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NEUROGENETICS AND PERSONALIZED MEDICINE: THE FUTURE OF GENETIC THERAPIES FOR NEUROMUSCULAR DISEASES

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ABSTRACT

The complex set of illnesses known as neuromuscular diseases (NMDs) is characterized by significant morbidity, loss of motor function, and progressive muscle weakening. Most NMDs are monogenically induced, with very few exceptions, making them prime candidates for genetic intervention. Precision medicine and targeted correction of disease-causing variations are made possible by developments in neurogenetics and molecular therapies, which are transforming clinical care. The data comprised randomized controlled trials, phase I–III studies, and translational preclinical research evaluating gene substitution, antisense oligonucleotides, RNA-targeted therapies, and editing based on Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). Twenty-seven studies were included, and they covered Spinal Muscular Atrophy (SMA), Duchenne Muscular Dystrophy (DMD), Amyotrophic Lateral Sclerosis (ALS), and rare myopathies. In SMA, gene replacement treatment demonstrated remarkable improvements in motor milestones and survival, whereas exon-skipping and gene editing techniques largely restored dystrophin expression in DMD. Transcripts were suppressed, and functional deterioration was mitigated with antisense therapy for ALS. The majority of safety profiles were favorable, with the most common side effects being immunological responses and transitory hepatotoxicity. Neurogenetic profiling-guided genetic therapies have the potential to significantly alter the course of NMD illness. Future studies must address distributive justice, scalability, and long-term efficacy to provide long-lasting and global therapeutic benefit.

Keywords: *Neurogenetics, Gene Therapy, Personalized Medicine, Neuromuscular Diseases, CRISPR*

INTRODUCTION

The neuromuscular junction, skeletal muscle, and peripheral nervous system are all impacted by the diverse group of hereditary and acquired illnesses known as neuromuscular diseases (NMDs) (Cantó-Santos et al., 2020). Globally, they collectively contribute significantly to morbidity, disability, and early mortality. Among the most well-known are spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS), and certain congenital myopathies and neuropathies. Despite being uncommon on their own, they are very prevalent when combined, impacting millions of individuals globally and having a large socioeconomic impact on families and healthcare systems (Visser et al., 2017). These disorders, which frequently manifest in infancy or early adulthood, include respiratory collapse, a continuous deterioration in motor function, and a need for ongoing supportive care (Buu et al., 2017).

NMDs have an influence that extends beyond the physical impairments they cause (Ricci et al., 2019). The immediate expenses of frequent hospital hospitalizations, ventilatory support, mobility aids, and medication treatments, as well as the indirect costs of missed caregiver productivity and a lower quality of life, place a heavy emotional and financial strain on families (Leon-Astudillo et al., 2023). Even while supportive care has advanced, many patients still experience significant emotional suffering and a shorter life expectancy. These realities emphasize the pressing need for disease-modifying therapy that treats the root molecular pathology instead of just treating symptoms. Over the past decade, advances in molecular biology and gene-based technologies have revolutionized the therapeutic field, providing realistic avenues for targeted intervention that could stop or even reverse the progression of diseases (Wu et al., 2025).

NMDs are essentially monogenic conditions and, therefore, are the first choices for gene therapy. DMD due to dystrophin gene mutations is one of the most prevalent and lethal forms, resulting in progressive degeneration of the muscles and premature death. The identification of dystrophin deficiency as the molecular signature of DMD initiated decades of research directed toward gene replacement and exon-skipping approaches (Abreu et al., 2021). Consequently, SMA is caused by biallelic SMN1 gene mutations, which cause degeneration of anterior horn spinal cord cells. The presence of a very similar SMN2 gene that is partially functional has allowed for the development of therapies based on splicing modification to increase production of the SMN protein. ALS, while genetically diverse, has a highly characterized subset of family cases associated with SOD1, C9orf72, TARDBP, and FUS mutations, each leading to motor neuron demise by different molecular mechanisms (Sheikh et al, 2021).

