Newborn Screening for Spinal Muscular Atrophy (SMA):Phase 2 Update of the Condition Review

Alex R. Kemper, MD, MPH, MS
K.K. Lam, PhD
Condition Review Workgroup

November 8-9, 2017

Nationwide Children's
When your child needs a hospital, everything matters.℠

Condition Review Workgroup

ERG Members	Role	Institution
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. Green, 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
Jelili Ojodu, MPH	Public Health Impact Task Leader	NBS & Genetics, Association of Public Health Laboratories
Lisa Prosser, PhD	Decision Analysis Leader, NBS Health Economist	Health Management & Policy/ SPH; Pediatrics/Univ of Michigan Med 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

SMA Evidence Review – Activities by Phase

MAY 11-12, 2017 Committee Meeting - Request for Evidence Review of SMA			
Phase 1 (Months 1-3) **AUG 3-4, 2017 Committee Meeting Interim Findings Presentation 1**	**SER**	**DA**	**PHSI**
Scope of Review / Case Definition	☑		
Analytic Framework Draft Key questions	☑		
Pilot Screening for SMA - Overview	☑		
Preliminary Search Results/PRISMA	☑	☑	☑
Draft Decision Analysis Structural Model		☑	
Draft Screening Fact Sheet			☑
Establish Technical Expert Panel (TEP) - 1, TEP 1	☑	☑	☑
Phase 2 (Months 4-6) **NOV 8-9 2017 AC Meeting Interim Findings Presentation 2**	**SER**	**DA**	**PHSI**
Assessment of Evidence	☑		
Major outcomes of interest	☑	☑	
Key Studies for Decision Model		☑	
Rev Decision Analysis Structural Model		☑	
Webinar & PHSI Survey Update, Final Screening Fact Sheet			☑
Update on follow up interviews			☑
TEP 2 Input	☑	☑	☑
Phase 3 (Months 7-9) **FEB 8-9, 2018 Committee Meeting Final Report of the Evidence Review for SMA NBS**	**SER**	**DA**	**PHSI**
Summary of Evidence and Quality Assessment, by Key Question	☑		
Decision Analytic Model		☑	
PHSI Survey Results and Follow Up Interviews			☑
Cost Assessment Results			☑
TEP 3 Input	☑	☑	☑

Overview

- Evidence review
  - Major outcomes of interest
- Decision Analysis Model
  - Draft Structural Model
  - Anticipated results
- Public Health System Impact (PHSI) Assessment
  - Screening Implementation Fact Sheet
  - PHSI survey rollout
  - Follow up interviews

Systematic Evidence Review: SMA Published Literature – 2000 through June 2017

- 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 June 2017 (n=2447)
  - PubMed (n=1414)
  - EMBASE (n=705)
  - CINAHL (n=215)
  - Cochrane (n=113)
- Articles screened for relevance (n=1941)
- Screening and full-text reviews completed
- Screening by two independent reviewers
- *Final evidence update January 2018, published and unpublished data*

