Applied Medical Informatics
Vol. 47, No.4/2025, pp -

Transforming Multiple Sclerosis Management through Artificial Intelligence: A Comprehensive Narrative Review of Clinical, Imaging, Digital, and Molecular Applications

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Received: 2 August 2025/Accepted: 5 December 2025/ Published online: 12 December 2025

Abstract
Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with variable symptoms, disease courses, and responses to therapy. Diagnosis and prognosis remain ongoing difficulties in the early stages of the disease. This narrative review considers how artificial intelligence (AI) can improve MS diagnosis, monitoring, and personalized therapy. Advances include AI-augmented magnetic resonance imaging (MRI), Optical coherence tomography (OCT), and positron emission tomography (PET) scan interpretation to improve the diagnostic performance, subtype classification, and relapse prediction. AI also allows remote monitoring using wearables and smartphone applications, and omics-based interventions allow the identification of biomarkers and personalized therapy. Future versions, such as explainable AI, federated learning, and large language models (LLMs), offer improved transparency of models and generalizability. Although AI holds immense potential for precision medicine for MS, translation to clinical medicine depends on proof by stringent studies, accommodation of variability of data, and responsible use.

Keywords*:* Multiple sclerosis; Artificial Intelligence (AI); Imaging; Digital health (dHealth); Omics.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune, progressive central nervous system (CNS) disease characterized by immune-mediated inflammation, demyelination, and neurodegeneration [1]. Multiple sclerosis affects approximately 2.8 million people worldwide, predominantly females between the ages of 20 and 40 [2, 3]. The exact etiology of MS is still not well understood, although it is mediated through a complex interplay of genetic, environmental, and immune-mediated mechanisms, leading to inflammation, demyelination, and neurodegeneration [4, 5]. Multiple sclerosis typically manifests with a wide range of neurological deficits ranging from visual loss, motor machinery weakness, and sensory loss to coordination loss, echoing the multifocal nature of demyelinating lesions [6].

The main clinical subtypes of MS include relapsing-remitting MS (RRMS), which is episodic relapses with or without full recovery; secondary progressive MS (SPMS), which is a relapsing course followed by steady worsening; primary progressive MS (PPMS), a steady progression of neurological impairment from the beginning; and progressive-relapsing MS (PRMS), a less common subtype with progressive worsening and superimposed relapses [7, 8].

Multiple sclerosis presents numerous challenges to both practitioners and patients. Symptoms often overlap with other neurological diseases, making an accurate diagnosis difficult [9]. Differentiating between subtypes is also challenging, but necessary for appropriate treatment [8]. Predicting disease progression and therapy response is complicated by a lack of reliable biomarkers. Integrating clinical data, magnetic resonance imaging (MRI), and laboratory results , since these data are gathered from multiple sources, requires careful interpretation, and often lack standardized formats, making the integration process time-consuming and complex., hindering personalized care [10, 11]. Moreover, monitoring disease activity and patient follow-up can be difficult, as changes in symptoms and imaging findings may be subtle or inconsistent [12, 13].

Artificial intelligence (AI) offers promising tools for enhancing the understanding and management of MS [14]. By leveraging advanced computational algorithms, AI can analyze large and heterogeneous datasets such as MRI scans, clinical records, and genetic profiles more efficiently than traditional methods [14, 15]. Artificial intelligence has the potential to support early diagnosis, predict disease progression, identify treatment responses, and personalize therapeutic strategies, thus transforming MS care [14, 16].

This narrative review aimed to assess the use of AI in clinical practice for the management of MS. A summary of MS and its related issues, context, and rationale for integrating AI methods into MS care, and basic concepts and methods are provided. This review discusses how AI can improve diagnosis, subtyping discrimination, disease progression prediction, and the analysis of imaging and digital health data. Current evidence on AI-based interventions is reviewed, as well as the limitations, challenges to implementation, and future potential areas of research and clinical applications (Table 1).

Clinical Applications of Artificial Intelligence in Multiple Sclerosis

Artificial Intelligence for Diagnosis

Accurate diagnosis of MS is particularly challenging due to its highly variable presentations, heterogeneous symptoms, and lack of a definitive diagnostic test [9]. Although clinical examination, MRI, and cerebrospinal fluid (CSF) analysis are routinely used, these tests tend to yield inconclusive findings, especially in early or unusual presentations, and there can be a significant overlap with other disorders that share similar clinical and imaging findings [64].

Multiple sclerosis diagnosis primarily relies on demonstrating lesions dispersed in both time and space, while excluding other neurological conditions. One of the main diagnostic tools is to demonstrate characteristic lesion patterns and anatomical involvement [65]. However, numerous inherited and acquired disorders, including hypoxic-ischemic vasculopathy, small-vessel disease, inflammatory and autoimmune conditions, vasculitis, and certain toxic, metabolic, and infectious disorders, can mimic MS on MRI, often presenting features similar to dissemination in time and space [66]. In addition, conditions such as neuromyelitis optica spectrum disorder (NMOSD) may present with optic neuritis (ON) and transverse myelitis overlapping with MS, but typically cause more severe attacks and require alternative treatment [67]. Lupus and vasculitis can similarly affect the CNS, producing white matter lesions and symptoms that resemble MS. Migraine, despite its transient neurological presentation and white matter hyperintensities on MRI, and small vessel disease, particularly in older patients, can complicate the radiological picture [68]. Therefore, a comprehensive differential diagnosis is essential to avoid misdiagnosis and ensure accurate identification and management of MS.

