TV-109-010720-90

SYLLABUS AND COURSE GUIDE

Clinical Insights on Recent Advances in Spinal Muscular Atrophy

A Free, 90-Minute CME/CNE/CPE/MIPS/ABIM MOC/ABP MOC Live and On-Demand Activity

Premiere Date: Tuesday, January 7, 2020

12:00 PM - 1:30 PM ET (live)

Credit Expiration Date: Thursday, January 7, 2021

On the Web: http://bit.ly/TV-109

LIVE FACULTY: John Brandsema, MD; Nancy L. Kuntz, MD, FAAN

MODERATOR: Emma Ciafaloni, MD, FAAN

Take advantage of our LIVE Q&A segment during this webcast!

During the webcast **type a question in the box under the presentation**

Email your question or comment: **questions@cmeoutfitters.com**

All other questions: Call CME Outfitters at 877.CME.PROS

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CME Outfitters

INFORMATION FOR PARTICIPANTS

Statement of Need

Spinal muscular atrophy (SMA) is a leading, fatal, autosomal recessive disorder that affects approximately one in 10,000 live births. Nusinersen was approved as the first targeted therapy for SMA, and since its groundbreaking approval data has been published that demonstrates its efficacy for both infantile- and later-onset SMA populations. Additionally, recent guidelines were published that provide evidence-based recommendations for the diagnosis and management of SMA.

However, despite these advances there are knowledge gaps among health care providers (HCPs) regarding current data on safety and efficacy of approved and emerging therapies, which can result in treatment delays. Closing these gaps will promote early and accurate diagnosis and optimal treatment of patients with SMA.

In this CME Outfitters live and on demand webcast, expert faculty will host a case-based panel discussion that focuses on screening and early diagnosis of SMA and the importance of utilizing the latest clinical data on the efficacy and safety of approved and emerging therapies.

Learning Objectives

At the end of this CE activity, participants should be able to:

- Review the pathophysiology and therapeutic targets of SMA.
- Apply the current recommendations for screening and early diagnosis of SMA.
- Evaluate the latest clinical data on the efficacy and safety of approved and emerging therapies for SMA.

The following learning objectives pertain only to those requesting CNE or CPE credit:

- Review the pathophysiology and therapeutic targets of SMA.
- Describe the current recommendations for screening and early diagnosis of SMA.
- Evaluate the latest clinical data on the efficacy and safety of approved and emerging therapies for SMA.

Target Audience

Pediatricians, neurologists, primary care physicians, physician assistants, nurse practitioners, nurses, and pharmacists.

Financial Support

Supported by educational grants from Biogen MA, Inc. and Genentech.

CREDIT INFORMATION

CME Credit (Physicians)

CME Outfitters, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CME Outfitters, LLC, designates this live activity for a maximum of 1.5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Universal Activity Number:
Live: 0376-0000-20-001-L01-P; Enduring: 0376-0000-20-001-H01-P
Type: knowledge-based

ABIM/MOC Credit:

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Formats:

Live activity
Enduring Material

ABPN/MOC Credit:

Note to ABPN Diplomates: ABPN Diplomates may select any activity relevant to their practice to count towards ABPN MOC requirements.

ABP/MOC Credit:

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Royal College MOC:

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

MIPS Improvement Activity:

This activity counts towards MIPS Improvement Activity requirements under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

CREDIT REQUIREMENTS

Post-tests, credit request forms, and activity evaluations must be completed online (requires free account activation), and participants can print their certificate or statement of credit immediately (75% pass rate required). This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit https://www.cmeoutfitters.com/privacy-and-confidentiality-policy.

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FACULTY BIOS & DISCLOSURES

Emma Ciafaloni, MD, FAAN (Moderator)

Dr. Ciafaloni is the Director of the Pediatric Neuromuscular Program and Co-Director of the MDA Clinic at URMC and has devoted her career to the diagnosis and treatment of adult and pediatric patients with neuromuscular disease, particularly patients with muscular dystrophies, Duchenne, SMA, ALS, and myasthenia gravis. As a Professor of Neurology and Pediatrics as well as the Program Director for the Neuromuscular Medicine Fellowship, she also takes pleasure in training Neurology residents and neuromuscular fellows in the diagnosis and treatment of patients with neuromuscular disease. Her research interests have focused on clinical trials in Myasthenia Gravis and Duchenne Muscular Dystrophy, as well as studying pregnancy outcomes in women with neuromuscular diseases.

After undergraduate training in Milano, Italy in Philosophy and ancient Greek, Dr. Ciafaloni obtained her medical degree at the Universita Statale of Milano, Italy, followed by a Fellowship in mitochondrial diseases at Columbia University in the laboratory directed by Dr. Salvatore Di Mauro. She then completed a neurology residency at Duke University in Durham, North Carolina. She completed her EMG/Neuromuscular Fellowship at Duke also, and became an attending there for two years, before accepting a position on the Neurology faculty at the University of Rochester in 2002.

