Clinical and research application of fluid biomarkers in autosomal dominant Alzheimer's disease and Down syndrome

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Summary

Autosomal dominant Alzheimer's disease (ADAD) and Down syndrome (DS) constitute genetic forms of Alzheimer's disease (AD). The study of these forms has been crucial in understanding the biomarker changes and disease progression, notably in advancing our knowledge of the natural history of AD. However, some specific characteristics of biomarkers in genetically determined forms and, most importantly, the near full penetrance and predictability of disease onset lead to a very different context of use for biomarkers in these populations. This article delves into the similarities and differences in biomarker profiles between genetically determined AD and sporadic cases, discussing the implications for research and clinical practice. It also emphasizes the need to account for factors that may affect biomarker reliability differently in genetically determined AD. Enhancing our understanding of the disease will pave the way for more personalized therapeutic approaches for affected individuals.

Keywords: Alzheimer; Autosomal dominant Alzheimer's disease; Down syndrome; Biomarkers; Biofluids

Introduction/rationale

In 1984, Glenner et al. made the first implicit statement of the amyloid cascade hypothesis, when β-amyloid (Aβ) protein was isolated from meningeal vessels of Alzheimer's disease (AD) cases and a case of Down syndrome (DS) with AD dementia and cerebral amyloid angiopathy (CAA).[1] This discovery suggested that the overproduction of Aβ could lead to AD and raised for the first time the possibility of a genetic origin of the disease.[1] In 1987, different groups cloned the *Amyloid Precursor Protein* (*APP*) gene and confirmed it was located on chromosome 21. Subsequently, duplications and different mutations in this gene were described in several families with early-onset AD. In 1995, other genes related to early-onset AD were reported in chromosomes 14 and 1, later known as *Presenilin 1* and *2* (*PSEN1/2*), respectively. The role of presenilins in the enzymatic cleavage of APP as a part of the γ-secretase complex was discovered shortly thereafter, solidifying the amyloid cascade hypothesis.[2]

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Autosomal dominant AD (ADAD) and DS are now both conceptualized as genetically determined forms of AD.[3,4] ADAD has been pivotal in advancing our understanding of AD pathophysiology, especially in characterizing the natural history of the disease.[5] Studies of ADAD have described the sequence of biomarker changes occurring in the long preclinical phase of AD, which lasts decades before symptom onset. This preclinical phase remains a key focus in AD research, offering valuable insights into early changes that precede clinical deterioration and representing an attractive time window for therapeutic intervention. Research on DS has corroborated findings from ADAD and offered new perspectives on AD progression and biomarker dynamics.[6,7]

Recent unprecedented research efforts and funding have enabled the emergence of international consortia and initiatives, fostering large-scale longitudinal studies that accelerate our understanding of AD progression in genetically determined forms of the disease.[7–9] Early studies with CSF and imaging biomarkers have led to more recent intensive research in plasma biomarkers. As in the general population, the newly developed plasma biomarkers will overcome the relatively low accessibility of these tests due to their demonstrated safety in staging the disease,[10,11] and accuracy in diagnosing and prognosticating patients.[12,13]

However, clinical and research use of fluid biomarkers in ADAD and DS differs from the general population. Asymptomatic AD mutation carriers and individuals with DS are considered to be in the AD continuum from birth.[4] Therefore, the context of biomarker use in these populations, both in research and in clinical practice, requires specific considerations as they can stage but not diagnose a disease status, which is present by definition.

This article explores the similarities and differences in biomarker findings and applications between genetically determined and sporadic forms of AD, focusing on tailoring approaches for more targeted and effective treatments and interventions.

Insights into the interpretation of biomarkers in genetically determined AD

The advent of biomarkers in genetically determined forms of AD has revolutionized our understanding of AD pathophysiology. The predictable sequence of biomarker changes along the AD continuum is fundamental to understand the natural history of the disease. ADAD and DS provide compelling evidence for the amyloid cascade hypothesis, as all mutations increase the production of β-amyloid (Aβ) protein or the relative ratio to longer forms, which are more prone to aggregation and plaque formation. Pathogenic mutations in *APP* and *PSEN1* and *PSEN2* genes show nearly 100% penetrance of AD dementia. However, ADAD phenotypes are heterogeneous, are influenced by the mutation position or the causative gene, and deserve separate analysis in observational research and clinical trials.[14]

Similarly, DS leads to the overproduction of Aβ due to the triplication of the *APP* gene on chromosome 21.[15] The triplication of the APP gene is both necessary and sufficient for the emergence of AD pathology, while other over-expressed genes on chromosome 21 may affect the risk. Although strictly defining the dose effect of the *APP* gene while examining biomarkers in DS could have some limitations, the complete trisomy of chromosome 21 is found in 95% of people with DS, while partial triplications–translocations or mosaicisms-that might not include APP triplication occur less frequently. Only two cases with partial chromosome 21 deletion have been reported, neither showing symptoms nor biomarker changes associated with AD at an older age, demonstrating the necessity of APP triplication for the development of AD pathology in DS.

