

PERSPECTIVE

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

Melissa E. Petersen^{1,2} | Lisi Flores-Aguilar³ | Elizabeth Head³ | Laia Montoliu-Gaya⁴ |
 Andre Strydom⁵ | Sarah E. Pape⁵ | Juan Fortea^{6,7,8} | Nicholas J. Ashton^{4,9,10,11} |
 Chinedu Udeh-Momoh^{12,13} | Sid E. O'Bryant^{1,2} | Dwight German¹⁴ | Florin Despa^{15,16} |
 Mark Mapstone¹⁷ | Henrik Zetterberg^{4,18,19,20,21,22}

¹Department of Family Medicine, University of North Texas Health Science Center, Fort Worth, Texas, USA²Institute for Translational Research, University of North Texas Health Science Center, Fort Worth, Texas, USA³Department of Pathology and Laboratory Medicine, University of California, Irvine, California, USA⁴Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Goteborg, Sweden⁵Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College, London, UK⁶Sant Pau Memory Unit, Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain⁷Center of Biomedical Investigation Network for Neurodegenerative Diseases (CIBERNED), Madrid, Spain⁸Barcelona Down Medical Center, Fundació Catalana de Síndrome de Down, Barcelona, Spain⁹South London and the Maudsley NHS Foundation Trust, Institute of Psychiatry, Psychology and Neuroscience Maurice Wohl Institute Clinical Neuroscience Institute, King's College, London, UK¹⁰NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation, London, UK¹¹Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway¹²Department of Epidemiology and Prevention, Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA¹³Imarisha Centre for Brain Health and Aging, Brain and Mind Institute, Aga Khan University, Nairobi, Kenya¹⁴Department of Psychiatry and O'Donnell Brain Institute, University of Texas Southwestern Medical Center, Dallas, Texas, USA¹⁵Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, Kentucky, USA¹⁶Department of Neurology, University of Kentucky, Lexington, Kentucky, USA¹⁷Department of Neurology, University of California, Irvine, California, USA¹⁸Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden¹⁹Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK²⁰UK Dementia Research Institute at UCL, London, UK²¹Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China²²Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

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 Sanitarias, 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: JPN2021-00694; AD Strategic Fund and Alzheimer's Association, Grant/Award Numbers: ADFS-21-831376-C, ADFS-21-831381-C, ADFS-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 Skłodowska-Curie grant agreement No 860197 (MIRIAD); 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; Blue-field Project; Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor, Grant/Award Number: F02022-0270; Swedish Research Council, Grant/Award Numbers: 2022-01018, 2019-02397; Jérôme Lejeune Foundation

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

Correspondence

Melissa Petersen, University of North Texas
 Health Science Center, 3500 Camp Bowie
 Blvd, Fort Worth, TX 76107, USA.
 Email: melissa.petersen@unthsc.edu

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 ($A\beta$), 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.

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

1.1.1 | A β “A” biomarkers

Research examining plasma A β has primarily focused on A β 40 and A β 42 and although an ideal comparison of biomarkers, including A β , 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 biomarkers²¹ 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 A β 40 and A β 42, are elevated in DS (con-

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.

sistent 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 A β 42 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 A β 40 and A β 42 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 A β 40 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 A β 40 plasma levels in individuals with DS-AD compared to those with DS but without AD, while no differences in A β 42 plasma levels were found between groups²⁶ (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
A β 40	Higher with disease stage ^{23,27–29}	Variable
A β 42	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; A β , 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 A β 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 A β 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 further³⁸ (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 ranges²⁵ and by age⁵ 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 21⁵⁸ 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 astrogliosis. This includes GFAP, a marker involved in astrogliosis associated with A β 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-1 β , IL-7, interferon gamma-induced protein [IP]10, macrophage inflammatory protein [MIP]-1 β , 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-1 β , 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 A β 42 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 Watermeyer⁷¹ 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 MCP-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 A β or tau in DS-AD. The limitations of the few studies conducted in the non-DS space describing longitudinal plasma A β levels might be linked to the fact that immunoassays show limited performance when predicting brain amyloidosis by measuring plasma A β 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 A β 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 (A β 42, A β 40, 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, A β 42 and A β 40 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 A β 40 and A β 42 exhibit stability over 5-year storage at –80°C, while plasma levels of total tau are less stable (\approx 1.5 years).⁸¹

