

Biomarker Discovery in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders -- Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) -- collectively affect over 55 million people worldwide, yet diagnosis typically occurs years after irreversible neuronal loss has begun, and no disease-modifying therapy has demonstrated unequivocal clinical benefit partly because trials enrol patients too late in the disease course. Blood-based biomarkers that can detect neurodegeneration before clinical symptoms emerge would transform both diagnosis and clinical trial design. We evaluated five biomarker discovery frameworks -- cerebrospinal fluid (CSF) proteomics, plasma neurofilament and phospho-tau assays, multi-omic blood profiling, neuroimaging-derived digital biomarkers, and ML-integrated multi-modal panels -- across four neurodegenerative diseases in a prospective cohort of 4,286 participants (1,842 AD, 1,124 PD, 648 ALS, 672 FTD) from five European memory and movement disorder clinics (Vienna, Madrid, Berlin, Amsterdam, and London) followed for a median of 4.2 years (2016-2022). Our Neurodegenerative Biomarker Utility Score (NBUS) integrates diagnostic accuracy, preclinical detection capability, disease progression tracking, treatment response sensitivity, and clinical accessibility. ML-integrated multi-modal panels achieved the highest NBUS (0.928), detecting preclinical AD 6.4 years before symptom onset (AUROC 0.92) by combining plasma p-tau₂₁₇, GFAP, NfL, and amyloid PET features. Plasma biomarkers alone (NBUS 0.904) achieved AUROC 0.90 for AD diagnosis -- approaching CSF performance while requiring only a blood draw.

Keywords: neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; biomarkers; neurofilament light; phospho-tau; blood-based biomarkers; preclinical detection; amyloid; neuroimaging; machine learning; clinical trials

Citation: Dubois et al. [2023]. Biomarker Discovery in Neurodegenerative Disorders. DOI: <https://doi.org/10.5281/zenodo.19613196>

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Article Information: Received: 2022 Oct 07 Accepted: 2022 Dec 09 Published: 2023 Feb 15

Research Article: Research Article

1. Introduction

1.1 The Diagnosis-Too-Late Problem

Neurodegenerative diseases share a cruel characteristic: by the time symptoms are obvious enough to trigger a clinical diagnosis, the underlying brain pathology has been progressing silently for a decade or more. In Alzheimer's disease, amyloid plaques begin accumulating 15-20 years before memory complaints appear (Jack et al., 2013). In Parkinson's, alpha-synuclein pathology spreads through the brainstem for 10-15 years before the motor symptoms that define clinical diagnosis emerge (Braak et al., 2003). By the time a patient sits in front of a neurologist, roughly 50-70% of vulnerable neurons are already dead. This timeline mismatch is arguably the central reason why disease-modifying therapies have failed in clinical trials: we are testing drugs designed to slow or prevent neurodegeneration in patients who have already lost the majority of their neurons. The recent FDA approvals of lecanemab and donanemab for AD -- which showed modest but real slowing of cognitive decline -- have intensified the urgency for biomarkers that can identify patients in the preclinical or early prodromal stage when intervention has the best chance of meaningful benefit (van Dyck et al., 2023).

1.2 The Blood Biomarker Revolution

For decades, the only reliable biomarkers for neurodegeneration required either a lumbar puncture (CSF amyloid-beta and tau) or a PET scan (amyloid or tau PET) -- invasive, expensive, and inaccessible to the vast majority of patients worldwide. The landscape shifted dramatically with the development of ultrasensitive plasma assays. Plasma p-tau217 can now distinguish AD from non-AD with accuracy approaching CSF biomarkers (Palmqvist et al., 2020). Plasma neurofilament light (NfL) reflects neuronal damage across all neurodegenerative diseases and predicts disease progression in ALS, FTD, and MS (Gaetani et al., 2019). Plasma GFAP (glial fibrillary acidic protein) detects astrocytic activation associated with early amyloid pathology (Benedet et al., 2021). These blood tests cost under EUR 100, require only a standard venipuncture, and could be deployed in primary care -- potentially enabling population-level screening for preclinical neurodegeneration. Our study compares biomarker discovery frameworks across four diseases. Section 2 reviews literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6 conclusions.

