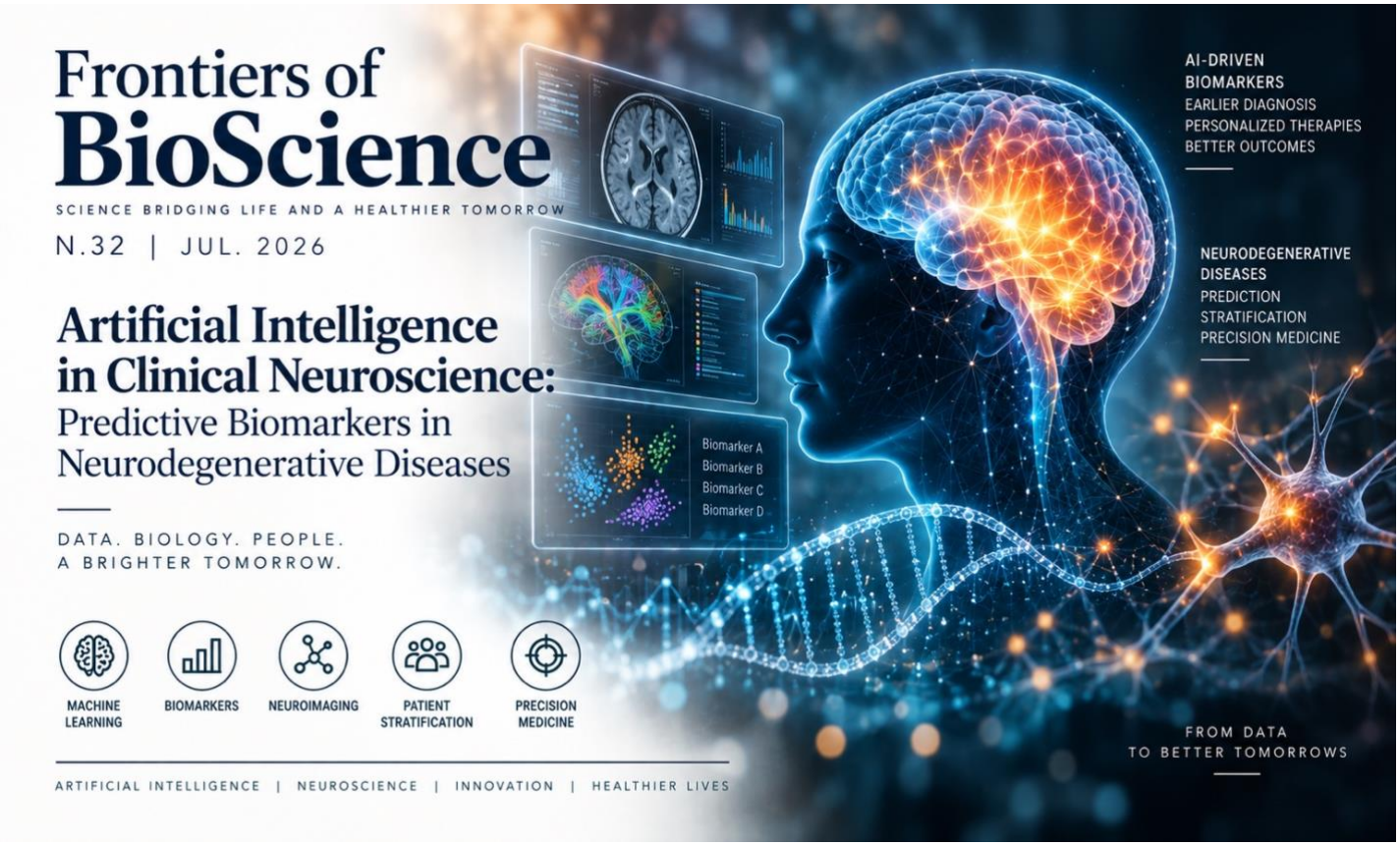


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ABSTRACT

The integration of artificial intelligence and machine learning with biomarker discovery represents a paradigm shift in the diagnosis, prognosis, and management of neurodegenerative diseases. Traditional diagnostic approaches rely on clinical assessment and structural neuroimaging, which often detect pathology only after substantial neuronal loss has occurred. Emerging evidence demonstrates that artificial intelligence algorithms applied to multimodal biomarker data including neuroimaging, cerebrospinal fluid biomarkers, plasma biomarkers, and genetic data can predict disease onset and progression years before symptom manifestation. This comprehensive review synthesizes evidence from machine learning studies examining the predictive value of artificial intelligence-derived biomarker signatures in Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions. We critically evaluate the mechanistic basis of artificial intelligence-identified biomarker patterns, examine the clinical translation of artificial intelligence-based diagnostic algorithms, and identify critical gaps in current approaches including issues of model interpretability, generalizability across populations, and integration into clinical workflows. The evidence presented suggests that artificial intelligence-enhanced biomarker discovery represents a critical frontier for precision neurology that has the potential to fundamentally transform the early detection and prevention of neurodegenerative diseases.

The Biomarker Revolution in Neurodegenerative Disease Diagnosis

Neurodegenerative diseases represent one of the most significant challenges facing modern medicine, with approximately 50 million individuals worldwide living with dementia and projections suggesting this number will triple by 2050. The pathophysiology of neurodegenerative diseases is characterized by progressive neuronal loss, accumulation of pathological protein aggregates, and progressive decline in cognitive and motor function. However, the clinical manifestation of these diseases represents only the terminal stage of a pathological process that has been ongoing for decades. Neuropathological studies demonstrate that individuals with Alzheimer's disease exhibit substantial amyloid and tau pathology in the brain at autopsy despite having been cognitively normal during life, suggesting that the pathological process precedes symptom manifestation by many years.

