

# Payer Perspectives on the Treatment Landscape of Spinal Muscular Atrophy (SMA)

*Findings from the AMCP Market Insights Program*

## Meeting Objective

- Understand how AMCP members identify and manage patients with SMA
- Identify how payers establish coverage criteria for new SMA therapies, including gene therapy
- Assess the role of real-world data to better understand the impact of current and emerging treatments for patients with SMA

## Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal recessive genetic disease that causes progressive muscle weakness and atrophy. Approximately 6,000 children and adults in the United States are affected, making SMA one of the most common rare diseases.<sup>1</sup> SMA is divided into subtypes based on age of onset and maximum function achieved. SMA types are classified as 0, 1, 2, 3 and 4 and are all associated with mutations in the Survival Motor Neuron 1 gene (SMN1) and SMN2 genes, which are located on chromosome 5q (Table 1).<sup>2</sup> SMN1 creates SMN protein, a protein essential for motor neuron development. SMN2 also produces SMN protein but only a small percentage of the protein produced by SMN2 can be used by the body. This deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor functions. These muscles are necessary for crawling, walking, sitting up and head control. The more severe types of SMA can affect muscles involved in feeding, swallowing and breathing.

Various medications are used to help those with SMA manage their symptoms but currently there is two therapies. The SMA drug pipeline includes treatment strategies to compensate fully or in part for the absence of SMN1 gene by increasing the level of functional SMN protein via multiple approaches. The high upfront costs and the cumulative budget impact of SMA treatments and the lack of long-term clinical durability data amplifies treatment uncertainties and complicate payer coverage and reimbursement determinations.

AMCP conducted a Market Insights program to identify perspectives of AMCP members on current and future therapies for SMA. The Market Insights program offered by AMCP is a blinded research program sponsored by corporate member to address current conditions that are a high priority among the AMCP membership. The payer experts in the SMA Market Insights Program represented a diverse mix of national and regional health plans, Pharmacy Benefit Managers, Integrated Delivery Networks, Physician

Groups and Employer Coalitions. Payers ranged in size from less than 500,000 insured lives to nearly 10-million and, in total, covered over 40-million lives (Figure 1). Discussions were led by two key opinion leaders who focused on best practices, the evolving SMA treatment landscape (including gene therapy) and the role of real world evidence on considerations for treatment decisions.

## Carrier and Newborn Screening

SMA was added to the federal Recommended Uniform Screening Panel (RUSP) for newborn screening in 2018.<sup>4</sup> The provision of carrier screening information is recommended by the American College of Obstetricians and Gynecologists for every pregnant woman.<sup>5</sup> Prenatal carrier screening does not replace newborn screening. Nor does newborn screening replace the potential value of prenatal carrier screening. Genetic counseling about potential reproductive outcomes should also be offered.

**“And it looks like earlier treatment is better—so support the prenatal screening.” –Health Plan**

Payer experts understood that timely newborn screening is a valuable tool to attain earlier treatment and stronger clinical benefit of preserved motor neuron function. Several payers noted that intuitional policies are already in place to support standard newborn screening for SMA.

## Care Management

The majority of people with SMA require constant support and attention by parents and caregivers. The condition is managed through multidisciplinary supportive care. However, supportive care strategies do not affect disease progression, but aim to minimize the impact of disability, address complications and improve quality of life. These may involve respiratory, gastroenterology, and orthopedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.<sup>3</sup>

Payers acknowledged that SMA has a substantial effect on the quality of life of patients, caregivers and their families. Some payers also noted their organizations were mindful during policy development and decision making of the specific need to take into account the child population, treatment timing, rarity and severity of the disease.

