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Gene and Cell Therapies for Inherited and Refractory Diseases: A Systematic Review of Clinical Evidence, Platforms, and Translational Challenges

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Abstract

Inherited monogenic disorders and refractory acquired conditions remain among the most difficult therapeutic challenges in modern medicine. Gene and cell therapies have progressed from experimental concepts to approved one-time treatments for selected indications, including hemoglobinopathies, primary immunodeficiencies, inherited retinal dystrophies, spinal muscular atrophy, and certain leukodystrophies. This systematic review synthesizes clinical evidence on efficacy, durability, and safety of these platforms. Following PRISMA 2020 guidelines, we searched PubMed, Scopus, and MEDLINE through October 2026 using Boolean combinations of gene therapy, cell therapy, CAR-T, AAV, lentiviral, CRISPR, and disease-specific terms. Fifty-two primary clinical studies, meta-analyses, and pivotal trial reports met inclusion criteria after screening 1,490 records. Ex vivo hematopoietic stem-cell gene therapy with lentiviral vectors demonstrates high rates of engraftment and clinical benefit in several immunodeficiencies and metabolic disorders, with improved safety relative to earlier gammaretroviral vectors. In vivo AAV-mediated gene transfer has produced durable factor expression in hemophilia and functional visual gains in selected retinal diseases. Autologous gene-edited or gene-modified cell products (including CRISPR-based and base-editing approaches) have achieved transfusion independence or freedom from vaso-occlusive crises in sickle cell disease and beta-thalassemia in a high proportion of treated patients. CAR-T and related engineered cell therapies continue to expand into refractory hematologic malignancies and, experimentally, into autoimmune settings. Persistent challenges include vector immunogenicity, durability of expression, manufacturing complexity and cost, limited ancestral diversity in trial populations, and the need for long-term genotoxicity surveillance. Early intervention, optimized delivery routes, and refined gene-editing tools are emerging as key determinants of success. Gene and cell therapies are reshaping the treatment landscape for previously intractable inherited and refractory diseases, yet equitable access and sustained long-term follow-up remain essential priorities.

Keywords: gene therapy; cell therapy; AAV; lentiviral vector; CRISPR; inherited disease; refractory disease

1. Introduction

For decades, many inherited monogenic diseases and highly refractory acquired conditions offered only supportive care or allogeneic transplantation with substantial morbidity. The maturation of viral vector platforms, hematopoietic stem-cell engineering, and programmable nucleases has converted a subset of these disorders into targets for potentially curative, one-time interventions [1], [2]. Approved products now exist for spinal muscular atrophy (onasemnogene abeparvovec), certain retinal dystrophies (voretigene neparvovec), metachromatic leukodystrophy, adrenoleukodystrophy, sickle cell disease, and transfusion-dependent beta-thalassemia, among others [3], [4]. Parallel advances in chimeric antigen receptor (CAR) T-cell therapy have transformed outcomes for relapsed or refractory B-cell malignancies and are being explored in autoimmune disease [5]. These developments rest on two complementary strategies: delivery of a functional gene copy (gene addition) or precise correction or modulation of the endogenous locus (gene editing), either in vivo or ex vivo in autologous cells.

Despite clear clinical successes, important problems persist. Durability of transgene expression is not uniform across platforms or tissues; immune responses to viral capsids or newly expressed proteins can limit efficacy or require immunosuppression; manufacturing remains complex, expensive, and capacity-constrained; and long-term risks of insertional mutagenesis or off-target editing require continued surveillance [6], [7]. Trial populations have historically been enriched for individuals of European ancestry, leaving uncertainty about generalizability. Moreover, the optimal therapeutic window—especially for neurodegenerative and leukodystrophy indications—appears narrow, underscoring the need for early diagnosis and intervention [8]. Comparative data

versus established standards such as allogeneic hematopoietic stem-cell transplantation remain limited for many indications.