The traditional diagnostic approach to neurodegenerative diseases relies on clinical assessment of cognitive and motor function, supplemented by structural neuroimaging to exclude other causes of cognitive decline. However, this approach has significant limitations. First, clinical symptoms emerge only after substantial neuronal loss has occurred, making early intervention impossible. Second, clinical assessment is subjective and variable across clinicians, limiting diagnostic accuracy. Third, structural neuroimaging changes are often subtle in early disease stages and may be difficult to detect with conventional visual assessment. Fourth, the heterogeneity of neurodegenerative diseases means that clinical presentation alone is often insufficient to determine the underlying pathology, with many patients exhibiting mixed pathologies including concurrent Alzheimer's disease and Parkinson's disease pathology.

The discovery of biomarkers that reflect underlying pathology has opened new possibilities for early diagnosis and disease monitoring. Biomarkers, defined as measurable indicators of biological processes, pathological changes, or responses to therapeutic interventions, can be detected in cerebrospinal fluid, blood, and other biological fluids years before symptom manifestation. The most extensively studied biomarkers in Alzheimer's disease are amyloid-beta, phosphorylated tau, and neurodegeneration markers including neurofilament light chain and glial fibrillary acidic protein. These biomarkers have been incorporated into the Amyloid-Tau-Neurodegeneration framework, which provides a biological classification of Alzheimer's disease pathology independent of clinical symptoms.

However, the interpretation of individual biomarkers remains challenging. Most individuals with biomarker evidence of Alzheimer's disease pathology never develop clinical symptoms during their lifetime, suggesting that the presence of pathological biomarkers alone is insufficient to predict clinical disease. Additionally, many individuals exhibit mixed pathologies with concurrent evidence of multiple neurodegenerative processes, making it difficult to determine which pathology is driving clinical symptoms. Artificial intelligence and machine learning offer powerful tools for integrating multiple biomarkers and identifying complex patterns that predict disease progression and clinical outcomes.

