TARGET AUDIENCE

This educational initiative is targeted to neurologists, neuromuscular specialists, physical therapists, nurses, nurse practitioners, physician assistants, and adult SMA patients and caregivers.

LEARNING OBJECTIVES

- Examine the genetic etiology, pathophysiology, and clinical phenotypes of spinal muscular atrophy (SMA) in adult patients.
- Evaluate unique clinical challenges faced by adults with SMA, emphasizing key distinctions from pediatric SMA.
- Appraise completed, ongoing, and planned clinical trial data for novel SMA disease-modifying therapies (DMTs) in adult patients, with a focus on FDA-approved agents.
- Identify how adaptive SMA therapeutic strategies incorporating novel DMTs can fulfill unmet needs and optimize outcomes in adult patients.
- Use real-world patient cases to design evidence-supported treatment plans for adults with SMA, highlighting the critical importance of patient engagement and shared decision making.

AGENDA

5 min	Welcome and Introductions/Pre-test
15 min	Characterizing SMA in Adults: Pathophysiology, Phenotype, and Patient Challenges
15 min	Where DMT Meets SMA: Exploring the Evidentiary Base and Clinical Impact of Disease-modifying Therapeutics for Adults
15 min	Power to the Patient: Practical Pearls for Employing Patient-centered Care and Novel Therapies in SMA
10 min	Conversations with the Experts/Audience /Q&A/Post-test

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

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IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 1 hour of Interprofessional Continuing Education (IPCE) credit for learning and change.

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CEC designates this live educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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This application-based activity is approved for 1.0 contact hour (0.10 CEUs) of continuing pharmacy education credit (JA0007101-0000-22-011-L01-P)

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Characterizing SMA in Adults

Pathophysiology, Phenotype, and Patient Challenges

Pathophysiology

Classic or 5q spinal muscular atrophy (SMA), the target of novel disease-modifying treatment (DMT), accounts for over 95% of genetic disorders causing SMA

SMA is caused by an autosomal recessive deletion or mutation of the survival motor neuron (SMN) 1 gene. The *SMN1* gene produces most of the SMN protein in the body, which is vital for survival.

Low SMN protein levels in 5qSMA results in progressive loss of spinal α-motor neurons, muscle denervation, weakness, and atrophy

The wide phenotypic spectrum of disease in 5qSMA is predicated on the number of *SMN2* gene copies, which in humans varies from 1 to 5. Because the *SMN2* gene produces a small amount of SMN protein, disease severity is inversely related to *SMN2* copy number

Kolb SJ, Kissel JT. *Neurol Clin*. 2015.

Clinical Classification of SMA

Type	Age of Onset	Requires Respiratory Support at Birth	Able to Sit	Able to Stand	Able to Walk	Life Expectancy
0	Prenatal	Yes	No	No	No	<6 months
1	<6 months	No	No	No	No	<2 years
2	6–18 months	No	Yes	No	No	10–40 years
3	>18 months	No	Yes	Yes	Assisted	Adult
4	>18 years	No	Yes	Yes	Yes	Adult

- In treatment-naïve patients, SMA is classified as types 0–4 based on age of onset and ultimate motor function, even if function is lost at a later time
- Type 0 is of prenatal onset and is classified by some as a subset of type 1 (1a)
- Type 1 are non-sitters, type 2 are sitters, type 3 are walkers, and type 4 occurs in adults
- Early treatment has altered the natural history of SMA, making this classification system less informative

Kolb SJ, Kissel JT. *Neurol Clin.* 2015; Talbot K, Tizzano EF. *Gene Ther. 2017.*

Prevalence of SMA

- Globally, SMA prevalence is estimated to be ~1–2 individuals in 100,000 with an incidence rate of ~1 in 10,000 live births
- SMA type 1 is the most common type, accounting for ~60% of cases
- According to the National Institutes of Health (NIH) Genetic and Rare Diseases Information Center (GARD), the prevalence of SMA type 4 is ~1 in 300,000; SMA type 4 is the mildest type of SMA disorder, representing less than 1% of all SMA cases

Verhaart IEC, et al. *Orphanet J Rare Dis.* 2017; https://rarediseases.info.nih.gov/diseases/564/spinal-muscular-atrophy-type-4.