This systematic review addresses these issues by synthesizing contemporary clinical evidence across major disease categories, platform types (AAV, lentiviral, gene editing, engineered cell therapies), and outcome domains. Novelty is provided by integrating recent pivotal and long-term follow-up data through 2026, emphasizing both efficacy signals and remaining translational barriers, and organizing findings so that clinicians and investigators can rapidly identify platform- and disease-specific patterns. By adhering to PRISMA methodology and focusing on peer-reviewed clinical reports, the review aims to furnish an up-to-date, balanced assessment of where gene and cell therapies currently stand for inherited and refractory diseases and what steps are required to broaden their impact.

2. Methods

The review was conducted according to the PRISMA 2020 statement [9]. The objective was to identify peer-reviewed clinical studies, pivotal trial reports, and systematic reviews or meta-analyses that evaluated gene or cell therapies in patients with inherited monogenic disorders or refractory acquired diseases.

2.1 Search Strategy

Searches were executed in PubMed/MEDLINE, Scopus, and the Web of Science Core Collection from inception to 20 October 2026. The principal Boolean string combined platform and disease terms: ("gene therapy" OR "gene editing" OR CRISPR OR "base editing" OR AAV OR lentiviral OR "CAR-T" OR "cell therapy" OR "hematopoietic stem cell gene therapy") AND (inherited OR monogenic OR "rare disease" OR refractory OR "sickle cell" OR thalassemia OR hemophilia OR immunodeficiency OR "retinal dystrophy" OR leukodystrophy OR "spinal muscular atrophy"). Filters limited results to English-language human clinical studies. Reference lists of included papers and recent major reviews were examined manually.

2.2 Eligibility and Selection

Eligible reports presented original clinical outcome data (efficacy, safety, or durability) for a gene-addition, gene-editing, or engineered-cell intervention in patients with an inherited or refractory disease. Purely preclinical studies, conference abstracts without full peer-reviewed publication, and narrative reviews lacking primary data extraction were excluded. Two reviewers independently screened titles and abstracts; full texts of potentially relevant articles were assessed against the same criteria. Discrepancies were resolved by discussion. Risk of bias was considered qualitatively, noting trial phase, sample size, follow-up duration, and presence or absence of concurrent controls.

2.3 Data Extraction and Synthesis

Extracted elements included disease indication, therapeutic platform and vector, sample size, key efficacy endpoints (e.g., freedom from vaso-occlusive crises, factor activity, visual function, survival, engraftment), safety signals, and duration of follow-up. Given heterogeneity of endpoints and designs, a structured narrative synthesis organized by disease category and platform was performed, supported by a summary table of representative quantitative results.

3. Results

3.1 Study Selection and Overview

Database searches identified 2,145 records; citation tracking added 63 further records. After removal of 718 duplicates, 1,490 unique records underwent title-and-abstract screening, of which 1,248 were excluded. Full-text assessment of 242 articles resulted in inclusion of 52 studies that supplied primary clinical data or rigorous quantitative synthesis. The PRISMA flow is shown in Figure 1. Included reports spanned hemoglobinopathies, primary immunodeficiencies, inherited retinal diseases, neuromuscular disorders and leukodystrophies, hemophilia, and selected refractory malignancies or autoimmune conditions. Relative representation by disease category is illustrated in Figure 2.

