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Progeria, Sanfilippo Syndrome, Epidermolysis Bullosa, & Cdkl5 Deficiency: AI-Driven 3D Facial Morphometry, Advanced Gene Therapies, Biomarkers, Genetic Pathologies, Etiology, Epidemiology, Diagnostic Odyssey, Machine Learning

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Abstract:

Rare genetic disorders, such as Hutchinson–Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (MPS III), Epidermolysis Bullosa (EB) and CDKL5 Deficiency Disorder (CDKL5), are often genetically complex, phenotypically variable and late diagnosed, leading to difficulties in diagnosis and treatment. The use of recent advances in artificial intelligence (AI), machine learning (ML), multi-omics technologies, and the discovery of biomarkers has enhanced early detection of disease, genotype–phenotype correlation, and precision diagnostics. This review covers the latest advancements in AI-assisted diagnosis, genetic pathology, biomarker identification, and the development of novel therapeutic strategies like gene editing, gene replacement therapy, RNA-based therapeutics, and AI-driven drug discovery. The review also touches upon the relevance of explainable AI, clinical decision support systems and integrated multi-omics for personalized medicine. Although progress has been made, there are still many obstacles, including small patient cohorts, disease diversity, efficacy and safety of therapy, ethical issues and regulatory standardization. In conclusion, the combination of AI and cutting-edge molecular medicine holds significant promise for improving the diagnosis, management, and individualized treatment of rare genetic diseases.

Keywords: Artificial intelligence (AI); Rare genetic disorders; 3D facial morphometry; Machine learning; Biomarkers; Gene therapy; Precision medicine; Multi-omics.

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1. INTRODUCTION

Rare genetic disorders are a diverse group of inherited disorders, each of which has a low prevalence, but together affecting millions of people worldwide[1]. Many of the disorders are extremely complex, due to the fact that they present with variable clinical symptoms, are progressive and affect patient survival and quality of life, such as Hutchinson–Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (Mucopolysaccharidosis Type III), Epidermolysis Bullosa (EB), and CDKL5 Deficiency Disorder (CDKL5). Despite new insights in the molecular genetics of these diseases, diagnosis remains delayed, there is a considerable degree of phenotypic variation, and disease-modifying therapies are still limited[2].

The management of rare genetic diseases is now undergoing a revolution as a result of recent advances in artificial intelligence (AI), machine learning (ML), three-dimensional (3D) facial morphometry, multi-omics technologies, biomarker discovery and the latest in advanced gene therapies[3]. The advent of AI-based diagnostic platforms has revolutionized the ability to identify characteristic facial phenotypes, incorporated genomic and clinical data and predicted disease progression, whilst new gene-editing technologies like CRISPR-Cas9 and RNA-based drugs offer great promise for precision medicine[4]. The present review focuses on the latest developments in AI-enabled diagnosis, molecular pathology, biomarker discovery and translational gene therapy research of HGPS, Sanfilippo Syndrome, Epidermolysis Bullosa, and CDKL5 Deficiency Disorder.

1.1 Background and Context

Rare genetic disorders can have many similar clinical presentations, which can make diagnosis challenging, and can result in extended diagnostic journeys. The conventional diagnostic methods of clinical examination and sequential genetic testing often are lengthy and can delay the proper therapeutic management[5]. Combining AI with genomics, medical imaging, and multi-omics technologies has enhanced diagnostic accuracy, leading to automated phenotypic analysis, variant interpretation, and personalized disease classification. At the same time, there are improvements in gene-editing technology and biomarker research making more and more progress with the shift from symptom management to targeted precision therapies.

1.2 Objectives of the Review

The objectives of this review are:

- To review the genetic pathophysiology, molecular mechanisms and clinical features of Hutchinson–Gilford Progeria Syndrome, Sanfilippo Syndrome, Epidermolysis Bullosa, and CDKL5 Deficiency Disorder.

- To learn about the application of AI supported 3D facial morphometry, machine learning and precision diagnostics in rare genetic disorders.
- To review recent developments in biomarker discovery, integration of multi-omics and molecular disease characterization.
- To assess the current progress in gene editing, gene replacement, RNA therapeutics and AI drug discovery.
- To emphasize current challenges, ethical issues and future directions of AI based precision medicine and gene therapy translation.

1.3 Importance of the Topic

In recent years, the merging of artificial intelligence, molecular genetics and precision medicine has paved the way for new opportunities to enhance the diagnosis and treatment of rare genetic disorders. The use of AI-powered diagnostic platforms, breakthroughs in biomarker discovery, and innovative gene therapies can help to shorten the time to diagnosis, enhance patient stratification, and enable personalized treatment approaches[6]. An extensive review of all these emerging technologies is therefore necessary to provide up-to-date evidence, highlight existing knowledge gaps and drive future research in the direction of clinically effective and personalized management of rare genetic diseases.

2. AI-DRIVEN DIAGNOSIS, GENETIC PATHOLOGY, AND BIOMARKER DISCOVERY

Advances in artificial intelligence (AI), genomics, and precision medicine have revolutionized the way rare genetic disorders are diagnosed and treated. Many of the rare diseases include Hutchinson – Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (Mucopolysaccharidosis Type III), Epidermolysis Bullosa (EB) and CDKL5 Deficiency Disorder (CDD), all of which have significant clinical heterogeneity, overlapping phenotypes and extended time to diagnosis. Lack of timely and accurate diagnosis is frequently due to conventional diagnostic strategies relying on clinical manifestations, and on sequential genetic testing[7]. Combination of AI-based facial phenotyping, machine learning (ML), multi-omics technologies and biomarker discovery has enhanced the recognition of diseases, genotype–phenotype correlations and individualized therapeutic planning. Such computational methods can provide quick analyses of complex genomic and phenotypical data, with the aim of diagnosing patient diseases earlier, stratifying patients better and developing precision medicine plans for ultra-rare diseases[8].

