

Payer Perspectives on the Treatment Landscape of Spinal Muscular Atrophy - Findings from the AMCP Market Insights Program

June 17, 2020



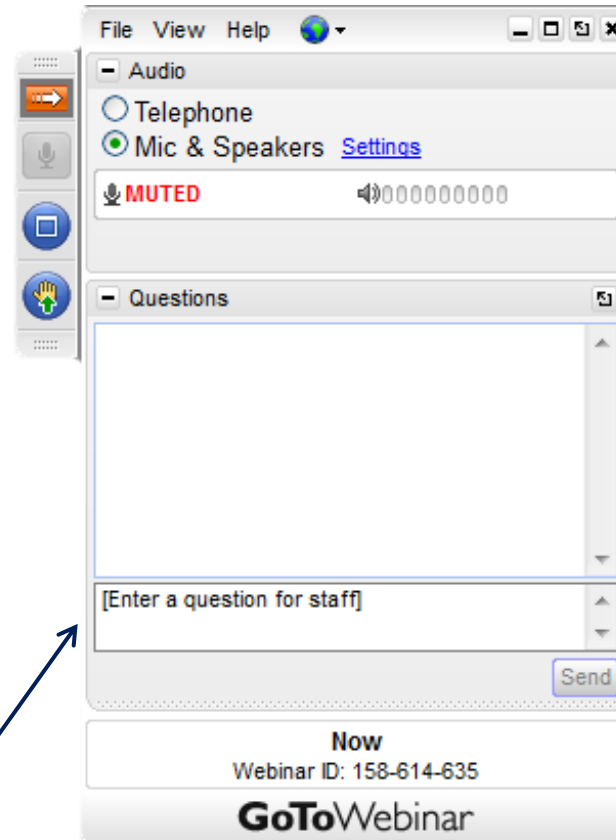
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Type your question in the 'Questions' area

AMCP Market Insights Overview



- **Association-led research** with AMCP members and non-members at regional and national plans
- **Blinded format** to allow participation and candid feedback
- **Topics are based upon category**, not product, to provide a holistic view of management
- Programs are **focus group meetings or virtual programs** with Clinical Key Opinion leader presentation
- **Current and future treatment options** are addressed to understand clinical and medical management utilization approaches



Payer Perspectives on the Treatment Landscape of Spinal Muscular Atrophy - Findings from the AMCP Market Insights Program

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Research Center

Agenda

Guest Speakers:

John Brandsema, MD

Neuromuscular Section Head
Children's Hospital of Philadelphia

Daniel C. Malone

Professor
University of Utah

Welcome & Setting the Stage for the Day

SMA Treatment Landscape: Today and Tomorrow

John Brandsema, MD
Neuromuscular Section Head, Children's Hospital of Philadelphia

Panel Questions

Discussion: Treatment Options

Real World Evidence Considerations for SMA Treatment Decisions

Daniel C. Malone, PharmD
Professor, University of Utah

Discussion: Gene Therapy

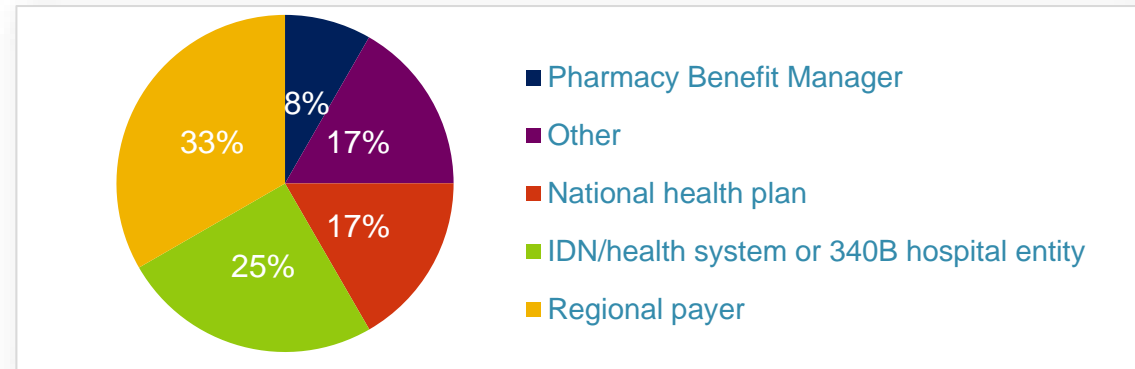
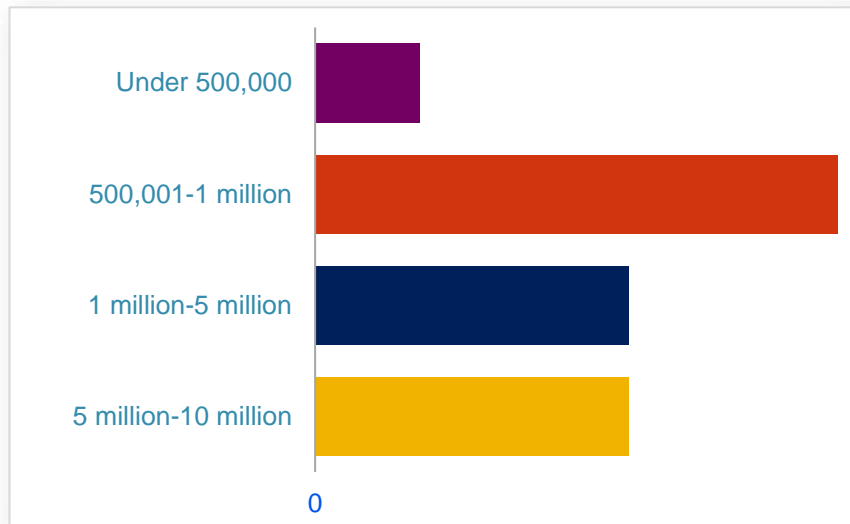
Wrap-up and Closing Remarks

Objectives

- 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

Methodology

- 5-hour virtual meeting on May 1, 2020
- Roundtable format, with presentations and group discussion
- > 40 million lives covered



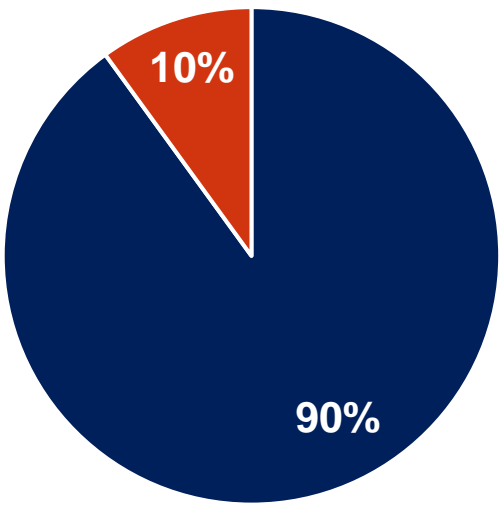
National and regional plans as well as broad range of PBMs- national and regional..



Pre-Survey

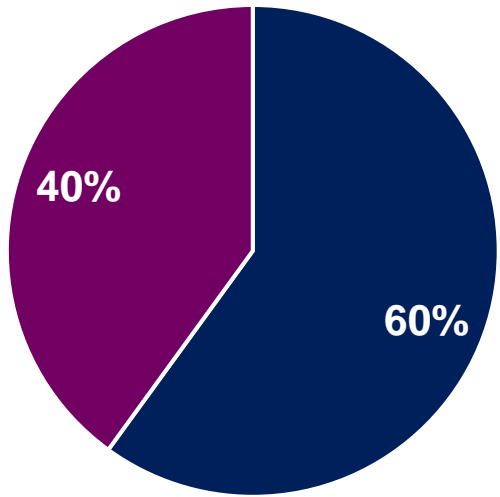
Pre Meeting Survey- Which product is currently used for each SMA Type?

