ISSN 2348-1218 (print)
International Journal of Interdisciplinary Research and Innovations ISSN 2348-1226 (online)
Vol. 14, Issue 4, pp: (14-20), Month: October 2026 - December 2026, Available at: www.researchpublish.com

# CRISPR- Cas9 for the Treatment of Monogenic Disorders: A Systematic Review of Therapeutic Efficacy, Genome - Editing Safety, Delivery and Translational Feasibility

Krupa Shah[1*], Keya Shah[2]

[1]Independent Researcher, Student IB Diploma, Surat, Gujarat, India

ORCID ID: 0009-0009-4830-6045

[2]Final Year MBBS Student, Kiran Medical College, Surat, Gujarat, India

ORCID ID: 0009-0004-2988-7423

**DOI:** https://doi.org/10.5281/zenodo.23689533

**Published Date: 27-October-2026**

***Abstract:*** **Background: Monogenic disorders are inherited diseases that are mainly caused by changes in a single gene. Lower the disease burden but they usually do not fix the original genetic problem. CRISPR-Cas9 genome editing offers a long-lasting therapy idea by changing DNA or its control routes.**

**Objective: This systematic review checked how well CRISPR-Cas9 therapies work how safe CRISPR-Cas9 editing is, how well CRISPR-Cas9 can be delivered and how ready CRISPR-Cas9 treatments are for real-world use in disorders.**

**Methods: We looked at papers from 2016 to 2025 in PubMed/MEDLINE, Embase, Scopus, Web of Science and Google Scholar. We pulled data on CRISPR-Cas9 efficacy, CRISPR-Cas9 editing efficiency, CRISPR-Cas9 safety, CRISPR-Cas9 delivery, CRISPR-Cas9 durability and CRISPR-Cas9 clinical translation. We used the PRISMA method for study selection. Of 300 records, we found 25 studies fit the criteria.**

**Results: CRISPR-Cas9 showed hopeful therapy results in blood, metabolism, liver, muscle and eye disorders. The best evidence was for sickle cell disease and transfusion-dependent β-thalassemia, where exagamglogene autotemcel (exa-cel; Casgevy) gave benefits. In conclusion, CRISPR-Cas9 has moved from a lab tool to a proven therapy platform for monogenic disorders.**

***Keywords:*** **CRISPR-Cas9, Sickle cell disease, DNA damage, monogenic disorder, Inclusion/Exclusion criterion, PRISMA.**

## 1. INTRODUCTION

Monogenic disorders, caused by pathogenic variants in a single gene, include sickle cell disease, β-thalassemia, cystic fibrosis, Duchenne muscular dystrophy, hereditary transthyretin amyloidosis, retinal disorders, and rare metabolic and immunological conditions. Conventional treatments can alleviate symptoms or replace deficient proteins, enzymes, or blood cells but rarely fix the genetic defect. Targeted genomic DNA modification with CRISPR-Cas9 genome editing may treat diseases. The discovery that guides RNA can program Cas9 to break site-Specific DNA [1] established the technology. After demonstrating clinical potential in sickle cell disease and β-thalassemia, exagamglogene autotemcel (exa-cel; Casgevy) became the first approved CRISPR-based therapeutic [2,3]. Despite these advances, clinical translation is difficult because therapeutic success depends on editing efficiency, genomic safety, delivery, durability, manufacturing, and long-term clinical outcomes. Off-target effects, genomic alterations, chromosomal abnormalities, and restricted tissue delivery of CRISPR components are concerns. Thus, systematic evidence evaluation is necessary. This review assesses CRISPR-

Cas9 therapy for monogenic disorders in four areas: therapeutic efficacy, genome-editing safety, targeted delivery, and translational feasibility to determine its clinical potential, limitations, and future applicability.

**Objectives**

The main goal of this review is to pull evidence about using CRISPR-Cas9 for monogenic disorders. The review looks at:

1. How well CRISPR-Cas9 works in preclinical models that is its therapeutic effectiveness.
2. How efficient and safe are different delivery methods, comparing delivery versus non-viral delivery when using CRISPR-Cas9.
3. Current milestones and the factors that determine whether CRISPR-Cas9 therapies can move from the lab to real patients.

