_____

Medical Biotechnology in Combatting Rare Genetic Disorders: A Review of Recent Advances

Mr. Prakash G. Ghewari,

Assistant professor, Krishna Institute of Allied Sciences, Krishna Institute of Medical Sciences "Deemed to be University," Karad, Maharashtra, India. Email: prakashghewari547@gmail.com

Dr. Abhay A.Ghatage,

Assistant professor, Krishna Institute of Allied Sciences, Krishna Institute of Medical Sciences "Deemed to be University," Karad, Maharashtra, India. Email: abhayghatage8@gmail.com

Dr. Rahul M. Sonavale,

Assistant professor, Krishna Institute of Allied Sciences, Krishna Institute of Medical Sciences "Deemed to be University," Karad, Maharashtra, India. Email: rahulsonavale777@gmail.com

Abstract. Rare genetic disorders pose significant challenges in healthcare due to their complex etiology and limited treatment options. Medical biotechnology has emerged as a transformative tool in combatting these conditions, offering innovative approaches for diagnosis, treatment, and management. This paper reviews recent advances in medical biotechnology and its application in addressing rare genetic disorders. Gene therapy, genome editing, RNA-based therapies, and personalized medicine approaches are discussed as key strategies in this endeavor. Through the synthesis of current research findings and clinical developments, this review highlights the potential of medical biotechnology to revolutionize the landscape of rare disease management. Despite challenges such as regulatory hurdles and technical limitations, ongoing advancements in medical biotechnology hold promise for improving outcomes and quality of life for individuals affected by rare genetic disorders.

Keywords: medical biotechnology, rare genetic disorders, gene therapy, genome editing, RNA-based therapies, personalized medicine

I. Introduction

Rare genetic disorders present a significant challenge to healthcare systems worldwide due to their complexity, diverse manifestations, and limited treatment options. These disorders, often caused by mutations in single genes or chromosomal abnormalities, affect a relatively small proportion of the population individually but collectively impact millions globally. Patients diagnosed with rare genetic disorders often face significant morbidity, reduced quality of life, and shortened life expectancy. Furthermore, managing these conditions poses substantial emotional and financial burdens on affected individuals, their families, and healthcare providers [1]. Traditionally, treatment options for rare genetic disorders have been limited, focusing primarily on symptomatic management rather than addressing the underlying genetic cause. However, recent decades have witnessed remarkable advancements in medical biotechnology, offering new hope for individuals affected by these conditions [2]. Medical biotechnology encompasses a broad range of techniques and technologies aimed at understanding, diagnosing, and treating diseases at the molecular level. In the context of rare genetic disorders, medical biotechnology has emerged as a powerful toolset for developing innovative therapeutic interventions tailored to individual patients' genetic profiles.

This work aims to provide an overview of recent advances in medical biotechnology and its application in combatting rare genetic disorders. Specifically, it will explore key areas such as gene therapy, genome editing, RNA-based therapies, and personalized medicine approaches. By synthesizing the latest research findings and

_____

clinical developments, this paper seeks to elucidate the transformative potential of medical biotechnology in reshaping the landscape of rare disease management [3]. Gene therapy stands out as one of the most promising avenues for treating rare genetic disorders. This approach involves delivering functional copies of defective genes or modifying gene expression to restore normal cellular function. Recent successes in gene therapy, such as the approval of Luxturna for treating inherited retinal dystrophy and Zolgensma for spinal muscular atrophy, highlight the therapeutic potential of this approach. Moreover, ongoing research efforts are exploring innovative gene delivery systems, gene editing technologies, and strategies to overcome immune responses to gene therapy vectors, thereby expanding the applicability of gene therapy to a broader range of genetic disorders [4].

