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Drug Repurposing for Neurodegenerative Diseases Using AI and Pharmacogenomic Approaches

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ABSTRACT

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive neuronal dysfunction and loss, leading to cognitive and motor impairments. Despite decades of research, effective disease-modifying therapies remain elusive, mainly due to complex pathophysiology, genetic heterogeneity, and translational challenges in drug discovery. Drug repurposing identifying novel therapeutic applications for existing drugs offers an efficient, cost-effective, and faster route for therapy development. Advances in artificial intelligence (AI) and pharmacogenomics are transforming this paradigm by enabling integrative data mining, predictive modeling, and patient stratification. This review highlights recent developments in AI-driven drug repurposing pipelines, the role of pharmacogenomic profiling in precision medicine, and emerging case studies demonstrating successful application of these approaches. Finally, we discuss future opportunities and challenges in integrating AI and pharmacogenomics to establish a robust framework for personalized therapeutics in neurodegeneration.

KEYWORDS: *Neurodegenerative diseases, Drug repurposing, Artificial intelligence, Pharmacogenomics, Precision medicine.*

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1. INTRODUCTION

Neurodegenerative diseases (NDs) - including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) - pose one of the most formidable challenges in modern medicine. Their prevalence rises as populations age: for example, the number of people with AD is projected to grow from tens of millions currently to more than 150 million by 2050 globally [1]. The burden of these disorders is not only clinical but also economic and societal, as they lead to progressive cognitive, motor, and behavioral decline, straining health systems and caregivers alike [2].

Despite decades of intense research, therapeutic breakthroughs remain elusive. Many promising candidates targeting canonical pathological hallmarks-such as amyloid-β accumulation, tau aggregation, or α-synuclein pathology-have failed in late-stage clinical trials [3]. These repeated failures highlight the complexity and multifactorial nature of NDs, and the limitations of traditional "target-centric" drug discovery. Moreover, development of first-in-class agents is a costly, high-risk, and time-consuming process: bringing a novel CNS drug from concept to market may take 10–15 years and cost upwards of a billion US dollars [4].

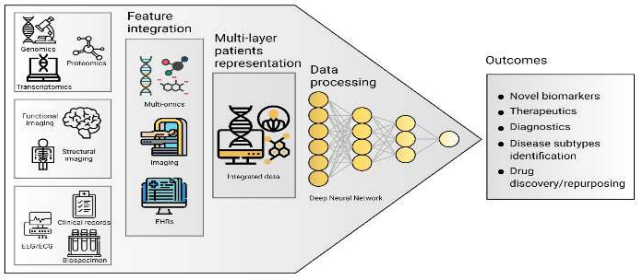

Figure 1. AI- and pharmacogenomics-driven drug repurposing framework for neurodegenerative diseases. Multi-omics and clinical data are integrated using machine learning and network

models to identify candidate drugs and stratify patient-specific therapies.

In this context, **drug repurposing** (also called drug repositioning) has emerged as a promising alternative or complement to de novo drug discovery. Rather than starting from scratch, drug repurposing seeks new therapeutic uses for existing compounds whose safety, pharmacokinetics, and toxicity profiles are already partially characterized. This reduces cost, risk, and development time [5]. Indeed, repurposed agents have a distinct advantage in the neurodegeneration field because the blood–brain barrier (BBB), CNS toxicity, and long-term safety hurdles are among the major obstacles for novel compounds [6].

However, repurposing is not a trivial "plug-and-play" strategy. To be effective, it must go beyond mere serendipity or trial-and-error screening. It should integrate mechanistic insights, network-level models, and patient heterogeneity [7]. Here is where **artificial intelligence (AI)** and **pharmacogenomics** converge to offer a transformative paradigm.

AI and computational intelligence enable scouring of vast biomedical datasets-such as genomics, transcriptomics, proteomics, metabolomics, imaging, electronic health records (EHRs), and drug–target databases-to uncover hidden or nonobvious associations between drugs and disease pathways [8]. Graph neural networks, knowledge graphs, deep learning, and network-based inference methods are increasingly being applied to generate repurposing hypotheses [9].

