Advancing Diagnosis and Therapy of Rare Monogenic Disorders through AI: Insights from Adrenoleukodystrophy

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Abstract

Background: Adrenoleukodystrophy (ALD) is a rare X-linked monogenic disorder caused by mutations in the ABCD1 gene, resulting in severe neurological and adrenal dysfunction. Its phenotypic variability and diagnostic complexity hinder timely intervention.

Objective: This review examines the role of artificial intelligence (AI) in improving the diagnosis, patient stratification, and therapeutic management of ALD, highlighting recent advances and challenges.

Methods: We discuss AI models such as Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), and Random Forest classifiers, focusing on their application to biomarker discovery, multi-omics integration, pathogenic variant identification, and disease modeling. The utility of AI in accelerating drug repurposing and enhancing CRISPRbased gene-editing strategies is also considered.

Results: AI-driven approaches have enabled earlier and more accurate diagnosis of ALD, improved patient stratification, identified potential therapeutic targets, and optimized gene-editing techniques. Integration of clinical and high-throughput multi-omics data enhances predictive modeling and personalized intervention strategies.

Challenges: Despite these advancements, limitations include small datasets, phenotypic heterogeneity, algorithmic opacity, and ethical concerns regarding AI deployment in rare disease management.

Conclusion: AI has transformative potential for ALD and other rare monogenic disorders, providing tools for early diagnosis, precision therapy, and drug development. Future work should focus on expanding datasets, improving interpretability, and addressing ethical considerations to maximize clinical impact.

Keywords: Adrenoleukodystrophy, Monogenic disorders, Artificial intelligence, Deep learning, CRISPR.

1. Introduction

Monogenic disorders, caused by mutations in a single gene, though individually rare (<1 in 2,000), collectively affect millions worldwide, with approximately 80% linked to genetic anomalies [1,2]. The wide range of mutations, which includes structural rearrangements and single nucleotide variations, pose significant difficulties for diagnosis and treatment. Recent advances in Next-Generation Sequencing (NGS) technologies, including whole-exome and wholegenome sequencing, have significantly improved the detection of pathogenic variants, in disorders such as propionic acidemia and other inherited metabolic diseases [3,4].

Among these conditions, X-linked Adrenoleukodystrophy (X-ALD) serves as a representative example of the complexity and heterogeneity associated with monogenic diseases. ALD results from mutations in the X-linked ABCD1 gene, which impair peroxisomal β-oxidation of very long-chain fatty acids (VLCFAs), leading to their toxic accumulation in plasma, brain, spinal cord, and adrenal cortex [5]. This biochemical dysfunction contributes to progressive central nervous system (CNS) demyelination, adrenal insufficiency, and spinal cord involvement. The estimated prevalence of ALD is approximately 1 in 15,000–25,000 males, while heterozygous females frequently develop milder, late-onset symptoms [6].

One of the main hallmarks of ALD is its phenotypic heterogeneity, with clinical outcomes ranging from mild to severe. Childhood cerebral ALD (ccALD), the most aggressive form of ALD, usually appearing between ages 4 and 10, leads to rapid neurodegeneration, worsening cognitive and motor function, and exhibiting high mortality within a few years in the absence of timely intervention [7]. In contrast, adrenomyeloneuropathy (AMN) generally appears in adulthood and manifests as progressive spastic paraparesis, neuropathy, and sphincter dysfunction [8]. Additionally, an Addison-only phenotype, presenting with isolated adrenal insufficiency, may remain stable or later progress to neurological involvement. This clinical variability, even among individuals harboring identical *ABCD1* mutations, suggests the influence of genetic, epigenetic, and environmental modifiers [9].

The insidious progression of the disease further complicates management, as the accumulation of VLCFAs often occurs well before the onset of overt symptoms. Adrenal insufficiency may emerge years before neurological deterioration, delaying recognition and intervention. Early diagnosis is crucial, given that hematopoietic stem cell transplantation (HSCT), the current standard therapeutic approach, offers the greatest benefit during presymptomatic or early cerebral stages. Unfortunately, the rarity of ALD, combined with its nonspecific early signs, frequently results in diagnostic delays, significantly narrowing the therapeutic window [10].

Against this backdrop, artificial intelligence (AI) has emerged as a transformative tool for addressing diagnostic and therapeutic challenges in rare monogenic disorders. AI-driven approaches, particularly machine learning (ML) and deep learning (DL) models such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), and random forests, have shown superior performance in imaging analysis, early disease detection, and drug discovery compared with conventional computational methods [11,12]. These frameworks also facilitate drug-target interaction prediction, virtual screening, and gene-editing optimization, paving the way for precision medicine [13]. However, despite these advancements, critical challenges persist, including the scarcity of annotated datasets, interpretability issues, and ethical concerns related to data privacy [14,15]. This review explores AI's role in overcoming diagnostic and therapeutic hurdles in rare monogenic disorders, using ALD as a model system. It highlights progress in early diagnosis, drug repurposing, and precision gene editing, compares AI-driven and traditional approaches, and outlines future directions toward personalized medicine.

