The Importance of Newborn Screening and Early Diagnosis to Maximize Clinical Outcomes in Spinal Muscular Atrophy

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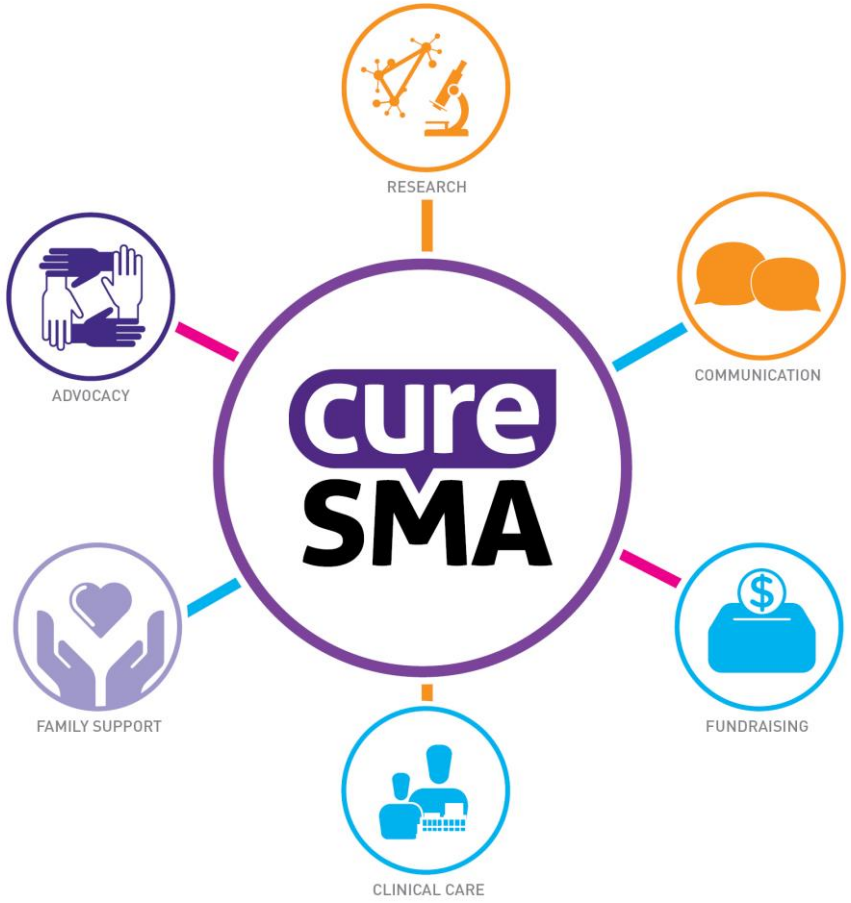
Cure SMA



Vision & Mission

- Cure SMA leads the way to a world without spinal muscular atrophy, the number one genetic cause of death for infants.
- We fund and direct comprehensive research that drives breakthroughs in treatment and care, and we provide families the support they need for today.

Acknowledgment

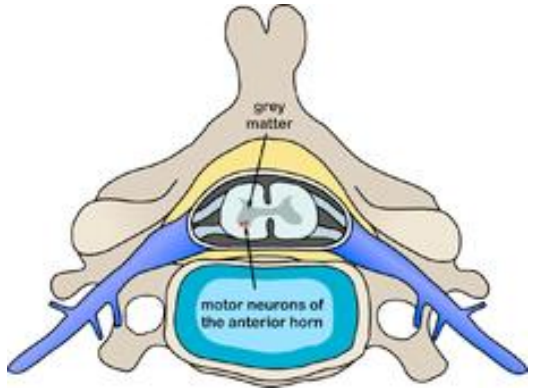
- **Cure SMA Industry Collaboration**
  - Established in 2016 to leverage the experience, expertise, and resources of pharmaceutical and biotechnology companies, and other nonprofit organizations involved in the development of spinal muscular atrophy (SMA) therapeutics to more effectively address scientific, clinical, and regulatory challenges.
  - Current partners include Novartis Gene Therapies, Biogen, Genentech/Roche Pharmaceuticals, Scholar Rock, and SMA Europe
  - Funding provided by Novartis Gene Therapies, Biogen, Genentech/Roche Pharmaceuticals, and Scholar Rock

Objectives Overview

- Recognize the early clinical presentation of Spinal Muscular Atrophy
- Describe the importance of early diagnosis and treatment in infants with SMA and the impact of diagnostic delays
- Describe the current status of newborn screening for SMA and the treatment algorithms for infants identified via newborn screening
- Describe FDA approved treatment options for SMA
- Identify on-demand resources available to enhance provider awareness of the early clinical presentation of SMA

Spinal Muscular Atrophy

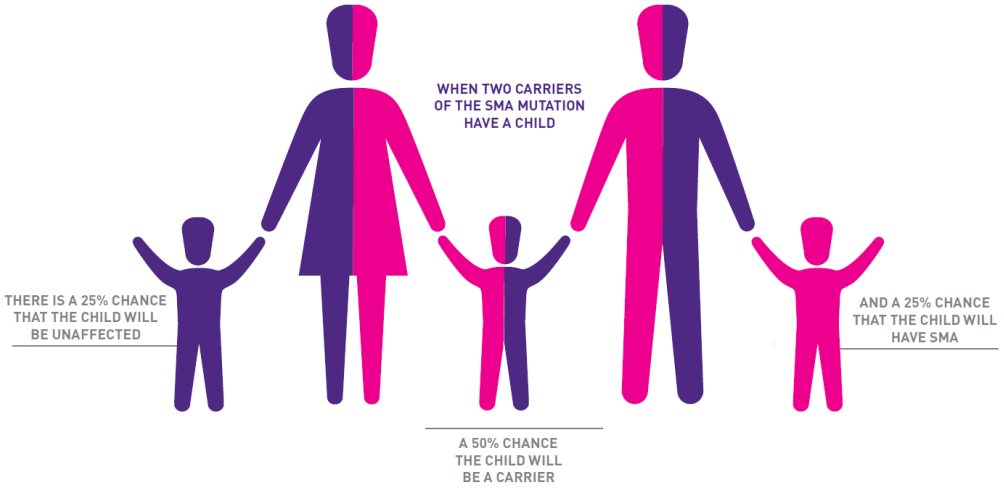
- **Underlying cause:**
  - Gene mutation → Survival Motor Neuron (SMN) protein deficiency
- **Disease of Motor Neurons – nerve disease**
  - Motor neurons send messages from the spinal cord to the muscles
- **Degenerative disease**
  - Fatigue and muscle weakness
- **Multiple parts of the body are involved**
  1. Musculoskeletal
  2. Respiratory -> failure is cause of death
  3. Swallowing, GI and nutrition
  4. Bone health



SMA Genetics

Autosomal recessive

- Carrier rate: 1 in 50
- Incidence estimate: 1/11,000 live births



Diagnose by gene mutation testing (>95%)

- Chromosome 5q
  - Homozygous deletion of SMN1 exon 7 and/or exon 8 (95%)
  - Remaining 5% have point mutation

