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Review

# Towards a Cure: Emerging Therapeutic Advances for DMD, LGMD, and GNEM- Insights from Pre-Clinical and Clinical Research

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## Abstract

Duchenne muscular dystrophy (DMD), Limb-girdle muscular dystrophies (LGMD), and GNE myopathy (GNEM) are progressive neuromuscular rare genetic diseases with differing etiologies either due to defects in structural muscle proteins or impaired metabolism and manifests through progressive weakening and deterioration of skeletal muscle tissues. This review summarizes current and recent clinical trials worldwide, highlighting curative approaches for neuromuscular diseases such as DMD, LGMD, and GNEM. We compiled and summarized latest and most promising outcomes from ongoing global clinical trials, using information from official websites, news sources, trial registries, databases and literature across four key therapeutic modalities: 1) palliative therapies: steroidal and non-steroidal 2) gene therapy and gene-targeted interventions, 3) cell-based regenerative strategies and 4) universal treatments (therapies not limited to the mutation type). We also highlighted the risks associated with gene therapy and discussed key regulatory considerations. Several current clinical trials show promise for muscular dystrophy treatments. RGX-202 gene therapy demonstrates early muscle strength improvement in DMD children. MyoPAXon, a stem cell therapy for DMD muscle regeneration, has FDA clearance to begin trials. Sevasemten (EDG-5506) trials report slowed DMD/BMD progression. SRP-9003 gene therapy targets protein restoration in LGMD. ACENOBEL, approved in Japan for GNEM, may delay disease progression if started early. These trials offer high potential to become widely available treatments improving quality of life and provide life-saving therapeutic options. Additionally, Indian specific founder mutations for the mentioned muscular dystrophies are highlighted to understand the disease etiology in Indian populations for precise diagnostics and therapeutics.

**Keywords:** gene therapy; drug therapy; cell based therapy; AAV; CRISPR/Cas; muscular dystrophy; founder mutations; rare genetic disease; orphan drugs

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### Key points:

**Comprehensive therapeutic evaluation:** This review provides a critical assessment on the promising emerging therapies for the muscular dystrophies “DMD, LGMD and GNEM” that included curative interventions, with particular emphasis on their clinical implications. Given the similarities in etiology and pathogenesis, we note the similarities in their therapeutic landscape.

**Global clinical trial catalogue:** We synthesize global clinical trial data from databases and literature across four key therapeutic modalities: 1) palliative therapies: steroidal and non-steroidal 2) gene therapy and gene-targeted interventions, 3) cell-based regenerative strategies and 4) universal treatments (therapies not limited to the mutation type)

**India-Specific Genetic Compilation:** This review presents, for the first time, a comprehensive census of all reported founder mutations for DMD, LGMD, and GNEM across Indian populations, synthesizing fragmented data from peer-reviewed literature and regional databases.

## 1. Introduction

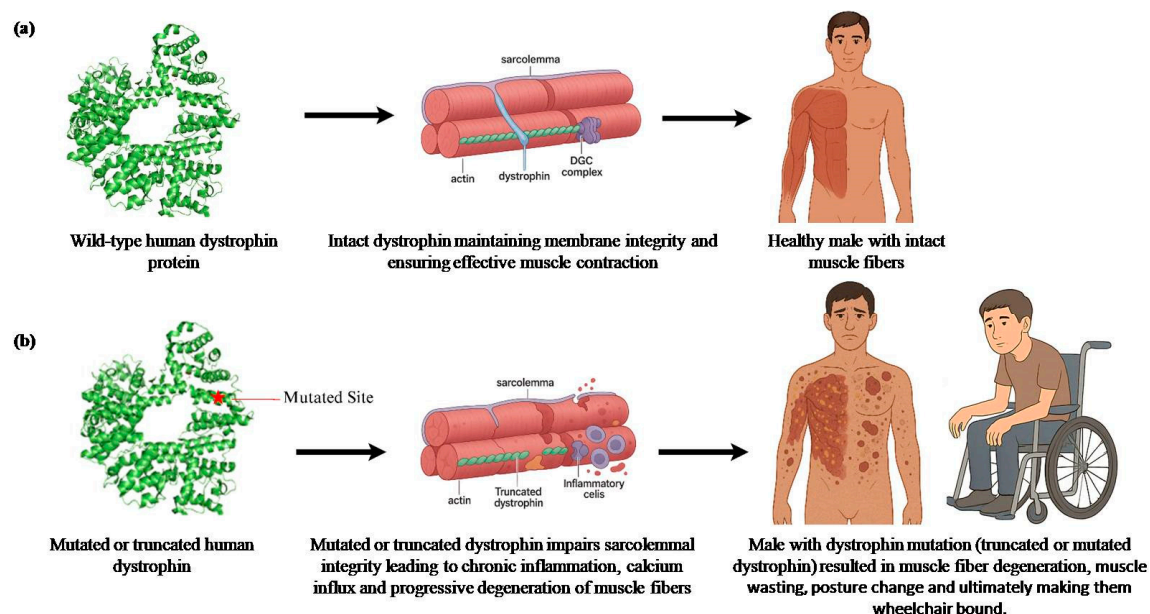
Neuromuscular disorders (NMDs) represent a diverse collection of predominantly genetic conditions marked by deteriorating muscle function, progressive physical disability, and reduced life expectancy (Iolascon et al., 2019; Kumar et al., 2025). These disorders encompass conditions that affect the nerves controlling voluntary muscles, the muscles themselves, or the communication between nerves and muscles (e.g., at the neuromuscular junction) (Liang, 2012; Mary et al., 2018). Neuromuscular disorders are subclassified into distinct categories based on their etiology (cause), pathogenesis (disease mechanism), and clinical phenotype (presentation). Muscular dystrophies, progressive disorders of muscle degeneration, caused by structural protein defects (e.g., dystrophin in DMD, Calpain3 in LGMD2A) (Murphy and Straub (2015); Falzarno et al 2018; Duan et al., 2021; Bouchard et al., 2023), while myopathies are primary muscle dysfunctions due to metabolic or contractile impairments (e.g., GNE enzyme in GNE Myopathy) (Malicdan et al., 2009) in absence of significant structural damage.

DMD and LGMD, as muscular dystrophies, and GNE myopathy, a metabolic myopathy, represent distinct yet interconnected challenges in neuromuscular medicine. All the three diseases are heritable (Tidball et al., 2018; Salih and Kang, 2020) due to mutations leading defective structural protein or enzyme rather than acquired muscular dystrophies which may be acquired in lifetime due to various factors such as auto-immune response (Preito and Grau, 2010). DMD demonstrates the highest disease burden of the three, with early symptom emergence and aggressive progression (Crisafulli et al., 2020; Duan et al., 2021). LGMD is a genetically heterogeneous group of disorders with variable onset and progression, representing a significant subset of muscular dystrophies worldwide (Murphy and Straub (2015); Nallamilli et al., 2018). GNE myopathy is an adult-onset, progressive distal myopathy with founder population clusters (Malicdan et al., 2009; Carrillo et al., 2018). This review will focus exclusively on three neuromuscular disorders that belong to the rare genetic diseases (RGDs): Duchenne (DMD), limb-girdle (LGMD), and GNE myopathy, due to their clinical and genetic significance in neuromuscular medicine. Recent reviews have extensively characterized the clinical and molecular features of DMD (Verhaart et al., 2012; Yiu et al., 2016; Duan et al., 2021), LGMD (Murphy and Straub (2015); Bouchard et al., 2023), and GNE myopathy (Nishino et al., 2015; Carrillo et al., 2018). While these disorders share overlapping pathogenic mechanisms and therapeutic approaches, this review specifically evaluates emerging treatment strategies through a critical analysis of ongoing and recently completed clinical trials worldwide. We systematically examine both palliative and curative interventions, with particular emphasis on their clinical implications. Furthermore, this work provides the first comprehensive synthesis of founder mutations identified in Indian populations for these three neuromuscular disorders, a critical yet understudied aspect, that has significant implications for developing population-specific therapies and understanding the mutational landscape of these diseases in the Indian subcontinent.

