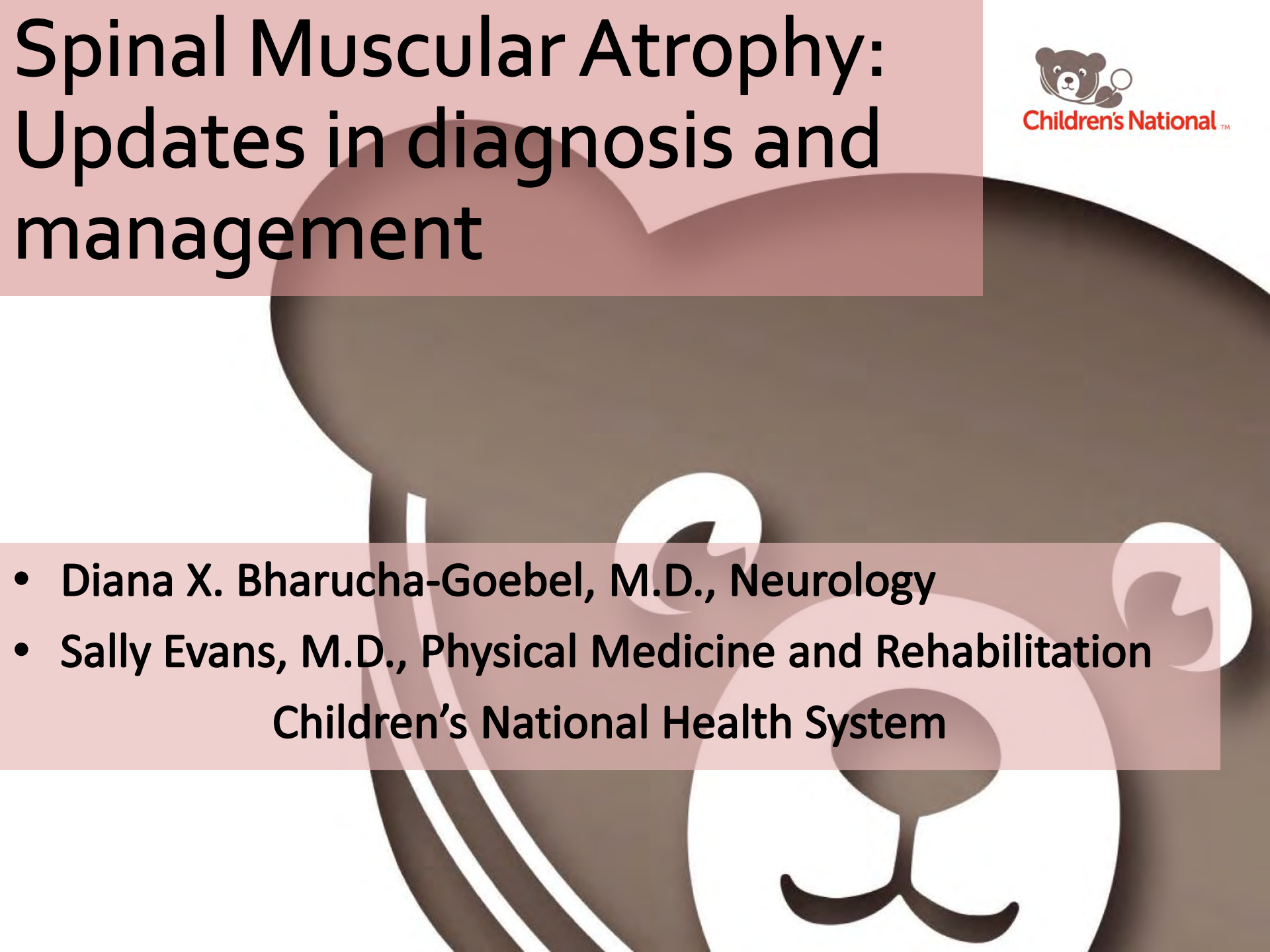
Spinal Muscular Atrophy: Updates in diagnosis and management



- Diana X. Bharucha-Goebel, M.D., Neurology
- Sally Evans, M.D., Physical Medicine and Rehabilitation

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Objectives

- What is SMA?
  - Pathophysiologic and genetic mechanisms
  - How to identify a case of SMA
- What can be done?
  - Review of advances in standards of care and treatment
  - Detailed review of treatment available regionally
- What to do if you have a suspected case?
  - How to refer a patient?
  - How to counsel a patient/ family?
  - Urgency of referral

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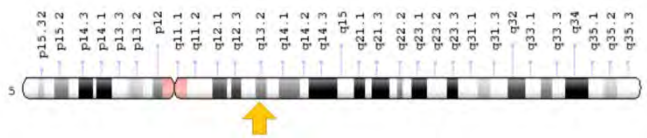
What is Spinal Muscular Atrophy?

