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REVIEW ARTICLE

CRISPR-Cas9 for Treating Genetic Blood Disorders: Promises and Limits

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ABSTRACT: Gene editing is a modern tool that shows promise in the treatment of genetic disorders. This review discusses major improvements in CRISPR regarding its mechanisms, delivery, safety, and clinical use. CRISPR alters DNA sequences to alter a gene's function. This is usually done by editing patient stem cells or immune cells through delivery methods. The clearest human efficacy signal comes from hemoglobinopathies, where editing increases production of protective fetal hemoglobin or corrects β-globin biology, leading to proven clinical benefit. In oncology, CRISPR's role is to enable more resilient cell therapies—by standardizing insertion sites and removing inhibitory checkpoints—rather than directly rewriting heterogeneous tumor genomes. Targeted delivery, preservation of stemness, genomic integrity, immune recognition of editing components, manufacturing complexity, and equitable access are examples of questions that surround CRISPR. New studies address these concerns with their inclusion of transient editors, double-strand-break-sparing technologies, orthogonal off-target assessments, and rigorous lot-release criteria. However, while these new studies are furthering CRISPR studies in the right direction, longer follow-up is still needed. Overall, the field has shifted from theory to clinical reality. CRISPR's next steps should revolve around targeting possible scientific improvements and prioritizing ethical use and access to the tool.

KEYWORDS: Cell Immunology, Cell and Tissue Engineering, Genetics, Genetic and Molecular Biology of Disease, Disease Treatment and Therapies.

Introduction

DNA is the building block that determines the composition of every living being, but small disruptions in this code can often lead to major health problems. Many genetic disorders—such as cystic fibrosis, sickle cell disease (SCD), and β-thalassemia—are caused by mutations in DNA that affect a gene's function.[1] Traditional treatments have only been able to target the symptoms of these disorders through methods such as bone marrow transplants, transfusions, and hydroxyurea rather than directly targeting their underlying genetic causes.[2] Despite countless years of research, there have been very few slightly curative solutions, leaving an issue in genetic medicine. There is a lack of an accessible, deliberate, and durable solution to correct pathogenic mutations at their root source.

In modern-day science, advances in molecular biology have begun to target this issue. Initial genome editing tools, such as zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), have demonstrated that human DNA can be modified, but these tools were too expensive, complex, and difficult to utilize to target each new mutation.[3] The discovery of CRISPR–Cas9 has revolutionized the field by providing a simpler, more programmable tool for site-specific DNA editing.[2,3] With the technology of programming RNA guides with enzymes, CRISPR has been able to target the root cause of several genetic disorders. This technology has given the scientific world the ability to repair pathogenic mutations in stem cells, allowing for a multitude of clinical possibilities to open up. Yet, as CRISPR-Cas9 advances and moves from preclinical research into human application, it becomes increasingly important to understand the technology's promises and its limitations. Identifying CRISPR-Cas9's abilities, such as allowing durable correction of monogenic mutations in accessible cell populations like hematopoietic stem cells, allows scientists to utilize the technology safely. Additionally, understanding the technology's limitations, such as its inability to target a plethora of genes without great cost, allows scientists to navigate the liabilities needed to translate clinical successes into safe, scalable, and ethical therapies.

As it stands, CRISPR is good at targeting single genes to attack a malicious tumor, while it falls short in terms of being able to edit complex genetic mutations.[4,5] This review argues that CRISPR-Cas9 has already achieved clinically durable benefit in monogenic hemoglobinopathies through *ex vivo* editing of hematopoietic stem and progenitor cells (HSPCs), but maintaining similar successes in polygenic blood cancers and improving the accessibility of CRISPR requires improvements in CRISPR itself, such as biological improvements and overall improved regulation of the tool.

Methodology

This is a narrative, problem-oriented literature review covering 2010–2025, the period in which the first reports of CRISPR–Cas9 editing in mammalian cells were reported, to the first regulatory approvals and late-phase results. PubMed, Google Scholar, and ClinicalTrials.gov were the primary sources from which journals and studies were obtained. A significant number of regulatory reports from the FDA/EMA were cross-referenced with sources and trials to check for approval status and safety monitoring.

