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MOVES



SMA DIAGNOSTIC TOOLKIT

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cure
SMA

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breakthrough.

Call to Action: The Need for Early Diagnosis in **Spinal Muscular Atrophy**

Spinal Muscular Atrophy (SMA) has been the most common genetic killer of infants. In the most severe form, SMA Type I (Werdnig-Hoffman disease), the majority of children died or were dependent on mechanical ventilation by 2 years of age. An infant with SMA is born approximately once a day.

The first **disease modifying treatment** of SMA was approved by the FDA in 2016, leading to improved outcomes for children with SMA, with the greatest benefit seen when the treatment is started early. This makes increased awareness of the early clinical presentation and diagnosis of SMA. ¹

A child with poor head control when pulled to sitting, or difficulty moving their legs or reaching for objects against gravity, yet is bright eyed, smiling, and socially engaging is a red flag for SMA. Given the rarity of this disease, and that its early symptoms in infants may also be associated with other neurologic or muscular disorders, the child and family can experience a “diagnostic odyssey” with many referrals and tests if the signs of SMA are not recognized. Literature reviews indicate *a significant diagnostic delay, during time periods that overlap with major motor neuron loss.*^{1,2} ***Urgent referral, early diagnosis, and the provision of a life-changing and life-saving therapy is required, as these motor neurons rapidly degenerate early in the progression of the disease.*** The future of SMA management is in your hands.

Despite persistent delays in diagnosis, ***pre-clinical and clinical data suggest that early pharmacological treatment dramatically increases benefit to the patient. Evidence suggests that the timing of administration has substantial impact on motor outcomes and life-expectancy.***^{3, 4, 5, 6} In infants with SMA type I, the onset of irreversible denervation occurs within the first three months with loss of 90% of motor units occurring within six months of age.⁷ Even when a FDA-approved treatment is administered. It is clear that early diagnosis is crucially important.

We are in the unique and exciting position to dramatically improve children’s lives with early diagnosis and early, effective treatment. This Spinal Muscular Atrophy Diagnostic Toolkit was designed to empower you, a health care professional, to recognize SMA in your patients, refer them urgently for diagnosis and treatment, and dramatically improve their outcomes. By utilizing this tool, you can make a significant impact. Early diagnosis and treatment is often the difference between life and death ***Join us in the fight to save our infants!!***

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What is SMA?

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease characterized by progressive deterioration of alpha motor neurons in the spinal cord.⁸ SMA is one of the most common monogenic disorders in the human population and historically has been the leading genetic cause of death amongst children under the age of two.⁹ The predominant symptoms of SMA include hypotonia and weakness in the trunk and limbs.¹⁰ In more severe cases, the respiratory muscles are compromised leading to respiratory insufficiency.

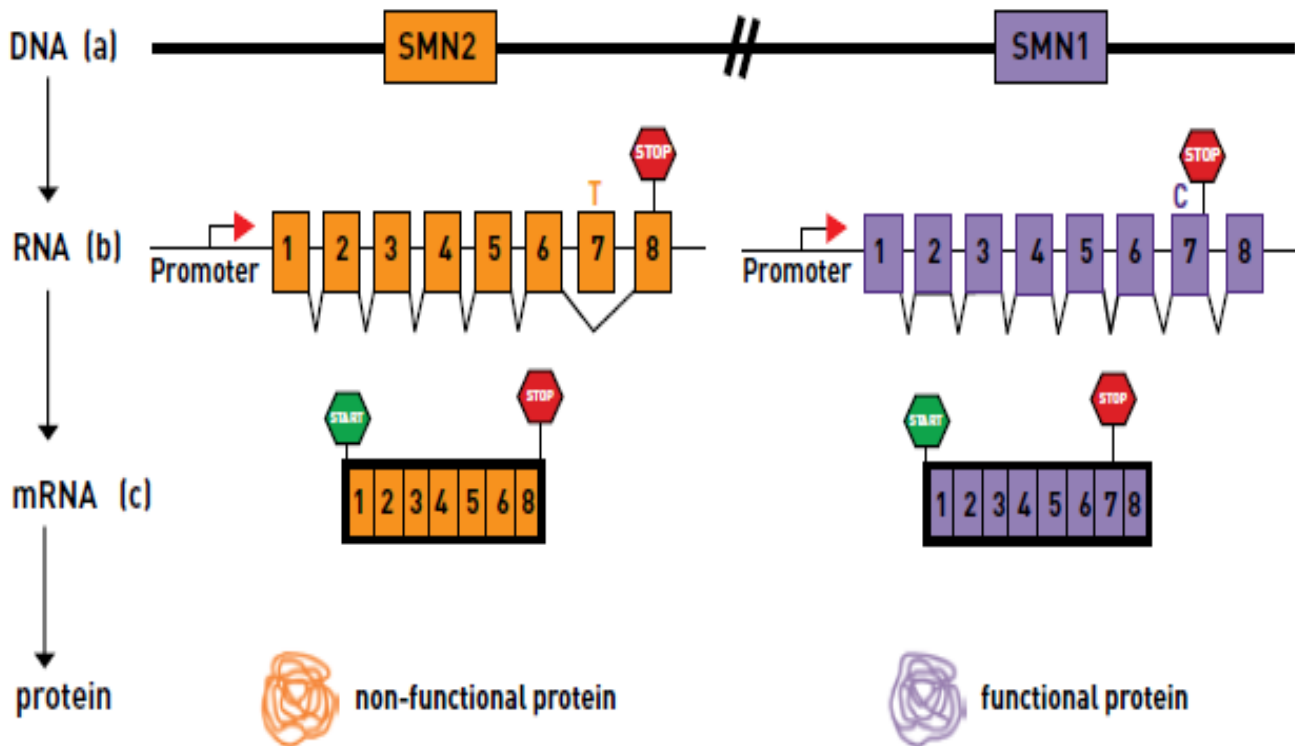


Figure 1. Schematic of SMN1 and SMN2 genes located on chromosome 5

Humans have two nearly identical copies of the survival motor neuron gene that have been named *SMN1* and *SMN2*.¹² SMA is caused by a mutation or deletion in the *SMN1* gene leading to a reduction of functional SMN protein. Despite ubiquitous expression of SMN1/2 throughout the body, decreased expression overtly impacts motor neuron function.^{8, 11, 13}

Although 95% of patients have the same homozygous deletion of the *SMN1* gene, a significant range in clinical presentation/phenotypes exists.^{12, 13} Much of the phenotypic variation in SMA can be explained by the existence of the *SMN2* back-up gene.¹² Although *SMN2* produces a poorly functioning protein, the total number and function of *SMN2* copies present in each individual is inversely correlated with phenotypic severity; a higher number of copies offers protection and decreases the severity of the disease.¹² Essentially,

More copies of SMN2 = less severe phenotype

SMA is typically categorized into five types that are based on age of onset and highest motor milestone achieved.^{12, 13, 14, 15, 16, 17} For instance, in infants with SMA type I, symptoms present before the age of three months and prior to an available treatment, never achieved the ability to sit independently, while other patients have a milder disease course.