- Autosomal recessive pediatric onset neurodegenerative disease
- Deletions (mutation) in 5q13 *SMN1* gene 'Survival of the motor neuron gene'



- SMN protein is important for motor neuron health and survival
  - Progressive loss of alpha motor neurons in the anterior horn cell of spinal cord

- Incidence 1:10,000

- Carrier frequency about 1:35 in the Caucasian population **
  - ** May be even higher because we may miss:
    - Asymptomatic individuals
    - Embryonic lethal subjects

Images:
www.clinicalgate.com
https://ghr.nlm.nih.gov/gene/SMN1#location

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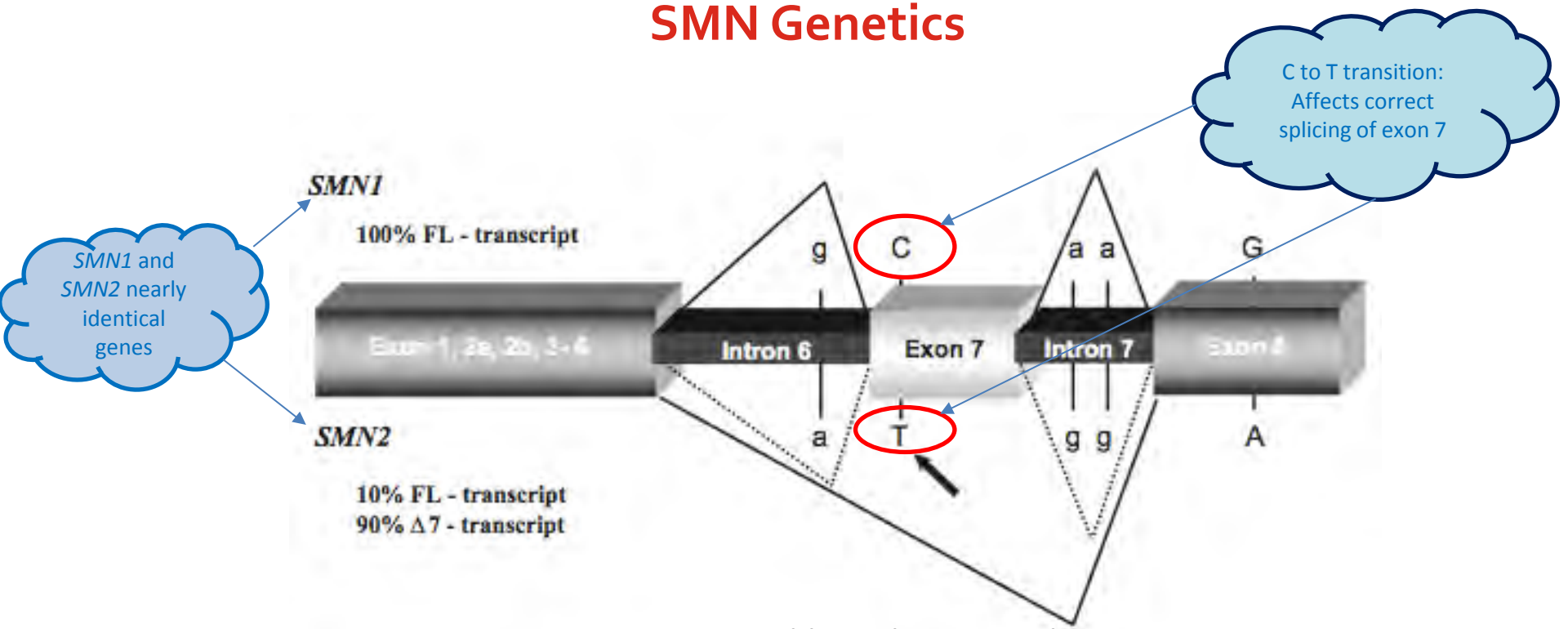
SMN Genetics



Exon 7 not recognized by splicing machinery
Get SMN2Δ7 transcripts

Truncated SMN protein (only 282 aa) is unstable and nonfunctional

***SMN2* gene allows for rescue (from embryonic lethality)**

Less efficient = each copy produces about 10-15% full length protein compared to SMN1 gene

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SMA Subtypes

The more SMN2 copies you have, the better….

