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Precision Medicine in Neurodegenerative Disorders: From Biomarkers to Therapeutic Strategies with Future Perspective and Challenges

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ABSTRACT:

Neurological diseases such as Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis have been radically transformed by precision medicine made possible by the human genome project and next-generation sequencing (NGS). More individualized care is possible with precision medicine since it adjusts medications based on patients' unique genetic profiles. When it comes to early diagnosis, illness progression prediction, and treatment efficacy monitoring, biomarkers—and microRNA in particular—are indispensable. With the use of these biomarkers, illness tracking and treatment can be improved. Gene therapy, immunotherapy, neuromodulation, and Al-driven diagnostics are among of the innovative medicines that provide fresh hope for treatment. Immunotherapy aims to destroy dangerous protein aggregation, whereas gene therapy targets the underlying genetic causes of neurodegenerative diseases. Improved motor and cognitive function can be achieved by neuromodulation treatments. Early detection and progression tracking are both improved by AI applications. Overcoming the blood-brain barrier, finding disease-modifying medications, and reducing the high failure rates of clinical trials are all obstacles that need to be addressed. To enhance the results for individuals suffering from neurological diseases, it is crucial to keep pushing the boundaries of what is known about biomarkers and how treatments are delivered.

HIGHLIGHTS

1. Precision medicine tailors treatment based on individual genetic profiles.
2. Biomarkers like microRNAs enable early diagnosis and treatment monitoring.
3. Emerging therapies include gene editing, immunotherapy, and neuromodulation.
4. Artificial intelligence enhances diagnostic accuracy and disease progression tracking.
5. Overcoming challenges such as the blood-brain barrier is crucial for future success.

INTRODUCTION

One significant development is the Human Genome Project. We have always discussed individualized treatment plans. But achieving that has been difficult. Next-generation sequencing (NGS) then emerged, opening up a whole new realm—precision medicine. The goal of precision medicine is to tailor treatment to each patient's unique circumstances, particularly when it comes to addressing the unique biological causes of disease [1]. Genetic and functional tests have revolutionized the way we identify and treat diseases in many different disciplines over the last few decades. However, we have found it difficult to completely comprehend the underlying causes of neurological diseases due to the difficulties in researching the nervous system through biopsies. Fortunately, new biological discoveries such as next-generation sequencing and the identification of biomarkers in cerebrospinal fluid (CSF) have created new opportunities for precision therapy in neurology [2]. Because neurodegeneration is the primary pathogenic characteristic of these well-known neurodegenerative disorders, they include Huntington's

Journal of Chemical Health Risks
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disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). Recently, several complex disorders that combine neurodegenerative components with other pathogenic processes, such as autoimmune neuroinflammation in multiple sclerosis (MS), have been categorized as NDDs [3]. Biomarkers are particularly useful for a variety of purposes. They can assist in determining risk, detecting disease, and tracking the effectiveness of therapies. Blood-based biomarkers are crucial for understanding the brain because they are used in clinical trials to select particular patient groups, ensure that medicines are reaching the proper targets, and assess the effectiveness of treatments. The blood-brain barrier first made people uncertain, but improved technology now allows us to measure minuscule levels of chemicals in various bodily fluids [4].

Among the new actors we have learned about in recent years, microRNAs (miRNAs) are particularly noteworthy. Because of their intriguing potential as biomarkers for diagnosis, outcome prediction, and therapy response, experts have thoroughly investigated them. It's amazing how miRNAs have become important actors in a number of illnesses that impact the central nervous system, igniting interest in finding novel biomarkers and therapeutic targets to monitor the course of the disease and customize treatment for each patient. By interacting with target mRNAs by base pairing and blocking translation, these tiny miRNAs—a unique class of short non-coding RNAs—play a crucial role in controlling gene expression post-transcriptionally [5].