Please note, as individuals receive treatment, the phenotype may change. However, for the purpose of this toolkit we will provide a general overview of the predominant observable symptoms in the five historical phenotypes and describe the early clinical presentation for each sub-group. For additional information regarding SMA typing, please see the subsequent section entitled, [Clinical Assessment of Symptoms](#) or visit the [Cure SMA website](#)^a

Type	Age at Symptom Onset	Incidence	Prevalence	Maximum Motor Function Achieved	SMN2 Copy Number *	Life Expectancy
0	in utero	<1%	<1%	Nil; Decreased Fetal Movement	1	Days - Weeks
1	<6 Months	60%	15%	Never Sits independently	1,2,3	<2 Years
2	6-18 Months	25%	70%	Sits independently, but Never Walks	2,3,4	20-40 Years
3	1.5-10 Years	15%	15%	Walks independently, then experiences regression	3,4,5	Normal
4	>35 Years	<1%	<1%	Slow Decline	4,5	Normal

Figure 2. Classification of SMA by Type

Table modified from EMA Briefing Document¹⁸

*Number in bold indicates the predominate copy number

^a <http://www.curesma.org/sma/about-sma/types-of-sma/>

Epidemiology

Despite being a rare disease, SMA is one of the most common genetic causes of death in infants

The reported birth prevalence ranges from 8.5 to 10.3 per 100,000 live births (approximately 1 in 11,000), with a reported carrier rate of 1/40–1/60.¹⁹ Due to autosomal recessive inheritance, both parents must be carriers for a child to inherit the condition, but the disease is not likely to have occurred in previous generations. Although SMA affects girls and boys equally, but the carrier rate varies somewhat by race. The reported carrier frequency ranges from 1/47 in the Caucasian population to 1/72 in the African American population.¹⁹

The Urgent Need for Early Diagnosis and Treatment

Diagnostic Delays in SMA are common and may put a significant financial, logistical, and emotional strain on families. Early recognition and diagnosis may mean the difference between life and death for an infant with SMA.

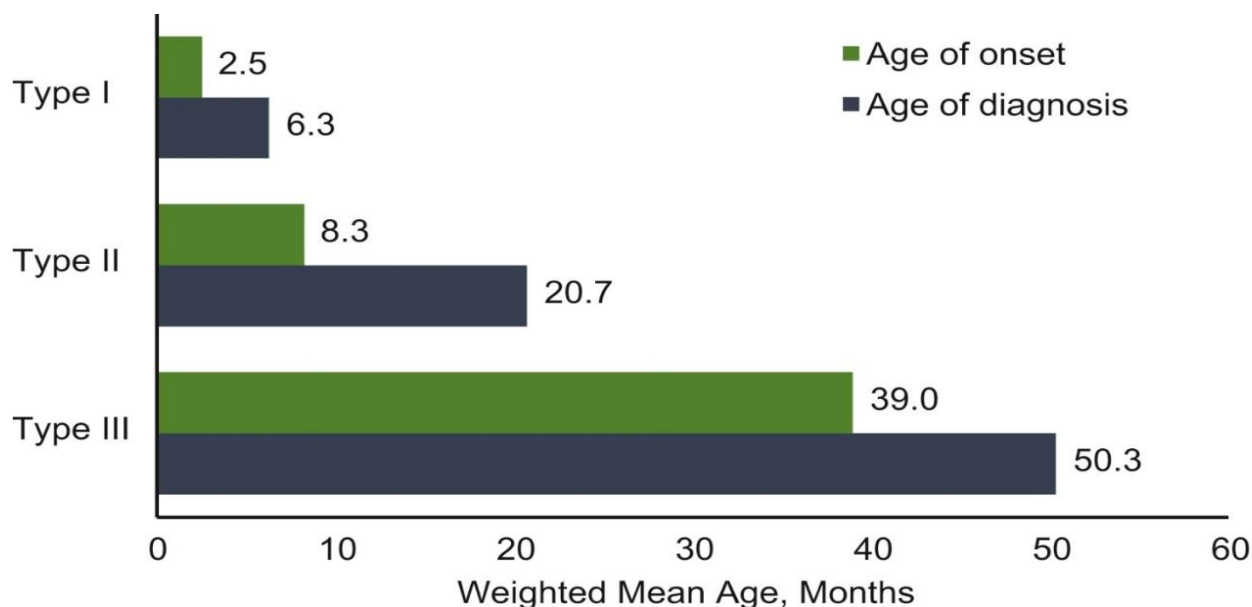


Figure 3. Diagnostic Delays in SMA by Type^b literature review examining the diagnostic delay in symptomatic children with SMA has reported the average age of diagnosis in SMA to be as follows, from 5.3 to 6.3 months (average delay of 3.6 months) in type I; in type II, from 20.7 to 22.1 months (average delay of 14.3 months) and from 50.2 to 97.8 months in type III (average delay of 43.6 months).^{1,2}

^b From Pediatric Neurology, Chia-Wei Lin MS, Stephanie J. Kalb PhD, Wei-Shi Yeh PhD. for Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review, Volume 53, Issue 4, October 2015, Pages 293-300. Copyright © (2015) Elsevier. Reprinted with permission from Elsevier via Creative Commons License.

Early provision of treatment is critical to modifying the rapid and irreversible loss of motor neurons and exponentially increasing chances of survival and functional gains to patients.

