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Review Article

CRISPR-Cas9 in Human Health: A Scoping Review of Therapeutic Applications, Safety Challenges, and Ethical Frameworks

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ABSTRACT

Background: CRISPR-Cas9 has revolutionized genome editing by providing an efficient, versatile, and comparatively accessible platform for targeted genetic modification. Its rapid progression from laboratory innovation to clinical application has generated substantial interest across multiple therapeutic domains, while simultaneously raising significant safety, ethical, and regulatory concerns.

Objective: This scoping review aimed to comprehensively map current evidence regarding the therapeutic applications, safety challenges, and ethical frameworks associated with CRISPR-Cas9 in human health.

Methods: A scoping review methodology guided by the Arksey and O'Malley framework and PRISMA-ScR guidelines was employed. Comprehensive searches were conducted across PubMed, Dimensions, and Embase for peer-reviewed English-language studies published between 2015 and 2026. Eligible studies focused on CRISPR-Cas9 applications in human health, including therapeutic interventions, safety evaluations, ethical analyses, and regulatory considerations. A total of 32 studies met the inclusion criteria and underwent thematic synthesis.

Results: CRISPR-Cas9 demonstrated substantial therapeutic promise across hematologic disorders, metabolic diseases, ophthalmologic conditions, oncology, immunotherapy, and rare genetic disorders. The most clinically advanced applications were observed in sickle cell disease, β-thalassemia, hereditary transthyretin amyloidosis, and hereditary angioedema, where clinical trials showed durable and potentially curative outcomes. However, major barriers remain, including off-target effects, genomic instability, delivery inefficiencies, immunogenicity, and limited long-term safety data. Ethical and regulatory concerns were prominent, particularly regarding germline editing, health equity, global governance, and accessibility.

Conclusion: CRISPR-Cas9 has demonstrated considerable clinical potential across a range of therapeutic applications, particularly for selected monogenic disorders in which the strongest clinical evidence is currently available. Although important advances have been achieved, broader clinical implementation will require continued improvements in editing precision, long-term safety evaluation, delivery technologies, ethical oversight, equitable access, and harmonized regulatory frameworks.

Keywords: CRISPR-Cas9; Genome Editing; Precision Medicine; Therapeutic Applications; Ethical Challenges

Introduction

Background to Gene Editing

Gene editing has emerged as one of the most transformative advances in modern biotechnology and medicine. It involves the precise modification of genetic material to correct mutations, regulate gene expression, or introduce beneficial genetic changes. Earlier genome-editing technologies such as Zinc Finger Nucleases (ZFNs) and Transcription Activator-Like Effector Nucleases (TALENs) provided important foundations for targeted DNA modification; however, their complexity, high cost, and limited efficiency restricted widespread clinical application (Aljabali et al., 2024).

The development of Clustered Regularly Interspaced Short Palindromic Repeats-associated protein 9 (CRISPR-Cas9) revolutionized genome engineering by providing a simpler, faster, and more efficient approach to gene editing. Adapted from a natural bacterial immune defense system, CRISPR-Cas9 enables precise targeting and modification of specific DNA sequences using guide RNA and the Cas9 nuclease enzyme. Its simplicity, affordability, and versatility have accelerated its adoption across biomedical research and therapeutic development(Khare et al., 2023).

CRISPR-Cas9 in Human Health

CRISPR-Cas9 has demonstrated enormous potential in the treatment of both inherited and acquired diseases. Inherited disorders such as sickle cell disease, β-thalassemia, cystic fibrosis, and Duchenne muscular dystrophy have become major targets for CRISPR-based therapies aimed at correcting disease-causing mutations. In oncology, CRISPR technology has contributed to the advancement of precision medicine and cancer immunotherapy, particularly through the development of engineered immune-cell therapies such as CAR-T therapy(Kolanu, 2024).

The technology has also shown promise in the treatment of infectious diseases, including HIV and hepatitis B virus infections, while emerging applications in regenerative medicine and stem-cell therapy continue to expand its clinical relevance. These developments position CRISPR-Cas9 as a promising tool in personalized medicine and future therapeutic innovation.

Safety Challenges

Despite its therapeutic promise, CRISPR-Cas9 raises significant safety concerns that continue to limit its widespread clinical implementation. One of the major challenges involves off-target effects, where unintended genetic modifications occur outside the intended target site, potentially resulting in harmful mutations or genomic instability. Additional concerns include immune responses to CRISPR components, inefficient delivery systems, mosaicism, and uncertainties regarding the long-term effects of genome editing (Uddin et al., 2020).

These challenges highlight the need for rigorous safety evaluation and optimization before CRISPR-Cas9 therapies can achieve broader clinical application.

Ethical and Regulatory Concerns

Beyond scientific limitations, CRISPR-Cas9 has generated major ethical and regulatory debates. Germline editing, which introduces heritable genetic changes, has raised concerns regarding human enhancement, designer babies, informed consent, and social inequality. Ethical concerns surrounding accessibility and potential misuse of gene-editing technologies have further intensified global discussions on responsible governance.

Regulatory approaches to CRISPR-Cas9 vary across countries, with some permitting limited research while others imposing strict restrictions on human germline editing. International organizations such as the World Health Organization (WHO) continue to emphasize the importance of ethical oversight and global cooperation in regulating human gene-editing practices (Wiley et al., 2025).

Rationale for the Scoping Review

The rapid growth of CRISPR-Cas9 research has produced a large and diverse body of literature spanning therapeutic applications, safety concerns, and ethical implications. Given the multidisciplinary and evolving nature of the field, there is a need to comprehensively map existing evidence and identify research gaps. A scoping review is therefore appropriate for synthesizing current knowledge and providing an overview of emerging trends, challenges, and future directions associated with CRISPR-Cas9 in human health.

Aim and Objectives

Aim

This scoping review aims to map current evidence on the therapeutic applications, safety challenges, and ethical frameworks associated with CRISPR-Cas9 in human health.

Objectives

1. To identify therapeutic applications of CRISPR-Cas9 in human health.
2. To examine safety challenges associated with CRISPR-Cas9 technologies.
3. To explore ethical and regulatory frameworks guiding the use of CRISPR-Cas9 in healthcare and biomedical research.

Methodology

Study Design

This study employed a scoping review design to systematically map and synthesize the breadth of available evidence regarding the therapeutic applications, safety challenges, ethical considerations, and regulatory frameworks associated with CRISPR-Cas9 in human health. A scoping review methodology was selected because of the rapidly evolving, multidisciplinary, and heterogeneous nature of CRISPR-Cas9 research, which spans preclinical experimentation, translational medicine, clinical trials, ethical scholarship, and policy development. The review was conducted in accordance with the methodological framework proposed by Arksey and O'Malley, with refinements from Levac et al. to strengthen methodological rigor, transparency, and reproducibility. Reporting was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. No formal review protocol was prospectively registered before conducting this scoping review.

