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PERSPECTIVE

The AT(N) framework for Alzheimer's disease in adults with Down syndrome

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Abstract

The National Institute on Aging in conjunction with the Alzheimer's Association (NIA-AA) recently proposed a biological framework for defining the Alzheimer's disease (AD) continuum. This new framework is based upon the key AD biomarkers (amyloid, tau, neurodegeneration, AT[N]) instead of clinical symptoms and represents the latest understanding that the pathological processes underlying AD begin decades before the manifestation of symptoms. By using these same biomarkers, individuals with Down syndrome (DS), who are genetically predisposed to developing AD, can also

be placed more precisely along the AD continuum. The A/T(N) framework is therefore thought to provide an objective manner by which to select and enrich samples for clinical trials. This new framework is highly flexible and allows the addition of newly confirmed AD biomarkers into the existing AT(N) groups. As biomarkers for other pathological processes are validated, they can also be added to the AT(N) classification scheme, which will allow for better characterization and staging of AD in DS. These biological classifications can then be merged with clinical staging for an examination of factors that impact the biological and clinical progression of the disease. Here, we leverage previously published guidelines for the AT(N) framework to generate such a plan for AD among adults with DS.

KEYWORDS
Alzheimer's disease, biomarkers, Down syndrome

1 | INTRODUCTION

A core purpose for the generation of the amyloid, tau, neurodegeneration (AT[N]) framework was to "enable a more precise approach to interventional trials where specific pathways can be targeted in the disease progress and in the appropriate people."[1] Recently, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed a "research framework" based on the AT(N) model[2] for observational and interventional research on Alzheimer's disease (AD).[3] Differently from the prior NIA-AA diagnostic criteria,[4] this framework defines AD as a biological rather than a clinical construct, characterized by extracellular deposits of amyloid-beta peptide (Aβ; "A"), intraneuronal aggregates of hyperphosphorylated tau ("T") and neurodegeneration ("[N]"). The "N" is placed in parentheses to emphasize that the biomarkers in the (N) group are fundamentally different from "A" and "T" biomarkers because they are: (1) not specific for neurodegeneration due to AD, (2) may be attributed to other possible comorbid conditions, and (3) do not map onto neuropathologic findings used to diagnose AD. The AT(N) model considers A, T, and (N) status relatively independent from one another with a known sequential order. However, the model then combines the clinically defined diagnostic classifications with AT(N) biomarker status for consistent terminology for research use.

Briefly, negative amyloid and tau along with the absence of neurodegeneration (A−T−[N]−) defines the normal biomarker profile, and amyloid negativity with either positivity for tau or presence of neurodegeneration corresponds to suspected non-Alzheimer's pathology. β-Amyloidosis (A+) is sufficient to identify the Alzheimer's continuum. Within this continuum, A+T−(N)− denotes Alzheimer's pathologic change (preclinical AD), while A+T+ (with or without [N]+) establishes definite AD. The AT(N) framework has the potential to enrich clinical trials with individuals who show objective evidence that they are on the AD continuum while also permitting the staging of individual patients and providing prognosis as well as stratification for precision-based clinical trials. The AT(N) classification system has been studied by multiple groups and has demonstrated utility in classifying individuals with late-onset sporadic AD on the basis of biomarkers.[5-7]

In 2013, the Food and Drug Administration (FDA) released draft guidance on drug development for AD. The guidance built on the understanding that AD is a progressive disease with clinical symptoms of dementia appearing decades after the AD pathophysiological process has begun and proposed a disease classification that acknowledged three stages of AD: the preclinical, prodromal, and dementia stages.[8] In 2018, the FDA revised the draft guidance and expanded the taxonomy of AD by recognizing four stages.[9] These include: Stage 1: "Preclinical AD"; Stage 2: "Preclinical/ Prodromal AD"; Stage 3: "Prodromal AD"; and Stage 4: "AD dementia." We are now poised to study these stages of AD in Down syndrome (DSAD) using the most advanced AD biomarkers available to refine the AT(N) classification for use in this population.