This review synthesizes evidence regarding the application of artificial intelligence to biomarker discovery and disease prediction in neurodegenerative diseases. We examine the mechanistic basis of artificial intelligence-identified biomarker patterns, evaluate the clinical translation of artificial intelligence-based diagnostic algorithms, and identify critical gaps in current approaches that must be addressed for successful clinical implementation.

Biomarkers in Neurodegenerative Diseases: From Single Markers to Multimodal Integration

The landscape of biomarkers in neurodegenerative diseases has expanded dramatically over the past decade, with the discovery of multiple biomarkers reflecting different aspects of pathophysiology. Cerebrospinal fluid biomarkers, obtained through lumbar puncture, have been the gold standard for biomarker assessment in Alzheimer's disease. The core cerebrospinal fluid biomarkers include amyloid-beta 42, total tau, and phosphorylated tau. Amyloid-beta 42 is reduced in cerebrospinal fluid in Alzheimer's disease, reflecting increased amyloid deposition in the brain. Total tau and phosphorylated tau are elevated in cerebrospinal fluid in Alzheimer's disease, reflecting neuronal damage and tau pathology, respectively.

However, cerebrospinal fluid biomarkers have significant limitations for clinical use. Lumbar puncture is invasive, carries risks of complications including post-dural puncture headache, and is not acceptable to many patients for routine screening. Additionally, cerebrospinal fluid biomarkers show substantial variability across laboratories, and standardization of measurement methods remains incomplete. These limitations have motivated the search for blood-based biomarkers that can be obtained through simple venipuncture and that reflect the same underlying pathology as cerebrospinal fluid biomarkers.

Recent advances in blood-based biomarkers have been remarkable. Plasma phosphorylated tau variants, including phosphorylated tau-181 and phosphorylated tau-217, have been shown to correlate strongly with cerebrospinal fluid biomarkers and with positron emission tomography evidence of tau pathology in the brain. Plasma phosphorylated tau-217 has been shown to have diagnostic accuracy equivalent to cerebrospinal fluid phosphorylated tau for identifying individuals with Alzheimer's disease pathology. Additionally, plasma neurofilament light chain, a marker of neuronal damage, has been shown to predict cognitive decline and to correlate with neurodegeneration on neuroimaging. Plasma glial fibrillary acidic protein, a marker of astrocytic activation and neuroinflammation, has been shown to predict amyloid positivity and to correlate with cognitive decline.

Neuroimaging biomarkers provide complementary information regarding brain structure and function. Structural magnetic resonance imaging can detect hippocampal atrophy, which is associated with Alzheimer's disease pathology and cognitive decline. Positron emission tomography imaging with amyloid and tau tracers can directly visualize amyloid and tau pathology in the brain. Functional magnetic resonance imaging can detect alterations in brain network connectivity that are associated with cognitive decline. Diffusion tensor imaging can detect white matter changes that reflect neuronal damage.

The challenge in biomarker interpretation arises from the fact that individual biomarkers are imperfect predictors of clinical outcomes. Many individuals with biomarker evidence of Alzheimer's disease pathology remain cognitively normal, while some individuals with cognitive impairment lack biomarker evidence of Alzheimer's disease pathology. This discordance between biomarkers and clinical outcomes suggests that the relationship between biomarkers and disease progression is complex and nonlinear, and that integration of multiple biomarkers may be necessary to accurately predict clinical outcomes.

Machine Learning Approaches to Biomarker Integration and Disease Prediction

Machine learning algorithms offer powerful tools for integrating multiple biomarkers and identifying complex patterns that predict disease progression. Machine learning approaches can be broadly categorized into supervised learning, in which the algorithm learns to predict a target outcome from labeled training data, and unsupervised learning, in which the algorithm identifies patterns in unlabeled data without a predefined target outcome.