2. Diagnostic Challenges

Diagnosis is complicated by phenotypic overlap with other disorders. Biochemical screening measures plasma VLCFA elevated C26:0 and altered C24:0/C22:0 and C26:0/C22:0 ratios followed by *ABCD1* mutation analysis [16]. MRI detects early cerebral lesions but may miss subtle changes, and VUS interpretation adds complexity. AI-driven integration of multi-omics and imaging biomarkers offers promising improvements in diagnostic accuracy and timeliness [17].

2.1 Role of AI in Diagnosis of Monogenic Disorders

AI has revolutionized the diagnosis of monogenic disorders by addressing the limitations of traditional methods in variant classification, phenotype prediction, and early detection. Integrating multi-omics data, clinical records, and imaging, AIdriven systems provide rapid, scalable, and accurate solutions, enhancing variant interpretation and uncovering complex genotype–phenotype relationships beyond conventional approaches (Table 1 [18]).

Table 1: AI Models and their applications in the studies of rare monogenic disorders.

Monogenic Disorders	AI Models Used	Purpose	Accuracy	References
Familial Hypercholesterolemia (FH)	Multivariable models (with/without LDL-C polygenic score)	Discriminating between FH carriers and non-carriers to identify at-risk individuals.	AUC of 0.77 (with PGS), AUC of 0.62 (LDL-C only), AUC of 0.71 (corrected for statin use)	[19]
Sickle Cell Disease (SCD)	GoogLeNet, ResNet18, ResNet50	Detecting sickle cell disease from microscopic blood smear images.	ResNet50: 94.90% accuracy	[20]
Retinitis Pigmentosa (RP)	Inception V3, Inception ResNet V2, Xception	Detecting the presence of retinitis pigmentosa from color fundus photographs.	AUROC: 96.74%, Accuracy: 91.45%, Sensitivity: 95.71%, F3 Score: 91.66%	[21]
Adrenoleukodystrophy (ALD)	CNN with 3D U-Net, Bayesian inference	Generating differential diagnoses from brain MRI scans,	91% accuracy for placing correct diagnosis in top three	[22]

		including detecting ALD.	differential diagnoses	
Cystic Fibrosis (CF)	2D and 3D nnU-Net	Detecting and segmenting airway alterations in CF patients from CT scans.	AUC: 0.683–0.886, DSC: 0.80 (3D) vs. 0.77 (2D)	[23]
Duchenne Muscular Dystrophy (DMD)	SDL-XGBoost	Automated detection and classification of muscular dystrophies using MRI data.	DMD: 96.18% accuracy, BMD: 94.25% accuracy	[24]
Menkes Disease (MD)	Targeted next generation sequencing (tNGS)	Detect pathogenic variants in the ATP7A gene for early diagnosis of Menkes disease, which is not easily identifiable through traditional biochemical newborn screening methods.	The sequencing method had a detection accuracy of 95.5%, correctly identifying 21 out of 22 cases.	[25]
Huntington's Disease (HD)	CNN	HD is classified by converting vGRF gait data into recurrence plot images, which are analyzed using a CNN.	HD: 96.74%	[26]
Amyotrophic Lateral Sclerosis (ALS)	Convolutional Neural Network (CNN)	ALS is classified by converting vGRF gait data into recurrence plot images, then analyzing them with a CNN.	ALS: 98.32%	[27]
Parkinson disease (PD)	CNN	Classifying PD using recurrence plots derived from gait vertical ground reaction force (vGRF) data. Gait data is transformed into images using recurrence plots and classified via CNN.	PD: 97.41%	[28]
Hypertrophic Cardiomyopathy (HCM)	RF and ANN	These models were aimed at early and accurate diagnosis of HCM by analyzing transcriptomic data from patient samples.	The ANN's performance, assessed via the ROC curve, showed strong predictive ability, although specific metrics like the AUC were not reported.	[29]

3. AI in Genomic Variant Interpretation

Accurate interpretation of pathogenic variants is essential for diagnosing monogenic disorders, but traditional methods are labor-intensive and lack scalability [30]. AI models such as RF, SVM, and ANNs trained on databases like ClinVar and HGMD predict the pathogenicity of SNVs and indels with higher efficiency [31]. Deep learning tools such as DeepVariant [32], SpliceAI [33], and MutPred2 [34] improve accuracy by considering sequence context, splicing effects, and conservation. CNNs excel in converting raw genomic sequences into annotated outputs, while RNNs analyze sequential data, including non-coding variants [35].