SMA Type 1



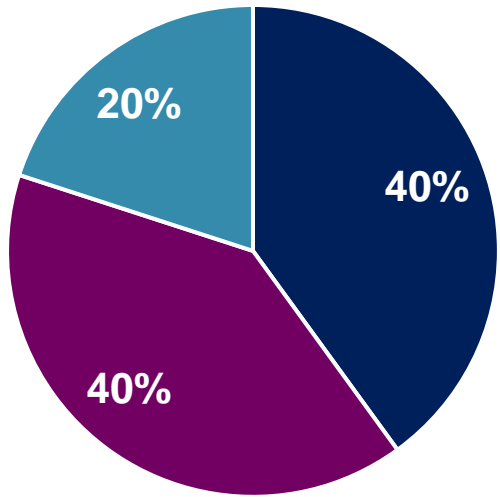
■ Both ■ Zolgensma only

SMA Type 2



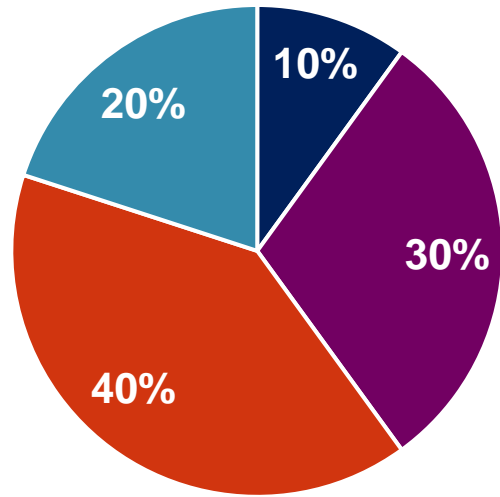
■ Both ■ Spinraza only

SMA Type 3



■ Both
■ Spinraza only
■ Niether

SMA Type 4



■ Both
■ Spinraza only
■ Zolgensma only
■ Niether

Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA)

- SMA = Leading Genetic cause of Infant Death
 - Autosomal Recessive, Incidence approx. 1:10,000
 - High Carrier Rate of approx. 1:35 - 1:50
- Degeneration of Survival Motor Neurons (SMN) in anterior horn
- Three clinical types in childhood
- Spectrum



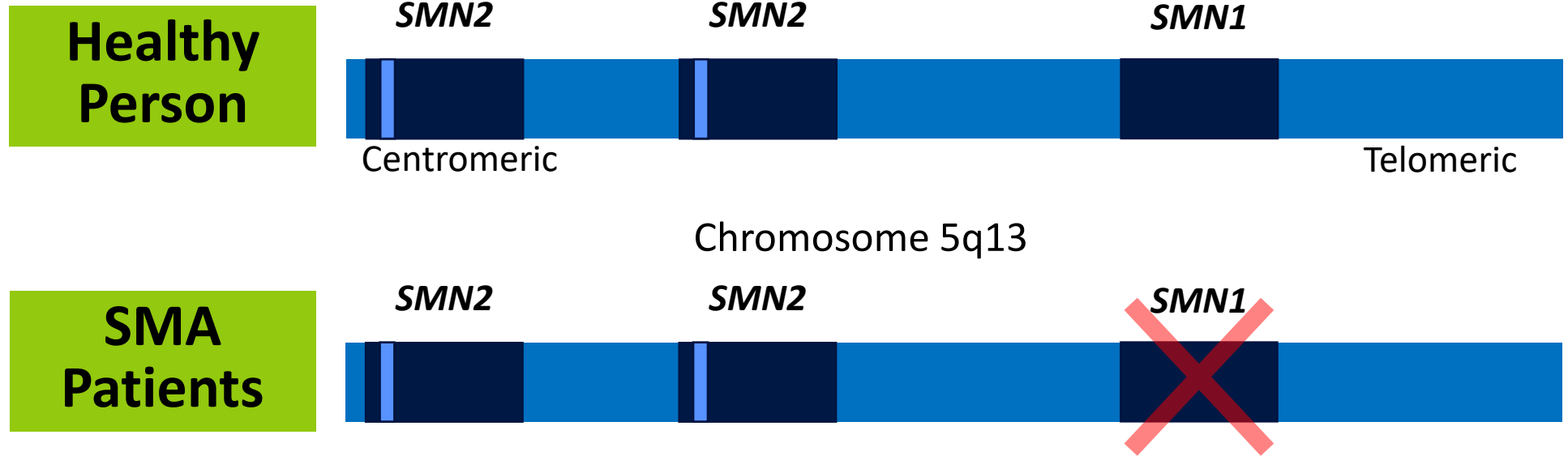
“We’re talking about a therapy without which children generally die by two years of age.”

Physician

SMA Type	Eponym	Age at Onset	Life Span	Highest Milestone Achieved	Proportion of Total SMA (%)
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

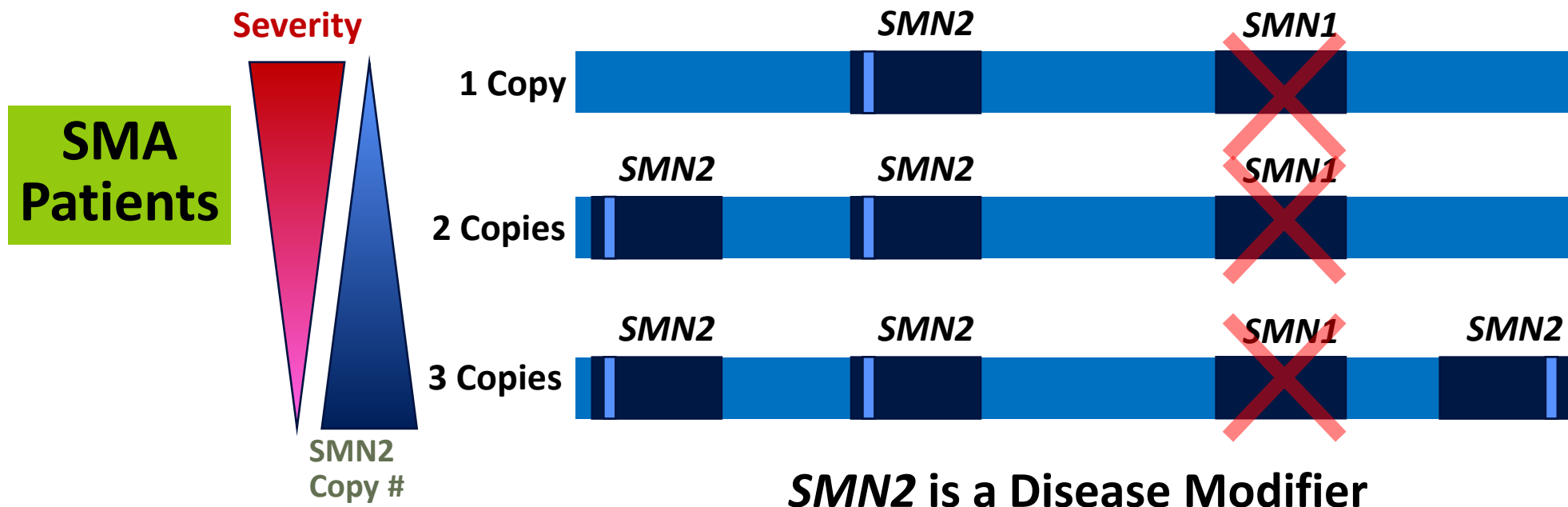
Neuromuscular Disorders of Infancy, Childhood and Adolescence. (2nd edition, 2015)

