Medical Management of Adults with SMA

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Disclosures

- *Dr. Elsheikh:*
  - Received grant/study support from Cure SMA and Biogen
  - Consultation for Stealth Bio-therapeutics
  - Grant/study support from RaPharma and UCB for myasthenia clinical trials.

- *Tina Duong:*
  - *Scientific Advisory Board: Biogen, Cytokinetics, Roche*
  - *Consultation: Roche, Audentes, ATOM International*

Outline

- Brief overview of presentation and diagnosis
- Discuss standard of care management
- Discuss preliminary data and access to Spinraza in the adult SMA population
- Overview of what is in the pipeline for adults

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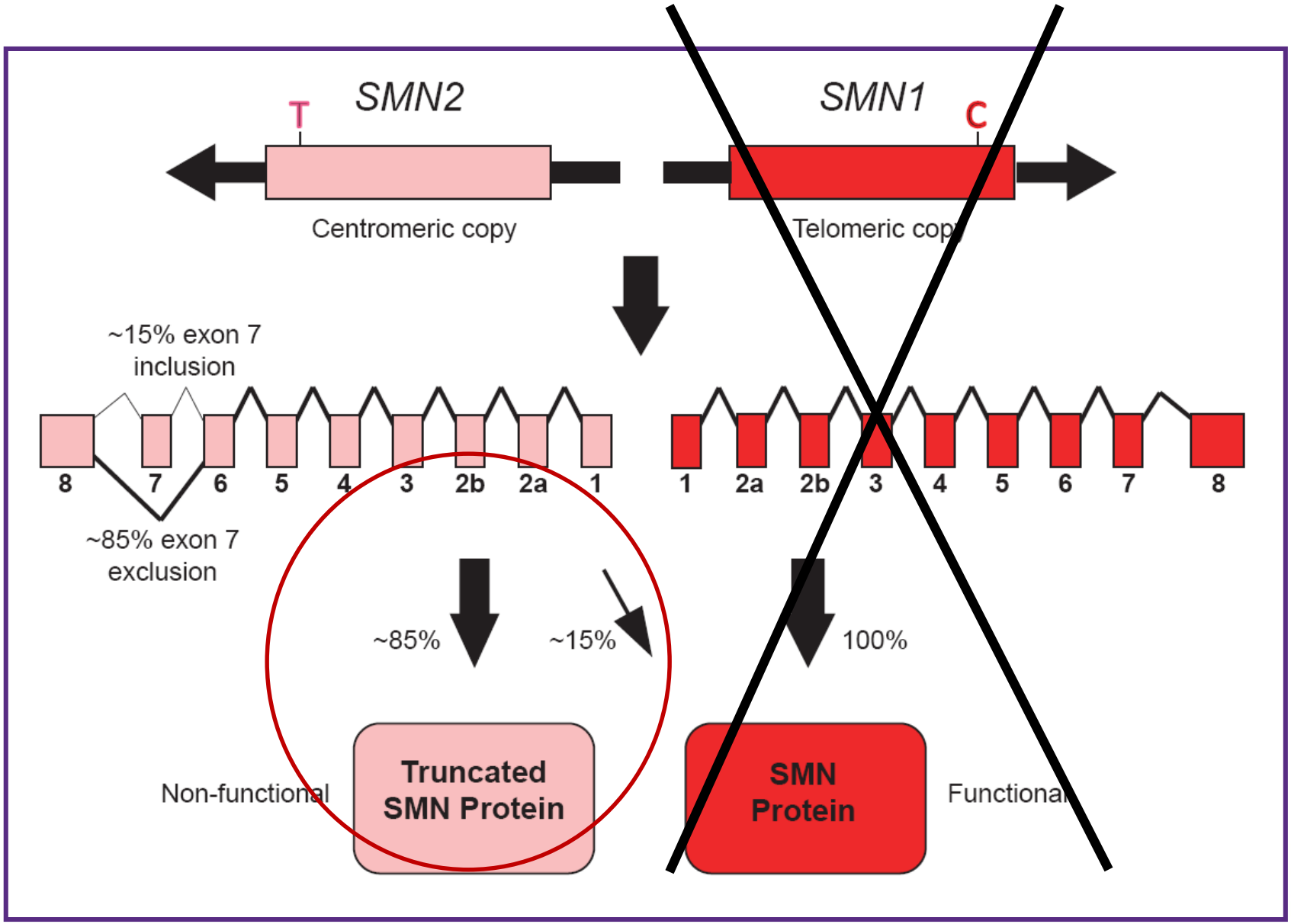
SMA appeal

- Clinical importance
  - Incidence is 1 in 6-10 000 live births
  - Carrier frequency is 1 in 40
  - Seven million carriers at genetic risk in USA
- Unique genetics
  - “Spare gene”
- Research support
  - Non- profit organizations (Cure SMA, SMA Foundation, MDA); NIH/NINDS & Pharma
- Disease modifying therapies era

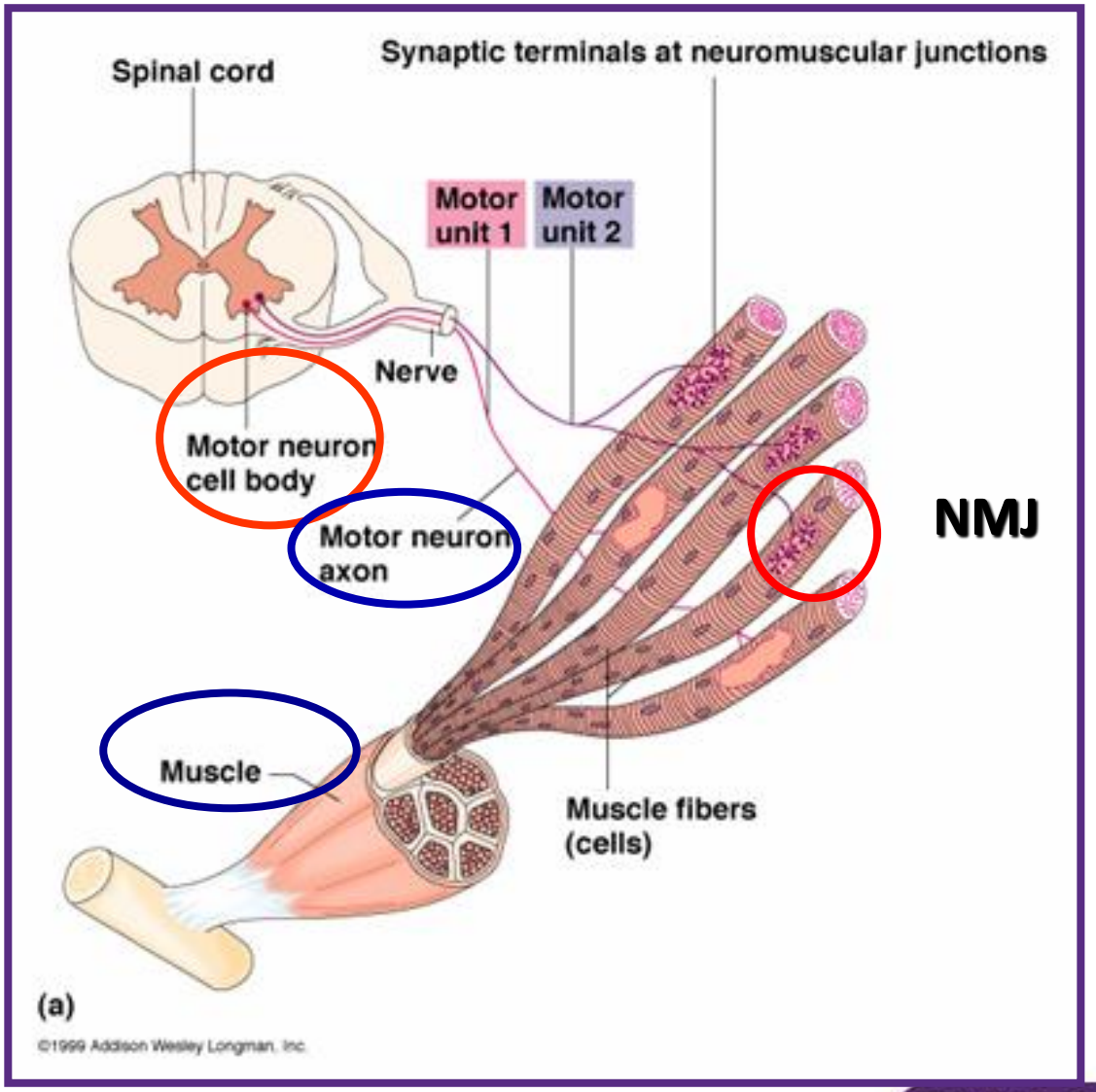
SMA Genetics



Kolb et al. Arch Neurol. 2011

SMN Function

- Does SMN function mainly on motor neuron at cell body?
- Or on motor axon?
- Or at NMJ?
- Or even in muscle?
- And ? supporting cells
  - ? astrocytes
  - Satellite cells
- **Burghes et al, 2009**



