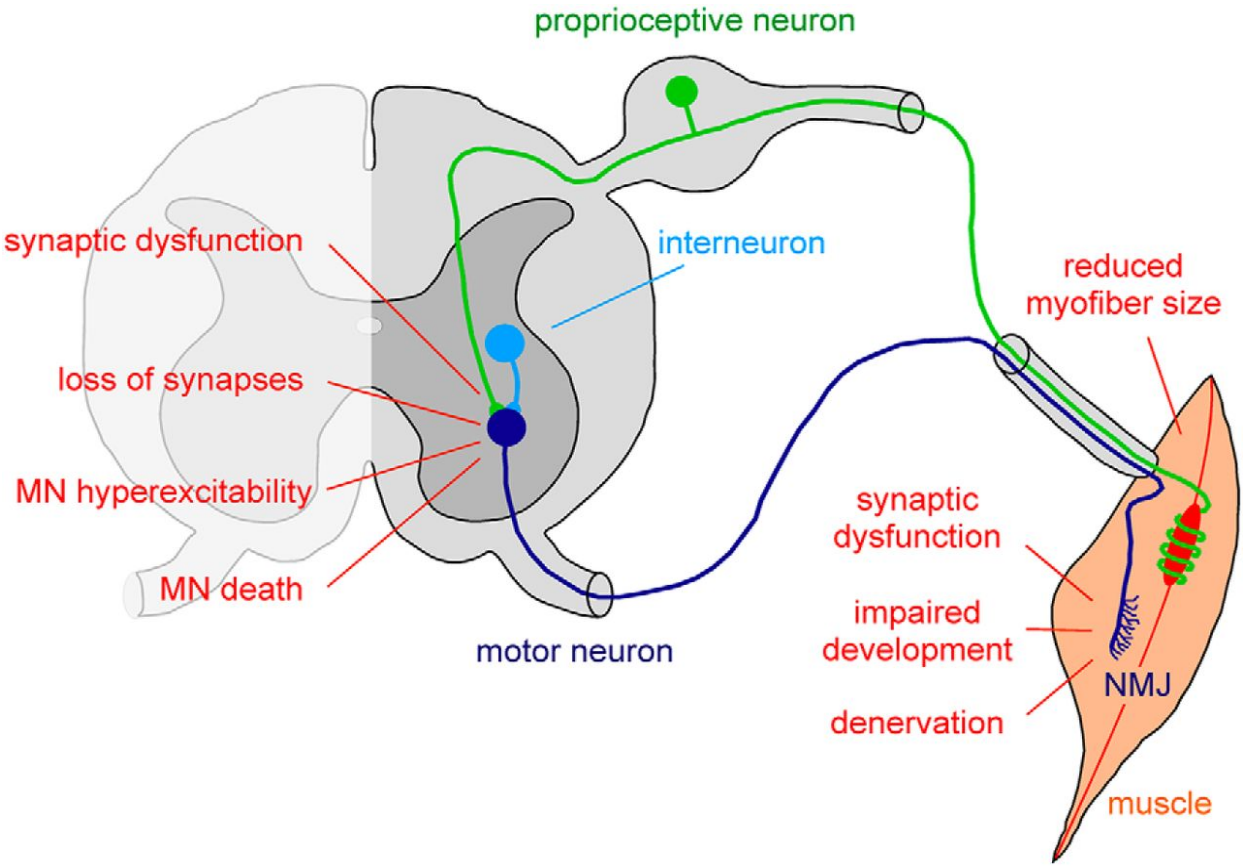
16:30 Inquadramento clinico, neurofisiologico e terapie nelle SMA E. Bertini (Roma)

