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GENE THERAPY AND THE CHALLENGES OF ITS CLINICAL APPLICATION: PERSPECTIVES IN BIOMEDICINE

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Abstract: Gene therapy, as an advanced therapeutic technique aimed at correcting genetic mutations associated with hereditary and acquired diseases, represents an important promise in the treatment of various pathologies. Despite the scientific and technological advances seen in recent decades, the clinical application of gene therapy faces significant challenges, both in terms of technical efficacy and ethical and social acceptance. The main objectives of this study were to analyze the scientific and ethical barriers that limit the use of this intervention and to understand the restrictions imposed by the regulatory and clinical context. To achieve these objectives, a literature review was carried out covering scientific publications on gene therapy, with a focus on studies on viral vectors, gene editing methods and analyses of the social and ethical acceptance of the technology. Articles and reviews published between 2000 and 2023 were selected, ranging from advances in technologies such as CRISPR/Cas9 to the most commonly used viral vectors, such as adenoviruses and virusesadeno-associated, with an emphasis on the adverse immune responses that often compromise the effectiveness of treatment. The results indicate that gene therapy has a high therapeutic potential, especially in monogenic diseases, but its full implementation depends on technological innovations that ensure immunological safety and improve the efficiency of the vectors. In addition, germ cell manipulation raises substantial ethical questions, especially in relation to hereditary impact and the associated long-term risks, which emphasizes the need for strict regulation. In conclusion, although gene therapy represents an innovative alternative in the field of medical interventions, overcoming the technical and ethical challenges is crucial for its definitive integration into clinical practice.
Keywords: *Gene therapy, Viral vectors, CRISPR/Cas9, Biomedical ethics.*

INTRODUCTION

Gene therapy, defined as a technique for inserting, altering or correcting genetic material to treat genetic and acquired diseases, has progressed considerably over the last few decades (SAYED *et al.*, 2022), consolidating itself as one of the most promising fields in biomedicine. This approach, which was initially limited to a theoretical perspective, is now at an advanced stage of development with real clinical applications, especially for hereditary genetic diseases such as β-thalassemia, sickle cell anemia and muscular dystrophyDuchenne.

CRISPR/Cas9 gene editing technology, for example, has been widely used to correct specific mutations in pre-clinical models and clinical trials, demonstrating high therapeutic potential. This system allows precise modifications to DNA and can be applied to correct mutations that would otherwise result in serious diseases, offering a possible cure for pathologies that were previously only treated palliatively (GONÇALVES; PAIVA, 2017).

The use of viral vectors, such as adenoviruses, viruses adeno-associated (AAVs) and lentiviruses, represents one of the main methods of delivering therapeutic genes to target cells, increasing the durability and precision of gene expression. However, the immunogenicity of these vectors, which can result in adverse immune responses, represents a significant challenge for the safe and effective implementation of gene therapy on a large scale. Recent studies have focused on improving the bioengineering of these vectors, seeking to minimize the risk of mutagenesis insertional and immunogenicity, while optimizing gene delivery to specific sites, such as the central nervous system and the hematopoietic system (OLIVEIRA et al., 2018).

Resistance to the use of gene therapy reflects ethical and safety concerns, as well as current technological limitations. Genetic tre-

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atment of somatic cells is widely accepted because their modifications are not hereditary; however, gene therapy of germ cells, which involves changes that can be passed on to future generations, is the subject of intense ethical debate. Genetic manipulation, especially in germ lines, raises concerns about the long--term genetic and environmental impact, including possible unwanted changes that could be passed on to offspring (SILVA; BARBOSA JÚNIOR, 2018); (GONÇALVES; PAIVA, 2017).

FUNDAMENTALS OF GENE THERAPY

Gene therapy is a constantly evolving field of research, offering new possibilities for the treatment of genetic diseases and other serious disorders. This study integrates fundamental concepts, technical advances and ethical challenges, organized based on a detailed analysis of five recent academic articles (MOTA, 2022).

