Evidence Review of Newborn Screening for Spinal Muscular Atrophy:

Final Report from the Condition Review Workgroup (CRW)

Alex R. Kemper, MD, MPH, MS
CRW Chair
February 8, 2018

Condition Review Workgroup

Name	Role	Organization
Alex R. Kemper, MD, MPH, MS	Chair	Nationwide Children's Hospital
Anne M. Comeau, PhD	State NBS Public Health Program	New England NBS Program, University of Mass Medical School
Nancy S. Greene, MD	Clinical Care Expert	Department of Pediatrics, Columbia University Medical Center
Scott Grosse, PhD	Federal Advisor, NBS Expert	CDC
Jennifer A. Kwon, MD	Clinical Care Expert, Long-term Follow up	University of Rochester Medical Center, Department of Neurology and Pediatrics
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Lisa Prosser, PhD	Decision Analysis Leader, NBS Health Economist	Health Management & Policy/SPH; Pediatrics/Univ of Michigan Medical School
Susan Tanksley, PhD	State NBS Public Health Program	Newborn Screening Laboratory TX Department of State Health Services
K. K. Lam, PhD	Project Director	Duke University

Committee Representatives – SMA Review	
Dietrich Matern, MD, PhD	**Beth Tarini, MD, MS, FAAP**

SMA Technical Expert Panel

Jeffrey R. Botkin, MD, MPH Professor of Pediatrics Chief, Division of Medical Ethics and Humanities	**Jill Jarecki, PhD*** Chief Scientific Officer, Cure SMA *(*Nomination team)*
Michele Caggana, ScD, FAC Director, Newborn Screening Program New York State Dept of Health	**Allison Kingsley** Family Advisory Council, Family as Faculty Nationwide Children's Hospital
Richard S. Finkel, MD Chief, Division of Neurology Nemours Children's Hospital	**Kathryn J. Swoboda, MD** Director, Neurogenetics, Ped Neurology Massachusetts General Hospital
Susan T. Iannaccone, MD, FAAN Chair in Pediatric Neurology & Learning Associate Director, UT Southwestern Wellstone Muscular Dystrophy Center	

TEP Meetings

- *Sept. 2017*
- *Oct. 2017*
- *Dec. 2017*

Topics

- Case Definition
- Natural History
- Prevalence, Phenotypes
- Screening & Diagnosis
- Treatment Initiation
- Available Evidence
- Unpublished data

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Questions to Consider

- What is the prognostic implication of *SMN2* copy number?
- What is the importance of detecting compound heterozygotes and carriers?
- What is the appropriate comparator to understand the impact of newborn screening compared to usual case detection?
- How convincing are data that are not available in the peer-reviewed literature?

Reminder of our Process

- Systematic evidence review
  - Focus on data, not expert opinion
- Modeling of expected outcomes
  - Limited to available data
- Public health system impact
  - Limited to state surveys
  - Cost of screening test implementation only

Reminder of our Process

- We present the evidence but do not make recommendations

Spinal Muscular Atrophy (SMA)

- Autosomal recessive disease affecting the motor neurons in the spinal cord and brainstem, resulting in motor weakness and atrophy
- Broad phenotype spectrum ranging in age of onset (birth to adulthood), severity, and clinical course
- Many types of SMA, distinguished primarily by maximum motor milestone achieved and age of symptom onset

Spinal Muscular Atrophy (SMA)

Type (Alt Names)	Age of Onset	Clinical Features	Affected Gene(s)
SMA Type 0 *(Congenital, Prenatal SMA)*	Prenatal (30-36 weeks)	Decreased fetal movements in utero, issues with asphyxia, severe weakness at birth	**SMN1**
SMA Type I *(Severe infantile acute; Werdnig-Hoffman disease)*	Birth to six months	Cannot sit independently, difficulty breathing	**SMN1**
SMA Type II *(Infantile chronic)*	Six to 18 months	Sit independently, but cannot stand or walk	**SMN1**
SMA Type III *(Juvenile, Kugelberg-Welander disease)*	After 12 months	May stand or walk, but with progressive weakness. Wheelchair assistance usually needed in later life.	**SMN1**
SMA Type IV *(Adult-onset)*	20-30 years	Mild to moderate muscle weakness, tremor, twitching in proximal muscles; difficulty breathing	**SMN1**
X-Linked SMA	Infancy	Joint deformities that impair movement	**UBA1**
SMA-LED *(SMA-Lower extremity, dominant)*	Infancy/early childhood, progresses slowly	Leg muscle weakness, esp in thigh muscles (quadriceps), unsteady gait, difficulty climbing stairs, rising from seated position	**DYNC1H1**
Adult-onset SMA	Early to mid-adulthood	Limb and abdomen cramping and contractions, leg muscle weakness	**VAPB**

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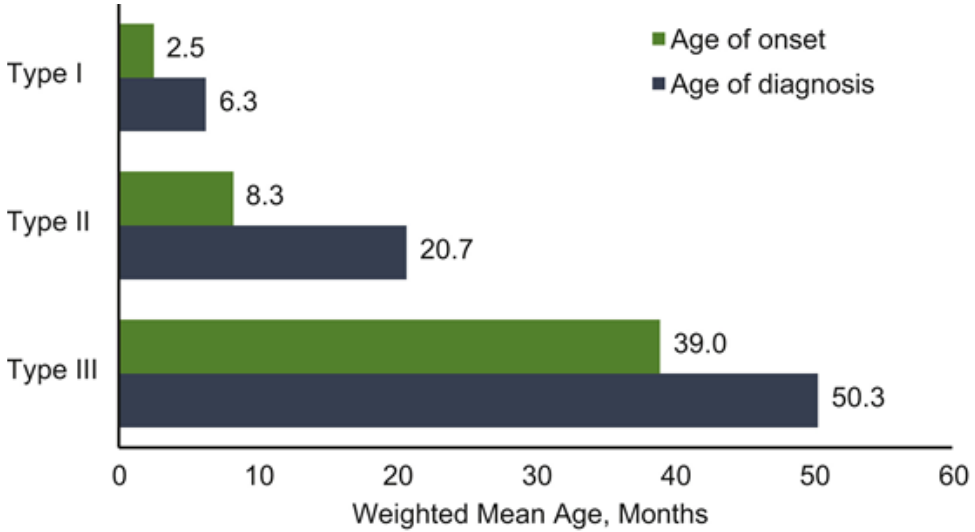
SMA – Age of Onset, Diagnosis by Type

- Review of studies 2000-2014, reporting mean ages of onset and confirmed diagnosis
- Delay in diagnosis (derived) greatest for less severe, later-onset forms



Lin et al. (2015). Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. *Pediatric neurology*. 53:293-300.

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SMA Classifications

SMA Type	Age of Onset	Highest Motor Milestone	*SMN2* Copy Number	Life Span
IA	<1 week	Never sits	1	<1 month
IB	1 week–3 months	Never sits	2, 3	<2 years
IC	3–6 months	Never sits	2, 3	<2 years
IIA	6–15 months	Sits independently Loses the ability to sit	2, 3, 4	>2 years
IIB	6–15 months	Sits independently Maintains the ability to sit	2, 3, 4	>2 years
IIIA	<3 years	Walks independently	3, 4	Adult
IIIB	>3 years	Walks independently	3, 4	Adult
IV	>21 years	Walks independently	4, 5	Adult

Munsat TL, Davies KE. Int'l SMA Consortium Meeting (26–28 June 1992, Bonn, Germany) *Neuromuscular Disorders*. 1992;2:423–428.

SMA Types and *SMN2* Copies

FIGURE 1.2 Diagram of frequency of patients with SMA Type I, II, and III by *SMN2* copy number. In 80% of children with SMA Type I, one or two copies of *SMN2* were found, 82% of patients with SMA Type II carried three *SMN2* copies, and 96% of patients with SMA Type III carried three or four copies of *SMN2*. *This image was published in Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy.* Am J Hum Genet. *2002;70(2):358–368.*

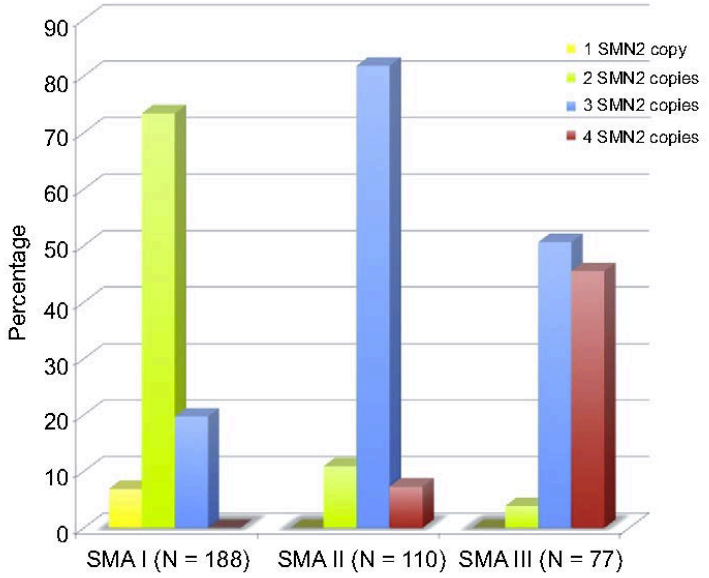

FIGURE 1.2 Diagram of frequency of patients with SMA Type I, II, and III by *SMN2* copy number. In 80% of children with SMA

Oskoui et al., 2017. Chapter 1. Spinal Muscular Atrophy: 125 Years Later and on the Verge of a Cure (pp. 3-19). In C. Sumner (Ed.). Spinal Muscular Atrophy: Disease Mechanisms and Therapy. Academic Press. https://doi.org/10.1016/B978-0-12-803685-3.00001-X

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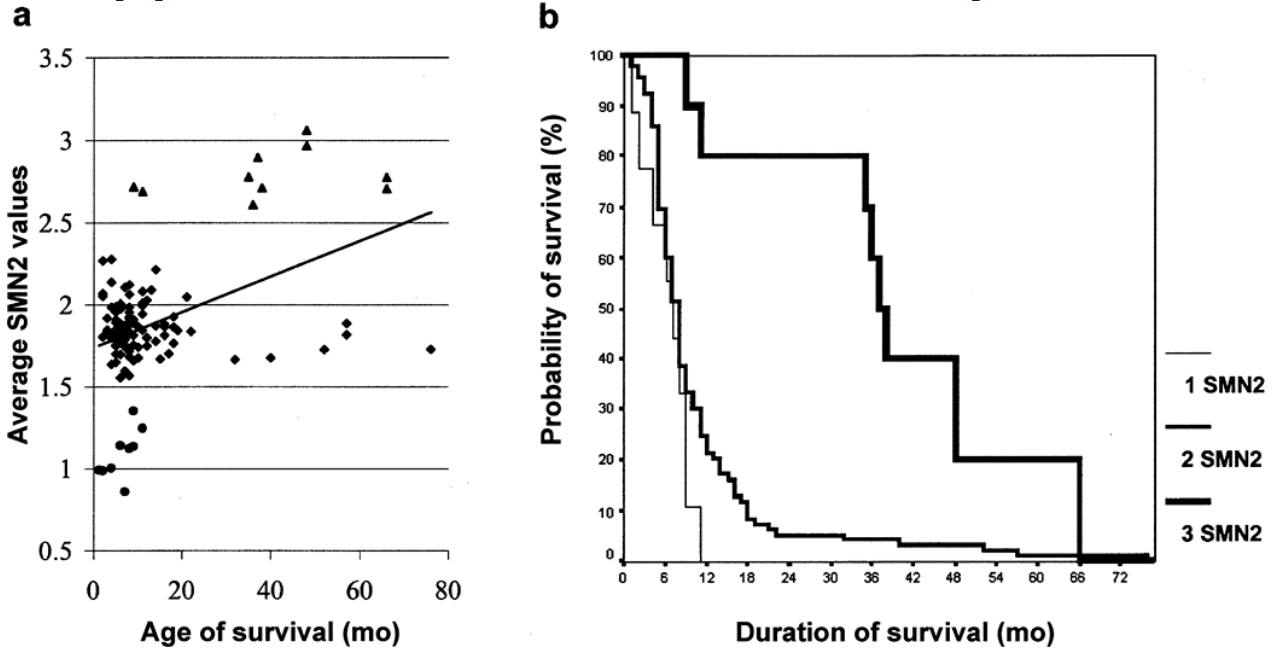
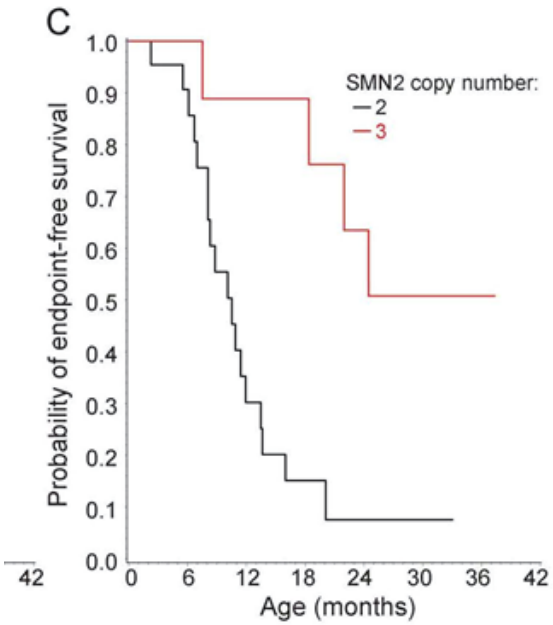
SMA Type I - Survival and *SMN2* Copies

SMN2 copy number correlates with severity and outcomes



Feldkotter et al., 2002. Quantitative Analyses of SMN1 and SMN2 Based on Real-Time LightCycler PCR: Fast and Highly Reliable Carrier Testing and Prediction of Severity of Spinal Muscular Atrophy. Am J of Hum Genet, 70, 358-368.

