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CRISPR-Based Genome Editing in Contemporary Clinical Medicine: Therapeutic Translation, Global Challenges and the Future of Precision Medicine

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ABSTRACT

CRISPR-based genome editing has transformed the therapeutic possibilities of genomic medicine by enabling programmable modification of disease-associated genes and regulatory pathways. This review analyzed the evolution, current clinical applications, emerging therapeutic strategies, safety limitations, ethical challenges, and future perspectives of CRISPR-based technologies within an international framework that incorporates Latin America. An integrative literature review was conducted using scientific evidence published between 2012 and July 2026, with emphasis on peer-reviewed studies indexed in major biomedical databases and relevant international and regulatory documents. The evidence showed a rapid progression from

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foundational CRISPR-Cas9 research toward base editing, prime editing, ex vivo cellular modification, and direct in vivo genome editing. Clinical translation was most advanced in hematology, particularly in sickle cell disease and transfusion-dependent β-thalassemia, where genome-edited autologous hematopoietic stem and progenitor cells have demonstrated clinically meaningful therapeutic outcomes. Applications in oncology and hereditary transthyretin amyloidosis further demonstrated the feasibility of engineered immune cells and systemic in vivo genome editing. However, broader clinical implementation remains limited by delivery and tissue targeting, off-target and unintended on-target modifications, immunogenicity, manufacturing complexity, long-term safety, regulatory requirements, and accessibility. The international analysis identified heterogeneous capacity for clinical implementation, emphasizing the need to strengthen genomic infrastructure, population representation, professional training, regulatory preparedness, and research participation in Latin America. CRISPR has therefore progressed from an experimental genome-engineering technology to a clinically relevant therapeutic platform, although its future impact will depend on the ability to combine molecular precision and durable therapeutic benefit with rigorous safety assessment, responsible governance, and equitable access across diverse populations and healthcare systems.

KEYWORDS

CRISPR-Cas9, genome editing, gene therapy, precision medicine, base editing, prime editing, clinical medicine, genetic diseases, bioethics, genomic safety, Latin America, personalized medicine

INTRODUCTION

The transition from conventional genetic engineering to programmable genome editing has substantially changed the therapeutic landscape of modern medicine. For decades, the possibility of correcting disease-associated genetic alterations was constrained by limitations in specificity, efficiency, scalability, and delivery. The development of clustered regularly interspaced short palindromic repeats (CRISPR)-associated systems introduced a comparatively versatile platform through which selected genomic sequences can be recognized and modified using RNA-guided molecular machinery. The demonstration that Cas9 could be programmed by RNA to induce targeted DNA cleavage established the molecular basis for a technology that rapidly expanded from experimental genetics into translational and clinical research [1]. Subsequent studies showed that CRISPR-Cas systems could be adapted for genome engineering in mammalian and human cells, facilitating targeted genetic modifications with a degree of programmability that substantially broadened the potential applications of genome editing [2], [3].

The relevance of CRISPR to clinical medicine extends beyond its technical efficiency. Many disorders encountered across internal medicine, hematology, cardiology, hepatology, neurology, immunology, and other specialties have genetic components that influence disease initiation, progression, therapeutic response, or prognosis. Historically, treatment for numerous inherited disorders has focused primarily on controlling manifestations, preventing complications, replacing deficient proteins, or providing long-term pharmacological therapy rather than directly addressing the underlying molecular alteration. Genome editing introduces a different therapeutic concept: intervention at the level of DNA or its functional regulation, with the possibility of producing durable biological effects after a limited number of therapeutic interventions. This distinction has positioned CRISPR-based technologies within the broader evolution toward precision medicine, in which therapeutic decisions increasingly incorporate molecular mechanisms, genomic variation, and individual disease characteristics [4].

CRISPR-Cas9 is based on a programmable RNA component that directs a Cas nuclease toward a complementary nucleic acid sequence adjacent to an appropriate protospacer adjacent motif. Once the target is recognized, DNA cleavage can initiate endogenous repair pathways that may be exploited to disrupt, remove, restore, or modify genetic information. Although the initial therapeutic paradigm was strongly associated with double-strand DNA breaks, contemporary genome editing has evolved considerably beyond this mechanism. Base editing enables specific nucleotide conversions without requiring conventional double-strand cleavage, thereby expanding the range of potentially correctable pathogenic variants [5]. Prime editing subsequently introduced a “search-and-replace” strategy capable of generating defined substitutions, insertions, and deletions without relying on donor DNA templates or

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conventional double-strand breaks [6]. These developments illustrate that CRISPR should no longer be regarded as a single editing technique, but rather as a growing family of programmable molecular platforms with distinct mechanisms, advantages, limitations, and potential clinical indications.

The clinical significance of these technologies has become particularly evident in hematology. Hemoglobinopathies provided an important setting for therapeutic genome editing because hematopoietic stem and progenitor cells can be collected, genetically modified ex vivo, characterized, and subsequently returned to the patient. Early clinical evidence demonstrated that CRISPR-Cas9-mediated modification of hematopoietic stem cells could produce sustained increases in fetal hemoglobin and clinically meaningful responses in patients with sickle cell disease and transfusion-dependent β-thalassemia [9]. More recent evidence from pivotal clinical studies of exagamglogene autotemcel has reinforced the therapeutic relevance of this approach. In severe sickle cell disease, treatment was associated with substantial prevention of vaso-occlusive events among evaluable patients, while in transfusion-dependent β-thalassemia, a large proportion of treated patients achieved transfusion independence [11], [12]. These findings represent a major milestone because they demonstrate that genome editing can move beyond molecular proof of concept and generate clinically meaningful outcomes in patients with serious inherited disorders.

The development of CRISPR-based therapies has also progressed beyond ex vivo modification. In vivo genome editing represents a particularly important frontier because it seeks to deliver editing components directly into the patient and modify target cells within the affected organ. Clinical investigation of CRISPR-Cas9 for transthyretin amyloidosis demonstrated that systemic administration of genome-editing components could produce substantial reductions in circulating transthyretin, providing early evidence that direct therapeutic genome editing within the human body is feasible [10]. This approach is especially relevant to internal medicine because several chronic and hereditary disorders affecting the liver, cardiovascular system, metabolism, and other organs may eventually become candidates for in vivo genomic intervention. Nevertheless, successful application depends not only on editing activity but also on efficient tissue-specific delivery, adequate biodistribution, durability, and acceptable immunological and toxicological profiles.

Oncology represents another important area of translational development. Genome editing can be used to modify immune cells, remove inhibitory pathways, introduce or optimize therapeutic receptors, and potentially generate cellular products with enhanced antitumor activity. Clinical investigations have demonstrated the feasibility of administering CRISPR-engineered T cells to patients with advanced malignancies [7]. Similarly, CRISPR-edited T cells have been evaluated in patients with refractory non-small-cell lung cancer, contributing early human evidence regarding feasibility and safety in cancer immunotherapy [8]. Although these studies involved limited populations and cannot be interpreted as definitive evidence of broad clinical efficacy, they established an important translational foundation for the development of increasingly sophisticated engineered immune-cell therapies.

These advances reflect a broader change in the therapeutic objectives of genomic medicine. Conventional gene therapy has frequently relied on introducing functional genetic material, whereas genome editing can directly alter endogenous genomic sequences or regulatory elements. This distinction creates opportunities to address diseases through multiple strategies, including disruption of pathogenic genes, restoration of physiological gene expression, correction of pathogenic variants, modulation of regulatory regions, and engineering of therapeutic cell populations. Consequently, CRISPR-based technologies are being investigated across inherited diseases, malignancies, cardiovascular disorders, neurological conditions, infectious diseases, immune-mediated disorders, and rare diseases. Their potential impact is therefore not restricted to clinical genetics; rather, genome editing is becoming relevant to multiple areas of medical practice and biomedical research [15], [18].

However, the transition from molecular editing to clinical treatment introduces challenges that cannot be assessed exclusively through measures of editing efficiency. One of the most persistent concerns is unintended genomic modification. CRISPR nucleases may interact with sequences that resemble the intended target, potentially producing off-target alterations. Genome-wide approaches such as GUIDE-seq were developed to characterize nuclease-induced double-strand breaks and improve the assessment of editing specificity [13]. Although technological improvements in guide design, nuclease engineering, delivery strategies, and analytical methods have reduced several risks, therapeutic genome editing requires a particularly high standard of safety because unintended changes may have persistent biological consequences.

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Safety assessment must also consider events occurring at the intended target. Genomic modification may produce heterogeneous repair outcomes, unexpected insertions or deletions, chromosomal alterations, or variable editing among cells. Furthermore, the biological consequences of a genomic intervention may differ according to the target tissue, developmental stage, delivery system, underlying disease, and persistence of the editing components. For these reasons, evaluation of genome-editing therapies requires a multidimensional approach that considers molecular specificity, cellular function, immunogenicity, toxicology, long-term clinical outcomes, and post-treatment surveillance. The clinical development of CRISPR therefore depends on the interaction between molecular genetics, clinical medicine, pharmacology, immunology, bioinformatics, and regulatory science rather than on editing performance alone [15], [18].

Delivery remains another major determinant of therapeutic feasibility. A genome-editing system that performs effectively in vitro does not necessarily translate into a clinically viable therapy unless its components can reach the appropriate cells in sufficient quantities while limiting exposure of non-target tissues. Ex vivo strategies partially address this problem by allowing cells to be manipulated outside the body; however, they may require specialized facilities, cell collection, conditioning regimens, and complex manufacturing procedures. In vivo strategies may broaden therapeutic applicability but introduce additional challenges related to tissue targeting, biodistribution, immune responses, dosage, and transient versus persistent expression of editing components. Viral vectors, lipid nanoparticles, electroporation, ribonucleoprotein complexes, and other delivery approaches have therefore become central components of therapeutic genome-editing development [14].

Technological diversification may help address some of these limitations. The contemporary CRISPR toolbox includes engineered Cas nucleases, transcriptional regulation systems, base editors, prime editors, and other platforms designed to modify genetic function with increasing precision [16], [17]. Rather than assuming that one editing system will be appropriate for every disease, clinical translation increasingly requires matching the molecular tool to the pathogenic mechanism. A loss-of-function variant may require restoration or correction, a dominant pathogenic allele may be approached through selective disruption, and disorders involving abnormal gene expression may potentially be addressed through regulatory editing. The therapeutic value of CRISPR is therefore closely connected to accurate molecular diagnosis and detailed understanding of disease biology.

At the same time, technical feasibility does not automatically establish clinical appropriateness. Genome editing raises ethical questions concerning acceptable levels of uncertainty, informed consent, long-term follow-up, access to advanced therapies, allocation of healthcare resources, and the distinction between treatment and human enhancement. These questions become particularly significant when considering interventions capable of producing persistent genetic changes. Somatic genome editing, in which modifications are limited to the treated individual, is fundamentally different from heritable genome editing involving germ cells, gametes, or embryos, where alterations could potentially be transmitted to future generations. The latter introduces broader questions regarding intergenerational consent, unpredictable long-term effects, social consequences, and the boundaries of legitimate biomedical intervention.

International governance has therefore developed alongside scientific progress. The World Health Organization has emphasized that human genome editing requires robust oversight, transparency, international cooperation, appropriate regulatory mechanisms, and attention to ethical and social implications [19], [20]. These principles are increasingly important as research becomes geographically distributed and therapeutic products move through multinational development pathways. Scientific progress in genome editing cannot be evaluated independently of the healthcare systems in which these interventions may eventually be implemented.

