

# Newborn Screening for Spinal Muscular Atrophy in New York State

## Clinical Outcomes From the First 3 Years

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*Neurology*® 2022;99:e1527-e1537. doi:10.1212/WNL.000000000200986

## Abstract

### Background and Objectives

Spinal muscular atrophy (SMA) was added to the Recommended Uniform Screening Panel in July 2018 largely on the basis of the availability and efficacy of newly approved disease-modifying therapies. New York State (NYS) started universal newborn screening for SMA in October 2018. The authors report the findings from the first 3 years of screening.

### Methods

Statewide neonatal screening was conducted using DNA extracted from dried blood spots using a real-time quantitative PCR assay. Retrospective follow-up data were collected from 9 referral centers across the state on 34 infants.

### Results

In the first 3 years since statewide implementation, nearly 650,000 infants have been screened for SMA. Thirty-four babies screened positive and were referred to a neuromuscular specialty care center. The incidence remains lower than previously predicted. The majority (94%), including all infants with 2–3 copies of survival motor neuron (*SMN*) 2, have received treatment. Among treated infants, the overwhelming majority (94%; 30/32) have received gene replacement. All infants in this cohort with 3 copies of *SMN2* are clinically asymptomatic posttreatment based on early clinical follow-up data. Infants with 2 copies of *SMN2* are more variable in their outcomes. Electrodiagnostic outcomes data obtained from a subgroup of patients ( $n = 11$ ) demonstrated either improvement or no change in compound muscle action potential (CMAP) amplitude at last clinical follow-up compared with pretreatment baseline. Most infants were treated before 6 weeks of age (median = 34.5 days of life; range 11–180 days). Delays and barriers to treatment identified by treating clinicians followed 2 broad themes: medical and nonmedical. Medical delays most commonly reported were the presence of AAV9 antibodies and elevated troponin I levels. Nonmedical barriers included delays in obtaining insurance and insurance policies regarding specific treatment modalities.

### Discussion

The findings from the NYS cohort of newborn screen-identified infants are consistent with other reports of improved outcomes from early diagnosis and treatment. Additional biomarkers of motor neuron health including EMG can potentially be helpful in detecting preclinical decline.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**DOL** = day of life; **mRNA** = messenger RNA; **NYS** = New York State; **qPCR** = quantitative PCR; **SCC** = Specialty Care Center; **SCID** = severe combined immunodeficiency; **SMA** = spinal muscular atrophy; **SMN** = survival motor neuron; **WHO** = World Health Organization.

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder characterized by progressive degeneration of spinal cord and brainstem motor neurons resulting in progressive muscle weakness and atrophy.<sup>1</sup> It is most commonly caused by homozygous loss of exon 7 of the *SMN1* gene encoding the survival motor neuron (SMN) protein. The clinical types of SMA are defined by motor milestone achievement: type 1 infants never achieve independent sitting, type 2 infants never achieve independent ambulation, and type 3 infants achieve independent ambulation and invariably lose this skill later on in life.<sup>1</sup> Type 0, the most severe form, refers to infants who are symptomatic at birth and have evidence of in utero weakness and immobility, such as arthrogryposis. Type 4 is the mildest form with symptom onset in adulthood. The phenotype is modified, in part, by the number of copies of a paralog gene, *SMN2*, such that increasing *SMN2* copy number correlates with milder phenotypes. For this reason, *SMN2* copy number is clinically used as a predictor of disease type.<sup>2,3</sup> However, the correlation is not absolute because of a variety of known and yet unknown mechanisms and requires thoughtful application in the era of molecular therapy.<sup>2,4</sup> Prior to May 2022, there were 2 Food and Drug Administration -approved therapeutic options for presymptomatic infants with SMA at birth: onasemnogene abeparvovec-xioi (Zolgensma; hereafter referred to as onasemnogene) and nusinersen (Spinraza). A third option, risdiplam (Evrysdi), was previously available for infants older than 2 months but recently received a label extension to include infants under 2 months of age. Nusinersen is an intrathecally administered antisense oligonucleotide that increases production of full-length SMN protein by altering splicing of *SMN2* premessenger RNA (mRNA).<sup>5</sup> Onasemnogene is a single-dose *SMN1* gene replacement therapy given via a peripheral infusion.<sup>6</sup> Risdiplam is a small molecule splicing modifier that selectively binds *SMN2* pre-mRNA, thereby promoting increased production of SMN protein.<sup>7</sup> All 3 treatment modalities have demonstrated superior survival and motor outcomes compared with the well-established natural history of SMA.<sup>8-10</sup> Early dosing appears to be critically important, and immediate treatment is recommended for patients with 2–4 copies of *SMN2*, including presymptomatic infants identified by newborn screening.<sup>11,12</sup> Despite these recommendations, insurance policies for coverage are widely variable, particularly with regard to treatment of 4-copy infants.

