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A Five Year Review of Newborn Screening for Spinal Muscular Atrophy in the State of Utah: Lessons Learned

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Background

Spinal Muscular Atrophy (SMA) is a progressive motor neuron disorder associated with muscle weakness and resulting motor impairments. SMA follows an autosomal recessive inheritance pattern and is caused by pathogenic variants in the *SMN1* gene. Copy number of the *SMN2* gene modifies the severity and age of onset for patients with higher copy numbers associated with less severe and later onset. Clinical symptoms can be identified in the first weeks to months of life in the most severe cases.[1] With multiple disease-modifying therapies available to prevent symptom development or slow disease progression, newborn screening (NBS) for SMA has been essential to identify individuals who can benefit from early treatment initiation.[2] In 2018, Utah was first to begin statewide newborn screening for SMA in the US. This study reviews our experience of SMA newborn screening and subsequent clinical follow up over the last five years in Utah.

Methods

Retrospective review of newborn screening results in the state of Utah from January 28, 2018-January 27, 2023 was completed. The newborn screening assay consists of real time PCR to detect presence or absence of *SMN1*. Data gathered for review included critical timepoints in our SMA NBS workflow, timing of clinical follow up, confirmatory genetic test results and treatment type. Descriptive statistics were derived using Microsoft Excel. Developmental outcomes following treatment were monitored with longitudinal measurements via the Bayley Scales of Infant and Toddler Development (BSID).[3]

Summary of Results

- **Total Screened Cases:** A total of 239,844 infants were screened in Utah from Jan. 2018-Jan. 2023 (Table 1). During this screening period, one case was determined to be a false positive. We are not aware of any false negatives. 13 cases screened positive for SMA and were clinically confirmed by genetic testing. One of these cases was previously known to our programs due to prenatal diagnosis. The incidence of SMA in Utah was approximately 1 in 20,000 live births.
- **Time to First Notification** of abnormal newborn screen from day of birth was a median of 6 days (Table 2). Median turnaround time for positive newborn screen reporting from time of collection was 5 days. One case was late to newborn screen (DOL18) due to home birth resulting in initial NBS sample collection at the 2 week well child check.
- **Initial Clinical Visit** for the majority of patients was within one day of abnormal screen notification (Table 2).
- **Time to Diagnosis** defined as receiving a positive clinical genetic testing confirmation was complete within a week of the initial clinical visit for all patients. The median was 4.5 days (Table 2). All patients were determined to have absent *SMN1*. Patient *SMN2* copy number counts are reported in Table 3.
- **Treatment** varied based on *SMN2* copy number and AAV9 antibody status. One patient with 1 copy of *SMN2* was symptomatic at birth with clinical presentation consistent with SMA type 0. Family opted for palliative care. Two patients with 2 copies of *SMN2* were positive for AAV9 antibodies and were initially treated with nusinersen. These patients later received onasemnogene abeparvovec once antibodies resolved. All other patients received onasemnogene abeparvovec as first line treatment.
- **Time to Treatment** for patients with 2 copies of *SMN2* was a median of 13.5 days from initial clinical visit. Time to treatment for patients with 3 copies and 4 copies of *SMN2* was a median of 39 days and 89 days respectively (Table 3).
- **Developmental Outcomes** were measured with the BSID during the 5 year study period. Treated patients with 2 copies of *SMN2* met early developmental milestones inconsistent with the natural history of SMA. Treated patients with 3 or 4 copies of *SMN2* are following normal developmental timelines (Figure 1-2).