## 2. Duchenne Muscular Dystrophy (DMD)

As one of the most common rare muscular dystrophies, DMD demonstrates progressive muscle weakness with an estimated global prevalence of 7.1/100,000 males and 2.8/100,000 overall population (Crisafulli et al., 2020). Symptoms start with the weakness of muscles by 4 years of age with rapid progression leading to ambulatory loss (Bushby et al., 2010). Mutations in dystrophin gene result in dystrophinopathies which include DMD, Becker muscular dystrophy (BMD) and Dilated cardiomyopathy (DCM) [19, 20]. The dystrophin protein stabilizes muscle fibers by linking the cytoskeleton to the extracellular matrix, enabling durability to contractile mechanical stress (Verhaart et al., 2012; Del Rio-Pertuz et al., 2022) (Figure 1). BMD is the milder dystrophinopathy with

symptoms appearing in the thirties, and much slower loss of mobility. DCM is a frequent age dependent complication in both DMD and BMD with prevalence ranging from 59% to 90% (DMD) and up to 61% in BMD (Nigro et al., 1990, Bello et al., 2016).

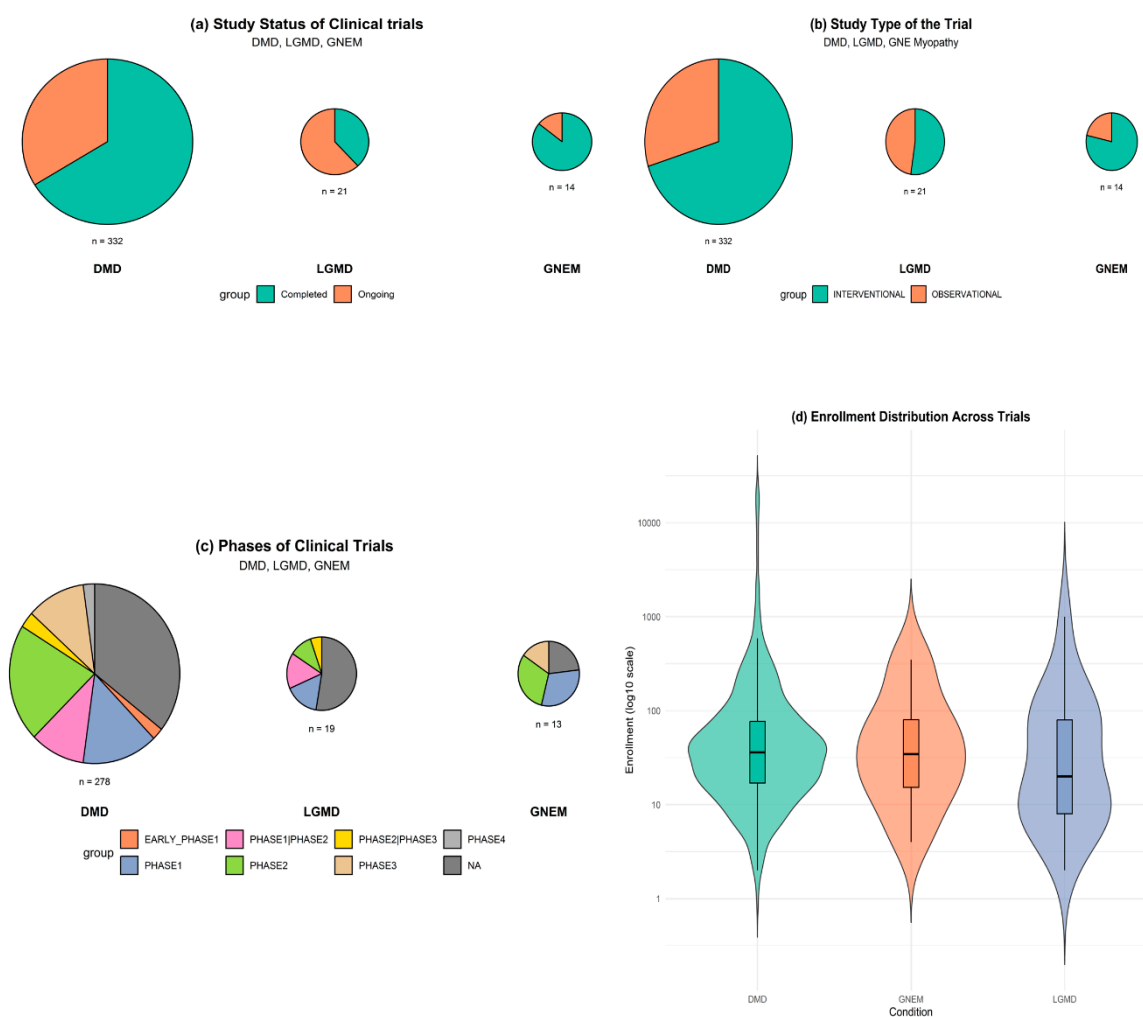


**Figure 1. Schematic representation of effect of normal and mutated dystrophin proteins on muscle integrity and clinical phenotype.** (A) Wild-type dystrophin protein maintains sarcolemma stability while (B) mutations trigger progressive muscle dysfunction.

While DMD predominantly affects males due to X linkage, female carriers can show some of the symptoms, such as increased risk of developing dilated cardiomyopathy (Suthar et al., 2021).

Earlier approaches to DMD primarily focused on symptom management using steroids, anticonvulsants, and immunosuppressants (Beytia et al., 2012), whereas recent advances in molecular biology facilitate the development of therapies that extend beyond palliative care, as illustrated in Figure 2. These novel approaches, like read-through therapy and exon skipping, aim to restore dystrophin production or function in muscle cells.

## Statistics of Clinical trials of LGMD, DMD and GNEM



**Figure 2. Statistics of clinical trials of DMD, LGMD and GNEM.** (a) Study status of clinical trials (completed/ongoing) (b) The study type of the trial (interventional/observational), (c) The phase of the completed/ongoing trial (d) The enrollment distribution of the trials.

The mutation spectrum of DMD mutations in Indian populations are very diverse with cohorts and carriers showing region specific mutational spectra (Basak et al., 2009; Goyal et al., 2021; Nagabhushana et al., 2021). However, there are no reported founder mutations for DMD in Indian populations indicating a need for more pedigree-based studies and wider genome-wide sequencing efforts. The difficulty to identify the founder mutations may also be attributed to the nature of progression of the disease which is characterized by early onset and demise of individuals before reaching adulthood (Bushby et al., 2010; Falzarano et al., 2015) and the genetic heterogeneity of the Indian populations (Papiha, (1996); Indian Genomic variation consortium (2005)). It is also speculated that DMD may be due to more de-novo mutations rather than inherited mutations (Polavarapu et al., 2019).

Searching for clinical trials on NIH site (<https://clinicaltrials.gov/>) after setting criterion for clinical trials that have not been withdrawn or terminated, we found 332 trials for DMD, 22 trials for LGMD and 14 trials for GNE Myopathy (Figure 2). Of these 332 trials, 220 are completed and 112 are ongoing. 233 of these trials were interventional in nature (i.e. they were examining some therapy or



its dosage) while 99 were observational. 37 of these were in advanced stages of clinical trials at Phase 3 (31) and at Phase 4(6). As Figure 1 shows that DMD is most well researched among the neuromuscular diseases with candidate therapies to enter market, if final phases are cleared. The complete list of clinical trials for the three neuromuscular disorders – DMD, LGMD and GNE Myopathy are given in the Supplementary Table (ST) 1, 2 and 3 respectively. As we note in ST1, ST2 and ST3, for all the three disorders, most of the clinical trials are coming from USA, China or Europe with other developing countries like India lagging behind. We shall elaborate on some of the promising therapies in the following sections.

### 2.1. Therapies Focused on Symptomatic Management (Palliative Therapies)

Palliative/symptomatic therapies primarily focus on relieving the patient's symptoms rather than addressing the underlying causes of the disease. For neuromuscular disorders there are steroidal and non-steroidal options for symptomatic management.