SMA and *SMN1*/*SMN2*



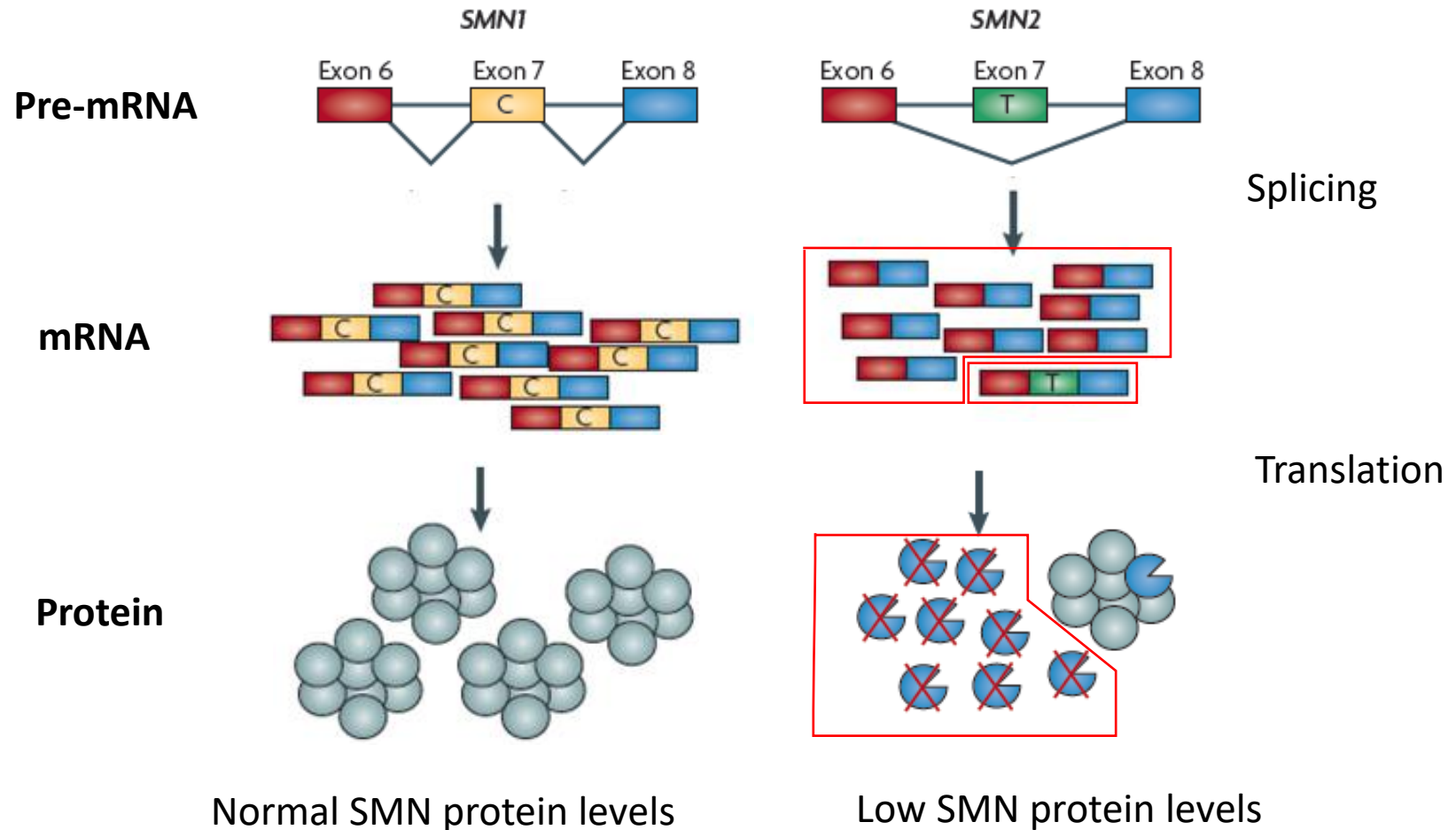
95% of 5q SMA

SMA and *SMN1/SMN2*



SMA Education Supported Greater Understanding of Genetics

- Two genes are essential for survival of motor neurons
 - SMN1
 - SMN2
- SMA is caused by a lack of a functional survival motor neuron (SMN1) gene. Severity varies by type and corresponds to the number of copies of the back-up gene (SMN2).



Participants Support Pre-symptomatic Diagnosis of SMA

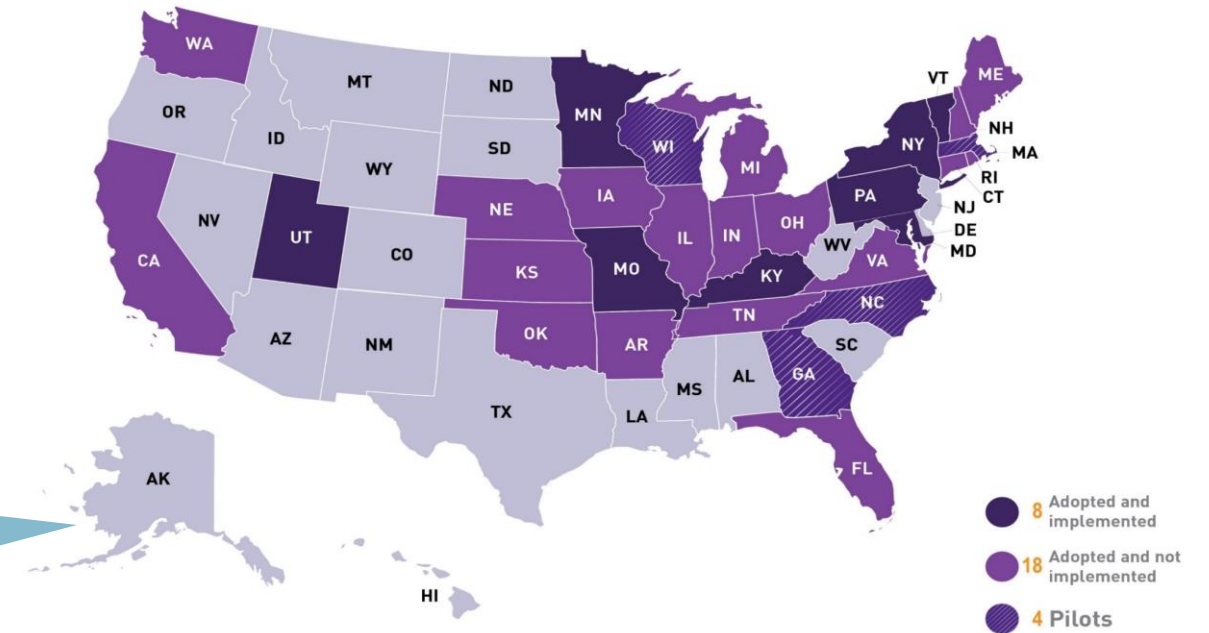
Carrier screening of parents

- ACOG and AGC Recommendations

“The earlier the diagnosis and treatment the better.”
-Integrated Delivery System



Newborn Screening Programs



www.cureSMA.org | 800.886.1762 | info@cureSMA.org Current as of September, 2019



Added to the federal Recommended Uniform Screening Panel (RUSP) for newborn screening in 2018.

Participants were Aware of and Sensitive to Patients' Care Needs

Managed through multidisciplinary supportive care

- May involve respiratory, gastroenterology, and orthopedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.

Supportive care does not affect disease progression but aims to minimize the impact of disability, address complications and improve quality of life.

- Payer experts acknowledged that SMA has a substantial effect on the quality of life of patients, caregivers and their families.