2.1 AI-Based 3D Facial Morphometry and Machine Learning for Rare Disease Diagnosis

In particular, the use of artificial intelligence facial phenotyping is one of the most promising diagnostic tools for rare genetic diseases, as many syndromic diseases have specific

craniofacial features that can be quantitatively assessed by three dimensional (3D) facial morphometry. Manually measuring thousands of geometric landmarks and measurements on a standardized facial photograph or 3D scan, as AI algorithms do, is a more objective approach than traditional clinical examination[9]. Deep learning models, such as convolutional neural network (CNN) models, have shown very good performance for identifying subtle facial dysmorphisms of HGPS, Sanfilippo syndrome, Epidermolysis Bullosa and CDKL5 deficiency; a useful tool for the clinician in identifying genetically inherited disorders early.

Machine learning models also improve the accuracy of the diagnosis by combining facial phenotype and clinical history, neurological examination, biochemical tests, and genetic data. While the signs of HGPS include mandibular hypoplasia, beaked nose, alopecia, and prominent scalp veins, signs of Sanfilippo syndrome may also include coarse facial features that may become more noticeable as the disease progresses. Facial characteristics may be unique in individuals with CDKL5 deficiency and are associated with profound neurodevelopmental delay, and in some EB subtypes, facial differences may be due to chronic tissue scarring and skin fragility[10]. Multicenter-based trained AI systems are able to differentiate these overlapping syndromes with more consistency than traditional visual assessment, minimizing interobserver variability and speeding up the diagnostic journey[11].

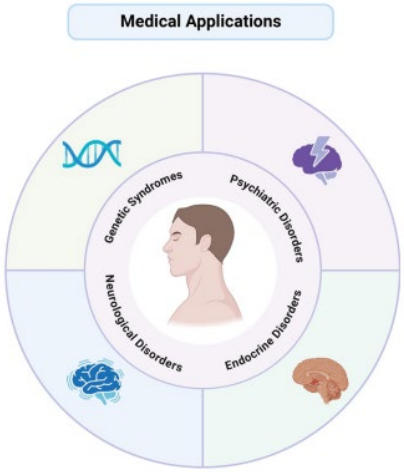

Figure 1. AI-based facial phenotyping for genetic disorder diagnosis

Cloud-based AI platforms and digital facial recognition software have opened up the opportunity for rare disease diagnosis, especially in areas where there are no clinical geneticists. As more patient data is shared with the continuous learning algorithms, the algorithms learn and improve, and the more patient data is shared with the explainable AI techniques, the more confident the clinician will be in their diagnostic prediction, because they will be able to identify the facial landmarks that contribute the most to the prediction[12]. However, image quality, ethnic variation, age variation in faces and balanced training sets are all critical to algorithm performance, and there is a need for internationally standardized facial databases and external, independent validation of the algorithms prior to their wide clinical use.

2.2 Genetic Pathogenesis, Molecular Mechanisms, and Biomarker Discovery

Molecular pathology of rare genetic disorders is a prerequisite for proper diagnosis, prognosis and directed therapy development. The abnormal production of progerin and accelerated cellular senescence are the primary cause of HGPS, due to the pathogenic mutation of the LMNA gene. The mutations in one of four genes (SGSH, NAGLU, HGSNAT, or GNS) that are involved in the lysosomal degradation of heparan sulfate lead to a progressive neurodegeneration, referred to as Sanfilippo syndrome[13]. Epidermolysis Bullosa is a genetically and clinically diverse group of disorders characterized by mutations in genes encoding structural proteins (COL7A1, KRT5, KRT14, LAMB3, ITGB4), while defects in the gene CDKL5 underlie CDKL5 deficiency, which is associated with disruptions in neuronal maturation, synaptic development, and signaling pathways in the cortex.

New molecular biology advances have made it possible to identify disease specific biomarkers that can reflect disease severity and therapeutic response. In HGPS, levels of circulating progerin, inflammatory cytokines, markers of telomeres, and markers of DNA damage have been promising. Heparan sulfate levels are still significant markers in CSF, plasma and urine. Biomarkers related to extracellular matrix remodeling, collagen degradation, wound inflammation and fibrosis have shown clinical relevance in EPA, while additional biomarkers such as neurofilament proteins, inflammatory mediators and transcriptomic signatures are being explored as biomarkers in CDKL5 deficiency[14]. These markers are objective indicators for disease monitoring, and for evaluating new therapeutic strategies.

AI can greatly speed up the discovery of biomarkers by analyzing high-dimensional data from genomes, proteins, metabolites, and transcripts, which are hard to interpret based on the traditional statistics approach. Machine learning algorithms discover patterns in molecular information that were previously unknown, rank candidate biomarkers and define genotype–phenotype relationships in diverse patient cohorts. The analysis of networks using AI also helps identify common pathways of disease to uncover new therapeutic targets and precision medicine strategies based on biomarkers. Nevertheless, it is still crucial to validate these molecular signatures in further multicenter studies and establish standardized biomarker protocols for their routine use in clinical practice[15].

