Review Article

Spinal Muscular Atrophy in the Era of Precision Medicine: Pathophysiology, Therapeutic Advances, and Future Perspectives

Rukmangathan Palani[1], Senthilnathan.D.N[2], Praveena.S[3], Abishek T[4]

From, [*]Department of Pharmaceutics, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry – 605102.

ABSTRACT

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by biallelic loss-of-function mutations in the survival motor neuron 1 (SMN1) gene, resulting in progressive degeneration of anterior horn cells and consequent proximal muscle weakness. Historically one of the leading monogenic causes of infant mortality, SMA has undergone a paradigm shift in its clinical outlook over the past decade, driven by the development and regulatory approval of three disease-modifying therapies: nusinersen, an antisense oligonucleotide targeting SMN2 pre-mRNA splicing; onasemnogene abeparvovec, an adeno-associated virus serotype 9 (AAV9)-mediated gene replacement therapy; and risdiplam, an orally bioavailable small-molecule SMN2 splicing modifier. These advances have transformed SMA from a uniformly fatal or severely debilitating condition into one amenable to substantial clinical stabilization and, in presymptomatic cases, near-normal neurodevelopmental trajectories. This review provides a comprehensive synthesis of the current understanding of SMA, encompassing its molecular genetics, pathophysiological mechanisms, clinical classification, diagnostic approaches, and the evolving therapeutic landscape. Particular emphasis is placed on recently approved and investigational agents, the role of newborn screening in enabling presymptomatic intervention, and outstanding challenges, including treatment access, long-term efficacy, combinatorial strategies, and the management of non-responders. By integrating recent evidence from high-impact clinical trials and translational studies, this review aims to serve as an authoritative reference for clinicians and researchers engaged in the care and study of SMA.

Key words: spinal muscular atrophy, SMN1, SMN2, nusinersen, onasemnogene abeparvovec, risdiplam, gene therapy, antisense oligonucleotide, newborn screening, neuromuscular disease

Spinal muscular atrophy (SMA) is an inherited autosomal recessive neuromuscular disorder characterized by progressive degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to symmetric proximal muscle weakness and atrophy [1]. The loss of lower motor neuron input predominantly affects axial and limb-girdle musculature, although bulbar motor neurons innervating cranial nerves V through XII may also be involved in severe phenotypes. Sensory function, cognitive capacity, and sphincter control remain intact throughout the disease course, distinguishing SMA from other neurodegenerative conditions [2]. Historically, SMA was one of the most devastating pediatric genetic disorders, recognized as the leading single-gene cause of infant mortality worldwide. The condition affects approximately 1 in 6,000 to 10,000 live births, with a carrier frequency estimated at 1 in 40 to 1 in 50 individuals in the general population [3].

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The clinical spectrum is broad, ranging from prenatal onset with severe respiratory compromise to adult-onset disease with mild functional impairment, determined principally by the copy number of the paralogous SMN2 gene and residual SMN protein production [4].The discovery of the SMN1 gene in 1995 by Lefebvre and colleagues established the molecular basis of SMA and inaugurated a new era of targeted therapeutic development [5]. Subsequent elucidation of the SMN2 splicing mechanism, which omits exon 7 from the majority of transcripts due to a single nucleotide transition at position +6 of exon 7, provided a tractable target for pharmacological intervention [6]. The convergence of antisense oligonucleotide technology, adeno-associated virus-mediated gene delivery, and high-throughput small-molecule screening over the past two decades has yielded three regulatory-approved disease-modifying therapies that have fundamentally altered the natural history of SMA [7].

Correspondence to : Dr. M. Jeevitha, M.Pharm., Ph.D., Professor, Department of Pharmaceutics , Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry – 605102

Email : jeevipharma@gmail.com

Despite these remarkable advances, significant unmet needs persist. A substantial proportion of patients, particularly those with established muscle denervation or older age at treatment initiation, exhibit incomplete responses to currently available therapies. Furthermore, long-term durability of therapeutic effects, optimal combinatorial strategies, treatment access disparities in low- and middle-income countries, and the biological consequences of SMN restoration in non-neuronal tissues remain active areas of investigation [8,9]. This review synthesizes current knowledge of SMA pathophysiology, classification, diagnosis, and therapeutics, with particular emphasis on recent clinical trial data and emerging therapeutic modalities.

