Virtual Roundtable on States' Experiences Screening for Spinal Muscular Atrophy (SMA)

Please note that all webinar summary notes captured below are reflective of the conversational format of the virtual roundtable discussion. If you have specific questions or clarifications regarding methodologies or techniques employed by states, please reach out to NewSTEPs staff at newsteps@aphl.org to be put in touch directly with the state representative. We also recommend viewing of the archived webinar video link, below.

Date: Thursday, October 24, 2019
Time: 2:00 – 3:30 pm ET

Time	Agenda
2:00 pm-2:05 pm	Welcome: Amy Gaviglio, George Dizikes, and Kshea Hale
2:05 pm-2:15 pm	Introductions: Speakers • Each speaker will briefly introduce themselves o Anne Marie Comeau (MA) o Fizza Gulamali-Majid and Jennifer Taylor (MD) o Joshua Featherston (MO) o Carrie Wolf (MN) o Jordan Shover (PA) o Sarah Bradley (NY) o Megan Wilde (MO)
2:15 pm-2:45 pm	**SMA Screening Overview** (Each speaker provided a summary of their SMA screening experience) **Webinar Summary:** • **What is your screening method?** o **Massachusetts Newborn Screening (NBS) program** uses a single-plex, two-tiered assay. The assay is designed to detect the homozygous absence of SMN1 Exon 7. Multiple analytes are included. Tier-one is run overnight, and tier-one and tier-two results are completed by the next afternoon. The repeat screens repeat the original test simultaneously with the other test showing Intron 7. o **Maryland NBS** uses a method developed by the Centers for Disease Control and Prevention (CDC) for multiplexing Severe Combined Immunodeficiency (SCID) and SMA. They punch 2-mm dried blood spots into the PCR plate and perform the assay on the same plate. RNaseP is used as a reference gene. Multiplexing with SCID was shown to not increase the re-test rate. Most specimens that are inconclusive for SMA are also inconclusive for SCID

	(results reported for both disorders instead of one). Maryland retests in duplicate – critical results are given to follow-up. o **Missouri NBS** also uses the method developed by CDC for multiplexing SCID and SMA – the method is almost identical to Maryland NBS (look for presence/ absence of SMN 1). Missouri NBS is set up a little differently in the sense that SCID and SMA testing is done in the molecular unit, and then reported to the NBS unit who sends results to providers. The biggest challenge has been adapting to the current setup to move into the typical NBS rhythm. ▪ Since **Missouri NBS** is only accepting presence or absence of SMN 1, they act upon all abnormal results. Follow-up calls the primary care physician (PCP) on record, and fax a packet of information regarding SMA for the PCP and parents. Once the packet is faxed, it is the duty of the PCP to get in touch with the specialist of the parents' choosing and arrange an appointment within 7 days. Referrals are not called out on weekends. o **Minnesota NBS** multiplexes SCID and SMA. They use RNaseP as a reference gene and look at the absence of SMN 1. o **Pennsylvania NBS** is different from the other presenting programs in that they contract screening with PerkinElmer Genetics. If there is a homozygous deletion on the first tier testing, the laboratory preforms a second test to confirm. If that happens, the second tier tests determines SMN copy numbers. The presumptive positive results from PerkinElmer are sent to genetic counselors who report out to PCPs and notify them of approved treatment centers/ where to refer the baby. After confirming with the physician, the nurses in follow-up work with treatment centers who must accept the patient within 72 hours, and report back once an evaluation has been performed. Once the baby gets to the treatment center, the center collects another sample to verify there was no mislabeling. Confirmed screen positives are sent back to PerkinElmer Genetics. Pennsylvania NBS relied on New York to get this treatment center process started. There has been a difficult time in getting gene therapies approved. o **New York NBS** use a custom real time assay multiplexed with SCID and are not reporting out carriers. The SMN 2 copy number analysis is done in house, and SMN 1 and 2 are reported on the same day (usually about two days after the sample was collected). They do intron 7 confirmatory testing as well. New York has run into challenges with multiplexing being more challenging than anticipated. They have found a higher retest rate for SCID, causing higher cost and greater staff time. New York is not referring babies straight to a genetic center because these patients have to be followed in the long-term with neuromuscular

specialists/ did not want to overburden the genetic centers. New York instituted a new group of specialty care centers, which was a long process that was a challenge, but not insurmountable.

