

Review

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An appraisal of emerging dystrophin restoration therapies in Duchenne muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is an X-linked, progressive muscle disorder caused by pathogenic variants in the DMD gene and resulting in a complete loss of dystrophin protein expression. As of now, there is no cure for DMD, and despite improvements in standard of care, there are significant unmet needs for disease modifying treatments. This article provides an overview of emerging therapies aimed at dystrophin restoration, emphasizing exon skipping and gene therapy, within the rapidly evolving landscape for Duchenne muscular dystrophy.

Keywords: Duchenne muscular dystrophy, dystrophin, gene therapy, exon skipping

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a devastating degenerative muscle disease that affects approximately 1:5,000~10,000 males. DMD prevalence reported in the literature is variable, ranging from 0.9 to 16.8 per 100,000 males. A recent meta-analysis showed a pooled global prevalence of 5.3 cases per 100,000 males^[1,2]. The disease is characterized by childhood-onset muscle weakness, which progresses to loss of motor function and premature death due to respiratory and cardiac insufficiency^[1]. Data from the Muscular Dystrophy Surveillance, Tracking and Research Network (MD STARnet) showed that over the



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last 15-20 years, the mean age at diagnosis in the United States has been 4.9 years. While there is no cure for DMD, advances in standard of care, including systemic corticosteroid use, cardioprotective interventions, non-invasive ventilatory support and a multidisciplinary management model, have been shown to slow disease progression and delay the onset of comorbidities^[1]. These improvements have led to a median life expectancy of 30 years, with reported variability ranging from 21 to 40 years^[3]. The time of diagnosis, access to available treatments, and other socio-economic factors can also affect survival.

Despite recent advancements, significant unmet needs remain in DMD treatment. Early diagnosis is essential, as it allows timely intervention, improves clinical outcomes, and enhances quality of life^[4].

MOLECULAR BASIS OF DISEASE

The DMD gene is located on the X chromosome and is the largest known human gene, comprising 79 exons (2.3 Mb) and encoding the protein dystrophin^[1]. Most mutations in the DMD gene are large deletions (68%) or duplications (11%), and the remaining 21% are small pathogenic variants. Half of that 21% are nonsense mutations, and small deletions, small insertions and splice site mutations represent 5%, 2% and 3%, respectively^[5]. Reports of variations in mutation-type frequency across different cohorts and countries suggest that ethnic background may contribute to mutation diversity^[6-9]. Deletions and duplications are concentrated with increased frequency in two hot spots in the DMD gene: exons 45-55 and exons 2-10^[10]. These regions have structural characteristics that increase susceptibility to instability and breakage, leading to a higher rate of rearrangements and an increased mutation frequency^[11-13].

Dystrophin is a cytoskeletal protein localized to the sarcolemma, connecting the dystrophin-associated protein complex (DAPC) and the intracellular cytoskeleton c-actin. This interaction protects the sarcolemma against damage that can occur due to the forces involved in muscle contraction. Dystrophin contains four functional domains: the actin-binding amino-terminal domain (ABD), a central rod domain, a cysteine-rich domain, and a carboxy-terminal domain. Pathogenic variants in the DMD gene also abolish dystrophin expression in stem cells, which affects cell polarity and mitosis. Stem cells lacking functional dystrophin undergo aberrant asymmetric division and impaired myogenic differentiation^[1,10].

The pathophysiological mechanisms involved in DMD secondary to the lack of dystrophin lead to (1) membrane instability, (2) calcium dysregulation within the muscle, (3) inflammation, (4) mitochondrial dysfunction, and (5) increased oxidative stress. With repeated injury and regeneration over time, chronic inflammation leads to muscle fiber fibrosis, reducing contractile function^[14].

HISTORICAL BACKGROUND AND NATURAL HISTORY OF THE DISEASE

DMD was the first genetic muscle disorder to be systematically described. Early reports in the first part of the 19th century were made by Meryon and Conte, followed by monographic works by Duchenne and Gowers^[15]. The first unequivocal clinical and pathological reports of DMD were by Edward Meryon in his paper, "On granular and fatty degeneration of the voluntary muscles" on November 28th, 1851. He also recognized the X-linked recessive inheritance of the disease^[16].