In addition to gene therapy, genome editing technologies have emerged as powerful tools for correcting disease-causing mutations at the DNA level. CRISPR-Cas9, in particular, has revolutionized the field of genome editing by enabling precise and efficient modification of target genes. Researchers are actively investigating the therapeutic potential of CRISPR-based approaches for various rare genetic disorders, including Duchenne muscular dystrophy, cystic fibrosis, and sickle cell disease. While genome editing holds tremendous promise, ethical considerations, off-target effects, and long-term safety concerns remain important areas of research and debate [5]. RNA-based therapies represent another exciting frontier in the treatment of rare genetic disorders. These therapies leverage the inherent regulatory functions of RNA molecules to modulate gene expression, alter protein production, or correct aberrant splicing events. RNA interference (RNAi) and antisense oligonucleotides (ASOs) are two prominent RNA-based approaches that have shown promise in preclinical and clinical studies for conditions such as Huntington's disease, amyotrophic lateral sclerosis, and rare neurogenetic disorders [6]. Continued advancements in RNA delivery technologies, chemical modifications, and therapeutic targeting strategies are driving the development of increasingly precise and efficacious RNA-based therapies.

Furthermore, personalized medicine approaches are revolutionizing rare disease management by tailoring treatments to individual patients' genetic makeup, disease characteristics, and clinical profiles. Advances in genomic sequencing technologies have facilitated the identification of disease-causing mutations, enabling clinicians to make informed decisions regarding treatment selection, dosage optimization, and patient stratification [7]. By integrating genomic data with clinical outcomes and biomarker information, personalized medicine holds the potential to enhance treatment efficacy, minimize adverse effects, and improve patient outcomes in the context of rare genetic disorders. The medical biotechnology offers a diverse array of tools and techniques for combating rare genetic disorders, ranging from gene therapy and genome editing to RNA-based therapies and personalized medicine approaches [8]. While significant progress has been made in recent years, challenges such as regulatory hurdles, accessibility issues, and technical limitations persist. Nevertheless, the collective efforts of researchers, clinicians, policymakers, and patient advocates continue to drive innovation and accelerate the translation of biotechnological advancements into tangible benefits for individuals affected by rare genetic disorders [9]. This review aims to provide insights into the current state of the field, highlight recent achievements, and chart a course for future research directions aimed at improving the lives of patients with rare genetic diseases.

II.   Gene Therapy for Rare Genetic Disorders

Gene therapy represents a promising approach for treating rare genetic disorders by addressing the underlying molecular defects responsible for disease pathogenesis. The fundamental principle of gene therapy involves delivering therapeutic genes or gene-editing tools to target cells, thereby restoring or modulating gene expression to ameliorate disease phenotypes. Recent advancements in gene delivery vectors, genome editing technologies, and our understanding of disease mechanisms have propelled gene therapy into the forefront of rare disease treatment. This section explores the recent progress, challenges, and future prospects of gene therapy in combatting rare genetic disorders.

Recent Advances in Gene Therapy:

•   Clinical Successes: The field of gene therapy has witnessed several notable clinical successes in recent years. For example, Luxturna (voretigene neparvovec) became the first FDA-approved gene therapy for an

_____

inherited retinal disorder, Leber congenital amaurosis, demonstrating significant improvements in visual function in treated patients. Similarly, Zolgensma (onasemnogene abeparvovec) has shown remarkable efficacy in treating spinal muscular atrophy (SMA), a devastating neuromuscular disorder, leading to improved motor function and survival outcomes in affected infants.

- Expanded Treatment Options: Beyond Luxturna and Zolgensma, gene therapy is being investigated for a diverse range of rare genetic disorders, including hemophilia, muscular dystrophies, metabolic disorders, and neurogenetic conditions. Clinical trials evaluating the safety and efficacy of gene therapy interventions are underway for diseases such as Duchenne muscular dystrophy, Huntington's disease, Rett syndrome, and Pompe disease, among others.

- Advancements in Gene Delivery: Innovations in gene delivery vectors have enhanced the efficiency, specificity, and safety of gene therapy approaches. Adeno-associated viruses (AAVs), lentiviral vectors, and non-viral delivery systems are among the most commonly utilized platforms for gene delivery. Researchers are continually optimizing vector design, serotype selection, and manufacturing processes to improve vector tropism, reduce immunogenicity, and minimize off-target effects.