Pharmacogenomics, which studies how individual genetic variation influences drug response, offers the means to tailor repurposed therapies to specific patient subgroups. Genetic differences in drug metabolism (e.g. cytochrome P450 variants), transporters, target binding, or downstream signaling may substantially modulate both efficacy and safety in the CNS [10]. By incorporating pharmacogenomic stratification, repurposed drugs can be optimized for personalized application, avoiding off-target toxicity or therapeutic nonresponders [11].

Thus, the integration of AI-driven repurposing strategies with pharmacogenomic insight has the potential to accelerate precision neuroscience therapeutics: discovering candidate repurposed drugs and predicting which patients are most likely to benefit or suffer adverse effects [12].

In recent years this integrative approach has gained momentum. For example, the DeepDrug method uses a graph neural network built on expert-curated biomedical graphs to propose combinations of repurposed drugs targeting multiple AD-relevant pathways [13]. Other studies have used transcriptomic reversal, knowledge graph embeddings, and large language model–augmented frameworks to infer drug–ND connections [14]. On the pharmacogenomic side, efforts to map genotype-phenotype relationships in CNS drug response and to integrate GWAS or variant data into repurposing pipelines are emerging, though still underexploited [15].

Nonetheless, this field faces several challenges: heterogeneity of data modalities, limited sample sizes in CNS cohorts, model interpretability ("black box" AI), regulatory and intellectual property constraints for repurposed generics, and the need for rigorous experimental and clinical validation [16].

In this review, we synthesize the state-of-the-art in AI-based drug repurposing for neurodegenerative diseases, detail how pharmacogenomics can be integrated, present key case studies, and highlight future prospects and major challenges. Our goal is to chart a roadmap toward more efficient, patient-centric repurposed therapies in the fight against neurodegeneration [17].

2. The Rationale for Drug Repurposing in Neurodegeneration

Drug repurposing has emerged as a promising strategy in neurodegenerative disease research, largely because of the high attrition rates associated with traditional drug discovery [18]. Despite substantial investments, most neurodegeneration-targeted drugs fail during Phase II or III clinical trials, often due to inadequate efficacy in humans despite encouraging preclinical results. This high failure rate reflects the complexity of disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, where multifactorial pathophysiology and poor translation from animal models remain persistent hurdles [19].

In contrast, repurposed drugs offer the advantage of well-established safety, pharmacokinetics, and toxicity profiles, which can significantly reduce the cost, risk, and time associated with clinical development [20]. Importantly, many approved drugs exhibit polypharmacology, meaning they interact with multiple targets and pathways rather than acting in a single linear fashion [21]. This pleiotropic nature is particularly advantageous in neurodegeneration, where disease progression involves interconnected mechanisms such as neuroinflammation, oxidative stress, excitotoxicity, and mitochondrial dysfunction [22]. For example, anti-inflammatory drugs, metabolic modulators, and certain oncology therapeutics have demonstrated beneficial off-target effects in preclinical models of neurodegeneration [23].

Finally, there is a pressing clinical urgency to identify viable interventions, as neurodegenerative disorders are progressive, irreversible, and associated with enormous societal and economic burdens [24]. For patients and caregivers facing declining quality of life, accelerating therapeutic development through repurposing offers a faster route to meaningful clinical benefit compared to conventional pipelines [25].

3. AI in Drug Repurposing for Neurodegenerative Diseases

3.1. Machine Learning and Deep Learning Models

Artificial intelligence has transformed drug repurposing by enabling the integration of large and diverse datasets [26]. Machine learning models can learn from known drug–target–disease interactions to predict novel associations, while unsupervised learning approaches cluster patients according to genetic, epigenetic, or transcriptomic profiles to identify subgroups that may respond to existing drugs [27]. Deep learning, particularly graph neural networks and transformer-based models, can capture complex nonlinear relationships across multi-omics data, neuroimaging, and clinical records [28]. For instance, deep learning algorithms have been applied to transcriptomic signatures to identify drugs capable of reversing disease-specific gene expression patterns in Alzheimer's and Parkinson's disease [29].