Nusinersen (Spinraza TM): the first-ever FDA-approved treatment for SMA

The data from SMA clinical trials demonstrate that early treatment increases benefit to the patient. Nusinersen (Spinraza), marketed by Biogen and currently the only FDA-approved drug for all types of SMA, is an antisense oligonucleotide (ASO) designed to increase production of fully functional SMN protein from the SMN2 gene. Both clinical and preclinical studies indicate that early treatment exposure is critical to modifying the rapid and irreversible loss of motor neurons, ultimately leading to muscle atrophy and weakness. Data from ENDEAR, a phase 3 sham-controlled trial that assessed the safety and efficacy of nusinersen in SMA type I infants with 2 copies of SMN2, showed that ***infants treated with nusinersen with a disease duration of ≤12 weeks showed greater improvements in motor function and motor milestones than untreated patients (Figure 4) (75% vs. 0%; p<0001).***⁴ In infants with disease duration greater than 12 weeks, the response rate still greatly favored the nusinersen treated group (32% vs. 0%; p=0.0026) but at a much lower rate.⁵ ***Nusinersen also had an impact on survival rate***, showing a treatment benefit in event-free survival (p=0.0004).⁵ Additionally, ***a few nusinersen-treated infants in the ENDEAR trial achieved milestones previously unseen in infants with SMA type I including supine to prone rolling and sitting without support.***⁵

Although all infants with SMA type I showed significant response to treatment with nusinersen, the ***administration of nusinersen prior to 6 weeks of age had even more substantial impact.*** Interim analysis of the data from the NURTURE trial, which enrolled pre-symptomatic infants (median age at first dose was 19 days), reports milestone achievement.³

All infants in the NURTURE trial have thus far achieved the motor milestone (Figure 4) of independent sitting and none have required permanent ventilation. As we compare the data from the NURTURE and ENDEAR studies, it is evident that early administration of treatment vastly alters the SMA phenotype, and encourages normal development.⁶

Milestone	Total number of infants achieving milestone, N (%)		
	ENDEAR (Symptomatic patients; N=73)	NURTURE* (Pre-symptomatic patients with 2 copies; N=15)	NURTURE* (Pre-symptomatic patients with 3 copies; N=13)
Head control (full)	16/73 (22)	14/15 (93)	9/9 (100)
Sitting (independent: stable, pivot)	6/73 (8)	12/12 (100)	7/7 (100)
Standing (stands with support, unaided)	1/73 (1)	10/12 (83)	7/7 (100)
Walking (cruising, independent)	0/73 (0)	5/12 (42)	5/5 (100)

Figure 4 Summary of Motor Milestone Achievements of Infants Receiving Nusinersen (Spinraza) during ENDEAR and NURTURE Trials

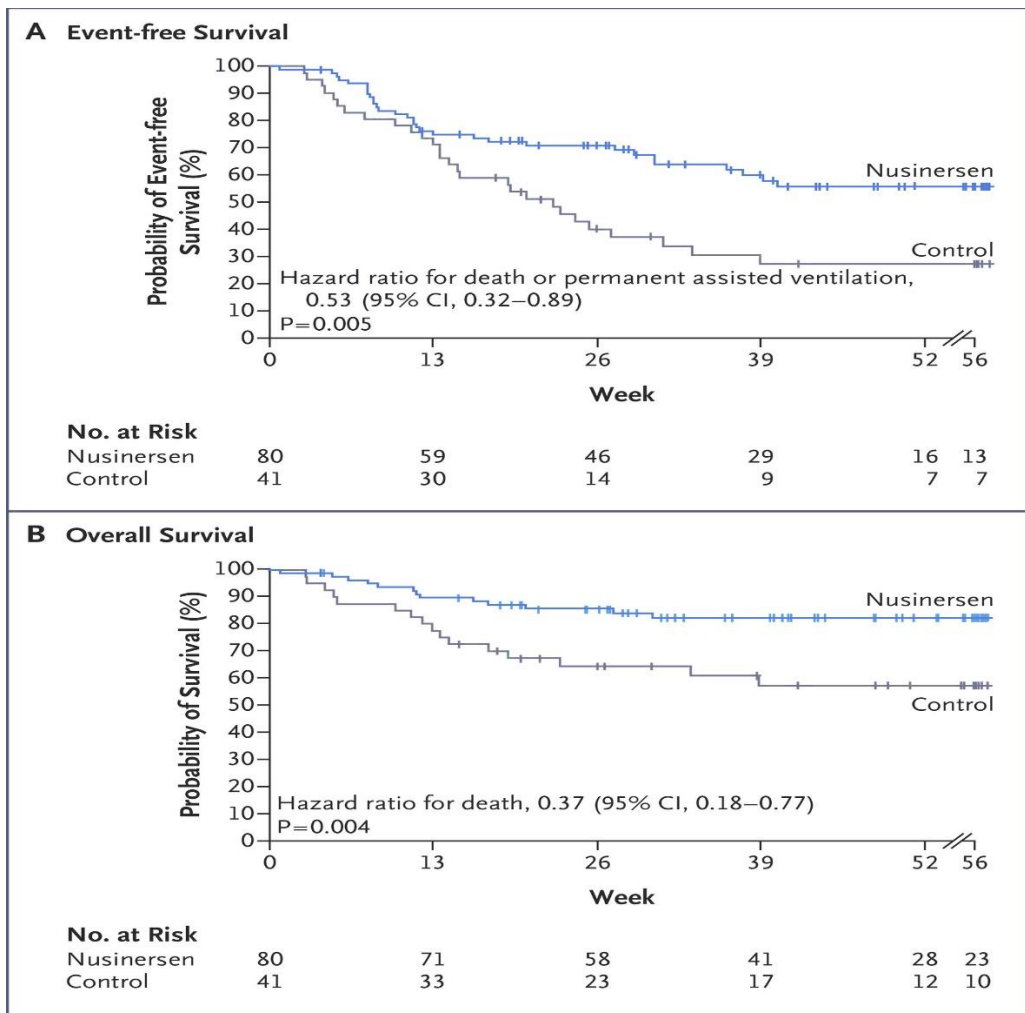


Figure 5 Event-free Survival and Overall Survival^c

Panel A shows the probability of event-free survival (the proportion of infants who were alive without the use of permanent assisted ventilation) and Panel B shows the probability of overall survival (the proportion of infants who were alive) in the nusinersen group and the control group. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group; the median time to death was not reached in either group.

