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CRISPR-Cas Systems in Functional Genomics and Therapeutics

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ABSTRACT

CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated proteins) systems have revolutionised functional genomics and therapeutic development by providing programmable, precise, and efficient tools for genome editing, transcriptional regulation, epigenome remodelling, and base editing across virtually all organism types. This review comprehensively surveys the mechanistic diversity of CRISPR-Cas systems--from the nuclease-active SpCas9 and SaCas9 to the RNA-targeting CasRx, the single-base editors BE3 and ABE, and the versatile prime editors PE2 and PE3--and evaluates their application across two transformative domains: functional genomics, including genome-wide CRISPR screens, CRISPRi/CRISPRa transcriptional perturbation libraries, and epigenome editing for gene regulatory network dissection; and therapeutics, covering ex-vivo haematopoietic stem cell editing for sickle cell disease and beta-thalassaemia, in-vivo liver-targeted delivery for transthyretin amyloidosis (NTLA-2001), CAR-T cell engineering, and emerging in-vivo CNS and muscle delivery approaches. Clinical trial progress as of 2025 is reviewed, including the landmark FDA and EMA approval of Casgevy (exa-cel) for sickle cell disease and beta-thalassaemia in December 2023--the first approved CRISPR therapeutic--and the expanding pipeline of 47 active clinical trials. Delivery systems, off-target safety profiles, immunogenicity, and regulatory considerations are critically evaluated. The review concludes by identifying the five most impactful near-term advances: prime editing clinical translation, in-vivo muscle CRISPR delivery, epigenome-only editing, pan-genome CRISPR libraries, and AI-guided guide RNA design.

Keywords: CRISPR-Cas9; Genome editing; Functional genomics; CRISPR screens; Base editing; Prime editing; Therapeutics; Sickle cell disease; CAR-T cells; Gene therapy

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1. Introduction

The discovery that bacteria and archaea employ clustered regularly interspaced short palindromic repeats (CRISPR) and their associated Cas proteins as an adaptive immune system against bacteriophage and plasmid invasion set the stage for one of the most consequential technological breakthroughs in the history of the life sciences (Barrangou et al., 2007). The 2012 demonstration by Jinek et al. that a two-component system consisting of the Cas9 endonuclease and a programmable single guide RNA (sgRNA) could be directed to cleave virtually any double-stranded DNA sequence bearing a protospacer-adjacent motif (PAM) established CRISPR-Cas9 as a universal genome editing platform accessible to any laboratory capable of synthesising a 20-nucleotide guide RNA sequence. The subsequent decade witnessed an extraordinary acceleration of CRISPR technology development, diversification, and application: from the first demonstrations of mammalian cell editing (Cong et al., 2013) to the landmark 2023 regulatory approval of the first CRISPR therapeutic, Casgevy (exagamglogene autotemcel; exa-cel), for sickle cell disease and transfusion-dependent beta-thalassaemia by the FDA and EMA--an event marking the transition of CRISPR from research tool to clinical medicine (Frangoul et al., 2021).

1.1 Scope of this Review

This review surveys CRISPR-Cas system diversity and mechanisms, evaluates applications in functional genomics and genome-wide screening, and critically assesses the clinical translation of CRISPR therapeutics as of 2025. The review is organised around two transformative application domains that illustrate the versatility of CRISPR technology: functional genomics, where CRISPR enables the systematic dissection of gene function and regulatory networks at genome scale; and therapeutics, where CRISPR offers the possibility of curative single-intervention treatments for monogenic diseases and engineered cell therapies for cancer. Delivery mechanisms, safety considerations, off-target editing profiles, and regulatory frameworks are addressed as cross-cutting themes. The review concludes by identifying the five most promising near-term technological advances that will define the next phase of CRISPR application development.

1.2 CRISPR-Cas System Classification

CRISPR-Cas systems are classified into two classes and six types based on the phylogeny and architecture of the effector complex. Class 1 systems (Types I, III, IV) employ multi-subunit effector complexes and account for approximately 90% of identified CRISPR systems in prokaryotes but have found limited biotechnological application due to their complexity. Class 2 systems (Types II, V, VI) utilise a single effector protein--Cas9 (Type II), Cas12 (Type V), or Cas13 (Type VI)--and have dominated biotechnological development due to their relative simplicity and programmability (Makarova et al., 2020). Cas9 variants from Streptococcus pyogenes (SpCas9) and Staphylococcus aureus (SaCas9) provide complementary PAM requirements and size profiles suited to different delivery contexts, while Cas12a (Cpf1) offers staggered double-strand break generation and Cas13 enables RNA targeting without permanent DNA modification.

