Review Article

Review Article

Gene therapy for rare diseases marks a new era in precision medicine: Insights from clinical trials

Suprianto Suprianto[1,2*], Yunita Messe[3], Raehan AH. Hamzah[4], Rose CMH. Ortega-Kindica[5], Dian A. Umaroh[6], Yusril IF. Wijaya[7], Suryani Musa[3], Ian I. Fidhatami[3,8], Ahmad Ikhsanudin[9] and Nurnisa Hamid[10]

[1]Department of Biomedical Sciences and Biotechnology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [2]Center of Excellence for Medical Genomics, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [3]Department of Tropical Biology, Faculty of Biology, Universitas Gadjah Mada, Yogyakarta, Indonesia; [4]Department of Public Health, School of Medicine, The University of Aberdeen, Aberdeen, United Kingdom; [5]Department of Biology and Environmental Science, College of Science, University of The Philippines, Cebu, Philippines; [6]Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Tanjungpura, Pontianak, Indonesia; [7]Bioinformatics Research Center, Institute of Bioinformatics Indonesia, Malang, Indonesia; [8]Faculty of Science and Health, Universitas Andi Sudirman, Bone, Indonesia; [9]Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Lampung, Lampung, Indonesia; [10]Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

*Corresponding author: supriantoupik1005@gmail.com

Abstract

Gene therapy represents an important advance in the treatment of rare diseases, offering precise and transformative therapeutic strategies. As many rare diseases are associated with well-defined genetic variants, they represent ideal candidates for targeted genetic interventions. The substantial unmet medical need associated with rare diseases has driven growing interest in gene therapy, with more than 300 clinical trials reported to date. The aim of this study was to evaluate the current evidence on gene therapy for rare diseases by examining therapeutic strategies, target diseases, clinical progress, clinical outcomes, and emerging research trends. Several approved therapies, including those for hemophilia B, spinal muscular atrophy, metachromatic leukodystrophy, and Wiskott–Aldrich syndrome, have demonstrated the clinical potential of gene therapy. Clinical evidence suggests that gene-based therapies in the management of rare diseases can achieve sustained functional benefits, reduce disease-related complications, and lessen dependence on long-term replacement or supportive treatments. However, challenges in ethical considerations, regulatory requirements, manufacturing complexity, treatment costs, and limited patient access remain. Continued clinical evaluation is essential to further establish long-term safety and effectiveness. Advances in gene therapy technologies and clinical applications continue to expand therapeutic opportunities for rare diseases while supporting the broader development of precision medicine.

Keywords: Gene therapy, rare diseases, clinical cases, therapeutic challenges, safety concerns

Introduction

Rare diseases represent a persistent public health challenge worldwide, affecting an estimated 300 million people globally and encompassing more than 7,000 distinct disorders [1,2]. Approximately 80% of rare diseases are genetic and manifest from an early age [3], involving a single gene, multiple genes, or chromosomal variations [4]. The growing number of rare disease cases poses significant clinical and research challenges due to the complexity of variants across diverse cases [5].

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The management of rare diseases remains challenging because many conventional therapies primarily focus on symptom control or delaying disease progression rather than addressing the underlying genetic cause [6]. In addition, substantial genetic variability among patients can influence disease manifestations and treatment responses [7]. These challenges have driven the adoption of personalized medicine, which uses genomic and molecular information to guide more individualized healthcare decisions [8]. In Asia, personalized medicine has advanced rapidly through developments in genomic technologies and precision healthcare initiatives, although implementation remains uneven due to differences in infrastructure, research capacity, regulatory frameworks, and healthcare resources. Regional collaborations such as Genome Asia have further supported genomic research and data integration across the region [9]. Within this framework, gene therapy has emerged as a promising approach for rare genetic diseases by targeting disease-causing genetic alterations [6].

In a published study, gene therapy has been reported to be successful in treating Leber congenital amaurosis, a disease caused by mutations in the RPE65 gene, indicated by significantly improved vision [10]. Furthermore, gene therapy for hemophilia B with etranacogene dezaparvovec has been associated with increased factor IX activity and fewer bleeding episodes in patients [11]. However, not all cases are significant. Some gene therapies fail clinical trials, necessitating reevaluation of continued treatment. Gene therapy for X-linked Severe Combined Immunodeficiency (SCID-X1) using a retroviral vector became quite phenomenal. This gene therapy caused patients to develop leukemia due to insertional mutagenesis. Therefore, the initial approach using a retroviral vector was discontinued and reexamined with safer alternative vectors [12]. Several gene therapies are still in the clinical trial stage [13], evaluated by relevant regulatory authorities for product safety before being eligible for distribution.

Gene therapy has become a key component of precision medicine, offering the potential to improve clinical outcomes and extend survival in patients with rare genetic diseases. By targeting the underlying genetic defects, gene therapy also provides a promising approach for disease modification and, in some cases, curative treatment. This review presents a comprehensive synthesis of evidence on gene therapy for rare diseases by integrating information from ClinicalTrials.gov and major scientific literature databases. The available evidence was evaluated to identify relevant clinical trials and published studies, enabling a comprehensive assessment of therapeutic strategies, target diseases, clinical progress, and key research findings. Therefore, the aim of this study was to systematically review the current evidence on gene therapy for rare diseases, summarize recent advances and clinical progress, identify emerging trends and research gaps, and discuss future directions for the field through a qualitative, descriptive, and comparative synthesis of the available literature.

Advances in the clinical translation of gene therapy for rare diseases

In recent years, gene therapy has emerged as a promising approach for the treatment of rare diseases. Gene replacement therapy with Zolgensma has demonstrated remarkable clinical efficacy in patients with spinal muscular atrophy [5], representing a major milestone in the clinical translation of gene therapy. Similarly, treatment with voretigene neparvovec has been shown to improve functional vision and visual mobility in patients with inherited retinal dystrophy caused by *RPE65* mutations [14]. Furthermore, etranacogene dezaparvovec has been reported to reduce bleeding episodes and decrease the need for routine factor IX replacement therapy in patients with hemophilia B [11].

The global distribution of 1,001 registered studies on rare diseases shows a substantial concentration of gene therapy research in North America and Europe (**Figure 1**), with North America accounting for the largest number of studies (425), followed by Europe (348). Asia contributed 105 studies, highlighting the increasing involvement of Asian countries in rare disease research and gene therapy innovation. The growing number of studies highlights a major shift in rare disease research, in which therapeutic strategies focus on correcting underlying genetic causes rather than merely managing symptoms [15-17]. Advances in viral vector systems, genome editing technologies, and cell-based therapeutic platforms have significantly expanded the potential of gene therapy across multiple rare disease categories [18]. However, despite this

rapid progress, the distribution of studies remains highly unequal. Asia has shown emerging growth in gene therapy research, whereas Africa, South America, and parts of Oceania continue to contribute relatively few studies, reflecting disparities in research funding, infrastructure, access to advanced technologies, and regulatory readiness [19-21].

