Newborn Screening for Spinal Muscular Atrophy (SMA):

Phase I Update of the Evidence Review

Alex R. Kemper, MD, MPH, MS
K.K. Lam, PhD
Evidence Review Group

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

August 3, 2017

Duke Clinical & Translational Science Institute

Nationwide Children's

Evidence Review Group (ERG)

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 Leader	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	☑	☑	☑
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Key Studies for Decision Model		☑	
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Webinar & PHSI Survey Update, Final Screening Fact Sheet			☑
Update on follow up interviews			☑
TEP 2 Input	☑	☑	☑
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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: Spinal Muscular Atrophy (SMA)

- Autosomal recessive disease affecting the motor neurons in the spinal cord and brainstem, resulting in progressive motor weakness and atrophy
- Broad phenotype spectrum ranging in age of onset (birth to adulthood), severity, and clinical course
- Estimated SMA incidence in the U.S.:
  - 1 in 6,000 to 1 in 11,000 *(~9 - 16 in 100,000)*

  Carrier frequency estimates: 1 in 40 to 1 in 60 *(~1667 - 2500 in 100,000)*
- Many types of SMA, distinguished by the pattern of features, severity of muscle weakness, and age of symptom onset

Types of SMA, Clinical Course, and Affected Gene

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** (extra SMN2)
SMA Type II *(Infantile chronic)*	Six to twelve months	Sit independently, but cannot stand or walk	**SMN1** (extra SMN2)
SMA Type III *(Juvenile, Kugelberg-Welander disease)*	After 18 months	Can stand or walk, but walking, stair-climbing become difficult. Wheelchair assistance usually needed in later life.	**SMN1** (extra SMN2)
SMA Type IV (Adult-onset)	20-30 years	Mild to moderate muscle weakness, tremor, twitching in proximal muscles; difficulty breathing	**SMN1** (extra SMN2)
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**

Types of SMA – Focus of Review

Type *(Alt Names)*	Age of Onset	Clinical Features	Life Expectancy	Affected Gene(s)
SMA Type 0 *(Congenital, Prenatal SMA)*	Prenatal (30-36 weeks)	Decreased fetal movements in utero, difficulty swallowing	Rarely past 6 months	**SMN1**
SMA Type I *(Severe infantile acute; Werdnig-Hoffman disease)*	Birth to six months	Cannot sit independently, difficulty breathing	24 months (med)	**SMN1** (2 SMN2 copies)
SMA Type II *(Infantile chronic)*	Six to twelve months	Sit independently, but cannot stand or walk	25 years (70%)	**SMN1** (3-4 SMN2 copies)
SMA Type III *(Juvenile, Kugelberg-Welander disease)*	After 18 months	Can stand or walk, but walking, stair-climbing become difficult. Wheelchair assistance usually needed in later life.	Normal	**SMN1** (3-4 SMN2 copies)
SMA Type IV (Adult-onset)	20-30 years	Mild to moderate muscle weakness, tremor, twitching in proximal muscles; difficulty breathing	Normal	**SMN1** (4-8 SMN2 copies)

SMA - Case Definitions

Genetics:	• 5q-SMA Types I-IV • ~95% - Homozygous deletion/gene conversion mutation of Survival Motor Neuron 1 (SMN1) exon 7 • ~5% - compound heterozygotes • Variable number of SMN2 genes, correlates with phenotype
Screening:	• Screening Target: homozygous deletion of SMN1 exon 7 • Method: Quantitative Real-time Polymerase Chain Reaction (qPCR) assay using Dried-blood spots • Confirmatory: SMN1 exon 7 deletion • Additional/optional testing: SMN2 dosage (informs phenotype)
Pilots:	NYS NBS Research Pilot (Krazsweski et al., 2017 *accepted for pub*), ~6,200 newborns • 1 of 6,200 screen positive, confirmed Taiwan NBS (Chien et al., 2017) – 120,267 newborns • 7 of 120,267 screen positive, confirmed (1 in 17,181)
Diagnosis:	Genetic Testing for SMN1 exon 7 deletions, SMN2 copy number, clinical exam
Treatment(s):	Nusinersen (FDA-approved Dec 2016) Clinical care support therapies