- Immunogenicity and Host Immune Responses: Immune responses to viral vectors remain a significant hurdle in gene therapy, particularly for AAV-based approaches. Pre-existing immunity, vector neutralizing antibodies, and cytotoxic T cell responses can limit the efficacy and durability of gene transfer. Strategies to mitigate immune responses, such as immune modulation regimens, capsid engineering, and vector capsid switching, are actively being pursued to improve the clinical outcomes of gene therapy interventions.

- Sustained Transgene Expression: Achieving durable and stable transgene expression is critical for the long-term success of gene therapy. Factors such as vector integration site, promoter strength, and immune-mediated clearance can influence transgene expression kinetics and persistence. Novel gene editing technologies, such as CRISPR-based approaches, offer the potential to precisely target genomic loci for site-specific integration or correction of disease-causing mutations, thereby improving the durability and safety of gene therapy.

- Scalability and Accessibility: The scalability and affordability of gene therapy remain important considerations for widespread clinical implementation. Manufacturing challenges, production costs, and regulatory requirements can impact the accessibility of gene therapy interventions, particularly for rare diseases with small patient populations. Collaborative efforts between academia, industry, and regulatory agencies are needed to address these challenges and streamline the translation of gene therapy from bench to bedside.

III. Genome Editing Technologies

Genome editing technologies have emerged as powerful tools for precisely modifying DNA sequences, offering unprecedented opportunities for treating rare genetic disorders at the molecular level. Among the various genome editing platforms, CRISPR-Cas9 has garnered significant attention due to its simplicity, versatility, and efficiency in targeting specific genomic loci. This section explores the recent advancements, applications, and challenges of genome editing technologies in combatting rare genetic disorders.

A. Recent Advances in Genome Editing:

CRISPR-Cas9 Revolution: The development of CRISPR-Cas9 has revolutionized the field of genome editing by enabling targeted modifications of DNA sequences with unprecedented precision and efficiency. CRISPR-based approaches offer the ability to introduce precise genetic changes, including gene knockout, gene correction, and gene insertion, in a wide range of cell types and organisms. Moreover, advancements such as base editing and prime editing have expanded the capabilities of CRISPR technology, allowing for precise nucleotide substitutions and multiplexed genome editing.

Applications in Rare Genetic Disorders: Genome editing holds tremendous promise for treating rare genetic disorders by correcting disease-causing mutations, restoring normal gene function, or modulating gene expression. Clinical trials utilizing CRISPR-based approaches are underway for various genetic conditions, including sickle cell disease, beta-thalassemia, cystic fibrosis, and Duchenne muscular dystrophy. Preclinical

_____

studies have also demonstrated the feasibility of genome editing for rare neurogenetic disorders, lysosomal storage diseases, and metabolic disorders.

Off-Target Effects and Specificity: Ensuring the specificity and accuracy of genome editing is paramount to minimize off-target effects and unintended genetic modifications. Despite significant improvements in CRISPR-Cas9 specificity, off-target cleavage events can still occur, posing safety concerns for clinical applications. Ongoing efforts to enhance CRISPR specificity include the development of high-fidelity Cas9 variants, engineered guide RNAs, and computational tools for predicting off-target sites.

Delivery Challenges: Effective delivery of genome editing components to target cells or tissues remains a major challenge for clinical translation. In vivo delivery strategies must overcome barriers such as immune responses, off-target effects, and inefficient delivery to specific cell types. Optimization of delivery vehicles, tissue-targeting strategies, and immunomodulatory approaches are essential for maximizing the therapeutic efficacy and safety of genome editing interventions.

Ethical and Regulatory Considerations: The ethical implications of genome editing, particularly germline editing, raise complex ethical, legal, and societal questions that must be carefully considered. Regulatory frameworks governing the use of genome editing technologies in human research and clinical practice vary globally, necessitating clear guidelines and oversight mechanisms to ensure responsible and equitable implementation. Stakeholder engagement, public education, and transparent communication are essential for fostering public trust and addressing ethical concerns surrounding genome editing.