2.3 AI Integration with Multi-Omics, Genomics, and Precision Diagnostics

AI and multi-omics technologies have revolutionized precision diagnostics for rare genetic disorders by offering a more holistic approach to analyzing biological systems, going beyond just genetic mutations. Whole genome sequencing, whole-exome sequencing, transcriptomics, proteomics, metabolomics, epigenomics and clinical phenotyping are all integrated into modern diagnostic workflows that provide multidimensional datasets allowing the study of complex disease. AI algorithms make use of these diverse data sources to find pathogenic variants, molecular pathways, disease subtypes, and potential therapeutic targets that might not be identified by traditional diagnostic methods.

Multi-omics analysis offers insights into disease mechanisms, response to treatment and molecular heterogeneity, which is especially valuable in disorders like HGPS, Sanfilippo syndrome, Epidermolysis Bullosa and CDKL5 deficiency. The computational frameworks based on AI algorithms combine genomic variations with transcriptomic changes, protein expression patterns, metabolic changes, and clinical features to create personal disease signatures[16]. This systems biology approach allows better genotype–phenotype correlation, more accurate disease classification and better selection of personalized treatments. Moreover, predictive machine learning models help to identify patients who might best benefit from gene therapy, RNA-based therapeutics, enzyme replacement therapy or targeted molecular therapeutics.

New precision diagnostic platforms will include real-time clinical data, wearable health monitoring devices, digital phenotyping, EHRs, and longitudinal biomarker data in integrated AI-based decision support systems. New technologies such as federated learning, digital twins, the explainable AI and cloud-based genomic analysis will further improve diagnostic accuracy and continue to safeguard patient privacy and foster collaboration between different centres[17]. While these developments have potential to improve the lives of patients, issues of data harmonization, algorithm transparency, interoperability, and regulatory standardization need to be addressed to ensure equitable, reliable, and clinically applicable AI-assisted precision medicine for patients with rare genetic disorders.

3. DISEASE-SPECIFIC CLINICAL ADVANCES

Rare genetic disorders have very different molecular defects, clinical symptoms and treatment approaches, which requires disease-specific diagnostic and management methods. The four inherited skin conditions, Hutchinson–Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (MPS III), Epidermolysis Bullosa (EB) and CDKL5 Deficiency Disorder (CDD), show the difficulties associated with late diagnosis, relentless progression and poor treatment. There have been recent developments in artificial intelligence (AI), molecular genetics, identification of biomarkers and gene therapy that have helped better identify the disease and developed precision medicine strategies[18]. The clinical picture, diagnostic progress and new treatment approaches in these disorders are summarized.

3.1 Hutchinson–Gilford Progeria Syndrome (HGPS)

Hutchinson–Gilford Progeria Syndrome (HGPS) is an extremely rare disorder of premature ageing that is mainly due to mutations in the LMNA gene which leads to abnormal accumulation of progerin within the nuclear envelope[19]. Usually, children with HGPS show signs of the disease within the first two years of life, such as growth retardation, alopecia, scleroderma-like changes in skin, skeletal abnormalities, joint stiffness, and characteristic craniofacial characteristics. Most patients live into their early teens, and progressive cardiovascular disease is the main cause of death.

Diagnosis is made based on clinical presentation and then molecular confirmation of mutations in LMNA. The use of AI-powered facial recognition technology, 3D facial morphometry and machine learning has greatly advanced the early diagnosis of disease, enabling the identification of subtle facial abnormalities before they become clinically apparent[20]. Other biomarkers like circulating progerin, inflammation markers, markers of oxidative stress, and markers of dysfunction of telomeres also play a role in disease monitoring and prognosis.

To date, the management is mainly supportive, focusing on cardiac treatment, physiotherapy, nutritional support, and multiple specialist follow-up[21]. The approval of lonafarnib has set a new benchmark in the field of survival and vascular function, and many emerging therapies, such as those based on artificial intelligence and drug discovery, base editing, and antisense oligonucleotides, are showing promise for disease-modifying treatment.

3.2 Sanfilippo Syndrome (MPS III)

In Sanfilippo Syndrome (MPS III), mutations in the genes SGSH, NAGLU, HGSNAT and/or GNS cause a failure to break down heparan sulfate, which leads to this disorder. It is mainly the central nervous system that is affected by progressive accumulation of glycosaminoglycans, which leads to developmental delay, behavioural abnormalities, cognitive decline, epilepsy, sleep disturbances and severe neurodegeneration[22]. Typically symptoms start early in childhood and gradually worsen over time.

Early signs and symptoms often mimic the signs and symptoms of autism spectrum disorder or developmental delay, leading to the delay in diagnosis. There have been advances in the diagnostic accuracy of AI-assisted clinical decision systems, digital phenotyping, genomic sequencing, enzyme assays, neuroimaging, and urinary heparan sulfate measurement. Clinical and genomic data can also be used to build machine learning models that help predict disease progression and disease subtypes.

Treatment is primarily supportive, such as seizure control, behavioral treatment, physiotherapy, and multidisciplinary treatment. But, with the recent advances in gene replacement therapy, enzyme replacement therapy, substrate reduction therapy and genome editing, there is new hope for therapeutic opportunities[23]. AI is gaining ground in finding therapeutic targets, optimizing vector design, and aiding the development of precise treatments.