Genes are defined as sequences of DNA (deoxyribonucleic acid) that contain the information necessary for the nature of proteins, which are essential for maintaining the biological and homeostatic functions of the organism. Gene expression, in turn, comprises the set of biochemical processes that convert the information contained in genes into functional products, such as proteins or RNA (ribonucleic acid) (FIGUEIREDO, 2020). Winter (WINTER, 2023) explores how the manipulation of gene expression can be used to correct genetic defects, highlighting the role of new gene editing technologies, such as the CRISPR/Cas9 system, which allows highly specific modifications to be made to the human genome.

Gene transfer techniques are crucial for the application of gene therapy, allowing the introduction of therapeutic material into target cells. These techniques can be defined in two broad groups: viral vectors and non-viral methods (BUTT et al., 2022) (figure 1)

Viral vectors, according to Winter (WINTER, 2023), such as adenoviruses and lentiviruses, have significant advantages in terms of efficiency in the delivery of genetic material. However, they also present challenges, such as potential adverse immune responses. In contrast, non-viral methods, such as nanoparticles and physical techniques, including electroporation, have the advantage of greater safety, although they often face limitations in terms of efficiency. To this end, he adds that hybrid strategies, which combine viral vectors and non-viral approaches, have been developed to overcome these limitations, offering a balance between safety and efficacy. The literature reinforces the need to adapt these technologies to the characteristics of the target gene and the specific conditions of each disease (FIGUEIREDO, 2020).

Gene therapy can be classified into two main types: somatic and germline, each with different characteristics and implications. Somatic gene therapy is applied to somatic cells, i.e. non-reproductive cells, with the aim of treating or correcting genetic defects in specific tissues of the individual. The changes made are not passed on to future generations, as they only affect the patient in question. This type of therapy aims to improve the patient's health and quality of life, without hereditary repercussions. In contrast, germline gene therapy involves modifying germ cells, such as eggs and sperm. In this case, the genetic modifications are passed on to future generations, affecting the patient's hereditary lineage. This approach raises more complex ethical and scientific questions, especially in relation to the potential long-term impact on subsequent generations and the risks of hereditary genetic manipulation (FIGUEIREDO, 2020). Each of these approaches has distinct technical and ethical challenges, and their application is regulated according to current legislation and ethical guidelines, with germline gene therapy largely a topic of debate due to its implications for public health and human genetics.