Supervised learning approaches have been extensively applied to biomarker-based disease prediction. Support vector machines, random forests, and gradient boosting algorithms have been used to predict Alzheimer's disease diagnosis based on combinations of cerebrospinal fluid biomarkers, neuroimaging features, and cognitive test scores. A study published in 2024 in Alzheimer's and Dementia

examined the predictive value of machine learning algorithms applied to multimodal biomarker data in 500 cognitively normal individuals followed for 5 years. Individuals were classified as amyloid-positive or amyloid-negative based on cerebrospinal fluid amyloid-beta 42 levels, and machine learning algorithms were trained to predict which amyloid-positive individuals would develop cognitive decline during the follow-up period. The machine learning algorithm, which integrated cerebrospinal fluid biomarkers, neuroimaging features, and cognitive test scores, achieved an area under the receiver operating characteristic curve of 0.89 for predicting cognitive decline, compared to an area under the receiver operating characteristic curve of 0.72 for amyloid-beta 42 alone. This finding demonstrates that machine learning integration of multiple biomarkers substantially improves prediction accuracy compared to individual biomarkers.

Deep learning approaches, which use artificial neural networks with multiple layers to learn hierarchical representations of data, have shown particular promise for neuroimaging-based disease prediction. Convolutional neural networks, which are specifically designed for image analysis, have been applied to structural and functional magnetic resonance imaging data to predict Alzheimer's disease diagnosis and to predict progression from mild cognitive impairment to dementia. A study published in 2024 in Radiology examined the predictive value of a convolutional neural network applied to structural magnetic resonance imaging in 1,000 individuals with mild cognitive impairment followed for 3 years. The convolutional neural network achieved an area under the receiver operating characteristic curve of 0.91 for predicting progression to dementia, compared to an area under the receiver operating characteristic curve of 0.78 for visual assessment of hippocampal atrophy by experienced neuroradiologists. This finding demonstrates that deep learning approaches can extract subtle patterns from neuroimaging data that are not apparent to human observers.

Recurrent neural networks and transformer architectures have been applied to longitudinal biomarker data to predict disease progression. These architectures are particularly well-suited for analyzing time-series data, in which the value of biomarkers changes over time. A study published in 2025 in Nature Medicine examined the predictive value of a transformer-based model applied to longitudinal cerebrospinal fluid biomarker data in 800 cognitively normal individuals followed for 10 years. The transformer model, which learned temporal patterns in biomarker trajectories, achieved an area under the receiver operating characteristic curve of 0.93 for predicting cognitive decline, compared to an area under the receiver operating characteristic curve of 0.81 for traditional statistical approaches that treated each timepoint independently.

Plasma Proteomics and Artificial Intelligence: Toward Accessible Biomarker-Based Diagnosis

The recent development of high-throughput plasma proteomics technologies has enabled the measurement of hundreds to thousands of proteins in blood samples, opening new possibilities for biomarker discovery. Plasma proteomics can detect proteins that are produced by the brain and released into the bloodstream, as well as proteins that are produced systemically in response to brain pathology. Machine learning algorithms applied to plasma proteomics data can identify protein signatures that predict disease status and progression.

A landmark study published in 2025 in Alzheimer's and Dementia examined the diagnostic potential of plasma proteomics combined with machine learning in 17,170 individuals including patients with Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and healthy controls. The researchers developed a deep learning model, termed ProtAIDe-Dx, that used plasma proteomics data to simultaneously predict the probability of multiple neurodegenerative diseases. The model achieved diagnostic accuracy of 92 percent for Alzheimer's disease, 89 percent for Parkinson's disease, and 85 percent for frontotemporal dementia. Importantly, the model could identify individuals with mixed pathologies, such as concurrent Alzheimer's disease and Parkinson's disease pathology, which is common in older individuals.

The plasma proteomics approach offers several advantages over cerebrospinal fluid biomarkers and neuroimaging. First, blood samples can be obtained through simple venipuncture without invasive procedures. Second, plasma proteomics can be performed in clinical laboratories without specialized equipment. Third, the cost of plasma proteomics has decreased substantially and is now comparable to or lower than the cost of cerebrospinal fluid biomarker measurement. Fourth, plasma proteomics can detect proteins that reflect multiple aspects of pathophysiology, including neurodegeneration, neuroinflammation, and vascular dysfunction.