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Key terms such as "CRISPR–Cas9 hematopoietic stem cells," "*BCL11A* enhancer editing," "fetal hemoglobin reactivation," "CTX001/exa-cel results," "base editing *HBG* promoters," "CRISPR off-target," "high-fidelity Cas9," "electroporation," and "CRISPR-engineered immune cells," etc., were used in the process of searching for reliable sources. Sources that contained well-characterized editing strategies and readouts (on-target rate, off-target profiling, functional rescue), clinically meaningful results in human trials (e.g., transfusion independence, VOC-free survival), or insight with applicability to blood disorders were prioritized in the source selection process. Non-academic sources were only included to verify the clinical usage of gene editing tools and to back up common claims, and peer-reviewed studies and governmental recognition verified all data from such sources. It is important to note that all sources were gathered online without any physical tools or materials.

Screening was done in three phases. Firstly, papers outside hematology or primary data were excluded. Second, trials that had rigorous specificity testing (e.g., GUIDE-seq), new enzyme innovations (e.g., eSpCas9, SpCas9-HF1), and good delivery/manufacturing methods were prioritized. Finally, the results were sorted by the topics that they discussed. Basic CRISPR mechanisms where editing is most useful (monogenic vs. complex disease); delivery methodologies (*ex vivo* electroporation, AAV6 donors, lipid nanoparticles), safety (off-targets, large on-target changes, immunity), and clinical translation (exa-cel results; building base-editing programs) were all topics of major interest.

Brief History and Mechanism of Gene Editing:

Gene editing has a long history that did not begin with CRISPR. Early tools, such as zinc finger nucleases (ZFNs) and transcription activators like effector nucleases (TALENs), allowed scientists to cut DNA at chosen sites. However, these technologies were hard to design and manipulate to work for each new target.[2,5,6] CRISPR-Cas9 changed the field by making targeting DNA simple. You swap a short guide RNA to point CRISPR-Cas9 to almost any DNA sequence, and then CRISPR-Cas9 makes a double-strand break at that site.[5] The cell then fixes that break by one of two main pathways. The first being non-homologous end joining (NHEJ).[4] NHEJ is fast, but it often isn't accurate.[5] It was common for NHEJ to delete or insert new letters and completely change a gene and cause mutations.[4,5]

Homology-directed repair (HDR) is slower but allows scientists to cause precise changes when a DNA repair template is provided.[4-6] The first landmark papers in 2012–2013 showed that CRISPR-Cas9 could work in bacteria and mammalian cells while allowing for multiplex editing, which meant that several genes could be changed at once.[2,3,7] Researchers then began mapping off-target cutting and building "high-fidelity" Cas9 variants to improve specificity in gene targeting and editing.[4] At the same time, gene editing technologies delivery went from viruses to electroporation and lipid nanoparticles, depending on the tissue.[7,8]

Together, these advances have turned gene editing from a niche lab technique into a mainstream platform with real clinical paths. Due to the biology of blood disorders, CRISPR is able to target their root causes with more ease compared to other types of disorders.[9] Blood stem cells can be collected, edited outside the body, where quality can be checked, and then reinfused after conditioning.[9] The practicality of this, plus strong genetic targets, explains why hematology became the first clinical proving ground for CRISPR.

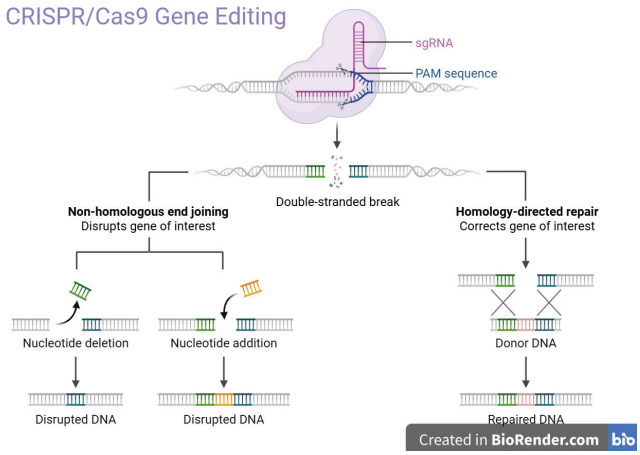

Figure 1: CRISPR-Cas9 Process. This figure shows the process of CRISPR-Cas9 gene editing with either non-homologous end joining or homology-directed repair. Created using BioRender.