3.3 Epidermolysis Bullosa (EB)

Epidermolysis Bullosa (EB) is an umbrella term for a set of inherited disorders of the skin which are caused by mutations in structural proteins involved in dermal–epidermal adhesion such as COL7A1, KRT5, KRT14, LAMB3 and ITGB4. Recurrent skin blisters, chronic wounds, scars, abnormalities of the nails, involvement with the mucous membranes, and susceptibility to aggressive squamous cell carcinoma. Subtype and affected gene determine varying degrees of severity.

The diagnosis is done through clinical exam, immunofluorescence mapping, electron microscopy and molecular genetic testing. In recent years, AI has been used in the field of wound image analysis, automated lesion segmentation, wound severity assessment, and wound healing prediction[24]. The identification of biomarkers of collagen degradation, inflammation, fibrosis and extracellular matrix remodeling is being more frequently studied to track disease activity and the response to treatment.

Today's treatment is geared toward prevention of infection, wound care, nutrition, pain management, and rehabilitation. New avenues of treatment involve ex vivo gene-corrected trans-planted skin grafts, genome editing with CRISPR, stem cells, protein replacement and regenerative medicine. AI also makes a significant contribution to optimizing gene therapy strategies and providing support for personalized wound management.

3.4 CDKL5 Deficiency Disorder (CDD)

CDKL5 Deficiency Disorder (CDD) is a severe developmental epileptic encephalopathy (DEE) syndrome that is caused by pathogenic variants in the CDKL5 gene. The disorder occurs early in infancy, with refractory epilepsy and severe developmental delay, hypotonia, intellectual disability, disturbance of motor control, cortical visual impairment and autistic features common features[25]. There is significant clinical heterogeneity in affected people depending on the underlying mutation.

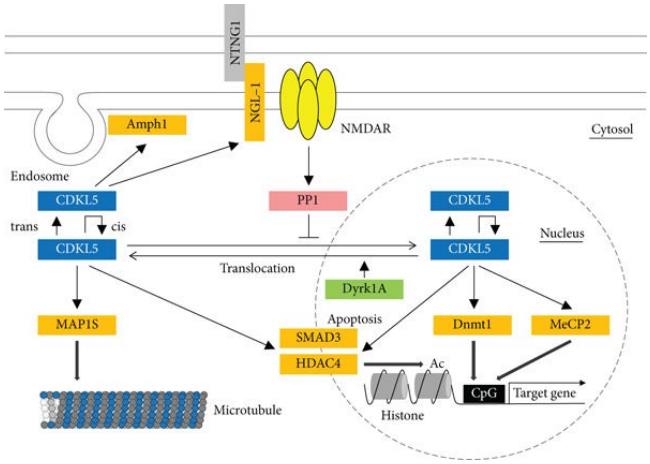

Figure 2. Molecular signaling pathways involved in CDKL5 deficiency disorder

Progress in whole-exome sequencing, neuro-imaging, electroencephalography and AI-aided seizure analysis has led to better early diagnosis. EEG recordings coupled with neurodevelopmental testing and genomic data can be incorporated into machine learning models to aid in distinction from other developmental epileptic encephalopathies. New biomarkers like neurofilament proteins and transcriptomic profiles also are being investigated for disease monitoring[26].

The main care provided is control of seizures, developmental rehabilitation, occupational therapy, speech therapy and supportive multidisciplinary care. There is promising potential for future treatment with recent breakthroughs in gene replacement therapy, RNA-based therapeutics, CRISPR genome editing and precision pharmacology. AI is driving significant advances in drug discovery, clinical trial optimization, and personalized treatment strategies.AI remains a game-changer in drug development, clinical trial optimization, and personalized treatment strategies.

Table 1. Comparative Clinical and Molecular Characteristics of the Four Disorders

Disorder	**Causative Gene(s)**	**Major Clinical Features**	**Key Biomarkers**	**AI Applications**	**Emerging Therapies**
Hutchinson–Gilford Progeria Syndrome (HGPS)	LMNA	Premature aging, growth failure, alopecia, cardiovascular disease	Progerin, inflammatory markers	3D facial morphometry, facial recognition	Lonafarnib, CRISPR gene editing, antisense therapy
Sanfilippo Syndrome (MPS III)	SGSH, NAGLU, HGSNAT, GNS	Neurodegeneration, developmental regression, behavioral abnormalities	Heparan sulfate, lysosomal enzyme activity	AI-assisted diagnosis, disease prediction	Gene replacement, enzyme replacement, substrate reduction
Epidermolysis Bullosa (EB)	COL7A1, KRT5, KRT14, LAMB3, ITGB4	Skin blistering, chronic wounds, scarring	Collagen VII, inflammatory markers	Automated wound assessment, lesion analysis	Gene therapy, stem cell therapy, regenerative medicine
CDKL5 Deficiency Disorder (CDD)	CDKL5	Early-onset epilepsy, developmental delay, motor dysfunction	Neurofilament proteins, transcriptomic markers	AI-assisted EEG analysis, precision diagnosis	Gene replacement, RNA therapeutics, CRISPR genome editing

4. ADVANCED GENE THERAPIES, AI, AND TRANSLATIONAL MEDICINE

In recent years, the development of precision therapeutics for rare genetic diseases has been greatly accelerated by molecular medicine and artificial intelligence. Given the complex genetic basis and progressive clinical course of Hutchinson–Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (MPS III), Epidermolysis Bullosa (EB) and CDKL5 Deficiency Disorder (CDD), conventional therapeutic strategies have been largely based on symptomatic management[27]. But with the advent of new technologies like gene editing, gene replacement therapies, RNA based therapies, and AI-assisted drug discovery, the emphasis has shifted to disease-modifying interventions. At the same time, AI has improved the accuracy of patient stratification or biomarker discovery, the prediction of new therapies, and clinical decision-making, all of which accelerate the translation from laboratory to patient.