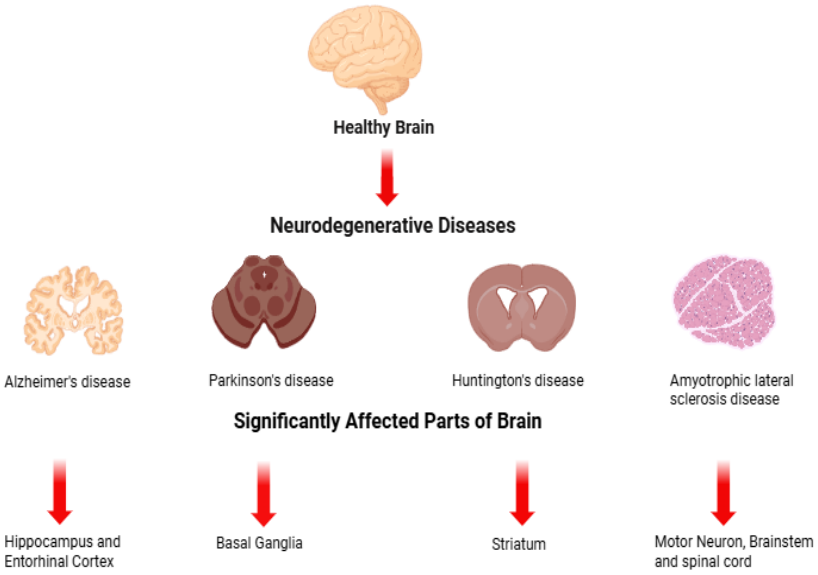

Fig 1.Therapeutic strategies in precision medicine for neurodegenerative

BIOMARKERS IN NEUROLOGICAL DISORDERS

The terms "biomarker" and "surrogate marker" have been appearing more often in the biological scientific literature in the last several years. There has been considerable confusion about the interchangeability of these terminologies, which has sparked discussions over the use of biomarkers as substitute endpoints [4,6]. In determining whether a biological process is normal or dysfunctional, biomarkers are vital. These unique alterations in pathologies, biochemistries, and genes shed light on the underlying causes of many diseases. For a biomarker to be considered ideal, it must be able to reliably discern between particular diseases and normal health, as well as distinguish between other diseases themselves. When it comes to forecasting illness risks, enabling early diagnosis, and setting standards for creating novel treatments, biomarkers are extremely promising. Scientists have been able to discover

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biomarkers for a variety of neurodegenerative illnesses due to recent technological advancements [7].

1. Alzheimer's disease

When it comes to dementia, Alzheimer's disease is far and away the most prevalent in the elderly. Among those over the age of 65, it is the sixth most common cause of death. Amyloid and tau proteins, in particular, are associated with Alzheimer's disease (AD) in some families. Unfortunately, studies for several medicines targeting these sites have had disappointing results. The reason is, AD is multi-faceted and manifests differently in each individual. For this reason, it is crucial to investigate novel approaches to tailored treatment that may impede the disease's progression. This approach to healthcare prioritizes tailoring treatment to each individual's needs. We want to discover new ways to treat Alzheimer's disease by customizing medicines such that they work best with the fewest negative effects. Patients suffering from this illness may find some relief with tailored treatments [8].

There have been about 53,000 scholarly articles published on the topic of Alzheimer's disease (AD) biomarkers since 1983 [9,10]. Conventional biomarkers like as genes, mutations, and end-stage neurotoxic substances fall within this category. Further indicators encompass microRNAs, inflammatory cytokines, lipid proteins, carbs, and chemokines. These indicators are crucial for understanding the development of Alzheimer's disease (AD) and for detecting dementia in its early stages [11,12,13].

2. Parkinson's disease

Parkinson's disease affects around 1% of persons over the age of 65 and has a late onset. It is the second most common neurological condition after Alzheimer's disease. Parkinson's disease (PD) is a degenerative, incurable disorder that gradually reduces a person's motor abilities. Parkinson's disease is thought to be an idiopathic or sporadic condition characterized by Lewy pathology as well as the degradation and death of dopaminergic neurons in the nigral striatal pathway. PD is frequently diagnosed clinically, and an autopsy is believed to be necessary to confirm the diagnosis [14,15].

There are various drugs available to treat Parkinson's disease. There is little evidence that drugs that target the dopaminergic system affect the course of the condition, even though they improve motor symptoms. This "one size fits all" approach might explain why clinical studies for disease modification in Parkinson's disease failed. The underlying pathophysiology must be addressed via therapy. Studies evaluating PD treatment on an individual basis should be undertaken because the etiology of PD varies from patient to patient. Thus, the precision medicine approach to Parkinson's disease is quite suited [16]. Medication therapy has less of an impact as Parkinson's disease advances into the intermediate and late stages, making early identification simpler. Finding PD patients in the preclinical stage might be more advantageous [17,18].

