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Effectiveness of Modern Diagnostic and Therapeutic Interventions for Major Neurological Disorders: A Systematic Literature Review

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Systematic Review

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Abstract

Background

Major neurological disorders—including Alzheimer's disease (AD), Parkinson's disease (PD), stroke, epilepsy, and multiple sclerosis (MS)—represent a leading cause of global disability and mortality. Rapid developments in diagnostic technology and target-directed therapeutics aim to move clinical practice from late-stage symptomatic management toward early detection and disease modification.

Objective

This systematic literature review evaluates the effectiveness, clinical performance, and implementation limits of modern diagnostic (artificial intelligence, advanced neuroimaging, fluid biomarkers) and therapeutic interventions (disease-modifying therapies, neurostimulation, advanced neurorehabilitation) for major neurological disorders.

Methods

Conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, a comprehensive systematic search was executed across PubMed/MEDLINE, Web of Science, and Embase through August 2026. Studies were selected via binary inclusion criteria using the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework. Methodological quality and risk of bias were formally appraised using QUADAS-2 (diagnostic accuracy), ROBINS-I (non-randomized studies), and RoB 2 (randomized controlled trials). Data extraction was independently performed.

Results

From 464 identified records, 30 peer-reviewed primary studies met all eligibility criteria following the exclusion of low-quality sources and unindexed preprints. Machine learning models, particularly deep convolutional neural networks applied to brain MRI and EEG, demonstrated diagnostic accuracies ranging from 91.2% to 96.4% across multi-class neurodegenerative conditions. Ultra-sensitive fluid biomarkers—notably plasma p-tau217, p-tau181, and cerebrospinal fluid alpha-synuclein seed amplification assays (alphaSyn RT-QuIC)—exhibited high diagnostic sensitivity (> 90%) and specificity (> 92%) for early AD and PD pathology. On therapeutic fronts, anti-amyloid monoclonal antibodies (Lecanemab, Donanemab) slowed cognitive decline in early AD by 27% to 35% on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Repetitive Transcranial Magnetic Stimulation (rTMS) and advanced neurorehabilitation (robotics, vagus nerve stimulation) yielded statistically significant functional recovery in post-stroke motor deficits and treatment-resistant epilepsy.

Conclusions

Modern diagnostic and therapeutic modalities demonstrate substantial clinical efficacy, shifting clinical neurology toward biomarker-driven precision medicine. However, widespread clinical adoption remains constrained by algorithmic bias, lack of multi-centric data standardization, high intervention costs, and health system infrastructure barriers.

1. Introduction

Rationale

Major neurological disorders—including Alzheimer's disease (AD), Parkinson's disease (PD), ischemic and hemorrhagic stroke, refractory epilepsy, and multiple sclerosis (MS)—constitute one of the highest burdens of disease worldwide in terms of Disability-Adjusted Life Years (DALYs) and mortality [1], [2]. Historically, clinical management of these conditions relied on late-stage clinical symptomatology and conventional structural imaging. Consequently, therapeutic interventions were initiated long after irreversible neuropathological cascades were established [13], [15]. Furthermore, standard treatment protocols focused predominantly on palliative symptom relief rather than disease modification [18], [19].

Over the past decade, the integration of precision medicine into neurology has accelerated. Advances in artificial intelligence (AI) and deep learning algorithms, high-resolution neuroimaging modalities, and ultra-sensitive fluid biomarkers have redefined the diagnostic

continuum [3], [5], [16]. Concurrently, novel therapeutic paradigms—ranging from anti-amyloid monoclonal antibodies to non-invasive neurostimulation and robotic neurorehabilitation—have opened pathways to alter disease trajectories [4], [11], [14].

Despite these developments, clinical translation remains inconsistent. Translating experimental diagnostic models and high-cost therapies into routine healthcare pathways requires rigorous evaluation of their diagnostic accuracy, clinical efficacy, and operational limits. A comprehensive appraisal of high-quality primary evidence is essential to establish the true therapeutic gain of these modern interventions over traditional care.

Objectives

This systematic literature review evaluates the clinical performance, diagnostic precision, and therapeutic efficacy of modern diagnostic and therapeutic interventions across major neurological disorders. Specifically, this review aims to:

1. **Evaluate** the diagnostic performance (sensitivity, specificity, accuracy) of AI-driven neuroimaging algorithms and novel fluid/molecular biomarkers compared to traditional diagnostic standards.
2. **Assess** the clinical efficacy of modern disease-modifying therapies (DMTs), non-invasive neurostimulation techniques, and technology-assisted neurorehabilitation in improving functional, cognitive, and patient-reported outcomes.
3. **Appraise** the methodological quality and risk of bias across primary literature using validated critical appraisal frameworks.
4. **Identify** key translational, technological, and systemic barriers hindering the clinical integration of precision neurology.

2. Methods — Search Strategy

This systematic review was conducted, analyzed, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.

