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# Innovations in Spinal Muscular Atrophy: From Gene Therapy to Disease-Modifying Treatments

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**Abstract**

While the recent development of disease-modifying treatments for spinal muscular atrophy arose from an understanding of scheme function, the achievement of adequate motor neuron molecule availability and proprioceptive feedback has always been crucial for the preservation of function and fitness of muscle units in childhood. Progress in neuroscience research, its methods, applications, and outcomes, together with growing interest in rare diseases, has considerably improved at least the length and quality of life in subjects affected by the most severe forms of spinal muscular atrophy, and for several of those with intermediate or later-onset (or milder) forms. Therefore, what had been for a long time predominantly a familial, parent-proven strategy, aimed at the optimization of rehabilitation and caring, and at the prevention of chronic complications chronically affecting the quality of life of subjects with more severe forms of spinal muscular atrophy, has now turned into a more multidisciplinary, hospital-coordinated and longer-term vision of spinal muscular atrophy management. This paper aims to present a practical description of the tools available today for the rehabilitation and management of spinal muscular atrophy patients from a motor, orthopedic, and cardiopulmonary perspective. Disease-modifying spinal muscular atrophy treatment with real-life effects will be discussed wherever available. Spinal muscular atrophy motor function, fitness, and quality of life are highly interdependent. Hence, optimizing management in the three connected areas may help in achieving a better quality of life for the individual patient. Achieving this objective with a multidisciplinary team possibly performed in the same location with the patients might bring improvement to the patients and families involved.

**Keywords:** Spinal Muscular Atrophy Disease-Modifying Treatments, Motor Neuron Molecule Availability, Proprioceptive Feedback in Muscle Function, Childhood Muscle Unit Fitness, Advances in Neuroscience for Rare Diseases, Quality of Life Improvements in SMA, Familial Care Strategies for SMA, Rehabilitation Optimization in SMA, Chronic Complication Prevention, Multidisciplinary SMA Management, Hospital-Coordinated SMA Care, Motor Rehabilitation Tools for SMA, Orthopedic Management in SMA, Cardiopulmonary Management in SMA, Real-Life Effects of SMA Treatments, Interdependence of Motor Function and Quality of Life, SMA Multidisciplinary Teams, Integrated Patient Care Approaches, SMA Patient and Family Support, Practical SMA Management Strategies.

## 1. Introduction

Spinal muscular atrophy (SMA) is a single-gene neurodegenerative disorder predominantly affecting lower motor neurons (LMNs) and resulting in muscle weakness and atrophy. With a prevalence of

1 in 6,000 to 1 in 10,000 live births, SMA is one of the most common genetic causes of mortality in infancy and childhood. The phenotypic spectrum of SMA ranges from severe infantile-onset with rapid disease progression to asymptomatic adults. The cause of SMA is a deficiency of the SMN protein due to homozygous loss of the telomeric SMN1 gene that is replicated in different numbers in all individuals by the centromeric SMN2 gene. Diseases with a monogenic etiology are obvious candidates for gene therapy, especially if they present in early life and are severely disabling and of short duration. These criteria apply to SMA, and they have been successfully met by the treatment with intrathecal delivery of antisense oligonucleotides or adeno-associated virus vectors during early life and infancy. Antisense oligonucleotides and adeno-associated viruses have also been used for SMN1 gene transfer in older SMA patients with residual SMN2 transcription for whom the disease-modifying effect is likely to be smaller. These successful SMA gene therapy experiences have inspired further efforts to treat other genetic neuromuscular diseases with antisense oligonucleotide or adeno-associated virus delivery.

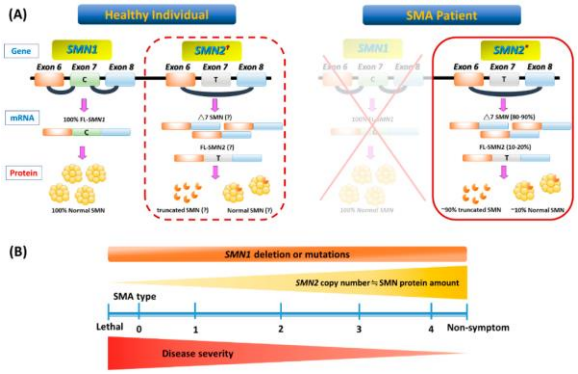


**Fig 1 : Therapies in Spinal Muscular Atrophy**

### 1.1. Overview of Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare, genetic disorder caused by a loss of motor neurons from the anterior horn of the spinal cord and is characterized by muscle weakness and atrophy. Most cases of SMA are caused by a deletion or mutation in the SMN1 gene that encodes the survival motor neuron (SMN) protein. SMN is essential for the function of all cells but is most highly concentrated in motor neurons and is believed to play a critical role in the function of the neuromuscular junction. SMA typically presents in infancy or childhood and the loss of the anterior horn cells leads to weakness and atrophy of muscle groups around the shoulders and hips, or proximal muscles, as well as neuromuscular junction-related defects affecting eye movements. The clinical spectrum of SMA ranges from infancy-lethal to adult-onset forms and can be categorized into five types, according to the age of presentation and maximum motor function achieved. Severe disease is characterized by weakness that presents before 6 months of age, with the inability to sit unsupported (type 1 SMA), and weakness that presents before 18 months of age with the inability to walk independently (type 2 SMA). Moderately severe disease is characterized by weakness that presents after 18 months of age but before 3 years with the ability to attain standing or walking (type 3 SMA) whilst milder disease presents with symptoms in late childhood to early adulthood, having the prognosis of being able to walk but do not stand or climb stairs (type 4 SMA). Interventions for SMA currently include technology and spine stabilization to support activities of daily living. No pharmacologic intervention had been available before December 2016, although disease-modifying treatment and curative therapy are approved modalities that alter the clinical trajectory of this devastating disease.

## 2. Understanding Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare, genetically driven neurodegenerative disorder that primarily impacts anterior horn motor neurons. The lifetime risk of having a child with SMA has been estimated to be approximately 1 in 11,000, with an additional 1 in 50 individuals carrying a mutation within the homozygous deletion region. SMA was first described in the mid-1800s and has undergone many descriptions and mischaracterizations since then. The phenotypic spectrum of SMA is now known to range from infants with neuronal loss and

weakness leading to early death due to respiratory failure, to adults with SMA who report vague ease of fatigue and minimal proximal muscle weakness. Major progress in our understanding of SMA has stemmed from insights gained over the fast-acting, patient-engaged gene therapy clinical trials that have brought to the forefront the previously esoteric concepts of toxic gene haploinsufficiency-driven pathology due to insufficient levels of mature SMN protein.

1. Pathophysiology of SMA

As a consequence of deletion or mutation in the SMN1 gene, SMA is caused by an SMN protein deficiency that leads to the degeneration of spinal motor neurons perikarya, and the denervation of muscle fibers and atrophy. SMA is classified based on age of onset and maximal motor function. The major subtypes of SMA are: 1) type 1 (SMA I), the most severe form of SMA that is prenatally apparent or apparent within 6 months of birth, with an inability to sit, poor head control, and muscle wasting; 2) type 2 (SMA II), a form of SMA that is apparent between 6-12 months of age, with an inability to stand, and proximal muscle weakness; 3) type 3 (SMA III), a form of SMA that is apparent after 12 months of age, with the ability to sit, proximal muscle weakness, and often loss of ambulation during the first to third decades of life; and 4) type 4 (SMA IV), a rare adult-onset form of SMA that presents in the late 20s or early 30s, primarily affecting proximal muscle groups. SMA is also classified as prenatal or early-onset (SMA I and SMA II), intermediate-onset (SMA III), or adult-onset (SMA IV), based on age of onset.