Critically, the large number of registered studies does not necessarily indicate successful clinical translation. Many therapies remain in preclinical or early-phase clinical development due to challenges related to long-term safety, immune responses, delivery efficiency, manufacturing complexity, and high treatment costs [22]. Furthermore, the limited participation of underrepresented regions raises concerns regarding global accessibility and equity in precision medicine. Therefore, while gene therapy has established a transformative direction for rare disease treatment, further efforts are needed to improve international collaboration, strengthen translational research, and ensure broader global access to emerging therapeutic innovations [19,23,24].

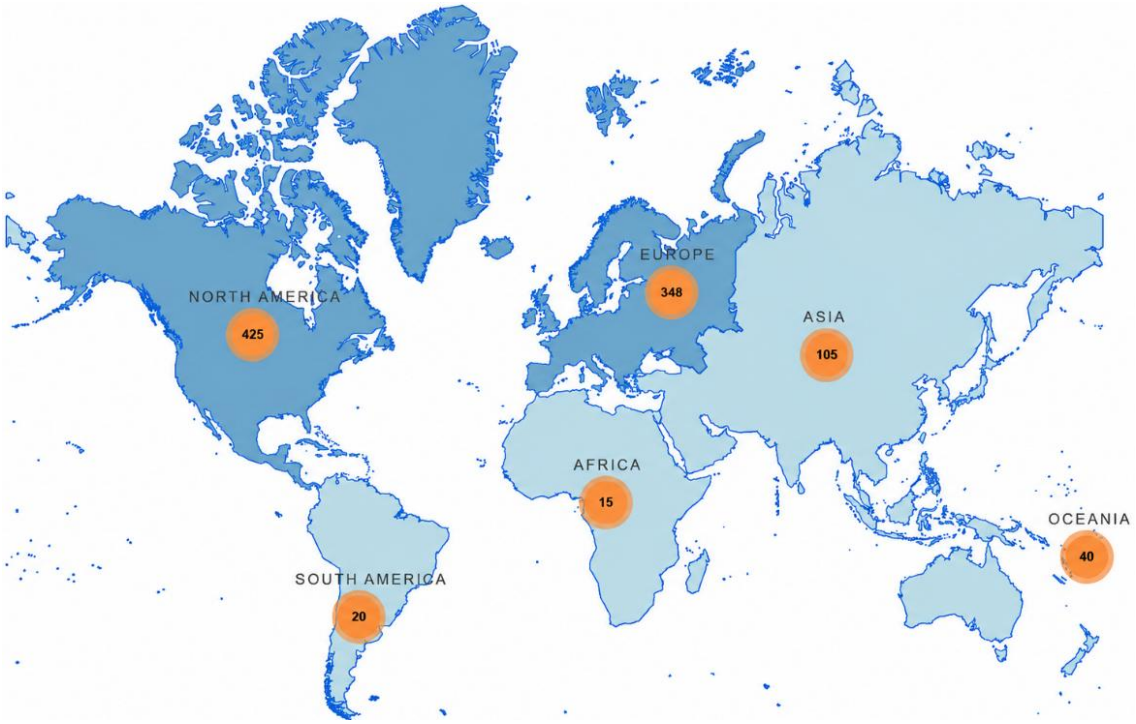

Figure 1. Global distribution of 1,001 registered trials on rare diseases across continents based on the records from clinicaltrials.gov.

Clinical studies of gene therapy for rare diseases are designed to establish the safety, efficacy, and clinical applicability of these therapies, thereby supporting their implementation as precision treatments [25]. According to the Food and Drug Administration (FDA), gene therapy for Wiskott-Aldrich syndrome was approved on December 9, 2025, for publication. This news represents a major success in gene therapy for Wiskott-Aldrich syndrome and marks broader clinical advances in gene therapy for rare diseases. A large number of gene therapies have been approved and are still in clinical trial stages. Approximately 3,900 gene therapies were undergoing clinical trials in 43 countries as of March 2023; some have been approved, and others are still in the clinical process toward approval [26]. The number of gene therapy trials continues to increase, and clinical studies are ongoing. Some emerging therapies targeting genetic blindness, hemophilia, muscular dystrophy, and cancer through gene editing approaches have been extensively highlighted and explored [27-30]. Gene therapy is currently not only a prospect but has made a substantial real contribution to the treatment of rare diseases. Information on registered gene therapy studies for rare diseases is presented in **Figure 2**.

Suprianto et al. Narra X 2026; 4 (2): e276 - http://doi.org/10.52225/narrax.v4i2.276