The accumulation of Aβ peptides leads to the downstream spread of tau pathology, synaptic loss, and neurodegeneration.[5,16] In genetically determined AD, by definition, the disease is present from birth, well before the onset of brain pathologic changes or symptoms. This is recognized in the Revised Criteria for Diagnosis and Staging of AD, defining stage 0 for individuals with causal gene mutations or DS but no symptoms and normal AD biomarker levels.[4] Therefore, in genetic cases, AD is a life-long pathological process (Fig. 1). The earliest signs of amyloid overexpression in DS result in accumulation within enlarged endosomes and lysosomes, potentially starting during gestation.[17] The neuropathological hallmarks develop in an ordered manner through different stages of increasing pathological burden, decades before the clinical presentation.[18] Neuroinflammation evolves through preclinical AD into the symptomatic stages,[19,20] while other processes such as CAA develop later closer to symptom onset.[21]

Biomarkers offer insights into this long AD continuum, each tracking specific processes at different stages of the pathological spectrum. Previous diagnostic criteria assumed equivalence between biofluid and imaging biomarkers within each AT(N) category,[22] but ample evidence, especially in genetic forms of the disease, disproves (Fig. 2). Particularly, cerebrospinal fluid (CSF) amyloid and tau biomarkers change almost a decade earlier than their PET counterparts,[5,6] indicating that imaging and fluid biomarkers within an AT(N) category are not interchangeable.[34,35] Furthermore, the natural history of pathological changes observed at autopsy indicates that some processes are not yet captured by *in vivo* biomarkers, and that different biomarkers have varied temporal windows. This evidence highlights the necessity of employing various biomarkers to capture the disease's full spectrum and to understand the

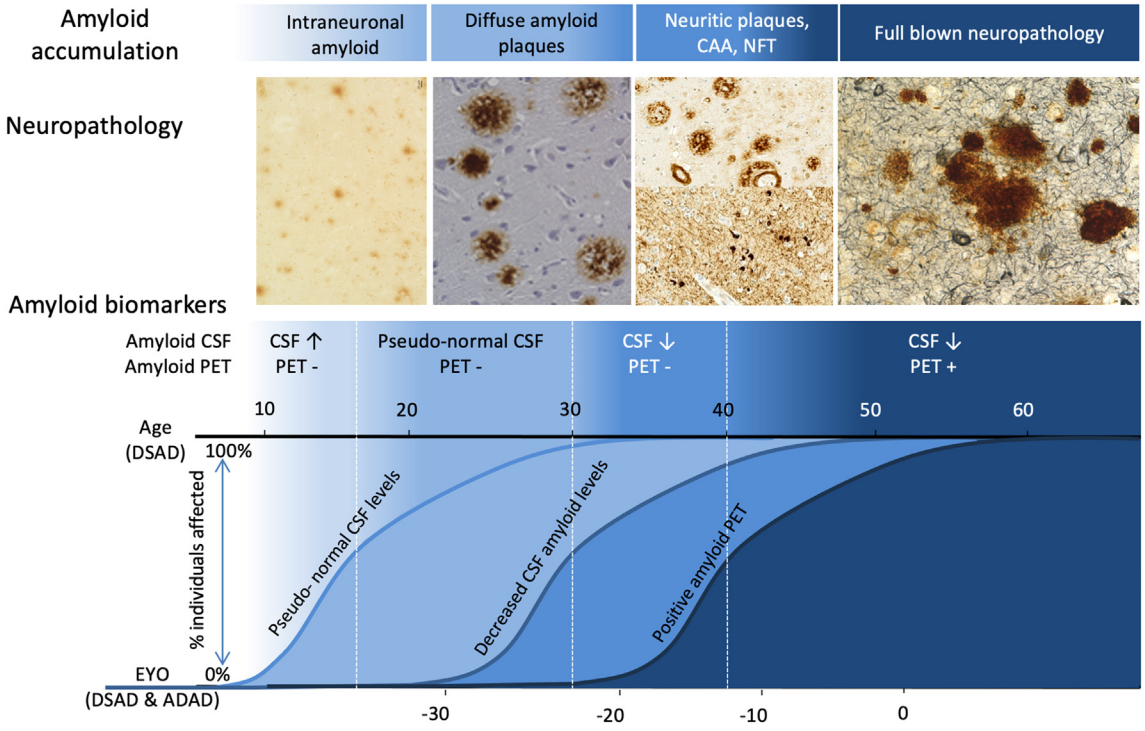

Fig. 1: **Lifelong accumulation of AD neuropathology in genetically determined forms of AD**. In early childhood, CSF Aβ levels are increased, then, from the second decade of life, intraneuronal amyloid accumulation starts, being accompanied by a pseudo-normalization in CSF Aβ levels. After the onset of the diffuse plaque formation, at the third decade of life, CSF Aβ levels start to decrease, while amyloid PET still remains negative. With the progressive accumulation of amyloid leading to the formation of neuritic plaques, 10 years later, becomes positive, while the rest of the neuropathological process (neurofibrillary tangles, cerebral amyloid angiopathy, etc.) continue to develop and lead to the clinical symptoms. Different approaches to detect amyloid accumulation are represented in each row: neuropathology, cerebrospinal fluid and amyloid PET. Their progress is shown according to estimated years to onset (for ADAD) and age (for DS). Aβ: β-amyloid protein; CAA: cerebral amyloid angiopathy; CSF: cerebrospinal fluid; EYO: estimated years to onset; NFT: tau neurofibrillary tangles; PET: positron emission tomography.

dynamics of each biomarker, potentially enabling earlier interventions at the different stages.

