Review of Newborn Screening Implementation for Spinal Muscular Atrophy Final Report

Prepared for
The Health Resources and Services Administration (HRSA)

Maternal and Child Health Bureau

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The Newborn Screening Translational Research Network (NBSTRN) is a key component of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Hunter Kelly Newborn Screening Research Program and develops tools and resources to support investigators engaged in newborn screening-related research. This project has been funded with in whole or in part with Federal funds from the NICHD, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN275201800005C.

EXECUTIVE SUMMARY

This report reviews the implementation of newborn screening for Spinal Muscular Atrophy (SMA) due to homozygous deletion of exon 7 in the Survival Motor Neuron 1 gene (*SMN1*). after it was recommended for the Recommended Uniform Screening Panel (RUSP) in 2018. SMA is a heterogeneous group of inherited neuromuscular disorders that affect control of muscle movement. Newborn screening for SMA detects the most common variant in the *SMN1* gene that leads to death in infancy (SMA type 1) or early childhood (SMA type 2) without intervention.

The Status of Newborn Screening Implementation
In 2018, two states offered universal newborn screening for SMA. By May 2020, 24 states offered universal screening with another 10 planning to do so within the next year. Most states multiplex SMA screening with newborn screening for Severe Combined Immunodeficiency Disease (SCID), another condition on the RUSP that is included in all state newborn screening panels. The adoption of screening for SMA has been faciliated by the ability to screen for SMA and SCID simultaneously in the same testing system and workflow.

After identification of SMA by absence of a region of messenger ribonucleic acid (mRNA) of the *SMN1* gene through newborn screening, determining the number of copies of a "back-up" gene, *SMN2*, is central to predicting the severity of the condition and planning treatment. One challenge to newborn screening programs is whether and how to include testing for *SMN2* copy number, which requires a separate assay. At least 8 of the 24 states screening for SMA determine the *SMN2* copy number as part of the newborn screening process , and the others defer this analysis as part of clinical follow-up care. The process for determining the *SMN2* copy number is complex and there is an ongoing effort to improve both the reliability of the process and the ability to better determine the count, which is often reported as 0, 1, 2, 3 or ≥4. Determining whether the count is 4 vs. >4 is technically challenging and has emerged as an important predictor of whether treatment should be offered to infants. At least two newborn screening programs using a droplet digital PCR method report *SMN2* copy numbers as 0, 1, 2, 3, 4 or 5.

Newborn screening programs also report challenges related to the availability of clinical experts after a positive newborn screen.

SMA Treatment
Nusinersen. Since the addition of SMA to the RUSP in 2018, additional reports support the benefit of nusinersen for infants with SMA type I identified presymptomatically. In a phase 2 open label study, an updated interim analysis reported continued survival of all patients (n=25, 100%) without permanent ventilator support and with improvements in motor function through a mean follow up of 2.9 years. All children were able to sit independently, and 88% could walk independently.[5] A published report from a phase 3 randomized clinical trial with SMA patients with type II or type III with symptom onset after 6 months of age (CHERISH trial, n=126) found significant improvements in motor function among patients 15 months after receiving nusinersen.[8] The study was stopped early due to the significant benefits of treatment relative to the sham-procedure control group patients. Additional reports have further reinforced the motor and respiratory function benefits of nusinersen.

Although nusinersen has been found to be a generally safe drug, administration requires intrathecal injections (lumbar puncture) every 3 months, with transient pain. A review of advsere events reported across 7 nusinersen trials (n=240 treated with nusinersen) did not identify excess risk of adverse events other than headaches.[10]

Gene Therapy. In May 2019, the U.S. Food and Drug Administration (FDA) approved a gene therapy (onasemnogene abeparvovec-xioi), for the treatment of patients with SMA less than 2 years of age.[11] Gene therapy appears to be effective, with all infants (12 of 12) in the phase 1 follow-up alive and not requring permanent ventilator support. Infants receiving treatment earlier (<3 months) achieved motor milestones at earlier ages than those treated after 3 months of age.[12] By 2 years, most (7 of 12) infants did not require any ventilator support.[13]

Gene therapy is administered as a single, one-time dose via intravenous infusion. Although gene therapy appears to be safe, the number of infants for whom treatment outcomes have been reported in published literature remains small (<20). Additional studies are underway for infants with SMA who are presymptomatic; interim results presented at a scientific conference on infants with 2 (n=10) or 3 (n=12) *SMN2* copies indicate 100% survival and typical motor milestone achievements through mean ages of 4 to 6 months.

There are no direct comparisons of health outcomes for nusinersen compared to gene therapy.

Other Treatments. Other potential treatments for SMA are in various stages of development and testing. One of these, risplidam, is in clinical trials for patients 1-7 months and 2-25 years. Like nusinersen, risplidam is intended to increase SMN protein production by improving efficiency of *SMN2* gene transcription. Unlike nusinersen and gene therapy, risplidam is an oral treatment that can be administered by patients or caregivers. No published reports of risplidam were identified in this review. Risplidam is under priority review by the FDA for benefits and harms, with a decision anticipated in August 2020.[1] Studies of risplidam are enrolling asymptomatic infants and older patients with SMA who have had other treatments (i.e., nusinersen or gene therapy).

Treatment Guidelines

An updated treatment guideline for newborns identified with SMA[14] recommends treating newborns with SMA and 1-4 *SMN2* copies. This reflects a shift toward treating those with a copy number of 4 rather than close monitoring for the development of symptoms. Because of the uncertainty regarding the net benefit of asymptomatic treatment for those with a copy number of 4, families should be engaged in shared decision making.[15]

Summary

There has been relatively quick adoption of SMA newborn screening, likely facilitated by the ability to combine it with newborn screening for SCID. The current evidence on nusinersen supports the benefits of early detection through 2.9 years (mean) after treatment initiation. Gene therapy offers another option for treatment of infants up to 2 years of age, with benefits reported through 2 year follow-up. New therapies also continue to be developed. One important challenge

[1] On 8/7/2020, the U.S. Food and Drug Administration (FDA) approved risdiplam (Evrysdi) to treat adults and children with SMA 2 months of age and older.

is determining the *SMN2* copy number, especially 4 copies, which has emerged as the upper limit for which treatment has been recommended for newborns diagnosed with SMA . Another important challenge is assuring the availability of clinical services for short- and long-term follow-up. Data registries for patients with SMA have been developed to facilitate understanding of treatment outcomes.

1 INTRODUCTION

Overview

In February 2018, the Advisory Committee on Heritable Disorders in Newborns and Children (Advisory Committee) recommended that newborn screening for spinal muscular atrophy due to homozygous deletion of exon 7 in the *SMN1* gene (SMA) be added to the Recommended Uniform Screening Panel (RUSP), after considering a nomination and full evidence review. The U.S. Secretary of Health and Human Services accepted this recommendation in July 2018, adding SMA to the list of conditions recommended to states for newborn screening.[16] In this communication, the Secretary also requested a follow-up report within two years:

> *In addition, I ask the Committee to provide a report to me within 2 years describing the status of implementing newborn screening for SMA and clinical outcomes of early treatment, including any potential harms, for infants diagnosed with SMA.*
>
> -Alex M. Azar, II
> U.S. HHS Secretary
> July 2018

Purpose

This report was developed in response to the Secretary's request for a follow-up of implementation of newborn screening for SMA. The focus of this report is to describe the status of state implementation of newborn screening for SMA and evidence regarding clinical outcomes of early treatment, including benefits and harms, for infants diagnosed with SMA.

This report addressed the broad areas outlined above with emphasis on the following:

- *The status of state implementation of SMA*, including the amount of time it has taken to implement screening for SMA, and challenges and facilitators of the implementation process;
- *The impact* of expanded screening to include SMA on patient and family outcomes; and,
- *The implications* of expanded screening for SMA for future conditions that might be added to the RUSP on public health systems and overall care delivery, with a focus on identifying strategies to improve future implementation.

2 APPROACH

An evidence-based review of the implementation of these conditions was conducted using multiple information sources. The review of evidence focused on the implementation of expanded newborn screening, impact on patients and families, public health, and systems of care, and implications for future conditions that may be added to the RUSP, and recommended strategies to facilitate and improve the implementation process of screening for other conditions in the future. For implementation, we considered the processes that newborn screening programs go through to expand their panel and the challenges and facilitators of expanding newborn screening. We explored common factors as well as the unique factors associated with screening for spinal muscular atrophy due to homozygous deletion of exon 7 in *SMN1* (SMA). To describe the impact of expanded screening, we included reported outcomes on patients and families, public health programs, and overall systems of health care.

The data sources for this report are described below. Further detail about the methods used to prepare this report (e.g., details of the systematic evidence review of literature, collaborating organizations/informants) can be found in Appendix A. Although the focus of this report is describing implications for newborn screening for SMA in the U.S., findings from other countries that provide insight into the process of newborn screening (e.g., screening test performance, outcomes of early intervention) that could be generalizable to the U.S. were included. This review also describes therapies approved for treatment of SMA to provide insight into benefits and harms related to early intervention following the Committee's evaluation of the net benefit of newborn screening for SMA.

Data Sources

1) *Review of the full evidence review report considered by the Committee when SMA was recommended for addition to the RUSP.* We started with the original evidence review report presented in February 2018, which informed the Committee's decision about recommending addition to the RUSP. That review reflects the evidence available at the time of the Committee's recommendation and provides context for the challenges and facilitators at the time of implementation.

2) *Technical Expert Panel*. A panel of Technical Experts (TEP) was identified to advise this review throughout its development; members are listed in Appendix B. We met with technical experts in October 2019 to review our scope of review and methods, to describe and understand current practice and impact of newborn screening and short-term follow-up of SMA since addition to the RUSP, and to identify current issues and challenges to inform future practice. Given the rapid changes and advances in newborn screening and treatments for SMA, additional input was gathered from the TEP and other stakeholders to gather updates available through the first quarter of 2020 to inform this final report.

3) *Systematic literature review updates.* Review of relevant peer-reviewed literature on newborn screening published since the original evidence review was conducted for SMA using the same search criteria. The 2018 review included literature published in PubMed, EMBASE, CINAHL, and Cochrane Reviews from January 1, 2000 through January 11, 2018. The search for this follow up report included literature published from December

11, 2017 through May 25, 2020. The key search terms first developed in the original review with consultation from medical librarians with expertise in systematic evidence reviews, were "spinal muscular atrophy," "newborn screening," and childhood age groups to include potential treatment outcomes for later-onset forms of SMA. Detailed search strategy and terms used for each database are presented in Appendix A. These search terms were further inclusive of key questions for this follow-up review related to implementation of newborn screening for SMA and related clinical outcomes. Key questions guiding the present review were adapted from the 2018 review to focus on observed impacts of newborn screening. Standard procedures for systematic evidence-based reviews were used (e.g., medical librarian consult, screening, full-text, and abstractions with 2 independent reviewers). Specific details about the searches and methods for this are included in Appendix A in the final report.

4) *Grey literature*. Conference abstracts, presentations, and other grey literature identified through relevant websites were reviewed to identify information about implementation and outcomes of comprehensive newborn screening, including short- and long-term follow-up and treatment for SMA.

5) *Expanded screening resources and technical assistance organizations.* We identified key organizations with initiatives providing technical and other assistance for SMA screening to gather information about these resources and activities. We also partnered with the Association for Public Health Laboratories (APHL) to collect information about the funding and assistance initiatives conducted through the HRSA-funded NewSTEPs 360, and the Newborn Screening Translational Research Network funded by the National Institutes of Health. These entities have played a central role in helping newborn screening programs in the U.S. adopt conditions added to the RUSP.

3 SUMMARY OF FINDINGS FROM THE 2018 EVIDENCE REVIEW ON NEWBORN SCREENING FOR SMA

SMA was first nominated for inclusion on the RUSP in 2008. At that time, the Committee's Nomination and Prioritization Workgroup recommended more evidence on the screening method through prospective pilot studies conducted in traditional public health laboratories to assess feasiblity, as well as on the availability of disease-modifying treatments beyond supportive care options. In May 2017, an updated SMA nomination package was accepted by the Committee for full review. The full evidence review was presented to the Committee in February 2018, at which time the Committee recommended to the Secretary of Health and Human Services (HHS) that SMA be added to the RUSP. In July 2018, the Secretary recommended expansion of the RUSP to include SMA.

Overview of Spinal Muscular Atrophy (SMA)

SMA is a heterogeneous group of inherited neuromuscular disorders that affect control of muscle movement. SMA is caused by degeneration of motor neurons in the anterior horn of the spinal cord that results in progressive motor weakness. Five clinical types of SMA (0, 1, 2, 3 and 4) have been defined that can be distinguished by the types of muscles and genes affected, as well as range in age of onset, severity of muscle weakness, and patterns of clinical features. Some clinical types of SMA may lead to death in early infancy, while some forms may appear as mild muscle weakness in adulthood. The 2018 evidence review focused on SMA caused by a variant (typically, deletion of exon 7) of the Survival Motor Neuron 1 (*SMN1*) gene located on chromosome 5q (locus 5q13), with infantile or childhood onset. This gene variant in *SMN1* account for most cases of SMA.