#### 2.1.1. Steroid-Based Palliative Therapies

Earlier therapies for DMD included corticosteroids such as prednisone, prednisolone, and deflazacort, which interact with glucocorticoid receptors suppressing the NF- $\kappa$ B pathway to control inflammation and muscle fiber necrosis (Matthews et al., 2016, Srinivasan et al., 2022). Patients on corticosteroids maintain muscle strength for longer periods aiding their locomotion. Use of corticosteroids in DMD patients has reduced severity of scoliosis, a curvature of the spine, minimizing the need for surgery (Duan et al., 2021). However, some side effects (Srinivasan et al., 2022) are associated with long-term corticosteroid use including hypertension, weight gain, cataracts, osteoporosis and stunted bone growth (Bianchi et al., 2005, Viviano et al., 2022). Corticosteroid therapy may elevate compression fracture risk, worsening clinical outcomes (Duan et al., 2021). To address the side effects of corticosteroids, new treatment options have emerged. Agamree (vamorolone) (Keam, 2024) and Deflazacort (Emflaza) (McDonald et al., 2020) are FDA-approved corticosteroids specifically designed for DMD. Agamree, a dissociative corticosteroid, aims to reduce the side effects while maintaining the anti-inflammatory properties of corticosteroids. Deflazacort and vamorolone (VBP15) are two more oral corticosteroids with similar objectives approved for DMD patients aged 2 and older.

#### 2.1.2. Non-Steroidal Palliative Therapies

In addition to corticosteroid-based treatments, non-steroidal options have also emerged for managing DMD. Duvyzat (givinostat) represents a significant advancement as the first non-steroidal drug approved for treating all genetic variants of DMD in patients aged six and older (Lamb, 2024). It functions as a histone deacetylase (HDAC) inhibitor, dampening chronic inflammation, fat infiltration and muscle fibrosis. Duvyzat was tested in a large-scale, 18-month study with muscle function evaluated using the North Star Ambulatory Assessment (NSAA) scale (Himba et al., 2023).

DMD impairs respiratory function, necessitating monitoring/ventilator support. Other symptoms include spasms, seizures, and contractures managed with anticonvulsants and physiotherapy (Duan et al., 2021). DMD patients have high risk of heart complications for which medications such as ACE (angiotensin converting enzyme) inhibitors, beta-blockers, and ARBs (angiotensin receptor blockers) are often prescribed (Birnkranz et al., 2018, Lee et al., 2022). The emerging technologies of virtual reality have found their applications in biomedical sciences as well, and they have been used to aid rehabilitate and improvise locomotor and co-ordination capabilities of the patients suffering from DMD and other muscular dystrophies (Baeza- Baragan et al., 2020; Kiper et al., 2024).

## 2.2. Therapies Focused on Restoring Dystrophin Expression and Function: Gene Therapy and Gene-Targeted Therapy

Newer therapeutic approaches such as read-through therapy, exon reframing, gene transfer and CRISPR gene editing aim to directly restore dystrophin expression and function (Shimizu-Motohashi et al., 2016). By targeting the root cause of the disease, these therapies hold the potential in finding a more durable cure for DMDs rather than palliative therapies which may offer only temporary relief.

Genetic studies of DMD cohorts showed that large deletions or duplications affecting multiple exons within the dystrophin gene leading to truncated and non-functional dystrophin proteins (Bladen et al., 2015, Zhang et al., 2019). Nearly 79% of the cases involve large-scale mutations, with large deletions (68%) and duplications (11%), with regions spanning exons 2-20 and 45-55 are particularly susceptible [46]. Rest are small-scale mutations - Nonsense mutations (11%), deletions (5%), insertions (2%), and splice site alterations (3%) (Flanigan et al., 2009, Sun et al., 2020, Zhang et al., 2021).

### 2.2.1. Read-Through Therapy

Read-through therapy targets nonsense mutations in DMD by bypassing premature stop codons thereby preventing mRNA degradation downstream. Studies have demonstrated that aminoglycosides, such as gentamicin, and compounds like ataluren can bypass these premature stop codons, generating complete dystrophin protein (Shimizu-Motohashi et al., 2016), with limited success in clinical trials (Landfeldt et al., 2020). Not much improvement was seen in timed function tests, though ambulatory loss was delayed (Mercuri et al., 2020).

### 2.2.2. Exon Skipping Therapy

Synthetic antisense oligonucleotide (ASO) drugs, correct dystrophin reading frames in DMD via exon skipping/reframing, offering targeted treatment for frameshift mutations (Mizobe et al., 2018; Ousterout et al., 2015; Chemello et al., 2021). ASOs target a specific exon, excluding them from the final dystrophin protein with function restored though shorter. It is worth noting that ASO therapy is not a complete cure for DMD, as it just slows the disease progression. AMONDYS 45 (casimersen), EXONDYS 51 (eteplirsen), Vyondys 53 (golodirsen) and Viltolarsen (VILTEPSO) are the few ASO drugs designed for DMD patients (Aartsma-Rus et al., 2020, Assefa et al., 2024;).

FDA-approved ASO therapies for DMD include AMONDYS 45 (casimersen) for exon 45 skipping (Vasterling et al., 2023). and EXONDYS 51 (eteplirsen) for exon 51 skipping, generating truncated dystrophin (Syed, 2016; Lim et al., 2017). XONDYS 51 gained FDA accelerated approval for boosting dystrophin levels, though its clinical efficacy remains under investigation, with reported adverse effects including contusions, rash, and respiratory symptoms [60,61]. Vyondys 53 (golodirsen) and Viltolarsen (VILTEPSO) are other FDA approved ASO therapies for patients amenable to treatment by skipping exon 53 (Heo et al., 2020). All listed ASO drugs were FDA-approved for orphan indications.

### 2.2.3. Adeno-Associated Virus (AAV) Vector-Based Gene Therapy

ELEVIDYS (delandistrogenemoxeparvovec-rokl) is an AAV vector-based gene therapy delivering microdystrophin ( $\mu$ Dys), a truncated (138 kDa instead of 427 kDa) dystrophin variant, for DMD treatment (Hoy, 2023). Developed by Sarepta Therapeutics, ELEVIDYS is based on the results from 3 clinical trial studies: NCT03375164, NCT03769116, NCT04626674, and is administered as a single intravenous infusion and has orphan drug designation.

However,  $\mu$ Dys lacks two-thirds of the dystrophin coding sequence, including critical rod and hinge domains required for proper protein interactions, resulting in incomplete protection of muscle integrity (Bostick et al., 2012; Wasala et al., 2023). Delivering full-length dystrophin (14 kb) was hindered by AAV's limited packaging capacity (~4.7 kb) (Srivastava et al., 1983). This was addressed using split intein-mediated protein trans-splicing (Tasfaout et al., 2024), where inteins (self-excising

polypeptides) and their flanking exteins reassemble separate protein fragments (Derbyshire et al., 1998; Fernandes et al., 2016).

Tasfaout et al. developed a split intein-mediated protein trans-splicing approach to express large dystrophins, using highly efficient intein pairs to assemble midi- or full-length dystrophin from two or three AAV-delivered fragments. Delivered systemically via the myotropic AAVMYO vector (Weinmann et al., 2020) at low doses ( $2 \times 10^{13}$  vg/kg), this method achieved body-wide expression in striated muscles, restoring function in young and old mdx mice more effectively than microdystrophin (Tasfaout et al., 2024). Similarly, Zhou et al. designed a triple-AAV system (MyoAAV4A) using orthogonal split inteins to deliver full-length dystrophin, rescuing expression in skeletal and cardiac muscles of mdxAcv mice (Zhou et al., 2024). To overcome neutralizing antibodies and transgene control challenges, emerging strategies include exosome-delivered CRISPR, immune-stealth capsids, and muscle-specific promoters (Saad et al., 2022).

#### AAV-NoSTOP Gene Therapy

Wang et al. (2022) used rAAV-delivered suppressor tRNAs (rAAV.sup-tRNA) to rescue nonsense mutations in mice by combining stop codon readthrough with NMD inhibition. In HEK293 cells, sup-tRNATyr, -Ser, and -Gln achieved up to 70% readthrough—outperforming G418 (Keeling et al., 2014). Notably, sup-tRNATyr restored full-length IDUA protein in W401X-mutant mIdua mRNA, demonstrating precise amino acid incorporation at PTCs. Optimized AAV capsids and delivery routes enabled therapeutic efficacy in liver, heart, muscle, and brain, with effects lasting >6 months—demonstrating promise as a durable genetic therapy.