**Equation 1 : Motor Function Preservation Model:** $M_p(t) = M_0 \times e^{-\mu(G_e+P_d)}$

$M_p(t)$ = Motor function at time $t$

$M_0$ = Baseline motor function

$\mu$ = Degeneration rate constant

$G_e$ = Gene expression deficiency (e.g., SMN protein levels)

$P_d$ = Progressive disease burden

**2.1. Pathophysiology of SMA**

SMA is characterized by the loss of motor neurons from the anterior horn of the spinal cord, which results in progressive wasting of skeletal muscle. Motor neurons, the largest type of neuron in human beings, control the movement of muscles along with the related muscle fibers. Due to the loss of functional spinal motor neurons, SMA is classified as a lower motor neuron disorder with a clear upper motor neuron deficit. A closer examination of the embryonic development of motor neurons reveals susceptibility to programmed cell death. Thus, SMA is primarily due to the insufficient support of motor neurons by surrounding skeletal muscle and lower motor neuron neuromuscular junction formation until the end of development into early life. Conversely, the majority of skeletal muscle atrophy and weakness observed during SMA disease onset is a consequence of denervation-reinervation cycles surrounding a small number of surviving motor neurons. Interestingly, despite the severe loss of spinal motor neurons, the surrounding central nervous system is relatively spared. It has been proposed that selective neuroinflammation may play a role in the neurological sparing of SMA. Microglial and blood-brain barrier dysfunction has also been implicated in neuroinflammatory differentiation towards SMA. Whether or not neuro infiltrative inflammatory T cells invade the brain in any neuronal injury model remains to be explored.

**2.2. Genetic Basis of SMA**

Spinal muscular atrophy (SMA) was discovered more than a century ago and has emerged as one of the most highly researched and medically advanced therapeutic areas in Pediatric Neurology, with the most recent outing of innovative therapies shifting its fate. Affected children with type I SMA now have significant chances for long-term survival thanks to recently discovered novel disease-modifying therapies disrupting its natural history. Although the first assumptions pointed toward the loss of motor neurons due to indiscriminate etiopathogenic mechanisms, the real SMA pathophysiology is incisive. The classic impairment

is located in the anterior horn of the spinal cord, where motoneurons undergo apoptosis. Mutations in the SMN1 gene ensured the focus of its research within the Developmental Biology area. Nowadays, SMA stands for a group of autosomal recessive genetic disorders affecting the motor neurons rich in the spinal cord anterior horn, leading to muscle weakness and atrophy. In the past decades, it became clear that the loss of SMN1 is counterbalanced by the presence of the SMN2 copy and by small molecular activators.

In 1995, groundbreaking research led to the inference that SMA stems from mutations in an autosomal recessive gene at 5q13, which was still so far untraced. In the last two decades, dozens of mutant genes related to various types of SMA more or less close to the classical description were discovered. Nowadays, although 80% of patients carrying a classic SMA phenotype have a homozygous deletion or mutation in the Survival of Motoneuron 1 (SMN1) gene at 5q13, twenty-eight genes have been identified. This review talks about the most frequent ones, and clinical practice must consider searching for those also as a cause of an SMA-like phenotype.

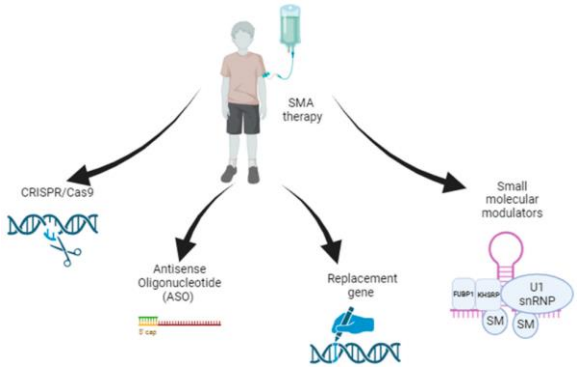


**Fig 2 : Spinal Muscular Atrophy**

### 3. Historical Perspective

1. Early Research and Discoveries

The first report with a description of a child with spinal muscular atrophy (SMA) was made in 1891, although the first historical evidence of disease naming was proposed in 1893. Later on, a description of the phenotype of affected children was made. It was only in 1956 that the hypothetical cause of death of these children was proposed - a loss of cortical inhibitory influences on spinal motor neurons - providing animal models that confirmed the leading role of anterior horn alteration in the disease development. A critical breakthrough in SMA research was related to the establishment of a linkage between SMA and the long arm of chromosome 5 in the early 1990s. Soon after, deletion of the survival motor neuron (SMN) 1 gene on chromosome 5q and its correlation with the SMA type and disease pathway were reported. Since the short-life mice model containing an SMN deletion was developed, there has been intensive work to establish the role of SMN in the neuromuscular junction, sensory interneurons, or motor neurons and to relate SMN with the presence of other resulting genes or other neuron-related pathways.

2. Evolution of Treatment Approaches

Because of the improved overall prognosis of patients with SMA, starting from the 1990s, a wide range of alternative therapeutic approaches have been developed. In the first place were new surgical techniques, leading to better scoliosis correction and spinal stability, a growth of life quality, and the prevention of cardiorespiratory failure that allowed the improvement of life expectancy, with about 80 % of affected patients thriving into adulthood. Intensive training of limb muscles with orthopedic and functional rehabilitation, associated with extensive supportive treatment during the child's development and the establishment of multidisciplinary teams to treat SMA, allowed those patients to lead a normal active life, depending on the severity of their disability and the acceptance of the family. During adult life, the reduction of kyphoscoliosis, especially in severely disabled patients, was achieved by resorting to night bracing. Limitation of increasing orthopedic deformities can also be done by respiratory physiotherapy or by using intrathecal baclofen infusion in patients with nocturnal respiratory failure and significant spasticity.

### 3.1. Early Research and Discoveries

In 1896, a patient was described with progressive weakness of lower limbs and atrophy of the muscles of the foot, and subsequently, children with progressive muscular atrophy and weakness associated with spinal cord changes were identified, giving it the name "spinal muscular atrophy". The clinicopathological studies suggested that motor neurons were involved, but they were not conclusive. Then in 1940, it was proposed that the disease was due to a group of diseases with degenerating anterior horn cell involvement, making it heterogeneous and non-familial. As the understanding of muscular dystrophies deepened, the links between SMA and muscular dystrophy associated with myopathy became clearer. The clinical identification of multiple cases revealed families with different clinical presentations. The clinical resemblances associated with mean age at onset and rate of progression led to a division of the disease into three or four types, although the latter number has varied considerably over the years.

The use of neurosurgical motor cortex stimulation plus the clinical findings, the denervation potentials on electromyography, and the denervation/innervation muscle neurogenic biopsy findings were exhaustively sufficient to establish the diagnosis during the patient's life. Studies that allowed the classification of SMA into proximal or distal, hereditary or acquired were fundamental for the classification of the lenses. In addition, the exclusion of diseases that may mimic SMA, such as botulism, acute poliomyelitis, or multiple acyl-CoA dehydrogenase deficiency – each has its embryological background and developmental problems with higher and lower birth rates – was determined. The natural history data on SMA development from the initial ages to late stages of development that were compiled for different types of SMA led the study to hope for therapeutic solutions that would attempt to alter the disease's natural history, maintaining motor function for longer and thus being crucial for future therapeutic approaches.