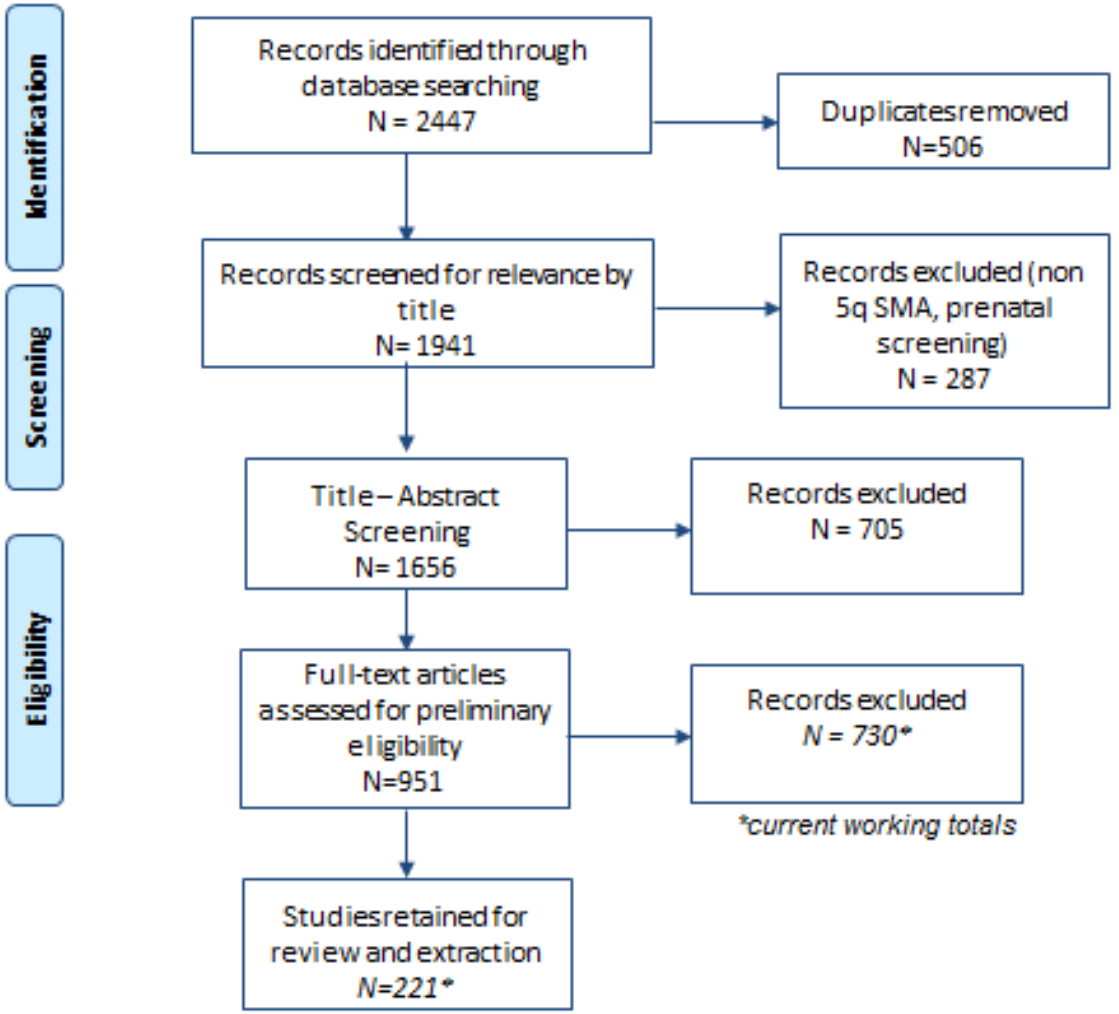


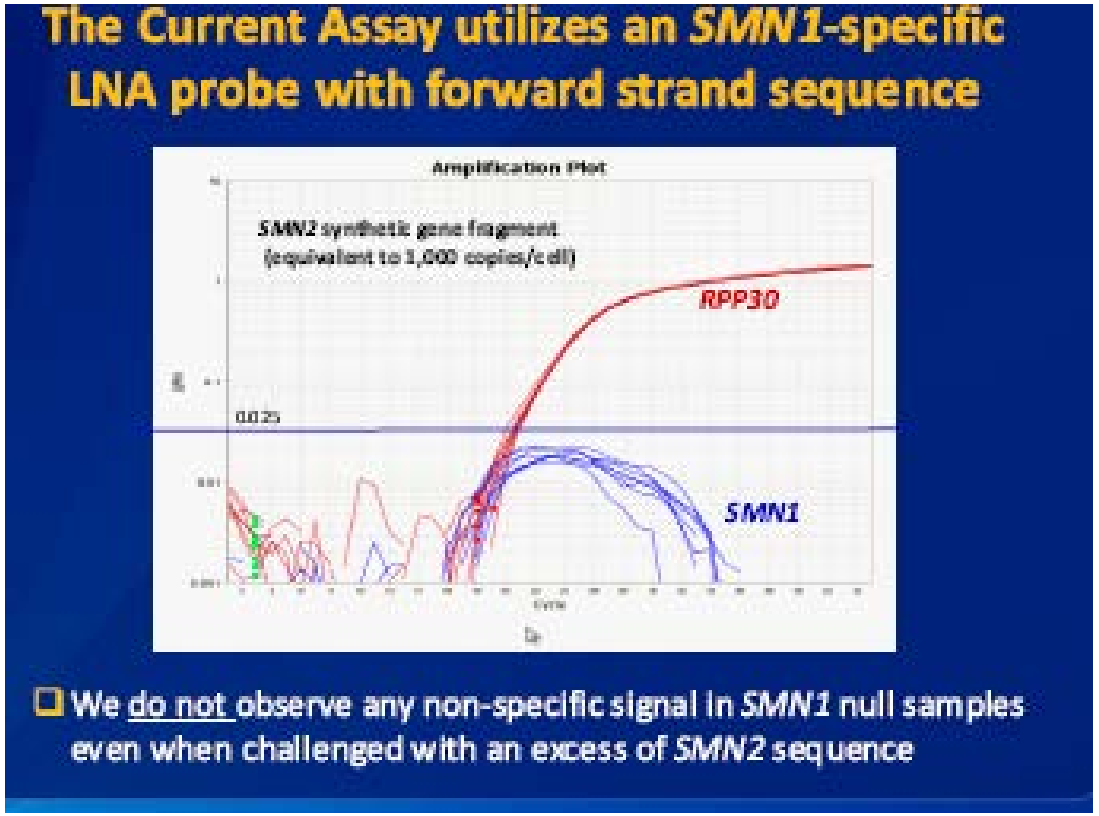
Figure 1. Preliminary PRISMA Diagram of Published Literature Search

Newborn Screening for SMA: Status in the U.S.

- **Targeted Research Pilots**
  - New York State NBS (3 NYC hospitals, since Jan 2016)
  - *Utah (opt-in)*
  - *Colorado (opt-out)*
- **Legislative Approval**
  - Missouri – July 10, 2017
  - Minnesota – October 12, 2017
- **States (known to be) considering SMA screening or pilot:**
  - Massachusetts
  - North Carolina
  - Wisconsin
  - Texas
- **CDC has developed screening method and proficiency testing materials**

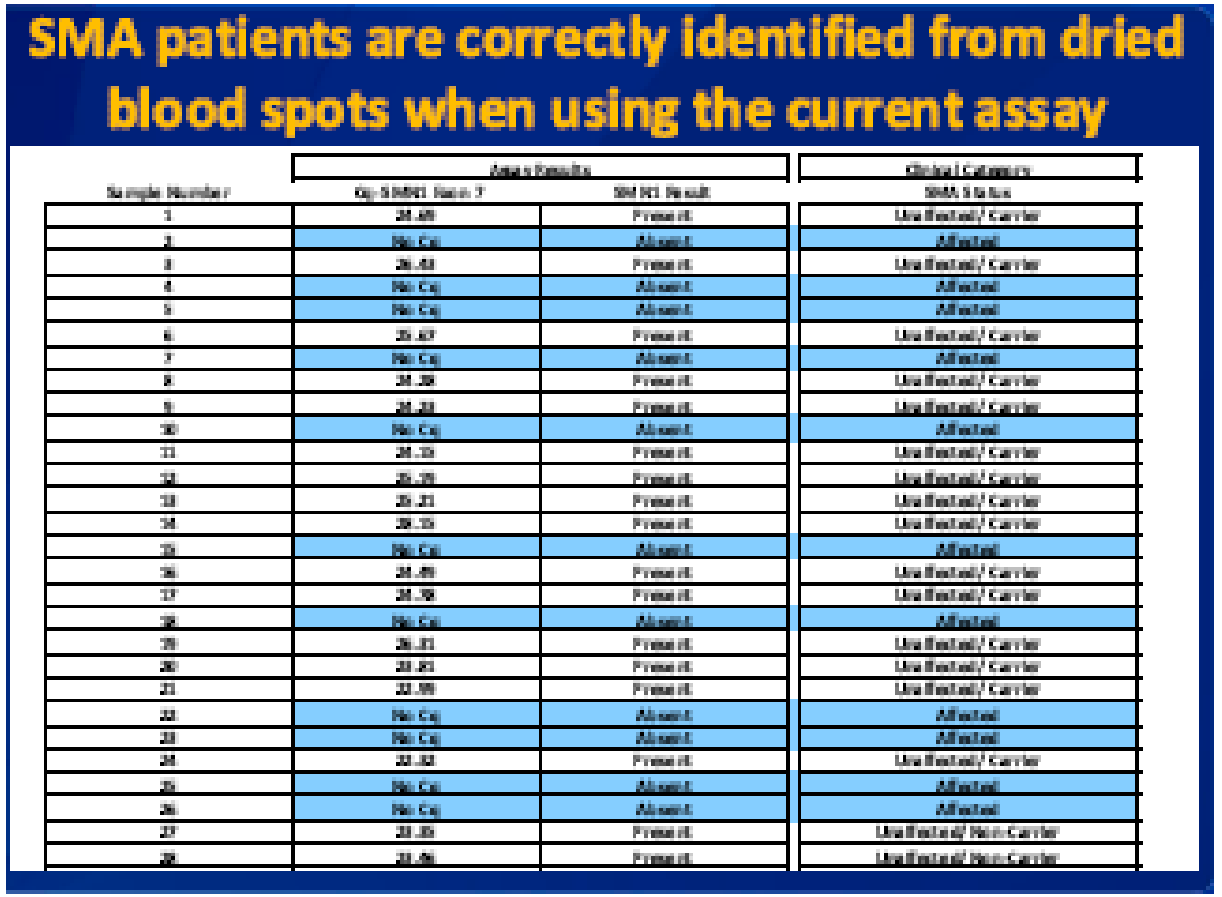
Screening – CDC-developed SMA Screening Assay