SMA affect all ages

Wide range of phenotypic variability

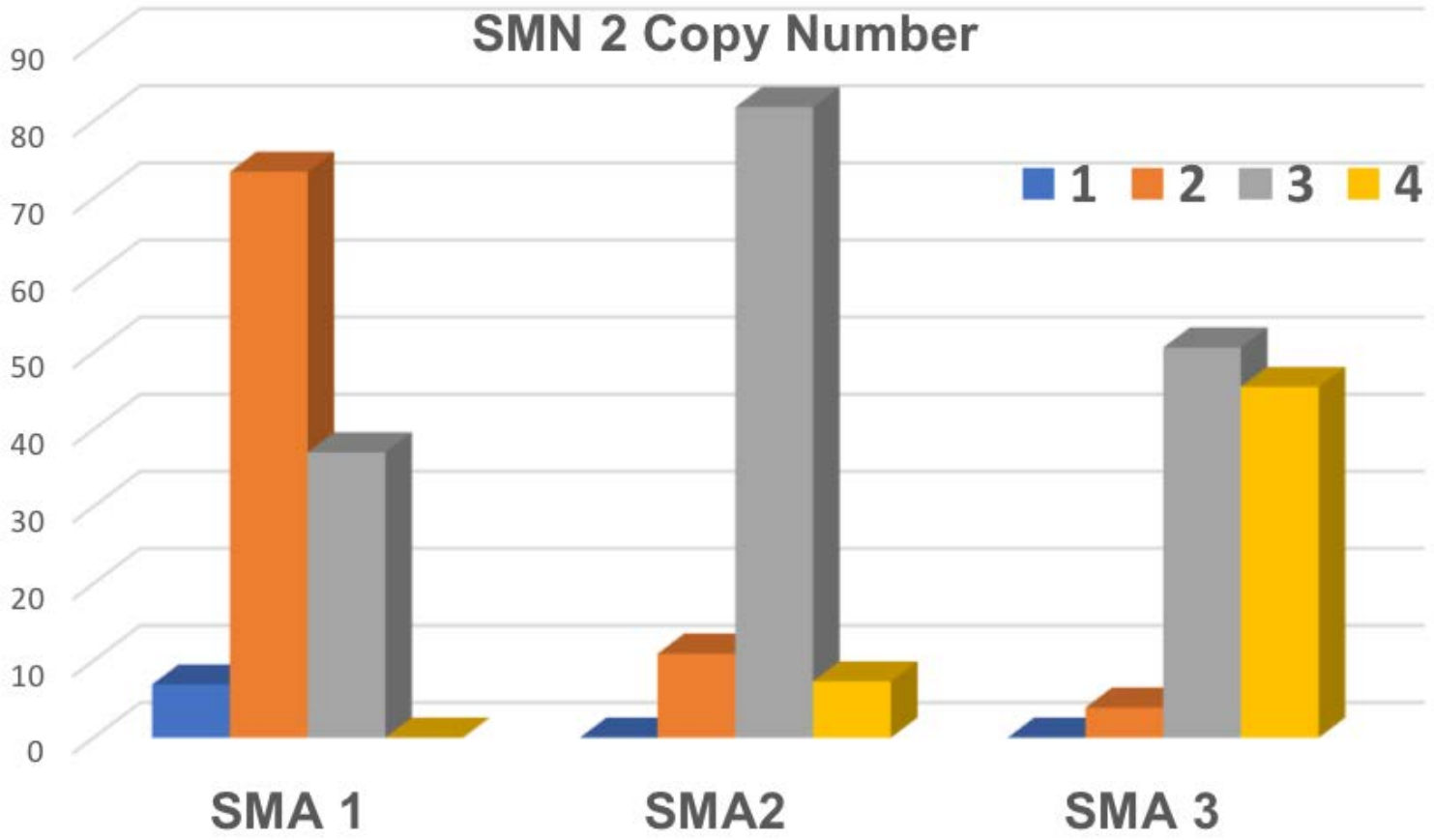
- SMA 1: Never sits
- Onset 0-6 months
- Severe hypotonia
- Respiratory distress
- Absent head control
- Severe weakness (>>P)
- Reflexes absent
- Bulbar weakness
- Tongue fasciculations

- SMA 2: Sitters
- Onset <18 months
- Weakness
  - (Legs>> arms)
- Rarely stand or walk with aid (type 2b)
- Reflexes absent (70%)
- Polyminimyoclonus

- SMA 3:Walkers
- Onset <3 years (3a
- > 3 years(3b
- Difficulty walking & climbing stairs
- Waddling gait
- Gower's maneuver
- Weakness
  - Legs> arms
- Limb fasciculations
- Reflexes reduced

- SMA 4: Adult
- Onset > 21 years
- Slowly progressive
- Limb girdle weakness
- Relatively benign course

Disease modifiers



- Not all SMN2 are the same
  - Variant SMNG859C increase the amount of full length SMN mRNA

Feldkotter et al. Am J Hum Genet. 2002
Prior et al. Am J Hum Genet. 2009

Adult SMA population

SMA type	Age at sx. onset	Maximal function attained	Survival
1c	3-6 months	Never able to sit unsupported	Occasional - adult
2a	6-18 months	Able to sit unsupported	20 year survival 77 to 93%
2b	6-18 months	Able to sit unsupported & stand or walk with support	
3a	18-36 months	Able to walk independently	Normal life span
3b	> 36 months	Able to walk independently	
4	> 21 years	Able to walk independently	

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Cure SMA membership database

SMA type N=1966	ALL subjects Type distribution	Average age at diagnosis /month	Deceased	Adults >21 N=91
SMA type 1	51.9%	5.2	96.2%	5%
SMA type 2	32.3%	22.1	3.6%	27%
SMA type 3	15.8%	97.8	0.2%	68%

Belter et al. Journal of Neuromuscular Diseases 2018

Adult phenotypes
Non-ambulatory/Severe

- Type 1, 2, and some 3a
- Very severe weakness
  - Quadriplegia
  - Trace movement limbs
  - Facial and bulbar weakness
  - Areflexic
- Contractures and severe scoliosis
  - Spinal fusion
- Severe restrictive thoracic disorder ± tracheostomy/ventilatory support/recurrent pneumonia/ aspiration

Adult phenotypes
Non-ambulatory/Intermediate

- Type 3a and some 2 and 3b
- Trace to absent leg movements
- Severe arm weakness
  - Proximal>>Distal
- Trace to absent reflexes
- Scoliosis
- Respiratory compromise
  - BiPap

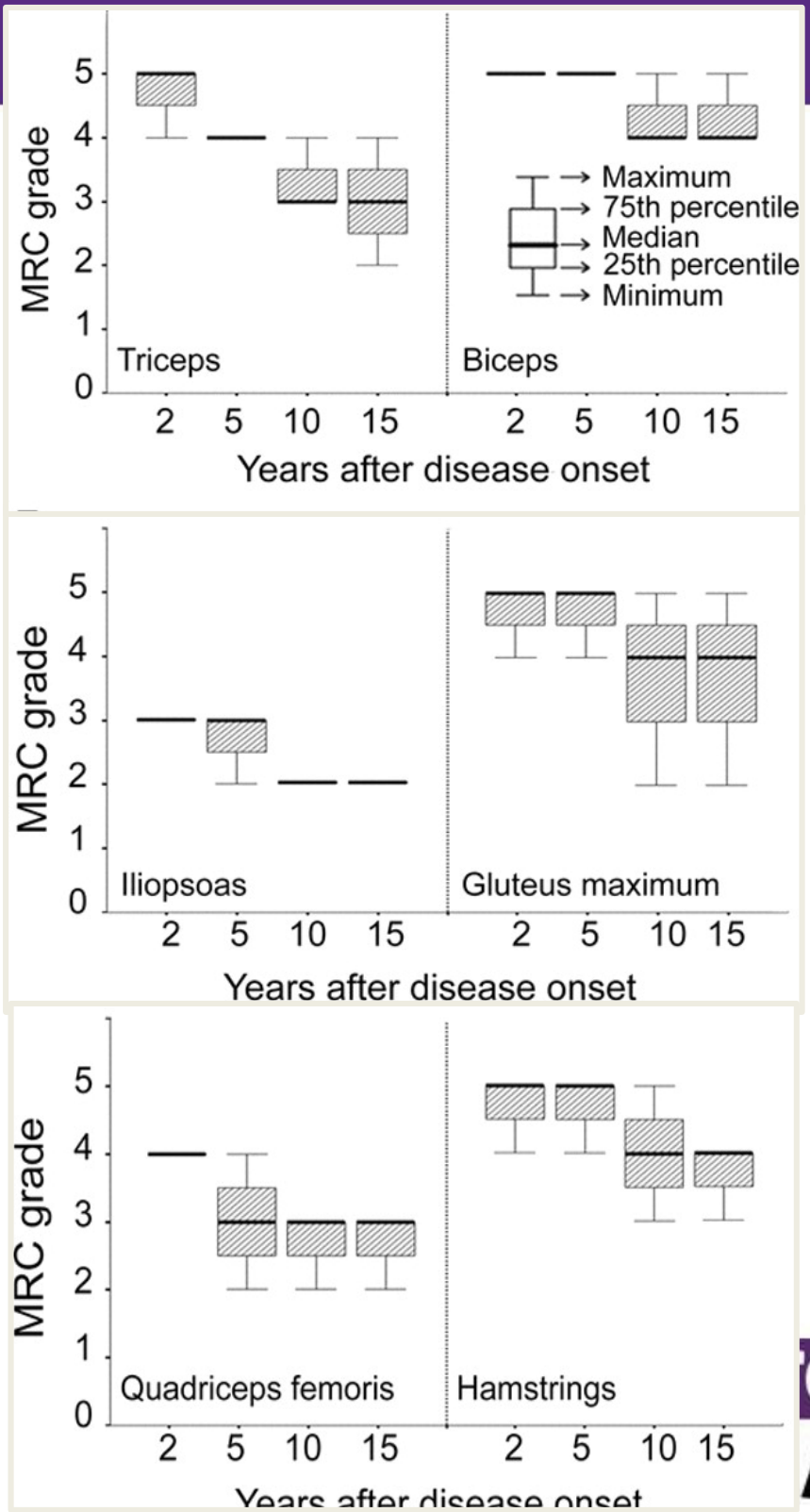
Adult phenotypes Ambulatory /Mild

- Type 3b, 4 and some 3a patients
- Weakness
  - Legs >arms / P>D
  - Triceps->biceps->deltoid
  - Thigh adductors->iliopsoas->quadriceps femoris> hamstrings>glutei
- Trace to absent reflexes in legs and normal in arms
- Calf hypertrophy
- No facial or bulbar weakness
- Normal respiratory function

