



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Recent Advances in Biomarkers for Early Diagnosis and Therapeutic Monitoring of Neurodegenerative Diseases: A Systematic Review

Archana Jorige, Kavitha Marati*

RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad-500027, Telangana, India

ARTICLE INFO

Published: 06 Oct 2026

Keywords:

Alzheimer's disease;
Amyotrophic lateral
sclerosis; Biomarkers;
Huntington's disease;
Parkinson's disease;
Neurofilament light chain;
Phosphorylated tau; α -
Synuclein.

DOI:

10.5281/zenodo.23202491

ABSTRACT

Neurodegenerative diseases are characterised by progressive neuronal dysfunction and loss, but clinically recognisable symptoms often emerge after substantial pathological change has occurred. Biomarkers can therefore complement clinical assessment by providing measurable evidence of pathogenic processes, disease activity, prognosis, target engagement, or treatment response. This narrative review synthesises established and emerging biomarkers across Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), with emphasis on early diagnosis and therapeutic monitoring. The review considers genomic, transcriptomic, proteomic, metabolomic, imaging, electrophysiological and fluid biomarkers, and distinguishes diagnostic, prognostic, monitoring and pharmacodynamic contexts of use. In AD, amyloid- β , phosphorylated tau and neurodegeneration biomarkers have evolved into a biologically anchored framework, while plasma phosphorylated tau—particularly p-tau217—has substantially improved the feasibility of minimally invasive biomarker assessment. In PD, α -synuclein seed amplification assays have strengthened the prospect of molecular diagnosis of synucleinopathy. In HD, CAG-repeat genotyping establishes inherited risk, whereas neurofilament light chain and mutant huntingtin are being developed for disease staging, prognosis and pharmacodynamic assessment. In ALS, neurofilaments are among the most consistently supported fluid biomarkers, with particular value for prognosis and treatment-response assessment. Across disorders, however, analytical variability, pre-analytical factors, comorbidity, biological heterogeneity, lack of universally accepted cut-offs, and incomplete qualification for specific clinical uses remain important barriers. Future progress will depend on standardised assays, longitudinal validation, multimodal biomarker panels and fit-for-purpose qualification within clinical trials and routine care.

INTRODUCTION

Neurodegenerative diseases comprise a heterogeneous group of disorders in which

*Corresponding Author: Kavitha Marati

Address: RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad-500027, Telangana, India

Email ✉: kavitha.marati@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



progressive neuronal dysfunction and neuronal loss produce cognitive, motor, behavioural or autonomic impairment. Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis represent major clinical and biological phenotypes; they differ in their dominant pathological proteins, genetic determinants, anatomical vulnerability and rate of progression. Despite these differences, clinical manifestations may become evident only after disease-associated molecular and structural changes have accumulated. Biomarkers are central to modern disease characterisation and to the development of mechanism-based therapies.^{1,3-5}

The term biomarker should be used precisely. The FDA-NIH BEST framework defines a biomarker as a defined characteristic measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Molecular, histologic, radiographic and physiologic measures can therefore qualify as biomarkers, whereas symptoms, functional status and survival are clinical outcomes rather than biomarkers. This distinction is particularly important in neurodegenerative disease research, where a measurable change in a biological marker may indicate target engagement or biological activity without necessarily proving clinical benefit.²

Earlier biomarker work focused heavily on cerebrospinal fluid (CSF) proteins and genetic variants, and the field has expanded to include plasma proteins, cell-free nucleic acids, transcriptomic signatures, metabolomics, neuroimaging, electrophysiology and

ultrasensitive assays. The most clinically consequential recent advances have been the emergence of high-performance blood biomarkers for AD, the development of α -synuclein seed amplification assays for PD, increasing validation of neurofilament light chain (NfL) across disorders, and the development of mutant huntingtin (mHTT) measures as pharmacodynamic biomarkers in HD.^{5,6,11}

In neurodegenerative diseases, a marker may show biological association without being sufficiently qualified for diagnosis, prognosis, treatment monitoring or use as a surrogate endpoint. Accordingly, the intended context of use, assay performance, population, sampling time and relationship to clinical outcomes are to be specified before a biomarker is incorporated into a clinical study.

2. Biomarker Concepts and Classification

2.1 Biological Basis and Major Platforms

Biomarkers may be classified according to the biological layer measured. Genomic biomarkers include pathogenic variants, repeat expansions and other DNA-level characteristics. Transcriptomic biomarkers quantify RNA abundance or expression signatures. Proteomic biomarkers measure proteins, protein fragments or post-translationally modified species. Metabolomic biomarkers quantify metabolites or metabolic intermediates. In neurodegenerative disorders, these molecular layers are complemented by imaging, electrophysiological and physiologic measures.^{1,3-5}

Table 1. Major biomarker platforms and their potential contexts of use

Biomarker class	Examples relevant to neurodegeneration	Principal value
Genomic	CAG expansion in HTT; pathogenic variants in APP, PSEN1/PSEN2, SOD1, C9orf72, TARDBP and FUS	Susceptibility, inherited diagnosis, molecular stratification



