Spinal Muscular Atrophy in 2017

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Disclosures

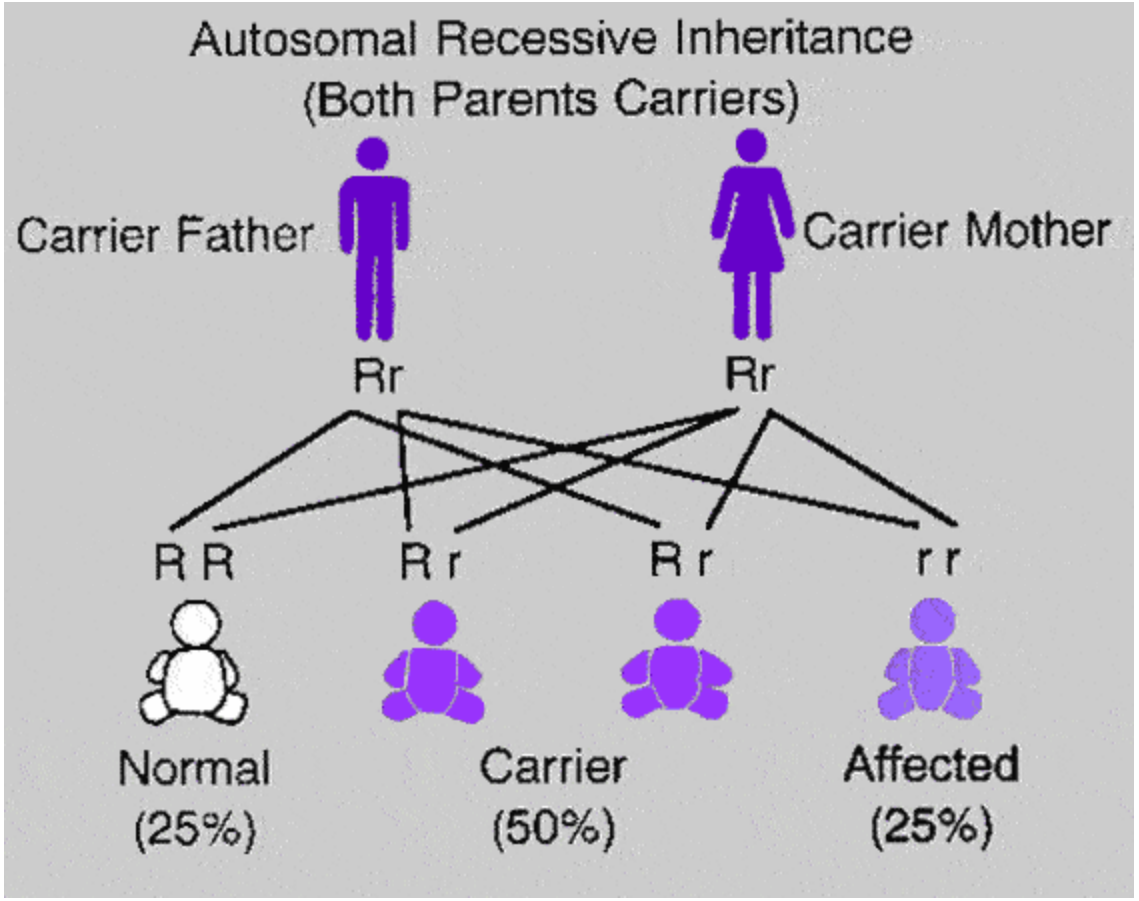
- MDA Care Center – Grant
- In this presentation, there are slides from both Sarepta Therapeutics and Biogen
- Parent Project Muscular Dystrophy Certified Care Center – Research Liaison Grant
- Local site for Sarepta Exon Skipping Trials 45 and 53
- PI for Santhera Idebenone study
- Medical Advisory Board Marathon Therapeutics
  - No personal honorarium payment received; did not partake in their snacks or wine
- Medical Advisory Board PTC Therapeutics
  - No personal honorarium payment received; honorarium redirected as a contribution to the neurology resident education fund