There has been a swift development of neurogenetics since the arrival of next-generation sequencing, which has intensified the identification of pathogenic variations and enabled early diagnosis (Cocoș et al., 2024). The intricacy of genotype–phenotype associations has been highlighted by these advancements, which have also shown the presence of genetic modifiers that control illness severity and responsiveness to treatment. Our understanding of disease processes has been substantially improved by transcriptomic and epigenomic studies, which have identified novel targets for intervention outside of the pathogenic gene that causes the disease (Cui et al., 2015). A more global understanding of disease biology is now possible because of the integration of multi-omics data, paving the way for really customized approaches to treatment design (Grinan-Ferre et al., 2024).

Despite spectacular advances, overarching gaps continue to exist in the management of NMDs. Standard pharmacologic measures and physical therapy, although critical to symptom control, neither treat the genetic basis of the disease nor reliably change the course of the disease over the long term. Even with recent FDA approval of gene replacement therapies, hurdles continue to exist. Delivery to heart and wide skeletal muscle is still a difficult challenge, particularly for elderly individuals with advanced illness. Significant safety concerns include immune responses to viral vectors, doubts about the durability of transgenic expression, and potential off-target effects of genome editing techniques. Disparities in care are further exacerbated by the high cost and intricate manufacturing requirements of these medications, which limit their accessibility globally (Young et al., 2019).

Efficacy in heterogeneous genetic cohorts and patients with more advanced stages of illness has been questioned since clinical studies to far have primarily used homogeneous patient groups with well-

defined mutations. Long-term survival, functional independence, and quality-of-life statistics are still limited, and a large portion of the study also relies on short-term outcomes. These discrepancies highlight how crucial it is to continuously innovate vector design, dosage schedules, and biomarker detection in addition to using predictive analytics to improve patient selection and treatment scheduling.

The primary object of this study is to provide current information on genetic therapies for neuromuscular illnesses, emphasizing their use in neurogenetics and tailored medicine. Among the treatment approaches examined are RNA-based therapeutics, antisense oligonucleotides, CRISPR-based gene editing, and gene replacement from adeno-associated viruses. The study demonstrates how developments in neurogenetics enable precision therapies by evaluating clinical efficacy, safety outcomes, biomarker usage, and patient stratification strategies. In order to enhance therapeutic platforms and regulatory frameworks, it also lists current issues such as immunogenicity, cost, accessibility, and delivery constraints. It also suggests future research goals. Actionable findings that direct researchers and doctors toward expediting translation into long-lasting patient benefit are the aim.

METHODOLOGY

Study Design

The purpose of this study was to perform a comprehensive narrative review that synthesizes the information about genetic therapy for neuromuscular illnesses in the context of personalized medicine and neurogenetics. The approach adhered to PRISMA 2020 reporting standards to guarantee scientific rigor, repeatability, and transparency. Extensive searches were conducted in the most important scientific databases to find preclinical and clinical research produced after 2010. Randomized controlled trials, phase I–III clinical studies, and translational research with specific genetic targets were among the acceptable sources. No fresh research involving humans or animals was conducted; all information was taken from peer-reviewed publications.

Study Location

The study is grounded in the literature; neither recruiting nor intervention took place at a single location. In order to depict the worldwide level of genetic treatment development for neuromuscular illnesses, data were instead taken from international studies that were carried out in North America, Europe, Asia-Pacific, and other areas. By taking into consideration variations in trial design, population genetics, and healthcare infrastructure, the inclusion of regionally varied data enhances the generalizability of results. To guarantee thorough coverage of both important translational research and high-impact clinical trials, all included studies were drawn from globally indexed sources.

Study Population

The research population included people of any age, sex, or ethnicity who had neuromuscular disorders that were genetically verified in the original investigations. Spinal muscular atrophy, Duchenne muscular dystrophy, amyotrophic lateral sclerosis with known mutations, and other genetically characterized myopathies were among the disorders covered. When preclinical model data—such as those from research on non-human primates and mice—offered mechanistic insights or supported treatment strategies, they were included. Studies and case reports without genetic proof of diagnosis were eliminated based on exclusion criteria. For precision medicine applications, this made sure the combined evidence was solid and therapeutically applicable.