2 | APPLICATION OF AT(N) TO THE DS POPULATION

To date, the AT(N) framework has been applied in limited ways to other populations that are at risk for AD as a method to expand this model and to enrich clinical trials for AD.[10] Given the unique features described below of AD among adults with DS, the framework may have utility for rapid advancement of precision medicine approaches to novel clinical trials in this population. DS is, by definition, a genetically determined form of AD as recognized in the International Work Group on Criteria for AD (IWG-2).[11] In DS, one of the most common forms of intellectual disability, the underlying genetic link between trisomy 21 and AD has been convincingly established.[12-15] By age 40 years, all adults with DS exhibit some degree of elevated brain amyloid.[16-18] The leading explanation for this link is tied to the triplication of chromosome 21 (trisomy 21) and the resulting overexpression of the amyloid precursor protein (*APP*) gene coded on this chromosome.[19] The excessive production of Aβ as a result is key to the pathogenesis of AD in adults with DS.[20] Although other genes coded on chromosome 21 may contribute to the early emergence of dementia and the phenomenon of accelerated aging seen in adults with DS,[21]

forms of partial trisomy 21 which do not result in triplication of *APP* (ie, the *APP*-containing portion of chromosome 21 is not present in the third copy) are not associated with clinical and pathological signs of AD.[14,15]

Despite these consistent AD neuropathologic changes, the timing of the development of dementia as part of AD in DS is quite variable,[22] suggesting the presence of other genetic and environmental risk and protective factors. Individuals with DS have a lifetime risk for dementia in excess of 90%, and DS is now acknowledged to be a genetic form of AD similar to the much less common autosomal-dominant causes of AD.[23,24] Although the development of dementia is not inevitable in all adults with DS, the risk increases incrementally with age.[25] Furthermore, as in the late-onset form in the general population, the AT(N) classification of adults with DS will be strongly influenced by the age of the individual.

Identifying cognitive impairment at an early stage of the AD continuum has become an increasingly important goal in AD research, as it is widely believed that the greatest chance for therapeutic success will be obtained by intervening early in the disease, before widespread and irreversible neurodegeneration has occurred.[26] As a result, the AT(N) framework describes AD across its full spectrum (ie, preclinical to dementia) in terms of biomarker positivity/negativity and is agnostic with respect to clinical symptoms. As more longitudinal data are collected in DS, correlations between the distinct AT(N) classifications with clinical and cognitive status will be possible as well as a richer understanding of the rates of change in each biomarker category: amyloid, tau, and neurodegeneration across the AD conitnuum in DS. This more precise assessment will facilitate primary, secondary, and tertiary prevention trials for ADin individuals with DS.[27-29]

In the general population[30-32] as well as in DS[33-36] the construct of mild cognitive impairment (ie, prodromal AD) as well as the identification of disease in the preclinical stage (eg, accumulation of amyloid in a cognitively stable individual) is central to the clinical diagnostic formulation of AD. Mild cognitive impairment (MCI) in the general population, as well as in DS, is generally regarded as the borderland between the cognitive changes of aging and early dementia where there is measurable decline in memory as well as some decline on instrumental activities of daily living (iADLs) but preservation of basic activities of daily functioning.[22,37-40] The characterization of preclinical and prodromal AD is now possible with the advancement of state-of-the-art biomarker modalities such as amyloid and tau assessment using positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) measures as well as emerging plasma biomarkers such as mass spectral Aβ assays[41,42] in the absence of or minimal cognitive decline.

Here we propose an application of the AT(N) framework for the full characterization of the AD continuum in DS using both state-of-the-art biomarkers and clinical assessments. Given the variability in cognitive assessments, the inclusion of biomarkers may facilitate the evaluation of potential efficacy of therapy in this population. Forthcoming data from the Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS)[43] and the European Horizon21 consortium[44] will inform the diagnostic accuracy and prognostic potential of AT(N) in DS.

