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# Hutchinson-Gilford Progeria Syndrome (HGPS): AI Models, 3D Morphometric Fingerprinting, Etiology, Epidemiology, Next-Generation Molecular Therapeutics, Microcephalic Osteodysplastic Primordial Dwarfism-II (MOPD-II)

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## Abstract:

Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II) are ultra-rare genetic syndromes associated with severe growth abnormalities, multisystem involvement and distinct molecular mechanisms. While the mutations of HGPS cause the accumulation of progerin and accelerated aging, the mutations for MOPD-II affect the function of the centrosome and proliferation of the cells. This review is aimed at summarizing the etiology, epidemiology, molecular pathology, and clinical manifestations of both disorders, and discussing recent developments in the field of artificial intelligence (AI), genomic analysis, three-dimensional morphometric fingerprinting, digital phenotyping, and multi-omics integration to better diagnose and characterize the disease. It also contrasts the clinical and molecular characteristics of HGPS and MOPD-II and touches on new treatment concepts, such as RNA-based approaches, antisense oligonucleotides and precision medicine with the help of artificial intelligence. The issues of clinical translation, small patient numbers and standardisation of data are also discussed. Overall, the integration of AI with molecular genetics and precision medicine offers promising opportunities for earlier diagnosis, personalized treatment, and improved clinical outcomes in these ultra-rare genetic disorders.

**Keywords:** Hutchinson-Gilford Progeria Syndrome (HGPS); Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II); Artificial Intelligence; 3D Morphometric Fingerprinting; Precision Medicine; Multi-Omics; Gene Editing.

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## 1. INTRODUCTION

Millions of people around the world suffer from rare genetic disorders, even though each disorder occurs only infrequently[1]. Of those disorders, two are extremely rare and have severe growth abnormalities and multisystem involvement, namely, Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II). The MOPD-II is caused by mutations in the PCNT gene which disrupt the centrosome function, cell division, and primordial dwarfism, while HGPS is caused by pathogenic mutations in the LMNA gene that cause abnormal accumulation of progerin and accelerated cell aging[2]. These disorders share some common features, including clinical and molecular heterogeneity and scarcity, which make them a therapeutic and diagnostic challenge.

In recent years, the study of rare genetic diseases has been revolutionized by the emergence of novel technologies such as the use of artificial intelligence (AI), genomic sequencing, 3D morphometric fingerprinting, and multi-omics technologies[3]. The application of machine learning, deep learning, digital phenotyping, and precision medicine approaches now allow earlier diagnosis, accurate variant interpretation, discovery of biomarkers, and development of individual treatment plan. Concurrently, new molecular treatments such as gene editing, RNA-based drugs, antisense drugs and targeted pharmacological treatments are emerging, which can provide novel strategies to treat the underlying genetic abnormalities rather than simply symptoms[4]. The advancements underscore the importance of AI-enabled translational medicine in enhancing the diagnosis, prognosis, and customization of treatment for extremely rare diseases like HGPS and MOPD-II.

### 1.1 Background and Context

Hutchinson-Gilford Progeria Syndrome and Microcephalic Osteodysplastic Primordial Dwarfism Type II have gained more and more scientific attention because of the insights that they provide into the molecular mechanisms of aging, growth regulation, DNA repair and cellular homeostasis. Progress in molecular genetics has defined how mutations in LMNA and PCNT are involved in the disease pathogenesis and next generation sequencing combined with computational biology has significantly enhanced diagnostic accuracy[5]. However, these disorders are not yet widely recognized and often go undiagnosed because of overlapping clinical signs and symptoms, lack of physician awareness, and the very low prevalence rates. The convergence of AI and precision diagnostics, digital phenotyping, and genomic medicine has thus become a promising approach to overcome these constraints and expedite clinical decision making.

### 1.2 Objectives of the Review

This review aims to:

- To review the etiology, epidemiology, clinical aspects and molecular mechanisms of Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II).
- To explore the latest developments in artificial intelligence, genomic analysis, 3D morphometric fingerprinting and multi-omics to enhance diagnosis and disease characterisation.
- To compare the clinical presentation, molecular diagnosis and evolution of HGPS and MOPD-II.
- To assess new molecular therapeutics, such as gene editing, RNA-based and AI-driven precision medicine.
- To determine the gaps in research, challenges to translative research, and future directions for AI powered precision medicine in HGPS and MOPD-II.

### 1.3 Importance of the Topic

This topic is important because there is increasing demand for accurate diagnosis and effective treatment of ultra-rare genetic disorders which are linked to substantial morbidity and premature mortality. The HGPS is a unique model to understand accelerated aging and cardiovascular disease, whereas the MOPD-II model offers valuable insights into growth regulation in humans and centrosome biology[6]. New challenges and opportunities for early diagnosis, personalized therapeutic strategies and translational research have emerged in recent years due to advances in artificial intelligence, molecular genetics and precision medicine. Advances in artificial intelligence, molecular genetics and precision medicine have presented new challenges and opportunities for early diagnosis, personalized therapeutic strategies and translational research. It is therefore important to conduct a detailed review that combines AI models, 3D morphometric fingerprinting, molecular pathology, comparative clinical characteristics, and next-generation therapeutics to summarize the existing evidence, pinpoint areas of knowledge gaps, and the future directions of research for enhancing patient care and clinical outcomes[7].

