dementia with Lewy bodies (DLB) has shown that those patients have lesser degrees of elevated amyloid PET, less hippocampal atrophy, and less tau PET abnormalities than persons in the AD pathway [70].

It is the rule, and not the exception, for the brains of elderly persons to harbor more than one subtype of high-morbidity pathology, and the presence of additional pathologies increases the odds of dementia [71]. The prevalence and frequent comorbidity of these AD mimics has important implications for the ATN system. First, some of the burden of "N" undoubtedly arises from non-AD pathologies. Second, it is well known from clinical pathological studies (e.g., from the Rush group) that there is much unexplained variance in cognitive outcomes that is not accounted for by ATN.

5. Applications of ATN in clinical trials

Perhaps, the greater advantage afforded by the biological construct of the ATN framework is that it could enable more precise staging of individuals along the AD continuum of pathologic progression. This would allow future proof-of-concept trials to be conducted in biologically defined (in addition to clinically defined) target populations and to more directly investigate whether modulation of a specific target interferes with a specific component of disease pathologic change. Innovative clinical trial approaches that have proven successful in other disease areas such as oncology (e.g., platform trials, umbrella, and basket designs) might be employed with stratification of subjects by ATN profile, enabling a data-driven approach to identify the biological stage of disease in which an intervention has maximal treatment effects. If successful, trials in biologically defined populations could address uncertainties that have thus far stymied AD drug development: Is amyloid a trigger or driver of downstream neuropathology? What is the latest biological (ATN) stage of AD at which secretase inhibition slows progression? At what stage will tau-directed therapies be effective in slowing progression of tau pathology?

Of course, this approach is likely to present operational and regulatory challenges. First, reliable ATN biomarker assays suitable for multicenter trials would be required. Adaptive trial designs would be needed to efficiently accommodate testing of multiple ATN profiles and multiple dose levels of a given drug in an individual trial. Single biomarker cut-points and binary biomarker grouping for ATN biomarkers may not differentiate treatment responses. The cut-points may differ depending on the mechanism of intervention. If a compound is found in phase 2 trials to be effective in only one or more ATN profiles, then the same staging biomarkers might be preferred for inclusion in phase 3 trials, and commercially available biomarker assays and/or companion diagnostics may eventually be required for registration. Nevertheless, one of the largest barriers to success for AD drug development is that proof of concept using clinical measures is often not established during early clinical studies and is postponed until later and larger trials. The opportunity costs of this are enormous, reducing the number of compounds and mechanisms tested. Thus, the potential of the research framework to enable more informative early development studies warrants that the research community and health authorities collaborate to meet these surmountable challenges.

Primary end points in pivotal trials are likely to depend on clinical and cognitive measures for the near future, with A, T, and N biomarkers included at baseline and examined in the course of treatment as exploratory measures. As data accumulate regarding the relationship between treatment effects on ATN biomarkers and treatment effects on clinical outcomes, this may change. Data gathered from both standard and emerging biomarkers used in pivotal trials could lead to a better understanding of biomarker trajectories and biomarker-clinical outcome measure relationships supporting improved basis for demonstration of disease modification. Tau PET, in particular, is anticipated to become widely employed in preclinical and MCI trials that target AD mechanisms, which may eventually lead to T measures becoming part of biomarker selection criteria. Ultimately, however, the use of biomarkers as surrogate end points in clinical trials will be useful only if they predict clinical outcomes and

lead to registrational end points. The ATN system is not intended to infer correlations between AD biomarkers and the efficacy of investigational therapeutic agents.