3.1 AI for Phenotype Prediction and Early Diagnosis

AI links genotype to phenotype by integrating genetic, biochemical, and clinical data, aiding prediction of disease risk, onset, and progression in heterogeneous disorders like ALD. Models such as Bayesian networks and ensemble learning frameworks improve patient stratification and help to identify therapeutic windows [36]. In rare genetic disorders, natural language processing (NLP) tools are increasingly used to extract early phenotypic indicators from unstructured clinical notes, accelerating diagnosis and enabling timely clinical interventions [37,38]. The integration of AI-driven analytics with clinical informatics thus offers a powerful strategy to reduce diagnostic delays commonly associated with rare diseases.

3.2 ALD-Specific Diagnostic Applications

ALD, a progressive X-linked peroxisomal disorder, increasingly benefits from AI-driven diagnostics. AI models integrated into newborn screening use tandem MS/MS data to detect elevated VLCFAs, reducing false positives and expediting genetic confirmation [39]. CNN-based neuroimaging models can identify early cerebral demyelination before symptoms, enabling timely interventions like hematopoietic stem cell transplantation [40]. Integrative AI frameworks combining genomic, metabolomic, and radiologic data aim to build comprehensive diagnostic platforms [41]. Repurposed tools like PICRUSt assist in metabolic profiling [42,43]. In practice, AI-enhanced MS/MS pipelines improve newborn screening throughput and accuracy, while tools such as PrimateAI and Exomiser prioritize pathogenic *ABCD1* variants by integrating allele frequency, evolutionary conservation, and phenotype-genotype match scores, refining ALD diagnostics [44].

3.3 AI-Driven Genome-Wide Association Studies (GWAS)

Genome-wide association studies (GWAS) are instrumental in identifying genetic variants linked to disease susceptibility and pathogenesis [45]. The integration of AI has significantly improved the sensitivity, specificity, and computational efficiency of GWAS. Machine learning (ML) and deep learning (DL) models, paired with robust statistical frameworks, enable detection of both common and rare variant associations, while reducing false positives via advanced filtering algorithms. AI has also enhanced polygenic risk score (PRS) estimation by incorporating multi-omics datasets, thereby refining risk stratification [46]. Deep neural networks and Bayesian models have uncovered novel variant–disease associations, aiding precision therapeutics, especially in rare monogenic disorders [47]. AI-driven frameworks capable of integrating genomic, transcriptomic, and epigenomic layers offer deeper insight into the functional consequences of variants, improving diagnostic accuracy and supporting personalized treatment strategies [48,49]. Moreover, AI-based infrastructures and interpretable models like GenNet accelerate NGS variant annotation, maintain clinical relevance, and offer transparent understanding of mutation impacts [50,51]. These models enhance phenotype prediction, variant classification, and multi-omics integration, reinforcing AI's role in both research and translational medicine [52,53]. As AI technologies evolve, their contributions to genomics and precision healthcare are expected to expand, enabling earlier diagnosis, tailored therapies, and improved patient outcomes [54].

3.4 Applications of AI and Deep Learning Models in Analyzing Monogenic Disorders

A rigorous comparison of AI models such as CNNs, Random Forests, and RNN-LSTMs is essential for rare disease diagnostics. Such evaluations not only reveal their technical performance but also assess clinical applicability. Incorporating mathematical formulations underlying diagnostic accuracy strengthens methodological rigor, enabling deeper insight into the computational architectures and decision-making processes of these models, particularly in the data-scarce settings of rare diseases [55].

3.4.1 Convolutional Neural Networks (CNN)

A CNN is a deep learning model with a generic architecture depicted in Figure 1 that is intended to analyze grid-like data, including images. Without requiring human feature extraction, it automatically recognizes and learns features from incoming data, including edges or textures, using convolutional layers [56].