## 2. AI-BASED DIAGNOSTIC FRAMEWORKS AND MOLECULAR UNDERSTANDING

Artificial intelligence (AI) has revolutionized the diagnosis and molecular characterization of rare genetic disorders such as Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II). Rare conditions can

often be missed when diagnosis is made by convention, which relies on clinical assessment, genetic sequencing, imaging and laboratory investigations. The recent development of machine learning, deep learning, computer vision, and multi-omics technologies has helped identify disease at an early stage, automating the identification of phenotypic traits, and interpreting the pathogenic variants. Combining genomic, transcriptomic, proteomic, metabolomic, and imaging data, AI-powered precision medicine offers an all-encompassing approach to comprehending the mechanisms of disease, enhancing diagnosis, and enabling tailored therapeutic interventions[8].

### 2.1 AI Models for Early Diagnosis, Genomic Analysis, and Variant Interpretation

A.I. has enhanced the diagnosis of rare genetic diseases by interpreting complex clinical, genetic and imaging data which is not possible through traditional diagnostic processes. In HGPS, affected children are frequently healthy at birth and diagnosis is delayed until clinical manifestations of the disease begin to become apparent. By analyzing subtle patterns in the disease, machine learning algorithms, able to see through the “noise” in the data, can help identify disease much earlier, even when using only a small amount of clinical data—such as findings from a clinical photograph or some anthropometric measurements along with lab tests. Diagnostic uncertainty is further minimized by using AI clinical decision support systems, which influence the choice of diagnosis, allowing for the differentiation of HGPS from other progeroid syndromes and skeletal dysplasias[9].

Next generation sequencing (NGS) has led to the generation of huge genomic datasets, which demand sophisticated computational analysis. Pathogenic variants are prioritized in AI-generated genomic pipelines through sequence conservation, splice-site alterations, changes to protein structure, and evolutionary information[10]. In HGPS, these models are able to correctly recognize the classical mutation in HGPS that produces progerin, the c.1824C>T (p.G608G) mutation in the LMNA gene. Similarly, AI helps identify pathogenic PCNT mutations that cause MOPD-II, making them more likely to be detected and enhancing the effectiveness of diagnostics.

The modern developments of the deep learning approach have reinforced the interpretation of variants with the incorporation of databases of genomes, annotations and phenotypes. Natural language processing (NLP) is used to extract disease-related evidence from biomedical literature and graph neural networks are used to find associations among genes, proteins, and signaling pathways. The AI frameworks enable variant classification, prioritization of candidate genes, and molecular reporting that is specific to an individual, offering a valuable backbone for precision diagnosis, genetic counselling and targeted therapeutic development[11].

### 2.2 3D Morphometric Fingerprinting and Digital Phenotyping

AI-based 3D morphometric fingerprinting is an important key technique for diagnosing craniofacial and skeletal abnormalities in rare genetic diseases. Patients with HGPS generally

have micrognathia, prominent scalp veins, alopecia and delayed craniofacial development, while patients with MOPD-II have severe microcephaly, facial disproportionality and skeletal dysplasia. The use of high-resolution 3D facial imaging and geometric morphometric analysis allows for accurate measurement of these abnormalities, and generates objective disease-specific phenotypic signatures.

Facial recognition systems based on deep learning have been found to hold great potential for automated diagnosis via digital phenotyping[12]. A convolutional neural network (CNN) is used to distinguish HGPS from similar diseases based on facial landmarks, morphology of the cranium, development of the mandible, and the characteristics of the skin. AI algorithms can score the probability of a disease by matching patient images with a reference database, aiding clinical diagnosis. Longitudinal facial imaging also provides objective documentation of disease severity and the response to treatment[13].

Digital phenotyping goes beyond facial recognition and encompasses radiological imaging, anthropometric measurements, gait analysis, dermatological markers, cardiovascular evaluations and clinical history in the development of comprehensive computational models. AI integrates these multi-dimensional datasets to create personalised phenotypic profiles, capturing the disease's severity and progression[14]. Wearable sensors and cloud-based healthcare platforms complement real-time monitoring and precision healthcare for these ultra-rare conditions.

### 2.3 Multi-Omics Integration, Biomarker Discovery, and Precision Medicine

Polygenism and intricacy of HGPS and MOPD-II is due to the interaction of genomic, transcriptomic, proteomic, metabolomic and epigenetic pathways. By integrating these data types, AI-driven multi-omics approaches can be used to understand molecular mechanisms that underlie premature aging, defective DNA repair, abnormal cell cycle regulation, and tissue dysfunction. Machine learning models find patterns in thousands of biological variables and better understanding of pathogenesis of disease and new potential targets for treatment.

AI has emerged as a key area of application in the field of rare disease research with the discovery of biomarkers. Advanced computational models integrate multi-omics data to identify proteins, metabolites, inflammatory mediators, microRNAs and epigenetic markers that are linked to disease progression[15]. In HGPS, AI has identified biomarkers indicative of progerin accumulation, oxidative stress, vascular dysfunction and cellular senescence. Likewise, investigations into MOPD-II have identified molecular markers associated with centrosome disruption, problems with mitosis and DNA damage repair, which could help with more accurate diagnosis and prognosis.