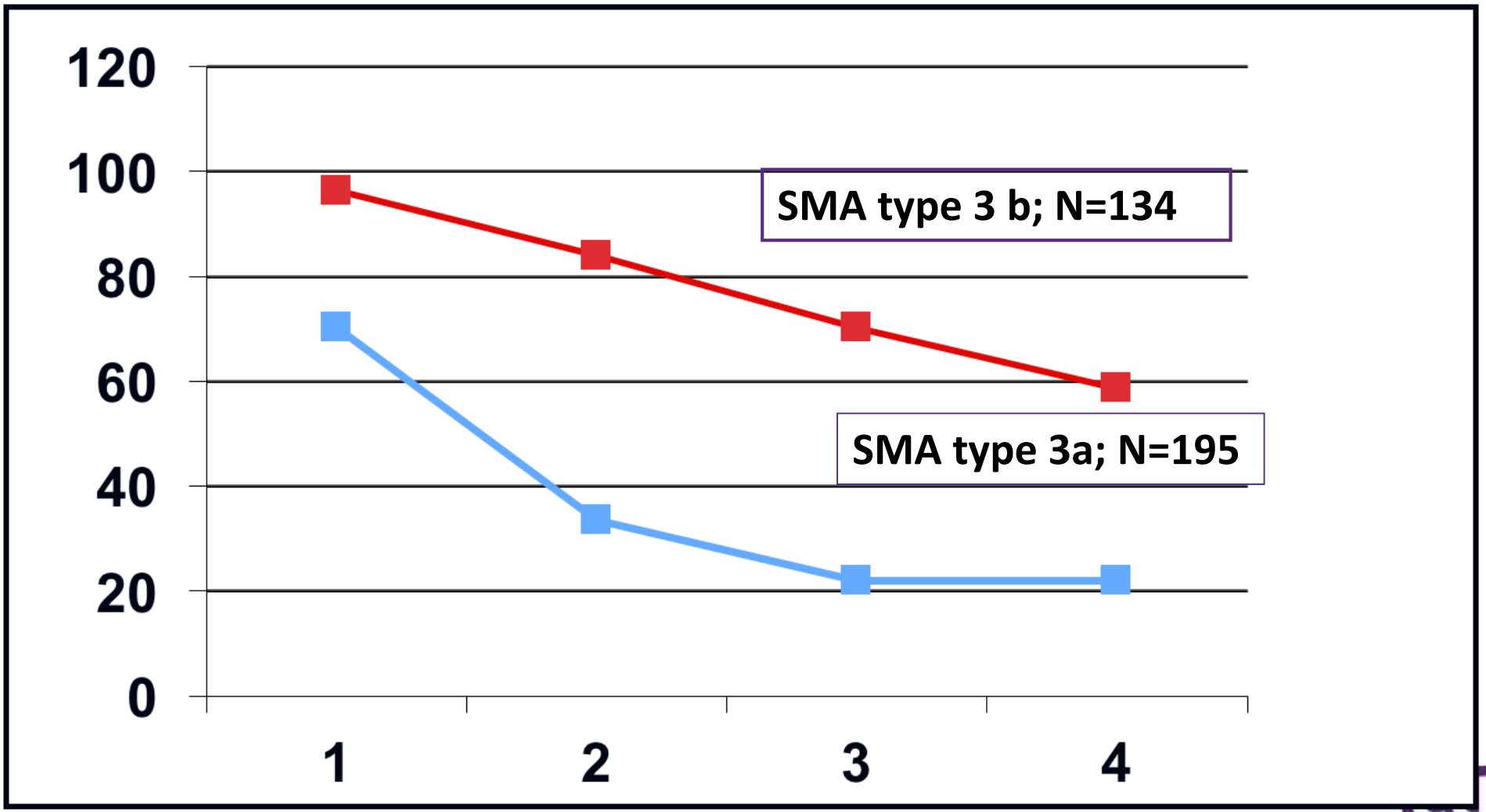
Longitudinal strength data in type 3b

- Small study (N=10; ages 9-18)
- Followed up to ~20 years
- First 5 years triceps, iliopsoas, thigh adductors, and quads weakness
- The MRC declined with years in all muscles
- The decline =/< one MRC grade for each 5-year period
- There were 5–10 year periods when some muscles appeared to remain stationary

Deymeer et al. Neurology. 2008

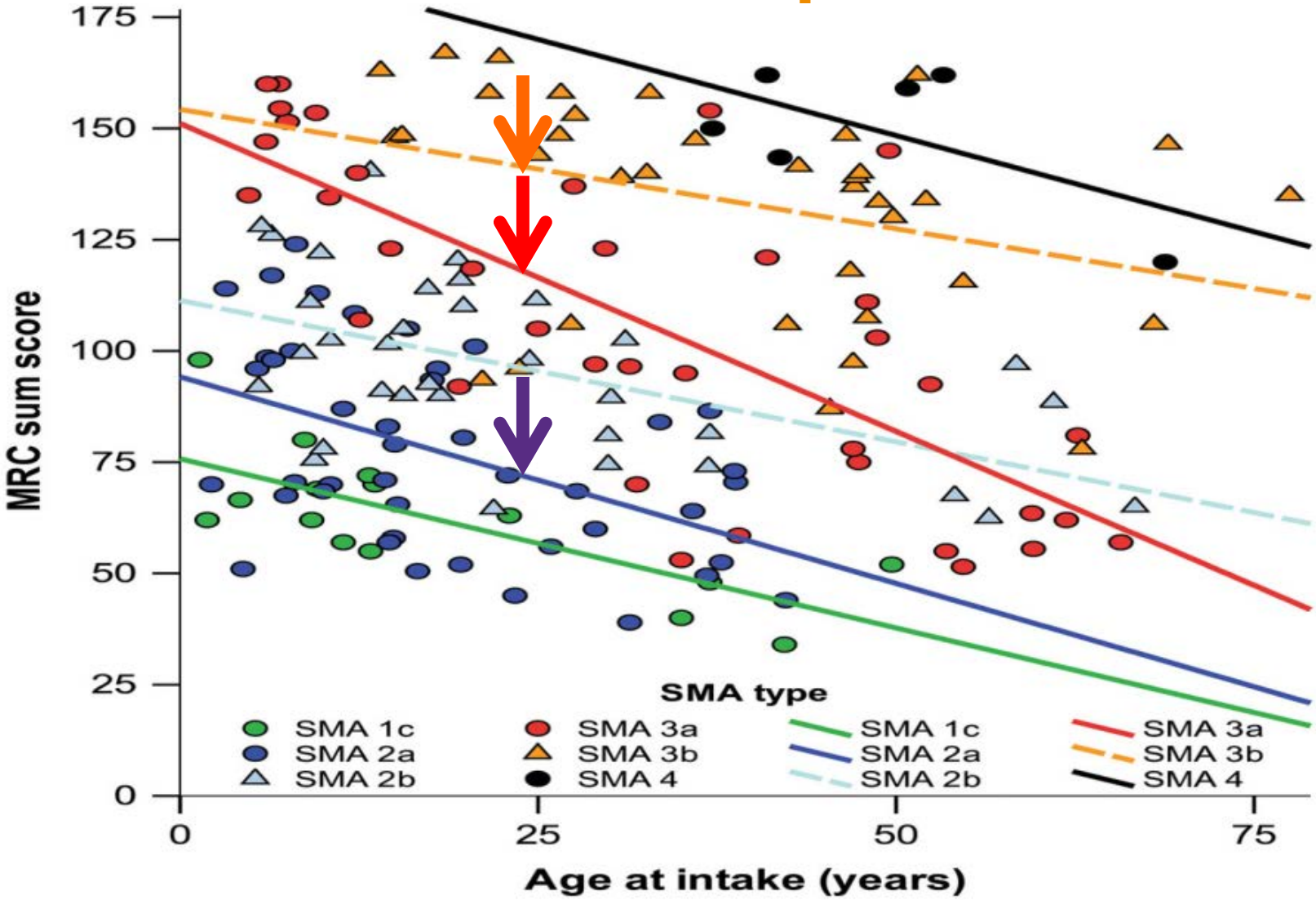


Probability of continued ambulation in SMA 3



Zerres et al. Neuromusc Disord. 1997

Muscle strength in cross sectional cohort of 180 SMA patients



Wadman et al. European Journal of Neurology. 2018

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Standards of care

Mercuri et al Neuromuscular disorders. 2017
Finkel et al. Neuromuscular disorders. 2018

Approach to treatment in adults vs. children

- Focus
  - Patient vs. family
- Decision making
  - Patient vs. parents
- Medical problems
  - Multiple vs. single organ system
- Tolerance for non adherence
  - Lower for adults

What can adult providers do?

- Follow a patient as they age
- See a patient for sick visits and well care
- Screen for and manage “adult diseases”
- Coordinate with specialists
- Admit to “adult” hospitals

Model of Rehabilitative Care

- **Habilitation**
  - Services that help a person **acquire, keep** or improve, partially or fully, and at different points in life, skills related to communication and activities of daily living. These services address the competencies and abilities needed for optimal functioning in interaction with their environments
- **Rehabilitation**
  - Rehabilitation refers to health care services that help a person keep, **restore** or improve skills and functioning for daily living and skills related to communication that have been lost or impaired because a person was sick, injured or disabled.
- **Maintenance**
  - Promote **retention** of skills attained through rehabilitation services is an established cost-effective component to maximizing patient functioning. The implementation of a maintenance program can delay deterioration of skills in progressive neurological diseases
- **Prevention**
  - Maintenance of function therapy can halt deterioration, help **prevent** harmful and costly **secondary conditions**, allow for independent living and greater participation in the community, all while limiting expensive inpatient admissions and readmissions, other costly care, and negative social effects.

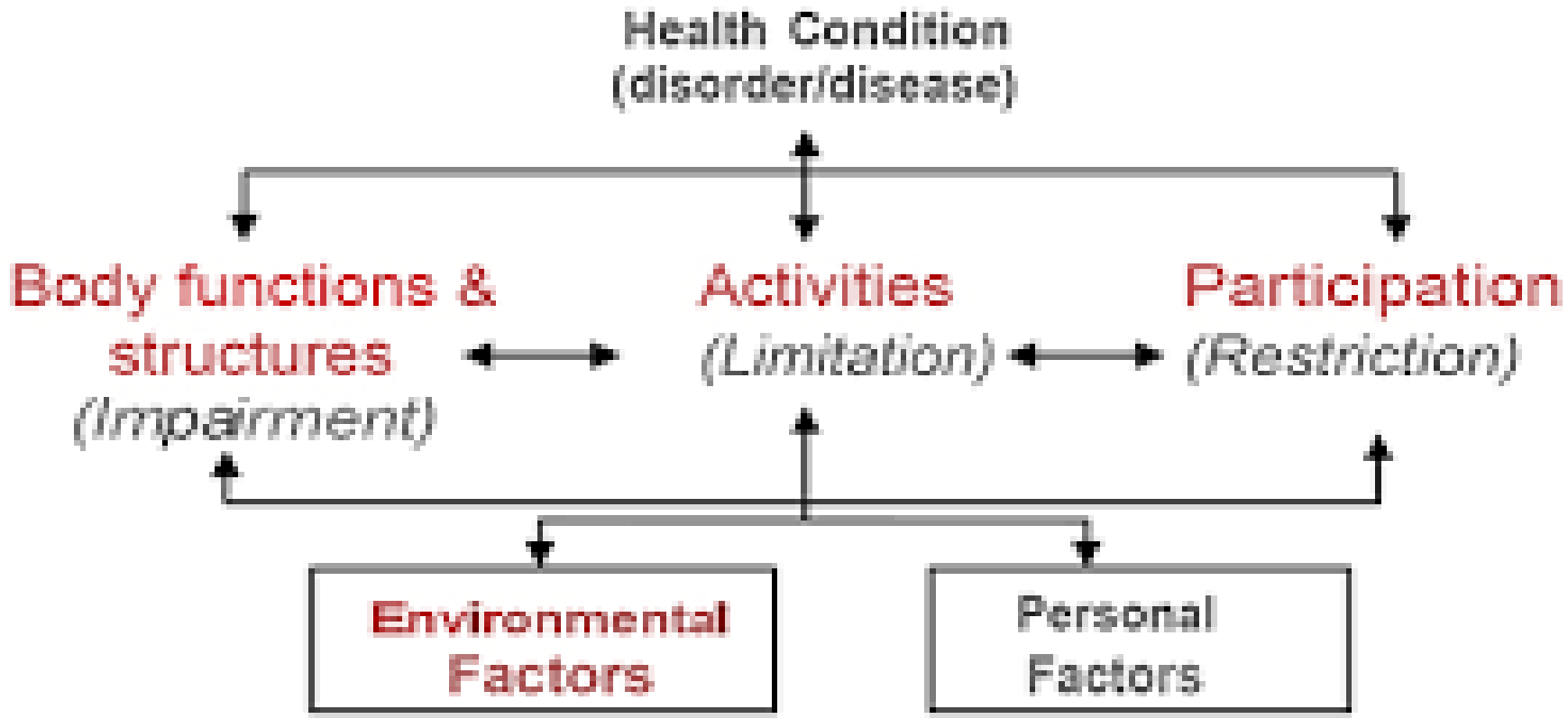
(NAIC Glossary of Health Insurance and Medical Terms)