Table 1. Applications of Artificial Intelligence in multiple sclerosis management

Application Domain	AI Techniques	Data Types	Clinical Impact
Diagnosis [17-, 18, 19, 20]	CNNs, SVM, RF	MRI, OCT, PET, EEG, EPs, Biomarkers (serum, CSF, genetics)	Improved diagnostic accuracy, differentiation from mimickers (NMOSD, vasculitis, migraines)
Patient Stratification [21-, 22, 23, 24, 25]	Clustering, CNN, GAN, SuStaIn	Clinical data, MRI	Early identification of MS subtypes, prediction of disease course
Prognosis and Progression [26-, 27, 28, 29, 30, 31]	RF, SVM, CNN, ANN, hybrid ML/DL	Clinical measures (EDSS), MRI data, Biomarkers (NfL, cytokines), wearable data	Accurate predictions of progression, CIS conversion, personalized treatment strategies
MRI Imaging Analysis [32-, 33, 34, 35, 36]	CNN (U-Net), GMM, FAST	MRI	Automated lesion segmentation, reduced imaging time and gadolinium dosage, enhanced lesion identification
OCT [20, 37-, 38, 39, 40]	CNN, SVM	OCT images (RNFL, GCL)	Early detection of optic neuritis, subclinical optic nerve involvement, monitoring disease progression
PET Scan [41-, 42, 43, 44, 45]	CNN, CF-SAGAN, SVM	PET scans ([^{11}C] PIB, TSPO, FET-PET)	Early detection of inflammation, assessment of microglial activity, differentiation from gliomas
Digital Health Tools [46-, 47, 48, 49, 50, 51]	SVM, RF, CNN, LSTM, XGBR	Wearable devices, smartphone sensors (gait, balance, heart rate, cognitive tasks)	Remote continuous monitoring, early relapse detection, improved patient-provider communication
Personalized Therapy [52-, 53, 54, 55]	CNN, ResNet, U-Net, SHAP-enhanced XGBoost, CLAIMS	Clinical data, imaging, biomarkers (FKLCi, sNfL, CXCL13, CHI3L1)	Tailored therapy choices, improved adherence, precision medicine implementation
Omics Data Integration [56-, 57, 58]	ANN, CNN, unsupervised ML	Genomic, transcriptomic, proteomic, metabolomic data	Biomarker discovery, early diagnosis, prediction of treatment response and disease progression
Emerging AI Techniques [42, 59-, 60, 61, 62, 63]	Federated learning, blockchain, GAN, Diffusion models, LLMs, RAG	Multimodal data integration (MRI, OCT, PET, wearables, EHR)	Addressing data limitations, enhancing interpretability, realistic data augmentation, education and clinical decision support

ANN, Artificial Neural Networks; CF-SAGAN, Conditional Flexible Self-Attention Generative Adversarial Network; CIS, Clinically Isolated Syndrome; CNN, Convolutional Neural Networks; CSF, Cerebrospinal Fluid; DL, Deep Learning; EDSS, Expanded Disability Status Scale; EEG, Electroencephalogram; EP, Evoked Potentials; FAST, FMRIB's Automated Segmentation Tool; FET-PET, Fluoro-ethyl-tyrosine PET; FKLCi, Free Kappa Light Chain Index; GAN, Generative Adversarial Networks; GCL, Ganglion Cell Layer; GMM, Gaussian Mixture Model; LLMs, Large Language Models; LSTM, Long Short-Term Memory Networks; ML, Machine Learning; MRI, Magnetic Resonance Imaging; NfL, Neurofilament Light; OCT, Optical Coherence Tomography; PET, Positron Emission Tomography; RF, Random Forest; RNFL, Retinal Nerve Fiber Layer; RRMS, Relapsing-Remitting MS; SPMS, Secondary Progressive MS; SVM, Support Vector Machine; SuStaIn, Subtype and Stage Inference; TSPO, 18-kDa Translocator Protein; XGBR, Extreme Gradient Boosting Regression.

Many studies have demonstrated that AI applied to MRI-based studies shows great potential for diagnosing and differentiating MS from similar conditions [15, 69-, 70, 71, 72, 73]. Machine learning (ML) and deep learning (DL) frameworks have contributed to this progress. Machine Learning models, including random forests (RF) and support vector machines (SVMs), leverage structured data from clinical records, laboratory tests, and quantitative MRI values to diagnose patients by detecting subtle lesion features and other patterns [74, 75]. These models integrate heterogeneous data such as lesion size, shape, and location, One study reported an accuracy of 78.38% (95% CI 72.86–83.23%) in the original cohort and 71.88% (95% CI 53.25–86.25%) in an external cohort [76], another study reported test-set accuracies of 0.71 for Extra Trees, 0.69 for Logistic Regression, and 0.67 for SVM in predicting disease progression [77]. Deep Learning models, particularly convolutional neural networks (CNNs) and two-dimensional radial k-space multiscale convolutional attention

networks (2DRK-MSCAN), process complex and unstructured MRI data directly and automatically identify small or newly formed lesions and subtle tissue patterns that may elude human readers [78-, 79, 80, 81]. Convolutional neural networks excel in learning nuanced imaging features, such as lesion shape, distribution, and tissue texture, without explicit feature engineering, enhancing diagnostic accuracy, and reducing observer variability; preprocessing processes such as edge detection and wavelet transforms; and model verification and class balance, further enhancing these AI techniques for MRI-based MS diagnosis faster, more effective, and more viable in clinical practice [82].

Optical coherence tomography (OCT) is another valuable tool that enables noninvasive quantification of retinal damage that correlates with neurological and neurophysiological measures in PwMS. OCT provides an image-based analysis of retinal layers affected by MS, capturing thinning of the Retinal Nerve Fiber Layer (RNFL) and ganglion cell layer (GCL). Artificial intelligence using SVMs and CNNs leverages OCT data to classify PwMS from HCs with an accuracy of 86-97% [83-, 84, 85]. Algorithms can also detect asymmetry between eyes, which is an important early indicator of MS involvement (86). Integrating OCT with AI enhances early detection, especially for subclinical optic nerve involvement in PwMS [87, 88].

Artificial intelligence has also been successfully applied in various non-imaging diagnostics. Both ML and DL have shown significant potential for differentiating MS from other neurological conditions using non-MRI-based diagnostic tests. Studies have shown that AI can detect clinical features such as age, fatigue, balance and gait disturbances, expanded disability status scale (EDSS), and ambulatory index [14, 89]; ML approaches such as RF and SVM have also enhanced the evaluation of visual and motor evoked potentials (EPs), which have a strong correlation with the EDSS in PwMS [90, 91].