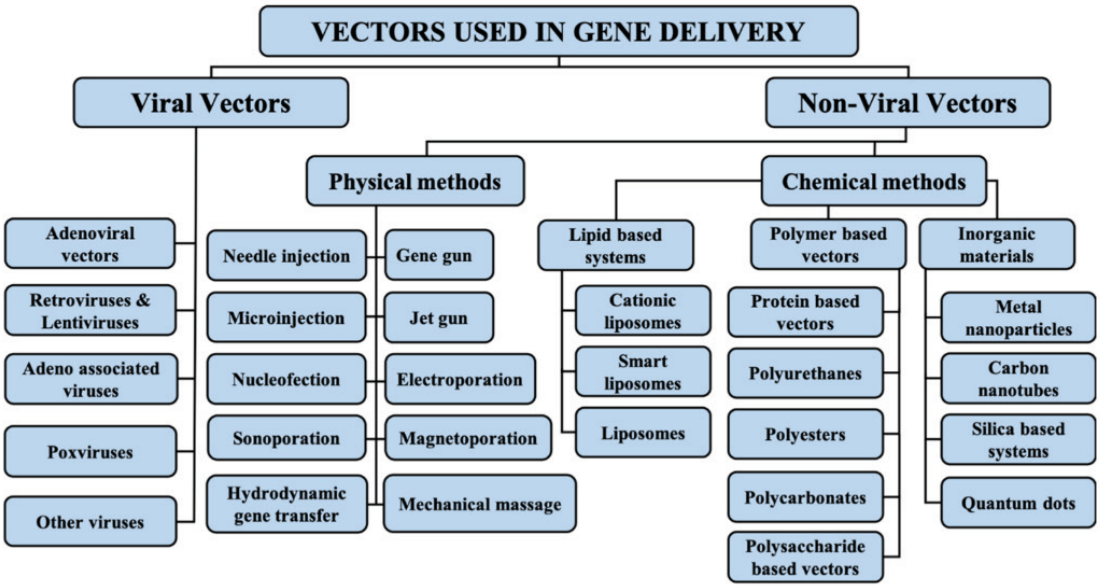

Figure1 : Types of vectors used for gene delivery, the selection of the vector for gene delivery is influenced by the type of genetic material to be transported, the desired gene therapy strategy, the amount of material to be delivered and the chosen route of administration (BUTT et al., 2022).

The most notable advances in gene therapy involve gene editing mechanisms such as CRISPR/Cas9, TALENs and ZFNs. The CRISPR/Cas9 system, as detailed by Winter (WINTER, 2023), has revolutionized gene editing by providing an efficient tool for specific modifications to the genome, allowing for the correction of genes responsible for a variety of medical conditions. With its high precision, this technology has proved crucial in advancing gene therapy, offering a new approach to treating hereditary and infectious diseases with unprecedented accuracy.

The advantages of CRISPR/Cas9 over other techniques, such as TALENs, which offer greater specificity in some situations but are more complex in terms of design and operation. Although TALENs may be preferred in contexts that require extraordinary precision, they lack the simplicity and versatility of CRISPR/Cas9. However, due to the accessibility and greater efficiency of CRISPR, ZFNs have been progressively replaced by this new generation of tools, which promise not only to simplify, but also to increase the precision and applicability of genetic modifications. These advances consolidate CRISPR/Cas9 as one of the most promising tools in genetic medicine, with a significant impact on both research and the treatment of genetic diseases.

Botas (BOTAS, 2021) emphasized the ethical and legal aspects associated with the application of gene editing in human embryos, especially in the context of germline gene therapy. They highlighted that issues such as justice, fairness and safety become essential as technology advances, as genetic modifications in embryos can have significant implications for future generations. Germ cell manipulation raises concerns about possible inequalities in access to these therapies, as well as the risks of unforeseen long-term consequences. This point is reiterated by Figueiredo (FIGUEIREDO, 2020), who notes that advances in gene editing technologies must be accompanied by rigorous ethical and legal discussions. He emphasizes that although tools such as CRISPR/Cas9 offer great potential for treating genetic diseases, it is imperative to ensure that the benefits are widely distributed, and that the risks are minimized, especially in a field as sensitive as the genetic manipulation

of embryos, which can affect the germ line and have implications for future generations. These debates highlight the need for a careful balance between scientific innovation and ethical responsibility, establishing clear guidelines for the safe and fair practice and application of these technologies are generously distributed and the risks are minimized.

CLINICAL APPLICATIONS OF GENE THERAPY

Advances in gene therapy have enabled effective treatments for monogenic diseases such as cystic fibrosis and muscular dystrophy Duchenne (LONG et al., 2014). In cystic fibrosis, according to the same authors, the use of adeno-associated vectors (AAVs) to deliver corrective genes to the respiratory epithelium has shown promise in correcting the dysfunction associated with the CFTR gene. In muscular Duchenne dystrophymini-dystrophins, therapies focused on the introduction of have shown partial functional recovery in clinical models.

(AJINA, 2019) et al.highlighted the effectiveness of CAR-T cells in fighting hematological tumors such as acute lymphoblastic leukemia. The study looks at the modification of T cells via viral vectors to chimeric receptors (CARs), allowing them to recognize and destroy cancer cells effectively. In addition, strategies to reduce cytokine release syndrome, a significant side effect, are being investigated to increase the safety of the therapy.