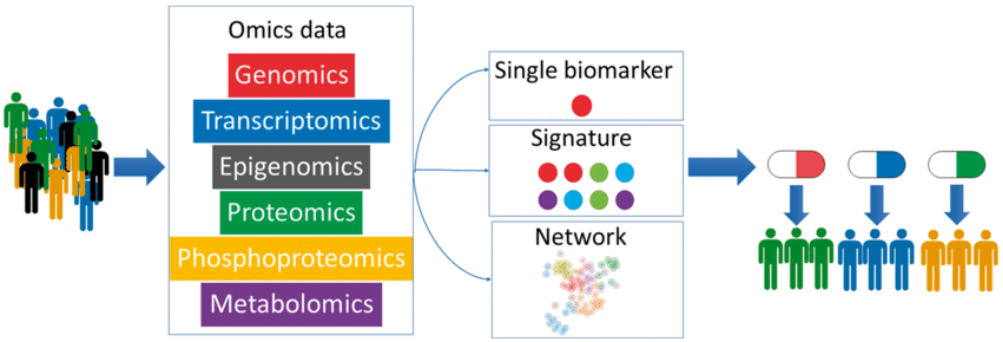


**Figure 1.** AI-Driven Multi-Omics Integration for Biomarker Discovery and Precision Medicine in Rare Genetic Disorders

AI in precision medicine can facilitate the use of molecular profiling to inform personalized treatment plans. Short-term disease progression, cardiovascular risk and treatment response can be estimated using predictive machine learning models based on genomic, clinical, imaging, and laboratory data[16]. AI can also help develop personalised therapies such as gene editing, antisense oligonucleotides and RNA therapeutics, as well as targeted molecular drugs. As the number of international genomic databases grows, AI-powered precision medicine will be expected to further speed up the translation of research into patient care and enhance results in patients with ultra-rare premature aging diseases.

## 3. CLINICAL FEATURES, COMPARATIVE DISORDERS, AND THERAPEUTIC ADVANCES

The Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II) are two rare inherited disorders of severe growth retardation and multisystem abnormalities, but they differ markedly in molecular basis, clinical features, and disease course[17]. The pathogenic variants in the LMNA gene that cause HGPS are characterized by abnormal levels of progerin and a premature ageing of the cells, while mutations in the PCNT gene disrupt centrosome function and cell division in MOPD-II. Recent developments in molecular genetics, imaging and precision medicine have contributed to understanding these disorders, and to earlier diagnosis and targeted therapy development. Their clinical and molecular features, when compared to each other, offer important clues on the disease mechanisms and help in designing personalized therapeutic approaches[18].

### 3.1 Hutchinson-Gilford Progeria Syndrome (HGPS)

Hutchinson-Gilford Progeria Syndrome is a very rare premature aging condition that affects about 1 in 4 to 8 live births in the world. The vast majority of cases are caused by a new defect in the LMNA gene, specifically the defect c.1824C>T (p.G608G) that results in the production of an abnormal lamin A protein called progerin. In the nucleus, progerin builds up, leading to nuclear instability, inability to repair DNA, chromatin alteration and premature cellular aging[19].

Affected children typically are normal at birth, but clinical features emerge during the first two years of life.

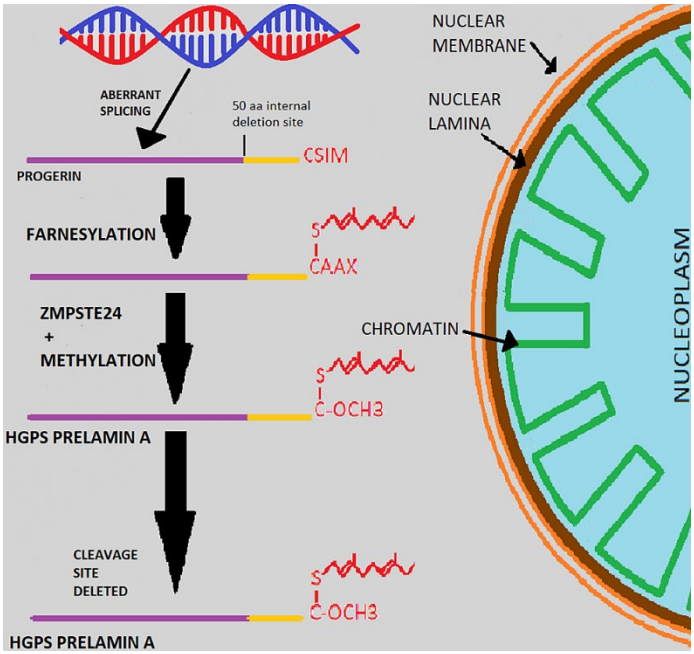


**Figure 2.** Molecular Pathogenesis of Hutchinson-Gilford Progeria Syndrome (HGPS): LMNA Mutation, Aberrant Progerin Processing, and Nuclear Lamina Dysfunction

Clinical features of the syndrome are characterized by severe postnatal growth failure, alopecia, scleroderma-like skin changes, lipodystrophy, association with joint contractures, delayed dentition and peculiar craniofacial abnormalities such as micrognathia, prominent scalp veins, beaked nose, and thin lips. Cardiovascular disease is the leading cause of morbidity and mortality, and during childhood or adolescence can lead to accelerated atherosclerosis, myocardial infarction, or stroke[20]. Although the body is very young, the mental development and intellectual function are largely normal, unlike many other developmental disorders caused by genes.

Recent advances in Molecular Research have greatly improved the understanding of pathogenesis of HGPS and therapeutic opportunities. The biomarkers of progerin accumulation, vascular dysfunction, oxidative stress, chronic inflammation, and DNA damage have aided in monitoring the disease and evaluating the effectiveness of treatment[21]. Farnesyltransferase inhibitors (FTIs) such as lonafarnib have been shown to benefit vascular stiffness, bone health and overall survival. There are several areas under investigation for correcting the underlying molecular defects that underlie premature aging, including RNA therapeutics, CRISPR-based genome editing, antisense oligonucleotides, and epigenetic modulation[22].