#### 2.2.4. CRISPR/CAS9

CRISPR/Cas9 employs sgRNA (guide RNA)-guided DNA cleavage for precise gene editing, enabling mutation correction or gene silencing (Keeling et al., 2014; Tycko et al., 2016; Hsu et al., 2019). A key challenge is off-target editing caused by sgRNA-DNA mismatches, which may disrupt genomic integrity and even trigger cancer (Tycko et al., 2016). This underscores the need for high-fidelity Cas9 variants with strict target specificity for safe clinical application. To address these limitations, engineered Cas9 variants have been developed. Acharya et al. (2024) created enhanced *Francisella novicida* Cas9 (FnCas9) derivatives with improved on-target efficiency, knock-in rates, and specificity. Their therapeutic potential was demonstrated by correcting RPE65 mutations in LCA2 patient-derived iPSCs using an optimized FnCas9 adenine base editor (Panda & Ray, 2022; Acharya et al., 2024).

CRISPR-Cas9 gene-editing technology has made significant strides in clinical applications, particularly in treating various genetic disorders such as sickle cell disease (Davies et al., 2024), cancer (Wang et al., 2021), cystic fibrosis (Wei et al., 2023) and muscular dystrophy (Laurent et al., 2024). Safe delivery of CRISPR tools to stem cells/iPSCs requires alternatives to DNA-based methods, with mRNA/nanoparticle approaches showing promise (De Masi et al., 2020).

Stadelmann et al. 2022 demonstrated that mRNA-delivered SpCas9 and adenine base editors achieved >90% editing efficiency in human muscle stem cells across donors, while maintaining myogenic function without cell enrichment (Stadelmann et al., 2022). Further, various nanoparticles, including lipid-based, polymer-based, inorganic, and extracellular vesicle-based systems have been explored as efficient delivery systems in advancing CRISPR/Cas9 technology for clinical applications and gene therapy (Emami et al., 2019; Agrawal et al., 2023). Biom mineralized and Polyrotaxane nanoparticles have been used to efficiently deliver cas9 systems without muscle damage (Agrawal et al., 2023)

Gustafsson et al. developed hPep cell-penetrating peptides for efficient RNP delivery of CRISPR tools (Gustafsson et al., 2024). These nanoparticles achieved near-complete editing in HEK293T (96%), iPSCs (74%), and muscle stem cells (80%), while maintaining cell functionality. The hPep system offers rapid bench-top preparation, lyophilized storage, and compatibility with standard lab techniques, representing a versatile synthetic delivery platform.



### 2.2.5. Vector Aided Gene Therapy

RGX-202, a vector-based gene therapy (NCT05693142), delivers a novel microdystrophin transgene containing functional C-terminal domains, showing promising clinical results [89]. A single IV dose of RGX-202 in 4–11-year-old DMD patients produced detectable microdystrophin in muscle by 12 weeks and reduced creatine kinase by 10 weeks, with improved muscle strength—particularly at higher doses. A long-term follow-up study (NCT06491927) is now underway (Braun, 2025).

While promising for ambulatory or younger patients with DMD, AAV-mediated CRISPR therapies carry severe risks from high systemic doses, which can overwhelm an inflamed system and trigger fatal innate immune responses, including acute respiratory distress syndrome (Lek et al., 2023). This unique risk profile emphasises the critical need for optimized dosing and proactive immunosuppression (Horn & Fehse, 2024), a strategy now being pursued to address similar toxicities. Following the exclusion of non-ambulatory patients from Elevidys' label due to liver toxicity, the FDA has approved a trial of an enhanced sirolimus-based immunosuppressive regimen to mitigate this risk and potentially restore access for this advanced patient population (Chwalenia et al., 2025; Swiderski et al., 2025). A young, ambulatory patient in Pfizer's DMD gene therapy trial suffered a fatal cardiac arrest, showing that severe risks may extend beyond advanced stage patients (<https://www.biopharmadive.com/news/pfizer-duchenne-patient-death-gene-therapy-trial/715450/>). The fatalities observed in both Pfizer's and Sarepta's gene therapy trials necessitate that regulatory agencies enforce more rigorous safety testing and adopt a more precautionary stance in their approval processes for high-dose AAV vectors.

### 2.3. Cell Based Therapy

Cell transplantation (e.g., satellite cells, myoblasts) offers potential for DMD by restoring dystrophin production (Siemionow et al., 2018; Tominari et al., 2023). However, challenges such as lack of suitable animal models for human cell studies (Sato et al., 2023) and impaired proliferative capacity of DMD patient-derived satellite cells (Blau et al., 1983) complicate its therapeutic use.

SAT-3247 (Satellos) is an oral AAK1 inhibitor that restores muscle stem cell polarity and regeneration in DMD models, demonstrating improved muscle strength. A completed Phase I study (NCT06565208) in 72 healthy volunteers established safety and translational pharmacokinetics, while an ongoing trial is assessing the same in 10 DMD patients over 28 days. (<https://ir.satellos.com/news/news-details/2024/Satellos-Announces-First-Participant-with-Duchenne-Muscular-Dystrophy-Dosed-in-the-Phase-1b-Clinical-Trial-of-SAT-3247/default.aspx>).

#### 2.3.1. Re-Engineering Cellular Medicine:

Vita Therapeutics' VTA-110, an FDA-designated orphan drug, is a first-in-class allogeneic iPSC therapy for DMD. Derived from somatic cells via Yamanaka factor reprogramming, it has demonstrated muscle repair/regeneration in preclinical studies. (<https://www.vitatx.com/all-news/vita-therapeutics-receives-orphan-drug-designation-from-fda-for-new-novel-treatment>).

#### 2.3.2. Chimeric Cell Therapy:

Dystrogen Therapeutics developed Dystrophic Expressing Chimeric (DEC) cell therapy for DMD—an allogeneic-autologous myoblast fusion approach that restores dystrophin expression independent of mutation type (Heydemann et al., 2023; Siemionow et al., 2024). DEC therapy expands functional myoblasts, reduces inflammation/fibrosis, and minimizes immune rejection. It offers broad applicability across all DMD patients without requiring gene editing or immunosuppression, and can be combined with other therapies (Siemionow et al., 2023, 2024).

### 2.3.3. One for All Stem Cell-Based Therapy

Myogenica has received FDA approval to initiate a clinical trial for MyoPAXon, a stem cell-based therapy derived from induced pluripotent stem cells (iPSCs) (<https://prnmedia.prnewswire.com/news-releases/fda-clears-investigational-new-drug-application-for-muscular-dystrophy-treatment-from-university-of-minnesota-startup-myogenica-302199393.html>). MyoPAXon therapy targets skeletal muscle regeneration in DMD patients, with initial trials assessing safety, tolerability, and engraftment. Successful engraftment will be indicated by dystrophin-positive myofibers. The durable persistence of MyoPAXon-derived cells suggests sustained therapeutic potential, demonstrating the utility of iPSC technology in regenerative medicine. Patient-specific iPSCs enable disease modeling and accelerate therapeutic development (Speciale et al., 2020).

### 2.3.4. Muscle Stem Cells (muSCs) and Piezo1 Ion Channels as Potential Therapeutic for Muscular Dystrophies Including DMD

Adult muscle stem cells (MuSCs) are essential for muscle repair, differentiating into myogenic cells to regenerate fibers. Ma et al. (2022) showed MuSCs transition between 'responsive' and 'sensory' states regulated by the mechanosensitive Piezo1 channel to mediate cell communication and environmental sensing. In DMD mice, the Piezo1 activator Yoda1 restored MuSC state distribution, increasing responsive cells and enhancing regeneration (Ma et al., 2022).

Piezo1 represents a promising therapeutic target for muscular disorders with impaired regeneration (Bernareggi et al., 2022), though further validation in larger DMD animal models is needed (Ma et al., 2022).

## 2.4. Therapies Not Limited to Dystrophin Mutation Type

Sevasesmen (EDG-5506) is an oral myosin inhibitor that protects dystrophin-deficient muscle fibers from contraction-induced damage in BMD/DMD patients (Russel et al., 2023; Donovan et al., 2025). Currently, four clinical trials are evaluating its efficacy across different age groups and treatment backgrounds (NCT05160415, NCT05291091, NCT05540860, NCT06100887).

