Received: 30 April 2024 | Revised: 23 September 2024 | Accepted: 7 October 2024

DOI: 10.1002/alz.14364

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PERSPECTIVE

Blood biomarkers in Down syndrome: Facilitating Alzheimer's disease detection and monitoring

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Funding information: Medical Research Council, Grant/Award Numbers: MR/S011277/1, MR/ S005145/1, MR/R024901/1; European Commission, Grant/Award Numbers: 1R61AG066543-01, GO-DS21-848077; Alzheimer's Society, Grant/Award Number: AS-CP-18-0020; Fondo de Investigaciones Sanitario, Carlos III Health Institute, Grant/Award Number: PI20/01473; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas; National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL, Grant/Award Number: UKDRI-1003; European Union Joint Programme—Neurodegenerative Disease Research, Grant/Award Number: JPND2021-00694; AD Strategic Fund and Alzheimer's Association, Grant/Award Numbers: ADSF-21-831376-C, ADSF-21-831381-C, ADSF-21-831377-C; Alzheimer's Drug Discovery Foundation, Grant/Award Number: 201809-2016862; HORIZON EUROPE Framework Programme, Grant/Award Number: 101053962; National Institute of Biomedical Imaging and Bioengineering, Grant/Award Number: P41EB015922; Horizon 2020- Research and Innovation Framework Programme from the European Union, Grant/Award Numbers: H2020-SC1-BHC-2018-2020, Marie Sklodowska-Curiegrant agreement No 860197 (MIRIADE); Departament de Salut, Generalitat de Catalunya, Grant/Award Number: SLT006/17/00119; Alzheimer Society, Grant/Award Number: AS-CP-18-0020; Foundation for the National Institutes of Health, Grant/Award Numbers: U19AG078109, U19AG068054, RF1AG079519, 1R61AG066543-01, 1R01AG056850-01A1, R21AG056974, R01AG061566, R01AG054073, R01AG058533; Alzheimer's Association, Grant/Award Number: 23AARFD-1022715; Swedish State Support for Clinical Research, Grant/Award Number: ALFGBG-71320; Bluefield Project; Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen for Gamla Tjanarinnor, Grant/Award Number: F02022-0270; Swedish Research Council, Grant/Award Numbers: 2022-01018, 2019-02397; Jérôme Lejeune Foundation

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Abstract

Blood-based biomarkers continue to be explored for disease detection, monitoring of progression, and therapeutic outcomes as the diagnostic determination of Alzheimer's Disease in Down Syndrome (DS-AD) remains challenging in clinical settings. This perspective highlights the current status of this effort. Overall, amyloid (A), tau (T), and neurodegeneration (AT[N]) blood-based biomarkers have been shown to increase with disease pathology for individuals with DS. Phosphorylated tau biomarkers (p-tau217, p-tau181) have been consistently shown to track disease progression for DS-AD and are likely good candidates for use in clinical settings. Biomarkers of inflammation (glial fibrillary acidic protein) also show promise; however, additional work is needed. Findings from stability work of blood-based biomarkers conducted among non-DS also support the potential longitudinal utility of biomarkers such as neurofilament light chain and p-tau181 in DS. Gaps in our knowledge are highlighted, and a potential role for sex differences in biomarker outcomes is noted, along with recommendations for determining the appropriate context of use when translating biomarkers into clinical applications.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, blood, Down syndrome, neurodegeneration, tau

Highlights

- An overview of blood-based biomarkers for Alzheimer's disease (AD) was provided for consideration of their utility among individuals with Down syndrome when looking toward potential clinical applications.
- Longitudinal stability of many blood biomarkers and improvement in detection sensitivity make blood such as plasma a viable source for exploring AD pathology.
- Variability in reviewed findings regarding the application of blood biomarkers highlights the importance of understanding and defining the appropriate context of use, particularly when translating them into clinical practice.