## Current and Emerging Therapies

Although recent progress has been made in understanding molecular mechanisms underlying the pathogenesis of SMA, there is currently no cure. Treatment involves prevention and management of

**Table 1. Clinical Classification of SMA<sup>2</sup>**

SMA Type	Eponym	Age at Onset	Life Span	Highest Milestone Achieved	Proportion of Total SMA (%)
0		Prenatal	< 6 months	None	< 1
1	Werdnig-Hoffman	Prenatal - 6 months	< 2 years without respiratory support	Never sits	60
2	Dubowitz	6-18 months	70% alive at 25 years	Sits independently-never stands	27
3	Kugelberg-Welander	> 18 months	Adulthood	Stands and walks	12
4	Adult-onset	Early adulthood (20s-30s)	Does not affect life expectancy	Walk through adulthood	< 1

Adapted from Verhaart et al. 2017.

the secondary effect of muscle weakness and loss. Clinically, even with early treatment, patients will continue to have symptoms of SMA. Developing therapeutics for SMA have shown positive clinical results in various phases of drug development and routes of administration.

**“We’re talking about a therapy without which children generally die by two years of age.” –Physician**

### Nusinersen

Nusinersen (Spinraza), an antisense oligonucleotide (ASO), was the first disease-modifying therapy to treat SMA when it was approved by the FDA in 2016.<sup>6</sup> It targets the SMN2 gene to enhance its effectiveness. Nusinersen is administered via lumbar puncture with four loading doses and maintenance doses every four months thereafter. An ICER review found there is high-quality evidence that nusinersen benefits children with Type 1 SMA, and it appears to benefit presymptomatic SMA.<sup>7</sup> Currently, the list price is \$750,000 for the first year and \$375,000 in subsequent years.

Payer experts stated nusinersen is covered for patients with SMA, although some require evidence that the patient has a specific number of copies of the SMN2 gene (e.g., at least two copies). However, coverage is variable across plans and there may be benefit limitations, such as nusinersen not being considered medically necessary for individuals previously treated with gene therapy. In addition, some plans have carved nusinersen out of the medical benefit and are only covering it under pharmacy benefits due to better affordability and management tools.

### Zolgensma

The gene replacement therapy, onasemnogene abeparvovec (Zolgensma), is FDA approved to treat patients less than two years of age with SMA.<sup>8</sup> It uses the adeno-associated virus serotype 9 vector to replace a copy of SMN in order to supplement the defective SMN1 gene. Onasemnogene abeparvovec is given as a one-time intravenous administration. The wholesale acquisition cost is \$2.1 million per patient and falls within the upper bound of ICER’s value-based price benchmark range.<sup>7,9</sup>

**“This (gene therapy) is not a cure in the sense of it is a one time treatment... There is still going to be impaired survival” –Physician**

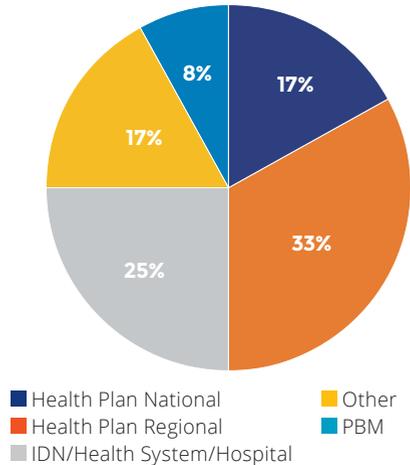
All but one of the payers stated that they have developed coverage criteria for onasemnogene abeparvovec. It was common for payers to require genetic testing results and to limit coverage to one dose per lifetime for a patient.

### Risdiplam

Risdiplam is an investigational SMN2 splicing modifier and is an orally-administered liquid. It is designed to durably increase and sustain SMN protein levels both throughout the central nervous system and in peripheral tissues of the body. It is being evaluated for its ability to help the SMN2 gene produce more functional SMN protein throughout the body. Risdiplam is expected to be submitted for FDA approval in 2020.

Payers are anticipating that risdiplam will have a broad label of SMA indications. They are anticipating managing it under the pharmacy benefit and to distribute it through

**Figure 1. Market Insights Participants**



specialty pharmacies under limited distribution. As an oral agent risdiplam may be preferred by patients, physicians and payers, as compared to the injectable treatment options. The difference in reimbursement timelines across the pharmacy and medical benefit may also play a factor in preferred product selection. Considerations for preferring one SMN2-enhancing product include the patient’s out-of-pocket cost for an oral product compared to a physician buying and billing for the injectable, as well as concerns around GI tolerability and adherence. However, the oral product may have advantages for adolescent and adult patients or those with complex spinal anatomy.