Eligibility Criteria

Studies were considered eligible for inclusion if they investigated CRISPR-Cas9 applications relevant to human health, with specific emphasis on therapeutic interventions, translational applications, safety evaluations, ethical analyses, or regulatory frameworks. Only peer-reviewed articles published in English between January 2015 and March 2026 were included. Studies were excluded if they focused exclusively on agricultural, environmental, veterinary, or non-human applications of CRISPR technology. Purely mechanistic or molecular studies lacking direct translational or clinical relevance were also excluded. In addition, editorials, commentaries, conference abstracts, opinion papers, letters, duplicate records, and non-peer-reviewed publications were removed during screening.

Information Sources

A comprehensive literature search was conducted across three major biomedical and interdisciplinary databases: PubMed, Embase, and Dimensions. These databases were selected due to their extensive coverage of biomedical science, translational medicine, clinical trials, and broader interdisciplinary healthcare research. Their combined scope ensured representation of foundational, translational, clinical, ethical, and policy-related CRISPR-Cas9 studies.

Search Strategy

A structured search strategy was developed using a combination of Medical Subject Headings (MeSH), controlled vocabulary, free-text keywords, and Boolean operators. Search terms were designed to capture literature related to CRISPR-Cas9, genome editing, therapeutic applications, safety concerns, ethics, and regulatory considerations. Key terms included "CRISPR-Cas9," "CRISPR," "gene editing," "genome editing," "human health," "therapy," "treatment," "clinical trial," "safety," "off-target effects," "ethics," and "regulation." Search syntax was adapted appropriately for each database to maximize sensitivity while preserving specificity.

The database search identified 1,124 records from PubMed, 986 records from Embase, and 903 records from Dimensions, resulting in a total of 3,013 records. No additional studies were identified through registry databases. The complete database-specific search strategies used for PubMed, Embase, and Dimensions are provided in Supplementary Table S1 to facilitate transparency and reproducibility.

Study Selection Process

The study selection process followed PRISMA-ScR recommendations and consisted of sequential phases of identification, screening, retrieval, eligibility assessment, and final inclusion. Following database searching, 412 duplicate records were removed before screening. The remaining 2,601 records underwent title and abstract screening according to predefined eligibility criteria. During this phase, 2,417 records were excluded because they were unrelated to therapeutic CRISPR-Cas9 applications in human health, focused on non-medical applications, lacked translational relevance, or were ineligible publication types.

Study screening was conducted independently by two reviewers. Titles and abstracts were initially screened against the predefined eligibility criteria, followed by full-text assessment of potentially eligible articles. Any disagreements regarding study inclusion were resolved through discussion and consensus, and when necessary, consultation with a third reviewer to ensure consistency in study selection.

A total of 184 reports were then sought for full-text retrieval, of which 21 reports could not be accessed. Consequently, 163 full-text articles underwent detailed eligibility assessment. Of these, 131 studies were excluded. Reasons for exclusion included lack of direct focus on therapeutic CRISPR-Cas9 applications in human health, basic science studies without sufficient translational, ethical, or safety relevance, editorial or commentary publication type, and inadequate alignment with the review's thematic objectives.

Ultimately, 32 studies satisfied all eligibility criteria and were included in the final scoping review. The complete study selection process is presented in Figure 1 in accordance with PRISMA-ScR guidelines.

The full study identification, screening, eligibility assessment, and final inclusion process are illustrated in Figure 1 according to PRISMA-ScR guidelines.

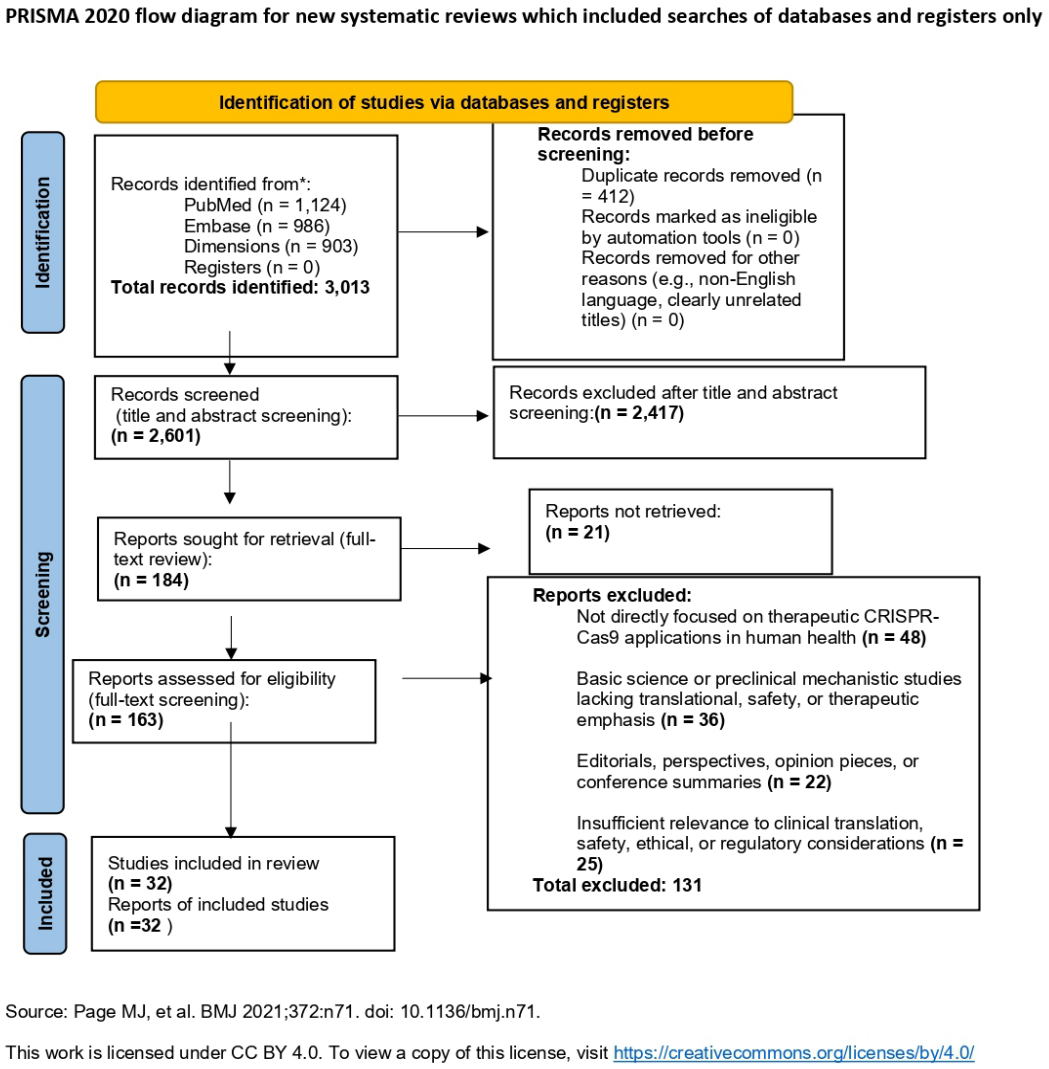

Figure 1. PRISMA-ScR Flow Diagram of Study Selection Process

Data Extraction and Charting

Data extraction was performed using a standardized data-charting form developed specifically for this review. Extracted variables included author, publication year, study design, country, disease focus, therapeutic application, delivery platform, study population, principal findings, safety concerns, ethical considerations, and study limitations where reported. To improve consistency, extracted information was cross-checked before thematic synthesis.