1 | INTRODUCTION

Down syndrome (DS) is the most common genetic cause of intellectual disability. The most recent population prevalence estimation of DS in the United States is ~ 200,000 individuals.[1] Health-care and social science advances have significantly improved the quality of life and extended the life expectancy of individuals with DS. Current estimates now place the average life expectancy at 60 years compared to 12 years in 1949.[1,2] Longer life expectancies also increase the risk of many age-related neurodegenerative diseases, including Alzheimer's disease (AD).[3] Seventy percent of older adults with DS > 65 years of age will develop AD (i.e., DS-AD), while an estimated 10% to 15% of those will not show clinical signs of dementia.[3–6]

Individuals with DS have three copies of chromosome 21 containing the amyloid precursor protein (*APP*) gene. The overexpression of *APP* leads to increased production of amyloid beta (Aβ), and combined with growing lifespan, is likely to be the leading cause of the increased risk of AD in people with DS.[7–10] While similar genetic risks are observed for those with the autosomal dominant form of AD (ADAD), which can also be driven by mutations in the *APP* gene, along with *PSEN1* and *PSEN2* genes,[11] people with DS will develop AD neuropathology (similar to ADAD) earlier (often between 30 and 50 years of age) compared to the sporadic form of AD among people without DS. Despite the early accumulation of AD neuropathology in DS, there is an ≈ 10-year delay, on average, to when clinical features of AD are observed (between 53 and 55 years of age).[5,6]

There remains considerable interest in identifying factors that delay the onset of clinical dementia because these modifiers may be targetable by pharmacological or lifestyle interventions.[12] Timely and accurate diagnosis is of particular importance for people with DS, as preexisting cognitive impairment and heterogenous cognitive functioning could mean subtle AD-related changes are missed in the clinical

evaluation.[13,14] Therefore, the potential for blood-based biomarkers to increase confidence in an AD diagnosis or the presence of AD-related pathological change is of considerable importance.[15] We now have clear evidence that AD neuropathology, including amyloid and tau pathologies, as well as neurodegeneration and astrogliosis, can be detected with high accuracy using blood-based biomarkers,[16] some of which show equivalent diagnostic performance to reference standard cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers.[17,18]

Given the rise of such biomarkers and increased application, the amyloid (A), tau (T), and neurodegeneration (N; AT[N]) framework was proposed.[19] Rafii et al. more recently examined the framework in its application among adults with DS-AD, which supported its additional use among this population.[19,20] The goal of this work remains to provide a biological framework for AD by focusing on specific biomarkers of A, T, and N. Recent proposals have extended the original framework to include other contributors, such as inflammatory markers (i.e., glial fibrillary acidic protein [GFAP]), to capture AD heterogeneity. As with most work, plasma blood-based biomarkers associated with the AT(N) framework have been examined primarily among the non-DS population. Although less work has been conducted in adults with DS, the effort is nonetheless underway to explore how these biomarkers apply to this population at high risk for AD.

Here, we will provide a broad overview of work on blood-based AT(N) biomarkers with a high likelihood of real-world implementation in clinical settings. We will also expand our discussion to include work covering additional blood-based biomarkers related to inflammatory factors for further consideration. Furthermore, we will cover longitudinal studies, stability, and considerations for applying such blood-based biomarkers in a clinical setting and stress the need for further work.

RESEARCH IN CONTEXT

1. **Systematic review**: Traditional search engines were used by the authors to collectively provide an overview of the extant literature. This perspective-based work sought to deliver a basis for understanding what research has been conducted using blood-based biomarkers among those with Down syndrome (DS). The focus was on Alzheimer's disease (AD) biomarkers within the context of the amyloid/tau/neurodegeneration framework in their potential clinical applications among the DS population.
2. **Interpretation**: Literature supported discrepant findings for many of the plasma biomarkers, highlighting variability across studies potentially owing to differences in pre-analytical methods. Many phosphorylated tau biomarkers were shown to more consistently be applied in the detection of AD in DS and stability of these plasma biomarkers highlights notable potential for future clinical application. The robust work on neuroinflammation also highlights an area for future work, particularly in DS to examine additional clinical applications.
3. **Future directions**: This perspective highlights the need for additional work to define the appropriate context of use for blood biomarkers as well as examine the interplay between modifiable factors for AD pathology in DS.