EDG-5506 significantly slowed DMD/BMD progression (improved NSAA scores, reduced CK/troponin I) with excellent tolerability in NCT05160415. Current pediatric trials include LYNX (ages 4-9; NCT05540860) [103] and FOX (ages 6-14 post-gene therapy; NCT06100887), demonstrating potential therapeutic use. This therapy is designed primarily as monotherapy but may exhibit complementary efficacy when combined with existing treatments.

### 2.4.1. Utrophin Modulators

Utrophin (a paralog of dystrophin) modulation offers a mutation-independent therapeutic strategy for DMD, as utrophin can functionally compensate for dystrophin deficiency (Blake et al., 1996). Ghosh et al. (2024) developed oral quinazoline/quinoline-based utrophin modulators (SG-02) that increase utrophin expression 2.7-fold in C2C12 cells and 2.3-fold in DMD patient cells enhancing myogenesis, with favorable bioavailability, positioning them as promising universal DMD treatments (Ghosh et al., 2024).

### 2.4.2. SERCA as a Therapeutic Target for DMD Cardiomyopathy

DMD cardiomyopathy is attributed to the dysregulated cytosolic calcium due to reduced sarcoendoplasmic reticulum calcium ATPase (SERCA) activity (Schneider et al., 2013). Morales et al. (2023) demonstrated a potential treatment for DMD cardiomyopathy by improving the SERCA activity using DWORF gene therapy (Morales et al., 2023). Dworf open reading frame (DWORF) is a regulator for SERCA with significantly reduced expression in mdx mice (Nelson et al., 2016). AAV serotype 9-DWORF vector was delivered to 6-week-old mdx mice ( $6 \times 10^{12}$  vector genome particles/mouse) via the tail vein which was shown to significantly enhance SERCA activity, thereby

reducing myocardial fibrosis, improved treadmill running, electrocardiography, and heart hemodynamics

### 2.5. *In Vitro* Disease Model Systems

A robust tissue model system is required to model the pathogenesis and response to therapeutic interventions for muscle dystrophies. To address this, Bou Akar et al. (2024) optimized a species-specific protocol to efficiently differentiate myoblasts from human induced pluripotent stem cells (hiPSCs) and murine embryonic stem cells (mESCs) with the help of specific maturation medium (Bou Akar et al., 2024).

## 3. Limb Girdle Muscular Dystrophies (LGMD)

LGMD are a group of rare progressive genetic disorders with heterogeneous etiology affecting skeletal tissues, mostly proximate muscles of hips and shoulders with different autosomal mutations (dominant or recessive; indicated by D or R respectively) responsible for each subtype (Straub et al., 2018; Muni-Lofra et al., 2023; Bouchard and Tremblay, 2023)]. LGMD is the 4th most common cause of muscular weakness and has a prevalence of around 2 per 100,000 worldwide (Narayanaswami et al., 2014; Wicklund, 2014; Parsipenny, 2018)] with notable variations in the frequencies across the populations (Nallamili et al., 2018; Liu et al., 2019). LGMD molecular markers, pathogenesis, and classifications have been extensively discussed by Bouchard and Tremblay, 2023, Samarasiri, 2023, and Aguti et al., 2024..

With >39 causative genes, LGMD is a highly heterogeneous neuromuscular disorder with subtype-specific etiologies, pathogenesis, and molecular markers (Murphy and Straub, 2015; Liu et al., 2019; Barton et al., 2020; Bouchard and Tremblay, 2023). LGMD treatment begins with genetic diagnosis (Polavarapu et al, 2021; Zidkova et al., 2023), as patients often harbor mutations in multiple interconnected genes (Blandin et al., 2013; Nallamilli et al., 2018) overlapping with other disorders (Uritzbera et al., 2007) alongside biopsy and imaging to characterize disease pathology (Samarasiri, 2023).

### 3.1. *Molecular Spectrum of LGMD Mutations in India*

Even amongst the rare genetic disorders the frequency of LGMD mutations have so far been low in Indian populations (Sheth et al., 2024). Khadilkar et al. 2017 provides a comprehensive review of previously identified LGMD mutations in the Indian population (Khadilkar et al. 2017) . Additional mutations, some of them founder mutations (Francis et al., 2014; Khadilkar et al., 2016; Polavarapu et al., 2021; Ganaraja et al., 2022) have been reported in Indian populations since then. Given India's vast ethnic diversity and high rates of endogamy (The Indian Genome Variation Consortium, 2005; Khadilkar et al., 2017; Macha et al., 2025), it is essential to investigate the mutational landscape and distribution of LGMD mutations across Indian subpopulations, (Ankala et al., 2013; Khadilkar, 2015) which is still under sampled in many regions (Sheth et al., 2024).

In the Indian patient cohorts, the predominant phenotypic presentations included LGMDR1 (CAPN3, Calpainopathy), LGMDR4 (SGCG, Sarcoglycanopathy), LGMDR2 (DYSF, Dysferlinopathy), and MMD1 (DMPK, Myotonic Dystrophy Type 1), with LGMDR1 and LGMDR4 being the most frequently identified subtypes (Manjunath et al., 2023). While many mutations observed in Indian populations have also been observed elsewhere in the world, a few novel ones attributed to founder effects are listed in Table 1. Some of the notable founder mutations in India are - Agarwal (Ankala et al., 2013; Khadilkar et al., 2016), South Indian ethnic communities (Polavarapu et al., 2021), Satwara community (Patel et al., 2024) affecting Calpain, Dysferlin, Lamin genes (Table 1). Agarwal mutations in Calpainopathy are the most extensively studied and well-documented founder mutations in India (Ankala et al., 2013; Khadilkar et al., 2016; Khadilkar et al., 2017).

**Table 1. LGMD Founder mutations catalogued so far in Indian populations.**

Mutation	Mutation Type	Gene	LGMD type	Community	Reference
c.1000G>A	Missense	GMPPB (GDP-mannose pyrophosphorylase B)	LGMDR23	South Indian	Polavarapu et al., 2021 [32]
intron 18/exon 19 c.2051-1G>T	Missense	CAPN3	LGMD2A/R1	Agarwal Community	Khadilkar et al., 2016 [125]
exon 22 c.2338G>C	Missense	CAPN3	LGMD2A/R1	Agarwal Community	Khadilkar et al., 2016 [125]
c.2051-1G>T and c.2338G>C in 9.7%, c.1343G>A, c.802-9G>A, and c.1319G>A	Missense	CAPN3	LGMD2A/R1	South Indian	Ganaraja et al., 2022 [127]
Chr 4:52894204C>T;	Missense	SGCB	LGMD2E/R4	Sathwara	Patel et al., 2024 [132]
EMD c.654_658dup*	duplication	LMNA	LGMD1B	Not mentioned	Baskar et al., 2024 [133]
c.847G>A	Missense	SGCG	LGMD2C/R5	Gypsies (Indian origin community)	Piccolo et al., 1996 [134]
SGCB c.544A>C	Missense	SGCB	LGMD2E/R4	11 different states in India and 1 individual from Bangladesh	Bardhan et al., 2022 [135]
Not available	NA	CAPN3	LGMDR1/2A	Mumbai	Khadilkar et al., 2022 [136]

### 3.2. LGMD Supportive and Symptomatic Treatments

Despite greater etiological heterogeneity than DMD, LGMD has fewer clinical therapies (Figure 1). However, research interest is growing, with 8 completed and 13 ongoing trials (21 total: 11 interventional, 10 observational). Currently, only 1 LGMD therapy is in late-stage trials.

LGMD patients experience chronic muscular pain and get fatigued easily (Vrist et al., 2022; Reelfs et al., 2023). Palliative \ remains a major domain of research (D'Este et al., 2024). LGMD patients receive tailored exercise regimens—combining strength and aerobic training—adjusted based on the affected protein (e.g., calpain, dysferrin) to mitigate fiber damage (Turken et al., 2022; D'Este et al., 2024). Personalized physiotherapy, including clinically-tested exercise regimens (Angelini et al., 2012; Turken et al., 2022), improves muscle strength, oxidative capacity, and daily function in LGMD patients, particularly subtypes 2I, 2L, and 2A (Siciliano et al., 2015). These supervised programs reduce fatigue and pain, even during pregnancy, while unsupervised eccentric exercise accelerates disease progression (D'Este et al., 2024).