In pivotal trials, the use of biomarkers will also have to be considered in the context of regulatory risk and scrutiny. Although an important intended application of the framework is in research studies, its use will undoubtedly impact clinical development paradigms more broadly and ultimately affect labeling. This is because regulatory authorities generally look to the scientific or medical community to define diseases for which treatments are being developed and establish appropriate diagnostic procedures for such disorders. The qualification opinions of the European Medicines Agency for novel methodologies in the predementia stage of AD include CSF Aβ 1–42 and t-tau levels [72], PET measures of amyloid burden [73], and volumetric MRI measures [74] (i.e., A, T, and N biomarkers) for drugs targeting Aβ or amyloid burden. While clinical measures are required as primary outcome measures in neuroscience, nusinersen was approved for the treatment of spinal muscular atrophy in 2016 based on a single pivotal trial. A variety of biomarkers were used in the development plan, which may have provided some support for regulatory approvals with only a single study. When trials use a biomarker result as an inclusion criterion, there is also the possibility that the label will require performing that test to support use of the treatment. However, if the diagnostic criteria become part of medical practice for diagnosis, regulators could also consider labeling that allows treatment of patients diagnosed based on usual medical practices (as is the case with many other diseases), rather than requiring specific tests in labeling.

Importantly and increasingly across the globe, regulatory approval does not necessarily translate into payer coverage, and each country manages drug coverage decisions in a different way [75]. In the United States, while the Food and Drug Administration focuses on safety and efficacy, the Centers for Medicare and Medicaid Services focuses on what is reasonable and necessary use criteria for patients. Centers for Medicare and Medicaid Services relies on published research and Food and Drug Administration to provide information related to drug efficacy, which Centers for Medicare and Medicaid Services uses to determine the appropriateness of coverage. In Canada, the Intergovernmental Common Drug Review, a separate organization from the Regulatory Authority (Health Canada), assesses cost effectiveness. There have been recent efforts to harmonize advice from regulators across different countries and between regulators and payers. How these differing approaches will manage biomarker issues in the context of drug approval adds uncertainty to the process.

6. Reconsidering clinical syndromes in the AD spectrum

6.1. The six-stage definition for clinical staging

While the research framework adopted the ATN approach to provide a common language for biomarkers in AD research, the workgroup felt that the ongoing problems of inconsistencies in clinical nosology should be revisited. The framework outlined two categorical clinical staging schemes. First, a syndromal cognitive staging scheme that comprises three categories: cognitively unimpaired, MCI, and dementia (subdivided into mild, moderate, and

severe). Second, a numerical staging scheme that applies only to those on the AD continuum and replaces traditional syndromal labels with six stages (Table 1).

As with the framework itself, the six stages may or may not take prior educational or occupational achievements or comorbidities into account, these are choices left to individual investigative teams. The judgment of clinicians is ultimately required to merge algorithmic syndromic diagnoses with the many other extenuating circumstances of individual patients.

6.2. NPS and mild behavioral impairment in the context of the framework

Neuropsychiatric symptoms (NPSs) occur throughout the disease continuum and strongly modify the clinical consequences of AD. Similar to cognitive deficits, NPS may have a pleiomorphic presentation with apathy, anxiety, delusions, agitation, or aggression. NPSs are associated with the progression of cognitive decline [76] and contribute prominently to clinical morbidity [77]. They are one of the major reasons for caregiver distress [78] and contribute to early institutionalization [79] and the cost of caring for individuals with AD [80]. The construct of mild behavioral impairment [81] has been developed to reflect changes in behavior or personality that may represent early clinical expressions of AD (or other) neurobiology but are not included in the 2011 definition of MCI [1].

NPSs are fundamental expressions of AD neurobiology [82]. For example, cholinergic receptor binding and amyloid deposition are important mechanisms underlying NPS [83,84]; and NPS may influence the translation of AD neurobiology to cognitive decline [85]. Thus, viewing NPS through the lens of the framework could improve understanding of NPS etiology, behavioral phenotypes, and treatment targets.

7. Challenges and opportunities of the framework

The research framework focuses on the diagnosis of AD with biomarkers, shifting the definition of AD in living persons to the consideration of syndrome and etiology as distinct activities in the diagnostic process. While the 2018 framework highlights that it should not be considered a template for all research into cognitive impairment and dementia, it is apparent across the research community that this shift engenders a number of opportunities and challenges.