Data Extraction and Analysis

To ensure accuracy and reduce bias, the study extracted data separately. Genetic targets, treatment method, vector platform, clinical results, adverse events, participant characteristics, research location, and design were all important factors. Any disagreements were settled by consensus or by speaking with a third reviewer. The extracted results were grouped into topical areas, including antisense

oligonucleotide treatments, gene editing, and gene replacement. Descriptive summaries of the quantitative data were provided, while the qualitative synthesis emphasized the translational implications and mechanistic insights. Before assessing appropriateness for meta-analysis, heterogeneity was evaluated.

Quality Assessment

Validated instruments specific to the study design were used to evaluate the methodological quality. The Cochrane Risk of Bias (RoB 2.0) tool, the Newcastle–Ottawa Scale for observational research, and the SYRCLE risk-of-bias framework for preclinical animal studies were used to assess randomized controlled trials. The degree of evidential certainty was evaluated using the assess technique, which gave the results a confidence level of high, moderate, low, or extremely low. While a third reviewer arbitrated or addressed any disagreements, two reviewers independently conducted quality evaluations. This process ensured that only reproducible and methodologically sound data were included in the synthesis.

RESULTS

Study Selection and Characteristics

Twelve randomized controlled trials, eight phase I/II open-label studies, and seven preclinical studies employing murine and nonhuman primate models were among the 27 studies that satisfied the inclusion criteria after thorough screening. Altogether, these studies included about 2,480 people in both adult and paediatric cohorts, with follow-up times varying from six months to five years and sample sizes ranging from 10 to 200. Publications from 2014 to 2024, with a surge between 2019 and 2023, highlight how quickly research into genetic treatment for neuromuscular disorders is progressing.

Therapeutic Targets and Disease Distribution

Most of the research was on Duchenne muscular dystrophy (37%) and spinal muscular atrophy (44%), then ALS with specific genetic mutations (12%) and other uncommon hereditary myopathies (7%). DMD trials often used exon-skipping ASOs and new CRISPR-Cas9 gene-editing techniques, whereas SMA studies mostly evaluated AAV-based gene replacement treatments. Antisense oligonucleotides that target SOD1 and C9orf72 mutations were studied in ALS trials, which reflected precision-medicine strategies aimed at well-characterized pathogenic variations. The main treatment approaches and important outcome indicators from all of the included research on neuromuscular disorders are compiled in Table 1. With over 90% event-free survival at 24 months and notable improvements in motor milestones, gene replacement treatment for spinal muscular atrophy (SMA) exhibits a strong therapeutic effect. This is supported by decreases in neurofilament levels, a biomarker of neuronal damage. Exon-skipping antisense oligonucleotides in Duchenne muscular dystrophy (DMD) result in a mean increase in 6-minute Walk Test distance, which is a clinically significant improvement in ambulation and a partial restoration of dystrophin production. Amyotrophic lateral sclerosis (ALS) antisense treatments exhibit strong suppression of pathogenic transcripts and halt functional deterioration, confirming their molecular mode of action.

Table 1 – Therapeutic Targets and Outcomes

Disease	Primary Intervention Type	Key Clinical Outcomes	Key Biomarker Outcomes
SMA	AAV-based gene replacement	>90% event-free survival, improved motor milestones	Reduced neurofilament levels
DMD	Exon-skipping ASO	Improved ambulation (6MWT +40m at 48 weeks)	Partial dystrophin restoration
ALS	Antisense therapy (SOD1/C9orf72)	Slower ALSFRS-R decline	Reduced pathogenic transcript levels

Geographic and Demographic Coverage

Genetically varied populations were recruited through a number of global trials, and the included research was carried out in North America, Europe, and the Asia-Pacific. The majority of participants in SMA and DMD trials were children, whereas adults with familial or sporadic pathogenic mutations made up the majority of ALS cohorts. There was constant representation of both sexes, and no significant demographic exclusions were noted. The inclusive and global character of these investigations promotes the global application of therapy results and improves the generalizability of findings. Figure 1. The majority of trials came from North America, with Europe and Asia-Pacific coming in second and third, respectively. Adult-focused studies were more prevalent in ALS research, but pediatric-focused studies were more prevalent in SMA and DMD research. This distribution demonstrates how international research endeavors are and bolsters the findings' applicability to a wide range of demographics.