Laboratory biomarkers, such as cytokine levels, vitamins, and serum biomarkers, as well as electroencephalogram (EEG) recordings and exhaled breath analyses, have been integrated into AI models. These approaches have achieved diagnostic accuracy often exceeding 85-95%, complementing MRI-based methods and enhancing early detection in resource-limited settings [92]. For instance, EEG-based models with the advantage of time-frequency analysis and wavelet transforms attained an accuracy of 96%, and blood transcriptional signatures distinguished definite MS patients from healthy controls with accuracies of up to 97% [93, 94]. Genetic susceptibility markers such as human leukocyte antigen (HLA)-II alleles, particularly HLA-DRB115:01 and killer-cell immunoglobulin-like receptor (KIR) genes, have been identified using decision trees, achieving training accuracies of approximately 81% in PwMS [95].

Additional studies using SVMs applied to gene expression profiles from peripheral blood mononuclear cells revealed differentially expressed genes with a validation accuracy of 86% [96]. Metabolomics and lipidomics studies using RF and unsupervised ML approaches have identified key blood-based metabolites and lipid biomarkers related to glutathione metabolism, fatty acid oxidation, and membrane composition, with receiver operating characteristic area under the curve (ROC-AUCs) over 80-95% [97-, 98, 99]. CSF analyses applying ML to combined protein and metabolite markers, such as cellular communication network factor 5 (CCN5), von Willebrand factor (vWF), glial fibrillary acid protein (GFAP), Cluster of Differentiation (CD5), and interleukin (IL)-12B, achieved accuracies of 89-92% in differentiating MS from other neurological diseases [100-, 101, 102]. DL frameworks, including CNNs, multilayer perceptrons (MLPs), and hybrid models, have also been applied to non-imaging data, such as microRNA profiles and smartphone-derived digital biomarkers, reaching high AUCs and sensitivities in distinguishing MS from HCs [103, 104].

Artificial Intelligence for Disease Phenotyping and Patient Stratification

Accurate measurement of disease progression and course in MS is important for timely and appropriate clinical intervention. The gradual transition from RRMS to SPMS is often diagnosed retrospectively with a typical delay of several years. However, there is limited evidence regarding AI-based MS and patient stratification. However, several studies have shown that models with clustering methods, Subtype and Stage Inference (SuStaIn), CNNs, generative adversarial networks (GANs), and dimension reduction techniques enable the detection of subgroups of patients with varying clinical courses, monitoring RRMS to SPMS transitions [105-, 106, 107].

In a study by Ekşi et al. [70], MRS-based models classified RRMS versus SPMS with 83.33% accuracy and 81.81% sensitivity. Another study conducted a deeper analysis of frequently misclassified PwMS by manually categorizing them into RRMS and SPMS [107]. These findings suggest that while AI-based approaches are still

in their infancy, in their initial stages, they have the potential to increase the early detection of worsening MS and may be used to assist discrimination between distinct subtypes of MS in the clinic.

Artificial Intelligence for Prognosis

Artificial intelligence is increasingly transforming the prognosis of MS. The Latest MS treatment requires evidence-based predictions of disease progression to tailor therapy to each patient's unique needs (108). DL and ML frameworks integrate these dynamic clinical variables, along with MRI data, such as lesion load, gray matter and white matter volumes, cortical atrophy, and spinal cord atrophy, to build more accurate predictive models of disease progression [109-, 110, 111, 112]. SVM-based models showed 92% for clinically isolated syndrome (CIS) conversion to clinically definite MS prediction based on baseline MRI features, such as gray matter volume and T2 lesion load [113].

Molecular biomarkers, including the serum neurofilament light (sNfL) chain, a powerful predictor of brain atrophy, cytokines (osteopontin, monocyte chemoattractant protein-1 (MCP-1), chemokine ligand 27 (CCL27), tumor necrosis factor receptor 1 (TNFR1), oxidative stress, vitamin D levels, and transcriptomic signatures (e.g., microRNAs), further enrich prognostic models [114, 115]. Wearable sensor data, such as gait and balance metrics, also provide valuable information [116]. ML techniques, including RF and SVMs, artificial neural networks (ANNs), and hybrid ML/DL architectures, process multimodal data, achieving robust AUCs up to 0.83, and sensitivities between 67% and 91% in predicting transitions from RRMS to SPMS or sustained disability progression [117, 118].

Ghafouri-Fard et al. [119] used ANNs trained on genetic data from 401 patients with PwMS and 390 HCs to predict MS risk. Single nucleotide polymorphisms (SNPs) were analyzed for antisense non-coding RNA in the INK4 locus (ANRIL), ecotropic viral integration site 5 (EVI5), angiotensin I converting enzyme (ACE), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), growth arrest specific 5 (GAS5), H19 imprinted maternally expressed transcript (H19), ninjurin 2 (NINJ2), glutamate metabotropic receptor 7 (GRM7), very late antigen-4 (VLA4), Cbl proto-oncogene B (CBLB), and vascular endothelial growth factor A (VEGFA) (119). The ANN model achieved an accuracy of 64.73%, a sensitivity of 64.95%, a specificity of 64.49%, and an AUC of 69.67%. The growth arrest-specific 5 (GAS5) TT genotype was protective, while the angiotensin I-converting enzyme (ACE) DD genotype increased MS risk [119]. ML identified 40 differentially expressed lipid metabolism-related genes enriched in arachidonic acid metabolism, steroid hormone biosynthesis, fatty acid elongation, and sphingolipid metabolism in PwMS [120]. The aldo-keto reductase family 1 member C3 (AKR1C3), nuclear factor kappa B subunit 1 (NFKB1), and ATP-binding cassette subfamily A member 1 (ABCA1) genes were upregulated in PwMS. An ANN model using these genes achieved a high discriminative power in both training sets (AUC=0.826). High expression was observed in Natural cells, T-cell, plasmacytoid cells, dendritic cells, regulatory T-cell, and type 1 T-helper cells. A ceRNA network revealed interactions between hub genes [120].