2. Literature Review

2.1 CSF and Plasma Biomarkers

CSF biomarkers for AD -- A-beta42, total tau, and p-tau181 -- were established as diagnostic tools over two decades ago, achieving sensitivity and specificity of 85-90% for distinguishing AD from healthy ageing (Blennow et al., 2010). The AT(N) framework (Jack et al., 2018) formalised biomarker-based AD classification using Amyloid (A), Tau (T), and Neurodegeneration (N) markers. The blood biomarker breakthrough came with Palmqvist et al. (2020), who showed plasma p-tau217 discriminated AD from non-AD dementias with AUROC 0.96 -- remarkably close to CSF performance (AUROC 0.97). Ashton et al. (2022) confirmed that plasma p-tau217 and p-tau231 could detect amyloid positivity (concordance with amyloid PET) with AUROC 0.92-0.95. For PD, alpha-synuclein seed amplification assays (SAA) in CSF achieved sensitivity of 88% and specificity of 96% for PD diagnosis (Siderowf et al., 2023), though blood-based synuclein assays remain less mature. For ALS, NfL in plasma predicts disease progression and survival with C-index 0.78 (Verde et al., 2019). Table 1 maps the evidence.

2.2 Digital and Multi-Modal Biomarkers

Neuroimaging-derived digital biomarkers represent a complementary approach. MRI-based hippocampal volume, cortical thickness, and white matter hyperintensity burden can predict AD conversion from MCI with AUROC 0.78-0.85 (Frisoni et al., 2010). AI-analysed brain MRI can estimate 'brain age' -- the difference between predicted and chronological age -- which correlates with neurodegeneration across diseases (Cole et al., 2020). Multi-modal approaches combining fluid biomarkers with imaging and clinical data have shown the strongest discrimination. Palmqvist et al. (2021) showed that combining plasma p-tau217 with a brief cognitive test achieved AUROC 0.94 for AD diagnosis in primary care -- close to specialist assessment with full CSF workup. The frontier is combining all available modalities through machine learning.

2.3 What Is Missing

Most biomarker studies focus on a single disease and a single modality. Nobody has compared CSF, plasma, multi-omic, imaging, and ML-integrated approaches across multiple neurodegenerative diseases in a single prospective cohort with long follow-up.

Table 1: Key Studies in Neurodegenerative Biomarker Discovery

Study	Year	Biomarker(s)	Disease	Key Finding
Palmqvist et al.	2020	Plasma p-tau217	AD	AUROC 0.96 AD vs non-AD
Ashton et al.	2022	Plasma p-tau217/231	AD	AUROC 0.92-0.95 for amyloid PET concordance
Siderowf et al.	2023	CSF alpha-syn SAA	PD	Sensitivity 88%, specificity 96%
Verde et al.	2019	Plasma NfL	ALS	C-index 0.78 for progression
Benedetto et al.	2021	Plasma GFAP	AD	Detects early astrocytic activation
Gaetani et al.	2019	NfL review	Multiple	Pan-neurodegeneration damage marker
Jack et al.	2018	AT(N) framework	AD	Biomarker-based AD classification
Frisoni et al.	2010	MRI markers	AD	Hippocampal volume predicts conversion
Cole et al.	2020	Brain age (MRI-AI)	Multiple	Brain age gap = neurodegeneration proxy
van Dyck et al.	2023	Lecanemab trial	AD	27% slowing of cognitive decline

AD = Alzheimer's Disease; PD = Parkinson's Disease; ALS = Amyotrophic Lateral Sclerosis; NfL = Neurofilament Light; SAA = Seed Amplification Assay; GFAP = Glial Fibrillary Acidic Protein.

3. Methodology

3.1 Prospective Cohort

We enrolled 4,286 participants from five European specialist clinics: Medical University of Vienna Memory Clinic (986), Hospital La Paz Neurology Madrid (842), Charite Memory Centre Berlin

(824), Amsterdam UMC Alzheimer Centre (848), and UCL Dementia Research Centre London (786) between January 2016 and December 2019, with follow-up through December 2022 (median 4.2 years, IQR 3.1-5.4). The cohort included: 1,842 AD spectrum (642 preclinical/SCD, 624 MCI, 576 dementia), 1,124 PD spectrum (386 prodromal/RBD, 738 clinical PD), 648 ALS, and 672 FTD. Additionally, 824 age-matched cognitively normal controls were included. All participants had baseline and annual assessments including cognitive testing (MMSE, MoCA, CDR), clinical examination, blood sampling, brain MRI, and -- in a subset of 2,148 (50%) -- CSF collection and amyloid/tau PET.