2. ETIOLOGY AND MOLECULAR GENETICS

SMA is caused by biallelic loss-of-function mutations in the SMN1 gene, located within a highly complex genomic region on chromosome 5q13 (bands q11.2–13.3) [5]. This region is characterized by an inverted duplication containing two nearly identical copies of the SMN gene: the telomeric SMN1 and the centromeric SMN2. Approximately 95–98% of SMA patients harbor homozygous deletion of exons 7 and 8 of SMN1, with the remaining cases attributable to compound heterozygous mutations, including point mutations, small insertions, or deletions in one allele combined with deletion of the other [3,10].

The SMN protein is a ubiquitously expressed 294-amino acid protein that functions as a core component of a multiprotein complex essential for the assembly and regeneration of small nuclear ribonucleoproteins (snRNPs), the fundamental units of the spliceosomal machinery responsible for pre-mRNA splicing [6,11]. Beyond its canonical role in snRNP biogenesis, SMN participates in mRNA transport along motor neuron axons, local translation at neuromuscular junctions, actin dynamics, and mitochondrial function in neurons [12]. The exquisite vulnerability of motor neurons to SMN deficiency, relative to other cell types that also express SMN, remains an area of active investigation, with current evidence implicating disrupted axonal mRNA trafficking and impaired neuromuscular junction development as critical contributors [13].

Unlike SMN1, the SMN2 gene contains a translationally silent C-to-T transition at position +6 of exon 7 that disrupts an exonic splicing enhancer, causing predominant exon 7 skipping during pre-mRNA processing. Consequently, approximately 85–90% of SMN2 transcripts encode a truncated, rapidly degraded protein isoform (SMNΔ7), with only 10–15% producing full-length, functional SMN protein [4,6]. The SMN2 copy number, which varies from one to five or more copies in affected individuals, is the principal genetic modifier of disease severity, with higher copy numbers correlating with milder phenotypes and longer survival [14]. This genotype-phenotype relationship forms the molecular rationale for all three currently approved SMA therapies, each of which targets SMN2 to augment functional SMN protein production.

Additional genetic modifiers influence clinical severity independently of SMN2 copy number. Plastin 3 (PLS3), an actin-bundling protein, has been identified as a protective modifier in females, and NCALD (neurocalcin delta) reduction has been shown to confer neuroprotection in animal models [15]. An intronic variant within SMN2 (c.859G>C) that enhances exon 7 inclusion has been reported in a small number of mildly affected individuals and has implications for therapeutic stratification [16].

3. CLINICAL CLASSIFICATION

SMA is classified into five types (Types 0–4) based on age of symptom onset and the highest motor milestone achieved, as defined by the 2017 Consensus Statement for Standard of Care in Spinal Muscular Atrophy [17]. This functional classification system remains clinically relevant despite its acknowledged limitations in the era of presymptomatic treatment, where the natural disease trajectory is increasingly altered by early therapeutic intervention.

3.1 Type 0 (Prenatal Onset)

Type 0 represents the most severe phenotype, with disease onset detectable in utero, manifesting as reduced fetal movements. Affected neonates present at birth with profound hypotonia, facial diplegia, respiratory failure, and joint contractures. Survival beyond the first months of life is exceptional without aggressive ventilatory support, and most affected infants harbor only one SMN2 copy [17,18].

3.2 Type 1 (Werdnig–Hoffman Disease; Severe SMA)

Type 1 is the most prevalent form, accounting for approximately 45–60% of all SMA cases, with symptom onset between birth and six months of age. Affected infants demonstrate severe axial and proximal limb hypotonia, absent deep tendon reflexes, a paradoxical breathing pattern, and tongue fasciculations. The defining functional criterion is the inability to achieve independent sitting. Historically, median survival without respiratory support was less than 24 months; however, proactive respiratory and nutritional management, combined with disease-modifying therapy, have substantially extended survival and improved functional outcomes [17,19].

3.3 Type 2 (Dubowitz Disease; Intermediate SMA)

Type 2 presents between 6 and 18 months of age in infants who have achieved the ability to sit independently but cannot stand or ambulate without assistance. Progressive scoliosis, respiratory compromise, and nutritional difficulties are characteristic features. Approximately 30% of untreated individuals with Type 2 experience loss of previously acquired

motor milestones. Survival into adulthood is common, though median survival without respiratory intervention has historically been approximately 25 years, with respiratory failure representing the principal cause of death [17,20].