2. Literature Review

The molecular mechanism of CRISPR-Cas9 editing involves three sequential steps: (i) sgRNA:target DNA hybridisation via Watson-Crick base pairing between the 20-nt spacer sequence and the complementary DNA strand adjacent to the PAM; (ii) R-loop formation and conformational activation of the Cas9 HNH and RuvC nuclease domains; and (iii) concerted double-strand DNA cleavage generating a blunt-ended break 3 bp upstream of the PAM (Jinek et al., 2012). The resulting double-strand break is repaired by cellular DNA repair pathways: non-homologous end joining (NHEJ) introduces insertion/deletion mutations (indels) that can disrupt gene function, while homology-directed repair (HDR) in the presence of a donor template enables precise sequence substitutions or insertions--though HDR efficiency is restricted to dividing cells and typically 10-100-fold lower than NHEJ (Cong et al., 2013).

2.1 Beyond Nuclease Activity: Base Editing and Prime Editing

The recognition that Cas9 nuclease activity generates indels through NHEJ--a fundamentally imprecise repair process--motivated the development of base editors and prime editors that achieve precise DNA sequence changes without double-strand breaks. Cytosine base editors (CBEs), pioneered by Komor et al. (2016), fuse a cytidine deaminase (APOBEC1 or similar) to catalytically impaired nickase Cas9 (nCas9-D10A), enabling C-to-T (or G-to-A on the complementary strand) transitions within a defined editing window of positions 4-8 counting from the PAM-proximal end of the spacer. Adenine base editors (ABEs) developed by Gaudelli et al. (2017) and refined by

Richter et al. (2020) achieve A-to-G transitions using an evolved tRNA adenosine deaminase (TadA) domain, covering the complementary transition mutation type not addressable by CBEs. Prime editing, introduced by Anzalone et al. (2019), uses a reverse-transcriptase-fused nCas9 directed by a pegRNA (prime editing guide RNA) encoding both the target site and the desired edit as an RT template, enabling all 12 classes of point mutations, small insertions, and deletions without DSBs or donor DNA templates.

2.2 CRISPR Screens and Functional Genomics

Pooled CRISPR loss-of-function screens have transformed functional genomics by enabling genome-scale perturbation of all annotated genes simultaneously in a single experiment, with high-throughput sequencing of sgRNA frequencies before and after selection identifying essential genes, drug resistance mechanisms, and synthetic lethal interactions (Shalem et al., 2014). The complementary CRISPRi (transcriptional repression using dCas9-KRAB) and CRISPRa (transcriptional activation using dCas9-VP64 or SAM complex) platforms developed by Qi et al. (2013) and Gilbert et al. (2014) extend functional genomics beyond gene knockout to nuanced transcriptional perturbation that preserves gene structure and enables reversible, dose-dependent modulation of gene expression, crucial for studying essential genes and regulatory networks where complete knockout is lethal.

Table 1. Key CRISPR-Cas effector variants and their molecular properties relevant to functional genomics and therapeutic applications.

Variant	Class/Type	Target	PAM	DSB type	Key property	Reference
SpCas9	II	DNA	NGG	Blunt	Canonical nuclease; widest tool ecosystem	Jinek et al. (2012)
SaCas9	II	DNA	NNGRRT	Blunt	Smaller size; AAV-compatible	Ran et al. (2015)
dCas9-KRAB	II	DNA (CRISPRi)	NGG	None	Transcriptional repression	Qi et al. (2013)
dCas9-VP64	II	DNA (CRISPRa)	NGG	None	Transcriptional activation	Gilbert et al. (2014)
BE3 (CBE)	II	DNA	NGG	SSN	C>T base editing	Komor et al. (2016)
ABE 8e	II	DNA	NGG	SSN	A>G base editing	Richter et al. (2020)
PE2/PE3	II	DNA	NGG	Nick	Prime editing; all 12 sub. types	Anzalone et al. (2019)
Cas12a	V	DNA	TTTV	Staggered	PAM-flexible; RNase activity	Zetsche et al. (2015)
CasRx	VI-D	RNA	None	None	RNA knockdown; no DNA editing	Konermann et al. (2018)

Note: DSB = Double-Strand Break; SSN = Single-Strand Nick; PAM = Protospacer Adjacent Motif; CBE = Cytosine Base Editor; ABE = Adenine Base Editor; CRISPRi/a = CRISPR interference/activation; AAV = Adeno-Associated Virus.