### 3.2 Microcephalic Osteodysplastic Primordial Dwarfism-II (MOPD-II)

Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPID II) is a rare, autosomal recessive condition, due to the presence of biallelic pathogenic variants of the PCNT gene encoding the protein pericentrin, which plays important roles in the organization of the mitotic spindle and in the segregation of chromosomes. The pericentrin dysfunction leads to abnormal cell division and tissue development and marked prenatal and postnatal growth restriction[23]. While the clinical features of MOPD-II are similar, the major difference is that it is a developmental growth disorder in contrast to HGPS which results in biological aging.

Patients with MOPD-II have extreme short stature, facial disproportionality, dental abnormalities, delayed bone maturation, microcephaly and reduced body weight. Other issues include cerebrovascular abnormalities, moyamoya disease, insulin resistance, renal anomalies and orthopedic deformities, which frequently require lifelong multidisciplinary care. The intellectual function is variable in affected persons, but most display normal intellectual functioning despite severe physical handicaps. Since many of the clinical features are variable, timely molecular diagnosis is crucial for correct diagnosis and clinical monitoring[24].

Recent advances in genomic sequencing and molecular diagnosis have significantly helped to identify pathogenic PCNT variants and increase knowledge of disease heterogeneity. Abnormalities in the integrity of the centrosome, DNA damage response, cell-cycle regulation and progression into mitosis have all been revealed through functional studies, offering clues to disease pathogenesis[25]. No single treatment yet has been developed that cures the disease, but the use of supportive medical treatment, along with frequent monitoring of the cardiovascular, neurological, orthopedic and endocrine systems, significantly enhances the quality of life. Research underway related to the use of gene replacement, modulation of molecular pathways and precision medicine based approaches will provide future therapeutic possibilities.

### 3.3 Comparative Clinical and Molecular Characteristics

While the clinical characteristics (severe growth retardation, physical retardation, skeletal abnormalities, and characteristic craniofacial features) are similar, HGPS is a clinically and pathogenetically different molecular disorder from MOPD-II. The mutations in LMNA cause abnormal processing of the lamin A, thus resulting in progerin accumulation, nuclear envelope defects and accelerated cellular senescence, which is the cause of HGPS. MOPD-II, on the other hand, is caused by mutations in the PCNT gene which affect the function of the centrosome, the assembly of the mitotic spindle and normal cellular proliferation. Such differences account for the different clinical course of the disease seen in case patients.

The clinical features of the two diseases also are significantly different. While cardiovascular disease, lipodystrophy, alopecia, skin tightening and premature ageing are the predominant features of HGPS, the key features of MOPD-II are severe microcephaly, primordial dwarfism,

skeletal dysplasia and developmental abnormalities[26]. In both cases, cardiovascular complications tend to occur due to rapid atherosclerosis, whereas patients with MOPD-II have a higher incidence of cerebrovascular complications including moyamoya disease and Intracranial Aneurysms. Still, it is crucial that both disorders be managed in a comprehensive and multidisciplinary fashion and monitored clinically over a period of time.

Comparative molecular studies have revealed similar processes related to genomic instability, DNA repair defects, oxidative stress, and regulation of cell cycle. Advancements in AI-driven genomic data analysis, digital phenotyping, and the integration of multi-omics approaches have facilitated better distinction between these disorders and improved diagnostic accuracy and biomarker identification[27]. The knowledge of both similarities and differences is essential to design disease-specific therapeutic strategies and to progress to precision medicine approaches for rare genetic growth disorders.

### 3.4 Next-Generation Molecular Therapeutics

Next generation molecular therapeutics have revolutionised research into rare genetic disorders, by tackling the underlying molecular defect instead of only the clinical symptoms. The goal of treatment in HGPS is to decrease progerin production, normalize nuclear structure, and prevent cellular senescence. Farnesyltransferase inhibitors such as lonafarnib have proven to have clinically relevant advantages by inhibiting abnormal protein farnesylation and thereby decreasing cardiovascular events[28]. Other strategies, such as antisense oligonucleotides, RNA interference, CRISPR-Cas genome editing, base editing and epigenetic manipulation are being explored to directly correct mutations in LMNA and normalize the processing of lamin A[29].

In MOPD-II, disease mechanism research is still most of the focus as there is no targeted molecular therapy for it yet in clinical practice. Recent developments in the science of gene-editing, stem-cell biology, and regenerative medicine have led to interest in targeting PCNT mutations and in restoring normal centrosome function. Experimental studies are probing modulation of cell-cycle regulators, DNA repair pathways and centrosomal proteins to optimize cellular proliferation and tissue development. While these methods are still in the preclinical phase, these are promising directions in which precision medicines might go from here[30].

AI is playing a vital role in the next generation of therapeutic development, speeding up the process of drug discovery, target identification, biomarker validation, and therapeutic optimization. Machine learning algorithms act on genomic, proteomic and transcriptomic data and on pharmacological data to identify candidate therapeutic targets, and to predict drug responses. The use of AI in precision medicine, digital twins and patient-specific molecular profiling is anticipated to aid in the personalization of treatment selection, design of clinical

trials, and a faster transition of innovative treatments for HGPS, MOPD-II and other ultra-rare genetic conditions.