Data Synthesis and Analysis

Data were analyzed using thematic synthesis to map major evidence domains and identify translational trends. Included studies were categorized into three overarching thematic domains: therapeutic and clinical applications of CRISPR-Cas9, safety challenges and technical limitations, and ethical, societal, and regulatory considerations. This approach enabled broad interdisciplinary synthesis while preserving the complexity of emerging evidence across scientific, clinical, and policy dimensions.

Methodological Strengths

The use of multiple high-coverage databases, clearly defined eligibility criteria, PRISMA-ScR reporting standards, and structured thematic synthesis substantially strengthened the methodological rigor of this review. By integrating foundational science, translational medicine, clinical implementation, ethics, and policy scholarship, this methodology provides a comprehensive evidence map of CRISPR-Cas9's evolving therapeutic landscape while minimizing methodological inconsistency between the review narrative and the PRISMA reporting framework.

Study Selection

The structured search strategy identified a total of 3,013 records from PubMed, Embase, Dimensions, and supplementary citation tracking. Following the removal of 412 duplicate records, 2,601 studies remained for title and abstract screening. Of these, 2,417 records were excluded because they lacked sufficient relevance to therapeutic CRISPR-Cas9 applications in human health, focused on non-medical or agricultural uses, represented purely mechanistic investigations without translational implications, or were editorial and commentary publications.

A total of 184 reports were sought for full-text retrieval, with 163 successfully assessed for eligibility after excluding inaccessible reports. Ultimately, 32 studies met all predefined inclusion criteria and were incorporated into the final scoping review, reflecting a broad multidisciplinary evidence base across therapeutic innovation, safety science, translational medicine, and ethical governance.

The included studies spanned publications from 2015 to 2026, thereby capturing the complete translational progression of CRISPR-Cas9 from foundational molecular optimization to regulatory-grade therapeutic implementation. Early foundational studies primarily focused on improving editing specificity, delivery efficiency, and comparative genome engineering feasibility. These investigations established the technical underpinnings necessary for later therapeutic translation and included critical work on delivery optimization, off-target minimization, and correction of monogenic hematologic disorders (Jo et al., 2015; Xu et al., 2015; Young et al., 2015). During this early developmental phase, translational feasibility was further strengthened by successful in vivo correction strategies for hemophilia B, demonstrating CRISPR-Cas9's initial movement toward clinical applicability (Nguyen & Anegon, 2016; Guan et al., 2016).

Between 2017 and 2019, CRISPR-Cas9 applications expanded substantially beyond foundational optimization into broader disease domains. Infectious disease applications emerged through HIV-targeted viral genome disruption studies, although resistance challenges remained significant (Zhao et al., 2017). Simultaneously, delivery engineering advanced through polymeric and nonviral strategies designed to improve translational safety and efficiency (Ryu et al., 2018). Metabolic, hematologic, and oncologic applications also expanded considerably, with successful preclinical studies in primary hyperoxaluria, β-thalassemia, ovarian cancer, and pancreatic cancer (Zabaleta et al., 2018; Shariati et al., 2018; He et al., 2018; Li et al., 2019). Ethical and conceptual scholarship likewise emerged during this period, broadening discourse beyond therapeutic science into governance and societal implications (Rogaev, 2018; Taguchi et al., 2019).

The transitional period from 2019 to 2021 marked increasing diversification into immunotherapy and advanced translational medicine. Studies involving multiplex T-cell engineering, endogenous receptor deletion, and improved cellular immunotherapy frameworks highlighted CRISPR-Cas9's growing role in engineered precision medicine (Sommer et al., 2019; Morton et al., 2020). Concurrently, landmark in vivo human therapeutic studies established lipid nanoparticle-mediated CRISPR delivery as a viable clinical strategy, particularly for transthyretin amyloidosis, representing one of the earliest major successes in systemic genome editing (Gillmore et al., 2021).

From 2024 onward, the evidence base became increasingly dominated by advanced translational studies, phase 1–3 clinical trials, and commercialization-focused therapeutic models. Breakthroughs were observed in hematologic disorders, particularly sickle cell disease and transfusion-dependent β-thalassemia, where ex vivo hematopoietic stem-cell editing demonstrated transformative and potentially curative outcomes (Frangoul et al., 2024; Locatelli et al., 2024; Ahmed et al., 2025). Additional high-impact applications included inherited retinal degeneration, congenital neutropenia, hereditary angioedema, dyslipidemia, ATTRv-PN, and allogeneic CAR-T therapies, collectively demonstrating rapid therapeutic diversification into ophthalmology, immunology, cardiometabolic medicine, and rare disease correction (Pierce et al., 2024; Ritter et al., 2024; Cohn et al., 2025; Laffin et al., 2025). Emerging ethical scholarship also continued to expand, particularly regarding genome editing governance and comparative ethical analysis (Alex & Winkler, 2024).

By 2025–2026, CRISPR-Cas9 had clearly evolved beyond proof-of-concept experimentation into a clinically validated therapeutic platform with expanding applications across multiple biomedical domains. Studies involving hepatocellular carcinoma, advanced immunotherapy engineering, long-term transthyretin suppression, and immunodeficiency correction underscored increasing commercialization, broader healthcare integration, and the field's movement toward sustained clinical maturity (Zhang et al., 2025; Iyer et al., 2025; Gillmore et al., 2025; Swaminathan et al., 2025; Duran et al., 2026).

Overall, the final dataset reflected substantial diversification of CRISPR-Cas9 from a foundational genome-engineering platform into an increasingly

mature therapeutic, safety, and ethical framework. This progression illustrates not only remarkable scientific advancement but also the parallel expansion of clinical implementation, regulatory discourse, and societal governance necessary for responsible integration into modern medicine.

Characteristics of Included Studies

The 32 included studies represented heterogeneous but complementary evidence categories, including phase 1–3 clinical trials, preclinical animal studies, ex vivo translational investigations, delivery platform optimization studies, systematic reviews, and ethical or regulatory analyses. Disease targets included hematologic disorders (sickle cell disease, β-thalassemia, congenital neutropenia, immunodeficiency), metabolic diseases (ATTR amyloidosis, hereditary angioedema, primary hyperoxaluria), ophthalmologic disorders (inherited retinal degeneration), infectious diseases (HIV), oncology (solid tumors, CAR-T, TCR engineering), and broader platform development.

Early studies (2015–2018) predominantly emphasized correction efficiency, sgRNA specificity, vector engineering, and comparative genome editing technologies, including TALEN versus CRISPR comparisons, polymeric and liposomal delivery, and substrate reduction approaches (Xu et al., 2015; Jo et al., 2015; Ryu et al., 2018; He et al., 2018; Zabaleta et al., 2018; Shariati et al., 2018). Mid-phase studies increasingly examined translational therapeutic design in oncology, infectious disease, and precision hematology (Zhao et al., 2017; Li et al., 2019; Morton et al., 2020). Recent literature was dominated by human clinical trial data, regulatory scholarship, and commercialization pathways, particularly for hemoglobinopathies, amyloidosis, cardiovascular risk reduction, hereditary angioedema, and engineered immunotherapies (Gillmore et al., 2021; Frangoul et al., 2024; Locatelli et al., 2024; Cohn et al., 2025; Gillmore et al., 2025; Laffin et al., 2025; Iyer et al., 2025).