- **How many newborns screened?**
  - **Massachusetts NBS** has screened 100,000 newborns.
  - **Maryland NBS** started screening on May 31, and are a two-screen state. They have screened over 31,000 newborns.
  - **Missouri NBS** has screened over 57,000 newborns for SMA.
  - **Minnesota NBS** has screened a little over 105,000 specimens.
  - **Pennsylvania NBS** has screened over 79,000 newborns.
  - Prior to statewide screening, **New York NBS** did a consented pilot study with 16,700 newborns screened (at that time, carriers were reported out). Immediately after the pilot study concluded they began statewide screening. In the first year, approximately 225,000 newborns were screened.

- **How many (what %) had results that prompted additional testing before release of results externally (to primary care physician (PCP)/specialist)?**
  - **Massachusetts NBS** had two per one thousand (.2%) prompting tier two; 198 of screens prompted retesting. The vast majority of newborns were shown to have in range results.
  - **Maryland NBS** has sent three cases to follow-up.
  - **Missouri NBS** had 274 results on the initial screen that prompted an additional screen. Of those, only five were released to the PCP as identified of having an absence of the SMN 1 gene. The majority of flagged cases were retested for reasons not indicative of SMA.
  - **Minnesota NBS** detected ten positive patients (one in 10,500). Ten samples had no amplification whatsoever (absence of SMN 1); Minnesota NBS repeats in triplicate the following day to confirm. Once confirmed, results are reported out.
  - **Pennsylvania NBS** has found five presumptive positives (1 per 16,000 screened).
  - During the **New York NBS** pilot study, they detected one true case of SMA. The baby started Spinraza quickly and is doing well. Additionally, 250 carriers were offered genetic counseling but the uptake was small. Since universal screening began, New York has referred eight newborns (three had two copies of SMN2, three has three copies, and two had four copies). The referral rate is less than expected.

- **What is the referral rate? How many (or what %) of released results to PCP/specialist yielded an SMA Diagnosis?**

	o **Massachusetts NBS** found four true positives, showing an overall frequency of 1 in 25,000. Of the true positives, one was shown to have four or more copies of SMN 2 (confirmed by a commercial laboratory); the others had two or three copies. All four infants are in pediatric neurology care. o All three cases in **Maryland NBS** had no amplification of SMN1 exon 7 in the initial and repeat specimen. o **Missouri NBS** has a referral rate of 1 in 14,000 o **Minnesota NBS** detected 10 positive patients (1 in 10,500). All ten babies have started treatment with Spinraza. The time from birth to the first injection is 19 days, which is a quick turnaround time from screening to treatment. o **Pennsylvania NBS** has found five presumptive positives (1 per 16,000 screened). o Once universal screening began, **New York NBS** has referred eight babies (three had two copies of SMN2, three has three copies, and two had four copies). The referral rate is less than expected. • **Have any False Negative results been reported to your program since you have started screening?** o **Massachusetts NBS** found no false negatives. o **Maryland NBS** found no false negatives. o **Missouri NBS** found no false negatives. o **Minnesota NBS** found no false negatives. o **Pennsylvania NBS** found no false negatives. o **New York NBS** found no false negatives.
2:45 pm-3:15 pm	State Questions & Discussion (questions were submitted in advance of the webinar) **Webinar Summary** **Analytical:** • **For states who have multiplexed with Severe combined immunodeficiency (SCID), have you seen an increase in SCID positive results - from what percentage to what percentage and in any certain population [e.g., Neonatal Intensive Care Unit (NICU)]?** o **Missouri NBS** has seen a decrease in referrals for SCID, which is most likely due to adjusting borderline cut-offs and that they switched to Quanta Extra Solution. In 2018, 2.3% of samples were high-risk or borderline vs. in 2019, .78% were high-risk or borderline. In 2018, they had 108 referrals for confirmatory testing vs. 29 in 2019.

- **New York NBS** initially had an increase in SCID referrals, which has subsided (issues were worked out with the assay). Re-test rate has been the bigger challenge.

- **For all states**
  - What have you used for calibration verification?
  - What material do you use for daily positive quality control (QC), and from where do you obtain it?
  - How did you validate your LIMS?
  - Is anyone doing SMN2 copy number within the screening lab? If yes – why and by what method? If no – why not?

    Tennessee NBS is in the process of validating. They are arranging to have SMN2 copy number done so that geneticists have access to this information.

    New York NBS provides SMN2 copy number and strongly requests specialists to have confirmatory testing done by an independent laboratory as soon as possible. New York is willing to do confirmatory analysis (sequencing) in-house if needed.

    Wisconsin NBS began screening in October 2019. They use the digital droplet PCR method to record SMN2 copy number. They can do 1 – 5 copy number. Wisconsin is interested in working with other programs for proficiency testing purposes.