Objectives

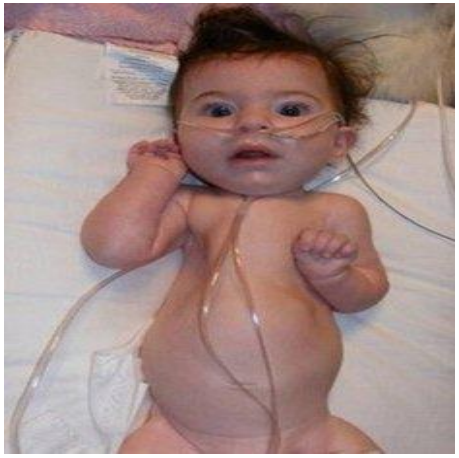
- Review Spinal Muscular Atrophy
- Discuss Nusinersen (Spinraza)
- Discuss Gene Therapy for Spinal Muscular Atrophy

Review of the Genetics of SMA

- SMN1 and SMN2 are found on the 5th chromosome
- There are other forms of spinal muscular atrophy that will not be covered

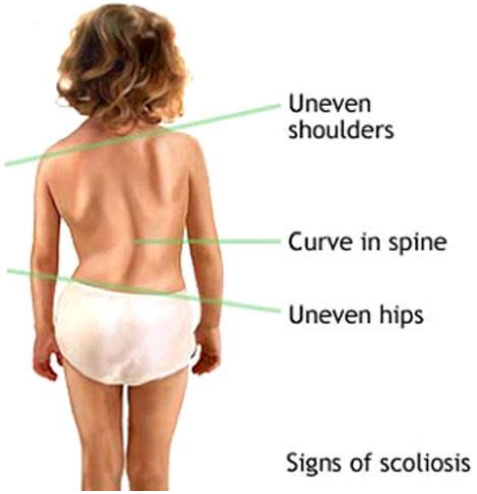

Autosomal Recessive Inheritance
(Both Parents Carriers)
Carrier Father
Carrier Mother
Rr
Rr
R R
R r
R r
r r
Normal
(25%)
Carrier
(50%)
Affected
(25%)

Clinical Spectrum of SMA



Orthopedic Care

- Unique challenges in this population; different for the different SMA forms
  - Hip subluxation
  - Contractures
  - Scoliosis (type 2)
  - Hypermobility (type 3)



Orthopedic Care

- Special scales exist for the abilities in patients with SMA
- Interventions
  - Bracing
  - mobility

The Clinical Trials

- Cherish – for type 2 SMA, Phase 3
- Endear – for type 1 SMA, Phase 3
- Embrace – “catch all trial”, Phase 2
- Nurture - pre-symptomatic newborns, Phase 2
  - Can have 2 – 3 copies of SMN2
  - This is a key study on the importance of prenatal screening and newborn screening

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SMN1 gene[3,6,7]