Duchenne examined a larger cohort of patients, refined the clinical observations and also introduced the needle muscle biopsy technique to aid in diagnosis^[17].

Over time, several natural history studies have described the clinical milestones of the disease including loss of ambulation, need for ventilatory support, scoliosis, cardiomyopathy and mortality. Factors that can impact the timing of key clinical milestones include the individual genotype and corticosteroid regimen^[18].

NEW APPROACHES ON DIAGNOSIS

Newborn screening initiatives

As the landscape for Duchenne muscular dystrophy is quickly evolving, new approaches for early diagnosis are of vital importance.

Newborn screening (NBS) for DMD is fully implemented in China. In the United Kingdom, a long-standing optional pilot program has been performed in Wales. In December 2019, the U.S. Food and Drug Administration (FDA) approved an assay using creatine kinase MM (CK-MM) isoform in dried blood test as a first tier for NBS. However, a second-tier or confirmatory test is necessary^[19-24].

As of now in the United States, two states - Minnesota and Ohio - have both approved and implemented NBS. Massachusetts, New York and Arizona have approved NBS but have not yet begun screening, while at least 12 other states have pending legislation^[25].

NBS provides significant advantages for both patients and their families. It can provide information to guide future reproductive planning, early access to mutation-targeted therapies (when available), and eligibility for clinical trials. Despite these advantages, the availability of this program in the United States remains restricted, with full implementation in only two states which limits the potential for early diagnosis and treatment.

Long-read sequencing

A variety of molecular techniques have been used to identify causative variants in DMD. Multiplex ligation-dependent probe amplification (MLPA) is the conventional method used to detect deletions and duplications, while next generation sequencing (short-read sequencing) can detect small variants and exon deletions/duplications; collectively, both methods have a diagnostic yield above 95%. Nevertheless, approximately 2%-7% of cases remain unsolved. Many of these undetected variants are deep intronic mutations that can generate pseudoexons, microindels, substitutions, large-scale deletions, and duplications. RNA analysis of muscle tissue might be able to identify some of these mutations; nevertheless, the invasive nature of this test and clinical availability present significant challenges. Lastly, given the presence of rare and complex structural variants, a subgroup of patients remains undiagnosed. The introduction of third generation technologies, long-read sequencing, through several platforms has significant advantages providing precise identification of structural and complex variants in the DMD gene. Long-read sequencing is a promising technology with potential to improve diagnostic yield, particularly in cases involving complex genomic variants^[26-29].

DISEASE MODIFYING TREATMENTS

Primary strategies in Duchenne Muscular Dystrophy treatment include: (1) restoring dystrophin at the sarcolemma; (2) upregulation of other genes to replace dystrophin, (homologue utrophin); and (3) managing the downstream effects from the lack of dystrophin which includes inflammation, fibrosis, and oxidative stress^[17]. There are several approaches to increase the expression of dystrophin including viral vector mediated gene therapy, exon skipping therapy, read-through of premature stop mutations, and gene editing, and each has advantages and challenges^[30] [see [Figures 1 and 2](#)].

DNA-mediated therapies

Gene editing

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-mediated gene editing is a promising therapy, theoretically allowing permanent restoration of dystrophin expression. The CRISPR system has

