

# Spinal Muscular Atrophy: Past, Present, and Future

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**AUTHOR DISCLOSURES** Dr Ross has disclosed that her spouse owns stock in General Electric and Bristol-Myers Squibb. Dr Kwon has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## ABBREVIATIONS

|         |   |
|---------|---|
| AAV     | adeno-associated virus  |
| AAV9    | adeno-associated virus serotype 9   |
| ACHDNC  | Advisory Committee on Heritable Disorders in Newborns and Children  |
| ACMG    | American College of Medical Genetics and Genomics   |
| CHERISH | A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants with Later-onset Spinal Muscular Atrophy        |
| ENDEAR  | Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy   |
| FDA     | Food and Drug Administration  |
| G-tube  | gastrostomy tube  |
| HRSA    | Health Resources and Services Administration  |
| ISS-N1  | intronic splicing silencer N1   |
| NBS     | newborn screening   |
| PCR     | polymerase chain reaction   |
| RT-PCR  | real-time polymerase chain reaction   |
| RUSP    | recommended uniform screening panel   |
| SCID    | severe combined immunodeficiency  |
| SHINE   | A Study for Participants with Spinal Muscular Atrophy Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies |
| SMA     | spinal muscular atrophy   |
| SMN     | survival motor neuron   |
| TREC    | T-cell receptor excision circle   |

## Practice Gaps

In December 2016, the United States Food and Drug Administration approved the use of nusinersen for the treatment of spinal muscular atrophy (SMA), a genetic disorder that is characterized by skeletal muscle weakness and atrophy. Although noncurative, intrathecal nusinersen has been shown to be effective in slowing down neuromuscular degeneration. In June 2018, SMA was added to the recommended uniform state newborn screening panel. However, its inclusion is not without controversy because SMA has wide variability in age at disease onset and no algorithm can accurately distinguish those who need early intervention from those who do not.

## Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by deletions or mutations in the survival motor neuron (*SMN1*) gene. SMA is characterized by loss of lower motor neurons (anterior horn cells) in the spinal cord and brainstem nuclei, leading to progressive symmetrical muscle weakness and atrophy. It affects approximately 1 in 6,000 to 1 in 10,000 individuals and is the most common inherited cause of childhood mortality, but this may soon change given recent developments. In December 2016, nusinersen, an antisense oligonucleotide drug, was approved by the United States Food and Drug Administration for the treatment of SMA, and in July 2018, SMA was added to the recommended uniform screening panel, a list of conditions that all states are encouraged to include in their newborn screening (NBS) panels. In this review, we begin with a brief clinical history of the diagnosis of SMA, discuss the current SMA clinical classification system, describe the current treatment, and discuss evolving treatment guidelines. We then discuss the path to include SMA in NBS programs as well as the controversies it engenders because the variability in age at symptom onset means early identification of asymptomatic patients who will not require therapy for years or decades. We also consider alternate population screening opportunities. Next, we consider experimental treatments. We conclude by supporting NBS for SMA with the caveat that a long-term follow-up registry is ethically essential to ensure that the benefits outweigh the harms for all screened infants, including those with milder and/or later-onset forms of SMA.

## Objectives After completing this article, readers should be able to:

1. Explain the indications, techniques, and limitations for newborn screening for spinal muscular atrophy.
2. Recognize the controversies associated with the introduction of new newborn genetic tests for conditions with variable presentation from the neonatal period through adult onset.
3. Describe the epidemiology, etiology, clinical presentation, clinical classification, and treatment of spinal muscular atrophy.

### INTRODUCTION

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disease caused by deletions or mutations in the survival motor neuron (*SMN1*) gene and is characterized by loss of lower motor neurons (anterior horn cells) in the spinal cord and brainstem nuclei, leading to progressive symmetrical muscle weakness and atrophy. There is wide variability in severity and age at onset. In this review, we begin with a brief clinical history of the diagnosis of SMA, discuss the current SMA clinical classification system, describe current treatment, and discuss evolving treatment guidelines. We then discuss the path to include SMA in newborn screening (NBS) programs, the controversies it engenders, and other possible screening opportunities. Next, we consider experimental treatments. We conclude by offering our own recommendations regarding screening and long-term follow-up given the current state of the science.

### CLINICAL HISTORY AND CLASSIFICATION OF SMA PHENOTYPES

Guido Werdnig of the University of Vienna presented the first case of SMA in an 1891 lecture titled “On a case of muscular dystrophy with positive spinal cord findings” and described 2 patients with progressive weakness in their lower extremities followed by tremors in their upper extremities and early death. (1)(2) Autopsies of these patients showed bilateral symmetrical loss of anterior horn cells. Johann Hoffman of Heidelberg University described patients with similar findings that year (3) and introduced the term, “Spinale Muskelatrophie” (“spinal muscular atrophy”), describing infants with progressive weakness, tremors, and death from pneumonia in early childhood. (4) Hoffman noted that these affected infants were born to healthy parents and that the same disease occurred in siblings. (4) Half a century later, Wohlfart et al (5) and

Kugelberg and Welander (6) described milder forms of SMA. In 1961, Byers and Banker provided the first classification of SMA, dividing patients into 3 groups (7):

Group 1: Intrauterine presentation or clinical signs in the first 2 postnatal months characterized by early weakness and early death