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=1943)
- Screening and reviews in progress
- Screening by two independent reviewers

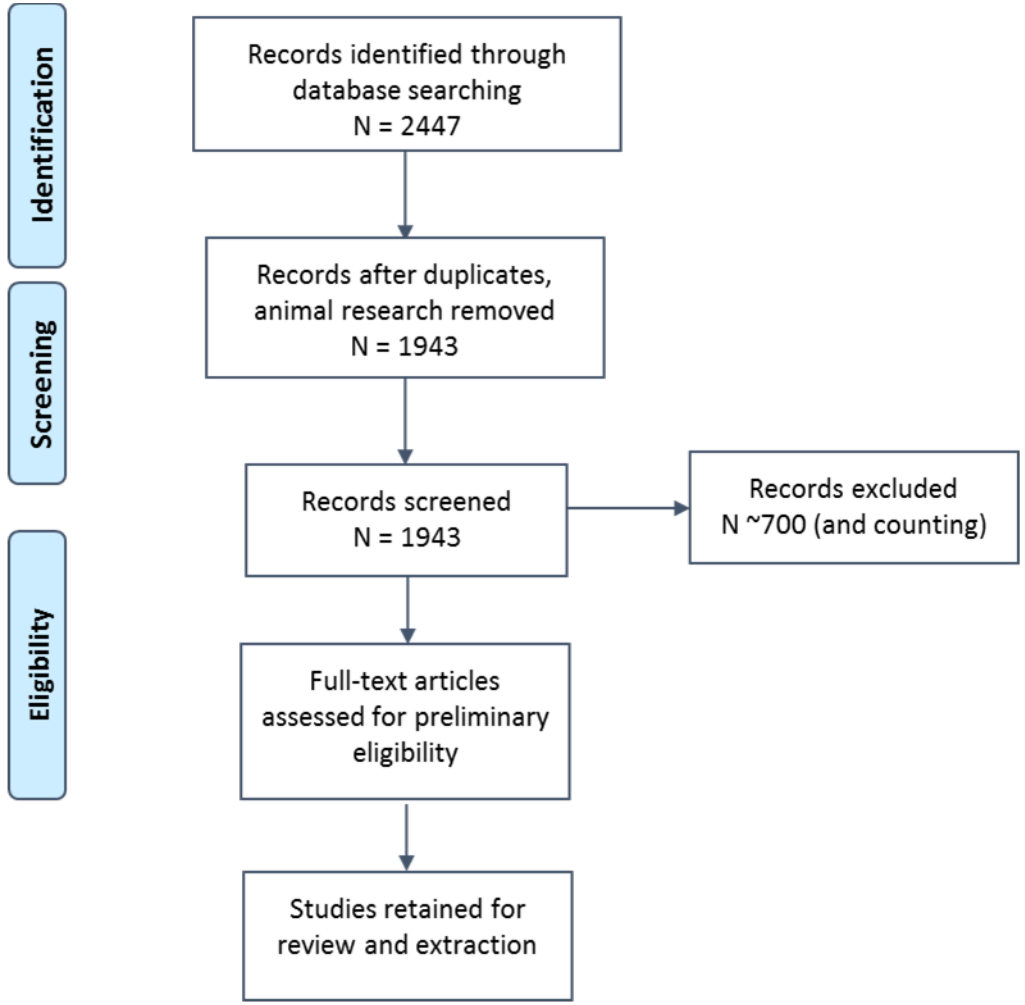
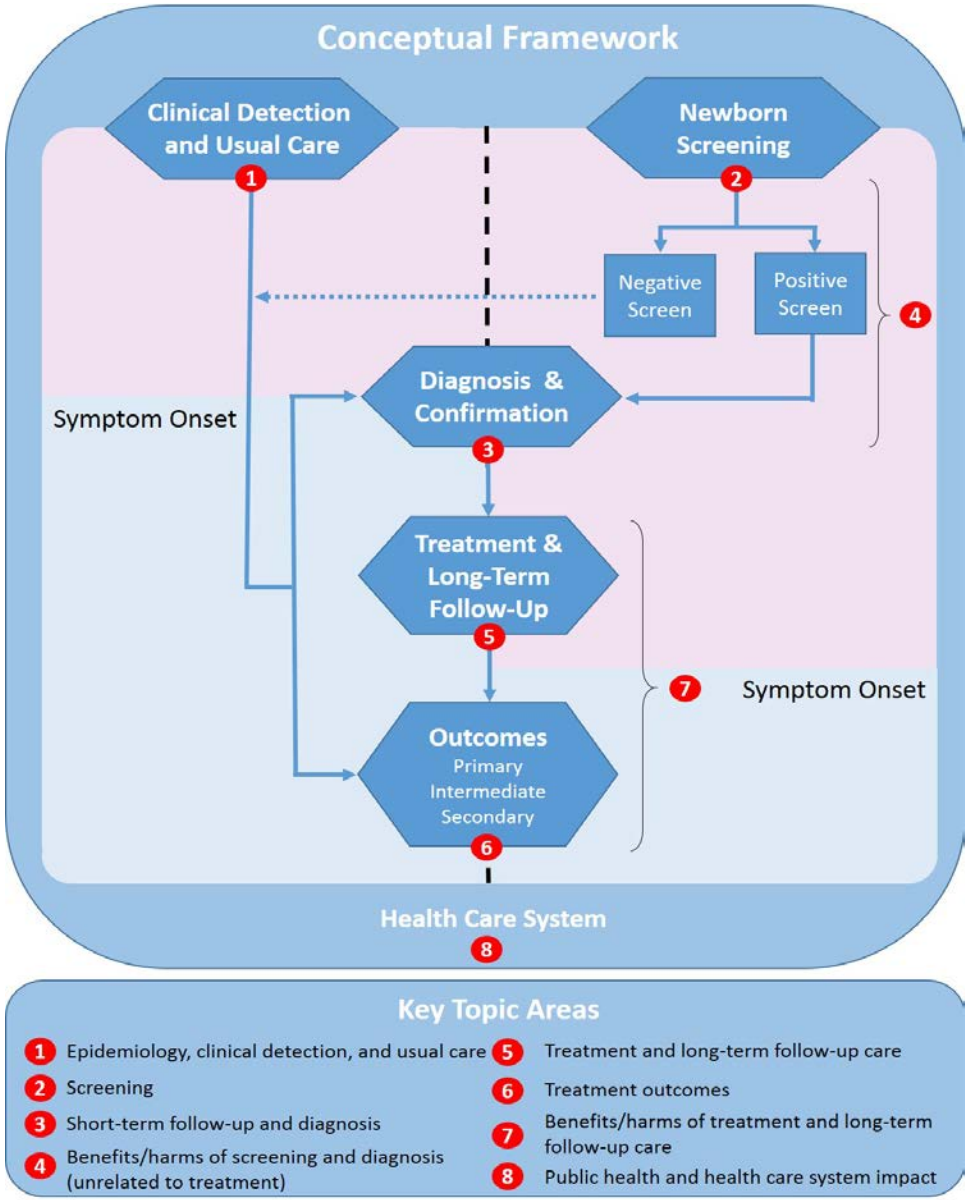


