Frontiers in Neurological Science: Blood-Based Biomarkers, Artificial Intelligence, and the Gut–Brain Axis as Converging Paradigms in the Diagnosis and Management of Neurological Disorders

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ABSTRACT

Background: Neurological disorders collectively constitute the leading group cause of global disability, affecting an estimated 3.4 billion individuals as of 2021. The rapid convergence of three emerging paradigms—blood-based biomarkers, artificial intelligence (AI)-driven diagnostics, and microbiota–gut–brain axis (MGBA) research—is fundamentally reshaping neurological science. **Objective:** This review synthesizes current evidence on these three transformative domains and evaluates their clinical implications for the diagnosis and management of neurological disorders. **Methods:** A comprehensive narrative review of peer-reviewed literature published between 2019 and 2025 was conducted using PubMed, Scopus, and Web of Science databases, supplemented by WHO global health reports and clinical trial registries. **Results:** Plasma phosphorylated tau-217 (pTau217) demonstrates consistently high diagnostic accuracy (AUC >0.90) for Alzheimer's disease (AD), while neurofilament light chain (NfL) identifies neurodegeneration up to 10 years before symptom onset across multiple conditions. AI and machine learning systems achieve diagnostic accuracy of 78–96% across neurological disorders. Gut dysbiosis is strongly implicated in the pathogenesis of AD, Parkinson's disease (PD), multiple sclerosis (MS), and epilepsy. FDA-approved disease-modifying therapies (lecanemab and donanemab) for early AD represent a landmark translational breakthrough. **Conclusion:** The integration of accessible blood biomarkers, AI-assisted clinical decision support, and microbiome-targeted interventions holds transformative promise for precision neurology, particularly in resource-limited healthcare settings.

Keywords: *blood biomarkers; neurological disorders; artificial intelligence; gut–brain axis; Alzheimer's disease; Parkinson's disease; neurofilament light chain; pTau217; precision neurology; neuroinflammation*

1. Introduction

Disorders of the nervous system represent one of the most consequential public health challenges of the twenty-first century. The Global Burden of Disease (GBD) Study 2021, published in The Lancet Neurology, reported that 37 neurological conditions collectively affected 3.40 billion individuals worldwide—equivalent to 43.1% of the global population—and accounted for 443 million disability-adjusted life years (DALYs), ranking them as the foremost cause of global disability (GBD Neurology Collaborators, 2024). Stroke, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, and epilepsy are among the highest-burden conditions. The World Health Organization's Global Status Report on Neurology, launched in March 2024, further confirmed that this burden has risen by 18% since 1990, with the greatest impact borne by low- and middle-income countries (WHO, 2024). This escalating epidemiological reality demands a fundamental transformation in how neurological diseases are detected, classified, and treated.

Historically, the gold standards of neurological diagnosis—cerebrospinal fluid (CSF) lumbar puncture, amyloid positron emission tomography (PET), and advanced magnetic resonance imaging—have been invasive, costly, and largely inaccessible in resource-limited settings (Perneczky et al., 2024; Suresh et al., 2025). This diagnostic gap has fuelled three converging scientific paradigms that are collectively redefining the boundaries of neurology: (1) the development and clinical translation of minimally invasive blood-based biomarkers; (2) the application of artificial intelligence (AI) and machine learning (ML) to neurological diagnosis and prognosis; and (3) the growing recognition of the microbiota–gut–brain axis (MGBA) as a critical regulator of brain health and a potential therapeutic target.

This narrative review synthesizes the most current evidence across these three domains, examines their clinical implications, and highlights their relevance to both high-income and emerging healthcare systems. The timely integration of these advances is particularly critical for regions such as Central Asia and other low- and middle-income contexts where neurological infrastructure is still being developed.