### 3.2. Evolution of Treatment Approaches

Exploring multiple avenues of treatment over the past century, SMA researchers have experimented with vitamin E supplementation, anti-inflammatory medications, and respiratory and nutritional support as potentially efficacious therapy options, albeit with limited to no clinical benefits. The hypothesis that SMA was a neurodegenerative disorder was exacerbated by the search for treatments for similar neurodegenerative disorders during the early 2000s. A drug for the treatment of ALS was subsequently used in SMA trials for infants, children, and adults but demonstrated no clinical efficacy. Over about 70 years, researchers utilized an inappropriate exploration of potential treatments, resulting in a prevalence of ineffective treatment for patients providing no clinical benefit. This evolved way too slowly for desperate patients, families, and advocates suffering from this ravenous disease. However, SMA highlighted for patients that a medical condition need not be the target of a proven clinical treatment to qualify for reimbursement over significant downtime through insurance or Medicaid.

In the late 1990s, preclinical data and a paradigm shift with the identification of the SCS gene led to a race of several research teams stemming from the same foundational discovery. This key biological fingerprint enabled a dramatic acceleration of clinical translation through drug development for targeted gene modification to initiate and publish common findings supporting SMA gene therapy in children and adults. Subsequently, the first large animal preclinical data described early treatment in SMA infants – not only in safety but from an efficacy perspective in non-human primates – launched multiple Phase 1/2 trials globally within 36 months.

## 4. Gene Therapy Innovations

1. Introduction to Gene Therapy

Gene therapy, which relies on the replacement of mutated genes with genes that encode the normal protein, has always been the holy grail of treatment for infants and children with spinal muscular atrophy (SMA). All Normal Function Studies had previously shown that trans-complementation of the SMN1 gene was able to reverse motor neuron degeneration and muscle atrophy in SMA models. The initial attempts using clinical gene therapy for SMA were scattered and with many failures. Innovative preclinical studies deciphered the following issues to be successful when using adeno-associated viral vectors for gene therapy in SMA: the choice of the vector serotype, the timing of the administration, the choice of the SMA model in which the gene therapy treatment was tested, the quantity of the administered vector particles, and the treatment combinations. The translation of these innovative discoveries into clinics occurred with the development of Zolgensma as a clinical product, designed for the treatment of SMA, which achieved the first successful use of gene therapy on patients with SMA.

2. Zolgensma: A Breakthrough Treatment

Zolgensma is the first gene therapy that was approved and marketed for the treatment of patients with SMA. Zolgensma is a one-time intravenous infusion of a high dosage of the AAV serotype 9 vector carrying a cDNA of the human SMN1 gene. The unprecedented efficacy and safety profile of Zolgensma in symptomatic SMA babies and toddlers who were enrolled in clinical trials led to its approval by the United States Food and Drug Administration in May 2020, followed by the European Medicines Agency in 2021 and 2022. However, Zolgensma has entertained many challenges that have limited its more extended development. The first challenge has included the short-term clinical effects of Zolgensma when it is used in symptomatic patients with SMA types 1 and 2. The second challenge has been the requirement of a mention of the low patient population, which would entail the single treatment of Zolgensma to these smaller SMA patients. The third challenge is the cost of Zolgensma and the health system's difficulties in reimbursing its high treatment cost. The last challenge is the clear risk of the multiple SMA parents couples' decisions who are inquiring about future pregnancies.

### 4.1. Introduction to Gene Therapy

Gene Therapy innovations in the 21st century heralded new avenues for genetic conditions. Spinal muscular atrophy (SMA) is a monogenic neurodegenerative condition with motoneuron loss. Almost all children with Type 1 SMA die from respiratory failure by 2 years of age when left untreated with supportive care. Gene therapy seeks to achieve a cure for SMA by directly targeting the underlying cause of the condition – mutations in the gene coding for the survival motor neuron (SMN) protein. SMA patients are genetically deficient in SMN, leading to congenital weakness, muscle wasting, and death from the sequela of neuromuscular respiratory failure. While traditional pharmacological treatments inhibit the downstream effects of genetic mutations, gene therapies address the root of the problem by introducing a functional copy of the faulty gene using viral vectors to deliver the transgene. These therapies can also introduce modified or chimeric genes using technology to edit the faulty genes in place. In addition to offering possible cures for conditions without currently available treatments, these innovative approaches also offer the promise of lasting treatment effects with high compliance as a single one-off treatment, rather than the daily lifelong doses required for traditional approaches. While gene therapy and genetic editing approaches have been studied for degenerative diseases of other organs, the highly specialized nature of the central nervous system (CNS) presents unique challenges. The brain is protected from circulating drugs by the blood-brain barrier (BBB). The motor unit – motoneuron, neuromuscular junction, and muscle – is innervated by large myelinated axons originating in the spinal cord. In SMA, loss of motoneuron survival leads to secondary denervation of the synaptic junction at

the muscle belly and, subsequently, muscle wasting. Our understanding of how to target gene therapies to these specific cells in the CNS and how to achieve efficient transgene uptake to enable lasting cellular correction is still in its infancy compared with the use of small molecule therapeutics and other macromolecules.

### 4.2. Zolgensma: A Breakthrough Treatment

On May 24, 2019, the FDA approved AAV9-scm-smn with the trade name Zolgensma as a breakthrough treatment for Spinal Muscular Atrophy. SMA is clinically classified into four types based on age of onset and clinical severity. The majority of patients have either later-onset Type 2 or Type 3 SMA which is associated with a steadier, albeit progressively debilitating and paralyzing disease trajectory. However, Type 1 SMA with onset of symptoms before 6 months of age is the most severe infantile form associated with significant morbidity and mortality. Symptoms include infantile-onset weakness, hypotonia, marked weakness of the bulbar muscles, and breathing issues. Without early intervention, approximately 50% of patients succumb to respiratory failure by 20 months, and up to 90% by 2 years of age. The added social burden placed on families, caregivers, and healthcare workers associated with the clinical course SMA is substantial. Therefore, consideration for premature Gene Therapy implementation of the most progressive form of the disease is probably justifiable as Zolgensma has demonstrated safety and efficacy in managing Type 1 patients under 2 years of age at the time of gene delivery.

Zolgensma is delivered as a one-time intravenous infusion through a peripheral vein to target the liver and CNS simultaneously. Once transduced, neuron cells should express SMN protein in therapeutic amounts for the patient's lifespan, theoretically eliminating the need for future additional doses. Zolgensma is engineered as a "self-limiting" gene vector that preferentially infects neurons and subsequently lowers the vector while producing full-length SMN transgenes carrying a potent synthetic enhancer and promoter. At the cellular and molecular level, Zolgensma should initially rescue pre-existing vulnerable and dying motor neurons due to low copies of SMN and after weeks to months lead to increased generalized expression of SMN in spinal, bulbar, and possibly cortical motor neurons and oligodendrocytes potentially converting Type 1 SMA to Type 2/3 disease decreasing morbidity and/or mortality.