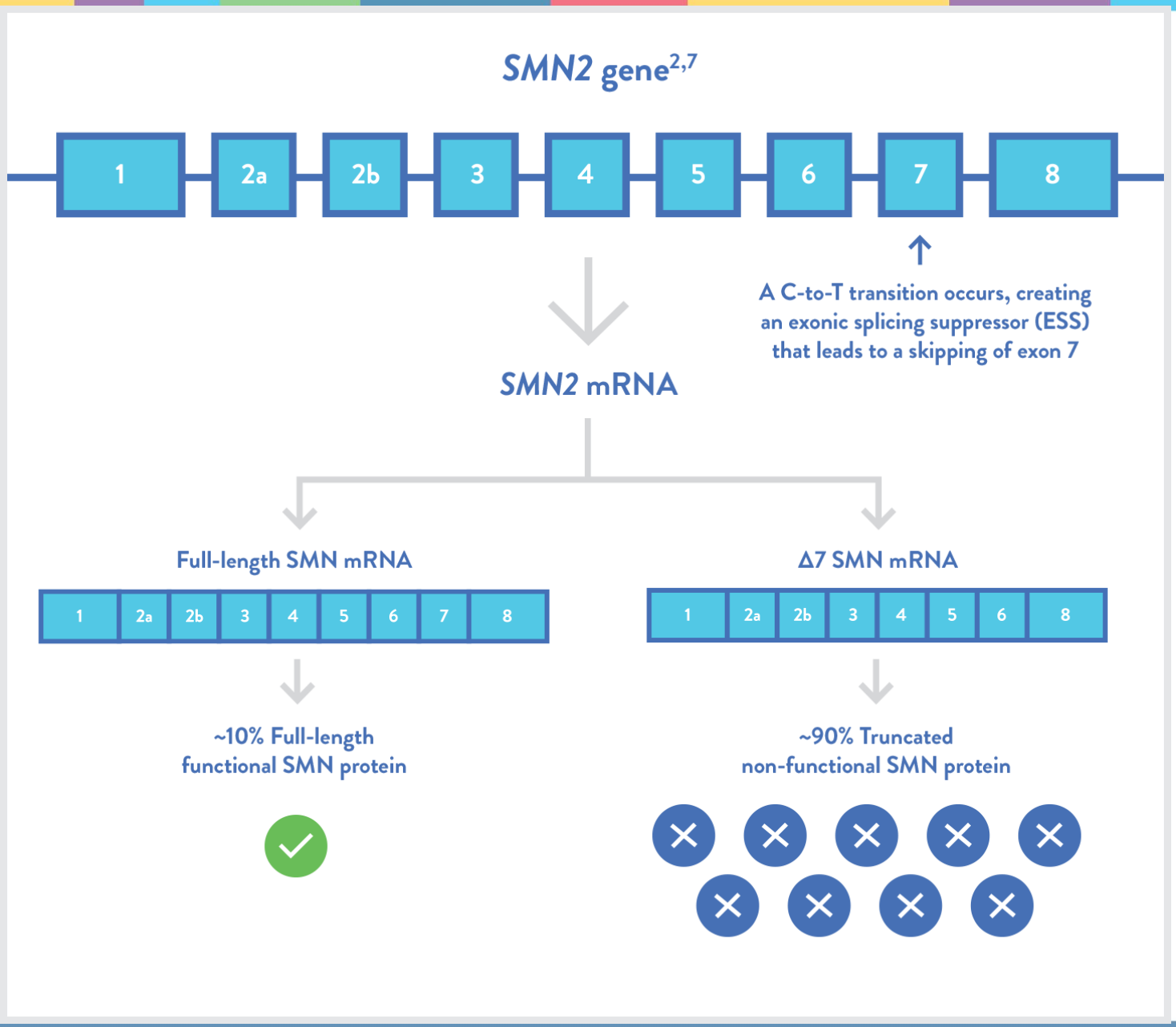
The *SMN1* gene is located on chromosome 5q13

SMN1 mRNA

100% Full-length functional SMN protein

Spinal Muscular Atrophy – Genetics

- SMN2 is a modifier gene also present on 5q
- Almost identical to SMN1, only 5 nucleotides different
  - C>T nucleotide change in SMN2 creates an exonic splicing suppressor (ESS) that leads to skipping of exon 7 during transcription
- SMN2 usually produces a truncated, non-functional, rapidly degrading, unstable protein
- 10-15% of the time, SMN2 includes exon 7
  - Gene product is identical to SMN1 transcript and is functional
  - Disease severity in SMA is inversely correlated with SMN2 gene copy number



https://www.togetherinsma-hcp.com

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

Nusinersen (Spinraza)