The use of gene therapy in cardiovascular diseases, especially in the context of heart failure, according to the authors Tessadori et al. (TESSADORI et al., 2018), is related to the delivery of genes to specific modular molecular pathways promotes tissue parts and improvements in cardiac function. In neurodegenerative diseases, therapies focused on suppressing toxic genes and increasing neuroprotective factors have demonstrated significant therapeutic potential (PLATT, 2018).

In the case of HIV, Xu (XU et al., 2019) explored the use of the CRISPR/Cas9 system to eradicate the provirus integrated into the host's DNA. In addition, editing the CCR5 gene, a critical receptor for the virus to enter cells, has shown efficacy in preventing the spread of infection in preclinical studies.

Gene therapy has been shown to be a revolutionary tool in the treatment of various clinical conditions, including monogenic diseases, cancer, chronic viral infections and cardiovascular and neurodegenerative diseases. Scientific progress in this area has enabled significant advances in its practical application, highlighting the beneficial potential of the technique in various pathologies.

In the context of monogenic diseases such as cystic fibrosis and muscular dystrophyDuchenne, gene therapy uses viral vectors to deliver functional versions of defective genes directly to target cells. According to Utkarsh et al. (UTKARSH et al., 2024)(, approaches using adeno-associated vectors AAVs) have been able to correct lung function in animal models of cystic fibrosis by introducing corrective CFTR genes, as well as promoting significant muscle improvement in patients with muscular dystrophyDuchenne. The combined use of techniques such as CRISPR/Cas9 and nanoparticles, as reported by Kaur et al. (KAUR et al., 2024), has also extended the efficiency of these therapies to allow more precise editing of genetic mutations.

Gene therapy also plays a key role in cancer treatment, especially through the application of CAR-T cells. The T cells genetically modified for chimeric expressed receptors (CARs) have been effective in treating leukemias and lymphomas. This FDA-approved approach uses viruses to modify T lymphocyte vectors, enabling them to target and destroy tumor cells. Sharma (SHARMA, 2023) details additional advances with the use of CRISPR/Cas9 to improve the expression of CARs, extending therapeutic efficacy while minimizing adverse effects such as cytokine release syndrome.

Cardiovascular and neurodegenerative applications have also benefited significantly from gene therapy. According to Roy et al. (ROY et al., 2024), the use of viral vectors to deliver genes that promote tissue regeneration has been shown to be effective in cardiac diseases, such as heart failure. In relation to neurodegenerative diseases such as Alzheimer's and Parkinson's, Kaur et al. (KAUR et al., 2024) highlight the use of vectors lentiviral to increase the expression of neuroprotective genes and reduce the accumulation of toxic proteins in the brain, providing functional improvements in experimental models.

The use of gene therapy in chronic viral infections, such as HIV, has also shown promising results. Sharma (SHARMA, 2023) states the effectiveness of CRISPR/Cas9 in deactivating the provirus integrated into the host's DNA, offering a specifically curative approach. In addition, editing the CCR5 gene, an essential receptor for HIV entry into cells, has been shown to significantly reduce viral replication in preclinical models. These advances demonstrate the transformative capacity of gene therapy to offer viable alternatives to infections previously considered incurable.

GENE THERAPY AND BIOMEDICINE

The development and application of gene therapy highlights the biomedical professional as an essential player in the research, molecular diagnosis and clinical implementation of these advanced technologies (PEREIRA, 2010). According to Winter (WINTER, 2023), the biomedical practitioner plays a central role in the use of techniques such as CRISPR/Cas9 for gene editing, carrying out not only the manipulation of genetic material, but also ensuring the integrity of biosafety processes. This responsibility includes technical training in specialized laboratories, as well as the adoption of strict ethical practices.