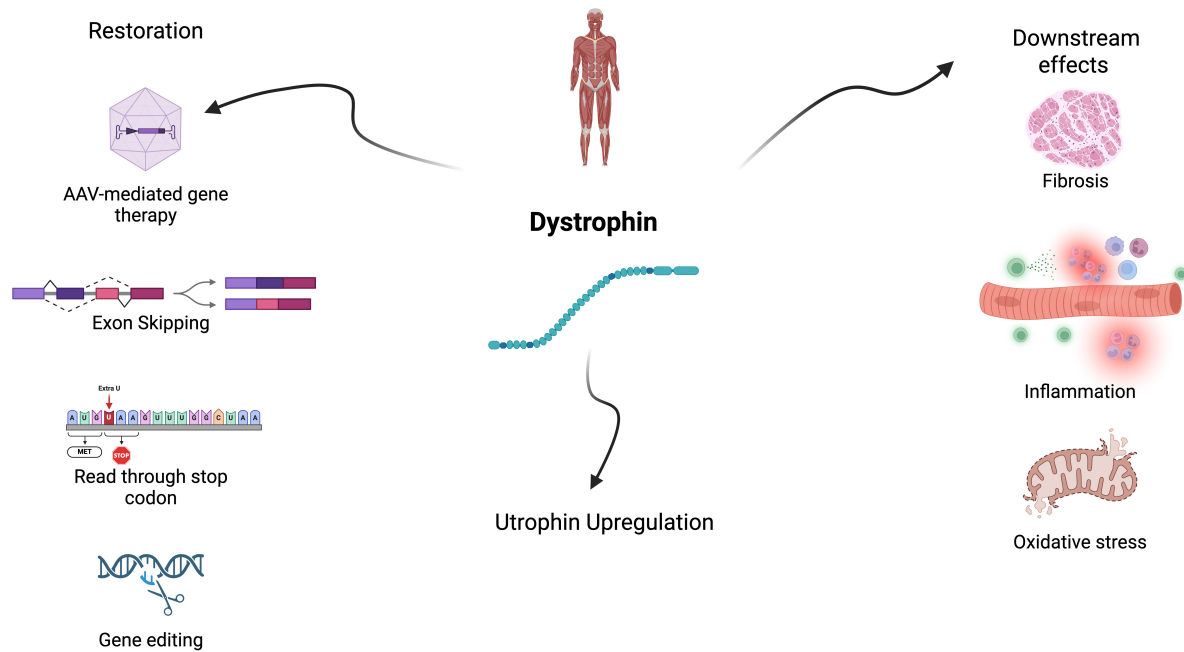


Figure 1. Treatment strategies for Duchenne muscular dystrophy. Created using BioRender (<https://BioRender.com/sfgOp18>).

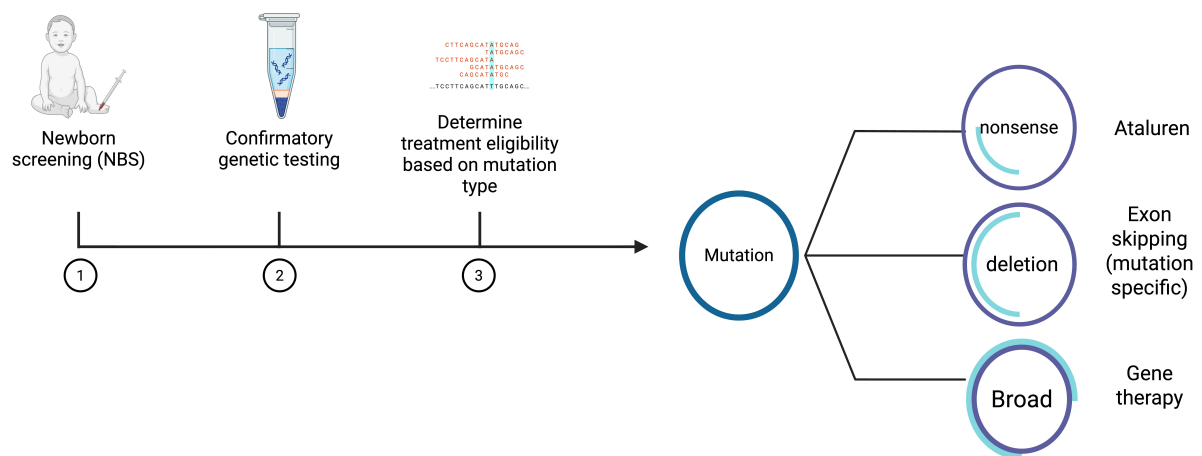


Figure 2. Diagnostic flowchart in Duchenne muscular dystrophy. Created using BioRender (<https://BioRender.com/8du86bo>).