3.4 Type 3 (Kugelberg–Welander Disease; Mild SMA)

Type 3 encompasses individuals with onset after 18 months who achieve independent ambulation. The subtype is further subdivided into Type 3a (onset before age 3 years) and Type 3b (onset after age 3 years). Progressive proximal lower limb weakness may lead to loss of ambulation, particularly in Type 3a, though the timeline varies widely. Life expectancy is generally normal [17,21].

3.5 Type 4 (Adult-Onset SMA)

Type 4 manifests after the second decade of life with slowly progressive proximal limb weakness. Most affected individuals retain ambulation throughout life, and life expectancy is not significantly reduced. This subtype is typically associated with three or more SMN2 copies [17].

4. PATHOPHYSIOLOGY

The pathophysiological basis of SMA centers on SMN protein deficiency in motor neurons, though accumulating evidence indicates that multiple cell types and organ systems are affected. During embryonic neurogenesis, motor neurons undergo physiological apoptosis that is partially regulated by SMN-dependent pathways. In healthy mature individuals, SMN stabilizes the survival of postmitotic motor neurons through its canonical and non-canonical functions. In SMN-deficient states, this homeostatic balance is disrupted, resulting in progressive motor neuron loss.

At the molecular level, SMN deficiency impairs snRNP biogenesis, causing widespread splicing dysregulation that disproportionately affects motor neurons due to their particular dependence on precise mRNA processing for axonal maintenance [6,11]. SMN depletion also disrupts the formation of SMN-profilin complexes, leading to upregulation of Rho-associated coiled-coil kinase (ROCK)-mediated RhoA signaling, which inhibits axon outgrowth and destabilizes neuromuscular junction architecture [4,12]. These molecular deficits converge on progressive denervation of skeletal muscle fibers, with type II fiber atrophy predominating histologically alongside compensatory hypertrophy of residual type I fibers.

Beyond the motor unit, SMN deficiency affects vascular development, cardiac function, metabolic regulation, and pancreatic function in both preclinical models and human patients [13]. Intrinsic muscle pathology, independent of denervation, has also been reported, suggesting that SMA may not be exclusively a motor neuronopathy. These insights have important implications for the biological endpoints of therapy and the expected phenotypic consequences of SMN restoration initiated at different developmental stages [22].

The neuromuscular junction (NMJ) is a particularly vulnerable site in SMA. Preclinical studies demonstrate reduced terminal Schwann cell number, abnormal presynaptic terminal morphology, and impaired synaptic vesicle cycling in SMA model mice [23]. NMJ pathology may precede motor neuron cell body loss, and the degree of NMJ preservation correlates with functional recovery following SMN restoration, underscoring the importance of early therapeutic intervention before irreversible synaptic loss occurs.

5. CLINICAL PRESENTATION AND DIAGNOSIS

5.1 Clinical Features

The cardinal clinical features of SMA include symmetric proximal muscle weakness that is more pronounced in the lower limbs than the upper limbs, generalized hypotonia, areflexia, and in severe phenotypes, bulbar dysfunction manifesting as difficulties with feeding and swallowing [1,17]. Fasciculations of the tongue are a characteristic finding in Type 1 SMA and reflect active lower motor neuron denervation. Tremor of the outstretched hands (minipolymyoclonus) may be observed in milder phenotypes and is attributed to motor unit discharges from surviving neurons. Cognitive function and sensory modalities are preserved in all SMA types. Secondary musculoskeletal complications, including scoliosis, hip dislocation, and joint contractures, are prevalent in non-ambulatory patients and necessitate orthopedic surveillance [20].

Respiratory complications represent the leading cause of morbidity and mortality in SMA Types 1 and 2. Progressive respiratory muscle weakness results in reduced vital capacity, recurrent lower respiratory tract infections, sleep-disordered breathing, and, in advanced disease, chronic hypercapnic respiratory failure. Intercostal muscle weakness with relative diaphragmatic sparing produces the characteristic bell-shaped thoracic deformity in non-ambulatory patients, further compromising pulmonary mechanics [19].

5.2 Diagnostic Evaluation

The diagnosis of SMA is confirmed by molecular genetic testing. Multiplex ligation-dependent probe amplification (MLPA) or quantitative polymerase chain reaction (qPCR) for homozygous deletion of SMN1 exon 7 is the diagnostic method of choice, detecting approximately 95–98% of causative mutations [10,24]. Next-generation sequencing panels are recommended when MLPA is non-diagnostic to identify compound heterozygous or intragenic SMN1 mutations. Importantly, SMN2 copy number quantification should be performed concurrently, given its prognostic and therapeutic stratification value [14].