Type	Frequency	SMN2 Copy	Age Onset	Max Motor	Survival	Comorbidities
0	<1 %	1	Prenatal	Never sit	< 6 mo	Respiratory failure Dysphagia Contractures Decreased fetal movement
1	50–60 %	2,3	0–6 mo	Never sit	< 2 yr	Respiratory failure Dysphagia Weak cough Paradoxical breathing Contractures Severe weakness
2	30 %	2,3,4	<18 mo	Sit	> 2 yr/Adult	Respiratory insufficiency Weak cough Tremor Scoliosis Contractures Weakness
3	10 %	3–4	18 mo – 21 yr	Walk	Adult	Variable weakness Joint contractures Scoliosis
4	1 %	4+	Late childhood-Adult	Walk	Adult	Mild weakness

SMA Type 1 (Werdnig-Hoffman Disease)

- Disease onset – within first 6 months of life
- Muscle weakness, hypotonia, areflexia – in limbs and trunk
- Clinical course:
  - Impaired head control (neck weakness)
  - Unable to sit or walk
  - Weak cry and cough
  - Difficulty with swallowing, feeding, and handling of oral secretions (before 1 year of age)
  - Die (or require > 16 hrs respiratory support) within first 2 years of life – due to bulbar dysfunction or pulmonary complications

SMA Type 2

- Intermediate Form
- Symptom onset after 6 months old
- Clinical Course:
  - Achieve sitting, but never able to walk unaided
  - Bulbar weakness; swallowing difficulties – can lead to poor weight gain
  - Intercostal muscle weakness → weak cough, difficulty clearing secretions
  - Fine tremors with extended fingers or when attempting hand grips
  - Kyphoscoliosis develops – requiring bracing or spinal surgery
  - Joint contractures over years
  - Lack of DTRs in about 70% of patients
  - Survival > 2 years

Wang C, et al. J Child Neurol 2007.

SMA Type 3 (Kugelberg-Welander Disease)

- Able to sit and walk (some lose ability to walk in childhood)
- Presenting Features:
  - Difficulties ascending and descending stairs at 2-3 years of age
  - Proximal Muscle weakness
  - Lower extremities more severely affected than upper extremities
  - Reduced or absent DTRs

  - Onset < 3 years – Type 3a
    - 44 % maintained walking by age 20 years
    - 22% maintained walking by age 40 years

  - Onset > 3 years – Type 3b
    - 90% maintained walking by age 20 year
    - 58% maintained walking by age 40 years
- Scoliosis can develop
- Swallowing, cough, and nocturnal hypoventilation (may occur)
- Muscle aches and joint overuse symptoms are common

Wang C, et al. J Child Neurol 2007.

Spinal Muscular Atrophy:

Making the Diagnosis

DNA Testing for SMA – 1st line

- *SMN* gene deletion test (Athena, Quest, Invitae)
  - Via molecular genetic PCR-based testing (2-3 weeks for result; now quicker)
  - 95% sensitivity, 100% specificity
  - 95% will have homozygous deletions of SMN1
    - 90% homozygous absence of exons 7 and 8
    - 10% show homozygous absence of exon 7 but not 8
  - ~ 4% of SMA patients exhibit intragenic *SMN1* mutations instead of deletion
- EMG → less used as first line; possibly more in later onset cases
- Prenatal diagnosis:
  - Carrier testing/ screening in expectant mother
  - Via CVS (10-12th week GA) or Amniocentesis (14-16th week GA)

Spinal Muscular Atrophy:

Updates in Management

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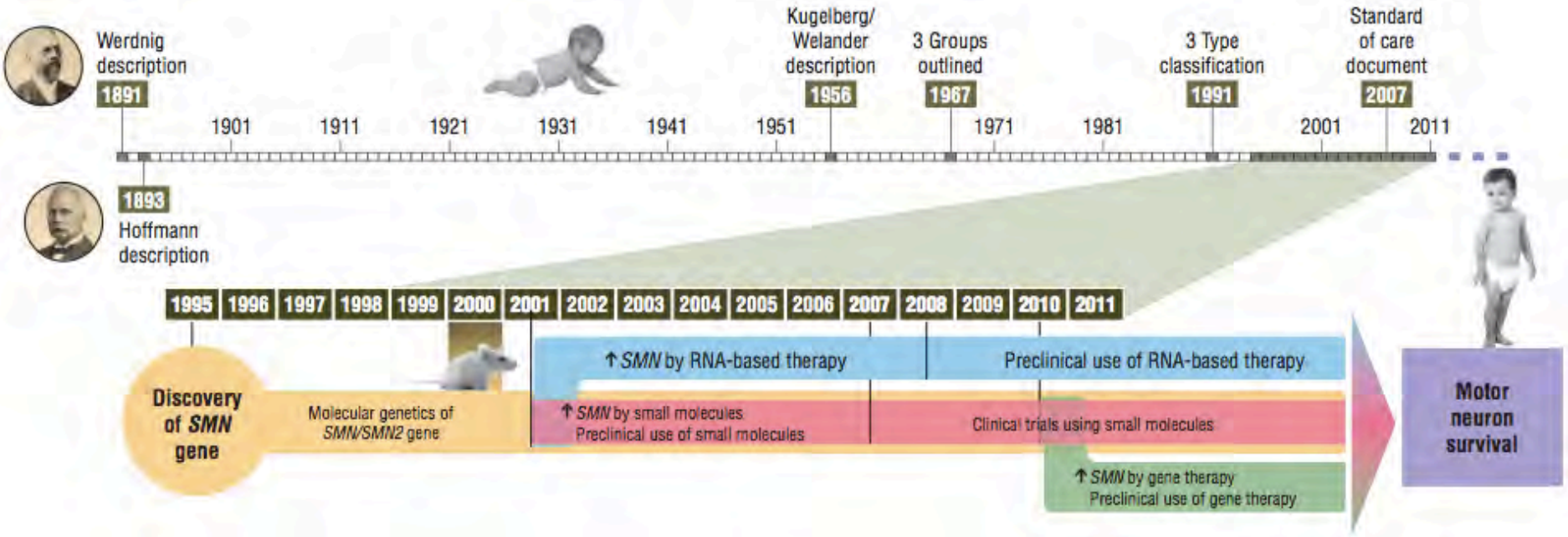
History