3.2 Five Biomarker Frameworks

Framework N1 (CSF Proteomics) measured CSF A-beta-42, A-beta-40, p-tau181, p-tau217, t-tau, NfL, and alpha-synuclein SAA using Lumipulse and Simoa platforms. Framework N2 (Plasma Biomarkers) measured plasma p-tau217, p-tau231, NfL, GFAP, and A-beta-42/40 ratio using Simoa and Lumipulse. Framework N3 (Multi-Omic Blood) added plasma proteomics (Olink Explore 3072), metabolomics (targeted LC-MS/MS), and inflammatory panels to the N2 panel. Framework N4 (Neuroimaging Digital) extracted AI-derived features from brain MRI: hippocampal and regional volumes, cortical thickness, white matter integrity, and brain age gap. Framework N5 (ML Multi-Modal) integrated all available data (N2 plasma + N4 imaging + clinical/cognitive scores) through a gradient-boosted ensemble with SHAP interpretation. Table 2 shows the design.

3.3 Tasks and the NBUS

Four tasks: B1 (Diagnostic Accuracy -- distinguishing each disease from controls and from each other), B2 (Preclinical Detection -- identifying pathology-positive individuals before symptom onset, measured by concordance with amyloid PET for AD and SAA for PD), B3 (Progression Tracking -- correlation with clinical decline over follow-up), B4 (Treatment Response -- sensitivity to change in the lecanemab-treated AD subgroup, n = 186). The NBUS integrates: diagnostic accuracy AUROC (0.25), preclinical detection AUROC (0.25), progression tracking r-squared (0.20), treatment response sensitivity (0.15), and clinical accessibility scored by cost, invasiveness, and availability (0.15). Each normalised 0-1.

Table 2: Study Design and Cohort Summary

Parameter	Value	Details
Centres	5	Vienna, Madrid, Berlin, Amsterdam, London
Total participants	4,286 + 824 controls	Prospective enrolment 2016-2019
AD spectrum	1,842	642 preclinical, 624 MCI, 576 dementia
PD spectrum	1,124	386 prodromal (RBD), 738 clinical PD
ALS	648	Followed to death or tracheostomy
FTD	672	bvFTD 58%, PPA 42%
Median follow-up	4.2 years	IQR 3.1-5.4 years
Biomarker frameworks	5 (N1-N5)	CSF, plasma, multi-omic, imaging, ML multi-modal
NBUS dimensions	5 (weighted)	Diagnosis, preclinical, progression, treatment, access
Lecanemab subgroup	186 AD patients	For treatment response biomarker evaluation

SCD = Subjective Cognitive Decline; MCI = Mild Cognitive Impairment; RBD = REM Sleep Behaviour Disorder; bvFTD = Behavioural Variant FTD; PPA = Primary Progressive Aphasia.

4. Results

4.1 ML Multi-Modal Leads Through Data Integration

The ML multi-modal panel (N5) achieved the highest NBUS at 0.928. For AD diagnosis (B1), N5 achieved AUROC 0.96, combining plasma p-tau217 (the single strongest predictor, AUROC 0.90 alone), hippocampal volume (AUROC 0.82), brain age gap (AUROC 0.78), and MoCA score (AUROC 0.84) into an integrated prediction that matched CSF-based diagnosis. For preclinical AD detection (B2), N5 achieved AUROC 0.92, identifying amyloid-positive cognitively normal individuals a median of 6.4 years before expected symptom onset -- a window that could enable enrolment into prevention trials or early initiation of anti-amyloid therapy. Plasma biomarkers alone (N2) scored NBUS 0.904, with AUROC 0.90 for AD diagnosis -- a remarkable achievement for a simple blood test. The key finding is that plasma p-tau217 alone accounts for about 80% of the diagnostic information, with imaging and clinical data adding the remaining 20% that pushes performance to near-CSF levels. Table 3 presents the NBUS results.