- Double blind placebo controlled trial 2:1
- 121 patients <7 months of age at the first dose
  - 80 treated, 41 controls
- All patients had to be symptomatic <6 months of age without ability to sit
- All patients had to have 0 copies SMN1 and 2 copies SMN2
- Planned for about a year (13 months)
- About 80 patients were evaluated in the interim
  - Because of the interim results, all patients started to get drug

Nusinersen (Spinraza)

- Patients could not be trach/vent dependent
- G-tubes were OK
- Hammersmith Infant Neurological Examination

Nusinersen (Spinraza) - HINE

Grasp: none, whole hand, immature, pincer

Kick: none, horizontal (no lift), vertical, touches leg, touches toes

Head Control: unable, wobbles, upright

Rolling: none, to side, prone to supine, supine to prone

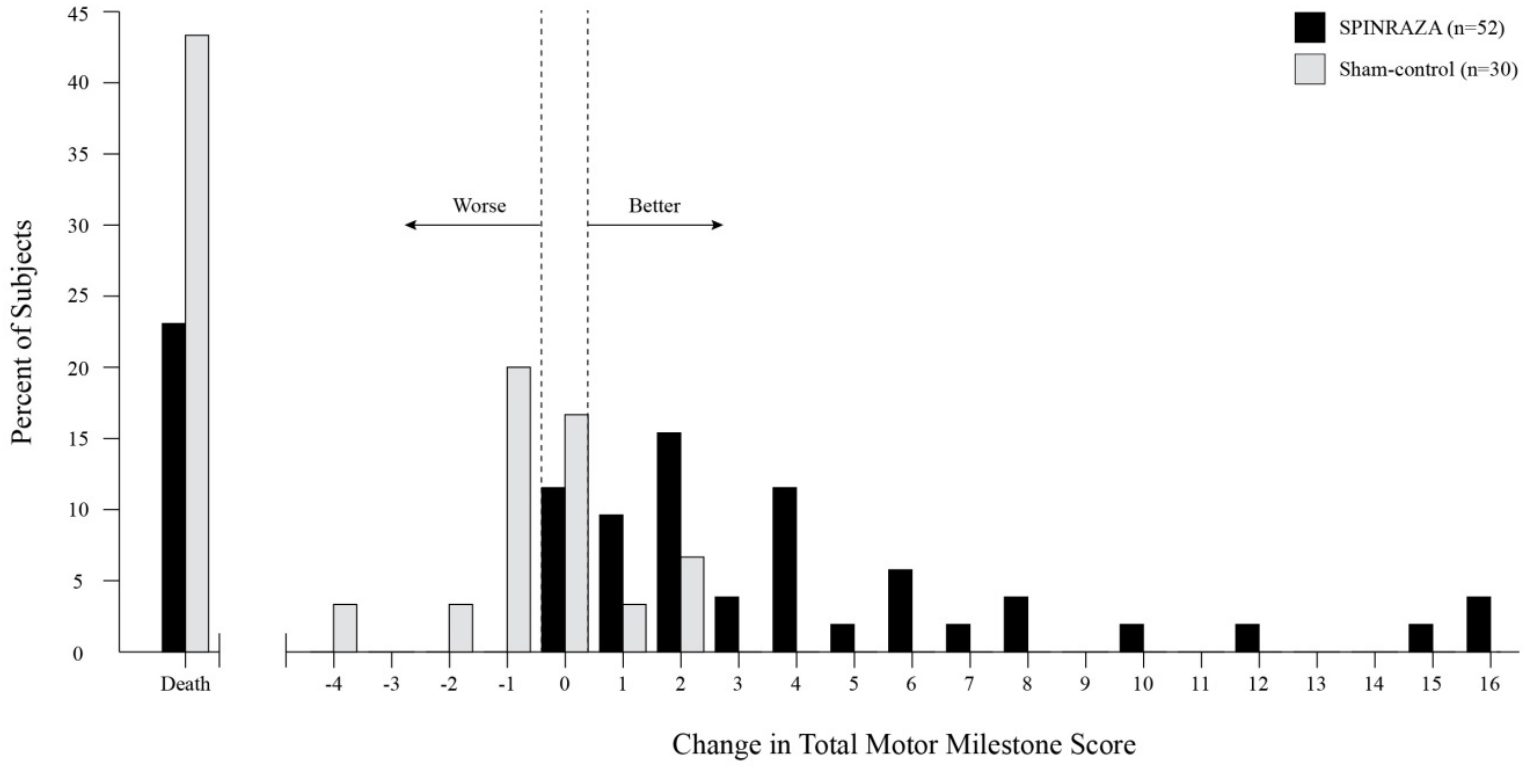
Sitting: none, hip support, props, stable, pivots