The contribution of biomedical to molecular research and diagnosis is highly recognized by professionals, who reports that professionals in this field have been essential in the advancement of DNA and RNA sequencing technologies. This progress has enabled the identification of genetic mutations associated with hereditary diseases and the development of targeted gene therapies. These initiatives reinforce the importance of biomedical professionals in personalizing treatments and improving patients' quality of life.Pereira (PEREIRA, 2010)

In terms of regulation and ethics, Bellarmino (BELLARMINO, 2018) points out that the work of biomedical professionals involves a careful analysis of the risks and benefits associated with genetic manipulation. This analysis is guided by bioethical principles that seek to balance technological innovation and patient safety. In addition, biomedical professionals are responsible for reviewing clinical protocols and validating experiments, ensuring compliance with local and international legislation.

Another critical aspect is the training of biomedical professionals in genetic manipulation techniques (BERNARDES *et al.*, 2021). The academic and technical training of these professionals must include not only theoretical knowledge, but also practical mastery of advanced technologies, such as the use of viral and non-viral vectors in gene therapy. This training is essential to ensure that scientific innovations are translated into safe and practical clinical interventions.

The role of the biomedical scientist in modern biomedicine transcends the simple application of laboratory techniques. They are positioned as a mediator between research and clinical practice, contributing to scientific advances, early diagnosis of genetic diseases implementation of cutting-edge therapies. andAs a scientist and researcher, they have great

potential in the development of CRISPR-Cas9 (BERNARDES *et al.*, 2021). By balancing technological innovation with ethics and regulation, the biomedical doctor promotes the responsible and sustainable development of gene therapy.

Biomedical professionals have played a strategic and multifaceted role in the advancement of gene therapy, a field that ranges from molecular research to clinical applications. According to Calliari (CALLIARI, 2018), biomedical professionals are one of the main players in the development ofmanipulation technologies genetic, such as CRISPR/Cas9, due to their interdisciplinary training that combines molecular biology and advanced laboratory techniques. This includes everything from designing genomic assays to implementing innovative therapeutic protocols, helping to personalize the treatment of genetic diseases.

The technical training of biomedical professionals is another fundamental pillar for the evolution of gene therapy. According to Pereira (PEREIRA, 2010), advanced training programs in biomedicine have integrated gene editing practices in their curricula, allowing professionals to acquire skills in technologies such as viral and non-viral vectors. This is particularly important for ensuring the efficiency and safety of innovative therapies, especially in clinical settings. In addition, biomedical professionals' active participation in translational research initiatives has been highlighted as essential for the effective clinical application of laboratory discoveries.

In field of molecular research and diagnosis, biomedical scientists have led efforts to identify genetic mutations associated with hereditary diseases, using technologies such as next-generation sequencing (NGS) and real--time PCR (BERNARDES *et al.*, 2021). These technologies not only facilitate early diagnosis, but also allow the selection of patients eligible for specific gene therapies. In addition, the biomedical practitioner acts in the validation of genetic biomarkers, which is crucial for the success of personalized interventions.

Ethics and regulation are central themes in the work of biomedical gene therapy professionals, who are often involved in ethics committees, assessing the risks and benefits associated with genetic experiments. The ethical responsibility of biomedical professionals also includes communicating with the public and promoting debates on the social and legal impact of genetic manipulation. In addition, Bellarmino (BELLARMINO, 2018) points out that compliance with national and international legislation is an integral part of the biomedical practitioner's work, especially in the validation of clinical studies involved in gene therapy.

Finally, Calliari (CALLIARI, 2018) argues that the continuous evolution of biomedicine requires biomedical professionals to be prepared to deal with the ethical and technical challenges posed by gene therapy. This includes the need to improve their skills through continuous training and constant updating in relation to regulatory standards. The convergence of training, research and ethics strengthens the role of the biomedical practitioner as a mediator between technological innovation and responsible clinical application.

RECENT ADVANCES AND FUTURE PROSPECTS

Gene therapy represents one of the greatest innovations in contemporary medical science, treating genetic and acquired diseases by altering the genetic material of cells (ROMA--RODRIGUES *et al.*, 2020). And, according to the same authors, when associated with nanotechnology, it takes on new contours, increasing its efficacy and safety, as well as introducing solution tools for the controlled release of therapeutic genes.