Three principal thematic domains emerged across the included studies: therapeutic and clinical applications, safety and technical limitations, and ethical, societal, and regulatory governance.

Table 1. Characteristics of the 32 Included Studies

Author (Year)	Study Design	Therapeutic Area	CRISPR-Cas9 Application	Key Findings	Theme	Evidence Level
Ahmed et al. (2025)	Systematic review of clinical trials	Hematology	Sickle cell disease and β-thalassemia	Demonstrated promising efficacy and safety of CRISPR-Cas9 therapies in hemoglobinopathies	Therapeutic applications	Secondary evidence (Systematic Review)
Alex & Winkler (2024)	Ethical review	Ethics	Genome and epigenome editing	Discussed ethical frameworks for responsible clinical implementation	Ethics	Secondary evidence (Review)
Aljabali et al. (2024)	Narrative review	Drug delivery	CRISPR delivery technologies	Summarized advances in delivery platforms and emerging technologies	Delivery systems	Secondary evidence (Review)
Amiri et al. (2024)	Narrative review	Oncology	CAR-T cell engineering	Reviewed the synergistic potential of CRISPR-Cas9 in cancer immunotherapy	Oncology	Secondary evidence (Review)
Cohn et al. (2025)	Clinical trial	Rare diseases	KLKB1 editing for hereditary angioedema	Demonstrated encouraging clinical efficacy of in vivo editing	Clinical therapeutics	Clinical evidence

Author (Year)	Study Design	Therapeutic Area	CRISPR-Cas9 Application	Key Findings	Theme	Evidence Level
Davis & Yeddula (2024)	Narrative review	General medicine	Human health applications	Reviewed therapeutic progress across disease areas	General applications	Secondary evidence (Review)
Duran et al. (2026)	Clinical study	Immunodeficiency	Hematopoietic stem-cell correction	Restored immune function using CRISPR-edited stem cells	Hematology	Clinical evidence
Frangoul et al. (2024)	Phase III clinical trial	Hematology	Exagamglogene autotemcel	Demonstrated durable therapeutic benefit in sickle cell disease and β-thalassemia	Hematology	Clinical evidence
Gillmore et al. (2021)	Phase I clinical trial	Metabolic disease	Transthyretin amyloidosis	Demonstrated successful in vivo genome editing	Metabolic disorders	Clinical evidence
Gillmore et al. (2025)	Clinical follow-up	Metabolic disease	ATTR amyloidosis	Reported sustained long-term efficacy and safety	Metabolic disorders	Clinical evidence
Guan et al. (2016)	Animal study	Hemophilia B	Somatic gene correction	Successfully corrected disease phenotype in mice	Gene therapy	Preclinical evidence
He et al. (2018)	Animal study	Oncology	Ovarian cancer gene therapy	Reduced tumor progression following CRISPR editing	Oncology	Preclinical evidence
Humbert et al. (2021)	Narrative review	Hematology	Clinical applications	Reviewed translation of CRISPR therapies to clinical practice	Hematology	Secondary evidence (Review)
Iyer et al. (2025)	Phase I clinical trial	Oncology	CD70 CAR-T therapy	Demonstrated favorable preliminary safety and activity	Immunotherapy	Clinical evidence
Jo et al. (2015)	Narrative review	Technology	CRISPR specificity and delivery	Reviewed improvements in specificity and delivery methods	Technology	Secondary evidence (Review)
Kalter et al. (2025)	Review	Safety	Off-target effects	Reviewed progress in minimizing off-target editing	Safety	Secondary evidence (Review)
Karimi et al. (2026)	Narrative review	Therapeutics	Therapeutic opportunities	Reviewed challenges and future applications	Future directions	Secondary evidence (Review)
Khare et al. (2023)	Book chapter	Biotechnology	Translational applications	Summarized broad applications of CRISPR	Biotechnology	Secondary evidence

Author (Year)	Study Design	Therapeutic Area	CRISPR-Cas9 Application	Key Findings	Theme	Evidence Level
Kolanu (2024)	Narrative review	Epigenetics	Gene editing	Reviewed therapeutic applications of CRISPR	Epigenetics	Secondary evidence (Review)
Laffin et al. (2025)	Phase I clinical trial	Cardiometabolic disease	ANGPTL3 editing	Demonstrated durable lipid reduction	Cardiovascular medicine	Clinical evidence
Li et al. (2019)	Animal study	Oncology	HIF-1α targeting	Suppressed pancreatic cancer metastasis	Oncology	Preclinical evidence
Locatelli et al. (2024)	Clinical trial	β-thalassemia	Exagamglogene autotemcel	Achieved transfusion independence in many patients	Hematology	Clinical evidence
Nguyen & Anegon (2016)	Commentary	Delivery systems	Viral vectors	Discussed delivery challenges and immune responses	Delivery systems	Expert opinion
Pierce et al. (2024)	Clinical trial	Ophthalmology	Retinal gene editing	Demonstrated feasibility of in vivo retinal editing	Ophthalmology	Clinical evidence
Ritter et al. (2024)	Experimental study	Hematology	ELANE correction	Restored granulopoiesis	Hematology	Preclinical evidence
Ryu et al. (2018)	Experimental study	Nanotechnology	PEI-mediated delivery	Improved CRISPR delivery efficiency	Delivery systems	Preclinical evidence
Sommer et al. (2019)	Experimental study	Immunotherapy	Multiplex T-cell engineering	Enhanced T-cell function	Immunotherapy	Preclinical evidence
Subica (2023)	Commentary	Public health	Health equity	Discussed the equity implications of CRISPR implementation	Ethics & policy	Expert opinion
Taguchi et al. (2019)	Cross-sectional survey	Ethics	Clinical genome editing	Assessed attitudes toward genome editing	Ethics	Primary observational evidence
Uddin et al. (2020)	Narrative review	Oncology	CRISPR gene therapy	Reviewed applications and future implications	Oncology	Secondary evidence (Review)
Wiley et al. (2025)	Systematic review	Ethics	Human embryo editing	Synthesized ethical arguments regarding embryo editing	Ethics	Secondary evidence (Systematic Review)
Xu et al. (2015)	Experimental study	β-thalassemia	HBB mutation correction	Demonstrated successful correction in iPSCs	Gene editing	Preclinical evidence

Abbreviations: iPSC = induced pluripotent stem cell; CAR-T = chimeric antigen receptor T cell; PEI = polyethyleneimine.