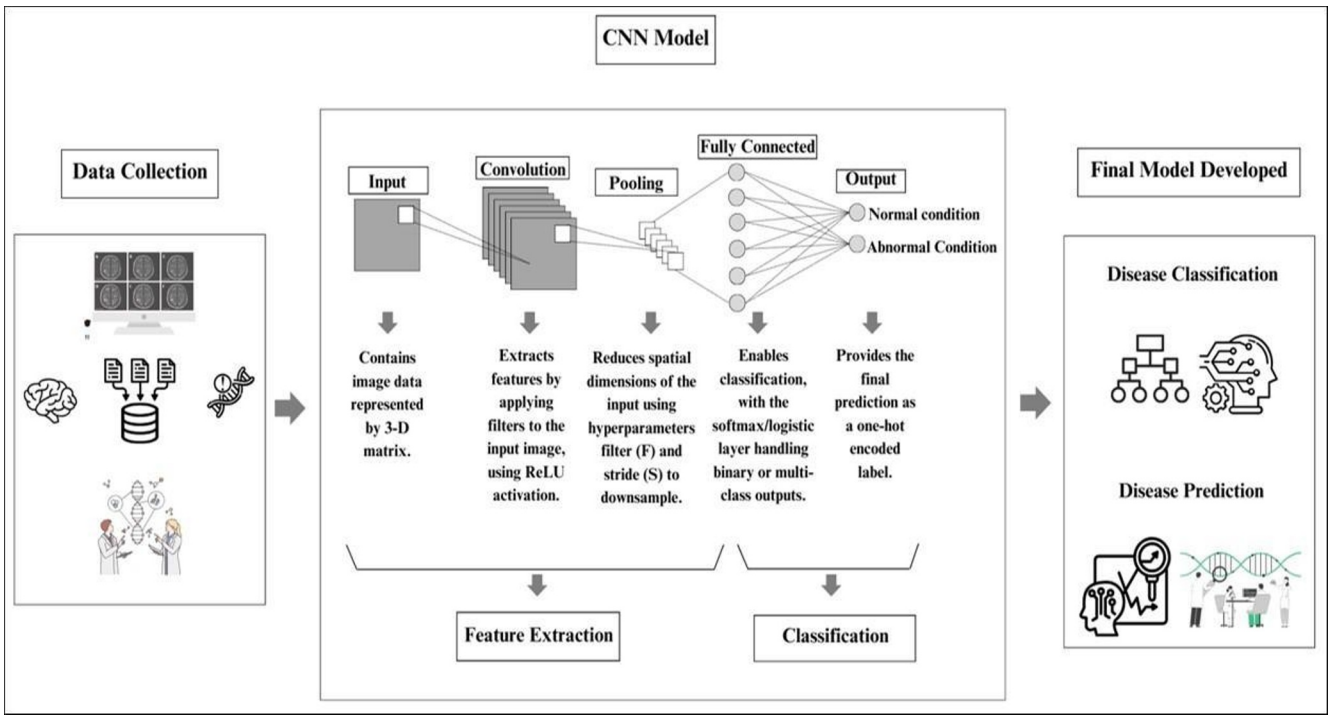

Figure 1: Overall structure of a CNN

3.4.2 Softmax Function

The softmax function transforms the output scores from the CNN into a probability distribution over N classes. Each value represents the predicted probability of the corresponding class. This function is essential for multi-class classification tasks [57]. The softmax ensures that the outputs are in the range [0, 1] and sum to 1, making them interpretable as probabilities, which is critical for accurate classification in studies related to monogenic disorders (Equation 1).

3.4.3 Cross-Entropy Loss Function

The cross-entropy loss measures the difference between the true class distribution and the predicted distribution generated by the CNN [58]. Minimizing this loss helps improve the CNN's ability to correctly classify cells and images (Equation 2).

3.4.4 Entropy Calculation for ROI (Region of Interest) Extraction

Equation 3 calculates the entropy of an image block, where p(i) is the probability of pixel intensity i in a region containing N pixels. High entropy indicates areas with rich information content, which can be used to identify regions of interest in images for further analysis.

3.4.5 Statistical Median Normalization

Median-based normalization is applied to adjust image intensity values, ensuring consistency across datasets. This step is crucial for reliable classification and analysis, particularly in identifying cellular abnormalities associated with monogenic disorders. Improved classification enhances understanding of disease progression and supports the development of personalized diagnostic and treatment strategies.

Random Forest (RF)

RF is a robust machine learning algorithm widely used in genetic studies to detect associations between genetic markers and disease traits. Its ensemble-based architecture, illustrated in Figure 2, enables high predictive accuracy and resilience against overfitting.