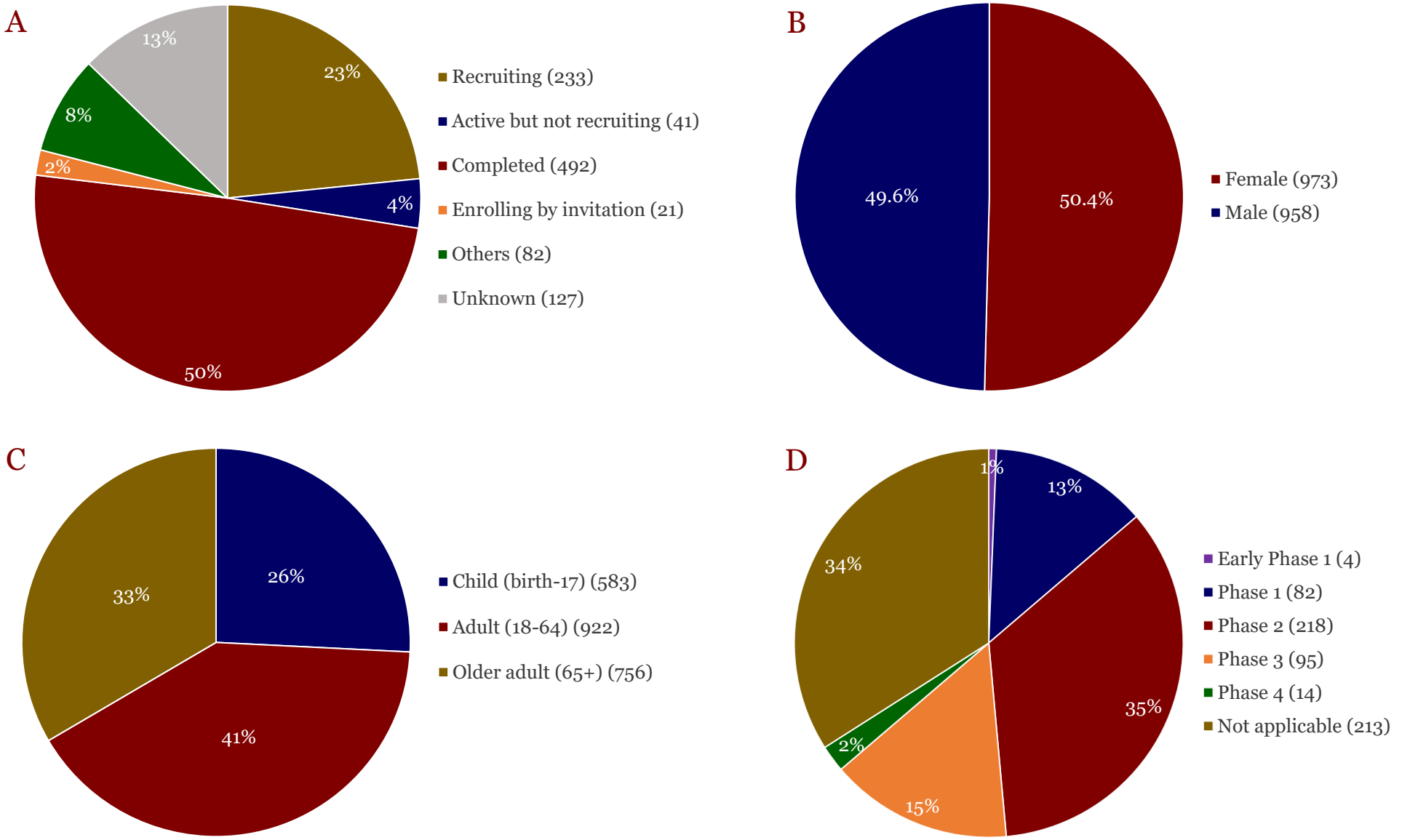

Figure 2. Overview of registered gene therapy studies for rare diseases. (A) Study recruitment status, including studies currently looking for participants and studies no longer recruiting participants. (B) Distribution of patients based on sex classification. (C) Patient classification according to age groups. (D) Clinical development phases of gene therapy studies. (E) Classification of study design types. (F) Distribution of funding sources supporting gene therapy studies for rare diseases [31].

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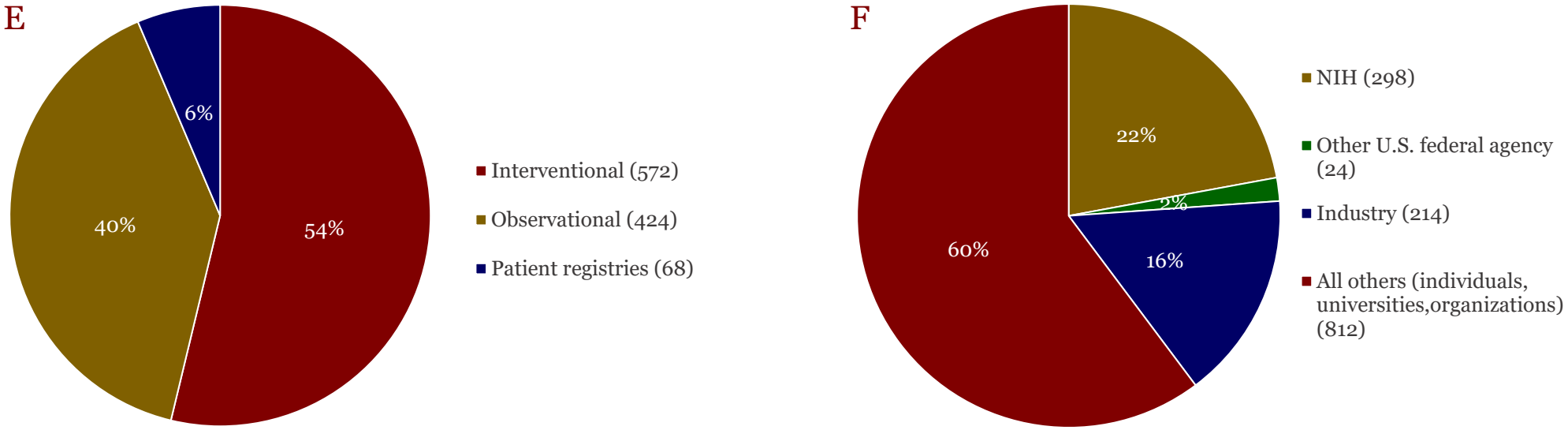

Figure 2 (continued). Overview of registered gene therapy studies for rare diseases. (A) Study recruitment status, including studies currently looking for participants and studies no longer recruiting participants. (B) Distribution of patients based on sex classification. (C) Patient classification according to age groups. (D) Clinical development phases of gene therapy studies. (E) Classification of study design types. (F) Distribution of funding sources supporting gene therapy studies for rare diseases [31].

Gene editing tools

Genetic modification is a fundamental step in gene therapy and is primarily achieved through gene-editing technologies [32]. Gene editing enables precise modification of genomic DNA by utilizing the cell's endogenous mechanisms for recognizing and repairing DNA double-strand breaks (DSBs). Through this approach, defective genes can be corrected, disrupted, or replaced to restore normal cellular function [33]. Several gene editing platforms have been developed, including Meganucleases (MNs), Zinc-Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated systems [34]. These technologies differ in their mechanisms of target recognition, editing efficiency, specificity, and clinical applicability.

Meganucleases are sequence-specific endonucleases that recognize relatively long DNA target sites (14–40 bp), resulting in high target specificity and low cytotoxicity [35]. They contain multifunctional domains that bind double-stranded DNA and induce DSBs [36]. However, their complex re-engineering process and relatively low editing efficiency have limited their widespread clinical application [37]. Meanwhile, ZFNs consist of engineered zinc-finger DNA-binding domains fused to a DNA-cleavage domain, enabling targeted induction of DSBs at specific genomic loci [32,38]. These breaks promote homologous recombination and facilitate genome modification [35]. Although ZFNs have a relatively small protein size (<1 kb) and sequence-based modular design, their development requires complex protein engineering, making the technology costly and time-consuming [39].

TALENs are engineered nucleases composed of customizable DNA-binding domains linked to the nonspecific FokI nuclease domain, allowing precise cleavage of selected DNA sequences [40,41]. TALENs offer high target specificity and relatively straightforward target-site selection [42]. Nevertheless, their large protein size (>3 kb), high production cost, and labor-intensive design process remain important limitations [43,44]. Among CRISPR-based systems, CRISPR-Cas9 remains the most extensively studied and widely applied platform for therapeutic gene editing [45]. It enables efficient and programmable genome editing in eukaryotic cells by introducing targeted double-stranded DNA cleavage guided by a single guide RNA (sgRNA). The resulting DNA breaks are repaired through non-homologous end joining (NHEJ) or homology-directed repair (HDR), allowing gene disruption or precise sequence correction [46].

Gene editing using CRISPR-Cas9 for disease treatment has become an innovative therapeutic approach to cure various genetic and other diseases [18]. CRISPR-Cas9 uses a guide RNA to recognize a specific DNA sequence and induce a double-strand break [47]. The cell resolves this DNA damage through two principal pathways: NHEJ, which frequently introduces small insertions or deletions, and HDR, which enables gene editing or targeted sequence insertion (**Figure 3**). Gene editing has become a major breakthrough in gene therapy [18,48]. This technique enables targeted modification of disease-associated genetic sequences and has shown therapeutic potential in the treatment of genetic disorders [49]. A previous study used CRISPR-Cas9-mediated gene editing in an in vivo gene therapy trial for transthyretin amyloidosis and reported favorable short-term safety outcomes together with reductions in serum transthyretin levels in a small patient cohort [50]. Furthermore, a previous clinical study investigating in vivo CRISPR-Cas9 gene therapy for hereditary angioedema reported substantial and sustained reductions in plasma kallikrein levels, supporting the therapeutic potential of this approach [51]. CRISPR-Cas9 enables targeted modification of specific genetic sequences and has been investigated for various therapeutic applications [52]. In a preclinical study of herpes simplex keratitis, direct in vivo CRISPR-Cas9-mediated editing of the HSV-1 genome demonstrated antiviral activity and favorable safety findings, highlighting its potential as a therapeutic approach for herpes keratitis [53]. Recent advances in gene modification technology provide new opportunities to create drugs that can meet unmet medical needs related to disorders of the central nervous system, including diseases affecting the aging brain [54].