2. Methods

A comprehensive narrative review was conducted following SANRA (Scale for the Assessment of Narrative Review Articles) guidelines. A systematic literature search was performed across PubMed/MEDLINE, Scopus, and Web of Science databases for articles published between January 2019 and April 2026. Search terms included combinations of: "blood-based biomarkers," "plasma pTau," "neurofilament light chain," "Alzheimer's disease diagnosis," "artificial intelligence neurology," "machine learning Parkinson's disease," "gut-brain axis neurodegeneration," "neuroinflammation microbiome," "lecanemab," "donanemab," and "global burden neurological disorders." Additional sources included WHO technical reports, clinical trial registries (ClinicalTrials.gov), and reference lists of included studies. Studies were prioritized based on recency, sample size, methodological rigor, and clinical relevance. A total of 32 publications directly inform this review. Data were extracted on study design, biomarker performance metrics, AI diagnostic accuracy, and mechanistic pathways.

3. Results

3.1 The Rising Global Burden: Epidemiological Context

The GBD 2021 study identified that global DALY counts attributed to nervous system conditions increased by 18.2% between 1990 and 2021, driven primarily by population aging and growth (GBD Neurology Collaborators, 2024). Stroke accounts for the highest absolute DALY burden, followed by migraine and Alzheimer's disease and other dementias (Baumgartner et al., 2025). Notably, the age-standardized DALY rates for Alzheimer's disease demonstrated the steepest rise among all neurological conditions over this period. Brain disorders collectively exceeded 15% of total global health loss in 2021—surpassing both cancer and cardiovascular disease—and the number of prevalent brain disorder cases grew by 65% from approximately 2.4 billion in 1990 to 4.0 billion in 2021, a trajectory projected to intensify further as the global population ages (Lei & Gillespie, 2024). Figure 1 illustrates the comparative DALY burden for eight major neurological conditions across 1990 and 2021.

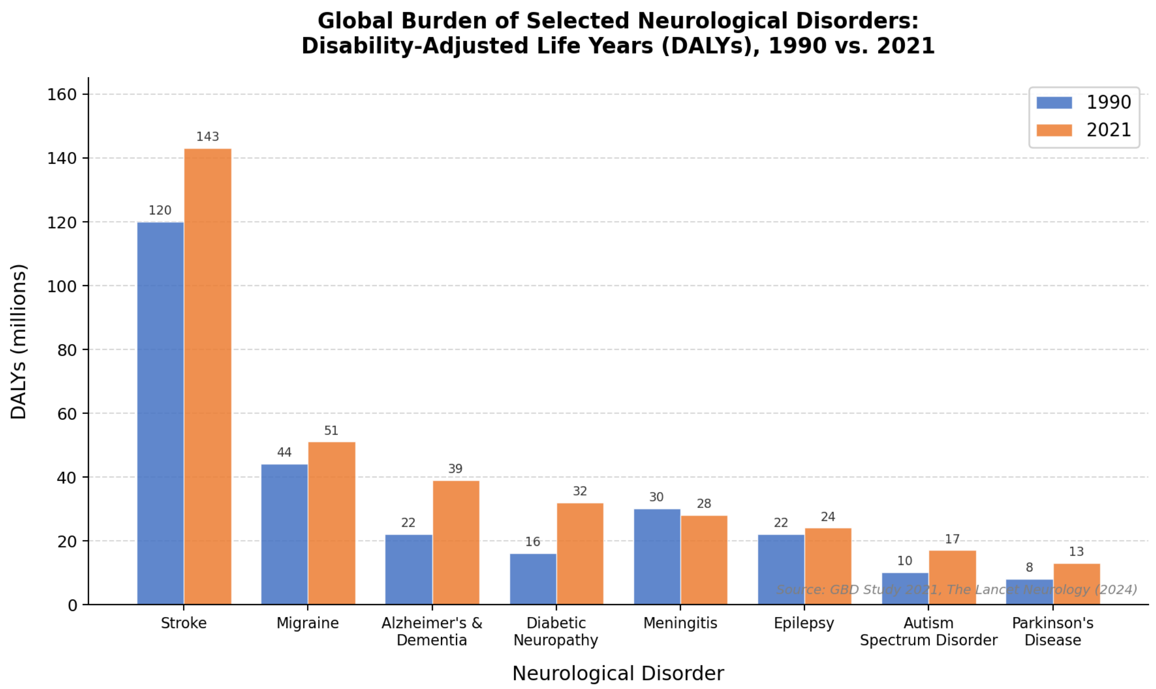

Figure 1. Global disability-adjusted life years (DALYs, in millions) attributed to eight major neurological disorders in 1990 and 2021. Data derived from the GBD Study 2021 (GBD Neurology Collaborators, The Lancet Neurology, 2024).