Corticosteroids like prednisone and dexamethasone provide therapeutic benefits in inflammatory LGMD subtypes, preserving muscle function and slowing disease progression (Aho et



al., 2015; Darin et al., 2021). While prednisone shows efficacy similar to DMD treatment (Quattrocelli et al., 2017, 2021; Zelikovich et al., 2022), dexamethasone enhances muscle contraction (Quattrocelli et al., 2021). However, their pleiotropic effects require careful dosage regulation to balance anti-inflammatory benefits with potential atrophy risks, ideally combined with tailored exercise (Quattrocelli et al., 2021).

LGMD patients—particularly children with early-onset symptoms and pregnant women—receive nutritional counseling as part of comprehensive palliative care. Late-stage sarcoglycanopathies often require ventilator support due to respiratory muscle weakness (Graustein et al., 2023). Ongoing trials are developing assistive devices (e.g., lower-limb exoskeletons) to improve mobility (Supplementary Table S2)

### 3.3. Therapeutic Approaches and Clinical Trials for LGMD

LGMD therapies fall into two categories: (1) Primary approaches targeting genetic/protein defects (exon skipping, CRISPR, cell therapy) and (2) Secondary approaches managing symptoms (physical therapy, respiratory support, anti-inflammatory drugs). Supplementary Table 2 provides an exhaustive list of clinical therapies targeting LGMD obtained from the data available from <https://clinicaltrials.gov>. The LGMD subtypes “LGMDR1 and LGMDR4” prevalent in Indian patient cohorts (Manjunath et al., 2023) has been reviewed in detail in next section.

**Table 2.** Founder mutations for GNE Myopathy in India.

Mutation	Mutation Type	Gene	Community	Paper
p.Val727Met	Missense	GNE	Gujarat and Rajasthan	Bhattacharya et al., 2018 [187], Khandilkar et al., 2022 [136]

#### 3.3.1. Treatment of LGMDR1/2A

##### Pharmacological and Small Molecule Therapies

##### Ubiquitin-proteasome as a therapeutic target for LGMDR1

LGMDR1 results from CAPN3 mutations, disrupting calpain-3 protease function (Richard et al., 1995). CAPN3 deficiency in mice triggers UPS-mediated SERCA degradation (Dayanithi et al., 2009), impairing calcium transport (Elgarresta et al., (2022)) and causing cytosolic calcium accumulation. Proteasome inhibition with bortezomib rescues SERCA2 levels and calcium homeostasis in CAPN3-deficient human myotubes (including G567W and R289W/R546L mutants), while also restoring mutant CAPN3 protein in patient cells (Lasa-Elgarresta et al., 2022). However, in CAPN3-KO mice, the same treatment (0.8 mg/kg every 72h for 3 weeks) failed to restore SERCA levels, indicating potential dose-dependent effects that require further investigation. Further studies are needed to validate proteasome inhibition's efficacy across missense mutations, including India-prevalent Agarwal mutations.

##### SERCA overexpression for LGMDR1 treatment

Given BTZ's narrow therapeutic index, alternative approaches warrant consideration, such as AAV-mediated SERCA gene therapy or pharmacological SERCA modulation via  $\beta$ -adrenergic agents, hormones, antioxidants, or direct activators (e.g., CDN1163) [(Zsebo et al., 2014; Mázala et al., 2015; Kang et al., 2016). Additionally, targeting ER stress with compounds like tauroursodeoxycholic acid, rapamycin, or DWORF may mitigate muscle atrophy (Kawakami et al., 2019; Luo et al., 2019; Fisher et al., 2021).

##### Drug therapies for LGMDR1

The WSiMD pilot trial (NCT04054375) evaluated weekly prednisone (0.75-1 mg/kg) in 20 LGMD/BMD patients over 24 weeks. Results showed trends of increased lean mass, reduced fat mass/CK levels, and improved motor function. Serum proteomics revealed prednisone-responsive markers (decreased muscle proteins, increased immune/matrix proteins), while MRI demonstrated fat fraction correlations with functional status. These findings support further investigation of low-dose weekly steroids (Zelikovich et al., 2019; Willis et al., 2024).

### **Small molecule approach**

In LGMDR1, calpain 3 deficiency disrupts CaMKII $\beta$  signaling and slow-oxidative muscle programming. The small molecule AMBMP reversed this defect in C3KO mice, restoring oxidative metabolism, increasing slow fiber size, and improving exercise capacity via selective CaMKII $\beta$  activation without affecting other growth pathways (Liu et al., 2020). These findings support CaMKII-targeted therapy development for LGMDR1.

## Gene and Genome Editing Therapies

### **Gene therapy approach for LGMDR1**

While AAV-mediated myostatin inhibition increased muscle mass and power in CAPN3-deficient mice (Bartoli et al., 2007), follistatin-based myostatin blockade in C3KO models worsened exercise tolerance and oxidative capacity despite modest hypertrophy (Kramerova et al., 2020). These contradictory results suggest limited therapeutic efficacy of myostatin inhibitors in LGMDR1, likely due to incomplete understanding of disease mechanisms [163].

### **AAV-mediated therapy**

Sahenk et al. (2021) demonstrated that systemic AAVrh74.tMCK.hCAPN3 gene therapy (1.17-2.35 $\times 10^{14}$  vg/kg) improved muscle function, contractility, and fiber size in CAPN3-KO mice after 20 weeks, with females showing a shift toward oxidative fibers. Safety studies confirmed no toxicity, supporting its therapeutic potential for LGMDR1 (Sahenk et al., 2021).

### **ATA-200, a gene therapy for LGMD**

Atamyo's ATA-200, an AAV8-based  $\gamma$ -sarcoglycan gene therapy for LGMD2C/R5, is currently in a Phase 1b pediatric trial (NCT05973630) assessing safety, protein expression, and functional outcomes. Parallel IND-enabling studies explore its application for LGMD2A/R1, building on preclinical evidence of dose-dependent muscle transduction without toxicity. (Atamyo, 2023; trial details: <https://atamyo.com/press-releases/ind-for-ata-200-a-gene-therapy-for-the-treatment-of-limb-girdle-muscular-dystrophy-type-2c-r5-lgmd2c-r5-cleared-to-proceed-by-fda/>)

### **CRISPR/Cas9 approach towards LGMDR1**

CRISPR/Cas9 enables direct gene-level editing (vs. mRNA-targeting approaches) by introducing double-strand breaks at specific loci, allowing defective gene excision and wild-type allele insertion for causal correction (Xiao-Jie et al., 2015; Chulanova et al., 2025). While widely used for knock-out/in models, its clinical translation for LGMD was limited by delivery challenges in higher organisms (Kim et al., 2024). Recent advances in non-viral delivery (nanoparticles, lipid particles) now enhance its therapeutic potential (Kim et al., 2024; Chulanova et al., 2025).

CRISPR/Cas9 has enabled generation of KO/KI animal models for studying LGMD pathogenesis and therapy development (Tanihara et al., 2019). Navarro-Serna et al. (2022) optimized electroporation-based CRISPR delivery in porcine oocytes to create LGMDR1 models with high mutation rates (Navarro-Serna et al., 2022). Similarly, a CRISPR-generated LGMDR1 mouse model (Capn3 c.635T>C variant) revealed impaired muscle repair due to mitochondrial dysfunction (Ma et al., 2023).

CRISPR/Cas9 can be integrated with cell replacement strategies. Mavrommatis et al. (2023) demonstrated CRISPR/Cas9-mediated correction of CAPN3 mutations (W130C, 550delA) in LGMDR1 patient-derived iPSCs using two approaches: (1) at the iPSC level, creating a functional chimeric exon 3-4 via CRISPR editing combined with FACS/Tet-based biallelic selection; and (2) in iPSC-derived CD82+/Pax7+ myogenic progenitors, specifically rescuing the prevalent exon 4 mutation. Both restored normal functions enabling autologous therapies (Mavrommatis et al., 2023).