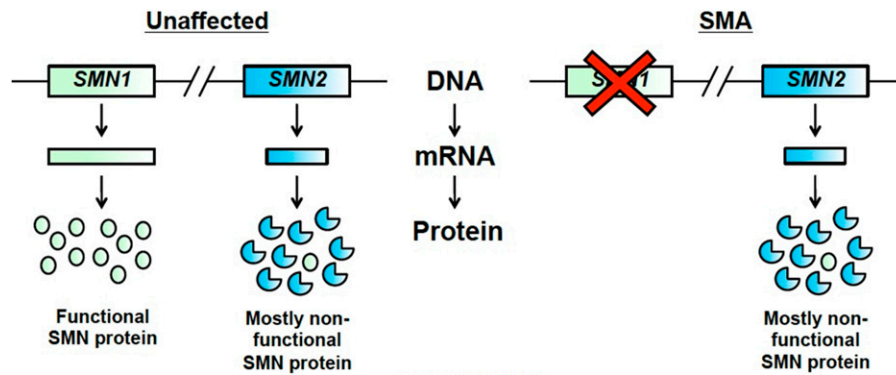
Group 2: Initial presentation between 2 and 12 months of age with more localized weakness and longer survival

Group 3: Presentation after 1 year of age

In 1992, a classification system was adopted in which different types of SMA were designated by the highest level of function (ie, sitting or standing). (8)

Today, we know that SMA is an autosomal recessive disorder that occurs in 1 in 6,000 to 1 in 10,000 individuals and is caused by loss of the SMN protein, which is encoded by the gene *SMN1*. (9)(10) The loss of *SMN1* causes SMA, with approximately 95% of affected individuals having homozygous deletions of *SMN1* exon 7. (10) Most of the remaining 5% of patients with SMA are compound heterozygotes for an *SMN1* deletion and *SMN1* point mutation. (10) Though not discussed further in this review, there are other forms of pediatric motor neuron dysfunction that are not caused by *SMN1* mutations. (10)(11)(12)

Although SMA is diagnosed by the presence of deletions and mutations in *SMN1*, the variability in clinical presentation depends on the presence of an adjacent and nearly identical gene, *SMN2*. (13) Both *SMN1* and *SMN2* genes can produce the full-length SMN mRNA transcript required to make normal SMN protein, along with other more unstable transcripts (Fig 1). However, while the full-length transcript is the major product of *SMN1*, *SMN2* produces smaller amounts of the full-length SMN mRNA transcript and hence smaller amounts of full-length (functional) SMN protein. (13)(14)



**Figure 1.** *SMN1* and *SMN2* genes and their respective mRNA transcripts and protein products. In the case of *SMN2*, mostly nonfunctional SMN protein is made but there is a small amount of functional protein. (Reprinted with permission from Dr. James Sleight, Spinal Muscular Atrophy UK website. <https://smauk.org.uk/blog/treatments-research/splicing-exons-and-the-smn2-back-up-gene>.)

In general, the more copies of *SMN2* that exist in a patient with SMA, the milder the symptoms. Without *SMN2* copies, the loss of *SMN1* function would be lethal whereas individuals with 5 or more copies of *SMN2* may have no symptoms at all. (15). However, the *SMN2* copy number does not completely correlate with phenotype, even within families. (10) (13) The current classification of SMA is determined by clinical manifestations (Table 1) based on highest attainment of function. (10)(16) SMA type 0 is the most severe form, often presenting with weakness in utero or at birth.

Patients with SMA type 1 present in the first few months of age with symmetrical limb weakness, intercostal muscle weakness, tongue fasciculations, and absent deep tendon reflexes. In contrast, affected patients have normal sensation (as is true for all forms of SMA). Untreated, these children never achieve the ability to sit. They have weak cries and difficulty handling oral secretions. Feeding becomes difficult and failure to thrive is common. Many have gastroesophageal dysmotility and gastroesophageal reflux disease, which can be life-threatening because of the risk of aspiration. As weakness progresses, decisions must be made about feeding methods, such as placement of a gastrostomy tube (G-tube) and the extent of ventilatory support. Historically, most of these children died in the first few years of age, but with the development of new therapies, the natural history is expected to evolve. Similar to all patients with SMA, patients with this type have intact cognition. (7)(8)(10)(16)

SMA type 2 is less severe than SMA type 1, with affected infants often presenting between 6 and 18 months of age. Although motor milestones are delayed, children with type 2 usually achieve the ability to sit, but cannot stand or walk independently. Respiratory issues ensue but are less severe than in patients with SMA type 1; most patients with SMA type 2 will require nighttime ventilation. Feeding and

swallowing difficulties are also common. Joint contractures develop over time from lack of movement. Many patients develop kyphoscoliosis, which exacerbates underlying respiratory dysfunction and leads to bracing or surgery. (7)(8)(10)(16)

SMA type 3 is an even milder form than SMA type 2, typically presenting after 18 months. Affected children achieve independent walking but most lose the ability over time (ranging from childhood to midlife). Scoliosis, falls, muscle and joint pain, and fatigue with activity are common. Less common are swallowing dysfunction and/or feeding difficulties. (10)(16)

Patients with SMA type 4 can present in adulthood, but, again, there is a wide range in the variability of onset of motor symptoms. Individuals with SMA type 4 can be ambulatory for decades, and they rarely experience respiratory or gastrointestinal symptoms. (10)(16)

Although the phenotypic descriptions of SMA focus on muscle weakness, hypoventilation, and gastrointestinal problems, now that patients with SMA are surviving longer, we are learning of other symptoms—disrupted sensory pathways, cardiac arrhythmias, vascular defects such as distal digital necrosis, decreased bone mineral content, and abnormal glucose metabolism—that indicate that low SMN levels affect other organ systems. (17)

## MANAGEMENT

Before 2017, the management approach in patients with SMA was supportive, with more invasive interventions (tracheostomy for airway protection and G-tube to address feeding difficulties) recommended in those with greater weakness. The 2007 consensus statement summarized the recommended approach to manage patients with SMA. (18) The guidelines recommended that patients with pulmonary disease, identified as the major cause of