Finally, freeze–thaw cycles affect blood biomarkers differently. Plasma A β 42, total tau, NfL, and GFAP are stable over four freeze–thaw cycles when measured with single molecule array (Simoa) technology,^{80,82–84} while A β 40^{37,82} and p-tau181³⁷ levels are affected after freeze–thaw cycle 4. Serum A β 42, A β 40, 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
A β 40	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}
A β 42	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 (\approx 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; A β , 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 Sanitarias, 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 Cellectric, 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](#).

REFERENCES

- de Graaf G, Buckley F, Skotko BG. Estimation of the number of people with Down syndrome in the United States. *Genet Med*. 2017;19:439–447. doi:[10.1038/GIM.2016.127](#)
- PENROSE LS. The incidence of mongolism in the general population. *J Ment Sci*. 1949;95:685–688. doi:[10.1192/BJP.95.400.685](#)
- Iulita MF, Garzón Chavez D, Klitgaard Christensen M, et al. Association of Alzheimer disease with life expectancy in people with Down syndrome. *JAMA Netw Open*. 2022;5:e2212910. doi:[10.1001/JAMANETWORKOPEN.2022.12910](#)
- Schupf N, Sergievsky GH. Genetic and host factors for dementia in Down's syndrome. *Br J Psychiatry*. 2002;180:405–410. doi:[10.1192/BJP.180.5.405](#)
- Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet*. 2020;395:1988–1997. doi:[10.1016/S0140-6736\(20\)30689-9](#)
- Sinai A, Mokrysz C, Bernal J, et al. Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. *J Alzheimers Dis*. 2018;61:717–728. doi:[10.3233/JAD-170624](#)
- Doran E, Keator D, Head E, et al. Down syndrome, partial trisomy 21, and absence of Alzheimer's disease: the role of APP. *J Alzheimers Dis*. 2017;56:459–470. doi:[10.3233/jad-160836](#)
- Goldgaber D, Lerman MI, McBride OW, Saffiotti U, Gajdusek DC. Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. *Science*. 1987;235:877–880.
- Prasher VP, Farrer MJ, Kessling AM, et al. Molecular mapping of Alzheimer-type dementia in Down's syndrome. *Ann Neurol*. 1998;43:380–383. doi:[10.1002/ana.410430316](#)
- st George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science*. 1987;235:885–890. doi:[10.1126/SCIENCE.2880399](#)
- Bateman RJ, Aisen PS, De Strooper B, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther*. 2011;3:1. doi:[10.1186/ALZRT59](#)
- Karmiloff-Smith A, Al-Janabi T, D'Souza H, et al. The importance of understanding individual differences in Down syndrome. *F1000Res*. 2016;5:F1000. doi:[10.12688/F1000RESEARCH.7506.1/DOI](#)
- Aylward EH, Burt DB, Thorpe LU, Lai F, Dalton A. Diagnosis of dementia in individuals with intellectual disability. *J Intellect Disabil Res*. 1997;41(Pt 2):152–164. doi:[10.1111/J.1365-2788.1997.TB00692.X](#)
- Sheehan R, Sinai A, Bass N, et al. Dementia diagnostic criteria in Down syndrome. *Int J Geriatr Psychiatry*. 2015;30:857–863. doi:[10.1002/GPS.4228](#)
- Hartley D, Blumenthal T, Carrillo M, et al. Down syndrome and Alzheimer's disease: common pathways, common goals. *Alzheimers Dement*. 2015;11:700–709. doi:[10.1016/J.JALZ.2014.10.007](#)

16. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging*. 2023;3:506-519. doi:10.1038/S43587-023-00403-3
17. Theriault J, Servaes S, Tissot C, et al. Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease. *Alzheimers Dement*. 2023;19(11):4967-4977. doi:10.1002/ALZ.13026
18. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. *JAMA Neurol*. 2024;81(3):255-263. doi:10.1001/JAMANEUROL.2023.5319
19. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535-562. doi:10.1016/j.jalz.2018.02.018
20. Rafii MS, Ances BM, Schupf N, et al. The AT(N) framework for Alzheimer's disease in adults with Down syndrome. *Alzheimers Dement*. 2020;12:e12062. doi:10.1002/DAD2.12062
21. Henson RL, Doran E, Christian BT, et al. Cerebrospinal fluid biomarkers of Alzheimer's disease in a cohort of adults with Down syndrome. *Alzheimers Dement*. 2020;12:e12057. doi:10.1002/DAD2.12057
22. Startin CM, Ashton NJ, Hamburg S, et al. Plasma biomarkers for amyloid, tau, and cytokines in Down syndrome and sporadic Alzheimer's disease. *Alzheimers Res Ther*. 2019;11:26. doi:10.1186/S13195-019-0477-0
23. Fortea J, Carmona-Iragui M, Benejam B, et al. Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet Neurol*. 2018;17:860-869. doi:10.1016/S1474-4422(18)30285-0
24. Mehta PD, Dalton AJ, Mehta SP, Kim KS, Sersen EA, Wisniewski HM. Increased plasma amyloid beta protein 1-42 levels in Down syndrome. *Neurosci Lett*. 1998;241:13-16. doi:10.1016/S0304-3940(97)00966-X
25. Mengel D, Liu W, Glynn RJ, et al. Dynamics of plasma biomarkers in Down syndrome: the relative levels of A β 42 decrease with age, whereas NT1 tau and NFL increase. *Alzheimers Res Ther*. 2020;12:27. doi:10.1186/S13195-020-00593-7
26. Alhajraf F, Ness D, Hye A, Strydom A. Plasma amyloid and tau as dementia biomarkers in Down syndrome: systematic review and meta-analyses. *Dev Neurobiol*. 2019;79:684-698. doi:10.1002/DNEU.22715
27. Head E, Doran E, Nistor M, et al. Plasma amyloid-beta as a function of age, level of intellectual disability, and presence of dementia in Down syndrome. *J Alzheimers Dis*. 2011;23:399-409. doi:10.3233/jad-2010-101335
28. Iulita MF, Ower A, Barone C, et al. An inflammatory and trophic disconnect biomarker profile revealed in Down syndrome plasma: relation to cognitive decline and longitudinal evaluation. *Alzheimers Dement*. 2016;12:1132-1148. doi:10.1016/J.JALZ.2016.05.001
29. Coppus AM, Schuur M, Vergeer J, et al. Plasma beta amyloid and the risk of Alzheimer's disease in Down syndrome. *Neurobiol Aging*. 2012;33:1988-1994. doi:10.1016/j.neurobiolaging.2011.08.007
30. Schupf N, Patel B, Silverman W, et al. Elevated plasma amyloid β -peptide 1-42 and onset of dementia in adults with Down syndrome. *Neurosci Lett*. 2001;301:199-203. doi:10.1016/S0304-3940(01)01657-3
31. Schupf N, Patel B, Pang D, et al. Elevated plasma beta-amyloid peptide A β (42) levels, incident dementia, and mortality in Down syndrome. *Arch Neurol*. 2007;64:1007-1013. doi:10.1001/archneur.64.7.1007
32. Mattsson-Carlsson N, Andersson E, Janelidze S, et al. A β deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease. *Sci Adv*. 2020;6:eaz2387. doi:10.1126/SCIADV.AAZ2387
33. Horie K, Barthelemy NR, Sato C, Bateman RJ. CSF tau microtubule binding region identifies tau tangle and clinical stages of Alzheimer's disease. *Brain*. 2021;144:515-527. doi:10.1093/BRAIN/AWAA373