Taiwan was among the first countries to successfully demonstrate the feasibility of population-based screening for SMA.<sup>13</sup> New York State (NYS) completed a pilot study for SMA screening between January 2016 and September 2018.<sup>14</sup> One infant was identified during the pilot study and enrolled in a

clinical trial for presymptomatic infants treated with antisense oligonucleotide therapy.<sup>15</sup> SMA was subsequently added to the Recommended Uniform Screening Panel by the Advisory Committee on Heritable Disorders in Newborns and Children in July 2018. In the United States, 44 states have implemented SMA newborn screening, accounting for 95% of newborns, as of April 1, 2022.<sup>16</sup> SMA was added to the NYS newborn screening panel on October 1, 2018. In the first year, 225,093 infants were screened, and 8 screened positive.<sup>17</sup> It has now been just over 3 years since the addition of SMA to the NYS screening panel. In this article, we present an update on the incidence, clinical outcomes, and challenges faced from the first 3 years of screening.

## Methods

Screening for SMA was accomplished using a modified version of the real-time quantitative PCR (qPCR) assay previously described.<sup>14,17</sup> Newborn screening for all babies born in NYS is performed by the NYS Newborn Screening Program at the Wadsworth Center, NYS Department of Health. Briefly, DNA was extracted from one 3-mm dried blood spot punch in a 96-well format. SMA screening was multiplexed with the current newborn screening assay for severe combined immunodeficiency (SCID), modified to include a primer/probe mix targeting the common *SMN1* exon 7 deletion (VIC labeled) to the primer/probe mixes targeting T-cell receptor excision circles (TRECc [molecular SCID biomarker]; FAM labeled) and *RPPH1* as an internal control (ABY labeled).<sup>18</sup> Primer/probe mixes were purchased from Thermo Fisher Scientific (Waltham, MA), and the assay was run in a 384-well format using PerfeCTa Multiplex qPCR ToughMix (QuantaBio, Beverly, MA) on an Applied Biosystems QuantStudio 12 K Flex Real-Time PCR System. Samples with *SMN1* Ct  $\geq$  30 and *RPPH1* Ct < 30 were considered screen positive. Heterozygous carriers of the exon 7 deletion and heterozygous individuals with SMA having a deletion on one allele and a pathogenic sequence variation on the other allele are not identifiable by this assay. Confirmation of the *SMN1* exon 7 deletion was performed in duplicate using fresh DNA preparations and the originally described qPCR assay with only the *SMN1* and *RPPH1* primer/probe mixes. *SMN2* copy number was determined in infants who screened positive using both the qPCR targeting *SMN2* exon 7 and *RPPH1* as previously described and a droplet digital PCR kit (ddPCR; Bio-Rad Laboratories, Hercules, CA). Results for *SMN2* were provided at the time of referral.

Retrospective data were collected by clinical providers at the individual NYS-designated Neuromuscular Specialty Care Centers (SCCs), and deidentified data were shared with the

University of Rochester site for aggregate analyses. Developmental milestones were assessed using parental recall and confirmed in the clinic. Developmental milestone delays were determined based on the upper limits of the World Health Organization (WHO) motor milestone window.<sup>19</sup> Among children with motor delays, developmental quotients were calculated as follows: developmental age (upper age limit for the highest level of function achieved) divided by chronological age then multiplied by 100 (22 month old with highest function achieved of walking with assistance: 13.7 months/22 months \* 100 = 62%.) We used 4 months as the window for reaching as per the Centers for Disease Control and Prevention guideline.<sup>20</sup>

For the purposes of this article, we defined presymptomatic as the absence of clinical examination findings of SMA, including evidence of hypotonia out of proportion with age, or reduced/absent reflexes in a patient prior to receiving treatment. The term asymptomatic is used in posttreatment babies without clinical examination evidence of SMA and normal acquisition of expected developmental milestones for age.

### Standard Protocol Approvals, Registrations, and Patient Consents

This study was reviewed by the University of Rochester Research Subjects Review Board (STUDY00006923) and determined to meet federal and University criteria for exemption. Waiver of consent was included in the protocol for exempt status.

### Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

## Results

### Screening

NYS screened approximately 650,000 infants from October 1, 2018, through September 30, 2021, and 34 screen-positive infants were referred by the newborn screening program for SMA. The referred cohort included 1 infant with 1 *SMN2* copy, 18 infants with 2 *SMN2* copies, 11 infants with 3 *SMN2* copies, and 4 infants with  $\geq 4$  *SMN2* copies (Table 1). Positive results were reported by NYS on median day of life (DOL) 7 (range 4–12 days). All infants with positive newborn screening results had confirmatory genetic testing, and there have been no false-positive results. All infants were referred to NYS Neuromuscular SCCs for facilitation of diagnostic confirmation, clinical evaluation, and treatment. Infants were seen for their first evaluation at an SCC at median DOL 9 (range 1–58 days). All positive screens were confirmed via diagnostic testing. Three infants were evaluated and seen at an SCC before NYS NBS results were available because of prenatally known risk from parental carrier testing or a family history of an affected sibling. One infant was formally evaluated at an

**Table 1** Treatment Modality Stratified by *SMN2* Copy Number

Treatment	Total infants (n)	<i>SMN2</i> copy number	Number of infants
None	2	4	1
		5	1
Onasemnogene alone	23	2	11
		3	10
		4	1
		5	1
Nusinersen alone	1	2	1
Risdiplam alone	1	1	1
Nusinersen bridge to onasemnogene	5	2	4
		3	1
Risdiplam after initial treatment with onasemnogene	2	2	2

Abbreviation: SMN = survival motor neuron.

SCC at 58 DOL but had confirmatory clinical testing by DOL 8 and was seen at an out-of-state clinic at DOL 9.

### Treatment

In our cohort, 94% (32/34) of infants diagnosed with SMA via newborn screening received treatment. Two infants have not been treated. A total of 23 infants (71%) were treated with onasemnogene alone, 1 infant (3%) is receiving nusinersen alone, 1 infant (3%) is receiving risdiplam alone, 5 infants (17%) were treated with nusinersen before onasemnogene, and 2 infants (6%) initially treated with onasemnogene were additionally started on risdiplam (Table 2). All infants who received nusinersen followed by onasemnogene have discontinued nusinersen. Two infants initially treated with onasemnogene were additionally started on risdiplam.

### Motor and Developmental Outcomes

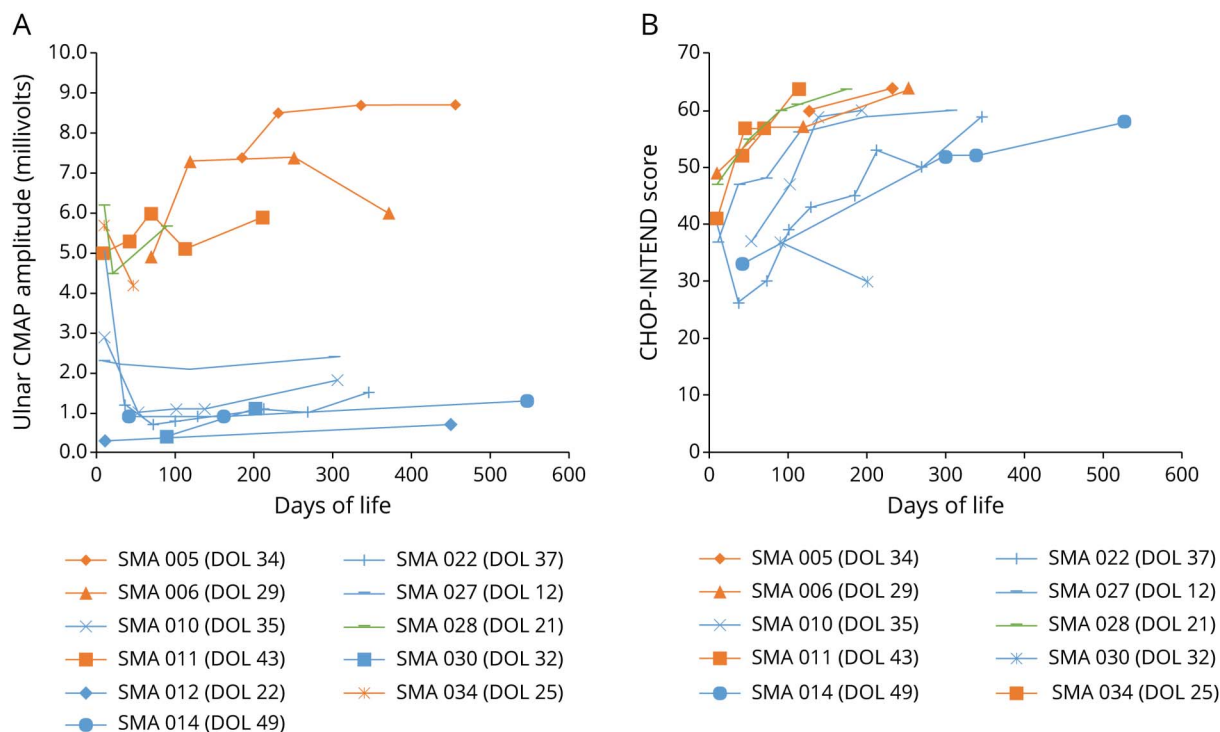
#### One-Copy *SMN2* Infants (n = 1)

This infant was noted to be severely affected at birth, including respiratory failure, dysphagia, immobility, diffuse contractures, and cardiac malformation. At parental request, risdiplam was started in the neonatal intensive care unit at 2.5 months of age. He remains ventilator dependent, is unable to feed orally, and has severe global weakness with minimal finger movement.