Transcriptomic	Blood RNA signatures; microRNA profiles	Disease-associated signatures; exploratory diagnosis and monitoring
Proteomic	A β 42/40, p-tau181/p-tau217, NfL, α -synuclein, mHTT	Diagnosis, prognosis, disease activity, pharmacodynamic assessment
Metabolomic	Urate, lipid and other metabolic signatures	Risk association, phenotyping and exploratory monitoring
Imaging	Amyloid PET, tau PET, MRI volumetry, dopaminergic imaging	Pathology localization, staging and longitudinal progression
Physiologic/ electrophysiologic	Electromyography, electrical impedance myography	Motor-neuron involvement and treatment monitoring

2.2 Biomarker Categories by Context of Use

For clinical and drug-development purposes, biomarkers should be linked to a predefined context of use. Diagnostic biomarkers identify or support the presence of a disease or pathological process. Prognostic biomarkers provide information about the likelihood or rate of a future clinical event or disease progression. Monitoring

biomarkers are measured serially to assess disease status or change over time. Pharmacodynamic/response biomarkers indicate a biological response to an intervention and are particularly important for demonstrating target engagement. Predictive biomarkers identify individuals more likely to respond to a specific intervention, whereas safety biomarkers indicate toxicity or injury.^{1,2,5}

Table 2. Biomarker categories and examples in neurodegenerative diseases

Context	Definition in practice	Neurodegenerative examples
Diagnostic	Indicates presence of a disease/pathological process	Plasma p-tau217 for AD pathology; CSF α -synuclein seed amplification for PD
Prognostic	Associated with future progression or clinical outcome	NfL in ALS and HD
Monitoring	Tracks biological or disease-state change longitudinally	Serial NfL; MRI measures; clinical-linked biomarker panels
Pharmacodynamic/ response	Shows biological response to treatment or target engagement	mHTT for HTT-lowering approaches; molecular target markers
Predictive	Identifies patients more likely to benefit from an intervention	Genotype/pathology-defined treatment eligibility in selected settings
Safety	Indicates treatment-related injury or toxicity	Drug-specific laboratory or imaging safety markers

2.3 Type 0, Type 1 and Type 2 Biomarkers

The source manuscript also describes a Type 0–2 framework. In this terminology, Type 0 biomarkers follow the natural history of disease, Type 1 biomarkers reflect biological activity or intervention effects, and Type 2 biomarkers are

surrogate measures intended to predict clinical benefit. The distinction is conceptually useful, but a biomarker should not be called a surrogate endpoint solely because it changes with treatment; surrogate status requires evidence linking biomarker change to clinical benefit.^{1,2}



Table 3. Type 0–2 Biomarker framework

Type	Concept	Interpretation
Type 0	Natural-history marker	Tracks disease biology or progression without necessarily responding to treatment
Type 1	Drug-activity/ intervention marker	Demonstrates biological activity, target engagement or pharmacodynamic response
Type 2	Surrogate endpoint	Biomarker change is intended to predict clinical benefit and therefore requires stronger validation

3. Practical Considerations in Biomarker Development

A useful biomarker must be analytically reliable, biologically plausible and clinically meaningful for its intended context of use. In neurodegenerative disease, additional challenges arise because the pathological process is spatially

compartmentalised, often develops over many years, and may be accompanied by substantial biological heterogeneity. Blood biomarkers are attractive as they are relatively accessible and repeatable, but concentrations can be influenced by age, renal function, body composition, peripheral expression, assay platform and other comorbidities.^{1,3-5}

Table 4. Advantages and practical concerns associated with biomarkers

Potential advantages	Important limitations/concerns
Objective quantitative assessment	Timing of sampling can materially affect interpretation
Potentially less dependent on subjective symptom reporting	Pre-analytical handling and laboratory error can alter measurements
Can provide mechanistic information	Reference ranges and clinically meaningful cut-offs may be difficult to establish
Can be repeated during longitudinal follow-up	Storage conditions and sample longevity require standardization
May enrich clinical trials and support target engagement	Biological heterogeneity may reduce sensitivity or specificity
Can complement clinical, imaging and pathological information	Ethical issues arise when preclinical results have uncertain clinical implications

3.1 Characteristics of an Ideal Neurodegenerative Biomarker

Biomarker development should address analytical validity, biological validity and clinical validity separately. A technically reproducible assay does not necessarily have sufficient disease specificity, and a statistically associated marker does not automatically provide clinically useful information. Fit-for-purpose validation is important when biomarkers are used for clinical trials or therapeutic decisions.

Biomarkers can provide objective measurements, reduce some forms of reporting bias, permit quantitative longitudinal assessment and provide mechanistic information about disease processes. However, timing of sample collection is difficult, specimen storage affects analyte stability, laboratory error can influence measurements, normal reference ranges may be difficult to establish, and ethical responsibilities arise when biomarkers identify individuals at risk without providing a clear therapeutic option.¹⁻⁵



4. Biomarkers Across Major Neurodegenerative Diseases

The four disorders considered in this review illustrate complementary biomarker strategies. AD has the most mature biological classification, with amyloid, tau and neurodegeneration domains now incorporated into disease-definition frameworks. PD is increasingly supported by direct detection of pathological α -synuclein. HD benefits from a definitive inherited genetic marker, while fluid markers such as NfL and mHTT add information about disease burden and therapeutic response. ALS has no single diagnostic laboratory test, but neurofilaments and other fluid measures are increasingly useful for prognosis and treatment development.^{6-10,18-22}