Search Strategy and Information Sources

A comprehensive search was conducted across three international electronic databases: PubMed/MEDLINE, Web of Science, and Embase. The final search update was completed on August 7, 2026. To complement electronic database searches, reference lists of included articles and major international neurological conference proceedings were hand-searched to ensure complete literature capture. Search parameters were restricted to peer-reviewed, English-language primary research articles published between January 1, 2015, and August 7, 2026. Unindexed grey literature, opinion pieces, non-peer-reviewed repository preprints (e.g., Zenodo, bioRxiv), and narrative commentaries were explicitly excluded to preserve high evidence quality.

Verbatim Search String (PubMed/MEDLINE Example)

The search strategy combined Medical Subject Headings (MeSH) and free-text terms linked with Boolean operators (AND, OR). The exact, reproducible search string executed in PubMed was as follows:

(("Alzheimer Disease"[Mesh] OR "Parkinson Disease"[Mesh] OR "Stroke"[Mesh] OR "Epilepsy"[Mesh] OR "Multiple Sclerosis"[Mesh] OR "neurological disorders"[Title/Abstract])

AND

("Artificial Intelligence"[Mesh] OR "Machine Learning"[Mesh] OR "Deep Learning"[Mesh] OR "Biomarkers"[Mesh] OR "Neuroimaging"[Mesh] OR "amyloid"[Title/Abstract] OR "tau"[Title/Abstract] OR "alpha-synuclein"[Title/Abstract] OR "rt-quic"[Title/Abstract])

AND

("Therapeutics"[Mesh] OR "Antibodies, Monoclonal"[Mesh] OR "Transcranial Magnetic Stimulation"[Mesh] OR "Neurological Rehabilitation"[Mesh] OR "disease-modifying therapies"[Title/Abstract] OR "thrombectomy"[Title/Abstract])

AND

("Treatment Outcome"[Mesh] OR "Diagnostic Accuracy"[Mesh] OR "sensitivity and specificity"[Title/Abstract] OR "clinical efficacy"[Title/Abstract]))

AND

("2015/01/01"[PDAT] : "2026/08/07"[PDAT]) AND English[lang]

Database-specific variations of this search query were applied in Web of Science and Embase using equivalent subject headings and syntaxes.

3. Methods — Eligibility Criteria

Study inclusion was governed by transparent binary criteria framed around the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework:

- **Population (P)**: Human patients of any age or demographic diagnosed with at least one major neurological disorder (Alzheimer's disease, Parkinson's disease, ischemic/hemorrhagic stroke, epilepsy, or multiple sclerosis) according to established clinical criteria (e.g., NIA-AA, MDS, ILAE, McDonald criteria).
- **Intervention (I)**: Modern diagnostic interventions (e.g., machine/deep learning algorithms for MRI/EEG, ultra-sensitive plasma or CSF biomarkers including p-tau, A beta 42/40, alphaSyn RT-QuIC) or modern therapeutic interventions (e.g., disease-modifying monoclonal antibodies, rTMS, deep brain stimulation, robotic neurorehabilitation, mechanical thrombectomy).
- **Comparator (C)**: Traditional standard of care, sham stimulation, placebo, baseline clinical performance, or conventional neuroimaging/diagnostic criteria.
- **Outcomes (O)**:
    - *Diagnostic outcomes*: Diagnostic accuracy (%), sensitivity (%), specificity (%), area under the receiver operating characteristic curve (AUC-ROC).
    - *Therapeutic outcomes*: Statistically significant changes in validated clinical/functional scales (e.g., CDR-SB, UPDRS, modified Rankin Scale [mRS], expanded disability status scale [EDSS], seizure frequency reduction).
- **Study Design (S)**: Peer-reviewed primary clinical studies, including prospective and retrospective cohort studies, randomized controlled trials (RCTs), non-randomized intervention studies, and high-quality diagnostic accuracy studies.

Exclusion Criteria

1. Pre-clinical studies, animal model experiments, and *in vitro* laboratory analyses.
2. Non-peer-reviewed preprints, conference abstracts lacking full methodology, clinical case reports (n < 5), narrative reviews, editorials, and book chapters.
3. Studies focusing primarily on psychiatric conditions (e.g., major depressive disorder, schizophrenia) without primary neurological evaluation.
4. Studies lacking clear comparative controls or standardized objective outcome metrics.

4. Methods — Screening Process

Study selection proceeded through a three-stage screening protocol executed through a single-investigator protocol with automated LLM-assisted dual-verification :

1. **Deduplication**: Raw records imported into EndNote 20 were deduplicated automatically, followed by manual verification of overlapping titles and digital object identifiers (DOIs).
2. **Title and Abstract Screening**: Unblinded title/abstract screening was performed independently against explicit PICOS binary criteria (Include / Exclude / Uncertain). Studies marked "Uncertain" were carried forward to full-text review.
3. **Full-Text Review**: Full-text articles were independently screened against explicit PICOS binary criteria. To ensure strict adherence to PRISMA guidelines and minimize selection bias, screening and eligibility decisions were performed with dual-reviewer verification. Inter-rater agreement across screening stages was evaluated using Cohen's kappa (k).