### 4.3. Challenges in Gene Therapy Implementation

While there are significant advantages to gene therapy, specifically an FDA-approved solution that treats the underlying genetic defect in most patients, only some regions of the world currently have access to these lifesaving treatments, and access to these programs continues to face challenges. The complexity and high costs involved in gene therapy development have led to significant disparities in the availability and distribution of these innovations. Additionally, ethical considerations as to whether gene therapy can cure a disease or if it simply changes the trajectory of the disease have led to uncertainty in potential availability for patients. Access to gene therapy relies heavily on inter-institutional support. Specialists at referring centers are responsible for making patients aware of the possibility of gene therapy, directing those patients to a referral center, and seeing patients for follow-up visits near their homes after treatment. Support from referral centers and multi-institution clinics is essential.

Gene therapy requires novel delivery methods to introduce the gene into cells and upregulate SMN protein expression. Adeno-associated viruses are one such delivery vehicle used by several ongoing clinical trials, and there are several advantages to using these as a gene delivery vehicle when compared to other viral vectors. They are non-pathogenic and nurture a broad tissue tropism, providing efficient transduction in multiple tissues. They are a closed and non-replicating ssDNA viral vector that maintains episomal status, allowing for

long-term gene expression. However, there are inherent limitations to using these. Compared to other viral vectors, this method is less efficient and has issues with transduction in cell types such as hepatocytes and neurons. Additionally, the availability of serotypes and flexible titered vectors on a large scale is still a concern. Furthermore, the need to inject a large volume of this delivery method is a practical concern with rare, infantile SMA types.

## 5. Disease-Modifying Treatments

In 2016, the first disease-modifying treatment for SMA was approved. This treatment is an antisense oligonucleotide that alters SMN2 splicing to increase full-length SMN2 mRNA production while decreasing the production of the truncated form that does not code for protein. Because SMN2 is expressed in virtually all cells, not just motor neurons, the predicted mechanism of action differs from that of other SMA treatments. Despite improving motor milestones in clinical trials, most patients assigned to receive this treatment still had some degree of disability. In SMA animal models, restoration of supraphysiological SMN expression during fetal development was needed to prevent nerve cell death and induce long-term motor function recovery. Therefore, near-future clinical trials testing combinations of therapies that target different pathways in SMA patients to achieve improved clinical status are warranted. Another treatment is an oral small-molecule splicing modulator of SMN2. In a trial, infants with SMA type 1 had improvement in survival and motor function from treatment with this modulator compared with historical controls.

Although the marketing approval of this treatment was a groundbreaking breakthrough for the treatment of SMA, there are still issues that remain. The greatest unmet need for SMA patients is the need for improvement in long-term clinical status and reduced disability. None of the Phase 3 trials performed with this treatment reported full resolution of SMA after treatment. Although motor milestone improvement may provide detectable clinical benefit, relatively few patients reach stage 3 or 4 on the relevant assessments. Moreover, the majority of infants with SMA type 2 or older children and adults with SMA are unable to achieve stage 3 or higher in these tests.

### 5.1. Nusinersen: Mechanism of Action

In total, there are nine exons in the SMN1 gene but they are spliced together differently, resulting in the inclusion or exclusion of a specific segment of exon 7, which is critical for the function of SMN protein. The full-length transcript that includes all the coding exons of SMN1 is designated as SMN1-fl; the two alternative splice forms are designated as SMN1-Δ7 and SMN1-Δ8. However, mutations in SMA are not primarily due to mutations in the SMN1 gene but are instead due to deletions or mutations of the SMN1 gene on chromosome 5. This phenomenon occurs because, similar to SMN1, there is a homolog gene (on chromosome 5) designated as SMN2 that contains eight introns and nine exons.

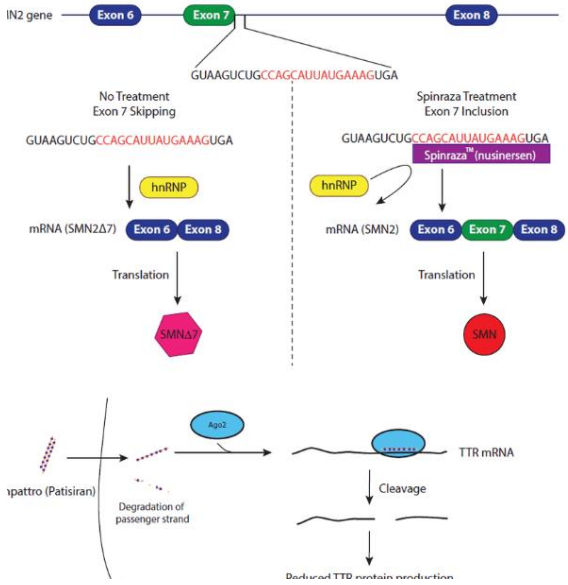


**Fig 3 : Mechanism of approved therapeutics.**

In contrast to SMN1, the SMN2 gene undergoes alternative splicing and its major translation product is a short transcript (designated as SMN2-Δ7) that lacks a critical part of the protein, resulting in a non-functional or poorly functional SMN protein.

Therefore, while SMN1 is responsible for the production of full-length transcripts of the protein SMN, the SMN2 gene is involved in low levels of production of the truncated SMN protein. Nevertheless, and although it is not sufficient to protect neurons from SMA, the SMN protein produced by SMN2 is important for the maintenance of the motor neurons, specifically the motor neurons of the ventral horns of the spinal cord, which are critical to regulating skeletal muscle function.

Nusinersen is an antisense oligonucleotide that is designed to induce, by base-pairing, the exclusion of the SMN2-Δ7 alternative splicing from the major translation product of SMN2. The exclusion of SMN2-Δ7 alternative splicing of the major SMN2 translation product has a two-fold benefit: increasing levels of the full-length SMN2 protein (designated as SMN2-fl), and decreasing levels of the short non-functional truncated SMA protein that is capable of exerting toxic gain-of-function effects although at low concentrations. Thus, the mechanism of action of Nusinersen consists of increasing levels of the full-length and functional SMN protein SMN2-fl while decreasing the levels of the truncated non-functional and toxic SMA protein SMN2-Δ7.

**Equation 2 : Gene Therapy Efficacy Score:**

$$G_t = \frac{S_e \times G_u}{T_r}$$

*where:*

- $G_t$ = Gene therapy efficacy score
- $S_e$ = SMN protein expression level post-treatment
- $G_u$ = Gene uptake efficiency
- $T_r$ = Time to therapeutic response

### 5.2. Risdiplam: A New Oral Treatment

Risdiplam is a new small molecule designed for mild, moderate, and severe SMA types, from newborns to adults. The compound was created to modify the splicing events of the SMN2 gene and allow it to produce sufficient amounts of functional SMN protein to address the deficiency in SMA patients. As with Nusinersen, the commercial interest in a product that is easy to deliver and approve worldwide is obvious. No other small molecule has reached SMA clinical development so far, and the development of oral narrow-spectrum splicing modifiers had at one point in time been suggested as a way to avoid any adverse effects associated with the use of broad-spectrum compounds. Risdiplam, a derivative of one of these early drugs, has moved into large trials with thousands of patients more quickly than feared since it was shown to be safe in adults and mostly effective in infants with the worst clinical presentations. In infants and young children, the duration of effect is expected to be maximal as SMN2 exon 7 skipping and the subsequent production of SMN protein occurs later at the presymptomatic stage and declines as muscle damage occurs. A phase 2/3 study in older children and adults with SMA types 2 and 3 is underway, utilizing an early and low-standardized assessment of SMA.