^c From New England Journal of Medicine, Richard S. Finkel, M.D., Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Anne M. Connolly, M.D., Nancy L. Kuntz, M.D., Janbernd Kirschner, M.D., Claudia A. Chiriboga, M.D., M.P.H., Kayoko Saito, M.D., Ph.D., Laurent Servais, M.D., Ph.D., Eduardo Tizzano, M.D., Ph.D., Haluk Topaloglu, M.D., Mår Tulinius, M.D., Ph.D., Jacqueline Montes, P.T., Ed.D., N.C.S., Allan M. Glanzman, P.T., D.P.T., P.C.S., Kathie Bishop, Ph.D., Z. John Zhong, Ph.D., Sarah Gheuens, M.D., Ph.D., C. Frank Bennett, Ph.D., Eugene Schneider, M.D., Wildon Farwell, M.D., M.P.H., and Darryl C. De Vivo, M.D. for the ENDEAR Study Group, Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy, Volume No. 377, Issue 18, Page No. 1723-1732. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Gene-Replacement Therapy – cutting edge technology offering a promising single dose treatment

Several additional therapeutic options are currently in clinical trials. Gene therapy offers the opportunity for single dose treatment of the disease.²⁰ In a phase 1, open-label, dose escalation trial, 15 patients with SMA Type 1 were treated with a single dose of AVXS-101, an intravenous adeno-associated virus serotype 9 which carried non-replicating SMN complementary DNA that encoded SMA protein.²⁰

The patients were enrolled into two cohorts that received different doses; cohort 1 received a low dose while cohort 2 received a high dose.²⁰ **Upon completion of the study, and two years post treatment, all 15 patients reached the age of 20 months without requiring permanent mechanical ventilation (Figure 6).**^{20, 21} The 12 patients enrolled in the higher dosed cohort achieved significant motor milestones, with 9 infants gaining the ability to sit unassisted for 30 seconds at the close of the phase 1 trial, and 2 additional infants achieving the milestone as observed at time of enrollment in a long-term follow-up study.^{20, 21}

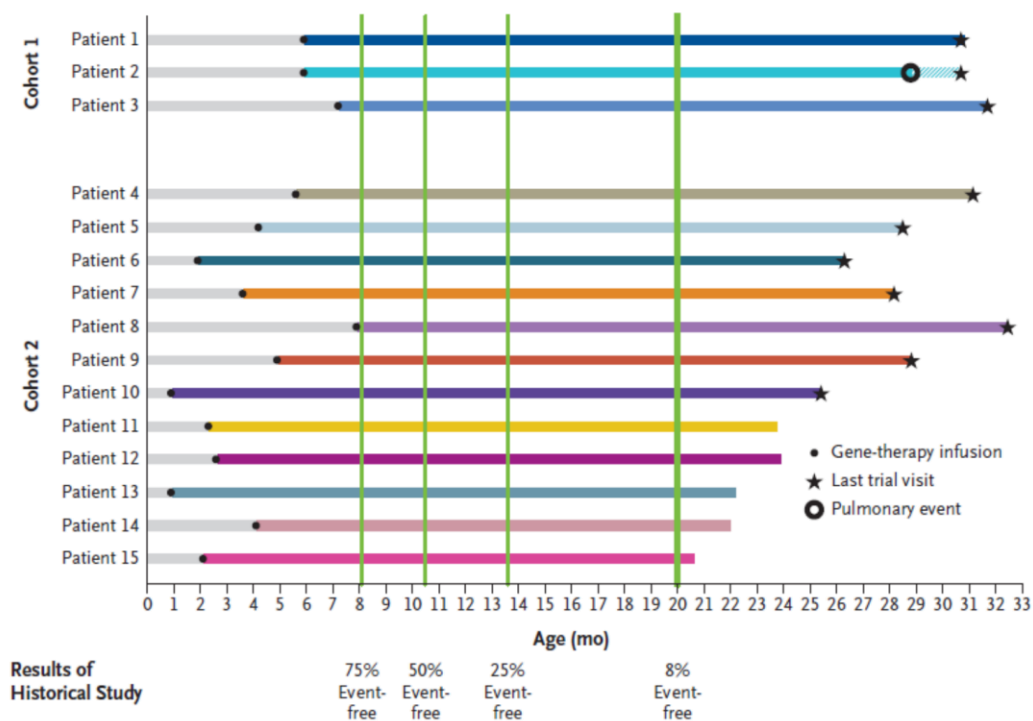


Figure 6 Survival Free from Permanent Ventilation in the 15 Study Patients (Phase 1 Trial for AVXS-101)^d

Shown is the duration of survival free from the need for permanent ventilation for the 3 patients in cohort 1, who received a low dose of adeno-associated viral vector containing DNA coding the SMN (6.7×10^{23} vg per kilogram), and the 12 patients in cohort 2, who received a high dose (2.0×10^{14} vg per kilogram). Stars indicated the completion of the ongoing 2-year safety follow-up. The percentages of patients who were event-free in a historical study of spinal muscular atrophy conducted by the Pediatric Neuromuscular Clinical Research Network are provided at the bottom of the graph for a control comparison, as indicated by the vertical green lines. The thicker vertical line indicates the benchmark of 20 months, at which time only 8% of the patients with the disease typically survive without permanent ventilation.

^d From New England Journal of Medicine, Jerry R. Mendell, M.D., Samiah Al-Zaidy, M.D., Richard Shell, M.D., W. Dave Arnold, M.D., Louise R. Rodino-Klapac, Ph.D., Thomas W. Prior, Ph.D., Linda Lowes, P.T., Ph.D., Lindsay Alfano, D.P.T., Katherine Berry, P.T., Kathleen Church, M.S.W., John T. Kissel, M.D., Sukumar Nagendran, M.D., James L'Italien, Ph.D., Douglas M. Sproule, M.D., Courtney Wells, B.S., Jessica A. Cardenas, Ph.D., Marjet D. Heitzer, Ph.D., Allan Kaspar, Ph.D., Sarah Corcoran, B.S., Lyndsey Braun, B.S., Shibi Likhite, Ph.D., Carlos Miranda, Ph.D., Kathrin Meyer, Ph.D., K.D. Foust, Ph.D., Arthur H.M. Burghes, Ph.D., and Brian K. Kaspar, Ph.D., Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy, Volume 377, Issue 18, Page No. 1713-1722 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Multicenter studies of AVXS-101 are currently underway. STRIVE, a phase 3, open-label, single-arm, single dose trial in patients with SMA Type 1, is designed to examine the efficacy of treatment in symptomatic patients less than 6 months of age.^{21, 22} As of April 11, 2018, 11 patients were enrolled into the study, 6 of which received treatment at a mean age of 3.2 months.²¹ All 6 that received AVXS-101 were alive and event free at the time of review.²¹

Small Molecule Therapy – opening the door to new methods of treatment administration and the potential development of combination therapy

A variety of small molecules are currently undergoing clinical trials. Branaplam and Risdiplam, two orally available small molecule have been developed and are currently undergoing clinical trials. These agents work similarly to Nusinersen by increasing SMN2 production^{23, 24, 25} Although the efficacy of Branaplam and Risdiplam has yet to be compared in pre-symptomatic and symptomatic patients, given their similar function to ASO and gene therapy, timing of administration will most likely affect clinical outcomes. Additional studies are required to confirm the impact of delayed treatment.