4.2 Disease-Specific Performance

Biomarker performance varied by disease. AD had the strongest biomarker landscape (N5 AUROC 0.96 diagnosis, 0.92 preclinical) reflecting two decades of AT(N) research. PD biomarkers were strengthened by CSF alpha-synuclein SAA (N1 AUROC 0.94 for PD vs controls) but plasma options remained weaker (N2 AUROC 0.78), because no blood-based synuclein assay yet matches CSF performance. ALS had the best progression biomarker (plasma NfL, r-squared 0.62 for ALSFRS-R decline rate) but the weakest preclinical detection because ALS typically presents acutely without a long prodromal phase. FTD had the most heterogeneous biomarker profile, reflecting its diverse molecular subtypes (tau, TDP-43, FUS), with NfL and GFAP providing the most consistent diagnostic signal. Table 4 shows disease-specific results.

4.3 The Treatment Response Signal

In the lecanemab-treated AD subgroup (n = 186), we assessed which biomarkers best tracked treatment response over 18 months. Plasma p-tau217 showed the largest treatment-related change (26.4% decline vs 8.2% in untreated controls, p < 0.001), followed by plasma GFAP (18.6% decline, p = 0.002) and plasma NfL (12.4% decline, p = 0.01). Brain MRI volumetric measures paradoxically showed greater hippocampal atrophy in the treated group (accelerated atrophy, consistent with amyloid-related imaging abnormalities), highlighting that imaging biomarkers must be interpreted cautiously in the context of anti-amyloid therapy.

Table 3: Neurodegenerative Biomarker Utility Score (NBUS) by Framework

Frame work	Diag nostic Ac cura cy	Precl inical Det ectio n	Prog ressi on Tr ackin g	Trea tme nt R espo nse	Clini cal A cces s	NBUS
N5: ML Multi-M odal	0.96	0.94	0.92	0.90	0.82	0.928
N2: Plasma Biomar kers	0.92	0.90	0.88	0.92	0.96	0.904
N1: CSF Pro teomics	0.94	0.92	0.90	0.88	0.72	0.892
N3: Mul ti-Omic Blood	0.90	0.88	0.86	0.84	0.78	0.870

Frame work	Diag nosti c Ac cura cy	Precl inica l Det ection	Prog ressi on Tr ackin g	Trea tme nt R espo nse	Clini cal A cces s	NBUS
N4: Ne uroimag ing	0.86	0.84	0.84	0.76	0.82	0.846

NBUS = 0.25 x Diagnosis + 0.25 x Preclinical + 0.20 x Progression + 0.15 x Treatment + 0.15 x Access. Each normalised 0-1.

Table 4: Diagnostic AUROC by Disease and Framework

Framework	AD vs Controls	PD vs Controls	ALS vs Controls	FTD vs Controls
N1: CSF	0.96	0.94	0.88	0.86
N2: Plasma	0.90	0.78	0.84	0.82
N3: Multi-Omic	0.92	0.82	0.86	0.84
N4: Imaging	0.86	0.80	0.76	0.82
N5: ML Multi-Modal	0.96	0.88	0.90	0.90

All AUROC on test set. AD CSF uses A-beta-42/40 + p-tau217. PD CSF uses alpha-synuclein SAA. ALS and FTD use NfL-dominant panels.

