Evidence Review following the Implementation of Newborn Screening Implementation for Spinal Muscular Atrophy (SMA)

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

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Alex R. Kemper, MD, MPH, MS

K.K. Lam, PhD

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Background and Purpose

- May 2017: Committee considers SMA Nomination and requests full evidence review
- February 2018: Committee considers the evidence review regarding SMA newborn screening and recommends to the Secretary, HHS, that SMA be added to the RUSP
- July 2018: Secretary, HHS, adds SMA to the RUSP and requests a report within 2 years (July 2020) describing
  - the status of SMA newborn screening implementation
  - clinical outcomes of early treatment, including any potential harms, for infants diagnosed with SMA.

Approach

- Update the systematic evidence review of published and gray literature (Jan 2018 - March 2020)
- Consult with expanded screening resources and organizations (e.g., APHL/NewSTEPs, CureSMA, NBSTRN) regarding SMA newborn screening
- Guidance from Technical Expert Panel (TEP), which convened in Jan 2019 with additional communication as needed

SMA NBS Implementation Review - Technical Expert Panel Members	
Mary Schroth, MD Chief Medical Officer	Cure SMA
***Michele Caggana, Sc.D., FACMG** Director	Division of Genetics, State of NY Newborn Screening Program
Stanton Berberich, PhD Prog Manager, Iowa Newborn Screening	Iowa State Hygienic Laboratory
Anne Connolly, MD Clinical Expert in SMA, Gene therapy	Division Chief, Neurology Nationwide Children's Hospital
Claudia Chiriboga-Klein, MD, MPH Clinical Expert, NY SMA Pilot Co-I	Dept of Neurology and Pediatrics Columbia University Medical Center
***Kathryn Swoboda, MD** Clinical Expert	Massachusetts General Hospital, Pediatric Neurology
Jennifer Kwon, MD Clinical Expert, SMA/NMD patient care	School of Medicine and Public Health University of Wisconsin
***Ms. Allison Kingsley** Parent of a child with SMA	Family Advisory Council Member Nationwide Children's Hospital
Francis Lee, MSc, PhD SMA Screening/Lab Methods	Centers for Disease Control and Prevention Newborn Screening and Molecular Biology Branch
(*) indicates members of TEP on original evidence review	

Evidence Regarding SMA Newborn Screening for SMA from 2018 (Highlights)

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Spinal Muscular Atrophy – Case Definition Target

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**

Spinal Muscular Atrophy (SMA)

Genetics:	• Most cases due to homozygous deletion of *SMN1* exon 7 • ~5% - compound heterozygotes • Variable copy number of *SMN2* genes, can modify the disease course by making ~10% of functional *SMN1* protein
Screening:	• Screening Target: Deletion of *SMN1* exon 7 in one or both alleles (detects at least 95% of the cases of SMA)
Pilots:	• New York Research Project • Taiwan newborn screening program
Diagnosis:	• *SMN1* exon 7 deletion, *SMN2* copy number, clinical exam
Treatment *(in 2018):*	• Nusinersen, FDA-approved Dec 2016

SMA Classification

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

~72% of SMA cases are Type I and II

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

Screening for SMA

- High-throughput screening with molecular testing for deletion of exon 7 in *SMN1* using qPCR
- Strong analytic and clinical validity for detecting homozygous deletion of exon 7 in *SMN1* when multiplexed with SCID or as stand-alone screen (PPV 100%, FP 0%)
- SMN2 copy numbers can inform severity and phenotype. Can be assessed in NBS/PH labs or through clinical testing
- When multiplexed with existing SCID screening, SMA NBS requires marginal additional resources and can share and screening time and labor
- Targeting presence or absence of homozygous deletion of exon 7 in SMN1 minimizes follow up compared to detecting only one copy of the deletion, which would detect carriers