There is a broad phenotypic spectrum, typically classified into five discrete types.

- Type 0 often leads to fetal loss or death in early infancy.
- Type I leads to progressive weakness in the first six months of life and, without targeted intervention including artificial feeding and respiratory support, death prior to 2 years of age.
- Type II is associated with progressive weakness by 15 months of life and, without targeted intervention, respiratory failure and death after the third decade of life.
- Types III and IV are associated with progressive weakness that develops after 1 year of life or in adulthood, and most individuals have a normal lifespan.

Although there are gaps in knowledge regarding the distribution of SMA by type, about 54% of clinically presenting cases are type I and 18% are type II. Another gene, *SMN2*, is similar to *SMN1* except for a single nucleotide change in exon 7 of *SMN2*, leading to most of the protein that is produced being an unstable form of the *SMN1* gene product. However, some (estimated <10%) of the protein is functional. Individuals vary in the number of copies of *SMN2* they have. If a patient carries a disease causing mutation in the *SMN1* gene, the disease course (i.e., SMA type) is influenced by the *SMN2* copy number. Historically, most cases of type I have genotypes characterized as one or two copies of *SMN2,* though some reportedly have three *SMN2* copies.

Newborn Screening and Treatment for SMA

Population-based screening for SMA is based on detection of a deletion in exon 7 in *SMN1* through molecular testing. Multiple screening methods are available to detect exon 7 deletions. The only method adopted statewide in the U.S. detects infants with deletions in both alleles (homozygotes), which comprise an estimated 95% of cases of SMA, resulting in an approximately 5% false negative rate, though other methods could be used to detect an exon 7 deletion in a single allele (heterozygote). Screening for SMA can be done as a stand alone procedure or multiplexed with screening for another RUSP condition, severe combined immunodeficiency (SCID). At present, all states screen for SCID.

When SMA was added to the RUSP in 2018, the only available treatment approved by the U.S. Food and Drug Administration (FDA) was nusinersen. Nusinersen was approved in December 2016 for all patients with SMA. Nusinersen is administered through intrathecal injections every three months. Other experimental treatments were in clinical trials, including a one-time dose of gene therapy for infants with early onset (i.e., type I and II), which has since been approved by the U.S. FDA in May 2019.

Patient-Level Outcomes

Evidence available for the 2018 review regarding patient-level outcomes focused on survival, ventilator dependence, and motor outcomes. Studies found that both nusinersen and gene therapy decreased the risk of ventilator dependence or death and improved motor outcome within the first 2 years of life in those with SMA type I. Data were limited regarding detection and treatment for later onset forms of SMA.

Most data regarding treatment outcomes were from unpublished reports. In addition, for most subjects, follow-up was limited to about 2 years of age, with many reports limited to about 1 year. No study directly evaluated whether outcomes varied by whether the subject was identified presymptomatically or based on the development of symptoms.

Evidence regarding the impact of early detection of SMA included:

- A post-hoc analysis not available in the peer-reviewed literature suggesting that nusinersen treatment outcomes are improved when symptoms have been present for no more than 12 weeks compared to treatment that begins later.
- Unpublished data regarding a phase 2 open-label study of nusinersen for asymptomatic subjects beginning therapy by six weeks of life, suggesting improved motor milestone development through about 1 year of life compared to symptomatic subjects at interim analysis with 9 of 20 patients.
- Published evidence identified adverse effects among patients on nusinersen; however, these effects were attributed to the procedure (intrathecal injections).

Population-Level Benefits and Harms

Population-level outcomes projected from decision analytic models were limited by the scarce data available for review. Based on the available evidence, compared to clinical detection, newborn screening for SMA was projected to result in earlier diagnosis and treatment for

patients who would experience disease progression and clinical onset of SMA type I symptoms before treatment, likely resulting in reduced deaths and cases of ventilator-dependence by 1 year of life. Other subtypes of SMA were anticipated to be detected through newborn screening rather than clinical onset.

Public Health System Impact

At the time of the original evidence review, population-based screening for SMA was considered feasible, with validated methods to detect *SMN1* exon 7 deletions. One site in New York was conducting a study of a small, research-based screening protocol for SMA in 4 hospitals. At least 4 states had approved legislative mandates in 2018 to screen for SMA, with one of these states mandated to begin population-based pilot screening with consent. At least 2 other states were planning pilot screening in 2018.

States identified the major facilitator to expanding newborn screening for SMA was the ability to multiplex screening with SCID with little to no additional equipment needed to detect exon 7 deletions. Challenges identified included follow-up with carriers if detected, and detection and clinical care of later onset cases.

Overall, most states reported readiness or developmental readiness to screen for SMA when the original evidence review was conducted.[2] When asked how long it would take to get authority to screen for SMA once it was added to the RUSP, the majority (66% of respondents, n=41) indicated that it would take them 1 to 3 years. When asked how long it would take after authorization to get funds allocated for SMA, 67% of respondents (n=39) responded it would take 1 to 3 years.

[2] The public health system impact survey was administered to states in 2017.

4 REVIEW OF NBS IMPLEMENTATION OF SMA

The following sections summarize screening implementation, and outcomes of SMA newborn screening since SMA was added to the RUSP in July 2018.

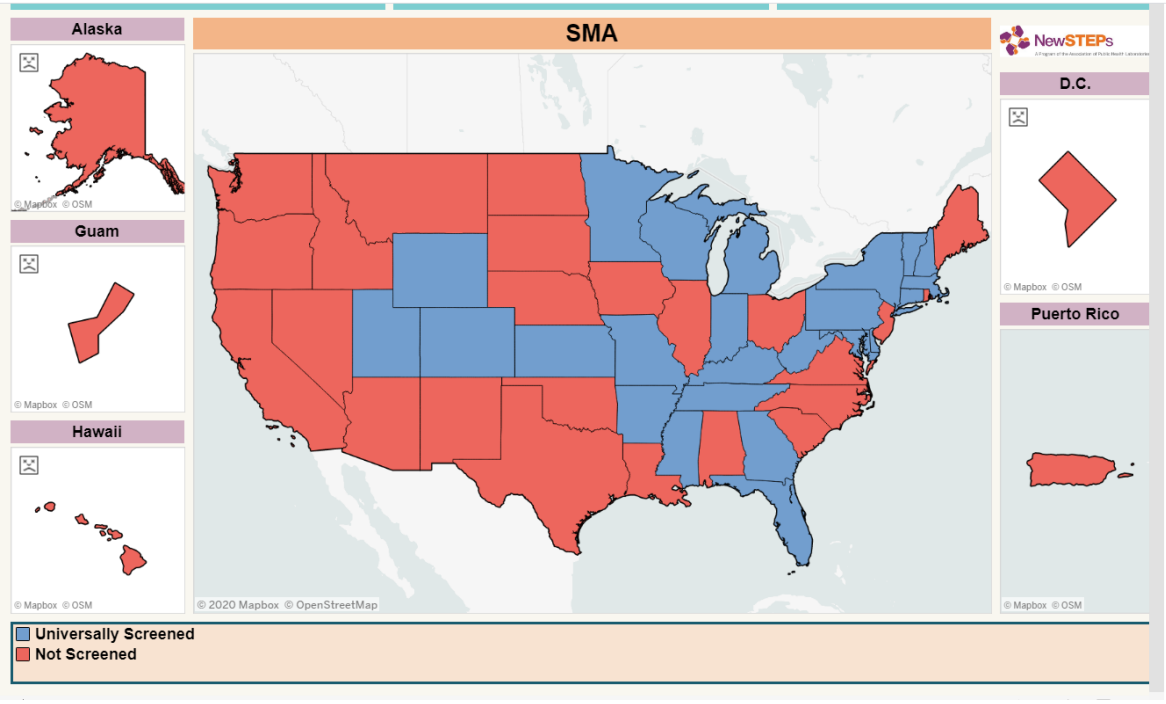
4.1 Status of State Implementation of Newborn Screening for SMA

Status of Expanded Screening for SMA in the United States

In July 2018, screening had just started in Massachusetts and Utah (January 2018) and 3 others (Minnesota, North Carolina, Wisconsin) were preparing to screen either statewide or as a pilot. At the time of the original evidence review, 41 (66%) of states responding to the public health system impact survey anticipated that their state would have authority to screen for SMA within 1 to 3 years, and 39 (67%) projected implementing SMA screening within 1 to 3 years after funding was in place.

As reported by NewSTEPs, 16 months after being added to the RUSP (December 2019), 13 states reported screening all newborns for SMA. By May 15, 2020, 24 of the 53 state/territory programs (45%) reported universally screening all newborns for SMA (see Figure 1). At least 10 additional states are either pilot screening or preparing for full implementation within the next year, pending approval of funds.[3]

Figure 1. Status of SMA Universal (Statewide) Screening in the United States (source: NewSTEPs, May 2020[4])



[3] Based on reports from the Newborn Screening Tranlational Research Network (NBSTRN) and/or NewSTEPs.
[4] As reported in APHL NewSTEPs (https://www.newsteps.org/resources/newborn-screening-status-all-disorders), accessed May 15, 2020).

Of the 24 states reported by APHL NewSTEPs and the Newborn Screening Translational Research Network (NBSTRN) to have implemented SMA statewide, most report multiplexing SMA screening with SCID. At least 8 assess *SMN2* copy numbers prior to clinical diagnosis (5 include *SMN2* copy number in the SMA screening algorithm, and 3 assess *SMN2* copy numbers through confirmatory testing).

State Experiences Implementing SMA: Challenges and Facilitators

Overall, state implementation of screening for SMA has expanded rapidly with the availability of screening assays and methods which can be multiplexed with SCID. Challenges to expanding newborn screening for SMA center around short-term follow up, in getting information to referring clinicians not required for a positive screen, yet critical to faciliate timely treatment decision-making. Availability of clinicians with expertsie in treating infants diagnosed with SMA presymptomatically also remains a challenge with early detection of these newborns. Facilitators and challenges of expanding newborn screening for SMA are detailed below.

Facilitators of Expanding SMA Newborn Screening

- Approaches identified as gold standards for genetic testing for SMA to assess *SMN1* and *SMN2* include quantitative polymerase chain reaction (qPCR), multiplex-ligation dependent probe amplification (MLPA), next generation sequencing (NGS),[17], and multiplex droplet digital PCR (ddPCR), which have high throughput applications suitable for newborn screening.[18]
- One of these approaches, qPCR, is the preferred method of high-throughput screening for SMA, a method used by most state newborn screening programs to screen for SCID.
- The Centers for Disease Control and Prevention (CDC) has developed and validated a specific screening assay appropriate for state newborn screening programs to multiplex SCID and SMA using real-time qPCR. This multiplex method requires few additional resources to expand screening for SMA. The CDC provides ongoing training, resources, and proficiency testing to states.[19]
- The screening method adopted by state programs screening for SMA yields screening results that report only whether there is an absence of *SMN1* exon 7 in both alleles, which simplifies interpretation and reporting of screening test results by not identifying carriers.
- Although not required to detect positive screens for SMA, some states assess *SMN2* copy number as part of a second tier newborn screen test or confirmatory testing to facilitate timely information for short-term follow up with the clinicians. Pilot funding opportunities to implement comprehensive newborn screening for SMA have been available from advocacy groups (e.g., CureSMA), federal agencies (e.g., CDC, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development), and other organizations (e.g., NewSTEPs/APHL).

Specific Challenges of Adding Comprehensive SMA Newborn Screening

- State newborn screening programs must decide whether to assess *SMN2* copy numbers, during screening or confirmatory testing, to inform disease severity. This information is

not required for identifying newborns screening positive for SMA, but is critical to determining disease severity and timely treatment.

- Obtaining clinical care for diagnostic confirmation can be challenging, especially in areas further from the major centers of expertise. For time-sensitive treatment decisions, this may leave initial guidance to physicians less experienced with navigating the approach for diagnosis and in determining the initial treatment plan.
- Treatment decisions for infants with 4 *SMN2* copies presents uncertainty, as classification of later-onset phenotypes (e.g., SMA type III or IV) remains unclear. Relating the *SMN2* copy number to an unambiguous natural history is a challenge requiring a systematic retrospective approach. As new patients are identified, determination of the type of SMA that they would have if untreated is dependent on a registry of well-characterized SMA patients whose DNA is available for systematic evaluation by a gold standard method. Prospective evaluation is confounded by treatment. In addition, current lack of precision and consistency in reporting of *SMN2* copy numbers in this range, as described below, contributes to this uncertainty.
- Insurance authorization for treatment can be lengthy and potentially delay treatment. With the very recent availability of expanded treatment options for SMA, evidence regarding comparative effectiveness or treatment combinations is lacking but crucial to informing treatment decisions.