In addition, a number of SMN-independent therapies are also in clinical development.²³ Two such treatments, reldesemtiv (CK-107) and SRK-015, both aim to enhance neuromuscular function, muscle fatigue, and muscle weakness.^{23, 26} Both treatments present a promising alternative to SMN targeted therapy, or may be used in combination. Additional studies are required to determine efficacy as a stand-alone treatment. The potential to combine these treatments with SMN-dependent treatments offers the potential to further enhance outcomes. However, early diagnosis remains crucial as we work to improve quality of life and prevent further loss of function. For additional information regarding the current SMA drug pipeline, please visit the [Cure SMA website^e](#).

Clinical Assessment of Symptoms

Early diagnosis of SMA heavily relies on the quick recognition of the cluster of physical signs and symptoms that is characteristic of SMA.

Although the presence of hypotonia in a ‘floppy infant’ is a diagnostic challenge, a thorough history and physical will help to isolate the cause.²⁷ Parents are frequently the first to recognize potential signs of motor delay and their concerns regarding a variety of symptomology including, muscle tone, strength, coordination, and poor feeding are accurate in more than 80% of cases.²⁸ A detailed family and past medical history that includes prenatal events can assist with localization of cause.²⁹ However, it is important to note that a parent’s description of concerns regarding their child’s development may be ambiguous and in these instances follow-up questions are required.²⁹ For additional information regarding parental descriptions of symptoms caused by neuromuscular disorders, please see the [Signs of Weakness: By Parent Report at ChildMuscleWeakness.org](#).²⁹

Physical exam findings will strengthen suspicions of neuromuscular disease and should include an assessment of age appropriate milestones as indicated in Bright Futures.³⁰ ***The most important signs to look for in a patient suspected to have SMA is weakness, tongue fasciculations, and diminished or absent deep tendon reflexes.*** Other signs and symptoms are illustrated in [Figure 7](#). For additional guidance regarding ways to exclude other disease states with similar features, please see the subsequent section, [The Differential](#).

^e <http://www.curesma.org/news/2018-sma-drug-pipeline.html>

System	Findings by Type at Presentation			
	SMA Type I (Werdnig-Hoffmann Disease)	SMA Type II	SMA Type III (Kugelberg-Welander disease / Juvenile SMA)	SMA TYPE IV (Adult Form)
Vital signs	Tachypnea Tachycardia possible hypoxemia	Possible tachycardia and tachypnea		
HEENT	Facial nerves intact Tongue Fasciculations Weak cry Possible high arched palate	Tongue fasciculations	Possible mild tongue fasciculations	
Pulmonary	Tachypnea Prominent abdomen relative to chest wall Abdominal breathing bell-shaped chest (due to weak intercostal muscles and diaphragm dependent breathing) Weak cough At risk for respiratory failure with viral respiratory infection. Possible “rattley” breathing (due to dysphagia)	Weak cough Possible abdominal breathing Possible bell-shaped chest (due to weak intercostal muscles and diaphragm dependent breathing)		
GI	Slow feeding Failure to Thrive Sloppy eating or dysphagia Possible aspiration	Possible failure to thrive Dysphagia		
Neurologic	Hypotonia and weakness Lying flat position: elbows bent and “frog legs” with hypotonia Difficulty lifting extremities against gravity Never achieves independent sitting	Slow movement of extremities, difficulty lifting extremities against gravity Delayed ability to sit independently and/or able to sit independently and then lose sitting. Never achieves weight bearing on legs nor standing Possible muscle tremors of extremities	Muscle tremor - can occur with any muscle, e.g., extremities and face	Diffuse muscle discomfort Progressive extremity muscle atrophy

System	Findings by Type at Presentation			
	SMA Type I (Werdnig-Hoffmann Disease)	SMA Type II	SMA Type III (Kugelberg-Welander disease / Juvenile SMA)	SMA TYPE IV (Adult Form)
	Head lag when pulled to sit Posture in vertical suspension: "Slip through" due to shoulder girdle weakness			
	Position in horizontal suspension: Extremities dangle in extension forming an inverted "U" posture.			
		Unable to Bear Weight on Legs and/or Walk	Gower's Sign	
		Unable to Bear Weight on Legs and/or Walk	Trendelenburg Gait Hyperlordotic Overpronation	
	Hypotonia Diminished strength	Hypotonia Diminished strength	Hypotonia Diminished strength	Hypotonia Diminished strength
	Absent or diminished deep tendon reflexes	Absent or diminished deep tendon reflexes	Absent or diminished	Absent or diminished
	Fatigues easily, most notable with oral feeding	Fatigues easily with eating and activity	Fatigue with exertion Frequent falls Loss of ambulation with disease progression	Fatigue with exertion

Figure 7. History and Physical Findings Observable in SMA

The Differential

The combination of symptoms and age of onset differentiates SMA from other disorders²⁷

Given the rarity of spinal muscular atrophy, and that its early symptoms in infants may also be associated with various other neuromuscular disorders, diagnosis remains difficult for primary care providers. Hypotonia is seen in many other conditions.²⁹ However additional clinical exam findings can help to exclude other disorders.²⁷ The combination of symptoms and age of onset helps to narrow the differential as seen in **Figure 8** below.²⁷