The small population of rare disease patients poses challenges to therapy feasibility, affecting the framework of drug development and related regulation [55]. The emergence of CRISPR-Cas9 technology has offered a second chance for gene therapy to move beyond its historical stigma and establish itself as a promising therapeutic approach [56].

Suprianto et al. Narra X 2026; 4 (2): e276 - http://doi.org/10.52225/narrax.v4i2.276

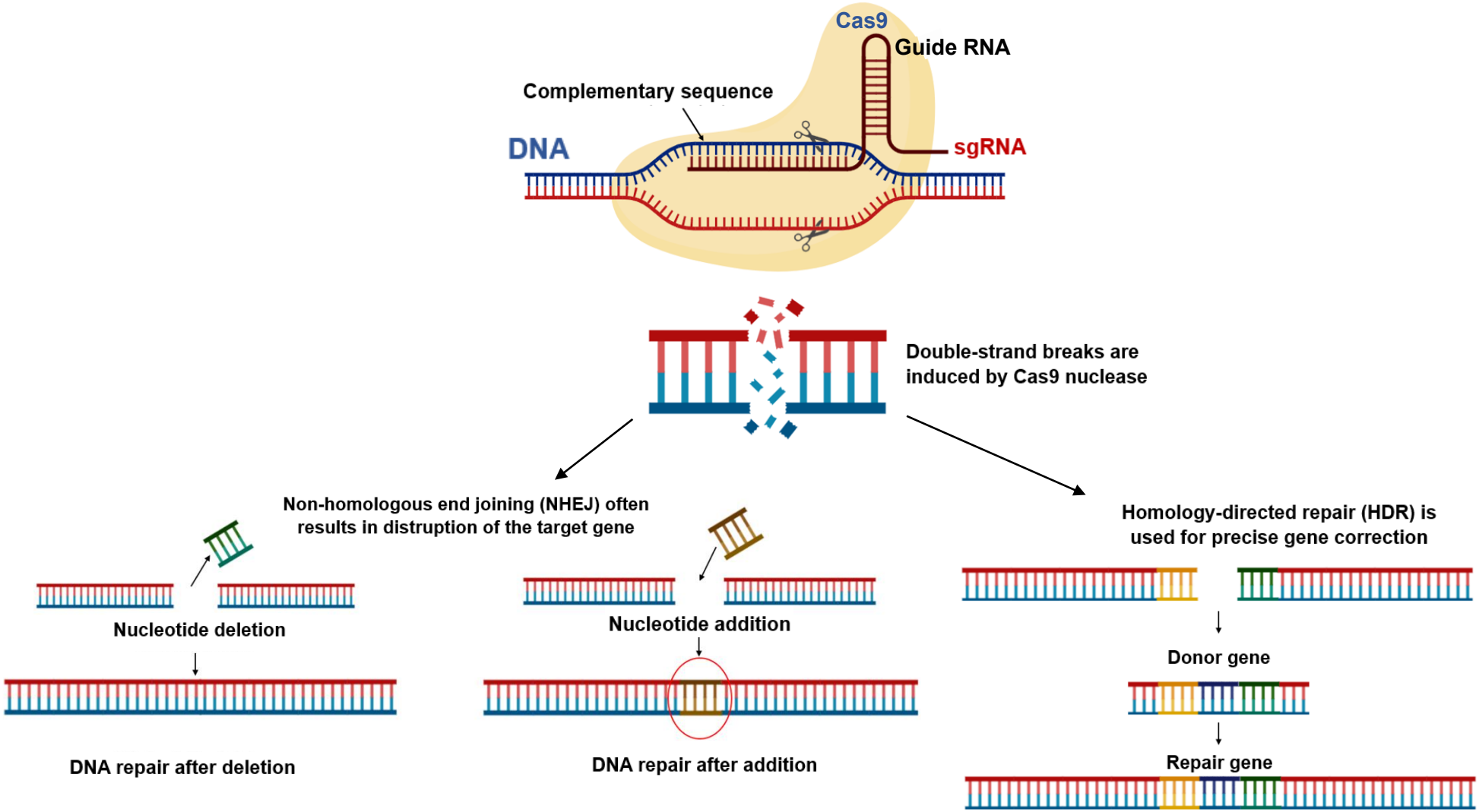

Figure 3. CRISPR mechanism. The guide RNA (gRNA) binds in a complementary manner to a specific target DNA sequence and recruits the Cas9 endonuclease, which induces a double-strand break at the designated site. This break is then repaired by the cell's intrinsic DNA repair mechanisms, either through HDR or NHEJ. These repair processes may introduce genetic modifications, including insertions or deletions through NHEJ, or precise sequence replacement via HDR when a donor template is provided. The donor template can incorporate reporter elements such as fluorescent proteins, epitope tags, antibiotic resistance genes, or restriction enzyme recognition sites for further analysis.

CRISPR has the ability to edit genes, providing valuable insights into the treatment of human genetic diseases [57]. Gene editing with CRISPR-Cas9 has become a reliable approach across various research timelines, including gene therapy methods relying on gene editing techniques for rare diseases. CRISPR-Cas9 is increasingly recognized as an innovative and effective genome-engineering approach with strong therapeutic potential for rare single-gene disorders and a broad range of inherited human diseases [58].

Although CRISPR-Cas9 remains the most widely used system in current gene therapy clinical trials for genetic disorders, its application is limited in multiplex gene targeting. In contrast, newer CRISPR systems such as Cas12 and Cas13 have been developed to address these limitations by enabling more efficient multiplexing and expanding the range of editable genetic targets [59]. However, these systems are still largely in the developmental and early translational stages, whereas Cas9 continues to dominate clinical applications in gene therapy. Despite this, Cas12 and Cas13 offer promising complementary advantages for future therapeutic strategies, particularly in overcoming current constraints of genome editing in complex diseases. Notably, these emerging systems show potential for treating ocular disorders such as glaucoma, retinal dystrophies, and age-related macular degeneration by enabling concurrent targeting of multiple genes [59,60].

Gene delivery strategies in gene therapy

Gene delivery methods are techniques used to deliver therapeutic genetic materials, such as DNA, mRNA, or CRISPR components, into patient cells [61]. These methods are broadly divided into viral vectors, non-viral vectors, and physical delivery approaches, and can be performed either directly in the body (in vivo) or outside the body before being reintroduced into the patient (ex vivo) [62,63]. Ex vivo therapies often face greater logistical and regulatory complexity related to personalized cell manipulation, while in vivo approaches are primarily challenged by vector safety and long-term systemic effects [63]. Editing control is more precise in ex vivo settings, whereas in vivo editing is more difficult to regulate spatially and temporally.