Multidisciplinary Approach

- **Therapies**
  - Speech, Occupational, Physical, Respiratory
- **Purpose**
  - Monitor Progression
  - Anticipatory Care
  - Maintenance of function
  - Prevention of
    - Contractures
    - Respiratory infections

Considerations

ICF: Interaction of Concepts



Adapting to a changing Natural history

- New treatment options= new phenotype
- Changing paradigm
  - Reactive Care vs ProActive Care
- Consider physical, occupational, speech therapy
  - Physical therapy
    - Functional strength and aerobic capacity
    - Motor learning and Neuromuscular education
    - Musculoskeletal health
  - Occupational Therapy
    - Improved fine motor tasks
    - Assistive technology
    - ADLs
  - Speech Language Pathologists
    - Articulation, voice, speech
    - Facial muscles and activation
    - Chewing

Combination Treatments

- Combination of treatments to increase strength function and independence
  - Exercise
  - Musculoskeletal health
    - Stretching/Bracing
    - Muscle extensibility
  - Assistive Technology
  - Robotics, Exoskeletons, Bracing

Adapt Environment as Necessary

- Enjoy LIFE…Don’t struggle when you may not have to

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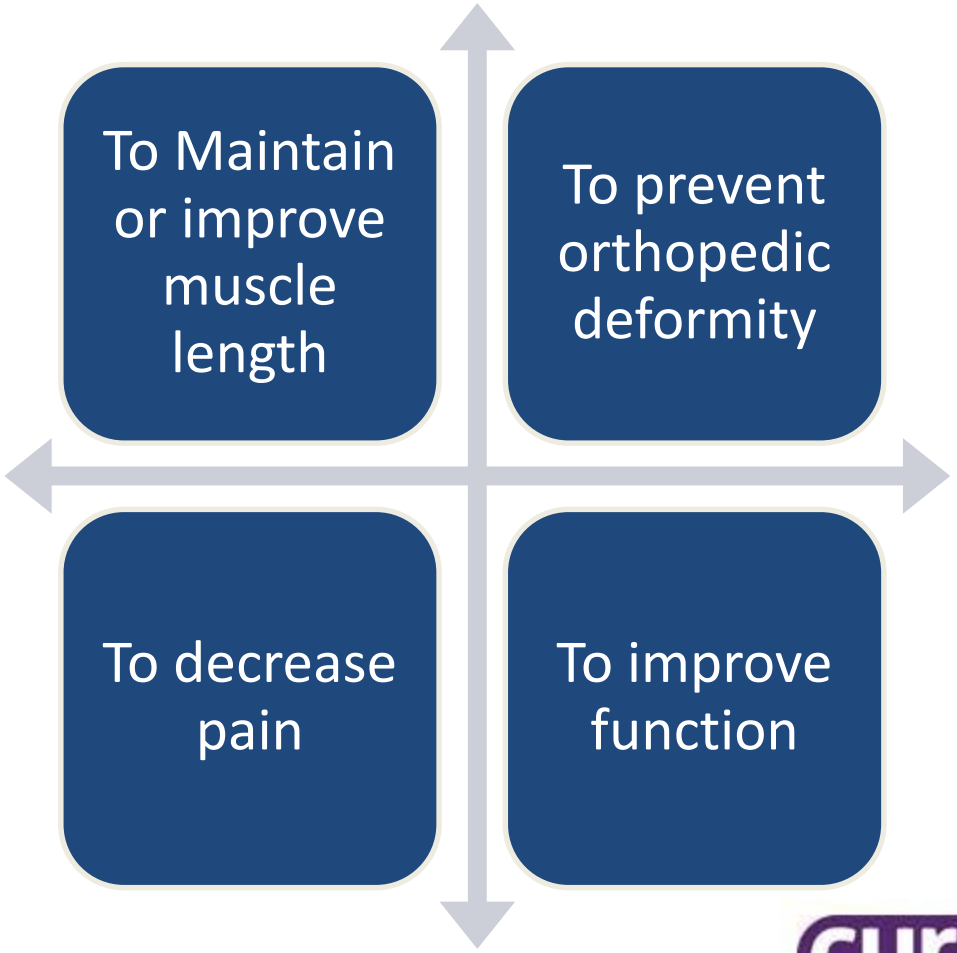
Contractures

- Causes
  - Positioning
  - Muscle Imbalances around a joint
  - Weakness
  - Physiological shortening

- Purpose of Management



Contractures

- Requires early intervention and initiation of management
- Regular periods of standing and/or walking
- Daily passive stretching of muscles and joints
- Positioning of limbs to promote extension
- Splinting for prevention and delay contractures

Joints at risk

- Lower Limbs
  - Knees
  - Hips
  - Ankles
- Upper limbs
  - Shoulders
    - Difficulty with hygiene management, dressing
  - Elbows
    - Inhibit function >30 degrees
      - Difficulty feeding self
  - Wrist flexion, Forearm pronation, ulnar deviation
    - Writing, typing, hand dexterity

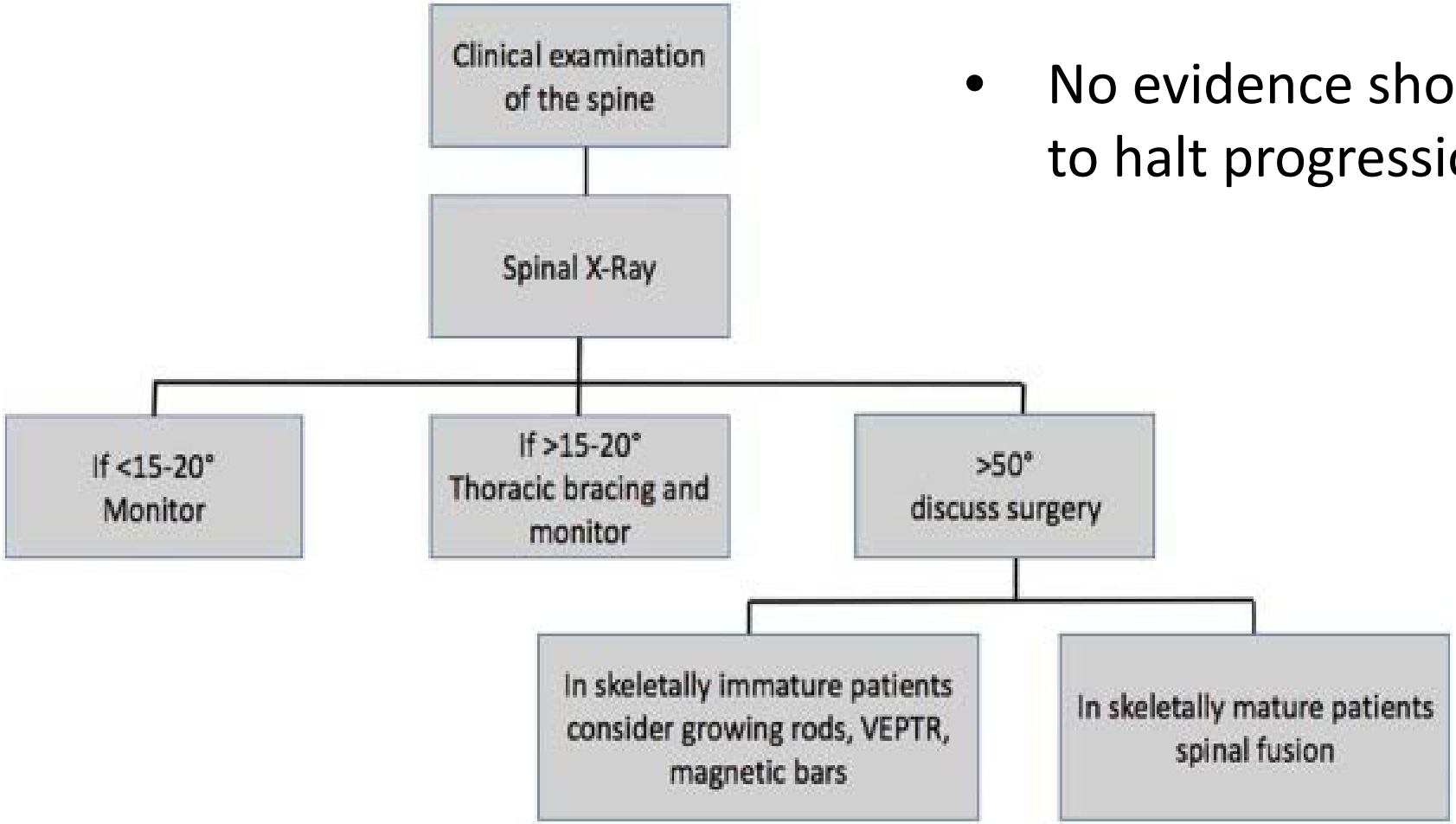
Approaches to Manage Contractures

Conservative	• Short Duration Stretches
	  • Manual Stretches
	  • At least 30 seconds x3
	• Long Duration Stretching
	  • Splinting
	  • Static/dynamic splints
	  • AFO/KAFO
	• Positioning
	  • Standing frames: Depends on tolerance(use AFOs)

Surgical	• Tendon lengthening and transfers
Frequency	• 3-5x/week: Optimal 5x/wk or daily

SMA

Scoliosis Management



- No evidence shown to halt progression

E. Mercuri et al. Neuromuscular disorders28 (2018), 103-115

Management of Scoliosis

Scoliosis in SMA II patients progresses by 8° per year and in non ambulant SMA III patients by 3° per year

- Management:
  - Bracing
  - Trunk Stabilization exercises
  - Good trunk Stab= improve
    - Breathing
    - Talking
    - Eating, use of upper limbs

Management of Scoliosis Surgical

- Based on curve progression
  - Pulmonary function
  - Bony maturity
- Curve >40 degrees
- Surgical intervention provides benefits in sitting balance, endurance, and cosmesis
- May alter function, balance, and respiration
- Careful consideration for those who are ambulant

Management of Hip Subluxation/Dislocation

- Subluxation
  - 30%–40% of SMA type II patients and 10%–30% of SMA type III patients.
- Dislocation
  - 30% of SMA type II

  patients and 20%–30% in SMA type III

- Operatively corrected hip joints= higher incidence for re-dislocations
- Treatment=conservative management
  - may preserve sitting balance, pelvic alignment and increase comfort, pain
- Varying surgical techniques and limited data effects surgical decision making and standards of care

Sporer et al 2003

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Exercise

- Yes! Do exercise!!
- **Strengthening**
  - Concentric and eccentric exercise with and without resistance for proximal, distal, core, and axial, and muscles with at least antigravity strength.
  - Cervical muscles and those without full range of motion, resistance NOT recommended
- **Aerobic exercise**
  - Recommended
    - Swimming, game-based activities (ie. Wii, Kinect), hippotherapy, upper and or lower extremity ergometry, walking, yoga / pilates, and wheelchair sports.
- **Duration:**
  - ≥ 30 min
- **Frequency:**
  - The 2-3x/week
  - Optimal= 3-5x/week

Standard of care (2018)

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Exercise Considerations

- Functional strength training
- Watch for fatigue and overuse weakness from over work
- Energy conservation
- Watch for:
  - Pain, and increased weakness
- Scheduling to optimize energy and strength
- Incorporate into daily activities
- With Strengthening and aerobic exercise, no evidence of improved strength
  - Improved aerobic capacity
  - NO deleterious effects

SMA Aerobic Exercise

- SMA Type 3
- Cycle ergometer training for 12 weeks; 4x/week
- n=6 SMA; n=9 controls
- Increased VO2 max (exercise capacity) by 27%
- Fatigue was a problem resulting in decrease in intensity
- Results
  - Significant improvement in exercise capacity
  - No muscle damage
  - Induces fatigue
    - Need for alternative exercise regiments
      - Shorter bouts? Higher intensity? Gradual increase in intensity?