- Real-time qPCR targeting SMN1 Exon 7 Deletion (*not Intron 7*)
- Utilizes SMN1-specific LNA probe to increase specificity in presence of SMN2



Screening – CDC-developed SMA Screening Assay - Validation

- Validation – case control study of 28 dried blood spots
- Discriminated SMA patient samples vs. Unaffected/Carriers
- Designed **not** to identify carriers

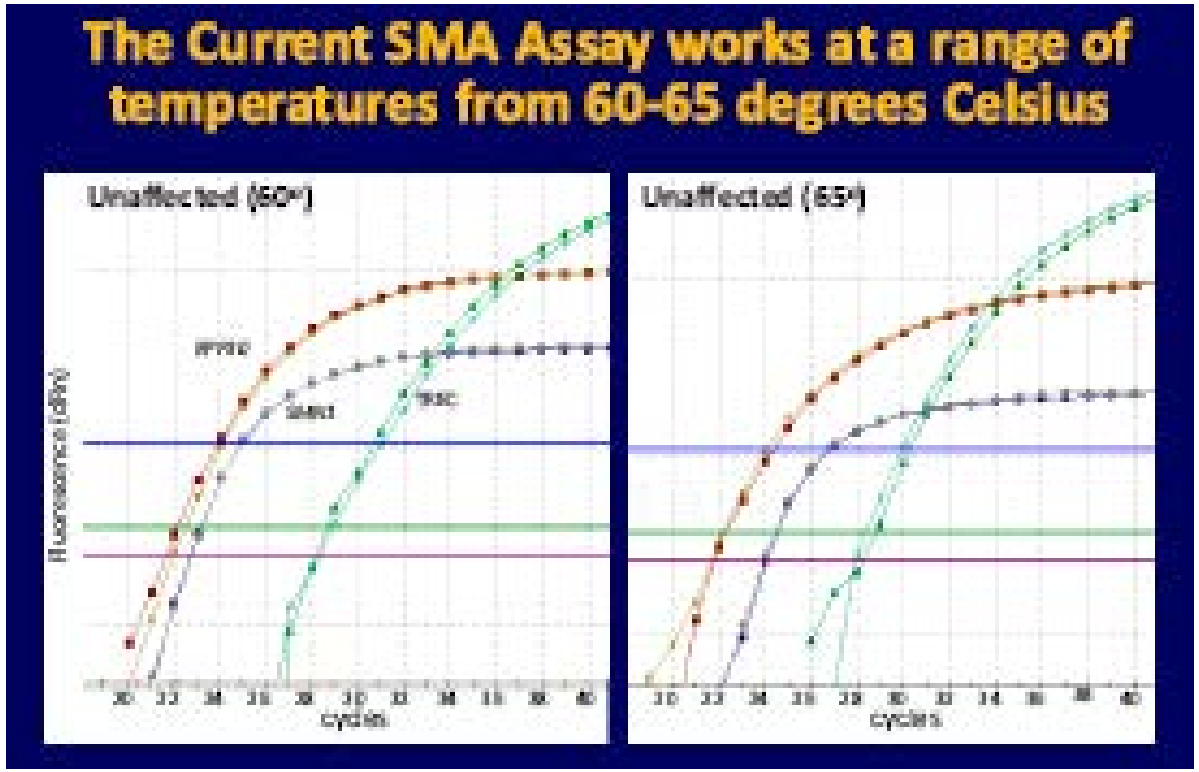


Sample Number	Assay Results		Clinical Outcomes
	Qty SMN1 Exon 7	SMN1 Result	SMA Status
1	24.69	Present	Unaffected/Carrier
2	No Cq	Absent	Affected
3	26.48	Present	Unaffected/Carrier
4	No Cq	Absent	Affected
5	No Cq	Absent	Affected
6	25.67	Present	Unaffected/Carrier
7	No Cq	Absent	Affected
8	24.28	Present	Unaffected/Carrier
9	24.43	Present	Unaffected/Carrier
10	No Cq	Absent	Affected
11	24.31	Present	Unaffected/Carrier
12	25.29	Present	Unaffected/Carrier
13	25.21	Present	Unaffected/Carrier
14	24.35	Present	Unaffected/Carrier
15	No Cq	Absent	Affected
16	24.49	Present	Unaffected/Carrier
17	24.78	Present	Unaffected/Carrier
18	No Cq	Absent	Affected
19	26.21	Present	Unaffected/Carrier
20	23.23	Present	Unaffected/Carrier
21	22.99	Present	Unaffected/Carrier
22	No Cq	Absent	Affected
23	No Cq	Absent	Affected
24	23.32	Present	Unaffected/Carrier
25	No Cq	Absent	Affected
26	No Cq	Absent	Affected
27	23.35	Present	Unaffected/Non-Carrier
28	23.26	Present	Unaffected/Non-Carrier