## 2. METHODOLOGY

**Search strategy and study selection**

A cross-sectional survey of literature relevant to the present study was conducted using several databases like PubMed/MEDLINE, Embase, Scopus, and Web of Science. Due to insufficient data of region-specificity and clinical outcomes, Google Scholar was verified for arriving at additional sample size for the systematic review. The search focused on papers published between 2016 - 2025. The search key terms involved the "Genome editing", "CRISPR-Cas9", "monogenic disorders", "treatment", "safety" and "delivery".

**Inclusion and Exclusion criteria**

**Inclusion Criteria**

1. Human, animal, or cellular studies evaluating **CRISPR-Cas9** as a therapeutic genome-editing intervention.
2. Studies involving **monogenic disorders**.
3. Clinical trials, cohort studies, case reports, case series, and relevant **preclinical studies**.
4. Studies reporting **efficacy, editing efficiency, safety, delivery, durability, or translational feasibility**.

**English-language, peer-reviewed studies** and authoritative regulatory documents with full text or translation.

1. **Exclusion Criteria**
2. Multifactorial or acquired diseases without a clear **monogenic basis**.
3. Non-therapeutic applications of **CRISPR-Cas9**.
4. Editorials, commentaries, letters, and publications **without supporting evidence**.
5. Studies lacking **therapeutic or translational outcomes**.
6. Studies with insufficient accessible information or **duplicate publications**.

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) approach was employed for study selection after merging the duplicates (Figure 1).

**Data Extraction and Quality Assessment**

The finalized data was standardized for ubiquitous management protocol and checked for ambiguities in quality of data. Further, an external examiner was assigned to recheck the studies for optimal clinical outcomes and derivations for future research.

**Screening Process**

The screening process used a two-stage method. The first 100 unique records were found after removing duplicates.

Title/Abstract Screening: 100 papers were checked against the inclusion criteria. 74 Papers were removed (45 because the population was not correct, 15 because the intervention was not right, and 14 because the outcomes were not enough).

Full-Text Review: 26 papers were looked at in detail to see if they met the eligibility requirements. One paper was not included because there was no translational data.

Final Inclusion: A total of 25 papers were added for data collection and analysis.

ISSN 2348-1218 (print)
International Journal of Interdisciplinary Research and Innovations ISSN 2348-1226 (online)
Vol. 14, Issue 4, pp: (14-20), Month: October 2026 - December 2026, Available at: www.researchpublish.com

**Data Extraction**

Standard data collection was done for each study that was included. The information collected included study type, target disease, delivery method, gene editing efficiency, phenotypic outcomes and safety or toxicity data reported.