IV.   RNA-Based Therapies

RNA-based therapies have emerged as a promising approach for treating rare genetic disorders by modulating gene expression, correcting aberrant splicing events, or targeting disease-causing RNA molecules. These therapies leverage the inherent regulatory functions of RNA molecules to modulate cellular processes and restore normal gene function. This section explores the recent advancements, applications, and challenges of RNA-based therapies in combatting rare genetic disorders.

A.   Recent Advances in RNA-Based Therapies:

RNA Interference (RNAi): RNA interference is a natural cellular process that regulates gene expression by degrading specific mRNA molecules, thereby inhibiting protein synthesis. RNAi-based therapies utilize synthetic small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) to selectively target and degrade disease-causing mRNA transcripts. Several RNAi-based therapeutics have been approved for rare genetic disorders, including patisiran for hereditary transthyretin-mediated amyloidosis and givosiran for acute hepatic porphyria.

Antisense Oligonucleotides (ASOs): Antisense oligonucleotides are synthetic single-stranded nucleic acids that hybridize with target RNA molecules, modulating their splicing, stability, or translation. ASOs can be designed to induce exon skipping, restore normal splicing patterns, or degrade disease-associated RNA transcripts. Nusinersen, an ASO-based therapy, has been approved for the treatment of spinal muscular atrophy, demonstrating improvements in motor function and survival outcomes in affected individuals.

mRNA-Based Therapies: mRNA-based therapies involve the direct delivery of synthetic mRNA molecules encoding therapeutic proteins or peptides into target cells. mRNA therapeutics offer advantages such as transient expression, rapid onset of action, and potential for dose adjustment. Recent advancements in mRNA delivery technologies, such as lipid nanoparticles and modified mRNA sequences, have improved the stability, translational efficiency, and immunogenicity profile of mRNA-based therapeutics, paving the way for their application in rare genetic disorders.

_____

B.   Applications in Rare Genetic Disorders:

Neurogenetic Disorders: RNA-based therapies hold promise for treating rare neurogenetic disorders characterized by abnormal protein aggregation, neurodegeneration, or impaired RNA processing. ASO-based approaches targeting disease-associated RNA transcripts have shown therapeutic benefits in preclinical models of Huntington's disease, amyotrophic lateral sclerosis, and spinocerebellar ataxias.

Muscular Dystrophies: RNA-based therapies offer potential treatment options for muscular dystrophies, a group of rare genetic disorders characterized by progressive muscle weakness and degeneration. Exon skipping strategies using ASOs or modified antisense compounds aim to restore dystrophin protein expression in patients with Duchenne muscular dystrophy or Becker muscular dystrophy, thereby mitigating disease progression and improving muscle function.

Metabolic Disorders: RNA-based therapies hold promise for treating rare metabolic disorders caused by enzyme deficiencies or metabolic dysregulation. ASO-mediated exon skipping approaches have shown therapeutic efficacy in preclinical models of lysosomal storage disorders, such as Pompe disease and Fabry disease, by restoring enzyme activity and reducing substrate accumulation in affected tissues.