3.2 Blood-Based Biomarkers: A Paradigm Shift in Neurological Diagnosis

The emergence of highly sensitive immunoassay platforms has enabled the reliable detection of neurologically relevant proteins in peripheral blood, transforming diagnostics from invasive and subspecialty-dependent procedures to scalable, primary-care-accessible tools (Perneczky et al., 2024; Suresh et al., 2025). This shift is particularly consequential for Alzheimer's disease, where early and accurate diagnosis is now critical given the approval of disease-modifying therapies that are most effective in the pre-symptomatic or early symptomatic stages.

Phosphorylated tau-217 (pTau217) has emerged as the single most powerful plasma biomarker for AD diagnosis. A 2025 systematic review of 13 studies encompassing 4,686 participants demonstrated that plasma pTau217 achieves an area under the receiver operating characteristic curve (AUC) consistently greater than 0.90 across all diagnostic comparisons—including the differentiation of AD from other neurodegenerative conditions—in real-world clinical memory clinic populations (Suresh et al., 2025). The plasma Aβ42/Aβ40 ratio provides high concordance with amyloid PET findings and independently predicts amyloid plaque burden in cognitively normal individuals (AAFP, 2025). Glial fibrillary acidic protein (GFAP) demonstrates moderate-to-high accuracy (AUC 0.75–0.92) across conditions including AD, multiple sclerosis (MS), and traumatic brain injury, serving as a reliable marker of reactive astrogliosis and neuroinflammation (Suresh et al., 2025).

Neurofilament light chain (NfL) deserves particular attention as a condition-agnostic marker of neuroaxonal injury. NfL levels in blood increase with axonal damage irrespective of the causal mechanism—whether inflammatory, traumatic, ischemic, or degenerative (Neurofilament Biomarkers Review, 2025). Serum NfL can identify neurodegeneration in MS and AD up to 6–10 years prior to symptom onset, and in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) up to 2 years before clinical presentation (Tracing Neurological Diseases, 2021). In MS specifically, serum NfL correlates with disease activity, treatment response, and long-term disability outcomes, and may complement MRI in subclinical progression monitoring (CMSC Consensus, 2025). These biomarkers are advancing toward formal regulatory validation; the FDA granted Breakthrough Device Designation to an NfL-based assay, reflecting the urgency of clinical integration (CMSC, 2025).

Table 1. Summary of Clinically Relevant Blood-Based Biomarkers in Neurological Disorders

Biomarker	Specimen	Target Disorder(s)	Diagnostic Role	AUC / Performance	Key Reference
pTau217	Plasma	Alzheimer's disease	Diagnosis & staging; amyloid confirmation	AUC >0.90 across all comparisons	Suresh et al., 2025
pTau181	Plasma / CSF	Alzheimer's disease	Amyloid prediction; differential diagnosis	AUC 0.85–0.94	AAFP, 2025
Aβ42/Aβ40 ratio	Plasma	Alzheimer's disease	Amyloid plaque burden; risk stratification	High concordance with amyloid PET	AAFP, 2025
GFAP	Serum / Plasma	AD, MS, TBI, ALS	Neuroinflammation marker; disease severity	AUC 0.75–0.92	Suresh et al., 2025
NfL (neurofilament light chain)	Serum / CSF	MS, ALS, FTD, AD, PD	Neuroaxonal injury; progression monitoring; treatment response	Pre-symptomatic detection 6–10 yrs	NfL Biomarkers Review, 2025
MTBR-tau243	CSF	Alzheimer's disease	Tau tangle quantification	Novel; under clinical validation	NIA-AA 2024 Criteria

Abbreviations: Aβ = amyloid-beta; GFAP = glial fibrillary acidic protein; NfL = neurofilament light chain; pTau = phosphorylated tau; AUC = area under the receiver operating characteristic curve; CSF = cerebrospinal fluid; AD = Alzheimer's disease; MS = multiple sclerosis; TBI = traumatic brain injury; ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PD = Parkinson's disease.