Precision in determining *SMN2* copy numbers. An additional challenge affecting treatment decision-making for SMA is that laboratory methods lack precision in determining *SMN2* copy numbers greater than or equal to 4. Most often laboratories report the copy numbers categorized as 0, 1, 2, 3, or ≥4. Recently published recommendations indicate that distinguishing 4 from >4 copies is important in predicting clinical severity and for disease management and the timing of intervention.[14, 15] Different laboratory methods have yielded discrepant results for *SMN2* copy numbers yet are widely applied among commercial laboratories.[20-22] Retesting laboratory results by a qualified reference laboratory found differences in the reported *SMN2* copy number in 9 of 20 samples (45%), with increased precision and accuracy found by the retest multiplex-ligation dependent probe amplification (MLPA) analysis. The MLPA method analyzes the whole genetic region relevant for SMA and is highly sensitive for quantitative DNA analysis, and has been suggested as a gold standard approach to determining both *SMN1* and the *SMN2* copy number. At least two newborn screening programs have developed and validated their *SMN2* assay using a droplet digital PCR method, and report *SMN2* copy numbers as 0, 1, 2, 3, 4 or 5.

Results of Newborn Screening Implementation for SMA

Since SMA was added to the RUSP in July 2018, the Newborn Screening Translational Research Network (NBSTRN) reports from informal polling of NBS programs participating in technical assitance calls that over 1 million newborns have been screened for SMA. Among states screening for SMA, informal reports to APHL NewSTEPs and the NBSTRN estimate that at

least 111 newborns have screened positive for SMA (85 from universal newborn screening, 26 from pilot or validation activities).[5]

Appendix C presents summarized information gathered about SMA newborn screening implementation status from APHL NewSTEPs as of May 15, 2020.[6]

Newborn Screening for SMA – Published Reports

One peer-reviewed publication reported outcomes of SMA newborn screening in the United States.[23] Two publications describing SMA newborn screening for SMA in Germany and in Australia were recently published.[24, 25]

United States

New York State. One publication reported on the first year of statewide screening for SMA in New York, which began October 2018.[23] Of the 225,093 newborns screened in the first year, the New York State program identified 8 newborns who screened positive for SMA (homozygous deletion of *SMN1* exon 7), three with 2 copies of *SMN2*, three with three copies, and two with four or more copies. Follow-up at the specialty center occurred at a median of 7.5 days after birth. All infants were asymptomatic at the time of referral. The infants with 2 or 3 copies of *SMN2* received gene therapy, two after initially receiving nusinersen. One of the infants with ≥4 copies also received gene therapy at a treatment center in a different state, although this infant was asymptomatic. No long-term outcomes were reported.

Based on the findings from the first year, the birth prevalence for SMA (with homozygous deletion of *SMN1* exon 7) is 1 per 28,137. Based on data through February 2020, the birth prevalence is 1 in 21,000 (based on 15 cases from ~314,000 screened). This birth prevalence from newborn screening is lower than the 1 in 11,000 birth prevalence estimated from clinical detection. However, additional screening results from other states are needed to increase precision of point estimates over time.

Other Countries

Germany. Screening for homozygous deletion in exon 7 was conducted in two German states from January 2018-February 2019. Screening did not significantly increase the observed incidence of SMA compared to clinical detection (1:7524 newborns after screening vs. 1:7089 newborns prior to screening). Patients with 2 or 3 copies of *SMN2* (45% and 19%, respectively) began treatment with nusinersen (n=10), starting prior to 39 days of age in all patients, 7 of whom were presymptomatic at the time of treatment initiation. Patients with 4 copies of *SMN2* (38% of positive screens) had close follow-up, and one of these became symptomatic at 8 months of age. All presymptomatically treated children had normal strength at the time of last evaluation (ages 1-12 months).

[5] Counts of newborns screening positive are estimates only, gathered through ongoing updates provided to the NBSTRN or APHL through technical assistance for expanded screening. The estimates from states may vary on last day of reporting screening results, presumptive vs. confirmed positive screens, etc.

[6] This information was gathered informally through the NBSTRN's ongoing calls with NBS programs involved with expanded screening. More detailed screening information and estimates of positive screens for SMA as collected from the NBSTRN and APHL NewSTEPS are available upon request.

Australia. Newborn screening for SMA in Australia was implemented in two states, New South Wales and Australian Capital Territory, from August 1, 2018 to July 31, 2019.[25] In the first year, 103,903 newborns were screened. Ten newborns screened positive for SMA, with genetic confirmation of SMA for 9 infants. Four of the 9 infants experienced clinical symptom onset within the first 4 weeks of life. Clinical treatment, including both disease modifying therapy or clinical follow up plans, were implemented within a median 26.5 days (range 16 to 37 days) from birth.

4.2 Clinical Impact of Screening and Treatment for SMA

Reported Outcomes

Outcomes reported in studies published and reviewed in the 2018 evidence review of newborn screening for SMA included survival and independence from ventilator support, and motor function. Specific motor function assessments included motor milestone achievement (e.g., able to sit up unassisted, walk independently), and other scales developed to evaluate neuromuscular function for patients with SMA. These scales included the The Hammersmith Infant Neurological Examination (HINE) and The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). These scales are briefly summarized in the Motor Function Scales sidebar.

Motor Function Scales

The **Hammersmith Infant Neurological Examination (HINE)** assesses neurologic and motor impairments in infants 2-24 months of age.[1] The second of three sections (HINE-2) has measures particularly relevant to SMA patients with a maximum possible score of 34. Infants with untreated SMA type I do not achieve the milestones measured at 12 months and beyond (including full head control, rolling, sitting),[2] and those with later-onset (type II and type III) SMA may demonstrate progressive decline in HINE-2 scores.[3]

The **Hammersmith Functional Motor Scale (HFMS)** was designed to measure motor function in SMA type II and III patients with limited mobility.[4]

The **Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)** was developed to assess children with SMA type I for children 4 months through 4 years of age. The total possible score is 64 and evaluates across 16 domains of motor function such as spontaneous movement, rolling pattern, head control and flexion of proximal joints.[6] Infants with SMA type I, compared to healthy controls, had lower CHOP-INTEND scores at 3-4 months of age [7] and scores declined over time in the affected infants.[7, 9]

Clinical Treatment with Early Detection for SMA – Recap of 2018 Evidence Review Findings

Nusinersen (approved Dec 2016 for all patients with SMA)

At the time of the 2018 evidence review, nusinersen was the only FDA-approved treatment for spinal muscular atrophy. The 2016 FDA approval for this *SMN2*-directed antisense oligonucleotide was based in part on a phase 3 randomized clinical trial ("ENDEAR") with infants (n=120) < 6 months of age with SMA type I diagnosed symptomatically.[26] The study was terminated early based on significantly different rates of event-free (i.e., no mechanical ventialtion) survival at 56-weeks and improvements in motor milestones. A secondary analysis of the ENDEAR trial presented at a conference also found an association between duration of symptoms and treatment outcomes.[27] Additionally, a conference presentation of interim results of a phase 2 trial of nusinersen with presymptomatic infants (n=9) <6 months of age showed improved motor development at 1 year follow up.[28]

Gene Therapy (approved May 2019 for patients up to 2 years)

The 2018 evidence review also included findings from a phase 2 efficacy trial of a then-experimental gene therapy with symptomatic infants (<6 months) with SMA type I.[29] Patients receiving the higher dose of this experimental gene therapy (n=12) showed significant benefits in survival, motor outcomes and developmental milestones through 20 months of age. Since addition of SMA to the RUSP in 2018, gene therapy was approved to patients less than 2 years of age with bi-allelic mutations in the *SMN1* gene.[11]

Clinical Treatment of Early Detected SMA: Updates on Evidence *(Dec 2017 to Mar 2020)*

Since addition of SMA to the RUSP in 2018, one report has been published with longer term follow up of presymptomatic infants treated with nusinersen that directly addresses potential benefits of newborn screening. In addition, reports on nusinersen have been published on SMA type I, II, and III, and from expanded access programs for infants with SMA in other countries. Published studies are reviewed on available outcome data for gene therapy for infants (<2 years of age) with SMA. Additionally, reports included in this update review present evidence on other key treatment factors (e.g., biomarkers, guidelines) identified since 2018.

Nusinersen

Nusinersen was first approved by the U.S. Federal Drug Administration (FDA) in December 2016 based on data from patients with SMA type 1. Since then, data from patients with later onset SMA (i.e., type II and III) and longer-term studies from expanded access programs have become available. Additional analysis has looked at treatment procedures, markers of disease severity, and treatment effects.

SMA Type I (pre-symptomatic treatment)

NURTURE is a phase 2 open label study of nusinersen treatment initiated in pre-symptomatic infants at risk of developing SMA type I or type II, with first dose given at <6 weeks of age. An updated interim analysis of 25 children (15 with two copies of *SMN2* and 10 with three copies, median age 34.8 months) at mean follow-up period of 2.9 years found that all (100%) were alive, and none received permanent ventilation.[5] Four patients (2 copies of *SMN2*) required ventilatory support ≥6 hours per day for ≥7 days during acute illness; however, ventilation was reversible in these patients. Assessed motor function also showed improvement. All children were able to sit independently, 92% walked with assistance, and 88% walked independently. Mean CHOP INTEND total (motor function) scores rose from baseline until reaching a plateau at day 183. At the time of analysis, most recent mean CHOP INTEND score was 62.1 in those with two *SMN2* copies and 63.4 in those with three *SMN2* copies. Plasma neurofilament heavy chain at baseline was the strongest predictor of motor score at Day 302 using HINE-2 and age of independent walking.

There were no adverse events related to the drug or that caused withdrawal from the study according to the publication. However, 8 of 25 patients had an adverse event related to lumbar puncture used to deliver nusinersen. One case considered as a serious adverse event (post-lumbar puncture syndrome) occurred before the first dose of study drug, and after a failed lumbar puncture attempt. There were no clinically relevant laboratory value abnormalities associated with treatment. No other serious adverse events were reported.

SMA Type II and III (symptom onset after 6 months of age)

Mercuri et al[8] conducted a multicenter, double-blind, sham-controlled, phase 3 trial ("CHERISH") of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure. The trial was stopped early due to the significant impact nusinersen had on motor function measured by the HFMSE at the interim analysis. By 15 months post-treatment, the nusinersen group increased by a mean of

4 points while the control group decreased by 1.9 points. In the final analysis, an increase of at least 3 points in the HFMSE was seen in 57% of the treated group and 26% of the sham-treated group. Frequency of adverse events were similar in the two groups (93% and 100% in the nusinersen and control groups, respectively). Serious adverse events were reported in 17% of children in the treated group, and 29% in the control group. No patient discontinued treatment or was withdrawn from the trial due to an adverse event. Adverse events associated with lumbar puncture reported within 24, 72, 120, and 168 hours after the assigned procedure were 9%, 14%, 15%, and 15%, respectively, in the nusinersen group and 3% for each time period in the control group. No clinically relevant changes related to nusinersen were noted in clinical laboratory test results.

An open-label extension trial reported in published conference proceedings followed 28 patients (11 SMA type II and 17 SMA type III) who received 12 mg of nusinersen over 715 days.[30] Between the initial and extension phases of the study, children were off treatment for up to 13 months. None of the children discontinued therapy due to adverse events. As with the previous study,[8] most adverse events related to the study were due to the lumbar puncture (headache, LP site pain, headache). The HFMSE, 6-minute walk test and upper limb strength improved while compound motor action potentials (CMAP) remained stable. Patients with SMA type II experienced a larger change in tests of motor function than type III patients; however, there was evidence of continued motor improvement over the course of the study in both groups. Mean HFMSE and upper limb motor scores in children with SMA type II and mean 6MWT distances in children with SMA type III increased over time in a relatively linear manner, which the authors interpreted as suggesting that nusinersen may not only prevent motor deterioration but could also allow for continued motor improvement. Two of the 4 children with SMA type III who had previously achieved independent walking but had lost that ability before the baseline assessment of the extension phase regained the ability to walk independently during the course of the study.

Fatigability is a measure of muscle function not typically reported in SMA studies. Montes et al.[31] evaluated the effect of nusinersen in patients with SMA II and III on fatigability by performing a post hoc analysis of performance on the 6MWT. A decrease in distance walked in minute 6 compared to minute 1 demonstrates fatigue. Patients who were ambulatory in the CHERISH trial [8] or the open-label extension [30] studies described above, were followed for 3 years. Median distance walked increased over time by 17.0 meters at day 253 and by 98.0 meters at day 1050, while change in fatigue was −0.1% and − 3.8% at the same time points, respectively. Patients with lower distances walked also demonstrated greater fatigue. Changes of ≥30 meters in 6MWT distance are considered clinically meaningful.

Nusinersen in Other Countries

SMA Type I

The results of three expanded access programs have been published from Germany, Italy and Australia. Pechmann et al [32] reported a prospective, longitudinal study of 61 SMA type 1 patients (mean age of 21 months) treated at seven centers in Germany. After 6 months of treatment, the mean increase in motor function as measured by CHOP INTEND scores was

9.0±8.0 points, with 77% improving ≥4 points. The major factor influencing the degree of improvement was the age of treatment initiation.