SMA Type I: Survival, *SMN2* Copies, Follow-up Period



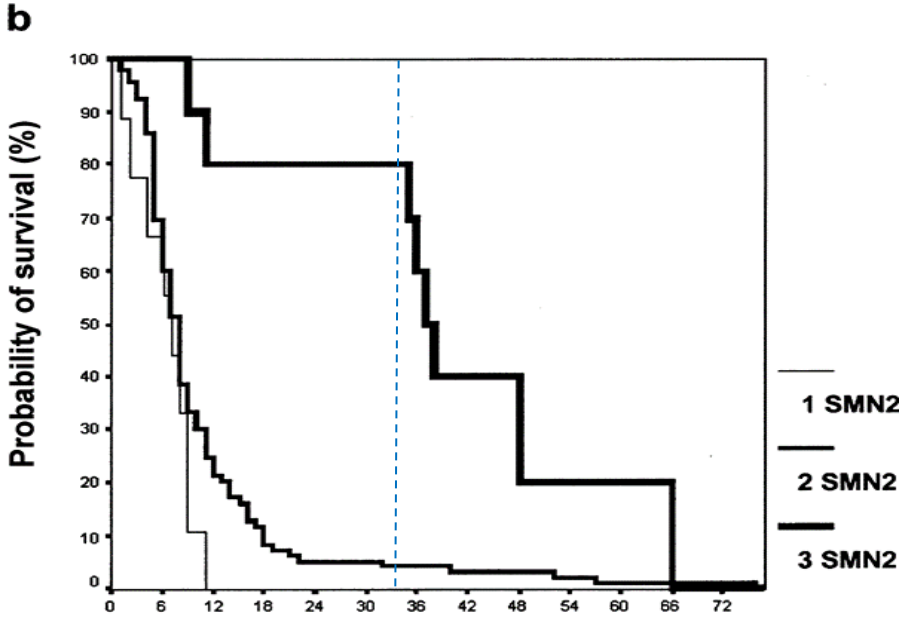
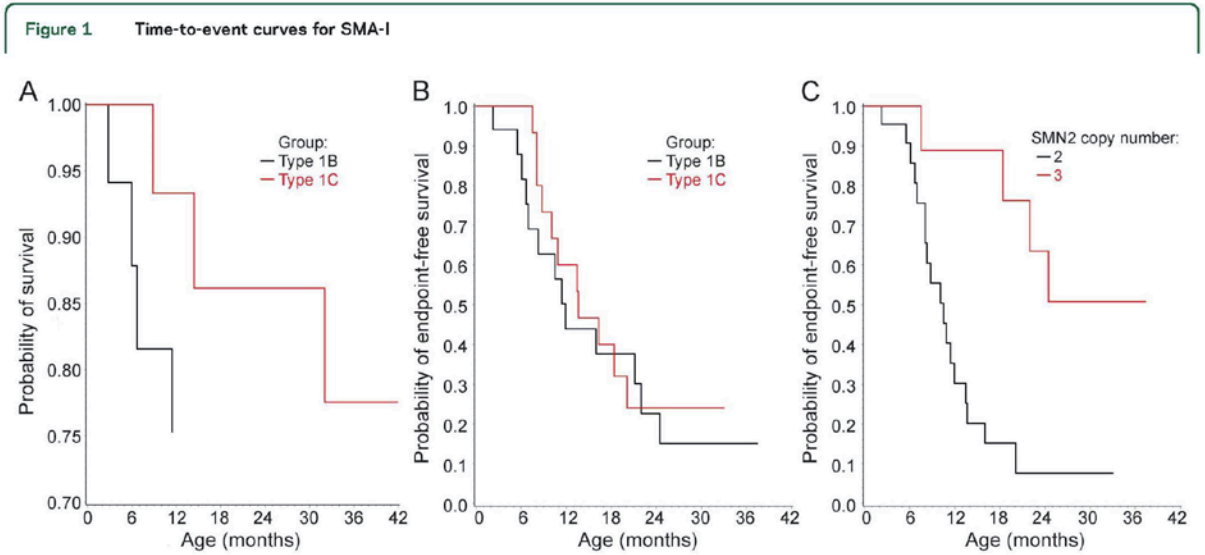


Fig c. Finkel et al. 2014. Observational study of SMA Type I and implications for clinical trials. Neurology, 83:810-817.
Fig b. Feldkotter et al., 2002. Quantitative Analyses of SMN1 and SMN2 Based on Real-Time LightCycler PCR: Fast and Highly Reliable Carrier Testing and Prediction of Severity of Spinal Muscular Atrophy. Am J of Hum Genet, 70, 358-368.

SMA Type IB, C – Survival, *SMN2* Copies

- ***SMN2* copy number correlates with severity and outcomes**



Kaplan-Meier curves for SMA-I. (A) Probability of survival with advancing age by SMA-I subtype (type IB, n = 18; type IC, n = 16). (B) Probability of not reaching the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days, in the absence of an acute reversible illness or perioperatively, with advancing age by SMA-I subtype. (C) Probability of not reaching the combined endpoint with advancing age by *SMN2* copy number (2 copies, n = 23; 3 copies, n = 9). SMA-I = spinal muscular atrophy type I.

Finkel et al. 2014. Observational study of SMA Type I and implications for clinical trials. Neurology, 83:810-817

Spinal Muscular Atrophy (SMA)

Genetics:	• Most cases due to homozygous deletion of *SMN1* exon 7 • ~5% - compound heterozygotes • Variable copy number of *SMN2* genes, which can modify the disease course
Screening:	• Screening Target: Deletion of *SMN1* exon 7 in one or both alleles
Pilots:	• New York Research Project • Taiwan newborn screening program
Diagnosis:	• *SMN1* exon 7 deletion, *SMN2* copy number, clinical exam
Specific Treatment:	• Nusinersen, FDA-approved Dec 2016

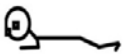
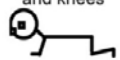
Outcome Measures

- Ventilator-free survival
- Validated Measures
  - Hammersmith Infant Neurological Examination (HINE)
    - Infants 2-24 months
    - 3 sections: neurologic examination, developmental milestones, behavioral assessment
  - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    - Children 4 months-4 years
    - Developed to assess SMA

HINE-2

- 8 domains (milestones)
- Total possible score, 34
  - *(26 points, HINE-2*, Finkel et al 2017)*
- % Milestone Responders

Infant Group	HINE-2 Score range (age at assessment)
‡Infants with no known perinatal risk (n=135)	24 – 34 (12 months) 31 – 34 (18 months)
Infants with SMA Type I †Untreated	0–3 (2 - 24 months)
††Treated/Nus, ClinDet	0 – ~17 (~6 -13 months) *[0-26 possible points]*

Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m
Rolling	No rolling	Rolling to side (normal at 4m)	Prone to supine (normal at 6 m)	Supine to prone (normal at 6 m)	
Crawling or bottom shuffling	Does not lift head	On elbow  (normal at 3 m)	On outstretched hand  (normal at 4m)	Crawling flat on abdomen  (normal at 8m)	Crawling on hands and knees  (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

‡Haataja et al. 1999. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J of Peds.,135, 153-161.

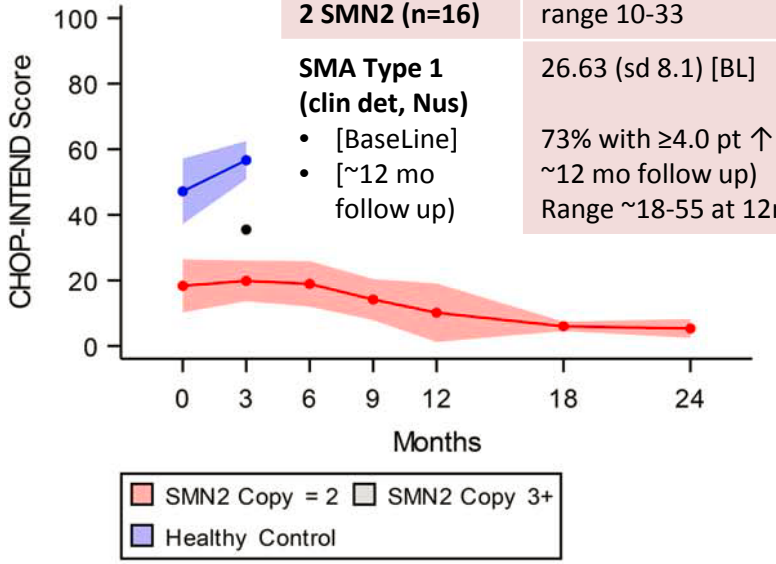
†De Sanctis et al. 2016. Developmental milestones in type I SMA. *Neuromuscular disorders* ,:26:754-759.

††Finkel et al., 2017. Nusinersen versus Sham Control in Infantile-Onset SMA. NEJM., 377:1723-1732.

CHOP INTEND

- 16 domains
- Total Possible Score, 64
  - Upper extremity spontaneous movement
  - Lower extremity spontaneous movement
  - Hand grip
  - Head in midline with visual stipulation
  - Hip adductors
  - Rolling elicited from legs
  - Rolling elicited from arms
  - Shoulder and elbow flexion and horizontal abduction
  - Shoulder flexion and elbow flexion
  - Knee extension
  - Hip flexion and foot dorsiflexion
  - Head control
  - Elbow flexion
  - Neck flexion
  - Head/neck extension
  - Spinal incurvation

CHOP-INTEND SCORES	
Healthy Infants (n=14)	50.1 (sd 10.2) range 32-62
SMA Type 1, 2 SMN2 (n=16)	20.2 points (sd 7.4) range 10-33
SMA Type 1 (clin det, Nus) • [BaseLine] • [~12 mo follow up)	26.63 (sd 8.1) [BL] 73% with ≥4.0 pt ↑ at ~12 mo follow up) Range ~18-55 at 12m)



Finkel et al. 2017. Nusinersen versus Sham Control in Infantile-Onset SMA. NEJM. 377:1723-1732.