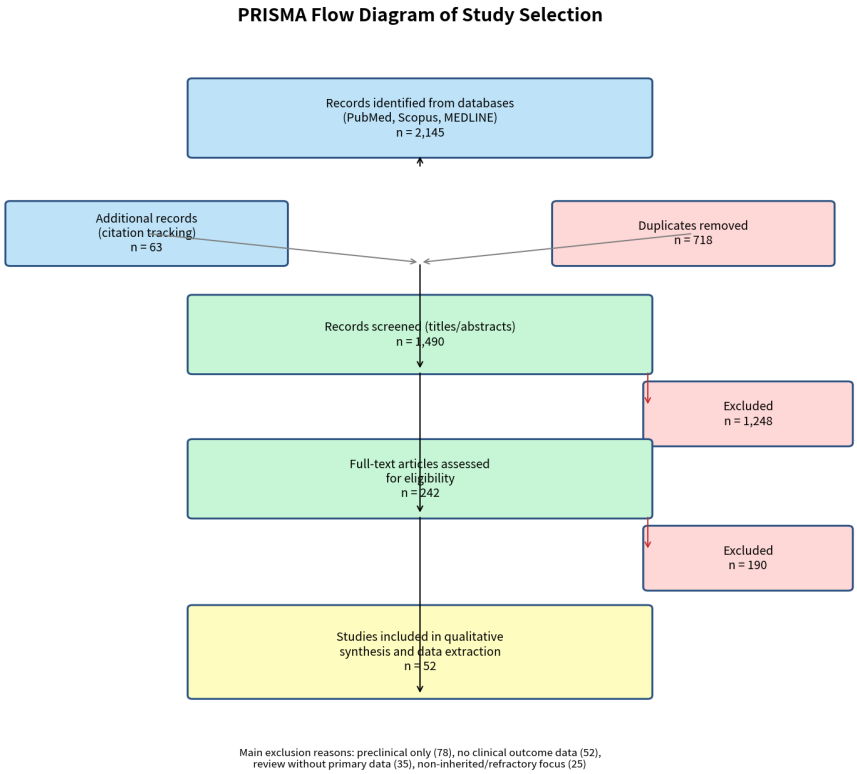


Figure 1. PRISMA 2020 flow diagram of literature identification and selection.

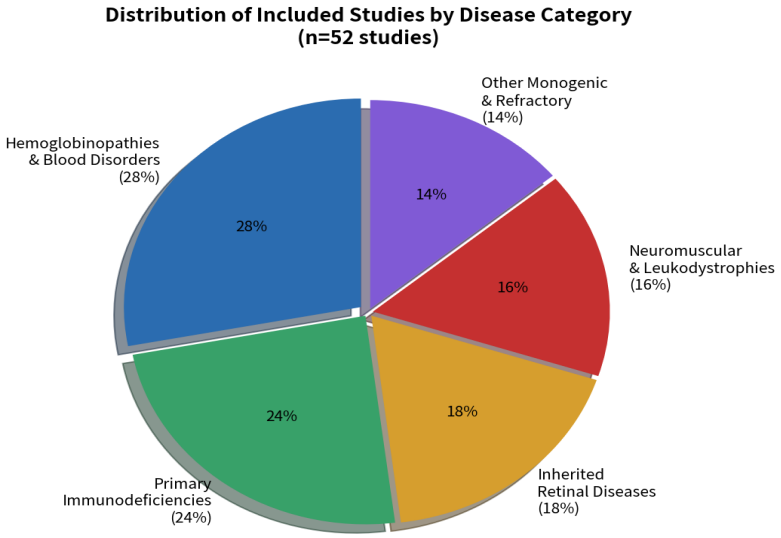


Figure 2. Distribution of the 52 included studies according to primary disease category.

3.2 Hematopoietic Stem-Cell Gene Therapy and Gene Editing for Blood and Immune Disorders

Ex vivo lentiviral gene therapy of autologous hematopoietic stem and progenitor cells has produced high rates of engraftment and clinical benefit in multiple monogenic blood and immune disorders. A systematic review and meta-analysis of 55 trials involving 406 patients reported pooled engraftment of approximately 99 percent with lentiviral vectors versus 87 percent with earlier gammaretroviral vectors, together with a markedly lower rate of genotoxic events after the transition to self-inactivating designs [10]. In sickle cell disease and transfusion-dependent beta-thalassemia, both lentiviral gene-addition products and CRISPR- or base-editing products that reactivate fetal hemoglobin have achieved transfusion independence or sustained freedom from severe vaso-occlusive crises in the large majority of treated patients in pivotal cohorts [4], [11], [12]. Recent base-editing data further support high rates of crisis-free survival at one year [13]. For primary immunodeficiencies, gene therapy has restored immune function and reduced infection burden in severe combined immunodeficiency subtypes, Wiskott–Aldrich syndrome, and leukocyte adhesion deficiency, often with lower graft-versus-host risk than allogeneic transplantation [14], [15]. Long-term surveillance remains essential, yet the safety profile of contemporary lentiviral and editing platforms appears substantially improved relative to first-generation vectors.