Zhou et al. (ZHOU et al., 2018) highlight the use of silica nanoparticles mesoporous as drug and gene delivery vehicles. These nanoparticles have unique characteristics, such as high loading capacity and convenient pores, allowing for controlled and targeted release. This advance is particularly relevant in the treatment of complex diseases such as cancer, where therapeutic specificity is essential to minimize damage to healthy cells. Osman et al. (OSMAN et al., 2018) corroborate this view by exploring the use of penetrating peptides PEGylated for lung therapies. These peptides act as highly efficient transporters, overcoming natural biological barriers and optimizing cellular delivery.

In addition, artificial intelligence (AI) has emerged as a powerful ally in the evolution of gene therapies. Bulaklak (BULAKLAK; GERSBACH, 2020) argues that AI enables advanced advances in the analysis of large volumes of genetic data, making it possible to optimize therapeutic vectors and predict potential risks. Thus, AI not only speeds up the development of new therapies, but also increases the safety of treatments by identifying possible prior complications.

In regenerative medicine, nanotechnology plays a central role. (ROMA-RODRIGUES., 2020) et alreport that nanoparticles designed for gene therapy can be used to reprogram cells in the fight against cancer, promoting tissue regeneration. Shein (SHEN; LI; QIAO, 2018) investigated magnetic nanoparticles, highlighting their ability to act as targeted delivery systems. These particles can be manipulated to target specific areas, promoting greater therapeutic efficiency. This advance is especially important in the treatment of degenerative diseases, where cell regeneration is key.

Despite progress, technical barriers still pose challenges. Francia et al. (FRANCIA et al., 2020) point out that the formation of biomolecular coronas on lipid nanoparticles can interfere with gene delivery. This unplanned interaction between nanoparticles and blood biomolecules reduces the effectiveness of the therapy and can trigger immune responses.

The risks of adverse effects associated with gene therapies are a constant concern. (ZHAO, 2021) et al.highlight the challenges in the combined use of photothermal and gene therapies, pointing out the need for strict control of application conditions to avoid collateral damage. Amreddy et al. (AMREDDY et al., 2018) warned that conventional therapeutic therapies can induce severe inflammatory responses, highlighting the need for constant monitoring and personalized adjustments to therapies.

ETHICAL AND REGULATORY CONSIDERATIONS

Gene therapy represents one of the greatest advances in modern biotechnology, bringing with it a series of ethical and regulatory challenges. This technology, which has the potential to transform medical practice by treating genetic and acquired diseases, requires a specific legal and regulatory framework to guarantee its ethical and safe application. At the same time, the social impact of gene therapy raises profound discussions about accessibility, equity and public acceptability (DELHOVE *et al..,* 2020)

The regulatory frameworks for gene therapy vary considerably between different jurisdictions, reflecting different political, social and cultural contexts. However, these regulations converge in a central objective: to guarantee the safety and efficacy of interventions, ensuring that the therapies applied do not compromise public health and patients' rights. In the context of the United States, Collins and Gottlieb (COLLINS; GOTTLIEB, 2018) point out that three gene therapies have already been approved by the *Food and Drug Ad-*

ministration (FDA). However, these therapies continue to be subject to strict supervision in order to prevent unethical use and to ensure that the benefits outweigh the potential risks. The FDA constantly monitors these therapies, considering the long-term impact on patients' well-being and on the healthcare system. From a global perspective, UNESCO's Universal Declaration on the Human Genome and Human Rights establishes broad ethical clauses relating to genetic research and the manipulation of the human genome. However, the declaration lacks binding regulatory force, which limits its practical implementation in different countries. Although it provides an important ethical basis for the field of gene therapy, the absence of a binding legal framework reduces its ability to directly influence the regulation of practices at national and global level.