RESEARCH IN CONTEXT

1. Systematic review: Alzheimer's disease (AD) is highly prevalent in Down syndrome (DS). The National Institute on Aging in conjunction with the Alzheimer's Association (NIA-AA) recently proposed a biological framework for defining the AD continuum. This new framework is based on key AD biomarkers (amyloid, tau, neurodegeneration, AT[N]) instead of clinical symptoms and represents the latest understanding that the pathological processes underlying AD begin decades before the manifestation of symptoms.
2. Interpretation: These biological classifications can then be merged with clinical staging for an examination of factors that impact the biological and clinical progression of the disease. We leverage previously published guidelines for the AT(N) framework to generate such a plan for AD among adults with DS.
3. Future directions: Further work on longitudinal AD biomarkers in DS should help clarify whether the AT(N) classification system can be applied to individuals with DS both for clinical trial stratification as well as for use as a potential staging and prognostic tool in the clinic, representing a fundamental tool for precision medicine.

3 | CLINICAL ASSESSMENT OF COGNITIVE STATUS

The defining feature of all causes of dementia is a decline from the baseline level of function and performance of daily skills. Although this may be straightforward to establish in the general population, it can be a much more complicated task in adults with DS because of lifelong intellectual impairment and significant variance in baseline cognitive functioning.[45,46] This is especially true for older adults with DS due to various factors impacting living arrangements in which there may be poor record keeping since childhood, lack of continuity in staff members supervising adults with DS over time, and a large number of physicians/health-care providers throughout his or her life span. In the absence of a personal historian who can accurately and comprehensively attest to an individual's baseline level of functioning, the assessment of a reported cognitive and behavioral change may be exponentially more difficult.[47,48] The early signs of dementia in adults with DS can be subtle and often require an astute observer to identify these changes. Often, individuals with DS are served by numerous caregivers throughout their lifetime, and often newly involved caregivers will presume that the current level of observed ability represents the individual's baseline level of functioning and, thus, miss signs of early decline that has already occurred.

In the clinical setting, accurate assessment of cognition and function depend upon a comprehensive history, which for individuals with DS

must be done in the context of knowledge and quantification of their historic level of intellectual disability.[49] It is important that a thorough history be obtained to compile evidence consistent with an emerging cognitive impairment while probing for potential factors contributing to decline. Pertinent historical information is useful from personal accounts of caregivers and family members who have known the individual for an extended length of time.[50] In addition, other sources of information, such as previous neuropsychological testing or school Individual Education Plan information, can greatly assist in accurately characterizing an individual's baseline level of functioning. In addition, medical history, medications, family history, social history, review of systems, laboratory evaluations, and brain imaging will be essential to rule out comorbidities that can masquerade as AD-related cognitive impairment. Objective evidence of memory decline will be essential for the diagnosis of MCI-DS and dementia. A number of cognitive assessment instruments are currently being evaluated in natural history studies of AD in DS, including the ABC–DS.[43] At this time, there is no single cognitive instrument that has been longitudinally validated in the context of AD biomarkers in DS but many are being presently intensely researched.[51-55]

Once arriving at the suspected clinical diagnosis of MCI or dementia, the AT(N) framework can be used to stage an individual with DS along the AD continuum with respect to extent of underlying biomarker changes (Table 1). This staging can be used to provide expected clinical prognosis, including an estimated duration of independent functioning, time to dementia, and to also enrich for more homogenous samples in clinical trials. The proposed clinical staging of the cognitive continuum was adapted from previously published guidelines for preclinical AD,[56] MCI,[57] and AD dementia.[58]

The difficulties with MCI diagnoses in the general population are well established. MCI in adults with DS (MCI-DS) is an even more challenging diagnosis and cross-sectional assessments can be unreliable. Therefore, longitudinal assessments are optimal and required. Additional work is needed to determine optimal psychometric assessment instruments, cutoff scores, and/or combinations of instruments in this population for refinement of the MCI designation. Specifically, the following points will need to be considered as the concept of MCI-DS evolves and will be informed by forthcoming data from ABC–DS: (1) Identification of the most informative cognitive assessment instruments for MCI varying based on severity of ID. (2) Quantification of decline needed to represent a clinically meaningful change. (3) Relationship between cognitive assessments and rates of change in various AD biomarkers. In order to confirm that MCI-DS is in fact prodromal AD, the use of biomarkers to confirm AD as the underlying etiology will be required.