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Screening Approaches

	Taiwan	New York (Research Pilot)
Question Asked	Is *SMN1* there?	Is *SMN1* there and if so, how does its quantity relate to other genes?
Testing	• a region of *SMN1* is targeted for amplification • amplification generates a fluorescent signal • if the fluorescent signal is sufficient, there is amplification and SMN1 is present. • The housekeeping gene (RNaseP) is only used to know that the specimen has amplifiable DNA	• A region of *SMN1* and a region of a housekeeping gene are targeted for amplification. Amplifications generate two different fluorescent signals • The intensity of the two signals are compared. If the signals are equal, there are 2 copies of *SMN1*. If the SMN1 signal is half that of RNaseP, there is one copy of *SMN1* (potential carrier). If the *SMN1* signal is less than half that of RNaseP, *SMN1* is likely not there (likely case) • All potential carriers are sequenced in order to determine whether the *SMN1* copy that appears to be there has a sequence variant that would make it one of the compound heterozygotes
Carrier Detection	No	Yes

Screening Approaches

- CDC-Developed Assay
  - qPCR targeting *SMN1* exon 7 deletion
  - Does not detect carriers
  - Can be multiplexed with SCID screening
  - CDC offers consultation, technical support, and reference materials

Systematic Evidence Review: SMA Published Literature – 2000 through June 2017, Update through Jan 12, 2018

- Keywords: "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]) *AND* "Pediatrics"[Mesh] *AND Limits: English.*
- Articles published 2000 to Jan 2018 (n=2782)
  - PubMed (n=1414 + 87)
  - EMBASE (n=705+186)
  - CINAHL (n=215+34)
  - Cochrane (n=113+18)
- Articles included: 240 review and synthesis
- Articles Abstracted and Assessed:
  - Treatment – 4 Nus, 2 exp.
  - Screening pilots – 2
  - (+ 4 grey lit)

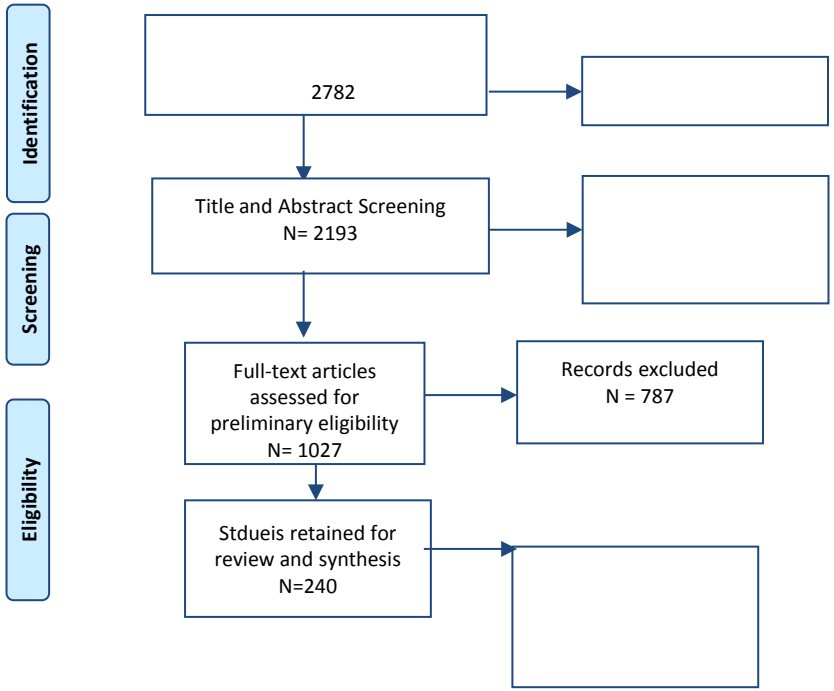

Figure 1. Preliminary PRISMA Diagram of Published Literature Search

SMA Systematic Evidence Review

- 4 of the 7 Key treatment and screening articles were published during the review (after Nov 2017)
- 5-8 key background articles reviewed and included published after Nov 2017
- 4 Grey literature/Conference presentations/posters included

SMA Newborn Screening Publications

Screening Pilot	NY State Pilot	Taiwan Pilot	Prior/Pilot with Anonymous DBS
Publication	Kraszewski et al. (2017), *Genetics in Medicine*.	Chien et al. (2017), *Journal of Pediatrics*	Prior et al. AJMG (2010).
Screening Results	n=3,826 newborns PPV = 100% FPR = 0% first tier positives = 1 second tier positives = 1 (1 in 3,826) heterozygous carriers = 59 (1 in 65, 1.5%) dates 1/2016 – 1/2017	n=120,267 newborns PPV = 100% FPR = 0% first tier positives = 15 second tier positives = 7 (1 in 17,181) heterozygous carriers = not detected dates = 11/2014 – 9/2016	n=40,103 Anonymous DBS (OH) PPV=100% FPR=0% First 'tier' = 7 required repeat testing Second tier positives = 4 (1 in 10,026) confirmed by genetic testing on DBS dates *NR*

DBS=Dried blood spots, SMA=Spinal Muscular Atrophy, SMN=Survival Motor Neuron, PPV=Positive Predictive Value, FPR=False-positive rate, FNR=False-negative rate

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DBS=Dried blood spots, SMA=Spinal Muscular Atrophy, SMN=Survival Motor Neuron, PPV=Positive Predictive Value, FPR=False-positive rate, FNR=False-negative rate

Screening Results

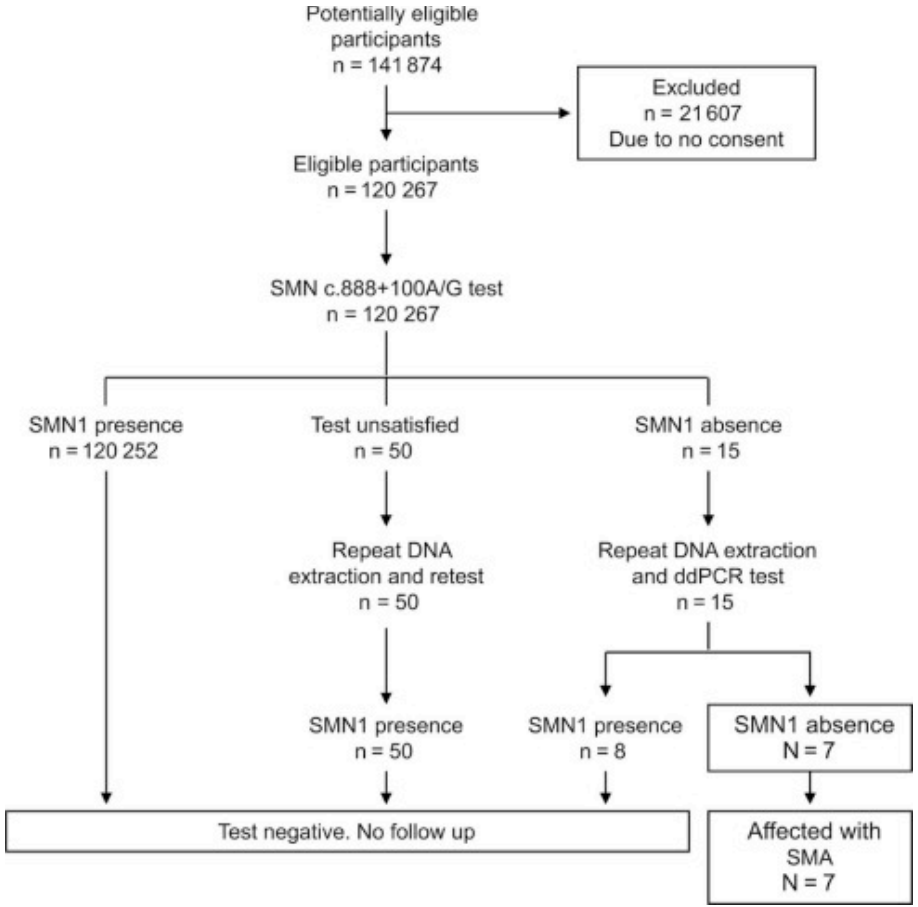
- New York: Updated January 2018
  - Total Screened: 10,362
    - False Positives: 0
    - Carriers: 144 (1:72 or 1.4%)
    - Cases of SMA: 1 (Homozygous deletion, 2 *SMN2* copies)
      - Diagnosed at age 7 days
      - First nusinersen treatment at 15 days
      - By 12 months of age, by report, no mechanical ventilation, developmental milestones met

Kraszewski et al. (2017). Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genetics In Medicine*
Updates – personal communication, Caggana Jan 2018.

Taiwan Pilot

- National Taiwan University Hospital newborn screening Center
- Feasibility trial for pre-symptomatic diagnosis of SMA
- Dates Nov 2014 – Sept 2016 *(before nusinersen approval)*

Taiwan – SMA Screening Algorithm



- 84.7% of parents approached gave consent for screening
- 1st tier (RT-PCR TaqMan SNP for SMN1 exon 7 deletion) positives (n=50 unreadable, n=15 1st tier positive)
- 2nd tier (ddPCR, MLPA) – 7 confirmed homozygous deletions of SMN1, 8 not homozygous deletions false positives, confirmed 7 *SMN1* homozygous deletions
- False negative rate (thus far reported)- 0%

Chien et al. (2017). Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening. Journal of Pediatrics

Screening Results

- Taiwan
  - Total Screened: 120,267
    - Test Unsatisfactory Retests: 50
    - Tier-One Positive: 15
    - Tier-Two Positive and Confirmed: 7
- Estimated Incidence: 1:17,181 (95% CI: 1 in 8,323 to 35,468)

Chien et al. (2017). Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening. Journal of Pediatrics

Taiwan Pilot: Follow up

- 7 SMA Patients
  - 6 presymptomatic at birth
  - Median age of diagnosis: 8 days of life (range: 4 – 11 days)

Table II. Outcomes of patients identified by newborn screening

Patients	*SMN2* copy number	Age at diagnosis, d	Condition at diagnosis	Age at latest visit, mo	Condition at latest visit
1	4	11	Normal	25	Normal
2	3	4	Normal but with imperforate anus	23	Walk with bilateral support at 13 mo, tongue fasciculation since 13 mo, unable to walk at 17 mo
3	2	4	Poor sucking and swallowing, no movement, on ventilator	3	Died at age 3 mo
4	2	7	Normal	1.5	Unable to kick since 1 month of age
5	4	11	Normal	2.5	Normal (older brother has SMA III diagnosed at age 2.5 y)
6	2	8	Normal	8	On trial treatment at age 3 wk, decrease in muscle power at 3 wk
7	3	11	Normal	6	Normal, on trial treatment since age 1.5 mo

Chien et al. (2017). Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening. Journal of Pediatrics

Treatment: Olesoxime

- One trial – rated strong quality
  - Subjects: 3-25 years old with Type 2 or Type 3 SMA
  - 108 randomized to olesoxime, 57 to placebo
  - After 25 months, no difference in motor outcome (p=0.0676)

Bertini et al. 2017. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 SMA: a randmised, led phase 2 trial. *The Lancet Neurology.*

Treatment – Gene Therapy

- Phase 1 study, infants with type 1 SMA, *2 copies SMN2*
- Single dose treatment
- Low (n=3) and High Dose (n=12)
- Moderate quality (lack of information about blinding of assessments)

Table 1. Demographic and Clinical Characteristics of the 15 Patients.*

Characteristic	Cohort 1 (N=3)	Cohort 2 (N=12)
Mean age (range) — mo	6.3 (5.9–7.2)	3.4 (0.9–7.9)
Mean weight (range) — kg	6.6 (6.0–7.1)	5.7 (3.6–8.4)
Sex — no. (%)		
Male	1 (33)	5 (42)
Female	2 (67)	7 (58)
Race — no. (%) †		
White	3 (100)	11 (92)
Other	0	1 (8)
Mean age at symptom onset (range) — mo	1.7 (1.0–3.0)	1.4 (0–3.0)
Mean age at genetic diagnosis (range) — days‡	33 (4–85)	60 (0–136)
Mean score on CHOP INTEND scale (range)§	16 (6–27)	28 (12–50)
Patients with clinical support — no. (%)		
Nutritional	3 (100)	5 (42)
Ventilatory	3 (100)	2 (17)