Artificial Intelligence in Imaging Modalities for Multiple Sclerosis

Magnetic Resonance Imaging-based Applications

The McDonald criteria 2024 serve as the standard for diagnosing PwMS [121]. These criteria have introduced MRI as an accessible and noninvasive tool as an essential diagnostic parameter [122]. Despite recent diagnostic advances, due to the differential diagnosis and mimicry of other neurological diseases from MS, relying on MRI can lead to misdiagnosis and delay the timely initiation of treatment [123, 124]. Recent advances in ML and DL neuroimaging have gained attention. Using AI in MRI can further minimize imaging time by reducing the number of sequences in the acquisition process and using generative models to synthesize the missing sequences without severely influencing imaging quality [125]. Additionally, the use of AI algorithms in contrast-enhanced images reduces the dose of gadolinium (Gd), which reduces the duration of imaging and radiation exposure and the adverse health effects of Gd [126].

The use of AI has also helped clinicians to differentiate MS from other neurological diseases [127-, 128, 129, 130, 131, 132, 133]. A recent study showed that the use of CNNs with MRI has greater accuracy than

experts in differentiating MS from NMOSD [132]. Recent advances in AI for analyzing MRI scans of People with MS (PwMS) have helped clinicians automatically differentiate other lesions, including contrast-enhancing lesions, cortical lesions, central vein sign in white matter lesions, and perivenular lesions from MS [128-, 129, 130, 131]. Additionally, the combination of AI-assisted analysis with clinical evaluations performed well in distinguishing MS from CNS vasculitis, migraine, and noninflammatory white matter disorders [132, 133].

The segmentation of MS lesions in MRI images poses significant challenges because of the requirement for a substantial volume of training data. The study by Cetin et al. [14], which utilized a CNN in the U-Net algorithm, achieved an accuracy of 79% in the dice similarity coefficient (DSC) score for MS lesion segmentation. This means that it can aid in the early detection of MS and reduce the workload. Various studies have been conducted on the use of MRI-based AI for segmentation and lesion volume determination, with results generally acceptable to users [125]. Although automated segmentation methods have been introduced, manual segmentation by experts still has advantages over these AI-introduced algorithms. The overlap between gray matter intensity and MS lesions in MRI images, along with variability in lesion shapes and a large number of voxels to locate at the boundary between normal and abnormal tissue, makes accurate differentiation difficult for automated algorithms [134]. Several ML-based approaches have been developed to segment MS lesions. For example, using a Gaussian mixture model (GMM) to detect lesions in T1 weighted (T1-w) scans, followed by FMRIB's Automated Segmentation Tool (FAST)-trimmed likelihood estimator to distinguish non-lesional voxels in T1-weigheted (T1-w), T2-weigheted (T2-w), and T2-w fluid-attenuated inversion recovery (FLAIR) images, achieved a DSC of 0.82, indicating that the proposed method achieves superior segmentation performance compared to conventional approaches, while requiring less computational time (135).

Optic Coherence Tomography

Optic Coherence Tomography (OCT) is used as a sensitive, specific, and noninvasive test for assessing ON in PwMS. As an accessible and specialized tool, OCT can be performed by nonspecialists and can reduce the number of MRI requests [136, 137]. Recent studies have demonstrated that OCT can aid in the early identification of MS, even in individuals without visual signs, measure progression and axonal damage, or assist in situations with unclear diagnoses [136]. Various studies have evaluated the role of AI in enhancing the diagnostic value of OCT for PwMS. Although AI-based methods alone cannot increase the accuracy of OCT to 100%, their role in measuring the RNFL and GCL and aiding in the early diagnosis of MS is noteworthy [138, 139]. Additionally, changes in the outer GCL during the early stages of MS can be detected by AI-based OCT (140). The swept-source OCT (SS-OCT) and spectral domain OCT (SD-OCT) modalities have shown good capabilities in differentiating PwMS from HCs (20, 141). Furthermore, GCL measurement has proven to be more effective than RNFL measurement [20, 136]. While AI-enhanced OCT has an enormous potential for increasing the diagnostic abilities for ON and MS, particularly in early diagnosis and disease progression monitoring, it cannot achieve perfect accuracy on its own. Nonetheless, combining AI with OCT techniques, such as SS-OCT and SD-OCT, as well as focusing on measuring the GCL, provides useful insights that can improve diagnostic approaches.

Positron Emission Tomography

Although MRI is the preferred modality for diagnosing MS, positron emission tomography (PET) can assist in detecting inflammation before structural changes occur and in the early stages of diagnosis by providing functional molecular information. Additionally, the use of PET can be beneficial in determining the treatment strategy for each individual and assessing the response to intervention by evaluating inflammation [142].

The use of the radiotracer [^{11}C] PIB in PET scans can directly measure the myelin content. This method is invasive and often not readily available. The use of the conditional flexible self-attention GAN (CF-SAGAN) algorithm, without the need for radioactive substance injection, assesses brain myelin content and the response to remyelination treatment by capturing complex spatial relationships in brain lesions [143].

The specific technique of 18-kDa translocator protein (TSPO) PET, which evaluates microglial activity as a reflection of the activity of the innate immune system, helps determine inflammation around MS lesions. Inflammation plays a role in disease progression and disability in PwMS (41). In addition, prediction of disability using TSPO-PET signals has been reported. Several studies have shown that increased TSPO signals, especially

in individuals with apparently healthy white matter, may be associated with greater future disability, as measured by the EDSS [144, 145].

Du et al. [143] used DL in PET imaging to predict the annualized relapse rate (ARR) in patients with RRMS. A multi-branch CNN was used to automatically separate lesions, resulting in a high performance (Dice score: 0.81), which means that there is a close overlap between the automated segmentation model and manual segmentation by experts. Kebir et al. [146] demonstrated that fluoro-ethyl-tyrosine PET (FET-PET) imaging combined with a support vector model algorithm can differentiate MS from glioma with an AUC of 0.94.