### Pipeline

The SMA drug pipeline includes treatment strategies to compensate fully or in part for the absence of SMN1 gene by increasing the level of functional SMN protein via multiple approaches (Table 2):

- i) Replacement or correction of the faulty SMN1 gene
- ii) Modulation of the low-functioning SMN2 gene
- iii) Muscle protection to prevent or restore the loss of muscle function in SMA
- iv) Neuroprotection of the motor neurons affected by loss of SMN protein
- v) Approaches that identify additional systems and pathways affected by SMA

The different mechanisms of action in investigational drugs focusing on muscular volume and muscular integrity further support the likelihood of additive therapy in SMA and highlight the need for clinical guidelines. Given the severity of the disease,

the majority of payers stated that their organizations would likely evaluate a new therapy for SMA in less than six months of FDA approval.

### Combination Therapies and Sequencing

The availability of treatments for SMA that target independent genes (SMN1 and SMN2) and the potential for new neuroprotective options has led to discussions around combining therapies in the hopes of better outcomes. Payers heard that the presence of SMN2 can compensate for the SMN1 deletion to some degree and the number of SMN2 gene copies is inversely related to the severity of SMA, which can be used to predict the course of the disease. Currently there is no clinical trial evidence to support using multiple therapies concurrently or sequentially. How effective treatments will be in the long term and which patients will benefit are not yet known.

**“When is it appropriate, or is it appropriate, to use Spinraza after gene therapy has already been used?”**  
**–Health System**

Payers are managing coverage requests for combination therapy with varying policies including requiring treatment with nusinersen to be discontinued prior to infusion of gene therapy. However, the discussion included the consideration that, since the available therapies have different mechanisms of action, that combination therapy may be reasonable on a patient-by-patient basis. Experts also cautioned about the potential safety concerns related to the unknown risks of providing too much SMN replacement, noting that ideally there would be clinical trial data (in animal models and humans) available to better inform safety and efficacy of combination therapy.

**“Without the data to preferentially place one treatment in front of the other, it is difficult to prefer one treatment... It is about the clinical efficacy data.”**  
**–Integrated Delivery Network**

### Current Payer Challenges

Payers identified several challenges with the available evidence and clinical guidance for differentiating treatment options in SMA. The lack of current clinical

**Table 2. SMA Drug Pipeline<sup>10</sup>**

	Preclinical: Discovery			Clinical Development			Market	
	Identification	Optimization	Safety & Manufacturing	Phase 1	Phase 2	Phase 3	FDA Approved	
Drug or Approach	Protein-Synthesis Enhancers	Small molecules	Gene-therapy	AVXS-1010	CK-2127107/reldesemtiv	Risdiplam	Nusinersen (Spinraza)	
	2nd Generation ASO		NU-p38aMAPK Inhibitor	BII110	LMI070/branaplam		Onasemnogene abeparvovec (Zolgensma)	
	Small molecules		E1 ASO		SRK-015			
	Long Non-coding RNA project				Olesoxime			
	Patten-Zebrafish Screen							
	Modifier genes							
	Calcium Channel modifier							

Adapted from Cure SMA. Last updated November 2019.

guidelines was noted as one issue, as standards of care recommendations for SMA were last published in 2018, before these newer treatments were available broadly.<sup>3</sup> Payers would like guidelines or treatment algorithms to address both treatment sequencing and combination therapy. Without broadly accepted guidelines determining medical necessity will likely be based on the product label and the inclusion/exclusion criteria in clinical trials.

The narrow eligibility criteria of clinical trials and the limited sample size were also discussed and there are concerns about generalizability of results to the wider population of patients with SMA. Payers noted the challenge of making evidence-based coverage policies based on the age of disease onset or age of treatment over 2 years, and find that there is stronger data for use in infants (types 1 and 2) and less clear evidence of benefit in older children and adults (types 3 and 4).

Additionally, there is a lack of data on the long-term safety and durability of effect for these treatments. Extension studies and registries could provide the longer-term efficacy and safety data being sought and should include payer-meaningful and actionable outcomes such as durability of effect, resource utilization, patient reported outcomes and safety information.