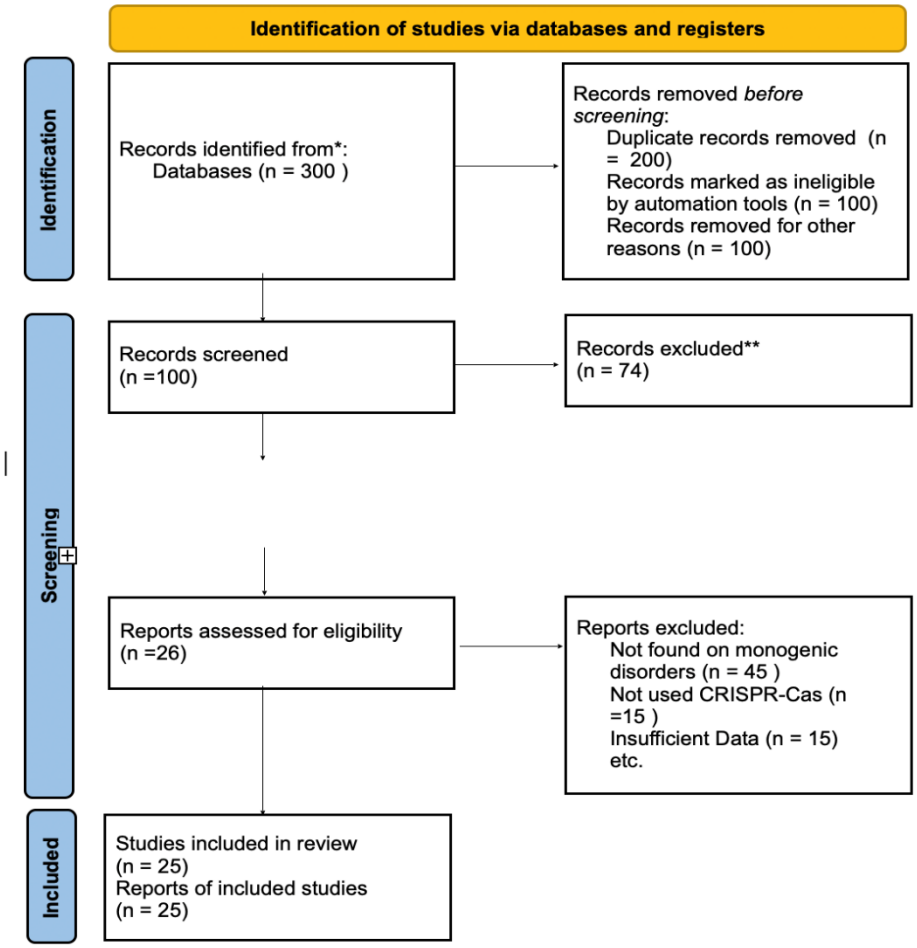



**Figure 1. PRISMA.**

## 3. RESULTS

**Study Selection**

The selection process is summarized in the PRISMA 2020 flow diagram below. From an initial pool of 300 records, deduplication and screening resulted in 25 studies that met all eligibility requirements.

**Study Characteristics**

The 25 included studies cover a range of monogenic conditions and stages of development:

1. Muscular Dystrophies: Studies focus on Duchenne Muscular Dystrophy (DMD) and use both in vivo animal models and ex vivo cell therapies (6) (7) (8).
2. Hematologic Disorders: A lot of the research is about Sickle Cell Disease (SCD) and Transfusion-Dependent β-thalassemia (TDT) (9) (10) (11)
3. Metabolic and Cardiovascular Diseases: Work includes Transthyretin Amyloidosis (ATTR) and Hemophilia A and B (12) (13). Familial hypercholesterolemia (14)
4. Other Genetic Conditions: There are also studies on Cystic Fibrosis (12) (15) and Dystrophic Epidermolysis Bullosa (DEB) (16).

The studies range from preclinical testing in animal models (mice, dogs, non-human primates) (13) to Phase I/II (17) and Phase III (9) clinical trials.

**Synthesis of Evidence**

The evidence base shows a shift from lab research to real-world medical use. The conditions that are most advanced in development include:

1. Sickle cell disease;
2. β-thalassemia;
3. Hereditary transthyretin amyloidosis;
4. Hereditary angioedema;
5. Selected inherited retinal disorders.

On the other hand, CRISPR-based treatments for DMD, cystic fibrosis, neurological disorders and many metabolic diseases are still mostly in the early research phase or early clinical trials.

**Therapeutic Efficacy**

CRISPR-Cas9 has shown strong results in different disease models. In Duchenne, Muscular Dystrophy studies have found that up to 90 percent of dystrophin can be restored to heart muscle. This restoration is linked with levels of creatine kinase and improved muscle function. Preclinical tests for DMD also show that base editing can fix nonsense mutations in 17 percent of muscle fibres (6).

When it comes to blood disorders, editing stem cells to increase fetal hemoglobin has worked well. The Exa-cel treatment (also known as Casgevy) showed improvements in clinical outcomes. Patients with β-thalassemia no longer need blood transfusions. People with sickle cell disease had vaso-occlusive episodes (9). For Hemophilia B, editing has been able to restore coagulation factor activity to more than 30 percent (18). Another trial found that CRISPR-Cas9 editing of the BCL11A enhancer led to increased γglobin expression in children (19).