Introduction to CRISPR-Cas9: Mechanism and Significance:

CRISPR-Cas9 is a two-part system. There is the guide RNA that finds a matching DNA sequence, and the Cas9 enzyme that cuts there, as shown in Figure 1.[6] This can be thought of as the "address" of the target and Cas9 as the "scissors" that edit the target. Because the guide is easy to design, CRISPR can be retargeted quickly across the genome.[4] After Cas9 makes a cut, cells repair the change either by NHEJ (which often disables the gene) or HDR (which allows for precise fixes), as illustrated in Figure 1.[7] Base editors chemically change a single DNA letter without cutting both strands, which can lower the risk of big changes to the DNA sequence.[10] Prime editors use a reverse transcriptase to "write" new sequences with fewer breaks.[6,10]

In the blood, editing is typically done *ex vivo* by electroporating CRISPR components into hematopoietic stem and progenitor cells (HSPCs) and then transplanting them back.[11] For liver diseases, lipid nanoparticles deliver CRISPR *in vivo*.[12] This approach was proven to work well in transthyretin amyloidosis.[12] Any accidental cuts are tracked with unbiased methods such as GUIDE-seq to eliminate unintentional edits caused by the editing.[4,7] The next-generation Cas9 variants significantly reduce spurious activity that was common in previous generations of the tool.[2]

While CRISPR seems to work in almost all use cases, scientists also must pay attention to immune responses against bacterial Cas9 proteins and to large off-target deletions that sometimes arise from double-strand break repair.[10,13,14] CRISPR matters because it mixes precision with practicality,

allowing for better treatment of genetic disorders. For blood disorders that have clear genetic drivers, it lets us either correct the mutation directly or change a regulatory switch that compensates for it, with results already strong enough to earn the early regulatory approvals that are already saving lives.[9,15]

Monogenic vs. polygenic blood disorders — where CRISPR fits best:

CRISPR works best when the target it's dealing with is simple and is vital to the creation of the disorder.[3] Single-gene (monogenic) diseases like sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) fit that category.[9] Well-understood changes in the β-globin locus drive both of them.[9] Editing a regulatory element to raise fetal hemoglobin (HbF) can bypass the defective adult hemoglobin and reduce symptoms in the disorder. Clinical trials with this strategy, as seen by the Exagamglogene Autotemcel (exa-cel/Casgevy) trials, show durable HbF induction, transfusion independence in TDT, and elimination of Vaso-occlusive crises that occur in most SCD patients.[9,15]

Polygenic or genomically complex diseases like acute lymphoblastic leukemia (ALL) are tougher to combat with CRISPR because ALL involves a plethora of mutations and clones that evolve.[16] That makes a single "fix" unrealistic. Instead, CRISPR's value in curing the disorder is often indirect. CRISPR-Cas9 engineers immune cells (like CAR-T cells) to work better; or by modeling resistance pathways or targets; and by combining edits (such as knocking out PD-1 or TCR chains) to kill a greater number of tumors with great effectiveness while limiting exhaustion.[16]

In short, monogenic blood disorders are the easiest to attack with CRISPR because CRISPR only has to edit one gene in order to be effective in removing the disorder. In polygenic disorders, specifically leukemias, CRISPR is more of a tool to assist the current cell therapies and to study disease genetics rather than being the final cure-all solution.

Snapshots of key blood disorders with single-gene drivers:

Many hematologic diseases are monogenic, making them natural candidates for CRISPR intervention, while others are syndromic or in predisposition states where editing may be feasible but ethically and technically complex.