**Table 1.** Comparative Clinical Profile of HGPS and MOPD-II

| **Characteristic** | **Hutchinson-Gilford Progeria Syndrome (HGPS)** | **Microcephalic Osteodysplastic Primordial Dwarfism-II (MOPD-II)** |
|---|---|---|
| **Causative Gene** | LMNA | PCNT |
| **Inheritance Pattern** | Usually de novo autosomal dominant mutation | Autosomal recessive |
| **Primary Molecular Defect** | Progerin accumulation and nuclear envelope instability | Centrosome dysfunction and defective mitosis |
| **Age of Onset** | Infancy (6–24 months) | Prenatal or at birth |
| **Growth Pattern** | Progressive postnatal growth failure | Severe prenatal and postnatal growth restriction |
| **Major Clinical Features** | Alopecia, lipodystrophy, skin tightening, joint contractures, cardiovascular disease | Microcephaly, primordial dwarfism, skeletal dysplasia, dental abnormalities |
| **Neurological Features** | Usually normal cognition | Variable; cerebrovascular complications may occur |
| **Major Complications** | Accelerated atherosclerosis, myocardial infarction, stroke | Moyamoya disease, aneurysms, orthopedic and endocrine complications |
| **Current Targeted Therapy** | Lonafarnib and emerging gene-based therapies | Supportive management; experimental molecular therapies |
| **Future Therapeutic Strategies** | CRISPR editing, RNA therapeutics, antisense oligonucleotides, precision medicine | Gene editing, regenerative medicine, AI-guided precision therapeutics |

## 4. TRANSLATIONAL MEDICINE, CLINICAL IMPLEMENTATION, AND FUTURE AI APPLICATIONS

To translate discoveries from the laboratory to clinical care, the fields of molecular genetics, artificial intelligence (AI), precision medicine, and multidisciplinary care need to be integrated in Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II). While great strides have been made in elucidating the molecular mechanisms and genetic etiology of these disorders, execution in the clinic is difficult due to the rarity, the small number of patients and the lack of disease-specific therapies. Clinical decision making, patient monitoring, and translation studies are currently being assisted by AI-driven diagnostics platforms, new and improved genomic technologies, and personalized therapeutic strategies[31]. The innovations are expected to help further the development of effective precision medicine approaches and increase the accuracy of diagnosis and beneficial outcomes for patients in the long term.

### 4.1 Human Evidence, Clinical Studies, and Diagnostic Workflow

The clinical experience with HGPS and MOPD-II has grown with patient registries from around the world, multicenter observational studies, genomic sequencing projects, and natural history studies. These studies have helped to understand better the disease progression, genotype-phenotype correlation, cardiovascular complications, growth abnormalities and survival outcomes. The value of longitudinal clinical data is also well exemplified in assessing effectiveness of new treatments and monitoring disease progression, as is illustrated in HGPS with targeted treatment of lonafarnib that has provided a clear clinical benefit.

The present diagnosis procedure is based on clinical examination and sophisticated molecular tests, in order to make the diagnosis as soon as possible and as precisely as possible. Initial assessment involves checking for key physical characteristics, growth, skeletal abnormalities and family history, followed by a radiological imaging and laboratory investigations. Next generation sequencing and molecular analysis of the LMNA gene in HGPS or of the PCNT gene in MOPD-II is used for confirmatory diagnosis[32]. The clinical, imaging, and genome data are increasingly integrated into AI-supported decision-support systems, which effectively prioritize genetic testing and enhance diagnosis.

In recent years, the development of digital health technologies has furthered the translational medicine and its potential in monitoring patients continuously and assessing clinical status remotely. AI platforms leverage genomic insights combined with imaging, lab tests, wearable sensors, and EHRs for lifelong disease surveillance. They are designed to support an integrated diagnostic workflow, enabling earlier intervention, a better tailored treatment plan and effective patient management, especially in rare, lifelong, multi-disciplinary disorders[33].

### 4.2 AI-Assisted Precision Therapeutics and Regulatory Considerations

AI is one of the key technologies that can speed up precision therapeutic development in rare genetic diseases. The machine learning algorithms are used to analyse the genomic,

transcriptomic, proteomic, pharmacological and clinical data to find potential therapeutic targets and predict treatment response. In HGPS, AI can help to develop treatments for the accumulation of progerin, dysfunction of the nuclear membrane, oxidative stress and vascular complications. In the case of MOPD-II, similar computational methods are being investigated to look for molecular pathways involved with centrosome dysfunction and impaired cell proliferation.

AI also plays a role in personalized treatment selection, by combining molecular profiles with clinical data and severity. Predictive models help distinguish patients that could potentially benefit from targeted therapies, RNA-based therapeutics, and gene-editing technologies, as well as future regenerative medicine treatments. Moreover, AI-based drug repurposing tools can quickly identify existing drugs with potential therapeutic applications, which can shorten drug development timelines and expedite clinical application for rare diseases that have few therapeutic options.

Regulatory oversight is essential for the clinical implementation of AI-assisted therapeutics to ensure safety, effectiveness, and reproducibility. Before AI systems can be used in clinical practice, regulatory agencies place a growing importance on the need for transparency of the algorithms, external validation, quality of the data, and performance monitoring. To facilitate reliable AI-guided precision medicine for rare genetic diseases, it is important to have genomic databases standardized, interoperability of healthcare systems, and accepted reporting standards throughout the world[34].

### 4.3 Challenges, Explainability, Ethics, and Clinical Translation

Despite significant technological advances, several challenges continue to limit the widespread clinical implementation of AI in HGPS and MOPD-II. Limited datasets for training and validating machine learning models is one of the greatest challenges as there are a very small number of affected persons across the globe. The clinical presentation is variable, different sequencing platforms are available, and reporting standards are inconsistent, which all contribute to making it more difficult to develop reliable AI algorithms. The restrictions underscore the need for cooperation between various nations and data sharing efforts.