John Brandsema, MD

Dr. Brandsema is an Attending Physician in Neuromuscular/ General Neurology & Electromyography and the Neuromuscular Section Head at the Children's Hospital of Philadelphia. He completed medical school as well as postgraduate training in Pediatric Neurology in Canada, followed by the Partners Neuromuscular Fellowship at Harvard in Boston. Dr. Brandsema has broad clinical and research interests in neuromuscular diseases, with a particular focus in clinical trials of novel therapies for childhood neuromuscular disorders. Outside of the hospital, he is a classically trained singer and musician, a budding Philadelphia sports fan, and helps his partner breed champion Lakeland Terriers.

Nancy L. Kuntz, MD, FAAN

Dr. Kuntz is a child neurologist with additional board certifications in pediatrics, electrodiagnostic medicine and autonomic medicine. She is Medical Director of the Mazza Foundation Neuromuscular Disorders Program, the PPMD Duchenne Care Center, and the MDA Care Center at Lurie Children's Hospital of Chicago. Dr. Kuntz is interested in the early diagnosis of neuromuscular disorders and the development of less invasive methods of neuromuscular diagnosis in children such as electrical impedance myometry, ultrasound, nerve excitability and motor unit mapping. She serves as site principal investigator in a number of natural history and clinical treatment trials for neuromuscular disorders including spinal muscular atrophy, Duchenne and Becker muscular dystrophies and X-linked myotubular myopathy. Dr. Kuntz is a professor of pediatrics and neurology at the Northwestern Feinberg School of Medicine in Chicago, Illinois.

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It is the policy of CME Outfitters, LLC, to ensure independence, balance, objectivity, and scientific rigor and integrity in all of their CE activities. Faculty must disclose to the participants any relationships with commercial companies whose products or devices may be mentioned in faculty presentations, or with the commercial supporter of this CE activity. CME Outfitters, LLC, has evaluated, identified, and attempted to resolve any potential conflicts of interest through a rigorous content validation procedure, use of evidence-based data/research, and a multidisciplinary peer review process. The following information is for participant information only. It is not assumed that these relationships will have a negative impact on the presentations.

Dr. Ciafaloni reports that she is on the advisory committee for AveXis, Inc. and Biogen. She is on the speakers bureau for Biogen.

Dr. Brandsema reports that he received a grant from Biogen (CHOP Neuromuscular fellowship). He receives research support from AveXis, Inc. and Biogen (Site PI for clinical trials) is on the advisory committee for AveXis, Inc. and Biogen and is a consultant for AveXis, Inc.; Biogen and Roche/Genentech, Inc.

Dr. Kuntz reports that she receives research support from Audentes Therapeutics; AveXis, Inc.; Biogen and Sarepta Therapeutics provided support for clinical research. Funds direct to institution. She is on the advisory committee for argenx; Audentes Therapeutics; Biogen; Cytokinetics, Inc.; F. Hoffmann-La Roche Ltd and Sarepta Therapeutics.

Tony Graham, MD (peer reviewer) has no disclosures to report.

Mae Ochoa, RPh (peer reviewer) has no disclosures to report.

Kavitha Ramachandran, PhD (planning committee) has no disclosures to report.

Evan Luberger (planning committee) has no disclosures to report.

Jan Perez (planning committee) has no disclosures to report.

Sharon Tordoff (planning committee) has no disclosures to report.

Disclosures were obtained from the CME Outfitters, LLC staff: No disclosures to report.

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Clinical Insights on Recent Advances in Spinal Muscular Atrophy

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CME Outfitters, LLC, gratefully acknowledges educational grants from Biogen MA, Inc. and Genentech in support of this CME/CE activity.

The course guide for this activity includes slides, disclosures of faculty financial relationships, and biographical profiles.

View and/or print the course guide from the ***Resources*** tab on the top right of your window.

To receive CME/CE credits for this activity, participants must complete the post-test and evaluation online.

Go to the ***Credit Tab*** at the top of the video box and click on the link to complete the process and print your certificate.

Please be sure to indicate the media format utilized and the date of participation when completing the online evaluation.

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any use not approved by the FDA) of products or devices.

Emma Ciafaloni, MD, FAAN
(Moderator)
Robert C. and Rosalyne H. Griggs Professor in Experimental Therapeutics of Neurologic Disease
Professor of Neurology, Pediatrics and Obstetrics and Gynecology
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Emma Ciafaloni, MD, FAAN
Disclosures

- ***Speakers Bureau:*** Biogen
- ***Advisory Committee:*** AveXis, Inc. and Biogen

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CONTINUING MEDICAL EDUCATION

John Brandsema, MD

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John Brandsema, MD
Disclosures

- ***Grants:*** Biogen (CHOP Neuromuscular Fellowship)
- ***Research Support:*** AveXis, Inc. and Biogen (Site PI for clinical trials)
- ***Advisory Committee:*** AveXis, Inc. and Biogen