Gene delivery into cells, both ex vivo and in vivo, is crucial to understanding gene roles and implementing gene therapy. For gene delivery to function effectively in the body, it is important to address degradation caused by nucleases and the uptake of DNA by non-target cells after systemic administration of exogenous DNA [64]. Many gene therapy strategies rely on viral vectors to introduce therapeutic genetic material into target cells. For successful expression of the introduced genes, the exogenous DNA must reach the cell nucleus, where it can be transcribed into functional proteins. In general, gene delivery systems are classified into two main categories: viral vectors and non-viral vectors. Viral techniques are associated with increased technical demands and potential toxicity risks related to viruses. However, viral vectors have been developed to ensure safety by rendering them replication-incompetent [65].

Non-viral vector–mediated gene delivery offers several advantages over viral systems, including improved safety, lower immunogenicity, larger genetic cargo capacity, and simpler, more cost-effective production, making it a promising alternative for gene therapy applications [62]. These systems are broadly categorized into physical and chemical approaches for delivering genetic material without viral particles. Chemical non-viral vectors, comprising both inorganic and organic materials, have been extensively explored. Inorganic nanoparticles, such as iron oxide nanoparticles, metal-based compounds, quantum dots, carbon nanotubes, and silica-based nanoparticles, provide structural stability and tunable properties that enhance nucleic acid protection and cellular uptake, often through surface modification or targeting ligands [63]. Organic systems, including lipid-based and polymer-based carriers, can form stable complexes with DNA or RNA and support intracellular delivery [62,63].

In contrast, viral vectors have been used in gene transfer applications since 1975 [66]. Owing to their high transduction efficiency and ability to target a wide range of tissues, viral vectors remain the primary choice for gene delivery [63]. Over the past 20 years, three commonly used viruses, lentivirus (LV), adenovirus (Ad), and adeno-associated virus (AAV), have supported significant preclinical and clinical achievements, such as the approval of Luxturna for inherited retinal disease and CAR-T therapy for blood cancers [67].

AAV is considered one of the most promising and widely used vectors in gene therapy. It exhibits strong transduction efficiency in both proliferating and non-proliferating cells, low immunogenicity and toxicity, and remarkable tissue specificity [54]. Gene delivery technologies for gene therapy, whether using viral vectors such as AAV and lentivirus or non-viral methods such as lipid nanoparticles, face various serious issues related to effectiveness and safety. Several major issues include immune reactions to vectors, low targeting efficiency, limited cargo capacity, and degradation of therapeutic materials, all of which hinder long-term treatment success [67].

Gene delivery strategies represent a pivotal component of gene therapy, as they govern the efficiency, specificity, and safety of therapeutic gene transfer to target cells. Viral vectors, particularly AAV and lentiviral systems, continue to dominate clinical applications owing to their superior transduction efficiency and demonstrated therapeutic efficacy across a range of genetic disorders. Nevertheless, significant challenges remain, including vector-induced immunogenicity, limited transgene packaging capacity, off-target biodistribution, and the instability of therapeutic genetic cargo, all of which may compromise long-term treatment outcomes. Therefore, continued refinement of both viral and non-viral delivery platforms is essential to enhance targeting precision, improve biosafety profiles, and achieve sustained therapeutic gene expression, thereby advancing the clinical translation and long-term success of gene therapy.

Recent clinical studies of gene therapy for rare diseases

Luxturna™ for Leber congenital amaurosis (LCA) in 2017, the first gene therapy utilizing AAV, received approval from the FDA for treating a hereditary blindness condition known as LCA. LCA consists of 23 distinct genetically defined retinal disorders that result in vision impairment [68]. Gene therapy clinical trials for rare diseases continue to advance, marking a new era of precision medicine (**Table 1**). Numerous clinical trials are currently underway evaluating gene therapy for a wide range of congenital and acquired disorders across multiple organ systems [22], including rare diseases.

Recent clinical studies, such as the application of CRISPR-Cas9 technology for sickle cell disease, demonstrate the clinical feasibility of ex vivo genome editing of hematopoietic stem cells. This approach does not directly correct the β-globin mutation but instead reactivates fetal hemoglobin production through modification of genetic regulators, thereby reducing the pathological consequences of sickle hemoglobin [15]. Furthermore, gene therapy for Metachromatic Leukodystrophy (MLD) using a lentiviral ex vivo approach that transfers the ARSA gene into autologous hematopoietic stem cells has shown that early treatment can alter the progression of a typically fatal neurodegenerative disease [69]. However, clinical cases also indicate that effectiveness is highly dependent on timing, with therapy being most ideal before the onset of severe neurological symptoms [16]. This emphasizes that gene therapy focuses not only on technology but also on early detection, neonatal screening, and integrated clinical strategies.

In other cases, such as hemophilia B, the in vivo approach using an AAV vector to deliver the factor IX gene to hepatocytes has become one of the most advanced models of systemic gene therapy. Clinical reports show a significant reduction in bleeding rates and the need for prophylactic therapy [11]. Nevertheless, issues such as AAV immunogenicity, elevated liver enzymes, and the potential decline of long-term transgene expression remain concerns [70,71]. This indicates that although gene therapy has reached the commercial stage, long-term safety monitoring remains an essential component.

The case of Duchenne muscular dystrophy (DMD) further emphasizes the complexity of the transition toward curative gene therapy. The use of micro-dystrophin delivered systemically through AAV has demonstrated improvements in motor function in some patients, but the gene applied is a truncated version and therefore does not fully replace the physiological function of natural dystrophin [17]. Variability in clinical responses and the possibility of systemic side effects underscore that biological innovation must be balanced with rigorous and continuous clinical evaluation.

The approval of novel gene therapy treatments by the FDA in 2025 indicates that the sector has entered a stage of significant clinical maturity. Various approaches, ranging from in vivo gene delivery using AAV to genetically engineered autologous cell therapies, are no longer limited to

early clinical experimentation but have become regulatory-recognized interventions for rare diseases that previously had very limited therapeutic options. This reflects a significant shift in medical practice, from supportive care toward molecular interventions focused on the genetic causes of disease. This progress also reflects important technological diversification.

A total of 73 gene therapies for rare diseases are currently in various stages of clinical development, with most still in mid-stage clinical trials (Phase II, approximately 55%), followed by Phase III (19%), therapies that have received regulatory approval (19%), and a small number still in Phase I (7%) [39]. This distribution shows that although many therapy candidates are still undergoing effectiveness and safety assessments, a significant proportion are already in advanced stages and have received approval. Recent gene therapy cases for rare diseases highlight variability in clinical conditions, therapy methods, and implementation details across different diseases, indicating promising yet heterogeneous outcomes that remain limited by clinical and translational challenges (**Table 2**).

During the period 2017–2023, several gene therapies have been approved for diseases such as beta- thalassemia, hemophilia A, spinal muscular atrophy, metachromatic leukodystrophy, and various types of blood cancer [72]. This demonstrates rapid progress in the application of gene therapy in clinical practice, although challenges in commercialization and market sustainability remain. Several recent gene therapy products approved by the FDA in 2025 are presented in **Table 3**.