This issue is particularly relevant from a global health perspective. The potential benefits of genome editing are substantial, but so are the risks of unequal distribution. Advanced genomic therapies require infrastructure for molecular diagnosis, sequencing, specialized laboratories, manufacturing, clinical monitoring, and long-term follow-up. The concentration of these resources in high-income settings could produce a situation in which diseases with a global burden become technically treatable while access remains geographically and economically restricted. The clinical success of genome editing must therefore be evaluated not only according to whether a genomic alteration can be corrected, but also according to whether safe and effective interventions can be implemented within diverse healthcare environments.

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Latin America occupies an important position within this discussion. The region combines substantial scientific and clinical capacity with marked heterogeneity in healthcare infrastructure, research investment, regulatory development, access to genomic testing, and availability of advanced therapies. Many countries in the region also face simultaneous burdens of chronic disease, inherited disorders, rare diseases, infectious diseases, and healthcare inequality. As CRISPR-based interventions progress toward broader clinical use, Latin American participation in research, regulation, bioethical deliberation, genomic surveillance, professional education, and clinical implementation will be important to prevent the emergence of a genomic medicine model in which innovation is concentrated in a limited number of healthcare systems.

The regional perspective is also relevant because genetic research and therapeutic development require representation of diverse populations. Underrepresentation can influence variant interpretation, diagnostic accuracy, identification of clinically relevant genetic associations, and ultimately the applicability of precision therapies. Expanding genomic research capacity and international scientific collaboration may therefore contribute not only to future access to CRISPR technologies but also to the generation of evidence that reflects the genetic and clinical diversity of populations across Latin America. International cooperation should consequently include participation in research design, genomic databases, clinical studies, regulatory frameworks, bioethical governance, technology transfer, and professional training rather than limiting regional involvement to eventual adoption of technologies developed elsewhere.

The rapid progression of the field further justifies a contemporary review. CRISPR has evolved within little more than a decade from programmable DNA cleavage demonstrated experimentally [1]–[3] to increasingly sophisticated editing systems [5], [6], clinical studies involving engineered human cells [7]–[9], direct in vivo editing [10], and therapies supported by pivotal clinical evidence [11], [12]. As Doudna emphasized, the promise of therapeutic genome editing is inseparable from the scientific, clinical, and societal challenges associated with controlling its effects and defining responsible applications [18]. The central question is therefore no longer simply whether the human genome can be edited, but how genome editing can be translated into interventions that are effective, sufficiently safe, ethically acceptable, and accessible across different healthcare settings.

Previous literature has extensively addressed individual dimensions of this field. Foundational studies established programmable CRISPR-Cas activity and its adaptation to human cells [1]–[4]. Subsequent research expanded editing capabilities through base and prime editing [5], [6], while clinical studies demonstrated applications in oncology, hematological disease, and systemic in vivo therapy [7]–[12]. Other investigations have focused on off-target detection, delivery systems, technological diversification, and the broader therapeutic potential of genome editing [13]–[18]. In parallel, international organizations have developed recommendations and governance frameworks intended to guide responsible human genome-editing research and clinical translation [19], [20]. Despite this extensive literature, the rapid convergence of technological innovation, clinical implementation, regulatory evolution, and global access creates a continuing need for integrated assessment.

Accordingly, this review examines CRISPR gene editing from an international clinical perspective, integrating evidence from molecular genetics, translational research, clinical medicine, and bioethics. Particular attention is given to the progression from foundational CRISPR-Cas systems toward base editing, prime editing, ex vivo cellular modification, and in vivo therapeutic strategies; the current and emerging applications across major areas of clinical medicine; the safety and delivery challenges that continue to influence translation; and the ethical and governance questions generated by increasingly powerful genome-editing capabilities. The analysis also incorporates Latin America within the broader international context, considering the implications of infrastructure, research capacity, regulatory preparedness, population representation, and equitable access.

The review is guided by several interconnected research questions: What level of clinical evidence currently supports CRISPR-based therapeutic interventions? Which diseases and clinical specialties have achieved the greatest degree of translation from experimental genome editing to human therapeutic application? What technological and biological limitations continue to restrict safety, precision, and scalability? How are emerging editing platforms changing the therapeutic possibilities originally established by CRISPR-Cas9? What ethical and regulatory considerations should accompany the expansion of human genome editing? Finally, how can the benefits of this technological transition be

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incorporated into diverse healthcare systems, including those of Latin America, without intensifying existing disparities in access to genomic medicine?

To address these questions, the review integrates foundational and contemporary peer-reviewed literature describing CRISPR mechanisms, technological development, preclinical-to-clinical translation, human therapeutic studies, safety, delivery, and emerging applications. Clinical evidence is interpreted together with relevant international recommendations and governance frameworks, allowing technological progress to be considered in relation to clinical applicability and responsible implementation. The structure of the review follows the translational trajectory of genome editing, beginning with biological and technological foundations, progressing through delivery strategies and clinical applications, and subsequently examining safety, ethical considerations, regulation, and future perspectives.

This approach is particularly important because the future of CRISPR in medicine will depend on more than technological sophistication. Therapeutic success will require precise identification of appropriate molecular targets, reliable delivery, rigorous evaluation of genomic consequences, demonstration of meaningful clinical benefit, long-term monitoring, transparent regulatory oversight, and strategies that enable equitable implementation. CRISPR gene editing has already demonstrated that targeted genomic intervention can produce clinically relevant therapeutic effects in selected diseases [9]–[12]. The next phase of development will determine how broadly these achievements can be translated across diseases, populations, and healthcare systems.

Therefore, the objective of this review is to critically examine the evolution, current clinical applications, emerging therapeutic opportunities, safety limitations, ethical challenges, and future perspectives of CRISPR-based genome editing in clinical medicine. By integrating evidence from genetics, internal medicine, translational research, and bioethics within an international framework that includes Latin America, this review seeks to provide a comprehensive understanding of the current position of CRISPR in medicine and the scientific, clinical, regulatory, and social conditions that will shape its transition from specialized genomic intervention toward a potentially broader component of precision healthcare.

DEVELOPMENT

CRISPR-based genome editing represents one of the most significant transitions in contemporary genomic medicine because it allows therapeutic strategies to move from compensating for genetic dysfunction toward directly modifying molecular mechanisms associated with disease. The original CRISPR-Cas9 platform demonstrated that RNA-guided nucleases could recognize selected genomic sequences and generate targeted DNA breaks [1]–[4]. Since then, the technology has expanded into a broader family of editing systems capable of disrupting genes, altering regulatory elements, correcting specific nucleotide changes, and modifying cellular functions. Base editing and prime editing have further increased the range of possible interventions by allowing defined genomic changes without depending exclusively on conventional double-strand DNA breaks [5], [6].

This technological evolution has direct clinical implications. The therapeutic value of genome editing depends on whether a genetic alteration contributes sufficiently to disease pathogenesis for its modification to generate a meaningful biological effect. Hemoglobinopathies have provided some of the clearest evidence of this principle. In sickle cell disease and transfusion-dependent β-thalassemia, ex vivo CRISPR-Cas9 editing of autologous hematopoietic stem and progenitor cells can modify the erythroid regulatory region of **BCL11A**, increasing fetal hemoglobin production and thereby compensating for abnormal or insufficient adult hemoglobin. Initial clinical evidence demonstrated sustained hematological responses and reduction of major disease manifestations [9]. Subsequent phase 3 studies of exagamglogene autotemcel provided stronger evidence of clinically meaningful benefit in both severe sickle cell disease and transfusion-dependent β-thalassemia [11], [12].

The progression of exagamglogene autotemcel also illustrates the transition of CRISPR from experimental technology to regulated clinical therapy. In the United States, Casgevy became the first FDA-approved therapy to use CRISPR/Cas9 genome editing, initially for selected patients with sickle cell disease and subsequently for transfusion-dependent β-thalassemia. By July 2026, the FDA had expanded its use to patients aged two years and older with either recurrent vaso-occlusive sickle cell disease or transfusion-dependent β-thalassemia, substantially widening its potential

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pediatric application. In the European Union, Casgevy is authorized for selected patients aged 12 years and older with transfusion-dependent β-thalassemia or severe sickle cell disease, particularly when hematopoietic stem-cell transplantation is appropriate and a matched related donor is unavailable.

The significance of these developments extends beyond hematology. CRISPR-based strategies are being explored across oncology, cardiovascular medicine, hepatology, neurology, ophthalmology, immunology, infectious disease, and rare genetic disorders. In oncology, gene editing has been used to modify T lymphocytes and investigate whether removal of inhibitory receptors or alteration of immune-cell characteristics can improve antitumor responses. Early clinical studies demonstrated that CRISPR-engineered T cells could be administered to patients with refractory malignancies and persist following infusion [7]. Similar investigations in refractory non-small-cell lung cancer demonstrated the feasibility of editing immune checkpoint-associated genes in autologous T cells [8]. These studies established proof of principle for combining genome engineering with cellular immunotherapy, although efficacy, manufacturing complexity, tumor heterogeneity, and long-term safety remain important limitations.

An additional shift has occurred with the development of **in vivo genome editing**, in which editing components are administered directly to the patient instead of manipulating cells outside the body. The study by Gillmore *et al.* demonstrated that systemic delivery of CRISPR-Cas9 components targeting the transthyretin gene could substantially reduce circulating transthyretin in patients with hereditary transthyretin amyloidosis [10]. This finding was especially relevant because it demonstrated that therapeutically meaningful genome editing could occur directly within human tissues. Such approaches may ultimately broaden the range of diseases suitable for CRISPR treatment, particularly disorders involving the liver and other organs accessible through targeted delivery systems.

Nevertheless, delivery remains one of the principal determinants of clinical applicability. Ex vivo editing provides greater control because cells can be collected, edited, evaluated, and selected before administration. However, this strategy is technically demanding and may require stem-cell mobilization, conditioning chemotherapy, specialized manufacturing, and highly trained clinical teams. In vivo editing may simplify certain aspects of treatment but introduces challenges related to biodistribution, tissue specificity, immune recognition, transient or persistent nuclease exposure, and unintended editing in non-target cells. Viral vectors, lipid nanoparticles, electroporation, and ribonucleoprotein delivery have therefore become integral components of genome-editing development [14].

Safety constitutes another major issue. CRISPR systems can potentially produce unintended genomic alterations at sequences that resemble the intended target. Genome-wide methods such as GUIDE-seq have contributed to systematic characterization of off-target nuclease activity [13]. Although improvements in guide-RNA design, engineered nucleases, computational prediction, and delivery methods have increased specificity, the absence of detectable off-target events in a particular assay cannot be interpreted as proof of complete genomic safety. Evaluation must also consider unintended consequences occurring at the intended target, including heterogeneous repair, large deletions, rearrangements, or other genomic alterations.

Newer editing platforms have been developed partly in response to these limitations. Base editors permit specific nucleotide conversions without producing conventional double-strand breaks [5], while prime editing combines Cas-derived targeting with reverse transcription to introduce defined sequence changes [6]. These technologies could theoretically expand the proportion of pathogenic variants amenable to correction while reducing some forms of DNA damage. Nevertheless, each platform introduces its own potential sources of unwanted editing, delivery challenges, molecular constraints, and safety considerations. Consequently, technological novelty should not be regarded as synonymous with clinical superiority; the appropriate editing system depends on the disease mechanism, cell type, target sequence, required duration of effect, and acceptable risk profile [16], [17].