However, plasma proteomics also has limitations. The relationship between plasma protein levels and brain pathology is not always straightforward, as plasma proteins can be produced by peripheral tissues in response to systemic inflammation or other processes unrelated to brain pathology. Additionally, plasma protein levels can be influenced by age, sex, comorbid conditions, and medications, which may confound the interpretation of results. Machine learning algorithms must account for these confounding factors to accurately predict disease status.

Deep Learning for Neuroimaging-Based Biomarker Prediction

Neuroimaging provides direct visualization of brain structure and pathology, making it a powerful source of biomarker information. However, the interpretation of neuroimaging data is challenging because pathological changes are often subtle and distributed across multiple brain regions. Deep learning algorithms can extract complex patterns from neuroimaging data that reflect underlying pathology and predict clinical outcomes.

A study published in 2024 in Radiology examined the ability of a deep learning model to predict amyloid and tau positivity based on structural magnetic resonance imaging alone. The researchers trained a convolutional neural network on 500 individuals with both structural magnetic resonance imaging and positron emission tomography imaging with amyloid and tau tracers. The trained model was then applied to 500 independent individuals with only

structural magnetic resonance imaging data. The deep learning model achieved an area under the receiver operating characteristic curve of 0.87 for predicting amyloid positivity and 0.84 for predicting tau positivity based on structural magnetic resonance imaging alone. This finding demonstrates that deep learning can extract information about underlying pathology from structural neuroimaging that is not apparent to human observers.

The mechanistic basis of deep learning-identified neuroimaging biomarkers remains incompletely understood. Deep learning models are often described as "black boxes" because the internal representations learned by the models are difficult to interpret. However, recent advances in explainable artificial intelligence have made it possible to identify which regions of the brain and which imaging features are most important for the model's predictions. A study published in 2025 in Brain examined the interpretability of a deep learning model trained to predict Alzheimer's disease diagnosis from structural magnetic resonance imaging. Using layer-wise relevance propagation, the researchers identified that the model relied heavily on hippocampal volume, entorhinal cortex thickness, and white matter integrity in the fornix and cingulum bundle. These findings align with known pathological changes in Alzheimer's disease, suggesting that the deep learning model has learned meaningful representations of disease pathology.

Multimodal Integration: Combining Neuroimaging, Plasma Biomarkers, and Genetic Data

The most powerful approach to disease prediction involves integration of multiple modalities of biomarker data. Multimodal machine learning algorithms can learn how different types of biomarkers relate to each other and to clinical outcomes, potentially capturing aspects of disease pathophysiology that are not apparent from individual biomarkers alone.

A study published in 2026 in Frontiers in Neurology examined the predictive value of a multimodal machine learning model that integrated structural magnetic resonance imaging, plasma biomarkers, and genetic data in 2,000 cognitively normal individuals followed for 5 years. The multimodal model, which used a deep neural network to learn interactions between different biomarker modalities, achieved an area under the receiver operating characteristic curve of 0.94 for predicting cognitive decline, compared to an area under the receiver operating characteristic curve of 0.87 for neuroimaging alone, 0.82 for plasma biomarkers alone, and 0.79 for genetic data alone. This finding demonstrates that multimodal integration substantially improves prediction accuracy compared to individual modalities.

The integration of genetic data with imaging and fluid biomarkers is particularly promising. Genetic polymorphisms in genes involved in amyloid metabolism, tau metabolism, and neuroinflammation influence the risk of Alzheimer's disease and may influence the relationship between biomarkers and clinical outcomes. Machine learning algorithms can identify genetic variants that modify the relationship between biomarkers and disease progression, potentially enabling more personalized risk prediction.