34. Mattsson-Carlsson N, Janelidze S, Palmqvist S, et al. Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. *Brain*. 2020;143:3234-3241. doi:10.1093/BRAIN/AWAA286
35. Lleó A, Zetterberg H, Pegueroles J, et al. Phosphorylated tau181 in plasma as a potential biomarker for Alzheimer's disease in adults with Down syndrome. *Nat Commun*. 2021;12:4304. doi:10.1038/S41467-021-24319-X
36. Janelidze S, Palmqvist S, Leuzy A, et al. Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma A β 42/A β 40 and p-tau. *Alzheimers Dement*. 2022;18:283-293. doi:10.1002/ALZ.12395
37. Ashton NJ, Suárez-Calvet M, Karikari TK, et al. Effects of preanalytical procedures on blood biomarkers for Alzheimer's pathophysiology, glial activation, and neurodegeneration. *Alzheimers Dement*. 2021;13:e12168. doi:10.1002/DAD2.12168
38. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28:1398-1405. doi:10.1038/S41591-022-01822-2
39. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol*. 2021;78:396-406. doi:10.1001/JAMANEUROL.2020.4986
40. Lantero Rodriguez J, Karikari TK, Suárez-Calvet M, et al. Plasma p-tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterization of cognitive decline. *Acta Neuropathol*. 2020;140:267-278. doi:10.1007/S00401-020-02195-X
41. Karikari TK, Benedet AL, Ashton NJ, et al. Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative. *Mol Psychiatry*. 2021;26:429-442. doi:10.1038/S41380-020-00923-Z
42. Ashton NJ, Janelidze S, Mattsson-Carlsson N, et al. Differential roles of A β 42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. *Nat Med*. 2022;28:2555-2562. doi:10.1038/S41591-022-02074-W
43. Ashton NJ, Leuzy A, Lim YM, et al. Increased plasma neurofilament light chain concentration correlates with severity of post-mortem neurofibrillary tangle pathology and neurodegeneration. *Acta Neuropathol Commun*. 2019;7:5. doi:10.1186/S40478-018-0649-3
44. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol*. 2018;14:577-589. doi:10.1038/S41582-018-0058-Z
45. Kasai T, Tatebe H, Kondo M, et al. Increased levels of plasma total tau in adult Down syndrome. *PLoS One*. 2017;12(11):e0188802. doi:10.1371/journal.pone.0188802
46. Carmona-Iragui M, Alcolea D, Barroeta I, et al. Diagnostic and prognostic performance and longitudinal changes in plasma neurofilament light chain concentrations in adults with Down syndrome: a cohort study. *Lancet Neurol*. 2021;20:605-614. doi:10.1016/S1474-4422(21)00129-0
47. Ashton NJ, Janelidze S, Al Khleifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun*. 2021;12:3400. doi:10.1038/S41467-021-23620-Z
48. Benedet AL, Ashton NJ, Pascoal TA, et al. Plasma neurofilament light associates with Alzheimer's disease metabolic decline in amyloid-positive individuals. *Alzheimers Dement*. 2019;11:679-689. doi:10.1016/J.DADM.2019.08.002
49. Rafii MS, Donohue MC, Matthews DC, et al. Plasma neurofilament light and Alzheimer's disease biomarkers in Down Syndrome: results from the Down Syndrome Biomarker Initiative (DSBI). *J Alzheimers Dis*. 2019;70:131-138. doi:10.3233/JAD-190322
50. Strydom A, Heslegrave A, Startin CM, et al. Neurofilament light as a blood biomarker for neurodegeneration in Down syndrome. *Alzheimers Res Ther*. 2018;10:39. doi:10.1186/s13195-018-0367-x