Most common lethal genetic disease of children under 2 years of age

SMA Gene - Normal

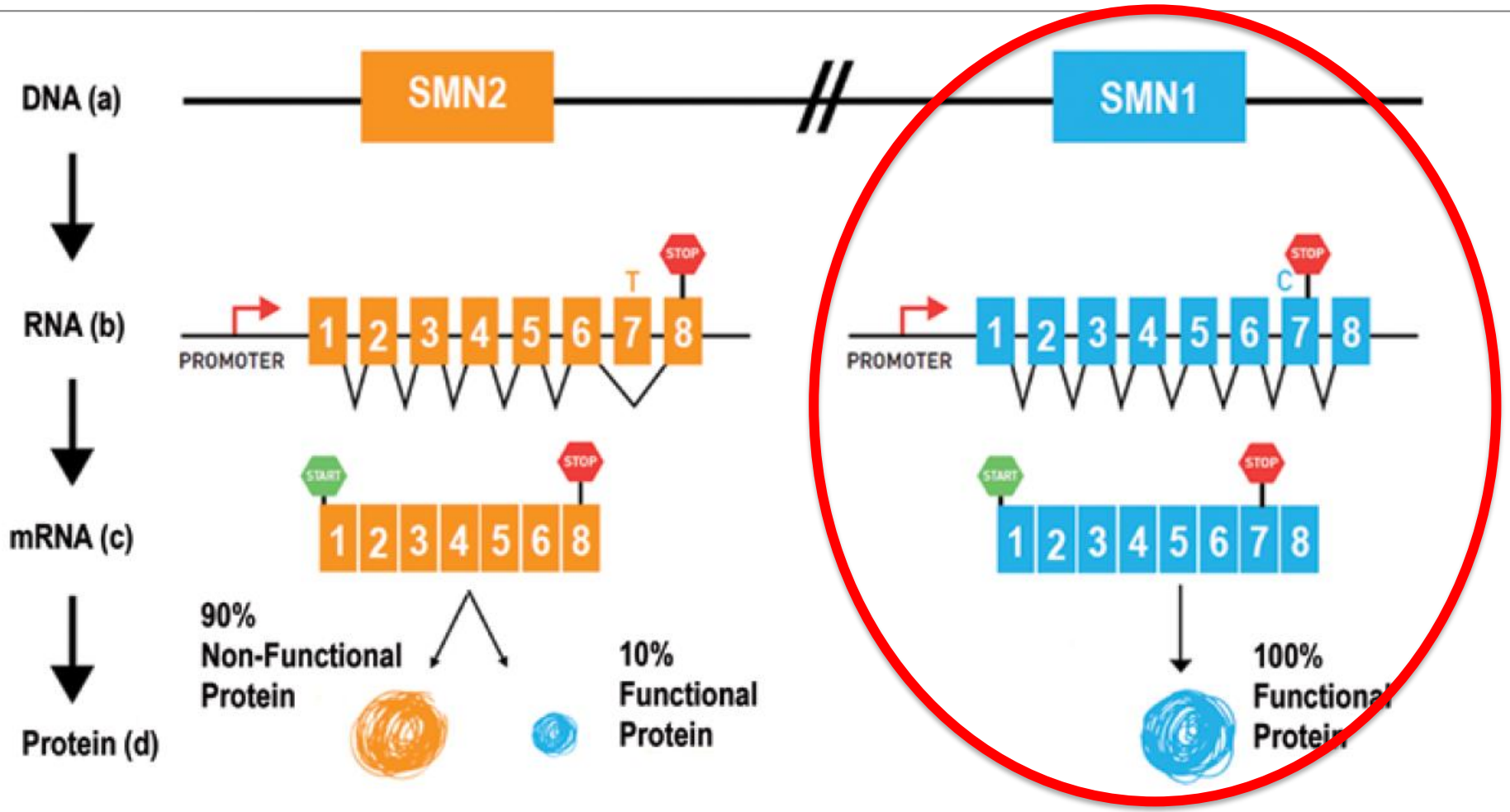
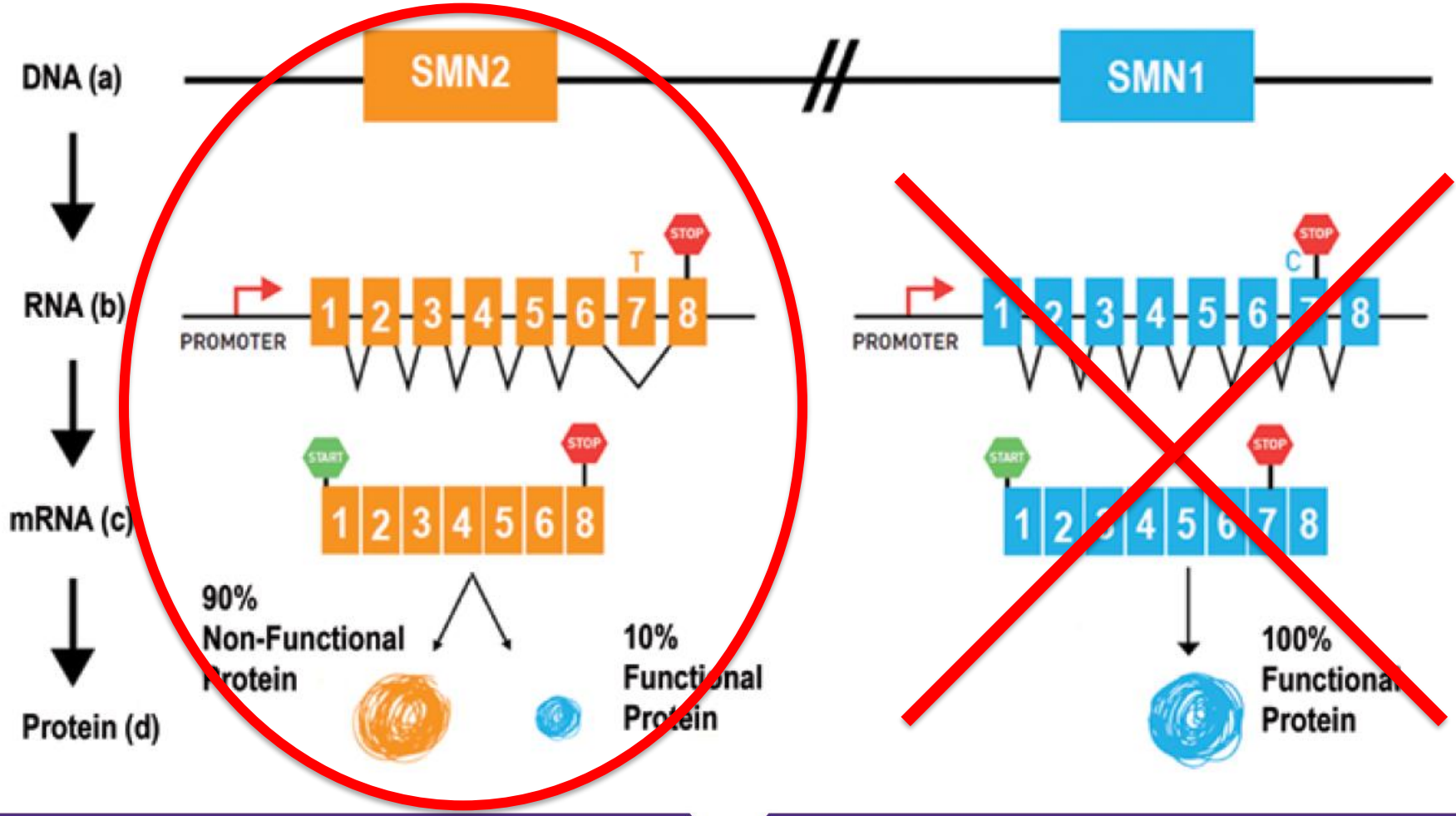