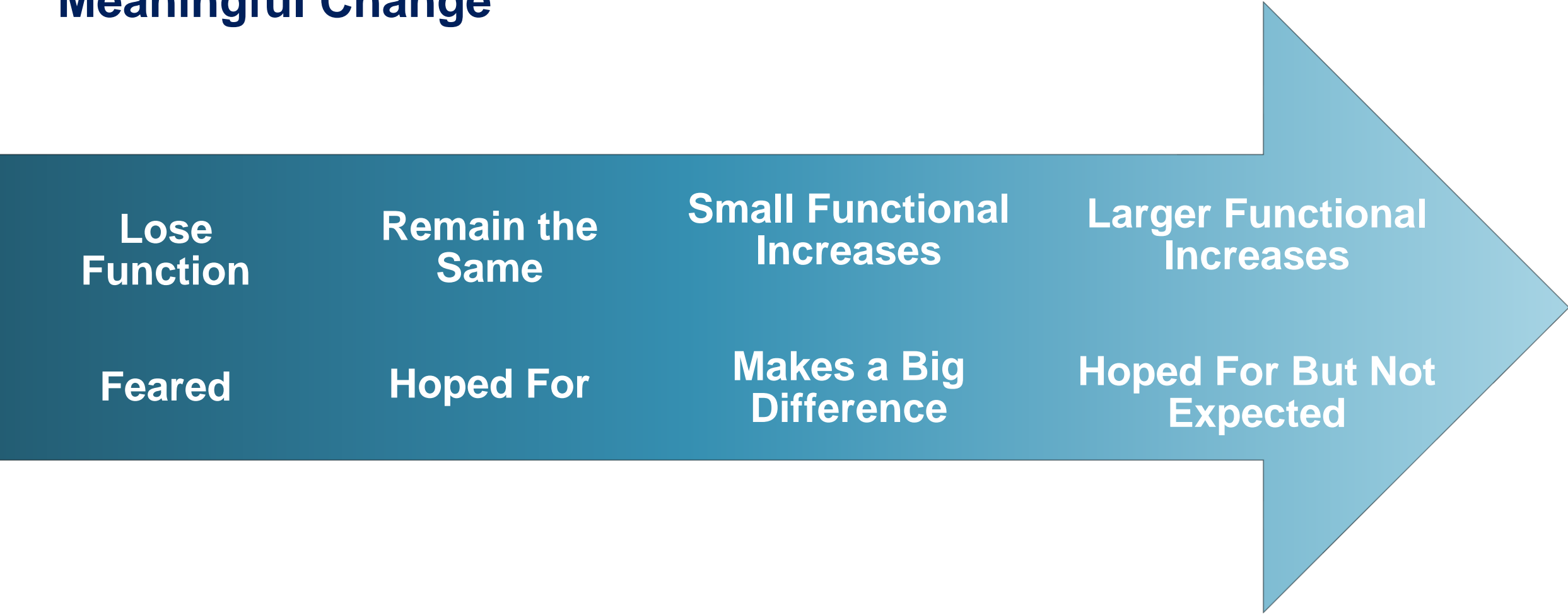
Delay in treatment increases risk for greater irreversible degeneration of motor neurons

- Organizations are mindful during decision making of the specific need to take into account the child population, treatment timing, rarity and severity of the disease.



Emerging Therapies

Meaningful Change



What Matters Most To Patients with SMA

- Type I
 - Ability to speak, communicate how child feels
 - Management of secretions
 - Respiratory Complications
 - Less dependence on machines
- Type II/III
 - Small changes / HUGE impact
 - Fatigue – Upper body strength/ diaphragmatic weakness
 - Respiratory Complications (type IIs)
 - Stopping disease progression, retaining mobility and function (Stabilizing disease)
- All Types
 - Muscle strength – stronger arms, legs, spine
 - Endurance



Lexi: With a Little Extra Neuromuscular Protein, Lexi Learns to Dance
<https://www.childrenscolorado.org/community/patient-stories/lexi-pacini-spinal-muscular-atrophy/>

Payers Understand the Clinical Benefits of Nusinersen, But Coverage is Variable Across Plans



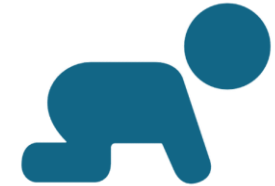
An antisense oligonucleotide (ASO) targeted to SMN2 pre-messenger ribonucleic acid (pre-mRNA).



Binds to SMN2 pre-mRNA to create a full-length SMN2 mRNA which produces a full-length SMN protein.



Administered intrathecally with 4 loading doses. Followed by maintenance doses every 4 months.



Improved motor function and motor milestones.

Payers Understand the Clinical Benefits of Nusinersen, But Coverage is Variable Across Plans

- List price is \$750,000 for the first year and \$375,000 in subsequent years.
- Coverage criteria is variable across payers
 - Some require evidence that the patient has a specific number of copies of the SMN2 gene (e.g., at least two copies) for coverage.
 - May not consider it medically necessary for individuals previously treated with SMN1 gene therapy.



“We want to make sure we understand the impact of the disease and what patients to prioritize in the treatment of their disease.” – *Health Plan*

Payers Understand SMN1 Gene Replacement is Transformative and Addresses Primary Genetic Cause Of SMA



Provides a functional copy of human SMN gene to halt disease progression through SMN protein expression.



Replaces the function of the missing or defective SMN1 gene.



Delivered as a single, one-time IV dose designed to provide long-term benefit.



Clinically transformative impact, showing achievement of motor milestones.

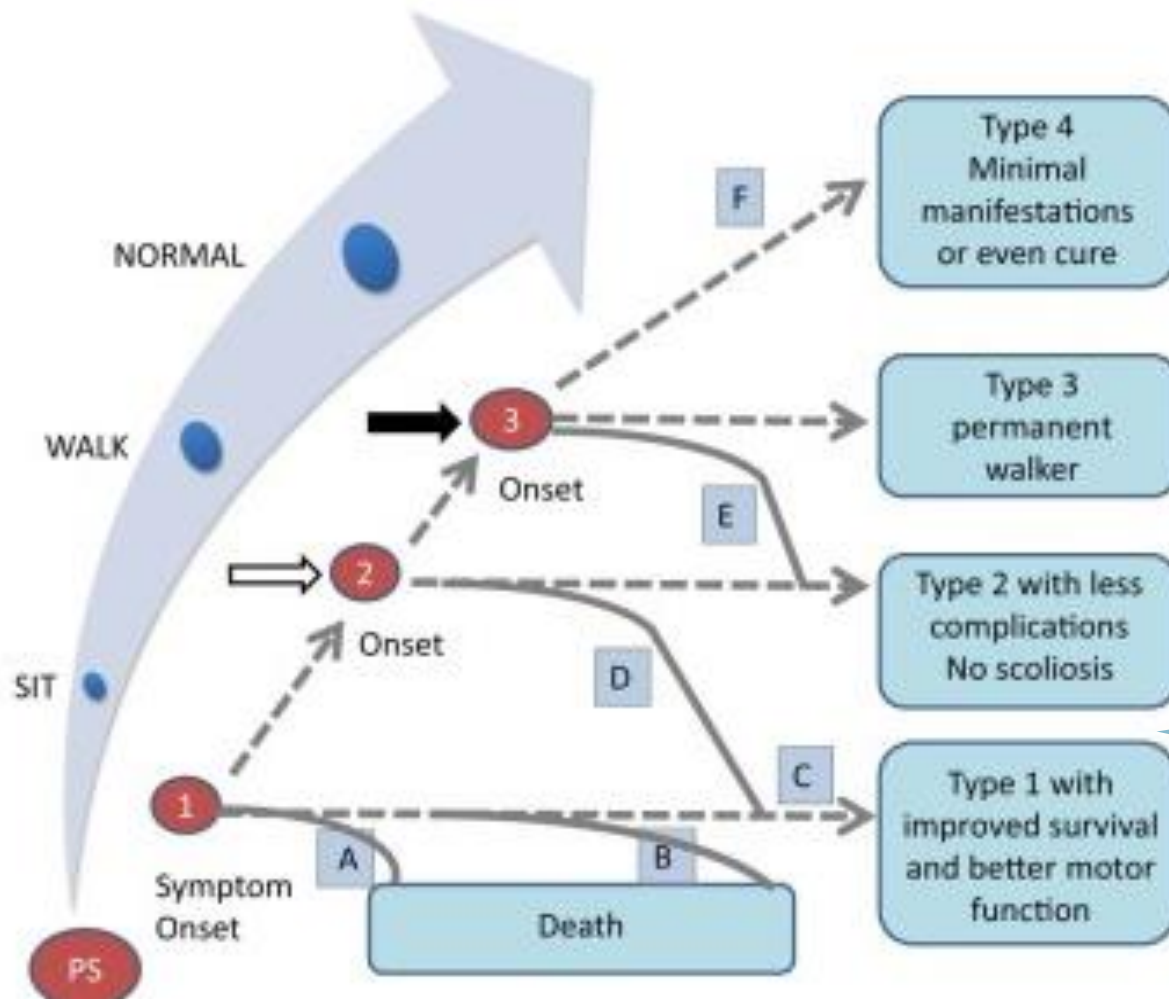
All But One Payer Has Developed Coverage Criteria for Gene Therapy

Considerations with onasemnogene abeparvovec (Zolgensma)

- IV vs. intrathecal
- Safety of higher doses by weight
- Vector manufacturing and dose, antibody titers in population
- Long-term safety, population genome effects
- Durability
- \$2.1 million per patient
- Limiting coverage to one dose per lifetime for a patient

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

Payers are Cautious about the Durability of Gene Therapy



“This is not a cure in the sense of its one time and these are going to be normal, healthy children that grow up into productive adults. There's still going to be impaired survival.” -Physician

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

Payers Anticipate Risdiplam will Have a Broad Label of Indications for use in SMA



Investigational survival motor neuron-2 (SMN2) splicing modifier, to help the SMN2 gene produce more functional SMN protein.



