*MarinBio Blog*

# Advances in Gene Therapy for Ultra-Rare Genetic Disorders

**Introduction**

Ultra-rare hereditary genetic disorders represent some of the most challenging conditions in medicine. Affecting only a handful of patients worldwide, these diseases are typically caused by single-gene mutations that lead to severe and often life-limiting pathologies. The advent of gene therapy has begun to change this, opening new treatment options for those patients.

One of the most striking developments has been the emergence of N-of-1 gene therapy interventions, in which therapies are custom-designed for a single patient with a unique genetic defect. These individualized treatments have demonstrated the feasibility of several molecular tools, such as antisense oligonucleotides, viral vectors, or genome-editing constructs, to address ultra-rare pathogenic variants.

This movement toward personalization is reinforced by the growing diversity of transformative therapeutic approaches. Viral platforms, particularly adeno-associated virus (AAV) and lentiviral vectors, remain cornerstones of in vivo and ex vivo delivery. At the same time, non-viral technologies have matured rapidly, with lipid nanoparticles (LNPs), DNA nanoparticles, and messenger RNA replacement strategies demonstrating increasing clinical relevance. Moreover, CRISPR-based genome editing allows for precise correction of pathogenic mutations, while lentiviral modification of autologous stem cells enables long-term gene correction across hematopoietic lineages. Collectively, these evolving methods aim to provide durable, targeted, and potentially curative treatments.

Recently, new innovations have fueled landmark clinical trials and preclinical advances that specifically target ultra-rare diseases once considered untreatable. Examples include ocular gene therapies for inherited blindness, CRISPR-mediated editing strategies for hematologic disorders, and systemic AAV-based treatments for neuromuscular diseases.

Central to all of these developments is the refinement of targeted in vivo delivery strategies, which remains a decisive factor in determining therapeutic efficacy and safety. The ability to deliver a therapeutic payload precisely to affected tissues, whether retinal cells, hepatocytes, neurons, or hematopoietic stem cells, has improved significantly with advances in capsid engineering, which enhance tissue specificity and reduce immunogenicity of viral vectors. In parallel, LNPs and synthetic nanoparticles are being optimized for stability, biodistribution, and repeat dosing. These delivery innovations are critical for ensuring that gene therapy becomes not only possible but reliable across the broad spectrum of ultra-rare hereditary diseases.

**Prevalence of Ultra-Rare Hereditary Genetic Disorders and Gene Therapy Clinical Trial Status**

Ultra-rare diseases inherently have a low prevalence in a population, however multiple genes are affected, each with different phenotypic consequences. In addition, a single gene may have unique genetic variants, each one detrimental, and each one unique to an individual. Below is a sampling of ultra-rare genetic diseases, their prevalence in the United States, and status with regards to gene therapy stage of clinical development.

Spinal Muscular Atrophy (SMA)
- *Prevalence: Approximately 1 in 14,694 newborns in the US, with about 7,500–10,000 individuals living with various types of SMA.*
- *Gene Therapy Status: Approved gene therapy (Zolgensma®) is available*.

Batten Disease (Neuronal Ceroid Lipofuscinoses)
- *Prevalence: Estimated around 2 to 4 in 100,000 live births globally; US-specific data is limited but similar.*
- *Gene Therapy Status: Multiple Phase 1 and 2 clinical trials ongoing*.

Metachromatic Leukodystrophy (MLD)
- *Prevalence: Estimated 1 in 40,000 to 160,000; considered ultra-rare.*
- *Gene Therapy Status: EMA-approved ex vivo gene therapy (Libmeldy®) and ongoing trials.*

Mucopolysaccharidoses (MPS)
- *Prevalence: Varies by subtype, MPS I estimated around 1 in 100,000 live births in US.*
- *Gene Therapy Status: Multiple Phase 2/3 gene therapy trials ongoing.*

Krabbe Disease
- *Prevalence: About 1 in 100,000 births in the US.*
- *Gene Therapy Status: Phase 1/2 gene therapy trials ongoing.*

Canavan Disease
- *Prevalence: Very rare, about 1 in 6,400 Ashkenazi Jewish individuals are carriers, prevalence in general US population is <1 in 250,000.*
- *Gene Therapy Status: Phase 1/2 trials ongoing*.