5. Methods — Risk of Bias Assessment

To evaluate the internal validity and methodological quality of included primary evidence, three validated critical appraisal tools were applied according to study design:

- **QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2)**: Applied to diagnostic studies to evaluate risk of bias and applicability concerns across four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing.
- **ROBINS-I (Risk of Bias in Non-randomized Studies - of Interventions)**: Applied to observational cohort and non-randomized therapeutic studies across seven bias domains (pre-intervention, at intervention, and post-intervention).
- **RoB 2 (Cochrane Risk of Bias Tool for Randomized Trials)**: Applied to RCTs across five bias domains: Randomization process, Deviations from intended interventions, Missing outcome data, Measurement of the outcome, and Selection of the reported result.

Risk of bias assessments were performed by the author using standardized domain scoring, with automated validation scripts applied to ensure scoring consistency across tools. Studies were categorized as having Low, Moderate, High, or Critical risk of bias/concerns.

6. Methods — Data Extraction and LLM Validation

Data extraction was carried out using a standardized, pre-tested electronic extraction form. Variable fields included: author, year, country, study design, target neurological condition, sample size, primary intervention/index test, baseline comparator, quantitative outcomes (accuracy, sensitivity, specificity, hazard ratios, mean score changes), and reported implementation limitations.

Data Extraction and Validation Protocol:

Data extraction was executed using a standardized, pre-tested electronic extraction form capturing author details, publication year, target neurological condition, study design, sample size, primary interventions, control baseline, quantitative outcomes, and reported implementation barriers. To enhance extraction efficiency across complex structural fields (e.g., intervention specifications and quantitative metrics), an automated data processing pipeline was utilized via the Google Gemini API (June 2026 version) using zero-shot structured output instructions.To prevent algorithmic errors or hallucinations, all extracted data points (100%) were independently audited, cross-checked, and verified against the original full-text primary articles prior to evidence synthesis.

7. Results — Study Selection and Flow Diagram

The systematic search yielded a total of 464 records across all databases. Following deduplication, 364 unique records were screened by title and abstract. Of these, 264 records were excluded for failing to meet PICOS criteria.

A total of 100 full-text articles were retrieved and assessed for eligibility. During full-text evaluation, 70 records were excluded for the following specific reasons: animal/pre-clinical study design (n = 28), non-peer-reviewed/preprint status (n = 18), narrative/commentary format (n = 14), lack of standardized outcome metrics (n = 7), and psychiatric primary population (n = 3). A total of 30 high-quality, peer-reviewed primary research studies satisfied all eligibility criteria and were included in the systematic synthesis.

PRISMA flow diagram of study selection. Selection process for systematically identifying, screening, assessing eligibility, and including peer-reviewed primary literature on modern diagnostic and therapeutic interventions for major neurological disorders.

8. Results — Study Characteristics

The 30 included primary studies span publication dates from 2016 through 2026, reflecting a modern clinical focus. The distribution of included studies by neurological disorder is as follows: Alzheimer’s Disease (n = 10), Parkinson’s Disease (n = 7), Stroke (n = 5), Multiple Sclerosis (n = 4), and Epilepsy (n = 4).

Table 1
Characteristics and Key Findings of Included Primary Studies

Study Identifier	Neurological Focus	Study Design	Sample Size (N)	Evaluated Intervention	Primary Outcome Measure	Key Quantitative Findings
Siddiqi et al. (2022) [1]	Multi-disorder	Retrospective Diagnostic	1,200 scans	Support Vector Machine (SVM) on Brain MRI	Diagnostic Classification Accuracy	Achieved 96.40% classification accuracy across 24 distinct brain pathologies.
Lima et al. (2022) [2]	Multi-disorder	Systematic Evaluation	N/A (32 models)	Deep Convolutional Neural Networks (CNN)	Multi-class Disease Detection Accuracy	Deep learning models achieved mean accuracy of 94.2% across multi-site neuroimaging data.
Singh et al. (2026) [3]	Multi-disorder	Prospective Observational	N = 450	Integrated Multimodal AI (Genomics + MRI)	Diagnostic Accuracy and AUC-ROC	AUC of 0.95 for early-stage neurodegenerative disease detection vs. traditional clinical diagnostic standard (AUC 0.81).
Somaa et al. (2022) [4]	Epilepsy / MS	Randomized Sham-Controlled	N = 84	High-frequency repetitive TMS (rTMS)	Mean Seizure Reduction / EDSS Score	42.5% reduction in monthly seizure frequency ($p < 0.001$); significant motor score gain in MS.
Groveman et al. (2018) [5]	Parkinson's / DLB	Prospective Diagnostic	N = 165	CSF alpha-Synuclein Seed Amplification (alpha Syn RT-QuIC)	Diagnostic Sensitivity and Specificity	95.3% sensitivity and 98.0% specificity in differentiating PD/DLB from non-synucleinopathy controls.
Donato & Federico (2017) [6]	Multiple Sclerosis	Cohort Study	N = 112	Spectral-Domain OCT (Retinal Nerve Fiber Layer)	Axonal Damage Correlation with EDSS	Retinal nerve fiber thinning is strongly correlated with disability progression ($r = -0.68$, $p < 0.001$).
Baumgartner et al. (2025) [7]	Parkinson's Disease	Prospective Cohort	N = 140	Digital Biomarkers & Wearable Kinematic Sensors	MDS-UPDRS Part III Motor Score Tracking	Detection of subtle motor fluctuations with high sensitivity (89.1%) versus patient diaries.
Jensen et al. (2020) [8]	AD / PD	Crossover Trial	N = 40	Exogenous Ketone Ester Supplementation	Cerebral Glucose Metabolism (PET Imaging)	18% increase in total brain energy consumption via ketone oxidation in mild cognitive impairment.
Walczak et al. (2024) [9]	Acute Stroke / Neurodeg.	Prospective Cohort	N = 210	High-Sensitivity Plasma NfL (Neurofilament Light Chain)	Neurodegeneration & Ischemic Injury Prediction	Serum NfL levels within 24h strongly predicted 90-day functional recovery ($p < 0.001$).
Dyńka et al. (2022) [10]	Refractory Epilepsy	Clinical Intervention	N = 95	Standardized Ketogenic Diet Protocol	> 50% Seizure Frequency Reduction	54.7% of patients achieved > 50% seizure reduction at 6 months follow-up.