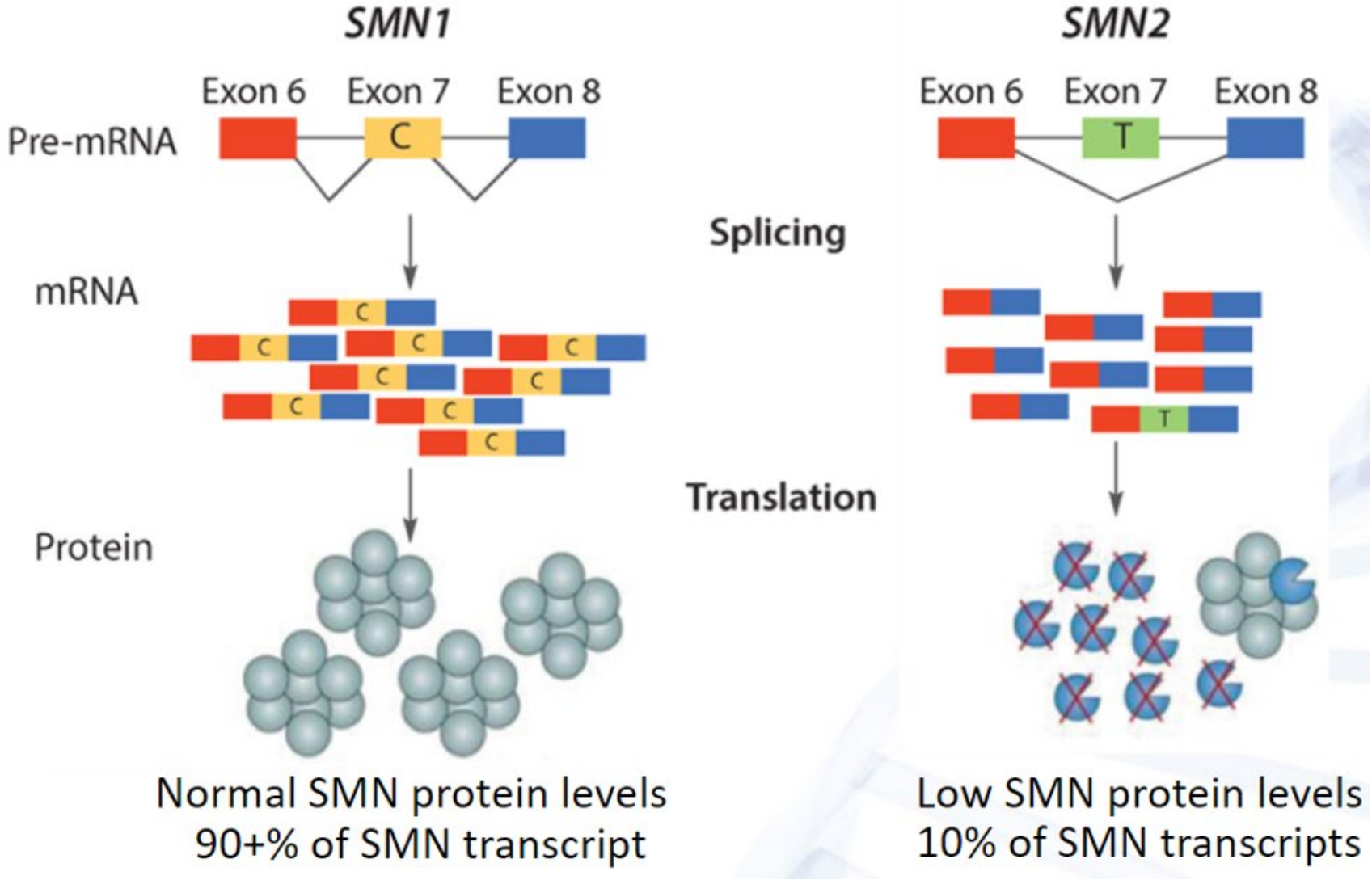
5q Spinal Muscular Atrophy

- One of the most common autosomal recessive neuromuscular disorders
- Progressive, frequently devastating—most common genetic cause of death in infants and children
- Caused by mutation in *SMN1* on chromosome 5 → reduction in SMN protein
- Number of *SMN2* copies (1 - 6) modifies phenotype
- Affects mainly lower motor neurons, but also affects proprioceptive neurons, neuromuscular junction, muscle
  - Highly selective neuronal death
  - Role of SMN in neuromuscular development unclear
- Outcomes without intervention
  - Progressive weakness/paralysis of trunk and limbs
  - Secondary spine and limb deformities
  - Respiratory compromise, early death in the most severe forms
  - Continuum of phenotypes from type 0 to type 4