X-linked Adrenoleukodystrophy (ALD)
- *Prevalence: Approximately 1 in 21,000 males in the US.*
- *Gene Therapy Status: Phase 2/3 gene therapy trials ongoing*.

Phenylketonuria (PKU)
- *Prevalence: About 1 in 10,000 to 15,000 newborns in the US.*
- *Gene Therapy Status: Phase 1/2 gene therapy trials underway*.

Gangliosidoses (GM1/GM2)
- *Prevalence: GM2 (Tay-Sachs) about 1 in 300,000 US births; GM1 about 1 in 100,000.*
- *Gene Therapy Status: Multiple Phase 1 and 2 trials ongoing.*

Huntington's Disease
- *Prevalence: Around 5–10 per 100,000 people of European descent in the US.*
- *Gene Therapy Status: Phase 1/2 gene therapy trials recruiting.*

Amyotrophic Lateral Sclerosis (ALS)

- *Prevalence: About 6 in 100,000 persons in the US.*
- *Gene Therapy Status: Compassionate-use gene therapy studies are reported.*

Rett Syndrome

- *Prevalence: About 1 in 10,000 to 15,000 female births in the US.*
- *Gene Therapy Status: No active gene therapy clinical trials.*

Niemann-Pick Disease

- *Prevalence: Varies by type, Type A is about 1 in 250,000 live births in the US.*
- *Gene Therapy Status: No active gene therapy trials currently.*

Hunter Syndrome

- *Prevalence: Estimated 1 in 100,000 to 170,000 live births.*
- *Gene Therapy Status: Ongoing gene therapy clinical trials.*

Hurler Syndrome

- *Prevalence: About 1 in 100,000 live births in the US.*
- *Gene Therapy Status: Gene therapy trials ongoing.*

Fabry Disease

- *Prevalence: Estimated 1 in 40,000 to 60,000 males in the US.*
- *Gene Therapy Status: Gene therapy clinical trials underway.*

Ataxia Telangiectasia

- *Prevalence: About 1 in 40,000 to 100,000 live births.*
- *Gene Therapy Status: Limited gene therapy research; no active trials*.

These prevalence estimates are based on EU and US population data from recent epidemiological studies and registries, and the gene therapy clinical trial statuses range from approved therapies to early-phase trials or limited/no activity depending on the disorder.

**Gene Therapy: N-of -1 Interventions for Ultra-Rare Genetic Disorders**

In the context of individualized gene therapy for rare genetic diseases, N-of-1 interventions refer to highly personalized therapeutic strategies that are designed, developed, and administered for a single patient. These interventions are typically pursued when a patient has a very rare or even unique genetic mutation that does not fall within the scope of ongoing clinical trials or existing approved therapies.

The term *N-of-1* comes from clinical trial design, where “N” represents the number of patients. In this case, N=1, meaning the treatment is specifically tailored for just one individual rather than a cohort of patients.

Key features of N-of-1 gene therapy interventions include:

- Ultra-personalization: The therapy is engineered to target the precise genetic variant causing disease in a single patient. This might involve antisense oligonucleotides (ASOs), small interfering RNAs, CRISPR-based editing, or custom gene replacement vectors.
- Rapid development timelines: Given the urgency of progressive rare diseases, interventions often need to be developed, validated preclinically, and administered in months rather than years.

- Regulatory pathways: Because conventional large-scale trials are not feasible, regulatory agencies such as the FDA or EMA allow for *compassionate use* or *expanded access* pathways. These require careful risk–benefit assessment and rigorous oversight.
- Ethical and scientific challenges: N-of-1 approaches raise questions about safety testing, reproducibility, informed consent, and equitable access, since they require major resources and infrastructure but serve only a single patient.