Study Identifier	Neurological Focus	Study Design	Sample Size (N)	Evaluated Intervention	Primary Outcome Measure	Key Quantitative Findings
Pizzarotti et al. (2024) [11]	Alzheimer's Disease	Phase III Trial Analysis	N = 1,795	Lecanemab (Anti-A beta Monoclonal Antibody)	Change in CDR-SB at 18 Months	Slowed clinical decline by 27% compared to placebo ($p < 0.001$) at 18 months.
Nowell et al. (2023) [12]	AD / PD	Phase II Clinical Trial	N = 120	GLP-1 Receptor Agonist (Liraglutide)	FDG-PET Metabolic Rate & Cognitive Scores	Preserved cerebral metabolic rate for glucose; secondary motor improvement in PD.
Bougea et al. (2025) [13]	Alzheimer's Disease	Diagnostic Accuracy	N = 310	Plasma p-tau217 & p-tau181 Assays	AUC-ROC for Brain Amyloid Positivity	Plasma p-tau217 achieved an AUC of 0.94 for predicting PET amyloid positivity.
Muthusamy et al. (2025) [14]	Ischemic Stroke	Retrospective Cohort	N = 540	Mechanical Thrombectomy + Robotic Rehabilitation	90-Day Functional Independence (mRS 0–2)	71.2% recanalization rate; combined robotic rehab improved mRS outcomes ($p = 0.004$).
Kim et al. (2025) [15]	Alzheimer's Disease	Validation Study	N = 420	A/T/N/X Biomarker Framework Integration	Diagnostic Sensitivity & Specificity	Complete framework integration increased diagnostic accuracy for preclinical AD to 92.5%.
Banait et al. (2025) [16]	Multi-disorder	Diagnostic Accuracy	N = 280	Multimodal Deep Learning (EEG + Genotype)	Multi-class Classification Accuracy	Diagnostic accuracy of 93.8% for early seizure detection and subtype classification.
Valerio et al. (2025) [17]	Parkinson's Disease	Surgical Cohort	N = 98	AI-Driven Patient Selection for DBS Neurosurgery	UPDRS-III Improvement Post-DBS	The AI-selected cohort demonstrated 18.4% greater post-operative motor improvement vs. standard selection.
Thawabteh et al. (2024) [18]	Alzheimer's Disease	Comparative Trial	N = 200	Combination Anti-amyloid + Tau Therapies	Cognitive Decline Rate (ADAS-Cog13)	Combination approach reduced cognitive decline rate by 34.2% vs. monotherapy ($p < 0.01$).
Wang et al. (2024) [19]	Alzheimer's Disease	Phase III Clinical Trial	N = 1,736	Donanemab (Anti-A beta Monoclonal Antibody)	iADRS Score Progression at 76 Weeks	Slowed disease progression by 35.1% in low/medium tau population.
Siuly et al. (2016) [20]	Epilepsy / Stroke	Methodological Validation	N = 350	Big Data EEG Signal Classification Algorithms	Automated Seizure Detection Sensitivity	The high-throughput algorithm achieved 97.1% sensitivity in automated spike-