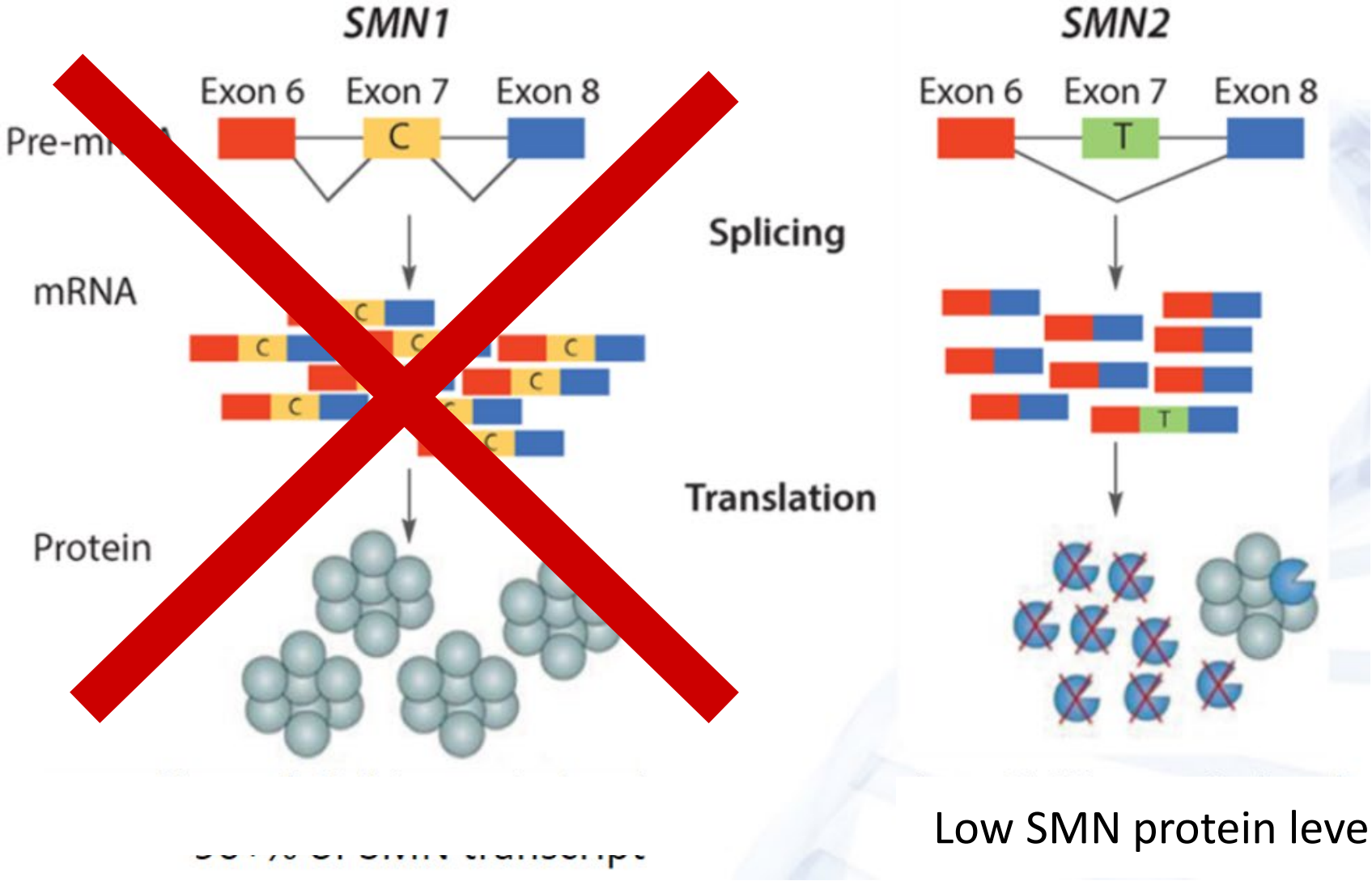
Tisdale S, Pellizzoni L. *J Neurosci* 2015;35(23) 8691-8700.

Normal Individual



Burghes AH, Beattie CT. *Nat Rev Neurosci*. 2009;10:597-609.