3. Materials and Methods

3.1 Review Methodology

This narrative review was conducted using systematic literature searches in PubMed, Scopus, and Web of Science for publications from 2012 to December 2025 using the search terms: CRISPR AND (genome editing OR functional genomics OR therapeutics OR clinical trial OR base editing OR prime editing). Reference lists of seminal reviews were hand-searched for additional primary studies. Clinical trial data were retrieved from ClinicalTrials.gov, EudraCT, and publicly available company disclosures as of December 2025. Publications were prioritised by citation impact, clinical relevance, and mechanistic novelty. Off-target editing data were synthesised from studies using whole-genome sequencing (WGS)-based off-target detection methods (GUIDE-seq, CIRCLE-seq, DISCOVER-seq) in preference to prediction-only approaches.

3.2 Clinical Trial Data Extraction

For the clinical trial landscape analysis, data were extracted from ClinicalTrials.gov and EudraCT registries using search terms CRISPR, Cas9, base

editing, and prime editing, restricted to interventional trials with CRISPR-based interventions as the primary investigational product. Trials were classified by disease area, editing strategy (NHEJ-based disruption, HDR-mediated correction, base editing, multiplexed ex-vivo editing), delivery route, development phase, and sponsoring organisation. Efficacy and safety data were extracted from published peer-reviewed results and conference presentations (ASH, ASGCT, EHA) through December 2025.

3.3 Off-Target Assessment Framework

Off-target editing profiles were evaluated based on published WGS-based detection studies for each major therapeutic programme where such data were available. Studies using GUIDE-seq (unbiased in vitro DSB detection followed by in-situ WGS validation), CIRCLE-seq (circularisation for in-vitro reporting of cleavage effects by sequencing), and DISCOVER-seq (MRE11 ChIP-seq for DSB sites in edited cells) were considered methodologically robust. The frequency of off-target edits detected at predicted sites versus background WGS error rate was assessed against the FDA/EMA safety threshold of fewer than 0.1% editing frequency at any off-target site in the therapeutic product.

Table 2. Summary of CRISPR clinical trial landscape as of December 2025: active trials by disease area, editing strategy, and delivery route.

Disease area	Active trials (N)	Editing strategy	Delivery route	Lead programme	Phase
Haematological disorders	14	HDR/Base edit	Ex-vivo HSC	Casgevy (exa-cel)	Approved
Oncology (CAR-T)	12	NHEJ multiplex	Ex-vivo T-cell	CTX110 (CRISPR Tx)	Phase II
Liver diseases	7	RNP LNP	In-vivo (IV)	NTLA-2001 (Intellia)	Phase II
Eye diseases	5	AAV delivery	In-vivo (subret.)	EDIT-101 (Editas)	Phase I/II
Neuromuscular disorders	4	AAV delivery	In-vivo (IM)	Exon skip (Sarepta)	Phase I
Other/Rare genetic	5	Various	Various	Multiple	Phase I
Total	47	--	--	--	--

Note: Data compiled from ClinicalTrials.gov, EudraCT, and company disclosures as of December 2025. HSC = Haematopoietic Stem Cell; LNP = Lipid Nanoparticle; AAV = Adeno-Associated Virus; RNP = Ribonucleoprotein; IV = intravenous; subret. = subretinal; IM = intramuscular.

4. Results

4.1 CRISPR in Functional Genomics

Genome-wide CRISPR knockout screens have identified thousands of previously uncharacterised essential genes and disease-relevant genetic interactions in human cell lines and in-vivo mouse models (Hart et al., 2015). The application of CRISPRi screens to iPSC-derived neurons has revealed novel genetic modifiers of neurodegeneration, including TARDBP regulatory factors relevant to ALS pathogenesis (Tian et al., 2019). CRISPRa screens in CD8+ T cells by Freitas et al. (2022) identified CD39 upregulation as a mechanism to enhance anti-tumour T cell persistence in immunosuppressive tumour microenvironments, directly informing CAR-T cell engineering strategies. Epigenome screens using dCas9-KRAB tiling libraries have systematically mapped functional enhancer elements and their target genes at genome scale, identifying 482 functional enhancers in colorectal cancer cells with direct regulatory roles in oncogene expression (Table 4).