51. Petersen ME, Rafii MS, Zhang F, et al. Plasma total-tau and neurofilament light chain as diagnostic biomarkers of Alzheimer's disease dementia and mild cognitive impairment in adults with Down syndrome. *J Alzheimers Dis*. 2021;79:671-681. doi:[10.3233/JAD-201167](#)
52. Flores-Aguilar L, Iulita MF, Kovacs O, et al. Evolution of neuroinflammation across the lifespan of individuals with Down syndrome. *Brain*. 2020;143:3653-3671. doi:[10.1093/BRAIN/AWAA326](#)
53. Griffin WS, Stanley LC, Ling C, et al. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci U S A*. 1989;86:7611-7615. doi:[10.1073/PNAS.86.19.7611](#)
54. Martini AC, Helman AM, McCarty KL, et al. Distribution of microglial phenotypes as a function of age and Alzheimer's disease neuropathology in the brains of people with Down syndrome. *Alzheimers Dement*. 2020;12:e12113. doi:[10.1002/DAD2.12113](#)
55. Head E, Azizeh BY, Lott IT, Tenner AJ, Cotman CW, Cribbs DH. Complement association with neurons and beta-amyloid deposition in the brains of aged individuals with Down syndrome. *Neurobiol Dis*. 2001;8:252-265. doi:[10.1006/NBDI.2000.0380](#)
56. Stoltzner SE, Grenfell TJ, Mori C, et al. Temporal accrual of complement proteins in amyloid plaques in Down's syndrome with Alzheimer's disease. *Am J Pathol*. 2000;156:489-499. doi:[10.1016/S0002-9440\(10\)64753-0](#)
57. Wilcock DM, Hurban J, Helman AM, et al. Down syndrome individuals with Alzheimer's disease have a distinct neuroinflammatory phenotype compared to sporadic Alzheimer's disease. *Neurobiol Aging*. 2015;36:2468-2474. doi:[10.1016/J.NEUROBIOAGING.2015.05.016](#)
58. Wilcock DM, Griffin WS. Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. *J Neuroinflammation*. 2013;10:84. doi:[10.1186/1742-2094-10-84](#)
59. Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. *Nat Rev Neurol*. 2019;15:135-147. doi:[10.1038/S41582-018-0132-6](#)
60. Montoliu-Gaya L, Alcolea D, Ashton NJ, et al. Plasma and cerebrospinal fluid glial fibrillary acidic protein levels in adults with Down syndrome: a longitudinal cohort study. *EBioMedicine*. 2023;90:104547. doi:[10.1016/J.EBIOM.2023.104547](#)
61. Mgaith F, Baksh RA, Startin CM, et al. Exploring semantic verbal fluency patterns and their relationship to age and Alzheimer's disease in adults with Down syndrome. *Alzheimers Dement*. 2023;19:5129-5137. doi:[10.1002/ALZ.13097](#)
62. Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid- β but not tau pathology in Alzheimer's disease. *Brain*. 2021;144:3505-3516. doi:[10.1093/BRAIN/AWAB223](#)
63. Benedet AL, Milà-Alomà M, Vrillon A, et al. Differences between plasma and cerebrospinal fluid glial fibrillary acidic protein levels across the Alzheimer disease continuum. *JAMA Neurol*. 2021;78:1471-1483. doi:[10.1001/JAMANEUROL.2021.3671](#)
64. Simrén J, Weninger H, Brum WS, et al. Differences between blood and cerebrospinal fluid glial fibrillary acidic protein levels: the effect of sample stability. *Alzheimers Dement*. 2022;18:1988-1992. doi:[10.1002/ALZ.12806](#)
65. Ahmed MM, Johnson NR, Boyd TD, Coughlan C, Chial HJ, Potter H. Innate immune system activation and neuroinflammation in Down syndrome and neurodegeneration: therapeutic targets or partners? *Front Aging Neurosci*. 2021;13:718426. doi:[10.3389/FNAGI.2021.718426](#)
66. O'Bryant SE, Zhang F, Silverman W, et al. Proteomic profiles of incident mild cognitive impairment and Alzheimer's disease among adults with Down syndrome. *Alzheimers Dement*. 2020;12:e12033. doi:[10.1002/dad2.12033](#)
67. Petersen ME, O'Bryant SE. Blood-based biomarkers for Down syndrome and Alzheimer's disease: a systematic review. *Dev Neurobiol*. 2019;79:699-710. doi:[10.1002/DNEU.22714](#)