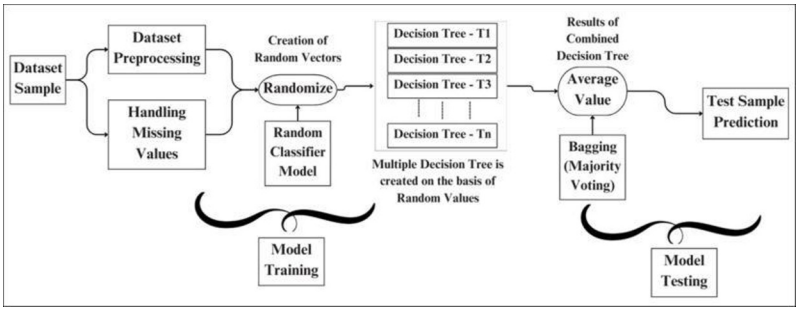

Figure 2: Overall structure of a Random Forest Classifier

3.4.6 Decision Tree (Gini Index)

For classification, the Gini Index is calculated as depicted in Equation 4, where p_i denotes the probability of class i. RF models use multiple decision trees trained on data subsets. Each tree splits data using criteria like Gini Index or Information Gain, enabling distinction between affected and unaffected cases and identifying key genetic markers [59]. Final predictions rely on ensemble voting, which reduces overfitting and enhances reliability in detecting diseaseassociated genes [60]. Equation 5 represents the ensemble prediction, where T is the total number of trees and $h_t(x)$ is the prediction from tree t.

RF uses a built-in method for error estimation without the need for a separate test set. OOB error helps assess how well the model generalizes, which is crucial for identifying reliable genetic associations. For each tree, the prediction error on the samples not used for training (Out-Of-Bag, or OOB samples) is calculated, as shown in Equation 6.

3.4.7 Long Short-Term Memory (LSTM)

LSTM is a type of machine learning algorithm that belongs to the category of RNNs. It is designed to address the issue of long-term dependencies by retaining historical information. The input gate, forget gate, control gate, and output gate are the four gates that make up an LSTM. As seen in Figure 3, i_t, f_t, c_t, and o_t stand for input gate, forget gate, control gate, and output gate, respectively [61].

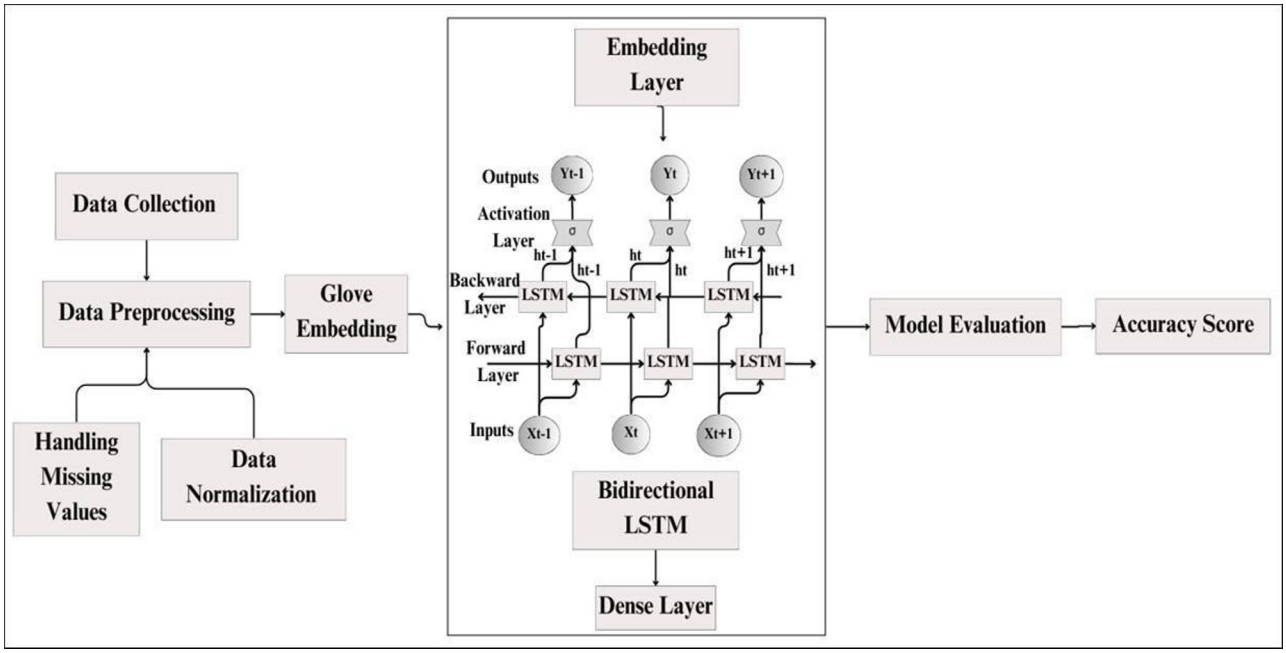

Figure 3: General architecture of Long Short-Term Memory (LSTM)

Input gate determines which information from the previous cell can be transferred to the current cell. It decides whether to retain or discard information from the previous memory input. The input gate is defined by Equation 7. The forget gate is represented by Equation 8. The control gate, responsible for updating the cell state, is described by Equation 9. The cell state update is represented by Equation 10. Finally, the output gate, which updates the hidden state and the output, is given by Equations 11 and 12.