4.1 Gene Editing, Gene Replacement, RNA-Based Therapeutics, and Precision Medicine

Direct targeting of the underlying genetic defect rather than symptoms alone makes gene therapy one of the most promising therapeutic strategies for inherited rare diseases. CRISPR-Cas9, base editing, prime editing, and viral vector-mediated gene replacement are a few of the technologies that are increasingly able to correct or replace the mutations responsible for diseases[28]. Gene-editing strategies that aim to decrease the production of progerin have been developed to treat HGPS, and gene replacement therapies are being explored for Sanfilippo syndrome and CDKL5 deficiency. In a comparable way, the ex vivo gene-corrected epidermal grafts have shown promising clinical results in a small number of patients with severe disease of EB.

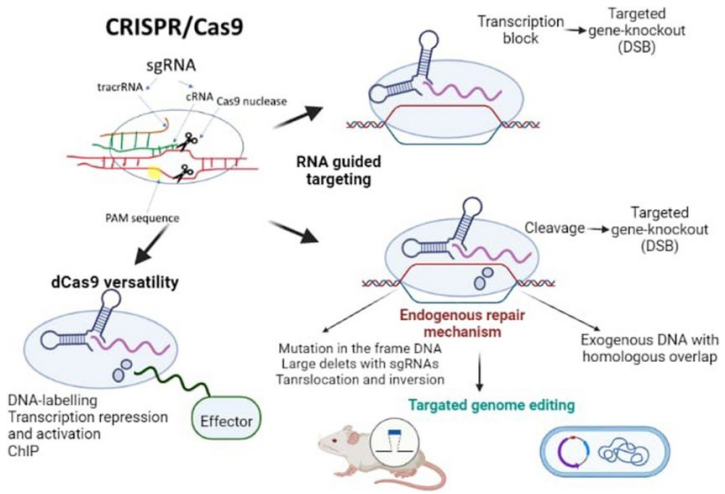

Figure 3. CRISPR-Cas9 genome-editing mechanism for targeted gene therapy

RNA-based therapeutics are new alternative strategies that can alter gene expression without changing the genomic DNA. Incorporating antisense oligonucleotides, messenger RNA (mRNA) therapies, RNA interference (RNAi) and splice-modulating therapies into the

treatment toolbox is under investigation to suppress mutant proteins, restore normal gene expression, and enhance cellular function[29]. These methods present significant benefits for gain-of-function mutations or production of abnormal proteins in diseases, and ongoing innovations in lipid nanoparticles and viral delivery systems are enhancing therapeutic efficacy and targeting.

Precision medicine involves leveraging genomic data, molecular markers, clinical features, and data from machine learning algorithms to create personalized treatment plans. Precision medicine, instead, allows the selection of the most appropriate therapeutic protocol, depending on the patient's genetic makeup and the severity of the disease. With the increasing availability of genome sequencing, personalised gene therapies are likely to be at the heart of managing rare diseases, making them more effective, but with fewer side effects[30].

4.2 AI in Clinical Decision Support, Drug Discovery, and Personalized Treatment

AI has proven to be a vital asset in the rare disease therapeutic journey, ranging from diagnosis to discovery of biomarkers, optimization of treatment strategies, and ongoing monitoring. The application of machine learning technologies uses clinical information, genomic sequencing, imaging, biochemical markers and electronic health records to aid clinical decisions. These AI-based systems enable early treatment, the identification of high risk patients, the prediction of disease course and the improvement of diagnostic accuracy, especially when dealing with diseases that have overlapping clinical phenotypes.

AI is also revolutionizing drug discovery, as it can quickly scan vast amounts of biomedical data to uncover disease-associated genes, molecular pathways, and therapeutic targets. Advanced screening techniques, such as computational screening, speed up the process of discovering commercially viable drug candidates and deep learning models can predict drug–target interactions, the efficacy of treatment and adverse effects before clinical trials are even conducted[31]. AI can also play a role in drug repurposing, as it can help identify existing drugs that might have therapeutic effects in rare genetic diseases, which can help to accelerate the process of translational research and increase the number of treatments available for these diseases.

In addition to therapeutic discovery, AI is also significantly contributing to personalized medicine by constantly merging patient history, data from wearable devices, biomarkers, and therapeutic outcomes. Predictive analytics help clinicians to make more personalized treatment decisions, track disease progression, fine-tune treatment plans, and adapt treatment based on the patient's response. AI combined with genomics and precision medicine is thus a game-changing strategy to enhance long-term care for patients with inherited rare diseases.

4.3 Challenges, Ethical Issues, Explainable AI, and Future Clinical Translation

While there are advancements in precision medicine and advanced gene therapies enabled by AI, certain scientific, clinical, and regulatory hurdles remain that hinder their broader adoption.