Because pathological changes may precede recognisable clinical symptoms, biomarkers have potential value for early detection, differential diagnosis, disease staging, prognosis, monitoring and therapeutic development. Current evidence supports these concepts while also showing that biomarker performance must be defined according to the disease, assay and intended clinical use.^{6-10,13-22}

The four prototypical disorders considered in the source manuscript illustrate distinct anatomical and biological patterns: AD involves prominent hippocampal and cortical neuronal loss with cognitive impairment; PD involves degeneration of the nigrostriatal dopaminergic system and motor impairment; HD involves basal-ganglia degeneration and abnormal involuntary movements; and ALS involves degeneration of spinal, bulbar and cortical motor neurons with progressive weakness and muscle atrophy.^{6,8,13,30,35}

Neurodegenerative disorders are a heterogeneous group of diseases characterised by progressive

dysfunction and loss of neurons in selectively vulnerable regions of the nervous system. The source manuscript highlighted genetic abnormalities, biochemical defects, chronic or environmental influences and incompletely understood causes as contributors to neurodegeneration. Clinical consequences may include progressive impairment of cognition, speech, vision, hearing, movement, feeding and other neurological functions.

5. Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised clinically by parkinsonism and biologically by α -synuclein pathology, dopaminergic neuronal loss and broader multisystem involvement. Loss of dopaminergic neurons in the substantia nigra pars compacta contributes to motor impairment, while non-motor manifestations such as REM sleep behaviour disorder, olfactory dysfunction and autonomic abnormalities may precede or accompany motor disease.

5.1 Pathophysiology Relevant to Biomarkers

The principal pathological hallmark is accumulation and misfolding of α -synuclein, accompanied by neuronal dysfunction and loss. This biological complexity explains why conventional clinical scales, although indispensable for patient care, do not capture all aspects of disease biology. Earlier biomarker approaches examined dopamine metabolites, CSF proteins, inflammatory markers, oxidative-stress markers and neuroimaging of dopaminergic pathways, but many lacked sufficient specificity for routine diagnosis.^{18-20,30,33}

5.2 Established and Emerging PD Biomarkers



α -Synuclein is the most disease-specific molecular target currently being developed for PD biomarker applications. Total α -synuclein concentration in CSF has shown group-level differences, but measurement of pathogenic aggregates using seed amplification assays has provided a more direct assessment of α -synuclein pathology. In the Parkinson's Progression Markers Initiative, CSF α -synuclein seed amplification substantially separated PD from controls and also revealed biological heterogeneity within clinically defined PD cohorts.¹⁸⁻²⁰

Other candidate biomarkers remain useful mainly as complementary measures. DJ-1, total tau, phosphorylated tau and A β -related measures have been investigated in CSF and blood, particularly when cognitive impairment or differential diagnosis is relevant. Metabolomic and proteomic panels, inflammatory cytokines, urate and RNA signatures have also been explored. However, these markers should not be presented as established standalone diagnostic tests without specifying the assay, population and context of use.^{15,18-20}

Table 5. Biomarkers investigated in Parkinson's disease

Biomarker	Specimen/modality	Potential role	Current interpretation
α -Synuclein seed amplification	CSF; other peripheral tissues under study	Molecular diagnosis/stratification	Strongly supported for detection of synucleinopathy; assay standardisation and broader clinical validation remain important
Total α -synuclein	CSF	Exploratory diagnosis/biology	Group-level differences reported, but less specific than seed amplification
NfL	CSF/plasma	Prognosis / neuro-axonal injury	Sensitive to neurodegeneration but not specific for PD
DJ-1	Plasma/CSF	Exploratory biomarker	Investigational; susceptible to assay and biological confounding
Urate	Serum	Risk/progression association	Observational association; not an established surrogate endpoint
Dopaminergic imaging	SPECT/PET	Pathway assessment	Useful for selected differential-diagnostic and research applications

Soluble, aggregated and post-translationally modified forms of α -synuclein, as well as DJ-1, dopamine-related metabolites, microRNAs, ST13 RNA, inflammatory markers, oxidative-stress products, total tau, phosphorylated tau, β -amyloid and serum urate are the markers which reflect different processes, including synaptic pathology, oxidative stress, inflammation, neuronal injury and metabolic alterations. Their usefulness varies by specimen and clinical context, and most should not be interpreted as established standalone diagnostic tests.^{15,18-20}

Clinical and neurobehavioral measures investigated as early markers include REM sleep behaviour disorder, olfactory loss and oculomotor

abnormalities. Neuroimaging approaches include SPECT and PET techniques for assessing dopaminergic pathways and metabolic alterations. Physiological measures and molecular analyses of CSF, plasma and other biofluids have also been investigated. These approaches are best considered complementary because none, by itself, captures the complete biological spectrum of PD.^{7,18-20}

PD is frequently difficult to recognise at an early stage because there may be a prolonged interval between initial dopaminergic neuronal injury and the appearance of clinical motor symptoms. The major pathological hallmarks are loss of neurons in the substantia nigra pars compacta and the



presence of intracellular α -synuclein aggregates associated with Lewy pathology.^{18-20,30,33}

6. Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia and is characterised pathologically by amyloid- β plaques and abnormal tau accumulation, together with progressive neurodegeneration. The biological definition of AD has increasingly shifted from a purely syndromal diagnosis toward biomarker-supported identification of underlying pathology.^{6,11-17}

6.1 Amyloid, Tau and Neurodegeneration

The NIA-AA AT(N) framework organises biomarkers according to amyloid deposition (A), pathological tau (T), and neurodegeneration or neuronal injury (N). This framework separates the biological disease process from its clinical expression and has been highly influential in research and therapeutic trials. The 2024 revised criteria further emphasise that AD can be diagnosed biologically by biomarkers of amyloid and tau pathology, while acknowledging that clinical implementation requires appropriate validation and context.^{6,13}

6.2 Fluid Biomarkers

CSF A β 42, A β 42/40 ratio, total tau and phosphorylated tau have long been central AD biomarkers. More recently, plasma p-tau217 and related phosphorylated tau measures have

demonstrated high accuracy for detecting AD pathology in well-characterized cohorts. In a 2024 multicohort study, plasma percentage p-tau217 showed performance comparable to clinically used CSF assays for classifying amyloid PET status and strong performance for tau PET status. Subsequent primary- and secondary-care validation has further supported the clinical potential of automated plasma p-tau217 assays.^{6,11-17}

Blood-based biomarkers are nevertheless not interchangeable with clinical diagnosis in every setting. Kidney dysfunction, cardiovascular and metabolic comorbidities, age and other factors can affect biomarker concentrations. Current evidence therefore supports a fit-for-purpose approach in which biomarker results are interpreted alongside clinical phenotype and, where appropriate, confirmatory CSF or PET testing.^{5,11-17,29}

6.3 Additional Biomarkers

As potential AD biomarkers, BACE1, soluble APP (sAPP), and anti-A β autoantibodies are still biologically significant but have not replaced the more reliable A β and phosphorylated-tau measurements. While data on sAPP and anti-A β antibody levels have been inconsistent across various studies, elevated levels and activity of BACE1 are associated with the production of amyloid. As a result, it is preferable to present them as experimental rather than proven clinical biomarkers..^{6,13-17}

Table 6. Alzheimer's disease biomarkers and their current contexts of use

Biomarker	Specimen/modality	Primary biological domain	Clinical/ research relevance
A β 42/40	CSF/plasma	Amyloid pathology	Core AD biomarker; plasma assays increasingly support minimally invasive assessment
p-tau181	CSF/plasma	Tau pathology	Diagnostic and biological staging support
p-tau217	Plasma/CSF	Tau/AD pathology	High-performing blood biomarker; increasingly relevant to clinical implementation



Total tau	CSF/plasma	Neurodegeneration/tau-related injury	Useful as part of biomarker panels; less disease-specific alone
NfL	CSF/plasma	Neuro-axonal injury	Prognostic/general neurodegeneration marker rather than AD-specific marker
Amyloid PET	Imaging	Amyloid deposition	Established reference biomarker in research and selected clinical pathways
Tau PET	Imaging	Tau pathology	Maps regional tau burden and disease progression
BACE1 / sAPP / anti-A β antibodies	CSF/plasma	Amyloid processing/immune response	Investigational; not established standalone clinical biomarkers

BACE1 is involved in amyloidogenic processing of APP, while sAPP and anti-A β antibody measurements have been investigated as indicators of altered amyloid metabolism or immune responses. These measures remain biologically relevant but are less clinically established than A β 42/40 and phosphorylated tau biomarkers.^{6,13-17}

The biological cascade described in the source material includes abnormal amyloid precursor protein processing, β -amyloid accumulation and fibrillar plaque formation, followed by tau-related neurodegeneration. These processes provide the rationale for biomarker development based on amyloid, tau and neuronal injury. Modern biomarker frameworks have subsequently strengthened this biological interpretation by distinguishing amyloid pathology, pathological tau and neurodegeneration.^{6,13-17}

Alzheimer's disease is the most common neurodegenerative cause of dementia and is characterised by progressive cognitive impairment associated with synaptic dysfunction, neuronal loss and characteristic amyloid and tau pathology. The source manuscript described early-onset and late-onset disease, age-related cerebral atrophy, hippocampal and cortical involvement, and the contribution of genetic and non-genetic factors to disease susceptibility.^{6,11-17}

7. Huntington's Disease

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder caused by expansion of a CAG trinucleotide repeat in the HTT gene. The pathogenic expansion produces mutant huntingtin (mHTT), and repeat length is associated with age at onset and disease trajectory, although it does not determine an exact clinical course for an individual.

7.1 Genetic and Clinical Biomarkers

Genetic testing for the pathogenic HTT CAG expansion provides a definitive molecular basis for diagnosis in appropriate clinical settings and identifies individuals at genetic risk. However, genotype alone is not a dynamic measure of disease progression. Clinical motor, cognitive and psychiatric measures therefore remain important endpoints, while MRI measures of striatal and other brain-region atrophy can detect structural changes before substantial clinical decline.