Fig. 1 reflects, through the amyloid pathology, that AD neuropathological changes are a life-long continuous process in where the dichotomization of a biomarker result leads to over-simplification and erroneous assumptions. Each biomarker measure has sensitivity and specificity depending on the temporality of the process it is tracking and a range of detection within which it can identify the process. A negative biomarker result does not exclude the presence of pathological lesions. Although the deposition of amyloid in diffuse plaques is present in teenagers with DS, amyloid PET positivity does not begin to be observed until the late 30s or early 40s, when plaques mature into neuritic plaques detectable with tracers (Fig. 1).[7] Also, the relationship between pathology and biomarkers is not always linear, e.g., in early stages of ADAD, CSF Aβ levels may fall within normal ranges, representing a transient pseudo-normalization, as these levels can temporarily normalize after being elevated compared to healthy controls. This insight challenges the conventional binary outlook of biomarker outcomes, highlighting the need for a nuanced understanding of biomarker dynamics. The age or stage of the disease at testing, the sensitivity and specificity of the biomarker and inter-individual biological variability can also influence biomarker levels. Thus, a negative biomarker finding should be contextualized within a broader diagnostic framework, incorporating multiple biomarkers and clinical evaluations.

Finally, the recent Revised Criteria, present objective criteria for diagnosis but also for staging AD.[4] These criteria distinguish between the clinical and biological severity staging. Biological staging using various biomarkers will help identifying groups of individuals with similar expected disease progression, guiding more tailored and effective treatment plans. These criteria underscore that biological AD stage and clinical severity are related but do not travel in lockstep. Comorbid pathologic change, resilience or cognitive reserve could impact this integration between biology and clinics. In genetically determined cases of AD, however, the earlier age of onset reduces the impact of confounding factors

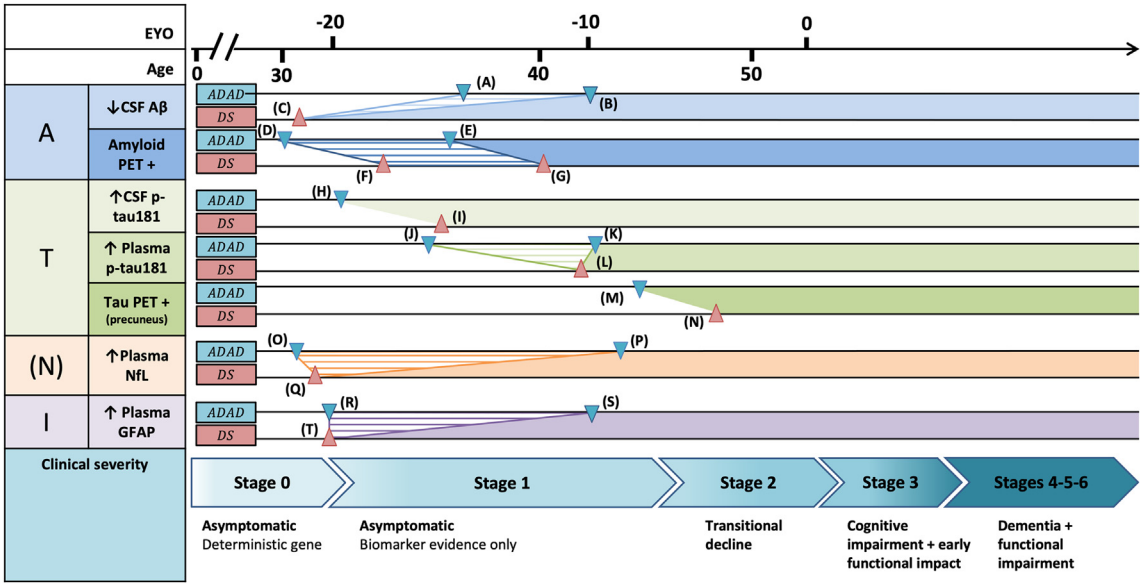

Fig. 2: **Temporal evolution of biomarkers in genetic AD**. This figure illustrates the progression of pathophysiological biomarkers in genetic forms of Alzheimer's disease, such as autosomal dominant Alzheimer's disease (ADAD) and Down syndrome-associated Alzheimer's disease (DSAD), using the AT(N) framework and inflammation markers. Biomarkers include cerebrospinal fluid (CSF) amyloid levels and amyloid PET for Aβ proteinopathy (A), CSF pTau-181 levels, plasma pTau-181 levels, and Tau PET in the precuneus for tau proteinopathy (T), plasma neurofilament light chain for neurodegeneration (N), and glial fibrillary acidic protein for astrogliosis (I). The clinical severity, shown in the last row, follows the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease. The figure uses blue to indicate changes in ADAD and red for DSAD, with letters referencing studies that report estimated years to symptom onset in ADAD or the age at which these changes occur in DSAD. These forms clearly show the temporality of biomarker changes leading to Alzheimer's dementia in genetically determined AD, which is strikingly similar across both conditions. The letters refer to the different studies which report the estimated years to symptom onset in ADAD or age in DSAD at which these changes occur: (A) Bateman et al. 2012[5]; (B) McDade et al. 2018[23]; (C) Fortea et al. 2020[6]; (D) Boerwinkle et al. 2023[24]; (E) Bateman et al. 2012, Wisch et al. 2024[5,25]; (F) Boerwinkle et al. 2023, Fortea et al. 2020[6,24]; (G) Wisch et al. 2024[25]; (H) Fagan et al. 2015, Barthelemy et al. 2020[26,27]; (I) Fortea et al. 2020[6]; (J) Barthelemy et al. 2020[26]; (K) Montoliu-Gaya et al. 2023[28]; (L) Montoliu-Gaya et al. 2023, Lleó et al. 2021[28,29]; (M) Wisch et al. 2024, O'Connor et al. 2023[24,25]; (N) Wisch et al. 2024[25]; (O) Quiroz et al. 2020[30]; (P) Preische et al. 2019[31]; (Q) Fortea et al. 2020[7]; (R) Montoliu-Gaya et al. 2023[28]; (S) Johansson et al. 2023, Chatterjee et al. 2023[32,33]; (T) Montoliu-Gaya et al. 2023.[28]

associated with ageing, allowing the pathological characteristics of AD to be better discriminated.[36] Our better understanding of the natural history of AD helps selecting participants for disease-modifying drug trials. Also, further development and validation of plasma biomarker signatures will increase the accessibility of AD staging systems in clinical settings to detect early disease.