In these equations, x_t represents the input, W denotes the weight matrices, b represents the biases, c_{t-1} is the previous cell state, c_t is the current cell state, h_{t-1} is the previous hidden state, and h_t is the current hidden state. The hyperbolic tangent function, tanh, scales the values between -1 and 1, while the sigmoid function σ outputs values between 0 and 1. Model performance is commonly assessed by Root Mean Square Error (RMSE) as shown in Equation 13. LSTM models overcome traditional RNN limitations in handling long-term dependencies by using memory cells. Nguyen et al. developed a bidirectional LSTM-based text-driven disease diagnosis system, which improved semantic feature extraction and sentence-level classification, achieving an AUC of 0.982 [62].

3.4.8 AI-Assisted Clinical Decision Support Systems (CDSS)

Integrating AI into CDSS enhances diagnostic accuracy and reduces delays for rare monogenic disorders. By combining clinical and genetic data, AI-driven CDSS minimizes errors and shortens the diagnostic journey by ~14% compared to conventional methods. Advances such as next-generation phenotyping and multidisciplinary teams further optimize workflows, though standardized frameworks for ultra-rare diseases remain needed [63].

4. AI in Drug Discovery and Repurposing

Drug discovery for rare monogenic disorders like ALD faces high costs, long timelines, and small trial populations. AI addresses these challenges by accelerating target identification, predicting drug–target interactions (DTIs), and enabling cost-effective drug repurposing [64,65]. Traditional development spans over a decade and billions in cost. AI-driven strategies integrate multi-omics data and computational tools to predict therapeutic candidates, improving target validation and prioritization. For ALD, caused by *ABCD1* mutations, AI platforms aim to restore peroxisomal function or reduce VLCFA accumulation, supporting precision medicine [66]. DTI prediction uses machine learning algorithms (Random Forests, SVMs) and deep learning models processing molecular graphs and SMILES strings. Tools such as DeepChem [67], DeepDTA [68], and MT-DTI [69], trained on DrugBank [70], BindingDB [71], and ChEMBL, enhance binding affinity prediction and candidate selection [72]. AI also drives drug repurposing for ultra-rare ALD by applying Bayesian learning and network pharmacology to identify compounds modulating VLCFA metabolism and neuroinflammation [73,74]. Bioinformatics platforms like DrugBank, ChEMBL, PubChem, and PharmGKB support virtual screening, toxicity prediction, and pharmacogenomics, enabling discovery of ABCD1-targeted therapies.

5. AI-Driven CRISPR Technologies for Precision Gene Editing in ALD

CRISPR-Cas9 has revolutionized genetic therapies by enabling precise genomic modifications, offering a promising strategy for treating monogenic disorders such as X-linked ALD. However, the effectiveness of CRISPR largely depends on guide RNA (gRNA) design, which determines editing specificity and minimizes off-target effects. Traditionally, gRNAs were designed using heuristic approaches, which often lacked predictive accuracy and scalability. The integration of AI has transformed this process by introducing data-driven optimization techniques. AI models including CNNs, RNNs, and Random Forest classifiers analyze large datasets of gRNA-target interactions, accounting for factors such as nucleotide composition, secondary structure, chromatin accessibility, and off-target risk [75,76]. These advanced models significantly improve CRISPR efficiency by reducing unintended edits and enhancing overall accuracy. Platforms like CRISPOR and Benchling leverage these AI-powered algorithms to streamline gRNA selection. In ALD, AI-assisted CRISPR strategies enable targeted correction of pathogenic *ABCD1* mutations, representing a pivotal step toward safe and effective gene therapy.

Despite these advances, a major challenge in CRISPR-based therapeutics is the risk of off-target edits, which can introduce harmful genomic alterations [77]. AI-driven models have been developed to address this issue by predicting and mitigating off-target cleavage. Techniques employing RNNs and Random Forest classifiers utilize large-scale CRISPR editing datasets to identify sequence motifs and chromatin states associated with off-target susceptibility [78]. Tools such as CRISPR-off integrate deep learning for genome-wide evaluation of off-target risks, outperforming traditional heuristic methods. In the context of ALD, minimizing such risks is crucial to prevent unintended disruptions in genes essential for neural and adrenal functions.

Beyond standard CRISPR-Cas9 editing, AI also enhances the development of next-generation precision technologies, including base editing and prime editing, which allow single-nucleotide modifications without introducing doublestranded breaks [79]. These advanced techniques are particularly suited for correcting specific *ABCD1* mutations in ALD patients. AI algorithms predict editing efficiency and guide the selection of optimal target sites by analyzing extensive datasets of successful and unsuccessful edits. Furthermore, AI-driven models optimize delivery strategies, such as viral vectors or lipid nanoparticles, tailored to efficiently target tissues affected in ALD, including the central nervous system and adrenal cortex. This ensures maximal therapeutic impact while minimizing systemic exposure and associated risks.