- **Limited datasets and disease heterogeneity:** The prevalence of rare genetic disorders is extremely low, leading to small patient populations and subphenotypic variability in clinical findings, which are challenging for robust AI model development, external validation, and accurate genotype–phenotype prediction.
- **Therapeutic safety and accessibility:** The first clinical trials of gene editing and gene replacement therapies have shown hopeful results but remain largely confined to the clinic due to potential off target effects, long-term safety, immune response concerns and the high costs of treatment.
- **Ethical and regulatory considerations:** Informed consent, patient privacy, security of genomic data, access to healthcare, and standardized regulations across different countries that regulate AI systems and cutting-edge genetic treatments are all critical concerns for responsible implementation[32].
- **Explainable AI and data integration:** Explainable Artificial Intelligence (XAI) is vital to create transparency and boost clinician trust, and harmonizing genomics, multi-omics, electronic health records, imaging and wearable-device data involves standardized and interoperable healthcare infrastructures.
- **Emerging digital technologies:** Collaborative research can be improved with new digital technologies that include federated learning, digital twins, cloud-based genomic analytics, and secure data-sharing platforms that reduce risks of patient data breaches.
- **Future clinical translation:** Multidisciplinary efforts are needed at clinical, genetic, computational, bioinformatic, regulatory, and pharmaceutical levels to create safe, effective and individualized treatments for rare genetic diseases.

Table 2. Recent Literature on AI, Gene Therapy, and Rare Genetic Disorders

Author(s) & Year	Study Focus	Key Findings	Contribution
Siri et al. (2021)[33]	CDKL5 Deficiency Disorder	Identified novel **CDKL5** variants and expanded genotype–phenotype correlations.	Supports molecular diagnosis and disease characterization of CDD.
Song et al. (2025)[34]	AI facial diagnostics	Reviewed machine learning and facial morphometry for genetic disease diagnosis.	Highlights AI-assisted early diagnosis of rare genetic disorders.

Srivastava (2023)[35]	AI and multi-omics	Discussed AI integration with multi-omics for biomarker discovery and precision medicine.	Supports AI-driven precision diagnostics and biomarker identification.
Uddin et al. (2019)[36]	AI in neurodevelopmental disorders	Demonstrated AI applications in genomic analysis and personalized treatment.	Supports AI-based clinical decision support for rare neurological disorders.
Van Bergen et al. (2022)[37]	CDKL5 therapeutics	Reviewed molecular mechanisms and emerging gene-based therapies.	Provides evidence for translational gene therapy in CDD.

5. DISCUSSION

In the current review, the authors emphasize the importance of artificial intelligence, advanced molecular diagnostics, biomarker identification, and precision gene therapies in the diagnosis and management of rare genetic disorders, such as Hutchinson–Gilford Progeria Syndrome (HGPS), Sanfilippo Syndrome (MPS III), Epidermolysis Bullosa (EB), and CDKL5 Deficiency Disorder (CDD). While these disorders are genetically distinct and present with different clinical features, they have some common challenges with delayed diagnosis, phenotypic heterogeneity, and few disease-modifying therapies[38]. The combination of AI, genomics, multi-omics, and precision medicine has seen a new era in disease characterization and the development of therapeutic approaches, fueling opportunities for personalized medicine[39].

5.1 Interpretation and Analysis of Findings

The review highlights the role of AI technologies in the diagnosis and understanding of rare genetic disorders, including facial morphometry, machine learning, genomic analysis, and marker identification. At the same time, the application of precision medicine has been changed from supportive care to gene editing, gene replacement therapy and RNA-based therapeutics. All this indicates that molecular medicine and computational intelligence are powerful tools that can be combined to boost early diagnosis, correlate genotype with phenotype, and enable customized therapeutic strategies[40].

5.2 Implications and Significance

Implications for the clinical care of patients with rare genetic disorders. AI can provide tools for diagnostics that help cut down on delays and enhance the ability to recognize the illness, and AI can help plan treatment and monitor the illness over time by analyzing biomarkers.

Moreover, new gene therapies offer potential to tackle the molecular defects directly instead of just disease symptoms, thus offering promise for better patient outcomes and quality of life.

5.3 Research Gaps and Limitations

Despite substantial progress, several limitations continue to hinder clinical translation. AI models are created from fairly small and heterogeneous datasets, which means that their predictions are not applicable to large populations. Likewise, there are numerous advanced gene therapies that are still at the early stages of clinical development and have limited long-term safety and efficacy data. To broaden the use of these technologies in real-world clinical settings, standardization of biomarkers, multicenter validation studies, explainable AI models, and harmonized regulatory frameworks are still needed.

5.4 Future Research Directions

Future investigations should explore the potential for using AI technologies to combine multi-omics, longitudinal clinical information, digital health tools, and high-throughput genomic sequencing to improve the ability to manage diseases more accurately and individualistically. The advancement of genome editing, RNA therapeutics, explainable AI and biomarker-guided precision medicine will continue to improve the clinical decision making process. The ability to transfer these new technologies into safe, available, and promising treatments for rare genetic diseases will require the collaboration of a global community, uniform data and research across multiple disciplines.