4 | BIOMARKER ASSESSMENTS OF AMYLOID, TAU, AND NEURODEGENERATION IN DS

Over the past few years, substantial progress has been made in elucidating the natural history of AD in people with DS using the latest biomarkers including amyloid and tau PET imaging, volumetric brain MRI, as well as biofluid markers in CSF and plasma.[59] There exist remarkable similarities between AD biomarkers in DS and other populations with AD.[60-64] Greater hippocampal atrophy is associated with a greater amyloid load.[61] Cognitive and functional measures do not correlate as strongly with amyloid deposition as they do with abnormalities on 18F-fluourodeoxyglucose (FDG) and tau PET.[61,65,66]

4.1 | Amyloid (A)

Amyloid PET positivity as observed using PET imaging in DS seems to resemble autosomal dominant AD more closely than sporadic AD. Specifically, Pittsburgh compound B (PIB) demonstrates an early and predominant basal ganglia signal[60,62,67,68]

although other tracers (eg, florbetabir) have shown a pattern more similar to sporadic AD.[61] The similarity of AD in DS and ADAD is thought to result from overproduction of Aβ. APP overproduction in DS leads to baseline plasma levels of Aβ40 and Aβ42 and Aβ42/Aβ40 ratios which are higher than those in non-DS individuals.[64,69,70] A positive correlation of tau and a negative correlation of CSF Aβ1-42 have been reported with age[71] and several studies have documented correlations of the changes in amyloid in DS with AD.[72-75] Higher levels of Aβ42 or the Aβ42/Aβ40 ratio appear to be associated with the onset of AD in DS,[76,77] although this is not entirely consistent in the literature.[78] CSF Aβ42 levels are first increased in early life and then become lower with age, representing deposition of Aβ into plaques.[64,79,80] Most studies seem to suggest that as with sporadic and autosomal-dominant AD, pathophysiological changes associated with AD in DS occur approximately two decades before the onset of symptoms of dementia.

Blood-based biomarkers have clear advantages as biomarkers as they are easily accessible. Individuals with DS have higher baseline plasma Aβ1-42 and Aβ1-40 concentrations compared to individuals without DS[81] due to the extra copy of the *APP* gene and the resulting overproduction of APP and Aβ. There have been a limited number of CSF studies in individuals with DS which show elevated levels of Aβ42 early in life, but with age, CSF Aβ42 levels decline (as expected with their deposition into plaques) while CSF tau levels progressively increase.[64,81]

4.2 | Tau (T)

Neurofibrillary tangles (NFTs)which are comprised of abnormal tau, are a key pathological hallmark of AD and correlate with the emergence of clinical symptoms more closely than amyloid plaques. This relationship has also been demonstrated in *post mortem* pathology of DS brains, where NFTs correlate with cognitive decline.[82] Tau PET signal in the DS brain appears to be similar to sporadic AD and can be assessed using standard Braak staging.[66] Specifically, tau deposition in adults with DS has been studied using the PET tracer (^{18}F) AV-1451.[66] Abnormal tau distribution (in the form of NFTs) first involves the medial temporal cortices and then spreads posteriorly,[66] similar in manner to that observed in sporadic AD. More recently, plasma and CSF tau have

TABLE 1 Clinical staging of cognitive continuum—Diagnostic recommendations

Cognitively Stable (Preclinical Alzheimer's Disease)

1. No report of cognitive decline that is greater than what would be expected with aging, based on informant or clinician report—subjective decline taken into account, but not a requirement
2. No objective evidence of cognitive decline that is greater than what would be expected with aging per se on formal neuropsychological testing (brief cognitive screening instruments are insufficient with this population)
   a. If first assessment, impairment is defined compared to estimated premorbid level of functioning (eg, functional measure, IQ measure)
      (i) Confidence of diagnosis is less
   b. If prior testing is available, impairment is defined based on decline from prior testing levels
      (i) Confidence of diagnosis is high
3. Preservation of premorbid level of functional abilities based on reliable informant report, unless functional decline is related to age-associated frailty unrelated to AD (ie, muscle weakness, etc.).