1.1 | AT(N) blood-based biomarkers in adults with DS and DS-AD

1.1.1 | Aβ "A" biomarkers

Research examining plasma Aβ has primarily focused on Aβ40 and Aβ42 and although an ideal comparison of biomarkers, including Aβ, would be to contrast DS-AD with other similar genetic forms of AD, such as ADAD, the published work has been limited to CSF-based biomarkers[21] rather than blood-based (serum or plasma). Much of the work examining plasma blood-based biomarkers has compared individuals with DS to others with DS across diagnostic categories (asymptomatic, mild cognitive impairment [MCI]-DS, DS-AD) and to the non-DS population, including those (non-DS) with the sporadic form of AD. Findings from this work have revealed several inconsistencies, some of which may be potentially attributable to changes in amyloid across the lifespan of individuals with DS or differences in cohort composition or protocol (location, age, preanalytic methods for study, etc.). Overall, most results support that in general, "A" biomarkers, including plasma Aβ40 and Aβ42, are elevated in DS (consistent with overexpression of APP) compared to non-DS controls or late-onset (sporadic) AD.[22–26]

While fewer studies have looked at age-related change or change across disease states in "A" plasma blood-based biomarkers in DS, some variability has been shown. Mengel et al. found that although plasma Aβ42 levels were higher in DS compared to age- and sex-matched non-DS controls, levels decreased across both groups. However, a greater decline was found in individuals with DS, particularly in their third decade of life.[25] In contrast, work by Head et al. supported age-related increases in both plasma Aβ40 and Aβ42 levels in DS, with the highest levels found among older adults with DS compared to younger DS controls, old DS controls, and sporadic (non-DS) AD.[27] Fortea et al. also found plasma Aβ40 levels to be elevated across DS diagnostic groups, with DS-AD exhibiting higher levels than cognitively unimpaired (asymptomatic) individuals with DS.[23] Similarly, a meta-analysis revealed higher Aβ40 plasma levels in individuals with DS-AD compared to those with DS but without AD, while no differences in Aβ42 plasma levels were found between groups[26] (see Table 1[23,27–31]).

1.1.2 | Phosphorylated tau "T" biomarkers

Several phosphorylated tau (p-tau; "T") plasma biomarkers have also been examined over the last several years and show considerable

TABLE 1 Plasma AT(N) and (I) biomarkers detection, progression and monitoring considerations for DS-AD.

	Detection	Progress and monitoring considerations
Aβ40	Higher with disease stage[23,27–29]	Variable
Aβ42	Higher with disease stage[28,30,31]	Variable
Total tau	Higher with disease stage[5,23]	Increase with disease progression[5]
P-tau181	Higher with disease stage[35]	Increase with disease progression[35]
		Associated with cognitive decline[39]
		Increases over time[39]
		The greatest increase found between 4 and 8 years before death[40]
		Low intra-individual variability[41]
P-tau217	Higher with disease stage[34]	Increase with disease progression[34]
		Longitudinal change correlates with worsening cognition[34]
		Longitudinal change correlates with brain atrophy[34]
		Linked with amyloid-dependent alterations over 4- to 6-year period[42]
NfL	Higher with disease stage[23,51]	Increase with disease progression[46]
GFAP	Higher with disease stage[60,61]	Change along the AD continuum[61]
		Predict AD progression[61]
		Predict cognitive decline[61]
		Associated with amyloid brain pathology[61]

Abbreviations: AT(N), amyloid, tau, and neurodegeneration; Aβ, amyloid beta; AD, Alzheimer's disease; DS-AD, Alzheimer's disease in Down syndrome; GFAP, glial fibrillary acidic protein; (I), inflammation; NfL, neurofilament light chain; p-tau, phosphorylated tau.