Adult SMA

- Adult SMA collectively encompasses both type 4 adult onset and those who develop SMA symptoms in childhood and survive beyond age 18 years
- An estimated 25% of patients with spinal muscular atrophy (SMA) are adults (age >18 years)
- The number of SMA patients reaching adulthood is likely to expand in light of improved outcomes observed with DMT
- The majority of therapies, disease management strategies, and related healthcare policies, however, primarily focus on pediatric populations

Butchbach ME. *Front Mol Biosci*. 2016; Verhaart IEC, et al. *J Neurol*. 2017; Walter MC, et al. *J Neuromuscul Dis*. 2021.

Multidisciplinary Approach

Clinical Issues That Can Be More Prevalent in Adults with SMA

- Fatigue
- Kidney stones
- Osteoporosis
- Acidosis
- Hypertension
- Weight management
- Sexual and reproductive health
- Hormonal issues

Mercuri E, et al. *Neuromuscul Disord.* 2018; Mongiovi P, et al. *Neurology.* 2018; LaMarca NH, et al. *J Child Neurol*. 2013; Darba J, Marsa A. *BMJ Open*. 2019.

Challenges for Adult SMA Patients

- Transitioning from pediatric to adult care
- Finding specialists and clinics for adults
- Finding financial assistance for equipment
- Being undervalued by the healthcare system
- Lack of support from society
- Relying on family and friends for support
- Access to mental health services

Wan HWY, et al. *Orphanet J Rare Dis*. 2020.

Where DMT Meets SMA

Exploring the Evidentiary Base and Clinical Impact of Disease-modifying Therapeutics for Adults

SMA Timeline

- **1967**—Three traditional types of SMA classified
- **1995**—Survival motor neuron (SMN) genes discovered
- **2015–2021**—Gene therapy and small molecule clinical trials
- **2016**—U.S. Food and Drug Administration (FDA) approves nusinersen for all SMA types and all ages
- **2019**—FDA approves gene replacement therapy (onasemnogene abeparvovec-xioi) for SMA in children age <2 years
- **2020**—FDA approves risdiplam for SMA patients age >2 months

Kolb SJ, Kissel JT. *Neurol Clin.* 2015; FDA Prescribing Information.

Nusinersen

Nusinersen is an mRNA-based therapy. Antisense oligonucleotide (ASO) targets specific site on survival motor neuron 2 (SMN2) mRNA that increases transcription of full-length SMN protein. It is approved for use in pediatric and adult patients.

It is administered intrathecally. Treatment is initiated with 4 loading doses, followed by a maintenance dose every 4 months. Warnings and precautions include thrombocytopenia, coagulation abnormalities, and renal toxicity.

The ENDEAR trial showed efficacy of nusinersen in infants, and the CHERISH trial showed efficacy in children age 2–12 years with SMA.

FDA Prescribing Information; Finkel RS, et al. *N Engl J Med*. 2017; Mercuri E, et al. *N Engl J Med*. 2018.

Nusinersen in Adult SMA

- Prospective cohort study of 173 SMA patients ages 16–65: 139 eligible for analyses
- Primary outcome: Hammersmith Functional Motor Scale Expanded (HFMSE)
- Secondary outcome: Revised Upper Limb Module (RULM) and 6-minute walk test (6WMT)
- Changes from baseline assessed at 6, 10, and 14 months were significant for all 3 outcomes

Clinically meaningful improvements in motor function were seen in this real-world cohort

Follow-up	**N** (%)	**Δ HFMSE from BL** (95% CI)	**% with ≥3-point increase in HFMSE**	**Δ 6MWT** (321–371 m BL)
6 months	124 (89%)	1.73 (1.05–2.41)	28%	22.1 m
10 months	92 (66%)	2.58 (1.76–3.39)	35%	31.1 m
14 months	57 (41%)	3.12 (2.06–4.19)	40%	46.0 m

Hagenacker T, et al. *Lancet Neurol*. 2020.

Nusinersen in Adult SMA

- Retrospective cohort study of 116 patients ages 18–72 years with SMA types 2 and 3
- Largest real-world study of SMA type 3 to date, with 103 adult patients

Percentage of Patients Who Were Responders to Nusinersen at 14 Months

SMA Type	% responders (HFMSE)	% responders (RULM)	% responders (6MWT)	Overall responders
All SMA	49%	35%	N/A	69%
SMA II	20%	60%	N/A	60%
SMA III	52%	32%	42%	70%

Maggi L, et al. *J Neurol Neurosurg Psychiatry*. 2020.

Risdiplam

Risdiplam is an mRNA-based molecule acting on SMN2 mRNA to increase inclusion of exon 7, thus increasing transcription of full-length SMN protein. It is indicated for SMA patients of all ages (approved in the United States for use under 2 months).