6. CONCLUSION

Artificial intelligence, 3-D facial morphometry, multi-omics technologies, biomarker discovery and advanced gene therapies are revolutionizing the diagnosis and management of rare genetic diseases including Hutchinson–Gilford Progeria Syndrome, Sanfilippo Syndrome, Epidermolysis Bullosa and CDKL5 Deficiency Disorder. Precision diagnostics powered by artificial intelligence (AI) have enhanced the ability to identify diseases early and stratify patients, and new gene-editing and RNA-based therapeutic options hold the potential to be the next generation of disease-modifying treatments. While these hurdles—such as data scarcity, clinical validation, ethical issues, and regulatory considerations—still exist, ongoing development of AI-driven molecular medicine is poised to advance precision healthcare and enhance clinical outcomes for patients with rare inherited disorders.

REFERENCES

1. Abbas, S. R., Abbas, Z., Zahir, A., & Lee, S. W. (2025). Advancing genome-based precision medicine: A review on machine learning applications for rare genetic disorders. Briefings in Bioinformatics, 26(4), bbaf329.

2. Abdallah, S., Sharifa, M., Almadhoun, M. K. I. K., Khawar Sr, M. M., Shaikh, U., Balabel, K. M., ... & Kanwar Sr, M. (2023). The impact of artificial intelligence on optimizing diagnosis and treatment plans for rare genetic disorders. Cureus, 15(10).
3. Ahmed, Z. (2020). Practicing precision medicine with intelligently integrative clinical and multi-omics data analysis. Human genomics, 14(1), 35.
4. Andrade, F., Aldámiz-Echevarría, L., Llarena, M., & Couce, M. L. (2015). Sanfilippo syndrome: Overall review. Pediatrics International, 57(3), 331-338.
5. Andreu-Montoriol, M., Pujol, M., Echeverry-Quiceno, L. M., Candelo, E., Heredia-Lidón, Á., Gómez, E., ... & Martínez-Abadías, N. (2025). 3D phenotyping in a Colombian population reveals unique population and ontogenic facial patterns in genetic and rare disorders. medRxiv, 2025-02.
6. Barbiero, I., De Rosa, R., & Kilstrup-Nielsen, C. (2019). Microtubules: a key to understand and correct neuronal defects in CDKL5 deficiency disorder?. International Journal of Molecular Sciences, 20(17), 4075.
7. Benetó, N., Vilageliu, L., Grinberg, D., & Canals, I. (2020). Sanfilippo syndrome: molecular basis, disease models and therapeutic approaches. International Journal of Molecular Sciences, 21(21), 7819.
8. Benke, T. A., Demarest, S., Angione, K., Downs, J., Leonard, H., Saldaris, J., ... & Haviland, I. (2025). CDKL5 deficiency disorder. In GeneReviews®[Internet]. University of Washington, Seattle.
9. Brasil, S., Pascoal, C., Francisco, R., dos Reis Ferreira, V., A. Videira, P., & Valadão, G. (2019). Artificial intelligence (AI) in rare diseases: is the future brighter?. Genes, 10(12), 978.
10. Dell'Isola, G. B., Perinelli, M. G., Frulli, A., D'Onofrio, G., Fattorusso, A., Siciliano, M., ... & Verrotti, A. (2025). Exploring neurodevelopment in CDKL5 deficiency disorder: Current insights and future directions. Epilepsy & Behavior, 171, 110504.
11. Dingemans, A. J., Hinne, M., Truijen, K. M., Goltstein, L., Van Reeuwijk, J., De Leeuw, N., ... & de Vries, B. B. (2023). PhenoScore quantifies phenotypic variation for rare genetic diseases by combining facial analysis with other clinical features using a machine-learning framework. Nature genetics, 55(9), 1598-1607.
12. Fedele, A. O. (2015). Sanfilippo syndrome: causes, consequences, and treatments. The application of clinical genetics, 269-281.
13. Germain, D. P., Gruson, D., Malcles, M., & Garcelon, N. (2025). Applying artificial intelligence to rare diseases: a literature review highlighting lessons from Fabry disease. Orphanet Journal of Rare Diseases, 20(1), 186.
14. Gurovich, Y., Hanani, Y., Bar, O., Nadav, G., Fleischer, N., Gelbman, D., ... & Gripp, K. W. (2019). Identifying facial phenotypes of genetic disorders using deep learning. Nature medicine, 25(1), 60-64.