From the perspective of internal medicine, genome editing is especially relevant because many systemic diseases involve genetically defined pathways that can potentially be modified. Hereditary transthyretin amyloidosis provides an established example [10], while experimental strategies targeting lipid metabolism, inherited hepatic disorders, immune pathways, and metabolic diseases illustrate the broader therapeutic potential of genomic intervention. In these conditions, CRISPR may complement rather than completely replace existing pharmacological or biological treatments. Clinical integration will therefore require comparisons with established standards of care regarding effectiveness, adverse events, durability, cost, feasibility, and quality of life.

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The therapeutic potential of CRISPR is also closely associated with precision medicine. Genome editing requires accurate identification of pathogenic variants or regulatory targets and therefore depends on molecular diagnosis, sequencing technologies, functional genomics, and increasingly sophisticated computational tools. This creates a reciprocal relationship: improvements in genomic diagnosis identify patients who may benefit from targeted therapies, while genome-editing technologies increase the clinical relevance of identifying disease-causing molecular abnormalities. However, this relationship also highlights disparities in access to sequencing and specialized genomic services.

These disparities are particularly relevant in Latin America. Although the region has growing expertise in genetics, molecular medicine, bioinformatics, and clinical research, capacity is unevenly distributed among countries and institutions. Advanced genome-editing therapies require not only regulatory authorization but also diagnostic laboratories, genomic characterization, cell-processing infrastructure, multidisciplinary clinical teams, long-term surveillance, and financing mechanisms capable of supporting high-complexity interventions. Therefore, participation of Latin American healthcare systems in the genomic medicine era depends on strengthening scientific infrastructure, regional collaboration, professional training, and representation of local populations in genomic research.

Population diversity itself has therapeutic implications. The interpretation of genomic variants depends heavily on the availability of representative genetic data. Populations that are insufficiently represented in genomic databases may experience greater uncertainty in variant classification and disease-risk interpretation. For Latin America, where populations reflect complex Indigenous American, European, African, and other ancestral contributions, increasing representation in genomic research is essential for ensuring that future precision therapies are applicable to regional populations rather than extrapolated exclusively from cohorts studied elsewhere.

Ethical analysis must develop in parallel with these clinical advances. Somatic genome editing is intended to modify cells of an individual patient without transmitting those changes to future generations, whereas germline editing introduces the possibility of heritable genomic alteration. The latter raises substantially different ethical and social concerns, including the absence of consent from future generations, uncertainty regarding long-term consequences, potential use for non-therapeutic enhancement, and possible amplification of social inequality. International governance frameworks therefore emphasize transparency, scientific responsibility, oversight, and mechanisms capable of responding to rapidly evolving applications [19], [20].

Equity is equally important for somatic therapies. A treatment may demonstrate remarkable efficacy but still have limited public-health impact if its availability is restricted to a small number of specialized centers or healthcare systems. The complexity of collecting and editing autologous cells, administering myeloablative conditioning, and monitoring patients after therapy illustrates this problem. Even in regions where CRISPR therapies receive regulatory authorization, clinical access may depend on infrastructure, reimbursement policies, availability of trained personnel, and capacity for long-term follow-up. Consequently, therapeutic innovation and equitable implementation must be considered together rather than as independent stages of development.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze the development, current clinical applications, therapeutic potential, safety limitations, ethical challenges, and future perspectives of CRISPR-based gene editing in clinical medicine through an integrative review of international scientific evidence, incorporating the Latin American context to understand its potential contribution to precision medicine and its implications for responsible and equitable healthcare implementation.

A. Cognitive Domain

To **identify and describe** the molecular principles underlying CRISPR-Cas systems and the technological evolution from conventional CRISPR-Cas9 editing toward base editing, prime editing, and other emerging genome-editing platforms.

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To **analyze and compare** the available scientific evidence regarding ex vivo and in vivo CRISPR-based therapeutic strategies, with particular attention to hematological disorders, malignancies, hereditary diseases, cardiovascular conditions, and other emerging clinical indications.

To **evaluate** the principal determinants of clinical safety, including off-target modifications, unintended on-target alterations, immunogenicity, delivery limitations, treatment durability, and potential long-term consequences associated with genome editing [13]–[18].

To **integrate** current clinical and translational evidence to determine the present position of CRISPR technologies within precision medicine and their potential evolution toward broader therapeutic applications [9]–[12].

B. Psychomotor Domain

To **organize and classify** the available scientific evidence according to editing technology, therapeutic strategy, target disease, delivery mechanism, stage of clinical development, and reported outcomes, enabling a structured comparison of CRISPR applications.

To **differentiate and interpret** the mechanisms of conventional CRISPR-Cas9 editing, base editing, prime editing, ex vivo modification, and in vivo intervention through systematic examination of their molecular and clinical characteristics [5], [6], [16], [17].

To **construct** an integrated framework connecting molecular mechanisms, therapeutic applications, clinical evidence, safety considerations, and implementation requirements to facilitate the understanding of genome editing within clinical practice.

C. Affective Domain

To **recognize and assess** the ethical responsibilities associated with human genome editing, particularly regarding patient autonomy, informed consent, long-term uncertainty, justice, and the distinction between somatic and heritable genetic modification [19], [20].

To **value** equitable access, population diversity, scientific transparency, and responsible innovation as essential components of the future implementation of genome-editing therapies.

To **examine** the challenges and opportunities associated with the participation of Latin America in genomic medicine, considering research capacity, healthcare infrastructure, professional training, regulatory preparedness, population representation, and access to advanced therapies within an international context.

OBJECT OF STUDY

The object of study of this review is the clinical translation of CRISPR-based genome editing, understood as the progression of programmable genetic modification technologies from their molecular foundations to their current and emerging therapeutic applications in human medicine. The analysis focuses on CRISPR-Cas systems and their technological derivatives, including conventional CRISPR-Cas9 editing, base editing, prime editing, and ex vivo and in vivo therapeutic approaches [1], [5], [6], [16].

The phenomenon under investigation encompasses the relationship between genome-editing mechanisms and their potential capacity to modify disease-associated genes or regulatory pathways with clinically meaningful consequences. Particular attention is given to applications in hematological diseases, cancer, hereditary and metabolic disorders, cardiovascular conditions, neurological diseases, and other areas in which genome editing may provide therapeutic alternatives. Clinical experiences in sickle cell disease, transfusion-dependent β-thalassemia, hereditary transthyretin

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amyloidosis, and engineered cellular therapies constitute relevant examples of the transition from experimental genome editing toward human therapeutic intervention [7]–[12].

The population of interest comprises patients with genetic, acquired, or multifactorial diseases for which CRISPR-based intervention has been investigated at preclinical or clinical levels, with particular emphasis on human clinical evidence. The review does not restrict its scope to a specific age group, sex, ethnicity, or geographical region, since the objective is to evaluate the international development of these technologies and their potential applicability across heterogeneous populations and healthcare systems.

The study also considers the technological and clinical conditions that determine the feasibility of genome editing, including target selection, editing precision, delivery systems, off-target activity, immunogenicity, durability, manufacturing requirements, and long-term safety [13]–[18]. These factors are examined as interconnected components of clinical translation rather than as isolated characteristics of the editing technology.

In addition, the object of study incorporates the ethical, regulatory, and social dimensions associated with human genome editing. Particular consideration is given to the distinction between somatic and heritable interventions, informed consent, risk-benefit assessment, long-term surveillance, equitable access, and international governance [19], [20]. Within this framework, Latin America is included as an essential regional perspective for examining differences in genomic research capacity, healthcare infrastructure, regulation, population representation, and access to advanced therapies.

Therefore, the object of study is defined as the **scientific, clinical, technological, ethical, and translational evolution of CRISPR-based genome editing and its incorporation into contemporary medicine**, evaluated through international evidence and complemented by the challenges and opportunities associated with its development and future implementation in Latin America.

METHODOLOGY

This study was conducted as an **integrative review of the scientific literature using the scientific method as the methodological framework**. This approach was selected because it allows evidence from different levels of research to be systematically identified, evaluated, compared, and synthesized, including molecular studies, technological developments, clinical trials, translational research, and ethical and regulatory documents. The methodology was designed to provide a reproducible overview of CRISPR-based genome editing and its current and emerging applications in clinical medicine.

The research process was structured around the following question: **What is the current state of CRISPR-based genome editing in clinical medicine regarding therapeutic applications, clinical evidence, safety, ethical challenges, and future perspectives within an international context that includes Latin America?** This question guided the identification of relevant evidence and the organization of the subsequent analysis.

A structured literature search was performed using **PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect** as the principal scientific databases. Complementary information was obtained from official documents and regulatory resources produced by the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and international clinical trial registries when required to contextualize therapeutic development, regulatory status, or governance.

The search strategy combined controlled vocabulary and free-text terms related to genome editing and clinical medicine. The principal terms included *"CRISPR," "CRISPR-Cas9," "genome editing," "gene editing," "base editing," "prime editing," "clinical applications," "gene therapy," "clinical trials," "sickle cell disease," "beta-thalassemia," "cancer," "cardiovascular disease," "genetic diseases," "off-target effects," "bioethics," "genome editing governance," "Latin America,"* and *"precision medicine."* Boolean operators **AND** and **OR** were used to combine concepts and increase the specificity or sensitivity of the search.

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The review primarily considered scientific literature published between **2012 and July 2026**, using the publication of the programmable RNA-guided Cas9 system as the starting point for the contemporary CRISPR era [1]. Seminal studies published during the initial development of the technology were retained because of their relevance to understanding the molecular and technological foundations of current therapeutic applications [1]–[4]. Priority was given to recent clinical evidence when multiple publications addressed the same therapeutic application.

Eligible sources included peer-reviewed original research articles, clinical trials, systematic or narrative reviews of substantial relevance, translational studies, and official regulatory or international governance documents. Publications were considered when they addressed CRISPR mechanisms, therapeutic genome editing, clinical applications, delivery systems, safety, emerging editing technologies, ethical implications, regulation, or implementation in healthcare. Evidence concerning Latin America was considered when relevant to genomic research capacity, clinical translation, population representation, regulation, bioethics, or access to advanced therapies.

Sources were excluded when they lacked a direct relationship with human health or therapeutic genome editing, contained insufficient methodological information, duplicated evidence reported in another selected publication, or consisted primarily of non-scientific commentary without relevant clinical, technological, or ethical evidence. Studies focused exclusively on agricultural, industrial, or environmental applications of CRISPR were outside the scope of this review.

The selection process was conducted in successive stages. Titles and abstracts were initially screened according to the research question and predefined eligibility criteria. Potentially relevant publications were subsequently assessed through full-text examination. Evidence was prioritized according to scientific relevance, methodological quality, clinical significance, publication source, and contribution to the objectives of the review. Particular attention was given to landmark molecular studies [1]–[6], early human investigations [7]–[10], and clinical evidence supporting the therapeutic translation of CRISPR technologies [11], [12].

Data extraction was organized according to predefined analytical categories: **editing technology, molecular target, therapeutic strategy, disease or clinical specialty, ex vivo or in vivo approach, delivery mechanism, stage of clinical development, reported therapeutic outcomes, safety findings, technological limitations, ethical considerations, regulatory implications, and future perspectives**. This structure enabled comparison between different applications despite heterogeneity in study design and clinical development.

The evidence was synthesized using a **qualitative and comparative approach**. Rather than combining heterogeneous outcomes through meta-analysis, findings were organized according to technological and clinical relevance. Relationships between molecular mechanisms and therapeutic applications were examined alongside evidence regarding delivery, specificity, off-target effects, durability, and safety [13]–[18]. Ethical and governance considerations were analyzed using internationally recognized frameworks, particularly recommendations developed by the WHO [19], [20].