The non-invasive route and self-administration through the mouth would certainly favor high compliance while dosing 3 to 4 times a day is laborious – to date, doses higher than 3 mg/day have been employed. The clinical effect should be similar to that of nusinersen, allowing some patients with SMA type 1 to exceed their predicted lifespan, although questions remain about the safety and dosing in infants with type 1 who are at risk of death from respiratory complications, especially as the early studies on the rescue effects of the drug gave higher doses. A complication of chronic daily dosing with a small molecule could be the development of immune tolerance or resistance.

### 5.3. Comparative Efficacy of Disease-Modifying Treatments

In the years following the approval of nusinersen by the FDA in 2016, there were several infants initiating treatment with nusinersen that subsequently developed symptoms of SMA and

commenced treatment with risdiplam. The observed limited efficacy of nusinersen upon initiation in SMA-affected patients led to a widespread desire to evaluate the comparative efficacy of the route of administration and dosing regimens in these therapeutics. With the more recent approvals of risdiplam and onasemnogene abeparvovec, several questions concerning the use of these different degenerative modifiers are now possible. Since SMA disease modifiers are an evolving field, with emerging data at any given time, it is difficult to provide an accurate up-to-date understanding of the comparative efficacy of available interventional drugs and how future drugs will fit into the current treatment paradigm.

In the initial study of nusinersen in the type 1 infant cohort 12 months of age or older, 22% of children failed to achieve motor milestones. In a similar age cohort of type 2 infants treated with risdiplam, there were only 4% of babies who did not achieve motor milestones. Therefore, children receiving risdiplam or nusinersen have a different clinical course that varies by SMA phenotype (type I or type II). Onasemnogene abeparvovec resulted in a higher rate of developmental milestones. However, as the SMA population ages, it will be more difficult to ascertain refined neurodevelopmental findings between naturally occurring disease course and active treatment; the key remaining question will be whether combination or multi-drug treatment will synergistically improve outcomes from degenerate therapy alone.

## 6. Clinical Trials and Research Advances

SMA is a rapidly advancing field, with numerous companies working on SMA therapeutics. Companies focused on gene therapies include a company developing an AAV9-delivered SMN1 gene therapy to treat infancy-onset SMA Type II-III; another company, which is working on an AAV-based gene therapy for SMA Type II; a third company, which has a small molecule in development for SMA Type I, and a fourth company, which is working to develop a proprietary glycoprotein technology for IV-delivered AAV gene therapies.

Another company, is developing a gene therapy product for SMA Type I, a different company, is using RNA-based technology to develop a therapeutic for SMA Type III, another company, is developing a small molecule for SMA Type I, yet another company, which is developing an AAV-delivered SMN1 gene therapy for SMA Type III, a company, which is developing an SME that is also a disease-modifying therapy for SMA Type I, another company, which is working on a gene therapy model for SMA Type III, and a final company, which is working on a 5-HT4 agonist for SMA Type I. These companies are only a small part of a growing ecosystem developing SMA therapies.

Ongoing trials in SMA Type I focus on early initiation of treatment and combination therapies. Preliminary research hints that using multiple disease-modifying drugs together may show increased efficacy compared to using drugs individually. Research studies are increasing in number, focusing on optimal drug combinations, demographic differences in treatment response, and gene-editing therapies. Recent breakthroughs in understanding SMN function and the discovery of multiple pathways downstream of SMN via SMN's interactome and post-translational modifications suggest that we may see newly developed SMA therapies targeting previously unexplored mechanisms in the future.

### 6.1. Ongoing Clinical Trials

The development of novel therapeutic modalities to restore motor function to SMA patients continues, with forms of direct and/or disease-modifying strategies in various stages of clinical and preclinical testing. Three SMA-targeting gene therapies have reached clinical testing: the lentiviral-based approach with a single administration to lead SMA type 1 patients into a correcting survival motor neuron 1/2 pre-mRNA splicing ecosystem; the 1:1 ratio AAV9-CB-1 and

AAV9-CB-2 alleles in patients and primate tissues in a corrected RNA context.

The AAV-MAP1B gene therapy for locomotor development and the AAV-GH gene therapy for SMA type 2 with a correction window of presymptomatic SMA type 1 patients but late symptomatic SMA type 2 patients for spine function and growth hormone deficiency responsible for lethargy, poor weight, and body mass index gain and sleep disturbance with long-term tattooing-dependent autophagy upregulation, also reached clinical testing with an initial small cohort in the clinical trial study. New formulations relying on proteoglycan positive charge-based inotrope-delivery of positively charged extended half-life combined ganglioside or highly-potent retinoic derivative type 1/2 allele-mRNA therapies for SMA-type 1 and 2 repurposing indications have effectively ameliorated SMA type 1 mouse and monkey premotor development and longevity, and have begun clinical testing with a single basal ganglia cerebral administration in SMA type 1 child.

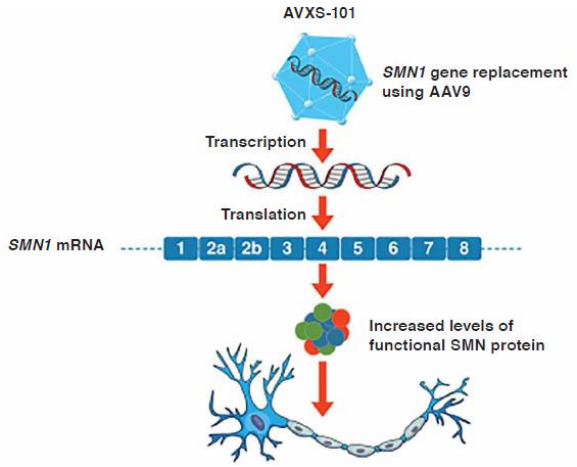


**Fig 4 : Gene Therapy for Spinal Muscular Atrophy**

### 6.2. Future Directions in SMA Research

Having established therapeutic options that significantly improve the outcomes of many patients with SMA, the field now shifts to studying several key questions. First and foremost are questions regarding the long-term impact of treatments that patients have only been receiving for a few years. Patient and caregiver-reported outcome measures among treated children, such as reduced caregiver burden and improved quality of life, are only part of this story. Some therapeutic effects, such as improving muscle function and replacing lost motor neurons, are irreversible. Patients still not walking or using their hands, or who still have feeding tubes, are unlikely to ever have this function return. Are there changes to expect in function in the coming decades? Will effects continue to be observed on motor neuron survival? How will patients fare neurologically as they age? Historically in SMA, late-in-life complications have included kyphoscoliosis, hip dislocations, and respiratory insufficiency. Will, and how, will these complications be more or less pronounced in treated individuals? What are the consequences of early treatment for those individuals with the most advanced and previously untreated disease? Presently, therapeutic trials are underway to collect information on some of the above questions. These trials aim to answer both questions of effect and safety by exploring the need for dose adjustments, how to best collaborate therapeutic strategies, and how to best follow treated individuals into adulthood.

Beyond the need for long-term information regarding existing treatments, a series of related questions directly inquire into new ones. SMA commonly presents in infant form, but milder forms of disease inexorably lead to symptoms at later points in development. While recognized, these usually remain underdiagnosed and underreported. With disease age, the involvement of the classical signs of SMA diminishes, only to be replaced with an unusual asymmetrical distribution of symptoms, including hyperreflexia of the head, a hearing disturbance, and mild learning disabilities. First-degree relatives and other non-separated individuals are likely to share low SMN levels but present with very mild disease. This offers a unique opportunity to study SMN levels in non-symptomatic individuals throughout life. Further, the discovery

of modifiers of disease, and the identification of experimental modifiers whose mechanism of action may defend vulnerable cells, also represent novel directions of research developments. Microglial cells, our resident immune cells, T-cells, and other factors in the inflammatory response have all been shown to play an important role in the shape of the SMA phenotype.