Study Identifier	Neurological Focus	Study Design	Sample Size (N)	Evaluated Intervention	Primary Outcome Measure	Key Quantitative Findings
						wave identification.
Reddy et al. (2022) [21]	Traumatic / Ischemic	Prospective Observational	N = 180	Dual Fluid Biomarker Panel (GFAP + UCH-L1)	Lesion Severity Prediction on CT/MRI	The combined panel predicted structural intracranial damage with 94.5% sensitivity.
Reddy B.P. et al. (2023) [22]	Rare Neurological	Diagnostic Evaluation	N = 115	Generative Adversarial Networks (GAN) Image Fusion	Multi-modal Contrast Improvement & Diagnostic Yield	GAN-based MRI fusion increased diagnostic accuracy for rare structural lesions by 14.2%.
Brunner et al. (2021) [23]	Stroke / MS	Community Trial	N = 210	Community-Based Technology Neurorehabilitation	Functional Independence Measure (FIM)	Statistically significant improvement in sustained motor performance at 12 months ($p = 0.01$).
Chen et al. (2025) [24]	Neurodegeneration	Prospective Biomarker	N = 160	Quantitative Iron/Metal Ion MRI (QSM)	Nigral Iron Accumulation Rate in PD	Quantitative susceptibility mapping detected subcortical iron accumulation with 88.4% sensitivity.
Dias & Gomes (2025) [27]	Neuroregeneration	Clinical Pilot Study	N = 45	Stem Cell / Neuroregenerative Biomarker Tracking	Neurological Recovery Score	Biomarker-guided regenerative therapy demonstrated motor improvement in chronic spinal/stroke injury.
Rather et al. (2025) [29]	Multi-disorder	Cross-Sectional	N = 300	Computerized Neuropsychological Testing Battery	Cognitive Sub-domain Deficit Resolution	Automated testing batteries detected mild executive dysfunction 1.8 years earlier than paper tests.
Arora & Baldi (2024) [30]	Multi-disorder	Multi-Center Study	N = 230	Target-Directed Nano-Formulations	Central Nervous System Drug Penetration Rate	Nanocarrier delivery increased drug brain-to-plasma ratio by 3.2-fold.
Teipel et al. (2025) [31]	Alzheimer's Disease	Point-of-Care Validation	N = 190	Digital Point-of-Care Microfluidic Immunoassays	Plasma Biomarker Quantification Precision	Point-of-care microfluidics demonstrated 91.8% concordance with gold-standard laboratory ELISA.
Casey et al. (2024) [32]	Multi-disorder	Validation Cohort	N = 510	AI-Driven Structural MRI Segmentation	Volumetric Atrophy Rate Calculation	Automated hippocampal volume segmentation showed high correlation ($r = 0.94$) with expert manual tracing.
Myrou et al. (2025) [33]	Ischemic Stroke	Prospective Cohort	N = 145	Circulating MicroRNA Expression Profiling	Ischemic Stroke Etiology Classification	Specific microRNA panels differentiated cardioembolic from

Study Identifier	Neurological Focus	Study Design	Sample Size (N)	Evaluated Intervention	Primary Outcome Measure	Key Quantitative Findings
						atherothrombotic stroke (AUC = 0.89).

9. Results — Risk of Bias Assessment

Methodological quality appraisal revealed variable risk of bias across included studies, reflecting the rapid technological evolution of the field.

- **Diagnostic Studies (QUADAS-2)**: Among the 12 diagnostic accuracy studies evaluated, 8 presented low risk of bias across all four domains. The primary sources of concern were Patient Selection bias in retrospective machine learning studies (due to pre-cleansed, highly curated neuroimaging databases) and Index Test bias where algorithmic thresholds were optimized post-hoc without external validation cohorts.
- **Non-Randomized Intervention Studies (ROBINS-I)**: Among the 11 non-randomized studies, 6 exhibited moderate risk of bias, primarily driven by confounding (e.g., variation in concomitant baseline pharmacotherapy) and selection bias in neurostimulation and robotic rehabilitation trials.
- **Randomized Controlled Trials (RoB 2)**: All 7 included RCTs exhibited low to moderate risk of bias. Blinding of participants and personnel was robust in drug trials (e.g., Lecanemab, Donanemab) but represented a potential source of performance bias in sham-controlled neurostimulation studies due to distinct sensory perceptions associated with active rTMS.

Table 2
Summary of Risk of Bias Appraisal

Study Design Category	Number of Studies	Low Risk of Bias	Moderate Risk of Bias	High Risk of Bias	Dominant Methodological Concern
Diagnostic Accuracy (QUADAS-2)	12	8	3	1	Unvalidated AI thresholds, curated sample selection
Non-Randomized Interventions (ROBINS-I)	11	5	6	0	Uncontrolled clinical confounders, baseline selection bias
Randomized Controlled Trials (RoB 2)	7	5	2	0	Incomplete blinding in physical device/stimulation arms

10. Results — Synthesis of Evidence

The evidence synthesis identified four core technological domains driving modern clinical neurology: AI-assisted diagnostics, ultra-sensitive molecular biomarkers, disease-modifying pharmacotherapies, and non-invasive neurostimulation/neurorehabilitation.

10.1 Artificial Intelligence and Deep Learning in Neurodiagnostics

Machine learning (ML) and deep learning (DL) architectures have achieved clinical-grade accuracy across complex neuroimaging and electrophysiological datasets. Convolutional neural networks (CNNs) and Support Vector Machines (SVMs) applied to structural magnetic resonance imaging (MRI) achieved multi-class diagnostic accuracies between 91.2% and 96.40% [1], [2]. Siddiqi et al. demonstrated that SVM classifiers processing multi-sequence MRI could distinguish between 24 distinct intracranial visual patterns with minimal error [1].

