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Editorial

Emerging Biomarkers and Approaches in Neurodegenerative Diseases

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Historically, neurodegenerative diseases (NDD) diagnosis relied heavily on clinical phenotyping and postmortem confirmation. The introduction of cerebrospinal fluid (CSF) biomarkers for AD—specifically amyloid-β (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau)—marked a pivotal transition toward biological definitions of disease. The 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework formalized this shift through the AT(N) classification system, categorizing AD based on amyloid (A), tau (T), and neurodegeneration (N) biomarkers rather than clinical presentation alone [1].

Recent advances extend beyond CSF. Blood-based biomarkers, particularly plasma p-tau isoforms (p-tau181, p-tau217, p-tau231), have demonstrated high diagnostic accuracy for AD pathology and strong correlation with amyloid positron emission tomography (PET) findings [2,3].

These minimally invasive assays hold promise for large-scale screening, early detection, and monitoring therapeutic response. Similarly, neurofilament light chain (NfL), a marker of axonal injury, has emerged as a transdiagnostic biomarker across AD, PD, ALS, and multiple sclerosis, reflecting disease intensity and progression [4].

In PD, α-synuclein remains central to biomarker development. Seed amplification assays (SAAs), such as real-time quaking-induced conversion (RT-QuIC), enable detection of misfolded α- synuclein aggregates in CSF and peripheral tissues with high sensitivity and specificity [5].

These assays are transforming early and prodromal PD diagnostics, including in individuals with REM sleep behavior disorder. For ALS and FTD, genetic biomarkers have become particularly relevant.

Hexanucleotide repeat expansions in C9orf72 represent the most common genetic cause of familial ALS and FTD [6].

The heterogeneity of neurodegenerative diseases poses a major obstacle to therapeutic success.

Patients with identical clinical diagnoses often exhibit distinct molecular drivers, rates of progression, and treatment responses.

Biomarkers offer a solution by enabling biological stratification. In AD, actually, the distinction between amyloid-positive and amyloid-negative mild cognitive impairment (MCI) patients is critical for enrollment in anti-amyloid therapeutic trials. The recent development and regulatory approval of monoclonal antibodies targeting amyloid plaques underscore the necessity of biomarker confirmation prior to treatment initiation [7].

Methodologically, reproducibility across laboratories, cross-ancestry genetics, and harmonized digital biomarkers remain under-built bridges; theoretically, the field still lacks a unifying systems model capable of weaving mitochondrial failure, α-syn misfolding, and neuroimmune crosstalk into one dynamic storyboard. Yet opportunity abounds [8].

In ALS, elevated serum and CSF NfL levels correlate with disease progression and survival, enabling prognostic stratification. Such markers are increasingly used as pharmacodynamic endpoints in clinical trials, potentially shortening trial duration and improving efficiency. Reliable biomarkers for amyotrophic lateral sclerosis (ALS) are urgently needed due to diagnostic and prognostic challenges. Neurofilament light chain (NfL) consistently demonstrated the highest diagnostic accuracy and high prognostic value in both blood and CSF. CSF chitinases and the p-tau/ t-tau ratio showed moderate utility. Other biomarkers, including interleukins, had limited clinical relevance [9].

Genomics, multi-omics, and systems approaches are reshaping personalized neurology. Genome- wide association studies (GWAS) have identified numerous risk loci for AD, including APOE ε4, TREM2, and CLU, highlighting pathways related to lipid metabolism and neuroinflammation [10].

The recognition of immune-related mechanisms in AD has shifted therapeutic strategies toward modulation of microglial function. In PD, mutations in LRRK2, GBA, and SNCA define genetically distinct subtypes with differential clinical features and potential responsiveness to targeted therapies. LRRK2 kinase inhibitors and GBA-directed treatments exemplify genotype-guided therapeutic development [11].

By integrating imaging, fluid biomarkers, genomics, and digital phenotyping data, predictive models can identify high-risk individuals and forecast disease trajectories. These approaches are particularly promising in preclinical stages, where intervention may be most effective. Digital and remote biomarkers: An emerging frontier in personalized neurology is digital biomarker development. Wearable sensors, smartphone-based cognitive testing, and passive monitoring technologies capture real-world motor and cognitive data continuously. In PD, wearable devices can quantify tremor amplitude, gait variability, and bradykinesia, offering objective measures beyond clinic-based assessments [12].

While biomarker-driven precision medicine offers transformative potential, it also raises ethical and logistical challenges. Early detection in asymptomatic individuals necessitates careful counseling, particularly in conditions without definitive cures. Genetic testing introduces implications for family members and requires robust ethical frameworks. Standardization and accessibility remain critical hurdles. Inter-laboratory variability in biomarker assays can limit reproducibility. International consortia and harmonization initiatives are essential to ensure reliability across clinical settings. Moreover, equitable access to advanced diagnostics must be prioritized to prevent widening healthcare disparities [13].

Surgical approaches in neurodegenerative diseases play a limited but important role in the management of selected neurodegenerative diseases, primarily for symptomatic control rather than disease modification. The most established intervention is deep brain stimulation (DBS), particularly in Parkinson's disease (PD). DBS of the subthalamic nucleus (STN) or globus pallidus interna (GPi) significantly improves motor symptoms, reduces motor fluctuations, and decreases medication requirements in advanced PD patients refractory to medical therapy [14,15].

While biologically promising, clinical outcomes have been variable, and these approaches are not yet standard practice [16].

For the future, the convergence of molecular biomarkers, genetic insights, and digital technologies is redefining neurodegenerative disease management. Biomarkers are shifting the field from symptomatic classification to pathophysiological precision, enabling earlier diagnosis, targeted therapy, and dynamic monitoring. To fully realize this vision, interdisciplinary collaboration among clinicians, neuroscientists, bioinformaticians, and ethicists is imperative. Investment in longitudinal cohort studies and diverse populations will enhance generalizability and equity.

Ultimately, the integration of emerging biomarkers into personalized therapeutic algorithms heralds a new era to identified earlier, treated more effectively, and understood more deeply at the molecular level.

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