Figure modified and provided courtesy of Louise Simard, PhD, University of Manitoba

SMA Gene - SMA



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SMA Clinical Classification
Pre-Gene Modifying Therapy

Wide range of symptom onset and rate of progression

Type	Age at Symptom Onset	Incidence	Prevalence	Maximum Motor Function Achieved	SMN2 Copy Number	Life Expectancy
0	Prenatally	?	0	None`	1, **2**	Weeks to few months
1	<6 Months	60%	15%	Never sits	1, **2**, 3	<2 years
2	6-18 Months	30%	50%	Never walks	2, **3**, 4	20-40 years
3	1.5-10 years	10%	35%	Walks, regression	**3**, **4**, 5	Normal
4	>35 Years	<1%	<1%	Slow decline	**4**, **5**	Normal

Why early diagnosis is important: SMA Treatments

- **3 FDA approved SMN enhancing treatments**
  - Increase SMN protein levels
- **Mechanism**
  - Replace the function of the SMN1 gene
    - Zolgensma (approved 2019)
  - Alter splicing of the SMN2 gene (backup gene)
    - Spinraza (approved 2016)
    - Evrysdi (approved 2020)
- **All disease modifying treatments**

SMA Treatments

	Spinraza™ Nusinersen	Zolgensma™ Onasemnogene abaparvovec	Evrysdi™ Risdiplam
FDA Approval Year	2016	2019	2020
Type	Antisense oligonucleotide	Single stranded SMN1 DNA via AAV9 vector	Small molecule
Mechanism	SMN2 mRNA splicing modifier	SMN1 functional replacement with SMN1 DNA episome	SMN2 mRNA splicing modifier
Approved age	All	<2 years old	>2 months old
Dose	12 mg/5 ml	1.1×10^{14} vector genomes/Kg body weight	2 months -2 years: 0.2 mg/kg >2 years and < 20kg: 0.25 mg/kg >2 years and >/=20 kg: 5 mg per day Concentration: 0.75 mg/ml
How given	Intrathecal	Intravenous	Enteral (oral or feeding tube)
How often	4 loading doses over 2 months, then every 4 months	One time	Daily
Body distribution	CSF	Blood stream – systemic	Enteral - systemic

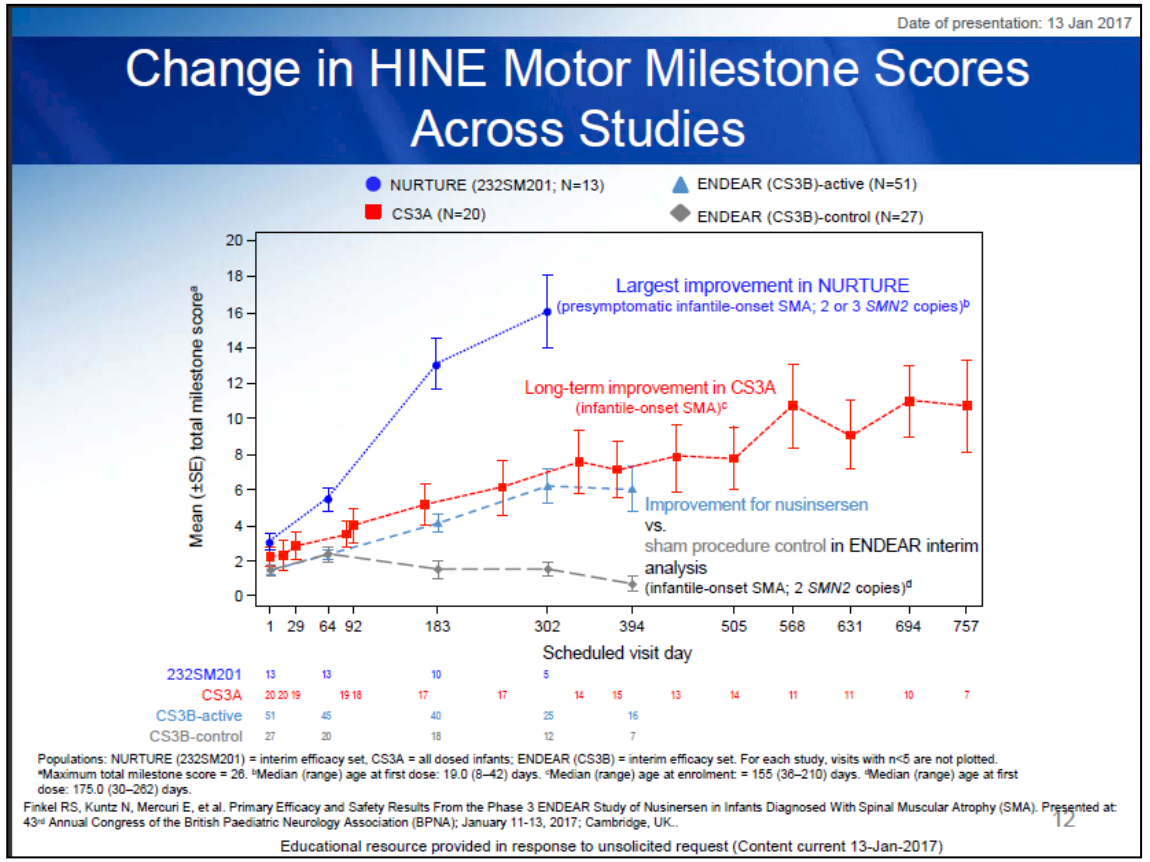
Nusinersin (Spinraza™)

SMA type I symptomatic trial (Endear)

- 51% of treated infants had a motor milestone response vs 0% of untreated group
- Risk of death or permanent ventilation 47% lower in nusinersen treated group

SMA Presymptomatic Trial (Nurture)

- Median 2.9 years of follow up: 100% sitting independently, 92% walking with assistance, 88% walking independently
- No deaths and no permanent ventilation



Finkel R et al, Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy, NEJM, 2017

De Vivo D et al, Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE Study, Neuromuscular Disorders, 2019