Kolb S. Arch Neurol. 2011

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Management – Supportive Care

- **First line**:
  - Clinicians can improve survival by optimal management of respiratory, nutritional, orthopedic health
  - Even in era of new drugs available

- This has dramatically improved since 2007 standard of care document by Wang et al.

- Referral for care to a specialized neuromuscular clinical program (Muscular Dystrophy Association/ MDA Clinical Program)

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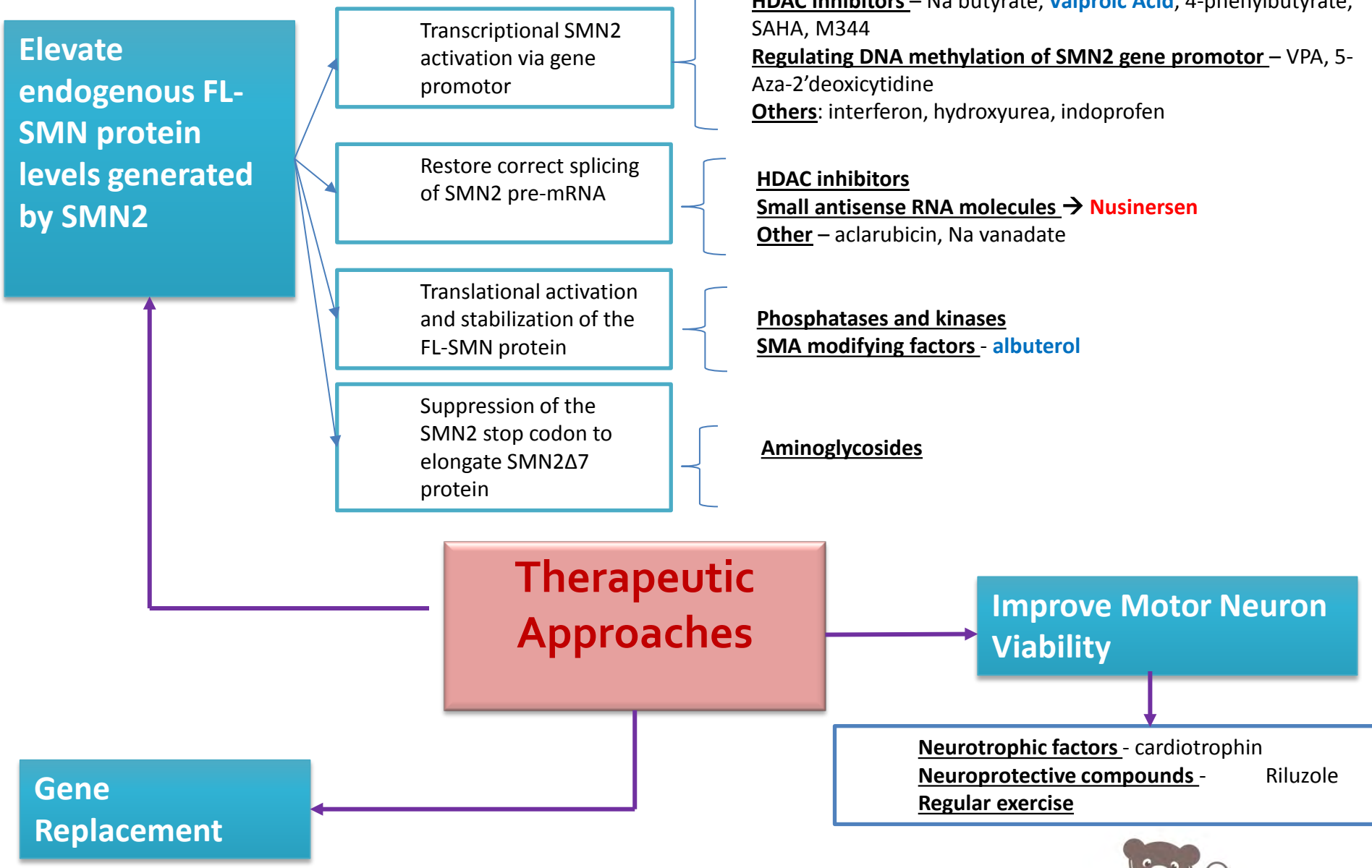
Drug Development