Increases SMN protein levels in the central nervous system and in peripheral tissues of the body.



Orally administered liquid.



Improved survival and motor milestones.

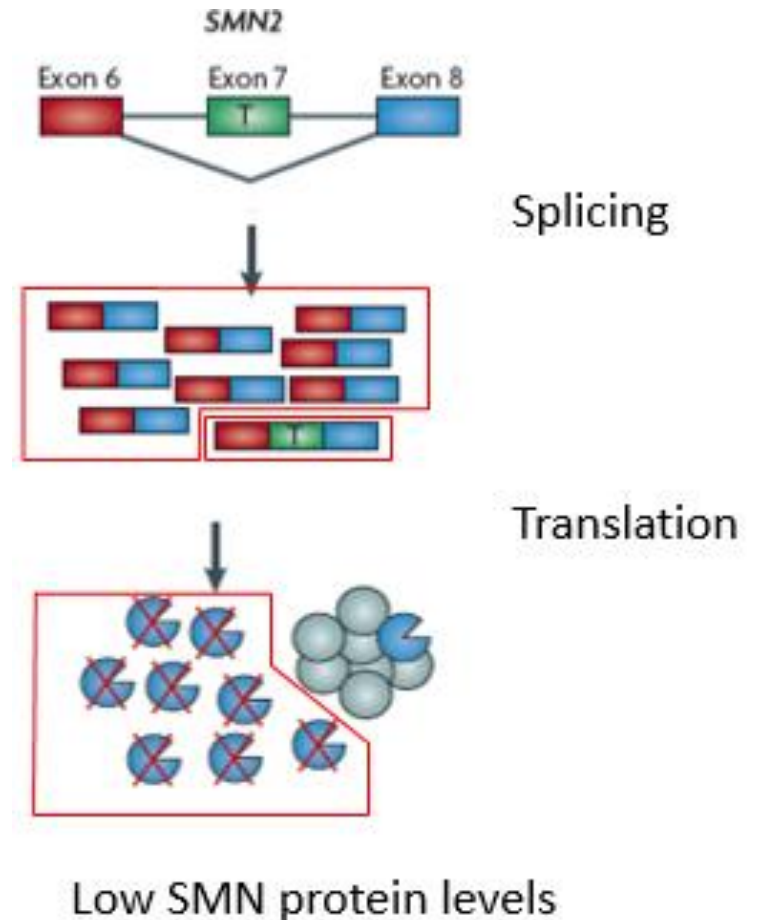
Payers Anticipate Managing Small Molecules Under the Pharmacy Benefit

Managed under the Pharmacy Benefit

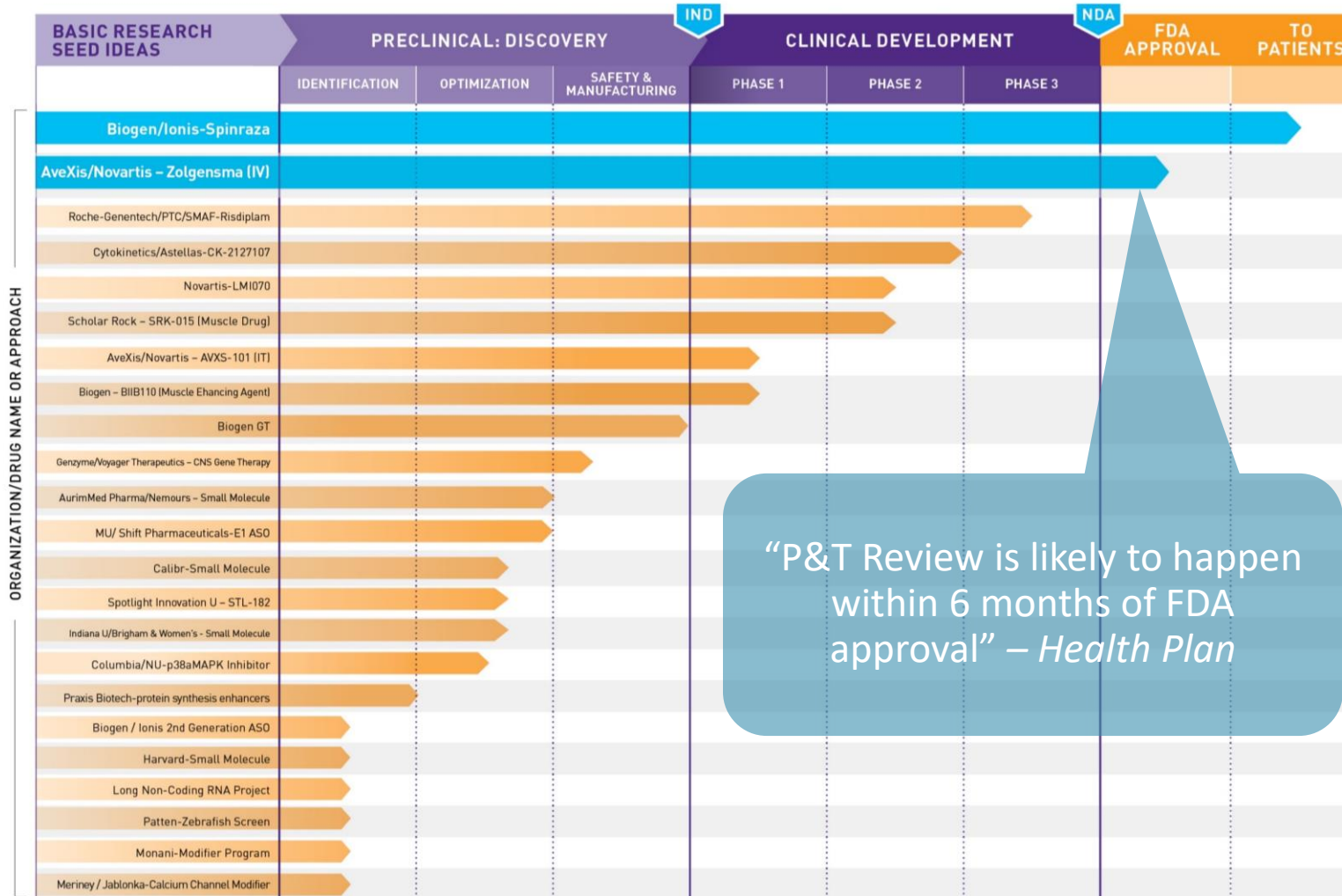
- Limited Distribution Drug, managed through Specialty Pharmacies.
- The difference in reimbursement across the pharmacy and medical benefit may also play a factor in preferred product selection.
- Payers will consider patient's out-of-pocket cost compared to a physician buying and billing for the injectable, as well as concerns around GI tolerability and adherence.

Possibly Preferred in Adolescents and Adult Patients

- Maybe a preferred treatment in those with complex spinal anatomy.



We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.