Crawling: none, elbows, outstretched hands, crawling flat on abdomen, on hands and feet

Standing: doesn't support weight, supports weight, stands with support, stands unassisted

Walking: none, bouncing, cruising, walking independently

Nusinersen (interim results)



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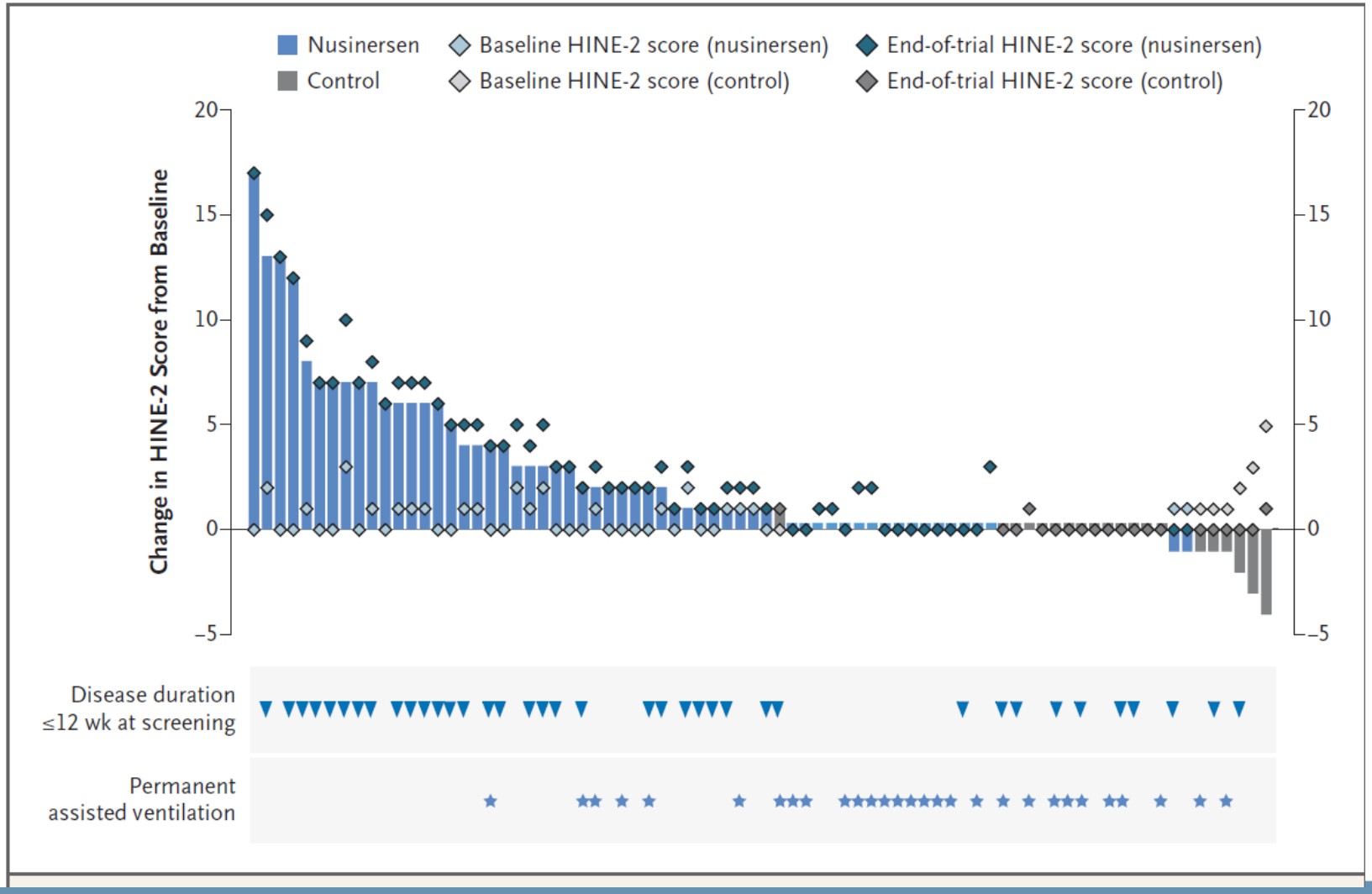
Nusinersen (final results)