An Italian report included 104 patients with SMA type I from 3 months to 19 years old. After 6 months of treatment, 55.7% of the patients had >2 point increase in CHOP INTEND motor function score. An increase of >2 points was seen in 20% on the HINE. Significant improvements from baseline to 6 months were observed on both the CHOP INTEND and HINE motor measures for the group as a whole ($p < 0.001$) as well as for the subgroups with two ($p < 0.001$) and three ($p < 0.001$) *SMN2* copies. An increase of ≥4 points was seen in 20/71 patients >2 years and 6/20 patients >10 years old.

The Australian expanded access program for SMA treatment included 20 Australian patients with SMA type I, of whom 16 consented to receive nusinersen.[33] The median age of treatment initiation was 20 months, and this was correlated with age of symptom onset. The median duration of treatment was 5 months. Treatment availability was associated with a shift in parental goals and clinical care. Parental goals shifted from palliative comfort and optimal positioning to active therapy to prevent contractures and promote mobility. Patients were more likely to be referred for elective procedures to treat other medical conditions.

Since the original 2018 evidence review, experts have differed in their guidance for treatment of patients with SMA and 4 or more copies of *SMN2*. The treatment algorithm from May 2018 recommended immediate treatment of SMA patients with 2-3 copies of *SMN2,* and treatment following symptom onset with close monitoring for patients with 4 or more copies of *SMN2.* [34] Experts in Germany highlighted differing patient and family preferences that further impact treatment decisions, recommendations for patients with 4 copies of *SMN2*.[15] Based upon data from newborn screening for SMA in Germany, these experts reported that 15 of 37 patients (40%) identified with SMA (homozygous *SMN1* deletion) had 4 *SMN2* copies, and followed the 2018 clinical guidelines (monitor for symptoms). Family responses and compliance with these guidelines varied, ranging from preferences for earlier treatment based on known family history or personal experience, to drop out of follow-up care due to stress of appointments or lack of symptoms after 13 months.

Other Treatment Considerations

Treatment guidelines and patients with SMA and 4 copies of *SMN2*

Guidance for treatment of patients with SMA and 4 or more copies of *SMN2* published in May 2018 (and reported in the original 2018 review) recommended immediate treatment of SMA patients with 2-3 copies of *SMN2,* and for patients with 4 or more copies of *SMN2*, recommended close monitoring, with treatment with symptom onset or signs of disease. [34]

These 2018 treatment guidelines were used in a German pilot of newborn screening for SMA, with mixed compliance with the recommendations by families[15] . Investigators reported that 15 of 37 patients (40%) identified with SMA (homozygous *SMN1* deletion) had 4 *SMN2* copies. Cargiver decisions about treatment for these babies reflected a range in preferences, with some opting for earlier treatment based on family history or personal experience, and others choosing to not initiate treatment immediately, due either to an absence of clinical symptoms through age 13 months, or drop out of follow-up care due to stress of appointments.

Based on additional data published from the NURTURE trial on presymptomatic patients with SMA who have 3 copies of *SMN2* described above,[5] the working group of expert clinicians who authored the 2018 guidelines, the American SMA NBS Multidisciplinary Working Group, convened by Cure SMA, recently published updated guidelines on SMA treatment.[14] Data from the NURTURE trial indicated that presymptomatic patients with 3 copies of *SMN2* treated with nusinersen appear to be free of many negative outcomes of SMA. The working group extrapolated that treatment of presymptomatic patients with 4 copies of *SMN2* would also prevent disease expression. As a result, this group recommends immediate treatment for patients with SMA with 2-4 copies of *SMN2* and close observation for patients with 5 copies.[14]

Both of the updated reports,[14, 15] cited methodological problems with obtaining a valid determination of the number of *SMN2* copies. Discrepancies have been reported between standard qPCR and ddPCR, with the latter being more precise.[20, 21] Given the reliance on *SMN2* copy number in treatment decision-making, both reports call for greater standardization and laboratory discrimination of *SMN2* copy number estimation.

Progress Toward Biomarkers of Disease and Treatment Efficacy for Nusinersen

Two groups evaluated the utility of biochemical markers of disease severity and treatment success. Phosphorylated neurofilament heavy chain (pNF-H) measured from plasma was elevated 10-fold in patients with SMA type I enrolled in ENDEAR compared to normal age-matched controls.[35] Although levels drop after 1 year of age, they remain elevated over the normal baseline in patients with SMA. Higher pNF-H levels corresponded to disease severity (age of symptom onset, CHOP INTEND, CMAPs) and dropped rapidly with treatment. However, neurofilament in cerebrospinal fluid did not correlate with disease state or treatment in 25 adolescents and adults with SMA type II and III treated with nusinersen compared to controls.[36]

Functional SMN protein can be isolated from peripheral blood cells (CD3+, CD19+ and CD33++) using flow cytometry.[37] SMN protein is much lower in nucleated blood cells from SMA patients compared to controls and has the potential to serve as a marker of treatment efficacy, although this requires further study.

Treatment Harms

Nusinersen– Safety and Adverse Events

Intrathecal Delivery. Some children with SMA develop scoliosis, making lumbar puncture more challenging and potentially even contraindicated. Nusinersen delivery by ultrasound-guided cervical puncture with only local anesthesia was reported in 4 adolescents with SMA (type not reported) who had 14 cervical infusions. Transient headache was reported in 2 patients. No other adverse events were reported.[38]

Two subsequent single-center retrospective studies of larger cohorts reviewed intrathecal delivery methods in adults and children with SMA types 1-3.[39, 40] In 10 children and 10 adults with SMA receiving 163 nusinersen injections, 55% had complicated spinal anatomy (fusion and hardware in 9 of 11, with two of these also having Ommaya reservoirs). Of the 163 injections performed in the cohort, 74% were fluoroscopically guided, 22% were delivered into a

reservoir, 1% were CT-guided, and 3% were performed with palpation and ultrasound guidance as per the usual protocol at the institution for intrathecal injection in all patients. None of the injections failed. Anesthesia was used in 29% of injections in children and in none of the adults. One patient reported chronic post-LP headache. In another study of 52 patients receiving nusinersen, 77.9% of the injections were performed with local anesthetic, 9.4% with moderate sedation and 8.6% with general anesthesia. Of the 265 injections, 65 were performed with CT guidance, 106 were fluoroscopically guided, and the rest were performed by palpation. During the course of the study, an intrathecal reservoir was placed in 3 patients, one of whom developed postoperative infection and required replacement of the device. Otherwise complications of injections were minimal with 2.2% of the injections associated with headache requiring medical management (none required blood patch).

Darras et al.[30] analyzed adverse events reported from 7 trials including 323 infants and children, of whom 240 were treated with nusinersen (100 with infantile-onset SMA and 140 with later-onset SMA) and 83 underwent sham procedures (41 infantile-onset, 42 later-onset). Median duration of nusinersen exposure was 449 days. The most common adverse events that occurred in >20% of patients treated with nusinersen included fever, upper respiratory tract infection, nasopharyngitis, vomiting, headache, and constipation. Of these, only headache was more common in the nusinersen treated group than the sham procedure group. Participants treated with nusinersen had a lower incidence of serious adverse events (41% vs. 61%), likely owing to their improved ventilatory status. Complications of lumbar puncture syndrome were more common in nusinersen-treated patients with later-onset SMA compared to younger infantile-onset SMA- patients receiving nusinersen or sham control procedures for post lumbar puncture syndrome, (19% versus 0%), vomiting (26% versus 22%), headache (37% versus 1%), and back pain (29% versus 1%), respectively. Infantile-onset SMA patients were also younger and less able to communicate symptoms. The authors point out that while liver, renal and platelet toxicities have been reported with some antisense oligonucleotides, these complications were not evident in laboratory tests performed in the trials analyzed.

Gene Therapy (approved May 2019**)**

In May 2019, the FDA approved onasemnogene abeparvovec-xioi (AVXS-101) as the first gene therapy for SMA, for use with children less than 2 years of age.[11] This decision was based on data from three reports – an initial study of safety and motor outcomes to 20 months that was presented in the 2018 review[29] and two additional reports reviewed below that followed the initial cohort of patients for up to 2 years and reported a variety of health outcomes.

<u>SMA Type I</u>

In the phase 2 trial [29] included in the initial evidence review, 15 patients with SMA type I (homozygous for exon 7 deletion, 2 copies of *SMN2*) received a single dose of intravenous adeno-associated virus serotype 9 carrying *SMN* complementary DNA. Three of the patients received a low dose (6.7×1013 vg per kilogram of body weight), and 12 received a high dose (2.0×1014 vg per kilogram). The primary outcome was safety. The secondary outcome was the time until death or the need for permanent ventilatory assistance. Patients with the c.859G→C disease modifier in exon 7 of *SMN2* were excluded. One screened patient was excluded due to AAV9 antibodies.

At 20 months of age, all 15 patients were alive compared to 8% of historical controls. High-dose gene therapy resulted in a rapid increase in CHOP INTEND scores with a mean gain of 9.8 points at 1-month post-dose and 15.4 points at 3 months. Of the 12 patients who received the high dose, 11 sat unassisted (9 for at least 30 seconds), 9 rolled over, 11 fed orally and could speak, and 2 walked independently. Elevation in serum aminotransferase resulted in a change in protocol to give prednisolone 1 mg/kg/d for 30 days starting the day prior to infusion.

Two subsequent publications identified in the present review reported 2-year outcomes of the 12 patients who received high dose gene therapy.

Lowes et al[12] reported a follow-up analysis of motor outcomes in the initial 12 children grouped according to age at dosing and baseline CHOP INTEND score (stratified by 3 months of age and scores of 20). The early dosing/high functioning group achieved sitting unassisted by a mean age of 9.4 months (CHOP INTEND from 44 to 60.3). The early dosing/low functioning group achieved unassisted sitting by a mean of 17 months (CHOP INTEND score from 15.7 to 50.7), which was earlier than the late dosing/high functioning groups (mean sitting age 22 months, CHOP INTEND from 26.5 to 49.8).

Additional health outcomes at 24 months in the initial high dose gene therapy group were reported by Al-Zaidy et al.[41] Among a group of 12 patients followed for two years after gene therapy, none required tracheostomy. Two required non-invasive ventilation at baseline and by 3 years of age, 3 of the 10 that did not require non-invasive ventilation at baseline did require it by two years.

Regarding nutritional interventions, 11 patients maintained the ability to swallow and to talk. One patient who did not require supplemental nutritional support required a feeding tube during the follow up period. Eleven (92%) of the 12 patients achieved and maintained full head control and unassisted sitting. Two (17%) of the patients walked independently. Patients remained vulnerable to respiratory infections and required a mean of 1.4 respiratory hospitalizations per year with a mean LOS of 6.7 days.

<u>Presymptomatic Infants with SMA (treatment ≤6 weeks of age, 2 or 3 *SMN2* copies)</u>
Interim data analysis of two phase 3 trials have been presented to scientific audiences but have not been published in the peer-reviewed literature. Conference presentations (posters) provided by the authors are described here.[42, 43] In the SPR1NT trial, gene therapy was delivered to pre-symptomatic infants with SMA ≤6 weeks of age.[43] Two of 33 infants screened were excluded due to anti-AAV-9 antibodies. Of the 10 patients with 2 copies of *SMN2* who were treated, mean age at treatment was 19.9 days and mean age at last follow up was 6.6 months. Of the 12 patients with 3 copies of *SMN2* who were treated, the mean age at treatment was 27.8 days and mean age at last follow up was 4.6 months. All patients had event-free survival (defined as no deaths and no permanent ventilation), none required feeding support, and all achieved independent sitting on time. CHOP-INTEND scores for 70% of patients with 2 copies of *SMN2* were 60-64. There were no treatment-related serious adverse).[43]

Symptomatic Infants with SMA (treatment <6 months of age, 1 or 2 *SMN2* copies)
The STR1VE trial was also a phase 3 study of gene therapy delivered to 22 infants <6 months old with SMA and 1-2 copies of *SMN2* was identified in a conference abstract, with information provided by the authors.[42] These subjects were symptomatic at the time of treatment (CHOP-INTEND mean 32) but did not require respiratory support > 6 hours per day. By the cutoff for reporting, 6 of 7 patients who could have reached 10.5 months of age had event-free survival (alive without permanent ventilator support) and continued to gain motor skills to the time of data presentation (median age of 12.6 months). Of the serious treatment-emergent adverse events, 3 of the 6 were related to treatment and all of these were transaminase elevations.[42] *Gene therapy (onasemnogene abeparvovec-xioi (AVXS-101)) vs Nusinersen*
A published secondary analysis compares gene therapy to nusinersen using data from two different studies.[44] The AVXS-101 phase 1 study[29] was compared to ENDEAR, a phase 3 trial.[26] From AVXS-101, outcomes from the 12 subjects who were treated with the proposed therapeutic dose were compared to 80 subjects in the ENDEAR trial. The main outcomes were the number needed to treat (NNT) across a wide variety of outcomes. The estimated number needed to treat (NNT) to prevent one additional death with gene therapy compared to nusinersen was 6.3 (95%CI 4.0-11.7). There are several important limitations of this post-hoc comparison of data from two different studies. There were some differences at baseline across the two studies. For example, there was nearly a two month difference in mean age at first dose (3.4 months for the AVXS-101 study versus 5.3 months for nusinersen). Interpreting the NNT for mortality depends critically on the time to outcome. For AVXS-101, the last study visit was 24 months, but 5 subjects had not reached this age. For the nusinersen trial, the last visit could be at 6, 10, or 13 months. The time frame to determine NNT was not clear and therefore, these findings, along with other reported outcome measures in this comparison study are difficult to interpret.