Figure 1. Preliminary PRISMA Diagram of Published Literature Search

Conceptual Framework of Adding Newborn Screening



Key Topic Areas Guiding the Evidence Review

1. **Epidemiology, Clinical Detection, and Usual Care**
   What is the typical course of SMA without newborn screening? How many people are diagnosed with SMA? What are the ages of onset, diagnosis, and treatment without newborn screening?
2. **Screening**
   What is the screening method to detect SMA among newborns? How well does it work? Can the severity or Types of SMA be predicted at the time of screening?
3. **Short-Term Follow-Up (Confirmatory Testing and Diagnosis)**
   How are positive screens confirmed and diagnosed? How well does it work? How long does confirmatory testing and diagnosis take? Are the testing procedures and clinical experts available to care for newborns who screen positive?
4. **Benefits and Harms of Screening and Diagnosis (Unrelated to Treatment)**
   What are the benefits and harms (not related to treatment) that could result from newborn screening and early diagnosis, to the infant and to family members?
5. **Treatment and Long-Term Follow-Up Care**
   What are the current treatments and guidelines for SMA, and do they address presymptomatic detection? Are there guidelines for treatment timing, types, details, changes, and duration? Are experts available to provide treatment?
6. **Treatment Outcomes of the Condition (Clinical Detection and Screening)**
   What are the outcomes of treatment with early detection? What factors influence how well treatment works?
7. **Benefits and Harms of Treatment and Long-Term Follow-Up (with Newborn Screening)**
   What are the benefits and harms of long-term follow-up and treatment, for newborns diagnosed with the condition after screening and their families?
8. **Public Health and Health Care System Impact**
   What is the expected impact of adding newborn screening on
   a) population health (e.g., how many infants would be affected by newborn screening?)
   b) the state public health programs responsible for implementing screening (what is the feasibility, readiness of, and costs for states to expand screening)?