Individual with SMA



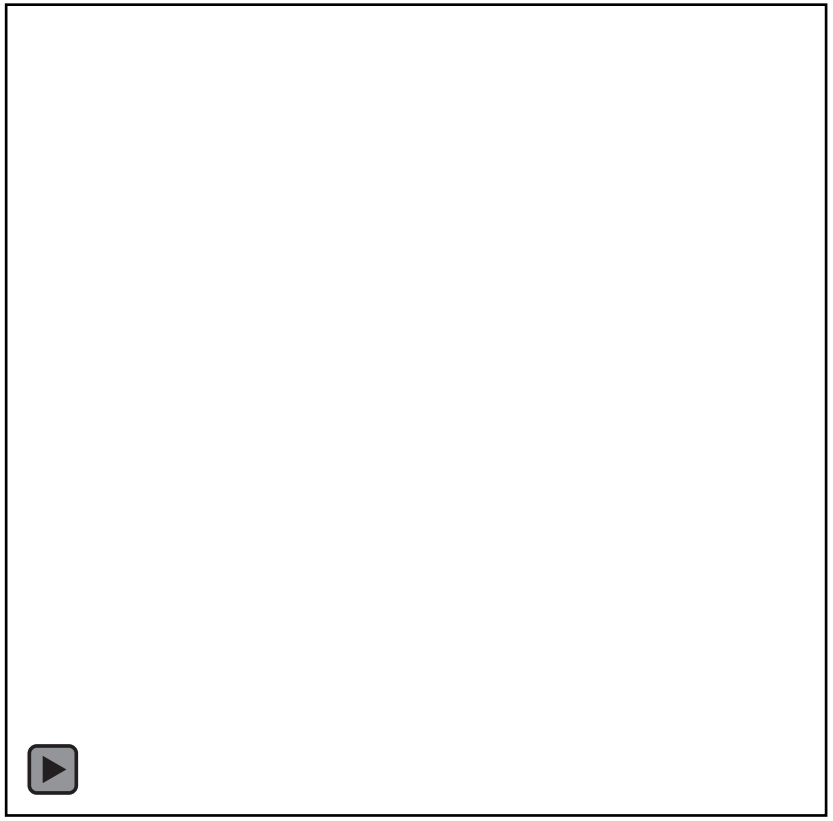
↑ SMN is a treatment goal/target

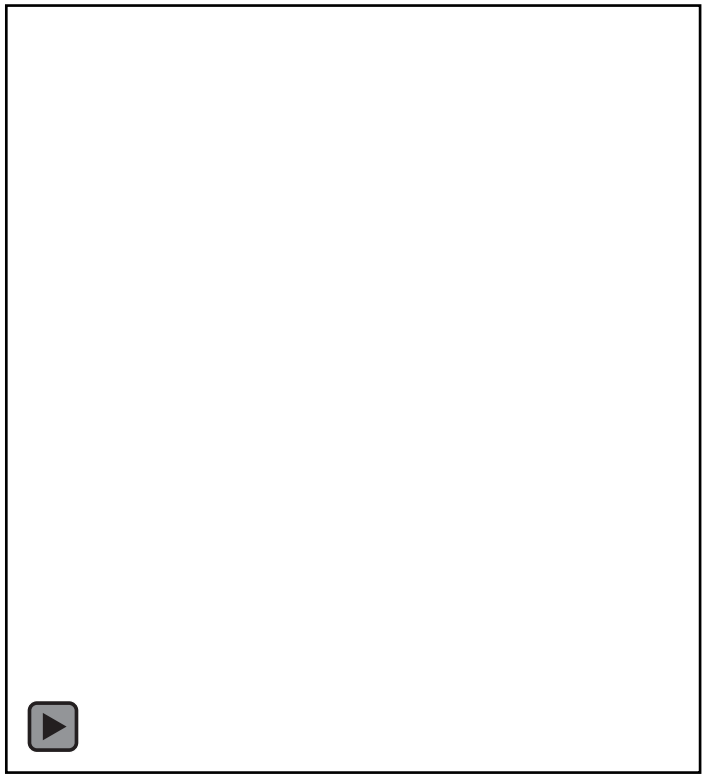
Low SMN protein levels

Burghes AH, Beattie CT. *Nat Rev Neurosci*. 2009;10:597-609.

Case 1: Infant Boy with SMA Type 1

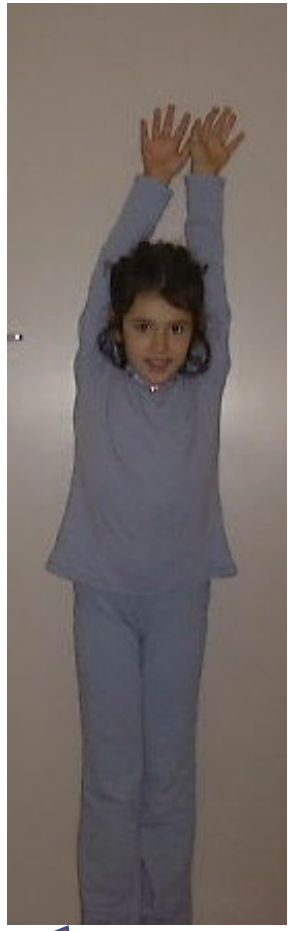
2 mo-old boy at first evaluation
Never able to achive head control (SMA 1 b)
No symptoms at newborn
Onset of respiratory and swallowing difficulties at the end of 7 months of age