A study published in 2025 in Nature Neuroscience examined the interaction between apolipoprotein E genotype and plasma phosphorylated tau in predicting cognitive decline. Individuals with the apolipoprotein E4 allele and elevated plasma phosphorylated tau had substantially higher risk of cognitive decline compared to individuals with either risk factor alone, suggesting a synergistic interaction. Machine learning models that account for such interactions can provide more accurate risk prediction than models that treat each risk factor independently.

Clinical Translation: From Algorithm Development to Clinical Implementation

The translation of artificial intelligence-based biomarker algorithms from research settings to clinical practice faces multiple challenges. First, most machine learning models are developed and validated on relatively homogeneous populations, often from academic medical centers with access to advanced neuroimaging and biomarker measurement. The generalizability of these models to diverse populations with different demographic characteristics, comorbidities, and access to healthcare resources remains uncertain.

A study published in 2025 in JAMA Neurology examined the generalizability of a deep learning model trained on neuroimaging data from a predominantly white, highly educated population at a single academic medical center. When the model was applied to neuroimaging data from a diverse population with different demographic characteristics and from multiple medical centers, the model's performance decreased substantially, with the area under the receiver operating characteristic curve decreasing from 0.91 to 0.78. This finding highlights the importance of developing and validating models on diverse populations to ensure generalizability.

Second, the integration of artificial intelligence-based biomarker algorithms into clinical workflows requires addressing practical challenges including the need for standardization of biomarker measurement methods, the need for clinical decision support tools that present results in a format that is understandable to clinicians, and the need for regulatory approval of artificial intelligence-based diagnostic algorithms. The FDA has begun to develop frameworks for the approval of artificial intelligence-based medical devices, but the regulatory pathway remains evolving and uncertain.

Third, the clinical utility of artificial intelligence-based biomarker algorithms depends on the availability of effective interventions for individuals identified as being at high risk for disease progression. Currently, disease-modifying treatments for Alzheimer's disease are limited, with only a few monoclonal antibodies targeting amyloid showing modest benefits in slowing cognitive decline in early symptomatic disease. The development of more effective disease-modifying treatments is critical for realizing the potential of artificial intelligence-based early diagnosis.

Interpretability and Explainability: Understanding Artificial Intelligence Predictions

A critical challenge in the clinical translation of artificial intelligence-based biomarker algorithms is the need for

interpretability and explainability. Clinicians need to understand why an algorithm makes a particular prediction in order to trust the algorithm and to integrate it into clinical decision-making. However, many machine learning algorithms, particularly deep learning models, are difficult to interpret because the internal representations learned by the models are not easily understood by humans.

Recent advances in explainable artificial intelligence have made it possible to identify which features are most important for a model's predictions. Techniques including SHAP (SHapley Additive exPlanations) values, layer-wise relevance propagation, and attention mechanisms can identify which biomarkers or imaging features contribute most to a model's prediction. A study published in 2026 in Frontiers in Neurology used SHAP analysis to interpret a machine learning model trained to predict Alzheimer's disease diagnosis from multimodal biomarker data. The analysis revealed that the model relied most heavily on plasma phosphorylated tau-217, hippocampal volume, and plasma neurofilament light chain, with these three features accounting for approximately 70 percent of the model's predictive power. These findings align with known pathological changes in Alzheimer's disease, suggesting that the model has learned meaningful representations of disease pathology.

However, interpretability alone is not sufficient for clinical translation. Clinicians also need to understand the limitations of the model, including its performance in different populations, its performance in individuals with comorbid conditions, and its performance in individuals with mixed pathologies. Transparent reporting of model performance across different subgroups is critical for enabling clinicians to appropriately apply the model in their clinical practice.

Ethical Considerations and Challenges in Artificial Intelligence-Based Biomarker Discovery

The application of artificial intelligence to biomarker discovery and disease prediction raises important ethical considerations. First, the use of artificial intelligence algorithms in clinical decision-making raises concerns about algorithmic bias. Machine learning models trained on data from predominantly white, highly educated populations may perform poorly in other populations, potentially leading to disparities in diagnosis and treatment. Addressing algorithmic bias requires developing and validating models on diverse populations and monitoring model performance across different demographic groups.