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Nancy L. Kuntz, MD, FAAN

Disclosures

- ***Research Support:*** Audentes Therapeutics; AveXis, Inc.; Biogen and Sarepta Therapeutics provided support for clinical research. Funds direct to institution.
- ***Advisory Committee:*** argenx; Audentes Therapeutics; Biogen; Cytokinetics, Inc.; F. Hoffmann-La Roche Ltd; Sarepta Therapeutics

CME for MIPS Improvement Activity

How to Claim this Activity as a CME for MIPS Improvement Activity

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- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation.
- Complete the follow-up survey from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

Claim ABIM MOC Credit

3 Things to Do

1. Actively participate in the meeting by **responding to ARS** and/or **asking the faculty questions**
   (It's ok if you miss answering a question or get them wrong, you can still claim MOC)
2. Complete your post-test and evaluation at the conclusion of the webcast
3. Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so we can submit your credit to ABIM.

ABIM CME MOC ACCREDITED

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CONTINUING MEDICAL EDUCATION

Clinical Insights on Recent Advances in Spinal Muscular Atrophy

Tuesday, January 7, 2020

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Learning Objective 1

Review the pathophysiology and therapeutic targets of SMA.

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Learning Objective 2

Apply the current recommendations for screening and early diagnosis of SMA.

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Learning Objective 3

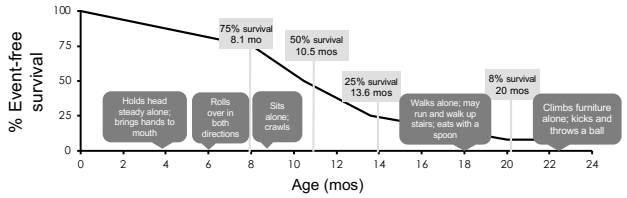
Evaluate the latest clinical data on the efficacy and safety of approved and emerging therapies for SMA.

SMA: Overview

- SMA is the leading genetic cause of infant death, with an estimated incidence of 1 in 10,000 live births in the United States
- In 2016, there were approximately 9,000 individuals with SMA (Types 1-3) living in the United States
- Heterozygous carriers 1:40 to 1:60

SMA = spinal muscular atrophy.
Lunn MR, Wang CH. *Lancet*. 2008;371(9630):2120-2133; Lally C, et al. *Orphanet J Rare Dis*. 2017;12:175; Sugarman EA, et al. *Eur J Hum Genet*. 2012;20(1):27-32; Prior TW, et al. *Am J Med Genet A*. 2010;152A(7):1608-1616.

Natural History of SMA Type 1



Onset of SMA Type 1 by 6 months

mos = months.
Finkel RS, et al. *Neurology*. 2014;83:810-817.

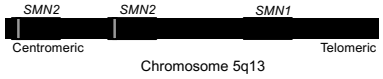
Classification of SMA (cont.)

- SMA type 1: infantile onset or Werdnig-Hoffmann disease
- SMA type 2: intermediate SMA or Dubowitz disease
- SMA type 3 and 4: juvenile-onset; slow progressive or Kugelberg-Welander disease
- SMA type 4: mild, adult-onset
- Other:
  - Congenital SMA
  - non5q SMAs and Kennedy's disease

Kolb SJ, Kissel JT. *Neurol Clin*. 2015;33(4):831-846.

SMA and *SMN1/SMN2*

Healthy Person



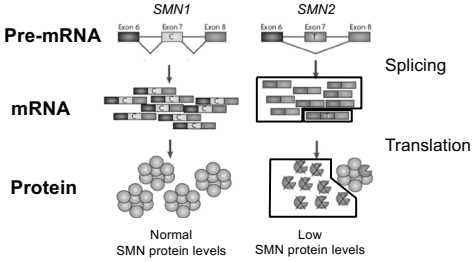
Chromosome 5q13

Patients with SMA

95% of 5q SMA

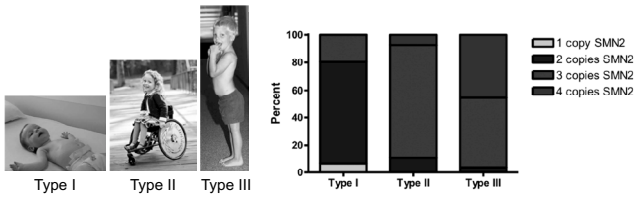
SMN = survival motor neuron.
Lefebvre S, et al. *Cell*. 1995;80(1):155-165; Verhaart IEC, et al. *Orphanet J Rare Dis*. 2017;12(1):124.

SMN Stability



mRNA = messenger RNA.
Ross LF, Kwon JM. *NeoReviews*. 2019;20(8):e437-e451; Butchbach MER, Burghes AHM. *Drug Discover. Today Dis. Models* 2004;(1)151-156.