Mild Cognitive Impairment–Down Syndrome (Prodromal AD)

1. Report of decline in cognitive functioning as reported by reliable informant or clinician AND
2. Objective evidence of impairment in one or more cognitive domains, based on extensive neurocognitive testing (brief cognitive screening instruments are insufficient with this population)
   a. Cognitive impairment may be in any of the following domains:
      (i) Impaired ability to acquire and remember new information
      (ii) Impaired reasoning and handling of complex tasks from premorbid level
      (iii) Impaired visuospatial abilities
      (iv) Impaired language functions
      (v) Changes in personality, behavior, or other neuropsychiatric symptoms that may include uncharacteristic fluctuations in mood (eg, agitation), depression, changes in motivation, apathy, social withdrawal, loss of interest in previous activities, among others
   b. If first assessment, impairment is defined as compared to estimated premorbid level of functioning (eg, functional measure, IQ measure)
      (i) Confidence of diagnosis is lower
   c. If prior cognitive testing is available, impairment is defined based on decline from prior testing levels
3. Confidence of diagnosis is high
4. Cognitive changes are not better explained by other factors such as significant life event (eg, environmental change, medical illness, etc.)
5. Preservation of premorbid level of basic functional abilities (basic ADLs) based on reliable informant report. There may be declines in iADLs in the DS population

Dementia in Down Syndrome

1. Cognitive concern reflecting a change as reported by reliable informant or clinician report–subjective decline taken into account if present, but not a requirement
2. Objective evidence of impairment in two or more cognitive domains, based on formal neurocognitive testing (brief cognitive screening instruments are insufficient with this population)
   a. Cognitive impairment may be in any of the following domains:
      (i) Impaired ability to acquire and remember new information
      (ii) Impaired reasoning and handling of complex tasks from premorbid level
      (iii) Impaired visuospatial abilities
      (iv) Impaired language functions
      (v) Changes in personality, behavior, or other neuropsychiatric symptoms that may include: uncharacteristic fluctuations in mood (eg, agitation), changes in motivation, apathy, social withdrawal, loss of interest in previous activities, among others
   b. If first assessment, impairment is defined as compared to estimated premorbid level of functioning
      (i) Confidence of diagnosis is less
   c. If prior testing is available, impairment is defined based on decline from prior testing levels
      (i) Confidence of diagnosis is high
3. Cognitive changes are not better explained by other factors such as significant life event (eg, environmental change), or active medical or mental illness, etc.
4. Changes in cognition and/or neuropsychiatric/behavioral symptoms interfere with previous level of daily functioning (basic ADLs) based on informant and/or clinician report – subjective decline taken into account but not a requirement.

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; DS, Down syndrome; iADL, instrumental activities of daily living.

been studied in individuals with DS, with their levels correlating with AD dementia in DS.[64,78,83-85]

4.3 | Neurodegeneration (N)

Markers of AD-specific neurodegeneration include regional hypometabolism on FDG PET9[86-88] or hippocampal atrophy[89-91] have been studied in DS and parallel findings from the sporadic and autosomal dominant forms of AD. More recently, plasma neurofilament light chain (NfL) levels (also a marker of neurodegeneration) have been shown to correlate with clinical status of AD in DS[92] as well as standard AD biomarkers such as amyloid PET and tau PET.[93] Specifically, plasma NfL levels appear to increase with age in but can still distinguish between normal aging and AD[81,92]. Plasma NfL levels have also been shown to correlate with other markers of neurodegeneration such as hypometabolism on FDG PET and hippocampal atrophy, as well as cognitive and functional decline.[93]

TABLE 2 Biomarker classification AT(N) pathology among adults with DS

**Biomarker classification is independent of Consensus Clinical Staging of Cognitive Continuum
AT(N) Biomarker Grouping
A: Aggregated Aβ or associated pathophysiologic state
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
Amyloid PET
T: Aggregated tau (neurofibrillary tangles) or associated pathophysiologic state
CSF phosphorylated tau
Tau PET
(N): Neurodegeneration or neuronal injury
Anatomic MRI
FDG PET
CSF total tau

Abbreviations: Aβ, amyloid beta; AT(N), amyloid, tau, neurodegeneration; CSF, cerebrospinal fluid; FDG, 18F-fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography

Thus, various biomarker modalities (eg, imaging, biofluids) can be used to characterize individuals with DS as exhibiting amyloid, tau, or neurodegeneration "positivity" in the AT(N) classification scheme. The biomarkers currently being used to characterize individuals with DS are listed in Table 2.