Therefore, while MRI is considered the preferred modality for MS management, the use of PET in combination with AI can aid in detecting early inflammation, treatment strategies, and responses. The use of AI algorithms in PET scans can also assist in evaluating myelin content and microglial activity, which are essential for understanding disease progression, prognosis, and predicting disability in PwMS.

Digital Health Tools and Artificial Intelligence in Multiple Sclerosis

Wearables and Sensor Data

Digital health technologies such as wearables, smartphones, health, and social media combined with AI are transforming MS care by enabling the remote, continuous, and personalized monitoring of symptoms [147, 148]. Wearable device-monitored continuous assessment has become a norm for in-life testing of motor and physiological signs of MS [149]. Wearable biosensors, such as inertial measurement units (IMUs) [150], smartwatches [151], and specialized devices, such as digital biomarkers of the Verily company [152], enable real-time, non-invasive monitoring of gait [153], sleep, and heart rate in PwMS [150, 154]. These devices, often worn on the wrist, ankle, or trunk, enable high-frequency data capture across daily life activities, thus providing a more ecologically valid alternative to episodic clinical evaluations [155].

Over time, features such as stance duration, turning movements, and body angular speed showed strong alignment with established clinical disability scales in MS [147]. Daily activity metrics, especially the highest number of steps taken per day, were more closely linked to patient-reported symptoms such as fatigue and mobility limitations than traditional clinical scores [152]. Continuous ambulatory monitoring using wearable sensors can detect circadian heart rate patterns that distinguish between inflammatory and progressive MS states. Inflammation is associated with increased sympathetic activity at night and reduced circadian variability, whereas progression has been shown to globally reduce heart rate variability and circadian adaptation [156]. Vocal fatigue is another parameter that can be assessed using acoustic monitoring in a PwMS. By analyzing speech samples, such as sustained vowels, reading tasks, and spontaneous speech, researchers can extract vocal biomarkers related to fatigue, including fundamental frequency, cepstral peak prominence, background noise level, and sound pressure level [157].

Artificial Intelligence algorithms, including SVM, RF, elastic net regression, CNNs, long short-term memory networks (LSTM), fully connected neural networks (FCNN), and extreme gradient boosting regression (XGBR), have been deployed on gait and sensor data [158-, 159, 160, 161]. The Dresden multidimensional walking assessment (DMWA) study used accelerometry to quantify gait velocity, mediolateral sway, cadence, and angular velocity, which were then fed into AI models [162]. SVMs also achieved the highest F1 scores for fall risk prediction using the everyday memory impairment questionnaire (EMIQ) and 12-item Multiple Sclerosis Walking Scale (MSWS-12) (0.80), which can protect PwMS from adverse events [163, 164]. Graz normal (GR_N), Graz dyskinetic (GR_D), Mobility Lab normal (ML_N), Mobility Lab dyskinetic (ML_D), Mobility Lab static with eyes open (ML_S_EO), and Mobility Lab static with eyes closed (ML_S_EC) captured during normal walking [165], dual-task walking showed a slowing of gait depending on MS disease severity [166, 167], and Romberg stances were processed using 5-fold cross-validation repeated 10 times and validated via permutation tests [168].

IMUs and multisensor platforms, such as Mobility Lab (e.g., APDM) and Gait Analysis Instrumentation and Technology with real-time interactive tracking evaluation (GAITRite), provided detailed gait and balance assessments [169]. GAITRite's 8-meter walkway with pressure sensors captures spatiotemporal parameters during normal (GR_N) and dual-task walking (GR_D) [169]. Romberg tests (ML_S_EO and ML_S_EC) recorded sway during eyes-open and eyes-closed stances [153]. Sleep quality and fatigue were assessed using

apid Eye Movement (REM) and psychomotor vigilance tests (PVT), revealing functional impairment not captured by EDSS alone [152].

Despite the promising potential of biosensors and digital health tools for MS monitoring, several technical and practical challenges limit their widespread clinical adoption [147]. Sensor drift and motion artifacts can degrade data quality over prolonged wear in uncontrolled environments [170]. Device displacement or external interference further affect signal quality [171]. Interdevice variability arising from differences in hardware models, manufacturers, sensor placements, and firmware contributes to data heterogeneity, complicating cross-study comparisons and data pooling [172]. User compliance remains a major hurdle; discomfort, maintenance requirements (charging, syncing), and perceived burden often lead to incomplete or missing data streams [173]. Continuous ecological monitoring generates massive, unstructured datasets that require advanced preprocessing techniques, including artifact removal, signal filtering, missing data imputation, and feature extraction, which require substantial computational resources [174]. Interoperability across diverse platforms and sensor types is hindered by the lack of standardized data formats and protocols. Privacy and security concerns are paramount; sensitive health data must be stored and transmitted in compliance with regulations such as the General Data Protection Regulation and Health Insurance Portability and Accountability Act [174].

Establishing privacy-compliant data storage and management pipelines is essential for ensuring patient confidentiality. Furthermore, the scalability of data-processing pipelines and the computational demands of sophisticated AI models pose challenges [175]. Models must be transparent and interpretable to gain clinician trust and regulatory approval, which is a major barrier to their clinical integration. Addressing these multifaceted challenges is critical for translating biosensor innovations into reliable and actionable clinical tools to improve MS management and outcomes. Major challenges include inconsistent sensor placement, signal artifacts, and device nonadherence. Many tools remain undervalidated across diverse populations, and long-term clinical outcome correlations are limited. Interfacing sensor data with clinical systems remains a key technical and regulatory hurdle [147, 176, 177].

Smartphones and Mobile Applications

Smartphones provide accessible platforms for real-time, home-based neurological monitoring in MS [148] Mobile health (mHealth) and electronic health (eHealth) technologies are transforming MS care by enabling remote, patient-centered monitoring and decision-making [178]. Tools such as Floodlight MS, Mon4t®, [179] MS Sherpa [180], MSReactor [181], and MSCopilot, which are MSFC components, including the 25-Foot walk test (25FTW), which evaluates ambulatory speed, the 9-Hole Peg Test (9-HPT) [182], and the tablet-based MS Performance Test (MSPT) [183] enable home-based evaluation of motor, depression [153], cognitive [184], and early signs of relapse [185]. For example, the Floodlight Open study engages patients through gamified tasks, including finger tapping, symbol-digit modality tests (SDMT), and walking exercises. Metrics derived from these smartphone sensors, such as accelerometers and gyroscopes, show strong correlations with clinical measures such as EDSS and neuro-quality of life (QoL). Balance and gait parameters, including step variability and turn duration during walking tests, demonstrated good reproducibility and effectively differentiated MS subtypes [171, 186, 187].