V.   Personalized Medicine Approaches

Personalized medicine, also known as precision medicine, tailors medical treatment to the individual characteristics of each patient, including their genetic makeup, disease phenotype, and environmental factors. In the context of rare genetic disorders, personalized medicine approaches aim to optimize therapeutic interventions based on the unique genetic profile and clinical presentation of each patient. This section explores the principles, applications, and challenges of personalized medicine in combatting rare genetic disorders.
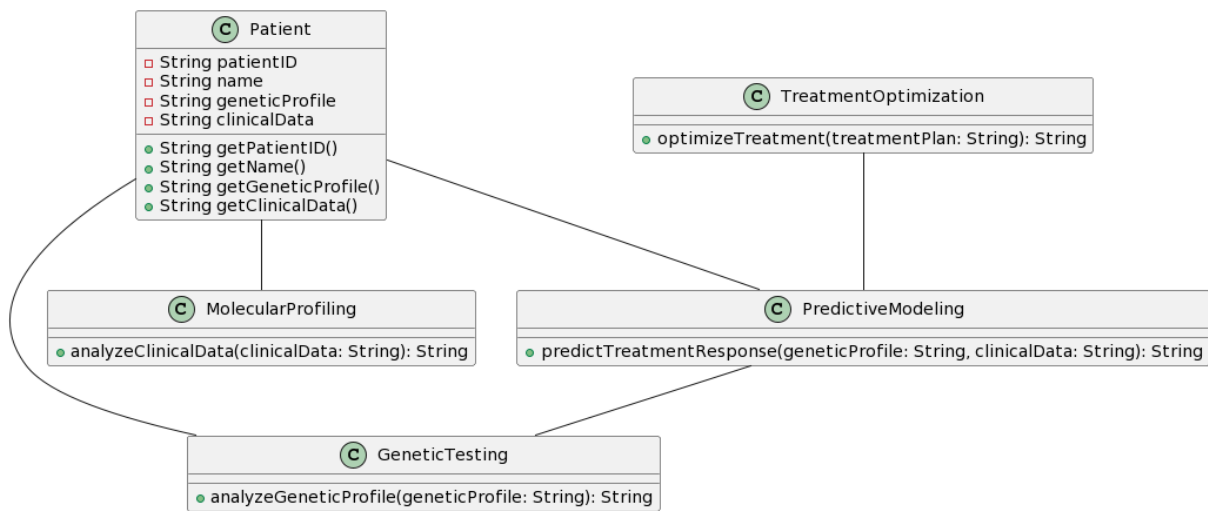

Figure 1. Personalized Medicine Approaches

A.   Principles of Personalized Medicine:

Genomic Characterization: Personalized medicine relies on genomic sequencing and molecular profiling to identify disease-causing mutations, genetic modifiers, and biomarkers associated with rare genetic disorders. Whole exome sequencing (WES), whole genome sequencing (WGS), and targeted gene panels are commonly used to interrogate the genetic architecture of rare diseases, enabling the identification of causative variants and guiding treatment decisions.

Treatment Optimization: Personalized medicine seeks to optimize therapeutic interventions by matching patients with the most effective treatments based on their genetic profile, disease subtype, and clinical characteristics.

_____

Treatment optimization strategies may include selecting targeted therapies, adjusting medication dosages, or implementing gene-specific interventions tailored to individual patient needs.

Predictive Modeling and Prognostication: Personalized medicine utilizes predictive modeling and prognostic tools to assess disease progression, treatment response, and long-term outcomes for patients with rare genetic disorders. Integrating genomic data, clinical variables, and biomarker measurements enables clinicians to develop personalized risk profiles and prognostic algorithms, guiding treatment decisions and patient counseling.

B.   Applications in Rare Genetic Disorders:

Genotype-Phenotype Correlation: Personalized medicine elucidates genotype-phenotype correlations by linking specific genetic variants to clinical manifestations, disease severity, and treatment outcomes in patients with rare genetic disorders. Understanding the molecular basis of disease enables clinicians to predict disease trajectories, anticipate complications, and tailor treatment regimens to individual patients' needs.

Targeted Therapies: Personalized medicine identifies targeted therapies that directly address the underlying molecular defects or pathogenic mechanisms associated with rare genetic disorders. Targeted therapies may include small molecule inhibitors, monoclonal antibodies, enzyme replacement therapies, or gene-specific interventions aimed at correcting or modulating disease-causing mutations.

Clinical Trial Design and Patient Stratification: Personalized medicine informs the design of clinical trials and patient recruitment strategies for rare genetic disorders by identifying patient subgroups with specific genetic mutations or biomarker profiles that may benefit from investigational therapies. Patient stratification based on genetic predictors of treatment response enhances clinical trial efficiency, increases statistical power, and improves the likelihood of successful therapeutic outcomes.