#### Two-Copy *SMN2* Infants (n = 18)

There were 18 infants with 2 copies of *SMN2*. All received treatment at a median age of 34 DOL (range 12–89 days). Ten were presymptomatic at the time of treatment, and 8 were symptomatic at the time of treatment. Of the 10 children who were noted to be presymptomatic at the time of treatment, 4 were noted to have symptoms at last follow-up. Symptoms

**Figure** Ulnar CMAP Amplitudes (A) and CHOP-INTEND Scores (B) Over Time



Orange: 3 *SMN2* copies and asymptomatic at last follow-up; green: 2 *SMN2* copies and asymptomatic at last follow-up; blue: 2 *SMN2* copies and symptomatic at last follow-up. Age at treatment for each patient is indicated in the graph legends. SMN = survival motor neuron.

reported for these infants include mild hypotonia and areflexia, but all 4 infants have achieved motor milestones respective to their age. The median initial CHOP-INTEND score for those reported ( $n = 8$ ) was 47 (range = 37–54).

Among symptomatic infants at the time of treatment ( $n = 8$ ), all are noted to be symptomatic at last follow-up. The median initial CHOP-INTEND score for those reported ( $n = 6$ ) was 35.5 (range = 14–47). Of these patients, 1 is independently walking, 1 is standing with minimal assistance, and 3 are sitting with support. Five infants are requiring respiratory support with noninvasive ventilatory measures like bilevel positive airway pressure. Three infants have required some degree of feeding assistance, but none have required gastrostomy tube placement. Of those with serial CHOP-INTEND scores, 1 infant has experienced a decline and has not achieved adequate head control or ability to roll or sit at 6 months of age (Figure, A).

Among the 2 *SMN2* copy infants old enough to assess motor development (had either achieved a motor milestone early or was over 6 months of age,  $n = 12$ ), 7 infants showed delayed motor development. Developmental quotients ranged from 30% to 95%. The mean developmental quotient among 2 *SMN2* copy children treated symptomatically was 50.6% ( $n = 5$ , range 30%–77%) and 86.5% (range 78%–95%) among those treated presymptotically.

### Three-Copy *SMN2* Infants ( $n = 11$ )

There were 11 infants with 3 copies of *SMN2*. All received treatment with a median age of 34 DOL (range = 11–94 days). All patients were presymptomatic at the time of treatment. Initial CHOP-INTEND scores were available for 5 infants and demonstrated a median of 49 (range = 40–60). All are reported to be clinically asymptomatic, meeting age-appropriate developmental milestones with normal neurologic examinations, at last follow-up. Seven are walking independently. The other 4 infants were less than 12 months old and reported to be meeting all age-relevant milestones. None in this group have required respiratory or feeding support.

### ≥Four-Copy *SMN2* Infants ( $n = 4$ )

Two infants were confirmed to have 4 copies of *SMN2*, and 2 confirmed to have 5 copies of *SMN2*. Two of these infants, 1 with 4 *SMN2* copies and 1 with 5 *SMN2* copies, were treated with onasemnogene. Two infants have not yet received treatment. One untreated infant with 5 copies of *SMN2* is being followed clinically. The patient achieved independent ambulation at 13 months and was presymptomatic at last clinical follow-up at 18 months of age. One untreated infant with 4 copies was last seen at 8 months of age and achieved sitting and crawling at 6 months of age.

### Electrodiagnostic Outcomes

Electrodiagnostic outcomes data were analyzed from a subgroup of patients for whom pretreatment and posttreatment



**Table 2** Clinical Summary of 34 Infants Identified in the First 3 Years of Spinal Muscular Atrophy Newborn Screening in New York State