15. Hong, W., Haviland, I., Pestana-Knight, E., Weisenberg, J. L., Demarest, S., Marsh, E. D., & Olson, H. E. (2022). CDKL5 deficiency disorder-related epilepsy: a review of current and emerging treatment. CNS drugs, 36(6), 591-604.
16. Hoskens, H., Liu, D., Naqvi, S., Lee, M. K., Eller, R. J., Indencleef, K., ... & Claes, P. (2021). 3D facial phenotyping by biometric sibling matching used in contemporary genomic methodologies. PLoS genetics, 17(5), e1009528.
17. Ilić, N., & Sarajlija, A. (2025). Artificial intelligence in the diagnosis of pediatric rare diseases: from real-world data toward a personalized medicine approach. Journal of Personalized Medicine, 15(9), 407.
18. Jain, N., Nagaich, U., Pandey, M., Chellappan, D. K., & Dua, K. (2022). Predictive genomic tools in disease stratification and targeted prevention: a recent update in personalized therapy advancements. EPMA Journal, 13(4), 561-580.
19. Jakimiec, M., Paprocka, J., & Śmigiel, R. (2020). CDKL5 deficiency disorder—a complex epileptic encephalopathy. Brain sciences, 10(2), 107.
20. Kadam, S. D., Sullivan, B. J., Goyal, A., Blue, M. E., & Smith-Hicks, C. (2019). Rett syndrome and CDKL5 deficiency disorder: from bench to clinic. International journal of molecular sciences, 20(20), 5098.
21. Katayama, S., Sueyoshi, N., Inazu, T., & Kameshita, I. (2020). Cyclin-Dependent Kinase-Like 5 (CDKL5): Possible Cellular Signalling Targets and Involvement in CDKL5 Deficiency Disorder. Neural plasticity, 2020(1), 6970190.
22. Khairnar, M., & Marda, S. (2025). Integrative Multi-Omics in precision medicine: from molecular interconnectivity to Single-Cell resolution. International Journal of Scientific Research and Technology, 2(7), 162-186.
23. Leonard, H., Downs, J., Benke, T. A., Swanson, L., Olson, H., & Demarest, S. (2022). CDKL5 deficiency disorder: clinical features, diagnosis, and management. The Lancet Neurology, 21(6), 563-576.
24. MacEachern, S. J., & Forkert, N. D. (2021). Machine learning for precision medicine. Genome, 64(4), 416-425.
25. Mahdi, S. S., Caldeira, E., Matthews, H., Vanneste, M., Nauwelaers, N., Yuan, M., ... & Claes, P. (2024). A 3D clinical face phenotype space of genetic syndromes using a triplet-Based Singular Geometric Autoencoder. Ieee Access, 13, 1-15.
26. Marouf, A. A., Rokne, J. G., & Alhajj, R. (2025). Integrating Multi-Omics and Medical Imaging in Artificial Intelligence-Based Cancer Research: An Umbrella Review of Fusion Strategies and Applications. Cancers, 17(22), 3638.
27. Marwaha, A., Chitayat, D., Meyn, M. S., Mendoza-Londono, R., & Chad, L. (2021). The point-of-care use of a facial phenotyping tool in the genetics clinic: Enhancing diagnosis and education with machine learning. American Journal of Medical Genetics Part A, 185(4), 1151-1158.

28. Muschol, N., Giugliani, R., Jones, S. A., Muenzer, J., Smith, N. J., Whitley, C. B., ... & MPS III Guideline Development Group. (2022). Sanfilippo syndrome: consensus guidelines for clinical care. Orphanet journal of rare diseases, 17(1), 391.

29. Nishat, S. M. H., Tanweer, A. S., Alshamsi, B., Shaheen, M. H., Tanveer, A. S., Nishat, A., ... & Ali-Mohamed, R. A. (2025). Artificial intelligence: a new frontier in rare disease early diagnosis. Cureus, 17(2).

30. Pammi, M., Aghaeepour, N., & Neu, J. (2023). Multiomics, artificial intelligence, and precision medicine in perinatology. Pediatric research, 93(2), 308-315.

31. Periyasamy, M. (2025, January). AI-driven multi-omics integration for enhanced drug discovery pipelines. In 2025 International Conference on Multi-Agent Systems for Collaborative Intelligence (ICMSCI) (pp. 1553-1558). IEEE.

32. Sharma, A., Kala, S., Kumar, A., Sharma, S., Gupta, G., & Jaiswal, V. (2024). Deep learning in genomics, personalized medicine, and neurodevelopmental disorders. Intelligent Data Analytics for Bioinformatics and Biomedical Systems, 235-264.

33. Siri, B., Varesio, C., Freri, E., Darra, F., Gana, S., Mei, D., ... & Alfei, E. (2021). CDKL5 deficiency disorder in males: five new variants and review of the literature. European Journal of Paediatric Neurology, 33, 9-20.

34. Song, J., He, M., Zheng, X., Zhang, Y., Bi, C., Feng, J., ... & Shen, B. (2025). Face-based machine learning diagnostics: applications, challenges and opportunities. Artificial Intelligence Review, 58(8), 243.

35. Srivastava, R. (2023). Applications of artificial intelligence multiomics in precision oncology. Journal of cancer research and clinical oncology, 149(1), 503-510.

36. Uddin, M., Wang, Y., & Woodbury-Smith, M. (2019). Artificial intelligence for precision medicine in neurodevelopmental disorders. NPJ digital medicine, 2(1), 112.

37. Van Bergen, N. J., Massey, S., Quigley, A., Rollo, B., Harris, A. R., Kapsa, R. M., & Christodoulou, J. (2022). CDKL5 deficiency disorder: molecular insights and mechanisms of pathogenicity to fast-track therapeutic development. Biochemical Society Transactions, 50(4), 1207-1224.

38. Winner, L. K., Rogers, M. L., Snel, M. F., & Hemsley, K. M. (2023). Biomarkers for predicting disease course in Sanfilippo syndrome: An urgent unmet need in childhood-onset dementia. Journal of neurochemistry, 166(3), 481-496.

39. Zack, M., Stupichev, D. N., Moore, A. J., Slobodchikov, I. D., Sokolov, D. G., Trifonov, I. F., & Gobbs, A. (2025). Artificial intelligence and multi-omics in pharmacogenomics: a new era of precision medicine. Mayo Clinic Proceedings: Digital Health, 3(3), 100246.

40. Zelei, T., Csetneki, K., Voko, Z., & Siffel, C. (2018). Epidemiology of Sanfilippo syndrome: results of a systematic literature review. Orphanet journal of rare diseases, 13(1), 53.