Looking ahead, AI-assisted CRISPR systems hold transformative potential for ALD therapy by enabling accurate correction of *ABCD1* mutations and addressing secondary pathological mechanisms like neuroinflammation [80,81]. Through intelligent gRNA selection, off-target risk prediction, precision editing modalities, and optimized delivery methods, the convergence of AI and CRISPR technologies is accelerating the transition from experimental approaches to clinically viable treatments. This integration represents a major leap toward safe, personalized, and durable genetic therapies for monogenic disorders.

6. AI-Driven Integration of Personalized Medicine and Multi-Omics

Personalized medicine tailors diagnosis and treatment to an individual's genetic, molecular, and environmental profile, offering a transformative approach for rare monogenic disorders where conventional therapies often fall short. By aligning interventions with disease-specific mutations, personalized medicine addresses significant unmet clinical needs despite historically limited investment in rare disease research. Whole-exome sequencing currently achieves diagnostic yields of approximately 25–30%, but precision care demands integration of genomic data with environmental and lifestyle factors through advanced bioinformatics frameworks [82]. Understanding the complexity of these disorders requires the integration of multi-omics layers — genomics, transcriptomics, proteomics, metabolomics, and epigenomics — combined with clinical data. Traditional single-omics analyses cannot capture the intricate molecular interactions driving phenotypic

variability. Here, AI, particularly ML and DL models, plays a pivotal role. AI algorithms can process vast, highdimensional datasets to uncover latent patterns, stratify patients, and predict therapeutic responses with high accuracy [83]. When integrated with electronic health records, these models generate multidimensional patient profiles that enhance clinical decision-making. For example, in X-linked ALD, pathogenic mutations in *ABCD1* initiate peroxisomal dysfunction, but disease progression is modulated by downstream metabolic and immune alterations. AI-enabled multiomics analysis allows dynamic tracking of these processes, supporting precision therapy tailored to disease stage and patient-specific risk factors [84].

Advanced AI frameworks further strengthen this paradigm by offering specialized capabilities: deep neural networks for complex feature extraction, Random Forests and Support Vector Machines (SVMs) for classification, Graph Convolutional Networks (GCNs) to model biological interactions, and Bayesian Networks for capturing probabilistic relationships within heterogeneous data [85]. These models enhance variant prioritization, biomarker discovery, and therapy optimization. The impact of AI-integrated personalized medicine is already evident in disorders such as Duchenne muscular dystrophy (DMD), Huntington's disease (HD), and cystic fibrosis (CF). For instance, AI tools predict individual responses to CFTR modulators in CF and identify optimal exon-skipping targets in DMD. Emerging ALD-focused studies leverage similar approaches to map peroxisomal dysfunction, immune dysregulation, and oxidative stress biomarkers, enabling refined diagnostics and novel therapeutic strategies. Collectively, these integrative approaches underscore AI's transformative potential in accelerating precision medicine for rare genetic disorders [86].

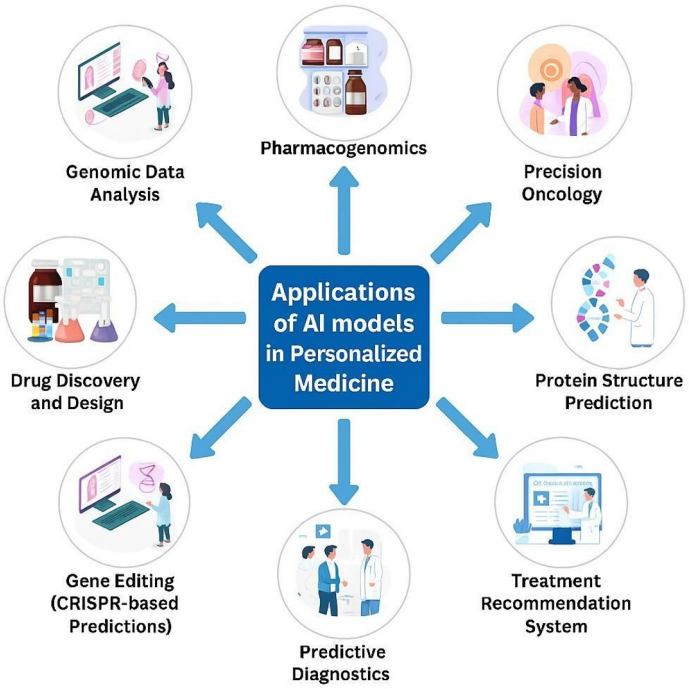

Figure 4: Applications of AI Models in Personalized Medicine.