Patient	SMN2#	Initial treatment	Age at treatment (d)	Symptomatic at treatment? (Y/N)	Age at last clinical f/u	Symptomatic at last f/u?	Motor milestone achieved	Respiratory involvement Y/N	Feeding assistance	Adjunct treatment
001	3	Onasemnogene (clinical trial)	39	N	2y	N	Walking independently (12m)	N	N	
002	2	Onasemnogene (clinical trial)	18	N	2y3m	N	Walking independently (14m)	N	N	
003 <sup>a</sup>	≥4 (5)	Onasemnogene	197	N	58 ds	N	Unknown	N	N	
004	2	Nusinersen (bridge)	35	Y	2y	Y	Walking independently	N	N	Onasemnogene (6 mos)
005	3	Nusinersen (bridge)	34	N	2y2m	N	Walking independently	N	N	Onasemnogene (after 4 loading)
006	3	Onasemnogene	29	N	2y	N	Walking independently	N	N	
007	2	Onasemnogene	39	N	2y	N	Walking independently	N	N	
008	≥4 (5)	None	NA	N	1y6m	N	Walking independently (13m)	N	N	
009	2	Onasemnogene	17	N	1y4m	N	Walking independently; stairs	N	N	
010	2	Onasemnogene	35	N	1y10m	Y	Standing independently; walking with minimal assist	N	N	
011	3	Onasemnogene	43	N	1y7m	N	Walking independently	N	N	
012	2	Onasemnogene	22	Y	1y1m	Y	Reaching	Y	N	Risdiplam (6m)
013	2	Nusinersen	89	Y	1y4m	Y	Standing and walking with assistance	N	N	
014	2	Onasemnogene	49	Y	1y6m	Y	Brief independent tripod sitting, close to independent rolling	Y	N	
015	3	Onasemnogene	94	N	15m	N	Walking	N	N	
016	3	Onasemnogene	18	N	17m	N	Walking independently (10m); stoop and recover (11m); stairs	N	N	
017	3	Onasemnogene	22	N	11m	N	Walking independently	N	N	
018	2	Onasemnogene	44	N	12m	Y, areflexia	Standing with support; able to get to sit from supine independently	N	N	
019	3	Onasemnogene	58	N	8.5m	N	Pulling to stand	N	N	
020	≥4 (4)	Onasemnogene	180	N	10m	N	Sitting independently; pulling to stand; walking with support	N	N	

Continued

**Table 2** Clinical Summary of 34 Infants Identified in the First 3 Years of Spinal Muscular Atrophy Newborn Screening in New York State (continued)

Patient	SMN2#	Initial treatment	Age at treatment (d)	Symptomatic at treatment? (Y/N)	Age at last clinical f/u	Symptomatic at last f/u?	Motor milestone achieved	Respiratory involvement Y/N	Feeding assistance	Adjunct treatment
021	2	Onasemnogene	19	Y	12m	Y	Rolling; sitting with support	Y	Y	
022	2	Onasemnogene	37	N	12m	Y	Sitting independently	Y	N	Risdiplam (6m)
023	2	Nusinersen (bridge)	33	Y	4.5m	Y	Neck control	N	N	Onasemnogene (91 d)
024	≥4 (4)	None	NA	N	7m	N	Sitting independently; crawling	N	N	
025	2	Nusinersen (bridge)	56	Y	7m	Y	Sitting with support	Y	N	Onasemnogene (8 wks)
026	2	Nusinersen (bridge)	39	N	6m	No	Sitting independently; bears weight	N	N	Onasemnogene (8 wks)
027	2	Onasemnogene	12	N	10m	Y, areflexia, hypotonia	Briefly sitting independently	N	N	
028	2	Onasemnogene	21	N	3.8m	N	Antigravity spontaneous movements	N	N	
029	3	Onasemnogene	39	N	2m	N	Head control	N	N	
030	2	Onasemnogene	32	Y	6m	Y	Spontaneous movements	N	N	
031	3	Onasemnogene	11	N	3m	N	N/A	N	N	
032	2	Onasemnogene	22	N	0.5m	N	N/A	N	N	
033	1	Risdiplam	67	Y	In NICU	Y	None	Y	Y	
034	3	Onasemnogene	25	N	1.5m	N	N/A	N	N	

Abbreviation: SMN = survival motor neuron.

<sup>a</sup> Infant moved out of state and has been lost to follow-up.

**Table 3** Summary of Infants Born Prematurely (<37w GA) Including Age at Treatment

Referral	#SMN2	Gestational age (GA)	Age at treatment (d)	GA at treatment	Symptomatic at treatment	Clinical status at last follow-up
003	5	34w2d	197	4.5m <sup>a</sup>	N	Lost to follow-up
005	3	36w5d	34	41w4d	N	Asymptomatic at 2y2m
015	3	34w1d	94	1m <sup>a</sup>	N	Asymptomatic at 15m
020	4	36w4d	180	5m <sup>a</sup>	N	Asymptomatic at 12m
022	2	34w6d	37	40w1d	Y	Symptomatic; brief independent sitting at 12m
028	2	34w1d	21	37w1d	N	Asymptomatic at 5m
031	3	35w4d	11	37w1d	N	Asymptomatic at 3m

Abbreviation: SMN = survival motor neuron.