**“Gene therapy is intended as a one-time treatment, but without long-term data, it’s not clear whether efficacy will wane.” –Physician**

As is often the case in clinical trials of rare diseases, there are currently no active comparator trials for SMA treatments. Therefore, payers commented that they may use indirect treatment comparisons. However this depends on the availability, quality, and relevance of outcomes published in trials across treatments.

Determining clinically-meaningful differences was also noted as a challenge for payers. Several payers use of SMA disease measurement scales (e.g., Hammersmith Functional Motor Scale-Expanded (HF MSE) in coverage criteria, while others stated that coverage determinations rely on the physician assessment of function and progression of the disease. In older patients (type 2/3), a reasonable milestone is likely stabilization or maintenance of motor function rather than improvement. The development of a validated response assessment tool that could be readily used in the clinic would be valuable to monitor patient progress at each visit. Payers generally found high value in hearing patient-specific stories of the benefits and recommended the continued use of patient interviews or video vignettes to demonstrate the relevance of surrogate endpoints and to help demonstrate the clinical impact of novel treatments.

Differentiation based on the cost of products that have similar mechanisms of action (e.g. SNM2 enhancer) is likely once there are multiple agents within a therapeutic class. Affordable treatment options is seen as a continued unmet need for SMA patients.

Finally, payers are seeking guidance around appropriate clinical criteria for starting, switching and discontinuing SMA therapy and outcomes for inclusion in outcomes-based contracts. Several outcome measures were discussed, including:

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- adverse effects
- biomarkers
- complications (e.g., scoliosis and muscle contractures)
- efficacy/motor function (e.g., age appropriate motor milestones)
- health-related quality of life
- mortality
- respiratory function or number of hours ventilation is needed

**“And thinking about SMA, what is a measure of response and at what point would we be measuring?”  
–Physician**

Ultimately, payers are seeking the same types of evidence for SMA treatments as with conventional disease treatments - Does this product safely and effectively address an unmet need? Is its value within the constraints on how we spend our healthcare funds? In order to answer these questions, the payer experts recognized the need for information about SMA treatment derived from multiple sources outside typical clinical research publications.

**Advancing Real World Evidence and Economic Modeling**

Payers heard from an expert about the potential benefits of using real world evidence (RWE) and economic modeling to support coverage decision making for SMA, including determining thresholds for cost-effectiveness, the importance of adjusting costs and benefits that occur in the future to present value (i.e. discounting) and its' impact on Quality Adjusted Life Years (QALYs). Considering the limited evidence on the long-term efficacy and safety of novel drug treatments for SMA and their costs, it is helpful for payers to collect real world data to improve the basis for clinical decision making and coverage determinations.

Payers recognize the value of RWE, but use of such studies to inform Pharmacy and Therapeutics (P&T) committee decisions varies from organization to organization. Relevance to payers, timeliness, and transparent methods are key concerns with RWE. Nearly all participants indicated that RWE was useful for monitoring safety and efficacy, conducting utilization management, and examining costs, but was less likely to be considered in P&T decision making, primarily due to timeliness.

Timeliness was just one of the identified limitations associated with RWE application to coverage decisions. Other challenges identified with RWE were the credibility

of the source, access to both pharmacy and medical claims data, and the lack of measurement standards in SMA. Benefits of RWE included using it to evaluate the durability of clinical benefit, assessing side effects over a longer period than clinical trials, exploring population subgroups in which there is greatest clinical benefit and gaining comparable evidence within a population.

Due to these challenges, payers stated they are using a variety of sources to develop coverage criteria including the FDA label, clinical trials, ICER reports, key opinion leaders and genetic testing requirements. Payers are using PROs as collected via their specialty pharmacies to inform decisions and both claims data and medical record data to monitor patient response to treatment.

**“It is difficult to get and to assimilate all of the RWE to make decisions. So we use pharmacy and medical claims, and PROs reported through our specialty pharmacy to pull in RWE.”  
–Pharmacy Benefit Manager**

Despite understanding the unique aspects of drugs developed for SMA, payers are managing finite healthcare resources under the steady increase in the number of orphan drugs approved across several diseases. Challenges on how to pay for innovative therapies remain, as do challenges in the economic modeling of SMA. Economic modeling can estimate life-time value of a product, however the uncertainty in cost-effectiveness estimates needs to be considered in the decision making and challenges remain on how to pay for these therapies going forward.