C.   Working parameters:

Genetic Heterogeneity: Genetic heterogeneity, characterized by the presence of multiple causative mutations or allelic variants within a single rare genetic disorder, poses challenges for personalized medicine approaches. Strategies to account for genetic heterogeneity, such as multi-gene panels, pathway-based analyses, and machine learning algorithms, are needed to improve diagnostic accuracy and treatment selection for genetically diverse disorders.

Data Integration and Interpretation: Integrating diverse data sources, including genomic data, clinical phenotypes, biomarker measurements, and environmental exposures, presents logistical and analytical challenges for personalized medicine approaches. Development of standardized data formats, interoperable electronic health record systems, and computational tools for data integration and interpretation is essential for realizing the full potential of personalized medicine in rare genetic disorder management.

Ethical and Social Implications: Personalized medicine raises ethical and social implications related to genetic privacy, data ownership, informed consent, and equitable access to genetic testing and targeted therapies. Addressing ethical concerns surrounding genetic discrimination, stigmatization, and disparities in healthcare access requires robust regulatory frameworks, patient education initiatives, and community engagement efforts to ensure responsible and equitable implementation of personalized medicine approaches.

VI.   Challenges and Future Directions in Personalized Medicine for Rare Genetic Disorders

While personalized medicine holds tremendous promise for the management of rare genetic disorders, several challenges must be addressed to realize its full potential and ensure equitable access to personalized interventions. Additionally, ongoing research efforts are needed to further advance the field and overcome existing limitations. This section discusses the key challenges and outlines future directions for personalized medicine in the context of rare genetic disorders.

_____

A. Challenges:

Limited Understanding of Disease Mechanisms: Many rare genetic disorders are poorly understood at the molecular level, making it challenging to develop targeted therapies or predict treatment outcomes accurately. Comprehensive characterization of disease mechanisms and pathways is essential for identifying therapeutic targets and optimizing personalized treatment strategies.

Access to Genetic Testing and Molecular Diagnostics: Access to genetic testing and molecular diagnostics is limited in many regions, particularly in low-resource settings. High costs, lack of infrastructure, and disparities in healthcare access contribute to inequities in genetic testing and diagnostic services, hindering the implementation of personalized medicine approaches for rare genetic disorders.

Data Interpretation and Clinical Implementation: Integrating genomic data into clinical practice poses challenges related to data interpretation, variant classification, and clinical decision-making. Clinicians may lack the necessary expertise in genetics and genomics to interpret complex genetic test results accurately. Moreover, incorporating genomic information into electronic health records and clinical workflows requires standardized protocols and infrastructure support.

Ethical and Legal Considerations: Personalized medicine raises ethical and legal considerations related to patient privacy, informed consent, data sharing, and genetic discrimination. Protecting patient confidentiality, ensuring informed consent for genetic testing, and safeguarding against misuse of genetic information are critical ethical imperatives in personalized medicine.

B. Future Directions:

Advancements in Omics Technologies: Continued advancements in omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, will enhance our understanding of rare genetic disorders and enable comprehensive molecular profiling of patients. Multi-omics integration holds promise for uncovering novel disease mechanisms, identifying biomarkers, and predicting treatment responses.

Development of Novel Therapeutic Modalities: Research efforts focused on developing novel therapeutic modalities, such as gene editing, RNA-based therapies, and small molecule inhibitors, offer new avenues for personalized treatment of rare genetic disorders. Innovations in drug discovery, delivery technologies, and precision medicine approaches will expand the therapeutic arsenal for rare diseases.

Implementation of Data Sharing Initiatives: Collaborative data sharing initiatives and international consortia facilitate the sharing of genomic and clinical data, enabling large-scale analyses, cross-validation of findings, and replication of research findings across diverse populations. Open-access data repositories and interoperable platforms promote transparency, reproducibility, and knowledge dissemination in personalized medicine research.