AI-powered platforms are transforming multi-omics integration and disease modeling, offering critical solutions for rare disorders where limited cohort sizes constrain traditional statistical approaches. Tools such as MOFA+ identify shared and dataset-specific patterns across diverse omics layers, facilitating a unified view of molecular interactions [87], while DeepMO leverages deep learning to enable patient stratification, phenotype prediction, and pathway inference with high accuracy [88]. In parallel, automated machine learning (AutoML) frameworks like TPOT and H2O.ai streamline pipeline construction for biomarker discovery and predictive modeling [89]. Network-based integrative tools, including OmicsNet and NetZoo, further extend this capability by incorporating molecular interaction networks, supporting comprehensive systems biology analyses [90].

These methods are particularly valuable for rare monogenic diseases, where small sample sizes and high biological complexity demand robust computational strategies. By linking multi-layered biological signals spanning genomics, transcriptomics, proteomics, metabolomics, and epigenomics to clinical phenotypes, AI-driven pipelines improve predictive accuracy and enhance model interpretability. Advanced architectures such as neural networks, GCNs, and Bayesian frameworks enable the construction of holistic disease models that capture intricate human pathophysiology. In X-ALD and similar conditions, these integrative approaches optimize patient classification, inform prognosis, and guide therapeutic decision-making, driving progress toward precision medicine. As the scale and complexity of multi-omics

datasets continue to expand, AI's role in rare disease research and personalized therapy will become increasingly indispensable.

7. Challenges and Future Directions for AI in Rare Monogenic Disorders

Despite its promise, AI adoption in rare monogenic disorders faces significant barriers. Limited, fragmented datasets and phenotypic heterogeneity reduce model accuracy, while lack of standardized protocols and low economic incentives contribute to underrepresentation — only 2.63% of AI-driven drug repurposing studies target rare diseases [91,92]. Ethical concerns, including algorithmic bias, model opacity, and unresolved issues in data privacy and consent, are particularly critical in prenatal and pediatric contexts. Integrating AI with CRISPR adds complexity, as safety, off-target effects, and validation across diverse genetic backgrounds remain unresolved challenges [93].

Future strategies focus on AI-augmented clinical decision support systems (CDSS) for real-time integration of genomic, phenotypic, and clinical data, enabling early detection and personalized care [94]. Combined with telemedicine, AI can improve access in resource-limited settings through automated screening and intelligent triage. Global initiatives such as GA4GH and ELIXIR are addressing data scarcity via standardized data sharing and federated learning. Synergies between AI, CRISPR, robotic surgery, and VR-guided interventions promise patient-specific therapies. Collectively, AI-driven multi-omics analysis, drug discovery, and precision gene-editing position AI as a cornerstone for next-generation diagnostics and therapeutics in rare disease care [95].

8. Conclusion

This review highlights AI's pivotal role in addressing diagnostic and therapeutic challenges in rare monogenic disorders. AI has proven valuable in genomic variant interpretation, phenotype prediction, drug discovery, gene-editing optimization, and multi-omics integration. Applications in ALD demonstrate its potential for mutation detection, drug repurposing, and precision gene-editing strategies. However, challenges remain, including limited and fragmented datasets, algorithm opacity, ethical issues around data privacy, and clinical adoption hurdles. Future efforts must prioritize transparency, fairness, and robust data protection. Advancements will rely on multimodal AI models, telemedicine integration, and global data-sharing collaborations to overcome these barriers. AI is evolving from a supportive tool to a transformative force in rare disease care, enabling faster diagnoses, personalized therapies, and improved patient outcomes worldwide.

Acknowledgement

We are thankful for Department of Biotechnology, Jaypee Institute of Information technology NOIDA for facilitating the necessary support; DBT, New Delhi [BT/PR 48077/BID/7/1025/2023] for financial assistance to carry out this work successfully.

Authors' Contribution

Conceptualization: BS, YG, SM, PK, CKJ. Formal analysis: BS, YG, PK, SM, CKJ. Writing – original draft: SM, YG, BS, CKJ. Writing – review & editing: CKJ.

Ethical Declaration Not applicable.

Conflict of Interest

All other authors declare they have no conflict of interest.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Abbreviations

AI – Artificial Intelligence | ML – Machine learning | DL – Deep learning | NGS – Next-Generation Sequencing | ALD – Adrenoleukodystrophy | SVM – Support Vector Machine | CNNs – Convolutional Neural Networks | RNNs – Recurrent Neural Networks | VLCFAs – Very long-chain fatty acids | ccALD – Childhood Cerebral ALD | AMN – Adrenomyeloneuropathy

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