Madsen et al 2014

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Exercise

Research Report

Single-Blind, Randomized, Controlled Clinical Trial of Exercise in Ambulatory Spinal Muscular Atrophy: Why are the Results Negative?

Jacqueline Montes[a,b,*], Carol Ewing Garber[c], Samantha S. Kramer[a], Megan J. Montgomery[a], Sally Dunaway[a,b], Shirit Kamil-Rosenberg[c], Brendan Carr[c], Rosangel Cruz[a], Nancy E. Strauss[b], Douglas Sproule[a] and Darryl C. De Vivo[a]

In all participants, there was an improvement in VO2 max with 6 months of exercise.

Percent-predicted VO2 max improved 4.9% in all participants.

Even greater changes (6.6%) were seen in the most compliant participants.

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2016;■:■■■-■■■

ORIGINAL RESEARCH

Exercise Intensity During Power Wheelchair Soccer

J.P. Barfield, DA,[a] Laura Newsome, PhD,[a] Laurie A. Malone, PhD[b]

From the [a]Department of Health and Human Performance, Radford University, Radford, VA; and [b]University of Alabama-Birmingham/Lakeshore Research Collaborative, Birmingham, AL.

11 participants with SMA (30 total)
Power Chair soccer ages 7-63
Assessed RPE and oxygen consumption (METs)

Table 2 Exercise intensity during power soccer game play (N=30)

Data Collection Conditions	n	Rest METs	Game play METs	RPE*
Unit 1	8	1.36±0.51	1.82±0.72	12.88±3.53
Unit 2	24	1.32±0.39	1.76±0.78	12.63±2.13
Practice	16	1.29±0.38	1.83±0.55	12.33±2.77
Tournament	14	1.41±0.56	1.78±0.76	13.42±3.26
Sample	30	1.35±0.47	1.81±0.65	12.80±3.11

NOTE. Values are mean ± SD.
* Borg RPE scale (6–20).

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SMA Resistive Training

- SMA type 2 and 3 (n=9)
- Improvements in motor function were seen in SMA type 2 and 3 3x/week for 12 week
- Progressive strengthening program
- Results

Strengthening program was safe and well tolerated…no adverse effects

Trend towards improvement in strength and function

(Lewelt et al 2015)

Pain- Overview

- Somatic
  - Nociceptive pain
  - Sharp, aching, stabbing, throbbing or pressure
  - Tissue injury or inflammation
  - Anti-inflammatory, acetaminophen, topical lidocaine
- Visceral
  - Nociceptive pain
  - Poorly localized
  - Colic, cramping, aching, or stabbing
  - Systemic treatment for somatic pain
  - Treatment of the cause: Reflux, constipation, renal stones
- Neuropathic
  - Somatosensory pathway
  - Burning sensation, pins and needles, or shooting pain
  - Anticonvulsants, antidepressants , local anesthetics

Managing Pain: Beyond Drugs

- Goal is to help restore functionality (Not cure)
- Message
- Relaxation techniques
  - Biofeedback
  - Breathing techniques
- Acupuncture
- Bed rest and bracing
- Exercise
- Heat
- Orthopedic Interventions

Pain in SMA

- National survey in Sweden
- 17 patients with SMA (10 SMA2, 7SMA 3; Age 12-18)
- Average pain intensity is mild and worst is moderate
- The pain typically occurred weekly
  - Frequently in the neck, back or legs
- General activity and mood were areas most affected by pain
- Common pain-exacerbating factors include
  - Sitting
  - Excess movement or activity
  - During lifting or transfer
- Pain relief
  - Resting
  - Position change
  - Use of analgesics
  - Message
  - Muscle stretching
  - Relaxing

Lager C. et al Eur J Paediatr Neurol. 2015

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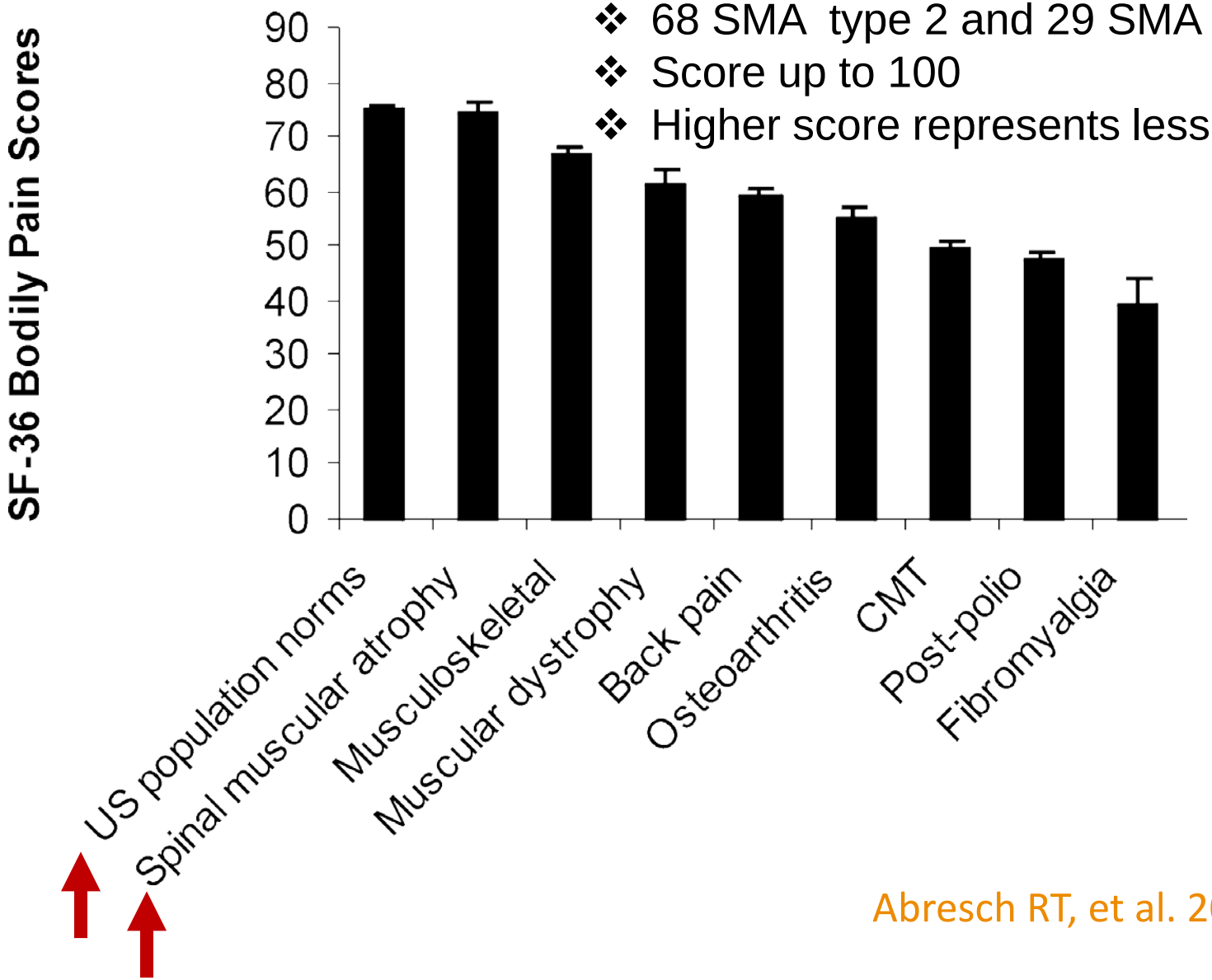
Pain in Adults with SMA

- 811 individuals with neuromuscular disease
- 68 SMA type 2 and 29 SMA type 3
- Score up to 100
- Higher score represents less pain



Abresch RT, et al. 2002

Pregnancy and child birth

- Several case reports of successful pregnancy in women with SMA
- Pulmonary function must be monitored, especially in 2nd and 3rd trimester
- Uterus has normal contractility, but pelvis deformity may prevent vaginal delivery
- Epidural anesthesia may be contraindicated depending on spinal deformity

Pregnancy and delivery in women with SMA

- Conducted a questionnaire based study sponsored by Cure SMA
- 32 females responded
- 19 experienced at least one pregnancy
  - Majority SMA type 3
  - 35 pregnancies
- Preterm labor and C section common in SMA type 2
- Increased weakness during pregnancy reported 74%
  - Persisted after delivery in 42%
- Overall positive experience
- Help with the decision should involve multidisciplinary team
  - Neurologist familiar with SMA
  - High risk obstetric physician
  - Pulmonologist