Age of Onset	Disorder	Gene(s) or Region	Method of Inheritance	Clinical Features	
				Overlapping w/SMA	Distinguishing from SMA
Congenital to <6 mos	X-linked infantile spinal muscular atrophy	<i>UBA1</i>	XL	Hypotonia, weakness, areflexia	Multiple congenital contractures, fractures
	Spinal muscular atrophy and respiratory distress 1 (SMARD1) 1 (OMIM 604320)	<i>IGHMBP2</i>	AR	Weakness, respiratory failure, hypo- or areflexia	Distal predominant weakness, diaphragmatic paralysis
	Prader-Willi syndrome	15q11.2-q13		Hypotonia	Poor respiratory effort is rare
	Myotonic dystrophy type 1	<i>DMPK</i>	AD	Hypotonia	Absence of tongue fasciculations
	Congenital muscular dystrophy	Many genes	AR AD	Hypotonia, weakness	CNS, eye involvement
	Peroxisome biogenesis disorders, Zellweger syndrome spectrum	PEX family of genes	AR	Hypotonia	Loss of skills, hepatosplenomegaly
	Congenital myasthenic syndromes	Many genes	AR AD	Hypotonia	Ophthalmoplegia, ptosis, intermittent respiratory failure
	Glycogen storage disease type II (Pompe disease)	<i>GAA</i>	AR	Hypotonia	Cardiomegaly
	Other: congenital myopathies, metabolic/mitochondrial myopathies, peripheral neuropathies				
>6 mos	Botulism	NA	NA	Proximal muscle weakness	Prominent cranial nerve palsies, acute onset
Later childhood	Guillain-Barré syndrome	Unknown		Muscle weakness	Subacute onset, sensory involvement
	Duchenne muscular dystrophy	<i>DMD</i>	XL	Hypotonia	Serum creatine kinase concentration 10-20x > normal
	Hexosaminidase A deficiency (juvenile, chronic, and adult-onset variants)	<i>HEXA</i>	AR	Lower motor neuron disease	Slow progression, progressive dystonia, spinocerebellar degeneration
	Fazio-Londe syndrome (see Riboflavin Transporter Deficiency Neuronopathy)	<i>SLC52A2</i> <i>SLC52A3</i>	AR	Progressive bulbar palsy	Limited to lower cranial nerves; progresses to death in 1-5 yrs.
	Monomelic amyotrophy (Hirayama disease) (OMIM 602440)	Unknown		Muscle weakness	Predominantly cervical; tongue may be affected (rare); other cranial nerves spared
	Other: peripheral neuropathies, muscular dystrophies				
Adulthood	Spinal and bulbar muscular atrophy	AR	XL	Proximal muscle weakness, muscle atrophy, fasciculations	Gradually progressive; gynecomastia, testicular atrophy, reduced fertility
	Amyotrophic lateral sclerosis	Many genes	AD AR XL	May begin w/pure lower motor neuron signs	Progressive neurodegeneration; involves both upper & lower motor neurons

Figure 8. Disorders to Consider in the Differential Diagnosis of Spinal Muscular Atrophy (SMA)^f

AD=Autosomal Dominant

AR=Autosomal Recessive

XL=X-Linked

^f Adapted from: Prior, T., & Finanger, E. (2000 Feb 24 [Updated 2016 Dec 22]). Spinal Muscular Atrophy. In M. Adam, H. Ardinger, R. Pagon, & e. et al., GeneReviews® [Internet]. Seattle, WA: University of Washington. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK1352/#sma.Diagnosis> ^f © University of Washington 1993-2017. GeneReviews® is a registered trademark of the University of Washington, Seattle. The content is used with permission. All rights reserved.

Testing Required to Diagnose SMA

Quantitative analysis of SMN1 and SMN2 – The gold standard of diagnostic testing

Upon suspicion of SMA, the process of ‘ruling in’ or ‘ruling out’ the disease is relatively straightforward by testing for the deletion of SMN1 on chromosome 5 (**Figure 9**). Only 5% of patients with SMA will have a different deletion.^{8, 9}

Children suspected of having SMA should be referred simultaneously to a neuromuscular specialist and for physical therapy at the same time that the test is being sent so as to not delay access to therapy.

Genetic testing is required to definitively diagnose SMA. Confirmation of the homozygous deletion of SMN1 can be obtained via PCR with subsequent restriction digest.³¹ However, this method does not quantify SMN1 or SMN2 copy number. If a homozygous deletion is identified, subsequent tests are required to confirm SMN2 copy number to assess prognosis and determine appropriate treatment.^{8, 32, 33, 34} Given the tests inability to rule out heterozygous deletion, PCR with restriction digest should not be utilized for carrier testing. **Quantitative analysis of SMN1 and SMN2, the ‘gold standard’ for SMA diagnosis and carrier testing, can instead be performed using multiplex ligation dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR), or next generation sequencing (NGS).**^{32, 35, 36, 37}

Once the presence of a homozygous SMN1 deletion confirms a diagnosis of spinal muscular atrophy, additional testing is required to predict phenotype (**Figure 9**).⁸ **Please note, as discussed in the section entitled “[What is SMA?](#)”, SMN2 copy does not perfectly correlate with SMA typing, but does help to predict the severity of the phenotype.** Ultimately, SMN2 copy number determines the course of treatment as described in the subsequent **[Standard of Care](#)** section.