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

- Targeted Research Pilot (3 NYC hospitals)
  - New York State NBS (since Jan 2016)
- Legislative Approval
  - Missouri – July 10, 2017
- States (known to be) considering SMA screening or pilot:
  - Massachusetts
  - North Carolina
  - Wisconsin
- CDC is developing QA/QC and proficiency testing materials for SMA.

NYS (Research) Pilot Screening for SMA

- 3 New York City Hospitals
- Research pilot (sponsor: Biogen, Inc., PI: Dr. Wendy Chung)
- 1 technician, consumables, coordinator (recruitment, follow up), genetic counselor
- Recruitment/Consent:
  - Consent: Opt-in parental (electronic) consent, noted on blood collection form.
  - Recruitment – recruiter approaches mom in post-partum, tablet-based video (English and Spanish), 5-10 minutes.
  - 93% of moms approached agreed to participate (across 3 sites).

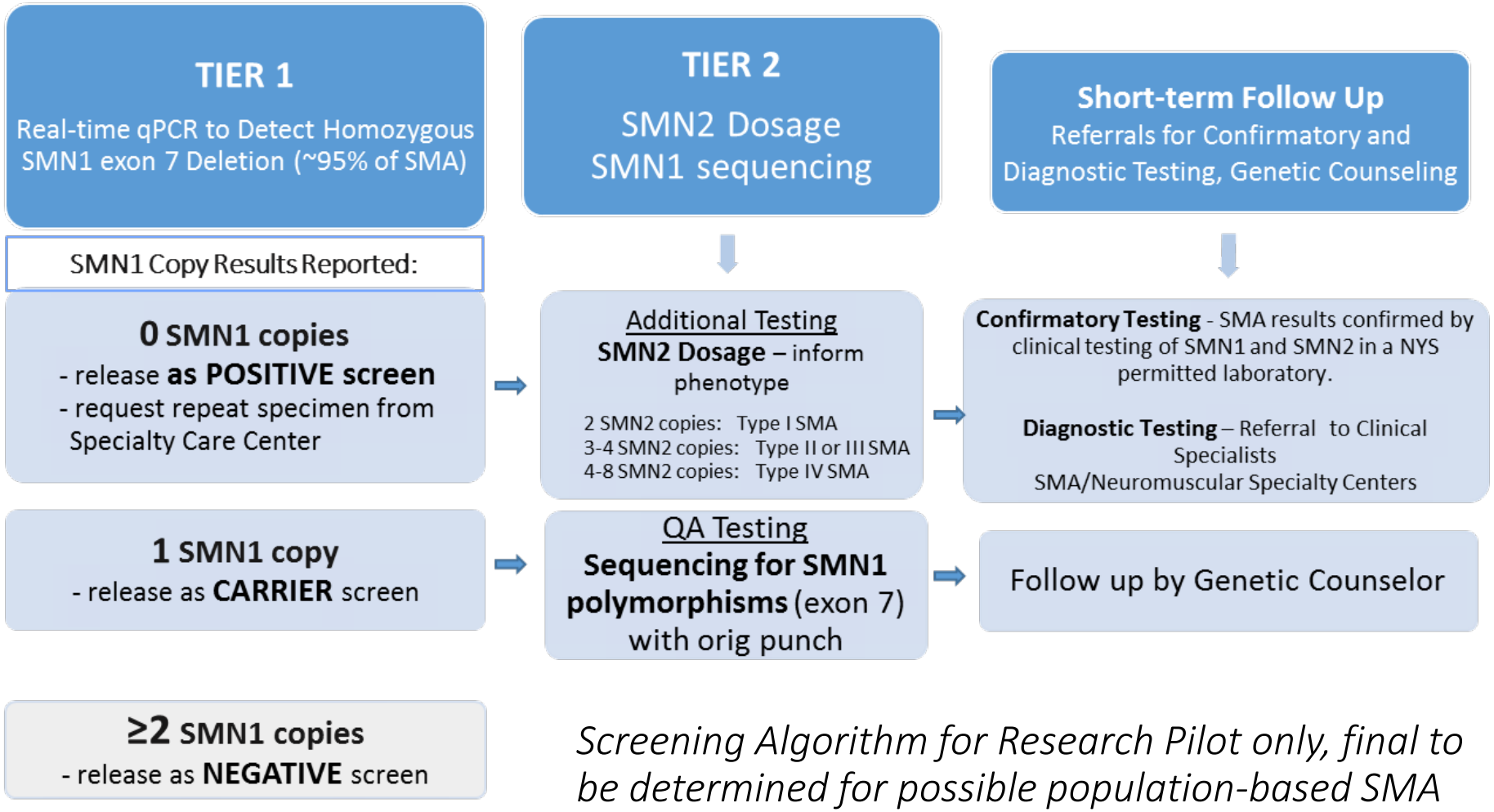
Kraszewski et al. (2017). Pilot study of population-based newborn screening for spinal muscular atrophy in New York State. Accepted for publication, GIM.