In the field of clinical genomics, EAI has gained significant relevance since health care practitioners need to comprehend how their computational models are producing diagnostic or therapeutic suggestions. By mapping the genetic mutations, imaging features, or molecular markers behind each prediction, transparent AI systems boost the confidence of clinicians. Explainable models also enable clinical validation, mitigate diagnostic bias and aid in informing decisions in genetic counselling and precision medicine applications.

Ethical and translational concerns continue to be core to the responsible application of AI to rare disease research. Before the widespread clinical use of large-scale data and new technologies, such as advanced diagnostics, issues of genomic privacy, informed consent,

secure data sharing, algorithm fairness, and equitable access need to be carefully considered. The advancement of AI into international rare disease registries, precision medicine programs, and multi-center clinical trials will be crucial for future developments[35]. Multidisciplinary efforts are likely to speed up therapeutic discovery, enhance patient care, and enable the successful delivery of innovative technologies to routine clinical car.

**Table 2.** Selected Recent Literature and Translational Contributions

| Author(s) & Year | Study Focus | Key Findings | Translational Contribution |
|---|---|---|---|
| Tesi et al. (2023)[36] | Precision medicine in rare diseases | Reviewed the integration of genomics, multi-omics, AI, and personalized therapeutic approaches for improving diagnosis and treatment of rare genetic disorders. | Demonstrates the importance of precision medicine frameworks for individualized diagnosis, biomarker discovery, and targeted therapeutic development in HGPS and MOPD-II. |
| Ullrich & Gordon (2015)[37] | Hutchinson-Gilford Progeria Syndrome | Provided a comprehensive overview of the clinical presentation, molecular genetics, cardiovascular complications, diagnosis, and current management of HGPS. | Serves as a foundational clinical reference supporting early diagnosis, multidisciplinary management, and development of targeted therapies for HGPS. |
| Villalón-García et al. (2020)[38] | Precision medicine in rare diseases | Discussed advances in genomic medicine, molecular diagnostics, biomarker identification, and individualized treatment strategies for rare diseases. | Highlights the clinical value of integrating genomic sequencing, molecular biomarkers, and personalized medicine to improve outcomes in rare genetic disorders. |
| Warudkar et al. (2024)[39] | Artificial intelligence in rare diseases | Reviewed recent applications of artificial intelligence, machine learning, and deep learning for disease diagnosis, genomic analysis, biomarker discovery, and | Demonstrates how AI-assisted diagnostic models and precision medicine approaches can accelerate early diagnosis and therapeutic decision-making |

| | | | |
|---|---|---|---|
| | | treatment prediction in rare disorders. | for HGPS, MOPD-II, and other ultra-rare diseases. |
| Zhou & Song (2025)[40] | LMNA gene mutations in Hutchinson-Gilford Progeria Syndrome | Summarized recent advances in the molecular pathology of LMNA mutations, progerin biology, disease mechanisms, and emerging therapeutic strategies. | Provides updated evidence supporting molecular-targeted therapies, gene-editing approaches, and future precision medicine strategies for HGPS. |

## 5. DISCUSSION

AI, molecular genetics, and precision medicine have made substantial strides, providing a much greater understanding of rare genetic diseases like Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II). This review aims to compile and summarize existing data on the etiology of the disease, molecular mechanisms, AI-based diagnostics, three-dimensional morphometric fingerprinting, multi-omics integration, comparative clinical characteristics, and novel therapeutic strategies. Overall, the results indicate that computational technologies complement genomic and clinical research, which has enhanced disease characterization, paved the way for earlier diagnosis, and facilitated the development of personalized treatment approaches. However, several scientific, clinical and translational challenges persist and underscore the need for ongoing multidisciplinary research and collaboration to improve patient outcomes in these ultra-rare disorders.

### 5.1 Interpretation and Analysis of Findings

This review illustrates the advances made in the understanding of the molecular biology, clinical features and therapeutic issues of HGPS and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II). The use of AI in conjunction with genomic sequencing, 3D morphometric fingerprinting and multi-omics technologies has significantly enhanced early diagnosis, pathogenic variant interpretation, and disease characterization. Comparative analysis also shows that the genetic defects of HGPS and MOPD-II are not the same; however, both disorders are characterized by disturbances to cellular homeostasis, DNA repair and tissue development. Therefore, molecular therapeutics and precision medicine with AI support give a solid basis for creating more personalised diagnosis and treatment approaches for these ultra-rare diseases.

### 5.2 Implications and Significance

Artificial intelligence has come to play an increasing role in precision medicine for rare genetic diseases, as evidenced by the results of this review. AI platforms for diagnostics, digital

phenotyping and computational genomics can aid in timely diagnosis, enhanced clinical decision making, and customize therapy. In addition, the newly developed technologies to modify genes, RNA-based therapeutics and targeted molecular interventions provide a promise in tackling the root cause of HGPS and perhaps even MOPD-II. Molecular medicine and AI are therefore likely to further support translative research and to optimize multidisciplinary patient care, as well as to increase the clinical benefit for patients suffering from these rare diseases in the long-term.

### 5.3 Research Gaps and Limitations

Despite significant progress, a number of limitations remain that impede clinical translation and therapeutic development in HGPS and MOPD-II. These disorders are very rare and therefore have few patients, which makes it difficult to get high-quality genomic and clinical data needed to build and validate strong artificial intelligence (AI) models. Furthermore, lack of standardized data collection, few long-term clinical trials and incomplete disease categorization limit the use of precision medicine strategies. The majority of emerging interventions are at the pre-clinical or early clinical stage and highlight the importance of increased collaboration on a larger scale internationally, standardized registries, and comprehensive multi-omics studies.