<sup>a</sup> Corrected GA provided in months

data were collected (n = 11). This included 7 infants with 2 copies of SMN2 and 4 infants with 3 copies of SMN2. Lower nadir compound muscle action potential (CMAP) amplitudes were seen in infants with 2 copies of SMN2 with a mean ulnar CMAP value of 1.4 mV (median 0.9 mV, range 0.3–4.5 mV). Higher CMAP values were recorded in 3-copy infants with a mean initial ulnar CMAP value of 5.8 mV (median 5.4 mV, range 4.9–7.4 mV). All infants had either improvement or no change in CMAP amplitude at last clinical follow-up compared with pretreatment baseline (Figure, A).

Of note, 2 infants with 2 copies of SMN2 were born prematurely (34 6/7 weeks, 34 1/7 weeks gestational age) and had relatively high ulnar CMAP amplitudes at first assessment (5.1 and 6.2 mV, respectively). The other five 2-copy infants who were born full term had initial mean CMAP amplitudes of 1.4 mV (median 0.9 mV, range 0.3–2.9 mV). One of these infants was noted to be significantly symptomatic at birth and had initial CMAP amplitude of 0.3 mV, which rose to 0.7 mV at 15 months of age with combinatorial onasemnogene and risdiplam treatment. One prematurely born infant was noted to have a precipitous drop in CMAP to 1.2 mV at the time of treatment (40 weeks GA), with posttreatment CMAP nadir at 0.7 mV, and subsequent slow improvement to CMAP of 1.5 mV at 11 months posttreatment. The other infant also had a drop in CMAP to 4.5 mV at the time of treatment (3 weeks of age) and has had improvement in CMAP to 5.7 mV at 2.4 months posttreatment.

### Prematurity (n = 7)

Seven infants in this cohort were born prematurely, defined as less than 37 weeks GA. Gestational age ranged from 34w1d to 36w5d. A summary of their treatment timeline and clinical symptoms is extracted and included in Table 3. One infant born at 34w6d was noted to be presymptomatic with a CHOP-INTEND score of 40/64 at 10 DOL. His examination on the day of treatment (40w1d) was notable for areflexia, hypotonia, weakness, and drop in the CHOP-INTEND score

to 26/64. The child was last seen at 11.5 months old and can sit independently for brief periods. The repeat CHOP-INTEND score was 59/64 at that time. The 6 other infants are reported to be presymptomatic at the time of treatment and remain clinically asymptomatic at their last clinical follow-up. No adverse side effects following onasemnogene were reported for the 2 infants treated at 37w1d GA.

### Treatment Timing

Most infants were treated before 6 weeks of age (median = 34.5 DOL; range 11–197 days). The significant outlier was an infant with 4 copies of SMN2 treated at 180 DOL. Of the infants with 2–3 copies of SMN2, treatment occurred between 11 and 94 days. Delays and barriers to treatment identified by treating clinicians followed 2 broad themes: medical and nonmedical. Medical delays most commonly reported were the presence of AAV9 antibodies and elevated troponin I levels. Nonmedical delays reported included, most commonly, delays in attaining insurance and insurance approval of requested treatment and, less commonly, delays in obtaining birth certificate during the COVID-19 pandemic and lack of contractual agreement between the patient's insurer and the specialty pharmacy.

### Discussion

After the first year of screening, the reported incidence was 1 in 28,137.<sup>17</sup> The incidence after data accumulation from 2 additional years of screening is approximately 1 in 19,000. However, the incidence remains lower than previously expected based on published estimates of 1 in 6,000–11,000.<sup>21</sup> The current estimate of 1 in 19,000 is likely closer to the true NYS incidence because of a larger sample size and more precise estimate. The authors maintain that the increase in prenatal counseling and informed reproductive decision due to advances in genetic testing capabilities contribute to this effect. All referrals were made before 2 weeks of life, and the

majority of infants were seen within a few days of a referral notification at a specialty care center demonstrating the practical feasibility of urgently establishing specialized care and treatment plans.

Of the 34 states offering population-wide screening for SMA as of June 2021, New York was 1 of 8 states simultaneously reporting *SMN2* copy number.<sup>22</sup> *SMN2* copy number must also be confirmed with repeat clinical testing, but it is helpful for risk stratification of infants at the highest risk of earlier clinical symptom onset.

This NYS cohort redemonstrates the consistently observed theme that early identification and treatment of newborns with SMA leads to improved motor outcomes. In our group, all infants with 3 copies of *SMN2* were treated before symptom onset and remained asymptomatic at follow-up. All infants in this group who are now older than 1 year are independently ambulating. We noted more variability in the outcomes of 2 *SMN2* copy infants, with some demonstrating rapid clinical decline over the first weeks to months of life, stressing the urgency of treatment initiation in this group. The youngest 2 *SMN2* copy infant in our cohort noted to be symptomatic at the time of treatment was 19 days old.