An economic analysis published to compare the cost effectiveness of the two treatments in the United States was identified. This study was excluded because insufficient specific information was provided to evaluate the underlying model assumptions including the probabilities assigned to the various outcomes that were considered. Furthermore, the model extrapolates far past an age for which data are available.

Experimental Therapies
At least two other pharmacological treatments for SMA are currently being evaluated in a series of human clinical trials for patients with SMA of different types. One of them, Risplidam, is currently under priority review by the FDA based on results with infants (1 to 7 months) and children (2 to 25 years). Risplidam[7] has a similar mechanism of action as nusinersen to increase SMN protein production through the *SMN2* gene, though unlike nusinersen, is an orally-administered liquid which patients would take at home. Evidence on these experimental therapies have not been reported in the peer-reviewed literature at this time.

Patient Registries
With the above therapies and the possibility of new therapies in the future, patient registries to facilitate the collection of long-term outcome data are increasingly important. A number of

[7] Update: On 8/7/2020, the U.S. Food and Drug Administration (FDA) approved risdiplam (Evrysdi) to treat adults and children with SMA who are 2 months of age and older.

registries for SMA have been established.[45-47] These efforts are multinational, seeking cooperation between medical centers, patient advocacy groups and industry. The registries aim to serve two purposes: to function as a central structure for conducting future academic investigations, and to collect and share real-world data with pharmaceutical partners, drug regulatory agencies, and advocacy groups for better understanding of treatment efficacy and safety of any SMA treatments. The RESTORE registry seeks to allow participation across registries, with consortuim agreements to facilitate this data sharing. [45]

5 SUMMARY AND CONCLUSIONS

Since the addition of SMA to the recommended newborn screening panel in July 2018, the number of states implementing statewide screening has increased from 2 to 24 within 20 months. Implementation of SMA screening is aided by the experience states already have in molecular testing from SCID implementation. Once the procedural and validation details of multiplexing SMA into the SCID assay are optimized for a given screening program, SMA screening requires little to no additional equipment or expertise. There have been no concerns related to the need to report carrier detection because the screening methods do not identify carriers. States report few inconclusive results with first tier testing because qPCR yields only whether there is an absense of *SMN1* exon 7 in both alleles.

Evidence from clinical treatment studies of nusinersen have offered further evidence of benefits for patients with earlier onset (type I), with benefits consistently related to age of treatment initiation. Evidence for nusinersen has also expanded to include benefits to patients with SMA with onset after 6 months of age (e.g., type II and III). Although nusinersen is not directly associated with serious adverse events, it requires intrathecal delivery, and therefore patients are at risk of harms due to that procedure.

The approval of gene therapy for treatment of SMA patients diagnosed before age 2 years has expanded therapeutic options. In principle, gene therapy requires a single dose treatment compared to the required intrathecal injections throughout life for nusinersen. However, evidence is insufficient to assess the durability of effects of a single-dose of gene therapy, or to compare the effectiveness of gene therapy to nusinersen. The U.S. experience is that families are choosing to use gene therapy in preference to nusinersen, sometimes after an initial treatment with nusinersen. Given that pattern, concern about potential harm from nusinersen injection may be moot in the U.S. newborn screening context. Ongoing challenges, which remain the focus of research, include approaches to facilitate the screening process, improving the precision of the *SMN2* copy number assessment, and assuring access to clinicians for short- and long-term follow-up.

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APPENDIX A: SYSTEMATIC EVIDENCE REVIEW METHODS

Published Literature Search
An experienced medical library conducted the initial literature search for evidence on newborn screening and treatment for each condition. We identified published literature from the PubMed, EMBASE, CINAHL, and Cochrane databases, from December 11, 2017 (1 month before the end date of the literature search covered in the original evidence review) through May 25, 2020.

An initial screening of titles and abstracts was conducted by two independent reviewers for preliminary exclusion and inclusion. A secondary screen of full-text articles was conducted by two independent reviewers, and disagreements were reconciled through discussion or a third independent reviewer. Both initial and secondary screening were conducted with pre-developed data abstraction forms in DistillerSR or Excel.

The exact search terms used in this report are listed in the next section.

Literature Screening: Inclusion and Exclusion Criteria
Inclusion criteria: Articles that reported on studies with human subjects and were published in English were included. All study designs were considered, including care reports, case series, observational studies, and uncontrolled and controlled intervention trials.

Case reports that directly informed evidence on net benefit of early detection and treatment were included.

Exclusion criteria: Non-human studies, studies without English language abstracts, and articles without original data were excluded. Case reports that do not inform evidence on net benefit of early detection and treatment.

Grey literature reports published in the databases described above were considered if they directly informed evidence on net benefit of early detection and treatment. To be included in the review, grey literature reports must directly inform evidence on net benefit of early detection and treatment, present new analyses or original data, and authors must provide full presentations (e.g., poster, presentation slides) and/or be able to provide sufficient information on study methods to report and assess the study.

Spinal Muscular Atrophy
PubMed-SMA, Newborn Screening and SMA

Update 1: 12/12/2017-3/31/2020		
Set	**Terms**	**Results**
#1	"Neonatal Screening"[Mesh] OR "Mass Screening"[Mesh] OR ((newborn[tiab] OR neonatal[tiab] OR mass[tiab] OR universal[tiab] OR communit*[tiab]) AND screen*[tiab])	203588
#2	"Muscular Atrophy, Spinal"[Mesh] OR "spinal muscular atrophy"[tiab] OR "spinal muscular atrophies"[tiab] OR Werdnig[tiab] OR Hoffman[tiab] OR Kugelberg[tiab] OR welander[tiab]	8658
#3	#1 AND #2	130
#4	#3 AND ("2017/12/12"[Date - Entrez] : "2020/03/31"[Date - Entrez])	**52**
Update 2: 3/31/2020 - 5252020		
Set	**Terms**	**Results**
#1	"Neonatal Screening"[Mesh] OR "Mass Screening"[Mesh] OR ((newborn[tiab] OR neonatal[tiab] OR mass[tiab] OR universal[tiab] OR communit*[tiab]) AND screen*[tiab])	204,522
#2	"Muscular Atrophy, Spinal"[Mesh] OR "spinal muscular atrophy"[tiab] OR "spinal muscular atrophies"[tiab] OR Werdnig[tiab] OR Hoffman[tiab] OR Kugelberg[tiab] OR welander[tiab]	8842
#3	#1 AND #2	132
#4	#3 AND ("2020/03/31"[Date - Entrez] : "2020/05/25"[Date - Entrez])	**3**

PubMed-SMA, Pediatrics and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**
#1	"Spinal Muscular Atrophies of Childhood"[Mesh] OR "Spinal Muscular Atrophies"[tiab] OR "Spinal Muscular Atrophy"[tiab] OR "Werdnig-Hoffman"[tiab] OR "Kugelberg-Welander"[tiab] OR (SMA[tiab] AND type[tiab])	8518
#2	("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab]) NOT	3969718

	("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]))	
#3	#1 AND #2	3066
#4	#3 AND English[la] AND ("2017/12/12"[Date - Entrez] : "2020/03/31"[Date - Entrez])	**400**
Update 2: 3/31/2020 - 5252020		
Set	**Terms**	**Results**
#1	"Spinal Muscular Atrophies of Childhood"[Mesh] OR "Spinal Muscular Atrophies"[tiab] OR "Spinal Muscular Atrophy"[tiab] OR "Werdnig-Hoffman"[tiab] OR "Kugelberg-Welander"[tiab] OR (SMA[tiab] AND type[tiab])	8626
#2	("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab]) NOT ("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]))	3,985,483
#3	#1 AND #2	3090
#4	#3 AND English[la] AND ("2020/03/31"[Date - Entrez] : "2020/05/25"[Date - Entrez])	**32**

Embase- Newborn Screening, and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**
#1	'newborn screening'/exp OR 'mass screening'/exp OR ((newborn:ab,ti OR neonatal:ab,ti OR mass:ab,ti OR universal:ab,ti OR communit*:ab,ti) AND screen*:ab,ti)	352,017
#2	'spinal muscular atrophy'/exp OR "spinal muscular atrophy":ab,ti OR "spinal muscular atrophies":ab,ti OR Werdnig:ab,ti OR Hoffman:ab,ti OR Kugelberg:ab,ti OR welander:ab,ti	59086
#3	#1 AND #2	1430
#4	#3 AND [12-12-2017]/sd NOT [1-4-2020]/sd	390
#5	#4 AND [embase]/lim NOT [medline]/lim	**139**
Update 2: 3/31/2020 – 5/25/2020		
Set	**Terms**	**Results**

#1	'newborn screening'/exp OR 'mass screening'/exp OR ((newborn:ab,ti OR neonatal:ab,ti OR mass:ab,ti OR universal:ab,ti OR communit*:ab,ti) AND screen*:ab,ti)	353,792
#2	'spinal muscular atrophy'/exp OR "spinal muscular atrophy":ab,ti OR "spinal muscular atrophies":ab,ti OR Werdnig:ab,ti OR Hoffman:ab,ti OR Kugelberg:ab,ti OR welander:ab,ti	59373
#3	#1 AND #2	1430
#4	#3 AND [31-03-2020]/sd NOT [26-05-2020]/sd	71
#5	#4 AND [embase]/lim NOT [medline]/lim	**44**

Embase- Pediatrics and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**
#1	'hereditary spinal muscular atrophy'/exp OR "Spinal Muscular Atrophies":ab,ti OR "Spinal Muscular Atrophy":ab,ti OR "Werdnig-Hoffman":ab,ti OR "Kugelberg-Welander":ab,ti OR (SMA:ab,ti AND type:ab,ti)	14,754
#2	([infant]/lim OR [child]/lim OR [adolescent]/lim OR pediatric:ti,ab OR pediatrics:ti,ab OR paediatric:ti,ab OR paediatrics:ti,ab OR juvenile:ti,ab OR juveniles:ti,ab OR infant:ti,ab OR infants:ti,ab OR infantile:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR preadolescent:ti,ab OR preadolescents:ti,ab OR prepubescent:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR youth:ti,ab OR youths:ti,ab OR teenager:ti,ab OR teenagers:ti,ab OR teenaged:ti,ab OR teen:ti,ab OR teens:ti,ab) NOT (([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) NOT ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim))	4,003,900
#3	#1 AND #2 AND [embase]/lim NOT [medline]/lim	1439
#4	#3 AND [english]/lim AND [12-12-2017]/sd NOT [1-4-2020]/sd	**524**
Update 2: 3/31/2020 – 5/25/2020		
Set	**Terms**	**Results**
#1	'hereditary spinal muscular atrophy'/exp OR "Spinal Muscular Atrophies":ab,ti OR "Spinal Muscular Atrophy":ab,ti OR "Werdnig-Hoffman":ab,ti OR "Kugelberg-Welander":ab,ti OR (SMA:ab,ti AND type:ab,ti)	14,877
#2	([infant]/lim OR [child]/lim OR [adolescent]/lim OR pediatric:ti,ab OR pediatrics:ti,ab OR paediatric:ti,ab OR paediatrics:ti,ab OR juvenile:ti,ab OR juveniles:ti,ab OR infant:ti,ab OR infants:ti,ab OR infantile:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR preadolescent:ti,ab OR preadolescents:ti,ab OR	4,015,588

	prepubescent:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR youth:ti,ab OR youths:ti,ab OR teenager:ti,ab OR teenagers:ti,ab OR teenaged:ti,ab OR teen:ti,ab OR teens:ti,ab) NOT (([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) NOT ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim))	
#3	#1 AND #2 AND [embase]/lim NOT [medline]/lim	1479
#4	#3 AND [english]/lim AND [31-03-2020]/sd NOT [26-05-2020]/sd	**80**

CINAHL-Newborn Screening and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**
#1	(MH "Health Screening+") OR TI((newborn OR neonatal OR mass[tiab] OR universal OR communit*) AND screen*) OR AB((newborn OR neonatal OR mass[tiab] OR universal OR communit*) AND screen*)	110,903
#2	(MH "Muscular Atrophy, Spinal+") OR TI ("spinal muscular atrophy" OR "spinal muscular atrophies" OR Werdnig OR Hoffman OR Kugelberg OR welander) OR AB ("spinal muscular atrophy" OR "spinal muscular atrophies" OR Werdnig OR Hoffman OR Kugelberg OR welander)	1729
#3	#1 AND #2	70
#4	#3; limit to 12/1/2017 – 3/31/2020	**18**
Update 2: 3/31/2020 – 5/25/2020		
Set	**Terms**	**Results**
#1	(MH "Health Screening+") OR TI((newborn OR neonatal OR mass[tiab] OR universal OR communit*) AND screen*) OR AB((newborn OR neonatal OR mass[tiab] OR universal OR communit*) AND screen*)	111,349
#2	(MH "Muscular Atrophy, Spinal+") OR TI ("spinal muscular atrophy" OR "spinal muscular atrophies" OR Werdnig OR Hoffman OR Kugelberg OR welander) OR AB ("spinal muscular atrophy" OR "spinal muscular atrophies" OR Werdnig OR Hoffman OR Kugelberg OR welander)	1734
#3	#1 AND #2	70
#4	#3; limit to 04/1/2020 – 5/31?2020	**0**