Results

Table 1. 5-Year Summary of SMA NBS Outcomes in Utah

Year	Samples Screened	Positive Samples
2018	48,218	2
2019	46,832	3
2020	46,862	3
2021	47,503	3
2022	46,754	2
2023-Jan	3,675	0
Total To Date	**239, 844**	**13**

Table 2. Critical Timepoints in SMA NBS Follow Up*

	Median (Range)
Time to First Notification (Days)	6 (3-18)
NBS TAT from collection (Days)	5(1-11)
Time to First Clinic Visit (Days)	1 (0-3)
Time to Diagnosis (Days)	4.5 (2-7)

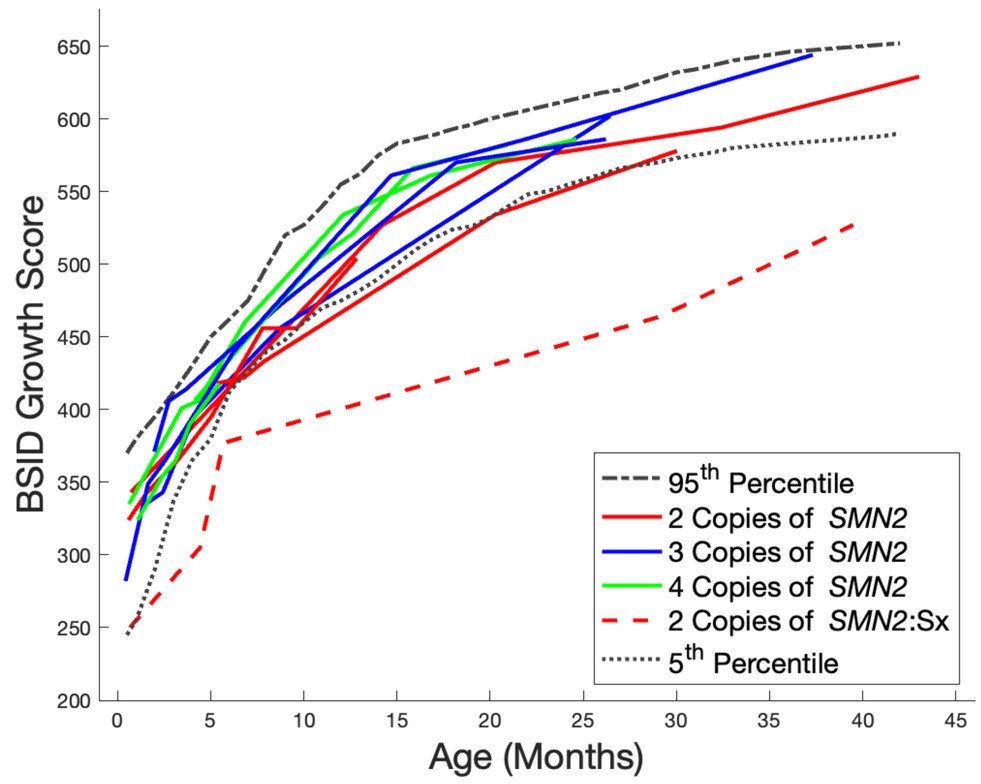
*One case was excluded as confirmatory testing was sent prior to return of positive NBS due to prenatal diagnosis.

Table 3. Treatment and Timing Stratified by *SMN2* Copy Number

SMN2 Copy Number	Number of Cases	Treatment			Median Time to Treatment from Birth in Days (Range)	Median Time to Treatment from Initial Visit in Days (Range)
		Palliative	NU-OA	OA		
1	1 (8%)	1			N/A	N/A
2	4 (31%)		2	2	19 (15-23)	13.5 (7-16)
3	5 (38%)			5	47 (23-210)	39 (15-201)
4	3 (23%)			3	106 (96-187)	89 (87-182)