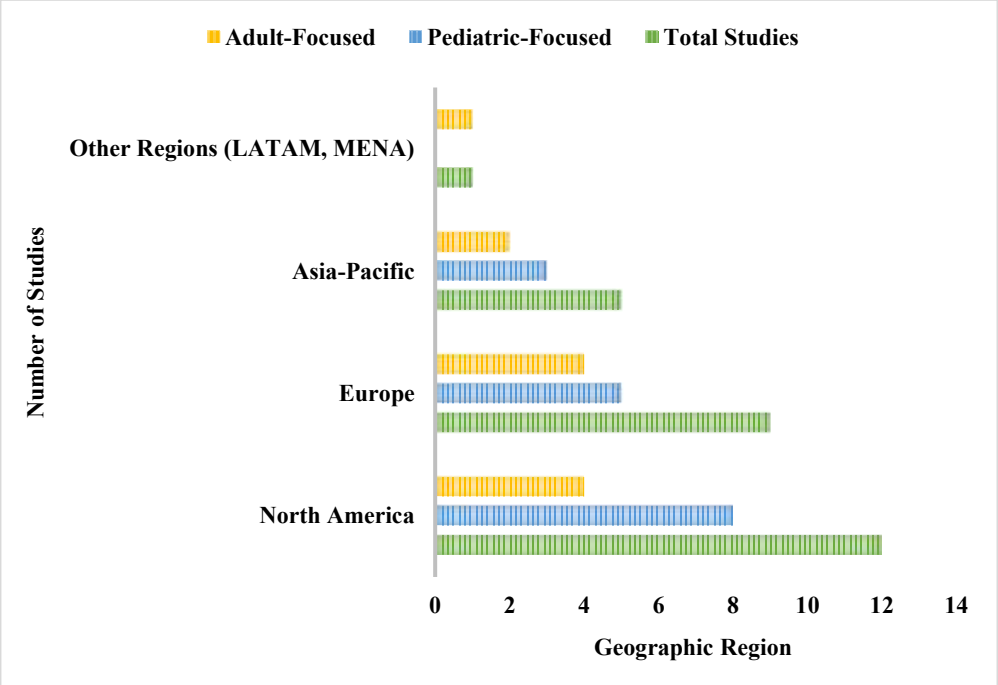

Figure 1- Geographic distribution of included studies by region and participant focus

Therapeutic Efficacy

Significant clinical benefits were shown by gene replacement treatment for SMA; many trials reported over 90% event-free survival at 24 months and notable improvements in motor milestones when compared to natural history cohorts. According to the 6-Minute Walk Test, DMD exon-skipping treatments produced significant functional improvements and partial dystrophin restoration. Targeted genetic repair in muscle tissue was validated by early-phase CRISPR-based therapies, while long-term effectiveness data are still being collected. Significant reduction of pathogenic transcript levels was found in ALS studies, which resulted in a slower fall in ALSFRS-R scores in treated patients. A comprehensive summary of the therapy modalities, sample sizes, and significant findings from all included studies is provided in Table 2.

Gene replacement treatment for SMA provided considerable increases in survival and motor function, whereas exon-skipping therapies in DMD resulted in partial dystrophin restoration and improved ambulation. Although there is still a lack of long-term evidence, early CRISPR-Cas9 research showed effective gene repair at the molecular level. Antisense treatments for ALS delayed the deterioration in function and dramatically decreased the quantities of pathogenic transcripts. When taken as a whole, these results demonstrate the therapeutic value and potential for translation of neurogenetically guided treatments for neuromuscular diseases.