CINAHL-Pediatrics and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**

#1	(MH "Muscular Atrophy, Spinal+") OR TI ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type)) OR AB ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type))	1,534
#2	TI (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens) OR AB (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens)	748,187
#3	#1 AND #2, limit to English and 12/12/2017 – March 2020	**105**
Update 2: 3/31/2020 – 5/25/2020		
Set	**Terms**	**Results**
#1	(MH "Muscular Atrophy, Spinal+") OR TI ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type)) OR AB ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type))	1,541
#2	TI (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens) OR AB (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens)	751,238
#3	#1 AND #2, limit to English and April 2020 – May 2020	**12**

Cochrane-Newborn Screening and SMA

Update 1: 12/11/2017-3/31/2020		
Set	**Terms**	**Results**
#1	[mh "Neonatal Screening"] OR [mh “Mass Screening"]	3660

#2	((newborn:ab,ti OR neonatal:ab,ti OR mass:ab,ti OR universal:ab,ti OR communit*:ab,ti) AND screen*:ab,ti)	9670
#3	[mh "Muscular Atrophy, Spinal"]	85
#4	"spinal muscular atrophy":ab,ti OR "spinal muscular atrophies":ab,ti OR Werdnig:ab,ti OR Hoffman:ab,ti OR Kugelberg:ab,ti OR welander:ab,ti	314
#5	(#1 OR #2) AND (#3 OR #4)	6
#6	#3 AND 2017 – present	2
Update 2: 3/31/2020 – 5/25/2020		
Set	**Terms**	**Results**
#1	[mh "Neonatal Screening"] OR [mh "Mass Screening"]	3660
#2	((newborn:ab,ti OR neonatal:ab,ti OR mass:ab,ti OR universal:ab,ti OR communit*:ab,ti) AND screen*:ab,ti)	9670
#3	[mh "Muscular Atrophy, Spinal"]	85
#4	"spinal muscular atrophy":ab,ti OR "spinal muscular atrophies":ab,ti OR Werdnig:ab,ti OR Hoffman:ab,ti OR Kugelberg:ab,ti OR welander:ab,ti	314
#5	(#1 OR #2) AND (#3 OR #4)	6
#6	#3 AND March 31, 2020 – May 26, 2020	**0**

Cochrane-Pediatrics and SMA

Update 1: 12/11/2017-3/31/2020		
Set	Terms	Results
#1	[mh "Spinal Muscular Atrophies of Childhood"]	24
#2	"Spinal Muscular Atrophies":ab,ti or "Spinal Muscular Atrophy":ab,ti or "Werdnig-Hoffman":ab,ti or "Kugelberg-Welander":ab,ti or (SMA:ab,ti and type:ab,ti)	267
#3	#1 OR #2, 2017 – March 2020	**90**
Update 2: 3/31/2020 – 5/25/2020		
Set	Terms	Results
#1	[mh "Spinal Muscular Atrophies of Childhood"]	24
#2	"Spinal Muscular Atrophies":ab,ti or "Spinal Muscular Atrophy":ab,ti or "Werdnig-Hoffman":ab,ti or "Kugelberg-Welander":ab,ti or (SMA:ab,ti and type:ab,ti)	267
#3	#1 OR #2, April 2020	**1**

SMA - Process	# Citations
Initial searches -> add to endnote	1,701
Dedup, quick quality check	1,078

Published Literature Search - Screening Flow of Records reviewed, excluded, and retained

Systematic Evidence Review – Published Literature Search, Newborn Screening for SMA		
Screening and Review Process	**# Citations**	Source
Records identified through database searching	N_0=1,701	PubMed, n=486
		Embase, n=787
		CINAHL, n=335
		Cochrane Reviews, n=93
Duplicates, non-human, non-SMA records removed (in Endnote)	(306)	
Records Screened (Title and abstract screen)	N_1=1395	
Duplicates, non-human, non-SMA, non-relevant grey literature and case reports	(616)	
Full-text Screen and Review - preliminary eligibility for key questions	N_2=779	
Records Excluded for non-relevance to key questions, other	(574)	
Full-text Review and Abstraction	N_3=205 (109 fulltext, 96 Grey Lit)	
Records Included in Review and Synthesis	N_F=30 (27 fulltext, 3 conference presentations)	

Key Questions for Evidence Review of Implementation and Impact of Added RUSP Conditions

The key topic areas and questions for the systematic evidence review were developed from the general analytic framework used by the Evidence-based Review Group (Condition Review Manual of Procedures-Rev v2.0, 2012, 2014) and the specific needs of the Advisory Committee. For consistency, this review of implementation adapted these Key Questions used in reviews of evidence to consider newborn screening. The Key Questions can be organized into four main topic areas, I. Natural History and Clinical Detection, II. Screening and Short-Term Follow-Up, III. Treatment and Long-Term Follow-Up, and IV. Public Health Impact. The final Key Questions are outlined below, with the refined inclusion and exclusion criteria listed within the Population, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) parameters consistent with standard evidence review methods.

Natural History and Epidemiology with Usual Clinical Detection

Key (Context) Question 1: What is the natural history and epidemiology with and without newborn screening?

Screening, Short-Term Follow-Up, and Diagnostic Confirmation

Key Question 2: What is the evidence that newborn screening for the disease leads to improved health outcomes compared to usual clinical care?

- Population: n>5, Newborns with no known risk for the condition and detected early, or newborns with increased family risk for the condition who were identified presymptomatically
- Interventions: Any care received subsequent to the screening test
- Comparators: Contemporaneous or historical controls affected by the condition
- Outcomes: Overall Survival; Survival with major morbidity
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 3: Screening and short-term follow-up/diagnostic confirmation methods

- What is the analytic validity or clinical validity of the newborn screening approaches used to detect different forms of the condition using high-throughput methods in generalizable populations?
- What diagnostic testing methods are available to confirm or identify these phenotypes?
- What screening or diagnostic methods, if any, are available to predict or inform age of onset or disease severity during newborn screening?

There are two standard measures of analytic validity, sensitivity and specificity. To estimate these requires validated proficiency testing samples. Few such data exist. Consequently, one must use screening studies, which represent the combination of analytic and clinical validity.

- Population: n>5, Newborns without known diagnosis of, or risk factor for the condition; de-identified dried-blood spots

- Interventions: Any screening methods for the condition conducted in the first month of life. For analytic validity, studies should also report proficiency
- Comparators: Diagnosis by genotype and follow-up evaluation or genotype alone
- Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value, reliability, and yield (i.e., prevalence)
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 4: What are the harms associated with newborn screening for the condition to the individual or the family?

- Population: n>5, Newborns screened for the condition and their families
- Interventions: Any newborn screening for the condition
- Comparators: Any population or none
- Outcomes: Systematic assessment of harms, including harm related to false-positive screening results, false-negative screening results, early identification of later-onset disease, or perceived harms or acceptability of screening for the condition
- Timing: Any duration of follow-up
- Settings: All settings

Treatment and Long-term Follow-Up

Key Question 5: What are the standard treatments for the condition and evidence for their effectiveness? Do follow-up protocols exist for the management of the condition that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes?

Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype?

- Population: n>3, Newborns and others diagnosed with the condition through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: Approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with the condition disease or no comparison
- Outcomes: Survival and key health status measures specific to the condition (e.g., motor function, time to ventilator dependence)
- Timing: Any duration of follow-up
- Settings: All settings

In assessing the impact of early intervention, it is important to distinguish whether cases were identified early through newborn screening or risk (e.g., family history) versus identification of symptoms under usual care (i.e., clinical detection). Those children detected based on symptom onset may have more severe disease, and thus could have worse outcomes.

Key Question 6: Does initiation of treatment modify the intermediate health outcomes when the condition is detected through newborn screening or other methods of presymptomatic detection

and diagnosis in childhood compared with usual clinical care? How does this vary by phenotype? How strong is the association between changes in intermediate outcomes of (e.g., biomarkers) of the condition and changes in health outcomes?

- Population: n>3, Newborns and others diagnosed with the condition through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: Approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with the disease or no comparator
- Outcomes: Changes in intermediate outcomes, such as improvements in biomarkers or physiologic changes which are related to other health outcomes.
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 7: What are the effects of treatment on secondary health outcomes?

- Population: n>3, Newborns and others diagnosed with the condition through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: Approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with the disease condition or no comparator
- Outcomes: Other important health outcomes, physical or psychosocial, for the patient or family members
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 8: What are the harms associated with treatments for the condition in early childhood, for symptomatic and presymptomatic patients? How does this vary by phenotype?

- Population: Any child (or caregiver of child) identified with the condition receiving a current treatment
- Interventions: Any approved disease-modifying therapies
- Comparators: Any population or none
- Outcomes: Any systematic assessment or description of harm
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 9: What is the impact of newborn screening on the Public Health of the population on projected numbers affected?

Key Question 10*:* What is the impact of implementing newborn screening of the condition on the U.S. Public Health System? What is the status of U.S. state newborn screening programs in expanding screening panels to include the condition?

APPENDIX B. TECHNICAL EXPERT PANEL MEMBERS

	Technical Expert Panel - SMA Newborn Screening Implementation Evidence-based Review
1	**Mary Schroth, MD** Chief Medical Officer Cure SMA
2	***Michele Caggana, Sc.D., FACMG** Division of Genetics Director, Newborn Screening Program 120 New Scotland Avenue Albany, NY 12208
3	**Stanton Berberich, PhD** Program Manager of Medical Screening State Hygienic Laboratory, University of Iowa Coralville, IA 52241
4	**Anne M. Connolly, MD** Division Chief, Neurology Nationwide Children's Hospital 700 Children's Dr. Columbus, OH 43205
5	**Claudia Chiriboga-Klein, MD, MPH** Professor of Neurology and Pediatrics Columbia University Medical Center
6	***Kathryn J. Swoboda, MD** Massachusetts General Hospital, Pediatric Neurology 55 Fruit Street Boston, MA 02114
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APPENDIX C. STATE IMPLEMENTATION OF NEWBORN SCREENING FOR SMA