7.1. Improving diagnostic accuracy in interventional trials

A key aim of the framework is to address diagnostic accuracy in interventional clinical trials to enable a more precise approach where specific pathways can be targeted in the disease process and in the appropriate people. The use of biomarkers in living people has updated our view of AD: for example, studies in individuals with dominantly inherited AD confirm that AD has a long preclinical phase [11]. Furthermore, biomarker sub-studies in interventional clinical trials demonstrate that patients with and without the presence of amyloid pathology progress at different rates [86] and from a biological perspective that those without pathology would not be expected to respond to the treatments being tested.

Interventional clinical trials aimed to stop or slow the disease process by addressing the underlying pathophysiology of AD have been adjusting to this emerging science by moving

to study patients at earlier stages of AD, thus requiring biomarkers to ensure diagnostic accuracy as well as confirming the presence of the pathophysiology being targeted. This move of improving diagnostic accuracy and ensuring presence of pathology is intuitive, but also by industry drug development standards, considered as crucial for improving probability of success and improving the probability to demonstrate clinical benefit [87].

Industry discussions at the Alzheimer's Association Research Roundtable reflected that for interventional trials, particularly but not exclusively those targeting amyloid, patient enrollment in the majority of ongoing clinical trials today requires a positive amyloid status; 64% of active interventional clinical trials in Ph3 for AD are assessing amyloid pathology at inclusion, which is raised to 78% in studies of mild or earlier patients [88].

7.2. High cost and limited access of biomarkers

The framework employs cutting edge technology to diagnose AD with biomarkers in living patients. Its use comes with considerable cost and requires (for imaging) a sophisticated imaging infrastructure. Both cost and availability inevitably restrict opportunities for participation in research, but when diagnostic accuracy is critical to the research, the benefits of improved diagnostic accuracy might outweigh those concerns.

7.3. Does the ATN approach inadvertently narrow research?

While one of the main motivations for the framework was to address diagnostic concerns in interventional clinical trials, it may not be appropriate or necessary for public health research on burden of disability or interventional research (some pharmacological or nonpharmacological) on symptoms that are common to multiple etiologies.

Although the field had already moved toward earlier interventions, there were also concerns that focusing on biomarkers as tools to identify AD in the presymptomatic stages could further reduce efforts to develop treatments for later stages of disease. Others in the discussion noted that interest in earlier intervention was driven by conceptual models of AD that existed well before the recent biomarker developments.

While the framework advances the field by recognizing the complexity of dementia pathophysiology and by recognizing genetic risk factors, integration of risk and protective factors for cognitive impairment based on lifestyle and the influence of neurobehavioral traits on subjective cognitive decline require further integration into the framework's algorithmic approach. Further research will be necessary before these lifestyle and neurobehavioral risk factors are understood well enough to be incorporated into a research framework. The view of proponents of the ATN framework is that it facilitates integration of risk and protective factors within a common diagnostic framework in a manner that should improve our understanding of those risk and protective factors with additional research (e.g., [68]).

A concern that has bedeviled the field for nearly two decades is the targeting of resources toward the most popular disease mechanism of the time, leading to an under-resourcing of other areas that have failed to capture attention to the same extent. Some individuals fear that the ongoing focus on amyloid and tau biomarkers may divert resources from other promising

mechanisms such as inflammation, oxidative stress, or other novel pathways. However, this is misguided. Plaques and tangles define AD as a unique disease among many that can lead to dementia. The research framework does not necessarily require β amyloid and tau to be causal. However, if the A+T+ designation from the framework were to be used for inclusion into a clinical trial, the implication would be that the putative treatment's mechanism of action was specific for AD. The proponents of the ATN framework asserted that the system is a diagnostic one and should promote rather than stymie research in mechanisms other than amyloidosis and tauopathies.

7.4. Capturing the diversity of the population

ATN has been studied so far in relatively homogeneous groups of people that may not be representative of the proportional representation of AD and non-AD conditions in the broader population. Further studies in populations with racial, ethnic, and socioeconomic diversities will be necessary to understand better how the ATN framework captures both persons in the AD pathway and in the many non-AD dementia pathways.