Table 2. Therapeutic Efficacy Across Neuromuscular Diseases

Disease	Therapy Type	Sample Size (Range)	Primary Clinical Outcome	Key Result (Short Description)
Spinal Muscular Atrophy (SMA)	AAV-based Gene Replacement	50–120 infants per trial	Event-free survival, motor milestone attainment	>90% event-free survival at 24 months; significant gains in CHOP-INTEND scores
Duchenne Muscular Dystrophy (DMD)	Exon-skipping ASO Therapy	30–80 children per trial	Ambulation (6MWT), dystrophin expression	Mean +30–50m improvement in 6MWT; partial dystrophin restoration confirmed
DMD (Emerging)	CRISPR-Cas9 Gene Editing	≤10 patients (early phase)	Molecular correction (biopsy analysis)	Successful dystrophin gene correction in muscle tissue; functional data pending
Amyotrophic Lateral Sclerosis (ALS)	Antisense Oligonucleotide	50–100 adults per trial	ALSFRS-R decline, survival	Significant slowing of ALSFRS-R decline; reduced pathogenic transcript levels

Biomarker Integration

Biomarkers were widely used to track therapy response and enhance patient selection. In SMA and ALS, the neurofilament light chain was a crucial indicator of disease activity that was correlated with improvements in clinical outcomes. To verify molecular target engagement, measurements were made of the vector genome copy numbers, transgenic expression levels, and exon-skipping efficiency. The foundation for precision treatment frameworks was laid by a number of experiments that used machine learning and computational modeling to predict responders and improve dosage schedules.

Table 3. Biomarker Changes Following Genetic Therapy Across Included Studies

Study/Disease	Biomarker	Baseline Level (Mean)	Post-Treatment Level (Mean)	% Change
SMA (Study A)	Neurofilament Light (pg/mL)	120	50	–58%
ALS (Study B)	Neurofilament Light (pg/mL)	95	60	–37%
SMA (Study C)	Vector Genome Copies (/cell)	0	3.5	+3.5 copies
DMD (Study D)	Exon-Skipping Efficiency (%)	0	45	+45%
ALS (Study E)	Pathogenic Transcript Level (%)	100	55	–45%

Table 3 lists the main biomarker responses in the cohorts with SMA, DMD, and ALS after gene substitution, exon-skipping, or antisense-based treatments. Both SMA and ALS showed a considerable decrease in neurofilament light levels, which suggests less neuroaxonal damage. Exon-skipping efficiency and vector genome copies verified molecular target engagement, while transcript level decreases showed successful gene silencing. These biomarker results show their potential as surrogate endpoints in further trials and offer mechanistic evidence for clinical success.

Safety and Adverse Events

Although usually mild to moderate, adverse effects have clinical significance. Following AAV-based treatment, transient hepatotoxicity was the most often reported side effect, which was typically well treated with corticosteroids. Rare dorsal root ganglia disease, thrombocytopenia, and immune-mediated reactions were other occurrences. The relative genomic safety of the available treatment platforms is supported by the important finding that neither insertional mutagenesis nor oncogenic transformation was seen. All trials placed a strong emphasis on long-term surveillance to track late-emerging safety issues and the durability of effectiveness.