CRISPR/Cas9 holds particular promise for LGMD treatment, as correcting even a fraction of nuclei in multinucleated muscle cells can yield therapeutic benefits. (Zhang et al., 2021).

### Patient-Specific iPSC-Derived Cellular Models of LGMDR1

Mateos-Aierdi et al. (2021) developed human myogenic models of LGMDR1 with diverse CAPN3 mutations using iPSCs (Mateos-Aierdi et al., 2021). Transient PAX7 overexpression enabled differentiation into myogenic progenitors and myotubes in vitro and in vivo. Despite inter-line variability, all patient-derived cells showed reduced DMD expression—critical for satellite cell regulation—providing a platform to study mutation-specific pathology and test therapies in a human myogenic context also helpful for LGMD.

### 3.3.2. Treatment of LGMDR4/2E

#### Gene and Genome Editing Therapies

LGMD2E/R4 or *beta*-sarcoglycanopathy is attributed to the mutations in the  $\beta$ -sarcoglycan (SGCB) gene, with consequential SGCB deficiency and muscle loss. A gene therapy “bidridistrogenexeboparvovec/SRP-9003” approach was developed based on SCB protein functional replacement. SRP-9003 is currently in Phase 3 evaluation (EMERGENE, NCT0624613), following prior Phase 1 (NCT05876780) and Phase 1/2 (NCT03652259) trials. SRP-9003 utilizes an AAVrh74 vector with MHCK7 promoter for systemic delivery of full-length  $\beta$ -sarcoglycan (SGCB) to skeletal, cardiac, and diaphragm muscles - particularly crucial for LGMD2E/R4 patients who often develop fatal cardiopulmonary complications.

Phase 3 study comprises ambulatory and non-ambulatory patients with LGMD2E/R4, aged 4 and older, monitoring changes in the expression of SGCB at 60 days (<https://www.cgtlive.com/view/sarepta-therapeutics-limb-girdle-muscular-dystrophy-gene-therapy-srp-9003-safety-5-year-data>) followed by study of secondary outcomes which includes functional outcomes through 60<sup>th</sup> month (<https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-completes-enrollment-emergene-phase-3>).

Interim Phase 1/2 data (NCT03652259) demonstrated dose-dependent SGCB expression (Cohort 1 [ $1.85 \times 10^{13}$  vg/kg]: 36.2%; Cohort 2 [ $7.41 \times 10^{13}$  vg/kg]: 62.1% at 60 days) using a self-complementary AAVrh74 vector with MHCK7 promoter driving codon-optimized full-length SGCB. All patients showed reduced CK levels (Cohort 1: -92.4%; Cohort 2: -94.9%) at 60 days, maintained through 2 years, with preliminary motor function improvements (NSAA) (Mendell et al., 2024).

#### Therapeutic Approaches Addressing the Secondary Causes of the Disease

##### **Redox-sensitive HMGB1 as a therapeutic target in sarcoglycanopathies**

Recent studies implicate redox-sensitive HMGB1 in sarcoglycanopathies, where its oxidized isoform (dsHMGB1) promotes inflammation over regeneration. In mdx and sgca-null mice, HMGB1 knockout or administration of 3S (a non-oxidizable HMGB1 variant) improved function, enhanced regeneration, and reduced inflammation/fibrosis (Careccia et al., 2021). While 3S-HMGB1 may broadly target sarcoglycanopathy mechanisms, validation in diverse models and humanized systems is needed given subtype variability.

##### **P2X7 receptor blockade as a therapeutic strategy in sarcoglycanopathies**

In sarcoglycanopathies, deficient ecto-ATPase activity elevates extracellular ATP (eATP), excessively activating P2X7 receptors and exacerbating inflammation. In sgca-null mice, blocking this pathway with either broad-spectrum oATP (Gazzerio et al., 2019) or selective P2X7 antagonist A438079 (Raffaghelo et al., 2022) attenuated dystrophic progression. This intervention reduced inflammation, increased FOXP3+ regulatory T-cell recruitment, improved muscle strength, and decreased necrosis/fibrosis (Pannicucci et al., 2020; Zablocki et al., 2023)

##### **Inhibition of FAP-driven fibrosis via nintedanib in sarcoglycanopathy models**

Fibro-adipogenic progenitors (FAPs; PDGFR $\alpha$ +) are essential for acute muscle repair but drive fibrosis in chronic dystrophies via persistent PDGF-AA/RhoA signaling (Fernández-Simón et al, 2022). Nintedanib, a PDGFR $\alpha$ / $\beta$ -FGFR2/3-VEGFR inhibitor, reduced fibrosis and improved muscle function in sgca-null mice by reshaping the inflammatory microenvironment (Alonso- Perez et al., 2022). Similarly, P2X7 antagonists (oATP, A438079) attenuated dystrophic progression in these models. These therapies may extend to other sarcoglycanopathies (LGMDR4/2E, LGMDR1/2A) given shared fibro-inflammatory pathways.

#### 4. GNE Myopathy (GNEM)

GNE myopathy (GNEM) is an ultra-rare (estimated prevalence: 1–9 per million), autosomal recessive disorder marked by progressive muscle wasting and ambulatory loss. While typically presenting with foot drop in the third decade of life (age range: 10–61 years), its hallmark pathological feature is the accumulation of rimmed vacuoles with concentric lamellar bodies, autophagic vacuoles, atrophic fibers, and 14–18 nm filamentous inclusions in skeletal muscle biopsies (Noguchi et al., 2004; Carrillo et al., 2018). Caused by biallelic mutations in the GNE gene—which encodes the bifunctional enzyme UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase—GNEM disrupts the rate-limiting step of sialic acid biosynthesis. This results in systemic hyposialylation of muscle glycoproteins, a key driver of pathology (Noguchi et al., 2004; Sparks et al., 2005; Malicdan et al., 2007; Malicdan et al., 2009).

Detailed mutation analysis of GNE gene showed that GNEM results from predominantly missense mutations (Chaouch et al., 2014, Zhu et al., 2017). Some of these are known to be population specific founder mutation, such as p.Met743Thr in Persian Jews (Eisenberg et al., 2001), p.Asp207Val in the Japanese (Nishino et al., 2002), p.Ile618Thr in Roma Gypsies (Kalaydjieva et al., 2004; Khadilkar et al., 2017) and p.Val727Met in populations of the Indian subcontinent (Nalini et al., 2013). As we can see from Table 2, the p.Val727Met is the only unique founder mutation which was detected in Indian populations and was observed under multiple cohorts (Bhattacharya et al., 2018; Khandilkar et al., 2022).

GNE mutations impair enzymatic function, causing sialic acid deficiency and GNEM pathogenesis (Noguchi et al., 2004). While no cure exists, therapeutic strategies aim to restore sialylation. In GNE mouse models, pre-symptomatic aceneuramic acid administration normalized motor function, muscle contractility, and histopathology (Malicdan et al., 2007, 2009). Similarly, sialic acid metabolites and IVIG (rich in sialylated glycoproteins) showed efficacy in preclinical studies (Sparks et al., 2007), supporting sialic acid supplementation as a viable therapeutic approach.

The candidate biomolecules/drugs evaluated in clinical trials included administration of intravenous immune globulin (IVIG) (NCT00195637, phase 1), Sialic Acid/aceneuramic acid/Neu5Ac (NCT01236898, phase 1), NeuAc extended-release tablet (Ace-ER) NCT01517880 (phase 2), NCT01830972 (phase 2), NCT02731690 (phase 2), NCT02377921 (phase 3), N-Acetylmannosamine (ManNAc) NCT01634750 (phase 1), NCT02346461 (phase 2), NCT04231266 (phase 2)) and 6'-Sialyllactose.

GNE Myopathy has 12 completed clinical trials and 2 ongoing. Three of the clinical trials of GNE Myopathy are observational in nature while rest are interventional. Two of these interventional clinical trials are in phase 3.