### 5.4 Future Research Directions

The integration of these technologies, such as AI, multi-omics technologies, digital phenotyping, and precision medicine, into comprehensive clinical workflows for rare genetic disorders should be a priority in future research. The potential of international genomic databases, federated learning systems, explainable AI models, and patient-specific digital twins could significantly enhance the ability to predict disease, choose therapies, and monitor outcomes over time. As further research into the use of CRISPR technology, RNA therapeutics, stem-cell technologies and novel molecular targets continues, the rate at which disease modifying therapies are developed should increase. Multidisciplinary studies, involving clinicians, geneticists, computational scientists and regulatory agencies, will be key to moving these advances forward into routine clinical care.

## 6. CONCLUSION

Hutchinson-Gilford Progeria Syndrome (HGPS) and Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD-II) are rare genetic syndromes that pose serious challenges in diagnosis and treatment due to their complex molecular mechanisms and limited options for treatment. The review discusses recent developments in the field of AI, genomic analysis, three-dimensional morphometric fingerprinting, multi-omics integration and precision medicine for diagnosis, molecular characterization and therapeutic development of diseases. An understanding of the different genetic pathways of these disorders as well as shared biological pathways that can guide future therapeutic innovation is reflected in

comparative evaluation. While there are still significant challenges to overcome, ongoing advances in AI-driven diagnostics, next-generation molecular therapeutics and translational medicine provide hope for earlier diagnosis, more personalized care, and better clinical outcomes for patients with these ultra-rare genetic diseases, in the end contributing to a step forward in precision healthcare.

## 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. Abdelnour, S. A., Xie, L., Hassanin, A. A., Zuo, E., & Lu, Y. (2021). The potential of CRISPR/Cas9 gene editing as a treatment strategy for inherited diseases. Frontiers in cell and developmental biology, 9, 699597.
3. Ahmed, M. S., Ikram, S., Bibi, N., & Mir, A. (2018). Hutchinson–Gilford progeria syndrome: a premature aging disease. Molecular neurobiology, 55(5), 4417-4427.
4. Arun, A., Nath, A. R., Thankachan, B., & Unnikrishnan, M. K. (2024). Hutchinson–Gilford progeria syndrome: unraveling the genetic basis, symptoms, and advancements in therapeutic approaches. Therapeutic Advances in Rare Disease, 5, 26330040241305144.
5. Ashapkin, V. V., Kutueva, L. I., Kurchashova, S. Y., & Kireev, I. I. (2019). Are there common mechanisms between the Hutchinson–Gilford progeria syndrome and natural aging?. Frontiers in genetics, 10, 455.
6. Benedicto, I., Dorado, B., & Andrés, V. (2021). Molecular and cellular mechanisms driving cardiovascular disease in Hutchinson-Gilford progeria syndrome: lessons learned from animal models. Cells, 10(5), 1157.
7. Beyret, E., Liao, H. K., Yamamoto, M., Hernandez-Benitez, R., Fu, Y., Erikson, G., ... & Izpisua Belmonte, J. C. (2019). Single-dose CRISPR–Cas9 therapy extends lifespan of mice with Hutchinson–Gilford progeria syndrome. Nature medicine, 25(3), 419-422.
8. Bhattacharya, R., & Khan, S. R. (2020). Review on Progeria: A Rare Genetic Premature Aging Disorder. Research journal of Pharmacology and Pharmacodynamics, 12(2), 73-82.
9. Cisneros, B., García-Aguirre, I., De Ita, M., Arrieta-Cruz, I., & Rosas-Vargas, H. (2023). Hutchinson-Gilford progeria syndrome: Cellular mechanisms and therapeutic perspectives. Archives of Medical Research, 54(5), 102837.
10. Collins, F. S. (2016). Seeking a cure for one of the rarest diseases: progeria. Circulation, 134(2), 126-129.
11. Dąbrowska, D., & Chlubek, D. (2022). Progeria (Hutchinson–Gilford syndrome)–review of current literature. Pomeranian Journal of Life Sciences, 68(3).