Appendix C. Table 1. SUMMARY OF SMA NBS IMPLEMENTATION STATUS ACROSS INFORMATION RESOURCES

	SMA NBS Implementation Status		SMA NBS Method/ Target	Univ Screening? State-reported in Listserv	SMA Screening Start Date State responses	SMA Screen(y/n)? NBSTRN
State NBS Program	†CureSMA, April 2020	‡NewSTEPs; April 2020	‡NewSTEPs; April 2020			
Alabama	No	No				
Alaska	No	No		0		
Arizona*	No	No				
Arkansas	Yes	Yes-**Mar 2020**		1	23-Mar-20	1
California	No	PI[1]- **Jun 2020**		0		0
Colorado	Yes	Yes- **Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***	1	20-Jan-20	1
Connecticut*	Yes	Yes-**Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***	1	1-Jan-20	1
Delaware*	Yes	Yes-**Jan 2020**		1	1-Jan-20	1
District of Columbia	No	No				
Florida	Yes	Yes- **Apr 2020**		1	27-Apr-20	1
Georgia	Yes	Yes- **Aug 2019**	1st Screen 1st Tier Test Method: **Real time PCR** 1st Screen 1st Tier Test Target: ***SMN1***	1		1
Guam	N/A	No				
Hawaii	No	No		0		
Idaho	No	No				
Illinois	No	PI[1]		0		0
Indiana	Yes	Yes- **Jul 2018**				1
Iowa	No	PI[3]- **Jan 2020**		0		0
Kansas	Yes	Yes-**Feb 2020**	1st Screen 1st Tier Test Method: **CDC qPCR Multiplex with SCID** 1st Screen 1st Tier Test Target: ***SMN1*** 1st Screen 2nd Tier Test Method: **Digital Drop PCR send-out to Wisconsin State Laboratory of Hygiene-NBS** 1st Screen 2nd Tier Test Target: ***SMN2*** **Number**	1	1-Feb-20	1
Kentucky*	Yes	Yes- **Aug 2019**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1*** **Exon 7**	1	13-Aug-19	1
Louisiana	No	No		0		
Maine	No	No		0		0
Maryland*	Yes	Yes- **Jun 2019**				1
Massachusetts	Pilot	Yes-**Jan 2018**	1st Screen, 1st Tier Test Method: **Real time PCR,** Target: ***SMN1*** **Exon 7 primer set one (performed as a duplex assay; RNaseP used for QC)** 1st Screen, 2nd Tier Test Method: **Real time PCR,** Target: ***SMN1*** **Exon 7 primer set two (performed as a triplex assay; Primers target different region of Exon 7 than is 1st tier, a region on intron 7 (data used to inform results from tier 1) RNaseP used for QC)**	1	Jan-18	1
Michigan	Yes	Yes- **Mar 2020**		1		1
Minnesota	Yes	Yes- **Mar 2018**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***			1
Mississippi	Yes	Yes- **Nov 2019**				
Missouri*	Yes	Yes-**Jan 2019**	1st Screen 1st Tier Test Method: **CDC qPCR** 1st Screen 1st Tier Test Target: ***SMN1***	1	1-Oct-19	1
Montana	No	No				
Nebraska	No	No		0		
Nevada	No	No		0		0
New Hampshire	Yes	Yes- **Dec 2019**				
New Jersey	No	No				
New Mexico	No	No				
New York	Yes	Yes- **Oct 2018**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1*** **Exon 7 Deletion** 1st Screen 2nd Tier Test Method: **DDPCR** 1st Screen 2nd Tier Test Target: ***SMN2*** **Copy Number**	1	1-Oct-18	1
North Carolina	Pilot	No		0		1
North Dakota	No	No				
Ohio	Pilot	PI		0	Pilot	0
Oklahoma	No	No		0		0
Oregon	No	No				
Pennsylvania	Yes	Yes- **Mar 2019**		1	1-Mar-19	1
Puerto Rico	No	No				0
Rhode Island	No	No		0		0
South Carolina	No	No		0		0
South Dakota	No	PI- **Jan 2020**				
Tennessee	Yes	Yes-**Feb 2020**	1st Screen 1st Tier Test Method: **RT-PCR** 1st Screen 1st Tier Test Target: **Exon 7** ***SMN1***	1	1-Feb-20	1
Texas	No	No		0		0
Utah*	Yes	Yes-**Jan 2018**		1	Jan-18	1
Vermont*	Yes	Yes- **May 2019**				1
Virginia	No	PI[2]				
Washington	No	No		0		0
West Virginia*	Yes	Yes- **Nov 2019**	1st Screen 1st Tier Test Method: **MS/MS non-derivatized**	1		1
Wisconsin	Yes	Yes		1	15-Oct-19	1
Wyoming*	Yes	Yes- **Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***	1	20-Jan-20	1
TOTALS	**23-Yes** 3-Pilots	**24-Yes** 6-PI		**18**		**23**
	Yes-Adopted and Implemented; **No**-Not Screened; **Pilot**- Conducted Pilot	**Yes**-Universally Screened; **No**-Not Screened; **PI**-Pursing Implementation; **PI[1]**-Required, but not fully implemented; **PI[2]**-Seeking authorization/funding; **PI[3]**-Addressing other barriers/or status not specified		1 = yes, full population screening started; 0 = no.		1 = yes, full population screening started; 0 = no.; Ohio- Population Study was excluded. (*)-Info obtained through NBSTRN/NewSTEPs.

† CureSMA *(https://www.curesma.org/newborn-screening-for-sma, accessed Apr 7, 2020)*

‡NewSTEPs *(https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders?q=resources/newborn-screening-status-all-disorders, accessed Apr 7, 2020)*

Appendix C. Table 1. SUMMARY OF SMA NBS IMPLEMENTATION STATUS ACROSS INFORMATION RESOURCES (cont'd)

Does you state get SMN2 copy numbers? NBS? CT? DX? State responses	SMN2 Copy # (y/n)? NBSTRN	Do they plan on including SMN2 Copy # NBSTRN	Positive cases through pop-screening? State responses	Positive cases through validation/pilot screening? State responses	Positive SMA Screens- NBSTRN	Total Screened- NBSTRN	If no, when will they start? NBSTRN	Annual Births- NBSTRN	% of US Births- NBSTRN
No			0					37,520	1.0
No		Y (Confirmation)					2-Jul-20	471,658	12.2
CT			5	2	8	30,000		64,382	1.7
No			0					35,221	0.9
Yes			0					10,855	0.3
DX/CT	Yes		1		N/A			223,630	5.8
CT	Yes		11		11	190,000		129,243	3.4
No				5					
N/A		N		1			1-Jul-20	149,390	3.9
	Yes (Confirmation)				7			82,170	2.1
No		N/A					1-Jul	38,430	1.0
CT	Yes		0	2	0			36,519	0.9
DX			8					54,752	1.4
N/A									
N/A		N/A					N/A	12,298	0.3
								71,641	1.9
Yes	Yes		6		6	135,000		70,702	1.8
No	Yes (Confirmation)		6		6			111,426	2.9
	Yes (Confirmation)				15	142,426		68,595	1.8
			10					73,034	1.9
N/A									
N/A		N					No timeline	35,756	0.9
Yes	Yes		15		15	400,000		229,737	6.0
No	N/A				0	7834		120,125	3.1
No	No	N/A		8		124,282	N/A	136,832	3.5
No		N					2020	50,214	1.3
Yes	Yes		12		9			137,745	3.6
								24,310	0.6
		Y					Summer 2020	10,638	0.3
		Y (Unsure if in-house or confirmatory					completion of Pompe, MPS I, and XALD	57,029	1.5
CT	Yes		1	2	3			81,016	2.1
		N/A					N/A	382,050	9.9
No			7					48,585	1.3
								5,655	0.1
No		Y (Confirmation)		5			Summer 2020	87,562	2.3
No			1					18,675	0.5
Yes	Yes		2		2	35,883		64,975	1.7
No				1				6,903	0.2
5-Yes 1-DX 4-CT 1-DX/CT	**11-yes**	**4- Yes**	**85**	**26**	**82**	**1,065,425**		**3,239,273**	**84.0**
NBS=Newborn screening in-house; CT=Confirmatory testing (outside lab); DX=Gathered by providers for diagnosis; Yes-state assesses *SMN2* copy number, collection method not specified; No- state does not assess *SMN2* copy numbers	(*)-Info obtained through NBSTRN/NewSTEPs	(*)-Info obtained through NBSTRN/NewSTEPs	*Positive cases during full population screening. Pilots reporting positive cases were excluded.	*Positive cases identified during validation/pilot screening ONLY.	*Pilots reporting positive cases were excluded (IL-1; OH-11; WA-5). (*)-NBSTRN/NewSTEPs	(*)-NBSTRN/NewSTEPs	(*)-NBSTRN/NewST	(*)-NBSTRN/NewSTEPs	(3,855,500 https://www.kff.org/other/state-indicator/number-of-births/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D#note-1) (*)-NBSTRN/NewSTEPs

Appendix C. Table 2. SMA NEWBORN SCREENING IMPLEMENTATION STATUS

	SMA NBS Implementation Status		SMA NBS Method/ Target
State NBS Program	†CureSMA, April 2020	‡NewSTEPs; April 2020	‡NewSTEPs; April 2020
Alabama	No	No	
Alaska	No	No	
Arizona*	No	No	
Arkansas	Yes	Yes-**Mar 2020**	
California	No	PI[1]- **Jun 2020**	
Colorado	Yes	Yes- **Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***
Connecticut*	Yes	Yes-**Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***
Delaware*	Yes	Yes-**Jan 2020**	
District of Columbia	No	No	
Florida	Yes	Yes- **Apr 2020**	
Georgia	Yes	Yes- **Aug 2019**	1st Screen 1st Tier Test Method: **Real time PCR** 1st Screen 1st Tier Test Target: ***SMN1***
Guam	N/A	No	
Hawaii	No	No	
Idaho	No	No	
Illinois	No	PI[1]	
Indiana	Yes	Yes- **Jul 2018**	
Iowa	No	PI[3]- **Jan 2020**	
Kansas	Yes	Yes-**Feb 2020**	1st Screen 1st Tier Test Target: ***SMN1*** 1st Screen 2nd Tier Test Method: **Digital Drop PCR send-out to Wisconsin State Laboratory of Hygiene-NBS** 1st Screen 2nd Tier Test Target: ***SMN2*** **Number**
Kentucky*	Yes	Yes- **Aug 2019**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1*** **Exon 7**
Louisiana	No	No	
Maine	No	No	
Maryland*	Yes	Yes- **Jun 2019**	
Massachusetts	Pilot	Yes-**Jan 2018**	1st Screen, 1st Tier Test Method: **Real time PCR,** Target: ***SMN1*** **Exon 7 primer set one (performed as a duplex assay; RNaseP used for QC)** 1st Screen, 2nd Tier Test Method: **Real time PCR,** Target: ***SMN1*** **Exon 7 primer set two (performed as a triplex assay; Primers target different region of Exon 7 than is 1st tier, a region on intron 7 (data used to inform results from tier 1) RNaseP used for QC)**
Michigan	Yes	Yes- **Mar 2020**	
Minnesota	Yes	Yes- **Mar 2018**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***
Mississippi	Yes	Yes- **Nov 2019**	
Missouri*	Yes	Yes-**Jan 2019**	1st Screen 1st Tier Test Method: **CDC qPCR** 1st Screen 1st Tier Test Target: ***SMN1***
Montana	No	No	
Nebraska	No	No	
Nevada	No	No	
New Hampshire	Yes	Yes- **Dec 2019**	
New Jersey	No	No	
New Mexico	No	No	
New York	Yes	Yes- **Oct 2018**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1*** **Exon 7 Deletion** 1st Screen 2nd Tier Test Method: **DDPCR** 1st Screen 2nd Tier Test Target: ***SMN2*** **Copy Number**
North Carolina	Pilot	No	
North Dakota	No	No	
Ohio	Pilot	PI	
Oklahoma	No	No	
Oregon	No	No	
Pennsylvania	Yes	Yes- **Mar 2019**	
Puerto Rico	No	No	
Rhode Island	No	No	
South Carolina	No	No	
South Dakota	No	PI- **Jan 2020**	
Tennessee	Yes	Yes-**Feb 2020**	1st Screen 1st Tier Test Method: **RT-PCR** 1st Screen 1st Tier Test Target: **Exon 7** ***SMN1***
Texas	No	No	
Utah*	Yes	Yes-**Jan 2018**	
Vermont*	Yes	Yes- **May 2019**	
Virginia	No	PI[2]	
Washington	No	No	
West Virginia*	Yes	Yes- **Nov 2019**	1st Screen 1st Tier Test Method: **MS/MS non-derivatized**
Wisconsin	Yes	Yes	
Wyoming*	Yes	Yes- **Jan 2020**	1st Screen 1st Tier Test Method: **qPCR** 1st Screen 1st Tier Test Target: ***SMN1***
TOTALS	**23-Yes**	**24-Yes**	
	3-Pilots	**6-PI**	
	Yes-Adopted and Implemented; **No**-Not Screened; **Pilot**- Conducted Pilot	**Yes**-Universally Screened; **No**-Not Screened; **PI**-Pursing Implementation; **PI**[1]-Required, but not fully implemented; **PI**[2]-Seeking authorization/funding; **PI**[3]-Addressing other barriers/or status not specified	

† CureSMA *(https://www.curesma.org/newborn-screening-for-sma, accessed Apr 7, 2020)*

‡NewSTEPs *(https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders?q=resources/newborn-screening-status-all-disorders, accessed Apr 7, 2020)*