To improve methodological consistency, the analysis followed four general principles: **relevance to the research question, scientific reliability, clinical applicability, and international representativeness**. Evidence from different geographical settings was considered when available, and Latin America was incorporated into the international analysis to identify regional opportunities and limitations related to genomic research, infrastructure, regulatory preparedness, professional training, population representation, and future therapeutic access.

Because this study consisted exclusively of a review and analysis of previously published literature and publicly available institutional documents, **no patients or research participants were recruited, no biological samples were obtained, and no individual clinical interventions were performed**. The methodological process was therefore centered on literature identification, critical evaluation, comparative analysis, and synthesis of existing scientific evidence.

This methodology provides a reproducible framework for examining the transition of CRISPR from experimental genome engineering to clinical medicine while integrating therapeutic evidence with technological, safety, ethical, regulatory, and global implementation considerations.

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PHASES OF DEVELOPMENT

The development of the review was organized into sequential phases derived from the scientific method and adapted to the characteristics of an integrative literature review. Each phase was designed to maintain consistency between the research question, the objectives, the selection of scientific evidence, and the final synthesis of CRISPR applications in clinical medicine.

Problem identification and research question formulation. The first phase consisted of defining the central problem of the review: the rapid transition of CRISPR-based genome editing from experimental molecular research to therapeutic applications in humans, together with persistent uncertainties regarding safety, delivery, ethical acceptability, regulation, and equitable access. Based on this problem, the research question was formulated to examine the current clinical status of CRISPR technologies, their emerging therapeutic potential, and the conditions required for responsible implementation within an international context that includes Latin America.

Definition of the analytical scope. The second phase established the conceptual boundaries of the review. CRISPR-Cas9, base editing, prime editing, ex vivo genome editing, and in vivo approaches were identified as the principal technologies of interest [1], [5], [6], [16]. Clinical areas were subsequently defined according to the available evidence and included hematology, oncology, hereditary and metabolic diseases, cardiovascular medicine, and other emerging therapeutic fields. Safety, bioethics, regulation, and accessibility were incorporated as transversal dimensions.

Systematic identification of scientific evidence. The third phase involved searching PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect using combinations of keywords and Boolean operators. The search covered literature published from 2012 through July 2026 and prioritized peer-reviewed evidence related to therapeutic genome editing. Seminal publications were retained to reconstruct the technological evolution of CRISPR [1]–[6], while more recent studies were prioritized for the evaluation of clinical translation [7]–[12].

Screening and eligibility assessment. Retrieved publications were examined according to predefined inclusion and exclusion criteria. Initial screening considered titles and abstracts, followed by full-text evaluation of potentially eligible studies. Publications were assessed according to their relationship with the research objectives, methodological quality, scientific relevance, clinical contribution, and reliability of the publication source. Duplicate or insufficiently relevant evidence was excluded.

Classification and extraction of information. Selected evidence was organized into standardized analytical categories, including editing technology, molecular target, disease, therapeutic strategy, delivery system, ex vivo or in vivo intervention, stage of clinical development, reported outcomes, safety findings, and principal limitations. Ethical, regulatory, and accessibility considerations were categorized separately to facilitate comparison across different therapeutic applications.

Critical analysis of clinical evidence. The fifth phase examined the progression from experimental genome editing toward clinical application. Particular attention was given to human studies involving hematological diseases, engineered immune cells, and in vivo editing [7]–[12]. Clinical findings were interpreted alongside evidence concerning off-target activity, delivery, molecular specificity, and technological limitations [13]–[18]. Differences between established therapeutic applications and emerging or experimental indications were maintained throughout the analysis.

Ethical and regulatory assessment. Scientific evidence was subsequently examined in relation to the ethical implications of human genome editing. Somatic and heritable editing were differentiated, and issues involving informed consent, long-term uncertainty, risk-benefit assessment, justice, accessibility, and international governance were considered. WHO recommendations and governance frameworks provided a reference for evaluating responsible clinical translation [19], [20].

International and Latin American contextualization. The evidence was then interpreted within the international development of genomic medicine. The Latin American context was incorporated to examine regional challenges involving research capacity, genomic infrastructure, regulatory preparedness, population representation, specialized

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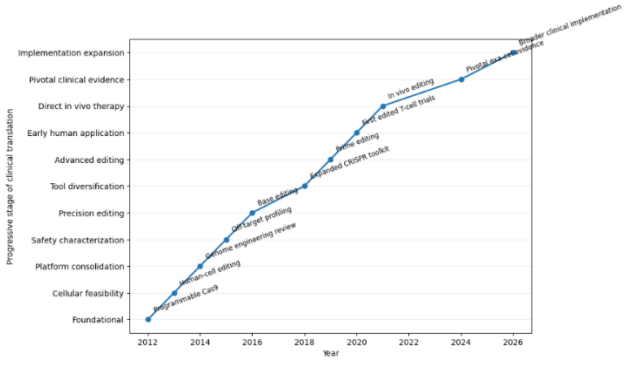
professional training, and potential access to advanced genome-editing therapies. This phase allowed technological progress to be analyzed in relation to different healthcare environments rather than exclusively from the perspective of countries where most clinical development has occurred.

Integration and synthesis of findings. Finally, the information obtained from the previous phases was integrated through qualitative comparative synthesis. Findings were organized according to the relationship between technological development, clinical applicability, safety, ethical considerations, and future implementation. Areas with stronger clinical evidence were differentiated from emerging applications for which evidence remains preliminary. This final phase provided the analytical foundation for presenting the results, discussing their clinical and bioethical implications, and establishing conclusions regarding the future role of CRISPR-based genome editing in international medicine.

RESULTS AND DISCUSSION

Figure 1.
Temporal evolution of CRISPR-based genome editing toward clinical medicine



The temporal pattern illustrated in Figure 1 shows a progressive transition of CRISPR from a molecular biotechnology platform toward clinically relevant therapeutic applications. The earliest stage corresponds to the demonstration that the CRISPR-Cas9 system could be programmed through RNA molecules to recognize and cleave selected DNA sequences. The study by Jinek *et al.* in 2012 represented a fundamental milestone because it established the principle of RNA-guided DNA targeting using Cas9, providing the mechanistic basis for later genome-engineering applications [1]. Shortly afterward, independent studies demonstrated that CRISPR-Cas systems could be adapted for efficient genome modification in mammalian and human cells, substantially accelerating interest in their potential biomedical applications [2], [3].

Between 2014 and 2016, the evidence shifted from basic demonstration of genome editing toward consolidation of CRISPR as a flexible biomedical platform. During this period, the scientific discussion increasingly focused on the possibilities of programmable genome engineering and the limitations that would need to be addressed before therapeutic use [4]. Safety became a central component of development because nuclease activity could potentially occur at genomic sequences similar to the intended target. The introduction of genome-wide analytical approaches such as GUIDE-seq provided a more systematic method for identifying off-target cleavage events and contributed to the development of increasingly rigorous strategies for evaluating editing specificity [13].

Another important transition occurred with the emergence of technologies designed to modify DNA without relying exclusively on conventional double-strand breaks. Base editing demonstrated that selected nucleotide substitutions could be introduced directly into genomic DNA using modified CRISPR-associated proteins coupled to nucleotide-modifying enzymes [5]. This development expanded the therapeutic potential of genome editing because many pathogenic variants result from single-nucleotide alterations. It also established a broader conceptual framework in which CRISPR-based medicine could involve precise molecular rewriting rather than only gene disruption.

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The diversification of CRISPR technologies continued during the subsequent years. The expansion of the CRISPR toolkit included engineered nucleases, transcriptional regulators, alternative Cas proteins, and increasingly specialized editing systems [16], [17]. Prime editing represented another major technological step because it enabled predefined substitutions, insertions, and deletions without requiring conventional double-strand DNA cleavage or donor DNA templates [6]. Together, these technologies progressively expanded the types of pathogenic genetic alterations that could theoretically become therapeutic targets.

The transition toward human clinical application became increasingly evident around 2020. Clinical investigations involving CRISPR-engineered T cells demonstrated that genetically modified immune cells could be produced, administered to patients, and monitored in therapeutic settings. Stadtmauer *et al.* reported the use of CRISPR-engineered T cells in patients with refractory cancer, providing evidence that multiplex genome editing could be integrated into cellular immunotherapy [7]. In parallel, Lu *et al.* evaluated CRISPR-edited T cells in patients with refractory non-small-cell lung cancer, further demonstrating the feasibility of applying genome editing within human oncological treatment protocols [8]. These investigations marked an important transition from technological feasibility to direct clinical experimentation.

A major milestone was reached with the development of CRISPR-based therapies for hemoglobinopathies. Early clinical evidence demonstrated that CRISPR-Cas9 editing of autologous hematopoietic stem and progenitor cells could increase fetal hemoglobin expression and produce clinically meaningful responses in patients with sickle cell disease and transfusion-dependent β-thalassemia [9]. This approach differs from direct correction of the pathogenic hemoglobin variant. Instead, it modifies the erythroid regulatory region of **BCL11A**, reducing repression of fetal hemoglobin and thereby compensating for abnormal adult hemoglobin production.

The clinical significance of CRISPR also expanded through direct **in vivo** genome editing. Gillmore *et al.* demonstrated that systemically administered CRISPR-Cas9 components could target the transthyretin gene in the liver of patients with hereditary transthyretin amyloidosis, producing marked reductions in circulating transthyretin [10]. This study provided important evidence that genome editing could be performed directly inside the human body rather than exclusively through ex vivo manipulation of harvested cells. The development of in vivo approaches broadened the potential therapeutic range of CRISPR but simultaneously increased the importance of delivery specificity, biodistribution, immunological responses, and control of editing activity.

The progression represented in Figure 1 culminates in the availability of stronger clinical evidence from pivotal studies. In 2024, phase 3 studies of exagamglogene autotemcel demonstrated substantial therapeutic benefit in severe sickle cell disease and transfusion-dependent β-thalassemia [11], [12]. These findings were particularly important because they represented a transition from proof-of-concept and early-stage clinical investigation toward therapeutic evidence capable of supporting integration of CRISPR-based intervention into regulated clinical practice.

Taken together, the trajectory depicted in the figure demonstrates that the development of CRISPR in clinical medicine has not occurred through a single technological event. Instead, it has resulted from successive advances in molecular programmability, genome-editing specificity, detection of unintended effects, precision-editing systems, cellular engineering, in vivo delivery, and clinical validation [1]–[18]. The progression also shows that improvements in molecular precision have occurred simultaneously with increasing clinical complexity. As CRISPR moved closer to therapeutic application, the relevant research questions expanded from whether DNA could be edited efficiently to whether such editing could be delivered safely, produce durable clinical benefits, and be incorporated into patient care.

The evidence further indicates that hematology has currently achieved one of the most advanced levels of clinical translation, largely because hematopoietic stem cells can be collected and edited ex vivo before reinfusion [9], [11], [12]. Oncology has provided important early evidence regarding engineered immune cells [7], [8], while transthyretin amyloidosis has demonstrated the feasibility of systemic in vivo genome editing [10]. These areas represent different therapeutic models and illustrate the increasing diversity of clinical CRISPR applications.