There are no sufficiently precise diagnostic markers available for the development of an efficient approach to detect Parkinson's disease early. Finding specific biomarkers in PD patients' body fluids would allow clinicians to trace the disease's progression without relying simply on structural, pathological, and functional brain imaging examinations. Finding biomarkers with high sensitivity and specificity will aid in early diagnosis, treatment, and tracking of Parkinson's disease progression. Here, we focus on several clinical diagnostic tests and kits commonly used in clinical practice, as well as potential biomarkers of Parkinson's disease (PD) in bodily fluids (cerebrospinal fluid (CSF), peripheral blood, saliva, and urine) and tissues (the brain, intestinal tract, and skin) [19,20].

3. Huntington's disease

Typically presenting in early to midlife, Huntington's disease (HD) is an autosomal dominant neurological disorder. Death follows a gradual deterioration in cognitive and motor function and is accompanied by severe mental health problems. Hypertrophy results from an expanded cytokines-adenine-guanine (CAG repeat in the huntingtin gene [21]. Predictive genetic testing can detect people who are carriers of HD, a rare neurological illness, long before symptoms appear. For these "pre-manifest" patients, neuroprotective treatment may postpone or halt the onset of clinical symptoms and functional impairment associated with Huntington's disease. Symptomatic, only partially effective therapies are available for HD at the moment because no disease-modifying drugs are on the market. The advancements in HD pathobiology are leading to the development of new therapeutics [22].

To evaluate the efficacy of disease-modifying treatments before symptoms appear, biomarkers play an essential role in therapeutic clinical trials. Suitable biomarkers for

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"pharmacology" or "efficacy" respond predictably to treatment. The pathobiology of a disease should be represented by state biomarkers, sometimes called "biomarkers of progression," which should track its clinical evolution. The best method to determine if potential indicators are associated with disease progression is to conduct longitudinal research, however, cross-sectional studies can find markers that are connected to disease stage [23]. Investigations on HD biomarkers have focused on the use of imaging modalities, such as PET and MRI, to detect brain abnormalities in both structure and function. Researchers are also researching molecular markers in physiological fluids, including blood, CSF, and saliva, including proteins, RNA, DNA, and metabolites. These biomarkers might assist in building non-invasive diagnostic tests, follow disease development, predict treatment results, and assess therapy effectiveness in HD patients [24]. New genomic technologies have enabled the finding of genetic biomarkers associated with Huntington's disease (HD). HD is currently diagnosed by genetic testing for huntingtin gene expression. To further understand the role of other genetic factors in HD onset and progression, more studies are required [23,25].

4. Amyotrophic lateral sclerosis (ALS)

The corticospinal tract, brainstem, and anterior horn cells of the spinal cord are the primary areas of progressive degradation in ALS, a neurodegenerative disease. Patients first experience localized weakness, which progresses to paralysis. In the European population, there are 2-3 cases of ALS for every 100,000 persons, and the lifetime chance of getting the disease is 1:400 [26,27]. Since the 19th century, the clinical definition of amyotrophic lateral sclerosis (ALS) has been constant. It is indicated by a gradual, painless loss of function, supporting EMG, normal imaging and indication of upper and lower neurons. Mutations in more than 20 genes, however, might result in symptoms and indicators that are clinically identical to those in sporadic cases of ALS, although a sizeable minority do not exhibit TDP-43 immunostaining [28,29]. Biomarker development efforts for ALS have been hampered by a number of issues, including small sample size, methodological variation, and lack of standardized techniques [30]. Numerous potential protein-based neurophysiological and neuroimaging biomarkers for ALS and has been found as a result of technological advancements [27,31,32]. Neurofilaments and tau two proteins generated when neurons die, have been investigated as potential markers for ALS [33-35]. Although its potential disease driving effects are yet unknown, inflammation is another general process that course in ALS and has been suggested as a source of biomarker candidates [36,37,38].

Table 2. Neurodegenerative diseases with their biomarkers.