Delhove et al. (DELHOVE et al., 2020) point out that international standards are often not aligned with local practices, which makes it difficult to carry out cross-border research. A clear example of this is the issue of freedom of germline therapies, which involve alterations to the human germline. This practice remains a point of global, with many countries banning it, while in others, it is allowed under strict conditions. The diversity in regulatory approaches reflects the different cultural, political and ethical views on genetic manipulation. controversyBrokowski and Adli (BROKOWSKI; ADLI, 2019) emphasize that the regulation of these interventions needs to evolve as technological advances become faster and more complex. The adaptation of regulatory standards must be continuous to ensure that existing gaps do not compromise either safety or ethical principles in the use of these emerging technologies. They suggest that a balance between scientific innovation and the safeguarding of ethical standards is fundamental to the safe conduct of genetic research and the clinical application of gene therapies.

In the Asian context, Sivagourounadin, Ravichandran and Rajendran (SIVAGOUROUNADIN; RAVICHANDRAN; RAJENDRAN, 2021) report that India has recently implemented national guidelines aimed at developing gene therapy products. These guidelines were drafted based on international standards, but were carefully adapted to address specific challenges faced by the country, such as limited infrastructure and issues of accessibility to innovative treatments. The adaptation of these standards aims to ensure that gene therapy is developed effectively and safely, taking into account local particularities and the needs of the many patients who could benefit from this technology.

The social impact of gene therapy goes beyond medical issues, involving accessibility, equity and public access. (MORADI., 2019) et alpoint out that although gene therapies have advanced significantly, their high cost makes them inaccessible to most populations in low- and middle-income countries. This economic barrier exacerbates global health inequalities, raising questions about social justice.

Delhove et al. (DELHOVE et al., 2020) explore the public acceptability of gene therapy and point out that fear of genetic manipulation and possible abuse still persists in many societies. These fears are exacerbated by ineffective scientific communication and a lack of transparency in some research. Pesapane et al. (PESAPANE et al., 2018) adds that in Europe and the United States, the integration of artificial intelligence in the management of gene therapies has raised concerns about the privacy of patient data, highlighting the need for robust legislation to protect sensitive information.

Hagerty and Rubinov (HAGERTY; RUBINOV, 2019) address the cultural impact of gene therapy, pointing out that different societies have different perspectives on its application, with religious and cultural values playing

a crucial role. For example, while some cultures see gene therapy as a violation of natural laws, others consider it an extension of modern medicine to save lives.

Hampson et al. (HAMPSON et al., 2018) discuss the economic sustainability of gene therapy in healthcare systems, emphasizing that public policies need to balance the costs of these innovative technologies with the long-term benefits. In this sense, approaches such as public funding and public-private partnerships can be key to ensuring that more patients have access to these transformative therapies.

CONCLUSION

The analysis of the advances and limitations of gene therapy highlights its great potential as a therapeutic intervention for genetic and acquired diseases, allowing the direct correction of mutations in patients' genetic material. The studies reviewed indicate that the application of viral vectors, such as adenoviruses and viruses adeno-associated (AAV), is a promising technique for the efficient transfer of therapeutic genes, with continuous improvements in gene editing and integration processes, especially in monogenic diseases such as β-thalassemia and muscular dystrophyDuchenne. However, the widespread implementation of gene therapy in clinical practice still faces technical and immunological obstacles, particularly due to the immunogenicity of the vectors, which can compromise the efficacy and safety of the treatment. Studies point to the need for improvements in viral capsids and vector manipulation, with the aim of reducing adverse immune responses and improving specificity in the delivery of therapeutic genes. In addition to the biotechnological challenges, the application of gene therapy also raises ethical issues, especially with regard to the modification of germ cells, which involves the risk of transgenerational effects and long-term repercussions. This approach requires strict regulation to guarantee safety and responsibility in therapeutic applications, considering the potential impacts on future generations. In this way, gene therapy is configured as an alternative with high clinical potential, but which depends on further advances to mitigate immunological and ethical limitations. Continued research in this area is essential to ensure the development of a safe, effective and widely applicable technology that meets the clinical and ethical requirements necessary for responsible implementation.

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