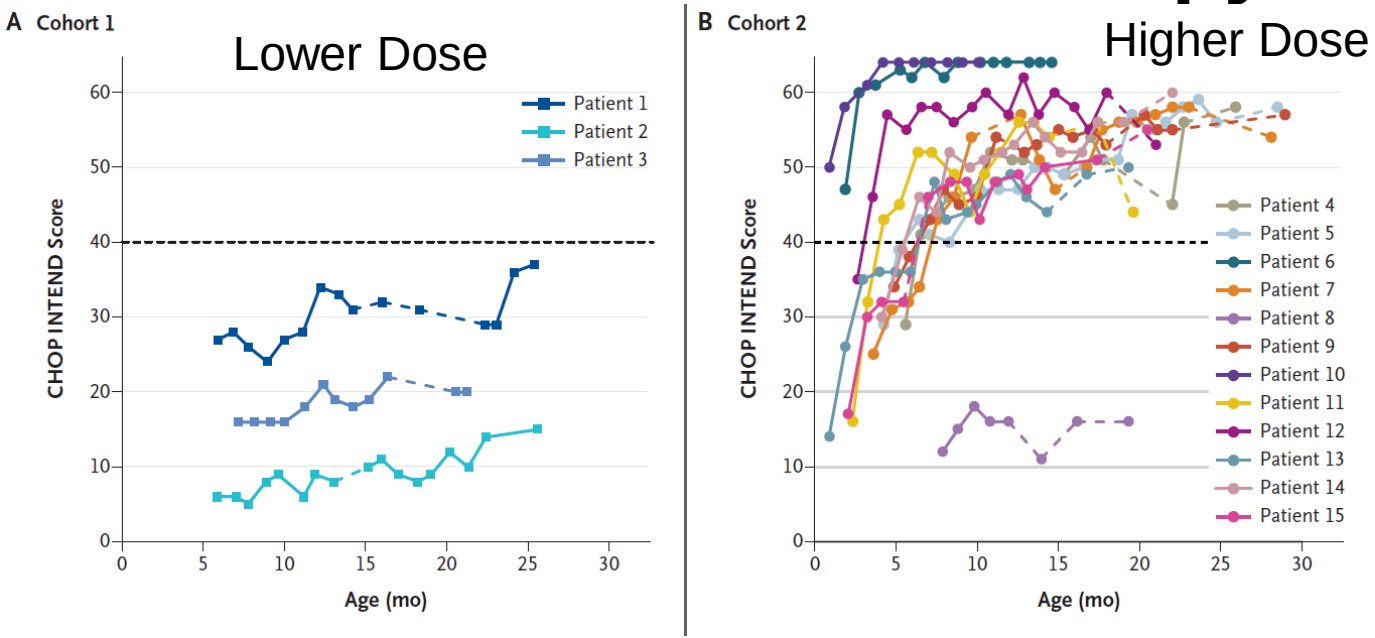
Mendell et al. 2017. Single-Dose Gene-Replacement Therapy for SMA. *NEJM.* 377:1713-1722.

Treatment - Gene Therapy Phase 1 Outcomes

- Event-Free Survival:
  - 100% EF Survival at age 20 months (20.6 – 32.4 months) *(8% in comparable natural history group)*
- Motor Function:
  - All increased scores (CHOP INTEND) from baseline
  - High dose group:
    - mean increases of 9.8 and 15.4 points at 1 and 3 months, 24.6 points at study cutoff (20 -32 months of age).
    - 11 of 12 attained CHOP INTEND motor scores >40 points
    - Milestones achieved
      - 11 could sit unassisted for 5 seconds
      - 9 could sit unassisted for at least 30 seconds
      - 11 had head control
      - 9 could roll over
      - 2 could walk independently
      - 11 could speak

Mendell et al. 2017. Single-Dose Gene-Replacement Therapy for SMA. *NEJM.* 377:1713-1722.

Treatment – Gene Therapy



- All increased scores (CHOP INTEND) from baseline
- Cohort 2: 11 of 12 attained CHOP INTEND motor scores >40 points

Mendell et al. 2017. Single-Dose Gene-Replacement Therapy for SMA. *NEJM.* 377:1713-1722.

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Treatment - Nusinersen

- Only FDA-approved treatment
- Alters splicing of the *SMN2* pre-mRNA, increasing the amount of functional SMN protein

Treatment - Nusinersen

- Overview of manufacturer-funded studies
  - CHERISH: Phase 3 trial in subjects with later-onset SMA
  - ENDEAR: Phase 3 trial in subjects with infantile-onset SMA
  - NURTURE: Phase 2 open-label study of subjects with pre-symptomatic SMA
  - EMBRACE: Phase 2 open-label study of subjects not eligible for other studies
  - SHINE: Open-label extension study

Treatment - Nusinersen

- Overview of manufacturer-funded studies
  - CHERISH: Phase 3 trial in subjects with later-onset SMA
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  - NURTURE: Phase 2 open-label study of subjects with pre-symptomatic SMA
  - EMBRACE: Phase 2 open-label study of subjects not eligible for other studies
  - SHINE: Open-label extension study

Treatment – Nusinersen: Infantile-Onset Trial

- Phase 3 trial (strong quality)
- Subjects
  - Symptoms before 6 months of age
  - Screening for study participation by 7 months of age
  - Two copies of *SMN2*

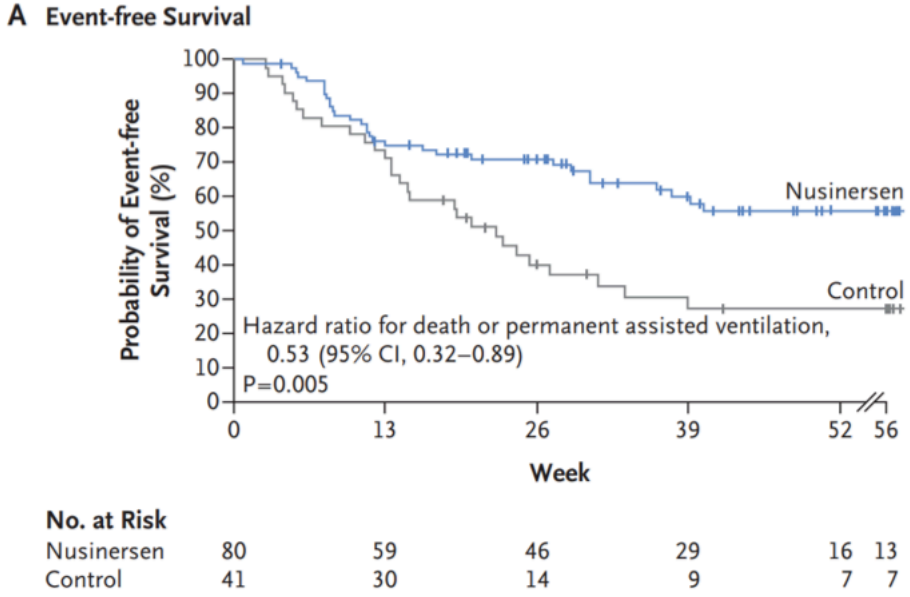
Finkel et al. 2017. Nusinersen versus Sham Control in Infantile-Onset SMA *The New England Journal of Medicine.* 377:1723-1732.

Treatment – Nusinersen: Infantile-Onset Trial

- Study terminated early
  - 80 in treatment group, 41 in the control group who received at least one intervention
- Event-free survival
  - Nusinerson Group: 61%; Control Group: 32%

Finkel et al. 2017. Nusinersen versus Sham Control in Infantile-Onset SMA *The New England Journal of Medicine.* 377:1723-1732.

Treatment – Nusinersen: Infantile-Onset Trial



Finkel et al. 2017. Nusinersen versus Sham Control in Infantile-Onset SMA. *The New England Journal of Medicine.* 377:1723-1732.

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Treatment – Nusinersen: Infantile-Onset Trial

- Motor-milestone response
  - Nusinersen Group: 41%; Control Group: 0%
- Response included
  - Full head control: 22%
  - Rolling over: 10%
  - Independent sitting: 8%
  - Standing: 1%

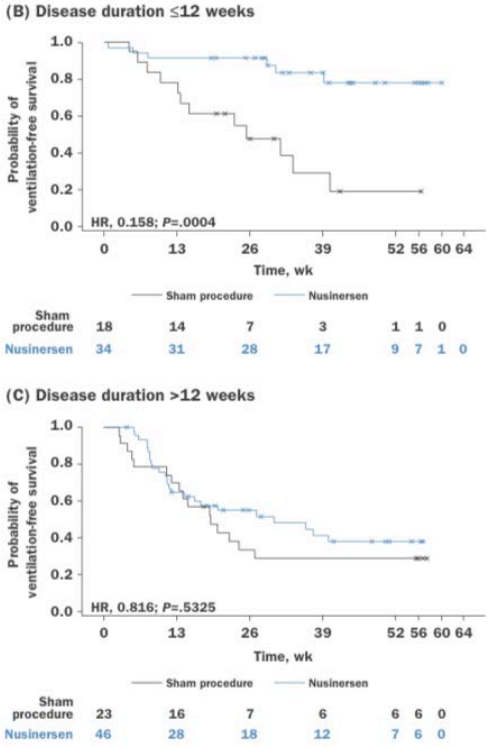
Finkel et al. 2017. Nusinersen versus Sham Control in Infantile-Onset SMA. *The New England Journal of Medicine.* 377:1723-1732.

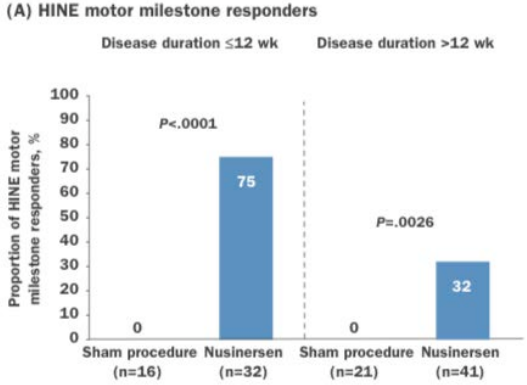
Treatment – Nusinersen: Infantile-Onset Trial

Grey literature suggests those with total disease duration ≤12 weeks before nusinersen treatment were more likely to have better outcomes than those with longer periods of disease duration

Servais et al. 2017. *Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With SMA*. Poster presented at the 22nd International Annual Congress of the World Muscle Society, 3-7 October 2017. Saint Malo, France.

Treatment – Nusinersen: Infantile-Onset Trial





Servais et al. October 2017. *Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With SMA*. Poster presented at the 22nd Int'l Annual Congress of the World Muscle Society, 3-7 October 2017. Saint Malo, France.

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Treatment - Nusinersen

- No peer-reviewed published reports comparing presymptomatic detection to usual clinical detection
- However, multiple presentations and abstracts from the ongoing phase 2 study of presymptomatic individuals

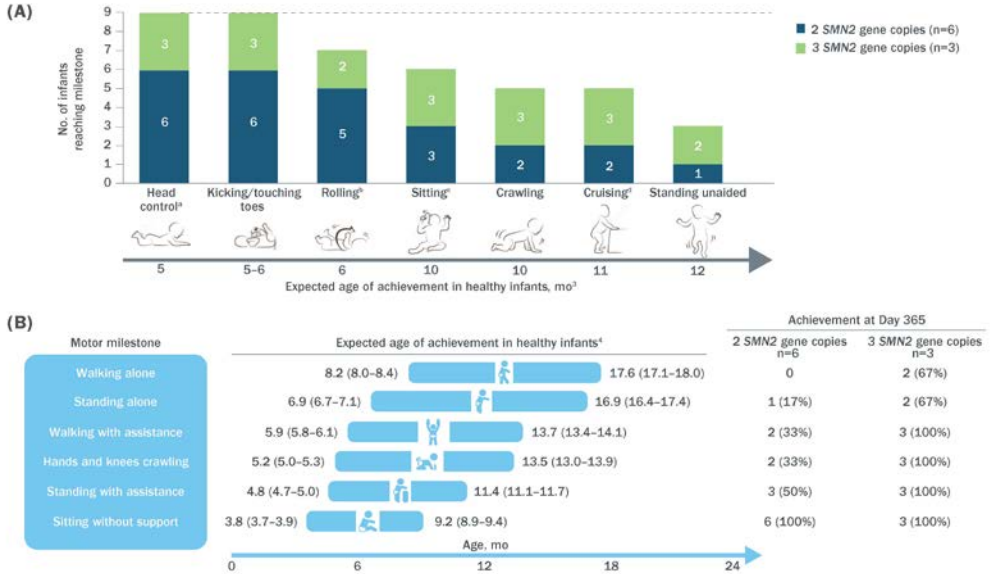
Treatment – Nusinersen: Presymptomatic

- Treatment ≤ 6 weeks
  - From one presentation: 20 subjects
    - 15: sibling
    - 3: Newborn screening
    - 1: Prenatal screening
    - 1: Other family member a known carrier

De Vivo et al. April 2017. *Interim efficacy and safety results from the Phase 2 NURTURE study evaluating nusinersen in presymptomatic*