Evidence of Net Benefit From Treatment Initiated Early

- No direct evidence comparing early detection vs. standard of care.
- Indirect evidence was limited in quality (grey literature, limited number of participants, no peer-reviewed publications, follow-up limited to <2 years of life.
- Indirect evidence suggested significant improvements (i.e., motor milestone responders, motor function) with treatment given earlier (age, shorter disease duration)

Nusinersen (reported in 2018 review)

Evidence source	Sample patients	Findings
Conference presentation	Post-hoc analysis of Phase 3 RCT (n=120) with infantile onset, symptomatic SMA patients	Infants with shorter disease duration (<12 weeks) before receiving nusinersen had better motor milestone response (p<.0001) than those with longer (>12 weeks) disease duration before treatment
Conference presentations, abstracts	Interim analysis on 9 of 20 participants in a Phase 2 open-label trial with infantile onset, asymptomatic SMA patients treated before 6 weeks of life	Interim findings -9 of 9 alive -suggested improved motor milestone development through 1 year of life (relative to symptomatic comparison group).

Experimental Gene Therapy (2018 review)

Evidence source	Sample patients	Findings
Peer-reviewed, scientific journal (NEJM)	Phase 1, open-label, single-arm, ascending-dose clinical trial, N=15 Infants up to ≤6 months old, with SMA type 1.	At 24-mo post-treatment, 12 of 12 higher dose patients were alive without vent support. All 15 patients in follow up study, followed annually per standard of care.

Projected Population-level Net Benefit

Summary – Projected Population-level Outcomes

- 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

Updated Evidence, 2018 - 2020

SMA Disease-Modifying Treatments

Treatment	Description	Status
Standard of Care		
Nusinersen (Spinraza®)	Intrathecally-administered antisense oligonucleotide; 4 loading doses in first 2 months, then repeat doses every 4 months; increases expression of functional SMN protein from *SMN2* transcript	FDA approved in December 2016 for all patients diagnosed with SMA (pediatric and adult, all forms of SMA)
Gene Therapy (Zolgensma®, AVXS-101)	Intravenously-administered AAV vector containing *SMN* gene; Single dose	FDA approved in May 2019 for children diagnosed with SMA <2 years of age, including those presymptomatic at diagnosis (single-dose only approved)
Experimental Treatments		
Risdiplam (experimental) (RO7034067)	Orally-administered, small molecular, splicing modulator of *SMN2;* daily dose	In development; Phase 2 open-lab studies in SMA Type 1, 2, and 3, in children and adults; Under priority review by FDA as of Nov 2019 (decision anticipated ~Aug 2020)
Branaplam (experimental) (LMI070, NVS-SM1)	Orally-administered, small molecule, splicing modulator of *SMN2*	In development; Phase 1/2 open-label trial underway

Nusinersen Studies

Trial	Study Design	Status/Findings
Evidence Review, 2018, published or vetted gray literature		
ENDEAR (n=121)* *terminated early*	Phase 3, RCT (2:1), infants with 3 copies of SMN2	Terminated early and moved to open-label (Nov 2016). Results in Finkel et al. Lancet 2017
NURTURE (n=25)* *as of May 15, 2018*	Phase 2, open-label, presymptomatic infants with 2 or 3 copies of SMN2	Active, est. end date Jan 2022. Interim results, n=9 of 25, conferences only.
Updated Evidence, 2018 – 2020, Published		
CHERISH (n=126) Mercuri et al., 2018	Phase 3, RCT, later-onset SMA (age 2-12).	Completed. Significantly greater increases in HFMSE scores with tx 15 months post-baseline for children with later-onset (med age at dx 18 mos, 8-94 mo rg)
NURTURE (n=25) DeVivo et al., 2019	• Phase 2, open-label, presymptomatic infants with 2 or 3 copies of SMN2 • Interim follow up analysis, median 2.9 years.	Interim analysis, n=25. At follow up, median age 34 months, 100% survival and free of vent support. 3/25 (92%) demonstrated walking with assistance, 22/25 (88%) achieved walking independently.