SMA Severity and Phenotypes

SMA Severity Types



Type 0:
- Most severe weakness
- Contractures; cardiomyopathy
- Death in weeks

Type 1A:
- Severe weakness
- Often respiratory problems at birth

Type 1B:
- Most typical type 1 form

Type 1C
- May develop head control
- Less rapid decline

Type 2:
- Able to sit but unable to achieve independent ambulation
- Variable severity (2A-2B)
- Survival strongly improved following NIV introduction and new standards of care

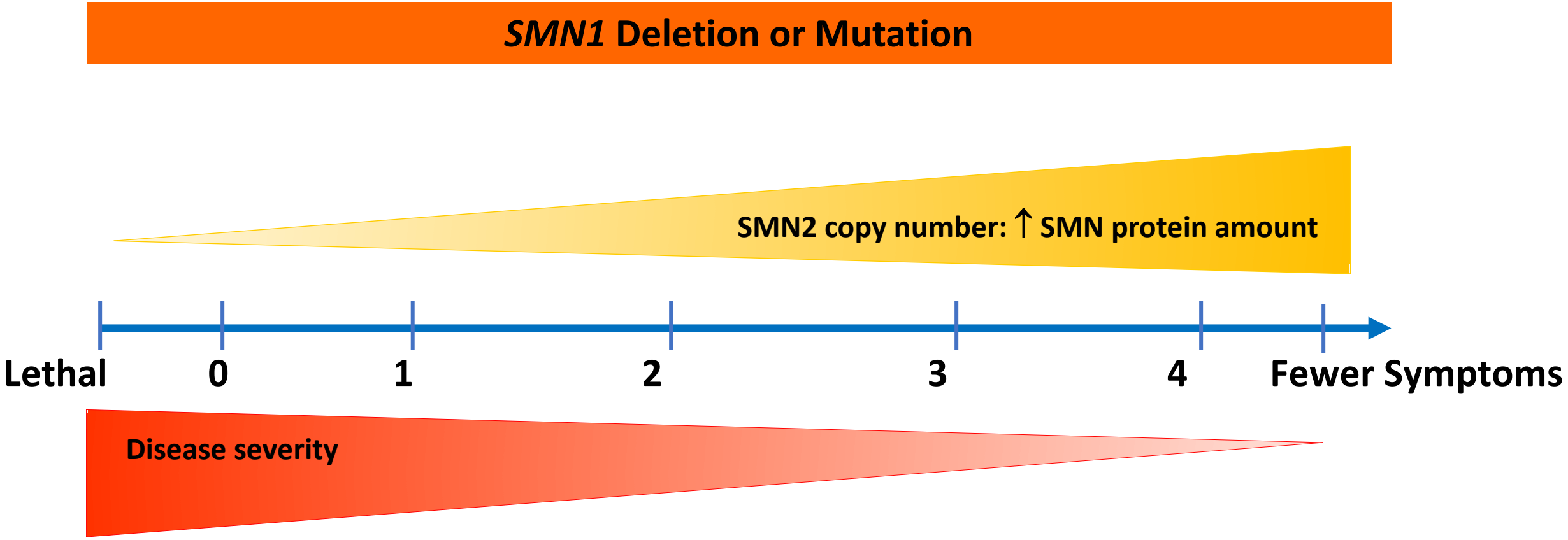
Type 3A/B:
- Early loss of ambulation
- Normal lifespan

Type 4:
- Ambulant until later in life
- Normal lifespan

Note: Phenotypes are changing with treatment

Talbot K, Tizzano EF. *Gene Ther*. 2017;24:529-533.