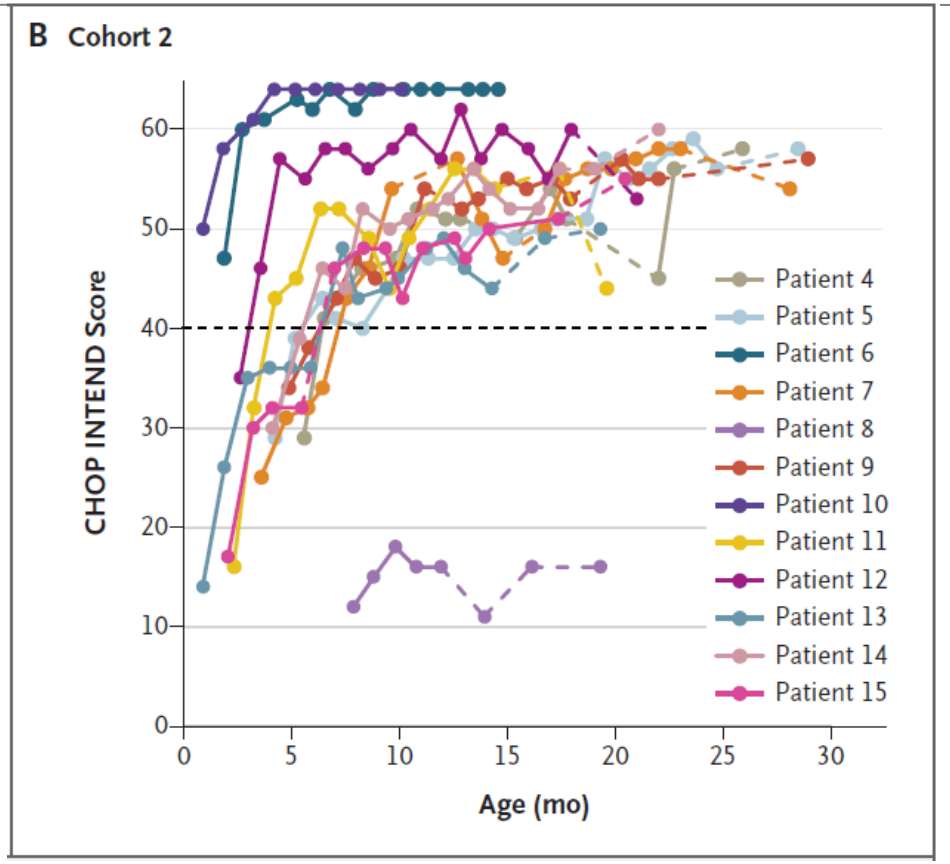
Onasemnogene abeparvovec-xioi (Zolgensma™)

SMA type I symptomatic trial (START)

- At 20 months of age:
  - 11/12 sat unsupported and
  - 11/12 fed orally and spoke
  - No deaths and no permanent ventilation

SMA presymptomatic trial (SPR1NT)

- At 15 months median age:
  - 2 copies SMN2: 79% age-appropriate sitting, 36% standing independently
  - 3 copies SMN2: 100% age-appropriate sitting, 53% standing independently, 40% walking independently
  - No deaths and no permanent ventilation



Mendell J et al, Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy, NEJM, 2017
https://www.novartis.com/news/media-releases/new-zolgensma-data-demonstrate-age-appropriate-development-when-used-early-real-world-benefit-older-children-and-durability-5-years-post-treatment

Risdiplam (Evrysdi™)

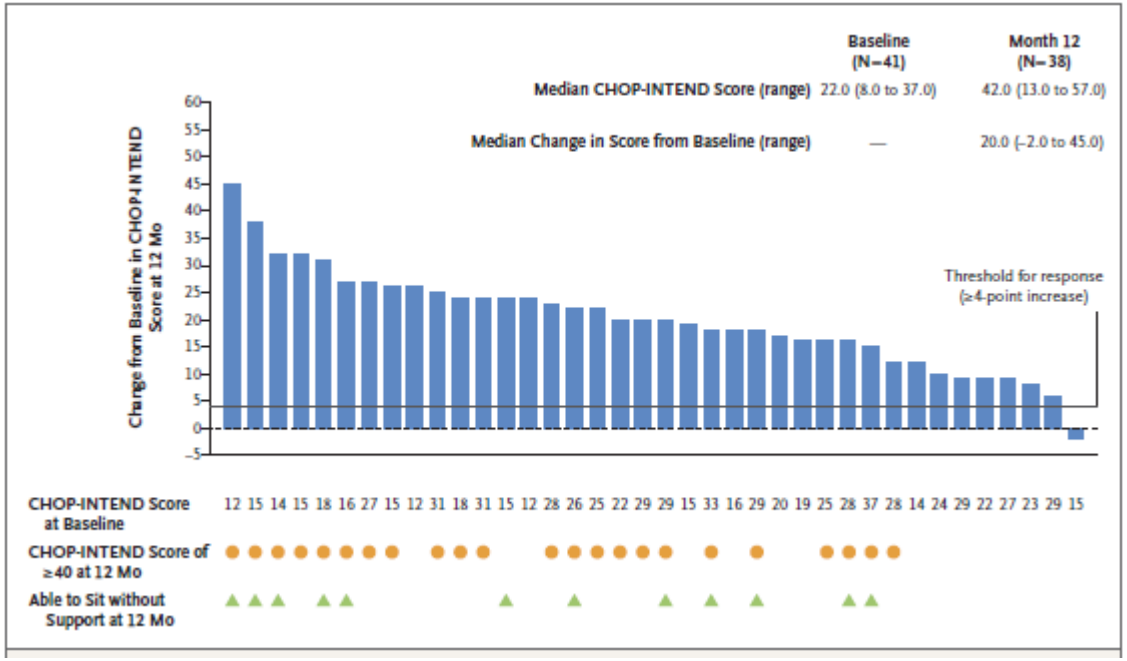
SMA type I symptomatic trial (FIREFISH)

- After 12 months of therapy:
  - 29% sat independently for >/=5 sec
  - 90% increased >4 points from baseline on CHOP-INTEND score
  - 56% CHOP-INTEND score of >/=40
  - 78% HINE-2 motor milestone response
  - 85% Event free survival

SMA presymptomatic trial (RAINBOWFISH)

- After 12 months of therapy:
  - 80% of infants scored maximum HINE-2 total score
  - Most achieved motor milestones within the WHO windows for healthy children
  - 100% reached maximum CHOP-INTEND score, and most achieved maximum score by 4-5 months of age
  - 100% survival
  - No treatment serious adverse events

Motor Function After 12 months of Risdiplam Treatment



Darras et al, Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls, NEJM, 2021
Finkel et al, RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA), presented at Cure SMA 2021 Virtual Research & Clinical Care Meeting

SMA Diagnosis

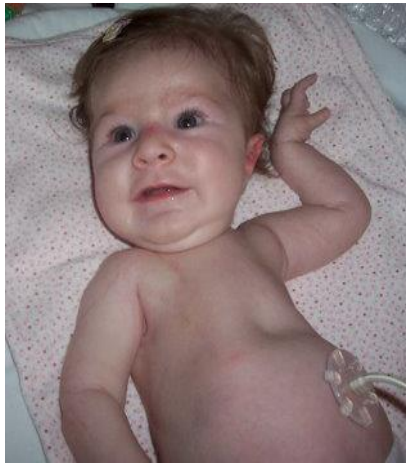
Clinical Emergency

Time is neurons!