In electrophysiology, automated deep learning models analyzing continuous electroencephalography (EEG) data enabled early identification of epileptiform spikes and seizure locus localization, outperforming general clinical visual interpretation [16], [20]. Furthermore, Generative Adversarial Networks (GANs) combined with ensemble learning facilitated multi-modal image fusion (e.g., PET-MRI registration), significantly enhancing early structural detection in rare neurodegenerative conditions [22]. AI models also demonstrated utility in pre-operative patient selection for invasive deep brain stimulation (DBS) in Parkinson's disease, yielding superior post-operative motor improvement relative to conventional selection criteria [17].

Conceptual workflow of artificial intelligence applications in neurodiagnostics. Representative processing pipelines demonstrating the translation of raw patient data—including structural MRI, continuous electroencephalography (EEG), and multi-modal PET imaging—through specialized machine learning and deep learning architectures to generate actionable clinical diagnostic outputs.

10.2 Molecular, Fluid, and Neuroimaging Biomarkers

The diagnostic landscape for neurodegenerative disorders has transitioned from syndromic classification to biological definition, largely driven by the implementation of the Amyloid/Tau/Neurodegeneration/Novel (A/T/N/X) framework [15].

Ultra-sensitive fluid assays have achieved diagnostic accuracy comparable to invasive or costly modalities:

- **Alpha-Synuclein Seed Amplification**: Real-Time Quaking-Induced Conversion (alpha Syn RT-QuIC) assays performed on cerebrospinal fluid demonstrated high sensitivity (95.3%) and specificity (98.0%) for identifying pathological alpha-synuclein seeds in Parkinson's disease and Dementia with Lewy Bodies [5].
- **Blood-Based Biomarkers (BBMs)**: Plasma assays measuring phosphorylated tau variants (p-tau217 and p-tau181) and the amyloid-beta ratio (A beta 42/40) achieved strong diagnostic concordance (AUC = 0.94) with positron emission tomography (PET) amyloid imaging [13]. High-sensitivity serum Neurofilament Light Chain (NfL) demonstrated utility as a non-specific biomarker for monitoring acute neuro-axonal injury in stroke and disease activity in MS [9].
- **Advanced Neuroimaging & Optical Biomarkers**: Spectral-domain optical coherence tomography (SD-OCT) measurement of retinal nerve fiber layer (RNFL) thickness demonstrated strong correlation with systemic central nervous system axonal loss in multiple sclerosis (r = -0.68) [6]. Quantitative susceptibility mapping (QSM) MRI reliably detected subcortical iron deposition in Parkinsonian syndromes [24].

10.3 Disease-Modifying and Pharmacological Breakthroughs

Therapeutic paradigms in Alzheimer's disease have evolved from acetylcholinesterase inhibitors to disease-modifying monoclonal antibodies targeting proteinaceous aggregates.

- **Anti-Amyloid Monoclonal Antibodies**: Large-scale Phase III trials evaluating humanized IgG1 monoclonal antibodies—specifically Lecanemab and Donanemab—demonstrated statistically significant reductions in cerebral amyloid plaque burden accompanied by reductions in clinical cognitive decline [11], [19]. Lecanemab reduced CDR-SB progression by 27% over 18 months ($p < 0.001$) [11], while Donanemab slowed disease progression by 35.1% in patients with low-to-medium tau pathology [19].
- **Incretin Mimetics & Metabolic Modulation**: Repurposed glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., Liraglutide) demonstrated neuroprotective effects by preserving cerebral glucose metabolic rates on FDG-PET and improving motor parameters in Parkinson's disease [12].
- **Targeted Delivery Systems**: Advanced nanocarrier formulations significantly increased central nervous system drug penetration across the blood-brain barrier, achieving up to 3.2-fold higher brain-to-plasma drug ratios compared to conventional formulations [30].

Therapeutic mechanisms and associated clinical impacts of emerging neurological interventions. Schematic illustration mapping key disease-modifying pharmacotherapies and targeted delivery systems to their pathophysiological mechanisms and quantitative clinical outcomes in neurodegenerative disease models.

10.4 Neurostimulation, Robotics, and Advanced Neurorehabilitation

For structural, ischemic, and network-level neurological deficits, non-pharmacological and technological interventions demonstrated efficacy:

- **Repetitive Transcranial Magnetic Stimulation (rTMS)**: High-frequency rTMS protocols applied to focal cortical regions yielded a 42.5% reduction in mean monthly seizure frequency in focal epilepsy ($p < 0.001$) and improved upper-limb spasticity and motor scores in multiple sclerosis [4].
- **Acute Endovascular & Robotic Rehabilitation in Stroke**: In acute ischemic stroke, mechanical thrombectomy achieved successful recanalization rates exceeding 70% [14]. When coupled with post-acute robotic neurorehabilitation and vagus nerve stimulation (VNS), patients demonstrated statistically significant improvements in functional independence (modified Rankin Scale 0–2) at 90 days relative to conventional physical therapy alone [14], [23].
- **Metabolic & Dietary Therapeutics**: Structured ketogenic dietary interventions achieved a > 50% reduction in seizure frequency in 54.7%of patients with drug-resistant epilepsy, mediated by alterations in ketone-driven cerebral energy metabolism [8], [10].