Nusinersen (CHERISH)

- Phase III multi-center trial
- 2 to 12 years
- Symptoms > 6 months at diagnosis
- Hammersmith Functional Motor Scale – Expanded
- Life expectancy greater than 2 years
- Primary endpoint is change from the HFSME baseline of which 3 points is considered significant
- The treatment group gained significantly more function than the untreated group.

What is measured in the HFMSE?

Chair sitting
Long sitting
One hand to head
Sitting, two hands to head
Supine to lying
Prone to supine right
Prone to supine left
Supine to prone left
Supine to prone left
Sitting to lying
Props on forearms
Prop on extended arms
Lifts head from prone
Lying to sitting
Four point kneeling
Crawling
Lift head from supine
Supported standing
Stand unsupported

Stepping
Right hip flexion in supine
Left hip flexion in supine
High kneeling to right half knee
High kneeling to left half knee
High kneeling to stand right
High kneeling to stand left
Stand to sitting on floor
Squat
Jumps 12 inches forward
Ascends 4 stairs with rail
Descends 4 stairs with rail
Ascends 4 stairs without rail
Descends 4 stairs without rail

Each is graded 0-2 with maximum score 66

Nurture Trial

Bertini (2016)

- Open label, multi-center, multi-national
- < 6 weeks before the 1st dose

Nurture Trial

- At 13 months, all infants were alive
- No infants required invasive ventilation, tracheostomy, or non-invasive ventilation >6 hours a day, 7 days a week
- 9/13 full head control
- 5/13 could now sit
- 3/13 could stand with support
- 1/13 walked
- Safety upheld – no one dropped out of the study because of side effects
- Of the studies, the Nurture trial also demonstrated the highest gain in function
- There is further information on this trial but is not yet public

Nusinersen (Spinraza)

- Submitted for NDA November 7, 2016
- Approved for use by the FDA on December 23, 2016

Nusinersen

- Indicated for all types of chromosome 5 SMN related SMA
- Given intrathecally
  - Same does for everyone
- Loading Dose
  - Once every 2 weeks x 3
  - 4^{th} dose in 30 days

Nusinersen side effects

Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients in the Controlled Study in Infants with Symptomatic SMA

Adverse Reactions	SPINRAZA 12 mg[1] N=80 %	Sham-Procedure Control N=41 %
Lower respiratory infection[2]	43	29
Upper respiratory infection[3]	39	34
Constipation	30	22
Teething	14	7
Upper respiratory tract congestion	6	2
Aspiration	5	2
Ear infection	5	2
Scoliosis	5	2

[1] Four loading doses followed by 12 mg (5 mL) once every 4 months
[2] Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia bacterial, bronchitis, bronchitis viral, pneumonia moraxella, pneumonia parainfluenzae viral, lower respiratory tract infection viral, lung infection, pneumonia influenza, pneumonia pseudomonal, pneumonia respiratory syncytial viral
[3] Includes upper respiratory tract infection, nasopharyngitis, rhinitis, pharyngitis, or tracheitis