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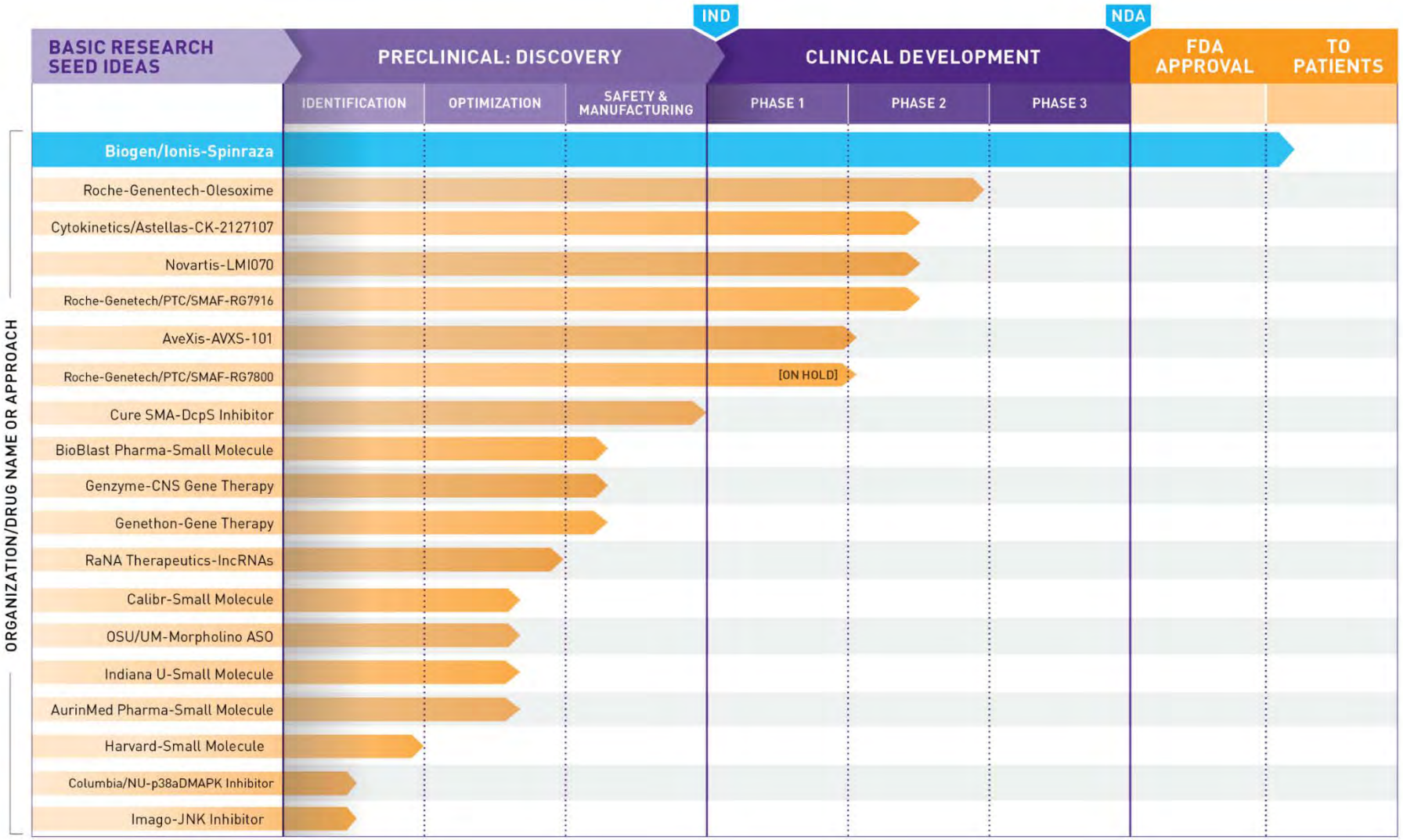
Drug Development Pipeline