Hereditary transthyretin amyloidosis (hATTR) is a dominant monogenic disorder caused by pathogenic TTR variants. Since the liver makes most of the transthyretin that circulates in the blood it is a target for in vivo CRISPR-Cas9 editing. NTLA-2001, a lipid nanoparticle that carries Cas9 mRNA and a guide RNA to TTR is designed to reach hepatocytes. In a in-human phase 1 study, this treatment led to average serum TTR reductions of 52% and 87% at day 28 when given at doses of 0.1 and 0.3 mg/kg respectively. The side effects were mostly mild, showing that in vivo CRISPR editing in humans can be done safely without needing to collect and modify cells, outside the body (20)

Hereditary angioedema HAE is a genetic disorder that causes repeated swelling that can be life-threatening because of too much kallikrein activity. NTLA-2002 is a treatment that uses CRISPR-Cas9, inside the body to target KLKB1. This treatment showed that it can lower levels in a way that depends on the dose. It also reduced HAE attacks (21).

**Safety and Genomic Integrity**

Safety is a priority when using CRISPR-Cas9 in clinical practice. The main worries that people keep talking about are off-target mutagenesis and genomic instability. Even though new Cas9 variants and better sgRNA designs have cut down these problems people still worry about deletions and the creation of micronuclei especially in human HSCs. New methods like base editing and prime editing are shown to help reduce double-strand breaks and the damage they cause (23). In one study scientists edited hematopoietic stem and progenitor cells and found that they could avoid large deletions while still editing precisely. The immune system can also be a hurdle. Studies show that people may react to the Cas9 protein or to the carriers, like AAV that bring the tool into cells. In some cases, giving a dose of AAV has been linked to liver problems and toxicity (24).

**Delivery Methods**

The efficiency of CRISPR-Cas9 depends largely on the delivery vehicle. Viral Vectors: Adeno-associated virus (AAV) AAV9 is used to target muscle and is a key delivery tool in both preclinical and clinical settings (22). Lentiviral and adenoviral vectors (23)

Non-Viral Systems: Lipid Nanoparticles (LNPs) are often used, especially for delivering NTLA-2001 for ATTR amyloidosis (22). Other non-viral methods include gold nanoparticles, electroporation and DNA nanocarriers (24). Ex Vivo Approaches: For blood disorders, electroporation of ribonucleoprotein (RNP) complexes into a patient's HSCs is the usual method used in therapies such as exa-cel (26, 27).

**Translational Feasibility and Clinical Progress**

A big step forward in this area happened in December 2023 when the US FDA approved exa-cel (Casgevy) for sickle cell disease and for people with transfusion-dependent β-thalassemia. This was the CRISPR-based product to get approval (28). Clinical studies are now growing in areas, such as pediatric thalassemia and heart-related treatments (29) The field is changing from experiments in labs to treatments used in hospitals. More studies are being done around the world. To fully use these new treatments, there are challenges. These include costs, problems from transplants and the need for rules that work the same in different countries (30).

## 4. DISCUSSION

The evidence reviewed shows that CRISPR-Cas9 has moved from being a lab tool to a treatment that has been proven in real patients for certain single-gene diseases. The approval of exa-cel is the proof of this change. It is important to note that the success of exa-cel does not require fixing the sickle-cell mutation. Instead, the treatment changes a part of the DNA that controls how much fetal hemoglobin is made. This shows that treating diseases with genome editing should be judged by how well it fixes the disease not just by fixing the mutation itself.

Another example comes from transthyretin amyloidosis. The study with NTLA-2001 shows that CRISPR parts can be put directly into the body using fat particles called lipid nanoparticles. This method can lower the protein a lot after just one dose. This opens the door for treating genetic diseases that affect the liver. NTLA-2002 adds proof that editing inside the body works. It shows that changing genes can greatly reduce the signs of hereditary angioedema.