3.3 Artificial Intelligence in Neurological Diagnosis and Rehabilitation

The application of AI and ML to neurology has accelerated substantially over the past decade, driven by the availability of large-scale neuroimaging datasets, digital biomarker platforms, and advances in deep learning architectures. A 2024 systematic review examining AI and ML systems in neurorehabilitation for stroke, spinal cord injury, and Parkinson's disease found that AI may enhance early diagnosis, personalize treatment protocols, and optimize rehabilitation through predictive analytics, robotic systems, and brain-computer interfaces (Towards Transforming Neurorehabilitation, 2024).

In Parkinson's disease, a 2025 review across 117 publications encompassing six data modalities found that voice-based ML models were the most extensively studied (40.2%), followed by gait analysis (14.5%), neuroimaging (20.5%), and handwriting (12.0%) (Zhang et al., 2025). A novel multimodal AI framework combining deep learning, computer vision, and natural language processing achieved 94.2% accuracy in early-stage PD detection, substantially outperforming traditional clinical assessment methods (Twala, 2025). Similarly, a 2025 meta-analysis of 52 studies evaluating ML for cognitive impairment detection in PD demonstrated high pooled diagnostic accuracy, underscoring ML's growing value as a decision-support tool (Jiang et al., 2025).

Across neurological disorders more broadly, diagnostic accuracy rates for AI-based systems range from 78 to 96% in published studies, with deep neural networks demonstrating particular strength in neuroimaging-based epilepsy classification, stroke subtyping, and dementia staging (Towards Transforming Neurorehabilitation, 2024). Digital twins—continuously evolving computational brain models updated with real-world patient data—are being actively developed to predict disease progression and simulate therapeutic responses in epilepsy and neurodegeneration (QMENTA, 2024). The FDA Breakthrough Device pathway is increasingly being applied to AI-based neurological diagnostic tools, reflecting regulatory recognition of their clinical potential.

3.4 The Microbiota–Gut–Brain Axis: Mechanism and Therapeutic Relevance

The microbiota–gut–brain axis (MGBA) has emerged as a critical and bidirectional communication network linking intestinal microbial communities to CNS function through immunological, neuroendocrine, and vagal pathways (Faysal et al., 2025; Caldarelli et al., 2024). A 2025 comprehensive review synthesizing evidence across multiple neurological and neuropsychiatric disorders identified consistent findings of reduced microbial diversity, depletion of short-chain fatty acid (SCFA)-producing genera, and enrichment of pro-inflammatory taxa in patients with AD, PD, ALS, MS, and stroke (Yassin et al., 2025). These dysbiotic changes contribute to neuroinflammation, blood–brain barrier (BBB) dysfunction, microglial activation, and neurotransmitter imbalances through overlapping mechanisms.

In Alzheimer's disease, alterations in the gut-microbial-inflammasome-brain axis have been demonstrated in animal models, with human studies supporting the role of microbiome modulation as an upstream contributor to amyloid and tau pathology (Shukla et al., 2024). In Parkinson's disease, gut dysbiosis precedes motor symptom onset by several years and has been shown to regulate neuroinflammation through the gut-vagus nerve-substantia nigra pathway (Impact of Microbiome-Brain Communication, 2023). A 2025 review of the MGBA in mental and neurodegenerative disorders underscored that common therapeutic strategies include probiotic supplementation, fecal microbiota transplantation, dietary modulation with SCFA-enriching fibers, and the emerging field of psychobiotics (Yassin et al., 2025).