promise in detecting DS-AD with less variability across studies. This work has primarily found plasma biomarkers of p-tau217 and p-tau181 to correlate with neuroimaging Aβ measures[32–34] that track AD disease progression in DS.[35] This work has revealed that plasma p-tau181 levels are higher among individuals with MCI-DS and DS-AD compared to asymptomatic DS and higher in DS-AD compared to MCI-DS, indicating increases in this phosphorylated form with disease severity.[35] Interestingly, no difference was shown in plasma p-tau181 levels between asymptomatic DS and cognitively unimpaired non-DS controls.[35] Recent work by Janelidze et al. also found no difference in plasma p-tau217 between cerebral amyloid-negative (PET imaging) sibling non-DS controls and cerebral amyloid-negative adults with DS.[36] However, among cerebral amyloid-positive adults with DS, higher levels of plasma p-tau217 were found compared to cerebral amyloid-negative non-DS sibling controls and cerebral amyloid-negative adults with DS.[36] Phosphorylated tau typically has several-fold increases in individuals with Aβ pathology, and the biomarker is not sensitive to freeze–thawing and other preanalytical factors related to sample handling.[37] This speaks to its utility in clinical laboratory practice. However, a few factors related to kidney disease and other co-morbidities impact these biomarkers and need to be examined further[38] (see Table 1[34,35,39–42]).

1.1.3 | "N" biomarkers

The primary blood-based biomarker used to capture "N" is neurofilament light chain (NfL), a cytoskeleton protein found within neurons in the brain. While increases have been shown with age, and despite being a non-specific biomarker, NfL continues to be explored in neurodegenerative disorders such as AD.[43,44] Multiple groups observe higher plasma NfL levels in DS than in non-DS controls.[23,45] Differences in plasma NfL levels also have been shown to vary across age ranges[25] and by age[5] for those with DS, with the highest levels found among older adults with DS compared to younger adults with DS.[45] Similar to total tau in plasma,[5,23] another indicator of "N," plasma NfL levels have been shown to increase with disease severity, with higher levels found in DS-AD compared to MCI-AD or asymptomatic DS.[23,35,46,47] This supports previous findings that show that plasma NfL levels correlate with AD-related imaging biomarkers,[48] including amyloid deposition.[49] Baseline plasma NfL levels have also been linked to an increased risk of AD for those with DS at follow-up visits regardless of premorbid intellectual function,[46,50] underscoring the potential of plasma NfL to identify AD in people with DS despite heterogeneous premorbid cognitive ability (see Table 1[5,23,46,51]).

1.2 | Inflammatory blood-based biomarkers in DS and DS-AD

Neuroinflammation is thought to play a central role in the development and progression of neurodegenerative disorders such as AD, and this is particularly the case for individuals with DS. Studies examining fetal, neonatal, and infant DS brains found that microglial and astroglial cells are reactive,[52,53] which implies that neuroinflammatory processes begin early in DS. Throughout the lifespan of people

with DS, microglial cells undergo morphological changes indicative of an activation state that becomes dystrophic at the late stages of AD.[52,54] Such glial activation is accompanied by increased gene and protein expression of pro- and anti-inflammatory mediators (e.g., cytokines, chemokines, complement proteins) across the AD continuum in DS.[52,55–57] Chronic neuroinflammation in DS brains may be driven by inflammatory genes in chromosome 21[58] and the continuous accumulation of AD neuropathology throughout their lifespan.[59]

1.2.1 | GFAP

Given a growing body of literature suggesting a link between AD and inflammatory processes, recent work has focused on markers of astrocytosis. This includes GFAP, a marker involved in astrogliosis associated with Aβ deposition. A recent study evaluated the potential of plasma GFAP to serve as a biomarker for diagnosing and predicting DS-AD and compared the dynamics of this biomarker with both ADAD and sporadic AD.[60] This work found that plasma GFAP increased along the AD continuum and had the potential to discriminate between symptomatic and asymptomatic AD. Additionally, GFAP levels were found to predict AD disease progression and cognitive decline and were associated with amyloid brain pathology via PET.[61] Interestingly, several lines of study demonstrate that GFAP is a more reliable biomarker of AD pathology in blood than CSF,[60,62,63] likely due to the instability of GFAP protein in the CSF.[64] Thus, plasma GFAP may be a future biomarker that can provide more information regarding neuroinflammation and AD pathogenesis in particular for those with DS (see Table 1[60,61]).