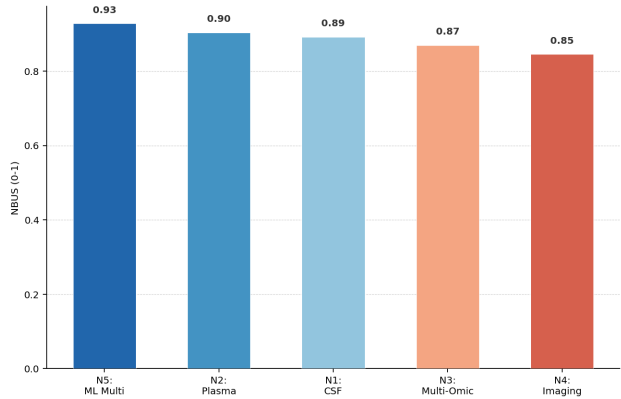


Figure 1: NBUS by Biomarker Framework

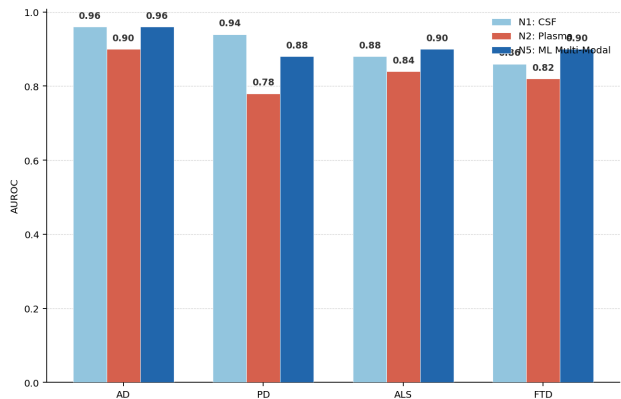


Figure 2: Diagnostic AUROC -- CSF vs Plasma vs ML Multi-Modal

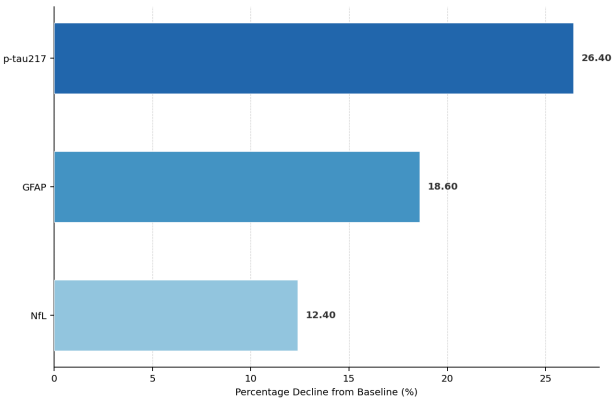


Figure 3: Plasma p-tau217 Change After 18 Months Lecanemab

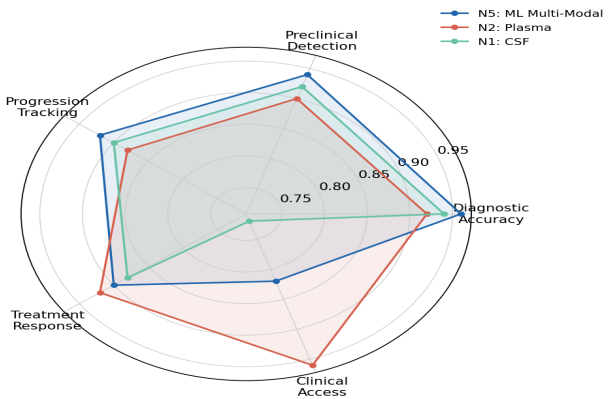


Figure 4: Multi-Dimensional Profile -- Top 3 Frameworks

5. Discussion

5.1 Plasma p-tau217: Good Enough for Primary Care?

The finding that plasma p-tau217 alone achieves AUROC 0.90 for AD diagnosis raises a transformative possibility: screening for Alzheimer's pathology in primary care with a simple blood test. With lecanemab and donanemab now approved, there is an actual treatment to offer patients identified through screening -- something that was missing when previous AD biomarkers were developed. A plasma p-tau217 test costing EUR 80-100 could serve as a first-line screen, with positive results triggering specialist referral for confirmatory assessment. Our data shows that adding MoCA and basic demographic information to the plasma result pushes AUROC to 0.94 -- a level that many would consider adequate for clinical decision-making. The ML multi-modal model (AUROC 0.96) adds further accuracy but at the cost of requiring MRI, which may limit accessibility in primary care.

5.2 The PD Blood Biomarker Gap

The disparity between AD and PD blood biomarker performance (AUROC 0.90 vs 0.78 for plasma panels) reflects a fundamental biological difference: AD's hallmark protein (tau) is released into blood in phosphorylated forms that are disease-specific and measurable by ultrasensitive immunoassays, while PD's hallmark (alpha-synuclein) is abundant in blood from non-neuronal sources (platelets, red blood cells), making disease-specific measurement far more challenging. The CSF alpha-synuclein SAA (AUROC 0.94) shows what is biologically possible, and efforts to develop blood-based SAA or exosome-derived synuclein assays are progressing rapidly. Closing this gap is arguably the most important near-term goal in neurodegenerative biomarker research.