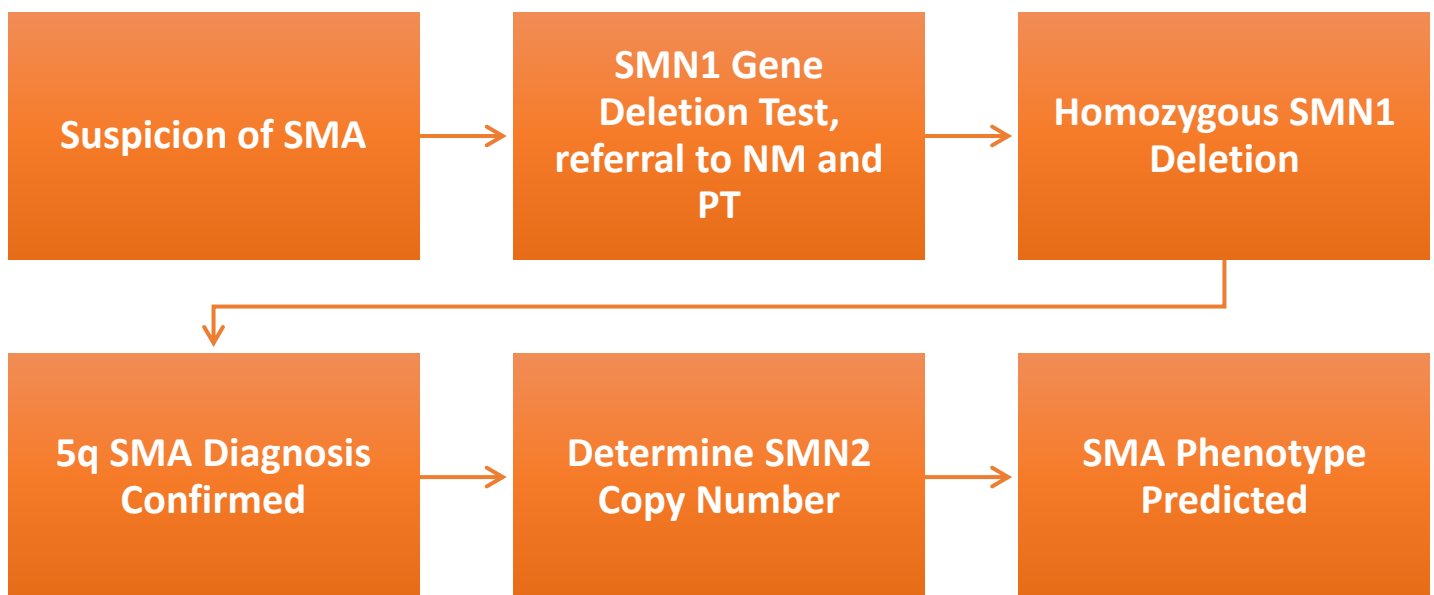


Figure 9 Diagnostic Process for Spinal Muscular Atrophy

Advent of Newborn Screening for SMA and Continuing Need for Early Symptomatic Treatment

In addition to enhanced understanding among practitioners regarding the early clinical signs of SMA, we are working to include SMA testing in the newborn screening panel, which would allow babies to begin treatment almost immediately after birth. SMA was recently added to the Recommended Uniform Screening Panel (RUSP). As each state works to implement SMA screening within their newborn screening panel, providers must continue to be vigilant for the early signs. If you reside in a state that has included SMA on the newborn screening panel, Glascock et al. recently published "[Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screen](#)", which provides guidance on treatment based upon SMN2 copy number.⁹

Standard of Care: Available Treatments and the Need for Multi-Disciplinary Care Teams

Supportive care, including respiratory and nutritional support, also play a significant role in improving the quality of life in patients with SMA. In 2007, the Journal of Child Neurology published the "[Consensus Statement for Standard of Care in Spinal Muscular Atrophy](#)"³⁸ created by an international, multidisciplinary SMA working.³⁸ This document established general guidelines for the management of SMA. The guidelines have become a practical roadmap for clinicians and emphasized the need for coordinated, individualized, **multidisciplinary care** from a variety of providers, specifically **neurologists, pulmonologists, orthopedic surgeons, gastroenterologists, dieticians, physical therapists, occupational therapists, speech therapists, and psychosocial support** for the patients and caregivers. **Palliative care** begins at the time of diagnosis and emphasizes quality of life and comfort measures. The primary care physician can play a prominent role in coordinating care, supporting the family, and implementing specialist recommendations.

Given the advances in treatment and supportive care of SMA, a recent update to standard of care was published in two parts: "[Diagnosis and management of spinal muscular atrophy: Part 1: Recommendation for diagnosis, rehabilitation, orthopedic and nutritional care](#)"³¹ and "[Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics](#)"³⁹ Given the changing phenotype with the provision or treatment, the recommendations are organized by the highest milestone achieved by the patient as follows: Non-sitters, Sitters, Walkers. ***A review of both documents is advised for those participating in the care of a patient diagnosed with SMA as this toolkit does not detail the care guidelines.***

In addition to the provision of immediate treatment following diagnosis, referrals to psychological support and genetic counseling should be offered not only to the patient (if age appropriate), but also the family as a whole.³¹ Receipt of a SMA diagnosis can have significant psychosocial impact. Qian et al, describes ten thematic areas related to the experienced burden which include confronting the possibility of premature death, making difficult treatment choices, fearing the loss of functional ability, social isolation, loss of sleep and stress, and the impact on family finances.⁴⁰ The provision of psychosocial support services is crucial, and can be provided via individual or family counseling, and support groups. Given their training in counseling, genetic counselors can provide psychosocial support to the patient and family, and can help the family understand the mode of inheritance, the risk of SMA reoccurrence in future pregnancies, and reproductive options.^{41, 42} However, despite the benefit of both psychosocial support and genetic counseling to families and patients, each individual is encouraged to pursue services in their own time and from a provider of their choice. For additional information regarding support and care for newly diagnosed families, please see <http://www.curesma.org/support-care>.

Appendix

Cure SMA is an irreplaceable resource for families facing SMA. We won't stop working toward a world without SMA, but until we have a cure, we'll do everything we can to improve quality of life for children and families affected by the disease today. We are experts in every aspect of this disease—from what it means for families to the genetics and the nuances of treatment options—and we offer unconditional support. We do not advocate any specific choices or decisions; we are here for anyone who wishes to talk through their options. All decisions related to SMA are highly personal, and every family needs to do what's best for them. We support every type of SMA and every affected person, from newborns to adults to families who have lost a child. We also help people who are carriers of the SMA gene understand the implications and explore their options. We recognize that the diagnosis can be overwhelming. Patients can request info packs and care packs tailored to meet the needs of each family by contacting infopack@curesma.org and familysupport@curesma.org.

Since 1984, we've led and invested in the research that has made today's breakthroughs possible. We focus on three different—yet equally critical and interdependent—research areas: basic research, to understand the cause and biology of SMA; drug discovery, to convert basic research ideas into practical new drug candidates; and clinical trials, to test the drug candidates. Cure SMA also funds clinical care research to understand the issues that affect daily life for people with SMA, from breathing to nutrition, and to improve their quality of life today. We have invested more than \$75 million in research and have funded half of all the ongoing new drug programs for SMA, including Spinraza, the first-ever approved therapy for SMA.

We educate health care professionals and the public about SMA, to enhance the quality of care and strengthen the support available to families. We work directly with clinicians, medical doctors, specialists, and skilled caregivers to ensure that patients have access to the best possible care. We're currently developing a network of SMA clinical care centers that will collaboratively collect patient care data. This data will help answer questions about the impact of SMA and develop additional strategies for optimal care for those affected by SMA. To further enhance SMA related knowledge amongst health care practitioners, patients, and families, additional resources can be found below. However, if additional questions or concerns persist, please contact Cure SMA staff at earlydiagnosis@curesma.org.