Impact of *SMN2* Copy Number

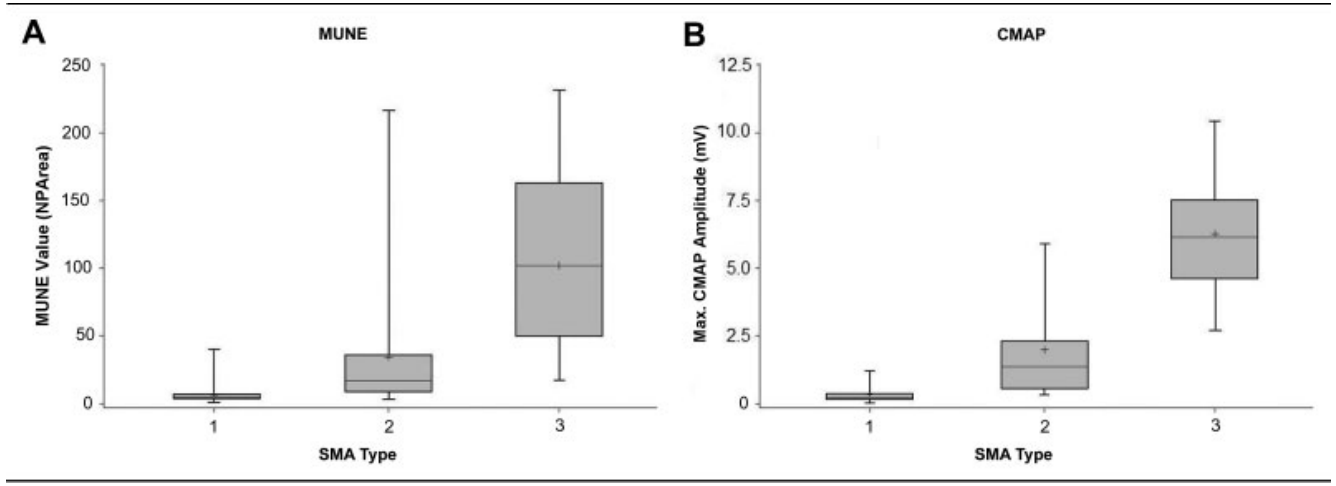


Adapted from Chen T-H. *Int J Mol Sci*. 2020;21(9):3297.

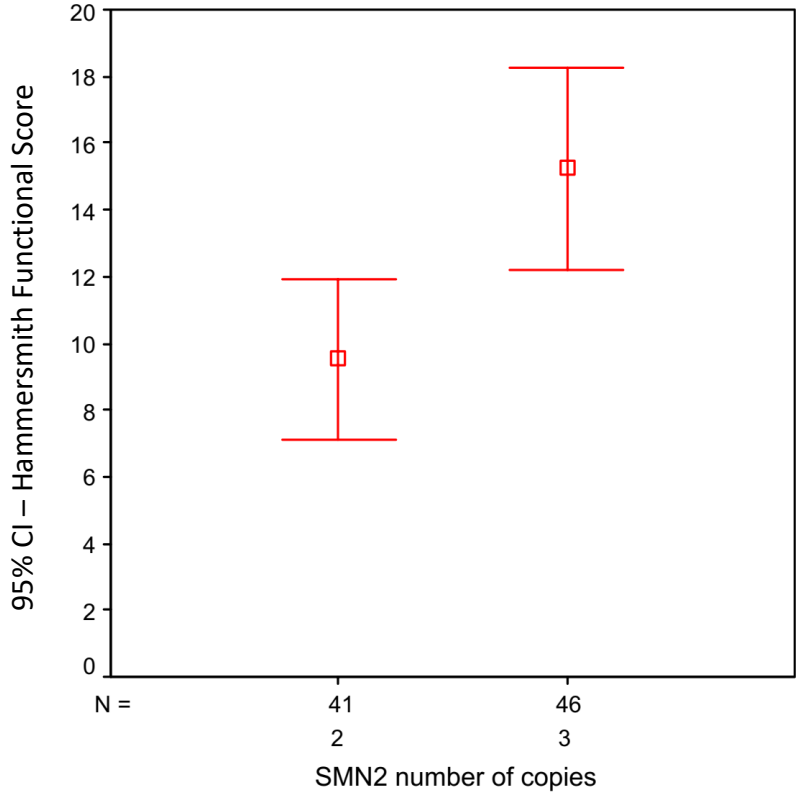
Inverse Relationship Between Disease Severity and *SMN2* Copy Number

MUNE				CMAP			
SMN2 Copy	Estimate	SE	*p*	SMN2 Copy	Estimate	SE	*p*
1 vs 2	−1.89	0.35	<0.0001	1 vs 2	−1.03	0.15	<0.0001
2 vs 3	−1.05	0.27	0.0001	2 vs 3	−0.78	0.11	<0.0001
3 vs 4	0.17	0.48	0.727	3 vs 4	−0.05	0.14	0.739
4 vs 5	−0.36	0.48	0.45	4 vs 5	−0.07	0.27	0.80

MUNE = motor unit number estimation; CMAP = compound motor action potential amplitude; SMN = survival motor neuron 1; SE = standard error.