Finally, Figure 1 should be interpreted as a **chronological synthesis of major translational milestones rather than as a quantitative measure of publication volume or therapeutic efficacy**. The upward progression represents the increasing level of clinical translation observed across the selected literature, beginning with molecular discovery and

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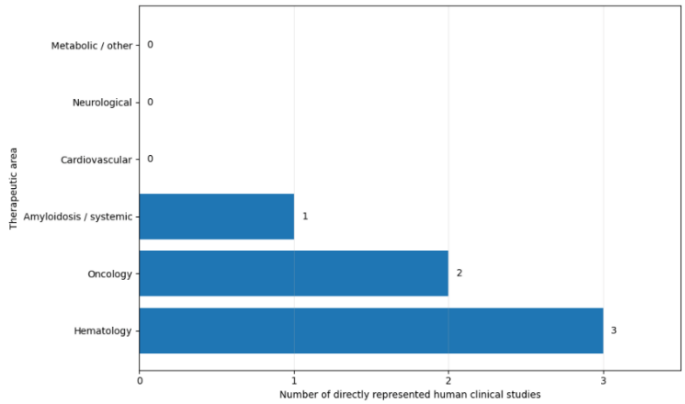
progressing through precision editing, human experimentation, direct in vivo intervention, and pivotal therapeutic evidence. The accumulated findings support the characterization of CRISPR as a technology that has undergone exceptionally rapid translational development within approximately one decade, while still retaining important limitations related to safety, delivery, durability, scalability, and equitable implementation [13]–[18].

Figure 2.
Distribution of selected human clinical evidence across therapeutic areas of CRISPR-based genome editing



The distribution presented in Figure 2 demonstrates that the human clinical evidence represented within the selected literature is not evenly distributed across therapeutic specialties. Hematology constitutes the most strongly represented area, followed by oncology and systemic hereditary amyloidosis. In contrast, cardiovascular, neurological, metabolic, and other potential applications remain less represented within the clinical studies included in the core evidence base of this review. This pattern reflects differences in the maturity of clinical translation rather than differences in the theoretical relevance of CRISPR to each specialty.

Hematology shows the highest concentration of directly represented clinical evidence, with three major studies included in the selected literature [9], [11], [12]. This predominance is explained in part by the biological and procedural characteristics of hematopoietic disorders. Hematopoietic stem and progenitor cells can be collected from the patient, genetically modified ex vivo, evaluated before administration, and subsequently reinfused. This workflow provides a level of control that is considerably more difficult to achieve when targeting cells located within solid organs or anatomically inaccessible tissues.

The study by Frangoul *et al.* provided early clinical evidence that CRISPR-Cas9-mediated editing of autologous hematopoietic stem cells could generate sustained fetal hemoglobin expression in patients with sickle cell disease and transfusion-dependent β-thalassemia [9]. The therapeutic strategy targets an erythroid-specific regulatory region of **BCL11A**, thereby reducing repression of fetal hemoglobin and compensating for defective adult hemoglobin production. The significance of this approach lies in its ability to modify a regulatory mechanism rather than directly repairing each disease-causing variant.

The later phase 3 studies of exagamglogene autotemcel strengthened this evidence. In severe sickle cell disease, the treatment produced clinically relevant control of vaso-occlusive events among evaluable patients, while in transfusion-dependent β-thalassemia a substantial proportion of treated patients achieved transfusion independence [11], [12]. These findings place hemoglobinopathies among the clearest examples of successful translation of CRISPR technology from experimental genome editing into therapeutic intervention.

Oncology represents the second most prominent field in the selected human evidence. Two studies included in the review evaluated CRISPR-engineered T lymphocytes in patients with advanced or refractory malignancies [7], [8]. These investigations demonstrated that immune cells could be edited outside the body and subsequently administered to patients, supporting the feasibility of combining CRISPR with adoptive cellular therapy.

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Stadtmauer *et al.* showed that CRISPR could be used to perform multiplex editing of human T cells for therapeutic application in patients with refractory cancer [7]. The study was particularly relevant because it demonstrated that several genomic targets could be modified within the same cell population while preserving the possibility of clinical administration and post-infusion monitoring. Lu *et al.* similarly investigated CRISPR-edited T cells in refractory non-small-cell lung cancer, providing additional evidence regarding feasibility and early safety of gene-edited immune-cell therapy [8].

However, the degree of clinical maturity observed in oncology differs from that of hematological genome editing. Cancer is biologically heterogeneous, and therapeutic effectiveness may be influenced by tumor evolution, immune escape, the tumor microenvironment, antigen variability, and the functional persistence of engineered cells. Therefore, although oncology has provided important evidence of feasibility, the available clinical experience represented in this review remains more preliminary than the evidence supporting genome editing in selected hemoglobinopathies.

The third directly represented therapeutic category is hereditary transthyretin amyloidosis. The study by Gillmore *et al.* demonstrated that intravenously administered CRISPR-Cas9 components could produce in vivo editing of the **TTR** gene in hepatocytes, resulting in substantial reductions in serum transthyretin concentrations [10]. This study was particularly important because it established a different model of therapeutic genome editing. Rather than removing and modifying cells ex vivo, the editing machinery was delivered systemically and acted directly within the patient's body.

The inclusion of transthyretin amyloidosis also illustrates the interdisciplinary nature of CRISPR-based medicine. Although the molecular target is primarily expressed in the liver, the disease can involve peripheral nerves, the heart, and other organ systems. Consequently, the application cannot be confined to a single conventional specialty and is relevant to internal medicine, neurology, cardiology, hepatology, and medical genetics. The successful reduction of a pathogenic circulating protein through in vivo genomic intervention broadened the conceptual scope of CRISPR therapy beyond diseases amenable to cellular manipulation outside the body [10].

The absence of directly represented human studies in the cardiovascular, neurological, metabolic, and other categories in Figure 2 should not be interpreted as evidence that CRISPR lacks potential within these fields. Rather, the figure is restricted to the clinical studies contained within the selected core bibliography of this review. Numerous preclinical and early translational approaches are investigating targets associated with lipid metabolism, hereditary cardiomyopathies, neurological disorders, metabolic diseases, infectious conditions, and rare genetic syndromes. The lower representation therefore reflects the stage of evidence included in the current review rather than the absence of scientific activity.

This distinction is important when interpreting the figure. The clinical translation of CRISPR is highly dependent on tissue accessibility and delivery. Diseases involving cells that can be isolated and manipulated ex vivo have progressed more rapidly because editing efficiency and cellular characteristics can be assessed before treatment. This advantage partly explains the prominence of hematology and engineered immune-cell therapies [7]–[9]. By comparison, treatment of cardiovascular or neurological diseases requires highly efficient and selective delivery to tissues within the body, where control over distribution and exposure is substantially more complex [14], [15].

The emergence of base editing and prime editing may alter this distribution in future clinical research. These platforms expand the types of genomic alterations that can be addressed and may reduce dependence on conventional double-strand DNA cleavage [5], [6]. Their clinical applicability, however, will remain dependent on effective delivery, molecular specificity, appropriate target selection, and demonstration of acceptable safety profiles. Therefore, technological capability alone does not determine how quickly a therapeutic field reaches clinical maturity.

Figure 2 also highlights the importance of distinguishing **clinical evidence from preclinical potential**. CRISPR has been investigated experimentally across a much broader range of diseases than those represented by the human studies analyzed here. Nevertheless, evidence derived from cellular models or animal studies cannot be considered equivalent to therapeutic outcomes observed in patients. For this reason, the present analysis separates areas supported by direct human clinical evidence from areas that remain predominantly developmental.

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From an international perspective, the concentration of clinical evidence in a small number of indications also reflects the complexity of bringing genome-editing interventions into clinical practice. Advanced therapies require regulatory approval, specialized manufacturing, genomic characterization, multidisciplinary clinical teams, and long-term monitoring. These requirements influence both which diseases are prioritized and which healthcare systems are capable of participating in clinical development.

The findings represented in Figure 2 therefore identify hematology as the most mature therapeutic area within the selected evidence base, followed by oncology and hereditary transthyretin amyloidosis. This distribution is consistent with the progression of CRISPR from controlled ex vivo cellular modification toward increasingly complex in vivo applications [7]–[12]. Other specialties retain substantial therapeutic potential, but the available human evidence remains less consolidated within the literature evaluated for this review.

Figure 3.

Comparative characteristics of ex vivo and in vivo CRISPR-based therapeutic strategies

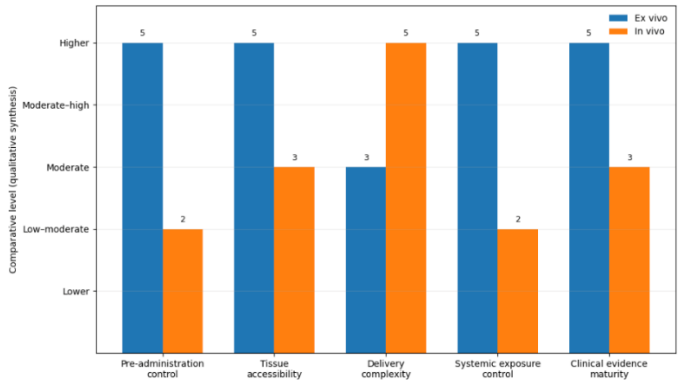

Figure 3 presents a comparative synthesis of the principal characteristics identified for ex vivo and in vivo CRISPR-based therapeutic strategies. The values represent an ordinal qualitative synthesis of the reviewed evidence rather than experimentally measured scores. Five dimensions were considered: pre-administration control, tissue accessibility, delivery complexity, control of systemic exposure, and maturity of clinical evidence. The comparison demonstrates that neither strategy is universally superior; instead, each presents characteristics that influence its suitability according to the disease, target tissue, therapeutic objective, and delivery requirements [9], [10], [14], [15].

Ex vivo editing showed the highest comparative level for pre-administration control. This characteristic derives from the possibility of obtaining target cells from the patient, modifying them under controlled laboratory conditions, evaluating the resulting cellular product, and subsequently administering the edited cells. The approach provides opportunities to assess editing efficiency, cellular viability, phenotype, and selected genomic characteristics before exposure of the patient to the final therapeutic product. This degree of control has contributed substantially to the clinical development of CRISPR in hematological disorders [9], [11], [12].

The therapeutic experience with sickle cell disease and transfusion-dependent β-thalassemia demonstrates the advantages of this model. Autologous hematopoietic stem and progenitor cells can be collected and edited to modify the erythroid regulatory region of **BCL11A**, thereby increasing fetal hemoglobin expression. The edited cellular product is subsequently reinfused following conditioning. Early clinical evidence demonstrated the feasibility of this strategy [9], while later studies provided stronger evidence of clinically meaningful outcomes [11], [12]. Consequently, the maturity of ex vivo clinical evidence was classified as higher within the comparative framework represented in the figure.

Tissue accessibility was also comparatively favorable for ex vivo strategies. This does not imply that all tissues can be treated through ex vivo editing. Rather, certain therapeutically important cell populations, particularly hematopoietic

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and immune cells, can be collected and manipulated outside the body. This accessibility has enabled CRISPR applications in both hematology and oncology. CRISPR-engineered T cells used in patients with refractory malignancies illustrate how immune cells can be genetically modified before therapeutic administration [7], [8].

However, ex vivo editing is not procedurally simple. The figure therefore assigns an intermediate level of delivery complexity to this strategy. Although direct delivery of the editing machinery to internal organs is avoided, treatment may require cell collection, specialized laboratory processing, quality control, preservation of cellular viability, reinfusion, and, in some applications, preparative conditioning. The therapeutic pathway consequently depends on advanced clinical and manufacturing infrastructure.