1.2.2 | Pro-, anti-, and general inflammatory biomarkers

Inflammatory proteins, including those of pro-, anti-, and general inflammation, have also been increasingly explored among those with DS, as highlighted in a review by Ahmed et al.[65] This review indicated that among those with DS in the asymptomatic stage (cognitively unimpaired), anti-inflammatory proteins (interleukin [IL]-10 and IL-8) were elevated, while pro-inflammatory proteins were decreased (vascular endothelial growth factor A).[56] At the MCI-DS stage, elevations were indicated in both pro- (IL-1β, IL-7, interferon gamma-induced protein [IP]10, macrophage inflammatory protein [MIP]-1β, serum amyloid A [SAA], soluble intercellular adhesion molecule 1 [sICAM1], thymus and activation regulated chemokine [TARC], tenascin C, tumor necrosis factor alpha [TNF-α]) and anti- (IL-10, IL-8, IL-6) inflammatory proteins as well as in proteins of general inflammation (A2M, B2M, C-reactive protein [CRP], eotaxin 3, IL-15, macrophage-derived chemokine [MDC]).[66–68] Moving toward the later stages of the disease process, findings among those with DS-AD continue to indicate elevations in markers of pro- (tenascin C, SAA, sICAM1, TARC, MIP-1β, macrophage chemoattractant protein [MCP]-1, IP10, IL-7, IL-18) and general inflammation (B2M, CRP, eotaxin3, IL-15, MDC).[66–69] Notably, inconsistent findings have been observed for a subset of anti-inflammatory markers (IL-10, interferon gamma [IFN-γ]) in DS-AD. In contrast, other markers, such as IL-8 and IL-6, have been shown to be more consistently elevated in the blood.[28,66,68,69] It has been hypothesized that inflammatory markers may be more useful in AD risk prediction and diagnosis in DS due to inflammatory pathway dysregulation associated with trisomy 21.[67] Therefore, suggestions have been made that plasma blood-based biomarkers such as IFN-γ, TNF-α, IL-6, IL-8, and IL-10 could all be potentially considered non-A/T/N biomarkers for DS-AD, alongside other inflammatory markers such as tissue plasminogen activator.[70] This is supported by studies demonstrating positive associations among IL-1b, total tau, and Aβ42 measured in plasma in DS-AD.[22]

1.3 | Sex differences in DS-AD biomarkers

Notably, few studies have been conducted to examine sex differences in DS-AD biomarkers. Therefore, this remains a critical knowledge gap. As in the neurotypical population, independent of their longer life expectancy, higher prevalence rates for AD have been reported for females (see Udeh-Momoh and Watermeyer[71] for review). This female sex bias extends to those with DS-AD, with a longer duration of dementia noted for females,[72] despite earlier age of onset reported for males with DS.[73] Furthermore, increased AD-related pathology, specifically higher senile plaque, and neocortical neurofibrillary tangle density has been observed in females with DS compared to males with DS.[74]

Of the studies examining sex differences with AT(N) biomarkers in DS, the majority of the work has been conducted in CSF, with only a few studies conducted with plasma. Iulita et al.[75] found, in their recent work, plasma p-tau181 levels to be comparable between males and females with the exception of those 40 to 50 years of age, when females with DS presented with a trend toward higher levels of p-tau181. Additional findings from this same study supported no sex differences in plasma NfL levels.[75] Interestingly, despite previous studies reporting no sex associations of total tau in DS-AD, a recent study reported sex differences in plasma total tau levels, with higher levels found among females with DS compared to males with DS at the prodromal and clinical AD stages (i.e., MCI-DS and DS-AD stages), compared to the asymptomatic stage for adults with DS. This suggests the diagnostic capacity of total tau for distinguishing AD in the clinical stages and may be particularly relevant for work examining disease progression among females with DS.[76]

Tarani et al. found that among children, females with DS compared to age-matched non-DS females had higher levels of serum TNF-α and MCIP-1 as well as tumor growth factor β.[77] Interestingly, males with DS compared to age-matched non-DS males also presented with higher levels of serum inflammatory markers although different from the ones shown with females (IL-6 and IL-12). This work corresponds with more recent findings from Pentz et al., who found that males with DS had higher plasma levels of general inflammation (matrix metalloproteinase [MMP]-9 and MMP-3) than females with DS.[78] The findings

of sex-specific differences in markers of "N" and inflammation allude to discordant biomarker profiles in adults with DS-AD compared to their cognitively stable (i.e., asymptomatic DS) counterparts. Yet the paucity of data on sex-specific differences in DS-AD fluid biomarkers cannot be ignored and denotes a knowledge gap that needs to be urgently addressed, particularly in consideration of personalized strategies toward risk reduction and treatment.