Fluid biomarkers in autosomal dominant Alzheimer's disease

Amyloid biomarkers are the first to change in ADAD. Specifically, reductions in CSF Aβ1-42 and in the Aβ1-42:1–40 ratio are closely associated with cerebral amyloid deposition, starting about two decades before symptom onset.[37] Interestingly, prior to cerebral amyloid accumulation, CSF Aβ1-42 levels are higher in mutation carriers compared to non-carriers, likely due to increased production of Aβ1-42.[37] This elevated Aβ production is also reflected in plasma, where Aβ1-42:1–40 ratio remains higher in mutation carriers compared to non-carriers, even after symptom onset and, in contrast to CSF, do not decline once cerebral amyloid deposition begins.[38] Plasma Aβ1-42:1–40 in ADAD might reflect peripheral production, serving as a marker of ADAD state as opposed to disease stage.

Different phosphorylated tau (p-tau) isoforms change at different stages of the AD continuum, each following distinct trajectories over time. CSF p-tau217 and CSF p-tau181 levels rise in mutation carriers compared to non-carriers soon after amyloid deposits, 21 and 19 years before symptom onset, respectively. These biomarkers can detect amyloid positivity with a high accuracy.[26] Conversely, increases in CSF p-tau205 occur later, 13 years before symptom onset, and are closely linked to neurodegeneration, evidenced by cortical atrophy and hypometabolism, persisting even after symptom onset.[26]

Similarly, early presymptomatic changes occur in plasma p-tau217 and p-tau181, elevated 20 and 16 years before symptoms appear, respectively.[39–41] However,

plasma levels of p-tau181 and p-tau217 plateau and possibly even decline after symptom onset.[26,42]

CSF total-tau (t-tau) changes are detected approximately 17 years before symptom onset, but longitudinal measures show variability and do not follow a linear trajectory, probably decreasing after symptom onset.[5,23,26] Increases in CSF t-tau correlate with disease progression as measured by cognitive decline and brain atrophy, and are more closely linked with tau accumulation on PET scans compared to p-tau measures.[26]

Neurofilament light chain (NfL) protein, a non-specific biomarker of neuronal damage, is likely to be indicative of symptomatic AD in genetically determined forms due to the low likelihood of other neurodegenerative processes co-existing at young ages. NfL can be measured accurately in CSF and blood,[43] correlating with disease progression (cortical thinning and declining cognitive performance).[31] Studies on plasma NfL levels show variable results regarding the earliest age of divergence between mutation carriers and non-carriers, ranging from 6 to 20 years before symptom onset.[30,31,44] As clinical onset approaches, longitudinal changes in NfL concentrations can more reliably detect early neurodegeneration in ADAD than a single measure.[30,31]

Synaptic markers such as synaptosomal-associated protein –25 (SNAP-25), neurogranin (Ng) and visinin-like protein 1 (VILIP-1), are elevated in mutation carriers approximately 15–19 years before the symptom onset, supporting their role as early biomarkers in the AD course. These biomarkers correlate with AD-related outcomes, including brain amyloid burden and cognitive performance.[37]

Regarding inflammatory changes, CSF levels of soluble Triggering receptor expressed in myeloid cells 2 (sTREM2) levels, a marker of microglial activity, increase soon after amyloid deposition begins, more than 20 years before symptom appear, and modulate the impact of Aβ aggregation on downstream processes (plaque accumulation, tau phosphorylation and neurodegeneration).[45] Microglial TREM2 activity likely starts right after or even during the earliest deposition of amyloid plaques,[45] making sTREM2 a promising marker for clinical trial design and interpretation. Astrogliosis, measured by the glial fibrillar acidic protein (GFAP), occurs a decade before symptom onset and is associated with cerebral amyloid accumulation in asymptomatic carriers.[32] Plasma and serum GFAP levels rise with clinical severity and predict cortical atrophy and cognitive change, outperforming CSF GFAP, serving as a prognostic measure. Of note, serum GFAP showed similar but less pronounced relationships compared to CSF GFAP.[32]

Fluid biomarkers in Down syndrome

AD in DS has a similarly predictable disease onset, as ADAD, with a median age of prodromal AD at 50.8 years and dementia diagnosis at 53.8 years.[7,46] DS is more common than ADAD, offering opportunities for well-powered studies to investigate biomarkers, genetic overproduction of APP, disease mechanisms, diagnostic performance, and neuropathologic measures.