Advances in ongoing clinical research on gene therapy show that this field is no longer focused on a single type of disease or a single technology but has transformed into a broad and organized translational ecosystem. Various therapeutic candidates target a spectrum of serious genetic diseases, from lysosomal storage disorders such as MPS IIIA and Pompe disease, neuromuscular conditions such as DMD and SMA, to bleeding disorders such as hemophilia A and B [73-77]. This reflects the expansion of gene therapy applications to various organ systems, the nervous system, skeletal muscles, liver, and hematological system. Conversely, indications such as immunodeficiencies, neuromuscular diseases, hemoglobinopathies, and other rare genetic conditions have represented a comparatively smaller proportion of the overall clinical trial landscape [78].

Many approaches continue to utilize AAV vectors with various serotypes (AAV5, AAV8, AAV9, AAV3), demonstrating that this platform remains the foundation of in vivo gene therapy [79]. Serotype optimization enables more precise tissue targeting, such as hepatocytes for hemophilia or skeletal muscle in DMD. According to the ClinicalTrials.gov database, 310 gene therapy studies for rare diseases were registered as Phase 2, Phase 3, or Phase 4 clinical trials (updated June 2026), indicating that gene therapy has moved beyond the initial exploratory phase and entered the stage of verifying effectiveness and safety in larger patient populations.

Challenges and concerns

Over the past three decades, gene therapy has evolved from early setbacks to providing durable and potentially curative treatments for both inherited and acquired diseases, including blood disorders, cancers, and conditions affecting the eyes and nervous system, using ex vivo cell modification and in vivo AAV-based approaches [22]. These advances demonstrate sustained clinical benefits that often surpass conventional treatments. However, when compared with gene therapy strategies targeting common or non-rare diseases, therapies for rare diseases face distinct challenges, particularly due to the small and highly heterogeneous patient populations, which limit statistical power, slow clinical validation, and reduce commercial incentives for large-scale development [80-82]. In contrast, non-rare diseases generally benefit from larger and more readily accessible patient cohorts, enabling faster recruitment, more robust clinical trial designs, and clearer endpoints [83,84].

Safety issues continue to be a major concern, particularly the innate and adaptive immune responses triggered by high-dose viral therapies in humans [85]. All gene therapy strategies necessitate long-term monitoring to ensure their safety, sustained efficacy, predictability, and durability of response [86]. Key risks include immune reactions against the delivery vector, the introduced genetic material, or the newly expressed therapeutic protein, as well as the residual risk of oncogenesis due to insertional mutagenesis.

Table 1. Registered gene therapy clinical trials for rare diseases on ClinicalTrials.gov (updated March 2026)

ClinicalTrials.gov ID	Conditions	Study start	Enrollment	Study type	Phase	Population
Completed						
NCT01802567	Neuroblastoma, medulloblastoma, brain tumors, and rare tumors	2013-03-04	52	Interventional	NA	American
NCT00004809	Familial hypercholesterolemia	1992-06	5	Interventional	1	American
NCT00004454	MPS II	1996-10	2	Interventional	1 and 2	American
NCT01344798	LGMD2C and Gamma-sarcoglycanopathy	2006-11	9	Interventional	1	European
NCT00004471	CF	1995-08	9	Interventional	1	European
NCT03855631	Kabuki Syndrome 1	2020-09-28	8	Observational	NA	European
NCT04148001	HoFH	2019-12-04	4	Observational	NA	American
NCT02736565	Ewing sarcoma, ESFT, STS, and other solid tumors	2016-10	7	Interventional	1	American
NCT03602079	HER2-associated and other solid tumors (including gastrointestinal, head and neck, genitourinary, gynecological, salivary gland, recurrent/metastatic cancers)	2018-07-16	49	Interventional	1 and 2	American
NCT04126005	Canavan disease	2019-10-10	67	Observational	NA	American and European
NCT04046224	Fabry disease	2019-07-23	36	Interventional	1 and 2	American, European, Oceanian, and Asian
NCT01414985	LINCL and Batten disease	2010-04-15	8	Interventional	1 and 2	American
Recruiting						
NCT06775561	Neuromuscular diseases, eye diseases, and genetic diseases	2023-05-20	100	Observational	NA	European
NCT05810181	SCD	2023-06-01	145	Observational	NA	American
NCT06860672	DD/ID and rare diseases	2025-02-19	1	Interventional	Early phase 1	Asian
NCT06826612	Huntington disease	2025-02-21	53	Interventional	1 and 2	American
NCT04998396	Canavan disease	2021-09-08	26	Interventional	1 and 2	American
NCT05770544	Hematological malignancies, lymphoproliferative disorders, brain neoplasms, ST, melanoma, glioma, and ST	2025-11-30	30	Interventional	2 and 3	European
NCT06065852	Hereditary nephropathies (AS, FD, cystinosis, IgAN, FSGS, and PKD)	2009-11-06	35000	Observational (patient registry)	NA	European
NCT05805202	aHUS	2023-05-03	112	Interventional	NA	European
NCT07180355	Friedreich's ataxia	2025-10-22	10	Interventional	1	American
NCT05722886	Hematological malignancies and ST	2023-03-01	825	Interventional	2 and 3	European
NCT04398628	Hematologic disorders, including hemophilia, thrombosis, VWD, thrombophilia, rare bleeding disorders, platelet disorders, FIXD, FVIIID, thalassemia, SCD, and MECP2 duplication syndrome	2020-09-30	3000	Observational	Not applicable	American
NCT06615206	MECP2 duplication syndrome	2024-10-30	6	Interventional	NA	Asian
NCT03340506	HGG, melanoma, NSCLC, rare cancers, and ST	2017-12-28	100	Interventional	4	American, European, and Asian
NCT07127978	DMD	2025-10-23	300	Observational	NA	American

ClinicalTrials.gov ID	Conditions	Study start	Enrollment	Study type	Phase	Population
NCT07176923	FCS	2025-10-15	15	Interventional	Early phase 1	Asian
Unknown status						
NCT03347591	Rare bleeding disorders	2017-11-07	300	Observational	NA	European
NCT04620980	Parkinson disease	2021-06-15	600	Observational (patient registry)	NA	European
NCT04080050	HoFH	2019-09-30	8	Observational	NA	American and European
NCT00004307	Amino acid metabolism, inborn errors	1999-12	66	Interventional	1	American
Active (not recruiting)						
NCT02978625	cutaneous malignancies, adnexal carcinomas, refractory/recurrent ST, MCC, SCC, BCC, extramammary PD, and vulvar SCC	2017-09-27	68	Interventional	2	American
NCT04628871	Hemophilia B, MPS I, and MPS II	2020-11-03	13	Observational	NA	American
Terminated						
NCT00004498	OTCD	1998-07	21	Interventional	1	American
NCT02651675	HoFH	2016-03	9	Interventional	1 and 2	American and European
NCT02465528	Tumors with ALK alterations, ALCL, inflammatory myofibroblastic tumor, and glioblastoma	2016-05-06	22	Interventional	2	European and Asian
NCT00004806	CF	1995-06	9	Interventional	1	European
NCT02702115	MPS I	2017-05-24	3	Interventional	1 and 2	American
NCT04171700	Solid tumor	2020-01-16	83	Interventional	2	American
NCT03495921	Solid tumors, ESFT, metastatic EWS, recurrent Ewing tumor, rare diseases, sarcoma, and connective and soft tissue neoplasms	2018-08-21	32	Interventional	3	American
NCT03041324	MPS II and MPS II	2017-05-11	9	Interventional	1 and 2	American

