GENETIC ENGINEERING AND CRISPR CAS9 TECHNOLOGY IN MODERN MEDICINE CLINICAL ADVANCES AND FUTURE THERAPEUTIC PERSPECTIVES

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Abstract: *Genetic engineering is changing medicine by allowing disease mechanisms to be addressed at the level of DNA and cellular function. CRISPR-Cas9 provides programmable targeting, while base editing and prime editing expand the range of possible genetic changes. This narrative review examines their biological principles, therapeutic applications, delivery strategies, and clinical limitations. Selected primary studies demonstrate substantial progress in sickle cell disease and transfusion-dependent beta-thalassemia, alongside early evidence in transthyretin amyloidosis, cancer immunotherapy, and an individually treated metabolic disorder. These applications differ in maturity and should not be interpreted as equally established treatments. Effective translation requires an appropriate genetic target, delivery to relevant cells, reproducible manufacturing, and durable clinical benefit. Genotoxicity, conditioning-related complications, affordability, and equitable access remain central considerations. The strongest prospects lie in matching the editing platform to the disease mechanism while evaluating patient outcomes rather than relying on editing efficiency alone.*

Keywords: *Genetic engineering; CRISPR-Cas9; genome editing; base editing; prime editing; precision medicine; gene therapy.*

Introduction

Many treatments control the consequences of disease without changing its underlying genetic cause. Genetic engineering offers another approach: adding genetic material, disrupting a harmful gene, correcting a pathogenic sequence, or modifying therapeutic cells. Gene addition and genome editing are related but distinct strategies. A functional gene may

be introduced without repairing the original mutation, whereas editing changes a selected genomic region.

The demonstration that Cas9 can be programmed with RNA established a practical foundation for targeted genome modification [1]. Subsequent innovations broadened the possible changes beyond DNA cleavage [2,3]. For modern medicine, the key question is whether a molecular intervention produces meaningful, durable benefit with acceptable treatment burden. This review connects editing mechanisms with clinical evidence and the requirements for wider therapeutic use.

Methods

This narrative review considers eight selected primary publications spanning programmable Cas9 activity, base and prime editing, and representative human therapeutic studies. Sources were chosen for their mechanistic or clinical relevance rather than through a systematic search protocol. Evidence is interpreted according to study design, sample size, outcome type, and follow-up. Laboratory findings, early clinical feasibility, and disease-specific therapeutic outcomes are distinguished throughout.

Molecular Principles and Editing Platforms

CRISPR-Cas9 combines a guide RNA with a DNA-targeting nuclease. Complementarity between the guide and target sequence, together with an appropriate protospacer-adjacent motif, enables recognition. Cas9 cuts both DNA strands, after which cellular repair determines the final sequence [1]. End joining can introduce small insertions or deletions that disrupt gene function. Template-directed repair can introduce a specified change when a suitable repair template and cellular conditions are available. A targeted cut therefore does not automatically produce precise correction.

Base editing couples a modified Cas protein to a base-modifying enzyme. The original cytosine base editor enabled selected C-to-T changes without requiring a double-strand break or donor template [2]. Different editor families extend this principle, but their capabilities depend on the desired substitution and local sequence. Unwanted nearby changes and unintended editing still require assessment.

Prime editing combines a Cas9 nickase with reverse transcriptase and a prime-editing guide RNA that specifies both the target and intended change. It can introduce substitutions and small insertions or deletions without the conventional double-strand break and donor-template approach [3]. These platforms complement one another. Choosing among them requires attention to the disease mechanism, target accessibility, expected byproducts, and feasibility of delivery.

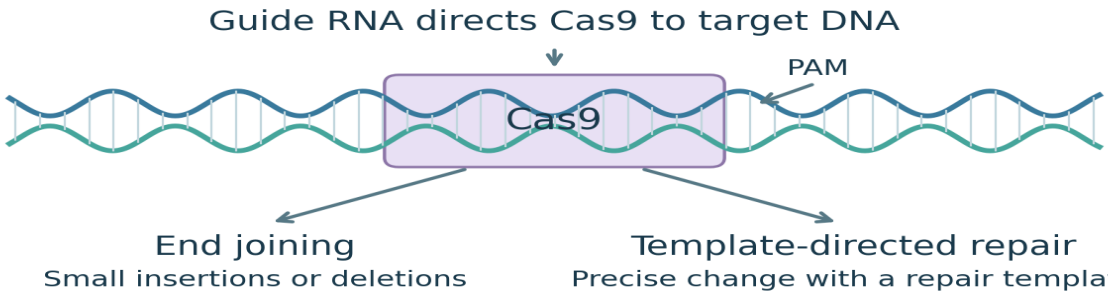


Figure 1. Programmable DNA Targeting and Repair

Clinical Applications and Strength of Evidence

Hemoglobin disorders illustrate how editing a regulatory element can compensate for a pathogenic mutation. Exagamglogene autotemcel modifies the erythroid-specific enhancer of BCL11A in a patient's hematopoietic stem and progenitor cells, increasing fetal hemoglobin rather than directly repairing the sickle mutation. In the reported sickle cell trial, 29 of 30 evaluable participants were free from severe vaso-occlusive crises for at least 12 consecutive months [4]. The denominator matters: 44 participants had received treatment, and the primary endpoint required sufficient follow-up.