The feasibility of performing lumbar punctures to study CSF biomarkers in adults with DS is well established.[11] Acceptance rates of lumbar punctures in research can be as high as 30%, as shown in the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI), where over 350 lumbar punctures have been performed.[6] Notably, the incidence of side effects, most commonly headache, in DS is similar or even lower than in sporadic AD.[11]

CSF Aβ levels are increased in early childhood, then decrease with a period of pseudo-normalization until the late 20s, when they drop below normal levels approximately two decades before dementia onset, reaching floor effects at prodromal stages.[7] Both CSF Aβ1-42 and Aβ1-40 levels are elevated due to the APP overproduction, showing different patterns of change with disease progression.[47] The CSF Aβ1-42 to Aβ1-40 ratio significantly decreases about 26 years before dementia diagnosis.[6,24]

Plasma Aβ1-42 and Aβ1-40 are consistently elevated in adults with DS compared to euploid adults across the whole age span, reflecting the APP gene dose effect. However, current evidence with immunoassays does not support their use for diagnosing symptomatic AD.[48] No studies with newer mass spectrometry techniques, which show better performance than immunoassays for detecting brain amyloidosis in sporadic AD and ADAD, have been conducted in DS. Finally, it is important to underscore that CSF and plasma Aβ1-42 and Aβ1-40 levels do not correlate,[49] highlighting the influence of the peripheral contribution to the plasma Aβ pool.

Young adults with DS have similar CSF p-tau181 concentrations compared to euploid peers, but levels begin to rise about 15 years before dementia onset, coinciding with amyloid PET SUVTs increases.[7,49] So far, no studies specifically examining other phosphorylated tau isoforms in CSF in DS are available. We anticipate, likewise to ADAD, that increases in p-tau217 and -possibly- p-tau231 will occur around the same time as amyloid PET positivity, with later increases in p-tau205 and, especially, MTBR-243 and non-phosphorylated tau fragments, closely associated with tau PET SUVR increases in late Braak stages and clinical symptoms. However, disease progression after amyloid positivity, with earlier tau PET elevations, may be more compressed in DS compared to ADAD.[25]

Plasma p-tau181 concentrations are significantly higher than in euploid controls around 10–15 years before expected prodromal AD diagnosis. Plasma p-tau181 levels correlate with core CSF biomarkers of AD, cortical thinning, and brain hypometabolism in

AD-related brain regions.[12] Both plasma p-tau181 and p-tau217 can identify symptomatic AD in DS, especially when combined with age, supporting their role for screening and enriching clinical trials.[50]

CSF and plasma t-tau and CSF NfL levels are similar in young adults with DS and young euploid controls, increasing early in the preclinical stage, even before amyloid PET positivity, and continuinng to rise in symptomatic AD, showing good diagnostic performance for detecting symptomatic AD.[49] Plasma NfL levels also have excellent prognostic performance in DS for predicting symptomatic AD and are highly indicative of symptomatic AD.[7,13]

When looking into synaptic dysfunction, SNAP-25 levels increase along the AD continuum, while the dynamics of Ng and VILIP-1 are less clear.[47] Neuronal Pentraxin Receptor 2 (NPTX2) levels, a recent CSF biomarker of inhibitory circuit dysfunction reduced in sporadic AD, are also decreased in CSF of adults with DS across all AD stages, supporting its role as a useful marker of AD-related changes prior to symptom onset.[51] Elevated levels of the presynaptic protein Vesicle-associated membrane protein 2 (VAMP-2) in adults with DS are a potential marker of synapse degeneration correlating with CSF amyloid and axonal degeneration markers and cognitive performance.[52]

Regarding neuroinflammation, although evidence about sTREM2 in DS is scarce, CSF sTREM2 levels are variable without clear differences along the AD continuum.[47] An exploratory study found that young adults with DS had significantly elevated plasma sTREM2 and inflammatory markers compared to age-matched controls,[53] while older adults showed lower levels.[54] These data suggest that, in DS, inflammation is altered since young ages, however as plasma can also reflect peripheral inflammation, more studies are needed confirming the central origin of inflammatory biomarkers in the context of the AD process. GFAP has demonstrated a very large dynamic range in AD in DS. Plasma GFAP levels increase in parallel to CSF Aβ changes, ten years before amyloid PET positivity, and continue to rise in symptomatic AD.[28] Plasma GFAP levels correlate with cortical thinning and brain amyloid pathology and also provide prognostic information.[28] In short, both peripheral and central chronic inflammation may be present across the lifespan of adults with DS, reflecting the predisposition to autoimmune disorders, but unique inflammatory responses to amyloid, tau, and other injuries including cerebrovascular disease may drive disease progression at specific stages of the disease.[55]

Comparison in biomarker findings between genetically determined forms of AD and sporadic AD

Although AD pathology and the sequence of biomarker changes are qualitatively similar in genetically determined AD and sporadic AD, there are subtle differences, such as more frequent cotton wool plaques and early striatal amyloid PET uptake in genetically determined AD compared to sporadic AD. The degree of overlap between clinical presentations, cognitive profiles, and biomarker patterns between genetically determined forms of AD also deserve further investigation. Table 1 summarizes the similarities and differences between the different forms of the disease.