7.2 Fluid Biomarkers

NfL has emerged as one of the most consistently supported fluid biomarkers in HD. CSF and plasma NfL concentrations rise with disease burden and are associated with clinical and imaging measures. mHTT can be quantified in CSF and has particular value for assessing target engagement of therapies designed to lower huntingtin expression. Recent evidence continues to support NfL as a prognostic biomarker, while



mHTT is particularly informative for (PDE10) remain of research interest, but their pharmacodynamic applications.^{8,9,21,22} clinical use is less established than genetic testing, MRI, NfL and mHTT.^{21,22}

H2AFY, inflammatory markers such as IL-8 and TNF- α , and imaging of phosphodiesterase-10

Table 7. Huntington's disease biomarker landscape

Biomarker	Domain	Potential role	Evidence status
HTT CAG repeat length	Genomic	Inherited diagnosis and genetic stratification	Established molecular diagnostic marker
NfL	CSF/plasma	Prognosis, disease burden, trial enrichment	Strongly supported; specificity for HD is limited
mHTT	CSF/plasma	Target engagement and disease biology	Important pharmacodynamic biomarker for HTT-lowering approaches
MRI volumetry	Imaging	Preclinical/early structural progression	Widely used in observational studies and trials
PDE10 PET	Imaging	Striatal pathway assessment	Research biomarker
H2AFY	Protein/transcription-related	Exploratory pharmacodynamic marker	Investigational
IL-8, TNF- α and related immune markers	Blood/CSF	Inflammatory phenotype	Investigational and context-dependent
Motor/cognitive measures	Clinical outcomes	Disease staging and efficacy endpoints	Essential clinical outcomes, not biomarkers under BEST terminology

Mutant huntingtin is particularly important because it is the pathogenic protein produced by the expanded HTT allele. Its detection in CSF, blood and saliva and its potential as a prognostic and pharmacodynamic biomarker, supports CSF mHTT as a target-engagement measure in studies of huntingtin-lowering therapies.^{8,21,22}

A histone-related protein called H2AFY was identified as having higher levels in HD and being responsive to sodium phenylbutyrate in the early stages of the illness. Although this observation has pharmacodynamic significance, it is still under investigation and shouldn't be used as a reliable clinical biomarker. Similarly, since transcriptional dysregulation and epigenetic mechanisms play a role in the pathophysiology of HD, histone deacetylase inhibition has been investigated experimentally.^{21,22}

The source manuscript described biomarker domains including clinical motor testing, anti-saccade error rate, digitomotography, cognitive testing such as the Symbol Digit Modalities Test, structural MRI, PDE10 imaging with [18F]MNI-659 PET, immune markers including IL-8 and TNF- α , H2AFY and mutant huntingtin. These measures interrogate different components of HD biology and disease progression.^{21,22}

CAG-repeat length is associated with age at onset, with larger expansions generally associated with earlier disease onset. These values should be presented as broad clinical ranges rather than absolute predictors because repeat length does not determine an individual's exact phenotype or age at onset.³⁵

Huntington's disease is an inherited neurodegenerative disorder caused by a



pathogenic CAG-repeat expansion in the HTT gene on chromosome 4. The major clinical domains are motor abnormalities, cognitive impairment and emotional or psychiatric changes, including involuntary movements, impaired coordination, difficulties with swallowing and speech, impaired concentration, memory and judgement, impulsivity, anxiety, depression and loss of initiative.³⁵

8. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive motor-neuron disease involving upper and lower motor neurons and leading to progressive weakness, muscle atrophy, bulbar dysfunction and, in many patients, respiratory failure. ALS is genetically heterogeneous. Pathogenic variants in genes including C9orf72, SOD1, TARDBP and FUS account for a substantial proportion of familial disease, while many sporadic cases remain genetically unresolved.

8.1 Pathophysiology Relevant to Biomarkers

ALS pathology includes motor-neuron degeneration, axonal loss, reactive gliosis, neuroinflammation and disturbances in protein homeostasis, RNA metabolism, excitotoxicity and mitochondrial function. Mutant SOD1 has been linked to mitochondrial abnormalities, oxidative stress and impaired cellular energetics, while no single biomarker represents the complete disease process.

8.2 Diagnostic, Prognostic and Monitoring Biomarkers

Diagnosis remains primarily clinical and electrophysiological, supported by neurological examination and electromyography and by exclusion of alternative diagnoses. The major unmet need is a biomarker that can shorten diagnostic delay and distinguish ALS from its mimics. Neurofilament light chain and phosphorylated neurofilament heavy chain are currently among the best-supported fluid biomarkers, with particularly strong evidence for prognostic use and increasing support for treatment-response assessment.

A blood gene-expression study involving 396 ALS patients, 75 patients with ALS-mimic disorders and 645 healthy controls reported 752 ALS-increased and 764 ALS-decreased differentially expressed genes. Individual neurofilament-gene measures (NEFH and NEFL) showed limited diagnostic accuracy in isolation, whereas a support-vector-machine approach using gene-expression features reportedly achieved 87% accuracy, with 86% sensitivity and 87% specificity. These findings are important as an example of a multigene approach, but they should not be interpreted as a clinically validated diagnostic test without independent replication and prospective validation.