Payers are using cost-effectiveness thresholds to help inform coverage decisions, but they are used in conjunction with clinical evidence and estimates of QALYs. As more treatment options for SMA enter the market, payers are anticipating that they will use the cost per QALY more often to inform preferred product selection. Payers are also looking for models that address the “right” research questions, such as estimating QALYs for combination therapy in SMA.

**“For a small employer, one gene therapy claim could potentially bankrupt them.” –Employer Group**

**Impact on Payers**

Payer concerns were namely around care management, financial risk, and pharmacy management. As a result, payers have already started to manage SMA

treatments using many of the management strategies they employ for other high-investment treatments. They are also looking at innovative reimbursement strategies, many of which prioritize improved predictability and smoothing of benefit costs. Payers are also planning to develop risk mitigation strategies with the goals to support appropriate patient access to SMA treatments and to manage financial risks.

**“With all of the gene therapies in the pipeline, solving the reimbursement issues and understanding the cumulative budget impact of all of the gene therapies is critical.”**  
–Regional Health Plan

### Care Management

There is recognized need for SMA treatment guidelines or algorithms that address the current evidence gap for treatment sequencing and combination therapy. Payers are looking for evidence-based algorithms to support selecting the right patient for the right product and identifying criteria for when to switch or discontinue therapy based on clinical benefit. Guidelines should also address the best measures of motor functioning in SMA by type or age at diagnosis. Lacking nationally recognized treatment algorithms, many payers are building specialized teams, similar to tumor boards, who have the right clinical expertise to evaluate rare disease treatments. Payers also realize the importance of identifying the subpopulations of patients that are going to be able to utilize a life-changing therapeutic regimen and ensuring that they start treatment appropriately.

The question remains whether patients will need supplemental SNM2 treatment following gene therapy, and whether patients will develop antibodies that will impact future treatments. Thus, the full impact of gene therapy on care management and patient lifetime costs remains unknown.

### Managing Financial Risk

Payers have long utilized the expertise of actuaries, but are now relying more on cost-effectiveness and budget impact models to evaluate the financial implications of SMA treatments. There is an interest in more proactive and predictive payment and insurance models, which may require outside expertise for management – especially for smaller plans and self-insured employers with limited ability to manage large upfront payments, therapeutic performance risk and/or actuarial risk.

The potential for patient migration between health plans underlines the need to consider alternative payment models for high-investment medications. Preferred strategies include value-based arrangements, such as outcomes-based agreements, in which the manufacturer assumes some of the risk for the outcomes associated with treatment. For example, the manufacturer could assume responsibility for the cost of any supplemental SNM2 treatment that is received within a defined time period after the patient receives gene therapy.

**“Our biggest challenge with this is development of criteria to ensure appropriate use, the appropriate patients are started, and when do you stop therapy”**  
–Pharmacy Benefits Manager

Annuity payments, in which the costs associated with gene therapy are amortized over time is another option. High risk pools, or reinsurance programs, are being utilized by smaller plans and self-insured employers. Subscription payment programs where a per-member per month (PMPM) fee is paid to a third party to provide patients with access to treatments is also an arrangement that most plans have considered.

Taking the point of view of the financial impact over the life of the patient and considering the total cost of care for treatments compared to the natural history of SMA is a perspective that was seen as helpful in assessing the financial impact to the plan and patient’s quality of life. However, in order to better manage the financial risk, there is a need to determine meaningful clinical outcomes that can serve as the basis for outcome-based contracts for patients with different types of SMA. Practically, agreements may need to use surrogates, such as the need for ventilation, rather than functional endpoints, and they will likely vary across SMA types.

A different risk mitigation strategy is to invest in coordinated pharmacy and medical benefits. This will allow the payer to monitor that non self-administered drugs are billed where intended and to survey for unapproved combination therapy.