TABLE 1. Spinal Muscular Atrophy (SMA) Classification Scheme (10)(13)(16)

| CHARACTERISTICS |                      |                                 |           | NATURAL HISTORY WITHOUT TREATMENT   |   |
|-----------------|----------------------|---------------------------------|-----------|---|---|
| SMA TYPE        | TYPICAL AGE AT ONSET | TYPICAL # OF SMN2 COPIES        | FREQUENCY | HIGHEST MOTOR FUNCTION EVER ATTAINED (EPONYMS INCLUDED, THOUGH USED LESS FREQUENTLY)  | TYPICAL AGE AT NATURAL DEATH (WITHOUT INVASIVE MEDICAL SUPPORT) |
| 0               | Prenatal/birth       | 0-1                             | <5%       | Presents in the fetal and neonatal period with lack of fetal movement, contractures and severe hypotonia<br>Early death without aggressive supportive intervention beginning at birth or shortly thereafter | Neonatal period   |
| 1               | 0-6 mo               | 1, 2 <sup>a</sup> , 3           | ~60%      | Werdnig-Hoffman disease: Never sits independently   | <2 y  |
| 2               | 6-18 mo              | 2, 3 <sup>a</sup> , 4           | ~10%      | Dubowitz disease: Able to sit; never able to walk independently   | >2 y  |
| 3               | >18 mo               | 3 <sup>a</sup> , 4 <sup>a</sup> | <5%       | Kugelberg-Welander disease: Shows marked variability in onset, symptom progression and function, but at some point are able to stand or even walk independently   | Normal life expectancy  |
| 4               | >21 y                | ≥4                              | ~20%      | Presents in adulthood.<br>Able to walk independently (individuals with >6 copies may be phenotypically normal)  | Normal life expectancy  |

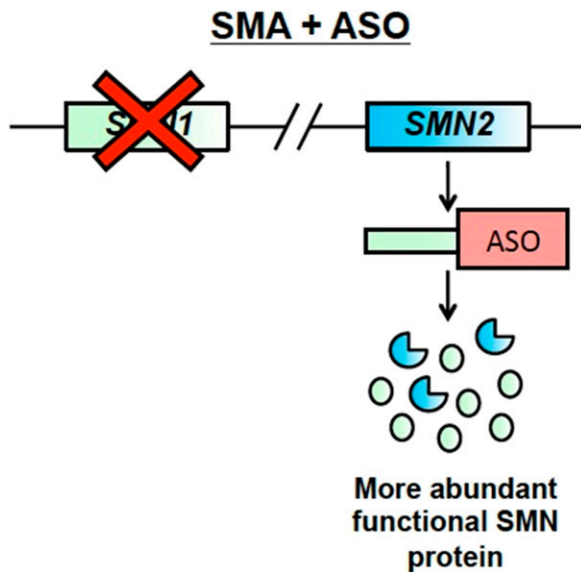
<sup>a</sup>The most frequent copy number for the SMA type (50) (see Table 2).

morbidity and mortality in SMA types 1 and 2, should receive a stepwise introduction of interventions, beginning with routine airway clearance with cough assistance and, with ongoing evidence of hypoxemia, progress to nocturnal, then continuous, noninvasive ventilation. Finally, invasive tracheotomy for chronic mechanical ventilation may be considered, “a decision that needs to be carefully discussed if requested by parents.” (18) The guidelines noted that feeding and swallowing difficulties were common in patients with SMA types 1 and 2. Clinicians were encouraged to optimize efficiency of feeding, manage gastroesophageal reflux disease, and treat abdominal distention resulting from infrequent bowel movements. However, the guidelines did not reach a consensus regarding when to refer a patient for G-tube placement.

In December 2016, the US Food and Drug Administration (FDA) approved the use of intrathecal nusinersen, the first medication designed to specifically treat patients with SMA by increasing the amount of SMN protein. The development of nusinersen began in 2004 with the identification of the intronic splicing silencer N1 (ISS-N1) sequence, which affects exon 7 skipping during splicing. (19) In 2010, Ionis Pharmaceuticals (Carlsbad, CA) was granted an exclusive

license by the University of Massachusetts Medical School, the patent holder, to develop a drug to treat patients with SMA that was based on the ISS-N1 target. (19)(20) Nusinersen is an antisense oligonucleotide designed to block ISS-N1, altering SMN2 splicing to include exon 7, producing more full-length transcripts and greater quantities of normal SMN protein (Fig 2). The efficacy of intrathecal nusinersen was first shown in the ENDEAR (Efficacy and Safety of Nusinersen [ISIS 396443] in Infants with SMA) study, a randomized controlled trial of patients with SMA type 1 younger than 7 months at the time of first administration of nusinersen or sham intrathecal injection. (21) Interim analysis found that 41% of patients treated with nusinersen were “motor milestone responders” (showing gains such as full head control, rolling, and sitting) versus 0% in the sham treatment arm ( $P < .001$ ). (21)

The sponsors sought rapid approval based on rare disease status. They submitted data from 5 trials of nusinersen. The FDA approved nusinersen on December 23, 2016, with data from fewer than 200 patient-subjects and using surrogate endpoints rather than final endpoints. (22) (23) At the time of approval, follow-up of at least 6 months' duration was available for only 78 (63.9%) of a planned 122 patients in



**Figure 2.** The antisense oligonucleotide (ASO), nusinersen, alters the mRNA transcript produced by *SMN2* to create normal protein. (Reprinted with permission from Dr. James Sleight, Spinal Muscular Atrophy UK website, <https://smauk.org.uk/blog/treatments-research/splicing-exons-and-the-smn2-back-up-gene>.)

the ENDEAR study. (23) The FDA approved nusinersen use in all classes of SMA, though clinical trial benefit was only shown in SMA type 1, and so degree and longevity of benefit for those with milder phenotypes was unknown. Since approval, additional data support the effectiveness of nusinersen in slowing (but not stopping) disease progression in SMA type 1. (24)