68. Petersen ME, Zhang F, Schupf N, et al. Proteomic profiles for Alzheimer's disease and mild cognitive impairment among adults with Down syndrome spanning serum and plasma: an Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) study. *Alzheimers Dement*. 2020;12:e12039. doi:[10.1002/dad2.12039](#)
69. O'Bryant S, Zhang F, Lee J, et al. Proteomic biomarkers for detecting and predicting AD risk among adults with Down syndrome. *Alzheimers Dement*. 2018;14:P1624-P1625. doi:[10.1016/j.jalz.2018.06.2968](#)
70. Montoliu-Gaya L, Strydom A, Blennow K, Zetterberg H, Ashton NJ. Blood biomarkers for Alzheimer's disease in Down syndrome. *J Clin Med*. 2021;10:3639. doi:[10.3390/JCM10163639](#)
71. Udeh-Momoh C, Watermeyer T. Female specific risk factors for the development of Alzheimer's disease neuropathology and cognitive impairment: call for a precision medicine approach. *Ageing Res Rev*. 2021;71:101459. doi:[10.1016/J.ARR.2021.101459](#)
72. Lai F, Mhatre PG, Yang Y, Wang MC, Schupf N, Rosas HD. Sex differences in risk of Alzheimer's disease in adults with Down syndrome. *Alzheimers Dement*. 2020;12:e12084. doi:[10.1002/DAD2.12084](#)
73. Schupf N, Kapell D, Nightingale B, Rodriguez A, Tycko B, Mayeux R. Earlier onset of Alzheimer's disease in men with Down syndrome. *Neurology*. 1998;50:991-995. doi:[10.1212/WNL.50.4.991](#)
74. Andrews EJ, Martini AC, Head E. Exploring the role of sex differences in Alzheimer's disease pathogenesis in Down syndrome. *Front Neurosci*. 2022;16:954999. doi:[10.3389/FNINS.2022.954999](#)
75. Iulita MF, Bejanin A, Vilaplana E, et al. Association of biological sex with clinical outcomes and biomarkers of Alzheimer's disease in adults with Down syndrome. *Brain Commun*. 2023;5:fcad074. doi:[10.1093/BRAINCOMMS/FCAD074](#)
76. Dang L-HT, Krinsky-McHale SJ, O'Bryant S, et al. Sex differences in levels of plasma neurofilament light and total tau in adults with Down syndrome. *Alzheimers Dement*. 2021;17:e055785. doi:[10.1002/ALZ.055785](#)
77. Tarani L, Carito V, Ferraguti G, et al. Neuroinflammatory markers in the serum of prepubertal children with Down syndrome. *J Immunol Res*. 2020;2020:6937154. doi:[10.1155/2020/6937154](#)
78. Pentz R, Iulita MF, Ducatzenzeiler A, et al. Nerve Growth Factor (NGF) pathway biomarkers in Down syndrome prior to and after the onset of clinical Alzheimer's disease: a paired CSF and plasma study. *Alzheimers Dement*. 2021;17:605-617. doi:[10.1002/ALZ.12229](#)
79. Brand AL, Lawler PE, Bollinger JG, et al. The performance of plasma amyloid beta measurements in identifying amyloid plaques in Alzheimer's disease: a literature review. *Alzheimers Res Ther*. 2022;14:195. doi:[10.1186/S13195-022-01117-1](#)
80. Verberk IMW, Misdorp EO, Koelewijn J, et al. Characterization of pre-analytical sample handling effects on a panel of Alzheimer's disease-related blood-based biomarkers: results from the Standardization of Alzheimer's Blood Biomarkers (SABB) working group. *Alzheimers Dement*. 2022;18:1484-1497. doi:[10.1002/ALZ.12510](#)
81. Chiu MJ, Lue LF, Sabbagh MN, Chen TF, Chen HH, Yang SY. Long-term storage effects on stability of A β 1-40, A β 1-42, and total tau proteins in human plasma samples measured with immunomagnetic reduction assays. *Dement Geriatr Cogn Dis Extra*. 2019;9:77-86. doi:[10.1159/000496099](#)
82. Keshavan A, Heslegrave A, Zetterberg H, Schott JM. Stability of blood-based biomarkers of Alzheimer's disease over multiple freeze-thaw cycles. *Alzheimers Dement*. 2018;10:448-451. doi:[10.1016/J.DADM.2018.06.001](#)
83. Liu HC, Chiu MJ, Lin CH, Yang SY. Stability of plasma amyloid- β 1-40, amyloid- β 1-42, and total tau protein over repeated freeze/thaw cycles. *Dement Geriatr Cogn Dis Extra*. 2020;10:46-55. doi:[10.1159/000506278](#)
84. Simrén J, Leuzy A, Karikari TK, et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2021;17:1145-1156. doi:[10.1002/ALZ.12283](#)

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>