Early treatment = best outcomes

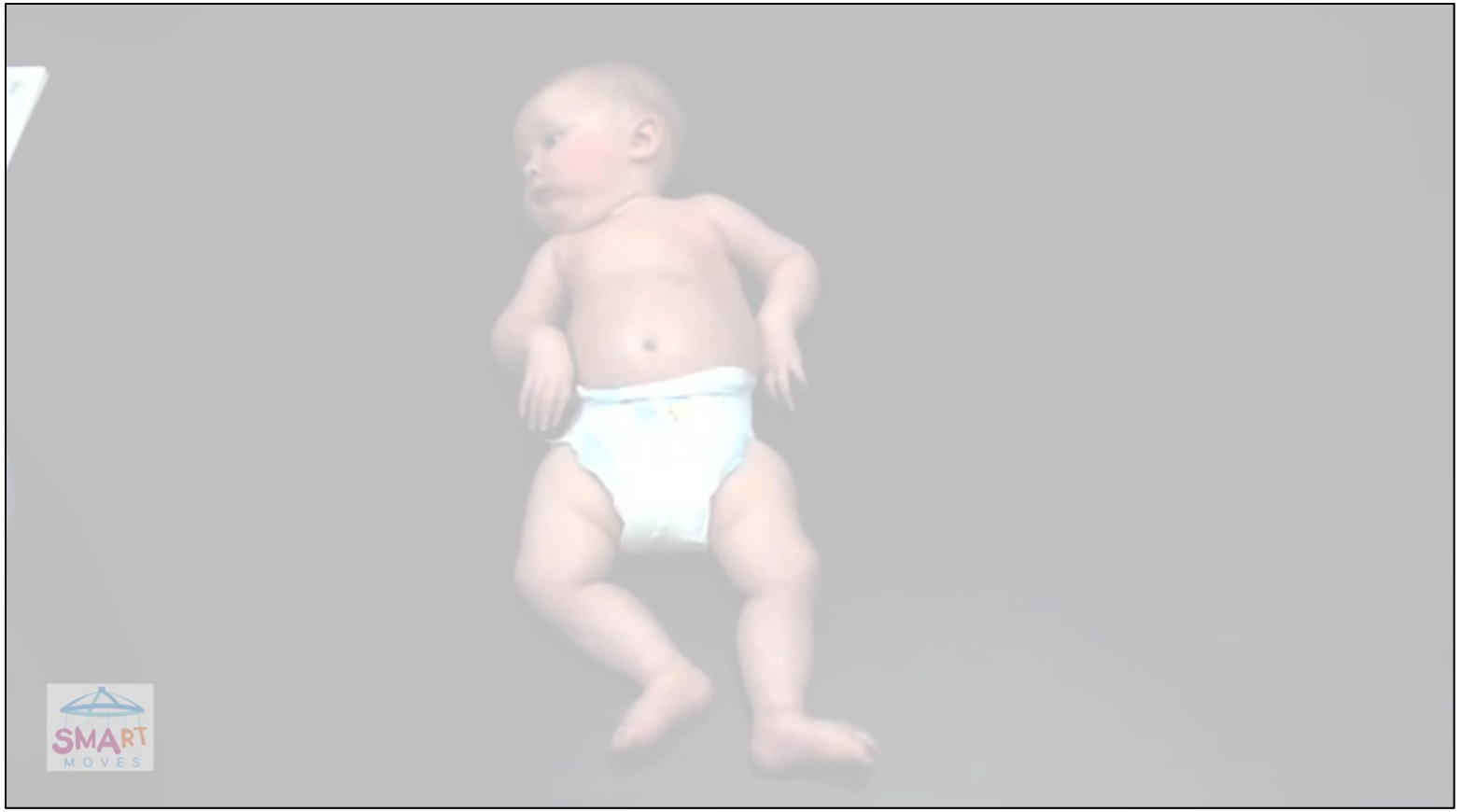
SMA Presentation

Smiling, socially engaging infant with diffuse hypotonia



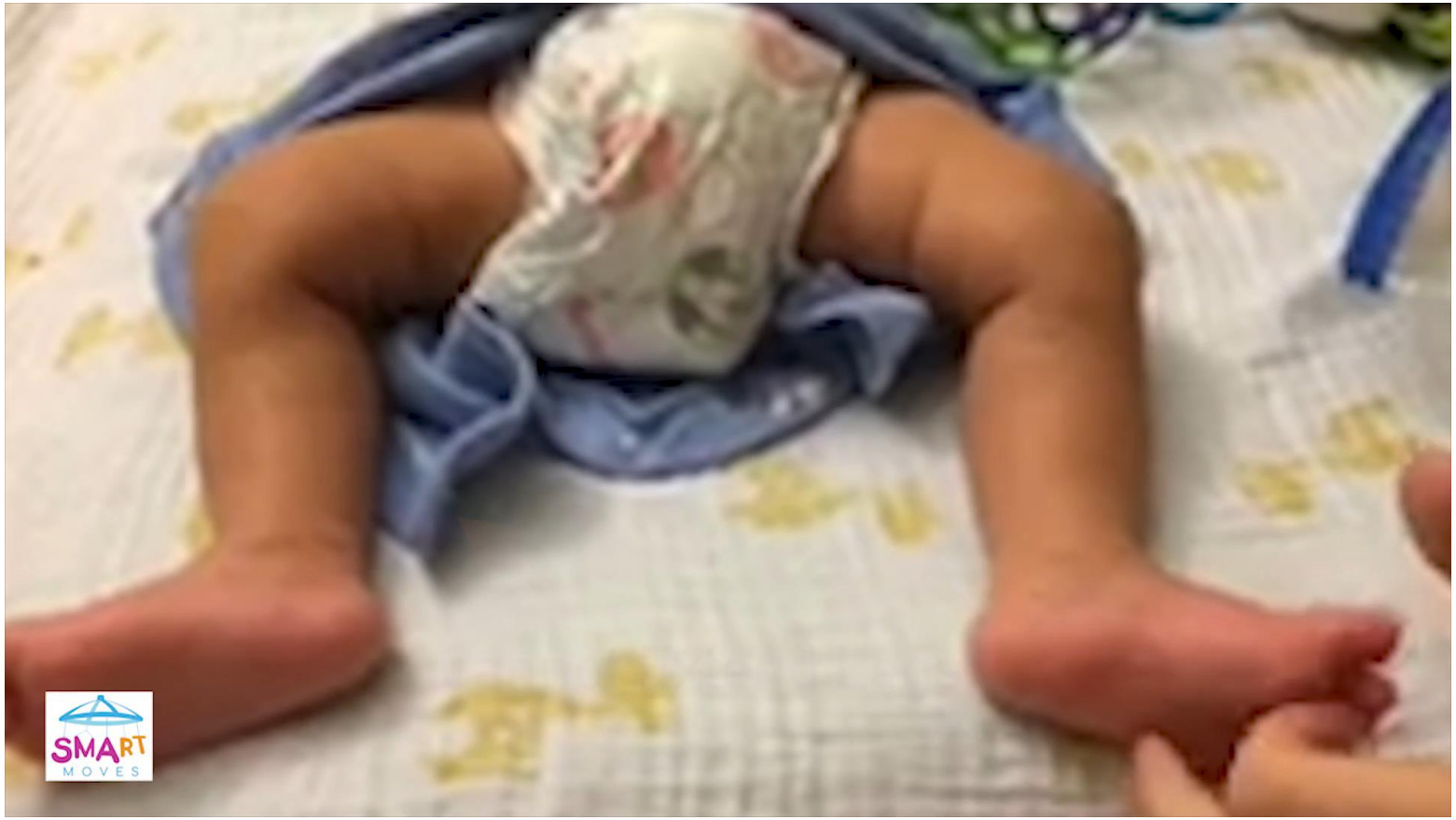
1. Proximal muscles weaker than distal
   - Limited anti-gravity movement
2. Legs weaker than arms
3. Tongue fasciculations
4. Absent deep tendon reflexes
5. Intercostal muscle weakness with diaphragm/belly breathing and chest wall collapse