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www.curesma.org

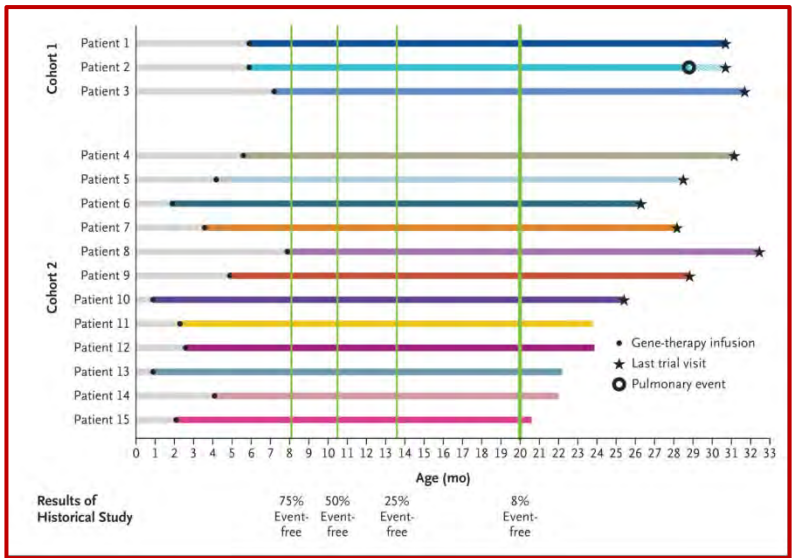
Clinical Trials

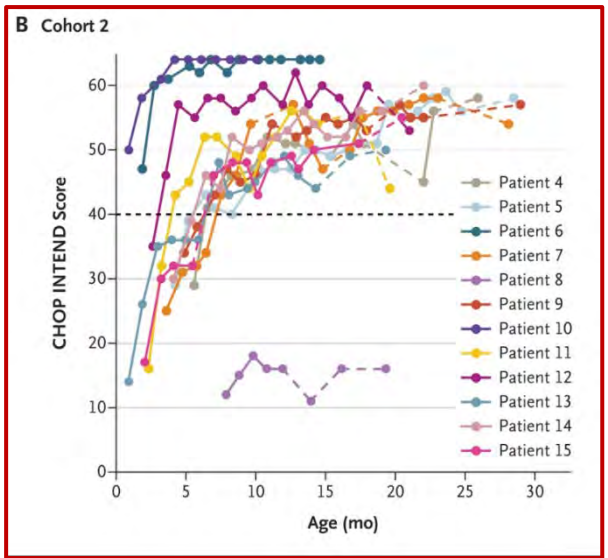
- **Olesoxime**: Cholesterol-oxime: NCT02628743
  - Targets mitochondrial integrity in stressed cells → promote motor neuron survival
  - Safe and well tolerated – 2 year study
    - 160 patients with Type 2 and nonambulant Type 3 ages 3-25 yrs
    - Primary endpoint not met, secondary endpoint suggests this may maintain motor function in patients with Type 2 or Type 3 SMA over 24 month period
- **Roche/ PTC: RG7800/** –
  - Selectively modulates inclusion of SMN2 exon 7 → orally bioavailable
  - Phase I – safe in HV
  - Phase Ib/IIa – randomized placebo control trial in adults and pediatric SMA patients → suspended due to unexpected eye condition
  - Modified compound: **RG7916/ R07034067** →
    - Phase I/II studies in infants with:
      - Type 1 SMA (NCT02913482)
      - Type 2 and Type 3 SMA patients (NCT02908685)

Clinical Trials

- **Cytokinetics/ Astellas**: CK-107/CK-2127107: NCT 02644668
  - Skeletal muscle troponin activator → slow calcium release → increased skeletal muscle contractility → enhance performance
  - Completed Phase I study in HV
  - In Phase 2 – DB/PC/ multi-dose study in patients with Types 2,3 and 4 SMA

- **Avexis: Gene Replacement:** AVXS101 (AAV9)
  - Strong preclinical data in mice (improved motor function, survival, weight, gene expression)
  - Strong phase I clinical data: Type 1 SMA (2 copies SMN2)
    - Mean age treatment 6.3 months





Outcomes:

- 11 sat unassisted
- 9 rolled over
- 11 fed orally and could speak
- 2 walked independently

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Clinical Trials: Gene Replacement: Enrolling

- Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT): NCT03505099
  - Pre-symptomatic Type 1, 2 or 3 SMA (2,3 or 4 copies SMN2); intravenous
- Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG): NCT03381729
  - Type 2 SMA (3 copies SMN2); intrathecal
- Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE): NCT03306277
  - Type 1 SMA (2 copies SMN2); intravenous

A rapidly evolving space for research and therapeutic development…

Approved Therapeutics

Antisense Oligonucleotide ('ASO')
(Nusinersen – Biogen/ Ionis)

- Goal – Manipulate RNA sequences to increase exon-7 incorporation during SMN2 RNA processing → therefore increase FL-SMN
- Need drug that can have effect within the CNS
- ASO's do not cross BBB
- With IT delivery – can get ASO's distributed into neurons, microglial cells, and astrocytes