Diseases	Biomarkers	Sample Type	Precision Medicine Approach	Diagnostic Tools
Alzheimer's Disease	-Amyloid-β (Aβ42, Aβ40) -Total tau (t-tau) -Phosphorylated tau (p-tau) -Neurofilament light chain (NfL)	CSF, Blood	-Anti-amyloid monoclonal antibodies (e.g., Aducanumab, Lecanemab) -Anti-tau therapies	-CSF analysis -PET scan -MRI
Parkinson's Disease	-α-Synuclein -Dopamine metabolites -Neurofilament light chain (NfL)	CSF, Blood	-Dopamine replacement therapy (Levodopa, Dopamine agonists) -α-Synuclein targeting therapies	-DAT-SPECT imaging -α-Synuclein analysis

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Huntington's Disease	-Mutant Huntingtin protein (mHTT) -Neurofilament light chain (NfL)	CSF, Blood	-Gene silencing therapies targeting mHTT	-Genetic testing -MRI
Amyotrophic Lateral Sclerosis	-Neurofilament light chain (NfL), pNfH -TDP-43 protein aggregates -Creatine Kinase	CSF, Blood	-SOD1-targeted therapy -Neuroprotective drugs (Riluzole, Edaravone)	-Electromyography (EMG) -CSF Biomarkers (NfL, pNfH)

THERAPEUTICS STRATEGIES IN PRECISION MEDICINE

1. Gene therapy

A game-changer in the fight against neurodegenerative diseases, gene therapy targets the biochemical and genetic factors at the root of the problem. In contrast to conventional treatment, which focuses on alleviating symptoms, gene therapy seeks for and destroys the disease's fundamental causes [39,40,41]. This method may produce therapeutic benefits that endure a long time, if not permanently. Gene editing, gene silence, and gene insertion are all part of this strategy for correcting genetic errors, preventing the production of harmful proteins, and filling in gene gaps. The use of viral vectors, particularly adeno-associated viruses (AAVs), is common due to their efficacy and potential safety concerns. They used to be unable to cross the BBB and reach CNS cells, but recent advancements have made that possible [42,43,44,45]. Researchers are also looking at non-viral vectors, such as lipid nanoparticles and polymeric systems, to circumvent the limitations of viral methods. It is possible to precisely target injured tissues using a variety of delivery modalities, such as intravenous, intrathecal, and intraparenchymal injections [46,47]. Localized injections are particularly helpful for compartmentalized organs like the retina and brain. Some examples of therapeutic aims include reducing neuroinflammation, enhancing mitochondrial function, and reducing protein misfolding and aggregation. In spite of tremendous progress, issues such as delivery challenges, off-target effects, and immune response persist. New advances in vector engineering, delivery methods, and early intervention approaches are continuing to drive the potential of gene therapy as a groundbreaking treatment for neurodegenerative illnesses [48,49,50].

2. Biomarker identification

The development of better diagnostic tools, more accurate prognoses, and novel therapies for neurodegenerative diseases depends on the identification of relevant biomarkers [51,52]. Biomarkers are measurable indicators of disease processes that help researchers understand the origins and progression of diseases. There, it is stressed how important genetic and transcriptome markers are for diseases like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. Some genetic indicators that are strongly associated with these diseases in families include rare mutations in genes such as SNCA, PSEN1, and C9orF72 [53-60]. Polygenic risk scores (PRS) are derived from genome-wide association studies and are used to assess an individual's susceptibility by combining several genetic risk variants [61,62,63]. Problems with insufficient penetration, low prevalence, and variability among populations restrict their therapeutic use. Circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) are three examples of transcriptomic biomarkers that are gaining attention due to their potential to regulate gene expression and their stability in biofluids [64–75]. Patients with certain diseases may be able to be distinguished from healthy controls or those with other illnesses based on dysregulated microRNAs, such as P-tau and neurofilament light chain (NFL) levels in Alzheimer's disease or miR-153 and miR-223 in Parkinson's disease [76,77]. Biomarkers based in blood are being sought after because of their scalability and lack of invasiveness, even if the current gold standard biomarkers are phosphorylated tau and β-amyloid in cerebrospinal fluid (CSF) [78,79,80]. The potential for multi-modal solutions to combine clinical, transcriptomic, and genetic data has been highlighted as

Journal of Chemical Health Risks
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JCHR (2025) 15(3), 1643-1659 | ISSN:2251-6727

a way to improve the utility of biomarkers and to more accurately manage neurodegenerative illnesses [81,85].