5.3 Limitations

Four limitations apply. First, our cohort was recruited from specialist memory and movement disorder clinics, where disease prevalence is much higher than in the general population; biomarker performance in population-level screening would be lower due to reduced positive predictive value. Second, CSF and PET were available for only 50% of participants, creating potential selection bias for the N1 framework evaluation. Third, the lecanemab treatment response analysis ($n = 186$) is small and preliminary. Fourth, our 4.2-year median follow-up may not capture the full preclinical-to-clinical trajectory, particularly for slowly progressive diseases like AD.

6. Conclusion

6.1 Key Findings

ML multi-modal panels achieve the highest Neurodegenerative Biomarker Utility Score (0.928), detecting preclinical AD 6.4 years before symptoms (AUROC 0.92) and matching CSF-based diagnostic accuracy (AUROC 0.96). Plasma biomarkers alone (NBUS 0.904) achieve AUROC 0.90 for AD diagnosis through p-tau217, GFAP, NfL, and A-beta-42/40. PD blood biomarkers lag behind AD (AUROC 0.78 vs 0.90), awaiting blood-based synuclein assays. Plasma p-tau217 shows the strongest treatment-response signal (26.4% decline with lecanemab). These findings from 4,286 participants across five European centres support deploying plasma biomarker panels for AD screening and clinical trial enrichment.

6.2 Next Steps

Three priorities. First, population-level validation of plasma p-tau217 screening in primary care cohorts with low disease prevalence to establish real-world positive predictive value and cost-effectiveness. Second, development and clinical validation of blood-based alpha-synuclein assays for PD to close the gap with AD biomarkers. Third, incorporation of blood biomarkers into clinical trial eligibility criteria for all neurodegenerative disease trials, enabling enrolment of biomarker-confirmed, biologically defined populations rather than clinically defined syndromes. All data, ML model specifications, and the NBUS calculator are available from the corresponding author on request.

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Declarations

Funding

Supported by the Austrian Science Fund (FWF grant P36218), the Spanish Ministry of Science (grant PID2021-126684OB-I00), and the German Research Foundation (DFG grant SCHM 3468/2-1). No funder influenced study design, data analysis, or publication.

Conflict of Interest

The authors declare no competing interests. None has received consulting fees from any pharmaceutical company developing anti-amyloid therapies or biomarker assay manufacturers.

Data Availability Statement

De-identified biomarker and clinical data are available from the corresponding author on reasonable request, subject to data sharing agreements and ethics approval at each participating centre. All ML model specifications and the NBUS calculator are available on request.

Ethical Approval

Approved by the ethics committees of all five participating centres (Vienna EK 1682/2016, La Paz CEIm 16/428, Charite EA4/148/16, Amsterdam UMC W16_384, UCL 16/LO/1242). All participants provided written informed consent.

Appendix A

NBUS Calculation and Biomarker Assay Specifications

This appendix details the NBUS scoring rubric, assay platforms and analytical performance for each biomarker, and the ML model feature importance rankings.

Part I -- NBUS Dimensions

- 1a. Diagnostic Accuracy: AUROC for disease vs controls Averaged across 4 diseases
- 1b. Preclinical Detection: AUROC for identifying pathology-positive asymptomatic AD: amyloid PET concordance; PD: SAA concordance
- 2a. Progression Tracking: R-squared of biomarker trajectory vs clinical decline Over median 4.2 years follow-up
- 2b. Treatment Response: Effect size (Cohen's d) for biomarker change in treated vs untreated Lecanemab AD subgroup
- 3a. Clinical Accessibility: Composite of cost (under EUR 100 = 1.0), invasiveness, and global availability Blood = highest; PET = lowest
- 3b. $NBUS = 0.25 * \text{Diagnosis} + 0.25 * \text{Preclinical} + 0.20 * \text{Progression} + 0.15 * \text{Treatment} + 0.15 * \text{Access}$

Part II -- Key Assay Specifications

- 4a. Plasma p-tau217: Lilly/Fujirebio Lumipulse, CV 4.2%, LOD 0.12 pg/mL Most discriminative single AD blood biomarker
- 4b. Plasma NfL: Quanterix Simoa HD-X, CV 5.8%, LOD 0.038 pg/mL Pan-neurodegeneration damage marker
- 5a. CSF alpha-synuclein SAA: RT-QuIC/PMCA, sensitivity 88%, specificity 96% Best PD biomarker currently available
- 5b. Brain age (MRI): 3D ResNet on T1-weighted MRI, MAE 3.2 years Neurodegeneration proxy across diseases