two main components: (1) an endonuclease protein (Cas9 is the most commonly used); and (2) a single-guide RNA complementary to the target sequence^[31,32]. Myo-editing can occur through homology-directed repair, which, in the presence of a DNA donor template, introduces the desired modification at the target locus; however, this mechanism is active only in proliferating cells. Another way is with nonhomologous end joining that can imprecisely repair the DNA by generating small insertion/deletions at the site of the DNA double strand breaks, which is active in both quiescent and proliferating cells. Myo-editing techniques have shown promising results in preclinical animal models and human cells^[33]. Dual-adenoviral-associated virus (AAV) systems can overcome the packaging limitations of AAV vectors for in vivo CRISPR delivery. However, they require high vector doses, which may limit clinical feasibility. Another major concern of

AAV-CRISPR gene therapy is the innate and adaptive immune responses evoked by AAV vectors and Cas proteins^[31,33].

Development of editing and delivery methods to reduce viral vector dosing to improve safety and reduce immunogenicity, while maintaining/improving dystrophin restoration efficacy, off-target related safety concerns and durability need to be addressed before clinical implementation^[33].

Gene replacement therapy

For monogenic diseases that lead to absent protein expression, the goal of gene replacement therapy is to deliver an intact copy of the mutated gene. In DMD, the transgene is delivered to muscle cells to allow the expression of functional protein and then restore or attenuate the phenotype^[15].

The DMD gene (2.3 Mb) and its full-length transcript (14 kb) exceed the carrying capacity of commonly utilized AAV vectors, which is approximately 5 kb. To overcome this limitation, a truncated version of dystrophin (mini/microdystrophin) was developed. The amount of functional microdystrophin required to achieve clinical efficacy varies, and multiple studies in animal models (mice and canines) indicate that approximately 20% of the normal dystrophin level may be sufficient to produce therapeutic effects^[1]. Different degrees of disease improvement have been seen in the mouse model with a wide range of dystrophin expression. Functional improvement was seen with as low as 4% dystrophin expression, while 20% levels prevented development of dystrophic symptoms. However, extrapolation of these data to human patients remains uncertain and challenging due to interspecies differences in muscle biology and correlations with clinical outcomes^[34]. Another factor to consider is that a truncated dystrophin is likely less effective than the wild-type, and the durability of dystrophin expression is not fully known^[35]. Additionally, the accuracy of dystrophin quantification techniques shows variability and sampling error should be considered due to the substantial variation of dystrophin expression within myofibers, between myofibers and even between muscles^[30].

In general, gene replacement therapies for DMD have focused on the delivery of various micro-dystrophin transgenes. Portions of the DMD coding sequence have been removed to preserve essential protein function while reducing the size to address AAV vector capacity limits. These constructs differ in terms of the micro-dystrophin structure, tissue-specific promoter and the AAV serotype, such differences may influence the transduction, efficacy and safety. [Table 1] summarize the distinctions between the FDA-approved gene therapy and other investigational drugs currently in clinical trials^[35,36].

The therapeutic potential of AAV gene therapy depends not only on vector design optimization but also on other strategies, including promoter selection, scaffold choice, and the use of adjunct peptides to enhance transgene expression and minimize toxicity^[37,38].

In 2020, Mendell *et al.* demonstrated in a phase 1/2 study that treatment with SRP-9001 led to improved microdystrophin expression, reduced creatine kinase levels, and increased NorthStar ambulatory assessment (NSAA) scores^[39]. In the subsequent phase 3 randomized trial (NCT05096221) with the same molecule, named delandistrogene moxeparvovec (Elevidys), part 1 - change from baseline NSAA score at 52 weeks - did not reach statistical significance. Some of the secondary endpoints showed numeric differences favoring treatment in time to rise (TTR), 10-meter walk/run (10MWR) and 95th percentile stride velocity^[39,40].