An example of such monogenic diseases would be Hemoglobinopathies (*HBB* locus). Sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) are caused by pathogenic variants in *HBB*. Editing either one reactivates fetal hemoglobin by disrupting the erythroid *BCL11A* enhancer or by altering *HBG* promoters. *Ex vivo* CRISPR tools have delivered durable HbF induction with the removal of Vaso-occlusive crises in SCD and transfusion independence in most TDT patients, leading to regulatory approval.[3,15,17]

Further diseases, such as Hemophilia A/B (*F8*/*F9*), are also monogenic diseases. Hemophilia A results from *F8* variants and Hemophilia B from *F9* variants, both X-linked genes and characterized by factor VIII or IX deficiency and bleeding diathesis.18 CRISPR strategies aim at editing the liver (e.g., AAV/LNP-delivered editors) to restore factor production and correct hotspot mutations. With this disorder, base/prime editing may reduce double-strand break risks.[18]

Inherited neutropenia is a monogenic blood disorder where pathogenic variants in *ELANE* (neutrophil elastase) can lead to cyclic or severe congenital neutropenia, with a high risk of infection and a measurable risk of MDS/AML in the congenital form.[19] Gene correction in autologous HSCs is the logical path to treatment, but it contains its dangers due to the chance that malignant mutations can occur independent of therapy.

Another monogenic blood disorder would be bone marrow failure/ribosomopathies. Diamond-Blackfan anemia is most often caused by haploinsufficiency, where a patient only has one functional copy of a gene, for ribosomal protein genes (e.g., *RPS19*), producing red cell aplasia with congenital anomalies.[20] The genetic heterogeneity (dozens of genes) complicates a single target edit, though base editing of specific founder alleles is being studied preclinically.[5]

Preclinical gene therapy groundwork in SCD and TDT:

Before the first human CRISPR trials, laboratory research demonstrated that genetic editing could correct the sickle cell mutation in human CD34+ cells and recreate healthy red blood cells.[21] Early research used HDR templates to fix the Glu6Val substitutions in *HBB*, leading to a restoration in adult hemoglobin levels in edited cells that could then be grafted into mice.[21,22] Concurrently, researchers discovered another method of correcting the sickle cell mutation. Instead of editing *HBB* directly (which is hard to scale with HDR), if a regulatory switch is disrupted, the fetal hemoglobin levels will rise. Through saturation mutagenesis, the small enhancer of the *BCL11A* gene in erythroid cells was mapped, and with that, scientists learned that editing this enhancer sharply increases HbF, which does not cause red blood cells to be sickled and can compensate for *HBB* defects.[17]

This strategy is the more commonly used one because it relies on NHEJ (efficient) and because HbF reactivation has a long clinical track record of success in hydroxyurea-treated patients. These preclinical successes led to the *ex vivo* design being used clinically.[23] The process is as such. First, HSPCs are mobilized, then CRISPR-Cas9 RNPs that target the *BCL11A* erythroid enhancer (or nearby HbF promoters) are electroporated, the product is verified and double checked to account for concerning off-targets, and finally, the product is reintroduced into the patient's body.[17] Animal models further confirmed long-term engraftment and normal HbF expression from edited stem cells. By 2020–2024, data from multicenter trials showed transfusion independence in TDT and near complete suppression of Vaso-occlusive crises in SCD, paving the way for widespread use of this method to combat SCD.[3,15] These studies also helped create the safety guidelines in these types of treatments.[23] By creating a process where off-targets are monitored with unbiased assays, large deletions are quantified and measured, and bank backup cells are stored in case re-collection is needed.

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Why BCL11A enhancer targeting works (and other promising targets):

BCL11A represses γ-globin in adult-type red cells. In people with certain natural mutations in the γ-globin genes, HbF levels stay high for the person's lifetime, and their cells are protected against SCD and TDT. CRISPR leverages this biology by disrupting a short, erythroid-specific enhancer within intron 2 of *BCL11A*. Because that enhancer is active primarily in red blood cell precursors, editing it raises HbF levels without removing *BCL11A* in the immune or nervous systems, where the gene has other important roles.[17]