    Question from Maryland: Do you have any problems resolving copy numbers using real-time PCR?

    Response: New York has not had a problem. They did have one baby that had confirmatory testing at two separate laboratories (one of these labs did not match NBS program – 2 vs. 3-copy number).

    Response: When New England NBS Program gets higher copy number, they say the baby has at least 4. MA will also request specialists conduct confirmatory testing.

    Question from Minnesota: Is reporting copy numbers as valuable as initially anticipated?

    Response from Tennessee: Tennessee does copy number to provide equity. Additionally, low copy numbers may help indicate urgency.

    Question from Tennessee: Is there a copy number where you can wait to provide treatment?

Response: Illinois is planning to go live with SMA in June 2020 and plans to multiplex. They do not plan to report carriers; however, it is something their genetic counselors really want them to do.

Response from clinician: Specialists are nearly as panicked if the copy number is 4 or greater. An important consideration to keep in mind is that some insurances may cover gene therapy which can only be given to children under the age of two vs. lifetime of Spinraza treatment (copy number can help detect urgency).

Question from Illinois: How do you detect carriers outside of digital droplet PCR?

Response from Minnesota: It is risky to automatically assume carrier if there is only one absence of exon seen.

Considerations for the Group: When do we go from screening to going to a diagnostic lab? Is the newborn screening system the most appropriate mechanism to report carriers?

CDC Response: The CDC is working towards developing a Proficiency Testing (PT) Program. They have developmental materials and put out a request for all laboratories that are interested to reach out to them to help with moving forward with developing a Proficiency Testing program in as short of a timeframe as they can.

Post-Analytical:

- **Follow-up Considerations**
  - What are your experiences with confirmatory testing? How well do they match screening results?
  - What follow-up data is being collected? Both upon diagnosis and after diagnosis?
    - Lab results? Clinical findings? Other?
    - Are programs/specialists trying to "type" SMA based on SMN2 copy numbers/clinical symptoms present at diagnosis?
  - Have any states worked with Medicaid on coverage of expensive treatment - especially gene therapy? If yes - what was outcome and who was involved?

***Question from* Amy Gaviglio: Have states noticed their issues with insurance companies have been related to copy number? Or**

	if there were insurance implications with parent treatment preference? **Response from Pennsylvania:** One case (of SMA) out of the five identified had difficulty because they were insured through Medicaid. This experience was not necessarily copy number related, though more urgency was shown to copy 3 vs copy 2. **Response:** In the above case, the insurance would not have covered costs for gene therapy if patient had started Spinraza. Dr. Jennifer Kwon shared that the issues she has noticed has not been related to copy number status. Noted that there are physicians in other parts of the country that put in prior authorization for multiple medications. Wonders how many of these scenarios are influenced by region ***Question from Amy Gaviglio: What are states experiences with diagnosing SMA? Are they categorized into SMA "buckets" (1, 2, 3, etc.). Amy Gaviglio noted that in Minnesota, they are not asking specialists to do so. Are others calling specialists based on symptoms or copy numbers?*** **Response from New York:** Not asking specialists what type they think baby has. They ask if baby has SMA. If there are abnormal clinical signs/symptoms? In addition, if baby has already started on treatment? If so, which treatment? **Response from Massachusetts:** Massachusetts does follow-up similar to New York's description. Noted the difficulty with typing based on symptoms, based on stage of treatment/intervention. Does not think there are tight correlations between SMN2 copy numbers and type. Therefore, until we can have more retrospective information, it will be a challenge to identify type. Also noted the need for improved case definitions. **Response from Texas:** The type of SMA was based on clinical symptoms and motor skills achieved by various ages. With interventions, typing may not be accurate **Response:** There is no correlation with SMN2, there is variability. Although more copies of SMN2 tends to result in a less severe disease**.**
3:15 pm- 3:28 pm	Participant Questions & Discussion (open dialogue) **Webinar Summary:** o Amy Gaviglio shared that some copies of SMA are being treated with gene therapy and inquired whether others thought gene