## 7. Patient Perspectives and Quality of Life

As the understanding of SMA, its nature, and its treatment increases, the perspective of the patients is gaining attention. Outcomes reported by patients or caregivers have grown to become a key consideration for drug development and regulatory decision-making. Clinical trials are normally designed around physical events that monitor disease progression, like motor and pulmonary functions, or consequences, like the onset of need for feeding or ventilatory support. While these milestones are important and require careful monitoring, they are seen as only a part of the story that may be far removed from the lived experience of the patients or their parents. Quantifying the effects of treatment on previously delayed or diminished functions in SMA patients may still not significantly impact the quality of life. For a congenital condition, in which most patients are bio-psycho-social adults trapped in bodies with loss of function and decay under the burden of neuromuscular symptoms, eventually, feeling like but not being a copy of their families and peers, it is difficult to understand the notion of living your best life. Existing ratings for SMA, like the quality of life indicator, were validated in prototypes for Adult SMA or Child SMA one or two decades ago, and have not been developed further to assess longitudinal changes in quality of life or treatment-specific kinds of impact.

Providing relatable experiences from individuals directly impacted by the various forms of SMA, through vlogs and videos, is becoming more common. Some commonly observed themes addressed in many of these viewer-voted videos are the burden of SMA and the impact on mental well-being. Considering the delay in neurodevelopmental milestones, practical help with extensive therapy regimens, accessibility issues, and the perceived burden on families, it is natural to assume that psychosocial concerns are very present at the forefront of the minds of both patients and families.

### 7.1. Impact of Treatments on Daily Life

Few untreated patients live beyond the first decade while most will have symptomatic disease by the second or third decade of life. SMA type 1 infantile-onset is marked by a longer survival now that treatments are available. In addition, older patients are pursuing therapy and perhaps a subset of these children may delay disease progression. Thus, qualitative assessments of the quality of life and experiences of those afflicted by SMA are greatly enriched by their parents.

Patient feedback regarding treatment experiences related to infantile-onset SMA type 1 disease changes over time. In the first year of life, there is uncertainty and chaos surrounding the diagnosis due to conflicting opinions on treatment options. Until therapy is started, deterioration continues with unrelenting disease symptoms. During the second year, with early treatment, there is optimism that treatment will improve the child's overall function. Once functional improvements plateau, allowing time to appreciate changes in milestones such as sitting or walking are typically small and there is variability among parents. Now there is a sense of having spoiled the child in a way because parents witness a child seeming to undergo a severe illness to receive the benefits of lifelong therapy with only small milestones in return. Consistent with this experience, some parents wish that they had started treatment sooner. By the end of the second year, caregivers' perceptions of certain levels of being at the peak become more tempered. Definitive conclusions are difficult to ascertain as most children remain in therapy with waning hopes. As new strategies are developed, the parent experience continues to evolve.

### 7.2. Psychosocial Considerations

There is no doubt that the rapid development of effective SMA treatments has had an incredibly positive impact on the quality of life of people with SMA and their families. Each of the successful drugs targets a different point, from restoration of SMN function to disease modification, and as such, each has a different mechanism of action, provides a different benefit set, and addresses a different group of patients. Each of the drugs currently in use is being delivered to patients who are spread around the world, generally under a CMS and within clinical use guidelines. These new drugs have become an integral part of SMA management.

Familial ACS is a well-described difficulty for families trying to manage their children with SMA. Some families, especially in regions of the world without easy access to the new drugs, have opted out of the new drugs because of their personal beliefs. The reasons for avoiding drug use are not entirely clear, but potential side effects, especially those of the gene therapy, which, at least initially, were significant have been described. Rarely, years of silence about the future of SMA treatment have generated feelings of being torn about using the new therapies, especially during the first months.

Family dynamics can be quite complicated and the perceptions and feelings of different family members are likely not to be homogeneous. To date, considerable discussion has already been had about the new therapies, and family support systems are understandably under some tension. Family involvement in the early phases of SMA treatment is likely to be critical in overcoming any sense of confusion or malaise. Taking the initial step as a family together will likely be one of the most important components of a positive experience going forward.

## 8. Regulatory and Ethical Considerations

At present, few gene replacement therapies for recessive disorders rely on exogenous copies of the mutated gene. Thus far, none has been approved for nonsense-mediated decay disorders such as SMA, so many ethical questions surrounding such use remain unexplored. The first step in therapeutic development is preclinical trials involving animal testing. Once researchers believe they have sufficient safety data, they can apply it to begin human trials.

Due to the extreme rarity of SMA, conducting pivotal trials to prove the safety and efficacy required to file for approval is especially challenging. Consequently, approval for new treatments relies on smaller-scale, shorter-duration studies, often with indirect measures. Accelerated approval pathways exist for such cases, allowing sponsors to show efficacy on a surrogate endpoint that will be further validated in confirmatory studies after approval. Additionally, for rare diseases, guidelines on expanded access programs allow patients to access unapproved therapies if no other options are available. Sponsors can also file a request for Breakthrough Therapy Designation if the new therapy shows preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies. Due to the successes of certain therapies, other companies are following suit with studies of their gene therapies.

### 8.1. Approval Processes for New Treatments

The development and approval of new therapies are subjected to extensive regulatory oversight at national and international levels. Historically, the process has included a series of preclinical and clinical studies progressing from small cohorts of healthy volunteers to larger cohorts of affected individuals, with data on safety and levels of pharmaceutical activity before moving into cohorts of affected individuals monitoring for efficacy and safety. At each stage, regulatory agencies review the data and approve the transition to the next stage. However, for ultra-rare diseases, there are relatively few affected individuals and the processes have thus far not been fully suffused with flexibility. The demand from patients and advocacy groups, often persisting for years as new treatment developments

struggle for funding, is nevertheless immense. This was seen most readily with the recent approval of gene-modifying therapies for SMA: both risk-benefit assessments as well as the need for follow-up data after approval need to consider the urgency for patients and families, the potential benefit for the risk, the maturity of the evolving science, and the proven efficacy and safety risk profile of similar successful approaches in other diseases. Further, the approval agencies must have the ability to require the collection of additional data in post-approval studies or to reverse their recommendations should the treatments fail to demonstrate long-term veracity and efficacy.

For SMA, the compelling need for safe, efficacious therapies in affected patients, supportive data from rapidly accumulated natural history studies, the gradual approval of similar approaches for other genetic diseases along with pre-marketing evidence for potential safety mitigations allowed SMA gene replacement therapies to progress relatively more rapidly into the clinic. Early results from clinical studies revealed safety and efficacy, spurring approval decisions and initial accessibility in some countries from the relevant agencies.

### 8.2. Ethical Implications of Gene Therapy

The approval of gene replacement therapy for children with SMA has stimulated interest amongst stakeholders not only in the safety and efficacy of treatment but also in ethical considerations of the provision of this treatment. Decisions have been made that affect the timing of treatment, the type of treatment provided, the plan for follow-up, and the provision of other healthcare services, as well as the governance of such decisions. Several groups have been forming guidance documents and frameworks, aimed at supporting decision-making in practice, which work to moderate the type and quality of data that should be submitted for approval before provision in clinical practice. By providing access to novel and innovative treatments with limited data sets to certain patients with diseases that are currently not treatable, these agencies are part of a careful balancing act between equitable access and exercising caution. In many countries and formulations, this access is relayed through the concept of Compassionate Use, the ability for sick individuals to request access to experimental therapies in the context of a clinical trial or before official marketing authorization.