Risdiplam is a liquid preparation, administered once daily by mouth or GT tube, that has widespread systemic distribution, including of CNS.

The most common side effects seen are fever, diarrhea, and rash.

FIREFISH is an open-label study that showed efficacy of risdiplam in infants ages 2–7 months.

FDA Prescribing Information; Darras BT, et al. *N Engl J Med*. 2021.

SUNFISH

Part 1

- Exploratory dose-finding study in 51 individuals with ambulant or non-ambulant type 2 or 3 SMA
- Enrolled individuals age 2–25 years
- Determined the dose used in part 2 of study

Part 2

- Multicenter, phase 3, double-blind, randomized, placebo-controlled trial
- Primary endpoint of change from baseline in motor function as measured by Motor Function Measure 32 (MFM-32)
- Secondary endpoints include marked improvement in MFM-32, change from baseline in RULM, HFMSE, forced vital capacity (FVC), Spinal Muscular Atrophy Independence Scale (SMAIS), and proportion of patients rated as "improved" on Clinical Global Impression of Change (CGI-C)

Mercuri E, et al. *Lancet Neurol*. 2022.

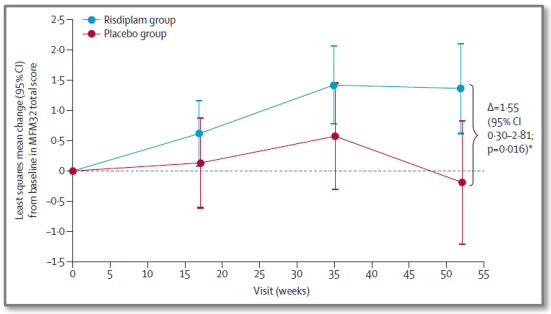
SUNFISH Part 2

Age Group	Risdiplam group (n=120)	Placebo group (n=60)
2–5 years	37 (31%)	18 (30%)
6–11 years	39 (33%)	18 (30%)
12–17 years	30 (25%)	16 (27%)
18–25 years	14 (12%)	8 (13%)

- Average score increase in patients on risdiplam compared to placebo
  - MFM32: 1.36 points vs -0.19 point
  - RULM: 1.61 points vs 0.02 points
- Using the novel SMA Independence Scale (SMAIS), risdiplam also improved independence in activities of daily living (ADLs), such as brushing teeth

This is the first treatment to have positive pivotal placebo-controlled data in a broad population of patients with SMA.

Least Squares Mean Change from Baseline in MFM32 Total Score



Mercuri E, et al. *Lancet Neurol*. 2022.

Ongoing Studies

SHINE is follow-up study of SMA patients (infants and late onset) who were enrolled in earlier **nusinersen** studies and continue to receive nusinersen. Expected completion is 2023.

JEWELFISH is an ongoing, exploratory, non-comparative, open-label study looking at the safety of **risdiplam** in 174 patients ages 1–60 years who had been previously treated with other SMA medications. Results are expected in 2024.

ClinicalTrials.gov. Identifiers: NCT02594124, NCT03032172.

Power to the Patient

Practical Pearls for Employing Patient-centered Care and Novel Therapies in SMA

Words from Adults with SMA

- "Many adults and teens speak to me as though I'm much younger or will talk to the person I'm with acting as though I'm not really there."
- "I feel like people judge me just by seeing the wheelchair. People treat me like I'm a baby or mentally disabled or too innocent, and I'm none of those things!"
- "It makes me sad when people stare at me. I know they're probably just 'curious,' but still, it makes me upset."
- "I was just diagnosed with depression and anxiety, mostly from the constant worrying about my life and having SMA. I think that in some cases having SMA makes me want to work harder and prove others wrong, but at the same time there are a lot of days where I just want to give up and say what's the point."

Mazzella A, et al. *Orphanet J Rare Dis*. 2021.

A Changing Landscape

With the recent approval of three DMTs, the phenotypic presentation and prevalence of SMA in adult patients is expected to change.

There are many uncertainties regarding best clinical practice, treatment response, and long-term outcomes for adults with SMA.

Healthcare providers involved in the treatment of adult SMA patients should be more cognizant of these issues and engage with patients to improve their care and treatment outcomes on a patient-centric basis.

While standards of care (SOC) do exist, they are generally geared toward pediatric patients and may overlook some or many of these adult considerations.

Sporer SM, Smith BG. *J Pediatr Orthop*. 2003; Mazzella A, et al. *Orphanet J Rare Dis*. 2021.