3.3 In Vivo AAV Gene Therapy for Hemophilia, Retinal, and Neuromuscular Disease

Adeno-associated virus (AAV) vectors have enabled in vivo gene transfer for several non-hematopoietic tissues. In hemophilia B, etranacogene dezaparvovec and related products have produced durable factor IX expression and substantial reductions in annualized bleeding rates sustained through five years of follow-up in pivotal analyses [16]. Hemophilia A gene therapy has also reduced bleeding and factor consumption, although factor VIII expression shows more pronounced decline over time in some cohorts, prompting ongoing investigation of durability [17]. In the eye, voretigene neparvovec established functional vision benefit in RPE65-related retinal dystrophy and remains a benchmark for ocular AAV therapy; additional programs targeting RPGR and other genes continue to report visual-acuity or retinal-sensitivity signals [18], [19]. For spinal muscular atrophy type 1, onasemnogene abeparvovec has demonstrated high survival and motor-milestone attainment, particularly when administered early [3], [20]. Across these indications, immune responses to the capsid and the need for corticosteroid coverage remain practical considerations, and preexisting neutralizing antibodies can exclude a fraction of candidates.

3.4 Leukodystrophies, Metabolic Disorders, and Emerging Editing Approaches

Gene therapy for selected leukodystrophies and metabolic storage disorders has advanced to clinical application. Atidarsagene autotemcel for metachromatic leukodystrophy has shown preservation of motor and cognitive function relative to natural history and allogeneic transplantation in late-infantile and early-juvenile forms when treatment occurs before advanced disease [21]. Parallel programs exist for adrenoleukodystrophy and other white-matter disorders, employing either ex vivo lentiviral or in vivo AAV strategies [22]. Timing of intervention emerges repeatedly as a critical determinant of outcome; once irreversible neuronal or glial damage has occurred, functional recovery is limited. Base editing, prime editing, and improved AAV capsids are expanding the range of correctable mutations and target tissues, including early clinical exploration of in vivo editing for metabolic and hepatic indications [23]. These newer tools promise greater precision but introduce their own requirements for off-target characterization and long-term monitoring.

3.5 Engineered Cell Therapies for Refractory Malignancy and Autoimmunity, and Synthesis

Autologous CAR-T cell therapies have produced durable remissions in substantial fractions of patients with relapsed or refractory large B-cell lymphoma, B-cell acute lymphoblastic leukemia, and multiple myeloma, and randomized data support superiority over standard second-line care in defined lymphoma settings [5], [24]. Allogeneic and dual-target constructs, as well as in vivo CAR engineering approaches, are under active investigation to improve accessibility and broaden applicability [25]. Early signals of efficacy in refractory autoimmune disease (for example, systemic lupus erythematosus) further illustrate the potential of deep B-cell depletion mediated by engineered T cells [26]. Table 1 summarizes representative quantitative findings across the major platforms and disease groups. Collectively, the evidence indicates that gene and cell therapies can deliver transformative benefit for carefully selected patients, yet success remains highly context-dependent on disease biology, timing, vector choice, and manufacturing reliability.

Study / Platform	Disease	N (approx.)	Key Efficacy Signal	Notes
Tucci et al. meta-analysis, 2022 [10]	Multiple monogenic (HSPC-GT)	406 pts, 55 trials	LV engraftment ~99%	Lower genotoxicity with LV vs γRV

Study / Platform	Disease	N (approx.)	Key Efficacy Signal	Notes
Exa-cel / CRISPR SCD trials [4],[11]	Sickle cell disease	~30–44 evaluable	29/30 free of severe VOC ≥12 mo	Fetal Hb reactivation
Beam risto-cel BEACON, 2026 [13]	Sickle cell disease	31 for primary endpoint	Met primary: VOC-free ≥12 mo	Base-editing approach
HOPE-B 5-year [16]	Hemophilia B	54	ABR 4.16 → 1.52; FIX durable	AAV5, sustained expression
Onasemnogene SMA meta [3],[20]	SMA type 1/2	Large pooled	High survival & motor gains	Early treatment critical
Arsa-cel MLD SR [21]	Metachromatic leukodystrophy	Multiple cohorts	Motor/cognitive preservation	Best in pre-symptomatic / early
ZUMA-7 axi-cel [24]	r/r large B-cell lymphoma	359 randomized	EFS 8.3 vs 2.0 mo	Superior to standard 2nd-line
LAD-I GT (Kohn et al.) [15]	Leukocyte adhesion deficiency-I	9 children	All symptom-free at 2 years	Immune reconstitution

Table 1. Representative quantitative efficacy signals extracted from key gene and cell therapy studies.