Gene Therapy

Trial/study	Study Design	Status/Findings
2018 Evidence Review, published		
START (n=15) Mendell et al., 2018	Phase 1, open-label, single-arm, ascending-dose clinical trial, Infants up ≤6 months old, with SMA type 1.	Complete. At 20 months of age, 100% survival (vs 8% historical controls). High dose gene therapy (n=12) patients had significant improvements in motor function at 1- and 3-months post treatment.
Updated Evidence 2018 – 2020, published		
START (n=15) Al-Zaidy et al. 2018	Follow up analysis of 24-month outcomes.	At 24-mo post-treatment, 12 of 12 higher dose patients were alive without vent support. All 15 patients in follow up study, followed annually per standard of care.
START (n=15) Lowes et al. 2019	Follow up analysis of motor outcomes from high dose patients (n=12).	Of the 12 higher dose patients, those treated earlier (<3 months) had greater motor outcomes than those treated later (>3months).

Gene Therapy

Trial/study	Study Design	Status/Findings
Updated Evidence 2018 – 2020, gray literature, press releases, abstracts*		
STR1VE (n=21) Conference presentation 2019	Phase 3, open-label, SMA Type 1, infants ≤6 months old at time of treatment, with 1 or 2 SMN2 copies	Active, est. end date Nov 2019. Continued improvements in CHOP-INTEND scores. 13 of 15 reached 13.6 months of age without perm vent support.
STRONG (n=27)	Phase 1, open-label study for children with *SMA type 2* (symptoms usually between 7-18 months), for sitting but non-ambulant children aged *6-60 months* with 3 copies of SMN2	Enrollment completed. Est. end date June 2021. Interim data (announced Oct 5 2019) demonstrating clinically sig and meaningful increases in baseline HFMSE scores at 9.3 months post-treatment for 2-5 year olds.
SPR1NT (n=18) 2019 Conf presentation	Phase 3 clinical trial for *presymptomatic infants less than 6 wks*, with SMA type 1, type 2, or type 3 (2 or 3 copies of SMN2)	Active, enrolling. Est. end date April 2021. Interim analysis (conference presentation 2019 AAN) showed 100% survival, increased motor function and milestone achievements.

**Press releases on industry website (non peer-reviewed) as of March 24, 2020 note that these studies were accepted for presentation at conferences that were cancelled due to COVID-19. Press releases state that information will be posted at a later date.*