Table 8. Biomarkers and outcome measures in amyotrophic lateral sclerosis

Biomarker	Potential role	Strengths	Important limitation
NfL	Prognosis; monitoring; pharmacodynamic assessment	Strong and reproducible association with neuro-axonal injury	Not ALS-specific; affected by age and other neurological disorders
pNfH	Diagnosis/prognosis	Strong CSF and blood evidence	Analytical and biological variability



NEFL/NEFH expression	Exploratory diagnosis	May contribute to multigene signatures	Individual-gene accuracy is insufficient for standalone diagnosis
ALSFRS-R	Clinical outcome	Established measure of functional progression	Clinical outcome, not a biomarker
Electrical impedance myography	Monitoring	Non-invasive physiologic measure of muscle involvement	Requires technical standardization and broader validation
SOD1 genotype / molecular target measures	Predictive/target engagement in genetic ALS	Directly linked to mechanism in SOD1-associated disease	Applicable to a genetically defined subgroup

For diagnosis, the current benchmark remains neurological history and examination supported by electromyography and established clinical criteria. Prognostic biomarkers are intended to identify progression patterns and improve stratification in therapeutic trials, while monitoring biomarkers may help identify ineffective interventions earlier. ALSFRS-R remains a key clinical outcome measure, and electrical impedance myography is an emerging physiological measure rather than a fully established standalone biomarker.^{10,28,32}

Glutamate excitotoxicity and mitochondrial abnormalities are associated with mutant SOD1. Mutant SOD1 can localise to mitochondrial compartments and is associated with altered mitochondrial membrane potential, impaired electron-transport activity, calcium and cytochrome-c dysregulation and increased reactive oxygen species. These mechanisms are relevant to interpret oxidative-stress and neuronal-injury biomarkers.^{25,26,27}

Corticospinal and bulbospinal motor-neuron degeneration, reactive gliosis, microglial and astrocytic responses, loss of large myelinated motor fibres, denervation and reinnervation of muscle, and pathological changes in the motor cortex, brainstem and spinal cord provide a biological basis for electrophysiological and neurofilament biomarkers.^{25,26}

Familial ALS is genetically heterogeneous. C9orf72, SOD1, TARDBP and FUS among major disease-associated genes are particularly useful for molecular classification and, in selected cases, treatment selection, but many ALS cases remain genetically unexplained.^{25,26}

Amyotrophic lateral sclerosis is a progressive motor-neuron disease involving upper and lower motor neurons, progressive muscle weakness, muscle atrophy, bulbar dysfunction and, in later stages, respiratory involvement. Frontotemporal dementia can occur in association with ALS, producing additional frontal and temporal cortical pathology.^{25,26}

8.3 ALS Pathology, Genetics and Biomarker Development

These findings illustrate the potential value of multigene signatures and cell-composition information, but the reported performance should be interpreted as evidence from the cited study rather than as a clinically validated diagnostic assay. Independent replication, prospective validation, assay standardisation, and evaluation in real-world diagnostic populations are required before such signatures can be adopted clinically.

Neurofilament-related genes including NEFH and NEFL were examined as candidate markers. The source manuscript reported individual-gene



diagnostic accuracy of approximately 50–53%. A support-vector-machine approach using gene-expression information reportedly distinguished ALS from mimic diseases and healthy controls with 87% accuracy, 86% sensitivity and 87% specificity.

The investigators reported 752 ALS-increased and 764 ALS-decreased differentially expressed genes. Increased genes showed higher exosome-related expression, neutrophil-specific expression and associations with translation-related processes, and overlapped with genes near ALS susceptibility loci including IFRD1, TBK1 and CREB5. Decreased genes showed lower exosome expression, erythroid-lineage specificity and associations with anaemia and blood disorders.

A blood-based gene-expression study designed to identify differentially expressed genes, characterise patient-to-patient heterogeneity and identify candidate biomarkers. The study included

396 patients with ALS, 75 patients with ALS-mimic diseases and 645 healthy controls.

9. Comparative Clinical Utility of Biomarkers

The four diseases demonstrate that biomarker maturity depends strongly on disease biology and context of use. A pathogenic genetic variant can be diagnostic in HD and in selected familial forms of ALS or AD, whereas protein or imaging biomarkers are needed to characterise sporadic disease biology. AD currently has the most developed multimodal biomarker framework, whereas PD is rapidly moving toward pathology-based molecular diagnosis through α -synuclein seed amplification. HD and ALS demonstrate the value of NfL as a cross-disease measure of neuro-axonal injury, but its lack of disease specificity means that it is better suited to prognosis, disease activity and treatment monitoring than to standalone diagnosis.^{5-10,18-22,28}

Table 9. Cross-disease comparison of biomarker utility

Disease	Most informative current biomarker domains	Early-disease utility	Therapeutic-monitoring utility	Key limitation
AD	A β , p-tau, amyloid/tau imaging, NfL	High and rapidly improving	Increasingly useful for disease characterisation and treatment eligibility	Pre-analytical/comorbidity effects; not all assays have identical performance
PD	α -synuclein seed amplification, imaging, NfL and multimodal measures	Promising for molecular confirmation	Mostly investigational for progression/response	Assay heterogeneity and incomplete longitudinal qualification
HD	HTT CAG repeat, NfL, mHTT, MRI	Strong genetic and premanifest research utility	mHTT for target engagement; NfL for progression	No single marker captures all disease dimensions
ALS	NfL/pNfH, genetics, electrophysiology, clinical scales	Useful mainly for differential/prognostic support	Strong potential for trial monitoring	No standalone diagnostic biomarker; NfL is nonspecific