Additional data also show efficacy of nusinersen for treating patients with SMA types 2 and 3. Chiriboga and colleagues performed a phase 1 escalating dose trial of nusinersen in children aged 2 to 14 years with SMA types 2 and 3. (25) Patients who received the highest dose had some improvement in the Hammersmith Functional Motor Scale–Expanded during a period when it would be expected that the children’s motor development would be flat or falling. (25) Although not available at the time of the FDA review, interim and final analyses data from CHERISH (A Study to Assess the Efficacy and Safety of Nusinersen [ISIS 396443] in Participants with Later-onset SMA) found that patients aged 2 to 12 years with types 2 and 3 SMA who received nusinersen had greater improvements in motor function than those in the control arm. (26) After FDA approval, children enrolled in ENDEAR, CHERISH, and other nusinersen trials were eligible to participate in a phase 3 extension study named SHINE (A Study for Participants with SMA Who Previously Participated in Nusinersen [ISIS 396443] Investigational Studies [NCT02594124]) in which all participants received nusinersen. Data presented at the

2018 American Academy of Neurology meeting showed continued safety and benefit. (27) Long-term follow-up is critical to determine if treatment continues to slow progression, if patients experience different effects depending on their disease severity, and if potential harms manifest over time. (22)(24)

Biogen has priced nusinersen at \$125,000 per dose. The regimen requires 6 intrathecal doses in year 1 and 3 intrathecal doses annually thereafter. Gerrity and colleagues note that patients may be at risk from unrecognized harms and burdens of paying for medications because of insufficient research. (23) Insurers may require documentation of disease stability or improvement, or at least a slower deterioration of muscle function than would be expected without treatment. The prior authorization process is complex, putting children at risk with delayed treatments, and exposing families to large out-of-pocket expenses. Already, several US insurers have declined requests for SMA types 3 and 4 because this regimen is still experimental for these types. (24)

The financial expense of the drug is only part of the cost. The intrathecal mode of therapy requires families to travel to centers that administer intrathecal infusions. There are wide differences in drug administration, with some centers administering the infusion in a clinic setting and others providing sedation in an operating room setting with continuous monitoring for respiratory and hemodynamic status both during and after the infusion. Access to the patient’s intraspinal space may become limited over time as a result of disease progression and/or repeated lumbar punctures. There are also concerns about the safety of multiple lumbar punctures in patients with significant comorbidities and the costs in terms of manpower, clinical resources, and cost of drugs. (22)(28)

With the approval of nusinersen and with promising early results from other experimental drug trials, new consensus care guidelines were developed and published in 2018. (29)(30) The guidelines provide detailed recommendations for physical therapy and rehabilitation, orthopedic care, nutrition, pulmonary care, and other organ involvement. As in the 2007 guidelines, (18) respiratory management and palliative care were the 2 most controversial issues. Tracheostomy ventilation is still described as “a decision focused individually on the clinical status, prognosis, and quality of life based on discussions with the family.” (30) Although there was no consensus about the role and timing of palliative care, especially in light of the most recent therapeutic approaches, the statement encourages the dismissal of “the dichotomous model,

which sets active treatment against palliative care in favor of a model of complementarity.” (30)

## NEWBORN SCREENING FOR SMA

Current research provides strong evidence that patients with SMA type 1 have irreversible motor neuron loss early in the perinatal period, which progresses to severe denervation in the first 3 months of age and a motor unit loss of more than 90% within 6 months of age. (31)(32) A delay in diagnosis is common; studies have shown that while the onset of symptoms occurs at a mean age of 2.5, 8.3, and 39.0 months for SMA types 1, 2 and 3, respectively, the diagnosis of SMA was confirmed later at weighted mean ages of 6.3, 20.7, and 50.3 months for types 1, 2, and 3, respectively. (33) Because animal and human studies found best outcomes when treatment was provided early in the disease course, (21)(32)(34)(35) newborn screening (NBS) is regarded as the best means to avoid the diagnostic odyssey reported by many families. (36)

However, NBS is not without controversy. The quest to include testing for SMA in NBS began over a decade ago with the development of the recommended uniform screening panel (RUSP). This panel was developed in 2005 through a joint effort between the American College of Medical Genetics (now the American College of Medical Genetics and Genomics) (ACMG) and the Health Resources and Services Administration (HRSA) and contained a list of disorders for which all newborns should be screened. (37) The ACMG/HRSA evaluated 81 conditions for inclusion in the RUSP based on the ability to perform a screening test, confirm the diagnosis, and treat the disorder. SMA was not on this list of potential conditions because no screening test and no treatment existed for SMA. Despite the controversies surrounding the process, (38)(39) 25 conditions and 29 secondary conditions were selected for the RUSP. (37) The RUSP was quickly endorsed by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), which has since agreed that a transparent evidence-based approach was necessary in considering additions to and removals from the RUSP. (38)(39)

In 2008, the ACHDNC was asked to consider SMA for inclusion. The ACHDNC concluded that it was premature to even conduct an evidence-based review because no effective treatments existed. (40) The technology for efficient population screening, not available at the time of the ACMG/HRSA report, had been developed. (41) In 2006, Pyatt and Prior had demonstrated the feasibility of population screening for SMA using real-time polymerase chain reaction (RT-PCR) as first-tier testing, which identified *SMN1* exon 7 deletions with sensitivity and specificity of 100%. (41) A

concurrently run assay detected *SMN2* copy numbers. However, at that time, “the use of DNA as a testing substrate and molecular techniques for deletion analysis” (41) as initial (first-tier) screening was rarely being used, but rather, was reserved for second-tier tests performed after metabolic screening. For example, molecular genetic testing for cystic fibrosis is conducted only after a newborn is identified as having elevated immunoreactive trypsinogen levels on the NBS blood spot.