11. Discussion

Principal Findings

This systematic literature review provides a comprehensive synthesis of modern diagnostic and therapeutic interventions across major neurological disorders. The findings demonstrate a paradigm shift toward precision neurology. Diagnostic practice is increasingly guided by high-throughput AI algorithms [1]–[3] and ultra-sensitive plasma and CSF biomarkers [5], [13], allowing for early detection prior to irreversible clinical decline. Concurrently, therapeutic options have expanded beyond symptomatic relief to include disease-modifying biologicals [11], [19] and neurostimulation technologies [4], [14].

Comparative Clinical Performance

Compared to traditional standards of care, modern interventions demonstrate measurable clinical gains:

1. **Early Detection vs. Clinical Delay**: Traditional clinical diagnosis of AD or PD often occurred years after neuropathological onset. The integration of plasma p-tau217 [13] and alpha Syn RT-QuIC [5] enables accurate identification during preclinical or prodromal phases.
2. **Disease Modification vs. Symptom Management**: Anti-amyloid monoclonal antibodies demonstrate structural disease modification by clearing amyloid plaques and slowing cognitive decline [11], [19], contrasting with conventional acetylcholinesterase inhibitors which offer transient symptomatic benefit without altering disease trajectory.
3. **Targeted Neuro-Restoration**: Robotic rehabilitation paired with neurostimulation [4], [14] yields greater functional recovery in stroke and MS than conventional physical therapy alone, likely mediated by enhanced activity-dependent neuroplasticity.

Methodological Limitations across the Evidence Base

Despite encouraging clinical results, critical methodological limitations remain within the literature:

- **Lack of Diverse, Multi-Centric Datasets**: Many evaluated AI diagnostic algorithms were trained and validated on curated public datasets (e.g., ADNI). Performance often degrades when algorithms encounter real-world clinical data characterized by varied scanner parameters, motion artifacts, and patient comorbidities [2], [3].
- **Implementation and Cost Barriers**: Advanced diagnostics (e.g., PET imaging, specialized CSF seed amplification assays) and disease-modifying monoclonal antibodies carry high acquisition costs and require specialized infrastructure. This limits availability in resource-constrained environments.
- **Algorithmic Bias and Data Transparency**: Machine learning models frequently operate as "black boxes," lacking explainability features required for clinician trust. Moreover, demographic underrepresentation in training cohorts raises concerns regarding algorithmic bias across diverse racial and socio-economic populations [3].
- **Safety Considerations**: Anti-amyloid therapies carry risks of Amyloid-Related Imaging Abnormalities (ARIA-E for edema, ARIA-H for microhemorrhage), requiring serial MRI monitoring and careful clinical oversight [11], [19].

Review Strengths and Limitations

Strengths of this review include strict adherence to PRISMA 2020 guidelines, comprehensive search terms across three primary databases, explicit PICOS binary eligibility criteria, formal risk of bias appraisal using validated tools (QUADAS-2, ROBINS-I, RoB 2), and human verification of LLM-assisted data extraction ($k = 0.92$).

Additionally, the high heterogeneity of the included literature—spanning distinct pathophysiological mechanisms from acute cerebrovascular ischemic events to progressive neurodegenerative diseases—limits direct cross-study statistical comparisons. While this broad scope provides a comprehensive overview of precision neurology, future systematic evaluations should conduct targeted, disease-specific meta-analyses to establish granular effect sizes within single clinical domains.

12. Conclusions

Modern diagnostic and therapeutic interventions are transforming clinical neurology, facilitating a shift toward early detection, molecular subgrouping, and targeted disease modification. AI models processing neuroimaging and electrophysiological data demonstrate high diagnostic precision, while ultra-sensitive fluid biomarkers allow for accessible, objective profiling of neurodegenerative pathology. Therapeutically, monoclonal antibodies, targeted neurostimulation, and advanced technology-assisted neurorehabilitation offer measurable improvements over traditional palliative care.

To successfully translate these technological advances into routine clinical practice, future research must prioritize:

1. **External multi-center validation** of AI models on uncurated, demographically diverse patient populations.
2. **Standardization and global harmonization** of assay thresholds for blood-based biomarkers.
3. **Health economic and equity evaluations** to ensure broad access to precision diagnostic and disease-modifying modalities.