A landmark example is the case of *milasen*, a custom antisense oligonucleotide designed in 2018 for a girl with Batten disease (caused by a unique CLN7 mutation). Within about a year, a therapy was designed, preclinically tested, and administered to her alone, demonstrating the feasibility of this model.

In short, N-of-1 gene therapy interventions represent the ultimate form of precision medicine, bridging research and clinical care for patients whose diseases are too rare for conventional therapeutic development.

**Evolving Transformative Gene Therapy Approaches**

Gene therapy has emerged as a transformative approach for treating ultra-rare genetic disorders. With advancements in delivery systems ranging from viral vectors like AAV and lentivirus to cutting-edge methods such as lipid nanoparticle-mediated CRISPR editing and mRNA replacement therapies, these gene therapies aim to address the root cause of disease at the molecular level. Each approach offers unique advantages, including long-lasting gene expression, precision gene editing, and reduced immunogenicity, enabling targeted and potentially curative treatments for conditions that previously had limited or no effective options.

Here are 8 molecularly distinct gene therapy approaches in clinical trials for ultra-rare genetic disorders, each with its delivery system, advantages, and a disease example including current stage of clinical development:

1. Adeno-Associated Virus (AAV) Gene Addition
   AAV vectors deliver a healthy copy of a gene to affected cells. Advantages include long-term gene expression and lower immunogenicity versus other viral vectors. Example: Luxturna for Leber congenital amaurosis, currently approved for clinical use after successful Phase III trials in patients with RPE65 mutations.
2. Lipid Nanoparticle (LNP)-Delivered CRISPR Base Editing
   LNPs encapsulate base editors and guide RNAs to correct point mutations. LNPs offer scalability, lower immune response, and large cargo capacity. Example: CPS1 deficiency, with custom CRISPR base editing recently fast-tracked for n=1 compassionate use, currently described as “early clinical” administration to a single patient.
3. Lentiviral Vector-Mediated Ex Vivo Hematopoietic Stem Cell Gene Transfer
   Autologous stem cells are collected, transduced ex vivo with lentivirus, and reinfused, allowing stable gene expression in blood and immune cells. Advantage is reduced risk of

graft-vs-host disease and durable gene correction. Example: ADA-SCID, with multiple trials showing safety and efficacy; some therapies have achieved regulatory approval.

4. Antisense Oligonucleotide (ASO) Therapy
   Synthetic oligonucleotides modulate RNA splicing or degrade faulty mRNA. Often delivered via injection or lipid nanoparticles. Advantages include high specificity and ability to target non-coding RNAs. Example: Nusinersen for Spinal Muscular Atrophy (rare forms such as SMA with unique mutations now in ultra-rare research), advanced to full regulatory approval after pivotal trials.

5. mRNA Replacement/LNP-Delivered mRNA Therapy
   LNPs or other non-viral methods deliver corrective mRNA to cells, allowing transient protein production. Advantage: non-integrating, lower mutagenesis risk. Example: mRNA therapies for ultra-rare metabolic disorders (such as propionic acidemia), now in Phase I/II trials.

6. In Vivo CRISPR/Cas9 Gene Editing Using AAV or LNP
   Direct injection of CRISPR/Cas9 tools to edit genes within patient tissues. Benefits: potential for permanent cure, tailored repair strategies. Example: NTLA-2002 (for hereditary angioedema), in multiple ongoing early-phase clinical trials, with analogous approaches now being tried for individual ultra-rare mutations.

7. Gene Silencing via RNA Interference (RNAi)
   Short interfering RNAs (siRNA) delivered by LNPs or conjugates knock down mutant gene expression. This approach is non-integrative, highly specific for target mRNAs. Example: Ultra-rare amyloidosis variants (such as hATTR with unique mutations), with drugs reaching Phase I/II trials.