In vivo genome editing presents a substantially different profile. Instead of removing cells for modification, the editing components must reach the intended cells within the patient. This characteristic explains the higher delivery complexity represented in Figure 3. Successful in vivo editing requires coordination between the molecular editor and an effective delivery system capable of protecting the therapeutic components, reaching the appropriate tissue, entering target cells, and producing sufficient editing while limiting unwanted distribution [14].

The clinical study of transthyretin amyloidosis provided an important demonstration of this principle. Gillmore *et al.* administered CRISPR-Cas9 components systemically to target the **TTR** gene in hepatocytes, resulting in substantial reductions in circulating transthyretin [10]. This evidence demonstrated that direct therapeutic editing within the human body was feasible and represented an important progression beyond cell-based ex vivo strategies.

Nevertheless, the feasibility of targeting the liver does not imply that comparable delivery can be achieved in every organ. Biological barriers differ substantially between tissues. Efficient editing of hepatocytes, skeletal muscle, myocardium, central nervous system cells, pulmonary tissue, or other cellular populations requires delivery platforms adapted to their anatomical and biological characteristics. Delivery therefore remains one of the major determinants of the future expansion of in vivo genome editing [14], [15].

The figure also identifies an important difference in control of systemic exposure. In ex vivo interventions, genome-editing machinery is primarily applied to isolated cells before administration, allowing greater control over the environment in which editing occurs. In contrast, systemic in vivo administration may expose multiple tissues to the delivery platform even when the therapeutic system is designed to preferentially reach a particular organ. Consequently, biodistribution, tissue selectivity, dose, duration of exposure, and clearance become important components of safety assessment.

This distinction is particularly relevant because genomic safety involves more than classical off-target activity. Unintended editing may occur when a nuclease recognizes sequences sufficiently similar to the intended target, and methods such as GUIDE-seq have demonstrated the importance of systematically assessing these events [13]. In vivo strategies introduce an additional dimension: determining not only **where in the genome** editing occurs, but also **in which tissues and cell populations** the editing machinery is active.

The comparative maturity of clinical evidence also differs between the two strategies. Ex vivo approaches have accumulated more advanced therapeutic evidence, particularly through applications in hemoglobinopathies [9], [11], [12]. In vivo editing has demonstrated important clinical feasibility [10], but its therapeutic development remains comparatively less mature across the broader spectrum of diseases considered in this review. The distinction reflects the current evidence base rather than a permanent limitation of in vivo genome editing.

The expansion of base editing and prime editing may progressively alter this relationship. Base editors can introduce selected nucleotide conversions without conventional double-strand DNA cleavage [5], while prime editing permits a broader range of predefined genomic modifications [6]. Their potential use in vivo is particularly relevant for diseases in which target cells cannot be readily collected and manipulated outside the body. Nevertheless, these molecular systems still require delivery technologies capable of transporting relatively complex editing machinery to the correct tissue.

The comparison further demonstrates why disease selection is fundamental in therapeutic genome editing. For a disorder affecting hematopoietic cells, an ex vivo strategy may offer substantial advantages because the target

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population is accessible and can be manipulated before administration. For a disease caused by hepatic production of a pathogenic protein, direct in vivo intervention may provide a more appropriate therapeutic model. The characteristics of the disease therefore determine whether the advantages of cellular control outweigh the procedural complexity of ex vivo treatment or whether direct tissue targeting justifies the additional delivery challenges of in vivo editing.

From a translational perspective, these differences also influence infrastructure requirements. Ex vivo therapies depend heavily on cell-processing facilities, specialized manufacturing, conditioning protocols, and multidisciplinary clinical management. In vivo approaches may eventually reduce some aspects of individualized cellular manufacturing, but they require sophisticated delivery technologies and rigorous assessment of biodistribution and systemic safety. These distinct requirements are relevant when considering future implementation across healthcare systems with different levels of genomic and therapeutic infrastructure.

The values displayed in the figure should therefore be interpreted as a **comparative qualitative synthesis of the reviewed evidence**, not as quantitative clinical efficacy or safety measurements. Their purpose is to summarize the relative characteristics consistently identified across the literature and to demonstrate how the route of genome editing influences the pathway from molecular intervention to clinical application [13]–[18].

Figure 4.

Principal challenges affecting the clinical translation of CRISPR-based genome editing

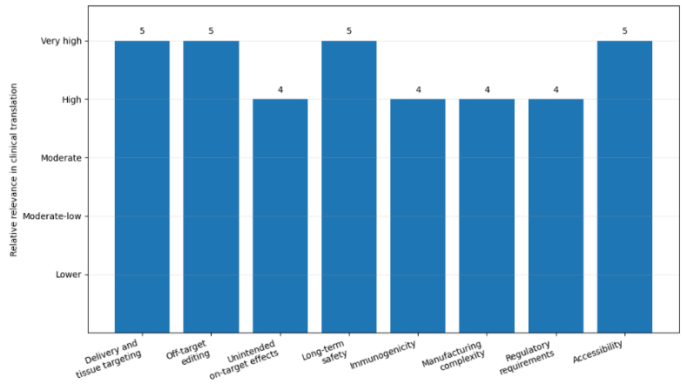

Figure 4 summarizes the principal challenges identified across the reviewed evidence that influence the transition of CRISPR-based genome editing from experimental and translational research to broader clinical application. Delivery and tissue targeting, off-target editing, long-term safety, and accessibility were classified as challenges of very high relative relevance, while unintended on-target effects, immunogenicity, manufacturing complexity, and regulatory requirements were classified as highly relevant. These levels represent an ordinal qualitative synthesis of the literature and should not be interpreted as numerical estimates of risk, incidence, or probability of adverse outcomes.

Delivery and tissue targeting emerged as one of the most important technological limitations. Genome editing requires the therapeutic machinery to reach a sufficient proportion of the appropriate cells while maintaining biological activity and minimizing exposure of tissues that are not intended to be modified. The problem is comparatively manageable in some ex vivo strategies because target cells can be isolated and manipulated under controlled conditions. In contrast, in vivo editing depends on delivery platforms capable of navigating biological barriers and achieving adequate tissue selectivity [14], [15].

The clinical experience with hereditary transthyretin amyloidosis demonstrated that systemic delivery can produce therapeutically relevant genome editing in humans. Targeting hepatocytes allowed CRISPR-Cas9 components to modify the **TTR** gene and reduce circulating transthyretin [10]. However, the feasibility of hepatic targeting cannot be generalized to other organs. The central nervous system, myocardium, skeletal muscle, lungs, kidneys, and other

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tissues present distinct anatomical and cellular barriers, making delivery a disease- and tissue-specific problem rather than a universal technical procedure.

Off-target editing was also classified among the challenges of very high relevance. CRISPR nucleases are designed to recognize specific genomic sequences, but interactions with sufficiently similar sequences can result in unintended cleavage. The development of GUIDE-seq and related genome-wide analytical approaches has enabled more systematic detection of potential off-target activity [13]. Improvements in guide design, computational prediction, engineered Cas proteins, and transient delivery have contributed to greater specificity, but safety evaluation remains necessary for each therapeutic product and genomic target.

Importantly, genomic safety cannot be reduced exclusively to off-target events. Modifications at the intended genomic locus may also generate outcomes different from the desired edit. DNA repair after nuclease-induced cleavage can produce heterogeneous insertions and deletions, and the biological consequences of editing may vary according to cell type and genomic context. This distinction explains the separate inclusion of unintended on-target effects in Figure 4. A therapy may demonstrate high target specificity while still requiring detailed characterization of the genomic alterations produced at that target.

Base editing and prime editing were developed partly to expand editing precision and reduce dependence on conventional double-strand DNA breaks [5], [6]. Base editors enable defined nucleotide conversions, while prime editors can introduce a broader range of substitutions, insertions, and deletions. These technologies provide important alternatives to nuclease-based editing, but they do not eliminate the requirement for safety evaluation. Unwanted nucleotide conversions, editing at unintended sites, variable efficiency, and delivery limitations remain relevant considerations [5], [6], [16], [17].

Long-term safety was classified as another challenge of very high relevance. Unlike medications whose pharmacological effects generally decline after discontinuation, successful genome editing may produce persistent modifications within treated cells. This durability is one of the principal therapeutic advantages of the technology, but it also means that unexpected biological consequences could persist for prolonged periods. Long-term follow-up is therefore particularly important when edited stem-cell populations are capable of self-renewal or when genomic modifications are intended to remain throughout the patient's lifetime [15], [18].

The available clinical evidence in hemoglobinopathies demonstrates the potential for sustained therapeutic benefit after ex vivo editing [9], [11], [12]. Nevertheless, increasing duration of follow-up remains important for evaluating persistence of therapeutic effects and identifying uncommon or delayed complications. The relative novelty of clinical CRISPR means that long-term evidence extending over several decades is inherently more limited than that available for established pharmacological treatments.

Immunogenicity was categorized as highly relevant. CRISPR-associated proteins originate from bacterial systems and may be recognized by the human immune system. Delivery vehicles may also generate immune responses depending on their composition, route of administration, dose, and previous exposure of the patient. Immunological considerations are especially relevant for in vivo approaches because editing components interact directly with the patient's biological environment. The significance of immune responses may vary considerably among technologies, making product-specific assessment necessary [14], [15].

Manufacturing complexity represents a different type of translational challenge. Ex vivo therapies require collection of patient cells, genome editing, processing under controlled manufacturing conditions, quality assessment, and subsequent administration. In hematopoietic applications, treatment may additionally require mobilization of stem cells and conditioning before reinfusion [9], [11], [12]. Such procedures are considerably more complex than conventional outpatient pharmacotherapy and require specialized infrastructure and trained multidisciplinary teams.

The manufacturing challenge also affects scalability. Autologous approaches produce a therapeutic product from the individual patient's own cells, which can increase logistical complexity compared with standardized medicines manufactured in large batches. Genome-editing strategies capable of producing standardized cellular products or more efficient in vivo delivery could modify this situation in the future, but clinical feasibility must continue to be established through appropriate evidence.

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Regulatory requirements were similarly identified as highly relevant. Genome-editing therapies combine characteristics of genetic medicines, advanced biological products, and, in some cases, cellular therapies. Regulatory evaluation must therefore consider product manufacturing, molecular specificity, potency, genomic integrity, clinical benefit, adverse effects, durability, and long-term surveillance. As technologies evolve from conventional Cas9 editing toward base and prime editing, regulatory frameworks must also accommodate mechanisms that differ substantially in their molecular actions [5], [6], [16].

The ethical dimension intersects with regulatory evaluation because genome editing can generate persistent genetic changes. International governance frameworks emphasize responsible oversight, transparency, scientific validity, appropriate risk-benefit assessment, and mechanisms to prevent inappropriate applications of human genome editing [19], [20]. The distinction between somatic and heritable genome editing remains particularly important because modifications capable of transmission to future generations involve substantially different scientific and ethical considerations.

Accessibility was classified as a challenge of very high relevance because clinical efficacy alone does not determine population-level availability. Genome-editing therapies may require molecular diagnosis, sequencing, specialized treatment centers, advanced manufacturing, multidisciplinary clinical management, and prolonged surveillance. These requirements may restrict access even after a therapy has demonstrated clinical effectiveness.

This challenge has particular relevance to the international and Latin American context. Countries and healthcare systems differ substantially in genomic infrastructure, research capacity, availability of specialized centers, regulatory experience, financing mechanisms, and access to molecular diagnostics. Consequently, the transition from successful clinical trials to routine care may occur at different rates across regions. The therapeutic potential of CRISPR therefore coexists with practical barriers that can influence which populations receive access to these technologies.