This attitude toward first-tier molecular testing changed in May 2010 with the approval of severe combined immunodeficiency (SCID) into the RUSP. (42)(43) First-tier screening for SCID is based on RT-PCR assays on DNA samples extracted from dried blood spots to measure T-cell receptor excision circles (TRECs), a byproduct of T-cell development. The need for state public health programs to adopt and implement new laboratory methodologies caused delays, and it was not until December 20, 2018, that all states had implemented SCID into their NBS program. (43)

In 2015, Taylor and colleagues modified a multiplexed RT-PCR TREC assay to allow concurrent testing of the presence or absence of the *SMN1* gene from a dried blood spot. (44) This promised to streamline the adoption of SMA into NBS programs by using already existing molecular equipment and workflows. An early pilot study in 2013-2014 by Swoboda, funded by the National Institute of Child Health and Human Diseases, was hampered by regulatory issues about whether the study could be done as an opt-out or required written consent (with different methodologies used in Utah and Colorado), and only managed to screen 16,736 infants (with no positive results), (45) despite the fact that research with parents in these two states supported an opt-out approach which would have garnered much greater participation. (46)

However, in 2017, 2 pilot NBS programs reported their experiences using PCR methods to screen newborns for SMA. Chien and colleagues described outcomes in 120,267 infants born and tested for SMA between November 2014 and September 2016 at the National Taiwan University Hospital Newborn Screening Center. (47) Of the 15 infants who screened positive, 8 were false positive for the disease (identified later as carriers) and 7 were diagnosed with SMA. In those diagnosed, 3 patients had 2 copies of *SMN2*, 2 had 3 copies, and 2 had 4 copies. The duration of patient follow-up ranged from 1.5 to 25 months. Some patients received treatment with nusinersen under a research protocol. In the 3 patients with 2 *SMN2* copies, 1 is currently receiving nusinersen, 1 died, and 1 patient’s family has declined participation in research. In the 2 who have 3 *SMN2* copies, 1 is receiving nusinersen and is well at 11 months and the other is not receiving nusinersen and lost ambulation at 17 months. The 2 patients who have 4 *SMN2* copies had

normal examination findings and were not receiving nusinersen at their last follow-up.

The second pilot study was reported by Kraszewski and colleagues and took place in 3 hospitals in New York City. (48) From January 2016 to January 2017, 3,826 (93% of eligible infants who were approached for consent) participated in a study to assess the ability of NBS to diagnose patients with SMA. Of the infants, 94.6% were screened as negative and did not require additional testing. The researchers identified 59 carriers and 1 infant homozygous for the *SMN1* exon 7 deletion who was immediately enrolled in a nusinersen trial. At 1-year follow-up, she had received 6 doses of nusinersen and was meeting all of her developmental milestones. (48)

In December 2016, nusinersen was approved by the FDA for the treatment of all types of SMA. In February 2017, armed with NBS pilot data and a therapy, Cure SMA (a national nonprofit support and advocacy organization for patients and families with SMA) reapplied to have SMA included in the RUSP. Because virtually all states were screening for SCID, (44) the infrastructure for first-tier molecular genetic testing for SMA was in place. The ACHDNC agreed to reevaluate the evidence and nominated it for inclusion into the RUSP in February 2018. This was approved 4 months later by the Secretary of the Department of Health and Human Services. Even before it was included in the national RUSP, 4 states were already screening newborns for SMA. (49)

SMA NBS avoids delays in diagnosis and allows treatment to be initiated before permanent axonal loss takes place. Cure SMA convened a group of experts to develop guidelines for initiating treatment in those identified with SMA by NBS and based treatment initiation on *SMN2* copy number because this is the best predictor of symptom onset and clinical severity. (32) The decision to treat infants with 1 copy of *SMN2* was deferred to the treating physician and family because these infants are likely to have SMA type 0 and may already show significant weakness at birth. In this setting, axonal damage may already be irreversible. In contrast, for infants with SMA type 1 (or patients who had 2 or 3 copies of *SMN2*), the guidelines recommend immediate treatment. (32) This is likely to result in overtreatment because copy number only roughly correlates with phenotype and some children who would not experience any symptoms for years will begin treatment as infants.

Another question that arises from early testing is: What proportion of infants with SMA with 3 *SMN2* copies will have a type 3 phenotype? Calucho and colleagues reviewed data from 625 unrelated Spanish patients and 2,834 patients identified from the literature (Table 2). (50) Most patients

(2,416 of 3,459 or 70%) had SMA type 1 or 2, and most of those with type 1 had only 1 or 2 copies of *SMN2* (1,007 of 1,256 or 80%). However, a person with 3 *SMN2* copies could present as type 1, 2, or 3 and in fact, a person with 3 *SMN2* copies has a 31% chance (515 of 1,662) of having SMA type 3, (50) which usually presents sometime in childhood, with some children having mild symptoms. (10)(16) It is important to monitor treated and untreated patients to determine whether those patients who truly require early treatment can be separated from those who will incur risks without benefit. Costs should be considered as well; the drug is far too expensive for the health care community to blindly treat all patients with a diagnosis of SMA. It is important to identify patients (as early as possible) who are unlikely to benefit from the medication.

If treatment is deferred in affected infants with 3 or more copies, changes in physical examination findings, including loss of tendon reflexes or other concerns of weakness, should trigger the need to start nusinersen treatment quickly. (32) Follow-up at a specialized pediatric neuromuscular clinic is essential to assess for subtle changes.

Consensus is lacking on how often patients with 4 or more *SMN2* copies should be followed and when, if ever, to start nusinersen treatment. In Taiwan's NBS pilot program, Chien and colleagues did not recommend routine clinical neurology follow-up for infants with 4 or more *SMN2* copies, but told families to return if symptoms develop. (47) In contrast, Kraszewski and colleagues were equivocal about what to do for children with 4 or more copy numbers: "it is still unclear whether patients with more than 4 *SMN2* copies should be treated as newborns and how frequently they should be treated. We believe it is likely that such children would derive benefit, but it is unclear exactly what the optimal treatment protocol should be." (48)

## CLINICAL CONTROVERSIES ARISING FROM EARLY DIAGNOSIS AND TREATMENT

The first controversial issue about using NBS to diagnose patients with SMA is that the methodology for early diagnosis might miss some cases of SMA. Most states are considering methods based on detection of homozygous deletions of *SMN1* exon 7, which will overlook some infants with SMA who are heterozygous for *SMN1* deletion and also have a point mutation. Thus, this cohort may not be diagnosed until symptoms develop, which would delay treatment.