Serial CHOP-INTEND scores were available from 1 center on 10 infants (Figure, B). All but 1 infant had improvement in CHOP-INTEND over time, although the rate of rise in score appears to be stratified by *SMN2* copy number.

In this cohort, all 2 and 3 *SMN2* copy infants received treatment concordant with expert recommendations that treatment initiation occurs as soon as possible after diagnosis.<sup>11</sup> Although the consensus statement was revised to include 4 *SMN2* copy infants, there is still practice variability among providers. Of interest, Germany's NBS program identified 15 children with 4 *SMN2* copies who were, by protocol, not treated pre-symptomatically. This included 1 infant who developed symptoms at 8 months of age. This patient was retested and found to have 3 *SMN2* copies, reminding us the importance of confirming *SMN2* copy number using orthogonal methods for a more accurate, albeit imperfect, prediction of disease type.<sup>23</sup>

Among the treated infants, the overwhelming majority (94%; 30/32) have received onasemnogene, either as initial therapy or following nusinersen bridge therapy. The only infant on nusinersen alone was noted to have persistently elevated AAV9 antibodies, precluding treatment with onasemnogene. This observation is likely reflective of both provider and parent choice. Recent studies have demonstrated that physician counseling, frequency of treatment, and method of delivery are important factors to caregivers for treatment decisions.<sup>24,25</sup>

All infants who received nusinersen followed by onasemnogene have discontinued nusinersen. Two symptomatic infants, who had initially received onasemnogene, received adjunct therapy

with risdiplam at 6 months of age because of a perceived plateau. No short-term adverse effects have been reported by the clinical teams following these infants. Still too little is known about the potential benefits and risks of combination therapy at this time.

Two infants in this cohort were treated within the first 2 weeks of life. In both cases, diagnosis was known before newborn screen results. One infant was screened prenatally via non-invasive prenatal testing for SMA because of a previous pregnancy with fetal demise. The other infant had clinical testing sent on DOL 1 because of known parental carrier status. Carrier screening for spinal muscular atrophy has been recommended by the American College of Medical Genetics and Genomics since 2008, but the practice of offering routine carrier screening for SMA is variable.<sup>26</sup> The American College of Obstetricians and Gynecologists recently reiterated their recommendation that all pregnant women be offered carrier screening for SMA.<sup>27</sup> Although the primary objective of carrier screening has historically been to inform risk and reproductive decisions, an increase in carrier screening rates may result in earlier diagnosis and treatment. As the treatment and care of SMA evolves and the new natural history of treated SMA emerges, pretest and posttest counseling will continue to have a critical role in this process.

When there was a treatment delay, recurrently encountered reasons leading to delay in treatment with onasemnogene included elevated troponin I levels and presence of AAV9 antibodies. It can be difficult to navigate the decisions about how long to wait when a medical barrier to treatment is encountered given the risk of rapid clinical symptom onset, particularly in infants with 2 copies of *SMN2*. Additional biomarkers of motor neuron health including CMAP can potentially be helpful in detecting preclinical decline.

Delays in treatment were also seen because of delays in obtaining insurance and insurance policies regarding specific treatment modalities. Of note, this led to treatment delay in a 2 *SMN2* copy preterm infant for whom insurance required the infant reach 40 weeks GA before treatment.

The premature infants in this cohort were born moderate to late preterm (32–37 weeks GA). No major neonatal complications were reported. No infants were treated before reaching term gestation (37 weeks as defined by the WHO). Early treatment with onasemnogene at 37w GA occurred in 2 infants, demonstrating feasibility. Both infants are reported to have tolerated treatment without significant short-term events. Long-term safety and neurodevelopmental outcomes will be important to follow.

Measurement of CMAP amplitude in SMA has been studied as a marker of motor neuron health and disease burden. The degree of innervation as reflected by maximum ulnar CMAP amplitudes has previously been shown to correlate with disease severity in children with SMA.<sup>28-30</sup> Early observations of prenatally identified infants with SMA type 1 also



demonstrated early and rapid decline in CMAP amplitudes that corresponded to development of symptoms.<sup>31</sup> Infants with SMA type 2 were observed to have slower decline in CMAP amplitudes.<sup>29</sup> Additional studies have shown that CMAP correlates with motor function on a variety of motor function assessments, with children obtaining higher motor function scores with higher CMAP amplitudes.<sup>28,32</sup> Since the implementation of newborn screening for SMA, new data reflecting CMAP changes with SMA treatment have been reported from the Taiwan and Germany newborn screening programs. A rapid decrease in CMAP amplitudes was observed in infants predicted to have SMA type 1 compared with infants predicted to have SMA types 2 or 3.<sup>33</sup> Infants who were already symptomatic at the time of treatment had ulnar CMAP amplitudes of less than 1 mV.<sup>34</sup> Both programs hypothesized that CMAP amplitude could be used as an early detector of the transition from being presymptomatic to symptomatic based on observations that CMAP amplitude decreased significantly just before development of weakness in some patients.<sup>33,34</sup> Both programs also noted improvement in CMAP after treatment.