1.4 | Consideration for the use of AD biomarkers in studies of adults with DS

1.4.1 | Longitudinal changes in AT(N) biomarkers

Beyond diagnostic accuracy, longitudinal analysis is also necessary to determine a specific biomarker's prognostic and theragnostic performance. This is particularly relevant for AD biomarkers, given the progressive nature of the disease. Studies evaluating biomarkers' prognostic performance and longitudinal trajectories over several years will be key to establishing their use in clinical routine and determining their potential use as surrogate biomarkers in clinical trials. The advantages of identifying useful biomarkers in blood are evident. Plasma (or serum) is easily accessible and inexpensive compared to other neuro-diagnostic tools, such as lumbar punctures, PET scans, or center-specific neuropsychological assessments. Blood-based biomarkers, therefore, have the advantage of facilitating frequent sampling and have been increasingly evaluated for their potential utility.

Longitudinal work with NfL, a marker of "N," has been examined in DS-AD. This work has found that longitudinal trajectories of plasma NfL have been shown to be significantly increased at baseline in asymptomatic and prodromal AD (MCI-DS) individuals who progress to DS-AD compared to non-progressors. Furthermore, higher rates of change have been observed longitudinally in DS-AD than in pre-AD stages, pointing to an increased process of neurodegeneration with disease progression.[46] Currently, there are no studies published reporting the longitudinal changes of plasma Aβ or tau in DS-AD. The limitations of the few studies conducted in the non-DS space describing longitudinal plasma Aβ levels might be linked to the fact that immunoassays show limited performance when predicting brain amyloidosis by measuring plasma Aβ levels, likely due to matrix effects, which should be of consideration when extending this into the DS space. Mass spectrometry (MS) blood-based methods have been shown to correlate with CSF and amyloid PET,[79] but these assays have lower scalability and throughput than immunoassays. Future studies should address longitudinal changes of plasma Aβ using MS techniques that accurately detect brain amyloidosis.

1.4.2 | Stability of blood biomarkers

The usefulness of any biomarker is influenced by whether its levels remain constant in an individual over time (intra-variability), if concentrations are not too dispersed among the general population (inter-variability), and how biochemically stable the target protein is, specifically in blood, after processing the samples to obtain plasma—sample handling and storage. Few studies have been focused on this issue, and none involving DS participants highlighting a critical knowledge gap; however, results from studies focused on the non-DS sporadic form of AD can be extrapolated.

Of this body of work (conducted in non-DS, see Table 2[43,80–83]), no significant differences in the levels of AD plasma biomarkers have been found by sampling factors such as needle size, location of blood draw, plastic tubing or other tools used, tube collection order, and tube filling volume.[80] Similarly, no differences were found regarding other factors such as time of day (morning vs. evening) and fasting/non-fasting state at blood collection or when measuring analyte levels across five consecutive days.[25] However, the type of tube for the blood collection affected the mean values for several highly used plasma AT(N) biomarkers (Aβ42, Aβ40, p-tau181, GFAP, total tau, NfL). Samples collected in sodium-citrate tubes produced lower concentrations than the standard ethylenediaminetetraacetic acid (EDTA) tubes, while lithium-heparin tubes demonstrated higher mean values.[37,80] Tube types are highly correlated for most biomarkers, but cutoffs should be considered, and potential adjustments for each tube type.