Screening – CDC-developed method Key Points

- Can be multiplexed with TREC/SCID
- Low marginal costs to multiplex with TREC (<~0.10/sample)
- Droplet digital PCR can be used to determine SMN1 and SMN2 copies

- CDC – offers consultation and technical support
  - Pre-assay development consultation, sequence info
  - Reference materials
  - Individual training at CDC



Treatment Evidence: Nusinersen

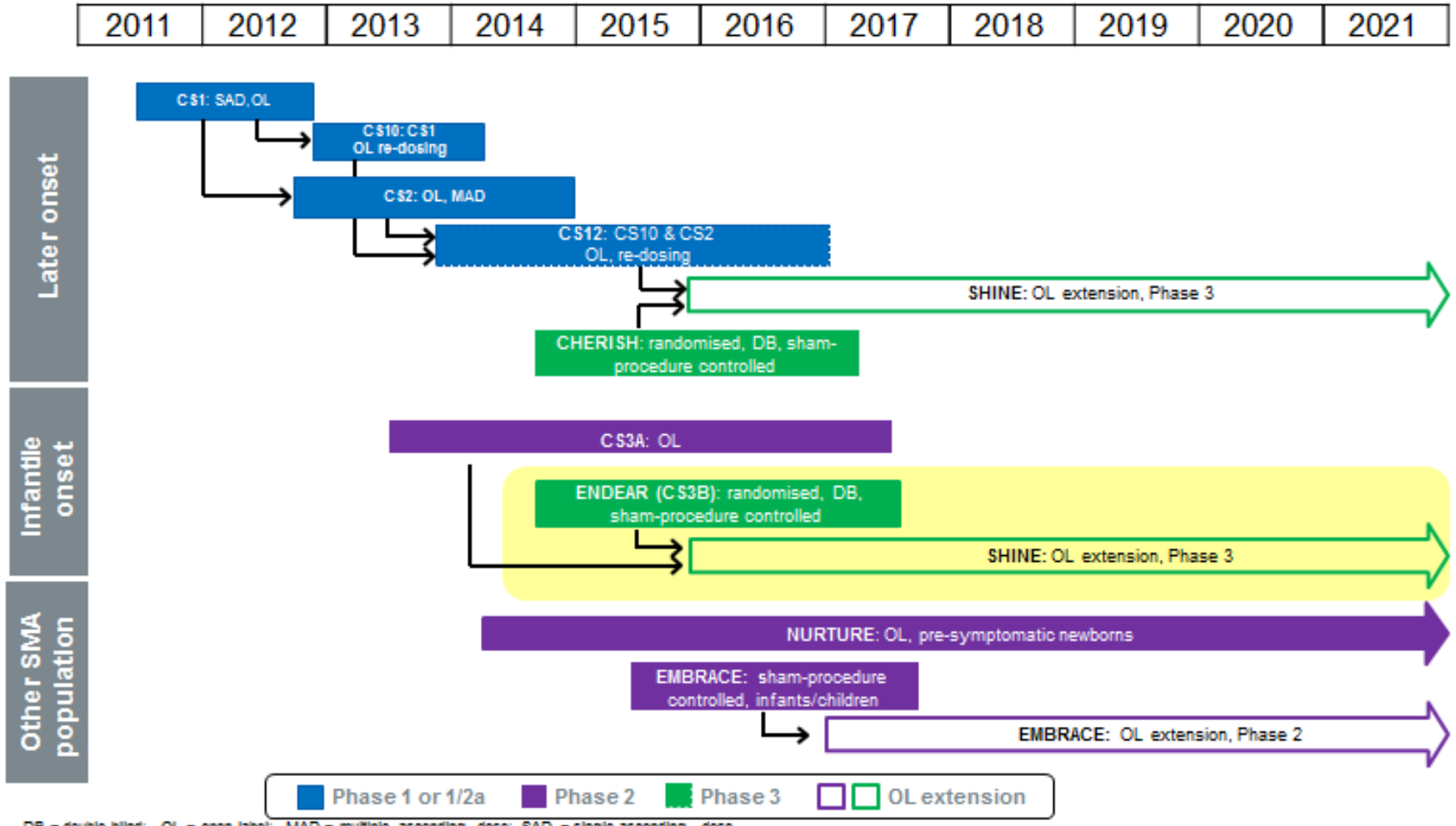
Published, Peer-reviewed scientific publications

- Chiriboga, C.A., et al. (2016). Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology, 86, 890-897.
- Hache, M. et al. (2016). Intrathecal injections in children with spinal muscular atrophy: Nusinersen clinical trial experience. Journal of Child Neurology, 31, 899-906.
- Finkel, R.A. et al. (2016). Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose escalation study. Lancet, 388, 3017-3026.

Published Abstracts/Presentations (Grey Literature)

ENDEAR (Final Results), NURTURE (Interim), CHERISH (Interim) trials

Nusinersen Clinical Development Program



DB = double-blind; OL = open-label; MAD = multiple ascending dose; SAD = single ascending dose.

Finkel RS, Kuntz N, Mercuri E, et al. Primary Efficacy and Safety Results From the Phase 3 ENDEAR Study of Nusinersen in Infants Diagnosed With Spinal Muscular Atrophy (SMA). Presented at: 43rd Annual Congress of the British Paediatric Neurology Association (BPNA); January 11-13, 2017; Cambridge, UK.

Educational resource provided in response to unsolicited request (Content current 13-Jan-2017)