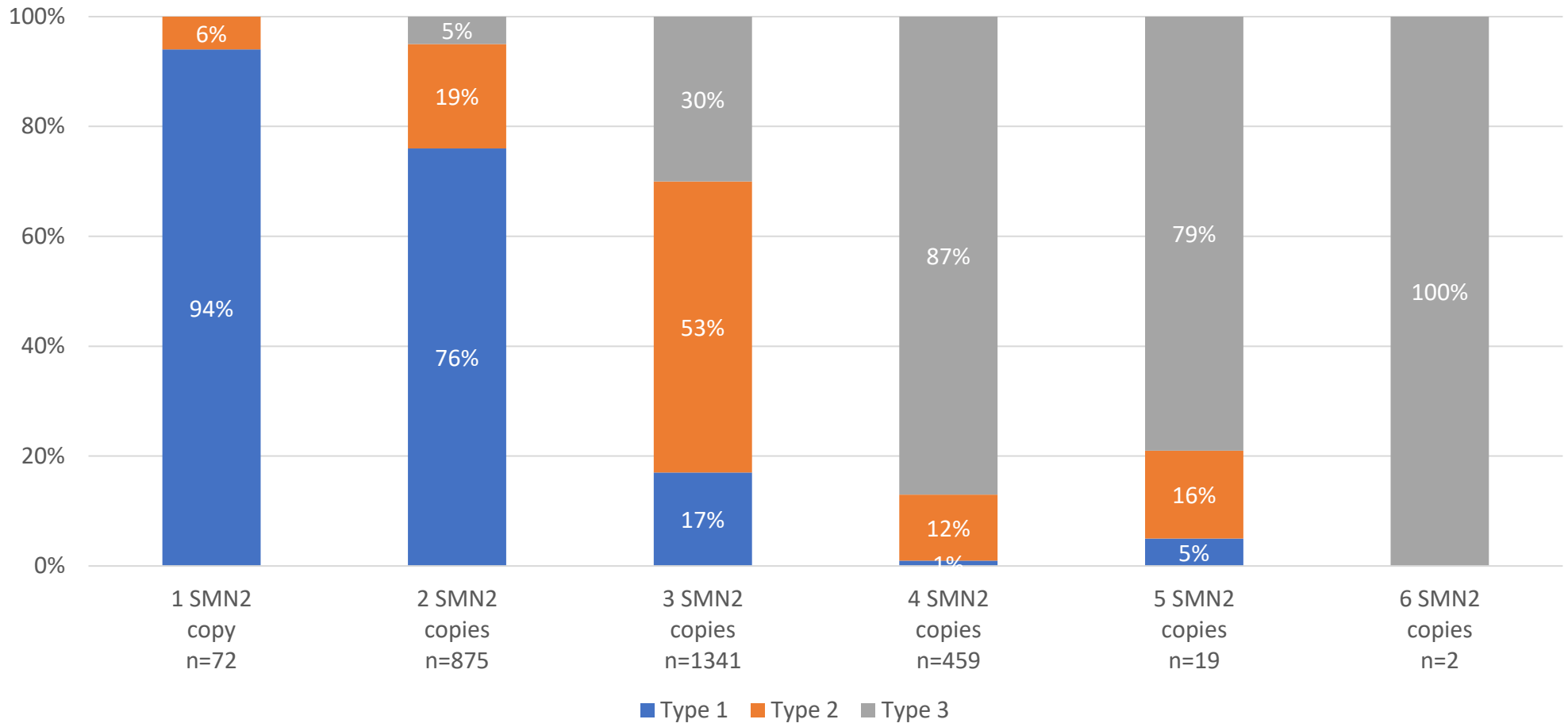


Swoboda KJ, et al. *Ann Neurol*. 2005;57(5):704-712.



Tiziano FD, et al. *Neuromusc Disord*. 2007;17(5):400-403.

Prediction of SMA Type According to Number of *SMN2* Copies – Large Spanish cohort of 2834 pts



Calucho M, et al. *Neuromuscul Disord*. 2018;28(3):208-215.

Discordant Phenotypes

Although *SMN2* copy number can predict disease severity, it does not account for intrafamilial variability in siblings, for example:

- Patients with severe disease (type 1) and 3 *SMN2* copies
- Patients with mild-to-moderate disease (types 2 - 3) and 2 *SMN2* copies
- Haploidentical siblings but with different evolution

Cuscó I, et al. *J Neurol*. 2006;253(1):21-25.