Early Warning Signs:
Tachypnea with Paradoxical Breathing



www.SMArtMoves.CureSMA.org

Early Warning Signs: Hypotonia, Difficulty Lifting Extremities Against Gravity, Areflexia

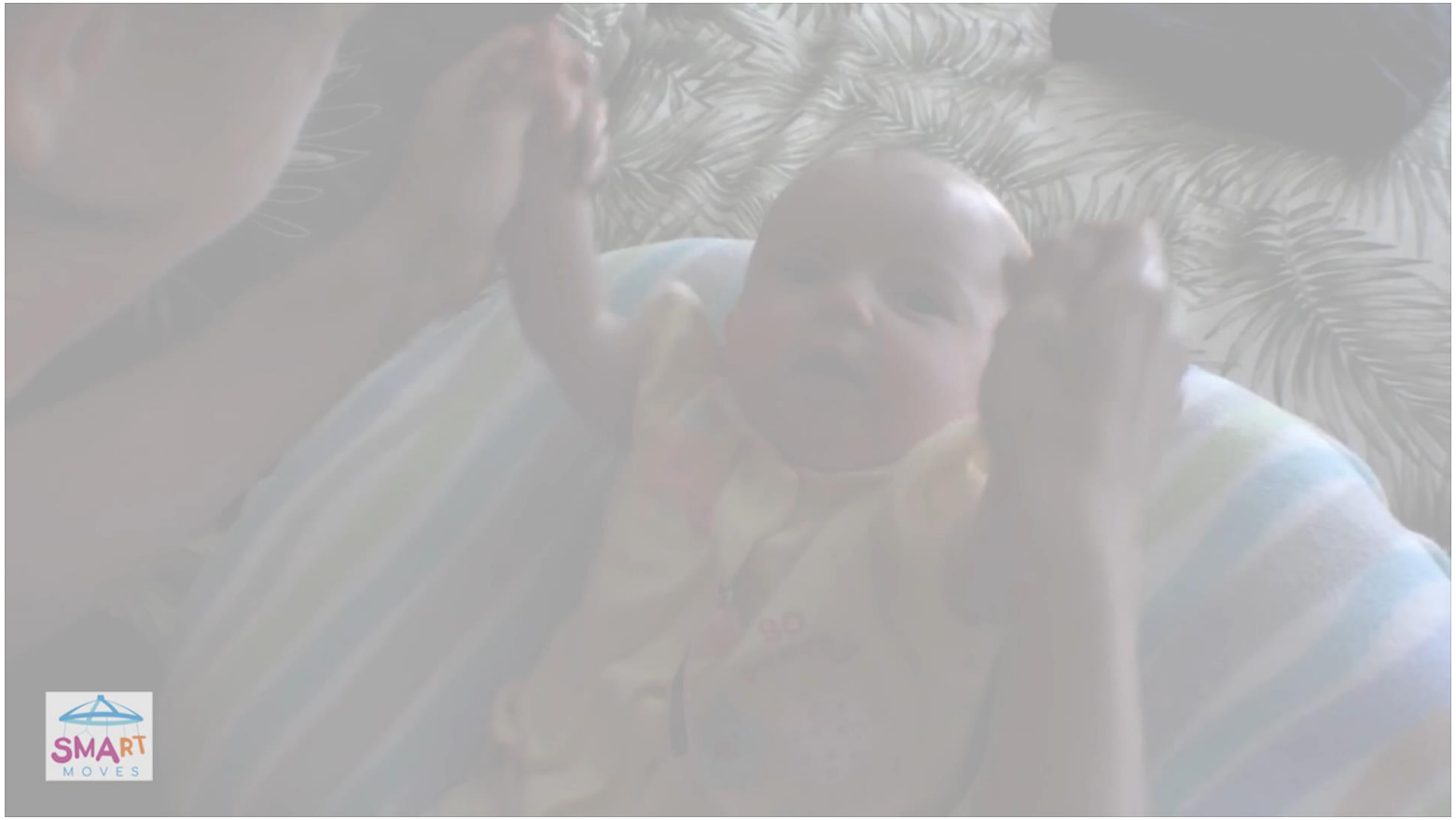


www.SMArtMoves.CureSMA.org

Early Warning Signs: Hypotonia, Lack of Squirming