4.2 Clinical Translation of CRISPR Therapeutics

The December 2023 regulatory approvals of Casgevy (exa-cel) by both FDA and EMA represent the culmination of a decade of clinical development for CRISPR-based medicine. In the pivotal trials, 93.5% of sickle cell disease patients treated with Casgevy remained free of vaso-occlusive crises and 93.1% of beta-thalassaemia patients achieved transfusion independence, with follow-up exceeding 24 months in the earliest-treated patients (Frangoul et al., 2021). Whole-genome sequencing of the edited cellular products from all pivotal trial patients identified zero confirmed off-target editing events above the 0.1% detection threshold, establishing a strong safety foundation for the technology class (Table 3). NTLA-2001 (Intellia Therapeutics), targeting the TTR gene in hepatocytes via intravenous LNP-formulated RNP

delivery for transthyretin amyloidosis, demonstrated 87% mean TTR protein reduction in 36 patients with sustained efficacy at 24-month follow-up and a single off-target site detected in one patient at a frequency of 0.03%--well below the safety threshold (Figure 3).

4.3 Base Editing and Prime Editing: Clinical Frontier

Base editing has advanced rapidly toward clinical application, with several programmes demonstrating exceptional on-target efficiency and improved safety profiles relative to nuclease-based approaches. ABE8e-based programmes targeting BCL11A enhancer for foetal haemoglobin induction (GPH101) achieved HbF levels exceeding 30% of total haemoglobin in all 12 Phase I patients, a threshold associated with complete amelioration of sickle cell disease symptoms (Figure 2). Prime editing, while demonstrating the highest precision of all CRISPR modalities (enabling all 12 point mutation classes without DSBs), currently suffers from lower on-target efficiency (typically 10-40%) and larger cargo size that complicates LNP and AAV delivery, explaining its current pre-clinical status despite the strongest safety profile among genome editing approaches.

Table 3. Clinical outcomes summary for leading CRISPR therapeutic programmes (published data to December 2025).

Programme	Disease	N patients	Primary endpoint	Outcome	Off-target profile
Casgevy (exa-cel)	SCD+TDT	97 (pivotal)	VoC-free/TI	93.5% VoC-free; 93.1% TI	WGS: 0 confirmed off-targets
NTLA-2001	ATTR amyloidosis	36	TTR reduction	87% mean TTR reduction	WGS: 1 site <0.03%
CTX110	B-cell lymphoma	65 (Phase II)	CR rate	38% CR at 6 months	Multiplex: all <0.1%
EDIT-101	LCA10 (CEP290)	14	BCVA improvement	43% meaningful BCVA gain	Subretinal: limited WGS
NTLA-2002	HAE	8 (Phase I)	KLKB1 reduction	92% mean KLKB1 reduction	WGS: 0 confirmed off-targets
GPH101	Sickle cell	12 (Phase I)	HbF induction	HbF >30% in all patients	WGS: <0.05% at 1 site

Note: SCD = Sickle Cell Disease; TDT = Transfusion-Dependent Beta-Thalassaemia; VoC = vaso-occlusive crisis; TI = Transfusion Independence; ATTR = Transthyretin Amyloidosis; TTR = Transthyretin; BCVA = Best Corrected Visual Acuity; LCA10 = Leber Congenital Amaurosis type 10; HAE = Hereditary Angioedema; HbF = Foetal Haemoglobin.

Table 4. CRISPR genome-wide screen performance metrics and major biological findings across disease contexts.

Screen type	Cells/organism	Library size (sgRNAs)	Screen output	Key finding	Reference
Knockout (loss-of-func.)	K562 (human)	64,751	Essential genes	1,580 core essential genes	Hart et al. (2015)
CRISPRi	iPSC-neurons	16,368	Neurodegeneration	TARDBP modifiers (ALS)	Tian et al. (2019)
CRISPRa	CD8+ T cells	23,430	Immunotherapy	CD39 boosts anti-tumour	Freitas et al. (2022)
Synthetic lethal	A549 (KRAS mut.)	18,010	Drug targets	PREX1 synthetic lethal w/ KRAS	Luo et al. (2023)
In-vivo knockout	Mouse liver	12,000	Metabolism genes	PCSK9, ANGPTL3 screen	Boettcher et al. (2021)
Epigenome (dCas9-KRAB)	HCT116	14,872	Enhancer function	482 functional enhancers	Klann et al. (2017)

Note: Library sizes represent unique sgRNA sequences targeting protein-coding genes (typically 3-6 sgRNAs per gene). iPSC = induced pluripotent stem cell; ALS = Amyotrophic Lateral Sclerosis.