Based on this data, Elevidys was granted accelerated approval (AA) from the FDA in June 2023 to treat patients with DMD aged four to five years. In June 2024, the label was expanded to a full approval for ambulatory patients and AA for nonambulatory patients over four years of age.

Table 1. Summary of different microdystrophin constructs*

Serotype	Tissue tropism	Promoter	Company	Development progress
AAV8	Skeletal, cardiac	Spc5.12	Regenxbio	Multicenter, phase I/II/III, open-label study. Entering pivotal phase
AAV8	Skeletal, cardiac	Spc5.12	Genethon	Completed Phase 1/2. Entering Pivotal phase
AAV9	Skeletal, cardiac, lesser extent CNS	CK8e	Solid Biosciences	Switched to a new generation vector (myo-AAV)
AAV9	Skeletal, cardiac, lesser extent CNS	CK7	Pfizer	Development was stopped (missed primary point in phase III clinical trial)
AAVrh74	Skeletal, cardiac	MHCK7	Sarepta/Roche	FDA approved in 2024 (Elevidys). Long-term outcome studies ongoing

*Adapted from Roberts *et al.*^[36].

AAV-mediated gene therapy replacement challenges

Durability

DMD is a chronic neuromuscular disease and, as such, requires sustained dystrophin expression. Several studies have shown that AAV vectors can persist in normal tissues, including muscle cells. However, there is some uncertainty regarding the long-term persistence of the transgene in the dystrophic muscle and animal model data might not be fully translatable to patients with DMD^[41,42]. Decline in transgene expression can presumably be related to immune response and vector dilution^[43]. As the vector genome is thought to remain episomal and not integrate into the host genome, the cell turnover rate in growing muscle, as seen in young patients, and repeated cycles of necrosis and regeneration in dystrophic cells can affect the persistence of the transgene and potentially lead to a dilution effect. It should also be noted that overactivation of the immune system in the microenvironment of dystrophic cells can limit AAV genome persistence^[41,44,45].

AAV- immunogenicity

Systemic delivery of high doses of AAV can trigger immune system-mediated toxicity. The complement system is a primary component of innate immunity and in vitro studies suggest that AAV capsid can interact and activate complement components. This activation can also happen through the classic pathway by immune complex formed from anti-AAV capsid antibodies^[45-48]. The adaptive immune response to AAV capsid has been reported in gene therapy trials for hemophilia, spinal muscular atrophy (SMA), and other diseases.

To date, two fatal cases of liver failure have been reported following treatment with Elevidys^[49]. The pathogenesis of liver injury is not yet fully understood. However, liver injury described in gene therapy clinical trials using AAV vectors could potentially be a result of both innate (possible complement system activation), and adaptive (T-cell mediated) immune response. Additionally, if the transgene is highly immunogenic, it could also trigger immune toxicity^[50,51].

Other toxicities related to gene therapy include myocarditis, liver injury and thrombotic microangiopathy (TMA), which can also be related to activation of both innate and adaptive responses against the AAV vector capsid^[51].

Some of the strategies under investigation to reduce AAV immunogenicity include inhibition of complement receptor^[52], AAV vector coating with a modified polymer to reduce interaction with neutralizing antibodies (Nabs)^[53], removal of CpG motifs from the AAV vector^[54], and the use of less immunogenic AAV serotypes^[55].

Transgene immunogenicity

Dystrophin-specific T cell activation is a major challenge in systemic gene therapy for DMD. Five patients with DMD enrolled in three trials (NCT0428148, NCT04626674, Eudra-CT number, 2020-002093-27), using different microdystrophin transgenes, promoters and AAV products (AAV9, AAV8 and AAVrh74), experienced suspected unexpected serious adverse reactions. These patients presented between 3 and 6 weeks post infusion with symptoms of severe myositis that led to loss of ambulation and weakness of the bulbar and respiratory muscles. The timing of these adverse reactions was consistent with transgene expression and further studies suggested a T-cell-mediated response against specific microdystrophin peptides contained within exons 8 through 11^[56,57].