SMA Newborn Screening – Research Pilot

- Aim – To demonstrate parental acceptance and feasibility of screening for SMA
- Uses dried-blood spots (DBS), DNA amplification
- Validation (~6 months)
  - 4,000 de-identified population samples
  - 47 positive controls (carriers, SMA-affected)
- Screening Methods

Screening	Description of methods
1st Tier	• Detection of homozygous SMN1 exon deletion • DNA amplification with Real-time qPCR with TaqMan probe
2nd Tier	• Detection of SMN2 copy number (to inform phenotype) • Digital droplet PCR • Targeted sequencing for SMN1 exon 7 polymorphisms
Confirmatory	• SMN1 and SMN2 by a NYS permitted laboratory

NYS – Research Pilot – SMA Screening Algorithm



Screening Algorithm for Research Pilot only, final to be determined for possible population-based SMA screening in NYS.

NYS Pilot Screening Results *(Jan 2016 – June 2017):*

- 93% of moms recruited (in 3 sites) agreed to participate
- ~6,200 newborns screened
  - 1 affected (2 SMN2 copies – SMA Type I)
  - 92 carriers (1 in 68)
- False positives – 0%
- False negatives – expected ~5-7%
  - 5% SMA cases - compound heterozygous for exon 7 deletion and other mutations- some currently detected as carrier
  - Possible other de novo mutations
- Follow up- identified baby with SMA in clinic at 7 days, treated at 15 days. Now 12 months old, asymptomatic, has met milestones appropriately.

NYS Pilot of Newborn Screening for SMA: Lessons Learned (*so far*)

- Pilot and completed/ongoing validation studies suggest:
  - Low false-positive rates, homozygous SMN1 deletion assay (for SMA) not technically challenging if some molecular screening experience
  - High-throughput feasibility
  - Sensitivity (false-negatives) uncertain –
    - Homozygous SMN1 deletions = ~95% of SMA causing mutations
    - ~5% heterozygote SMN1 deletions detected (*in this pilot*)
    - ~2-3% de novo SMA mutations projected, not detected
  - High carrier rates (~1 in 40 to 1 in 60 estimated, 1 in 68 in NYS pilot)
  - Multiplexing with SCID screening (TREC PCR) – straightforward, additional set of probes (NY and other states validating now, good preliminary results)
  - Highly scalable with SCID screening – no additional technicians or instruments if added to SCID