10. Biomarkers in Therapeutic Development and Clinical Trials

Biomarkers can improve neurodegenerative disease trials by enriching biologically defined populations, demonstrating target engagement, supporting dose selection, reducing heterogeneity



and providing earlier evidence of biological activity. However, biomarker change should not automatically be equated with clinical benefit. The evidentiary burden depends on the intended use and the strength of the relationship between the biomarker, disease mechanism and clinical outcome.

In AD, biomarker confirmation of amyloid pathology is increasingly important because disease-modifying anti-amyloid therapies are directed at a defined pathological substrate. In HD, mHTT is particularly relevant to trials of huntingtin-lowering approaches because it can provide direct evidence of molecular target engagement. In ALS, NfL has become an important pharmacodynamic and prognostic measure, including in studies of genetically targeted therapies. In PD, α -synuclein assays may eventually allow molecular stratification of synucleinopathy trials, but their role as validated surrogate endpoints remains to be established.^{7-10,28,34}

11. Future Directions

The next stage of neurodegenerative biomarker development is likely to involve multimodal and longitudinal approaches rather than reliance on a single analyte. Combining molecular pathology markers with measures of neuronal injury, imaging, genetics and clinical phenotype may improve diagnostic confidence and disease staging. Machine-learning approaches may further improve composite biomarker performance, but model development should include independent validation, transparent reporting and clinically meaningful endpoints.

Blood-based testing is likely to expand substantially because it is less invasive and more scalable than CSF collection or PET. The most important requirement is not simply higher

analytical sensitivity but clinically validated performance in representative populations, including patients with comorbidities and overlapping syndromes. Standardisation of specimen collection, assay calibration and reporting will therefore be as important as biomarker discovery itself.^{5,11,16,17,29}

For therapeutic development, biomarkers should be selected according to the pathological condition they are intended to treat. A diagnostic biomarker should identify disease or pathology; a prognostic marker should predict progression; a pharmacodynamic marker should demonstrate biological response; and a surrogate endpoint should have substantially stronger evidence connecting biomarker change to clinical benefit. This fit-for-purpose principle can prevent overinterpretation and improve the efficiency of biomarker-driven clinical trials.

12. Discussion

The original manuscript correctly emphasised the expanding range of biomarker modalities and the need for biomarkers that can detect disease earlier and improve therapeutic development. The current evidence, however, requires a more differentiated interpretation. Not every measurable biological difference is a clinically useful biomarker, and not every biomarker is suitable for diagnosis, prognosis and treatment monitoring simultaneously. Biomarker performance depends on disease stage, specimen, assay and context of use.

Among the disorders reviewed, AD provides the clearest example of a transition from exploratory biomarkers toward a biologically anchored clinical framework. The combination of amyloid and tau biomarkers can identify disease pathology before advanced clinical decline, while plasma p-tau217 has emerged as a particularly promising scalable



measure. PD demonstrates a different trajectory: direct detection of pathological α -synuclein is changing the field from symptom-based diagnosis toward molecular characterisation. HD benefits from a definitive genetic cause, while NfL and mHTT address complementary questions of neurodegeneration and target engagement. ALS illustrates the challenge of a biologically heterogeneous disorder in which neurofilaments are highly informative but insufficiently specific for diagnosis on their own. ^{6-10,13,18-20}

A single biomarker may be highly sensitive to neuronal injury but nonspecific, while another may be disease-specific but less suitable for longitudinal monitoring. Multimodal panels can potentially compensate for these limitations, provided that they are prospectively validated and their added value over established clinical measures is demonstrated.

CONCLUSION

Biomarkers are becoming central to the modern characterisation and therapeutic development of neurodegenerative diseases. Progress is most evident where biomarkers directly reflect disease-defining pathology, as illustrated by amyloid and phosphorylated tau in AD and α -synuclein seed amplification in PD. NfL has emerged as a broadly useful marker of neuro-axonal injury with important prognostic and pharmacodynamic applications in HD and ALS, while mHTT provides a mechanistically informative target-engagement measure in HD. Nevertheless, clinical translation requires rigorous analytical standardisation, validation in diverse populations, longitudinal assessment and a clearly specified context of use. The future of neurodegenerative biomarker research will therefore depend not only on discovering new molecules but also on demonstrating that each biomarker provides

reproducible, clinically interpretable and decision-relevant information.

Acknowledgement

The authors acknowledge the academic support of RBVRR Women's College of Pharmacy, Hyderabad, Telangana, India.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Kavitha Marati: literature compilation, drafting and organisation of the manuscript. Archana Jorige: conceptual supervision, critical review and final approval of the manuscript.