**12.** 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.
**13.** Gonzalo, S., & Kreienkamp, R. (2015). DNA repair defects and genome instability in Hutchinson–Gilford progeria syndrome. Current opinion in cell biology, 34, 75-83.
**14.** Gonzalo, S., Kreienkamp, R., & Askjaer, P. (2017). Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. Ageing research reviews, 33, 18-29.
**15.** Gordon, L. B., Brown, W. T., & Collins, F. S. (2019). Hutchinson-Gilford progeria syndrome.
**16.** Harhouri, K., Frankel, D., Bartoli, C., Roll, P., De Sandre-Giovannoli, A., & Lévy, N. (2018). An overview of treatment strategies for Hutchinson-Gilford Progeria syndrome. Nucleus, 9(1), 265-276.
**17.** Hisama, F. M., & Oshima, J. (2018). Precision medicine and progress in the treatment of Hutchinson-Gilford progeria syndrome. Jama, 319(16), 1663-1664.
**18.** James, K. N., Phadke, S., Wong, T. C., & Chowdhury, S. (2020). Artificial intelligence in the genetic diagnosis of rare disease. Advances in Molecular Pathology, 3, 143-155.
**19.** Jamuar, S., Palmer, R., Dawkins, H., Lee, D. W., Helmholz, P., & Baynam, G. (2023). 3D facial analysis for rare disease diagnosis and treatment monitoring: proof-of-concept plan for hereditary angioedema. PLoS Digital Health, 2(3), e0000090.
**20.** Johnson, H., & Jacob, D. A. (2025). Hutchinson–Gilford Progeria Syndrome (HGPS): A Review Article. International Journal of Nursing Education and Research, 13(3), 204-208.
**21.** Kumar, B. P., Chaturvedhi, D. L., Prasad, U. S., Rajasekhar, A., & Reddy, D. R. B. (2019). Progeria or hutchinson-gilford progeria syndrome [hgps]: a review.
**22.** Lai, W. F., & Wong, W. T. (2020). Progress and trends in the development of therapies for Hutchinson–Gilford progeria syndrome. Aging Cell, 19(7), e13175.
**23.** Lamis, A., Siddiqui, S. W., Ashok, T., Patni, N., Fatima, M., & Aneef, A. N. (2022). Hutchinson-Gilford progeria syndrome: a literature review. Cureus, 14(8), e28629.
**24.** Larizza, L., & Cubellis, M. V. (2023). Rare diseases: Implementation of molecular diagnosis, pathogenesis insights and precision medicine treatment. International Journal of Molecular Sciences, 24(10), 9064.
**25.** Matthews, H., de Jong, G., Maal, T., & Claes, P. (2022). Static and motion facial analysis for craniofacial assessment and diagnosing diseases. Annual Review of Biomedical Data Science, 5(1), 19-42.
**26.** Mendez, C. A. (2025). Artificial Intelligence in Pediatric Rare Disease Diagnosis and Treatment: From Early Screening to Personalized Therapy. Al in Medicine and Health.
**27.** Nandy, A. (2025, March). Advancements in Machine Learning for Predictive Modeling of Genetic Disorders. In 2025 3rd International Conference on Disruptive Technologies (ICDT) (pp. 1200-1204). IEEE.

**28.** Naqvi, S., Hoskens, H., Wilke, F., Weinberg, S. M., Shaffer, J. R., Walsh, S., ... & Claes, P. (2022). Decoding the human face: progress and challenges in understanding the genetics of craniofacial morphology. Annual review of genomics and human genetics, 23, 383-412.

**29.** Okawa, Y., Matsuo, M., Kosaki, R., Tonoki, H., Fujimoto, M., Ozono, K., ... & Ihara, K. (2025). National survey of Hutchinson-Gilford progeria syndrome and progeroid laminopathy in Japan. Aging (Albany NY), 17(7), 1667.

**30.** Pachajoa, H., Claros-Hulbert, A., García-Quintero, X., Perafan, L., Ramirez, A., & Zea-Vera, A. F. (2020). Hutchinson–Gilford progeria syndrome: clinical and molecular characterization. The Application of Clinical Genetics, 159-164.

**31.** Piekarowicz, K., Machowska, M., Dzianisava, V., & Rzepecki, R. (2019). Hutchinson-Gilford progeria syndrome—current status and prospects for gene therapy treatment. Cells, 8(2), 88.

**32.** Qureshi, M. D. A., Ahmed, W., & Mehdi, S. (2024). Bioinformatics and Genomics in Rare Disease Diagnosis: Leveraging AI and Next-Generation Sequencing for Identifying Novel Genetic Disorders. Biosciences Research Reviews, 1(01), 46-59.

**33.** Rahman, M. M., Ferdous, K. S., Ahmed, M., Islam, M. T., Khan, M. R., Perveen, A., ... & Uddin, M. S. (2021). Hutchinson-Gilford progeria syndrome: an overview of the molecular mechanism, pathophysiology and therapeutic approach. Current Gene Therapy, 21(3), 216-229.

**34.** Roman-Naranjo, P., Parra-Perez, A. M., & Lopez-Escamez, J. A. (2023). A systematic review on machine learning approaches in the diagnosis and prognosis of rare genetic diseases. Journal of biomedical informatics, 143, 104429.

**35.** Sharma, V., & Shukla, R. (2020). Progeria: A rare genetic syndrome. Indian Journal of Clinical Biochemistry, 35(1), 3-7.

**36.** Tesi, B., Boileau, C., Boycott, K. M., Canaud, G., Caulfield, M., Choukair, D., ... & Lindstrand, A. (2023). Precision medicine in rare diseases: What is next?. Journal of Internal Medicine, 294(4), 397-412.

**37.** Ullrich, N. J., & Gordon, L. B. (2015). Hutchinson–Gilford progeria syndrome. Handbook of clinical neurology, 132, 249-264.

**38.** Villalón-García, I., Álvarez-Córdoba, M., Suárez-Rivero, J. M., Povea-Cabello, S., Talaverón-Rey, M., Suárez-Carrillo, A., ... & Sánchez-Alcázar, J. A. (2020). Precision medicine in rare diseases. Diseases, 8(4), 42.

**39.** Warudkar, S., Jalit, R., Shende, S., Muppawar, H., Vaywhare, H., Rizvi, N., & Tiwari, S. (2024, December). Artificial intelligence in rare diseases: A review of recent advances in diagnosis and treatment. In AIP Conference Proceedings (Vol. 3188, No. 1, p. 080010). AIP Publishing LLC.

**40.** Zhou, X., & Song, J. (2025). Unraveling the mysteries of Hutchinson-Gilford progeria syndrome: a comprehensive review of LMNA gene mutations. Biogerontology, 26(5), 186.