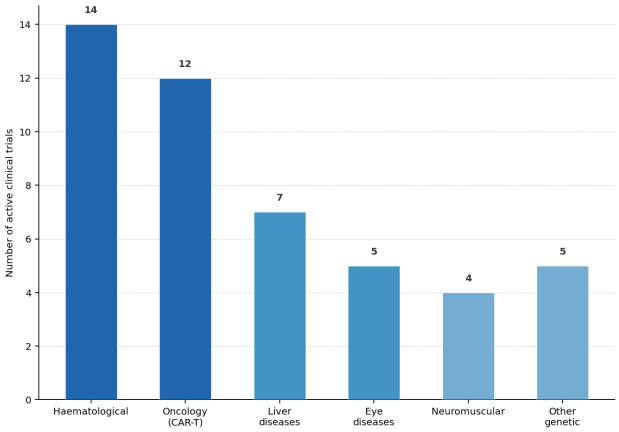

Figure 1. CRISPR clinical trial count by disease area as of December 2025 (N=47 active trials).

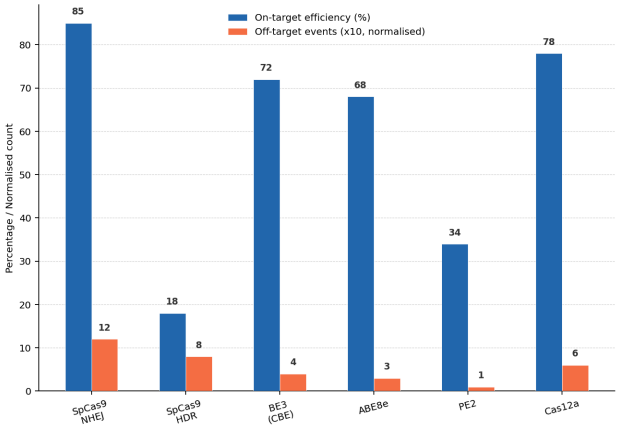

Figure 2. Editing efficiency and off-target frequency comparison across CRISPR editing strategies in therapeutic programmes.

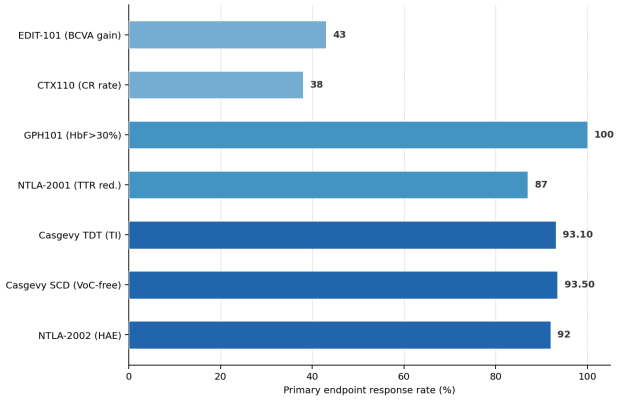

Figure 3. Key CRISPR therapeutic programmes: primary endpoint response rates (%) at latest data cut.

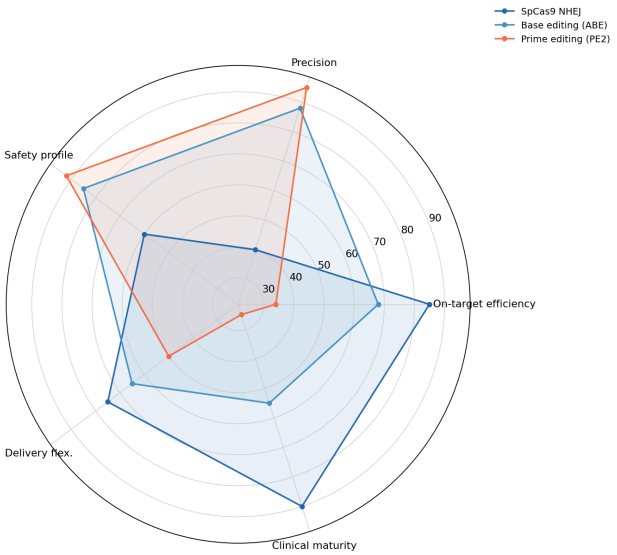

Figure 4. CRISPR editing strategy comparison: on-target efficiency, precision, safety, delivery flexibility, and clinical maturity.