Treatment – Nusinersen: Presymptomatic

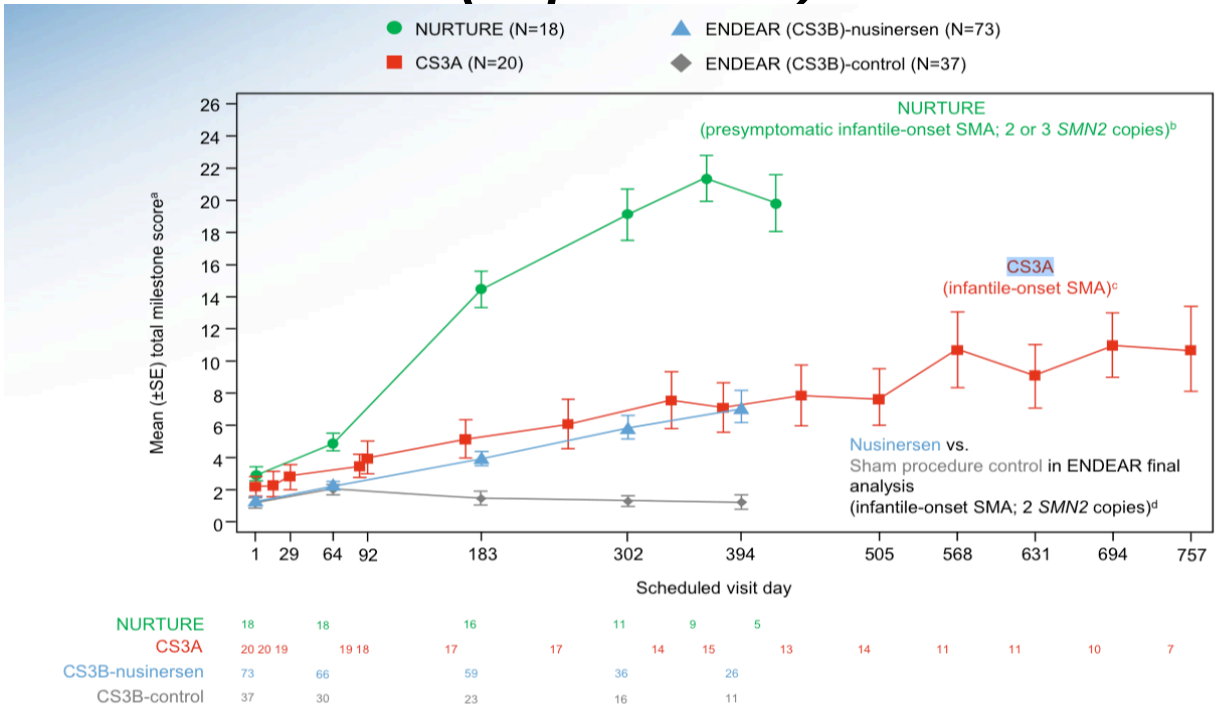
- At one year: 9/9 alive, motor development appears to be a function of *SMN2* copy numbers



Hwu et al. Oct 2017. *Outcomes After 1 Year of Treatment in Infants Who Initiate Nusinersen in a Pre-symptomatic Stage of SMA: Interim Results From the NURTURE Study*. Poster presented at the 22nd Int'l Annual Congress of the World Muscle Society, 3-7 October 2017. Saint Malo, France.

Treatment – Nusinersen: Overall

*(Unpublished)**

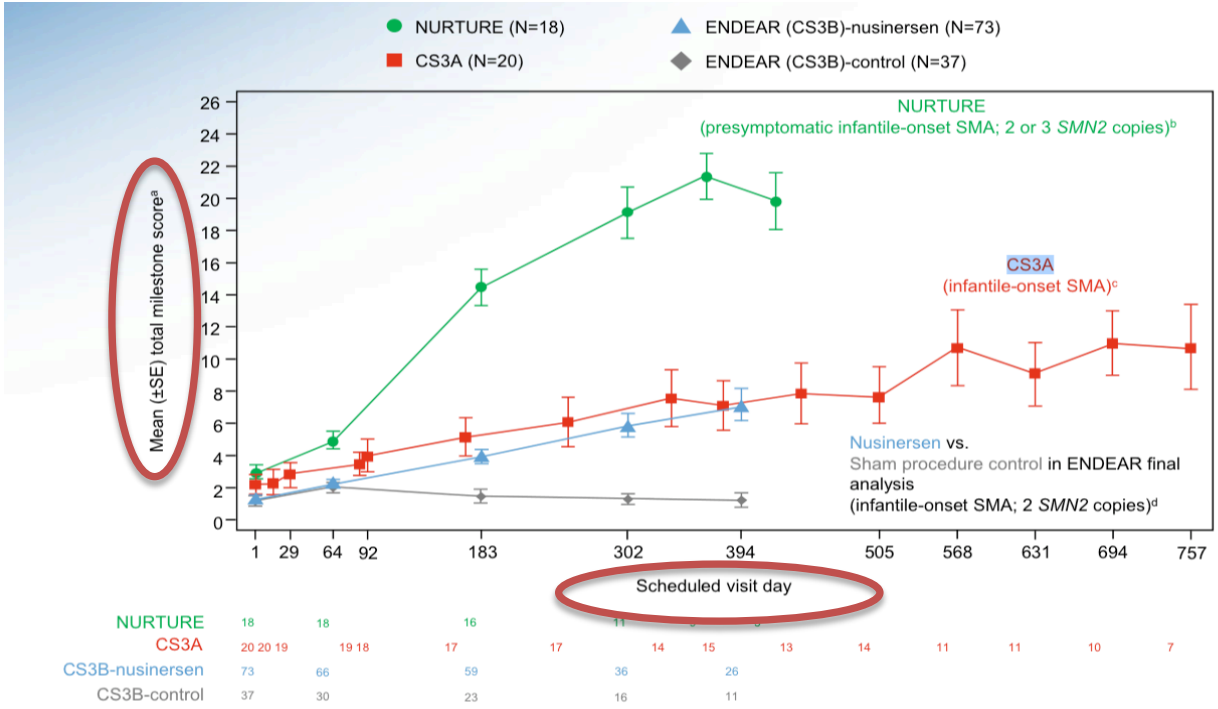


Crawford TO. July 2017. Efficacy and Safety of Nusinersen in Genetically Diagnosed Infants With Presymptomatic SMA: Results From the 2nd Interim Analysis of the Ongoing, Phase 2 NURTURE Study. *Presented at the 2017 Annual SMA Conference Orlando, FL. June 29-July 2,* 2017. (Unpublished).

Kuntz et al. April 2017. Nusinersen in Infants Diagnosed with SMA: Study Design and Initial Interim Efficacy and Safety Findings from the Phase 3 Int'l ENDEAR Study. *Presented at the 69th Annual Meeting of the American Academy of Neurology April 22–28, 2017. Boston, MA.*

Treatment – Nusinersen: Overall

(Unpublished)



Crawford TO. July 2017. (Unpublished).
Kuntz et al. April 2017.

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Treatment – Nusinersen: Overall

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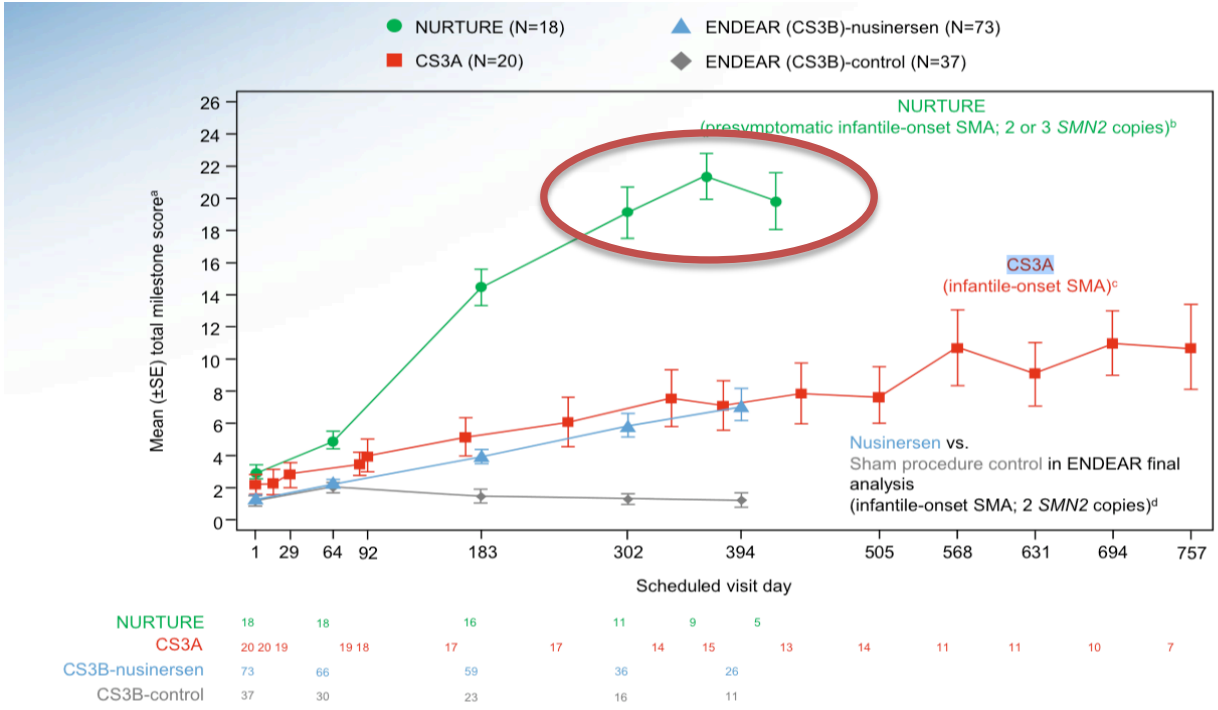

Crawford TO. July 2017. (Unpublished).
Kuntz et al. April 2017.

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Key Points

- Screening can detect cases of SMA in newborns
  - Compound heterozygote and carrier detection?
- Treatment can modify the course of SMA
  - Few data regarding presymptomatic identification
  - Presymptomatic treatment alters the “natural history”
  - Outcomes generally limited to around the first year of life
  - Magnitude of motor development changes difficult to assess
  - More work is needed to understand the role of *SMN2* copy number for risk stratification or prognosis

Additional Information

- Treatment guidelines have been developed by an “SMA NBS Multidisciplinary Workgroup” using a modified Delphi technique with 13 voting members*
- The Project Cure SMA Data Repository, including longitudinal natural history data as well as data from investigator-initiated clinical trials will reside in the LPDR Data Commons (Swoboda)

*Glascock et al. under review, 2018. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *Manuscript submitted for publication.*

Population-Level Outcomes for Newborn Screening of Spinal Muscular Atrophy

Lisa A. Prosser, Ph.D., M.S.