### Pharmacy Management

Payers are considering a wide range of clinical evidence from multiple sources outside typical clinical research settings to make coverage decisions in SMA, including taking into account the young population, the rarity and severity of the disease, and the considerable impact on families and caregivers. Some payers are considering the benefits and differences in management tools and costs across

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pharmacy and medical benefits. The buy-and-bill process for medical benefit drugs may be viewed as less desirable due to the different reimbursement schemes, time lag with data to support clinical and coverage decisions and patient cost-sharing.

With many rare diseases and orphan drugs, payers are considering more robust management criteria. Prior authorizations, for example, may restrict drug use to the drugs clinical trial inclusion/exclusion criteria rather than the FDA-approved label. Renewal processes may require more detailed documentation, and prescribing may be limited to specific specialties (e.g. neurologist). Payers are also evaluating the risk and benefit of restructuring the formulary to include multi-specialty tiers for orphan drugs and/or gene therapies. However, due to the rarity and complexity of SMA, payers do not expect to use traditional utilization management tools beyond prior authorization (such as step therapy or therapeutic class preferred products), even with the new treatments entering the market in the coming years.

### Summary

The treatment of SMA is undergoing a period of important advancement: new treatments for SMA, like splicing modification and gene therapy are allowing the clinical course to be substantially modified. Additional therapeutic approaches are currently in advanced stages of clinical development and are likely to expand the spectrum of drug treatment options. However, the existing evidence base contains many of the common limitations pervasive in rare disease areas. Lacking head-to-head clinical trials, payers are using indirect comparisons and RWE to inform coverage policies, and they are seeking evidence to better inform starting, switching and discontinuation rules and the appropriateness of combination therapy.

Various traditional management strategies are being employed by payers to identify and manage patients with SMA, including following nationally recommended screening, clinical evidence review, utilization management programs and RWE data collection. To mitigate financial risk, payers are looking to cost-effective modeling, alternative payment models and re-insurance or carve-out programs. The emerging treatments options for SMA are fundamentally altering the natural history of the disease and improving the quality of life for the affected patients and their families. But with these innovations comes a substantial economic impact to the health care system; managed care experts are working diligently to ensure patient access and continued affordability through evidence-based medicine strategies.

### Disclosures

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## Key Summary Findings

- Clinicians and payers need more guidance on appropriate patient selection, starting, switching and discontinuation rules, and differentiated by SMA type or patient age (e.g. infant, adolescent, and adult).
- Current treatments are not a cure, but clinical trials have shown efficacy allowing patients to develop stronger muscles and survive for longer without breathing support.
- Due to limited published data, RWE may need to be incorporated into decision making.
- Due to the lifesaving nature of the treatments and because the disease is so rare, payers are likely to cover all SMA treatments with limitations based on evidence of benefits.
- Emerging treatments options for SMA are fundamentally altering the natural history of the disease and improving the quality of life for the affected patients and their families.
- Extension studies and registries could provide the longer-term efficacy and safety data and should include actionable outcomes such as durability of effect, resource utilization, patient reported outcomes and safety information.
- Financial models need to consider the impact of treatments on the total cost of care and over the lifetime of a patient.
- New clinical treatment guidelines are needed to address combination or sequencing of novel treatments.
- The underlying challenge with high drug prices and affordability are not solved by alternative payment arrangements, but they can be useful in mitigating risk.

## Impact to Treatment and Coverage Decisions

- Challenges remain in understanding the appropriate algorithm of care based on available clinical data.
- Collect data from multiple sources outside typical published clinical research for developing coverage policies.
- Combination or sequenced therapy coverage requests are likely based on the novel MOAs and agents in the drug pipeline.
- Evaluate restructuring the formulary to include multi-specialty tiers for orphan drugs and/or gene therapies.
- Limited distribution of therapies will impact payers contracting and negotiation strategies.
- Multiple agents coming to market within a therapeutic class will support competition, but utilization management may not go beyond prior authorizations.
- Route of administration alone may not be a significant factor in product preference as plans shift coverage for SMA treatments to the pharmacy benefit.
- Treatment selection and coverage determinations will be made on a case-by-case basis.