##### 4.1. Early-Stage Trials (2005–2010)

Early clinical trials (2005–2010) of IVIG and free sialic acid supplements (Neu5Ac/aceneuramic acid) showed limited efficacy due to rapid renal excretion (Sparks et al., 2007; Suzuki et al., 2018). This prompted development of Ace-ER, a slow-release sialic acid formulation designed to improve bioavailability.



#### 4.2. Extended-Form Sialic Acid and Aceneuramic Acid Extended-Release (Ace-ER) Treatment

While a Phase 2 trial of extended-release sialic acid (Ace-ER) showed promise, the Phase 3 study (NCT02377921; n=89) failed to meet primary endpoints. Patients received oral Ace-ER (6 g/day, TID) for 48 weeks, with no significant improvement in upper/lower extremity composite scores versus placebo (Argoy et al., 2016; Lochmuller et al., 2019). However, subsequent research suggests potential efficacy with modified sialic acid formulations.

#### 4.3. Sialic Acid Precursors

##### 4.3.1. ManNAc and Sialyllactose

The poor efficacy of sialic acid may be due to its low uptake, therapeutic focus shifted to precursors like N-acetylmannosamine (ManNAc) prodrugs (targeting de novo synthesis) and sialyllactose, which offer improved lipophilicity and bioavailability (Yonekawa et al., 2014; Xu et al., 2017; Carrillo et al., 2021; Pertusati and Morewood, 2022). ManNAc serves as the first committed precursor in sialic acid biosynthesis.

A Phase 1 trial (NCT01634750) demonstrated that oral ManNAc (3-10 g/day) significantly increased plasma sialic acid levels in humans (Xu et al., 2017). An open-label Phase 2 trial (NCT02346461) in 12 GNEM patients demonstrated that oral ManNAc was safe, slowed extremity strength decline, and increased plasma Neu5Ac/sarcolemmal sialylation (Carrillo et al., 2021). The ongoing MAGiNE trial (NCT04231266), a Phase 2 randomized, double-blind, multicenter study by Leadiant Biosciences, is evaluating long-term safety and efficacy of ManNAc (12 g/day) in 51 GNEM patients (2:1 randomization) over 24 months. Assessments include QMA, IBMFRS, PROs, and functional tests, with completion expected October 2025.

##### 4.3.2. ManNAc and Neu5Ac

Neu et al. (2024) demonstrated tissue-specific sialic acid metabolism in GNE-KO models: while HEK293 cells utilized ManNAc for sialic acid synthesis, murine myoblasts (C2C12/Sol8) required Neu5Ac for sialylation rescue (Neu et al., 2024). GNE deficiency also caused irreversible myogenesis defects, suggesting fundamental limitations of precursor supplementation therapies for skeletal muscle.

##### 4.3.3. 6'-Sialyllactose (6SL) Supplements

6 g/day 6'-sialyllactose (6SL) supplements outperformed 3 g/day in maintaining muscle strength and reducing fatty infiltration in GNEM patients over 48 weeks (Park et al., 2023). Their follow-up placebo-controlled study (Park et al., 2025; n=11, 6SL=5/placebo=6) confirmed these findings: MRI revealed significantly increased fat fraction in placebo thigh muscles ( $P=0.0004$ ), while the 6SL group showed slower progression (24–36 weeks). Biochemical and lectin-binding assays confirmed successful resialylation with 6SL.

#### 4.4. ACENOBEL, a Sustained Release of Aceneuramic Acid Tablet Approved in Japan for GNEM

Japan recently approved ACENOBEL, a sustained-release aceneuramic acid tablet for GNEM, based on a Phase II/III trial (n=20) showing significant improvement in upper limb function versus placebo. (Suzuki et al., 2023). A subsequent 72-week open-label extension study found SA-ER was well-tolerated but showed gradual UEC decline in both SA-ER/SA-ER and placebo/SA-ER groups, suggesting partial disease-modifying effects (Suzuki et al., 2024).

Pre-symptomatic treatment in animal models show normalized muscle function, contraction, and histopathology, highlighting the potential benefits of early intervention (Mori-Yoshimura et al., 2023; Suzuki et al., 2024).

#### 4.5. Gene Delivery Approaches for GNEM

Gene therapy approaches for GNEM include liposomal (Nemunaitis et al., 2011) and AAV-mediated (Mitrani-Rosenbaum et al., 2012; Crowe et al., 2021) delivery of wild-type GNE. While AAV vectors show long-term efficacy in murine/human muscle cells, challenges remain: 50% of patients have pre-existing AAV antibodies (Zygmunt et al., 2017), and risks of toxicity/oncogenicity (Berns et al., 2017). Recent work Zygmunt et al., 2023 demonstrates that rAAVrh74.CMV.GNE can systemically target skeletal muscle at safe doses, using a MyoD-inducible Lec3MyoDI cell line to quantify sialic acid production and vector potency .

Solve GNE ([www.solvegne.org](http://www.solvegne.org)) and Genosera are developing a novel bicistronic AAV gene therapy for GNE myopathy, to halt disease progression and potentially reverse muscle damage. (<https://www.globenewswire.com/news-release/2023/08/14/2724542/0/en/Solve-GNE-and-Genosera-Sign-Agreement-to-Develop-a-Novel-Bicistronic-AAV-Gene-Therapy-Targeting-HIBM.html>).

#### 4.6. Other Emerging Strategies

In addition to sialic acid supplementation, GNE myopathy therapeutic strategies include N-acetylcysteine (NAC) and mutant enzyme activation. Rimmed vacuoles (RVs), resulting from protein misfolding (Raben et al., 2012), impair muscle function by promoting oxidative stress. NAC alleviates this pathology in mouse models by reducing oxidative damage (Cho et al., 2017). Its broader application in mitochondrial disorders (Sahasrabudhe et al., 2017) further supports its therapeutic potential. These approaches complement efforts to restore sialic acid biosynthesis through targeted enzyme modulation. While GNE p.Met743Thr mutation reduces epimerase activity without causing hyposialylation in cultured muscle cells (Salama et al., 2005; Sharma et al., 2022) identified mutation-specific enhancement of GNE enzymatic activity using plant phenolics and antidiabetic compounds, with metformin showing particular efficacy in restoring epimerase function.

Supplementary Table S3 gives complete list of ongoing and completed clinical trials focused on GNE Myopathy.

## 5. Conclusions

Muscular dystrophies (DMD, LGMD, GNEM) represent a spectrum of genetic disorders characterized by progressive muscle degeneration. While current therapies primarily aim to slow disease progression, recent advances in gene editing and regenerative medicine have enabled curative strategies targeting underlying genetic defects. These include AAV-mediated gene replacement, CRISPR-Cas9 genome editing, exon skipping, and innovative approaches like split intein-mediated large-gene delivery. Notably, for AAV-mediated gene therapy, stringent caution is required regarding vector dosage and the patient's disease stage, as these factors are critical to mitigate the risk of severe adverse events, including clinical fatalities. Cell-based therapies utilizing iPSCs and small molecule modulators targeting muscle repair pathways (e.g., Piezo1 channels) show particular promise. However, significant challenges remain, including immune responses to viral vectors, off-target effects of gene editing, tissue-specific delivery limitations, and the complexity of personalized therapies. Additionally, translating preclinical success to diverse patient populations requires addressing genetic heterogeneity and founder mutations. Prioritizing therapies for high-prevalence mutations while ensuring scalable manufacturing will maximize population level impact for neuromuscular disorders.

## 6. Future Directions

The integration of AI/ML with multi-omics profiling holds significant potential to identify novel therapeutic targets and enable personalized treatment strategies for muscular dystrophies. Future innovation will likely focus on three key areas: (1) enhancing the safety and efficiency of gene delivery systems, (2) developing non-viral delivery platforms, and (3) optimizing genome editing precision.

Realizing this potential will require sustained interdisciplinary collaboration among clinicians, researchers, and regulatory bodies to translate scientific advances into accessible, durable therapies.

For efficient therapy development, regulatory frameworks must account for national variations in rare genetic disease (RGD) definitions and orphan drug designation criteria. Given disparities in healthcare infrastructure and resources between developed and developing nations, uniform global regulations may prove ineffective. Instead, each country should establish tailored RGD strategies that align with local healthcare priorities, economic realities, and ethical considerations to ensure equitable therapeutic access for patients.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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