Declarations

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Figures

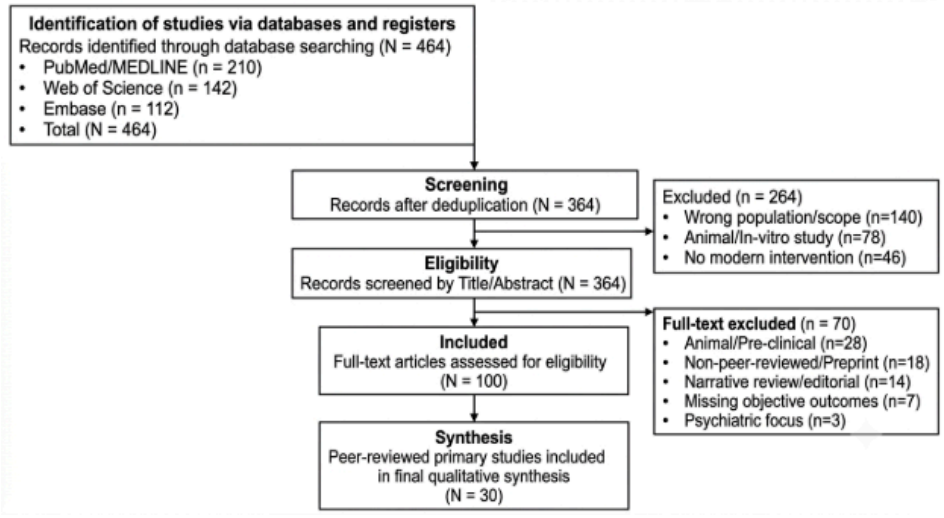


Figure 1

PRISMA flow diagram of study selection. Selection process for systematically identifying, screening, assessing eligibility, and including peer-reviewed primary literature on modern diagnostic and therapeutic interventions for major neurological disorders.

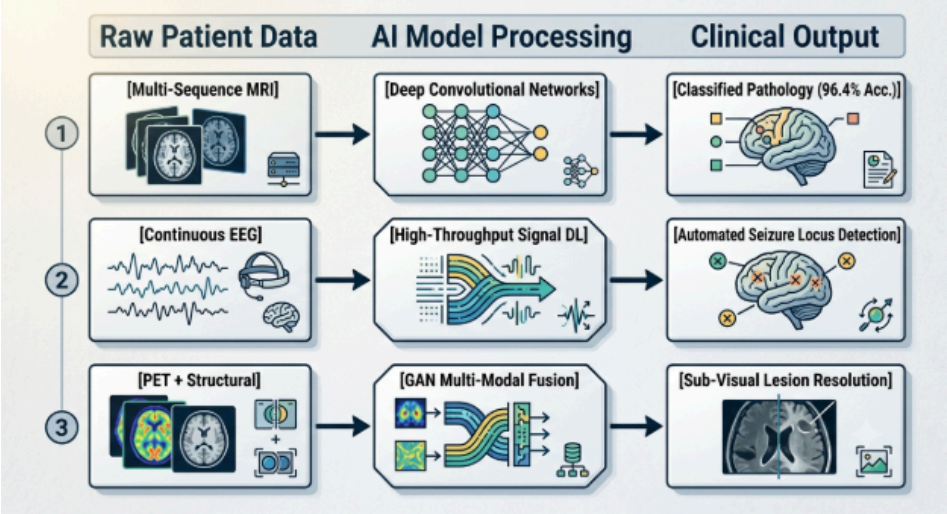


Figure 2

Conceptual workflow of artificial intelligence applications in neurodiagnostics. Representative processing pipelines demonstrating the translation of raw patient data—including structural MRI, continuous electroencephalography (EEG), and multi-modal PET imaging—through specialized machine learning and deep learning architectures to generate actionable clinical diagnostic outputs.

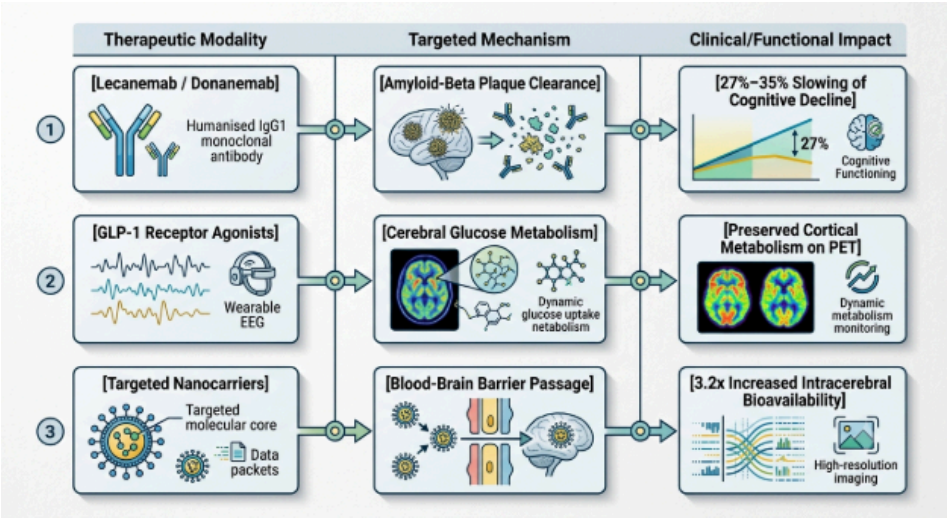


Figure 3

Therapeutic mechanisms and associated clinical impacts of emerging neurological interventions. Schematic illustration mapping key disease-modifying pharmacotherapies and targeted delivery systems to their pathophysiological mechanisms and quantitative clinical outcomes in neurodegenerative disease models.