3. Immunotherapy

Immunotherapy is a prospective approach for addressing neurodegenerative disorders by targeting the atypical accumulation of certain proteins, such as tau, alpha-synuclein (α-syn), and amyloid-beta (Aβ) [86,87]. The pathogenesis of disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia (FTD) is significantly affected by the toxic aggregates produced by these proteins. The strategies include passive immunization, which entails the direct administration of monoclonal antibodies, and active immunization, wherein vaccines stimulate the immune system to produce antibodies [88-91]. These therapies diminish the dissemination of extracellular protein aggregates, enhance their clearance, and mitigate neuroinflammation and synaptic injury. The most advanced objective is extracellular plaques associated with Alzheimer's disease (AD) and targeting Aβ [92,93]. Mixed findings from clinical trials highlight concerns regarding limited clinical efficacy and adverse immunological reactions [94,95,96]. Innovative antibody engineering aims to target tau and α-syn, reducing intracellular aggregates and facilitating intracellular penetration and lysosomal route degradation [97]. Innovative approaches simultaneously address protein synthesis and aggregation by integrating immunotherapy with gene editing or antisense oligonucleotides. Recent findings indicate that addressing the coexisting diseases in neurodegenerative illnesses is essential. Combinatorial immunotherapies targeting inflammation and aging-related processes, alongside Aβ, tau, and α-syn, are gaining popularity [98,99]. These techniques can transform the management of complex and multifactorial neurodegenerative disorders by providing personalized and multi-targeted therapeutics [100].

4. Neuromodulation

Neuromodulation approaches mitigate motor and cognitive impairments caused by neurodegenerative diseases by capitalizing on the brain's plasticity [101, 102]. Some examples of non-invasive brain stimulation (NIBS) methods include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and more recent developments like transcranial alternating current stimulation (tACS) [103-106]. The hippocampus and the dorsolateral prefrontal cortex (DLPFC), two regions of the brain associated with motor and cognitive functions, are the targets of these methods [107,108]. For the best results, treatments often include computer-based cognitive training; repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have shown improvements in memory and executive functioning for Alzheimer's disease. These methods, when combined with specific cognitive or physical therapy for Parkinson's disease (PD), improve motor symptoms, quality of life, and executive functioning [109–112]. Transcranial alternating current stimulation is a relatively new technique that modulates gamma oscillations and can decrease the accumulation of harmful proteins like tau in Alzheimer's disease (AD) [113-114].

5. Artificial intelligence and machine learning

Neurodegenerative disease diagnosis and therapy are being revolutionized by AI and ML, which offer scalable approaches for early identification, progression tracking, and personalized treatment strategies [115,118]. Analysis of genetic, vocal, gait, and neuroimaging data, among other modalities, using machine learning techniques such as deep learning models, support vector machines (SVMS), and random forests [119–121]. For example, SVM-based classifiers have demonstrated efficacy in distinguishing between normal movement and motor symptoms of Parkinson's disease [122-125], and convolutional neural networks (CNNS) have demonstrated high accuracy in differentiating between healthy controls and Alzheimer's disease using MRI and PET scans. In order to identify biomarkers like Aβ and tau levels in AD or gait abnormalities in PD, machine learning models are being employed with the help of wearable sensors and data from many imaging models [126,127]. In addition to improving early disease detection, these approaches allow for comprehensive progression tracking throughout several phases of neurodegeneration, such as the transition from mild cognitive impairment to Alzheimer's disease [128–130]. With the use of machine learning, it is now possible to combine data from many models, such neuroimaging and speech analysis, to provide more accurate diagnoses [131].