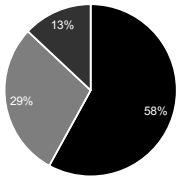
Disease Correlates with *SMN2* Copy Number



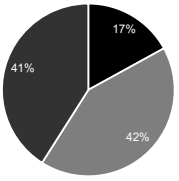
Stabley DL, et al. *Mol Genet & Genomic Med.* 2015;3(4):248-257; Calucho M, et al. *Neuromuscul Disord.* 2018;28(3):208-215.

Incidence and Prevalence of SMA Type I, II, and III

SMA Incidence: estimated incidence per live birth

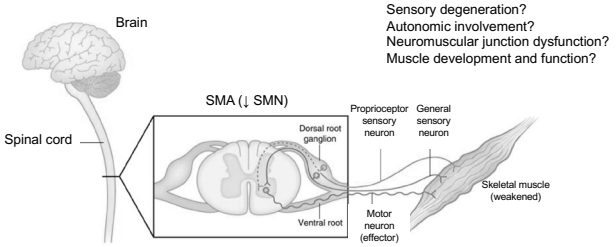


SMA prevalence: estimated number of all patients with SMA living in the population



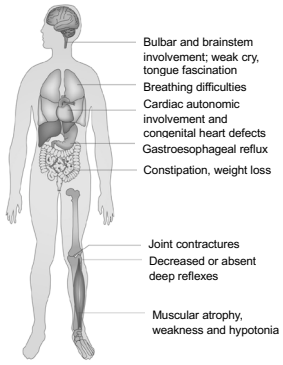
Lally C, et al. *Orphanet J Rare Dis.* 2017;12:175; Ogino S, et al. *Eur J Hum Genet.* 2004;4(1):1015-1029.

SMN1-Related SMA Pathogenesis



Lewelt A, et al. *Curr Neurol Neurosci Rep.* 2012;12(1):42-53.

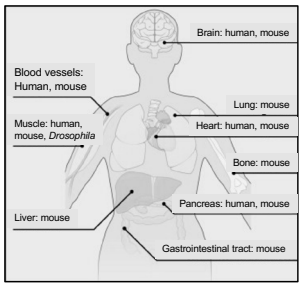
Other Body Systems



Faravelli I, et al. *Nat Rev Neurol.* 2015;11(6):351-359.

Multisystemic in Severe SMA

- Heart/ vessels
  - Arrhythmias
  - Cardiomyopathy
  - Vasculopathy
- Liver
  - Low IGF-1
  - Iron overload
- Spleen/ thymus
- Cognitive/ brain
  - No IQ difference between SMA types or with controls
  - Migrational disorders
  - Thalamus
  - Hippocampus



IGF-1 = insulin-like growth factor 1.
Hamilton G, Gillingwater T. *Trends Mol Med*. 2013;19(1):40-50.

Parent/Caregiver Perspectives

"It took us about 2 ½months to get a correct diagnosis. We were first diagnosed with low muscle tone. We knew there was issues right away. Our doctors were not well versed on it at all. We ended up hitting the emergency room at two and a half months with two collapsed lungs. We actually asked them to test them for SMA. So he was about two months, three weeks old when we got our diagnosis officially. A lot of damage had already been done."

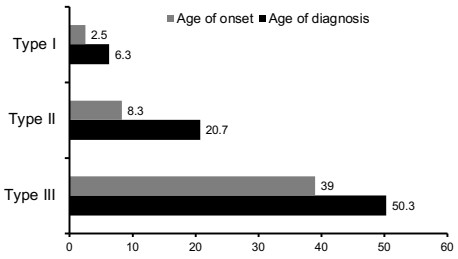
"From the time the blood work was done until we got the diagnosis was about three weeks. I do not feel that the doctor who diagnosed this was well-informed."

"I was diagnosed at 18 months. I started showing symptoms around 12 months old, so it took about six months to get a diagnosis and accurate diagnosis of SMA type 3."

Brandon

- First noted to have poor tone and head control at 2 months
- Difficulty gaining weight
- Hospitalized at 3 months for pneumonia and work-up of his failure to thrive and hypotonia
- Genetic testing confirmed a homozygous *SMN1* deletion and an *SMN2* copy number of 2
- Initial CHOP INTEND score was 20

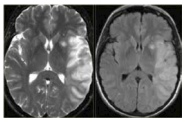
Diagnostic Delay in SMA



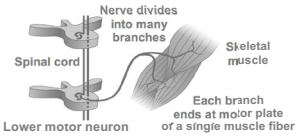
Lin C, et al. *Pediatr Neurol*. 2015;53(4):293-300.

Time Equals Motor Neurons

Time =



Time =



Govoni, A, et al. *Mol Neurobiol.* 2018;55:6307-6318; Shorrock HK, et al. *Front Mol Neurosci.* 2019;12:59.