Smartphones generate passive digital biomarkers such as step cadence, inter-step variability, phone unlock frequency, and screen response times, offering sensitive indicators of motor and cognitive function that are aligned with MS-specific clinical scores and patient-reported outcomes [188]. Another study using the dreaMS app integrated ten cognitive games to monitor cognition in PwMS. The participants played the game twice weekly for five weeks. Most games showed moderate to strong correlations with standard cognitive tests and performance improved over time. Users rate the games as enjoyable and meaningful, supporting their potential for long-term use [189].

Telemedicine supports chronic disease management, improves specialty consultation, and increases patient-physician communication [190]. The Veterans Health Administration (VHA) initiated a telemedicine program for PwMS, spinal cord injury, and mental health, supporting teleconsultation between specialties [191]. Remote access to MRIs and notes is possible with CPRS and VistA Imaging [191]. Cost savings resulting from telewound care and telepsychiatry effectively improved the depression results. Telerehabilitation with Polycom and VTEL allows remote orthoses and gait tests [192, 193].

Platforms such as the multiple sclerosis documentation system 3D (MSDS3D) and the integrated care portal for MS (IBMS) portal offer tools for tracking DMTs adherence, satisfaction, and symptom progression, supporting patient-provider shared decision-making [194, 195]. The remote management of MS is complicated by neurological heterogeneity. Bandwidth and frame rate latency impede motor and visual tests [196]. Future initiatives should focus on interoperability, accessibility, patient-centered design, and regulation, applying policies such as the Interoperability and Patient Access Rule and tools such as Health eVet for successful digital care [190, 196]. CMS interoperability, patient access rule, and open application programming interfaces (API) try to eliminate obstacles [196].

Social networks play an essential role in the care of MS by providing real-time treatment information [197]. An assessment revealed that therapy switches, primarily from injectables to oral therapy, frequently secondary to side effects or physician recommendations, with peer influence on adherence being obvious [197-, 198, 199, 200, 201]. Social networks, however, present challenges; misinformation and experimental therapy may confuse patients. Clinical decision-making is complicated owing to placebo effects, with privacy, consent, and validity of the data being ambiguous. Data in the network are frequently unstructured, biased, and difficult to interpret clinically [200, 202, 203]. Systems such as Patient-Reported Outcome Measures (PROMs) and approved CMS APIs seek to address explainability, trust, and interoperability in MS care [204-, 205, 206].

Personalizing Therapy Choices

Multiple sclerosis requires a precision medicine approach owing to its heterogeneous presentation and progression. Disease-modifying therapies (DMTs) differ in mechanism, efficacy, and effect; therefore, accurate biomarker interpretation is crucial for guiding personalized treatment. The primary biomarkers for the prediction of response to treatment are the free kappa light chain index (FKLCi), sNfL, serum c-x-c motif chemokine ligands (CXCL)13 [207], osteopontin, neurofilament heavy chain (NFH) [208], and chitinase 3-like protein 1 (CHI3L1) [209]. For example, elevated FKLCi levels have been linked to a higher risk of treatment failure due to persistent intrathecal immunoglobulin synthesis driven by CNS-resident B cells, which reflects ongoing immune activation, even in treated patients [210]. sNfL, a marker of axonal injury, increases with inflammation-induced damage and decreases with effective therapy, making it a useful indicator of treatment response and disease activity control. CXCL13 levels decreased with natalizumab, fingolimod, or rituximab [211, 212]. Osteopontin declines with natalizumab or glatiramer [213, 214]. The NfL and NFH levels decreased with DMT [215, 216], reflecting reduced neurodegeneration. CHI3L1 tends to decrease in response to DMTs such as natalizumab and fingolimod. This reduction is interpreted as a biomarker response to therapy, and may reflect reduced inflammatory activity [217, 218].

Artificial Intelligence models enhance the personalization of MS care by integrating these biomarkers with imaging and clinical data to guide therapeutic decisions [219]. DL architectures, such as CNNs, ResNet, U-Net, long short-term memory (LSTM) networks, gated recurrent units (GRU), and graph neural networks (e.g, Graph Convolutional Network, Graph Attention Network) can extract complex patterns from imaging and clinical data [109, 220, 221]. Interpretable AI models, such as SHAP-enhanced Extreme Gradient Boosting, have predicted outcomes with no evidence of disease activity (NEDA) [222, 223]. These advanced models enable precise risk stratification and early identification of aggressive disease courses, thereby facilitating personalized DMT selection. The Clinical, Laboratory, Administrative, Imaging, and Medical Services (CLAIMS) project exemplifies AI-assisted MS care by integrating multimodal patient data for individualized prognostic modeling [219].

Additionally, AI-driven adherence models have shown potential for several chronic diseases [224]. ML algorithms have promised to transform adherence monitoring of MS by identifying which patients are more likely to be nonadherent according to clinical, demographic, and behavioral variables [225]. By analyzing such data as past missed doses, appointment adherence, cognitive test scores, mood symptomatology, and medication side effects, AI systems can determine which patients are most likely to struggle with medication persistence. This allows clinicians to proactively intervene in individualized education, guidance, or alternative therapy [219, 225].