Therapeutic Applications of CRISPR-Cas9

Hematologic and Monogenic Disorders

Hematologic diseases represented the most clinically advanced and therapeutically successful CRISPR-Cas9 applications. Exagamglogene autotemcel (exa-cel) demonstrated transformative efficacy in both sickle cell disease and transfusion-dependent β-thalassemia through ex vivo BCL11A enhancer editing, producing durable fetal hemoglobin induction, elimination of vaso-occlusive crises, and transfusion independence in most treated patients (Frangoul et al., 2024; Locatelli et al., 2024; Ahmed et al., 2025). Additional therapeutic models included β-thalassemia mutation correction in patient-derived iPSCs, SOX6-mediated fetal hemoglobin reactivation, and gene correction strategies for severe congenital neutropenia and Artemis deficiency, demonstrating broader applicability across inherited hematologic syndromes (Xu et al., 2015; Shariati et al., 2018; Ritter et al., 2024; Duran et al., 2026).

Hemophilia B studies further demonstrated the feasibility of direct in vivo hepatic gene correction, though vector immunogenicity and repair efficiency remained important limitations (Nguyen & Anegon, 2016). Together, these findings establish hematologic disorders as the most mature CRISPR therapeutic category due to favorable stem-cell accessibility, monogenic architecture, and established transplantation frameworks.

In Vivo Editing for Metabolic, Cardiovascular, and Rare Diseases

Systemic in vivo CRISPR therapies have rapidly expanded therapeutic scope beyond ex vivo models. NTLA-2001 and Nexiguran ziclumeran demonstrated substantial and durable TTR suppression in hereditary transthyretin amyloidosis, achieving >90% serum reduction following a single infusion (Gillmore et al., 2021; Gillmore et al., 2025). NTLA-2002 targeting KLKB1 significantly reduced hereditary angioedema attack burden, while CTX310 targeting ANGPTL3 showed promising lipid-lowering potential for dyslipidemia and cardiovascular prevention (Cohn et al., 2025; Laffin et al., 2025).

Primary hyperoxaluria type I studies demonstrated successful glycolate oxidase disruption as a substrate-reduction strategy, highlighting alternative therapeutic paradigms for metabolic disorders (Zabaleta et al., 2018). These data collectively confirm liver-directed CRISPR editing as one of the most scalable near-term clinical models.

Ophthalmology and Sensory Disorders

EDIT-101 provided one of the earliest demonstrations of successful in vivo CRISPR application in ocular tissue, producing clinically meaningful visual improvements in CEP290-associated retinal degeneration (Pierce et al., 2024). This represented a critical milestone for tissue-specific editing beyond hepatic systems.

Oncology and Cellular Immunotherapy

Oncology-focused studies explored both direct oncogene disruption and enhancement of immune therapeutics. Tumor-targeted CRISPR platforms suppressed HIF-1α, DNMT1, and PD-L1 signaling pathways in pancreatic, ovarian, and hepatocellular carcinoma models, often through nanoparticle or liposomal co-delivery systems (He et al., 2018; Li et al., 2019; Zhang et al., 2025).

Parallel advances in immunotherapy included endogenous TCR deletion, safer TCR engineering, and allogeneic CAR-T manufacturing platforms, improving efficacy, scalability, and safety for hematologic malignancies (Morton et al., 2020; Iyer et al., 2025; Swaminathan et al., 2025). These studies suggest oncology may represent the next major frontier, though delivery and tumor heterogeneity remain substantial barriers.

Infectious Diseases and Emerging Therapeutics

CRISPR strategies targeting HIV demonstrated additive suppression when combined with RNA interference approaches, although rapid escape mutations and cross-resistance highlighted major antiviral limitations (Zhao et al., 2017). Emerging investigations also explored neurodegeneration, epigenome editing, and broad therapeutic expansion, though these remain less clinically mature (Rogaev, 2018; Alex & Winkler, 2024).

Safety Challenges, Technical Constraints, and Delivery Barriers

Off-Target Activity and Genomic Integrity

Off-target mutagenesis remained among the most consistently cited safety concerns. Comparative analyses revealed variable specificity across CRISPR platforms relative to TALENs and other editing systems, with risks including unintended indels, chromosomal abnormalities, and oncogenic transformation (Jo et al., 2015; Xu et al., 2015; Ritter et al., 2024). Advances such as GUIDE-seq, allele-specific editing, high-fidelity Cas9 variants, and optimized sgRNA architecture improved precision but did not eliminate long-term genomic concerns.

Delivery Platform Limitations

Delivery remained a universal translational bottleneck. Viral vectors, particularly AAV systems, offered strong transduction but introduced concerns regarding immune activation, limited payload capacity, and insertional risks (Nguyen & Anegon, 2016). Nonviral systems—including PEI polymers, lipid

nanoparticles, receptor-targeted liposomes, and polymeric nanoplatforms—improved safety and repeat-dosing potential but often sacrificed editing efficiency (Ryu et al., 2018; He et al., 2018; Li et al., 2019; Zhang et al., 2025).

Immunogenicity and Procedure-Related Toxicity

Clinical trials generally reported manageable short-term safety, though infusion reactions, conditioning toxicity, transient hepatotoxicity, and immune activation persisted (Gillmore et al., 2021; Frangoul et al., 2024; Cohn et al., 2025; Laffin et al., 2025). Long-term immunologic consequences remain insufficiently characterized.

Durability and Surveillance Needs

While many interventions demonstrated sustained medium-term efficacy, most studies emphasized the need for prolonged surveillance regarding genomic stability, malignant transformation, durability of correction, and intergenerational implications where applicable.

Ethical, Societal, and Regulatory Dimensions

Ethical and governance scholarship emphasized that technological capability has progressed more rapidly than regulatory harmonization. Surveys among genetic professionals in Japan revealed cautious support for somatic therapeutic use but strong opposition to enhancement-oriented applications and germline modification (Taguchi et al., 2019). Comparative ethical analyses further highlighted nuanced distinctions between genome editing and epigenome editing, particularly regarding reversibility, risk burden, and societal misuse (Alex & Winkler, 2024).

Key recurring ethical concerns included the boundary between somatic and germline intervention, risks of enhancement misuse, fragmented international regulation, informed consent complexity, health equity challenges, and the concentration of advanced therapies in high-resource settings.

These concerns were amplified by the disproportionately high projected costs of approved therapies and infrastructural barriers in low- and middle-income settings despite disease burden concentration.

Emerging Trends and Research Gaps

Major translational trends included the shift from proof-of-concept studies to regulatory-grade therapeutics, increasing dominance of liver-targeted in vivo editing, expansion of multiplex immunotherapy engineering, progressive refinement of delivery platforms, commercialization of one-time genomic medicines, and parallel growth in ethical scholarship and governance discourse.

Persistent research gaps included limited long-term safety outcomes, underrepresentation of diverse ancestries in clinical trials, incomplete delivery solutions for extrahepatic tissues, inadequate affordability and equitable access frameworks, limited durability in infectious disease applications, fragmented global governance, and insufficient standardized post-approval surveillance systems.