Clinically, gene enhancer edits lift HbF levels to a level that dilutes or replaces sickling hemoglobin, which leads to improving anemia and preventing crises in the blood. Alternative targets follow the same logic. By editing the *HBG1/2* promoters to weaken *BCL11A* binding (base editing with BEAM-101), or by tweaking other transcriptional regulators in the fetal hemoglobin to adult hemoglobin switch.[24] Outside hemoglobinopathies, targets depend on disease biology. In immune cells, edits to *TRAC* (to standardize CAR expression), edits to *PDCD1* (PD-1, to sustain activity), or edits to checkpoint pathways can boost antitumor effects in cells.[25,26]

In leukemias, some groups test the editing of surface antigens or resistance nodes, but the difficulties are greater when changing malignant genomes.[16] Overall, *BCL11A* enhancer targeting works due to its nature, which is mechanistically grounded, efficient with NHEJ, and tissue-restricted, which explains its success compared with more invasive genome rewrites. Base editing and prime editing may improve treatments further by avoiding double-strand breaks and reducing risks like large DNA sequence deletions.

Emerging trials: exa-cel (CTX001/Casgevy) and next-gen editors:

The most advanced gene editing program as of right now is Exagamglogene Autotemcel (exa-cel; formerly CTX001, now Casgevy), which edits the *BCL11A* erythroid enhancer in autologous HSPCs.[9,15,27] In pivotal studies, most SCD patients became free of Vaso-occlusive crises, and most TDT patients achieved durable transfusion independence by using this therapy.[15] The U.S. and U.K. authorized the therapy in late 2023, allowing for it to become mainstream.[8,10,27] Now, base editors aim to raise HbF levels while avoiding double-strand breaks. BEAM-101 base edits *HBG* promoters to reduce *BCL11A* bindings with early reports showing a strong HbF induction (above 60%), rapid engraftment, and no post-engraftment crises in small trial cohorts, though data is still being collected.[24]

Editas's Reni-cel (formerly EDIT-301) uses an AsCas12a nuclease to cut *HBG* promoters. Early updates in the trial also suggest high HbF levels and crisis freedom with limited follow-ups for patients. For cancers, CRISPR enables "armored" T cells and precise CAR attacks at defined loci like TRAC, which produce more uniform, less exhausted cells in preclinical models, and the first human polygene editing has shown proof that it may be successful.[25,26] Trials conducted, such as this one focusing on NTLA-2001, which uses lipid nanoparticles delivering Cas9 mRNA and guide RNA to the liver, reduce transthyretin protein levels in patients with ATTR amyloidosis and validated systemic editing in humans.[5,28]

Together, these studies outline a future with tailored editors (Cas9, Cas12, base, prime), smarter cell therapies, and broader applications, given that long-term safety in gene editing remains possible.

Delivery methods - viral vectors, nanoparticles, and electroporation:

The method of delivery matters just as much as the genetic edit itself. For blood disorders, the standard approach of delivery is to edit cells outside the body (*ex vivo*). Doctors collect a patient's blood stem cells ($CD34^+$ HSPCs), then use electroporation to briefly open the cell membrane and push in a CRISPR-Cas9 guide RNA ribonucleoprotein (RNP).[29] Because the nuclease is present only for minutes to hours, this reduces off-target risk and avoids long-term enzyme expression.[3,30]

If a precise insert is needed, such as placing a CAR at the *TRAC* site, a short DNA "template" will be supplied during the repair, with AAV6 often being used to deliver that template for homology-directed repair (HDR).[25] Many groups avoid viral delivery of the nuclease itself when used, as AAV6 is typically just a donor for HDR, not the editor.[3] *In vivo* delivery is different as the solution is directly inserted into the target region. Lipid nanoparticles (LNPs) that carry Cas9 mRNA and guide RNA to the liver enabled the first systemic CRISPR editing in people (NTLA-2001), demonstrating that infusion-based editing is feasible.[28] As it stands, bone-marrow targeted LNPs are under active study, but most hematology programs still use *ex vivo* editing because it's auditable and allows strict lot release testing before cells are returned to the patient.[3,12] Quality control typically checks editing efficiency, off-targets, vector copies (if any), and cell function (stemness for HSPCs, killing capacity for T cells). As base and prime editors mature and the methods of delivery improve, more *in vivo* hematology applications may appear, but the current clinical standard remains clean, virus-free *ex vivo* manufacturing.[12,31]