Elsheikh et al. Int J Neurosci 2017

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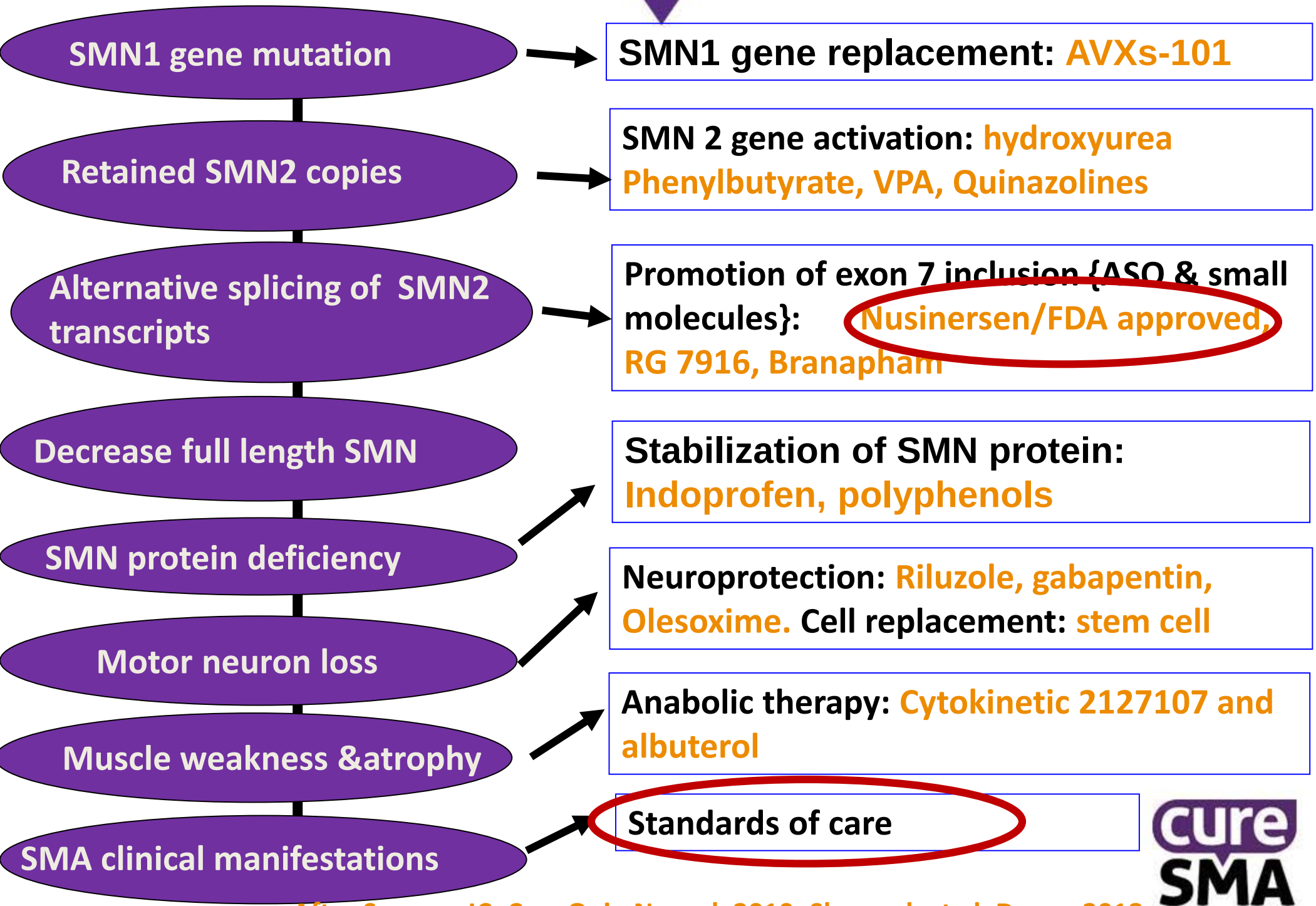
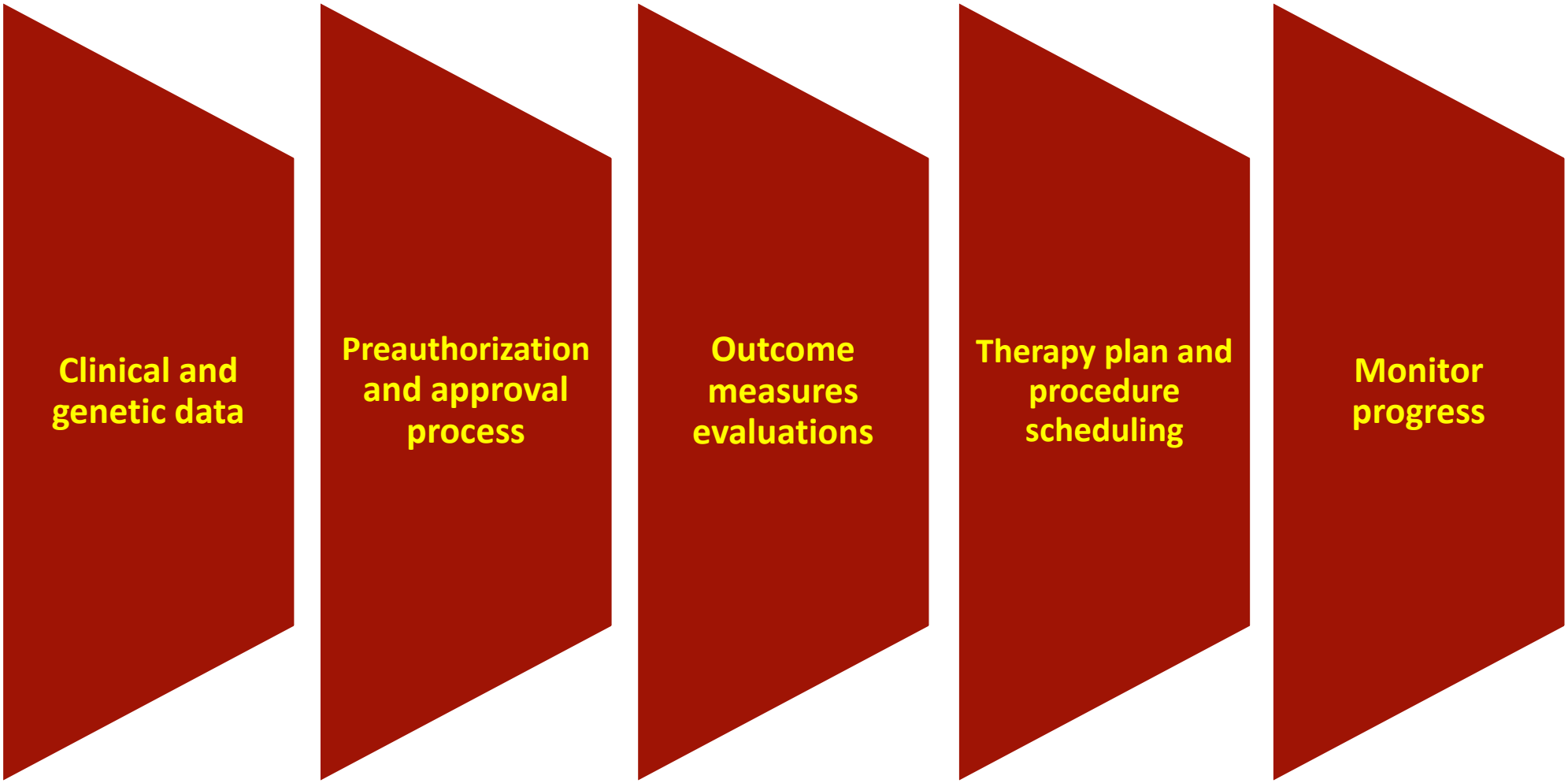
Treatment Strategies

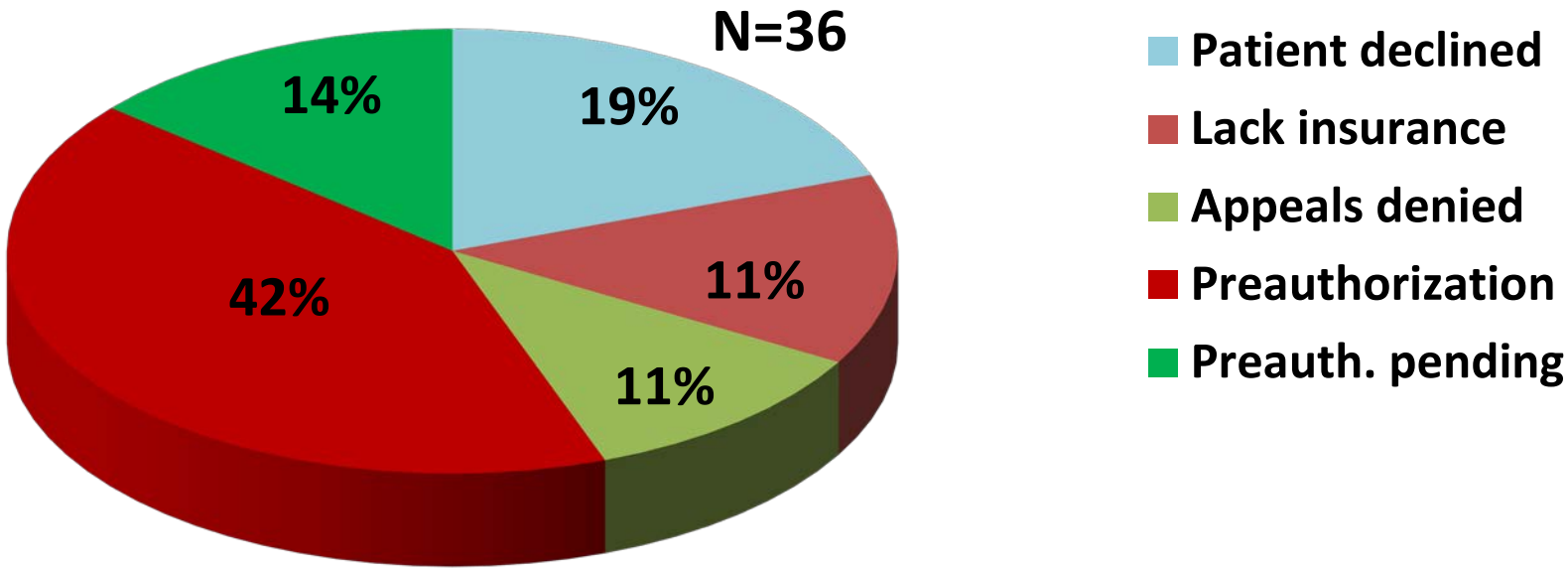


After Sumner JC. Curr Opin Neurol. 2010; Shorrock et al. Drugs. 2018

OSUWMC Adult SMA Nusinersen Program



OSUWMC Access to treatment Preliminary data



- ~20 % declined citing lack of data and concerns about side effects from the procedure
- 19 patients completed the approval process
- 17 patients received total of 68 injections
- 18 of these were cervical C1-2 injection (5pts)