Summary of Findings

Across the 32 included studies, CRISPR-Cas9 has evolved from a disruptive experimental technology into a therapeutic platform with growing clinical evidence currently available for hematologic disorders and selected liver-directed therapies. However, therapeutic maturity varies considerably across disease categories, with many applications in oncology, infectious diseases, and neurology remaining at the preclinical or early clinical stages. The current evidence indicates that CRISPR-Cas9 represents one of the most promising advances in genome editing, although continued evidence generation is required to support broader clinical implementation. Continued advances in delivery technologies, ethical governance, equitable implementation, and international regulatory coordination will be essential to support the safe and responsible translation of CRISPR-based therapies into routine clinical practice.

Discussion

Interpretation of Principal Findings

This scoping review demonstrates that CRISPR-Cas9 has undergone a remarkable transformation from an experimental genome-engineering tool into a clinically viable therapeutic platform with expanding applications across multiple domains of human health. The evidence synthesized from the 32 included studies reveals a clear translational trajectory, progressing from foundational studies focused on editing efficiency, sequence specificity, and delivery optimization toward regulatory-grade therapeutic implementation in severe human diseases. This evolution highlights CRISPR-Cas9 as one of the most significant biomedical innovations of the modern era.

The strongest therapeutic advances were observed in monogenic disorders, particularly hematologic and metabolic diseases, where disease mechanisms are well-defined, and target tissues are relatively accessible (Murphy et al., 2013). Clinical

successes in sickle cell disease, transfusion-dependent β-thalassemia, hereditary transthyretin amyloidosis, and hereditary angioedema suggest that CRISPR-Cas9 has moved beyond theoretical promise to deliver durable and, in some cases, functionally curative clinical outcomes (Frangoul et al., 2024; Locatelli et al., 2024; Gillmore et al., 2025; Cohn et al., 2025). These findings represent a paradigm shift from conventional disease management toward direct molecular correction of pathogenic mechanisms.

Importantly, therapeutic maturity remains uneven across disease categories. While hematology and liver-targeted systemic diseases currently dominate successful translation, applications in oncology, infectious disease, and neurodegeneration remain comparatively early-stage due to challenges such as tissue heterogeneity, immune complexity, and delivery barriers. Thus, CRISPR-Cas9's present success appears highly dependent on biological context, with simpler monogenic disorders offering the clearest path to implementation (Karimi et al., 2026).

Therapeutic Implications Across Disease Categories

Hematologic disorders currently represent the most advanced and clinically validated CRISPR-Cas9 therapeutic domain. Ex vivo hematopoietic stem-cell editing has demonstrated exceptional translational success because it combines precise gene correction with established transplantation infrastructure. The efficacy of exa-cel in both sickle cell disease and β-thalassemia establishes CRISPR-Cas9 as a credible, potentially curative approach for inherited blood disorders and may fundamentally reshape treatment paradigms for numerous monogenic diseases (Humbert et al., 2021; Dickson, 2026).

One of the most important observations emerging from this review is the marked disparity in the pace of clinical translation across different therapeutic areas. CRISPR-Cas9 has advanced most rapidly in hematological disorders, whereas progress in solid tumors has been comparatively slower. This difference reflects fundamental biological, technical, and clinical factors rather than differences in the potential value of genome editing itself.

Hematological disorders provide particularly favorable conditions for CRISPR-based therapeutic development. Many inherited blood disorders, including sickle cell disease and β-thalassemia, are caused by well-characterized mutations in a single gene or a limited number of genetic targets, making them highly amenable to precise genome editing. Furthermore, hematopoietic stem cells can be harvested from patients, edited ex vivo under carefully controlled laboratory conditions, extensively assessed for editing efficiency and potential off-target effects, and subsequently reinfused following established transplantation protocols. This ex vivo strategy substantially reduces uncertainties associated with in vivo delivery while allowing rigorous quality control before clinical administration. In addition, blood-based biomarkers, hemoglobin levels, and clinical outcomes such as transfusion independence or reduction in vaso-occlusive crises provide objective and relatively straightforward measures of therapeutic efficacy, facilitating both clinical evaluation and regulatory assessment.

In contrast, the translation of CRISPR-Cas9 for solid tumors remains considerably more challenging. Solid malignancies are characterized by extensive intratumoral heterogeneity, with genetically distinct cell populations coexisting within the same tumor. Consequently, editing a single molecular target is often insufficient to achieve durable therapeutic responses. Efficient delivery of CRISPR components throughout the entire tumor mass also remains a major obstacle because physical barriers within the tumor microenvironment limit penetration of viral and non-viral delivery systems. In addition, the immunosuppressive tumor microenvironment, the presence of multiple oncogenic pathways, and the emergence of treatment resistance further complicate the development of durable genome-editing strategies. These biological complexities explain why many oncology applications remain in the preclinical or early clinical stages despite encouraging experimental findings.

Consequently, therapeutic translation has progressed considerably faster in hematological disorders than in solid tumors, highlighting how disease biology, delivery feasibility, and clinical infrastructure collectively influence the successful implementation of CRISPR-Cas9 therapies.

To provide an overview of the current clinical maturity of CRISPR-Cas9 across major therapeutic areas, Figure 2 summarizes the principal disease categories together with their corresponding stages of translational development.