www.SMArtMoves.CureSMA.org

Early Warning Signs:
Bright-eyed and Smiling with Hypotonia



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SMA Diagnostic Algorithm

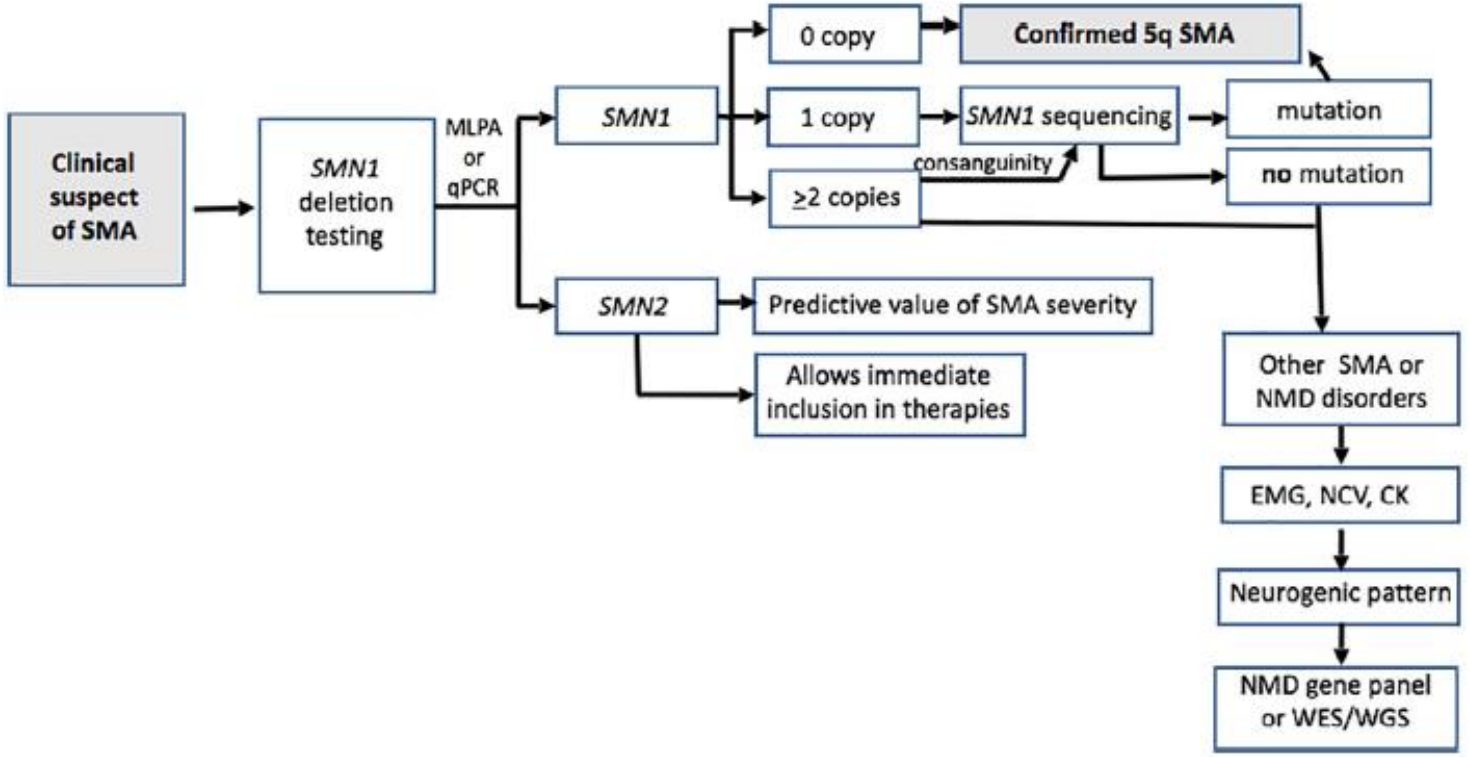
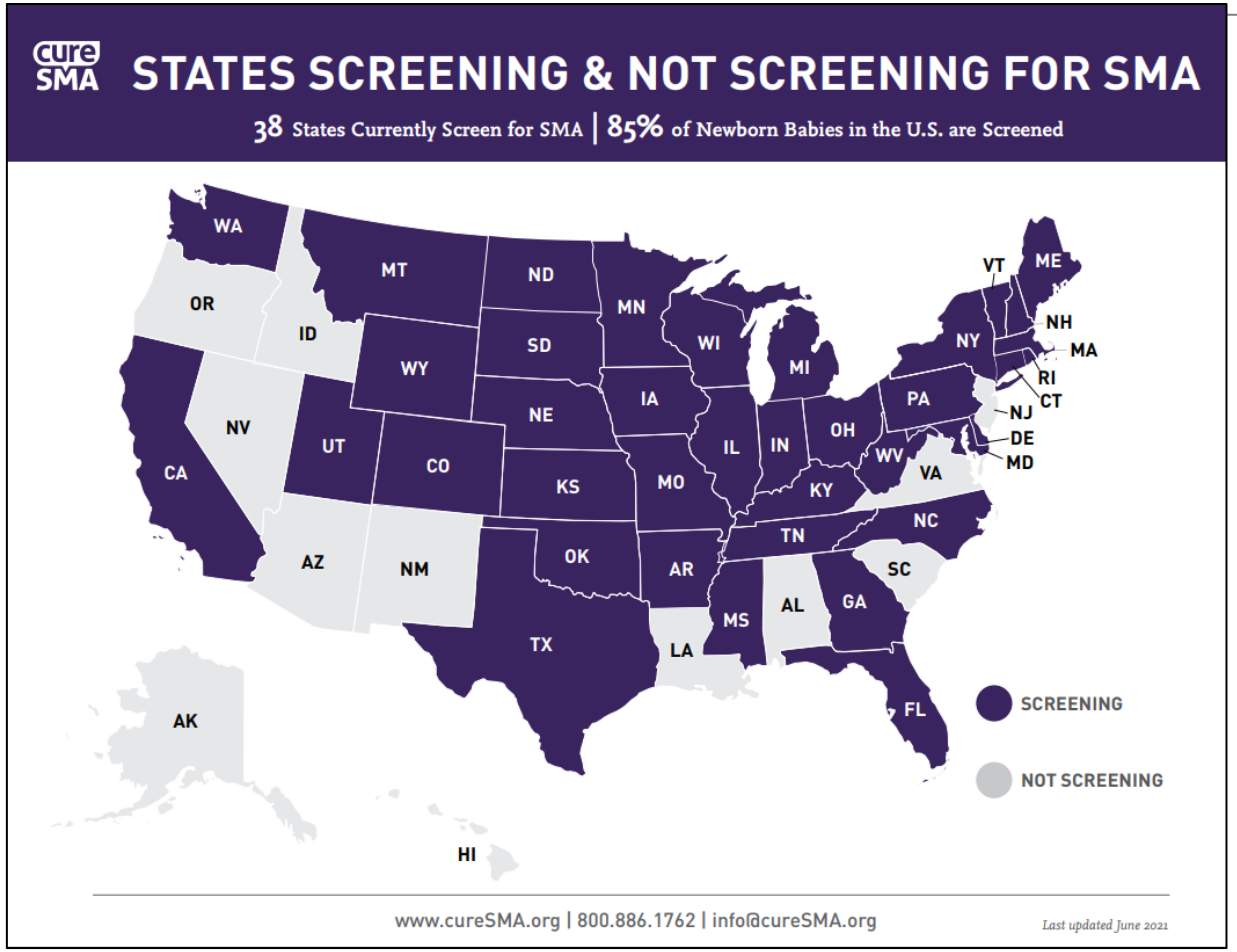
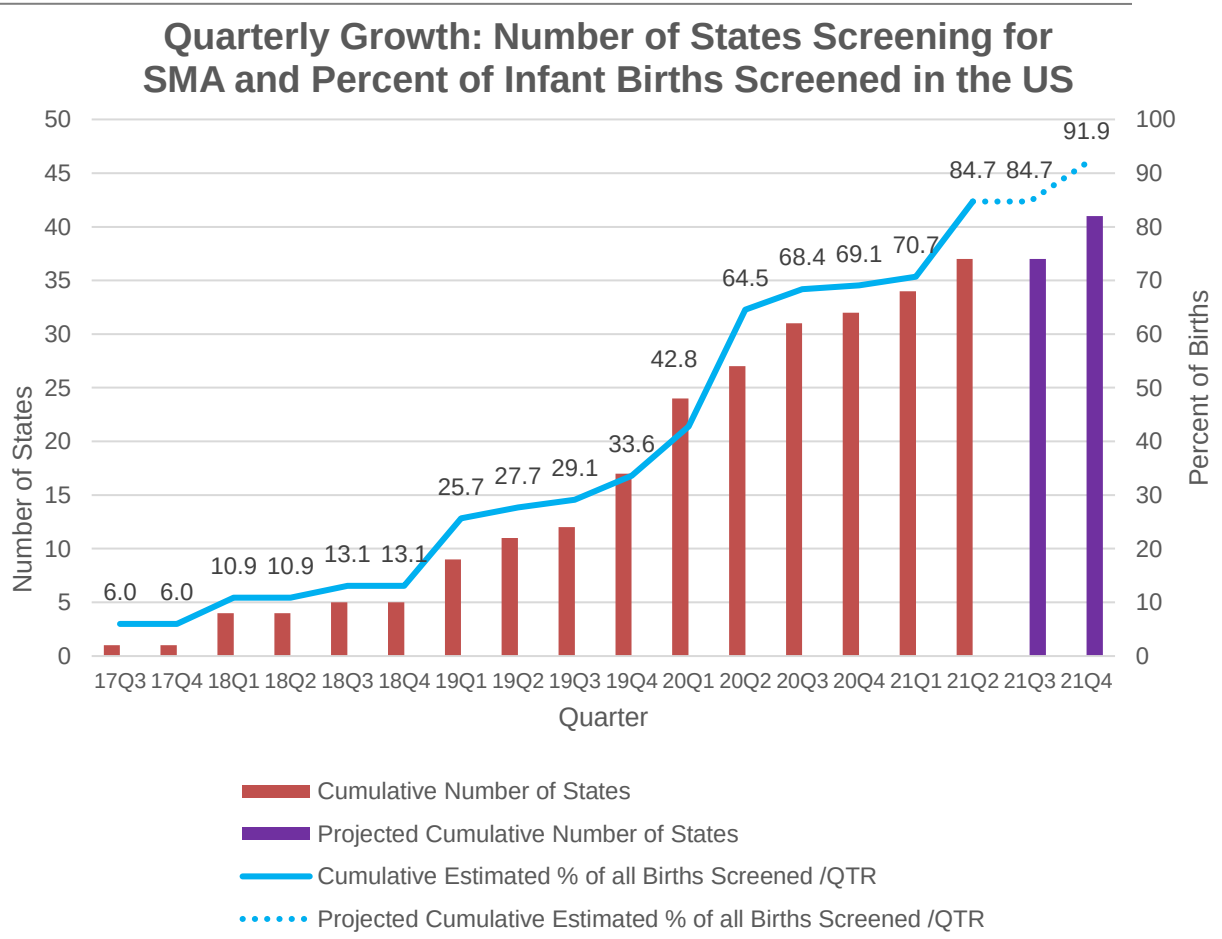