Aspirations

- A group of clinical SMA leaders recently published a call to action to improve care and empower adults living with SMA

Provide age-appropriate and comprehensive care that delivers the most meaningful health outcomes and QoL for adults living with SMA

→

Establish more integrated pathways that enable adults living with SMA to optimally manage their multifaceted healthcare needs

→

Strengthen social and financial support systems that empower adults living with SMA and their caregivers to fulfill their personal goals

- It is important to emphasize a patient-centered approach to treating adults with SMA, recommending therapies that are specific to that patient's symptoms and lifestyle

Walter MC, et al. *J Neuromuscul Dis*. 2021; Farrar MA, et al. *BMJ Open*. 2018.

Conversations with the Experts

Case of GR

GR is a 20-year-old female who was diagnosed with SMA at age 12 months and is fully confined to her power wheelchair. She recently moved to the area with her parents and is establishing care with you as her healthcare provider.

How would you classify GR's adult SMA?

A. Type 1
B. Type 2
C. Type 3
D. Type 4

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- Early treatment has altered the natural history of SMA, making this classification system less informative

Kolb SJ, Kissel JT. *Neurol Clin.* 2015; Talbot K, Tizzano EF. *Gene Ther. 2017.*

Case of GR

GR reports that prior to moving she received the majority of her care from her pediatric neurologist. She does some mobility exercises on her own that she found on the internet, and she has a history of recurrent respiratory infections. She also reports she recently created a dating profile and is excited to meet some new people in the area.

Which referrals would be most appropriate for GR?

A. Physical therapy
B. Pulmonary
C. Sexual and reproductive health
D. All the above

Multidisciplinary Approach

Clinical Issues That Can Be More Prevalent in Adults with SMA

- Fatigue
- Kidney stones
- Osteoporosis
- Acidosis
- Hypertension
- Weight management
- Sexual and reproductive health
- Hormonal issues

Mercuri E, et al. *Neuromuscul Disord.* 2018; Mongiovi P, et al. *Neurology.* 2018; LaMarca NH, et al. *J Child Neurol*. 2013; Darba J, Marsa A. *BMJ Open*. 2019.

Case of GR

GR is currently being treated with nusinersen for her SMA. She reports she has been on it for several years and has noticed her muscle weakness has been progressing recently. She also reports severe anxiety leading up to each intrathecal administration of the drug.

Which of the following is most appropriate to recommend?

A. Switch nusinersen to risdiplam
B. Switch nusinersen to onasemnogene abeparvovec-xioi
C. Add risdiplam to the nusinersen
D. No changes needed at this time

SUNFISH Part 2

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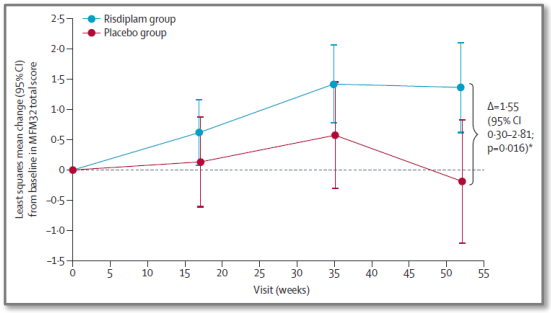

Mercuri E, et al. *Lancet Neurol*. 2022.

Case of GR

GR's parents are worried about her physical and mental health as GR ages. They want to support her in any way that they can.

Which of the following is the most appropriate response?

A. There are very few uncertainties regarding best clinical practice, treatment response, and long-term outcomes for adults with SMA. We have an abundance of data in this patient population.

B. The standards of care (SoC) for SMA are geared toward adult patients and are an informative resource for caregivers and healthcare professionals

C. Some helpful resources include Cure SMA, the Muscular Dystrophy Association, and the National Organization for Rare Disorders (NORD)

D. It is not important to emphasize a patient-centered approach to treating adults with SMA; continued care through pediatric providers is recommended

Resources

- Cure SMA
- Muscular Dystrophy Association
- SMA My Way
- National Organization for Rare Disorders (NORD)
- SMA News Today

Optimizing Outcomes for Adults with Spinal Muscular Atrophy

Patient-centric Strategies for the Multidisciplinary Treatment Team

Bibliography

Butchbach ME. Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. *Front Mol Biosci*. 2016;3:7.