As alluded to earlier, whom to treat soon after early diagnosis is controversial. If expert guidelines recommend "immediate treatment" for an infant who has 2 or 3 *SMN2*

TABLE 2. Summary of Combined Data on Types of Spinal Muscular Atrophy<sup>a</sup>

| SMN2 COPY NUMBER | TYPE 1 (N=1,256)<br>N (%) | TYPE 2 (N=1,160)<br>N (%) | TYPE 3 (N=1,043)<br>N (%) |
|------------------|---------------------------|---------------------------|---------------------------|
| 1                | 88 (7)                    | 4 (<1)                    | 0 (0)                     |
| 2                | 919 (73)                  | 192 (16)                  | 54 (5)                    |
| 3                | 245 (20)                  | 902 (78)                  | 515 (49)                  |
| 4                | 3 (<1)                    | 59 (5)                    | 455 (44)                  |
| 5                | 1 (<1)                    | 3 (<1)                    | 16 (2)                    |
| 6                | 0 (0)                     | 0 (0)                     | 3 (<1)                    |

<sup>a</sup>Data extracted from articles published from 1999 to date.

Reprinted with permission from Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord.* 2018;28(3):208–215. (50)

copies, then some infants with SMA type 3 will be treated even though they may not present for years and their progression may be slow. Given the cost of the drug and its invasive administration, this will mean excessive treatment for some. Based on the data from Calucho and colleagues, in the 2,827 infants with 2 or 3 SMN2 copies, 569 or 20.1% were diagnosed as having SMA type 3 (50).

Some identified with NBS may not present until adulthood. The number is generally assumed to be small because SMA type 4 is considered a relatively rare presentation, (10)(16) (50) However, as population screening becomes more commonplace, the number of individuals diagnosed with adult-onset disease is likely to rise. This is because many of these individuals may have never been diagnosed and therefore not included in the medical literature or in databases. Current pediatric genetic testing guidelines discourage early diagnosis of children with adult-onset conditions because it takes away their right to decide for themselves whether they want to get tested and their right to privacy about their adult health risks. It also exposes them to the risks that they will be treated as if they are ill even while asymptomatic (“vulnerable child syndrome”). (51)(52)(53)(54)

The following logistical challenges arise from identifying infants with adult-onset conditions: 1) how to ensure that individuals asymptomatic in childhood are aware of their diagnosis; 2) how to ensure that health information diagnosed at birth is available to their adult physicians; and 3) how to establish and maintain the infrastructure needed to ensure that this information follows these individuals for life so that they might benefit from early treatment if and when their symptoms appear. (51)(55)(56)

Expecting asymptomatic patients to pass on this information to clinicians during adulthood is unrealistic because it assumes that their parents informed them about the diagnosis, that patients know to share this information with all of their physicians, and that they are aware of symptoms that should lead to further evaluation. This is further complicated in the patchwork health care system that exists in the United States.

A major controversy of early SMA diagnosis arises in children who are eligible to be treated but the family is unwilling to have their child treated. This may be especially concerning if the clinicians involved feel a sense of urgency to start treatment when it can be the most effective. It is important for clinicians to understand why a family refuses treatment and to make sure that the family is cognizant of the risks and benefits of forgoing medication. Some parents may refuse treatment because of lack of sufficient information, lack of long-term safety data, risks related to repeated lumbar punctures, and repeated anesthesia exposure. Some may want to participate in other treatment trials or to delay treatment to see if symptoms are likely to develop (some infants with 3 SMN2 copies may not develop symptoms for years). Others may refuse because of financial and logistical burdens if they live far from administration sites or the administrative sites are out of network, which would require negotiation with insurers and possible large out-of-pocket expenses. We believe it is premature to argue that refusal in the first weeks after birth is inherently medically neglectful. However, parents must be counseled about the risks and benefits of delaying treatment and signs and symptoms of disease progression that should trigger immediate follow-up.



The use of ventilation in symptomatic children is also controversial. Although we hope that with early diagnosis and treatment, children with SMA will never have to face the need for invasive ventilation, there are many children with SMA who progress or are already too weak to benefit from the many advances described. The consensus for the use of noninvasive ventilation, including airway clearance using mechanically assisted coughing for infants with SMA is unanimous; however, the data show that a significant percentage of physicians did not support more invasive tracheostomy and ventilation. (57)(58)(59)(60)(61) Physicians have raised concerns about the quality of life of children receiving ventilation, because it often removes their ability to speak. Given that this disease is also associated with bulbar weakness, individuals receiving ventilation may have severely limited communication abilities. (62)(63) Still, it should be noted that numerous studies show that patients and parents view quality of life for those with disabilities as much better than their physicians rate them. (64)(65)(66)(67)

A final question is whether NBS is the appropriate time to screen for SMA. An alternative strategy is prenatal screening to inform parents of health risks to the fetus as early as possible or even preconception screening to provide couples with reproductive options. Carrier frequency varies by race/ethnicity, occurring in 1 in 40 Asians, 1 in 50 whites, 1 in 100 blacks, and 1 in 76 Hispanics. (68)(69)(70) That is, SMA is relatively frequent in all ethnicities. SMA carrier screening has been supported by the ACMG since 2008 (71) and by the Association for Molecular Pathology since 2011. (72) In 2009, the American College of Obstetrics and Gynecology supported targeted testing of those with a family history, (73) but since 2017, this organization supports offering universal prenatal screening in all ethnic communities. (74) Whether couples offered screening will take advantage of this option, and, if testing is done, how they will use the information, is not yet known. Clearly, counseling will need to discuss the diverse phenotypes as well as the current and developing treatments. All professional societies support parental and prospective parental rights to nondirective counseling and freedom in reproductive decision making. (71)(72)(74)

Of course, the ideal timing of screening for SMA may not be either during the prenatal/periconception or neonatal period but rather, screening might be best if offered in both periods because they serve different purposes. (75) Prenatal/periconception screening provides couples with reproductive options. These types of screenings should be voluntary with pre- and postnatal counseling. NBS, in contrast, serves to provide information about health conditions affecting

infants, and fairness demands that it be universally provided to allow for maximal benefit to the infant, especially when life saving treatments exist.