“P&T Review is likely to happen within 6 months of FDA approval” – *Health Plan*

SMA drug pipeline includes treatment strategies

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

IND = Investigational New Drug NDA = New Drug Application Last updated: June 2019

Education Altered the Perception of Combination and Sequencing of Therapies

- Tailor combination therapies to the individual patient based on genotype and age of diagnosis/ symptoms prenatal therapies
- Varying payer policies exist, including requiring treatment with nusinersen to be discontinued prior to infusion of gene therapy.
- Many patients are living with symptomatic SMA
- Cautioned about the potential safety concerns related to the unknown risks of providing too much SMN replacement
- Ideally clinical trial data (in animal models and humans) would be available to better inform safety and efficacy of combination therapy

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

“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*

Changing The Outlook For Patients

“We are unfortunate that Céline has this disease, but at the same time we are really lucky that we got an early diagnosis and could get the medication and gene therapy.” - *Celine’s Mother*

“While SMA remains a serious and life-threatening disorder, Spinraza and Zolgensma are changing the outlook for patients, they can stop progression of disease, making early diagnosis and rapid treatment critical to ensuring the best outcomes. While they are still not cures, they allow for continued motor improvement, particularly in the setting of supportive families and a commitment to rehabilitative therapy.” - *Celine’s Neurologist*



<https://www.chop.edu/stories/gene-therapy-treatment-spinal-muscular-atrophy-celines-story>



Payer Challenges

Payers are Challenged by Lack of Head-to-Head Studies and Treatment Guidelines

- Standards of care recommendations for SMA were last published in 2018, before these newer treatments were available broadly
- Need to address:
 - treatment sequencing and combination therapy
 - criteria for starting, switching and discontinuing SMA therapy
 - long-term safety and durability of effect
 - measurement scales or validated response assessment tool
 - SMA Type (1,2,3,4) or age of onset

“Our biggest challenge is development of criteria to ensure appropriate use, the appropriate patients are started, and when do you stop therapy.” -PBM

“At what point in therapy is there still clinical benefit?” -Regional Health Plan

“This is not a cure in the sense of its one time and these are going to be normal, healthy children that grow up into productive adults. There's still going to be impaired survival.”
-Physician

Payers Are Seeking Guidance Around Appropriate Outcomes for Inclusion In Outcomes Based Contracts

Several outcome measures were discussed, including:

- 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 – especially for gene therapy that may not really be a cure?” -*Physician*



Economic Models & Real World Evidence

Presentation Overview

- Role of RWE in Decision Making
- The ICER Institute's Role in evaluating Cost-effectiveness
- Economics and Evidence for SMA/Challenges in Modeling
- ICER SMA report
- SMA Cost-utility Study vs. Nusinersen

Real-World Evidence: *What is it?*

“...information on health care that is derived from multiple sources outside typical clinical research settings including...

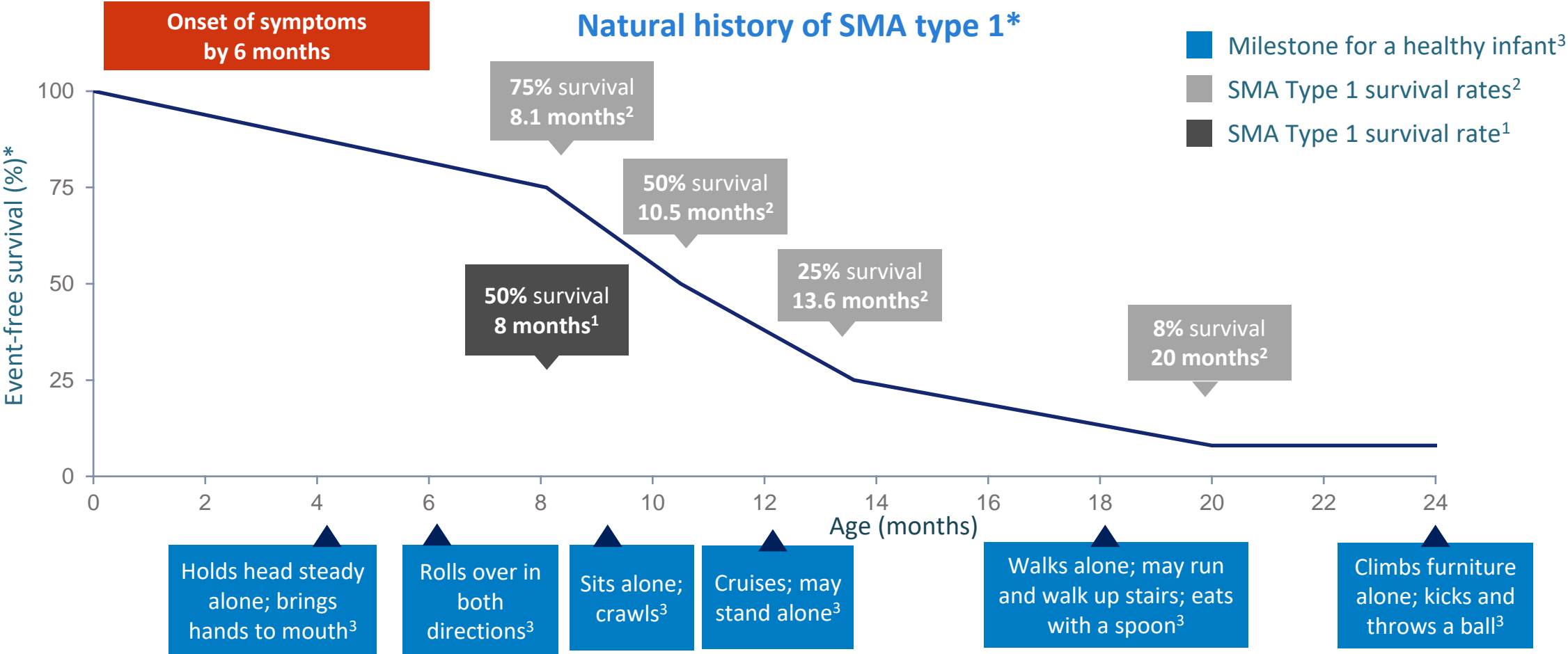
– Sherman RE, et al. Real-world evidence - what is it and what can it tell us? NEJM. 2016; 375: 2293-97. (All authors employed by the FDA)

Can you think of examples of RWE data sources?

- Electronic health records (EHRs)
- Claims and billing data
- Product and disease registries
- Data gathered through personal devices and health applications



Historical Context: More Than 90% of SMA Type 1 Patients Will Not Survive or Require Permanent Ventilator Support by 2 Years of Age



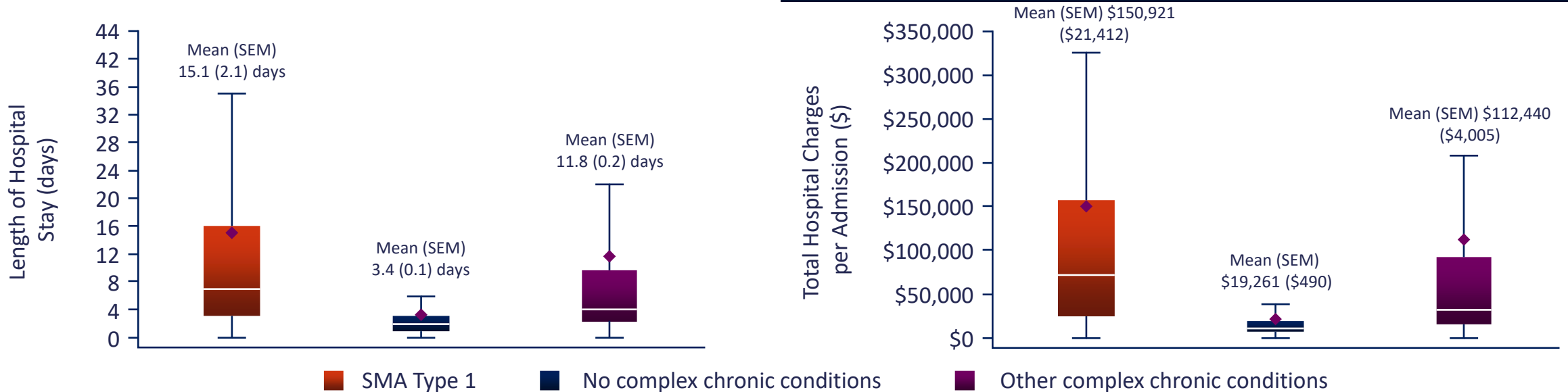
*Survival for Finkel² = no death, or no need for ≥16-hours/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (2 copies of *SMN2*). Survival for Kolb¹ = no death, or no tracheostomy; n=20. SMN, survival motor neuron.