Presentation and Differential Diagnosis

Hypotonic Infants

- Frequently presents with decreased spontaneous movements and failure to meet new motor milestones
- Slow weight gain/failure to thrive/choking with feeding
- Increased work of breathing with paradoxical abdominal movements

Differential:
- SMARD
- Non 5q- SMAs
- Congenital muscular dystrophy
- Congenital myasthenic syndrome
- Pompe disease
- Infantile botulism
- Prader-Willi syndrome
- Congenital myotonic dystrophy

Prior TW, et al. National Center for Biotechnology Information Website. 2019. https://www.ncbi.nlm.nih.gov/books/NBK1352/.

Presentation and Differential Diagnosis

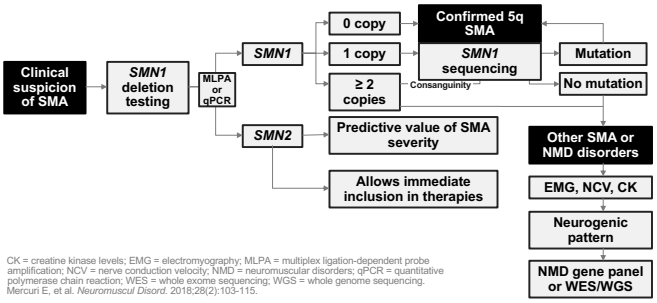
Older Ambulatory Child

- Children may first show difficulty running, climbing steps, rising from a chair, or walking
- Proximal leg muscles are usually affected first
- A fine tremor can be seen during UE use
- Frequently, loss of previously achieved motor skills and/or falls are presenting complaints

Differential Diagnosis:
Myopathy: dystrophinopathies, limb girdle muscular dystrophy, metabolic myopathies, or inflammatory myopathies
Neuropathy: inflammatory neuropathies
Neuromuscular junction disorders: myasthenia gravis or congenital myasthenic syndromes
Other motor neuron disorders: non-5q form of SMA or late-onset hexosaminidase A deficiency

Arnold WD, et al. *Muscle Nerve.* 2015;51(2):157-167.

Diagnostic Algorithm



CK = creatine kinase levels; EMG = electromyography; MLPA = multiplex ligation-dependent probe amplification; NCV = nerve conduction velocity; NMD = neuromuscular disorders; qPCR = quantitative polymerase chain reaction; WES = whole exome sequencing; WGS = whole genome sequencing.
Mercuri E, et al. *Neuromuscul Disord.* 2018;28(2):103-115.

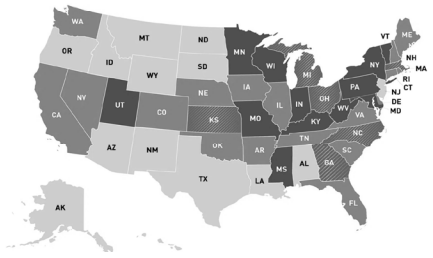
Presymptomatic Diagnosis of SMA

- Prenatal parental carrier testing
- Family history
- Newborn screening

Prenatal Testing

- Carrier testing of expectant parents for SMA recommended by Obstetrics and Genetics guidelines
  - Based on results, also can test fetus within standard windows for sampling methods
- Complex genetic counseling discussion if results are positive
  - Recommend referral to a Pediatric SMA care center to also discuss today's treatment landscape regarding educating parents

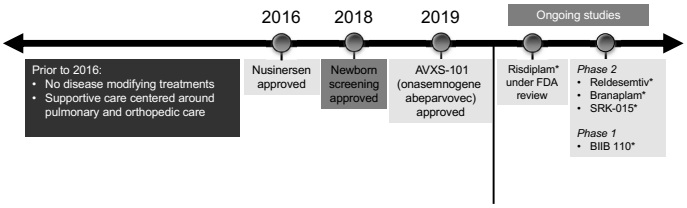
Presymptomatic Diagnosis of SMA



Double *SMN1* deletion detection will not detect 5% of affected individuals

Cure SMA Website. 2019. https://www.curesma.org/newborn-screening-for-sma/.

Treatment Landscape



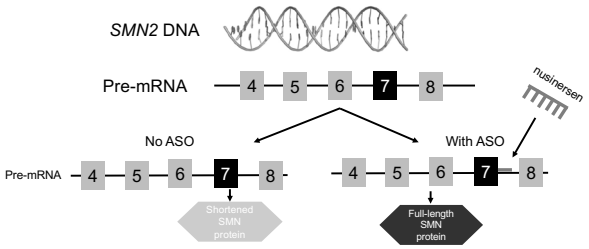
*Not approved by the FDA.

Parent/Caregiver Perspectives

"Our diagnosing doctor, she was very unaware that there were treatments very close to approval..."

"I actually brought it up to his neurologist. His neurologist knew nothing about treatment. And it took 11 months after it was approved by the FDA to get him injections..."

Nusinersen: Mechanism of Action



ASO = allele-specific oligonucleotide.
Wurster CD, Ludolf AC, et al. *Ther Adv Neurol Disord.* 2018;11:1-3.