The AT(N) classification scheme can then be applied to such individuals as depicted in Table 3. Briefly, individuals with DS with stable cognition who have no elevations in brain amyloid or tau and no evidence of neurodegeneration would be classified as A−/T−/N−. Therefore, they would not be on the AD continuum. However, an individual with stable cognition who has elevated brain amyloid but no evidence of elevated tau or any neurodegeneration (A+/T−/N−) would be categorized as preclinical AD. An individual who has symptoms consistent with MCI-DS who has elevated brain amyloid but no elevated tau or evidence of neurodegeneration (A+/T+/N) would be classified as Prodromal AD. Finally, an individual with MCI-DS but who is A−/T+/N− would be considered as having a neurodegenerative disease other than AD (non-AD) as the basis for their symptoms. Therefore, by use of the A/T(N) framework, it is anticipated that we will be able to conduct clinical trials in a more finely characterized participant sample.

5 | ESTIMATING A+/T+(N)+ PREVALENCE IN DS

We intend to look at AT(N) classification across the different clinical diagnostic categories, that is, Cognitively Stable, Mild Cognitive Impairment, and Dementia in the ABC-DS Study to calculate A+/T+/(N)+ prevalence and to correlate the various classifications with clinical and cognitive status. Based on a review of the literature,[20,36,41,42,59-93] we estimate that, between ages 35 to 55 years, there will be 80% A+, 40% T+, and 10% (N)+ for cognitively stable adults with DS; 80% A+, 60% T+, and 20% (N)+ for MCI-DS; and 80% A+, 80% T+, and 60% (N)+ for dementia in the DS group (Figure 1).

There may be limitations specific to the A/T(N) classification system. For example, amyloid imaging may underestimate true amyloid positivity. In addition, some biomarkers indicating tau pathology may become positive at different stages of the disease (ie, CSF becoming abnormal before PET imaging). And, there appears to be a potential discrepancy between timing of positive MRI indicators of

TABLE 3 AT(N) Framework for adults with Down syndrome

			Combined syndromal cognitive and biomarker categorization		
AT(N) profiles	**Biomarker category**	**Part of Alzheimer's continuum (Y/N)**	**Stable cognition**	**MCI**	**Dementia**
A-/T−/(N)−	Normal biomarkers	No	Stable cognition + normal AD biomarkers	MCI-DS + normal AD biomarkers	Dementia + normal AD biomarkers
A+/T−/(N)−	AD pathological change	Yes	Preclinical AD pathological change	MCI-DS + AD pathological change	Dementia + AD pathological change
A+/T+/(N)−	AD	Yes	Preclinical AD	Prodromal AD	AD + dementia
A+/T+/(N)+	AD	Yes	Preclinical AD	Prodromal AD	AD + dementia
A+/T−/(N)+	AD and concomitant suspected non- AD pathological change	Yes	Preclinical AD*	Prodromal AD*	AD* + dementia
A−/T+/(N)−	Non-AD pathological Change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia
A−/T−/(N)+	Non-AD pathological Change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia
A−/T+/(N)+	Non-AD pathological Change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia

NOTE: AD* = AD and concomitant suspected non-AD pathological changes
Abbreviations: AT(N), amyloid, tau, neurodegeneration; AD, Alzheimer's disease; MCI, mild cognitive impairment.