The field should not think that CRISPR can treat every disease. Far success is mainly in diseases where the part of the body that needs treatment is easy to reach or where it is possible to take cells out, hange them and put them back. Blood diseases are candidates for taking cells out of the body changing them and putting them back. This is because the cells that make blood can be taken out worked on checked and put back in. Liver diseases are candidates for editing inside the body because the fat particles naturally go to the liver cells. On the other hand, diseases that affect the brain, the muscles or parts of the body spread out are much harder to treat. So, the future of CRISPR medicine will depend on balancing three things: precision, delivery and scalability. Precision is needed to reduce the risk to DNA. Delivery decides whether the treatment can get to the cells. Scalability decides if the treatments can help people beyond a small group of patients.

**Limitations**

Several limitations were identified in the body of evidence:

1. Long-term Safety: While short-term safety profiles (1-9 months) for some therapies like DEBCT appear favorable [12], there is a lack of long-term data regarding the persistence of edits and potential delayed genotoxicity or oncogenesis.
2. Delivery Efficiency: In vivo targeting remains suboptimal for organs requiring high viral doses that increase the risk of inflammatory responses
3. Cost: The complexity of ex vivo manipulation and the high cost of current clinical products (e.g. Casgevy) limit accessibility, particularly in resource-limited settings

## 5. CONCLUSIONS

CRISPR-Cas9 has emerged as a promising therapeutic platform for monogenic disorders, with clinical evidence supporting durable benefits in sickle cell disease, β-thalassemia, hereditary transthyretin amyloidosis, and hereditary angioedema. Approval of exa-cel established its clinical potential, while in-vivo approaches such as NTLA-2001 and NTLA-2002 demonstrate the potential of lipid nanoparticles for systemic delivery. However, off-target effects, unintended genomic changes, immune responses, delivery challenges, manufacturing complexity, long-term safety, high costs, and unequal access remain major barriers. Future progress requires organ-specific delivery, standardized safety assessment, scalable manufacturing, streamlined regulation, long-term monitoring, and equitable access. Ultimately, CRISPR-Cas9 offers the potential to transform molecular diagnoses into precise, durable, and potentially curative therapies.

## REFERENCES

[1] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable Dual-RNA-Guided DNA endonuclease in adaptive bacterial immunity. Science. 2012 June 28;337(6096):816–21.

[2] Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et al. Multiplex Genome Engineering using CRISPR/cas systems. Science. 2013 Jan 3;339(6121):819–23.

[3] Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, et al. RNA-Guided human genome engineering via Cas9. Science. 2013 Jan 3;339(6121):823–6.

[4] Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016 Apr 20;533(7603):420–4.

[5] Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019 Oct 21;576(576).

[6] Erkut E, Yokota T. CRISPR therapeutics for duchenne muscular dystrophy. International Journal of Molecular Sciences. 2022 Feb 6;23(3):1832.

[7] Happi Mbakam C, Lamothe G, Tremblay G, Tremblay JP. CRISPR-Cas9 gene therapy for duchenne muscular dystrophy. Neurotherapeutics. 2022 Feb 14;19(3).

[8] Laurent M, Geoffroy M, Pavani G, Guiraud S. CRISPR-Based gene therapies: From preclinical to clinical treatments. Cells. 2024 Jan 1;13(10):800.

[9] Levesque S, Bauer DE. CRISPR-based therapeutic genome editing for inherited blood disorders . Nature Reviews Drug Discovery. 2025 July 14;24(12):907–25.

[10] Wang Z. CRISPR-Cas9 technology in the treatment of sickle cell anemia (SCA). Academic Journal of Science and Technology. 2025 Dec 28;18(1):272–7.

[11] Ahmed R, Alghamdi WN, Alharbi FR, Alatawi HD, Alenezi KM, Alanazi TF, et al. CRISPR/Cas9 system as a promising therapy in thalassemia and sickle cell disease: A systematic review of clinical trials. Molecular Biotechnology. 2025 Jan 10;68(1):23–32.

[12] Zhang X. The CRISPR-Cas9 technology used for the treatment of single-gene genetic diseases. Theoretical and Natural Science. 2025 Sept 3;129(1):84–90.