Age at symptom onset in genetically determined forms occurs decades earlier than in sporadic AD, even when compared with early-onset sporadic AD cases, reducing the likelihood of other concurrent age-related co-morbidities. Atypical clinical presentations are more common in early-onset sporadic AD but are rare in genetically determined forms.[56] Conversely, neuropsychiatric symptoms and motor disturbances might be more frequent in genetically determined forms than in late onset sporadic AD.[56,57]

Biological sex differences might affect the clinical phenotype and progression of sporadic and genetic AD. Women may have greater risk for AD, with more tau accumulation, faster hippocampal volume loss and greater metabolic dysfunction.[58,59] Female carriers of PSEN1 E280A tend to perform better on memory tasks initially but experience faster cognitive decline and greater neurodegeneration as the disease progresses.[59,60] In DS, biological sex does not seem to influence clinical and biomarker profiles of AD.[61]

Regarding fluid AD biomarkers, overall, the changes in ADAD and DS are like those in sporadic AD. However, recent evidence suggests that ADAD shows lower CSF Aβ42 levels and higher CSF levels of p-tau181 than other forms of AD but no significant differences in t-tau and other markers of neurodegeneration.[7,56,62,63] Also, the temporal sequence of changes and progression of biomarker patterns are similar in genetically determined AD and sporadic AD but, although there are only a few direct comparisons between ADAD, DS and sporadic-early and late onset- AD,[56,62–65] tau changes in DS may occur closer to amyloid deposition, suggesting a compressed disease timeline.[25,46,66]

DS deserves some additional considerations. Beyond the causal role of the *APP* gene dose effect on AD, trisomy 21 is associated with co-occurring conditions that can affect AD biomarker levels. For example, intellectual disability is one of the most salient features of the syndrome, with interindividual variability. Also, DS is associated with some neurodevelopmental differences in brain anatomy or in the immune response that must be considered when studying the sequence of biomarker changes and especially when comparing the results with euploid individuals. Individuals with DS show smaller hippocampal volumes than euploid individuals, however, importantly, the AD-related hippocampal atrophy occurs around 5–10 years before

Feature	Sporadic AD	ADAD	DS
Age of onset (mean age)	LOAD (80.2) EOAD (54.8)	Depending on the mutation: PSEN1 (43.3) APP (47.6) dAPP (51.5) PSEN2 (58.1)	50.2 (prodromal AD) 53.7 (AD dementia)
Disease duration (average years)	10	11.6	4.6
Most frequent clinical presentation	Episodic memory loss, predominant Atypical presentations in EOAD	Episodic memory loss, predominant	Episodic memory loss, predominant
Other symptoms			
Visuo-perceptual skills impairment	Early stages	Late stages	Early stages
Attention deficits	Present	Very early stages	Early stages
Language deterioration	Present	Present, depending on the mutation	Present (frequently baseline impaired)
Motor symptoms	Less common (more common in EOAD)	32.5% Parkinsonism, tremor, early falls and/or pyramidal signs	More common
Neuropsychiatric symptoms	80%	60%	>80%
Other			Decline in functional skills
Co-existing conditions			
Inflammation	–	–	Chronic inflammatory state
Sleep apnea disease	50%	Not available data	65–100%
Epilepsy	1.5–12.7% Focal seizures with altered level of consciousness	2.8–47% Generalized motor seizures >> focal with impairment of consciousness	41.1–75% LOMEDS: Myoclonus, BTC seizures
Other	–	–	Neurodevelopmental differences Baseline level of intellectual disability
Fluid biomarkers:		Similar order and timing	
Biological staging			
Initial stage biomarkers	↓CSF Aβ42/40 ↑p-tau181/Aβ42 ↑t-tau/Aβ42 and accurate plasma analysis	↓CSF Aβ42/40 ↑p-tau181/Aβ42 ↑t-tau/Aβ42 and accurate plasma analysis	↓CSF Aβ42/40 ↑p-tau181/Aβ42 ↑t-tau/Aβ42 and accurate plasma analysis
Early stage biomarkers	↑CSF p-tau205[a]	↑CSF p-tau205[a]	↑CSF p-tau205[b]
Intermediate stage biomarkers	↑CSF MTBR-243[a]	↑CSF MTBR-243[b]	↑CSF MTBR-243[b]
Advanced stage biomarkers	↑Non phosphorylated tau[a]	↑ Non phosphorylated tau[b]	↑ Non phosphorylated tau[b]
Neuroimaging			
Initial Striatal Aβ deposition	No	Yes	Yes
Aβ deposition map (amyloid PET)	Parieto-temporal, precuneus, posterior cingulate, frontal cortex	Parieto-temporal, precuneus, posterior cingulate, frontal cortex	Parieto-temporal, precuneus, posterior cingulate, frontal cortex
Hypometabolism (FDG-PET)	Parietal, precuneus, posterior cingulate cortex	Parietal, precuneus, posterior cingulate cortex	Parietal, precuneus, posterior cingulate cortex
Atrophy map (MRI)	Posterior dominant cortical thinning with atrophy of hippocampus, thalamus and striatum	Posterior dominant cortical thinning with atrophy of hippocampus, thalamus and striatum (accelerated)	Posterior dominant cortical thinning with atrophy of hippocampus, thalamus and striatum
Tau distribution (Tau PET, histopathology)	Follows Braak staging	Follows Braak staging More tau burden in medial temporal lobe	Follows Braak staging More tau burden in subcortical and medial temporal regions
Other particularities	–	–	Connatal neurodevelopmental abnormalities
Co-pathology			
Cerebral amyloid angiopathy (moderate to severe)	50%	63% (higher in PSEN1 mutations beyond codon 200 and highest in APP duplications)	60%
TDP-43	11% EOAD, 29% LOAD	9%	6%
Lewy body	6–42%	50%	50% of cases with dementia

[a]Validation of p-tau205, MTBR-243 and non-phosphorylated tau as early, intermediate and advanced stage fluid markers respectively is conceptual for now, awaiting further studies. [b]Validation of p-tau205, MTBR-243 and non-phosphorylated tau as early, intermediate and advanced stage fluid markers respectively is conceptual for now, awaiting further studies and, to our knowledge, have not still been tested in this form of AD.