Cost of Hospital Admissions for SMA Type 1 Patients As Compared to Controls

Retrospective analysis of the Kids' Inpatient Database)

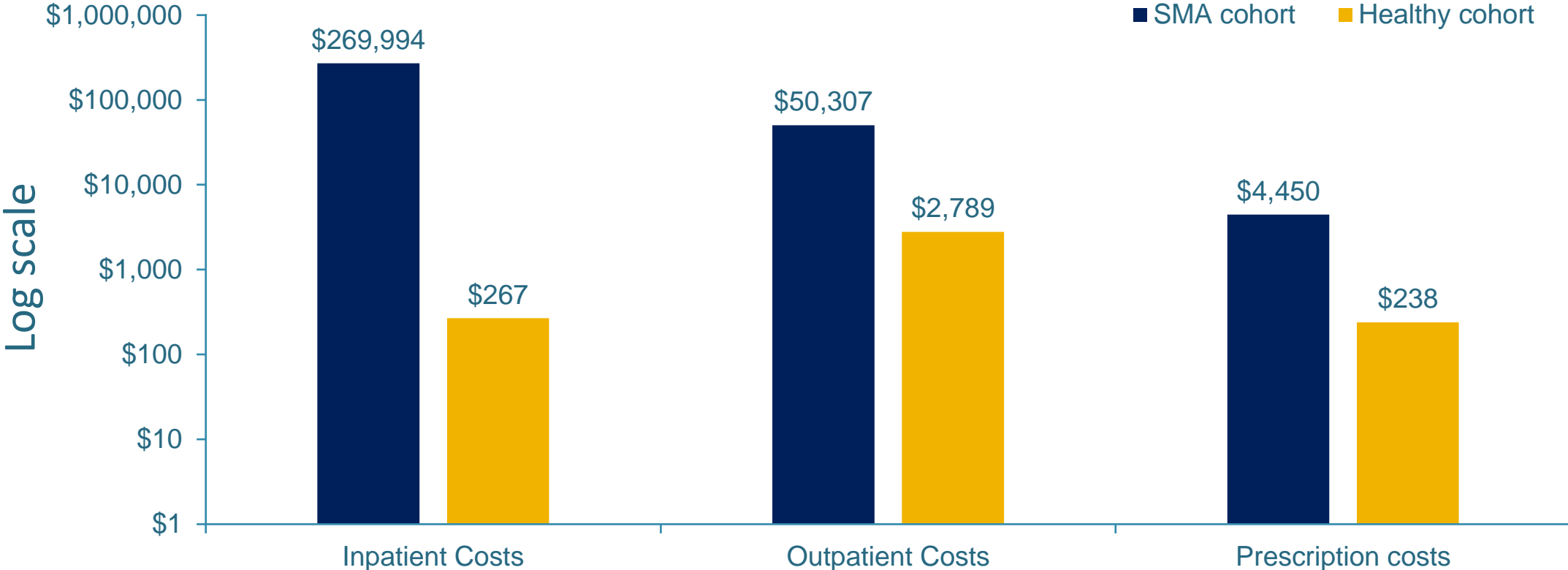
Hospitalizations for Type I SMA patients were longer than those for children without and with other complex chronic conditions

Cost per admission for SMA Type 1 patients significantly more expensive compared to children without and with other complex chronic conditions



Infants with Type 1 SMA were hospitalized 4.2 to 7.6 times/year compared to 1.7 in patients without SMA^{2,3}

Healthcare Expenditures for SMA Type 1 Compared to Non-SMA Controls



Payers Understand The Unique Value of Drugs for SMA

However they are managing finite healthcare resources under the steady increase in the number of orphan drugs approved across several diseases.

- The specialty drug trend continues to outpace that of traditional pharmaceuticals and remains a key priority of payer management
- Gene therapy forecasts demonstrate a significant cost impact on the specialty trend, including in SMA
- Cost-effectiveness thresholds to help inform coverage decisions
- Consider impact of newly-approved treatments on underwriting assumptions

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

“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*

Payers Have Challenges in Economic Modeling of SMA

- Identifying clinical care in presence of new therapies
 - Assume that patients monitored similar to clinical trials
 - Standard of care changes rapidly and may affect outcomes
- Determining baseline treatment
 - ICER evaluation of Zolgensma based on standard of care without nusinersen
 - Malone et al. used nusinersen as baseline therapy
- Converting health outcomes to utility values
 - Can't directly measure utility (quality of life) in infants
 - Few studies / limited evidence
- Utilizing the expertise of actuaries to set premiums

"It's not just the \$2 million upfront; it's the continuing \$500,000 [per year for combination therapy]."-
Regional Health Plan

Payers Rely on Cost-Effectiveness Experts to Understand Adjusting Costs and Benefits that Occur in the Future to Present Value

- Adjusts costs and benefits that occur in the future to present value (generally > 1 year)
- Based on concept of time preference for money
 - Uncertainty
 - Preference for goods today vs. delayed purchase
- Discount rate will vary: usually 3% or 5%
- QALYs Increase Dramatically When Discounting Is Reduced



Impact of Various Discount Rates on Quality Adjusted-Life Years

Comparator	Discount Rate						
	Quality-Adjusted Life Years						
	3%	2.5%	2%	1.5%	1%	0.5%	0%
Zolgensma	15.87	17.33	19.05	21.10	23.56	26.55	30.25
Nusinersen	5.29	5.54	5.81	6.11	6.44	6.81	7.21
Best Supportive Care	2.65	2.73	2.83	2.92	3.03	3.14	3.27

ICER's Study of SMA Treatments

Table ES11. Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	\$2,231,000	\$1,653,000	\$3,884,000	3.24	7.64	\$1,112,000	\$590,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table ES12. Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	\$2,000,000*	\$1,657,000	\$3,657,000	12.23	18.17	\$243,000	\$182,000
BSC	\$0	\$789,000	\$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment

Purpose: To evaluate the cost-effectiveness of AVXS-101 in patients with SMA1 in the United States and compare it with that of nusinersen, from a commercial payer perspective