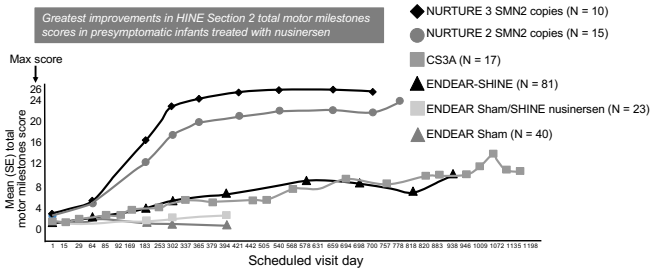
Nusinersen: Clinical Studies

Name of the Trial	Trial Design	SMA Population
ENDEAR[1]	Pivotal, phase 3, international, multicenter, double-blind, sham-controlled	Infantile onset SMA (type 1)
CHERISH[2]	Pivotal, phase 3, randomized, double-blind, sham-controlled	Age 2-9 years, non-ambulatory
NURTURE[3]	Phase 2, open-label, international, multicenter	Presymptomatic infants, age 0-6 weeks with a genetic diagnosis of SMA type 1 or 2
SHINE[4]	Open label extension study	Patients who previously participated in nusinersen investigational studies
CS3A[5]	Phase 2	Age 21 days to 7 months with infantile-onset SMA
CS2/CS12[6,7]	Phase 1/2, open label, multiple-dose, dose-escalation	Type 2 and 3, ambulatory and non-ambulatory

[1]ClinicalTrials.gov Website. Updated 2017. https://clinicaltrials.gov/ct2/show/NCT02193074. [2]ClinicalTrials.gov Website. Updated 2018. https://clinicaltrials.gov/ct2/show/NCT02292537. [3]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT02386553. [4]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT02594124. [5]ClinicalTrials.gov Website. Updated 2018. https://clinicaltrials.gov/ct2/show/NCT01839656. [6]ClinicalTrials.gov Website. Updated 2017. https://clinicaltrials.gov/ct2/show/NCT01703988. [7]ClinicalTrials.gov Website. Updated 2017. https://clinicaltrials.gov/ct2/show/NCT02052791.

Effect of Nusinersen on HINE Motor Milestone Scores Across Studies

Greatest improvements in HINE Section 2 total motor milestones scores in presymptomatic infants treated with nusinersen



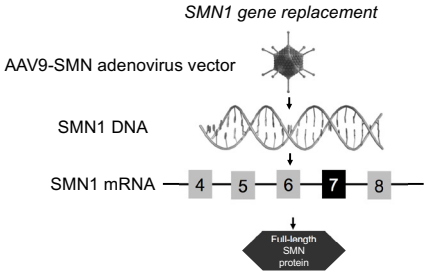
Finkel RS, et al. 71st AAN Annual Meeting; 2019. Abstract No. S25.004.

WHO Motor Milestone Development in NURTURE Presymptomatic Onset of Treatment with Nusinersen

Motor milestone	Expected age of achievement in healthy infants 5th-95th percentile[1]	Caregiver-reported site-confirmed achievement in NURTURE participants		Median (95% CI) age of first achievement (mo)	
		3 *SMN2* copies	2 *SMN2* copies	3 *SMN2* copies	2 *SMN2* copies
Sitting without support	4.3–8.0 mo	10/10 (100%)	15/15 (100%)	6.4 (5.1–7.9)	7.9 (5.9–9.2)
Standing with assistance	5.5–10.1 mo	10/10 (100%)	15/15 (100%)	8.3 (3.5–9.5)	10.0 (5.1–13.5)
Hands and knees crawling	6.1–11.3 mo	10/10 (100%)	13/15 (87%)	8.7 (7.2–10.5)	15.5 (8.9–20.9)
Walking with assistance	6.9–11.8 mo	10/10 (100%)	13/15 (87%)	9.6 (8.0–11.8)	16.1 (11.8–18.8)
Standing alone	8.1–14.4 mo	10/10 (100%)	12/15 (80%)	11.4 (10.3–14.6)	18.6 (12.9–25.9)
Walking alone	9.4–15.3 mo	10/10 (100%)	12/15 (80%)	12.3 (11.2–14.9)	20.4 (15.5–29.7)

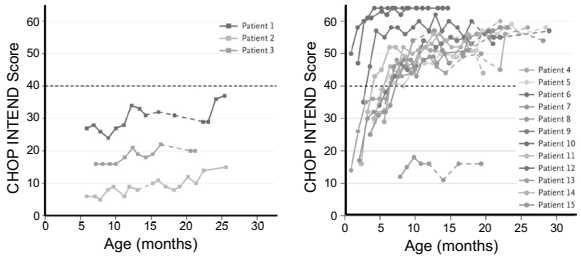
WHO = World Health Organization. NURTURE study interim analysis data cutoff date: March 29, 2019.
[1]WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl.* 2006;450:86-95. DeVivo DC, et al. 71st AAN Annual Meeting; 2019. Abstract No. S25.001.