State Newborn Screening for SMA – Implementation Status

State NBS Implementation for SMA

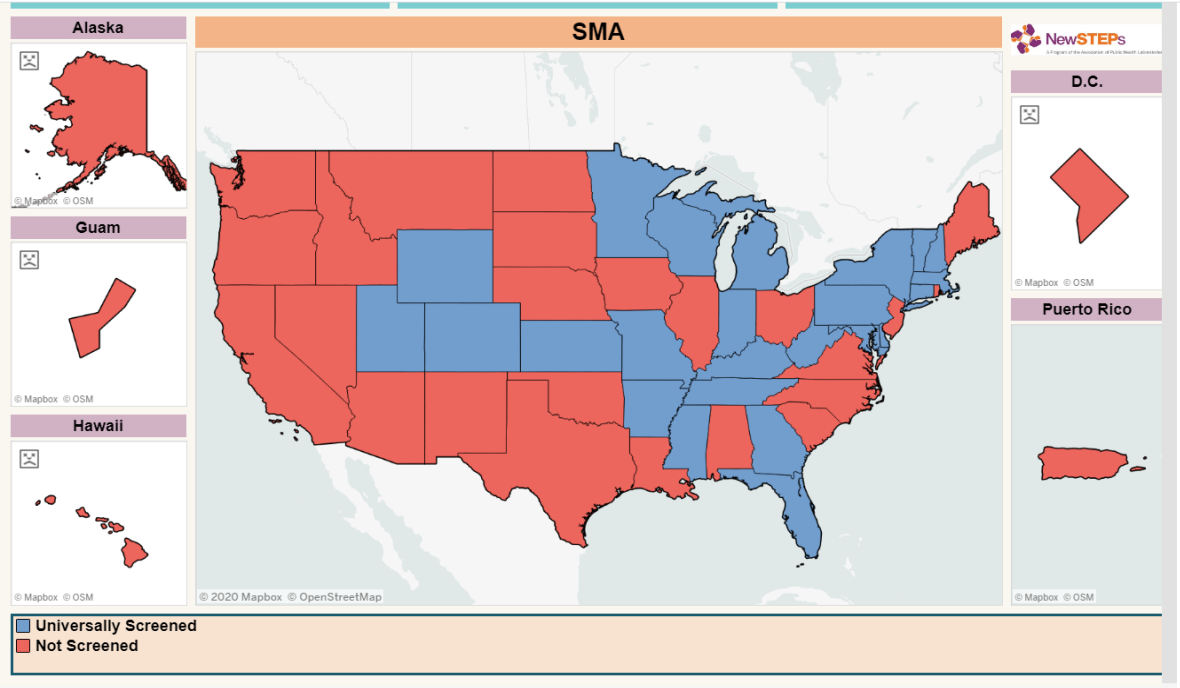
As of **July 2018**,

- 2 states had adopted and just started implementing statewide screening for SMA (Massachusetts and Utah, January 2018).
- 4 states (MN, NC, WI, MO) were planning or preparing to screen either statewide or through a pilot.

State NBS Implementation Status (per APHL Data Repository

As of **May 2020**

- **24** states report to the APHL data repository that they are universal screening for SMA NBS



APHL Data Repository, May 2020

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State NBS Implementation Status (per NBSTRN Reports, as of May 2020)

State NBS for SMA Implementation:

- 24 state NBS programs had adopted and were implementing newborn screening, most multiplexed with SCID
- 8 of 24 assess *SMN2* copy numbers prior to clinical diagnosis (5 in the SMA screening, and 3 through confirmatory testing).
- At least 10 state NBS programs were planning or preparing (including pilots)

SMA Screening Results since July 2018

- Over 1 million newborns screened for SMA
- ~111 of these newborns have screened positive and been diagnosed with SMA (85 from universal screening, 26 from pilot or validation screening)

State NBS Implementation for SMA

Rapid expansion of SMA newborn screening across states!

- Ease of screening procedures and multiplexing with SCID
- CDC development and assistance with procedures for statewide screening
- National technical assistance and expanded screening infrastructure to support and facilitate peer networks among states
- Advances in SMA treatments for newborns diagnosed at birth
- Limited clinical expertise for early treatment initiation decisions for newborns diagnosed with early onset SMA

Summary and Conclusions

- Advancements in SMA therapies
  - New gene therapy for infants with SMA (0-2 yrs)
  - Another therapy (oral, self-administered medication [pill]) under priority FDA review
  - Expansion of nusinersen to later-onset, older SMA patients
- Gene therapy for 0-2-year-olds with SMA appears to have significant benefit.
- Nusinersen benefits for asymptomatic infants with SMA (n=25) appear to be maintained through median 2.9 years follow up after treatment initiation. Drug appears safe but requires intrathecal delivery.
- SMA newborn screening has been rapidly adopted across states, with universal screening increasing from 2 states (Feb 2018) to 24 states adopting SMA (May 2020).

Summary Conclusions

- Availability and accessibility of clinical expertise for newborns with SMA is limited. Training more professionals is needed. Establishing centralized network of providers may provide access to expertise.
- Treatment guidelines have been updated (2020) to recommend immediate treatment for infants with SMA and 4 *SMN2* copies (some might have adult-onset disease).
- Laboratory results for numbers of *SMN2* copies is not reported with sufficient accuracy for *SMN2* copies ≥4. Evidence and laboratory reporting to support identification of 4 *SMN2* copies is needed to inform treatment decisions (although may be less critical than ≤3 copies).
- Families may need to make time-sensitive treatment decisions. Developing educational and training materials for treatments and shared decision-making may facilitate this process.

Questions?