ClinicalTrials.gov. A study for participants with spinal muscular atrophy (SMA) who previously participated in nusinersen (ISIS 396443) investigational studies (SHINE). Identifier: NCT02594124. ClinicalTrials website. https://clinicaltrials.gov/ct2/show/NCT02594124. Accessed August 2022.

ClinicalTrials.gov. A study of risdiplam (RO7034067) in adult and pediatric participants with spinal muscular atrophy (JEWELFISH). Identifier: NCT03032172. Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT03032172. Accessed August 2022.

Cure SMA. Voice of the patient report: spinal muscular atrophy. January 10, 2018. Cure SMA website. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf. Accessed August 2022.

Cruz R, Lenz M, Belter L, et al. Voice of the patient report: spinal muscular atrophy. January 10, 2018. Cure SMA website. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf. Accessed January 2023.

Darba J, Marsa A. Patient characteristics and hospitalisation costs of spinal muscular atrophy in Spain: a retrospective multicentre database analysis. *BMJ Open*. 2019;9(11):e031271.

Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, et al. Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls. *N Engl J Med*. 2021;385(5):427–435.

Farrar MA, Carey KA, Paguinto S-G, et al. Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives. *BMJ Open*. 2018;8(5):e020907.

FDA-approved drug: nusinersen. Revised December 2016. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf. Accessed August 2022.

FDA-approved drug: onasemnogene abeparvovec-xioi. Revised October 2021. U.S. Food and Drug Administration website. https://www.fda.gov/media/126109/download. Accessed August 2022.

FDA-approved drug: risdiplam. Revised April 2021. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213535s001lbl.pdf. Accessed August 2022.

Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1723–1732.

Hagenacker T, Wurster CD, Günther R. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study (see appendix). *Lancet Neurol*. 2020;19(4):317–325.

Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin*. 2015;33(4):831–846.

LaMarca NH, Golden L, John RM, et al. Diabetic ketoacidosis in an adult patient with spinal muscular atrophy type II: further evidence of extraneural pathology due to survival motor neuron 1 mutation? *J Child Neurol*. 2013;28(11):1517–1520.

Maggi L, Bello L, Bonanno S, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1166–1174.

Mazzella A, Curry M, Belter L, et al. "I have SMA, SMA doesn't have me": a qualitative snapshot into the challenges, successes, and quality of life of adolescents and young adults with SMA. *Orphanet J Rare Dis*. 2021;16(1):96.

Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378(7):625–635.

Mercuri E, Deconinck N, Mazzone ES, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial [published correction appears in *Lancet Neurol*. 2022;21(2):e2] [published correction appears in Lancet Neurol. 2022;21(3):e3]. *Lancet Neurol*. 2022;21(1):42–52.

Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* 2018;28(2):103–115.

Mongiovi P, Dilek N, Garland C, et al. Patient reported impact of symptoms in spinal muscular atrophy (PRISM-SMA). *Neurology.* 2018;91(13):e1206–e1214.

Rouault F, Christie-Brown V, Broekgaarden R, et al. Disease impact on general well-being and therapeutic expectations of European type II and type III spinal muscular atrophy patients. *Neuromuscul Disord.* 2017;27:428–38.

Ozge Ozkaya. Spinal Muscular Atrophy: SMA Type 4. Rare Disease Advisor Website. Available at: https://www.rarediseaseadvisor.com/hcp-resource/spinal-muscular-atrophy-type-4/#:~:text=Spinal%20muscular%20atrophy%20%28SMA%29%20type%204%20is%20the,be%20approximately%201%2F300%2C000.%203%20SMA%20Type%204%20Causes. Last reviewed July 2021. Accessed January 2023.

Sporer SM, Smith BG. Hip dislocation in patients with spinal muscular atrophy. *J Pediatr Orthop*. 2003;23(1):10–14.

Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. *Gene Therapy.* 2017;24:529-533.

Verhaart IEC, Robertson A, Leary R, et al. A multi-source approach to determine SMA incidence and research ready population. *J Neurol*. 2017;264(7):1465–1473.

Verhaart IEC, Robertson A, Wilson IJ. et al. Prevalence, incidence, and carrier frequency of 5q–linked spinal muscular atrophy—a literature review. *Orphanet J Rare Dis.* 2017;12(124).

Walter MC, Chiriboga C, Duong T, et al. Improving care and empowering adults living with SMA: a call to action in the new treatment era. *J Neuromuscul Dis*. 2021;8(4):543–551.

Wan HWY, Carey KA, D'Silva A, et al. Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. *Orphanet J Rare Dis*. 2020;15(1):70.