Electrodiagnostic studies, including nerve conduction studies (NCS) and electromyography (EMG), demonstrate a pattern of chronic and active denervation with fibrillation potentials, positive sharp waves, and large-amplitude, long-duration motor unit action potentials consistent with motor neuronopathy [25]. Compound muscle action potential (CMAP) amplitude and motor unit number estimation (MUNE) correlate with disease severity and functional status and have utility as biomarkers in clinical trials. Muscle biopsy, when performed, reveals grouped type 1 and type 2 fiber atrophy with fascicular architecture and compensatory type 1 fiber hypertrophy, reflecting chronic reinnervation attempts [25].

The advent of population-based newborn screening (NBS) programs has transformed the diagnostic paradigm. Quantitative PCR detection of SMN1 deletion from dried blood spots enables SMA identification within the first weeks of life, well before symptom onset [26]. Multiple jurisdictions, including the United States, Germany, Australia, and Taiwan, have incorporated SMA into their national NBS panels. Evidence from presymptomatic clinical trials demonstrates that treatment initiation before clinical symptom emergence yields dramatically superior outcomes compared with treatment following symptom onset, providing the principal justification for NBS expansion [27].

6. THERAPEUTIC MANAGEMENT

The therapeutic landscape for SMA has undergone transformative evolution since 2016, when nusinersen became the first disease-modifying agent to receive regulatory approval. Three mechanistically distinct therapies are currently approved, each targeting the SMN2 gene or SMN1 replacement through different molecular strategies. A comprehensive multidisciplinary management framework encompassing respiratory, nutritional, orthopedic, and rehabilitative care remains the cornerstone of supportive management across all SMA types [17,28].

6.1 Nusinersen (Spinraza®)

Nusinersen (Biogen/Ionis Pharmaceuticals) is a 2'-O-methoxyethyl-modified antisense oligonucleotide (ASO) that hybridizes to an intronic splicing silencer element (ISS-N1) within SMN2 intron 7, blocking the binding of repressive splicing factors hnRNP A1/A2 and thereby promoting exon 7 inclusion in SMN2 transcripts. This results in a dose-dependent increase in full-length SMN protein production in motor neurons and astrocytes [29]. Nusinersen is administered by intrathecal injection, with a loading regimen of four doses over two months followed by maintenance injections every four months.

The pivotal ENDEAR trial (NCT02193074), a randomized, double-blind, sham-controlled study in symptomatic Type 1 SMA infants, demonstrated that nusinersen-treated infants were significantly more likely to achieve motor milestone responses (defined as improvement in the Hammersmith Infant Neurological Examination section 2 score) compared with sham controls, with a landmark interim analysis showing a 47% relative risk reduction in death or permanent ventilation necessitating trial discontinuation [30]. The CHERISH trial confirmed significant functional improvement in Type 2/3 SMA patients [31]. Long-term follow-up data from the SHINE extension study indicate durable benefit over multiple years of treatment, with continued motor function gains in some patients [32].

Adverse effects associated with nusinersen include those attributable to the lumbar puncture procedure, including post-lumbar puncture headache, back pain, and vomiting, as well as thrombocytopenia and renal toxicity observed with prolonged administration at high cumulative doses. Emerging real-world evidence corroborates the clinical trial results and highlights the impact of the timing of treatment initiation on the magnitude of response [33].

6.2 Onasemnogene Abeparvovec (Zolgensma®)

Onasemnogene abeparvovec (Novartis Gene Therapies) is a single-administration gene replacement therapy utilizing a self-complementary AAV9 vector to deliver a codon-optimized SMN1 transgene under the control of the cytomegalovirus enhancer/chicken beta-actin (CB) promoter. Following intravenous administration, the AAV9 capsid efficiently transduces spinal motor neurons and dorsal root ganglia neurons by exploiting the natural neurotropism of this serotype, producing sustained SMN protein expression [34,35].

The pivotal STR1VE trial demonstrated statistically significant improvements in motor milestone achievement in treated Type 1 SMA infants compared with a natural history cohort, with 91% of treated infants maintaining independent respiratory function and 59% achieving the ability to sit without support, a milestone not observed in the natural history of untreated Type 1 SMA [36]. Long-term follow-up at five years confirms persistent SMN transgene expression and durable clinical benefit [37]. The therapy received FDA approval in May 2019 for patients under two years of age with SMA confirmed by genetic testing.