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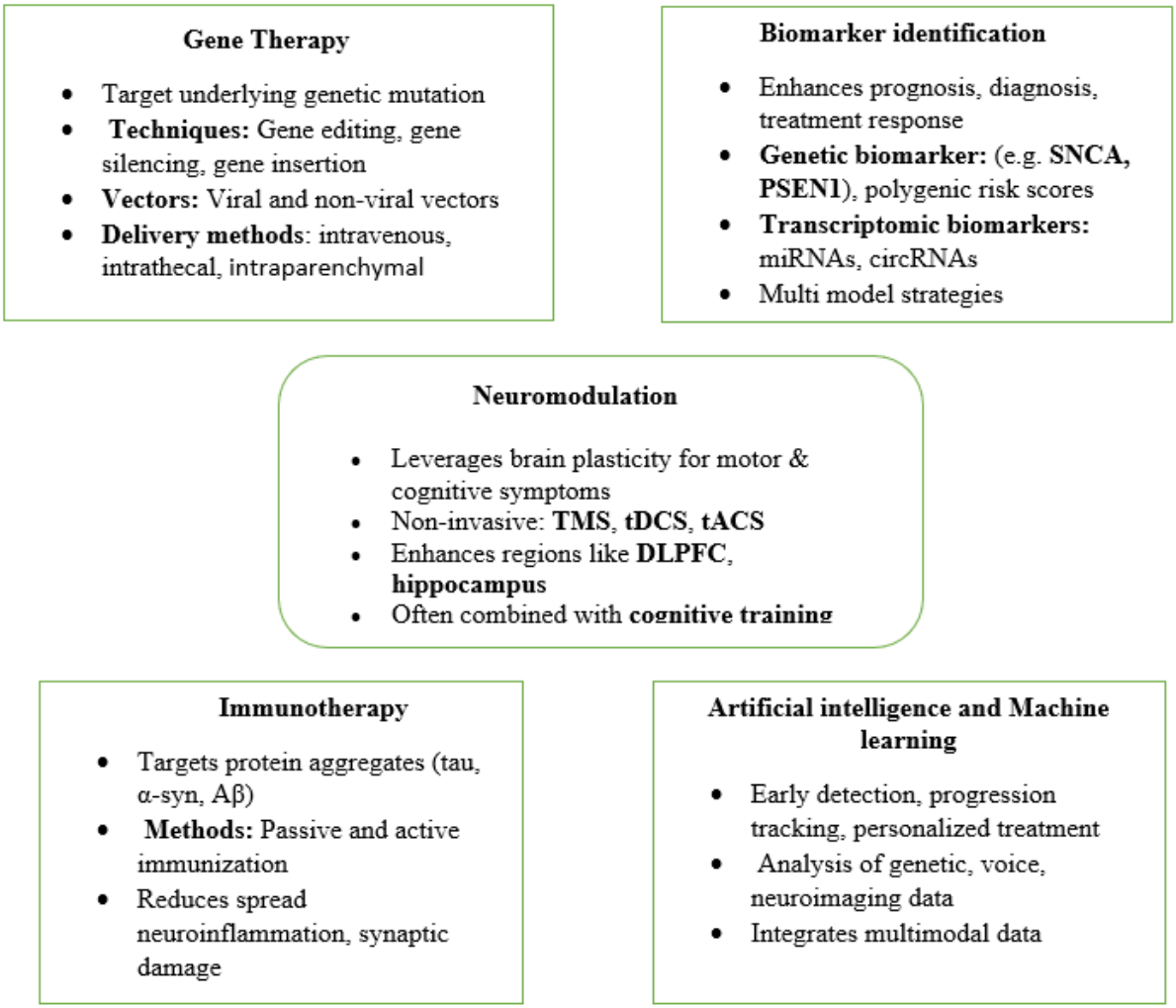

Fig2.Therapeutic strategies in precision medicine for neurodegenerative diseases.

CHALLENGES AND FUTURE PERSPECTIVES

For neurodegenerative illnesses to be effectively treated in the future, gene-based therapeutics such as antisense oligonucleosides and better delivery mechanisms utilizing nanocarriers and chemical modifications are crucial [132-135]. A more rapid and less expensive solution may be possible through the use of medication repurposing and integrative approaches that combine state-of-the-art strategies with existing therapy options [136-137]. Better biomarkers for early detection and real-time monitoring are essential for guiding precision medicine and enhancing clinical trials [138-140]. However, problems persist, including a lack of disease-modifying drugs, challenges in crossing the blood-brain barrier, high rates of failure in clinical trials, and the complexity of individual heterogeneity. These issues need to be tackled through innovation, collaboration, and readily available treatment choices in order to boost patient outcomes and progress the field [141-145].

CONCLUSION

The use of next-generation sequencing, advanced biomarkers, and novel treatments has brought about a paradigm shift in the treatment of neurological disorders under precision medicine. In diseases including Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis, biomarkers like microRNAs allow for early diagnosis and individualized treatment. Promising new approaches to illness management are emerging in the fields of gene editing,

immunotherapy, neuromodulator, and AI-driven diagnostics. The intricacy of neurodegeneration, difficulties in delivering medications, and a lack of disease-modifying therapies are all ongoing problems. In order to enhance outcomes for larger populations, future work should center on making it easier to access, improving delivery systems, and combining data from several models.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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