SMA Newborn Screening Methods

Screening Pilot	NY State Pilot	Taiwan Pilot	PerkinElmer (in development)
Description	Uses Real-time qPCR to detect homozygous SMN1 exon7 deletion, and uses RNAseP as reference	detects SMN1 exon7 deletion	detects SMN1 exon7 deletion, SMN2 copy number, TREC (SCID), KREC (XLA), uses RNaseP as reference
First-tier/ Primary Assay	Real-time qPCR with TaqMan probe	Real-time PCR with TaqMan probe	5-plex real-time PCR assay with LNA probe
Instrument	RT-PCR platform such as ABI7900 (Applied Biosystems) or QuantStudio 12K Flex Real-Time PCR System (Thermo Scientific)	StepOne Plus 96-well System (Applied Biosystems)	96-well or 384-well QuantStudio 5 or QuantStudio DX (Thermo Scientific)
FDA status	LDT, not FDA approved	LDT, not FDA approved	N/A, laboratories may source raw materials for LDT from PerkinElmer
Second-tier Assay	targeted Sanger sequencing of SMN1 gene, and TaqMan assay or digital droplet PCR to detect SMN2 copy number	digital droplet PCR to exclude false positives and measure SMN2 copy number	No second-tier test Mulitplex single-tier assay combines detection of SMN1 exon 7 deletion and SMN2 copy number.
Sensitivity	test will detect 95% of SMA causing mutations, other 5% heterozygotes detected (carriers)*	test will detect 95% of SMA causing mutations, other 5% will not be detected	test will detect 95% of SMA causing mutations, other 5% will not be detected

SMA Newborn Screening Methods

Similarities

- Real-time PCR (RT-PCR) detection of SMN1 exon7
- Detection of SMN2 copy number
- Similar reagents required
  - (DNA oligonucleotides to SMN1 exon7 for PCR amplification, and TaqMan probe or locked nucleic acid (LNA) probe to specifically measure SMN1 exon7 levels)

SMA Newborn Screening Methods

Major Difference:

- Single- vs. Two-tier Screen
  - Multiplexed Single-tier Screen - PerkinElmer
    - SMN2 copy numbers determined in multiplexed 1st-tier
  - Two-tier Screening - Taiwan and NY State
    - 1st tier – PCR detection of SMN1 exon 7
    - 2nd tier - confirm SMN1 homozygous deletion, determine SMN2 copy number

Issues:

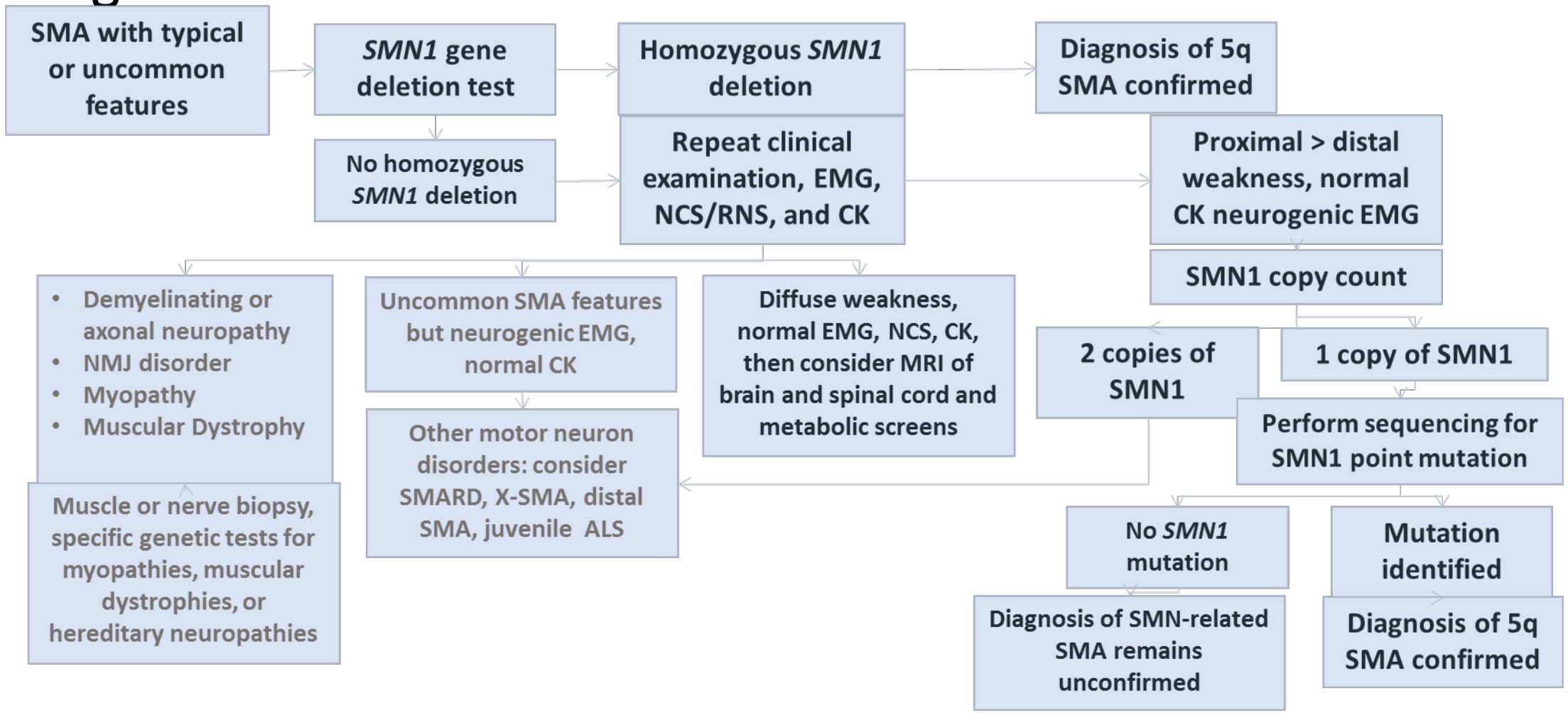
- Carrier status detection and reporting
- SMN2 copy number detection and reporting