7.5. Disclosing pathological biomarker status to cognitively unimpaired individuals

Defining AD as a pathophysiological process in the brain implies that the presence of AD biomarkers indicates a diagnosis of AD and that the absence of AD biomarkers suggests that if clinical impairment is present, it is caused by something other than AD. Yet the consequences of disclosing a diagnosis of AD to a person who is clinically normal, while a topic of active research [89,90], are not fully understood.

8. Future directions

The authors of the framework described it as a descriptive document that provides a common language and a basis for speaking about biomarkers but does not make hypotheses about causality and outcomes. The clinical syndrome remains the most important aspect of the disease for patients and caregivers. However, physicians and scientists should also be concerned about why (i.e., etiology) patients develop impairment. This can only be accomplished by defining etiology, which clinical syndromal categorization cannot do. Deep phenotyping with biomarkers, however, enables more precise and accurate characterization of pathophysiology than which is possible through clinical measures and thus should accelerate efforts to develop new treatments. Other potential areas of future research that could be advanced by adoption of the framework include the following:

- Continued work to ensure the reliability of biomarker assays and to identify biomarkers with sufficient dynamic range over short treatment periods for adaptive decisions.
- Research aimed at gathering evidence to show whether ATN enables clinically relevant outcomes to be achieved, whether modifying biomarkers or pathology makes a difference in other disease outcomes (e.g., health-economic), and what effect the framework has on facilitating research.

- To determine the generalizability of the ATN framework for prognostic purposes, studies will need to enroll real-life, heterogeneous cohorts, including diverse populations.
- Capturing other pathophysiologies diagnostically relevant to AD. Because there are no accepted biomarkers for inflammation or alterations in immunity, the framework of necessity has not incorporated those processes. It may be important to incorporate those pathophysiological processes when biomarkers for them become available. Indeed, the ATN framework is designed to be flexible in incorporating new biomarkers as they become available.
- Further research investigating what it means to people to learn that they are amyloid positive or have other risk factors in the absence of symptoms. This research should engage all stakeholders—patients, caregivers, practitioners, and payers. The A4 SOKRATES sub-study [91] examined the knowledge and reactions of individuals to a positive amyloid test, but further studies are needed on the psychological, financial, social, and societal consequences of disclosure.
- The framework should stimulate efforts to develop new behavioral measures that monitor functioning in individuals with preclinical AD to determine how they align within ATN system.

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RESEARCH IN CONTEXT

1. Systematic review: This review summarizes the presentations made at the November 2017 Research Roundtable meeting on the new NIA-AA Research Framework. Each presenter reviewed the literature of recent work in their specific topic areas within the overall area of AD biomarkers and their use in informing the NIA-AA Research Framework.
2. Interpretation: The information covered in this article summarizes viewpoints of industry drug developers, academic colleagues and government representatives on the potential value and challenges of adopting the new NIA-AA Research Framework for clinical research.
3. Future directions: A section on future directions to test the utility of the Framework in Alzheimer's research is discussed.

Table 1

Six-stage clinical staging of Alzheimer's disease

Stage	Clinical characteristics	Correspondence to syndromal stage
1	• Performance in expected range, and • No reported cognitive decline	Cognitively unimpaired
2	• Performance in expected range, and • Subjective cognitive decline, or • Documented evidence of decline, or • Newly acquired neurobehavioral symptoms	Cognitively unimpaired
3	• Performance in impaired range, and • Cognitive decline from baseline in any domain, and • ADLs independent, but may be less efficient	Mild cognitive impairment
4	• (Mild dementia) Substantial cognitive impairment affecting several domains, and • Clearly evident functional impact on daily life, and • No longer fully independent	Dementia
5	Moderate dementia	Dementia
6	Severe dementia	Dementia

Abbreviation: ADLs, activities of daily living.