Table 1: **Similarities and differences between sporadic AD, ADAD and DS.**

symptom onset, in accordance with the temporality described in sporadic AD.[6] The earlier decline in renal function in adults with DS might also impact plasma AD biomarker levels.

CAA, defined by the aggregation of Aβ within the walls of leptomeningeal and cortical vessels, is more commonly and severely found in ADAD and DS than in sporadic AD or healthy ageing.[21,67] Consequently, CAA

clinical and neuroimaging features, such as intracerebral haemorrhages, lobar microbleeds and cortical superficial siderosis, are more frequently found in adults with genetically determined AD than in those with early onset sporadic AD and might also affect the biomarker levels.[68,69] CAA has drawn particular importance in the context of clinical trials with anti-amyloid therapies due its relationship with its most important side effect, amyloid-related imaging abnormalities (ARIA). ARIA are closely related to CAA and there are exclusion criteria based on imaging findings of CAA.[70] There is a pressing need to develop biochemical biomarkers able to predict and monitor ARIA as to diagnose CAA. Reduced CSF-Aβ40 levels have been proposed for the diagnosis of sporadic CAA not related with AD, however, in the context of genetic AD, CSF-Aβ40 is not a reliable specific biomarker for CAA.[68,71]

Another differential factor could be neuroinflammation, as DS is its itself a proinflammatory condition because some immunoregulatory genes are coded on chromosome 21, such as those in the chromosome 21 critical region and 3 out of 4 interferon receptors.[72] Consequently, there are dysregulated pathways involved in the immune system that result in chronic inflammation. This particular inflammatory phenotype differs from age-matched neurotypical controls and reflects an increase in pro-inflammatory gene expression,[73] probably leading to significant differences when comparing to sporadic and ADAD forms of AD.

Epilepsy and sleep disorders-mainly sleep apnea disease-are more frequent in ADAD and, especially, DS than in late-onset sporadic AD.[74,75] Whether epilepsy and sleep disruption are causes or consequences (or both, in a feed-forward cycle) of neurodegeneration remains under investigation. While seizures could be the consequence of the pro-epileptogenic effect of Aβ deposition, epilepsy and sleep probably impact AD pathophysiology,[76] as cortical hyperexcitability may increase release of Aβ and tau, and slow wave sleep reduction and sleep fragmentation lead to Aβ aggregation.[76,77] How epilepsy and sleep impact biochemical biomarkers is currently under investigation in genetic forms of dementia.

Finally, the presence of concomitant α-synuclein aggregates is also more frequent in ADAD than in sporadic AD, although it seems to be a late phenomenon in the course of the disease. In DS, α-synuclein aggregates might be found in up to 50% of the cases with dementia.[78]

Recommendations for the use the biomarkers in genetic forms of dementia in clinical practice

The recognition of ADAD and DS as a genetically determined AD from birth has profound implications.[3,4] The use of AD biomarkers as state biomarkers is the most frequent use in the general population as they help identify those individuals with AD pathophysiology from those that do not have it. Stage biomarkers, however, help to determine disease severity. As genetically determined forms of AD have an underlying AD pathophysiology (whether it is detectable by AD biomarkers or not), in this context biomarkers can only be used as stage biomarkers. Within this framework, we discuss potential contexts of use of AD biomarkers in clinical practice or in research settings for genetic forms of dementia (see key messages in Table 2).

The long natural history of AD, in which biomarker change occur in a predictable sequence, offers unique opportunities to stage disease severity. AD biomarkers will need different tailored cut-off points deepening to the context of use. Thus, a precise understanding of the positive predictive value (PPV) and negative predictive value (NPV) of each biomarker in their context of use is essential for optimizing the biomarker interpretation. PPV refers to the probability that individuals with a positive biomarker have the neuropathological hallmark it is meant to identify; while NPV-more relevant in genetic forms of AD-denotes the likelihood that subjects with a negative biomarker do not have the pathology. These values, however, are not static, they are affected by the prevalence of the disease or the prevalence of a stage for a given age-range in our context. This dynamic interplay underscores the need for age-specific or even stage-specific interpretation of biomarker results, setting the rationale for optimizing biomarker cut-off points, depending on what we aim to accomplish with the biomarker. The use of various cut-off points provides more nuanced information about the natural history of AD beyond the oversimplified dichotomization. As mentioned, the clinical use of AD biomarkers in genetic forms of dementia should focus first on the NPV of these biomarkers. Negative amyloid biomarkers, for instance, discard the possibility that the symptoms of an individual carrying a pathogenic mutation in *PSEN1*, *PSEN2*, or *APP*, or trisomy 21, should be attributed to AD. Cognitive and behavioural symptoms might be caused by other factors (e.g., depression or hypothyroidism) that do not affect AD biomarker levels. Then, the use of stage biomarkers with appropriate thresholds could provide acceptable PPV that enhance our diagnostic certainty. A given biomarker can have different threshold depending on our purposes. For instance, the threshold for p-tau217 to detect amyloid positivity will probably be different and lower than that to diagnose AD dementia. NfL has a very high diagnostic performance for the clinical diagnosis of symptomatic AD in DS and ADAD.[13,31,44] This probably stems from its dynamic range, that continues to increase non-linearly in the symptomatic stages of the disease, enabling higher thresholds that better differentiate asymptomatic from symptomatic individuals.[79] Of note, the usefulness of NfL might be higher in genetically determined AD

than sporadic AD. Not only it is showing higher fold-changes, but also because of the rarity of other neurodegenerative conditions that increase NfL levels at these young ages.