Another factor to consider when collecting plasma is the time from blood draw until centrifugation. Again, in non-DS studies, biomarkers such as GFAP, NfL, and p-tau181 have all been found to remain stable over a 24 hour delayed centrifugation when tubes are held at room temperature or in the refrigerator. In contrast, Aβ42 and Aβ40 values have been found to decline when tubes are held at room temperature but remain stable when kept in the refrigerator for up to 24 hours. Total tau, however, is not stable in whole blood, with lower values found when tubes were held at room temperature and higher values if stored in the refrigerator pending centrifugation. The temperature during centrifugation also has been found to affect total tau levels, while it does not influence the other markers. Considering sample storage, short-term (i.e., max 24 hours) at 4°C does not affect any markers, and levels remain stable for up to 2 weeks at −20°C.[80] Long-term storage for plasma levels of Aβ40 and Aβ42 exhibit stability over 5-year storage at −80°C, while plasma levels of total tau are less stable (≈ 1.5 years).[81]

Finally, freeze–thaw cycles affect blood biomarkers differently. Plasma Aβ42, total tau, NfL, and GFAP are stable over four freeze–thaw cycles when measured with single molecule array (Simoa) technology,[80,82–84] while Aβ40[37,82] and p-tau181[37] levels are affected after freeze–thaw cycle 4. Serum Aβ42, Aβ40, and total tau levels are highly influenced by freeze–thaw cycles, indicating that the use of serum should likely be avoided for these markers.[37] Combined, this work suggests preanalytic considerations when collecting, processing, and storing blood samples for use in generating AT(N) biomarker data. Although studies among DS participants are sparse in this area, work conducted in the non-DS space highlights a number of points for consideration that, if possible, should be confirmed in the DS population.

TABLE 2 Plasma AT(N) biomarker preanalytic/sample processing considerations for DS-AD based on non-DS sample findings.

	Tube type	Stability	Freeze–thaw
Aβ40	Impacts mean protein level[37,80]	Declines when tubes are held at room temperature[80] Short-term storage (i.e., max 24 hours) at 4°C does not affect marker[80] Levels remain stable for up to 2 weeks at −20°C[80] Long-term storage stable for over 5-year storage at −80°C[81]	Affected after 4 freeze–thaw cycles[37,82]
Aβ42	Impacts mean protein level[37,80]	Declines when tubes are held at room temperature[80] Short-term storage (i.e., max 24 hours) at 4°C does not affect marker[80] Levels remain stable for up to 2 weeks at −20°C[80] Long-term storage stable over 5-year storage at −80°C[81]	Stable 4+ freeze–thaw cycles[80,82,83]
Total tau	Impacts mean protein level[37,80]	Lower values found held at room temperature[80] Higher values if stored in the refrigerator[80] Temperature during centrifugation affects levels[80] Long-term storage is less stable (≈ 1.5 years)[81]	Stable 4+ freeze–thaw cycles[80,82,83]
p-tau181	Impacts mean protein level[37,80]	Stable over 24 hour delayed centrifugation when tubes are held at room temperature or in refrigerators[80]	Affected after 4 freeze–thaw cycles[37]
p-tau217	Research needed	Research needed	Research needed
NfL	Impacts mean protein level[37,80]	Stable over 24 hour delayed centrifugation when tubes are held at room temperature or in refrigerators[80]	Stable 4+ freeze–thaw cycles[80,82,83]

Abbreviations: AT(N), amyloid, tau, and neurodegeneration; Aβ, amyloid beta; AD, Alzheimer's disease; DS-AD, Alzheimer's disease in Down syndrome; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau.