As a result, AAV clinical trials have been modified to exclude patients who have DMD deletions that significantly overlap with those transgene sequences.

Pre-existing immunity

One of the major difficulties in AAV-mediated gene therapy is the presence of pre-existing Nabs against the viral capsid; overall, up to 80% of the human population has antibodies against various serotypes^[46].

Pre-existing immunity to AAV vectors is a barrier for treatment eligibility and is primarily due to prior exposure to the wild-type AAV which leads to the formation of Nabs. Seroprevalence differs among serotypes, with studies reporting 32%, 36% and 47% prevalence for AAVrh74, AAV9 and AAV8, respectively. Given the degenerative nature of the disease, it is likely that redosing might be needed in the future. Development of strategies such as pharmacological modulation, removal of circulating antibodies (plasmapheresis), blocking innate immunity (complement antagonist), use of different AAV serotypes and AAV capsid engineering are under investigation^[45,58].

RNA-mediated therapies

Exon skipping

Antisense oligonucleotides (ASOs) are short, single-stranded nucleotides that are capable of binding to a specific region of RNA to promote exon-skipping. The main goal is to restore the disrupted reading frame of the dystrophin gene, producing an internally truncated but functional dystrophin protein^[1,59].

These therapies are mutation-specific and benefit a subset of patients, approximately 27% of the DMD population. Currently, there are four FDA-conditionally approved ASOs that target exons 45, 51 and 53 [Table 2]. Clinical trials have shown that ASOs restore dystrophin in patients with DMD, albeit at very low levels. The FDA approval was granted based on the surrogate endpoint of dystrophin expression in muscle biopsies of treated patients. However, none of these ASOs has received approval in Europe. Clinical data on Eteplirsén, the first FDA-approved exon skipping therapy, has demonstrated slowing disease progression compared with matched external controls^[60]. However, the data remains controversial and it is not yet fully clear if the low levels of dystrophin restoration (even with high intravenous doses) are sufficient and further clinical trials are ongoing to further assess the long-term functional efficacy and safety^[61].

ASO treatments have several limitations related to delivery efficiency to the skeletal and cardiac tissues. Approved ASOs are based on phosphorodiamidate morpholino oligomer (PMO) chemistry, which is uncharged and does not bind to serum proteins, thereby limiting tissue distribution and bioavailability due to renal clearance^[31]. Delivery to skeletal and cardiac muscle can be improved through pPMO peptide conjugates, transferrin receptor-targeted antibody conjugation, and chemical modifications (see Table 3)^[62-64].

Table 2. Summary of current FDA conditionally approved exon skipping therapies*

Treatment	Exon	Year of FDA approval	Dose	% DMD patients amenable to treatment	% Dystrophin restoration
Eteplirsen (exondys)	51	2016	30 mg/kg	14%	0.9% after 180 weeks
Golodirsen (vyondis)	53	2019	30 mg/kg	8%	1% after 48 weeks
Vitolarsen (viltepso)	53	2020	80 mg/kg	8%	5.9% after 25 weeks
Casimersen (amondys)	45	2021	30 mg/kg	9%	4.25% after 48 weeks

*Adapted from Chwalenia *et al.* [64].

Table 3. Summary of ASOs in development*

ASO	Type of modification	Exon targeted	Company	Current development
Vesleteplirsen	conjugate	51	Sarepta	Phase 2 multidose ascending dose. Program was discontinued in 2024 due to safety concerns
PGN-EDO51	conjugate	51	PepGen	Phase 2 trial was discontinued
ENTR-601-044	conjugate	44	Entrada Therapeutics	FDA hold was removed in February 2025
DYNE-251	Transferrin 1 Antibody associated	51	Dyne Therapeutics	Phase 1/2 clinical trial (Active, not recruiting)
AOC1044	Transferrin 1 antibody associated	44	Avidity	Phase 1/2 clinical trial (Active, not recruiting)
BMN351	Phosphorothioate chemical modifications	51	BioMarin	Phase 1/2 clinical trial (recruiting)
WVE-N531	Inclusion of phosphoryl guanidine (PN), chemical modification	53	Wave Life Sciences	Phase 1b/2 open-label study (Active, not recruiting)

*Adapted from Roberts *et al.* [36] and Aartsma-Rus [62].