Elsheikh et al. AAN 2018

Monitoring disease progression

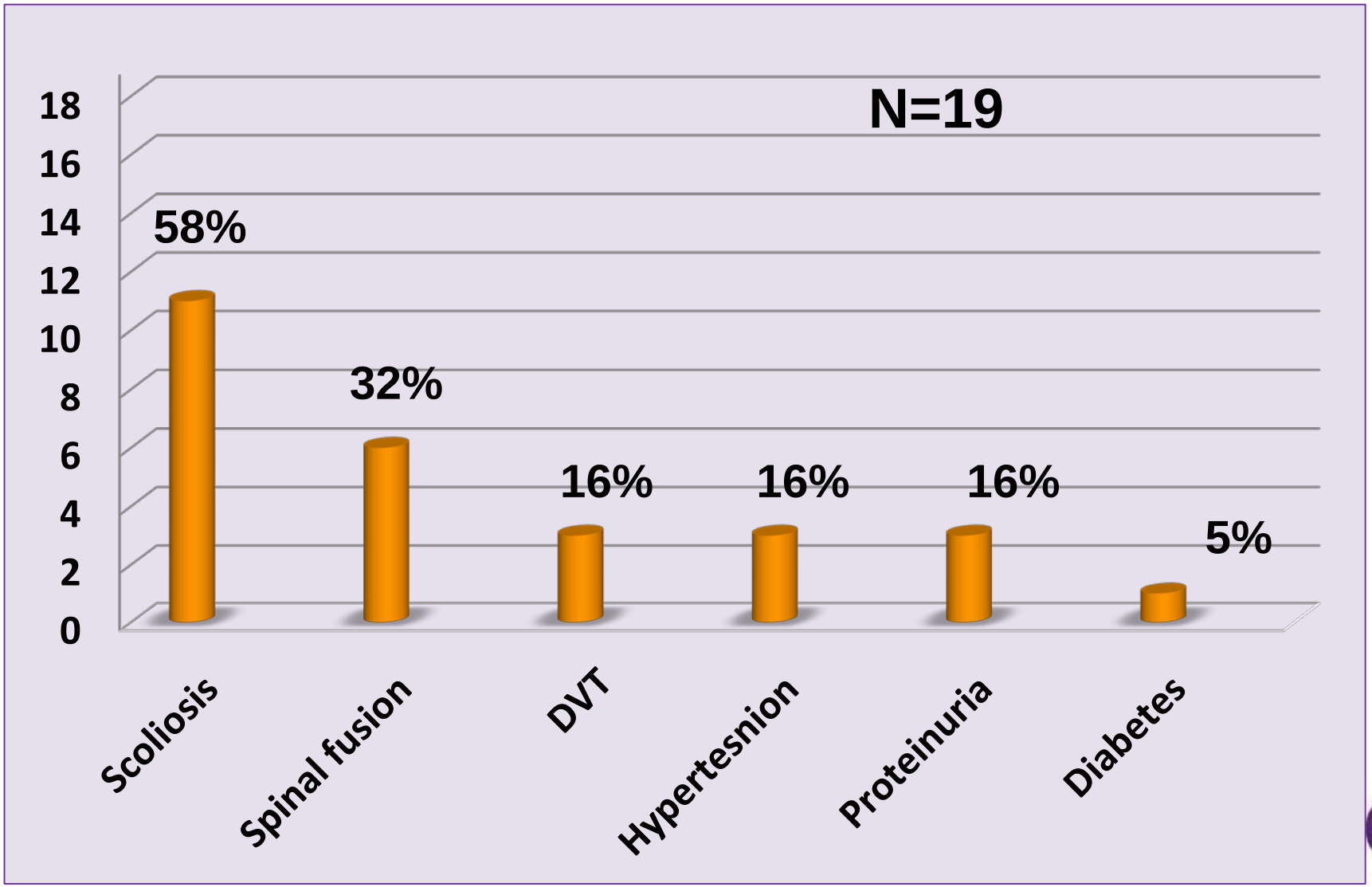
- **Motor function**
  - 6 Minute walk test (6MWT)
  - Hammersmith Functional Motor Scale Expanded (HFMSE)
  - Revised upper limb module (RULM)
  - SMA Functional Rating Scale (SMAFRS)
- **Strength measurements**
  - Manual Muscle Testing (MMT)
  - Voluntary Isometric Contraction (MVICT)
  - Handheld Dynamometry (HHD)
- **Pulmonary Function Tests (PFT)**
- **Electrophysiology**
  - Compound Muscle Action Potential (CMAP)

Participants characteristics Preliminary data

	Total N=19	Ambulatory N=8	Non-ambulatory N=11
Age (Mean ± SD)	38 ± 12 (18-64)	35± 9 (18-44)	40 ± 15 (26-64)
Gender (F/M)	8/11	4/4	4/7
SMA type			
2	7	0	7
3a	1	0	1
3b	11	8	3
SMN 2 copy			
2	1	0	1
3	11	1	10
4	7	7	0

Elsheikh et al. AAN 2018

Medical comorbidities
Preliminary results



Adverse Events/Preliminary data

- Overall well tolerated
- Similar to younger patients headache and back pain were most common
- Headache was rare in patients who received cervical injection
- One patient hospitalized for bronchitis
- One patient hospitalized for pneumonia
- One patient with recurrent UTI
- No change in platelet count or coagulation profile
- Increase baseline urine protein/creatinine ratio without significant change on treatment

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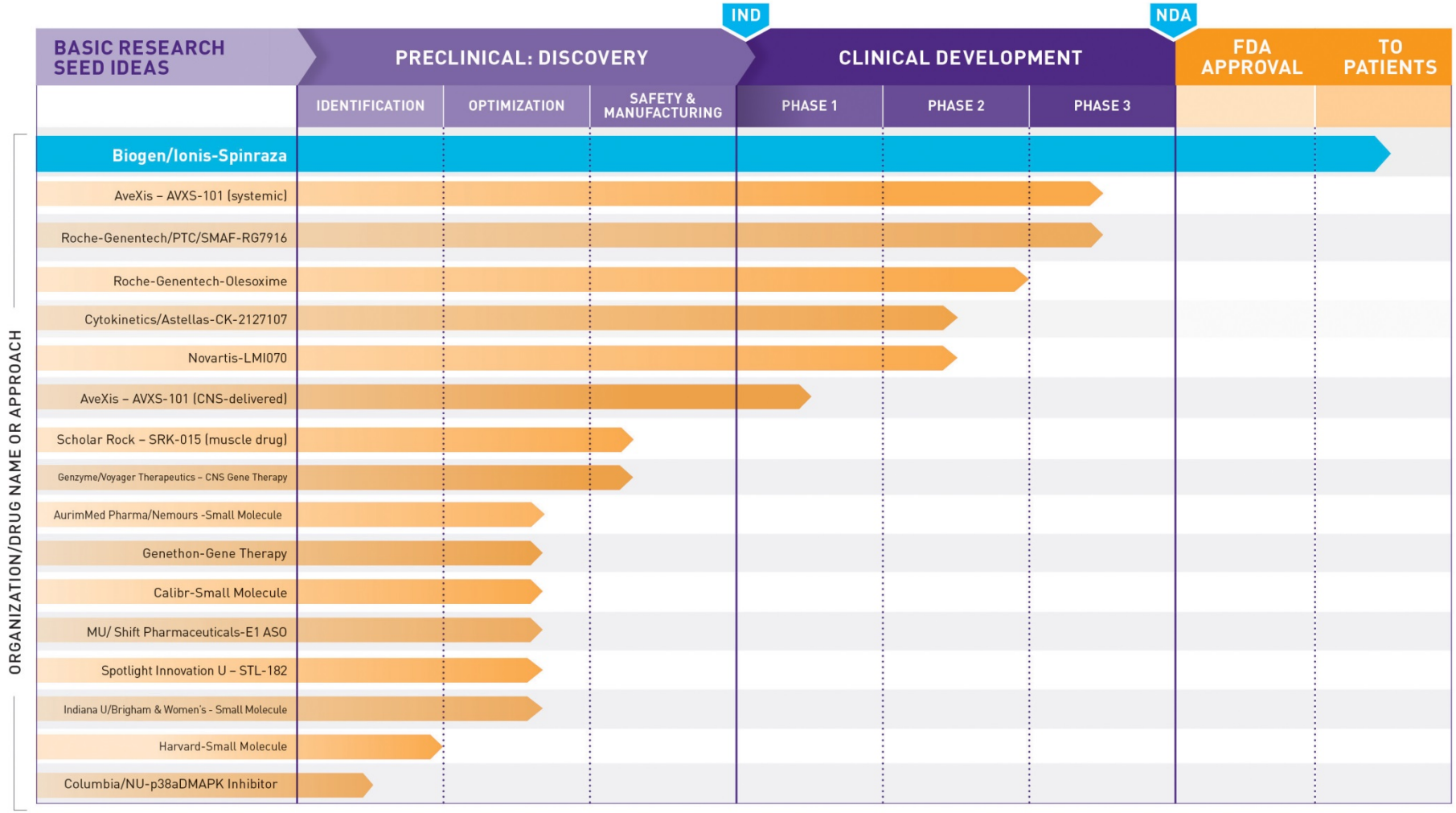
SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.



IND = Investigational New Drug **NDA** = New Drug Application

Last updated: January 2018

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Single Dose Gene Replacement Therapy for Spinal Muscular Atrophy AVXS 101

- Single-site, Phase I gene transfer trial in SMA type1
- N = 12 clinically affected subjects, <9 mo of age, proven SMN1 mutation (bi-allelic) with 2 copies of SMN2
- scAAV.CB.SMN delivered intravenously
  - Cohort 1 (Low Dose) 6.7 X 10^{13} vg/kg (n=3)
  - Cohort 2 (High Dose) 2 X 10^{14} vg/kg (n=6 + 6)
- Primary Outcome measure: Safety
- Secondary outcome measures:
  - Time to ≥ 16-hour resp. assist/day or death
  - Efficacy : 50% subjects alive/ventilator free at 2 yrs
  - **Compared to natural history**

Mendell JR et al. N Engl J Med 2017;377:1713-1722.