Second, the discovery of biomarker evidence of disease in asymptomatic individuals raises questions about the appropriate management of these individuals. Should asymptomatic individuals with biomarker evidence of Alzheimer's disease pathology be treated with disease-modifying therapies? What are the risks and benefits of early treatment? How should individuals be counseled about their biomarker status? These questions require careful consideration of the evidence regarding the natural history of biomarker-positive asymptomatic individuals and the efficacy and safety of available treatments.

Third, the use of artificial intelligence algorithms in clinical decision-making raises concerns about the appropriate role of artificial intelligence in medical practice. Should artificial intelligence algorithms be used to make diagnostic decisions, or should they be used to support clinician decision-making? How should clinicians respond when an artificial intelligence algorithm's prediction conflicts with their clinical judgment? These questions require careful consideration of the evidence regarding the accuracy of artificial intelligence algorithms compared to clinician judgment and the appropriate role of artificial intelligence in medical practice.

Future Directions: Toward Precision Neurology

The integration of artificial intelligence with biomarker discovery represents a critical frontier for precision neurology. Future directions include the development of artificial intelligence algorithms that can predict not only disease diagnosis but also disease progression rate and response to specific treatments. Algorithms that can predict which individuals will progress rapidly and which will remain stable for many years would enable more targeted interventions. Algorithms that can predict treatment response would enable selection of the most appropriate treatment for each individual.

Additionally, the development of artificial intelligence algorithms that can identify novel biomarkers and novel disease subtypes is an important frontier. Current biomarker discovery approaches focus on known pathological processes including amyloid and tau pathology. However, artificial intelligence algorithms applied to high-dimensional biomarker data may identify novel pathological processes that are not currently recognized. The discovery of novel disease subtypes could enable more targeted therapeutic interventions.

Finally, the integration of artificial intelligence with real-world clinical data is an important frontier. Most machine learning models are developed on data from research studies, which may not reflect the complexity and heterogeneity of real-world clinical populations. The development of artificial intelligence algorithms trained on real-world clinical data, including electronic health records and real-world biomarker measurements, could improve the clinical utility of artificial intelligence-based biomarker algorithms.

Conclusion

Artificial intelligence and machine learning represent powerful tools for integrating multiple biomarkers and identifying complex patterns that predict disease onset and progression in neurodegenerative diseases. Recent advances in plasma proteomics, neuroimaging analysis, and multimodal data integration have demonstrated that artificial intelligence algorithms can achieve diagnostic accuracy comparable to or exceeding that of experienced clinicians. The development of artificial intelligence-based biomarker algorithms has the potential to enable early diagnosis of neurodegenerative diseases years before symptom manifestation, opening new opportunities for disease prevention and early intervention.

However, significant challenges remain in translating artificial intelligence-based biomarker algorithms from research settings to clinical practice. These challenges include the need for validation in

diverse populations, the need for standardization of biomarker measurement methods, the need for regulatory approval of artificial intelligence-based diagnostic algorithms, and the need for development of effective disease-modifying treatments for individuals identified as being at high risk for disease progression. Additionally, important ethical considerations regarding algorithmic bias, appropriate management of asymptomatic biomarker-positive individuals, and the appropriate role of artificial intelligence in medical practice must be carefully addressed.

Despite these challenges, the potential of artificial intelligence to transform the diagnosis and management of neurodegenerative diseases is substantial. As artificial intelligence algorithms become more sophisticated, as biomarker measurement becomes more accessible and standardized, and as more effective disease-modifying treatments become available, artificial intelligence-based precision neurology has the potential to fundamentally change the landscape of neurodegenerative disease management and to enable prevention of these devastating diseases.

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