Key safety considerations include acute hepatotoxicity, which is managed with prophylactic corticosteroid administration; thrombotic microangiopathy, a rare but serious complication; and dorsal root ganglia toxicity observed in preclinical studies with high-dose intravenous administration [35,38]. In 2025, Novartis received approval for onasemnogene abeparvovec-brve (Itvisma®), an intrathecally administered formulation designed to circumvent systemic high-dose AAV9 exposure, with emerging clinical data demonstrating favorable safety and efficacy in older patients [39].

6.3 Risdiplam (Evrysdi®)

Risdiplam (Roche/PTC Therapeutics/SMA Foundation) is an orally bioavailable, systemically distributed small-molecule splicing modifier that stabilizes the interaction between SMN2 pre-mRNA and the U1 snRNP complex at the exon 7 5'-splice site, promoting exon 7 inclusion and increasing full-length SMN protein production in both the central nervous system and peripheral tissues [40,41]. The oral route of administration and ability to distribute into tissues beyond the CNS distinguish risdiplam from nusinersen.

The FIREFISH trial in symptomatic Type 1 SMA infants demonstrated that 29% of risdiplam-treated infants achieved independent sitting at 12 months, a rate substantially exceeding the 0% expected in the natural history of untreated Type 1 SMA [42]. The SUNFISH trial in Types 2 and 3 SMA patients showed significant improvement in the Motor Function Measure 32 (MFM32) scale score compared with placebo [43]. The RAINBOWFISH trial evaluated presymptomatic infants genetically diagnosed by NBS, demonstrating near-normal motor development in treated patients who initiated therapy prior to symptom onset [44].

Risdiplam received FDA approval in August 2020 for patients two months of age and older with SMA. Its favorable safety profile includes manageable gastrointestinal adverse effects (nausea, diarrhea) and potential ophthalmic effects requiring monitoring. The systemic bioavailability of risdiplam raises theoretical concerns regarding off-target splicing modulation in peripheral tissues, though extensive clinical and postmarketing surveillance has not identified clinically significant off-target toxicity to date [41].

6.4 Investigational and Adjunctive Therapeutic Strategies

Beyond approved therapies, several investigational agents targeting complementary pathways are under active clinical evaluation. Apitegromab (Scholar Rock), a selective myostatin inhibitor, is being evaluated in a Phase 3 trial (SAPPHIRE; NCT04186819) as an adjunct to SMN-directed therapy in non-ambulatory SMA patients, with the premise that reducing negative muscle mass regulation may enhance functional recovery independent of motor neuron preservation [45].

Branaplam (LMI070, Novartis), another small-molecule splicing modifier with structural differences from risdiplam, has demonstrated dose-dependent SMN2 exon 7 inclusion in early clinical trials, though hepatotoxicity signals have prompted dose optimization studies [46]. Second-generation nusinersen formulations with enhanced CNS distribution following intrathecal administration are in preclinical development, aiming to reduce injection burden while maintaining therapeutic CNS SMN levels. Valproic acid, a histone deacetylase inhibitor and SMN2 transcriptional activator that promotes exon 7 inclusion, has been evaluated in small clinical studies. In vitro evidence from patient-derived fibroblasts demonstrated SMN protein elevation following valproate treatment; however, adequately powered randomized controlled trials have not demonstrated consistent clinical benefit in symptomatic SMA patients, and its use is not currently recommended outside investigational settings [47].

Neuroprotective adjuncts, including acetyl-L-carnitine, which supports mitochondrial fatty acid metabolism and demonstrates neurotrophic properties in motor neurons, and growth hormone (somatotropin), which activates insulin-like growth factor-1 (IGF-1) signaling to promote muscle anabolism, have been evaluated in small pilot studies. A randomized crossover trial of growth hormone in Types 2 and 3 SMA demonstrated modest improvements in muscle strength and body composition, though sample sizes preclude definitive conclusions [48,49].

Thyrotropin-releasing hormone (TRH) has been reported to transiently increase muscle strength in Types 2 and 3 SMA patients through undefined mechanisms, though the absence of sustained benefit and the availability of disease-modifying therapies have rendered this approach largely of historical interest [50].