Nusinersen Cost

- $125,000 per vial
- $750,000 for the first year
- $375,000 for the subsequent years

Buy and Bill did not work for CHLA

- There is a significant financial risk
  - CHLA would have to shell out approximately 21 million for the first year to accommodate our patients population
  - The budget for Neurology (one division) is a lot less than that
  - Alternative was offered - Specialty Pharmacy

The NEW ENGLAND JOURNAL of MEDICINE

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Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

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Single-Dose Gene Replacement Therapy for SMA1

- 15 patients
- AAV 9 cDNA encoding SMN protein
- 3 low dose; 12 high dose
- Primary outcome = safety
- Secondary outcome = time to death or permanent ventilatory support
- CHOP Intend (scored from 0 to 64)

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At 20 months, all patients gained milestones

Table 2. Event-free Survival and Motor and Other Milestones among the 12 Patients in Cohort 2.*

Variable	Age at Study Entry	Event-free Survival†	Motor Milestones							Other Achievements			
			Brings Hand to Mouth	Controls Head	Rolls Over‡	Sits with Assistance	Sits Unassisted§			Speaks	Swallows	No NIV Use	No Nutritional Support¶
	mo						*≥5 sec*	*≥10 sec*	*≥30 sec*				
Patient no.													
4	5.6	31.1	+	+	+	+	+			+	+		
5	4.2	28.5	+	+	+	+	+	+	+	+	+	+	+
6	1.9	26.1	+	+	+	+	+	+	+	+	+	+	+
7	3.6	28.1	+	+	+	+	+	+		+	+	+	
8	7.9	32.4	+										
9	4.9	28.9	+	+	+	+	+	+	+	+	+	+	+
10	0.9	25.3	+	+	+	+	+	+	+	+	+	+	+
11	2.3	23.8	+	+	+	+	+	+	+	+	+		
12	2.6	23.9	+	+	+	+	+	+	+	+	+	+	+
13	0.9	22.1	+	+		+	+	+	+	+	+		
14	4.1	22.0	+	+	+	+	+	+	+	+	+	+	+
15	2.1	20.6	+	+		+	+	+	+	+	+		
Patients with outcome (%)													
This study		100	100	92	75	92	92	83	75	92	92	58	50
Natural-history studies		8 by 20 mo‖	NA	0	0**	0**	0**	0**	0**	NA	NA	NA	8 by 20 mo‖

SUNFISH Phase 2 Trial Part 1- RG7916

- Double-blind, placebo controlled trial in ambulatory and non-ambulatory patients with SMA 2/3
- Orally administered “small molecule”
  - Mechanism: forces alternative splicing of SMN2
  - Results in expression of full SMN2 mRNA transcript and SMN protein
- Interim analysis of 4 cohorts treated with RG7916 for ≥28 days demonstrated an exposure-dependent increase in SMN protein
  - Up to a median of 2.5-fold increase in SMN protein
- Well tolerated without side effects
- SUNFISH part 2: 150 non-ambulatory patients
  - Safety and efficacy of the dose level selected in part 1

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Summary

- Spinal Muscular Atrophy (SMA) has various clinical presentations
- Patients with SMA require multidisciplinary care
- Nusinersen (Spinraza) is an anti-sense oligonucleotide treatment that is now FDA approved with impressive study results
- There is promise in an oral medication for SMA
- A new gene therapy is in the process of development/clinical trials also shows incredible promise

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- https://www.spinraza-hcp.com
- http://www.ionispharma.com
- https://www.biogen.com
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- Osman EY, et al. Optimization of morpholino antisense oligonucleotides targeting the intronic repressor element1 in Spinal Muscular Atrophy. Molecular Therapy. 24 (9), p1592-1601, September 2016