Trials

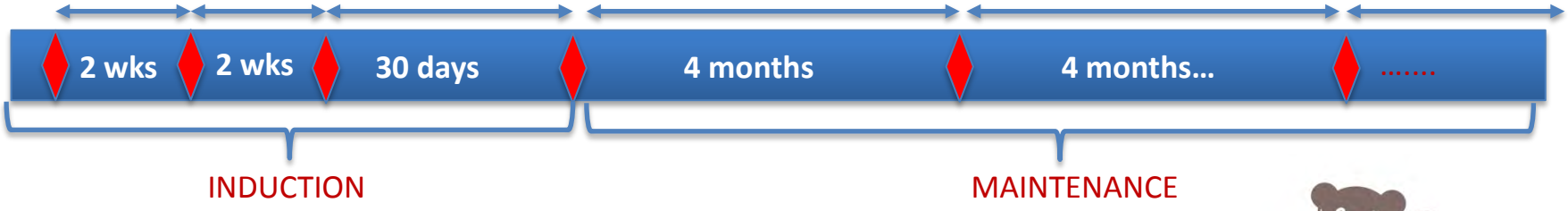
- Double blind controlled clinical trial in 121 patients with SMA type 1 dosed < 7 months of age:
  - IT administration
  - Analysis in 82 patients showed motor improvement in 40% of patients on treatment vs none in sham group
  - Trial halted, all patients rolled into open label extension

- Study in presymptomatic patients with 2 or 3 copies of SMN2 showed favorable results

- FDA approval December 2016

Spinraza ® (nusinersen)

- Antisense oligonucleotide
- Modifies the transcription of *SMN2* to produce a full-length SMN protein.
- Only effective for SMA caused by deletions/ point mutations of *SMN1*
- Approved for use in patients of all ages with 5q SMA
- Given via intrathecal injection, 12 mg (in 5 mL solution) – single dose vial
- Induction phase, then maintenance every 4 months for life



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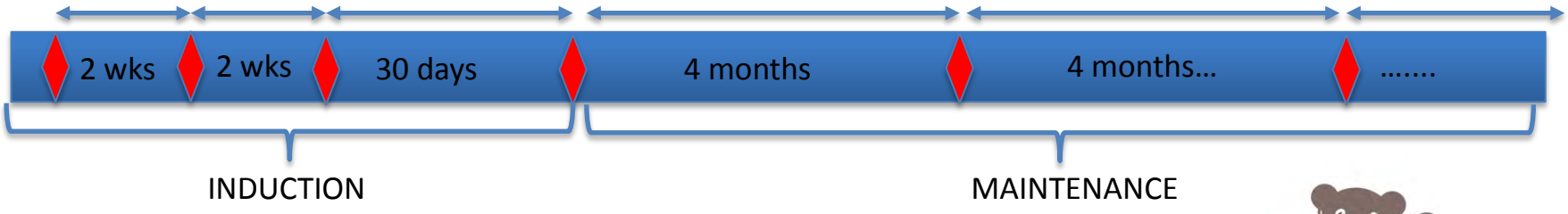
Treatment

- Genetic Testing
- Baseline evaluation with laboratory testing
- Clinical documentation and consent for treatment/financial review
- Payer authorization
- White bag process for drug acquisition
- Scheduling (!)
- Loading doses
  - Weeks 1,3,5,9
  - Safety labs
  - Biobanking
- Multidisciplinary f/u
- Maintenance dosing every 4 months

Spinraza ® (nusinersen) at Children's National

- 32 patients on drug (8 Type 1, 10 Type 2, 14 Type 3 SMA patients)
- 28 in maintenance, 3 in loading, 1 awaiting first loading dose
- 1 international patient
- One of largest injecting sites in region (total 164 injections)
- One of earliest sites to initiate clinical dosing of Spinraza in 3/2017
- Tracking motor function, respiratory function, speech/ communication, and biomarkers
- All patients showing subjective and objective functional gains; better tolerance to respiratory infections; increased energy; improved motor milestones
- 1 prenatally diagnosed patient → prenatal referral → baby seen immediately postnatally, predicted type 2 or type 3 SMA → Dosed by 5 weeks of life