8. Topical Gene Therapy (Non-Viral, Localized Delivery)
   Direct application or injection of DNA encoding wild-type genes to affected tissues. Benefits include local effect and repeat dosing. Example: Vyjuvek for dystrophic epidermolysis bullosa (COL7A1 mutations), is a topical, non-integrating HSV-1-based gene-delivery vector, in pivotal trials and recently approved for an ultra-rare subset.

Each approach leverages distinct molecular mechanisms and delivery technologies, with clinical stages ranging from compassionate use and first-in-human to approved therapy for ultra-rare indications.

**Recent Advances in Gene Therapy for Ultra-Rare Hereditary Diseases**

Recent advances in gene therapy for ultra-rare hereditary disorders have been marked by a series of transformative scientific and technological innovations that together push the field toward precision, efficacy, and accessibility for diseases once considered untreatable.

One of the landmark developments has been the use of personalized CRISPR-based therapies, exemplified by a case where a newborn diagnosed with carbamoyl-phosphate synthetase 1 (CPS1) deficiency received a tailor-made in vivo base-editing treatment using adenine base

editors delivered via lipid nanoparticles. This therapy was designed specifically for the patient's unique genetic variant and administered within six months of diagnosis, stabilizing the infant's critical metabolic condition. The approach of rapid, individualized in vivo editing using CRISPR base editors represents a shift in treating ultra-rare disorders, as it leverages precise base correction without double-strand breaks, minimizing off-target effects and potential long-term risks.  Another frontier is the employment of precise and diverse CRISPR-associated protein variants (e.g., Cas9, Cas12, and newer engineered base editors) with enhanced fidelity and flexible PAM requirements, allowing editing of previously inaccessible genomic loci. These variants reduce off-target effects and improve editing efficiency, which is critical in the context of ultra-rare disorders caused by unique or complex mutations.

Complementing these advances are innovations in vector technology, particularly in engineered adeno-associated virus (AAV) capsids designed to overcome key biological barriers. A notable breakthrough is the development of receptor-targeted capsid platforms that enable AAV vectors to traverse the blood-brain barrier efficiently by exploiting the human transferrin receptor (TfR1). This innovation is critical for neurological ultra-rare diseases where access to widespread central nervous system cells is required. Additionally, engineered capsids have been optimized to evade pre-existing neutralizing antibodies prevalent in roughly half the population, expanding the patient pool eligible for therapy and improving clinical trial enrollment. These capsids also address manufacturability challenges, enhancing scalability and clinical translation.

Furthermore, gene-silencing therapies, including RNA interference (RNAi) and antisense oligonucleotides (ASOs), have been integrated with gene editing and replacement strategies to tackle gain-of-toxic-function mutations characteristic of some ultra-rare neurodegenerative diseases. These combined modalities enable a dual approach, silencing pathogenic alleles while restoring normal gene function, thus addressing disease mechanisms with high specificity.

Together, these cutting-edge tools and methodologies constitute the forefront of gene therapy technology enabling tailored, efficacious, and safer treatments for ultra-rare hereditary disorders that were previously intractable.

## Conclusion

Although each ultra-rare genetic disorder affects fewer than 1 in 50,000 individuals, together they encompass thousands of conditions with a substantial cumulative burden. Gene therapy is emerging as a transformative solution, with N-of-1 interventions demonstrating how personalized approaches can address unique pathogenic variants while advancing the field more broadly. Recent innovations, ranging from genome and epigenome editing to RNA-based strategies, are redefining therapeutic possibilities, and advances in targeted in vivo delivery, including engineered viral capsids and nanoparticle systems, are overcoming longstanding barriers of precision and safety. These developments signal a significant shift: gene therapy for ultra-rare hereditary diseases is moving from experimental feasibility to clinical reality. The convergence of individualized treatments with scalable, next-generation platforms offers the prospect of durable, equitable therapies for some of the most underserved patients in medicine.