February 8, 2018

Background: Decision analysis

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Explicitly identify assumptions and key areas of uncertainty

Modeling analysis

Overall goal: To quantify screening outcomes and health outcomes for newborn screening of SMA compared with clinical identification

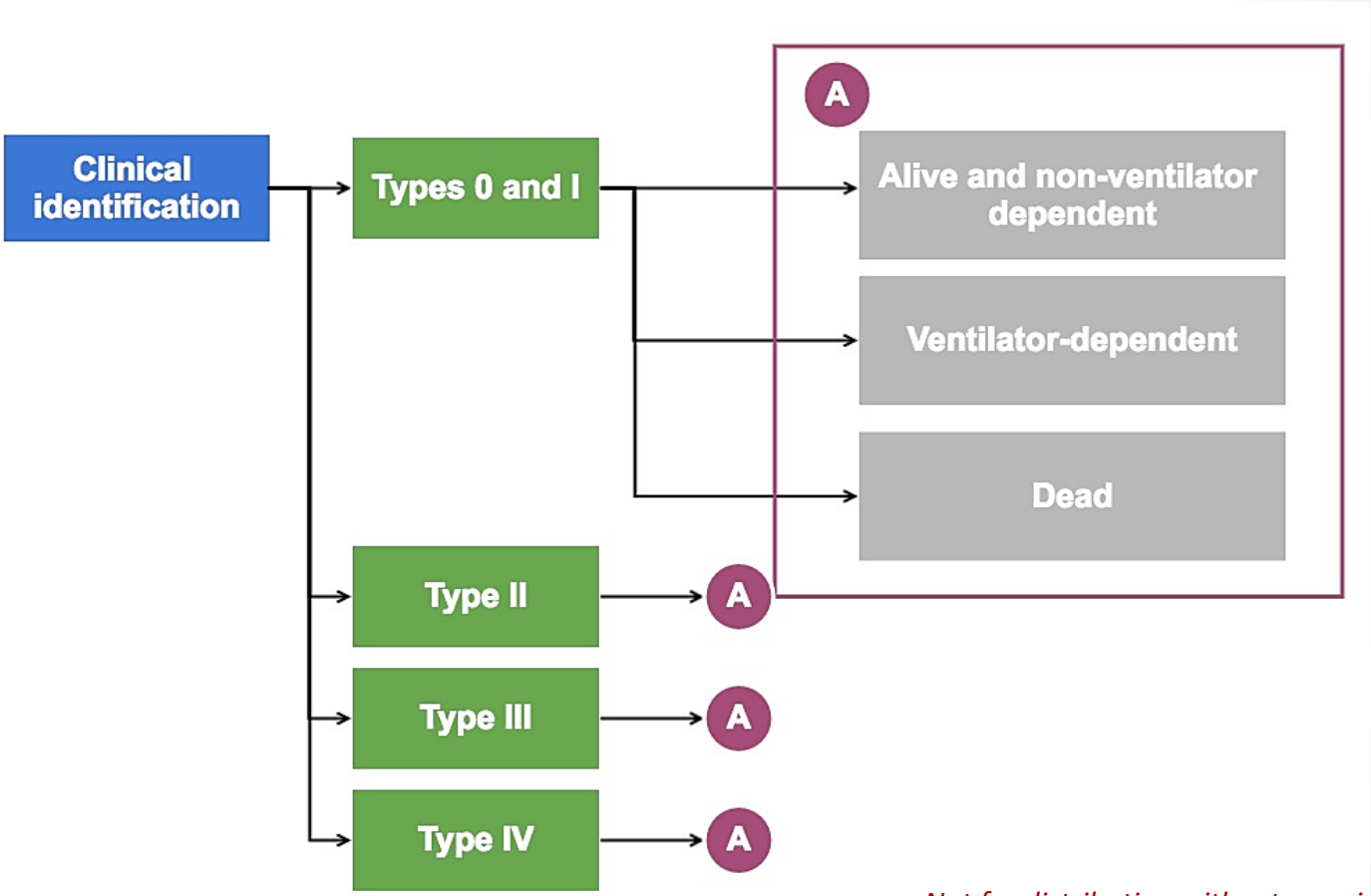
Health outcomes

- Mortality
- Ventilator-dependence
- Motor function (not modeled)

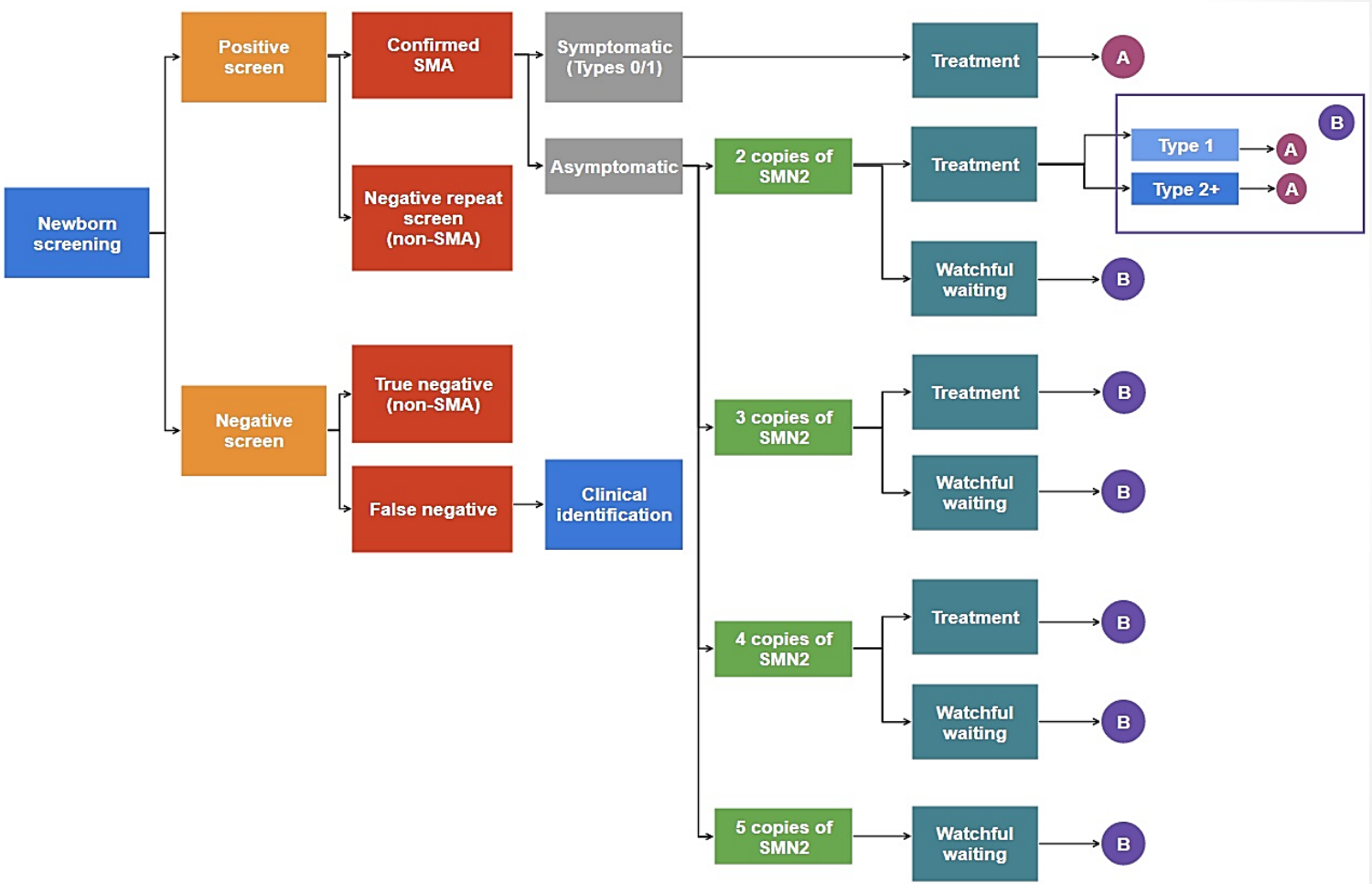
Scope

- Focus on SMA Type I
  - Projected cases identified
  - Projected health benefits
- Quantify screening outcomes and projected cases for “non-Type I”
- 1-year endpoints

Model Schematic: CI Submodel



Model Schematic: NBS Submodel



Modeling Assumptions

- Screening projections based on NY pilot program
- Other model inputs derived from evidence review, expert panel, assumptions, Taiwan pilot
- Potential benefits of earlier treatment include:
  - Improved survival
  - Improved respiratory (modeled) and motor function (not modeled)
- Estimates of treatment effectiveness
  - Symptomatic: Early v. late treatment (ENDEAR)
  - Asymptomatic: Single-arm trial (NURTURE)

Results: Annual Cases of SMA identified[1,2]

	Clinical Identification	NBS
SMA Type I	196 (82-413)	196 (82 - 413)
Symptomatic	196 (82-413)	45 (1 - 192)[3]
Asymptomatic	--	151 (133 - 363)[3]
SMA Type II+	167 (70 - 351)	167 (70 - 351)[4]
Total SMA	**364 (152 - 764)**	**364 (152 - 764)**

[1]Assuming healthy annual newborn cohort of 4 million, not at higher risk of SMA
[2]Ranges represent one-way sensitivity analysis on each parameter
[3]By 11 days of life
[4]All asymptomatic at time of diagnosis (11 days)

Results: Outcomes at 52 Weeks, Type I SMA1[1,2]

	Clinical Identification	NBS	Cases or Deaths Averted
Ventilator-dependent cases	52 (17 - 109)	4 (0 - 18)	48 (16 - 100)
Deaths	36 (15 - 75)	3 (0 - 13)	33 (14 - 68)

[1]Assuming healthy annual newborn cohort of 4 million, not at higher risk of SMA
[2]Ranges represent one-way sensitivity analysis on each parameter

Summary

- Projected population-level outcomes
  - 364 (range: 152 - 764) cases of SMA identified annually
  - 196 (range: 82 - 413) Type I SMA cases identified
  - Reduced deaths and cases of ventilator-dependence for newborn screening compared with clinical identification for Type I SMA
- Additional benefits will likely accrue to other subtypes
- Limited data for modeling:
  - 52 weeks treatment effectiveness
  - 52 weeks for “new” natural history
  - Uncertainty for long-term outcomes

Analysis. Answers. Action.

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Public Health System Impact Assessment

Spinal Muscular Atrophy (SMA)

Jelili Ojodu, MPH

February 8, 2018

Overview

- Background
- Role of APHL
- Methods
- Results
- Summary

Public Health System Impact: Background

- Recommendations are based on
  - Certainty of net benefit.
  - Feasibility and Readiness of implementing comprehensive newborn screening.

Definition of Readiness

- Ready
  - Most NBS programs could implement within 1 year.
- Developmental Readiness
  - Most NBS programs could implement within 1–3 years.
- Unprepared
  - Most NBS programs would take longer than 3 years to implement.

Components of Feasibility

- An established and available screening test.
- A clear approach to diagnostic confirmation.
- Acceptable treatment plan.
- Established approach to long-term follow-up.

Why is this Assessment Important?

- Opportunity to
  - Understand both the “real world” barriers and the facilitators related to screening.
  - Evaluate opportunity cost.

Methods

- SMA factsheet.
- Webinar and outreach.
- Survey to 53 US states and territories + DC.
- Informant interviews with 5 state NBS programs that are conducting/planning pilots, or have mandates for SMA newborn screening; conducted a sixth interview with a state NBS program that is not screening for Severe Combined Immunodeficiency (SCID).

NBS Programs with Mandates/Pilots

State	Target Start	Select or Whole Pop	Funds	Method	Carriers	Costs
*Massachusetts	Jan/Feb 2018	Whole PILOT	N/A	RT-PCR	Will not report	N/A
Minnesota	Mar 2018	Whole	None identified	RT-PCR (CDC)	Will not report	< $1.00
Missouri	Dec 2018	Whole, no reporting initially	None identified	RT-PCR (CDC)	Undecided	~$1.00
North Carolina	Apr 2018	Select, research PILOT, consent	NICHD contract	RT-PCR (CDC)	Will not report	N/A
New York	Jan 2016	Select- 3 hospitals, consent, PILOT	Biogen	RT-PCR with outside confirm; second tier ddPCR	Reporting for pilot; Undecided future	.15-$1.00
*Utah	Jan/Feb 2018	Whole		RT-PCR, TREC/SCID	--	--
Wisconsin	May 2018	Whole population PILOT	Cure SMA Grant	RT-PCR (CDC); possible second tier ddPCR	Will not report	N/A

(*) MA and UT did not complete interviews. Other info sources.
RT=Realtime; PCR=Polymerase Chain Reaction; dd=digital droplet

Results: Interviews

Challenges from NBS programs conducting pilots, planning pilots and those with mandates:

- Legislative buy-in and approval for funds.
- Reporting algorithm (reporting carriers or not).
- Securing genetic counseling resources.
- Establishing relationships with new group of specialists (pediatric neurologists).
- Ensuring that patients have access to evaluation and treatment.

Results: Interviews

Factors aiding implementation from NBS program screening:

- Existing infrastructure/expertise.
- Ability to multiplex with SCID.

Results: Interviews

- Basic cost information was gathered from five NBS program directors (program conducting pilot, those planning pilots and those with mandates).
- It was estimated that the addition of SMA will add between 10 cents and $1 to the cost of the NBS test when multiplexed with SCID.

Results: Interviews

- The higher end of the 10 cents to $1 range for the addition of SMA was from a program that is currently considering purchasing equipment (i.e., digital droplet PCR) to include second-tier screening to assess *SMN2* copy number.
- Purchase of this equipment was estimated at approximately $93,000 to $140,000 in the start-up year, and about $50 per specimen for each affected baby.