Safety concerns - off-targets, immune responses, and large edits:

Most major safety concerns regarding CRISPR-Cas9 can be grouped into three main groups. First, off-target edits. RNA guides can sometimes send Cas9 to similar DNA sites, leading to further damage from CRISPR.[7] Researchers lower this risk with improvements in guide design, high-fidelity Cas9 variants, and unbiased mapping tools like GUIDE-seq before products reach patients.[32]

Second, immune responses. Because Cas9 comes from bacteria, some people already have T cells or antibodies that recognize it.[30] This is one of the main factors as to why *ex vivo* products use transient RNPs. Early trials have shown that edited cells can persist without obvious immune rejection, disproving this concern.[33]

Third, large on-target changes. Double-strand breaks can occasionally cause big deletions or rearrangements at the intended cut site that basic PCR might miss. Long-read sequencing and

other assays have detected such events in HSPCs and T cells at low to moderate rates depending on the locus.[10]

Doctors work to minimize double-strand breaks (short Cas9 exposure, high-fidelity enzymes), use DSB-free editors when a single-letter change will do (base/prime), and add release assays to screen out risky alleles to alleviate these concerns.[10,20,33] For cell therapies, the usual CAR-T toxicities (cytokine release syndrome and neurotoxicity) still apply and are monitored as standard of care.[26]

Table 1: Collection of clinical trials from clinicaltrials.org, evaluating gene editing therapies in select blood disorders.

Product / Name	Condition(s)	Editing modality	Genetic target	Key Findings
Exagamglogene Autotemcel (exa-cel, CTX001) - CLIMB THAL-111	Transfusion-dependent β-thalassemia(TDT)	CRISPR-Cas9	*BCL11A* erythroid enhancer	Most patients achieved durable transfusion independence; Hb typically >11 g/dL; safety consistent with busulfan conditioning.[34]
Exagamglogene Autotemcel (exa-cel, CTX001) - CLIMB SCD-121	Sickle cell disease (SCD)	CRISPR-Cas9	*BCL11A* erythroid enhancer	97% of evaluable pts free from severe VOCs for ≥12 months; HbF ~40% with pancellular distribution; safety consistent with conditioning.[35]
CLIMB-131 long-term follow-up (LTFU)	SCD and β-thalassemia long-term follow-up of CTX001 recipients	CRISPR-Cas9	*BCL11A* erythroid enhancer (parent studies)	Edited allele levels stable in blood & marrow; sustained clinical benefit reported in follow-up cohorts.[36]
EDIT-301 (Reni-cel) - RUBY	Severe sickle cell disease	CRISPR-Cas12a (Cpf1)	*HBG1/2* promoters (γ-globin upregulation)	Early data show robust HbF (~40–50%), total Hb ≥11 g/dL, and elimination of VOCs in most evaluable pts to date.[37]
EDIT-301 - EdiTHAL	Transfusion-dependent B -thalassemia	CRISPR-Cas12a (Cpf1)	*HBG1/2* promoters	Early participants show increased HbF and reductions in transfusion needs; some achieve transfusion independence.[38]
BEAM-101 - BEACON	Severe sickle cell disease with recurrent VOCs	CRISPR adenine base editing	*HBG1/2* promoter	Initial cohorts show increased HbF (>40% in many) and reductions in VOCs; safety is acceptable so far.[39]
BIVV003 - PRECIZN-1	Severe sickle cell disease	Zinc Finger Nuclease	*BCL11A* erythroid enhancer	Early pts showed HbF elevation (e.g., ~45% in one improved-manufacture pt) and VOC reduction; program deprioritized pending partner.[40]
Long-term safety/ efficacy follow-up for BIVV003 / ST-400	LTFU in SCD (BIVV003) & β-thalassemia (ST-400) recipients	ZFN	*BCL11A* enhancer (parent)	LTFU safety/efficacy monitoring of prior ZFN-treated participants.[41]
ST-400 - THALES	Transfusion-dependent B-thalassemia	Zinc Finger Nuclease	*BCL11A* erythroid enhancer	Prompt engraftment; HbF induction observed; mixed clinical benefit; limited dataset.[42]
SB - FIX	Hemophilia B	Zinc Finger Nuclease	Albumin locus knock-in of *F9*	First-in-human *in vivo* ZFN editing; no sustained FIX expression; program discontinued.[43]
OTQ923	Sickle cell disease	CRISPR-Cas9	*BCL11A* (HbF induction)	Proof-of-concept *BCL11A*-targeting program; study ended; no posted outcomes on registry.[44]
Exa - cel pediatric - CLIMB - 151	Pediatric severe SCD (ages 2-11)	CRISPR-Cas9	*BCL11A* erythroid enhancer	Pediatric expansion of exa-cel; results pending.[45]
Exa - cel in HbSC	Severe SCD, Bs/ Bc genotype (HbSC)	CRISPR-Cas9	*BCL11A* erythroid enhancer	Early-stage CRISPR program; no human efficacy data yet.[46]
CS - 101 (CorrectSequence)	Severe sickle cell disease	Base editing	HBG promoter (*BCL11A* binding site)	Early-stage CRISPR program; no human efficacy data yet.[47]