Healthcare Policy and Regulatory Reform: Healthcare policy reforms and regulatory initiatives are needed to address challenges related to reimbursement, insurance coverage, and regulatory approval pathways for personalized medicine interventions. Streamlining regulatory processes, incentivizing investment in rare disease research, and promoting innovation in personalized medicine will accelerate the translation of scientific discoveries into clinical practice.

The personalized medicine holds immense promise for transforming the diagnosis, treatment, and management of rare genetic disorders by tailoring interventions to the individual genetic makeup and clinical characteristics of each patient. However, addressing challenges related to limited disease understanding, healthcare access, data interpretation, and ethical considerations is essential for realizing the full potential of personalized medicine in rare disease management. By fostering interdisciplinary collaboration, leveraging technological innovations, and implementing policy reforms, personalized medicine can revolutionize healthcare delivery and improve outcomes for patients with rare genetic disorders.

_____

VII.   Conclusion

Rare genetic disorders present significant challenges due to their complexity, limited treatment options, and the often-devastating impact on affected individuals and their families. However, the emergence of personalized medicine, driven by advancements in genomics, molecular diagnostics, and therapeutic interventions, offers new hope for patients with rare genetic disorders. Through the tailored approach of personalized medicine, treatments can be optimized based on the unique genetic makeup, disease phenotype, and clinical characteristics of each patient. The integration of genomic sequencing, molecular profiling, and predictive modeling enables clinicians to identify disease-causing mutations, predict disease trajectories, and select targeted therapies with greater precision. From gene therapy and genome editing to RNA-based therapies and small molecule inhibitors, personalized medicine approaches are revolutionizing the treatment landscape for rare genetic disorders, offering novel therapeutic modalities and improved outcomes for patients. Despite the remarkable progress achieved in personalized medicine for rare genetic disorders, several challenges remain to be addressed. These include limited understanding of disease mechanisms, disparities in healthcare access, data interpretation hurdles, and ethical considerations. Addressing these challenges will require collaborative efforts from researchers, clinicians, policymakers, and patient advocates to advance scientific knowledge, improve healthcare infrastructure, and ensure ethical and equitable implementation of personalized medicine approaches. Looking ahead, continued investments in research, technological innovations, and healthcare policy reforms are essential for realizing the full potential of personalized medicine in rare disease management. By overcoming existing limitations and embracing future opportunities, personalized medicine has the potential to transform the lives of patients and families affected by rare genetic disorders, offering hope for a brighter future where tailored treatments provide relief and improved quality of life for all.

References

[1] Adams, D., & O'Regan, M. (2020). RNA Therapeutics for Rare Genetic Disorders. In RNA Therapeutics (pp. 389-405). Springer, Cham.

[2] Doudna, J. A., & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR-Cas9. Science, 346(6213), 1258096.

[3] Groft, S. C., & Posada de la Paz, M. (2010). Rare diseases–avoiding misperceptions and establishing realities: the need for reliable epidemiological data. Advances in experimental medicine and biology, 686, 3-14.

[4] Kim, J. S. (2018). Precision genome engineering through adenine and cytosine base editing. Nature plants, 4(3), 148-151.

[5] Ledford, H. (2018). First CRISPR clinical trial gets green light from US panel. Nature, doi:10.1038/d41586-018-05279-y.

[6] Mendell, J. R., Al-Zaidy, S., Shell, R., Arnold, W. D., Rodino-Klapac, L. R., Prior, T. W., ... & Finkel, R. S. (2017). Single-dose gene-replacement therapy for spinal muscular atrophy. New England Journal of Medicine, 377(18), 1713-1722.

[7] Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines—a new era in vaccinology. Nature reviews Drug discovery, 17(4), 261-279.

[8] Wirth, T., Parker, N., & Ylä-Herttuala, S. (2013). History of gene therapy. Gene, 525(2), 162-169.

[9] Zou, J., Mali, P., Huang, X., & Dowey, S. N. (2011). Site-specific gene correction of a point mutation in human iPS cells derived from an adult patient with sickle cell disease. Blood, 118(17), 4599-4608.