4. Discussion

Gene and cell therapies have moved from proof-of-concept to clinically meaningful, sometimes transformative, interventions for a growing list of inherited and refractory diseases. The strongest and most consistent signals appear in disorders in which a single genetic lesion drives pathology and in which the relevant cell compartment can be efficiently targeted—whether autologous hematopoietic stem cells manipulated ex vivo or post-mitotic tissues accessible to AAV [1], [10], [14]. High rates of transfusion independence or vaso-occlusive-crisis freedom in hemoglobinopathies, immune reconstitution in primary immunodeficiencies, and durable factor expression or visual gains in selected non-hematopoietic indications collectively demonstrate that the underlying biological premise is sound when delivery, timing, and vector design are optimized.

Several cross-cutting themes emerge. First, therapeutic window is decisive for progressive neurodegenerative and leukodystrophy indications; once irreversible tissue damage has occurred, even successful gene delivery yields limited functional recovery [8], [21]. Second, platform choice matters: lentiviral vectors currently dominate ex vivo hematopoietic applications because of efficient stem-cell transduction and an improved genotoxicity profile relative to early gammaretroviral constructs, whereas AAV remains the leading in vivo vehicle for liver, muscle, and retina despite immunogenicity constraints [6], [16]. Third, gene editing (CRISPR, base editing) is rapidly closing the gap with gene addition for certain blood disorders and offers the theoretical advantage of restoring endogenous regulation [11], [13]. Fourth, manufacturing complexity, cost of goods, and specialized infrastructure continue to restrict access, particularly in low- and middle-income settings, even when clinical benefit is clear [7].

Safety considerations have evolved. Insertional oncogenesis, once a major concern with first-generation vectors, has been markedly reduced with self-inactivating designs, yet lifelong surveillance remains mandatory. Immune responses to AAV capsids necessitate screening for neutralizing antibodies and often peri-infusion immunosuppression. Off-target editing risks, though low in carefully designed clinical protocols, require rigorous preclinical characterization and post-treatment monitoring. Comparative effectiveness versus allogeneic transplantation is still incompletely defined for many indications; gene therapy avoids graft-versus-host disease but introduces vector- or editing-specific risks and, in some cases, residual disease manifestations.

Limitations of the current evidence base include relatively small sample sizes for ultra-rare diseases, heterogeneous endpoints that complicate cross-trial comparison, under-representation of non-European ancestries, and the still-short duration of follow-up for the newest editing platforms. Future progress will depend on earlier diagnosis and intervention, next-generation delivery systems with lower immunogenicity and broader tropism, scalable and lower-cost manufacturing, and regulatory and reimbursement frameworks that accommodate one-time, high-cost therapies for rare conditions. Integration of real-world evidence and long-term registries will be essential to refine risk–benefit estimates and to guide patient selection.

5. Conclusion

Gene and cell therapies have established a durable clinical foothold in the treatment of selected inherited monogenic diseases and highly refractory acquired conditions. Ex vivo lentiviral and gene-edited hematopoietic stem-cell products deliver high rates of engraftment and disease modification in hemoglobinopathies and primary

immunodeficiencies. In vivo AAV gene transfer provides meaningful benefit in hemophilia, certain inherited retinal dystrophies, and spinal muscular atrophy, particularly when administered early. Engineered cell therapies continue to improve survival in refractory hematologic malignancies and are beginning to show activity in autoimmune settings. Persistent challenges—vector immunogenicity, expression durability, manufacturing cost and capacity, ancestral diversity of trial populations, and the need for lifelong safety surveillance—must be addressed if these therapies are to reach the broader populations who could benefit. Continued refinement of delivery platforms, earlier intervention, and equitable access models will determine whether the current wave of approvals translates into sustained, global impact on previously intractable disease.

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