aHUS: atypical hemolytic uremic syndrome; ALCL, anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; AS: Alport syndrome; BCC: basal cell carcinoma; CF: cystic fibrosis; DD/ID: developmental delay/intellectual disability; DMD: Duchenne muscular dystrophy; ESFT: Ewing sarcoma family tumors; EWS: Ewing sarcoma; FCS: familial chylomicronemia syndrome; FIXD: factor IX deficiency; FSGS: focal segmental glomerulosclerosis; FVIIID: factor VIII deficiency; HER2: human epidermal growth factor receptor 2; HGG: high-grade glioma; HoFH: homozygous familial hypercholesterolemia; IgAN: immunoglobulin A nephropathy; LGMD2C: limb-girdle muscular dystrophy type 2C; LINCL: late infantile neuronal ceroid lipofuscinosis; MCC: Merkel cell carcinoma; MPS I: mucopolysaccharidosis type I; MPS II: mucopolysaccharidosis type II; NSCLC: non-small cell lung cancer; OTCD: ornithine transcarbamylase deficiency; PD: Paget disease; PKD: polycystic kidney disease; SCC: squamous cell carcinoma; SCD: sickle cell disease; ST: solid tumors; STS: soft tissue sarcoma; VWD: von Willebrand disease.

Table 2. Gene therapy approaches and findings in rare disease cases

Trial registry number	Disease	Clinical condition	Gene target	Therapy method	Trial phase	Outcomes	Product and approval status
NCT03745287	Sickle cell disease	Genetic hemoglobin disorder causes vaso-occlusion and organ damage	BCL11A	CRISPR-Cas9-mediated genome editing in hematopoietic stem cells	2 and 3	The therapy stably increased HbF levels	Casgevy® received FDA approval in 2023
NCT01560182	MLD	ARSA deficiency causes progressive CNS/PNS demyelination	ARSA	Ex vivo lentiviral ARSA gene transfer into	1 and 2	Encapsulated hARSA-secreting cells reduced neuroinflammation	Libmeldy® received EMA approval in 2020 and FDA approval in 2024

Trial registry number	Disease	Clinical condition	Gene target	Therapy method	Trial phase	Outcomes	Product and approval status
				autologous CD34+ HSCs		and sulfatide accumulation	
NCT03488394	Mucopolysaccharidosis type I (MPS I, Hurler syndrome)	IDUA deficiency leads to glycosaminoglycan accumulation and neurodegeneration	IDUA	Neonatal ex vivo gene therapy in MPS-I mice	1 and 2	Increased IDUA activity improved metabolic correction and skeletal abnormalities	Not yet approved
NCT03569891	Hemophilia B	Factor IX deficiency causes recurrent bleeding	F9	AAV-mediated liver-directed gene therapy delivering functional F9	3	Sustained FIX expression reduced bleeding frequency and prophylactic factor use	HEMGENIX® approved by FDA in 2022
NCT05096221	Duchenne muscular dystrophy	DMD mutation causing progressive muscle degeneration	DMD	AAV-mediated micro-dystrophin gene delivery	3	Phase 3 studies demonstrated improved motor outcomes and strong microdystrophin expression	Elevidys® received FDA approval in 2023

AAV: adeno-associated virus; ARSA: arylsulfatase A; BCL11A: B-cell lymphoma/leukemia 11A; CNS: central nervous system; CRISPR: clustered regularly interspaced short palindromic repeats; DMD: Duchenne muscular dystrophy; EMA: European Medicines Agency; F9: factor 9; FDA: U.S. Food and Drug Administration; HBF: fetal hemoglobin; IDUA: alpha-L-iduronidase; MLD: metachromatic leukodystrophy; MPS I: mucopolysaccharidosis type I.

Table 3. The latest FDA-approved gene therapy products for rare diseases in 2025

Product	National clinical trial numbers	Biologics license	Company	Indication	Therapy type	FDA approval
Itvisma (onasemnogene abeparvovec-brve)	03381729, 03421977, 04042025, 05089656, 05335876, 05386680.	BL 125856/0	Novartis Gene Therapies	Spinal muscular atrophy (SMA) expanded indication ≥2y	AAV9 gene therapy	November 2025 [87]
Zevaskyn (prademagene zamikeracel)	01263379, 04227106, 05708677, and 05725018.	BL 125807/0	Abeona Therapeutics	Recessive dystrophic epidermolysis bullosa (RDEB)	Autologous cell-based gene therapy	April 2025 [88]
Revakinagene taroretcel (Encelto)	01327911, 01949324, 03071965, 03316300, 03319849, and 04729972.	BL 125798/0	Neurotech Pharmaceuticals, Inc.	Macular telangiectasia type 2	AAV gene therapy	March 2025 [89]
Waskyra (etuvetidigene autotemcel)	01515462 and 03837483.	BL 125846/0	Fondazione Telethon ETS	Wiskott-Aldrich syndrome (WAS)	Autologous gene-modified HSCs	December 2025 [90]

AAV: adeno-associated virus; BL: biologics license; FDA: U.S. Food and Drug Administration; HSCs: hematopoietic stem cells; RDEB: recessive dystrophic epidermolysis bullosa; SMA: spinal muscular atrophy; WAS: Wiskott–Aldrich syndrome.

In addition, ethical and regulatory considerations must be carefully addressed, and innovative reimbursement frameworks are needed to mitigate the substantial financial burden on healthcare systems [86]. Beyond scientific and clinical challenges, patient recruitment represents a major bottleneck in gene therapy trials for rare diseases, as the low prevalence of patients often results in geographically dispersed populations and delayed enrollment [91,92]. To address this limitation, emerging digital health strategies, including blockchain-based patient registries, have been proposed to improve transparency, data security, and cross-institutional data sharing, thereby potentially enhancing patient identification and recruitment efficiency, as has been explored in initiatives in the United Kingdom [93,94].

The ability to modify the genomes of human embryos has generated substantial scientific and ethical debate. While this technology holds promise for preventing or treating genetic disorders, both research and potential clinical applications raise serious ethical concerns, regulatory barriers, and safety issues [95]. Ethical discussions in gene therapy focus on applying genetic science for the benefit of humanity while preventing avoidable harm [96]. Current concerns include the protection of genetic data privacy, potential discrimination against individuals with identified genetic disorders, and equitable access to beneficial genetic treatments [96]. One of the most significant ethical concerns, as underscored by the National Institutes of Health (NIH), in the field of genome editing is the possibility of off-target effects. These unintended mutations can cause insertional mutagenesis and lead to unanticipated changes in the genome [97]. Bioethicists and researchers emphasize that genome editing is still an emerging and unpredictable technology, with incomplete understanding of gene regulation and embryonic development. Therefore, germline interventions may carry severe or even lethal consequences [98]. Genome editing in human embryos carries a significant risk of inducing pathological conditions that may affect both the individual and future generations.