[13] Chakravarthi S, Judson JP, Karikalan B, Gopalakrishna PK, SS A. CRISPR-Cas9 mediated gene editing in inherited hematologic disorders. Journal of Pharmacology, Genetics and Molecular Biology. 2025 Aug 4;1(4):12–23.

[14] Lu X, Zhang M, Li G, Zhang S, Zhang J, Fu X, et al. Applications and research advances in the delivery of CRISPR/Cas9 systems for the treatment of inherited diseases. International Journal of Molecular Sciences. 2023 Jan 1;24(17):13202.

[15] Sharma A, Singh P. CRISPR-Cas9 technology for combating genetic disorders. In: CRISPR-Cas9 Technology for Precision Medicine. 2026. p. 147–74.

[16] Neumayer G, Torkelson JL, Li S, McCarthy K, Zhen HH, Vangipuram M, et al. A scalable and cGMP-compatible autologous organotypic cell therapy for Dystrophic Epidermolysis Bullosa. Nature Communications. 2024 July 11;15(1).

[17] Fu B, Liao J, Chen S, Li W, Wang Q, Hu J, et al. CRISPR–Cas9-mediated gene editing of the BCL11A enhancer for pediatric β0/β0 transfusion-dependent β-thalassemia. Nature Medicine. 2022 Aug;28(8):1573–80.

[18] Miesbach W, Klamroth R, Oldenburg J, Tiede A. Gene therapy for hemophilia—Opportunities and risks. Deutsches Ärzteblatt international. 2022 Dec 27;119(51–52):887–94.

[19] Demirci S, Leonard A, Essawi K, Tisdale JF. CRISPR/Cas9 to induce fetal hemoglobin for the treatment of sickle cell disease. Molecular Therapy - Methods & Clinical Development. 2021 Oct;23(1):276–85.

[20] Gillmore JD, Gane E, Taubel J, Kao J, Fontana M, Maitland ML, et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. New England Journal of Medicine. 2021 June 26;385(6):493–502.

[21] Jalal L, Taimuri MA, Sumbal A, Ikram A, Ali T, Khan A, et al. CRISPR-Cas9 gene editing for hereditary angioedema: Current treatments and emerging therapies. Annals of Medicine & Surgery. 2025 Nov 7;87(12):8671–7.

[22] Lee BC, Lozano RJ, Dunbar CE. Understanding and overcoming adverse consequences of genome editing on hematopoietic stem and progenitor cells. Molecular Therapy. 2021 Nov;29(11):3205–18.

[23] Buffa V, Alvarez Vargas JR, Galy A, Spinozzi S, Rocca CJ. Hematopoietic stem and progenitors cells gene editing: Beyond blood disorders. Frontiers in Genome Editing. 2023 Jan 9;4(9):97142.

[24] He X, Urip BA, Zhang Z, Ngan CC, Feng B. Evolving AAV-delivered therapeutics towards ultimate cures. Journal of Molecular Medicine. 2021 Feb 16;99(5):593–617.

[25] Cetin B, Fulya Erendor, Yunus Emre Eksi, Ahter Dilsad Sanlioglu, Salih Sanlioglu. Advancing CRISPR genome editing into gene therapy clinical trials: Progress and future prospects. Expert Reviews in Molecular Medicine. 2025 Mar 31;1–96.

[26] Pérez-Maroto J, Sepp-Lorenzino L, Castaño-Esteban D, Palacios D, Sot B. Advancements in nonviral gene editing strategies for rare diseases. Human Gene Therapy. 2025 Sept;36(17–18):1118–37.

[27] Office of the Commissioner. FDA approves first gene therapy for young children with sickle cell disease. U.S. Food and Drug Administration. FDA; 2026.

[28] Frangoul H, de la Fuente J, Chopra Y, Meisel R, Amrolia PJ, Algeri M, et al. Exa-cel in children with transfusion-dependent β-Thalassemia or sickle cell disease. New England Journal of Medicine. 2026 June 10;.

[29] Zhang S, Wang Y, Mao D, Wang Q, Zhou H, Pan Y, et al. Current trends of clinical trials involving CRISPR/Cas systems. Frontiers in Medicine. 2023 Nov 10;10.