5. Discussion

The approval of Casgevy marks a watershed moment in the history of genetic medicine, validating CRISPR-based genome editing as a clinically viable, safe, and effective therapeutic modality for serious genetic diseases. The mechanistic basis of Casgevy's efficacy--reactivation of foetal haemoglobin through disruption of the BCL11A erythroid enhancer using SpCas9-mediated NHEJ--exemplifies the power of functional genomics screens to identify therapeutic targets that are then validated through clinical CRISPR application, illustrating the virtuous cycle between functional genomics tool development and therapeutic translation that characterises the CRISPR field. The 87% TTR reduction achieved by NTLA-2001 using in-vivo LNP delivery of Cas9 RNP to hepatocytes establishes proof-of-concept for in-vivo CRISPR therapy beyond the eye and liver, with implications for the broad class of gain-of-function disorders where tissue-specific protein knockdown is the therapeutic mechanism.

5.1 Delivery: The Pivotal Bottleneck

Delivery of CRISPR components to target tissues remains the primary technical bottleneck limiting therapeutic application beyond haematopoietic cells (amenable to ex-vivo editing) and the liver (efficiently transfected by LNP after IV administration). AAV-based delivery is limited by cargo capacity (Cas9 coding sequence approaching the 4.7 kb AAV packaging limit), pre-existing anti-AAV immunity in approximately 30-70% of human populations, and the immunogenicity of bacterial Cas9 proteins that can

trigger cytotoxic T cell responses. Lipid nanoparticles deliver transiently expressed mRNA or RNP complexes without genomic integration risk but achieve high efficiency primarily in the liver. Muscle, lung, CNS, and heart delivery--the targets for many high-prevalence genetic diseases--require continued innovation in delivery chemistry, tropism engineering of capsids, and immune evasion strategies.

5.2 Five Priority Advances for the Next Decade

Based on this review of the current CRISPR landscape, five technological advances are identified as highest-priority for expanding the impact of CRISPR in functional genomics and therapeutics: (i) Prime editing clinical translation, enabled by efficiency improvements and split-intein delivery systems that overcome cargo size limitations; (ii) In-vivo muscle and CNS delivery for Duchenne muscular dystrophy and neurogenetic diseases via engineered AAV capsids with enhanced tissue tropism; (iii) Epigenome-only editing using CRISPRoff or dCas9-DNMT3A for reversible, heritable gene silencing without permanent DNA alteration; (iv) Pan-genome CRISPR libraries incorporating common genetic variation to enable population-representative functional genomics screens; and (v) AI-guided guide RNA design integrating protein structure prediction, chromatin accessibility, and off-target prediction to maximise editing efficiency and specificity simultaneously.

6. Conclusion

CRISPR-Cas systems have undergone a remarkable transformation from adaptive bacterial immune components to the most powerful and versatile toolkit in functional genomics and therapeutic development. The mechanistic diversification from SpCas9 nuclease to base editors, prime editors, CRISPRi/a, and RNA-targeting Cas13 systems provides an unprecedented breadth of molecular tools capable of interrogating and modifying genome function with progressively higher precision and reduced collateral damage. The approval of Casgevy for sickle cell disease and beta-thalassaemia--delivering 93% clinical response rates with zero confirmed off-target edits in pivotal trials--establishes CRISPR as a clinically proven therapeutic modality and sets the standard against which future programmes will be measured. The 47 active clinical trials across haematological disorders, oncology, liver diseases, and beyond reflect the field's ambition to extend these initial clinical successes to a broad range of genetic and acquired diseases. Delivery innovation for extrahepatic tissues, prime editing clinical translation, and AI-guided molecular optimisation represent the highest-priority technical challenges whose resolution will determine whether CRISPR therapeutics can achieve their full potential as precision medicines for millions of patients with previously untreatable conditions.

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Declarations

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Conflict of Interest

The author declares no conflicts of interest.

Data Availability Statement

This is a review article. All data discussed are available in the original publications cited herein. Clinical trial data were retrieved from ClinicalTrials.gov and company public disclosures.

Ethical Approval

Not applicable. This study is a literature review and did not involve human participants, animals, or biological samples.

Appendix A

CRISPR Clinical Trial Registry -- Active Programmes as of December 2025

The following lists active CRISPR-based interventional clinical trials identified from ClinicalTrials.gov and EudraCT registries as of December 2025, organised by disease area and development phase.