AVXS-101: Mechanism of Action



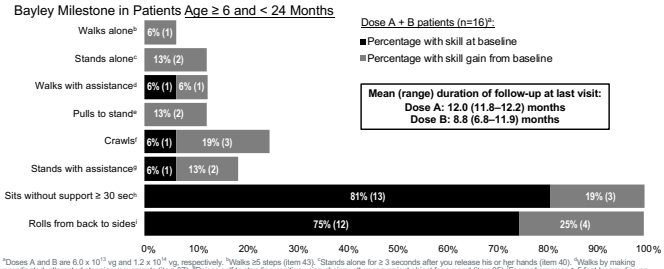
Farrar MA, et al. *Ann Neurol*. 2017;81:355-368.

Effect of AVXS-101 on Motor Function in SMA 1



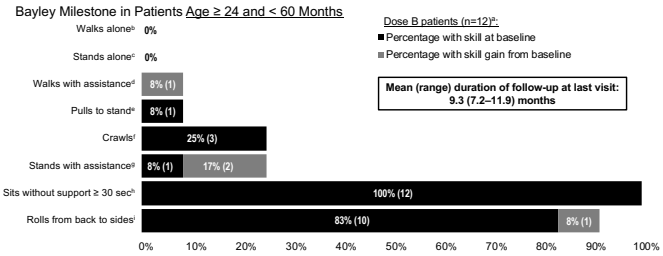
Mendell JR, et al. *N Engl J Med*. 2017;377:1713-1722.

Bayley Milestones Gained During AVXS-101 IT Treatment in Patients Age ≥ 6 and < 24 Months (as of 31 May 2019)



[a]Doses A and B are 6.0×10^{13} vg and 1.2×10^{14} vg, respectively. [b]Walks ≥5 steps (item 43). [c]Stands alone for ≥ 3 seconds after you release his or her hands (item 40). [d]Walks by making coordinated, alternated stepping movements (item 37). [e]Raises self to standing position using chair or other convenient object for support (item 35). [f]Forward progress ≥ 5 feet by crawling on hands and knees (item 34). [g]Supports own weight for ≥ 2 seconds (item 33). [h]Item 26: 'Rolls from back to both right and left sides (item 20). Milestones were confirmed by a central reader.
IT = intrathecal.
Mendell J, et al. *Can J Neurol Sci.* 2019;46(S1): S32. doi:10.1017/cjn.2019.166

Bayley Milestones Gained During AVXS-101 IT Treatment in Patients Age ≥ 24 and < 60 Months (as of 31 May 2019)



[a]Doses A and B are 6.0×10^{13} vg and 1.2×10^{14} vg, respectively. [b]Walks ≥5 steps (item 43). [c]Stands alone for ≥ 3 seconds after you release his or her hands (item 40). [d]Walks by making coordinated, alternated stepping movements (item 37). [e]Raises self to standing position using chair or other convenient object for support (item 35). [f]Forward progress ≥ 5 feet by crawling on hands and knees (item 34). [g]Supports own weight for ≥ 2 seconds (item 33). [h]Item 26. [i]Rolls from back to both right and left sides (item 20). Milestones were confirmed by a central reader.
Mendell J, et al. *Neuropediatrics* 2018;49(S 02)S1-S69.

Treatment Monitoring

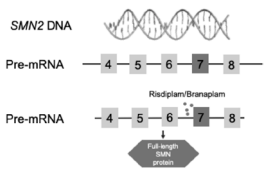
- Side effects of treatment
  - nusinersen: clotting abnormalities, urine protein, rare hydrocephalus
  - onasemnogene abeparvovec: hypertransaminitis, complement-mediated thrombocytopenia, HSP-like reaction
- Clinical response
  - CHOP INTEND
  - HINE
  - MFM-32
  - WHO motor milestones
  - Pulmonary function

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; HSP = Henoch-Schönlein purpura; MFM = Motor Function Measure.

Small Molecules for the Treatment of SMA

- Oral *SMN2* splice modulators
  - Risdiplam/RG7916*
  - Branaplam/LMI070*
- Early data presented at recent academic meetings
- Advantages: oral/tube administration, systemic distribution
- Various studies are in progress in the United States, Europe, and elsewhere

Mechanism of Action



*Not approved by the FDA.
Farrar MA, et al. *Ann Neurol*. 2017;81:355-368; Ratni H, et al. *J Med Chem*. 2018;61:6501-6517; Cheung AK, et al. *J Med Chem*. 2018;1(24):11021-11036.