3.2. Network-Based Approaches

Network pharmacology leverages gene–drug–disease interactomes to identify drugs capable of modulating entire biological networks rather than focusing on a single target [30]. This approach is highly relevant to neurodegenerative diseases, which involve multiple converging pathways such as protein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation [31]. Network-based inference has highlighted drugs like pioglitazone, an antidiabetic agent, and minocycline, an antibiotic with anti-inflammatory properties, as candidates for repositioning in Alzheimer's and Parkinson's disease [32].

3.3. Natural Language Processing (NLP) and Knowledge Graphs

Natural language processing is increasingly used to mine the enormous volume of biomedical literature, patents, and clinical trial reports for hidden drug–disease relationships [33]. Knowledge graphs then integrate these findings with curated biomedical databases, linking drugs, genes, pathways, and clinical phenotypes into structured networks [34]. This enables context-specific repurposing predictions and accelerates hypothesis generation [35]. Such approaches have already produced comprehensive resources for Alzheimer's and Parkinson's disease research, improving predictive accuracy and guiding experimental validation [36].

3.4. Case Studies

AI-driven repurposing has already yielded several promising candidates in neurodegenerative diseases. Sildenafil, originally developed for erectile dysfunction, has been identified as a potential therapeutic for Alzheimer's disease based on population-scale data and computational modeling that highlight its effects on amyloid and tau-related pathways [37]. Metformin, widely used for type 2 diabetes, has emerged as a candidate neuroprotective agent due to its capacity to regulate mitochondrial metabolism, activate AMP-activated protein kinase (AMPK), and exert anti-inflammatory effects, with several clinical trials currently assessing its efficacy in cognitive decline [38]. Similarly, minocycline, a tetracycline antibiotic, has demonstrated neuroprotective and anti-inflammatory properties, showing promise in models of Parkinson's disease and amyotrophic lateral sclerosis [39]. These examples illustrate how AI methodologies-ranging from transcriptomic reversal to network inference-can uncover non-obvious therapeutic opportunities and accelerate the transition from computational predictions to experimental validation and clinical evaluation.

4. Pharmacogenomics in Drug Repurposing

4.1. Role in Precision Medicine

Pharmacogenomics examines how individual genetic variations influence drug absorption, distribution, metabolism, excretion (ADME), target interactions, and downstream signaling pathways. In neurodegenerative diseases, this field provides a critical foundation for moving beyond generalized treatment strategies toward precision medicine approaches that align with genetically defined patient subgroups [40].

For instance, cytochrome P450 polymorphisms (particularly CYP2D6 and CYP3A4/5) are among the most studied pharmacogenes, and their variants can dramatically alter plasma and CNS concentrations of many neuroactive drugs, shifting them between therapeutic, subtherapeutic, or toxic ranges [41]. The APOE ε4 allele, a major genetic risk factor in Alzheimer's disease, has been linked to variability in drug responses, influencing lipid homeostasis, neuronal repair, and cerebrovascular function that affect drug delivery to the brain [42]. In Parkinson's disease, LRRK2 and GBA mutations define molecular subtypes with distinct pathological trajectories, influencing lysosomal and mitochondrial function. These variations may affect how repurposed drugs

perform across patient groups, highlighting the need for genotype-informed therapeutic strategies [43].

By incorporating pharmacogenomic data into drug repurposing strategies, researchers can stratify patients into likely responders and non-responders, personalize drug selection and dosing, and minimize adverse effects. This ensures that therapies are not only effective at the population level but also safe and optimized for individual patients.

4.2. Integration with Repurposing Pipelines

To fully harness the potential of pharmacogenomics in repurposing, integration is required at every stage of the discovery and development pipeline [44]. During candidate filtering, predicted repurposed drugs should be prioritized if their mechanisms or metabolic pathways overlap with known pharmacogenomic markers relevant to the disease cohort (for example, CYP2D6-metabolized drugs in populations with common CYP2D6 variants). In silico modeling can then incorporate genotype-specific parameters such as predicted enzyme activity or transporter polymorphisms, simulating heterogeneous drug responses across genetic subgroups.

Pharmacogenomic insights also guide biomarker selection, with markers used as covariates or stratification factors in preclinical validation or clinical trial design. Finally, adaptive trial designs represent a particularly powerful application: they allow dynamic reassignment of patients or dose adjustments based on emerging genotype–response data, ensuring that patients are not unnecessarily exposed to ineffective regimens while maximizing the chance of clinical success.