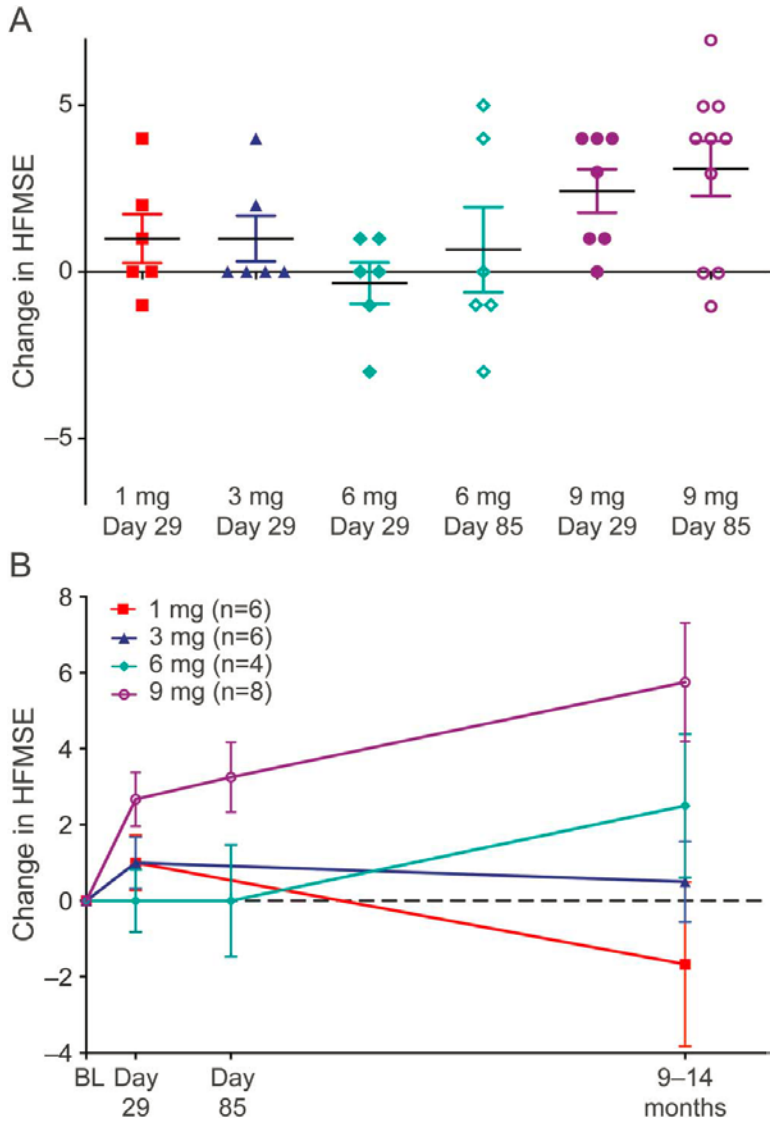
Results from a Phase 1 Study of Nusinersen in children with SMA

ELIGIBILITY:
- SMA Type 2 or 3
- Ages 2 to 14 years
- Symptomatic, Medically stable

SAMPLE (N=28):
- 39% Male, 82% Caucasian
- Med Age at baseline (yrs): 6.1 (2-14)
- 4 groups: 1 mg, 3 mg, 6 mg (n= 6 in each), and 9 mg (n=10).

RESULTS:
- Safe, well-tolerated, all doses
- Prelim Efficacy: Significant improvement in motor development (HFMSE) in 9mg dose cohort (n=10) at 3 mos (3.1 points) and 9-14 mos (5.8 points)
    - Clinically meaningful, diverge from typical SMA course of stable, slight declines

Changes in Hammersmith Functional Motor Scale Expanded (HFMSE) scores by treatment group



Chiriboga C.A., et al. (2016). Chiriboga, C.A., et al. (2016). Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology, 86, 890-897.

Treatment of infantile-onset SMA with Nusinersen: A phase 2, open-label, dose escalation study.

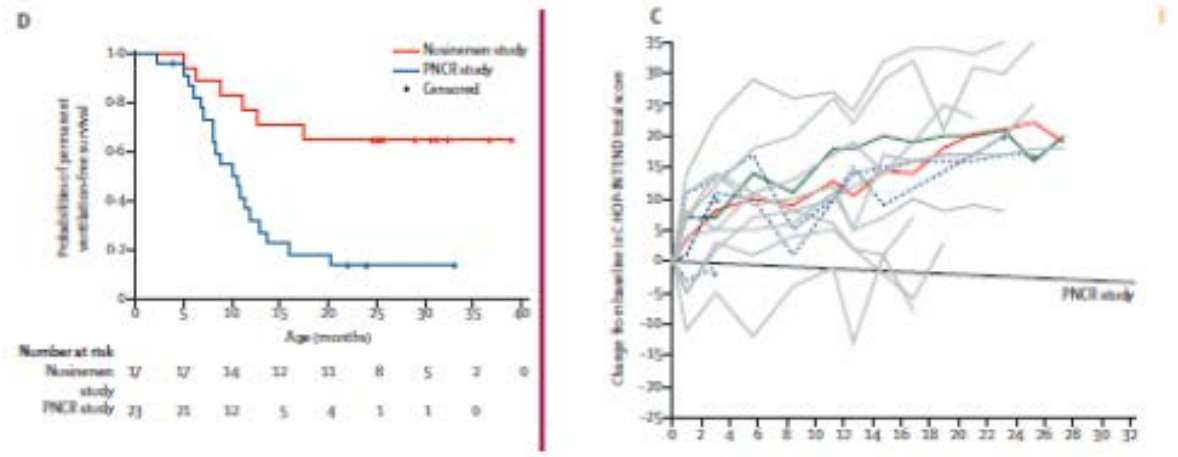
Eligibility	SAMPLE (N=20)
SMA infantile-onset	SMA infantile-onset, SMN2 copy number (2/3/UNK): 17/2/1
Ages 3 weeks to 7 months	Mean age at enrollment (days): 141 (36-210), 60% male
Clinical onset 3 weeks to 6 months	Mean age at clinical symptom onset (days): 60 (21-154)

Design: 2 groups, consecutively assigned: 6 mg (n=4), 12 mg (n= 16)

RESULTS:

Survival. Kaplan-Meier curve, participants with infantile-onset SMA and 2 SMN2 gene copies: nusinersen-treated vs. untreated infants with SMA from the PNCR natural history study (log-rank test, *p*=0.0014).