As the therapeutic landscape for SMA continues to evolve rapidly with several innovative interventions becoming available shortly, the need for a comprehensive and accessible governance document will become increasingly pressing. If gene therapy is to become a part of the repertoire of treatments for SMA in clinical practice, the initiation of the provision of such treatment will need to be adaptable, equitable, easy to follow without requiring ethical deliberation in every case, clinically appropriate, and safe.

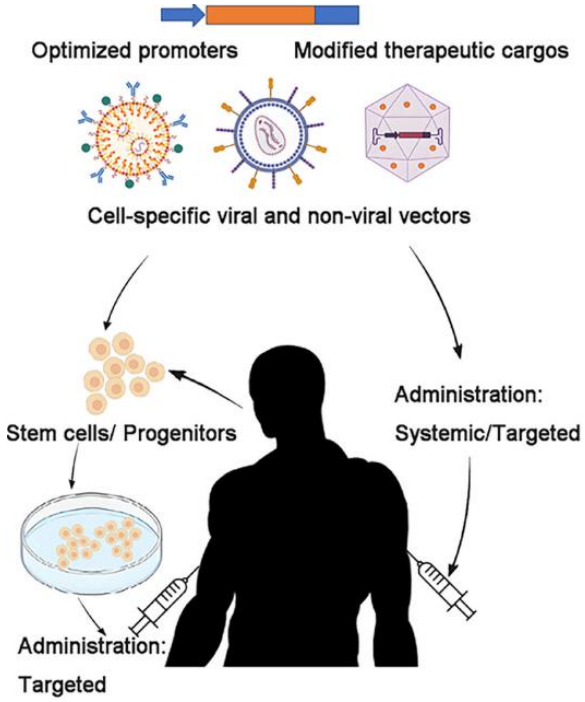


**Fig 5 : Gene therapy for genetic diseases**

### 9. Economic Aspects of SMA Treatments

New strategies of SMA treatment promise increased efficacy but at an extreme cost per treatment. The longest-standing and most performance-changing are FDA-approved disease-modifying agents. The future may tell us whether other more recently filed products increase performance or are considered

disease-modifying, primarily indicating maintenance treatment. Various treatments, but especially the earlier FDA-approved treatments, will have cost and efficacy implications. Treatment cost is a major economic aspect once efficacy is considered. For the treatment of a broader patient population, economic issues will impact insurance coverage, accessibility, and pharmaceutical incentives. Gene therapies are extremely costly, but as single interventions, justify their cost over a lifetime, especially if treatment is delivered in the pre-symptomatic phase.

On the other hand, the orphan status of many SMA treatments and factored high-cost coverage in the small acquisition market are often raised arguments challenging gene therapy development and pragmatic considerations for SMA patients, especially regarding non-molecule pathway management options, physical, nutritional, and general support for the holistic needs of SMA patients and families that often are at the border of economic and social difficulties induced by SMA disease burden. Moreover, the disparity in local access to molecule or disease direction treatments may widen the gap between SMA disease course amelioration in wealthier countries and in lower-income areas, where supportive care still is the backbone for patients and families. Would collaborative policy at a more equal level encourage a less opportunistic approach from pharmaceutical companies, especially in lower-resourced settings?

### 9.1. Cost of Gene Therapy vs. Traditional Treatments

Given the exceptional cost of gene therapy, issues of health economics regarding SMA therapy have arisen. Zolgensma came at a list price of 2.125 million dollars, and the estimated total expenditure for gene therapy is 3 million dollars. These numbers are interpreted as exaggerated when compared to the annual costs of non-gene treatment of approximately 200,000 dollars. Genetic testing adds up to approximately 5,000 to 7,000 dollars, and initial diagnosis costs have been estimated at 8,000 dollars, with presenting symptoms being diagnostic in approximately one-third of symptomatic patients. Clinical exome sequencing, including SMA genes, costs approximately 1,000 dollars.

Costs for SMA are likely to exceed the additional expenses for gene therapy in the long run due to the burden of care for severely affected SMA patients. It has also been shown that the implementation of disease-modifying therapies would drive down the costs of SMA morbidity. This perspective has led several other authors to model the potential economic impact of SMA gene therapy. Findings indicate SMA gene therapy QALY results to be economically attractive. This modeling occurs in the context of health economic models currently under development, which are designed to estimate the costs associated with early childhood mortality due to SMA.

### 9.2. Insurance and Accessibility Issues

Insurance companies across the United States and around the world are attempting to limit their exposure to costs associated with the approval of novel therapies. In doing so, they provide reasoning and rationale to limit patients' access to life-saving treatments. In heme-oncology, there have been attempts to restrict access to CAR-T therapy due to the cost with limited success; perhaps this will be the case for SMA as well, except for neurological diseases where the long-held paradigm is that treatments impact the quality of life but do not modify the natural history of the disease. The unprecedented nature and cost of a single, one-time treatment for SMA have led payers to create treatment guidelines outlining specific requirements a patient must meet before receiving gene therapy. Proposed guidelines for access to Zolgensma include age restrictions, clinical phenotypic criteria, and molecular genetic criteria. Insurance companies have specific requirements for treatment receipt and are beginning to create different reimbursement pathways including value-based care contracts to mitigate their risk.

The goal of Zolgensma is to prevent disease progression in Type 1 patients and ultimately make them "low-responders" with stable weight gain, improved strength, and delayed disease course and function on testing. However, the ramifications of insurance company treatment guidelines in SMA is the applicability of the guidelines to older patients and in some cases presymptomatic patients, or those with high-risk but asymptomatic SMA perhaps due to genetic carriers in the infant's family. Furthermore, many parents who enroll their child in an SMA clinical trial in hopes of providing treatment for the child may find difficulty obtaining Zolgensma therapy because their child is no longer in the approved clinical trial age bracket or weight limit and may miss the opportunity for gene therapy altogether.

## 10. Future Perspectives

Over the past 30 years, gene therapy approaches have been discussed as a potential option for the treatment of almost all genetic disorders. Before recent advances, this elusive goal had remained unrealized for a multitude of reasons. Encouragingly, we are no longer in that era: transplantation of engineered hematopoietic stem cells is becoming routine to treat immune deficiencies, thalassemias, sickle cell disease, β-hemophilia, and lysosomal storage disorders, to name a few. The application of these same tools to treat rare neurological diseases, such as spinal muscular atrophy and Duchenne muscular dystrophy, has also made great progress. Now with the first rare neurological diseases entering mainstream clinical practice, and with definable endpoints for success, the time is ripe for other conditions to follow. Currently, 66 AAV-SMA tools have been registered in the clinical trials database, with approximately half in Phase I-II studies.

Despite the FDA approvals of gene therapy for SMA and the treatment of SMA with disease-modifying drugs, the field is still evolving, with numerous questions remaining. What about the other motor neuron diseases? Could you expand these tools to patients with different MNDs, such as spinal and bulbar muscular atrophy, Amyotrophic lateral sclerosis, or hereditary neuropathy with liability to pressure palsies? This type of research will require collaboration among the HSC, gene, and neurological research communities. When you go beyond childhood SMA, the modules will need to be reworked to ameliorate the severity of the disease in both children and adults presenting later in life. Perhaps with a collaborative approach, failure of clinical development in adults with SMA may be avoided.