When implemented systematically, this integration enhances the efficiency of drug repurposing pipelines, reduces attrition, and accelerates the identification of precision therapies in genetically heterogeneous populations.

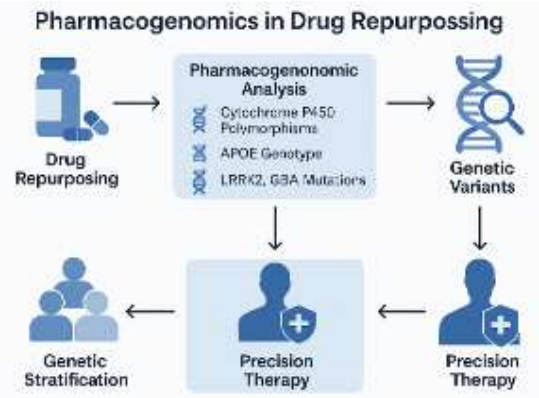

Figure 2. Pharmacogenomics-guided drug repurposing: integrating genetic variants and stratification to enable precision therapy in neurodegenerative disease

4.3. Examples

Several illustrative cases highlight how pharmacogenomics has shaped therapeutic outcomes in neurodegenerative contexts. Donepezil, a widely prescribed acetylcholinesterase inhibitor for Alzheimer's disease, demonstrates marked interindividual variability in efficacy. Variants in CYP2D6 strongly influence drug metabolism: for example, the rs1080985 promoter polymorphism has been linked to differential responses, with G-allele carriers exhibiting faster metabolism and reduced drug exposure, resulting in diminished cognitive benefit [45]. Conversely, patients with intermediate or poor metabolizer genotypes may show improved therapeutic responses due to prolonged drug exposure. These findings are supported by pharmacokinetic studies demonstrating that CYP2D6 activity scores correlate with steady-state plasma levels of donepezil [46].

Other drug–gene interactions provide prospective insights, even if direct evidence in repurposed neurotherapeutics remains limited. Agents such as valproic acid (mood stabilizer with repurposing potential in ALS), modafinil (wake-promoting agent with potential cognitive benefits), and other metabolic modulators show variable efficacy depending on genetic background [47]. Variants in genes encoding mitochondrial proteins, oxidative stress regulators, or transporter proteins (e.g., ABC family) can alter drug distribution, efficacy, or toxicity in neurodegenerative disease contexts [48]. These examples illustrate both the promise and current limitations: pharmacogenomics has the capacity to meaningfully guide drug repurposing decisions, but large-scale, consistent evidence remains to be established.

5. Synergistic Use of AI and Pharmacogenomics

The integration of artificial intelligence with pharmacogenomics represents a paradigm shift in the rational design of repurposing strategies for neurodegenerative diseases. AI excels at handling the scale and complexity of multi-omics datasets-including genomics, transcriptomics, proteomics, metabolomics, and epigenomics-and can generate predictive biomarkers and stratification strategies [49]. By embedding these data into machine learning models, AI can identify which repurposed drugs are most likely to benefit genetically defined subgroups.

A particularly promising development is the creation of virtual patient cohorts-in silico populations generated from real-world genomic and clinical data-that allow researchers to test candidate drugs across heterogeneous subgroups before human trials [50]. Such computational avatars simulate variability in

efficacy and toxicity, reducing the risk of costly trial failures.

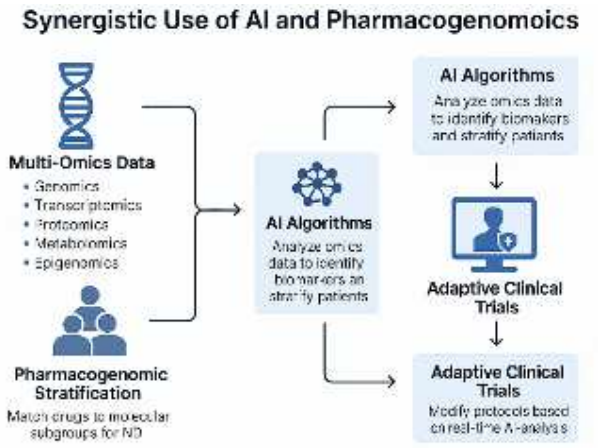

Figure 3. Synergistic use of AI and pharmacogenomics in drug repurposing for neurodegenerative diseases. Multi-omics data are analyzed by AI algorithms to identify biomarkers, enable pharmacogenomic stratification, generate virtual patient cohorts, and guide adaptive clinical trials, ultimately facilitating precision repurposed therapies.