The challenges represented in Figure 4 are also interconnected. Improvements in delivery can reduce systemic exposure but may introduce new manufacturing requirements. Increased editing precision can reduce certain genomic risks while creating more complex molecular products. Long-term surveillance strengthens safety assessment but requires healthcare infrastructure capable of maintaining patient follow-up. Regulatory rigor supports responsible implementation but must adapt continuously to rapidly evolving technologies [13]–[20].

Figure 5.

International landscape of CRISPR clinical translation and implementation readiness

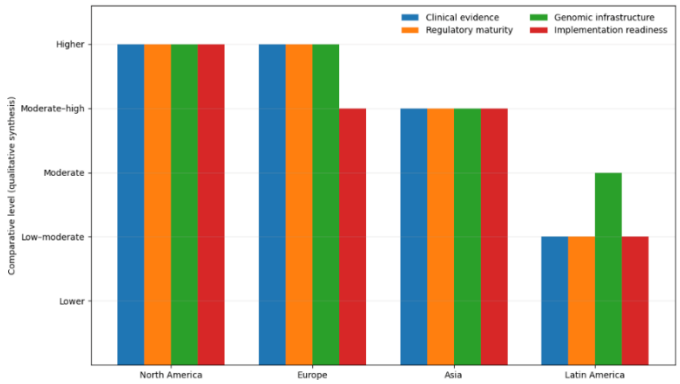

Figure 5 summarizes the international landscape of CRISPR-based genome editing across four broad regions—North America, Europe, Asia, and Latin America—using four dimensions relevant to clinical translation: clinical evidence, regulatory maturity, genomic infrastructure, and implementation readiness. The comparative levels represent an ordinal qualitative synthesis of the evidence reviewed and are intended to describe broad patterns rather than provide numerical measurements of regional performance.

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North America showed the highest comparative level across the four dimensions considered. The region has played a central role in the development of CRISPR technologies, from foundational genome-engineering research to clinical studies and the development of advanced therapeutic products [2], [3], [7], [9], [11], [12]. The presence of established genomic research networks, biotechnology industries, specialized clinical centers, and regulatory structures has facilitated the transition from laboratory research toward human therapeutic application.

The clinical evidence represented in the review also reflects this concentration. Studies involving CRISPR-engineered T cells, hematopoietic stem-cell editing, and advanced therapeutic development have included institutions and research programs located in the United States [7], [9], [11], [12]. These studies contributed to the demonstration that CRISPR-based interventions could move from experimental genome manipulation toward clinically meaningful therapeutic strategies.

Europe demonstrated a similarly high level of scientific and regulatory maturity. European research institutions have contributed substantially to molecular genetics, advanced therapies, clinical trials, and regulatory evaluation of gene-based medicinal products. The region also possesses established frameworks for the assessment of advanced therapy medicinal products, creating an environment in which genome-editing therapies can be evaluated within existing regulatory structures.

The slightly lower comparative level assigned to European implementation readiness reflects the distinction between regulatory capacity and uniform clinical availability. Even within regions with mature regulatory systems, access to complex genomic therapies may vary among countries because healthcare financing, specialized infrastructure, reimbursement, treatment-center availability, and national implementation policies are not identical. Therefore, regulatory authorization does not necessarily translate immediately into equivalent access across all healthcare systems.

Asia also demonstrated substantial participation in the development of CRISPR-based medicine. Early clinical investigations of CRISPR-edited T cells in refractory non-small-cell lung cancer provided evidence of the feasibility of therapeutic genome editing in China [8]. The region has considerable research capacity in genomics, biotechnology, cellular therapy, and precision medicine, although scientific and regulatory conditions vary markedly among individual countries.

The Asian context is particularly relevant to the international development of genome editing because rapid scientific expansion has occurred alongside intense debate regarding governance of human genomic intervention. These experiences reinforce the importance of internationally coordinated standards that distinguish responsible somatic therapeutic research from applications involving heritable human genome modification. WHO governance frameworks emphasize the need for transparency, oversight, international collaboration, and mechanisms capable of addressing activities that may cross national regulatory boundaries [19], [20].

Latin America displayed a different pattern. Genomic infrastructure was positioned above the other regional dimensions in the qualitative synthesis, reflecting the existence of universities, research centers, sequencing capacity, biomedical laboratories, and professional expertise capable of supporting genomic research in parts of the region. However, clinical evidence, regulatory maturity specifically related to advanced genome editing, and readiness for broad therapeutic implementation were comparatively less developed within the literature considered.

This pattern should not be interpreted as an absence of scientific capacity in Latin America. The region contains heterogeneous healthcare and research systems, and several countries have developed substantial capabilities in genetics, molecular biology, bioinformatics, rare-disease diagnosis, transplantation, oncology, and advanced biomedical research. Nevertheless, the transition from genomic research to routine therapeutic genome editing requires additional components, including specialized manufacturing, validated genomic diagnostics, regulatory expertise in advanced therapies, long-term patient surveillance, and sustainable financing.

The difference between genomic infrastructure and implementation readiness is particularly important. Sequencing a genome, identifying a pathogenic variant, or conducting molecular research requires substantial technical capacity, but administering an individualized genome-editing therapy introduces additional clinical and organizational demands. Ex vivo interventions may require collection of hematopoietic cells, specialized processing, genome editing, quality

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control, conditioning, reinfusion, and prolonged monitoring [9], [11], [12]. These requirements can limit implementation to highly specialized centers even in countries with established genomic laboratories.

In vivo therapies introduce a different set of requirements. The clinical evidence obtained in hereditary transthyretin amyloidosis demonstrates the feasibility of systemic genome editing [10], but broader application depends on highly specialized delivery technologies, molecular monitoring, safety assessment, and regulatory oversight. Consequently, adoption of in vivo editing in Latin America would depend not only on the availability of genomic diagnostics but also on access to advanced therapeutic platforms and the institutional capacity to monitor their long-term effects.

The international comparison also highlights the importance of population representation. Genome editing depends on accurate molecular diagnosis and characterization of pathogenic variants. Genomic databases have historically contained unequal representation of global populations, which can influence variant interpretation and the identification of clinically relevant genetic alterations. Greater inclusion of Latin American populations in genomic research is therefore relevant to the future development of precision medicine and gene-editing therapies.

Latin American populations are genetically heterogeneous, reflecting varying contributions from Indigenous American, European, African, Asian, and other ancestral populations. This diversity has implications for genomic medicine because pathogenic variants, allele frequencies, pharmacogenomic characteristics, and genetic modifiers may differ between populations. Increasing regional genomic research can therefore strengthen the scientific basis for evaluating whether therapeutic strategies developed in other populations can be appropriately applied to Latin American patients.

The international pattern represented in Figure 5 also demonstrates that clinical translation depends on more than scientific discovery. The foundational molecular mechanisms of CRISPR are internationally reproducible, but therapeutic implementation occurs within healthcare systems with different economic resources, regulatory structures, clinical infrastructure, and research capacities. Consequently, the same genome-editing technology may reach clinical practice at substantially different rates across regions.

Regulatory maturity represents a particularly important component of this process. Genome-editing therapies require assessment of molecular specificity, manufacturing quality, delivery, potential off-target modifications, clinical efficacy, durability, and long-term safety [13]–[18]. Regulatory agencies must therefore combine expertise in genetics, cellular therapy, pharmacology, toxicology, bioinformatics, and clinical medicine. Building this capacity is relevant for regions seeking to participate actively in advanced genomic medicine rather than depending exclusively on regulatory decisions generated elsewhere.

International governance adds another layer to this process. WHO recommendations emphasize that human genome editing requires mechanisms that promote responsible research, scientific transparency, appropriate oversight, and equitable consideration of potential benefits and risks [19], [20]. Such principles are particularly important as genome-editing technologies become increasingly accessible to laboratories worldwide and therapeutic development becomes more geographically distributed.

The comparative regional differences observed in Figure 5 therefore describe different stages of translational development rather than fixed technological divisions. North America and Europe currently show a stronger combination of clinical evidence, regulatory experience, infrastructure, and implementation capacity, while Asia demonstrates substantial scientific and clinical development with considerable internal heterogeneity. Latin America possesses emerging genomic capacity but continues to face important challenges in translating that capacity into widespread access to advanced genome-editing therapies.

As with the preceding comparative figures, the levels shown in Figure 5 should not be interpreted as measured regional indices or formal rankings. They represent a **qualitative synthesis of the international translational context described by the evidence analyzed in this review**, providing a structured visualization of regional differences that will be examined more critically in the discussion.

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DISCUSSION

The findings of this review demonstrate that CRISPR-based genome editing has undergone an unusually rapid transition from molecular discovery to clinical application. Within slightly more than a decade, the field progressed from programmable RNA-guided DNA cleavage [1] to human genome engineering [2], [3], increasingly precise editing platforms [5], [6], therapeutic modification of human cells [7]–[9], direct in vivo intervention [10], and pivotal clinical evidence supporting genome-editing therapies for selected hematological diseases [11], [12]. This trajectory suggests that CRISPR has moved beyond its original role as an experimental biotechnology and has entered a new stage in which its clinical value must be assessed according to therapeutic benefit, safety, durability, feasibility, and accessibility.

One of the most relevant findings was the unequal distribution of clinical maturity among therapeutic areas. Hematology currently represents the clearest example of successful translation, particularly in sickle cell disease and transfusion-dependent β-thalassemia [9], [11], [12]. This predominance is not attributable exclusively to the molecular effectiveness of CRISPR-Cas9. Hematopoietic stem and progenitor cells provide a particularly favorable therapeutic model because they can be collected, genetically modified ex vivo, characterized before administration, and reinfused into the patient. Thus, the biological accessibility of the target cell has been almost as important as the availability of the editing technology itself.

The success of exagamglogene autotemcel is particularly relevant because it demonstrates that therapeutic genome editing does not necessarily require direct correction of the pathogenic mutation. Modification of the erythroid regulatory region of **BCL11A** increases fetal hemoglobin expression and functionally compensates for defective adult hemoglobin [9], [11], [12]. This strategy illustrates a broader principle for genomic medicine: therapeutic targets may include regulatory pathways and genetic modifiers rather than only the primary disease-causing sequence. Such an approach could expand the number of diseases amenable to genome editing when direct variant correction is technically difficult or when multiple pathogenic variants produce a common phenotype.

Nevertheless, the clinical success observed in hemoglobinopathies should not be generalized to all genetic diseases. Ex vivo treatment involves complex procedures that may include stem-cell collection, individualized manufacturing, conditioning, reinfusion, and prolonged follow-up. Consequently, a highly effective molecular intervention can remain difficult to implement at scale. The therapeutic performance of genome editing must therefore be distinguished from the feasibility of delivering the entire treatment pathway to eligible patients.

The comparison between ex vivo and in vivo strategies further supports this interpretation. Ex vivo editing currently provides greater control over the cellular product and has accumulated more mature clinical evidence, whereas in vivo editing offers the possibility of treating tissues that cannot be practically removed and manipulated outside the body. The results reported for hereditary transthyretin amyloidosis represented an important milestone because systemic administration of CRISPR-Cas9 components demonstrated that direct editing of human tissues could produce a substantial biological effect [10].