Resources for Providers

- [Cure SMA Provider Microsite](#)
 - SMartMoves.CureSMA.org
- [Quick Resource Guide](#)
 - An abbreviated version of the HCP toolkit
 - [//cureSMA.org/SMartmoves-JIT](http://cureSMA.org/SMartmoves-JIT)
- ChildMuscleWeakness.org
 - Designed by Neuromuscular Disorder Task Force, funded by the Center for Disease Control (CDC).
 - Website designed to help pediatricians recognize the early signs of neuromuscular disease

- **[The Floppy Infant: Evaluation of Hypotonia](#)**²⁷
 - Provides guidance regarding the clinical evaluation of a hypotonic infant
 - Peredo, D. E., & Hannibal, M. C. (2009, September). The Floppy Infant: Evaluation of Hypotonia. *Pediatrics in Review*, 30(9). doi:10.1542/pir.30-9-e66
 - <http://pedsinreview.aappublications.org/content/30/9/e66>

- **[Spinal Muscular Atrophy: A Timely Review](#)**¹²
 - Offers a comprehensive review of SMA and current efforts to develop treatment
 - Kolb, S. J., & Kissel, J. T. (2015, November). Spinal Muscular Atrophy. *Neurologic Clinics*, 33(4), 831-846. doi:10.1016/j.ncl.2015.07.004
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860273/>

- **[Motor Delays: Early Identification and Evaluation](#)**⁴³
 - Algorithm for developmental screening and surveillance
 - Noritz, GH; Murphy, NA; NEUROMOTOR SCREENING EXPERT PANEL. (2013, June). Motor Delays: Early Identification and Evaluation. *PEDIATRICS*, 131(6). doi:10.1542/peds.2013-1056
 - <http://www.pediatrics.org/cgi/doi/10.1542/peds.2013-1056>

- **Cure SMA's Annual Conference**
 - Largest SMA conference in the world.
 - Bring together researchers, healthcare professionals, and families to network, learn, and collaborate
 - Offers a Research and Clinical Care Track

- **[Diagnosis and management of spinal muscular atrophy: Part 1: Recommendation for diagnosis, rehabilitation, orthopedic and nutritional care \(2018\)](#)**³¹
 - Part 1 of current standard of care document
 - Reviews standard practices in 7 areas: Rehabilitation, Orthopedic Management, Nutritional Care, Pulmonary and Acute Care, Medications/Supplements/Immunizations, Other Organ Systems, and Ethics
 - Mercuri, E., Finkel, R. S., Muntoni, F., Wirth, B., Montes, J., Main, M., . . . Group, S. C. (2018, February). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*, 28(2), 103-115. Doi: 10.1016/j.nmd.2017.11.005.
 - [https://www.nmd-journal.com/article/S0960-8966\(17\)31284-1/fulltext](https://www.nmd-journal.com/article/S0960-8966(17)31284-1/fulltext)

- **[Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics \(2018\)](#)**³⁹
 - Part 2 of current standard of care document
 - Reviews standard practices in 7 areas: Rehabilitation, Orthopedic Management, Nutritional Care, Pulmonary and Acute Care, Medications/Supplements/Immunizations, Other Organ Systems, and Ethics
 - Finkel, R. S., Mercuri, E., Meyer, O. H., Simonds, A. K., Graham, R. J., Kirschner, J., . . . Group, S. C. (2018, March). Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*, 28(3), 197-207. doi: 10.1016/j.nmd.2017.11.004.
 - [https://www.nmd-journal.com/article/S0960-8966\(17\)31290-7/fulltext](https://www.nmd-journal.com/article/S0960-8966(17)31290-7/fulltext)

- [Consensus Statement for Standard of Care in Spinal Muscular Atrophy \(2007\)](#) ³⁸
 - Reviews standard practices in 5 care areas: *Diagnostic/New Interventions, Pulmonary, Gastrointestinal/Nutrition, Orthopedics/Rehabilitation, and Palliative Care.*
 - Wang, C. H., Finkel, R. S., Bertini, E. S., Schroth, M., Simonds, A., Wong, B., . . . Care, P. o. (2007, August). Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *Journal of Child Neurology*, 22(8), 1027-1049. doi:10.1177/0883073807305788
 - <http://journals.sagepub.com/doi/pdf/10.1177/0883073807305788>

- [218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19–21 February 2016](#) ⁴⁴
 - Update to standard of care practices previously established by the “*Consensus Statement for Standard of Care in Spinal Muscular Atrophy*”
 - Finkel, R. S., Sejersen, T., Mercuri, E., & Group, E. S. (2017, June). 218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. *Neuromuscular Disorders*, 27(6), 596-605. doi:10.1016/j.nmd.2017.02.014
 - [https://www.nmd-journal.com/article/S0960-8966\(17\)30138-4/pdf](https://www.nmd-journal.com/article/S0960-8966(17)30138-4/pdf)

- [Treatment algorithm for Infants Diagnosed with Spinal Muscular Atrophy through New Born Screening](#) ⁹
 - Provides a detailed treatment algorithm for SMA-positive infants based on SMN2 copy number
 - Glascock, J., Sampson, J., Haidet-Phillips, A., A, C., Darras, B., Day, J., . . . Jarecki, J. (2018). Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screen. *Journal of Neuromuscular Disease*. doi:10.3233/JND-180304
 - <https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd180304>

- [SPINRAZA SITE LIST:](#)
 - Cure SMA offers a comprehensive Spinraza site list that is searchable by state
 - <http://www.curesma.org/spinraza/>.

Resources for Patients

- **Cure SMA’s “Parent Checklist”**
 - Quick checklist that parents can utilize to help identify potential signs of motor delay and recognize red flags that may indicate a life-threatening condition
 - Specific to two age groups:
 - **0 to 6 months** (<http://www.curesma.org/documents/support--care-documents/parent-checklist-0-6mo.pdf>)
 - **7 to 12 months** (<http://www.curesma.org/documents/support--care-documents/parent-checklist-7-12mo.pdf>)
- **Cure SMA’s “Parents with Concerns” Website**
 - Provides pictures and videos that illustrate the observable differences between normal and abnormal motor development
 - Urges parents to trust their gut and discuss all concerns with their child’s pediatrician
 - <http://www.curesma.org/for-concerned-parents/>
- **Cure SMA Care Packages**
 - Please call our office at 800.886.1762 or email infopack@curesma.org to request or receive additional information about the resources available to newly diagnosed families.
- **SPINRAZA SITE LIST:**
 - Cure SMA offers a comprehensive Spinraza site list that is searchable by state
 - <http://www.curesma.org/spinraza/>.
- **Family Guide to Consensus Statement for Standard of Care in Spinal Muscular Atrophy**⁴⁵
 - Offers a clear and concise version of the “*Consensus Statement for Standard of Care in Spinal Muscular Atrophy*”
 - <http://www.curesma.org/documents/research-documents/family-consensus-statement.pdf>

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