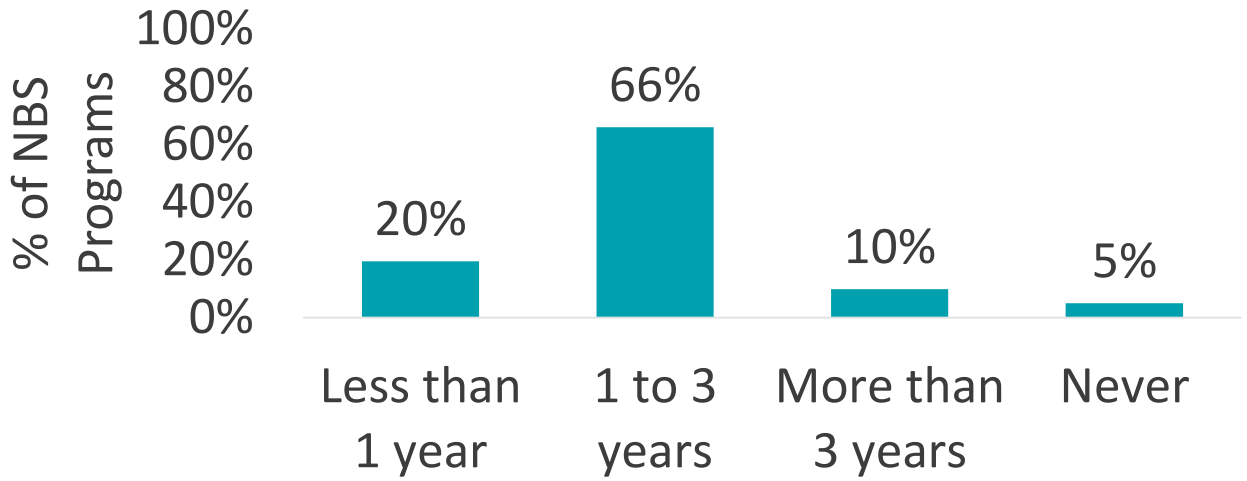
Results: Interviews

- Additional marginal costs to screen included expenses for disposable supplies (i.e., reagents, primers, probes) and added labor for laboratory technician (ranging from 0 to 1.0 FTE initially) and short-term follow-up (ranging from 0-0.3 FTE initially).
- Sustained screening labor costs are more difficult to estimate.

Results: Survey

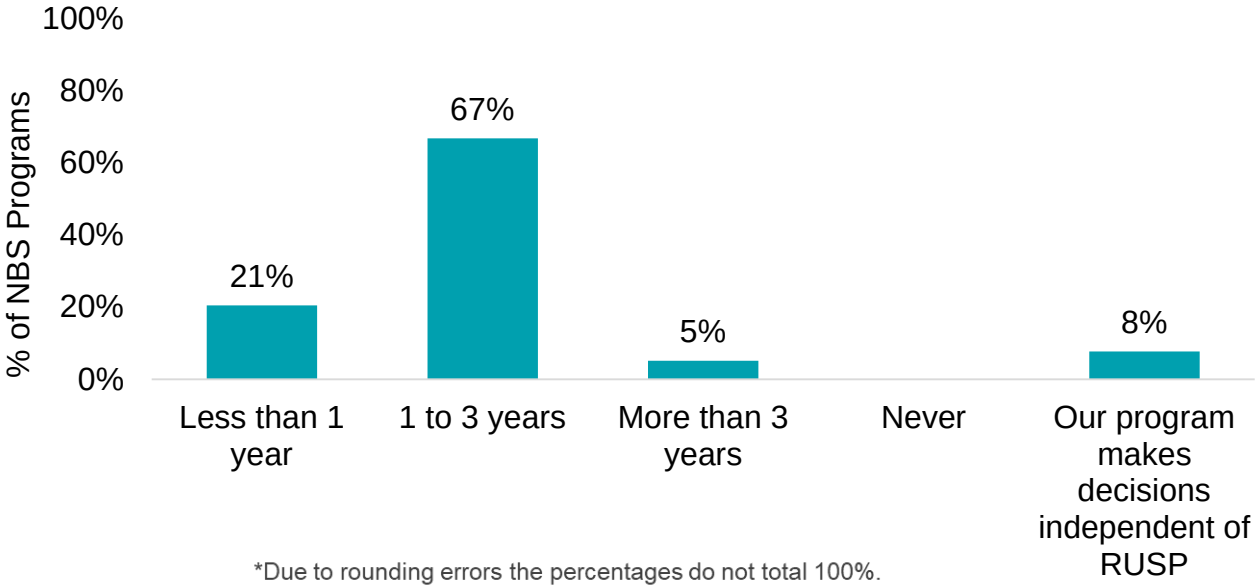
- Response rate of 87%.
  - 27 responses from state NBS programs.
  - 14 responses from programs that contract commercially or regionally.
- Five states NBS programs were excluded from the analysis because they participated in the interview.

Results: Duration between addition to the RUSP and State authorization



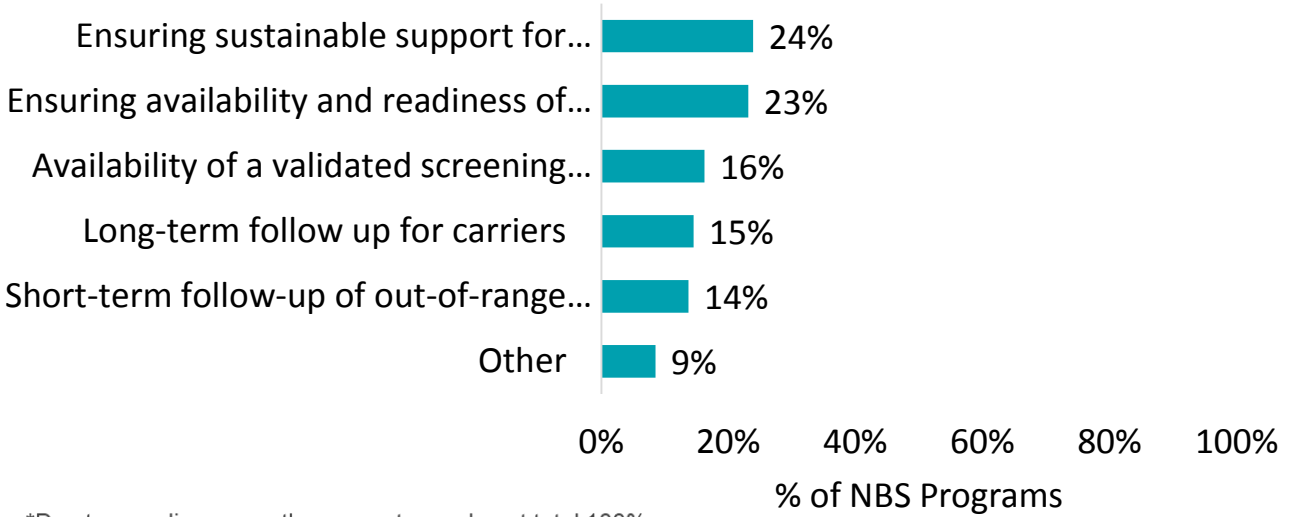
*Due to rounding errors the percentages do not total 100%.

Results: Duration between authorization and allocation of SMA Funds



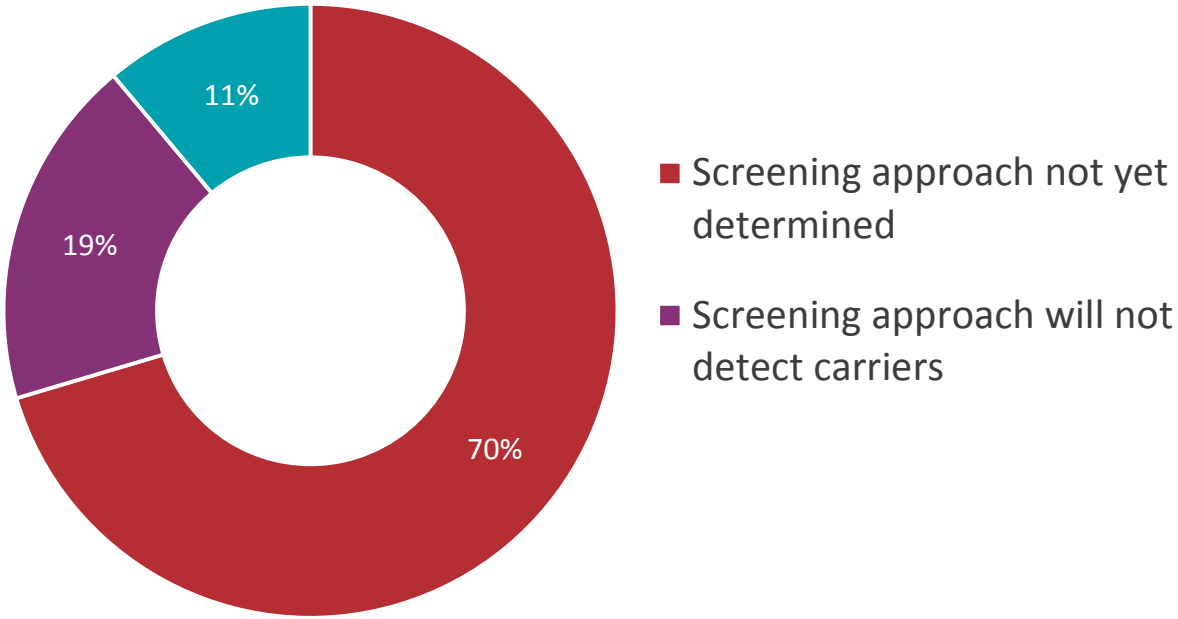
*Due to rounding errors the percentages do not total 100%.

Results: Implementation Challenges

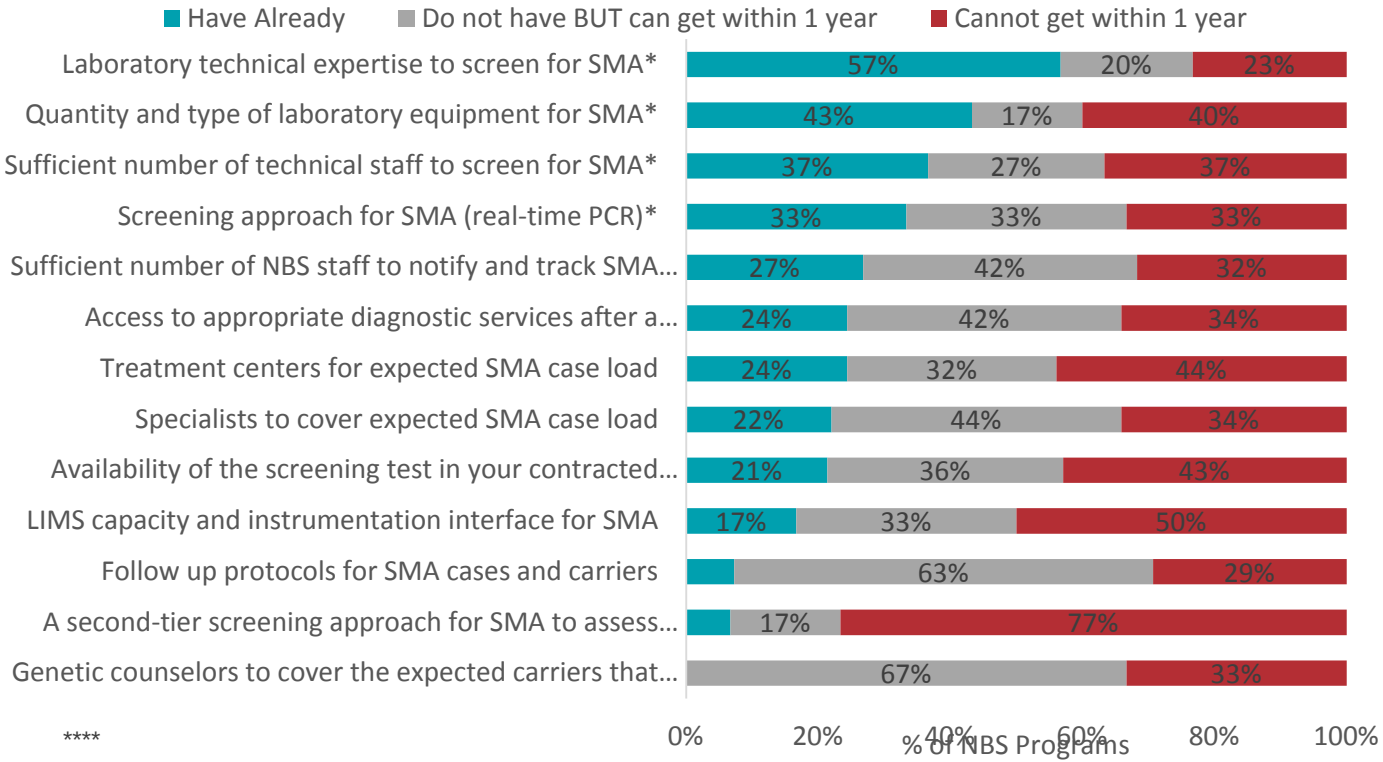


*Due to rounding errors the percentages do not total 100%.

