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
# Condition Review Workgroup

<table>
<thead>
<tr>
<th>ERG Members</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex R. Kemper, MD, MPH, MS</td>
<td>Chair</td>
<td>Nationwide Children’s Hospital</td>
</tr>
<tr>
<td>Anne M. Comeau, PhD</td>
<td>State NBS Public Health Program</td>
<td>New England NBS Program, University of Mass Medical School</td>
</tr>
<tr>
<td>Nancy S. Green, MD</td>
<td>Clinical Care Expert</td>
<td>Department of Pediatrics, Columbia University Medical Center</td>
</tr>
<tr>
<td>Scott Grosse, PhD</td>
<td>Federal Advisor; NBS Expert</td>
<td>CDC</td>
</tr>
<tr>
<td>Jennifer A. Kwon, MD</td>
<td>Clinical Care Expert, Long-term Follow up</td>
<td>University of Rochester Medical Center, Department of Neurology and Pediatrics</td>
</tr>
<tr>
<td>Jelili Ojodu, MPH</td>
<td>Public Health Impact Task Leader</td>
<td>NBS &amp; Genetics, Association of Public Health Laboratories</td>
</tr>
<tr>
<td>Lisa Prosser, PhD</td>
<td>Decision Analysis Leader, NBS Health Economist</td>
<td>Health Management &amp; Policy/ SPH; Pediatrics/Univ of Michigan Med School</td>
</tr>
<tr>
<td>Susan Tanksley, PhD</td>
<td>State NBS Public Health Program</td>
<td>Newborn Screening Laboratory, TX Department of State Health Services</td>
</tr>
<tr>
<td>K.K. Lam, PhD</td>
<td>Project Director</td>
<td>Duke University</td>
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</tbody>
</table>
# SMA Evidence Review – Activities by Phase

**MAY 11-12, 2017 Committee Meeting - Request for Evidence Review of SMA**

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


• 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

*We do not observe any non-specific signal in SMN1 null samples even when challenged with an excess of SMN2 sequence*
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
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


Published Abstracts/Presentations (Grey Literature)

ENDEAR (Final Results), NURTURE (Interim), CHERISH (Interim) trials
Nusinersen Clinical Development Program


Later onset

C31: SAD, OL
C10: CS1
OL re-dosing

C31, CS1, OL MAD

C31: CS10, OL re-dosing

SHINE: OL extension, Phase 3

CHEESE: randomised, DB, sham procedure controlled

Infantile onset

CS3A: OL

ENEAR (CS3B): randomised, DB, sham procedure controlled

SHINE: OL extension, Phase 3

CS3A: OL

Other SMA population

NUTURE: OL, pre-symptomatic newborns

EMBRACE: sham procedure controlled, infants/children

EMBRACE: OL extension, Phase 2

DB = double-blind; OL = open-label; WAC = multiple ascending dose; SAC = single ascending dose

Finkel RS, Kordik N, Mercouf E, et al. Primary Efficacy and Safety Results From the Phase 1 ENEAR Study of Nusinersen in Infants Diagnosed With Spinal Muscular Atrophy (SMA). Presented at 45th Annual Congress of the British Paediatric Neurology Association (BPNA), 11/12, 2016 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

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

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

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 PNCNR 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 \( (p=0.0013) \).

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

Figure 1. ENDEAR study design

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

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

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

AE = adverse event. *Investigators assessed whether the AE was related to study drug. A serious AE was any untoward medical occurrence that resulted in death, life-threatening events, 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.
AIM: To assess efficacy and safety of nusinersen in infants with SMA (from ENDEAR) by disease duration (≤12 or >12 weeks).

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

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).

**Figure 2B**
Event-free Survival
≤12 weeks Disease Duration

Significant treatment benefit of nusinersen in event-free survival in infants with disease duration ≤12 weeks (hazard ratio [HR], 0.158; P=.0004).

**Figure 2C**
Event-free Survival
>12 weeks Disease Duration

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 - Clinical Identification - Working DRAFT

Clinical Identification

- Type 0
- Type 1
  - Motor Deficits*
  - Pulmonary Function Deficits (Ventilator assistance)
  - Dead
- Type 2
- Type 3a
- Type 3b
- Type 4

*May not be included in the final model
## Potential Results Tables: SMA Cases Identified

<table>
<thead>
<tr>
<th>Type</th>
<th>NBS</th>
<th>Clinical Identification</th>
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<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td># (#-#)</td>
<td># (#-#)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td># (#-#)</td>
<td># (#-#)</td>
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<tr>
<td>Type 2+</td>
<td># (#-#)</td>
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# Potential Results Table: Health Outcomes

## Projected survival

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Screened / Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Likely (min, max)</td>
<td># (#-#)</td>
<td># (#-#)</td>
</tr>
<tr>
<td>Clinically Diagnosed / Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Likely (min, max)</td>
<td># (#-#)</td>
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</table>

## Projected cases of ventilator dependence

<table>
<thead>
<tr>
<th></th>
<th>Survival without ventilator dependence</th>
<th>Ventilator dependence deaths</th>
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</thead>
<tbody>
<tr>
<td>Screened / Treated</td>
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<td></td>
</tr>
<tr>
<td>Most Likely (min, max)</td>
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</table>
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?