Following early adverse events in gene therapy clinical trials in 1999, informed consent in clinical research has become a central concern [99]. Any research aiming for therapeutic advances must strictly adhere to ethical standards of informed consent [100]. Since James Watson raised concerns in 1991 about the potential enhancement of human genetics, gene therapy has progressed through improvements in vector systems, the use of induced pluripotent stem cells combined with the application of advanced genome-editing tools, including CRISPR-Cas9, and experimental applications in germ cells, which introduce complex ethical and moral implications [101].

A major concern remains the possibility of off-target effects, which may result in unintended mutagenesis and serious diseases such as cancer. The technology is still relatively new and not fully understood, particularly in relation to gene regulation and embryonic development, making it difficult to predict long-term outcomes, especially in germline editing, where genetic modifications can be inherited by future generations and potentially cause lasting pathological consequences. Past adverse events in clinical trials have underscored the necessity for strict safety oversight and transparent informed consent. Therefore, beyond technical limitations, gene therapy raises profound ethical, safety, and intergenerational responsibility issues that require careful and ongoing consideration.

Current access and regulation of gene therapy

Gene therapy signifies groundbreaking progress in healthcare, offering unique opportunities to tackle the underlying causes of genetic disorders and broadly enhancing regenerative medicine. Nevertheless, unmonitored generation of therapeutic genes may result in reduced clinical effectiveness because of different complications [102]. The high price of licensed gene therapies poses a significant burden even for high-income countries (HICs) and makes widespread access in low- and middle-income countries (LMICs) nearly unattainable [103]. For instance, Glybera, the first gene therapy approved in Europe, was priced at approximately €1 million and was eventually withdrawn because no country agreed to reimburse it due to its cost [104,105]. By 2021, at least 15 gene therapy products had received approval [103]. Nevertheless, access to these treatments remains highly restricted in LMICs, where they are primarily available through compassionate use or managed access programs. Furthermore, the substantial costs and

specialized clinical infrastructure required to administer gene therapies present major obstacles to delivering treatment in underserved regions [103].

These challenges are particularly evident in Tier 3 countries across Asia, where limited genomic infrastructure, inadequate regulatory capacity, shortages of trained personnel, and dependence on external laboratories significantly constrain the implementation of advanced precision medicine and gene therapy programs [9]. In these settings, access barriers extend beyond treatment costs to include insufficient diagnostic capabilities, lack of specialized treatment centers, and restricted participation in genomic research networks. These issues require continuous dialogue about when, why, and where gene therapy is suitable and warranted, with gene regulation technologies anticipated to be crucial to that conversation concerning safety and effectiveness [102].

Gene therapy must possess a validated companion diagnostic test sanctioned by regulatory bodies, with availability potentially varying by country [106]. The most frequently cited barrier in literature pertains to affordability, particularly highlighting the expensive nature of therapy (84%) and issues concerning therapy payment/reimbursement (51%). Crucially, the evidence creation concentrating on restricted trial results (81%) appears to be a significant barrier to patient access to these treatments [107]. Tier 3 countries, defined as countries without independent genomic facilities, frequently face constraints in generating locally relevant evidence due to limited involvement in clinical trials and inadequate genomic databases, which can hinder regulatory approval, reimbursement processes, and the clinical adoption of gene therapies [9].

Recently approved gene therapies in the US and Europe provide single-treatment solutions for severe or terminal illnesses that supposedly yield lasting advantages [108]. Preclinical and clinical research has consistently shown that inflammation associated with rAAV treatment, especially from subretinal and intravitreal injections, appears to depend on dose [109]. Fortunately, mild inflammation after AAV administration can often be reduced using topical, local, or systemic steroid treatment [110]. Guaranteeing the long-term safety of gene therapy is crucial, as off-target effects and unanticipated outcomes of genetic manipulation are being extensively studied. Creating effective and precise delivery mechanisms, especially for nonviral vectors, presents a major hurdle. Additionally, immune reactions to the vector or the newly added gene may reduce therapy efficacy and present possible hazards to patients [111].

Gene therapy requires a far more complex oversight system than conventional drugs. The production of viral vectors and genetically modified cells must comply with strict pharmaceutical quality standards to ensure consistency, safety, and efficacy. Scientific evidence that largely originates from clinical trials with limited populations also becomes a barrier to expanding access, as regulators and healthcare payers require long-term data on durability and safety. Regulatory frameworks for advanced therapy medicinal products (ATMPs) remain underdeveloped in countries that have not yet established independent genomic facilities, including comprehensive genomic databases and the necessary infrastructure and equipment, creating additional challenges for the evaluation, approval, and post-marketing surveillance of gene therapy products [9]. Regional and international collaboration has therefore been proposed as a practical strategy to strengthen regulatory capacity and facilitate technology transfer in resource-limited settings.

Long-term safety remains a primary focus in gene therapy regulation. The risk of immune responses to viral vectors, particularly AAV, dose-related inflammatory effects, and the possibility of off-target effects or unforeseen genetic consequences necessitate long-term patient monitoring [112]. Although gene therapy has demonstrated promising clinical success and even curative potential, challenges related to access, financing, regulation, and long-term safety assurance remain major barriers to widespread implementation. These barriers are disproportionately experienced by Tier 3 countries, highlighting the need for capacity building in genomic medicine, expansion of diagnostic infrastructure, and greater integration into regional precision medicine initiatives [9]. Therefore, progress in this field depends not only on biotechnological innovation but also on health policy reform, flexible reimbursement systems, and international regulatory harmonization to ensure fair and sustainable access to the benefits of gene therapy.

Conclusion

Gene therapy has transitioned from an experimental concept to a clinically validated precision treatment for rare diseases, supported by strong evidence from successful therapies, increasing clinical trials, and regulatory approvals. Advances in gene editing technologies, particularly CRISPR-Cas9, as well as improvements in vector design and delivery systems, have contributed to increased precision and therapeutic potential in specific contexts. However, important challenges remain. Safety concerns, including immune responses and off-target effects, continue to require careful evaluation. In addition, the high cost of treatment and limited availability restrict broader access, particularly in resource-limited settings. Regulatory and ethical considerations further add complexity, as frameworks must ensure patient safety while accommodating emerging innovations. Clinical outcomes are also influenced by factors such as the timing of intervention and the durability of therapeutic effects, both of which vary across diseases and treatment strategies. Long-term data are still limited for many gene therapy approaches, highlighting the need for continued monitoring and evaluation. Gene therapy represents a promising therapeutic approach for rare diseases; however, its long-term clinical impact will depend on overcoming current challenges related to safety, accessibility, and long-term efficacy.

Ethics approval

Not required.

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Competing interest

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools in the following capacity: AI-based language tools, including QuillBot, were employed for language refinement to improve grammar, sentence structure, and overall readability of the manuscript. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the content, and the final decisions, interpretations, and conclusions presented in this article were solely made by the authors.

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