Results: Cost-Effectiveness

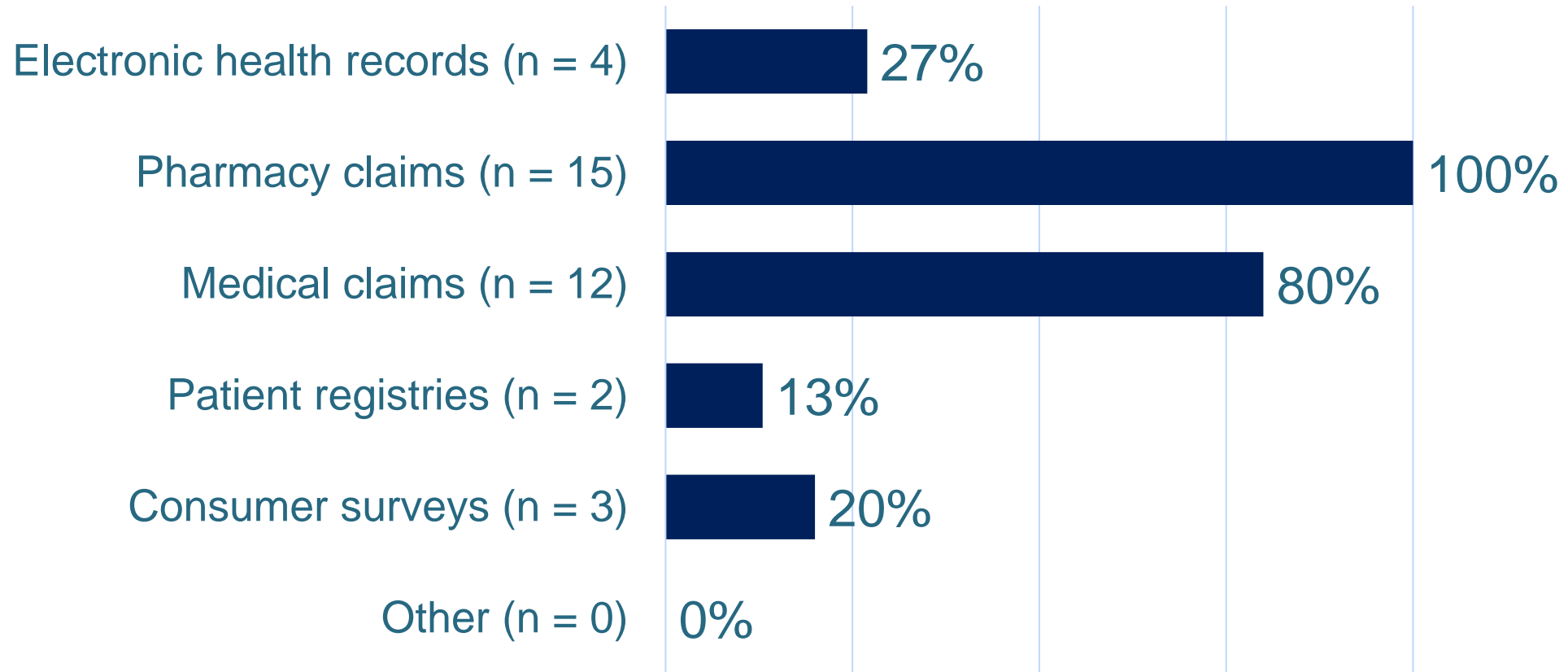
Treatment	Costs (discounted)	Life Years	QALYs (discounted)	ICER
Nusinersen	\$6.3 million	9.68	5.29	Base case
Zolgensma	\$4.2 million	37.20	15.65	Dominate

Payers See Evidence Challenges for Treatments of SMA

Considering a wide range of clinical evidence from multiple sources to make coverage decisions, including taking into account the young population, the rarity and severity of the disease, and the considerable impact on families and caregivers.

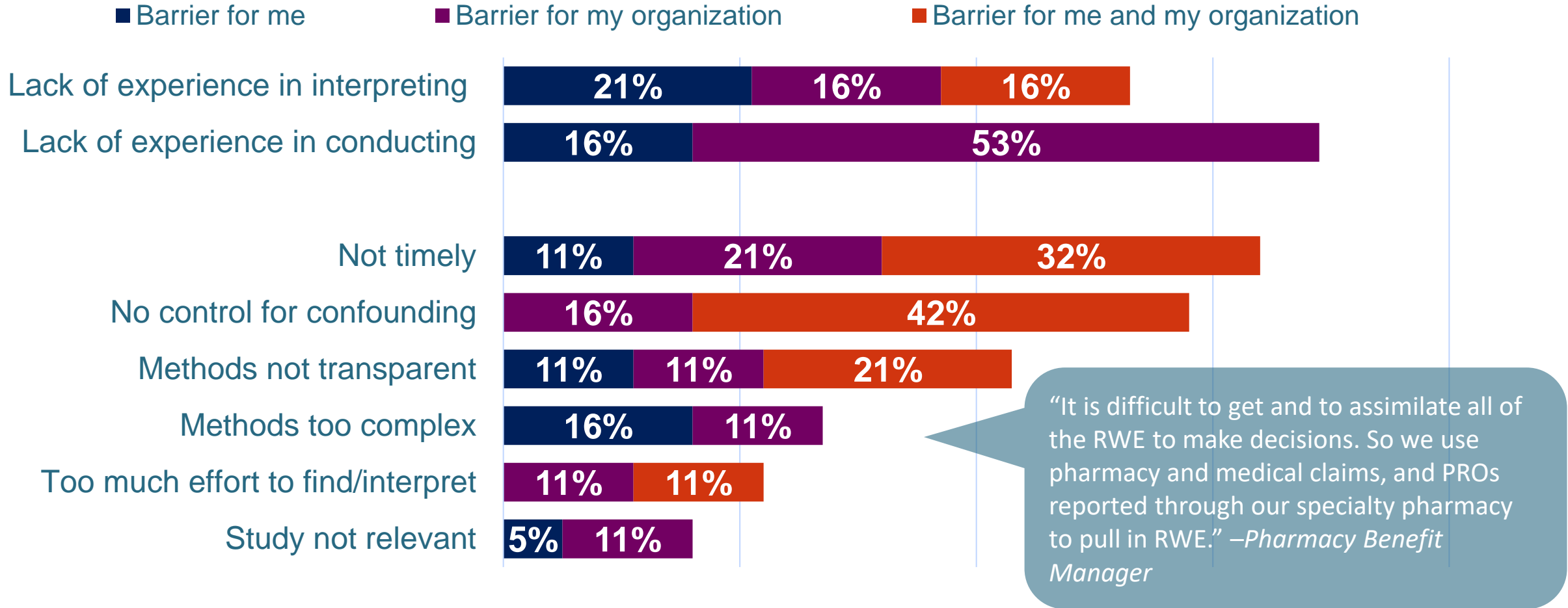
- Limited sample size
 - Rare disorders have limited number of available subjects
- Limited duration
 - Data from studies limited compared to duration of disease / benefit?
- No control group
 - Historical control
- Guidelines or treatment algorithm

Payers Use Different Types of Real World Data for Internal Analyses to Inform Coverage Decisions



Proportions of survey participants reporting on the types of data used for internal analyses to inform coverage decisions (N = 15).

Payers See Barriers with RWE



Perceived barriers to use of observational studies in decision making (N = 19).

Payers are Interested in Proactive and Predictive Payment and Insurance Models

- High-investment medications, in addition to the potential for patient migration between health plans, necessitates innovative payment models
 - Consider potential impact of gene therapy cost on access to other treatments
- Potential strategies
 - Outcomes-Based Agreements
 - Consider need for collection and tracking of real-world evidence
 - Gene-therapy manufacturer becomes responsible for other treatment costs (e.g., any necessary Factor costs) within a defined time period
 - Alternative Payment Models: Annuity payments, high risk pools, reinsurance programs, subscription payment programs where a per-member per month (PMPM) fee is paid to a third party
 - Take 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

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.

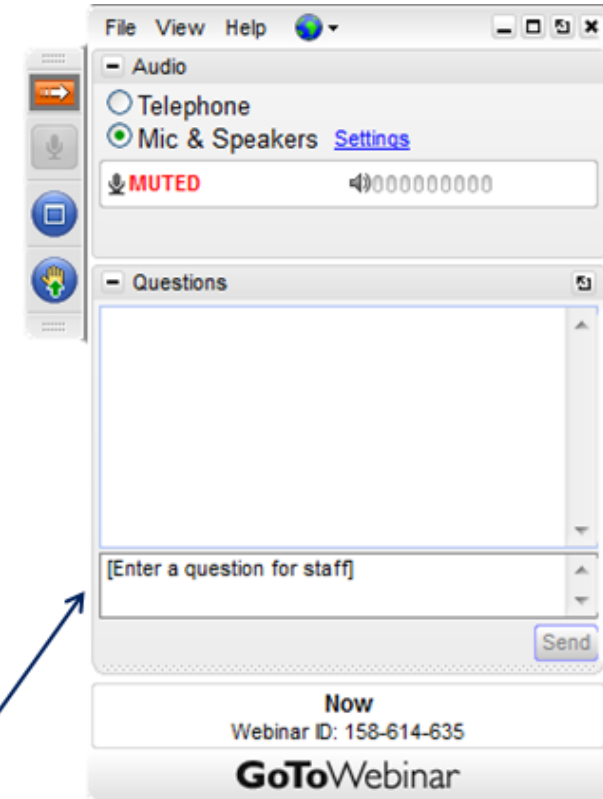
Summary

- 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.

How to Ask a Question

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Type your
question in the
'Questions' area



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