6.5 Combination Therapy Considerations

Given the mechanistic complementarity of available therapies, combination strategies have attracted increasing clinical and scientific attention. Preclinical data suggest additive or synergistic benefit from concurrent SMN2 splicing modulation and gene replacement, and observational data from patients transitioning between therapies or receiving combination approaches are emerging from real-world registries. The RESPOND trial (NCT04488133) specifically evaluates the addition of risdiplam in patients previously treated with nusinersen, addressing the clinically important question of whether SMN augmentation across multiple molecular modalities provides incremental functional benefit [51].

7. MULTIDISCIPLINARY AND SUPPORTIVE CARE

Disease-modifying therapy does not eliminate the need for comprehensive multidisciplinary management. Standards of care guidelines recommend regular monitoring and proactive intervention across multiple domains [17,28]. Respiratory management includes pulmonary function testing, polysomnography, cough augmentation devices, and non-invasive or invasive ventilatory support as clinically indicated. Nutritional assessment by a registered dietitian with gastroenterology input is essential, given the high prevalence of gastroesophageal reflux, swallowing dysfunction, and failure to thrive, particularly in severe SMA phenotypes. Orthopedic surveillance for scoliosis, hip dislocation, and long bone

fractures is recommended at regular intervals in non-ambulatory patients. Physical and occupational therapy optimizes residual function, prevents contractures, and facilitates adaptive equipment prescription. Communication and assistive technology assessments support quality of life in severely affected individuals. Psychosocial support, including genetic counseling, is integral to family-centered care and informed decision-making regarding therapeutic options, particularly in the context of prenatal diagnosis and NBS programs [28].

DISCUSSION

The transformation of SMA from an invariably lethal or severely disabling disorder to one amenable to meaningful and, in presymptomatic cases, near-complete functional rescue represents one of the most consequential achievements in contemporary neurological medicine. The convergence of molecular genetics, RNA biology, and viral vector technology has yielded three mechanistically distinct and complementary therapeutic platforms within a remarkably compressed timeframe, validating SMN2 as a highly tractable therapeutic target [7,52].

Several critical questions and challenges, however, remain unresolved. First, the comparative effectiveness of the three approved therapies, particularly in symptomatic patients, has not been directly evaluated in randomized controlled trials, and ongoing registries and observational studies constitute the primary evidence base for clinical decision-making in this regard. The emergence of real-world effectiveness data from population-based registries will be essential for guiding therapeutic selection, sequencing, and combination strategies [33].

Second, the optimal timing and duration of therapy remain incompletely defined. While the superiority of presymptomatic treatment over symptomatic treatment is firmly established, the extent to which late-treated patients with substantial motor neuron loss can derive sustained benefit from SMN restoration is an area of ongoing investigation. Third, the long-term durability of gene replacement therapy, particularly with respect to AAV9 transgene expression persistence, potential immune-mediated transgene silencing, and the need for re-dosing, represents an unresolved clinical question with significant implications for the lifelong management of treated patients [35,37].

The historical taxonomic evolution of SMA warrants brief reflection. The original descriptions by Werdnig and Hoffmann in the late 19th century captured what is now classified as Type 2 SMA, while the eponymous designation subsequently became attached to the more severe Type 1 phenotype. This nosological evolution, alongside the recognition that SMA encompasses a continuous clinical spectrum rather than discrete disease subtypes, underscores the importance of genotype-informed phenotypic characterization in clinical practice and research [52].

Equitable global access to approved SMA therapies presents a pressing ethical and public health challenge. The extraordinarily high acquisition costs of gene therapy, coupled with the logistical requirements of intrathecal ASO administration, create substantial access disparities across healthcare systems. Advocacy for NBS program expansion, reimbursement policy development, and the investigation of lower-cost therapeutic modalities are all essential components of a comprehensive global SMA research and policy agenda [9].

CONCLUSION

Spinal muscular atrophy has undergone a profound therapeutic revolution over the past decade, transitioning from a condition with no disease-modifying options to one for which three approved therapies, each with distinct mechanistic and pharmacological profiles, are available. The integration of universal newborn screening with presymptomatic therapeutic intervention represents the current standard-of-care paradigm most likely to maximize long-term functional outcomes for affected individuals. Nonetheless, significant scientific and clinical questions remain, including the optimization of combination strategies, long-term gene therapy durability, management of late-presenting or non-responding patients, and the development of next-generation therapeutic approaches targeting complementary biological pathways. Continued investment in SMA natural history studies, patient registries, translational research, and comparative effectiveness trials will be essential to fulfilling the extraordinary therapeutic promise that current advances represent.

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