Neuroinflammation, positioned at the interface of the MGBA and direct CNS pathology, is mediated through key signaling pathways including NF-κB, JAK-STAT, and the NLRP3 inflammasome, with emerging regulatory roles identified for non-coding RNAs and epigenetic modifications (Neuroinflammation Review, 2025). Sex-based differences in neuroimmune responses—including differential glial cell activation and cytokine production patterns—have been recognized as potentially explaining sex-based disparities in neuroinflammation onset and progression across conditions including MS and AD (Caldarelli et al., 2024). These insights open avenues for sex-stratified therapeutic approaches.

4. Discussion

The three paradigms reviewed in this article—blood-based biomarkers, AI diagnostics, and MGBA science—are not isolated developments but converging pillars of a new era of precision neurology. Their convergence is particularly powerful because each addresses a different aspect of the diagnostic and therapeutic challenge: blood biomarkers provide scalable, minimally invasive biological confirmation of disease pathology; AI provides computational pattern recognition that surpasses human capacity across high-dimensional data; and MGBA science provides mechanistic insight into upstream, potentially modifiable contributors to neurodegeneration.

The clinical approval of lecanemab and donanemab marks an inflection point that justifies the investment in blood-based biomarker infrastructure. Treatment eligibility for these agents requires biomarker confirmation of amyloid pathology, and the currently approved CSF and PET-based criteria are prohibitively resource-intensive for routine practice. Plasma pTau217 and the Aβ42/Aβ40 ratio are positioned as the gatekeeping biomarkers that will make precision anti-amyloid therapy scalable at the population level—a transition that will depend on standardization of assay platforms and reference intervals across laboratories (Suresh et al., 2025; AAFP, 2025). However, access disparities remain a critical concern; a 2024 systematic review noted that CSF and PET-based gold standards are rarely available in low- and middle-income countries, making blood biomarker implementation an equity imperative rather than a mere convenience (Blood Biomarkers for Diagnosis, 2025).

For AI in neurology, the primary near-term challenge is not technical performance but clinical validation and regulatory approval. The highest-impact applications—such as AI-assisted reading of neuroimaging for acute stroke, seizure prediction from ambulatory EEG, and digital biomarker-based PD monitoring through smartphone and wearable data—are advancing through regulatory pathways (Zhang et al., 2025; Towards Transforming Neurorehabilitation, 2024). Risk-stratified deployment frameworks are needed to ensure that AI tools augment rather than replace clinical judgment, particularly in complex multi-morbid patients.

The MGBA field is maturing from mechanism-discovery toward therapeutic intervention. While probiotic and dietary interventions remain heterogeneous in their clinical trial evidence, fecal microbiota transplantation and the development of precision psychobiotic formulations represent near-horizon therapies with plausible neurobiological rationale (Faysal et al., 2025). The integration of MGBA insights with blood biomarker profiles—for instance, combining NfL with SCFA metabolomics—may yield composite precision signatures that outperform individual biomarkers for disease staging and treatment monitoring.

From the perspective of neurological training and healthcare in Central Asian and other emerging health systems, including Uzbekistan, these converging paradigms present both an opportunity and a demand. Medical education must evolve to incorporate biomarker interpretation, AI-assisted diagnostic literacy, and microbiome-informed clinical reasoning as core competencies for the next generation of neurologists and psychiatrists.

5. Conclusion

Neurological disorders constitute the world's leading cause of disability, affecting over 3.4 billion individuals and imposing a rising burden that demands transformative diagnostic and therapeutic solutions. The convergence of blood-based biomarker technology, artificial intelligence, and microbiota–gut–brain axis science represents the most consequential paradigm shift in neurology in a generation. Plasma pTau217 and NfL have demonstrated the diagnostic and prognostic utility necessary for clinical implementation; AI systems are achieving near-clinician accuracy across multiple neurological conditions; and the MGBA has established itself as a mechanistically plausible and therapeutically tractable pathway in neurodegeneration. The landmark FDA approvals of lecanemab and donanemab validate these converging investments and underscore the urgency of biomarker infrastructure development. Realizing the promise of precision neurology—particularly in resource-limited settings—will require coordinated action in assay standardization, regulatory harmonization, digital health infrastructure, and neurological workforce development globally.

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