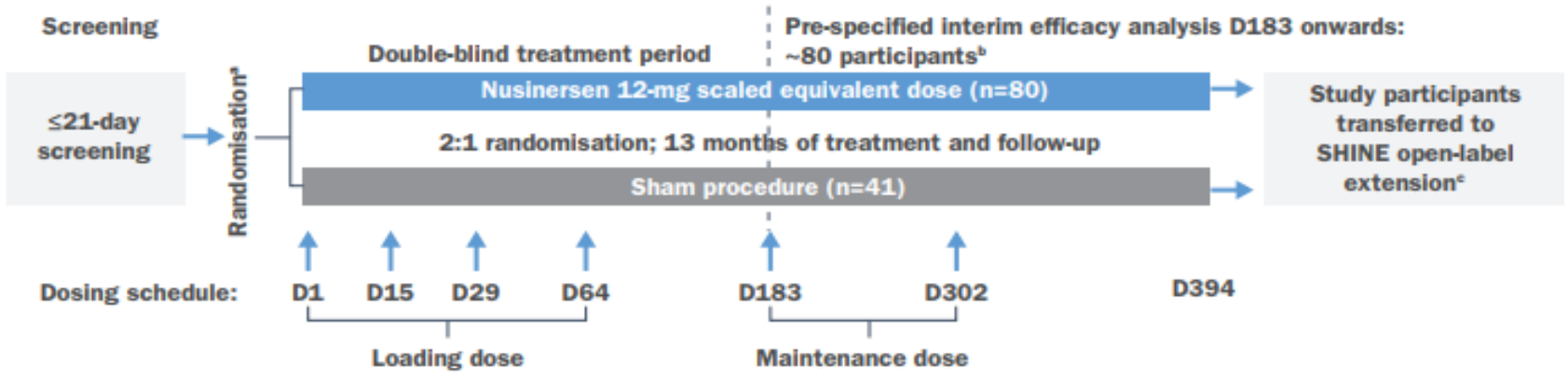
Motor function. Significant improvements from BL to last eval (*p*=0.0080), and compared with Ped Clin Neuromuscular Res (PCNR) natural history for SMA patients (*p*=0.0013).



Finkel, RA, et al. (2016). Treatment of infantile-onset SMA with nusinersen: a phase 2, open-label, dose escalation study. *Lancet*, 388, 3017-26.

ENDEAR Study (Phase 3 RCT) of Nusinersen in infants with SMA

Figure 1. ENDEAR study design



Study Design	Key Eligibility Criteria	Outcomes
Phase 3 randomized clinical trial	Infants with genetic diagnosis of SMA	Significant benefit for Nusinersen > Control
2:1 nusinersen vs. sham-procedure control	2 SMN2 copies	Motor milestone responders, motor function
Double-blinded	Clinical symptom onset ≤6 months	Event-free (vent-free) and Overall Survival
Intent-to-Treat Analysis and safety population	Age ≤ 7mos at study screening	Other biomarker and safety endpoints
Nusinersen group received ≥1 dose of study drug	No hypoxemia at study screening	

Kuntz et al., Apr 2017, Final Results of the Phase 3 ENDEAR Study: Assessing the Efficacy and Safety of Nusinersen in Infants With SMA. Presented at the 69th Meeting of the Amer Acad of Neur, April 22-28, 2017, Boston, MA.

ENDEAR Study (Phase 3 RCT) of Nusinersen in infants with SMA

Adverse Events (AEs)

- No AEs considered related to treatment by the investigator
- All AEs that led to discontinuation were AEs with fatal outcomes

AE, n (%)	Sham procedure control n=41	Nusinersen n=80
Any AE	40 (98)	77 (96)
AEs leading to discontinuation	16 (39)	13 (16)
Treatment-related AE[a]	0	0
Possibly treatment-related AE[a]	6 (15)	9 (11)
Severe AE	33 (80)	45 (56)
Serious AE	39 (95)	61 (76)
Serious AE with fatal outcome	16 (39)	13 (16)
Respiratory, thoracic and mediastinal disorders	12 (29)	7 (9)
Cardiac disorders	3 (7)	2 (3)
General disorders	1 (2)	2 (3)
Nervous system disorders	0	2 (3)

AE = adverse event. [a]Investigators assessed whether the AE was related to study drug. A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalisation/prolonged hospitalisation, persistent or significant disability/incapacity or that resulted in a congenital anomaly/birth defect. Severe AEs were defined as symptoms causing severe discomfort, incapacitation or significant impact on daily life; participants reporting >1 AE were counted once for total incidence, using the highest severity.

Kuntz et al., Apr 2017, Final Results of the Phase 3 ENDEAR Study: Assessing the Efficacy and Safety of Nusinersen in Infants With SMA. Presented at the 69th Meeting of the Amer Acad of Neur, April 22-28, 2017, Boston, MA.

ENDEAR Study (Phase 3 RCT) of Nusinersen in infants with SMA: Treatment Group X Disease Duration

AIM: To assess efficacy and safety of nusinersen in infants with SMA (from ENDEAR) by disease duration (≤12 or >12 weeks).

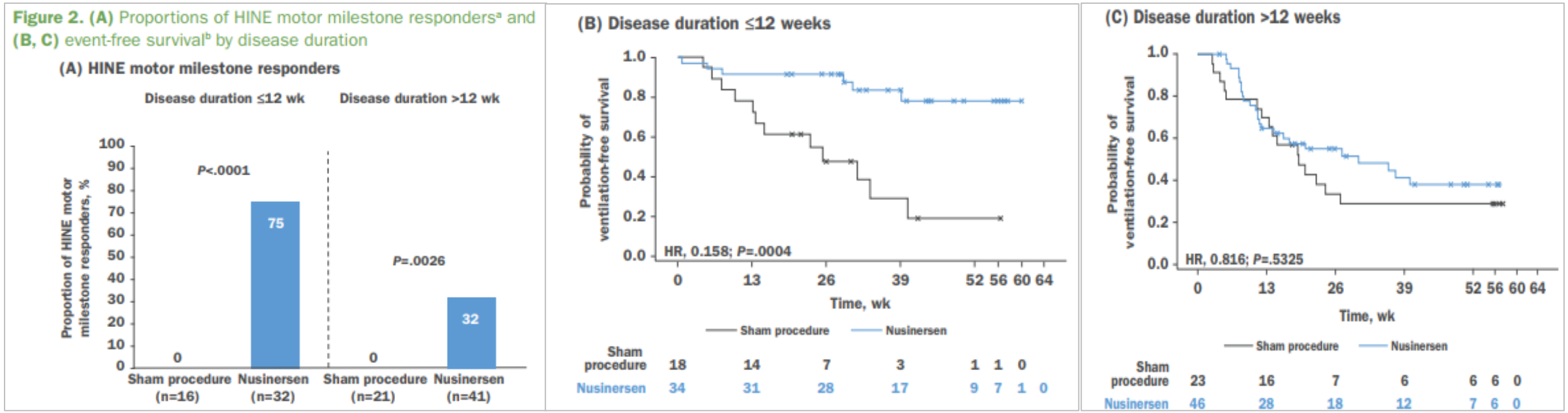
Table. Baseline characteristics by disease duration