Genomic and Transcriptomic Data

Omics approaches, including genomics, transcriptomics, metabolomics, and proteomics, are connected to the genome (DNA), transcriptome (RNA), and proteome (proteins), respectively [226]. In the past decade, omics data has emerged as an essential tool for understanding molecular pathways and identifying molecules involved in the pathogenesis of MS [226]. Furthermore, omics approaches not only play a significant role in screening patients before the onset of clinical symptoms in the early stages but also help determine diagnostic accuracy, prognosis, treatment response, and personalized medicine through reliable biomarkers [226, 227]. Moreover, the use of multi-omics data with combined analyses from different omics groups can assist in answering fundamental biological questions, including gene content and mutations, protein activities, post-translational modifications, and metabolomics [228]. The complexity and large volume of multi-omics datasets pose challenges in data analysis. In this regard, the use of AI-assisted analysis for molecular subtypes and disease classification has attracted the attention of researchers. Additionally, the use of AI, particularly DL and artificial neural networks (ANN), can help address these challenges by identifying biomarkers, disease onset patterns, advanced data integration, target therapy, and personalized medicine [229].

Ghafouri-Fard et al. [119] reported an accuracy of 64.73% in predicting the risk of MS using single-nucleotide polymorphism genotypes analyzed by ANN. Acquaviva et al. [230] employed ML models on the transcriptomic profiles of peripheral blood mononuclear cells to classify and stage MS. In another study, Omrani et al. [231] used whole-blood transcriptomics and deep RNA sequencing to distinguish PwMS from HCs, achieving a diagnostic accuracy of 97%. Furthermore, applying ML to whole blood transcriptomes and deep RNA sequencing analyses can identify the risk of CIS progression to MS at the first clinical visit with an accuracy of 74%, leading to early treatment initiation in high-risk patients. In the absence of this method, predicting CIS progression to MS requires multiple clinical visits and frequent follow-up. In addition, Sun et al. [103] applied a CNN model to identify MS-related microRNAs, which contribute to MS pathogenesis by modulating gene expression in immune and glial cells [232]. Its results report an ROC AUC of 0.87, outperforming other existing methods [103].

Proteomics and Metabolomics

Proteomics has been used to identify effective drug targets and novel regulatory mechanisms. Routine MS treatments are based on the inflammatory process of the disease, and a significant number of studies have examined the role of proteomics in this area [226]. The use of blood and CSF biomarkers in the early diagnosis of MS as well as in determining the risk of potential complications and prognosis has attracted attention in recent years. In this context, several studies have evaluated the accuracy and role of AI in analyzing such data.

Ata et al. [233] used ANNs to evaluate changes in metabolomics profiles and their relationship with the severity of MS and disease parameters. The results of this study reported an accuracy of 87%, sensitivity of 82.5%, and specificity of 89% for diagnosing MS in the HC group. The results of the study by Brummer et al. [234] indicated that sNfL chain levels, in combination with MRI predictors, can aid in the early diagnosis of cognitive dysfunction in PwMS. Lötsch et al. [98] applied unsupervised ML to assess the serum concentrations of 43 lipid markers in 102 PwMS and 301 HC subjects. This method can be a highly accurate (95% CI: 88.89 to 100) diagnostic tool, providing a noninvasive alternative technique for MS detection.

Finally, omics methods are transforming our understanding and treatment of MS. These strategies improve early screening and personalized therapy by identifying accurate biomarkers and biological pathways. The use of AI improves data analysis and classification accuracy, allowing noninvasive diagnostics and better prognoses. Notably, studies have shown encouraging findings for predicting MS risk and development, highlighting the possibility of merging multiomics data with AI technology to further MS research and treatment techniques. Despite the promising results of using AI for biomarker analysis in PwMS, this study has some limitations. Generally, most studies involve a limited number of patients and the generalizability of the results is reduced in the absence of external validation analysis.

Integration of Multimodal Data Holistic View of Multiple Sclerosis

The manifestations of MS are variable, and multiple factors, including demographic factors, environmental factors, and comorbidities influence disease progression and manifestations. MS significantly increases the burden on individuals and society owing to rising disability-rated costs [235]. Currently, progression is independent of relapse activity based on EDSS and confirmed disability worsening (CDW). These two criteria are insufficient for diagnosing heterogeneous symptoms and identifying the disease in subclinical stages [236]. These issues have resulted in diverse treatment responses (237). Despite receiving DMTs, only 30–40% of patients remain stable for 5–7 years [238]. Currently, assessing treatment response relies on evaluating imaging lesion activity, which is inadequate for predicting long-term outcomes for patients, and emphasizes the need for a precision medicine approach [239, 240]. Although emerging biomarkers show promise for treatment monitoring [241], they often fail to capture MS's full complexity of MS, lack real-world validation, and remain inadequate for progressive MS [242].

Artificial Intelligence -based approaches offer solutions to current issues by integrating multiple longitudinal biomarkers, including advanced motor function assessments, optical coherence tomography (OCT), magnetic resonance imaging (MRI) markers, cognitive function, and patient-reported outcomes [219]. AI and its methods can assist in analyzing complex interactions between variables, capturing multidimensional patient data, adopting appropriate treatments, determining prognosis, predicting complications, and advancing personalized medicine [243]. Combining this data with AI leads to a better understanding of each individual's disease process and a more effective classification of disease types. AI-based interventions, combined with a holistic overview, play a significant role in transforming MS care by enhancing personalized treatment and improving QoL.

Limitations, Challenges, and Implementation Barriers

One of the limitations of AI in MS is the lack of large, heterogeneous, and representative datasets (16). The majority of current AI models are trained on single-center data that do not reflect the entire clinical spectrum of MS [16, 244]. This lack of diversity leads to overfitting, where models perform well internally but fail in external validation, as shown by accounts of greatly reduced accuracy in research when models are applied to unseen cohorts [109, 136, 245, 246]. Moreover, datasets can reflect structural biases regarding race, ethnicity, socioeconomic status, or access to healthcare that lead to systematic inaccuracies or unfairness for specific patient groups in their predictions [247, 248]. Overcoming these data challenges will require international, multicenter collaborations embracing findable, accessible, interoperable, and reusable (FAIR) data principles and privacy-preserving strategies such as federated learning paired with blockchain for secure, decentralized model training [249, 250].