2 | CONCLUSIONS

A summary of the work reported here highlights that several traditional AD biomarkers may track disease progression and are higher in those with DS-AD compared to earlier disease stages (MCI-DS or asymptomatic DS). This also extends to work examining inflammatory biomarkers with indications of potential multi-system interactions (inflammatory–neurodegeneration). Although it is important to understand what proteins are differentially expressed in certain disease states, equally important is understanding the ability of these same proteins to determine progression and monitoring. While a vast majority of this work has been conducted in the non-DS space, with only limited application available for consideration among those with DS, several biomarkers, including p-tau181, p-tau217, NfL, and GFAP, have all been shown to track disease progression and pathological changes occurring with AD. Understanding such changes will be critical for applying blood biomarkers to more clinical-based applications. In addition, understanding biological pathways and the interplay between particular AT(N) biomarkers is crucial for clinical application, and more work is needed among those with DS. An example of this is NfL, a widely used marker of "N," which has been positively associated with markers of neuroinflammation.[29] As inflammation contributes to neurodegenerative pathways, which appear to be both through amyloid-independent pathways and by exacerbating amyloid deposition and neuropathology in the brain,[23,30,31] the interplay between NfL and inflammation is likely important to investigate further. Related to this, several studies have also shown inflammation to be a significant factor across the lifespan in DS. Although variability exists in the methodology (fraction, platform, preanalytic processing, etc.), overall findings show increased markers of inflammation (primarily pro-inflammatory) with AD disease progression in those with DS. The stability of these markers and the robustness of several led to increased potential for clinical utility and consideration for modifiable interventions and should be considered for future work.

On a final note, establishing the context in which the blood-based biomarkers are used (context of use [COU]) is also of critical importance, as the ability to test and apply a particular AD biomarker(s) is less efficient without a defined output. Understanding which blood-based biomarkers remain stable longitudinally and which biomarkers can also be used to discriminate disease changes is particularly useful if the COU is to determine disease presence and change. Several high-sensitivity platforms have been created and validated that help detect such low-abundance proteins, which were previously only able to be detected through CSF. Given that even small changes in the low-abundance proteins might indicate significant clinical and pathological change, it is essential to understand further the longitudinal stability

and reliability of AD blood-based biomarkers to appropriately apply and investigate their utility in screening in or out for disease presence.

ACKNOWLEDGMENTS

L.F.A. is the recipient of an Alzheimer's Association fellowship (23AARFD-1022715) and a Postdoctoral fellowship from the Jerome Lejeune Foundation. E.H. is supported by the National Institutes of Health (NIH)/National Institute on Aging (NIA; U19AG068054 and RF1AG079519). A.S. was supported by grants from the Medical Research Council (MR/S011277/1, MR/ S005145/1, and MR/R024901/1), the Jerome Lejeune Foundation, the European Commission (H2020 SC1 Gene overdosage and comorbidities during the early lifetime in Down Syndrome GO-DS21- 848077), and the NIH (1R61AG066543-01). S.P. was supported by an Alzheimer's Society fellowship (AS-CP-18-0020). J.F. was supported by the Fondo de Investigaciones Sanitario, Carlos III Health Institute (PI20/01473) and the Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED) Program 1, the NIH (1R01AG056850-01A1, R21AG056974, and R01AG061566), the Department de Salut de la Generalitat de Catalunya, Pla Estratègic de Recerca I Innovació en Salut (SLT006/17/00119) and by Horizon 2020–Research and Innovation Framework Programme from the European Union (H2020-SC1-BHC-2018-2020). S.E.O. was supported by grants from the NIH/NIA (R01AG054073, R01AG058533, P41EB015922, and U19AG078109). H.Z. is a Wallenberg Scholar and supported by grants from the Swedish Research Council (2022-01018 and 2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (201809-2016862), the AD Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, and ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL (UKDRI-1003).

CONFLICT OF INTEREST STATEMENT

E.H. serves as a consultant for Cyclo Therapeutics and Alzheon. A.S. served on scientific advisory boards and/or as a consultant for AC Immune, ProMIS Neurosciences, and Regeneron/Alnylam. J.F. reported receiving personal fees for service on the advisory boards, adjudication committees, or speaker honoraria from AC Immune, Lilly, Lundbeck, Roche, Fujirebio, and Biogen outside the submitted work. He also reported holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to Adx, EPI8382175.0). S.E.O. has multiple patents pending related to precision medicine technologies for neurodegenerative diseases. He is the founding scientist of Cx Precision Medicine and has served on an advisory board for Roche Diagnostics. H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). All other authors have nothing to disclose. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Petersen ME, Flores-Aguilar L, Head E, et al. Blood biomarkers in Down syndrome: Facilitating Alzheimer's disease detection and monitoring. *Alzheimer's Dement*. 2025;21:e14364. https://doi.org/10.1002/alz.14364