A second use of biomarkers that could be implemented in clinical practice is prognosis. Health plans recommend variable frequency of assessments in individuals with DS based on the age as a proxy for predicted distance from symptom onset at the individual level.[80] Biomarkers could personalize these plans according to the biomarker profile, facilitating early and personalized care and identifying critical windows for intervention that could, potentially, delay the onset of the disease.

The third use in research, or advanced clinical use, would be in clinical trials. Biomarkers are essential to stage AD, enabling not only the determination of the disease severity and estimating prognosis, but also establishing the eligibility of participants for primary or secondary prevention trials. Also, fluid biomarkers will be paramount in evaluating target engagement and the biological effect of drugs and treatment response or even guiding therapeutic decisions. Depending on the predicted biological pathways targeted by the different drugs, different biomarkers could be of interest. Again, the understanding of biomarkers changes over time in relation to disease progression and treatment efficacy, could guide the design of preventive clinical trials including tailored therapies, optimizing outcomes, and minimizing adverse effects.

Outstanding questions

The integration of biomarkers into clinical practice for individuals with ADAD and DS holds a promise in personalized medicine. However, the transition from research to clinical practice is challenging, particularly in establishing precise and meaningful cut-offs for biomarker levels. The complexity of AD, viewed as a continuum rather than a binary state, underscores the importance of establishing variable thresholds for different stages of the disease. These thresholds are critical for distinguishing not only between normal and pathological states, but for characterizing and staging the severity of the disease. The use of biomarkers with different thresholds extends beyond the selection of arbitrary values (Fig. 2).

The development of age-dependent biomarker cut-offs and the identification of the factors that affect biomarker levels will require extensive clinical and epidemiological data and sophisticated statistical modelling. Such approach would not only refine the diagnostic process but also pave the way for personalized medicine, where biomarker interpretation is finely tuned to the individual's demographics and co-occurring conditions. The use of biomarkers in this context will maximize the clinical utility and enabling an accurate individual diagnosis and prognosis. Currently, the lack of defined thresholds and a nuanced interpretation of biomarker results hamper the application of these tools in clinical settings for ADAD and DS.

AD biomarkers are increasingly used in clinical practice in ADAD and DS, but more work is needed to refine the use of biomarkers in a more personalized medicine approach. This involves not only the scientific determination of cut-offs through empirical research but also the consideration of how these thresholds can be applied in a clinical context to provide meaningful, actionable information to healthcare providers and patients. Addressing this gap is essential for advancing the use of biomarkers in the personalized management of AD, particularly in populations with genetically determined AD.

From a research perspective, genetic forms of AD are the best populations in which to investigate the dynamics of any biomarker in the AD continuum. However, for individuals with these genetic forms, the most important research use is in the context of clinical trials: for patient selection (e.g., primary vs. secondary prevention), target engagement, disease monitoring, endpoints of efficacy, but also safety.

In conclusion, the future of AD management, particularly for its genetically determined forms, is intricately linked to the advancement in biomarker research. The potential to improve diagnostic and prognosis accuracy enable early intervention, and tailor treatments to individual genetic makeups highlights the importance of continued investment in this area. As we move forward, a multidisciplinary approach that combines genetic, biochemical, and computational sciences will be paramount in harnessing the full potential of biomarkers in transforming AD management and patient medical care.

ADAD and DS are genetically determined forms of AD. In these populations, AD biomarkers can be used with staging purposes, instead of diagnosis, as individuals with ADAD or DS are part of the AD continuum since birth.
The predictability in the order and temporality of biomarker alterations during the AD continuum renders genetically determined forms of AD an excellent population for investigating—specially- the preclinical stages of the disease.
In genetically determined forms of AD, biomarkers become abnormal in a predictive order along age. In this context, different tailored cut-off points according to what process or stage they are aimed to track instead of a binary categorization would enable a more accurate estimation of the stage of the disease.
AD biomarker's negative predictive value is useful for discarding the possibility that symptoms in an individual carrying a pathogenic mutation in PSEN1, PSEN2, APP or trisomy 21 should be attributable to AD.
AD biomarkers could be implemented as prognostic tools that could personalize health plans facilitating early and personalized care and identifying critical windows for intervention.
Staging AD through biomarkers can enable the measure of disease severity, estimate prognosis, determine eligibility for clinical trials and guide clinical care.
A deeper knowledge on the fluid biomarker dynamics will improve diagnostic and prognosis accuracy and will facilitate early intervention and tailored treatments to individual genetic makeups.

Table 2: **Key Messages Panel.**

Search strategy and selection criteria

We searched PubMed for research studies published since database inception until Dec 2023. All relevant articles relating to autosomal dominant or familial Alzheimer disease (AD) and AD in individuals with Down syndrome (DS) were identified for consideration. Search terms include: ("autosomal dominant Alzheimer disease" OR "autosomal dominant Alzheimer's disease" OR "familial Alzheimer disease" OR "familial Alzheimer's disease") AND biomarkers on one hand and ("Down syndrome" OR "Down's syndrome" OR Downs) AND (Alzheimer OR Alzheimer's OR dementia) AND biomarkers on the other hand. Additional search terms for specific sections were considered. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Contributors

MCI, JF and RSV devised the paper and invited the other authors to provide parts of the text according to their expertise. MCI and RSV collated and edited the contributions and did additional literature searches. MCI, PL, JLG, AOC, JF, and RSV contributed to parts of the paper, reviewed the full paper, and gave final approval.

Declaration of interests

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