These studies might also serve as the dogs that bark in the night-time, sounding the alarm for other MNDs. As we pursue new treatment pathways for other types of MNDs, innovative personalized medicine approaches that go beyond the current disease-modifying drugs would be welcomed.

**Equation 3 : Disease Progression Risk Index:**

$$D_r = \gamma(A_o + S_m + T_i)$$

*where:*

- $D_r$ = Disease progression risk
- $\gamma$ = Scaling coefficient
- $A_o$ = Age of onset
- $S_m$ = Severity of motor milestones missed
- $T_i$ = Treatment initiation delay

### 10.1. Emerging Therapies in Development

Numerous innovative therapies are undergoing phased clinical trials to address unmet challenges with current SMA treatments. Encouragingly, these clinical trials also attempt to account for diverse factors exacerbating SMA clinical heterogeneity and treatment response. For instance, several recent studies have concluded that SMA treatment may increase the risk of developing secondary musculoskeletal morbidities, such as scoliosis, hip dysplasia, and joint contractures, highlighting the need for a multidisciplinary team approach in the management of SMA.

Many new therapies are aimed at harnessing the power of the SMN expression from cis-acting elements or alternative splicing events. Large concentrations of systemically injected SMN2 splice-switching oligonucleotide corrected the splicing of the highest SMA patient-derived fibroblast in vitro. A subsequent trial treated six infants with SMA1, resulting in increased ambulation, oxygenation, and retention of modified bipedal motor tasks, but the trial was terminated early due to a lack of funding and ethical concerns. This therapy may require frequent injections, owing to the short half-life and rapid clearance of the SSO. However, a subsequent phase 1 trial of treatment in two children suggested tolerability due to the established safety of SSO therapies.

A clinical trial suggested that adeno-associated virus-delivered SSO would have a more beneficial safety profile than the unapproved SSO. Encouragingly, AAV-delivered SSO treatment improved ambulation, survival, and bulbar functions; however, it was associated with a reduced increase in overall skeletal muscle strength, leading to SMA recruitment for predicting therapeutic efficacy. Another trial is testing the same therapy in individuals with SMA. Other clinical trials focus on methylated enhancements or ASO diastereomeric sequences to transiently boost SMN expression in targeted areas.

### 10.2. Personalized Medicine Approaches

As stronger SMN-dependent therapeutic interventions for SMA are developed, personalized medicine approaches are likely to play a role, in supporting or leading to more optimal clinical outcomes. At the moment, most of our efforts in this area have focused on exploring ways to dispose of newer, stronger SMN1-independent therapeutic strategies for SMA. However, that choice, taken out of innocent ignorance, might not turn out to be optimal. For example, while significant concerns over the pharmacological consequences of administering an SMN-dependent therapeutic strategy together with an SMN1-independent strategy have already been raised, the only trial carried out has provided inconsistent data suggesting that it is safe.

Almost all SMN1-independent therapeutic interventions, whether currently in development or just based on fantasy, have the same or similar constraints. In short, they are not able to ameliorate or restore NMJ dysfunction due to SA. Likewise, they will be less effective in more severely affected SMA patients, such as those with SMA types 2 or 3, than in SMA patients with isolated weakness due to a primary motor neuron defect. However, a critically important question is whether and how early we should center treatment strategies dedicated to restoring NMJ function due to the chronic effect of SA. The same caveat applies to SMN1-independent interventions that ameliorate muscle weakness by curing muscle pathology. In brief, these temporally correspond to developmental time windows when both SA levels and muscle pathology would be strong enough to warrant treatment and effective pharmacological strategies are available for SMA to consider restoring NMJ function due to a chronic effect of SMN–SA, before initiating damage control of NMJs by NMJ repair strategies. Outlining a road map for answering these questions is essential for a practice that is quickly becoming excessive.

## 11. Conclusion

Over the past few years, SMA has witnessed significant therapeutic advances. The increased understanding of SMN role, the identification of SMN-dependent mechanisms causing motor neuron degeneration, of SMN-related long non-coding RNA genes, and the advances in the development of SMA rodent models and patient-derived induced pluripotent stem cells have led to the development of novel and efficacious SMA therapies. Gene therapy using AV-encoded SMN1 can locally and systemically address the root cause of the disease when applied early in the disease course. More recently, oral medications to increase levels of SMN protein are also able to alter disease course

concerning historical natural history cohorts, although the treatments do not target the root cause of the disease. The use of SMN large dose manipulation following gene delivery also seems to augment efficacy, allowing the treatment of patients that would otherwise not qualify due to pre-symptomatic diagnosis cutoff dates or late-onset symptoms.

Continued biomarker development, natural history documentation, and identification and treatment of SMA subtypes will aid gene therapy and therapy development toward the next set of approved products. The field is currently working on lowering the age of treatment initiation and increasing the number of treated patients. New AV designs, novel PROMs to follow older children and adults, combination strategies to induce nerve fiber regeneration, and engineering therapy delivery to further augment effect sizes and broaden the SMA patient population are also essential for an even brighter future for SMA patients. It has been an amazing past few years, and we envision that this will only continue with more years of progress ahead, to allow an even greater expansion of treatment options that are effective for all SMA subtypes.

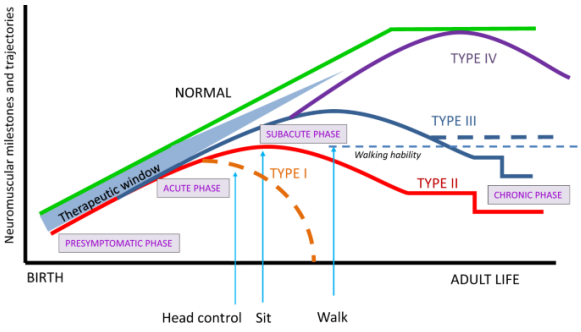


**Fig 6 : Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era**

### 11.1. Summary and Final Thoughts on SMA Management

Neuro-muscular disorders, including spinal muscular atrophy (SMA), covering a wide spectrum of clinical presentation, burden of care, and support needs, create a high burden for patients and caregivers despite disabled life expectancy extending with timely interventions. The advent of disease-modifying treatments for SMA has transformed the outlook, burden of care, and support needs of many affected by this condition. At the same time, as is the case with other diseases traditionally viewed as whole-body conditions, these treatments do not offer a cure, and physical care and support for a variety of symptoms and co-morbid conditions is still required both at the patient level and from healthcare services. The ultimate goal of intervention in SMA is for the individual to achieve their hoped-for engagement and participation, and physical function in achieving this needs to be carefully monitored, adopting developmental milestones, age, comorbidities, and specific needs. Disease-modifying treatments have altered clinical pathways so that interventions that may have been appropriate in the past may not be appropriate today, known modalities of intervention may become available earlier in life for eligible babies and infants, and novel modalities of intervention may need to await development and testing. Tools and assessments based on a single dimension, such as strength, may no longer be appropriate and consideration needs to be given to multi-dimensional assessments and monitoring of both engagement/participation and underlying physical function. It is hoped that international consensus development on physical care strategies and outcomes of individual importance may help to guide the lack of evidence currently available and it is important to remember that international collaboration between patients, caregivers, and family members is fundamental to prevent the two-tiered approach currently experienced from being perpetuated post-treatment transition.

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