## THE FUTURE

Although nusinersen was initially the only therapy approved for SMA, many other therapies are under development. Gene replacement therapy is being developed, which uses self-complementary adeno-associated virus (AAV) serotypes that cross the blood-brain barrier and can target brain cells. (76)(77)(78) In October 2018, AveXis (Chicago, IL) filed for FDA approval for single-dose intravenous infusion of AVXS-101. AAV serotype 9 (AAV9), in particular, shows active transport across the blood-brain barrier as well as high transgene expression and spread in the central nervous system, with particular tropism for motor neurons. (76) Animal studies using AAV9-mediated delivery of *SMN1* confirmed that transgene expression is stable after a single dose and successfully corrected the phenotype in the mouse model. (78)

Based on this work, a phase 1 trial was conducted in infants with SMA type 1 using AAV9 carrying *SMN1* (the modified virus called AVXS-101), and recently reported by Mendell et al. (79) The first cohort of 3 patients (mean age 6.3 months) received a low dose and the next 12 patients (cohort 2; mean age 3.4 months) received a higher dose. Follow-up at a median age of 27.8 months and 30.7 months for patients in cohorts 2 and 1, respectively, found all patients alive and without need for permanent ventilation. (80) In follow-up, the patients in cohort 2 showed a reduced need for nutritional and ventilatory support and improvement in swallowing function. Of the 12 patients in cohort 2, 11 (92%) could feed orally, with 6 (50%) able to maintain full nutritional needs with oral feedings exclusively, and 11 (92%) able to speak. (80) These were remarkable outcomes after a single-dose trial, given the natural history of SMA type 1.

These outcomes prompted AveXis (owned by Novartis, Basel, Switzerland) to submit a biologic license application with the FDA to allow for the marketing of AVXS-101 to treat SMA. The FDA accepted the application for priority review in October 2018; and on May 24, 2019, Zolgensma (onasemnogene abeparvovec-xioi), was the first gene therapy approved to treat children older than 2 years of age with an expected price tag of 2.125 million dollars. (81) Similar applications have been submitted in Europe and Japan and await approval.

Animal models of SMA have suggested that the intravenous delivery of AAV9 may work best in animals at an early developmental stage (76)(78); intrathecal delivery of AAV9 requires less volume and less total dose of the drug and has been promising in animal models of SMA. (82) AveXis is

currently sponsoring a phase 1 clinical trial of intrathecal AVXS-101, which is a potentially useful route for older and heavier patients who would otherwise require large volumes with the weight-based intravenous dosing. (82)

Apart from direct replacement of the *SMN1* gene, there have been other avenues of drug development for patients with SMA, primarily looking at small molecules that have nonspecific actions such as muscle preservation, neuroprotection, or target *SMN2* splicing. (83) A neuroprotective agent considered promising for SMA was olesoxime, which interacts with mitochondrial membranes to preserve mitochondrial function. (84)(85) It had been studied for several years but in 2018, Roche Holding AG (Basel, Switzerland) announced that they were halting further development. (86) Outcome data in SMA type 2 and nonambulatory patients with SMA type 3, which were initially promising at 12 months, (84) showed declines in motor function of treated patients at 18 months. (85)

The efficacy of nusinersen has prompted additional investigation into other agents that might affect SMN type 2 before mRNA splicing. (87) Two promising agents have been identified: risdiplam (formerly, RG7916) (88)(89)(90) and brana-plam (formerly LM1070). (87) Both agents can be administered orally, providing many potential advantages over the cumbersome intrathecal delivery of nusinersen. Given the prominent loss of muscle that results in motor neuron disease, 2 agents that prevent muscle atrophy are in early stages of testing. Reldesemtiv (also called CK-2127107) activates troponin in fast skeletal muscle and appears to improve muscle force and exercise tolerance. (83)(91)(92)(93) SRK-015 is a monoclonal antibody that inhibits myostatin (a muscle growth inhibitor), and in animal models, SRK-015 has been shown to increase muscle mass. (94)

## HOW TO ETHICALLY PROCEED WITH SMA NBS

SMA testing as part of mandatory NBS warrants several ethical considerations. There needs to be a plan to follow the 15% or 20% (or more) of infants who test positive but are asymptomatic and may not require treatment for years or decades. Late-onset and milder phenotypes may be even more common than we currently believe. Thus ethically, comprehensive long-term follow-up databases are needed. We must acknowledge that for some individuals, the harms of predictive information and the psychological and emotional costs that they cause, as well as the potential harms of unnecessary or even inappropriate treatment that parents may impose on their children, may outweigh the diagnostic benefit, particularly because treatment benefit for late-onset presentation has not yet been proven.

The variability in clinical presentation of patients with SMA also supports the importance of more research on the psychosocial harms and benefits of informing parents at birth that their infant is at risk for a late-onset health problem. (22) This diagnostic approach creates patients in waiting with all the psychosocial risks and harms that this can cause, including unnecessary invasive testing and treatment. (95)

Unfortunately, the type of comprehensive and publicly transparent follow-up registry that is needed has traditionally been difficult to develop and maintain. (96)(97) It is imperative that national and international data are collected to understand the impact of screening and treatment. Because of the rarity of this disease, the data need to be collected in such a way as to combine information from the various registries around the world.