Fig. 1. Diagnostic algorithm for spinal muscular atrophy (SMA: spinal muscular atrophy; SMN1: survival motor neuronon 1; SMN2: survival motor neuron 2; NMD: neuromuscular disorders; EMG: electromyography; NCV: nerve conduction velocity; CK: creatine kinase levels; WES: whole exom sequencing; WGS: whole genome sequencing).

Mercuri et al, Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care, Neuromuscular Disorders, 2018; 28:103

SMA Newborn Screening



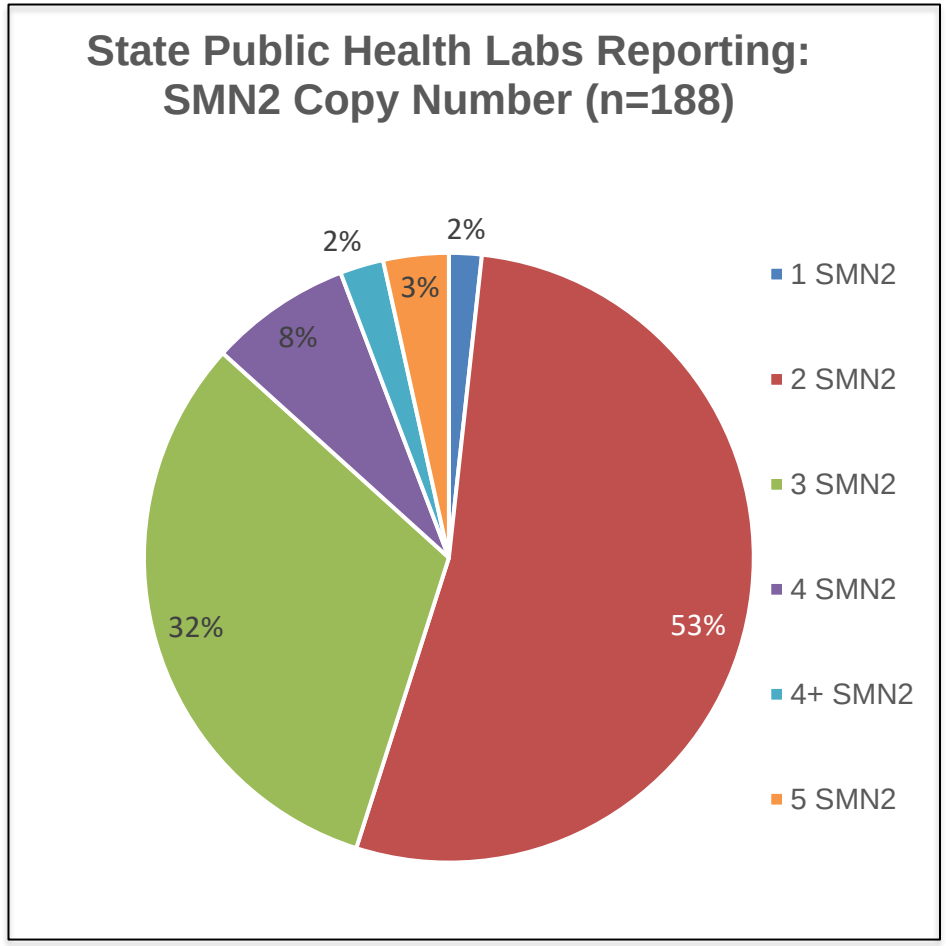


Positive SMA Newborn Screening Follow Up

- **Requires urgent/emergent referral to Neuromuscular Care Center**
  - Confirmatory testing
    - SMN1 and SMN2 copy number
  - Treatment options discussion
    - 2 disease modifying treatments available for infants < 2 months
      - Zolgensma™
      - Spinraza™
    - Treatment should be offered to all infants with SMN2 copy number 1-4 (Glascock et al, Journal of Neuromuscular Disorders, 2020)
  - Genetic counseling

SMA NBS Incidence

- **36 states with permanent SMA NBS**
- **2 states with pilot or population screening**
- **30 states reporting:**
  Preliminary estimated SMA incidence ~1:14,700 births
- **4,029,770 infants screened for SMA**
  - 274+ infants identified
  - 166 families have contacted Cure SMA



RESOURCES

To Help Bridge the Gap: SMArt Moves

Cure SMA awareness campaign

- **Reduce diagnostic delays** in SMA by **recognition of the early signs**
- Intended to **bridge the gap** until universal inclusion of SMA on NBS panel
- Equips parents and healthcare professionals with tools to promptly diagnose SMA and facilitate treatment
- **On-demand materials** include:
  - Videos highlighting the early symptoms
  - SMA Diagnostic Toolkit
  - SMA 1-Page Quick Reference Guide
  - CME Activities
- www.SMArtMoves.CureSMA.org

SMART MOVES

EARLY ACTION, EARLY TREATMENT, SAVES LIVES.

SMA NBS Registry

- Survey questions developed by Cure SMA with input from multiple SMA experts
- IRB Approved protocol
- Families can consent to allow providers to enter information
- Separate portals for physicians and caregivers
- www.curesma.org/NBSR

Access and Treatment Sites

Website Site Locator Tool:

- **229 Spinraza Sites**
- **65 Zolgensma Sites**
- **100 Evrysdi Providers**
- **19 Care Center Network Centers**
- **https://www.curesma.org/find-a-location/**

SMA Standard of Care Guidelines: revised 2018

Diagnosis and management of spinal muscular atrophy; Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Neuromuscular Disorders 28: 103-115, 2018

Diagnosis and management of spinal muscular atrophy; Part 2: Pulmonary care and acute care; medications, supplements and immunizations; other organ systems; and ethics

Neuromuscular Disorders 28:197-207, 2018

https://www.curesma.org/clinical-guidelines/

Summary

- **Spinal muscular atrophy**
  - Treatable disorder with FDA approved gene modifying treatments, but not cures
  - Suspected SMA is an emergency referral to a neuromuscular clinic for diagnostic confirmation
  - Resources:
    - www.curesma.org
    - www.SMArtMoves.CureSMA.org
    - https://www.curesma.org/find-a-location/

THANK YOU

- **For additional questions, please contact:**
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  - mary@curesma.org


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