Moreover, adaptive trial designs powered by AI-pharmacogenomic frameworks represent a dynamic alternative to traditional static protocols. These designs allow iterative modifications of dosage, inclusion criteria, or subgroup stratification in response to real-time data [51]. Together, these approaches illustrate how AI and pharmacogenomics can work synergistically to accelerate precision repurposing in neurodegenerative diseases.

6. Challenges and Limitations

Despite its transformative potential, this convergence faces key challenges. Data integration is a persistent barrier, as omics, imaging, and clinical records are often fragmented across platforms and lack standardized formatting [52]. Model interpretability is another limitation: while deep learning models achieve high predictive accuracy, their "black box" nature reduces mechanistic transparency and slows clinical adoption [53].

Ethical and regulatory concerns also remain pressing. Pharmacogenomic data is highly sensitive, raising issues of privacy, ownership, and algorithmic bias. Without proper governance, AI models risk reinforcing health disparities by underperforming in underrepresented populations [54]. Furthermore, most regulatory frameworks are not yet equipped to validate AI-driven pipelines, creating uncertainty regarding evidentiary requirements for approval [55].

Finally, a substantial clinical validation gap exists. Many AI-predicted drug candidates perform well in silico or preclinically but fail in human trials due to disease heterogeneity, poor biomarker translation, or unanticipated side effects [56]. Closing this gap requires robust validation frameworks, large-scale longitudinal cohorts, and close alignment with regulatory science.

7. Future Perspectives

Several emerging strategies could overcome these limitations. Federated learning enables multi-institutional collaborations without direct data sharing, allowing models to be trained across diverse datasets while preserving privacy [57]. This is particularly important for rare genetic subgroups and for ensuring inclusivity of underrepresented populations.

The integration of single-cell omics with AI provides an unprecedented resolution of cellular heterogeneity in neurodegeneration. Single-cell transcriptomics and proteomics reveal the dysfunction of specific neuronal and glial subtypes, enabling repurposed drugs to be targeted with higher precision [58].

Another promising frontier is the development of digital twins-computational avatars of patients that incorporate genomic, molecular, and clinical data to simulate disease trajectories and drug responses [59]. These models could allow clinicians to virtually test repurposed drugs before prescribing them, reducing trial-and-error approaches in clinical practice.

Finally, the establishment of pharmacogenomic-informed repurposing consortia will be essential for uniting academia, industry, regulators, and patient advocacy groups. Such collaborations can standardize data collection, address ethical concerns, and ensure rapid clinical translation [60]. Together, these innovations could firmly establish repurposing, augmented by AI and pharmacogenomics, as a cornerstone of precision medicine in neurodegenerative diseases.

8. Conclusion

Drug repurposing offers a pragmatic and high-impact avenue to address the persistent unmet needs in neurodegenerative disorders. Unlike conventional drug development, which is protracted, costly, and prone to high attrition, repurposing leverages known compounds with established safety profiles, thereby accelerating the path to clinical translation [61].

The integration of AI and pharmacogenomics adds unprecedented depth to this approach. AI models can interrogate vast and complex datasets, uncover novel drug–disease associations, and simulate heterogeneous drug responses, while pharmacogenomics provides the precision medicine lens needed to match therapies with genetically defined patient subgroups [62].

Yet, challenges remain-including data fragmentation, interpretability of AI models, privacy concerns, and the validation gap between computational predictions and clinical success. Addressing these issues will require collaborative frameworks, transparent AI systems, and adaptive clinical trial designs informed by pharmacogenomic markers [63].

If successfully implemented, the convergence of AI and pharmacogenomics in drug repurposing has the potential to redefine therapeutic development in neurodegeneration-delivering safer, more effective, and personalized treatments to patients in need [64].

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