## CONCLUSION

Much progress has been made in understanding, diagnosing, and treating SMA since it was first described in 1891. While the only currently available treatment is nusinersen, other treatments may be available soon. Both the cost of treatment and the timing of initial therapy raise concerns about equitable access. Justice also requires equitable access to screening, and yet, screening is not without its problems. First, carrier screening does not pick up all at-risk individuals. Second, NBS may miss approximately 5% of infants with point mutations. Third, screening identifies at least 20% of infants who may be asymptomatic for years or decades and the psychosocial, emotional, and even clinical risks and benefits of such knowledge have not been well-studied. A long-term follow-up registry is ethically essential to ensure that the benefits outweigh the harms for all screened infants, including those with milder forms of SMA.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the basis for (including genetic) clinical and laboratory features (including associated abnormalities), differential diagnosis, evaluation, management, and outcomes of neonatal hypotonia/neuromuscular weakness.
- Recognize the controversies associated with the introduction of new genetic tests for rare and common diseases that present in the neonatal period.
- Recognize the controversies associated with the development of gene-based therapies to treat neonatal conditions.

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1. Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by loss of survival motor neuron (SMN) protein encoded by the *SMN1* gene. In 95% of affected patients, the genetic mechanism for SMA is a homozygous deletion of the *SMN1* exon 7, while the remaining 5% of cases are caused by heterozygous *SMN1* deletions or *SMN1* point mutations. The timing and severity of the clinical presentation depends on the number of *SMN2* gene copies. Which of the following statements regarding the classification and presentation of SMA is correct?
  - A. SMA type 0 presents with stillbirth, and by definition, these patients always have 0 copies of *SMN2*.
  - B. SMA type 0 is increasingly recognized as an important subtype of SMA, representing about 25% of all SMA cases.
  - C. Patients with SMA type 1 typically present immediately after birth with symptoms and patients can have 0 or 1 copy of *SMN2*.
  - D. SMA type 2, also known as Kugelberg-Welander disease, presents between 6 and 18 months of age.
  - E. In general, the more copies of *SMN2* that exist in a patient with SMA, the milder the symptoms.
2. SMA type 1 is the most common type of SMA, representing approximately 60% of all SMA cases. Despite current evidence that patients progress to severe denervation by age 3 months followed by more than 90% motor unit loss by age 6 months, delays in diagnosis remain common. What is the mean age at diagnosis in patients affected by SMA type 1?
  - A. Prenatally, usually at the ultrasound visit at 20 weeks of gestation.
  - B. 1 month.
  - C. 6 months.
  - D. 12 months.
  - E. 24 months.
3. With the approval of nusinersen by the US Food and Drug Administration (FDA) in 2016, the management of SMA has moved beyond supportive care alone. Nusinersen is an antisense oligonucleotide that prevents exon 7 skipping during splicing by blocking the intronic splicing silencer N1. This results in the production of more full-length transcripts and thereby more SMN protein. Which ONE of the following statements regarding nusinersen is correct?
  - A. In December 2016, the FDA approved nusinersen for the treatment of all classes of SMA.
  - B. In the ENDEAR (Efficacy and Safety of Nusinersen [ISIS 396443] in Infants With Spinal Muscular Atrophy) trial, an interim analysis revealed that 10% of patients with SMA type 1 treated with nusinersen were "motor milestone responders."
  - C. Patients enrolled in the ENDEAR trial had to be younger than 1 week of age at the time of first intrathecal administration of nusinersen.
  - D. Recommended treatment protocols suggest that only 1 intrathecal administration of nusinersen, with the timing suggested to be prior to 2 months of age, with a recommendation against use of the drug if the treatment has not been given by that age.
  - E. The CHERISH (A Study to Assess the Efficacy and Safety of Nusinersen [ISIS 396443] in Participants with Later-onset Spinal Muscular Atrophy) trial found no benefit of nusinersen in patients with any type of SMA, with increased adverse effects in SMA type 2.

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4. With the development of therapies such as nusinersen and the importance of early SMA diagnosis to optimize outcomes, there has been a renewed interest in including SMA in the newborn screen. Which ONE of the following statements regarding newborn screening for SMA is correct?
- A. Although there have been several pilot studies, no newborn screening program or similar work has led to any identified cases of SMA.
  - B. Carrier states cannot be identified with the current methods of screening.
  - C. Newborn screening for SMA relies on quantitative real-time polymerase chain reaction to identify *SMN1* exon 7 deletions.
  - D. The addition of SMA testing to the recommended uniform screening panel will require all states in the United States to purchase new equipment.
  - E. The methodology for SMA screening allows for the detection of all causes of SMA including heterozygous *SMN1* deletions and point mutations.
5. SMA was approved by the Secretary of the Department of Health and Human Services for inclusion in the recommended uniform screening panel in February 2018. With the recommendation to include SMA, new guidelines have been developed for the use of nusinersen in this patient population. Which ONE of the following statements regarding the use of nusinersen in patients identified via newborn screening is correct?
- A. All patients with SMA, particularly those with 4 or more copies of *SMN2*, should be followed in a specialized neuromuscular clinic every month starting at birth until 5 years of age.
  - B. Because approximately 50% of patients with 3 copies of *SMN2* will have type 3 SMA, immediate treatment with nusinersen is not recommended.
  - C. Current recommendations are to initiate nusinersen treatment immediately for all patients with 2 copies of *SMN2*.
  - D. Newborn siblings of patients who have been diagnosed with SMA should receive treatment with nusinersen prior to newborn screening as a prophylactic.
  - E. Treatment with nusinersen is contraindicated in infants with only 1 copy of *SMN2*.

## Spinal Muscular Atrophy: Past, Present, and Future

Lainie Friedman Ross and Jennifer M. Kwon

*NeoReviews* 2019;20:e437

DOI: 10.1542/neo.20-8-e437

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