In vivo editing may ultimately have broader clinical implications because many disorders encountered in internal medicine involve organs that cannot be treated through conventional ex vivo cellular manipulation. Cardiovascular, hepatic, metabolic, neurological, and multisystem hereditary diseases could theoretically benefit from direct genomic intervention. However, this potential depends heavily on delivery. A molecular editor can only produce therapeutic benefit when it reaches the appropriate cells in sufficient quantities and with adequate specificity [14], [15]. For this reason, future advances in delivery systems may influence clinical expansion as strongly as improvements in the editing enzymes themselves.

The development of base editing and prime editing also changes the therapeutic framework established by conventional CRISPR-Cas9. Base editing enables selected nucleotide conversions without conventional double-strand DNA cleavage [5], while prime editing permits a wider variety of predefined substitutions, insertions, and deletions [6]. These technologies potentially increase the number of pathogenic variants that can be addressed and may reduce some consequences associated with double-strand breaks. However, they should not be considered intrinsically risk-free.

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Their clinical value will depend on editing specificity, efficiency, delivery, molecular consequences, and evidence obtained through appropriately designed studies [16], [17].

Safety therefore remains one of the central issues identified by this review. Off-target activity has received considerable attention since genome-wide detection methods demonstrated that CRISPR nucleases may interact with unintended genomic sites [13]. Improvements in guide design, engineered nucleases, computational prediction, and transient delivery have increased control over editing, but therapeutic safety cannot be reduced to the absence of detectable off-target cleavage. Unintended alterations may also occur at the intended locus, and their biological significance may depend on the affected cell population and genomic context.

Long-term safety deserves particular consideration because genomic interventions are designed to produce durable biological effects. In conventional pharmacotherapy, treatment can often be discontinued when adverse effects occur, whereas successful genome editing may generate persistent changes within long-lived cells. This characteristic is therapeutically attractive but increases the importance of long-term surveillance. The current evidence supporting CRISPR therapies is clinically significant [9]–[12], yet the relatively recent introduction of these interventions means that several decades of longitudinal observation are not yet available. Continued follow-up will therefore remain essential even after short- and medium-term efficacy has been established.

Oncology illustrates both the versatility and the complexity of CRISPR-based medicine. Early clinical studies demonstrated that edited T cells could be manufactured and administered to patients with refractory malignancies [7], [8]. However, cancer differs substantially from monogenic disorders because tumor heterogeneity, clonal evolution, immune escape, and the tumor microenvironment can influence therapeutic response. Genome editing may therefore become particularly valuable as a component of engineered cellular immunotherapy rather than as an isolated intervention.

Another major implication concerns the relationship between CRISPR and precision medicine. Genome editing depends on accurate identification of molecular targets, making genomic diagnosis increasingly relevant to therapeutic decision-making. As editing technologies become more specific, the capacity to distinguish pathogenic variants, regulatory abnormalities, and disease-modifying pathways will become increasingly important. Consequently, the future clinical development of CRISPR will likely occur alongside advances in sequencing, functional genomics, bioinformatics, molecular diagnostics, and individualized therapeutic design.

However, this relationship introduces an important equity problem. A patient cannot benefit from a genotype-specific therapy when molecular diagnosis is unavailable, and a healthcare system cannot implement advanced genome editing without appropriate laboratory, clinical, regulatory, and financial infrastructure. Therefore, disparities in genomic medicine may arise before the therapeutic intervention itself. Unequal access to sequencing, genetic counseling, specialized diagnostics, clinical trials, and treatment centers can determine which populations ultimately benefit from genome-editing technologies.

This issue is particularly relevant to Latin America. The region should not be considered scientifically peripheral to the development of genomic medicine, as several countries possess established capabilities in genetics, molecular biology, bioinformatics, clinical research, oncology, transplantation, and rare-disease diagnosis. Nevertheless, regional capacity is heterogeneous, and the implementation of advanced genome-editing therapies may be limited by differences in infrastructure, funding, regulatory preparedness, specialized manufacturing, and long-term clinical monitoring.

Greater Latin American participation is also necessary from a scientific perspective. Genomic databases and biomedical research have historically underrepresented several populations. Given the complex ancestral diversity of Latin America, increasing regional representation is relevant for variant interpretation, identification of disease-associated genetic patterns, and evaluation of precision therapies. A future in which genome-editing interventions are developed primarily from genomic information derived from limited populations could reproduce existing disparities in precision medicine.

International collaboration may therefore play an important role in reducing these differences. Collaboration should extend beyond access to finished therapeutic products and include genomic research, clinical trial participation,

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technology transfer, professional training, regulatory development, bioinformatics capacity, and representation in international governance. Such participation could allow Latin American institutions to contribute actively to the generation of evidence rather than functioning solely as eventual recipients of technologies developed elsewhere.

The ethical challenges identified in this review become increasingly important as technical capability expands. Somatic genome editing can be evaluated within established principles of therapeutic risk, benefit, autonomy, and informed consent, although the durability and novelty of genomic interventions introduce additional considerations. Heritable genome editing presents a fundamentally different problem because modifications could affect individuals who cannot consent and potentially persist across generations. WHO governance frameworks therefore emphasize responsible oversight, transparency, international coordination, and mechanisms capable of addressing inappropriate applications [19], [20].

The distinction between treatment and enhancement is similarly relevant. The increasing precision of genome editing could eventually make it technically possible to modify biological characteristics unrelated to the treatment of serious disease. Scientific capability alone does not determine whether an intervention is medically justified. Decisions regarding acceptable applications require consideration of clinical necessity, proportionality of risk, autonomy, justice, social consequences, and international governance.

Accessibility represents perhaps the strongest point at which clinical, economic, and ethical considerations converge. A genome-editing therapy may produce durable therapeutic benefit but still have limited global impact when its implementation requires infrastructure available only in highly specialized healthcare systems. The international differences identified in this review suggest that successful development of CRISPR does not automatically guarantee equitable implementation. The benefits of genomic medicine could become concentrated among populations with access to molecular diagnostics, advanced treatment centers, financing, and long-term monitoring unless accessibility is incorporated into translational planning.

The findings also indicate that the future of CRISPR will probably not be defined by a single editing platform. Conventional CRISPR-Cas9, engineered nucleases, base editors, prime editors, transcriptional modulation, and future technologies may coexist, with selection determined by the molecular mechanism of each disease [5], [6], [16], [17]. The relevant clinical question may therefore shift from whether CRISPR can treat a disease to which editing strategy provides the most appropriate balance between precision, therapeutic effect, delivery feasibility, and risk.

Several limitations should be considered when interpreting this review. The field is evolving rapidly, and the maturity of evidence differs substantially among therapeutic areas. Direct comparison between early-phase studies, pivotal trials, molecular investigations, and technological studies is inherently limited by methodological heterogeneity. Furthermore, clinical evidence remains concentrated in selected diseases, and several promising applications are supported primarily by preclinical or early translational research. The regional comparison should also be interpreted cautiously because research capacity and healthcare infrastructure vary considerably within North America, Europe, Asia, and Latin America, preventing broad regional categories from representing every country or institution.

Despite these limitations, the evidence consistently demonstrates that CRISPR has crossed an important threshold in clinical medicine. The central challenge is no longer demonstrating that targeted human genome editing is technically possible. The emerging challenge is determining where it provides a meaningful advantage over existing therapies, how its genomic and long-term safety can be established, which delivery systems can expand its therapeutic reach, and how healthcare systems can incorporate these interventions responsibly.

CRISPR-based genome editing therefore represents both a therapeutic opportunity and a test of the capacity of modern medicine to translate molecular innovation responsibly. Its future clinical relevance will depend on maintaining a balance between technological progress and rigorous evidence, between therapeutic durability and long-term safety, and between innovation and equitable access. The experience accumulated in hematology, oncology, and transthyretin amyloidosis provides an important foundation [7]–[12], but broader clinical integration will require continued technological refinement, international research collaboration, regulatory adaptation, ethical oversight, and inclusion of diverse populations and healthcare systems, including those of Latin America.

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CONCLUSION

CRISPR-based genome editing has evolved from a programmable molecular tool into a clinically relevant therapeutic platform capable of modifying disease-associated genetic mechanisms with potentially durable effects. The evidence analyzed in this review demonstrates that this transition has been driven by the progressive refinement of CRISPR-Cas systems, the development of base and prime editing, improvements in delivery strategies, and the accumulation of human clinical evidence. These advances have expanded genome editing beyond experimental genetics and established its relevance to clinical medicine, precision therapeutics, and the future management of genetically influenced diseases.

Among the therapeutic areas examined, hematology currently presents the strongest evidence of clinical translation. The experience obtained in sickle cell disease and transfusion-dependent β-thalassemia demonstrates that ex vivo modification of autologous hematopoietic stem and progenitor cells can generate clinically meaningful and sustained therapeutic effects [9], [11], [12]. These findings provide an important proof of principle that modifying a disease-associated genetic or regulatory pathway can alter the clinical course of severe inherited disorders.

Clinical investigations in oncology and hereditary transthyretin amyloidosis have further expanded the therapeutic scope of CRISPR. Engineered T-cell approaches demonstrated the feasibility of integrating genome editing with cellular immunotherapy [7], [8], while direct in vivo editing of the **TTR** gene established that systemic administration of genome-editing components can produce measurable biological effects within human tissues [10]. Together, these developments indicate that the future of therapeutic genome editing will include both ex vivo and in vivo strategies selected according to disease biology, target-cell accessibility, and delivery requirements.

Nevertheless, broader clinical implementation remains constrained by important challenges. Off-target modifications, unintended on-target alterations, immunogenicity, delivery efficiency, tissue specificity, manufacturing complexity, and uncertainty regarding long-term effects require continued investigation [13]–[18]. The durability that makes genome editing therapeutically attractive simultaneously increases the importance of genomic characterization and long-term clinical surveillance. Future development should therefore prioritize therapeutic benefit alongside molecular precision and sustained safety.

Base editing, prime editing, engineered CRISPR systems, and emerging delivery technologies may progressively expand the range of treatable genetic abnormalities [5], [6], [16], [17]. Their development suggests that genome editing will increasingly move toward disease-specific platforms in which the selected molecular strategy is adapted to the pathogenic mechanism rather than applying a single editing approach across different conditions. Integration with genomic diagnostics, bioinformatics, and precision medicine will be essential to this process.

The ethical and regulatory dimensions of genome editing are equally important. Somatic therapeutic editing and heritable genomic modification involve substantially different implications, and technological capability should not be interpreted as sufficient justification for clinical use. Patient autonomy, informed consent, proportionality between benefits and risks, long-term monitoring, scientific transparency, and international oversight must accompany technological development. International governance frameworks provide an essential foundation for responsible progress while recognizing that regulatory approaches will require continuous adaptation as editing technologies evolve [19], [20].

Equitable access represents another central challenge. Advanced genomic therapies depend on molecular diagnosis, specialized infrastructure, trained professionals, regulatory capacity, and sustainable financing. Without strategies to address these requirements, the therapeutic benefits of CRISPR could remain concentrated in a limited number of institutions and healthcare systems. Clinical success should therefore be evaluated not only by the capacity to produce a desired genomic modification but also by the possibility of delivering safe and effective treatment to the populations that may benefit from it.

Within this context, Latin America has an important opportunity to participate actively in the development of genomic medicine. Strengthening regional genomic research, population representation, professional education, clinical infrastructure, regulatory preparedness, international collaboration, and access to molecular diagnostics will be necessary for the region to contribute to and benefit from future genome-editing therapies. The genetic diversity of

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Latin American populations further reinforces the importance of regional participation in generating genomic evidence applicable to diverse patients.

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