Discussion

This collection of trials revolving around monogenic blood disorders shows that, as discussed before, the CRISPR-Cas9's efficacy is strongly backed by the evidence from the results discovered by these trials, as summarized in Table 1. Looking at the table, the *ex vivo* editing of autologous $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) has consistently delivered durable clinical benefit in both β-thalassemia and sickle cell disease (SCD).[9,15,24] In transfusion-dependent β-thalassemia, Exagamglogene Autotemcel (exa-cel; Casgevy) treatment led to transfusion independence in around 91% of patients, with mean hemoglobin concentrations around 13 g/dL and pan-cellular HbF distribution.[15] Similarly, in sickle cell disease, roughly 97% of participants were free from severe Vaso-occlusive crises (VOCs) for more than 12 consecutive months, and 100% avoided VOC-related hospitalizations over the same time period, with sustained increases in HbF and improvements in hemolysis markers.[3,21,22] Table 1 highlights a consistent association between CRISPR-based editing and increases in fetal hemoglobin. These findings, as well as regulatory approval for public use by the U.S Food and Drug Administration in 2023, give reason to believe that *ex vivo* CRISPR-Cas9 editing of CD34+ HSCs can be used commercially to produce persistent benefits in humans.[27]

However, translating these same clinical successes to blood cancers requires that the role of CRISPR be more indirect. Rather than directly repairing malignant genomes—which are often unstable and polyclonal—CRISPR is used to enable the precise engineering of immune effector cells.[14,33] For example, targeted integration of chimeric antigen receptor (CAR) constructs at the *TRAC* locus reduces tonic signaling, promotes uniform CAR expression, and enhances antitumor persistence in acute lymphoblastic leukemia.[16,25] Multiplex editing has allowed for the simultaneous removal of inhibitory receptors such as PD-1 and TCR chains, producing armored T cells with improved resilience and reduced cell fatigue.[26] In pivotal studies on anti-CD19 CAR-T therapies—such as tisagenlecleucel and Brexucabtagene autocel—continue to set clinical benchmarks, with complete response (CRi) rates around 70%, drastically improving survival outcomes in patients.[48] CRISPR-enabled T-cell engineering contains the potential to eventually standardize manufacturing, minimizing variability between batches of solutions, and overall lead to "off the shelf" allogeneic cell therapies that can be used as regular medicine that can be more widely accessible.