Our data are consistent with previous studies that demonstrated correlation between CMAP amplitudes and predicted disease severity. This highlights the importance of early treatment, particularly in infants predicted to have SMA type 1 because symptom onset can be rapid. Based on observations comparing our premature and term infants with 2 copies of *SMN2*, we also postulate that motor neuron function may be more likely to be preserved before 40 weeks gestation. This notion is supported by high CMAP values seen in the 2 premature infants (mean initial CMAP amplitude = 5.6 mV) compared with term infants (mean initial CMAP amplitude = 1.6 mV). Additional long-term data will be needed to see whether the CMAP and clinical outcome differences persist with time. Overall, CMAP amplitude appears to be a useful marker of motor neuron health. In the era of SMA treatment, it can also potentially be used to stratify treatment response and help guide the use of adjunctive therapies.

The clinical outcomes from the NYS cohort of newborn screen-identified infants are consistent with previous studies and reports. Risk stratification by *SMN2* copy number, albeit imperfect, appears to be clinically helpful in identifying infants at the highest risk for early decline and argues for the addition of *SMN2* copy number reporting along with initial screening results. Our cohort illustrates the rapidity at which neonatal screening to initial specialty evaluation can feasibly occur. However, the presence of real-life clinical and system barriers and the complexities of treatment decisions must be recognized and addressed. Additional biomarkers of motor neuron health including electrodiagnostic measures should be considered for detection of preclinical decline and could be a useful posttreatment outcome marker. Additional long-term follow-up data will be critically important in the era of the new treated SMA phenotypes. Standardization of recommended clinical follow-up

measures will help inform continued improvement of clinical SMA care and management.

The authors recognize the limitations of a retrospective, descriptive study and the small sample size. Some data points were unavailable because of limited access to medical charts and some visits occurring via telemedicine during the height of the COVID-19 pandemic. Additional long-term follow-up data will be informative with regard to sustainability of motor benefit and incidence of long-term side effects or complications of therapy.

## Acknowledgment

The authors thank the laboratory and follow-up staff of the New York State Newborn Screening Program, especially April Parker, Allison Brown-Madole, Robert Sicko, and Virginia Sack. The authors thank additional members of the Neuro-muscular Disease Specialty Care Center staff, especially Dawn Dawson, Debra Guntrum, Erin Collins, and Joan Mountain.

## Study Funding

Funding for universal SMA newborn screening was provided by the New York State Department of Health with additional funding from the Centers for Disease Control and Prevention (CDC) (NU88EH001319).

## Disclosure

B.H. Lee has received funding from AveXis, AMO Pharma, Sarepta, and Sanofi Genzyme; she received personal compensation for serving on advisor boards for Roche. C.A. Chiriboga has received funding from AveXis, Biogen, and Roche; she is a consultant (advisory board) for AveXis/Novartis, Genentech, Roche, and PTC Therapeutics; she has served as an educational speaker for Biogen and Roche. D.M. Kay's work has been funded by the CDC and Biogen Idec. M. Caggana's work has been funded by the CDC and Biogen Idec. C.F. Stevens's work has been funded by the CDC and Biogen Idec. E. Ciafaloni has received personal compensation for serving on advisory boards and/or as a consultant for AveXis, Biogen, Medscape, Pfizer, PTC Therapeutics, Sarepta Therapeutics, Ra Pharma, Wave, and Strongbridge Biopharma; she has received personal compensation for serving on a speaker's bureau for Biogen and has received research and/or grant support from the CDC, CureSMA, Muscular Dystrophy Association, National Institutes of Health, the Patient-Centered Outcomes Research Institute, Parent Project Muscular Dystrophy, PTC Therapeutics, Santhera, Sarepta Therapeutics, Orphazyme, and the US Food and Drug Administration; she has received royalties from Oxford University Press and compensation from MedLink for editorial duties. The other authors have no relevant disclosures. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

## Publication History

Received by *Neurology* February 3, 2022. Accepted in final form June 3, 2022. Submitted and externally peer reviewed. The handling editor was Renee Shellhaas, MD, MS.

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