Risdiplam*: Ongoing Studies

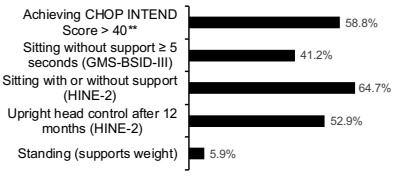
Name of the Trial	Trial Design	SMA Population
FIREFISH[1]	Open-label, 2-part, pivotal	Infants with Type 1 SMA
SUNFISH[2]	Double-blind, 2-part placebo-controlled, pivotal	Age 2-25 years with Types 2 or 3 SMA
JEWELFISH[3]	Open-label exploratory	Age 6 months–60 years who have been previously treated with SMA-directed therapies
RAINBOWFISH[4]	Open-label, single-arm, multicenter	Age 0-6 weeks with genetically diagnosed SMA, non-symptomatic

*Not approved by the FDA.
[1]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT02913482. [2]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT02908685. [3]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT03032172.
[4]ClinicalTrials.gov Website. Updated 2019. https://clinicaltrials.gov/ct2/show/NCT03779334.

FIREFISH: Risdiplam* in Type-1 SMA

FIREFISH Part 1 (N = 17)

Motor Function and Key Milestones



No loss of ability to swallow
No tracheostomy/ permanent ventilation
Event-free survival: 15 (88.2%)
Common adverse events
- Fever (pyrexia; 52.4%)
- URI (42.9%)
- Diarrhea (28.6%)
- Vomiting (23.8%)
- Cough (23.8%)
- Pneumonia (19.0%)
- Constipation (19.0%)

*Not approved by the FDA. **Median change in CHOP INTEND over 1 year: 17.5 points. CHOP INTEND score: 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months.

GMS-BSID-III = Gross Motor Scale Bayley Scales of Infant and Toddler Development, Third Edition; HINE-2 = Hammersmith Infant Neurological Examination Module 2; URI = upper respiratory infection.
Baranello G, et al. 71st American Academy of Neurology Annual Meeting; 2019. Abstract S25.003; Servais L, et al. 71st American Academy of Neurology Annual Meeting; 2019. Abstract S25.008.

SUNFISH: Risdiplam* in Type 2/3 SMA

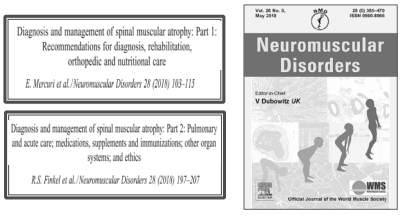
Motor Function Achieved in Part 1 Dose Escalation (N =51)			
Endpoint	> 12 months treatment		
MFM-32	All patients	Age 2-11	Age 12-25
Achieved improvement (change from baseline score ≥ 3), %	58%	71%	42%
Serious adverse events: nausea (4%), upper respiratory tract infection (4%) and vomiting (4%)			

- SUNFISH Part 2: Confirmatory; N = 180
- **Met primary endpoint** of change from baseline in the MFM-32 scale after 1 year of treatment with risdiplam compared to placebo (announced 11/2019)

*Not approved by the FDA.
Mercuri E. 71st American Academy of Neurology Annual Meeting; 2019. Abstract S25.007; Roche Website. 2019. www.roche.com/media/releases/med-cor-2019-11-11.htm; Mercuri E, et al. 23rd International Annual Congress of the World Muscle Society Congress; 2018. Poster No. 255.

SMA Consensus Care Guidelines

- Stated goals
  - Improve quality of life
  - Reduce disease burden
- Updated classification system
  - Non-sitters
  - Sitters
  - Walkers


Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

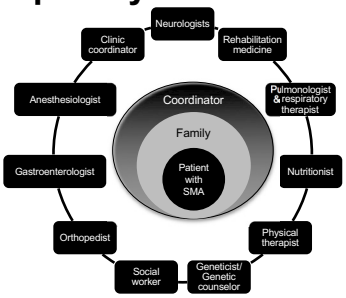
E. Mercuri et al./Neuromuscular Disorders 28 (2018) 103–115

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

R.S. Finkel et al./Neuromuscular Disorders 28 (2018) 197–207

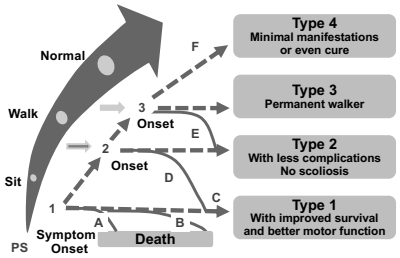
Parent/Caregiver Perspectives

SMA Management Requires a Multidisciplinary Team



Mercuri E, et al. *Neuromuscul Disord*. 2018;28(2):103-115.

Hypothetical Effects of Novel Therapeutics on SMA



Tizzano EF, Finkel RS. *Neuromuscul Disord.* 2017;27(10):883-889.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Simple genetic testing will pick up 95% of cases of SMA
- There are disease modifying therapies available and data suggest that early diagnosis and treatment lead to optimal outcomes
- Implement strategies for multidisciplinary care coordination for patients with SMA guided by a neuromuscular specialist

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with Emma Ciafaloni, MD, FAAN (Moderator); John Brandsema, MD; Nancy L. Kuntz, MD, FAAN

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