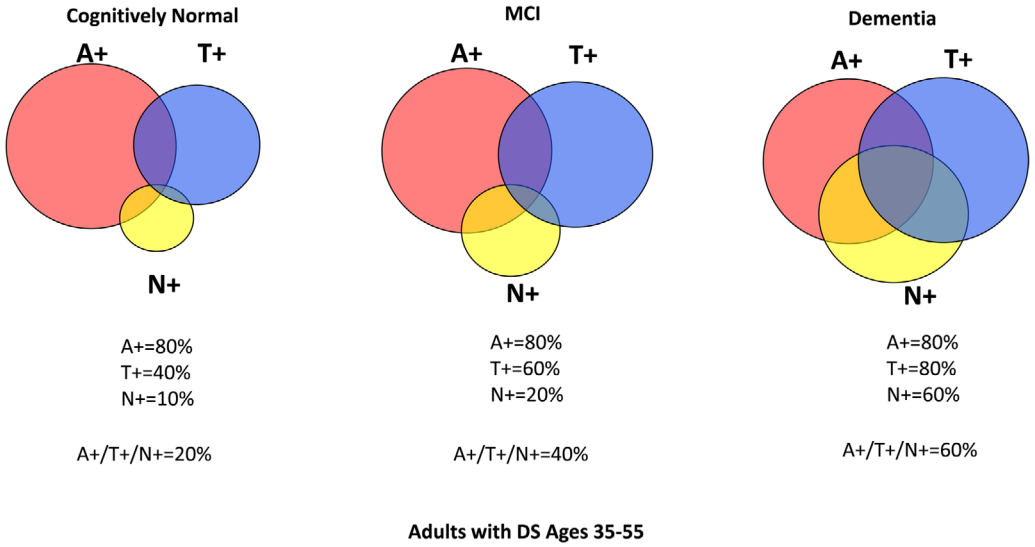

FIGURE 1 Estimated prevalence of A/T(N) positivity across clinical diagnoses. We estimate that between ages 35 to 55 years, there will be 80% A+, 40% T+, and 10% (N)+ for cognitively stable adults with Down syndrome (DS); 80% A+, 60% T+, and 20% (N)+ for mild cognitive impairment (MCI)-DS; and 80% A+, 80% T+, and 60% (N)+ for the dementia in DS group. A+ = elevated brain amyloid, T+ = tau pathology present, (N) = neurodegeneration present

atrophy (and hence neurodegeneration) versus increased levels of plasma NfL. Finally, these differences indicate that dichotomization may potentially decrease sensitivity to changes in cognition.

As longitudinal data become available, the utility of the AT(N) classification scheme will be compared with each individual's clinical status over time. We will test if there are differences between the biochemical and neuroimaging measures of AT(N) . We will confirm prevalence of AD biomarker positivity across different ages and clinical diagnoses. Additionally, we will assess how best we can operationalize the biomarker binarization to ensure the external validity of the results. Finally, we will evaluate the impact of cerebrovascular disease, including microhemorrhages related to cerebral amyloid angiopathy; neuroinflammation; and, as *post mortem* data accrue, other pathologies such as TDP-43 and Lewy bodies on A/T(N)'s accuracy in staging disease and predicting clinical status. A similar longitudinal AD biomarker study (Horizon21) is ongoing in Europe with plans to harmonize some elements with ABC-DS going forward.[44]

6 | CONCLUSIONS

Recent work on the AT(N) frameworkin the general population suggests that individuals exhibiting abnormalities on all three biomarkers are at the greatest risk of developing AD dementia. The AT(N) model considers A, T, and (N) status relatively independent from one another with a known sequential order. The current framework is proposed as a starting point for use of A/T(N) classificationin the DS population. It is understood that this is not a final model and as new data emerge, the framework will be revised and updated accordingly in order to parallel the state of current knowledge. As with the original AT(N) Framework, this staging system is intended to aid in the refinement of clinical trials and to facilitate a better understanding of the biology ofAD in adults with DS. This research framework is not intended for clinical use at this time.

Further work on longitudinal AD biomarkers in DS should help clarify whether the AT(N) classification system can be applied to individuals with DS both for clinical trial stratification as well as for use as a potential staging and prognostic tool in the clinic, representing a fundamental tool for precision medicine.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest that are relevant for this manuscript.

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