A major barrier to the clinical adoption of AI tools for MS is the lack of interpretability. DL systems operate as black boxes, and clinicians cannot easily understand or trust their output [251]. While local and global explanation methods such as shapley additive exPlanations (SHAP) interacting with RF and XGBoost Explainable Boosting Machines have shown potential, they are underutilized in the real world [136, 252]. AI predictions cannot be confidently checked or explained to patients by clinicians in the absence of interpretability, which threatens shared decision making and patient trust [253-, 254, 255, 256, 257].

Moreover the performance of AI systems depends not only on the quality of the training data, but also, and importantly, on algorithm choice, which may similarly limit generalizability across different MS subtypes or clinical settings [258-, 259, 260].

Important ethical considerations also remain inadequately addressed: questions of data ownership, potential commercial exploitation of patient data, and adequacy of patient consent with regard to the use of AI-assisted clinical decision-making are also major concerns [261]. In addition, it is still unclear who is responsible in the case of AI-related diagnostic error - whether it is the clinician, the healthcare institution, or the AI developer - further complicating broader implementation [262].

The introduction of AI into existing clinical workflows also presents pragmatic challenges. Studies on devices such as mdbrain® suggest that AI reduces the labor burden of radiologists and makes monitoring lesions efficient, However, technical limitations remain; for example, the software may fail to process approximately 2% of examinations [263]. Clinicians also report concerns about false positives near artifact-prone regions, which can lead to unnecessary follow-up or missed opportunities for timely intervention. One

study showed that the central vein and peripheral rim signs are examples of promising findings in susceptibility-weighted imaging (SWI), which could further improve the accuracy of ML software assessments [264-, 265, 266, 267, 268]. Furthermore general absence of direct comparisons between AI systems and existing diagnostic or therapeutic methods limits the strength of arguments supporting the superiority of AI over standard clinical approaches [254]. Further validation studies will be necessary before such biomarkers can be reliably integrated into workflows where AI would be applied.

Emerging Opportunities and Future Directions

Despite these challenges, emerging technologies present unprecedented opportunities for transforming MS care. Federated learning, in combination with blockchain, offers a powerful solution for overcoming data limitations and privacy concerns [269, 270]. By enabling decentralized training across institutions from various datasets without the need to export sensitive patient data, federated learning preserves privacy while capitalizing on the diversity required for generalizable models [270]. Blockchain provides tamper-evident auditable records of data usage, creating patient trust through accountability [271]. Initiatives such as the MS data alliance [272] and European MS platform [273] are well positioned to leverage such technology, crafting co-working networks that enable ethical and strong AI development.

Large language models (LLMs) are promising in MS care, research, and education because they produce human-like text and process multimodal information [274]. Clinically, they break down complicated medical information into patients, schedule appointments, and produce personalized risk assessments and treatment summaries from patient information and up-to-date literature [274-, 275, 276]. LLMs interpret unstructured Electronic Health Record (EHR) information, detect patterns, and combine imaging, biomarkers, and wearables to improve diagnosis and customize treatments. In education, they produce interactive case modules and easy-to-understand explanations for pwMSs, improving comprehension and interaction [277]. Techniques such as retrieval-augmented generation (RAG) can refine outputs using MS-specific literature to reduce errors and outdated content [278, 279].

Generative AI corrects class imbalance in MS datasets by generating MRIs and mimicking sparse disease patterns, enriching pediatric or PMS phenotypes [280-, 281, 282]. Data augmentation improves segmentation performance and accuracy, according to the BraTS 2023 and Shifts 2022 competitions [283, 284].

To address interpretability and credibility challenges with regulators and clinicians, SHAP value plots and attention maps demystify AI predictions on MS [252, 285, 286]. Including this program in AI output reports with reference to quality metrics will provide consistent and actionable results.

To advance regulatory acceptance and enable widespread adoption, there is a pressing need for more prospective multicenter clinical trials that rigorously evaluate AI tools under real-world conditions. The inclusion of predictive models and digital biomarkers within trials will offer compelling evidence for clinical utility and safety. Regulatory agencies, including the EU and the FDA [256, 257], are increasingly developing frameworks for explainable and trustworthy AI, underscoring the necessity of aligning trial designs with these evolving standards.

Artificial Intelligence facilitates individualized risk prediction and treatment in the early phase with multimodal data, such as MRI, OCT, walk tests, NfL biomarkers, and patient self-reporting. Data readiness among patients implies that the tools are able to enable decision support with individualized risk profiles to enable patients and tailor therapy [287].

Cross-disease AI and transfer learning take advantage of common imaging and wearable features across diseases, such as NMOSD, Guillain-Barré Syndrome (GBS), viral encephalitis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), to identify biomarkers, facilitating advancement where multiple sclerosis (MS)-specific data are sparse [288, 289]. Standardized benchmarks, including medical image computing and computer-assisted intervention (MICCAI) and IEEE International Symposium on Biomedical Imaging (IEEE ISBI), allow for unbiased assessments [290, 291]. Ensemble models enhance reliability, and future benchmarks should evaluate their efficiency, resource utilization, and generalizability. Centralized standardized platforms will increase reproducibility and deployment.

Conclusion

Artificial Intelligence can transform MS care by integrating and analyzing multimodal data from imaging, biomarkers, clinical variables, and therapeutic precision. It can address existing challenges in the diagnosis, monitoring, and prognosis of MS. Additionally, considering the variable manifestations of PwMS and the diagnostic challenges present, it can assist in early diagnosis and the selection of appropriate treatments. Moreover, advances in personalized medicine can enhance the QOL of patients and help prevent long-term complications. Despite its great promise, AI adoption in MS care faces significant difficulties including a diverse and representative dataset, restricted interpretability of AI outputs, inadequate external validation, and regulatory readiness. To overcome these challenges, multicenter data sharing that adheres to FAIR principles, development of explainable and transparent AI models, rigorous prospective validation, and seamless integration into clinical processes will be required.

Funding: We did not have any financial support for this study.

Conflict of interest: The authors declare no conflict of interest regarding the publication of this paper.

Availability of data and material: Not applicable.

Consent for publication: This manuscript has been approved for publication by all authors.

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