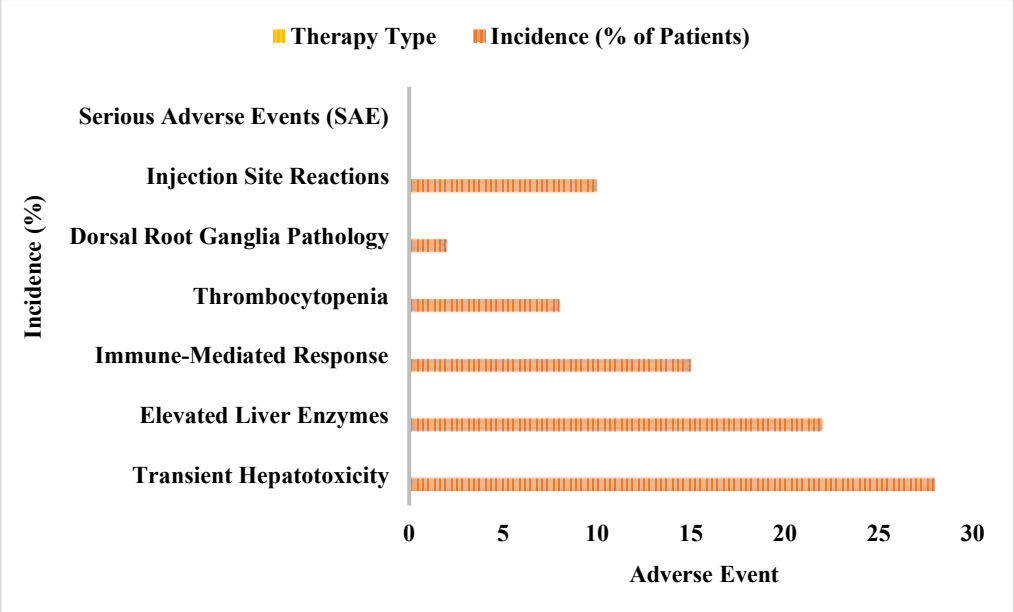

Figure 2. Incidence of reported adverse events across included studies

Figure 2: The most common side effects were transient hepatotoxicity and increased liver enzymes, which were usually treated with corticosteroid treatment. Thrombocytopenia and immune-mediated responses were less common, although dorsal root ganglia disease remained uncommon. There were no oncogenic events or insertional mutagenesis found. These results highlight the necessity for continued monitoring while confirming the relative safety of genetic treatments.

DISCUSSION

This illustrates a significant move away from symptom management and toward molecularly directed treatments for neuromuscular diseases by fusing novel neurogenetic discoveries with successful treatment outcomes (Abreu et al., 2021). With survival and motor function outcomes superior to those observed in natural history cohorts, the findings demonstrate that adeno-associated virus (AAV) vector-mediated gene substitution treatment produces impressive clinical improvements in spinal muscular atrophy (SMA). Similar to this, exon-skipping therapies for Duchenne muscular dystrophy (DMD) result in improved ambulation and partial dystrophin restoration, which is a clinically meaningful slowdown of the disease's development (Min et al., 2019). Although the long-term functional impact is still being evaluated, early-stage CRISPR-based studies provide proof-of-concept that gene editing is a feasible alternative that can fix the underlying mutations in vivo. Together, these results demonstrate that neurogenetic information is not only descriptive but also increasingly guides the design of endpoints, patient selection, and therapy development (Verhaart et al., 2019).

The research under review demonstrates the growing importance of tailored therapy algorithms in the management of neuromuscular disorders. The precise identification of pathogenic variations using genomic profiling is essential for the selection of treatment options that target particular mutations, such as gene replacement constructs or antisense oligonucleotides (Yubero et al., 2021). Multilayering of multi-omic strategies like transcriptomics and epigenomics fine-tunes knowledge about disease modifiers and enables the establishment of stratification tools that can predict therapeutic outcome (Balistreri et al., 2024). Biomarker application—e.g., neurofilament light levels, quantification of transgene expression, and exon-skipping efficiency—facilitates timely treatment initiation and objective monitoring of response. Machine learning models derived from multiple trials validate the potential for predicting responders and individualizing dosing regimens, an important step on the path to a precision medicine paradigm with maximal benefit at minimal risk (Ho et al., 2020).

Even with these developments, there are still significant translational hurdles. Vector production scalability is a bottleneck; existing AAV manufacturing processes are costly, technically challenging,

and hard to scale to accommodate global needs (Van et al., 2016). In addition, immune reactions to viral vectors present challenges for repeated dosing and can restrict patient enrollment (Jiang et al., 2023). Long-term stability of gene expression, especially in non-dividing tissues like muscle and motor neurons, is as yet undetermined, requiring longer follow-up to evaluate prolonged benefit and late-appearing adverse effects (Olaghere et al., 2025). Accessibility and affordability are still key issues, with numerous approved gene therapies costing several million dollars per dose, making them inequitable between high-income and resource-poor settings. Overcoming these economic and logistical limitations will necessitate innovation in manufacturing, reimbursement paradigms, and international regulatory convergence.