Read-through of premature stop mutations

Nonsense mutations replace an amino acid codon in the messenger RNA (mRNA) by one of the three stop codons - UAA, UGA or UAG, resulting in an inactive, truncated protein. Drugs that induce suppression of these nonsense mutations during translation can increase the read-through of the premature stop signal and produce a full-length protein [65,66].

This therapeutic approach, applicable to all nonsense mutations in DMD, can treat 10%-15% of all DMD patients.

Ataluren is an oral treatment that promotes full-length dystrophin synthesis through ribosomal read-through of an in frame premature stop codon. It is not approved in the United States, and the European Medicines Agency (EMA) is not going to renew its approval in Europe, as clinical trials have failed to prove its effectiveness [67].

Gene replacement surrogates

Utrophin is a cytoskeletal protein that is an autosomal paralogue of dystrophin. Upregulation of utrophin A, the predominant form in skeletal muscle, can potentially compensate for the absence of dystrophin. Several pathways involved in utrophin regulation and expression are currently under investigation [68,69].

Regulatory divergence in treatment approvals

The FDA and the EMA have high concordance in decisions on marketing approvals. However, there are also divergent authorization decisions based on clinical data, efficacy, safety conclusions and regulatory authority differences^[70].

Both the FDA and EMA have expedited approval pathways for therapies intended for serious, life threatening and rare diseases. In the United States, the AA program allows authorization based on a surrogate endpoint that is likely to predict a clinical benefit. By contrast, the conditional marketing authorization (CMA) pathway in the European Union requires a higher level of clinical evidence and does not rely on surrogate endpoints. These distinctions are illustrated by the FDA's approval of exon skipping therapy based on surrogate endpoint and the EMA's initial approval of Ataluren based on preliminary efficacy evidence and the benefit-risk balance^[71].

MEASURES OF MOTOR FUNCTION IN CLINICAL TRIALS AND CLINICAL PRACTICE

Determination of treatment efficacy based on motor function changes must consider many factors. Understanding the natural history and progressive nature of the disease, the effects of standardized administration, and patient behavior or cognition on effort-based motor performance, as well as perception of change and impact on quality of life, are all important when interpreting changes in motor function measures. Clinical outcome assessments (COAs) have been validated to quantitatively measure clinically meaningful functional changes in boys with DMD^[72-74]. To better understand true change in response to intervention and interpret clinical trial outcomes, estimates of minimal detectable change (MDC) and anchored minimal clinically important differences (MCIDs) highlighting the relevance of function to patient perception have been established for multiple COAs^[73,75-77]. The North Star Ambulatory Assessment (NSAA) incorporates items that may be gained in boys with DMD treated with disease modifying therapies (DMTs) that would typically be lost with typical disease progression. Based on MDC and MCID estimates, score thresholds may be applied to define clinical progression of disease and may aid in distinguishing non-transient functional change using the NSAA. Additionally, timed function tests such as time to climb 4 stairs (4SC) and the Six Minute Walk Distance (6MWD) utilizing continuous data can be sensitive to change. These may be used to convert data to calculate movement velocity and can be interpreted in the context of maturation, using percent-predicted results relative to normative values^[78]. The Performance of Upper Limb 2.0 (PUL 2.0) was designed to measure upper extremity function across the range of severity in patients with DMD including those who are nonambulatory^[79,80]. The scale measures gross and fine motor function with items that relate to daily function utilizing upper limbs. Results of COAs administered to assess changes in function must incorporate clinical reasoning, knowledge gained from scale validation, and lessons learned from previous clinical trials and clinical care to set realistic expectations for functional prognosis, which may influence clinical decision-making and the recommendations provided to patients and their caregivers.