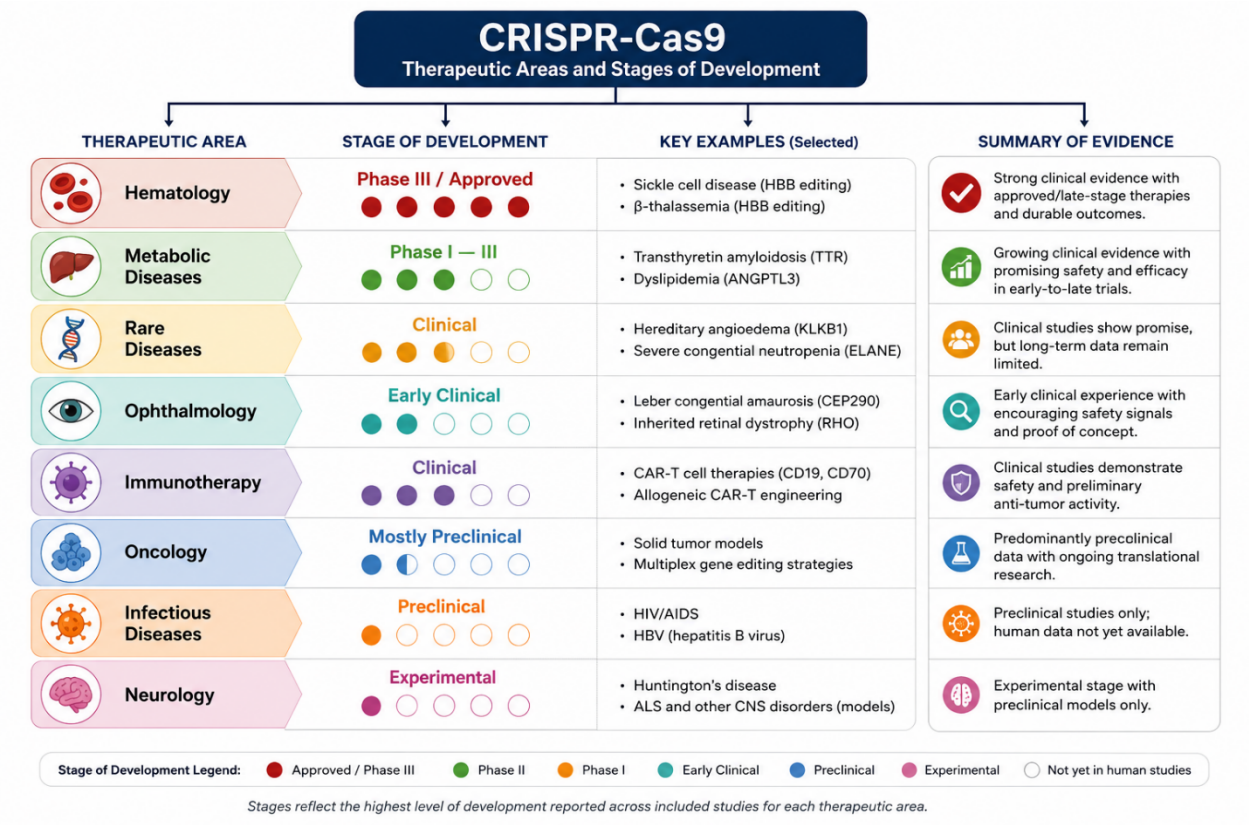

Figure 2. Current Therapeutic Applications of CRISPR-Cas9 and Stages of Clinical Development.

Summary of the major therapeutic applications of CRISPR-Cas9 according to their current stage of clinical development. Hematological disorders represent the most clinically advanced applications, supported by late-stage clinical trials and regulatory approvals for selected indications. Metabolic diseases, rare genetic disorders, ophthalmology, and immunotherapy have demonstrated encouraging clinical progress, whereas most oncology applications remain predominantly preclinical because of challenges related to tumor heterogeneity, delivery efficiency, and treatment resistance. Infectious disease and neurological applications are largely at the experimental stage, reflecting ongoing technological and translational development.

Top of Form

Bottom of Form

Similarly, liver-targeted in vivo editing platforms have emerged as highly promising strategies due to the liver's accessibility and compatibility with lipid nanoparticle delivery systems. Therapies targeting TTR, KLKB1, and ANGPTL3 suggest that CRISPR-Cas9 may soon expand beyond rare genetic disorders into broader chronic disease prevention, including cardiometabolic medicine (Gillmore et al., 2025; Laffin et al., 2025). This broadening scope substantially increases the public health relevance of genome editing.

Oncology presents a more complex but highly promising frontier. While direct tumor editing remains constrained by biological complexity and delivery inefficiency, CRISPR-mediated cellular immunotherapy engineering, including CAR-T and TCR optimization, may offer a more immediately scalable pathway. The capacity for multiplex engineering, endogenous receptor disruption, and allogeneic manufacturing suggests that CRISPR could substantially improve the safety, consistency, and accessibility of next-generation immunotherapies (Amiri et al., 2024).

Safety as the Primary Limitation to Broader Clinical Expansion

Despite extraordinary therapeutic progress, safety remains the principal determinant of CRISPR-Cas9's long-term viability. Across the included literature, off-target effects consistently emerged as the most significant technical barrier. Unintended genomic alterations, chromosomal rearrangements, insertional mutagenesis, and potential oncogenic transformation remain major concerns that could undermine broader clinical adoption(Kalter et al., 2025).

Although innovations such as high-fidelity Cas9 enzymes, optimized sgRNA design, allele-specific targeting, GUIDE-seq, and next-generation editing systems have improved precision, no platform has fully eliminated long-term genomic uncertainty (Jo et al.,

2015; Ritter et al., 2024). This challenge becomes increasingly important as CRISPR therapies expand into broader populations and preventive medicine contexts where acceptable risk thresholds may be lower.

Delivery challenges further complicate expansion. Viral vectors remain highly efficient but introduce concerns related to immunogenicity, payload limitations, and insertional risks, whereas nonviral systems often improve safety at the expense of efficiency. Consequently, future CRISPR progress will likely depend heavily on advances in safer, tissue-specific, and scalable delivery technologies.

Ethical, Regulatory, and Societal Considerations

A major finding of this review is that scientific innovation has advanced more rapidly than global ethical and regulatory harmonization. While somatic therapeutic applications have gained increasing legitimacy, germline editing remains deeply controversial because of irreversible heritable consequences, enhancement concerns, and broader societal implications. Ethical scholarship consistently emphasizes that governance structures must evolve in parallel with technological capability to prevent misuse and preserve public trust (Taguchi et al., 2019; Alex & Winkler, 2024).

Equity emerged as a particularly important translational issue. Many diseases most likely to benefit from CRISPR interventions, such as sickle cell disease, are disproportionately prevalent in lower-resource settings, yet therapy development and commercialization remain concentrated in wealthier healthcare systems. Without deliberate efforts to improve affordability, manufacturing scalability, and equitable implementation, CRISPR-Cas9 may risk exacerbating existing global health disparities (Subica, 2023).

Therefore, responsible translational progress must be evaluated not solely by scientific success, but also by distributive justice, accessibility, and sustainable healthcare integration.

Comparison With Earlier Genome Editing Technologies

Compared with preceding technologies such as zinc finger nucleases and TALENs, CRISPR-Cas9 offers substantially greater programmability, affordability, scalability, and multiplexing potential. These advantages have accelerated research productivity and clinical translation. However, broader accessibility also increases ethical complexity and misuse potential, particularly in inadequately regulated environments (Aljabali et al., 2024).

Thus, CRISPR-Cas9's true significance lies not merely in technical superiority but in its establishment as a flexible therapeutic framework capable of broad application across multiple disease systems.

Limitations of Current Evidence

Despite rapid progress, the evidence base remains constrained by several limitations. Long-term safety data remain sparse due to the relatively recent emergence of many clinical applications. Several therapeutic studies involve small patient populations, limiting broad generalizability. Geographic and demographic diversity remains insufficient, potentially constraining global relevance. Additionally, many applications in oncology, infectious disease, and neurologic medicine remain predominantly preclinical, highlighting persistent disparities in translational maturity across disease domains.

As a scoping review, this study maps broad evidence landscapes rather than quantitatively comparing treatment efficacy, which may limit direct comparative interpretation.

An additional limitation of this review is the restriction to English-language publications, which may have resulted in the exclusion of relevant studies published in other languages. Consequently, language bias may have been introduced, potentially limiting the representation of evidence from non-English-speaking regions and reducing the global comprehensiveness of the review. Furthermore, consistent with the objectives of a scoping review, no formal critical appraisal of methodological quality or risk of bias was undertaken for the included studies. As a result, the findings should be interpreted as a broad mapping of the available evidence rather than an assessment of the strength or certainty of the evidence supporting individual therapeutic applications.

Future Directions

Future CRISPR-Cas9 research should prioritize long-term genomic surveillance, safer extrahepatic delivery systems, broader inclusion of diverse populations in clinical trials, improved affordability, and stronger international governance.