In transfusion-dependent beta-thalassemia, the same regulatory strategy supported sustained transfusion independence in most evaluable participants [5]. Both studies provide strong disease-specific evidence, but their single-arm designs and follow-up do not establish lifelong benefit or eliminate the risks of intensive treatment.

In vivo editing offers a different route. Gillmore and colleagues delivered Cas9 components in lipid nanoparticles to reduce hepatic transthyretin production. Early reductions in circulating transthyretin demonstrated biological activity [6]. A biomarker response, however, does not by itself establish reversal of organ damage.

Oncology applications include engineering immune cells. A phase 1 study of multiplex-edited T cells in three patients demonstrated feasibility and persistence of modified cells, rather than definitive survival benefit [7]. In 2025, a patient-specific base-editing intervention for an infant with carbamoyl-phosphate synthetase 1 deficiency illustrated rapid individualized development and early clinical improvement [8]. A single case cannot establish broad effectiveness, but it expands the practical possibilities for rare diseases.

Table 1. Genome Editing Platforms and Medical Applications

Gene addition	Introduces a functional genetic sequence	May restore function without correcting the original variant.
Cas9 nuclease [1,4,5]	Targeted DNA cleavage followed by repair	Clinical hemoglobin applications; repair outcomes require assessment.
Base editing [2,8]	Selected single-base conversions	Variant-specific potential; editing window and byproducts constrain use.
Prime editing [3]	Substitutions and small sequence changes	Broad laboratory capabilities; delivery and efficiency remain important.
Multiplex editing [7]	Modifies several genomic targets	Immune-cell engineering; added genomic complexity requires testing.

Delivery and Clinical Safety

Ex vivo treatment allows cells to be collected, edited, and assessed before infusion. This supports product testing and characterization, although it cannot guarantee that every rare unintended event will be detected. Hematopoietic applications also require successful engraftment. In the exagamglogene studies, conditioning was an important component of the treatment pathway and its adverse-event burden [4,5]. Evaluation must therefore consider the complete procedure, not only the molecular editor.

In vivo delivery avoids external cell processing but places greater demands on tissue targeting and dose control. Lipid nanoparticles have enabled liver-directed editing in clinical studies [6,8]. Comparable delivery to other organs cannot be assumed. The number and type of cells reached, persistence of editing components, immune effects, and unintended distribution influence therapeutic performance.

Safety assessment should examine both unintended genomic sites and unexpected outcomes at the intended site. Multiplex editing adds complexity because several genomic cuts may interact; chromosomal rearrangements were specifically investigated in the engineered T-cell study [7]. Clinical follow-up must also assess disease control, organ function, and late adverse events. A high percentage of edited cells is useful evidence of activity, but it is not a substitute for a favorable clinical outcome.

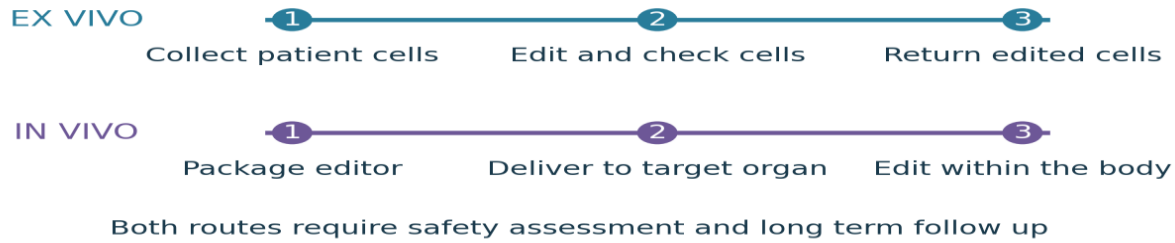


Figure 2. Ex Vivo and In Vivo Treatment Pathways

Future Perspectives and Responsible Translation

The next stage of development will depend on making editing more predictable and practical. Base and prime editing expand the range of addressable variants, but their foundational laboratory results do not establish equivalent clinical readiness across diseases [2,3]. Future studies need to show that the intended edit occurs in the relevant tissue and changes the natural history of illness.

Personalized editing creates a particular challenge: a treatment may be designed for very few patients, while manufacturing, quality assessment, and follow-up remain demanding [8]. Reusable development frameworks could improve feasibility, provided that each new target receives appropriate evaluation. Broader access will also depend on specialist infrastructure, reliable supply chains, and the affordability of the entire care pathway.

The therapeutic applications discussed here concern somatic cells. Their results do not justify extending clinical claims to heritable embryo editing. Informed consent should distinguish established outcomes from uncertain durability and experimental benefit. For research priorities, the most useful measure of progress is the relationship between patient benefit, treatment burden, and long-term safety.

Conclusion

Genetic engineering has progressed from programmable DNA targeting to clinically meaningful genome-editing interventions. Hemoglobin disorders provide compelling examples, while liver-directed editing, engineered immune cells, and individualized treatment demonstrate additional possibilities. Continued progress requires platform selection grounded in disease biology, effective delivery, and careful interpretation of clinical evidence. CRISPR-based medicine will achieve its greatest value when durable benefit becomes reproducible and accessible.

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