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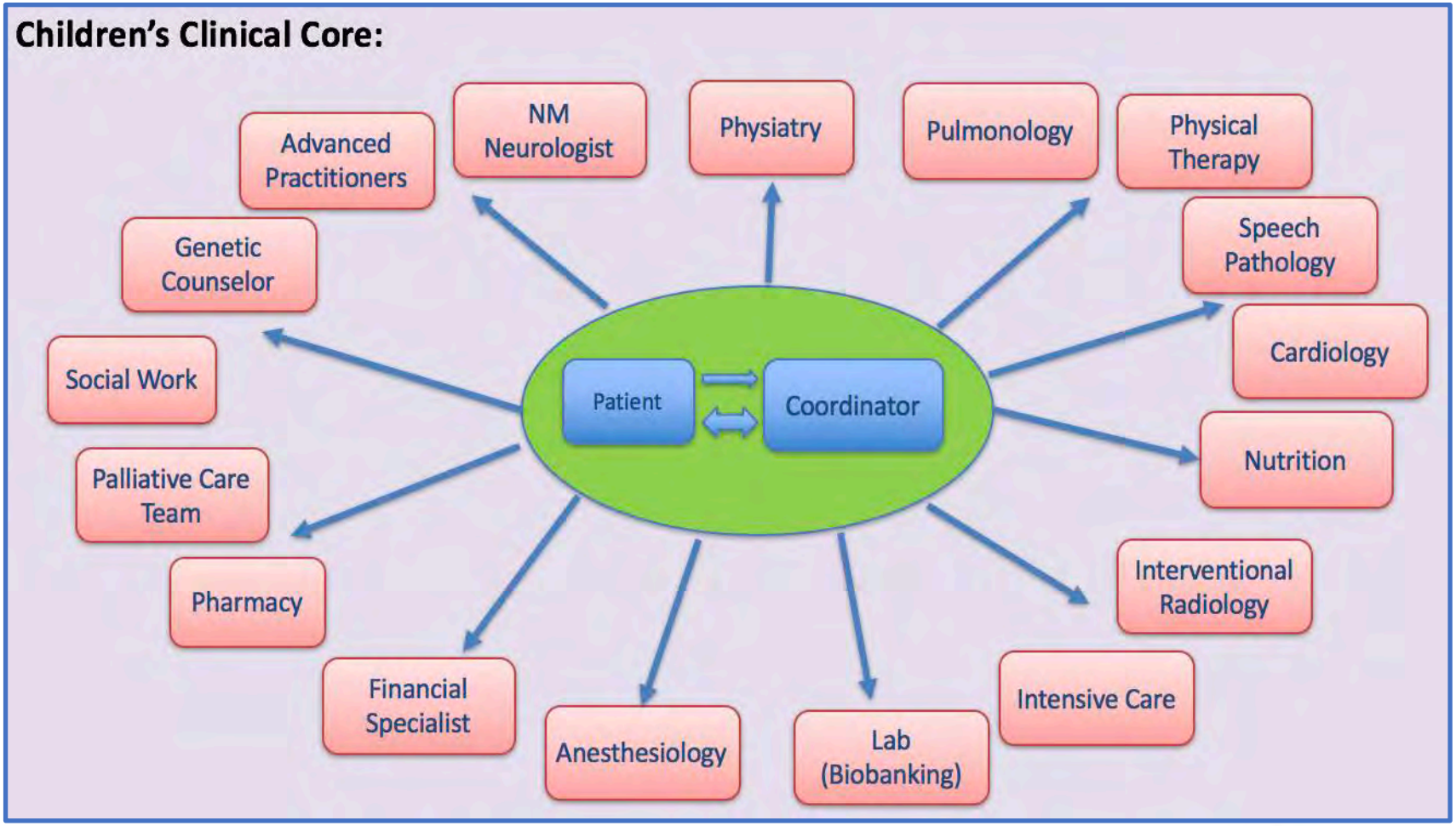
Cure SMA Center Designation - 2018



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Patient Management

- Medical treatment: Spinraza
- Nutrition: swallow, feeding, fluids, calories
- Respiratory: adequate ventilation and pulmonary toilet
- Communication: dysarthria, phonation, devices
- Self Care: occupational therapy, adaptive equipment
- Mobility: physical therapy, mobility devices +/- power
- Positioning: joint integrity, scoliosis

When to Treat?

- Based on electrodiagnostic studies in pre-symptomatic patients (Finkel R. 2012, Swaboda K. 2005):
  - Early preservation of the motor unit
  - Precipitous drop
  - Then more gradual decline
- There may be a critical window for treatment based upon natural history and timing of motor neuron loss
  - This is further reinforced by trial data
  - EARLIER IS BETTER!!!
- Benchmark for prenatally/ NBS neonatally identified cases:
  - Predicted Type 1 SMA: Dose within 3-4 weeks of life
  - Predicted Type 2 or Type 3 SMA: Dose within 2 months of life

Take Home Points

- When to suspect SMA?…. Weakness, hypotonia, areflexia, tongue fasciculations, fine tremor (on reaching), relative facial sparing

- What to do?…… Referral to neuromuscular specialist
  Children's National Health System:
  Neuromuscular Coordinator:
  Kathleen Smart: 202-476-6193
  ksmart@childrensnational.org

- Counseling/ information?.... www.curesma.org

- When to treat?.... Earlier is better!!

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Thanks!

- ksmart@childrensnational.org ***1st contact****
  - Neuromuscular/ MDA/ Cure SMA coordinator
- dbharuch@childrensnational.org
  - Neuromuscular Neurology, Co-director Cure SMA Center
- shevans@childrensnational.org
  - Chief, Physical Medicine & Rehabilitation, Co-director Cure SMA Center

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