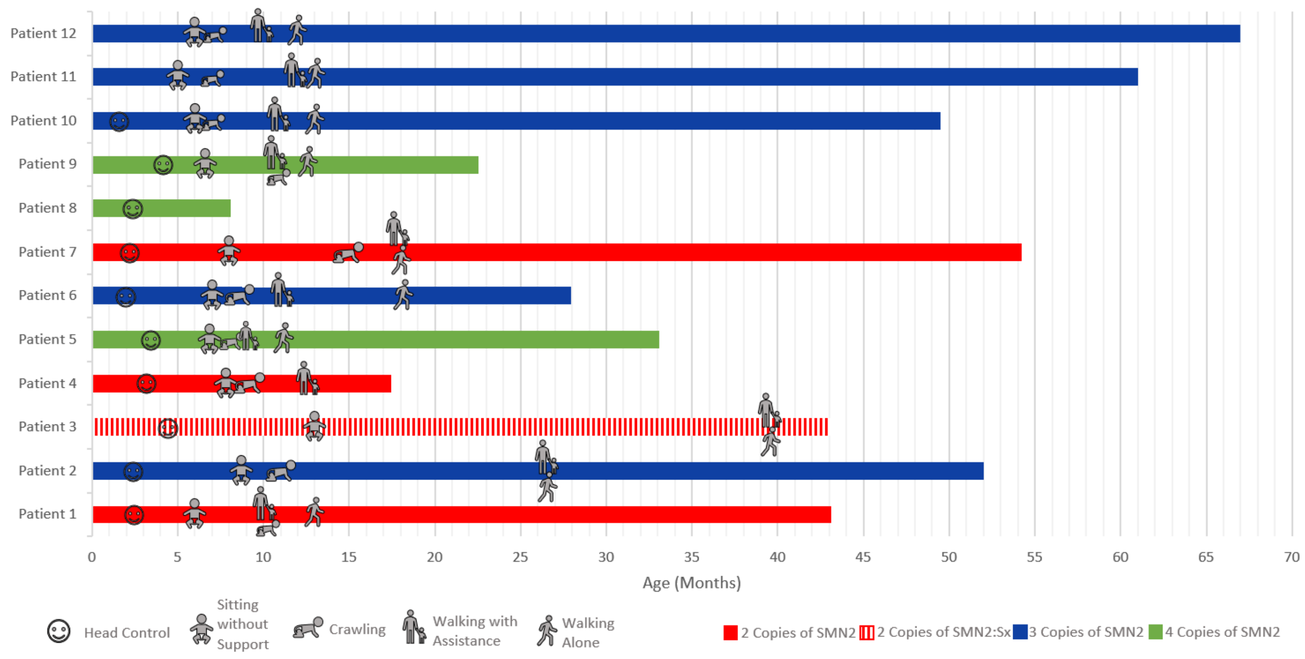
Abbreviations: NU, nusinersen; OA, onasemnogene abeparvovec; NU-OA, initial treatment with nusinersen with subsequent onasemnogene abeparvovec; N/A, not applicable

Figure 1. Longitudinal Developmental Outcomes (BSID Scores)**



**Two patients were excluded from analysis due to treatment on clinical trials; thus, detailed developmental outcomes were unavailable. However, both are reported to be typically developing. A third patient with SMA Type 0 clinical presentation was also excluded due to BSID score of 0.

Figure 2. Observed Attainment of Developmental Milestones in Commercially Treated Patients***



***Developmental milestones were observed as obtained by the above time as assessed and/or recorded during routine PT/neurology follow up or by parent report. End of bars represents current patient age. Patient 3 was symptomatic at treatment at 21 days old. One patient with SMA Type 0 clinical presentation was excluded from this figure as patient did not meet any developmental milestones.

Conclusions

- The incidence in our population was approximately 1 in 20,000 live births which is consistent with published epidemiological data on SMA.[4]
- Newborn screening is an effective tool for early identification and treatment of patients with SMA.
- Treatment before symptom onset results in a dramatic shift in natural history of patients with SMA, with most patients meeting appropriate developmental milestones. Identification of patients with two copies of *SMN2* identified through newborn screen constitutes a neurogenetic emergency.
- Due to complexities of follow up, a multidisciplinary team, including close communication with the newborn screening program, is required to facilitate diagnosis and treatment in a timely manner.

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