SMA Newborn Screening – Population Pilots

Screening Pilot	NY State Pilot	Taiwan Pilot	PerkinElmer *(in development)*
Publication	Kraszewski et al. (2017) accepted for publication., *Genetics in Medicine*.	Chien et al., (July) 2017	None currently.
Validation	De-identified DBS from 4,000 population-based samples, and 47 positive controls (SMA, carriers) 100% concordance with controls	DBS of 2,937 anonymous newborns and 9 samples with known SMN1 / SMN2 copy numbers	DBS of 1,080 newborns and samples with known SMN1 / SMN2 copy numbers
Published 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%) FNR = ~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 FNR = ~5% dates = 11/14 – 9/16	None currently.

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

Diagnosis of SMA with Clinical Detection



Wang et al. (2007). Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *J of Child Neurology.*

Establishing the 5-q SMA Diagnosis

- Genetic testing for homozygous SMN1 gene deletion
- Detection of SMN2 copy number to inform phenotype
- Clinical assessment
  - Physical exam (Clinical and Neurological)
  - Biomarkers
  - Family history

Treatment and Clinical Care for SMA

FDA-approved treatment –

- Spinraza (Nusinersen) FDA-approved 12/23/2016 - first disease-modifying therapy for SMA patients, all types and ages.
- antisense oligonucleotide drug, alters SMN2 to increase SMN protein.

Clinical care approaches improve survival and quality of life

- nutritional support and monitoring of intake and swallow function
- respiratory support
- pulmonary care
- orthopedic and rehabilitation care
- Palliative care

Other therapies in development

- SMN1 gene replacement therapy
- small molecules designed to alter SMN2 mRNA splicing and to protect motor neurons and enhance muscles.

SMA Technical Expert Panel

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

Next Steps for SMA Evidence Review, Phase 2

Convene the TEP (August)

A. Systematic Evidence Review

- Complete Systematic Review & Evidence Tables

B. Decision Analysis/Population Health

- Develop the Preliminary Decision Analytic - Structural Model (for public health impact on the population)
- Determine Target Health Outcomes

  (*prelim*: overall survival, motor function/mobility/ventilator-free)

C. Public Health System Impact Assessment (PHSI)

- Finalize screening implementation fact sheet
- Webinar and Survey administration
- Begin Interviews with Screening States

  (cost, readiness/implementation)

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Questions or Comments?

Thank you!

Alex Kemper, MD, MPH, MS
alex.kemper@nationwidechildrens.org

K.K. Lam, PhD
kk.lam@duke.edu
Ashley Lennox (PhD Candidate)
Emily Miller, PhD

Duke CTSI