	therapy would be a helpful approach in treating other copies of SMA. o George Dizikes shared that a low copy number of SMA decreases urgency in proceeding with follow-up screening. Asked if there is a copy number where other's wait before proceeding? o The **Maryland NBS program** and George Dizikes highlighted the potential of doing a second part of this webinar to discuss how SMA copy number potentially effects treatment. o The **Illinois NBS program** is aiming to go live with SMA next June/July with multiplexing and is currently trying to differentiate between screenings for SMA versus diagnosing SMA. The program has found that some of their conversations on screening for SMA falls in line with the diagnostic part of things rather than screening. The Illinois NBS lab also shared that their genetic counselors want them to begin screening for SMA carriers, which will require reporting on a large number of carriers. The lab asked the group if there is an alternate way to report carrier information outside of PCR. **In response to the Illinois NBS lab, the panel shared:** o That only the exon 7 deletions specifically for SMA were added to Recommended Uniform Screening Panel (RUSP). No other forms of SMA are on the RUSP. o Additional testing is needed to screen for carriers. o Screening for carriers would also raise concern for many parents who may have normal genetic makeup. o Assuming other versions of SMA make an individual, a carrier is not necessarily true. o Best to go route of not identifying carriers and just screen for the disease. o **Wisconsin NBS program** shared that they started screening for SMN2 copy numbers in October 2019 using PCR. The lab inquired whether other states would be interested in developing Proficiency Testing material for SMN2. o One participant shared that for SMN1 exon 7 deletion, CDC will not be providing Proficiency Testing material and instead has been training states to prepare their own. However, this training is currently suspended. o George Dizikes shared that his lab is working with PerkinElmer to create Proficiency Testing material for his state. George asked if other state agencies are doing this with other vendors. o Mei Baker (Wisconsin) wants to plan solution to accommodate needs of SMN2 Proficiency Testing program. Mei asked if there are states currently working on SMN1 material also working in collaboration with CDC or other states.

- CDC clarified that they are working on Proficiency Testing and developing materials and that the CDC has reached out to states interested in developing these materials. CDC said that they are aiming to send out 30 specimens. The goal is to develop Proficiency Testing program and QC program. Materials will be for research use only.
- One participant shared that clinicians are not concerned with 4 or greater copies of SMA but 2 or 3 copies cause concern. However, a patient with copy 4 may have late onset.

Question: A number of reimbursements from insurers, for patients with SMA, are at the local level. For those states that have issues with infants getting insurance coverage, do we see infants with certain level of copy numbers given priority?

- **Response from Pennsylvania**: Medicaid gives priority to patients with copy 1 and 2.
- **Response:** Hold up with insurance does not seem to be based on copy number.
- **Response:** In order to attain Spinraza need to get prior authorization from doctor.

Question: One participant asked if states are categorizing SMA type as 0, 1,2,3,4, is type based on SMA copy numbers, or based on symptoms before treatment? In response to this question:

- **Response from New York**: The information currently being collected does not ask for the type of SMA. The baby is observed for symptoms.
- **Response from Massachusetts**: There may be a few babies that type in the first few weeks of life but this is a major challenge and hard to do. There are no type correlations and there need to be better case definitions.
- **Response from Texas:** The type of SMA is based on motor skills at different ages. With interventions, typing will go away. Will need to think about this differently because once intervention happens the outcome is no longer the same.

Question: Participant asked states to share what Proficiency Testing values are used and how they clarify their SMA positives.

- The **Minnesota NBS program** shared that they use a conservative cutoff of 30, higher, with reflex, or repeat. This is done just in case amplification was not great or was not working as well. There have been zero amplification of false positives. RNA P is very close to inconclusive or unsaturated weight.

	o The **Missouri NBS program** shared that his lab cutoff is 0.10 which shows that there SMA is present or not. o **Response from New York:** 30 but the lab is very dependent on reaction and master mix. o **Response from Massachusetts:** cut-off is undetermined. **Question from Massachusetts NBS program to New York NBS program: Is it correct that the New York lab has a cutoff of 30, only received 10 positives and no amplifications.** o **Response from New York:** Yes, this is correct and shared that the median is 24. o **The Massachusetts NBS program** shared that they liked the use of the multicomponent plot and that it is very important to keep language clear. Massachusetts added that the Massachusetts lab has very few retest if they had not ordered retesting for some of their not so great results. Retesting may lead to perfectly good exon and can clear sample. o **The Massachusetts NBS program** shared that the cutoff of 24 and extraction methods may be reason for lower retest rate. The quality control (PCR quantitation cycle value) for exon 7 for Massachusetts's lab is 31, which is normal population average.
3:28 pm-3:30 pm	Concluding Remarks: Amy Gaviglio, George Dizikes and Kshea Hale **Upcoming Webinar:** Spinal Muscular Atrophy (SMA) Treatment and Outcomes- Thursday, November 21 at 2:00 pm ET. Please register for this webinar online at the **SMA Treatment and Outcomes** registration page.
3:30 pm	Adjourn

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