Emerging Genome Editing Technologies

Conventional CRISPR-Cas9 has established itself as the most clinically advanced genome-editing platform and currently underpins the majority of approved or late-stage clinical applications. Its versatility, relative simplicity, and ability to generate targeted double-strand DNA breaks have enabled therapeutic development across a broad range of inherited, metabolic, hematologic, and oncologic diseases. However, the induction of double-strand breaks may also increase the risk of unintended insertions or deletions (indels), chromosomal

rearrangements, and off-target genomic alterations, thereby motivating the development of next-generation genome-editing technologies.

Base editing has emerged as an important refinement of CRISPR technology by enabling the direct conversion of one DNA base into another without generating double-strand DNA breaks. Because most known pathogenic genetic variants are single-nucleotide substitutions, base editors offer a highly attractive strategy for correcting disease-causing point mutations while reducing the frequency of indels and large genomic rearrangements. Nevertheless, their clinical application remains constrained by relatively narrow editing windows, dependence on compatible target sequences, and the inability to correct all mutation types.

Prime editing represents a further advancement by combining a Cas9 nickase with a reverse transcriptase enzyme and a prime-editing guide RNA to introduce precise genetic modifications without requiring double-strand DNA breaks or donor DNA templates. Unlike conventional CRISPR-Cas9 or base editing, prime editing can generate targeted insertions, deletions, and all possible base substitutions, thereby substantially expanding the range of potentially treatable genetic disorders. Despite these advantages, prime editing currently demonstrates lower editing efficiency in many cell types, involves more complex editing machinery, and continues to face important delivery challenges that must be overcome before widespread clinical implementation.

Although these next-generation technologies show considerable promise, CRISPR-Cas9 currently possesses the strongest body of preclinical and clinical evidence, particularly in hematologic disorders and liver-directed therapies. Base editing and prime editing should therefore be viewed as complementary rather than replacement technologies. As improvements in editing efficiency, specificity, and delivery continue, these emerging platforms may overcome several limitations associated with conventional CRISPR-Cas9 and further expand the therapeutic landscape of precision genome editing.

As approved therapies increasingly transition from specialized trials into broader healthcare settings, implementation science will become central. Considerations, including health economics, infrastructure readiness, patient accessibility, and global scalability, will play critical roles in determining CRISPR-Cas9's ultimate public health impact.

Beyond scientific advancement, the successful integration of CRISPR-Cas9 into mainstream healthcare will require addressing broader clinical implementation, policy, and equity considerations.

Clinical and Policy Implications

The rapid clinical advancement of CRISPR-Cas9 therapies carries profound implications not only for biomedical innovation but also for healthcare systems, regulatory infrastructures, and global public health policy. As genome editing transitions from experimental trials to approved therapeutic modalities, successful implementation will increasingly depend on the capacity of healthcare systems to integrate these highly specialized interventions into routine clinical practice. This includes the development of advanced genomic medicine infrastructure, specialized workforce training, long-term surveillance systems, and multidisciplinary treatment frameworks capable of managing both therapeutic delivery and post-treatment monitoring (Davis & Yeddula, 2024).

A major policy challenge identified across the current evidence base is the absence of harmonized international regulatory standards. While several countries have established evolving frameworks for somatic genome editing, global governance remains fragmented, particularly regarding germline editing, clinical oversight, long-term safety monitoring, and commercialization practices. Inconsistent regulations may create ethical loopholes, encourage medical tourism, and increase the risk of misuse or inequitable deployment. Therefore, stronger international coordination will be essential to ensure responsible innovation, patient safety, and public trust.

Economic barriers represent another critical limitation to broad clinical adoption. Many currently approved or emerging CRISPR-based therapies involve highly individualized manufacturing, specialized conditioning regimens, and complex delivery systems that may result in exceptionally high treatment costs(Dickson et al., 2026)

. Without substantial advances in manufacturing scalability, reimbursement strategies, and pricing reform, these therapies may remain inaccessible to the majority of global patients. This challenge is particularly concerning for diseases such as sickle cell disease, which disproportionately affect populations in lower-resource settings where access to advanced therapeutics may be most limited(Uddin et al., 2020).

Health equity must therefore remain central to future policy planning. If CRISPR-Cas9 therapies are commercialized primarily within high-income healthcare markets, existing global disparities in healthcare access may widen significantly. Equitable implementation will require targeted investment in infrastructure development, international partnerships, differential pricing models, and policies that prioritize accessibility in underserved populations. Expanding

access to genome editing therapies should be viewed not solely as a scientific objective, but as a broader public health and social justice imperative.

Commercialization also introduces important strategic considerations. As biotechnology companies increasingly drive CRISPR therapeutic development, balancing innovation incentives with affordability and ethical stewardship will become increasingly important. Intellectual property constraints, proprietary delivery platforms, and market exclusivity may accelerate innovation while simultaneously restricting accessibility. Policymakers, regulators, and healthcare stakeholders must therefore work collaboratively to establish frameworks that encourage continued therapeutic advancement without compromising equitable public benefit.

Overall, the future success of CRISPR-Cas9 will depend not only on scientific refinement but also on the development of sustainable healthcare implementation models, globally coordinated regulatory systems, equitable access strategies, and ethically grounded commercialization pathways. Integrating these clinical and policy dimensions will be essential to ensuring that the transformative potential of genome editing is realized broadly, responsibly, and inclusively.

Conclusion

CRISPR-Cas9 has emerged as one of the most promising advances in genome editing and precision medicine, with rapidly expanding applications across hematologic, metabolic, ophthalmologic, cardiovascular, oncologic, and immunologic diseases. This scoping review demonstrates that the strongest clinical evidence currently supports its use in selected monogenic disorders, particularly hemoglobinopathies and liver-directed diseases, where early clinical trials have reported encouraging therapeutic outcomes. However, the maturity of the evidence varies considerably across therapeutic areas, with many applications remaining in the preclinical or early stages of clinical development.

Despite substantial progress, important translational challenges remain. Persistent concerns regarding off-target effects, genomic instability, delivery efficiency, immunogenicity, and limited long-term safety data continue to constrain broader clinical implementation. In addition, ethical considerations surrounding germline editing, equitable access, regulatory harmonization, and affordability remain central to the responsible development and implementation of CRISPR-based therapies.

Overall, the available evidence indicates that CRISPR-Cas9 has entered clinical practice for selected indications and has demonstrated considerable therapeutic potential. Nevertheless, broader clinical implementation will depend on continued technological refinement, robust long-term safety evaluation, equitable access to treatment, and internationally coordinated ethical and regulatory oversight. As genome-editing technologies continue to evolve, CRISPR-Cas9, together with emerging approaches such as base editing and prime editing, is expected to play an increasingly important role in the future of precision medicine. Continued multidisciplinary collaboration among researchers, clinicians, policymakers, industry, and patient communities will be essential to ensure that these technologies are translated into safe, effective, and equitable healthcare solutions.

Supplementary Materials

Supplementary file available via: https://www.aubiomed.org/suppfile/766/Supplementary-Table-aubm024.pdf

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Okechukwu assisted with data interpretation and manuscript editing. Daniel Obinna Eke contributed to policy analysis, editorial refinement, and final manuscript review.

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