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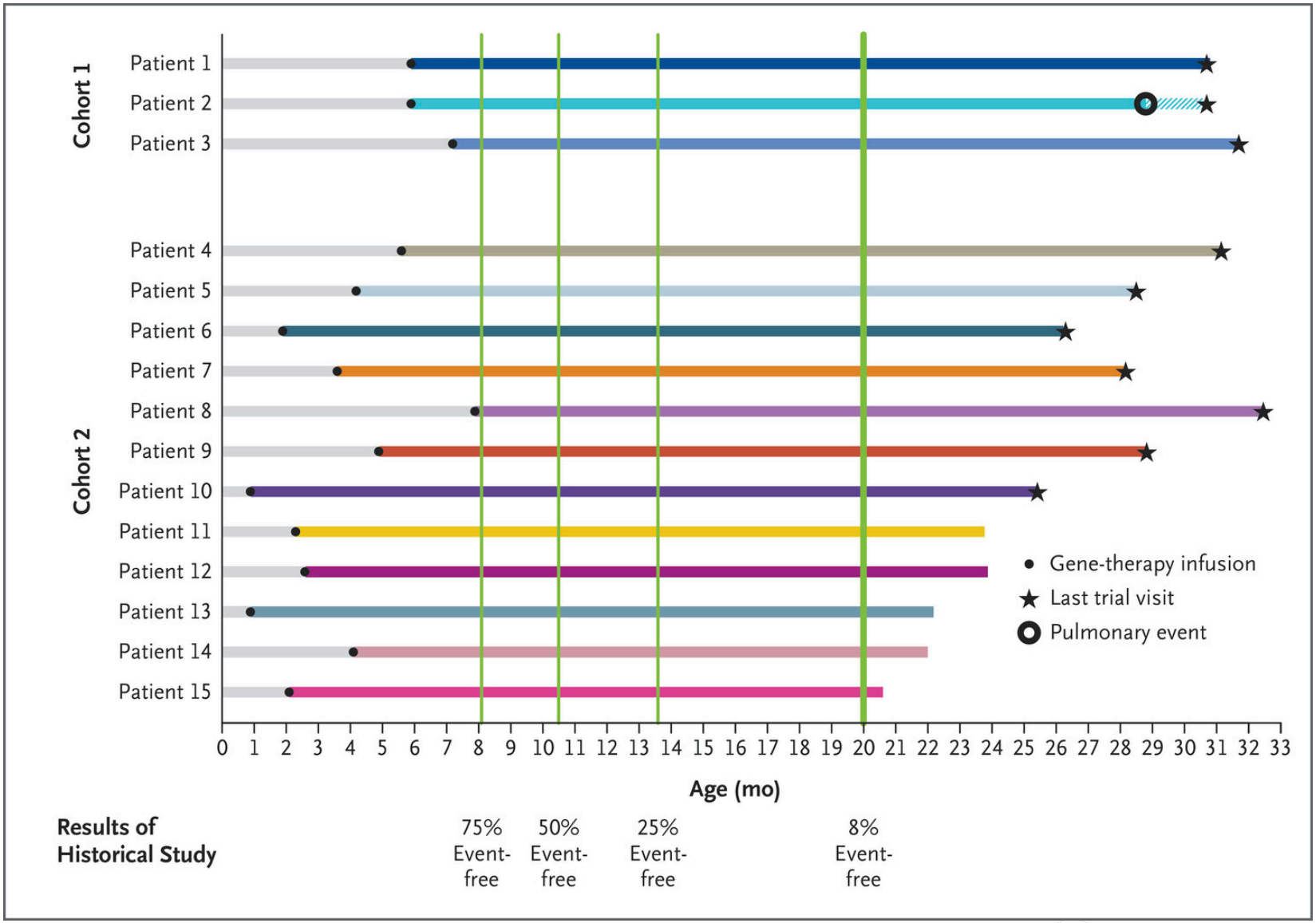
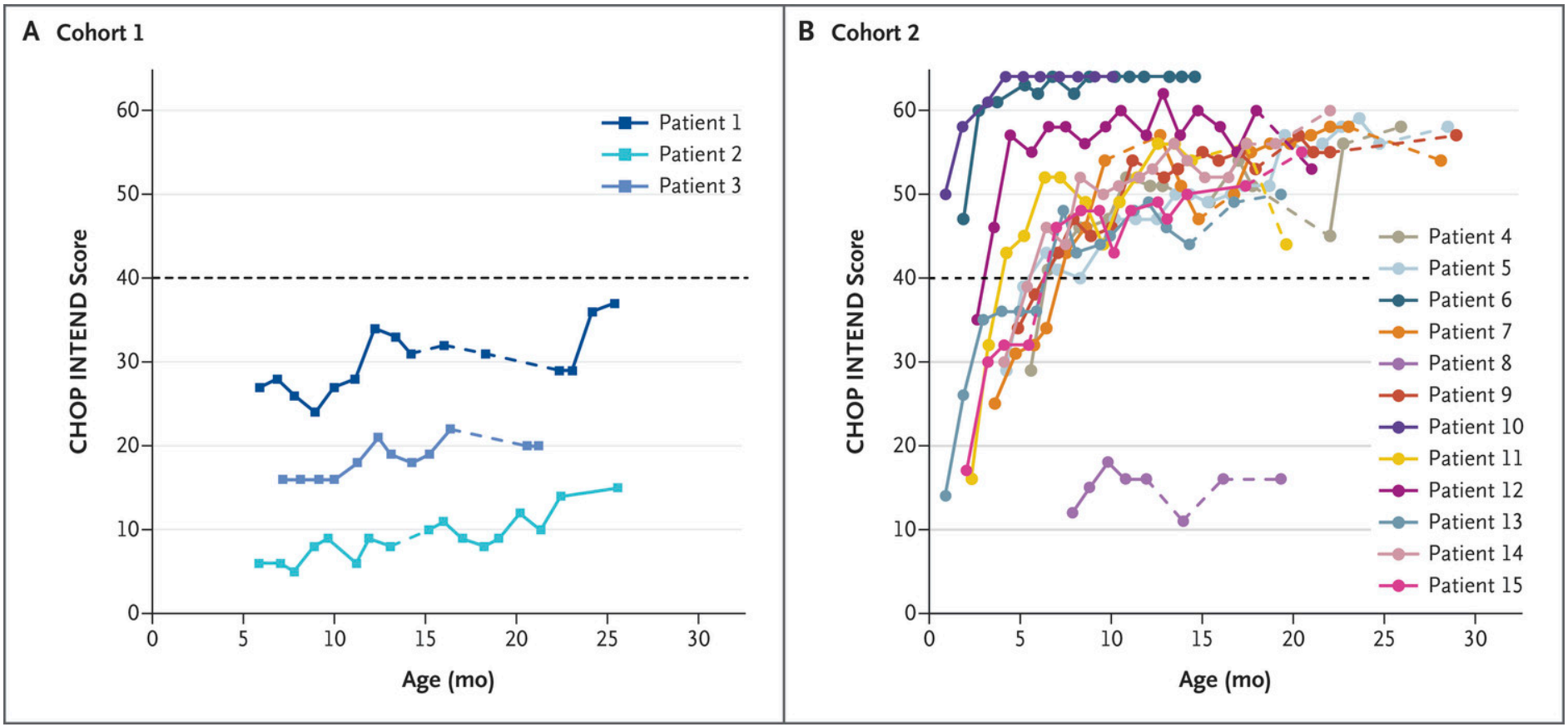
Survival Free from Permanent Ventilation in SMA-1 Patients



Mendell JR et al. N Engl J Med 2017;377:1713-1722.

Motor Function after Gene Therapy



Mendell JR et al. N Engl J Med 2017;377:1713-1722.

RG 7916 (Hoffmann-La Roche)

- SMN2 splicing modifier
- Oral daily dosing
- **Firefish:** SMA type 1, age 1-7 months, open label
- **Sunfish:** SMA type 2 &3, age 2-25 years, ambulatory and non-ambulatory, PRDBPC
- **Jewelfish:** SMA type 2 & 3, age 12-60, open label trial investigating safety, tolerability and efficacy in patient's previously treated with other SMN 2 targeting small molecule therapies
  - Increase SMN2FL/SMNΔ7 ration
  - Up to four fold SMN protein increase over 4 weeks
- Safe, well tolerated, increase full length SMN2 mRNA level
- Some benefit suggested

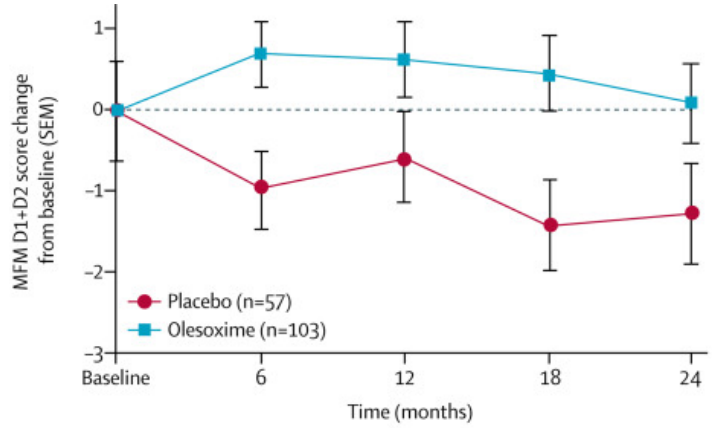
Mercuri et al. 21st Annual SMA researcher meeting. 2017
Chiriboga et al. AAN meeting 2018

Branaplam (LM1070, Novartis)

- SMN2 splicing modifier
- Oral weekly dosing
  - Dose finding, safety and tolerability over 13 weeks
  - Followed by 13 months extension for safety monitoring and to assess efficacy
- SMA type 1 with 2 SMN2 copies
- Parallel chronic animal toxicity studies showed nerve injury
- N=13 on treatment
  - 5 died and 8 on treatment for 16-29 months
- Initial results mild reversible adverse events
- Suggested some improvement in motor function

Olesoxime (Hoffmann-La Roche; Trophos SA)

- Neuroprotective agent
- Bind to components of mitochondrial permeability pores
- Prevent excess permeability under stress condition
- PRDBPC, SMA type 2 and non-ambulatory type 3, age 3-25 years
- Daily10mg/kg oral liquid for 24 months



Difference between treatment groups at timepoint	2·41	1·77	2·74	2·00*
p value	0·0039	0·0711	0·0075	0·0676*

Overall treatment difference 2·23, p=0·0084

- Adverse events: vomiting, cough, fever and naso-pharyngitis
- Maintain motor function

Bertini et al. Lancet Neurology, 2017

CK 107 (CK-2127107; Cytokinetics)

- Fast skeletal muscle troponin complex activator
- Slows the rate of calcium release from the regulatory troponin complex resulting in sensitization of the sarcomere to calcium
- Increase force output at submaximal frequencies of motor nerve stimulation.
- Preclinical study reduced fatigability in rat muscle in vivo
- PRDBPC, SMA type 2-4, age ≥12
- Oral suspension
- Cohort 1:150mg BID vs. Placebo
- Cohort 2: Up to 450mg BID

The combination of therapies in SMA

SMN2 splicing modifier approach
Antisense oligonucleotides molecules
Oral small molecules
(Oral [systemic] and/or intrathecal delivery; increased expression of full-length *SMN2* transcript)

SMN independent pharmacological approach
Neuroprotectors/ Neurotransmission enhancers / Myoactivators

Gene replacement
Intrathecal or systemic *SMN1* gene transfer/ Stem cell therapy?

Tizzano EF, Finkel RS. Neuromuscul Disord. 2017 Oct;27(10):883-889.

Take Home points

- Play an active role in your care
- The new standard of care documents are valuable
  - Consider sharing the information with your local neurologist and primary care physician
- FDA approved nusinersen to all patients with SMA including adults
- Overall the treatment and procedures are well tolerated with no safety concerns
- Emerging efficacy data in adults is encouraging
- Consider participating in research studies to address gaps in medical knowledge pertinent to the adult SMA population