Appendix C. Table 3. SMA NBS PROGRAM INFORMATION FROM STATES PROVIDED BY THE NBSTRN

State	Note	Annual Births	% of US Births (3,855,500)†	SMA Screen(Y/N)	Do they plan on including SMN2 copy #	SMN2 Copy # (Y/N)	Positive SMA screens	Total Screened	If no, when will they start?
Alabama									
Alaska									
Arizona									
Arkansas	Screening' per NewSTEPs (5/10/20)	37,520	1.0	Y					
California	Report to NBSTRN	471,658	12.2	N	Y (Confirmatory)				2-Jul-20
Colorado	Report to NBSTRN	64,382	1.7	Y			8	30,000	
Connecticut	Screening' per NewSTEPs (5/10/20)	35,221	0.9	Y					
Delaware	Screening' per NewSTEPs (5/10/20)	10,855	0.3	Y					
District of Columbia									
Florida	Report to NBSTRN	223,630	5.8	Y		Y	NA		
Georgia	Report to NBSTRN	129,243	3.4	Y		Y	11	190,000	
Guam									
Hawaii									
Idaho									
Illinois	Report to NBSTRN	149,390	3.9	N	N		1‡		1-Jul-20
Indiana	Report to NBSTRN	82,170	2.1	Y		Y (Confirmatory)	7		
Iowa	Report to NBSTRN	38,430	1.0	N	NA				1-Jul
Kansas	Report to NBSTRN	36,519	0.9	Y		Y	0		
Kentucky	Screening' per NewSTEPs (5/10/20)	54,752	1.4	Y					
Louisiana									
Maine	Report to NBSTRN	12,298	0.3	N	NA				NA
Maryland	Screening' per NewSTEPs (5/10/20)	71,641	1.9	Y					
Massachusetts	Report to NBSTRN	70,702	1.8	Y		Y	6	135,000	
Michigan	Report to NBSTRN	111,426	2.9	Y		Y (Confirmatory)	6		
Minnesota	Report to NBSTRN	68,595	1.8	Y		Y (Confirmatory)	15	142,426	
Mississippi									
Missouri	Screening' per NewSTEPs (5/10/20)	73,034	1.9	Y					
Montana									
Nebraska									
Nevada	Report to NBSTRN	35,756	0.9	N	N				No timeline
New Hampshire									
New Jersey									
New Mexico									
New York	Report to NBSTRN	229,737	6.0	Y		Y	15	400,000	
North Carolina	Report to NBSTRN	120,125	3.1	Y		NA	0	7834	
North Dakota									
Ohio	Report to NBSTRN	136,832	3.5	Y (*Population Study)	NA	N	11‡	124,282	NA
Oklahoma	Report to NBSTRN	50,214	1.3	N	N				2020
Oregon									
Pennsylvania	Report to NBSTRN	137,745	3.6	Y		Y	9		
Puerto Rico	Report to NBSTRN	24,310	0.6	N					
Rhode Island	Report to NBSTRN	10,638	0.3	N	Y				Summer 2020
South Carolina	Report to NBSTRN	57,029	1.5	N	Y (Unsure if in-house or confirmatory)				Post-completion of Pompe, MPS I, and XALD
South Dakota									
Tennessee	Report to NBSTRN	81,016	2.1	Y		Y	3		
Texas	Report to NBSTRN	382,050	9.9	N	NA				NA
Utah	Screening' per NewSTEPs (5/10/20)	48,585	1.3	Y					
Vermont	Screening' per NewSTEPs (5/10/20)	5,655	0.1	Y					
Virginia									
Washington	Report to NBSTRN	87,562	2.3	N	Y (Confirmatory)		5‡		Summer 2020
West Virginia	Screening' per NewSTEPs (5/10/20)	18,675	0.5	Y					
Wisconsin	Report to NBSTRN	64,975	1.7	Y		Y	2	35,883	
Wyoming	Screening' per NewSTEPs (5/10/20)	6,903	0.2	Y					
		3,239,273	84.0				82	1,065,425	

†https://www.kff.org/other/state-indicator/number-of-births/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D#note-1)

‡ detected during pilot screening

Appendix C. Table 4. STATE NBS REPORTS ABOUT SMA NBS ACTIVITIES THROUGH APHL/NEWSTEPS LISTSERV

State	Q1: Does your state screen for SMA?	Universal screening?		Q2: If yes, do you determine the *SMN2* copy #?	*SMN2* testing? NBS, CT, DX	Q3: How many positives have been recorded?	#positive cases identified through population screening	Positive cases through pilot screening? State responses
Alabama								
Alaska	Alaska does not currently screen for SMA.	**0**						
Arizona								
Arkansas	Yes, we started screening March 23, 2020	1	23-Mar-20	No, but this part of the diagnostic follow up	DX	None	0	
California	(No) Here in California we are just about to start screening for SMA and our goal is the last week of June or the first week of July. (Our mandate is by July 2, 2020)	0	No	We will include *SMN2* copy number with our confirmatory testing that the program will cover, but will be done on a whole blood sample at a contract lab. The lab is interested in making it part of screening in the future.	CT planned	N/A		
Colorado	Colorado and Wyoming went live with SMA testing on January 20, 2020	1	20-Jan-20	Our contracted follow-up providers confirm *SMN1* and *SMN2* copy numbers. State lab currently only tests for *SMN1* deletion. We are piloting *SMN2* copy number testing by ddPCR.	CT	In our 2019 validation study, we discovered 2 cases in Colorado that were not previously known. Since going live in January, we have found 5 additional cases in Colorado. Note: Birth rate for Colorado is approx. 68,000/yr. Current incidence rate 1 in about 5000.	5	2
Connecticut	Yes - we started our validation with samples received as of 10/1/2019 and went live 01/01/2020	1	1-Jan-20	No	No	0 - CT info provided to CureSMA: Reporting period of 10/1/2019-4/30/2020: 20,073 infants screened; 0 screened positive with confirmatory testing; annual birth rate of ~36,000 infants/year…. Reporting period of 01/01/2020-04/30/2020: 11,343 infants screened; 0 screened positive, same birth rate	0	
Delaware	DE started screening for SMA (and X-ALD, MPS0I, Pompe) 1/1/2020	1	1-Jan-20	Yes, we do report *SMN2* copy number (lab reports 1, 2, 3, or > 3 copies)	YES	~3500 screened to date, NO positives	0	
D.C.								
Florida	Yes, we went live 4/27/2020	1	27-Apr-20	No - The clinics will order the *SMN2* copies (followup contract dollars) and if we have sufficient specimen left on the first screen, we will send it to cut down time.	DX/CT	1	1	
Georgia	(Yes) Georgia completed the NIH-sponsored pilot for SMA and is continuing with state-funded universal screening	1	yes	(No) - *SMN2* copy number is not part of our screening test. It is obtained with confirmatory testing combined with *SMN1* common deletion testing.	CT	(Yes) We have identified 11 true positive cases of SMA. False positives and inconclusive results are being examined now. LOTS of inconclusive (meaning the internal control RNAseP was also abnormal)). Some false positives, but not many.*	11	
Guam								
Hawaii	Same as Washington state: No, we do not yet screen for SMA. We anticipate starting in Summer 2020.	0	No	Same as Washington state: *SMN2* copy number will be part of the confirmation testing, but not on the NBS sample.	CT planned	Same as Washington state: We've screened 3,000+ in an anonymous pilot study with five positive results (likely first and second screens for some of them).		5
Idaho								
Illinois	(Not screening for SMA yet) Illinois will begin screening for SMA by July 1, 2020	0	No			We did find 1 case that was confirmed with diagnostic testing during our validation study.		1
Indiana								
Iowa	Iowa is scheduled to begin an SMA pilot July 1, 2020 (all babies will be included and screened as part of the pilot)	0	No	(No) We will not be including *SMN2* as part of the screen.	No	N/A		
Kansas	Yes, Kansas started screening for SMA on February 1, 2020	1	1-Feb-20	Yes, our Advisory Council definitely wanted *SMN2* copy number. Our positive screens are sent to another lab to determine *SMN2* copy number (Wisconsin State Laboratory).	CT	We have not had any positives since Go Live date of February 1, 2020. We did have two positives screened during the pilot phase	0	2

Kentucky	KY has been screening for SMA since 8/13/2019.	1	13-Aug-19	*SMN2* copy number is determined as part of the diagnostic follow-up process.	DX	We've had 8 positive SMA cases with two presumptives that have yet to be confirmed. This is out of approximately 40,400 specimens.	8	
Louisiana	Louisiana's Genetic Diseases Program recommended screening for SMA on May 8, 2020. We soon start the process for adding this condition to the newborn screening panel.	0	No			N/A		
Maine	Not screening for SMA yet	0	no					
Maryland								
Massachusetts	Massachusetts has been screening for SMA since January 2018	1	2018- Jan	Yes, we do provide *SMN2* copy number using the modified sequencing protocol we presented at the national symposium.	YES-NBS	135,000 screened, six cases identified	6	
Michigan	Yes, we screen for SMA	1	yes	No, we do not determine *SMN2* copy number (it's done as part of diagnostic follow-up)	NO	We have had 6 positives	6	
Minnesota								
Mississippi								
Missouri	Yes, prior to pilot for SMA (January 2, 2019, went live with screening October 1, 2019)	1	1-Oct-19		?	10 babies have been identified in Missouri since screening started in January 2019. Our laboratory estimates we have screened approximately 100,000 babies for SMA since screening began in January 2019.	10	
Montana								
Nebraska	Not screening for SMA yet. However, screening for SMA is part of a pending priority bill that the Nebraska legislature is considering, and it will be voted on when their legislative session resumes.	0	no			N/A; we anticipate that once we have a signed bill in place, we will be able to begin testing within two days.		
Nevada	Not screening for SMA yet	0	no					
New Hampshire								
New Jersey								
New Mexico								
New York	Yes, NYS began universal SMA screening 10/1/2018	1	1-Oct-18	Yes, we determine *SMN2* copy number and report at the time of referral.	YES	15 positives; 349,725 screened	15	
North Carolina	Not yet. We are targeting implementation early 2021.	0	no	We do not intend to implement copy number detection.	no	N/A		
North Dakota								
Ohio	Ohio has not yet added SMA to the Ohio Administrative Code that lists disorders included in the state screening panel. However, since mid-January 2019, every specimen has been screened for homozygous deletion of exon 7 of the SMN1 gene as part of a population study.	0	pilot	No	No	In 2019, 124,282 infants were screened, and 2 were identified with SMA-1 and 6 were identified with a later onset form of SMA. So far in 2020, there have been 3 infants with abnormal screening results for whom diagnoses are pending.		8
Oklahoma	Not currently screening for SMA; but we do have plans to begin screening later this year. No definite time frame yet.	0	No	(No) - We will not be determining *SMN2* copy number	No	N/A		
Oregon								
Pennsylvania	Yes, Pennsylvania began screening all newborns for SMA on 3/1/2019	1	3/1/2019	YES	YES	Number of infants screened: 148,911 / Number of screen positives: 12 / Confirmed SMA Dx: 9 / Dx pending: 3 (Reporting period: 3-1-2019 to 4-20-2020)	12	
Puerto Rico								
Rhode Island	Not screening for SMA yet	0	no	N/A		N/A		
South Carolina	Not screening for SMA yet; on hold until we can complete the addition of Pompe, MPS I, and X-ALD to our panel between now and 2021.	0	no	N/A; unaware if the copy number will be provided in-house or via confirmatory testing at this time.		N/A		
South Dakota								
Tennessee	Tennessee began screening for SMA February 1, 2020.	1	1-Feb-20	Our lab sends a bloodspot to an outside lab to determine the number of *SMN2* copies and this information is sent to the tertiary center for follow-up.	CT	Tennessee had 2 positives during validation and 1 positive since screen began. All 3 cases have been confirmed as disease.	1	2

Texas	Not screening for SMA yet	0	no					
Utah	Utah began screening for SMA in January 2018	1	Jan-18	(No) - Screen for homozyous deletions of *SMN1* only	No	To date, we have identified 7 cases	7	
Vermont								
Virginia								
Washginton	No, we do not yet screen for SMA. We anticipate starting in Summer 2020.	0	NO	*SMN2* copy number will be part of the confirmation testing, but not on the NBS sample.	no	We've screened 3,000+ in an anonymous pilot study with five positive results (likely first and second screens for some of them).		5
West Virginia	Yes	1	Yes	No	no	1+	1	
Wisconsin	Yes, since 10/15/2019	2	10/15/2019	Yes, *SMN1* zero specimens undergo the *SMN2* copy numbers assessment by a ddPCR in-house	YES-NBS	2 positive cases during Oct 15, 2019-May 15, 2020 with 35,883 infants screened	2	
Wyoming	Colorado and Wyoming went live with SMA testing on January 20, 2020	1	20-Jan-20	Our contracted follow-up providers confirm *SMN1* and *SMN2* copy numbers. State lab currently only tests for *SMN1* deletion. We are piloting *SMN2* copy number testing by digital PCR.	no	In our 2019 validation study, we discovered 1 case in Wyoming that were not previously known. Note: Birth rate for Wyoming is approx. 68,000/yr. Current incidence rate 1 in about 5000.		1
TOTALS		**19**			**4-YES *(not specified)*** **1-NBS** **7-CT** **12-NO** **1-Don't Know**		**85**	**26**

*NOTES: GEORGIA - Inconclusives are a bit different than false positives – they are really more reflective of a bad sample and not an abnormal result – for those kids we always ask for a repeat sample and they ALWAYS turn out normal. Internally at the NBS lab, any abnormal result is automatically repeated from that same card in duplicate to confirm before reporting it. Again, we are running the numbers NOW as we are trying to generate our report to the NIH from the pilot. So we will have more info soon…

*NOTES: GEORGIA - continued: Georgia (Emory Dept of Human Genetics and GA Dept of Public Health) was awarded a grant from NIH to do a pilot screening for SMA. We recently transitioned to state funding. At the end of April we had screened 181,661 specimens (~140,000 babies). We have had 11 confirmed SMA cases. SMN2 copy number is determined as part of the diagnostic workup, not from the dried blood spot specimens.

*NOTES: CT - providing two sets of numbers—the number of infants that have been tested since our validation began and the number of infants that have been tested since we officially went live with screening. During the validation stage before going live we tested all infants received 10/1/2019-12/31/2019 so there was no gap between the end of our validation testing and our go-live date. During the validation we had Wisconsin on standby for verification of our validation screening results for anything that was abnormal so that we could act on any results outside of normal limits and did not run a blinded validation. Wisconsin does test for the *SMN2* copy number for abnormal results and would have done this testing for any out of range results if we had any during our validation. We did not have any abnormal SMA results during our validation.