REFERENCES

1. Hulka BS, Griffith JD, Wilcosky TC. Overview of biological markers. In: Hulka BS, Griffith JD, Wilcosky TC, editors. *Biological Markers in Epidemiology*. New York: Oxford University Press; 1990. p. 3-15.
2. US Food and Drug Administration. About biomarkers and qualification [Internet]. Silver Spring (MD): FDA; 2025 [cited 2026 Sep 27].
3. Naylor S. Biomarkers: current perspectives and future prospects. *Expert Rev Mol Diagn*. 2003;3(5):525-529.
4. Verbeek MM, De Jong D, Kremer HP. Brain-specific proteins in neurological disease: the potential of CSF biomarkers. *Ann Clin Biochem*. 2003;40(Pt 1):25-40.
5. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gatringer T, et al. Neurofilaments as biomarkers in neurological disorders—towards clinical application. *Nat Rev Neurol*. 2024;20:269-287.
6. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.



7. Siderowf A, Concha-Marambio L, Lafontant DE, Farris CM, Ma Y, Urenia PA, et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α -synuclein seed amplification: a cross-sectional study. *Lancet Neurol.* 2023;22(5):407-417.
8. Wild EJ, Boggio R, Langbehn D, Robertson N, Haider S, Miller JRC, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. *J Clin Invest.* 2015;125(5):1979-1986.
9. Byrne LM, Rodrigues FB, Johnson EB, Wijeratne PA, De Vita E, Alexander DC, et al. Neurofilament light protein in blood as a potential biomarker of Huntington's disease. *Lancet Neurol.* 2017;16(10):784-791.
10. Benatar M, Wu J, Andersen PM, Atassi N, David WS, Schoenfeld D, et al. Neurofilament light chain in ALS: theory and practice of biomarker qualification. *Ann Neurol.* 2024;95(2):211-216.
11. Mielke MM, Fowler NR. Alzheimer disease blood biomarkers: considerations for population-level use. *Nat Rev Neurol.* 2024;20:495-504.
12. Barthélemy NR, Salvadó G, Schindler SE, He Y, Janelidze S, Collij LE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med.* 2024;30:1085-1095.
13. Jack CR Jr, Andrews SJ, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for the diagnosis and staging of Alzheimer's disease. *Nat Med.* 2024;30:2121-2124.
14. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA.* 2020;324(8):772-781.
15. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to tangle pathology and clinical utility. *Nat Med.* 2020;26:379-386.
16. Mielke MM, et al. Plasma p-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. *Nat Med.* 2025;31:2036-2043.
17. Barthélemy NR, et al. Diagnosis of Alzheimer's disease using plasma biomarkers adjusted to clinical probability. *Nat Aging.* 2025;5:215-227.
18. Berg D, Klein C. α -synuclein seed amplification and its uses in Parkinson's disease. *Lancet Neurol.* 2023;22(5):369-371.
19. Chahine LM, Beach TG, Adler CH, Hepker M, Kanthasamy A, Appel S, et al. Central and peripheral α -synuclein in Parkinson disease detected by seed amplification assay. *Ann Clin Transl Neurol.* 2023;10(5):696-705.
20. Bellomo G, et al. α -Synuclein seed amplification assays for diagnosing synucleinopathies: the way forward. *Neurology.* 2022;99(5):195-205.
21. Rodrigues FB, Wild EJ. Huntington's disease clinical trials and biomarkers. *Curr Opin Neurol.* 2017;30(5):510-516.
22. Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RAC, Durr A, Craufurd D, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol.* 2009;8(9):791-801.
23. Shahim P, et al. Neurofilaments in sporadic and familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Genes (Basel).* 2024;15(4):489.
24. Verde F. Neurochemical biomarkers of amyotrophic lateral sclerosis: recent developments. *Curr Opin Neurol.* 2025;38(4):331-337.
25. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature.* 1993;362:59-62.
26. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol.* 2015;7:181-193.
27. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of

- failure. Are we any closer to registering a new treatment? *Front Aging Neurosci.* 2017;9:68.
28. Benatar M, Ostrow LW, Lewcock JW, Bennett F, Shefner J, Bowser R, et al. Biomarker qualification for neurofilament light chain in amyotrophic lateral sclerosis: theory and practice. *Ann Neurol.* 2024;95(2):211-216.
 29. Global CEO Initiative on Alzheimer's Disease. Acceptable performance of blood biomarker tests of amyloid pathology—recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol.* 2024;20:426-439.
 30. De Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *Lancet Neurol.* 2006;5(6):525-535.
 31. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Mov Disord.* 2010;25(16):2695-2703.
 32. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov.* 2004;3(3):205-214.
 33. Goedert M. Alpha-synuclein and neurodegenerative diseases. *Nat Rev Neurosci.* 2001;2(7):492-501.
 34. Griffiths HR, Møller L, Bartosz G, Bast A, Bertoni-Freddari C, Collins A, et al. Biomarkers. *Mol Aspects Med.* 2002;23(1-3):101-208.
 35. Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell.* 1993;72(6):971-983.

HOW TO CITE: Archana Jorige, Kavitha Marati, Recent Advances in Biomarkers for Early Diagnosis and Therapeutic Monitoring of Neurodegenerative Diseases: A Systematic Review, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 898-913. <https://doi.org/10.5281/zenodo.23202491>