FROM CLINICAL TRIALS TO REAL-WORLD: LESSONS LEARNED

Extrapolating clinical trial findings to real-world patients is challenging due to multiple influencing factors. The perception of gene therapy benefits can differ among patients, caregivers, and providers. Therefore, it is essential to establish clear definitions and set realistic expectations.

Increases in dystrophin levels after treatment occur gradually over time, and clinical effects might not be apparent until the first year post-treatment. High-dose steroids used in gene therapy can affect short-term functional outcomes. This may create inaccurate perceptions of improvement among patients and families. Discouragement may arise if progress appears to stall during steroid tapering.

A further consideration is the initial expanded label for Elevidys in nonambulatory boys. Families may anticipate outcomes comparable to those observed in younger, ambulatory patients. However, in later disease stages, functional gains are less likely.

This underscores the need for risk stratification for potential cardiac and liver events following gene therapy, particularly in older patients. This should be addressed during the screening process to ensure informed decision-making.

Large-scale registries, such as the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry and the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS), provide robust data to help differentiate between perceived and actual efficacy. For example, in the STRIDE registry, patients receiving ataluren plus standard of care showed a delay in loss of ambulation. On the other hand, data from the CINRG DNHS has shown that glucocorticoid treatment for ≥ 1 year increases median age at loss of ambulation and other functional milestones by 2.1-4.4 years^[81,82].

Although gene therapies offer life-changing benefits for patients, the unprecedentedly high cost represents a challenge for reimbursement. Some payers may deny coverage, and others might include several filters before approval which can delay treatment. Various alternative payment models have been proposed and used to pay for these therapies in the United States and internationally. Some of these models address the high budgetary impact of gene therapies by spreading costs over multiple years (amortization) or across multiple patients (risk spreading), to make the cost among the population of patients more predictable. Other models focus on the clinical uncertainty of high-cost therapies by using performance-based agreements. In an outcome-based payment model, compensation is directly linked to the drug's performance and payment is adjusted based on a predefined outcome, either at the individual level or across the treated population^[83]. This model has also been combined with amortization, allowing the benefit of spreading costs over time.

More efforts to implement innovative solutions are needed to ensure patient equitable access to treatment^[83].

CONCLUSIONS

Variable results have been reported from multiple clinical trials targeting dystrophin restoration. In general, modest clinical benefits were observed, showing slowed disease progression, but long-term efficacy and durability remain uncertain. Emerging therapies for dystrophin restoration hold promise to address limitations of current treatments, including transfection efficacy, immunotoxicity, alternative immunosuppression regimens, and AAV delivery. Future advancements in dystrophin restoration will require both optimization of current therapeutic strategies and integration of sensitive biomarkers and comprehensive outcome measures to accurately assess clinical response. Additionally, real-world data will be essential to understand the impact across diverse patient populations and guide evidence-based clinical implementation. Nevertheless, multidisciplinary care and steroids remain the mainstay of treatment.

DECLARATIONS

Authors' contributions

Initial draft, conceptualization, writing and editing: Gonzalez Castillo Z

Writing and editing: Nelson L

Writing, editing and supervision: Batley K, Iannaccone ST

All authors have reviewed and agreed to the published version of the manuscript.

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Conflicts of interest

Iannaccone ST is an Editor and Editorial Board Member of *Journal of Translational Genetics and Genomics*. Iannaccone ST was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making, Iannaccone ST has served as a consultant for Sarepta Therapeutics, TRINDS, Merck, BioMarin, Broadstreet and Astellas; Gonzalez Castillo Z has served on advisory boards for ITF Therapeutics and Sarepta Therapeutics; Batley K has received research funding from Catalyst Pharmaceuticals, Sarepta Therapeutics, and NS Pharma. She has served on advisory boards and/or as a speaker for Catalyst Pharmaceuticals, ITF Therapeutics, Sarepta Therapeutics, Pfizer, and Regenxbio; Nelson L declares that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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