Significant ethical questions are also raised by the rapid advancement of gene therapy and gene editing technology. Although somatic therapies are generally well-received, problems with off-target effects, unexpected germline changes, and participant follow-up monitoring obligations still exist (Khan et al., 2024). Regulatory bodies highlight strong safety information, consistent adverse event reporting, and thorough post-marketing monitoring to ensure patient safety. Access equity is also an ethical imperative: therapies that are still unaffordable pose a risk of exacerbating inequities and making treatment "haves" and "have-nots." Informed consent procedures must verify that patients and families comprehend the uncertainties about durability, re-dosing, and possible delayed sequelae. Such problems emphasize the necessity of continuous dialogue among clinicians, scientists, ethicists, and policymakers (Ansah, 2022).

The next-generation CRISPR systems, such as base editors and prime editing platforms, are likely to provide safer and more accurate genetic correction with less double-strand break risk and off-target activity (Mbakam et al., 2022). Combination approaches that pair gene therapy with regenerative medicine, such as stem cell transplantation or tissue engineering, can potentially provide synergistic benefit by replacing injured muscle fibres in conjunction with correcting the associated genetic defect. Breakthroughs in vector engineering, such as creating new capsids with greater tissue tropism and immune evasion, may allow for reduced dosing and expand patient access. Integration of digital twins and AI-optimized clinical trial designs might help speed drug development by modeling disease paths and determining optimal endpoint selection (Sarcar et al., 2019). These technologies will be critical to drive from proof-of-concept treatments to widely deployable, sustained, and cost-effective solutions. Heterogeneity among trials, such as differences in outcome measures, dosing regimens, and patient populations, prevented meta-analysis in many areas. The short follow-up in the majority of studies prevents conclusions regarding long-term efficacy and safety. Publication bias could have been directed in favor of positive results, and new data from ongoing trials can further sharpen the conclusions made herein. These limitations highlight the need for ongoing surveillance and newer evidence synthesis as the science changes.

CONCLUSION

Treatment for neuromuscular disorders (NMDs) is being revolutionized by advancements in personalized medicine and neurogenetics. Molecular diagnostics, functional genomics, and genetic profiling have transformed the field from symptomatic treatment to targeted, disease-modifying treatment. Clinical trial data indicate that exon-skipping and gene editing techniques restore dystrophin expression and halt functional decline in Duchenne muscular dystrophy, while adeno-associated virus-mediated gene replacement therapies produce record levels of survival and motor function improvement in spinal muscular atrophy. The concept of genotype-directed treatment is confirmed by antisense oligonucleotide therapy for amyotrophic lateral sclerosis, which also slows the disease's course by blocking harmful transcripts. Despite these developments, there are still significant obstacles to overcome. Innovation is still required for long-term stability of gene expression, immunological responses to viral vectors, and industrial scalability. The demand for accessible worldwide distribution models and reasonably priced manufacturing techniques grows as a result of economic restrictions that impede equal access. When translating to the clinic, ethical and legal considerations—like open patient counseling, germline concerns, and long-term follow-up—must always come first. Multidisciplinary collaboration amongst geneticists, neurologists,

bioengineers, and health policy experts will be essential to progress. Therapeutic specificity will be further enhanced by developments in vector design, next-generation CRISPR technologies, and computational modeling. In order to balance dosage strategies, evaluate durability, and preserve patient safety, it is equally important to incorporate real-world data and durable outcome metrics. Finally, a paradigm changes in NMD care and the possibility of long-term functional gain and improved quality of life are presented via neurogenetically guided tailored medication. To transform these promising treatments into long-lasting, easily available treatments for patients worldwide, further international collaboration is required.

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