While the promise of allogeneic CRISPR solutions is one of success and feasibility, the transition from autologous to allogeneic CRISPR platforms will require careful evaluations of individual immune compatibility and graft versus host risks.[30-32] Nuanced approaches to these issues, such as multiplex knockouts of *HLA* genes or the additions of edits to improve the stealth of edited cells to evade a host's immune system, are currently being explored. At the moment, ensuring the genomic stability of heavily edited cells is a priority in research regarding CRISPR. Long-term sequencing and orthogonal mapping methods have detected multiple low-frequency large deletions in DNA sequences and rearrangements at target loci, which might carry unpredictable long-term consequences.[10] Therefore, there must be a balance between the ambition of multi-gene editing and the safety guidelines that have been established for clinical trust.

While CRISPR technology may be feasible scientifically, there are significant discussions regarding the ethical aspects of CRISPR usage. While Exa-cel may have received authorization to be used in the market, the therapy's estimated list price of around 2.2 million USD illustrates the unethical divide between members of differing socioeconomic groups, determining access to life-saving treatments.[49] Even with managed access agreements, treatments are restricted to a small number of specialized centers in high-income countries. For low and middle-income nations where hemoglobinopathies are most

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common, these economic barriers are prohibitive. If CRISPR is to be fully realized as what it is meant to be, scientists must scale manufacturing, simplify conditioning regimens, and build global infrastructure for genomic therapies. While the ethical concerns of access exist, there is a much larger debate over whether genome editing is a moral practice. Both the U.S. National Academies (2017) and the WHO (2021) emphasize that somatic genome editing should only be conducted with strict frameworks in the usage of this tool, with no margin for error.[50,51] In order to practically implement this technology, there should be rigorous informed consent procedures, community engagement, and global data sharing to track the long-term outcomes of genome editing. As the field shifts towards *in vivo* editing approaches and base or prime editors that blur the line between somatic and heritable changes, there must be ethical oversight over this whole process. With CRISPR having the ability to not only edit the genes of one individual but also their bloodline, genome editing should be used with care.

Finally, while CRISPR's success in hemoglobinopathies is evident, the next step for the technology involves extending its reach. This includes refining delivery systems such as bone marrow tropic lipid nanoparticles, exploring gentler conditioning methods, and applying double-strand break-free editors for more predictable outcomes. CRISPR's future now depends not only on molecular innovation but on the whole field of bioengineering, regulatory policy, and social equity.

Conclusion

In conclusion, CRISPR-Cas9 has proven its reliability in delivering consistent, durable clinical benefits when treating monogenic blood disorders, specifically sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT). Furthermore, when the results from the trials were analyzed, the *ex vivo* editing of cells led to positive results being found within patients. With these results being combined with the fact that some CRISPR-Cas9 treatments, such as exa-cel, have received regulatory authorization in the United States and the United Kingdom, CRISPR-Cas9 establishes itself as one of the leading modern tools in the battle against genetic disorders.

In polygenic blood disorders, CRISPR shows potential in the treatment of these genomically complex malignancies, such as leukemias and lymphomas, by utilizing its ability to adapt to a multitude of scenarios. With researchers using CRISPR-Cas9 to improve immune systems and support other systems within the body, CRISPR-Cas9 can still fight against polygenic disorders through unconventional routes. Site-specific integration of chimeric antigen receptors (CARs) at the *TRAC* locus and the multiplex deletion of inhibitory receptors like TCR chains enhance the ability of CAR-T cell therapies.

Finally, CRISPR-Cas9 has advanced from being a theoretical concept to a critical clinical tool. From its success in monogenic disorders to its adaptability in the treatment of polygenic blood disorders, the evidence shows that genome editing can produce sustainable cures when used with precision, safety, and ethical oversight. As the various aspects of CRISPR, such as its delivery methods and global accessibility, continue to be improved, CRISPR will redefine how medicine approaches the treatment of blood disorders.

While this is a comprehensive review regarding the subject of CRISPR and blood disorders, there is a plethora of limitations. Firstly, it must be recognized that while there are a multitude of sources within this review, this review cannot include and compare all the sources available regarding this subject. The decision in choosing which sources to reference and use in the review may have led to some information biases. The rapid nature of this field, in which discoveries are constantly being made, leads to this review being unable to account for current discoveries from Aug 25th, 2025, and onwards. Finally, due to many of the trials being analyzed still being continued as those trials mature, the conclusions established in this review may need to be revisited.

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