Results: Screening Approach for Carriers



Results: Implementation Resources



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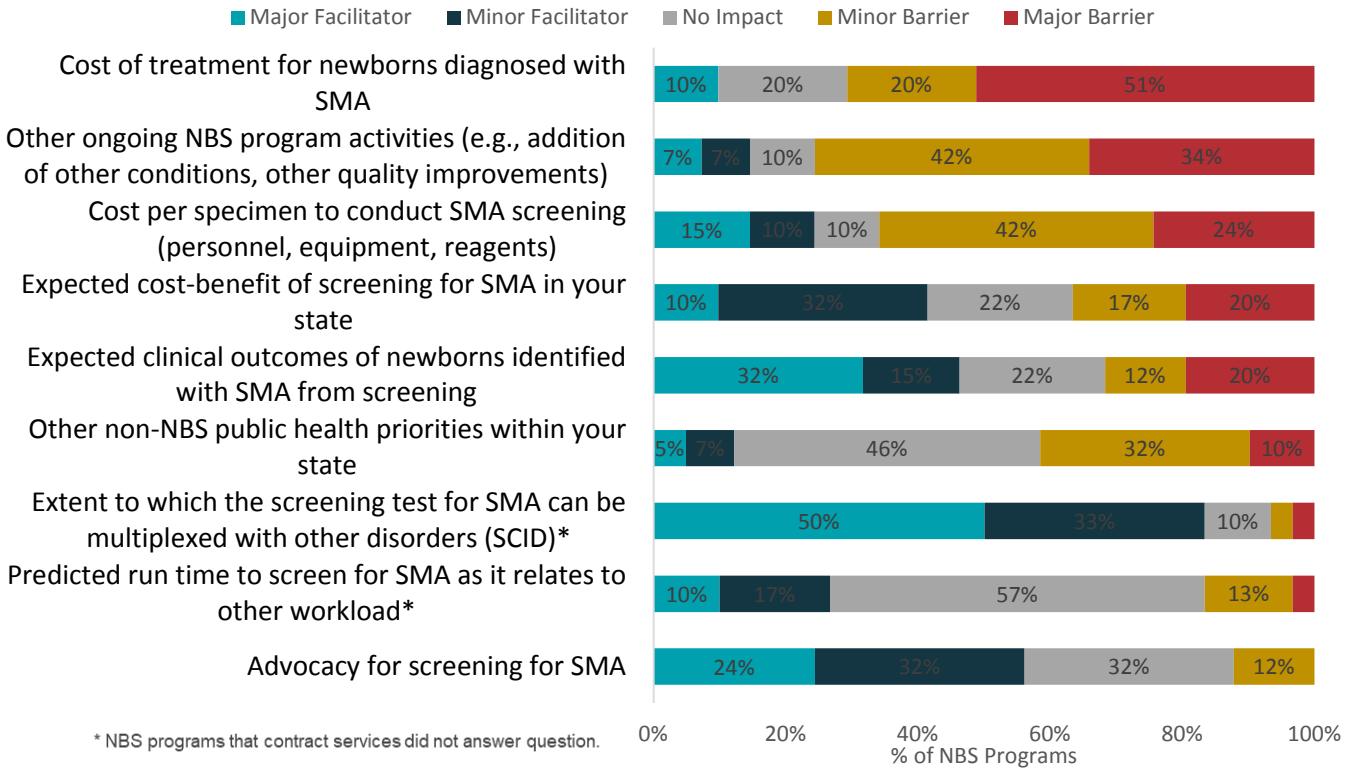
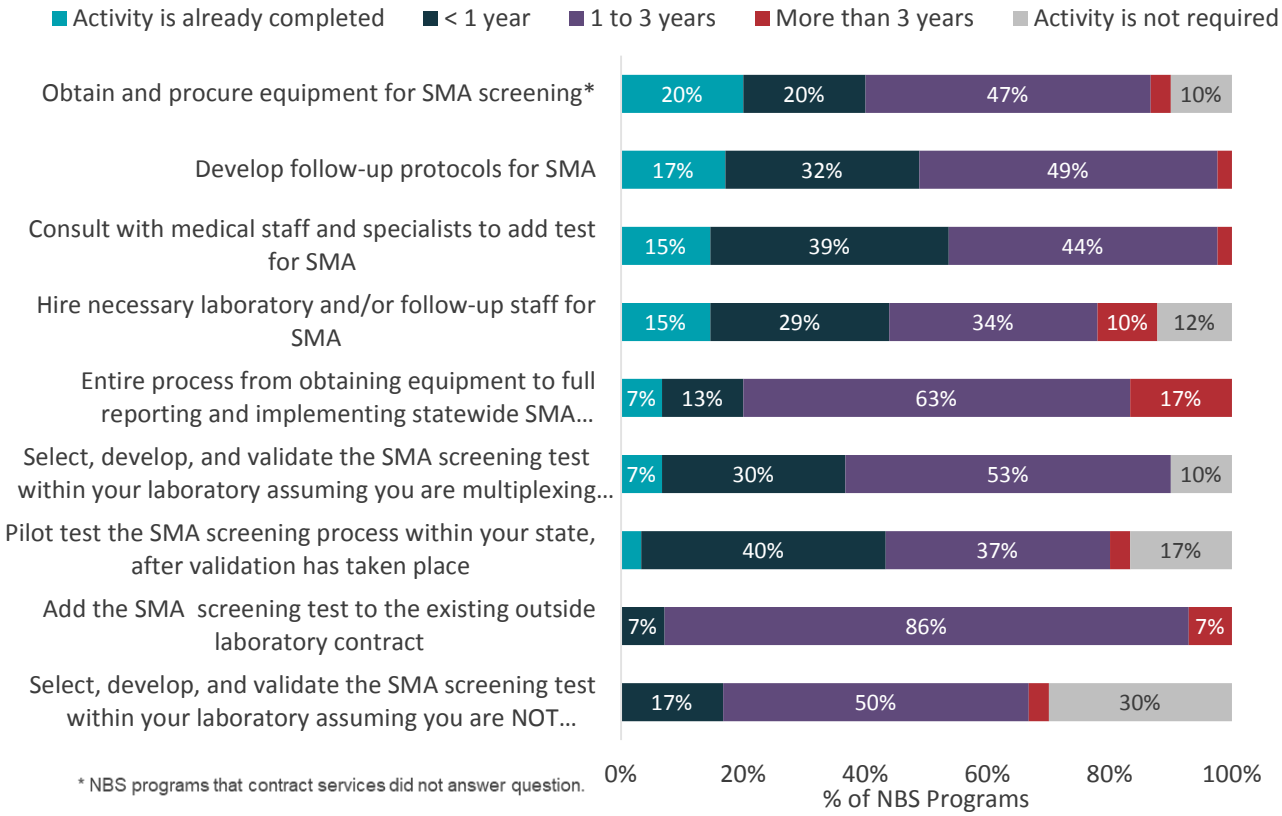
* NBS programs that contract services did not answer question.

Results: Implementation Factors



* NBS programs that contract services did not answer question.

Results: Duration For Activities



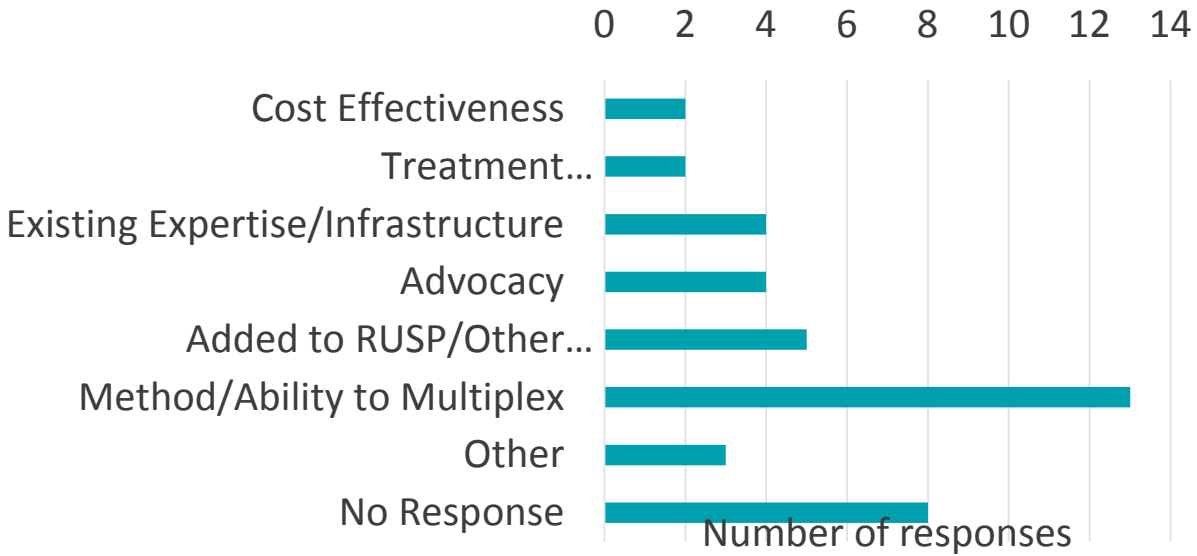
* NBS programs that contract services did not answer question.

Results: Most Significant Barrier

Open-ended and multiple responses captured.

Results: Most Significant Facilitator

Open-ended responses captured.



Strengths of PHSI

- Survey response rate of 87%.
- Webinar and factsheet for survey responders.
- Survey assessed perceptions about implementation based on experiences with other disorders.
- Interviews assessed real world experiences.

Limitations of PHSI

- **Assumption that approval had occurred and funds were allocated.**
- Hypothetical survey questions and subjective responses.
- Limited data on screening for SMA in NBS setting.

Conclusions: Readiness

- The majority of NBS programs reported that it would take between 1 and 3 years to implement screening for SMA **after approval** and **allocation of funds.**
- Quite a bit of variation among NBS programs.
- Administrative processes (increasing NBS fee, meeting with committees) can delay process.

Conclusions: Feasibility

- The method (quantitative real-time PCR) has shown to be reliable and have 0% false positive rate.
- Rate of missed cases are anticipated to be 5-7% (based on the reported frequency of babies who are not compound homozygous for the SMN1 exon 7 deletion).
- The false negative rate will not be known until screening begins.
- The CDC prepared to provide quality control materials, however if a large number of states implement at once supply could become limited.

Conclusions: Feasibility

- Diagnostic confirmation with SMN1 gene and SMN2 copy number.
- Nusinersen is an FDA approved treatment, but there is a lack of understanding of long-term outcomes.
- May be cost issues with treatment and issues with treatment coverage by insurance and Medicaid.
- Long-term follow-up of patients is unclear.

Summary

- The NBS states interviewed who are conducting/preparing pilot studies or population screening have begun implementation activities and plan to all be screening, at least select populations by December 2018.
- Screening for carriers, determining what to do with late-onset cases, cost of treatment, and treatment equity were commonly reported challenges.

Summary

- Administrative barriers can delay the implementation process.
- The state NBS program that has begun to offer screening for SMA has identified 1 SMA case since 2016 and provides important lessons about implementation challenges and facilitators.

Summary

- Factors that aid in implementation include existing infrastructure, multiplexing the screening test, and expected clinical outcomes for newborns diagnosed early.
- Strong collaborations among NBS programs and guidance coming from the RUSP will likely bolster implementation activities.

Questions?

Evidence Review of Newborn Screening for Spinal Muscular Atrophy
Final Report from the Condition Review Workgroup
February 8, 2018

Acknowledgements

The CRW thanks all those who provided input on this review, especially TEP members, NYS and other NBS programs, and the SMA and NBS communities.

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