Characteristic	Disease duration ≤12 wk		Disease duration >12 wk	
	Sham procedure n=18	Nusinersen n=34	Sham procedure n=23	Nusinersen n=46
Female, n (%)	7 (39)	18 (53)	17 (74)	25 (54)
Median (range) age at first dose, d	136.0 (30–228)	117.0 (52–235)	213.0 (143–262)	196.0 (127–242)
Median (range) age at symptom onset, wk	8.0 (1–20)	6.0 (3–18)	8.0 (4–16)	8.0 (2–16)
Median (range) disease duration, wk	9.9 (0–12)	8.7 (0–12)	18.0 (13–23)	16.3 (12–26)
Median (range) age at SMA diagnosis, wk	10.5 (2–25)	9.5 (0–22)	20.0 (12–30)	12.0 (2–29)

Servais et al., Oct. 2017. Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With SMA. Presented at the WMS Meeting, France.

ENDEAR Study (Phase 3) of Nusinersen in infants with SMA: Disease Duration

Figure 2A **Motor milestones (HINE)** Treatment group x disease duration	**Figure 2B** **Event-free Survival** ≤12 weeks Disease Duration	**Figure 2C** **Event-free Survival** >12 weeks Disease Duration
Significant between-group differences (nusinersen vs. control) in the proportion of HINE responders observed in infants with disease duration ≤12 weeks (75% vs. 0%; P12 weeks (32% vs. 0%; *P*=.0026).	Significant treatment benefit of nusinersen in event-free survival in infants with disease duration ≤12 weeks (hazard ratio [HR], 0.158; *P*=.0004).	Trend favoring nusinersen treatment in those with disease duration >12 weeks (HR, 0.816; *P*=.5325, *ns).*



Servais et al., Oct. 2017. Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With SMA. Presented at the WMS Meeting, France.

Public Health System Impact Assessment

- Screening Implementation Fact Sheet
- Webinar – October 4, 2017 (live and recorded, 72 registrants)
- Presenters:
  - Jelili Ojodu, APHL Director of NBS
  - Alex Kemper, Chair, Condition Review Workgroup
  - Denise Kay, NYS NBS Program Laboratory
- Topics:
  - PHSI background information
  - SMA – overview
  - PHSI Survey overview
  - SMA Screening Implementation Factsheet
  - Q/A and Summary

Public Health System Impact Assessment

- PHSI Survey: online survey opened ~Oct 5 to Nov 17
- Invitations sent to all NBS programs, input from all relevant sources encouraged

- PHSI Survey responses (as of ~October 18):
  - 53 NBS Programs invited
  - 11 opened/partially completed
  - 12 completed surveys
  - 5 states report actively considering or mandate to screen for SMA

- Follow-up interviews will be invited with states reporting mandate to screen (or states planning/estimating costs)

Modeling Analysis

Overall Goal:

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

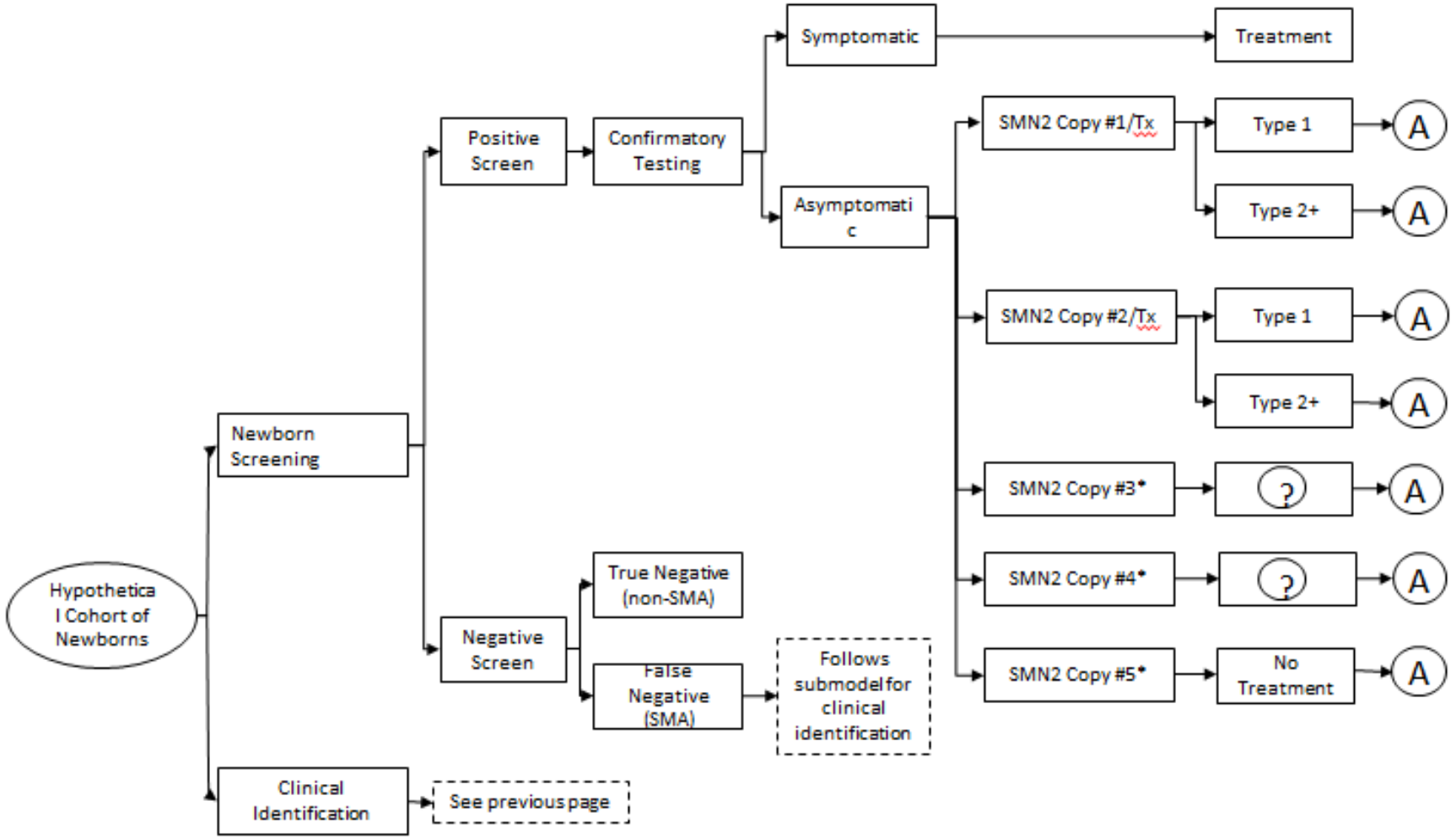
Health Outcomes:

- Mortality
- Ventilator Assistance
- (May also include Motor Deficits contingent on available data)

Scope of the Analysis:

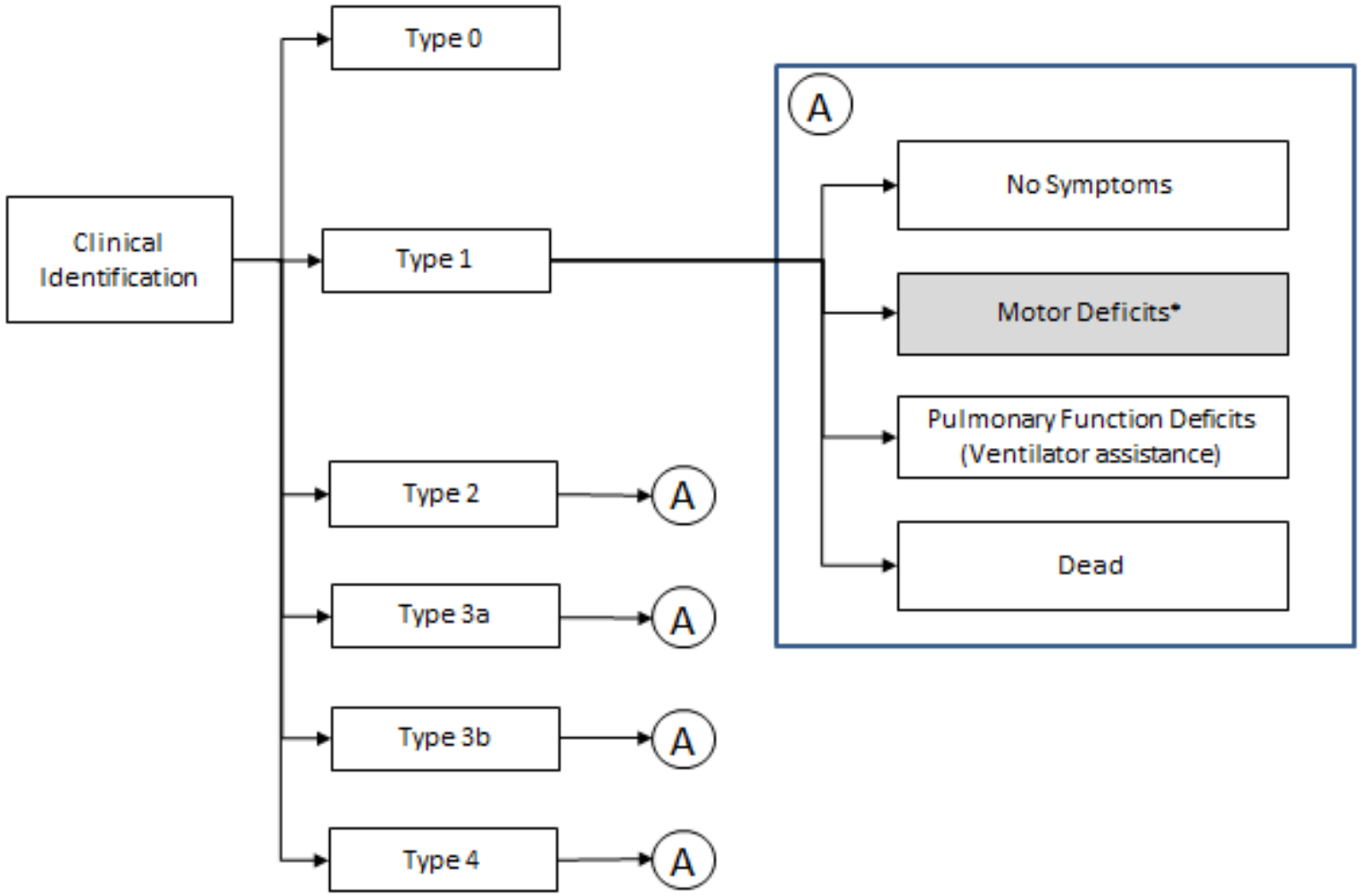
- Focus on Type 1 SMA
  - Projected cases identified
  - Projected health benefits
- Quantify screening outcomes and projected cases for “Non-Type 1”

SMA Model Schematic- Newborn Screening- Working DRAFT



*Assume type 2+

SMA Model Schematic- Clinical Identification- Working DRAFT



*May not be included in the final model

Potential Results Tables: SMA Cases Identified

	NBS	Clinical Identification
Type 1		
Symptomatic	# (#-#)	# (#-#)
Asymptomatic	# (#-#)	# (#-#)
Type 2+	# (#-#)	# (#-#)

Potential Results Table: Health Outcomes

Projected survival

	Survival	Deaths
Screened / Treated		
Most Likely (min, max)	# (#-#)	# (#-#)
Clinically Diagnosed / Treated		
Most Likely (min, max)	# (#-#)	# (#-#)

Projected cases of ventilator dependence

	Survival without ventilator dependence	Ventilator dependence deaths
Screened / Treated		
Most Likely (min, max)	# (#-#)	# (#-#)
Clinically Diagnosed / Treated		
Most Likely (min, max)	# (#-#)	# (#-#)

Decision Analysis: Next Steps

- Develop estimates for modeling parameters (via systematic evidence review and expert interviews)
- SMA Technical Expert Panel Meeting #3: Dec 13
- Review parameter inputs with expert panel
- Conduct base case and sensitivity analyses to obtain ranges for projected outcomes

Questions?