Emerging Factors that Modulate Severity of SMA Phenotype

- *SMN2* coding variants[1,2] (few have been found)
  - Best characterized: rare missense variant in exon 7 (c.859C>G, MAF:0.003), which reduces exon skipping
  - 3 variants in intron 6 are significantly associated with milder phenotypes
- PLS3[3] (plastin 3): gender-related positive modifier
- CORO1C[4] (coronin 1C): overexpression has a protective effect in a pre-clinical model of SMN knock-down
- Outside the SMN locus, 2 SNPs in NCALD[5] (neurocalcin delta) have been associated with severity in a mouse model of severe SMA
- Roles for some miRNAs[6] as biomarkers and potential therapeutic targets are under study

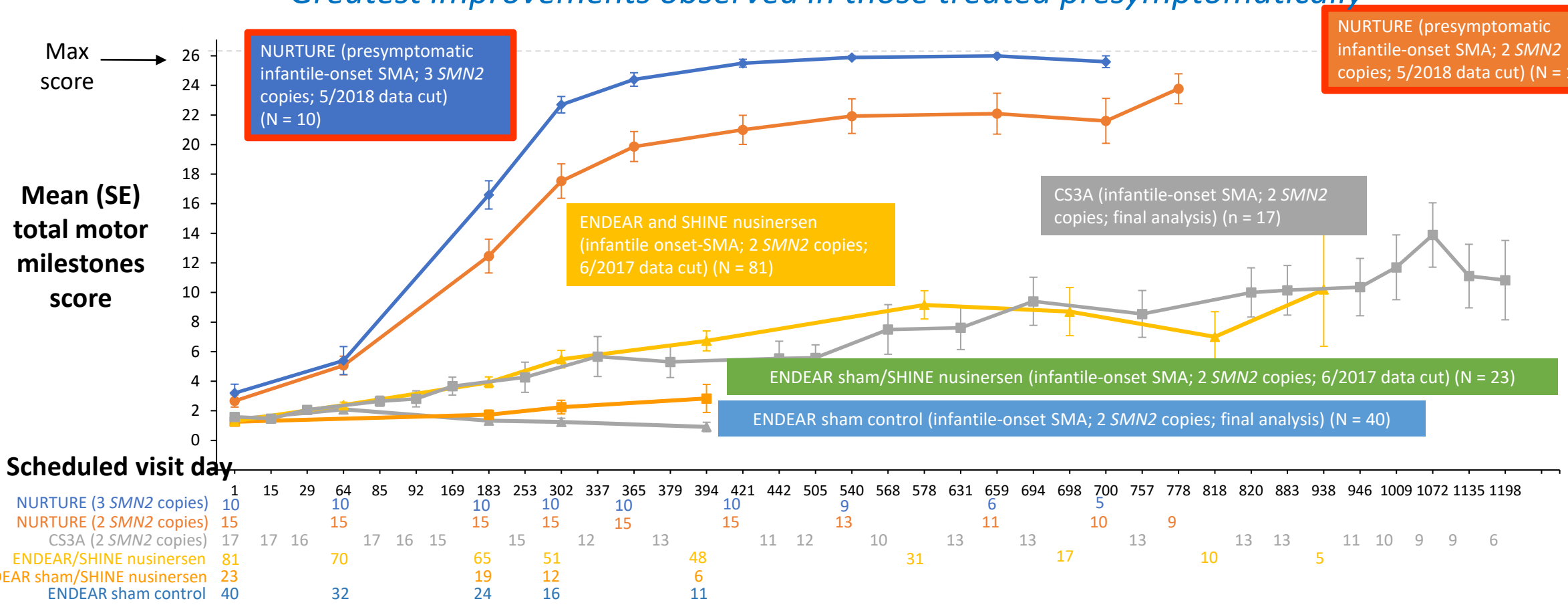
1. Prior TW. et al. *Am J Hum Genet*. 2009;85:408-413.
2. Ruhno C, et al. *Hum Genet*. 2019;138:241-256.
3. Oprea GE, et al. *Science*. 2008;320:524-527.
4. Hosseinibarkooie S, et al. *Am J Hum Genet*. 2016;99:647-665.
5. Riessland M, et al. *Am J Hum Genet*. 2017;100:297-315.
6. Chen TH, Chen JA. *eLife*. 2019;8:e50848.

Importance of Early Diagnosis and Screening in SMA

Evidence Supporting Early Diagnosis/Treament in SMA: Nusinersen Clinical Trials

HINE Motor Milestone Scores Over Time Across Studies

Greatest improvements observed in those treated presymptomatically



HINE-2 = Hammersmith Infant Neurological Examination – section 2.

For each study n ≥ 5 were plotted.

Swoboda KJ, et al. Presented at the Annual International Congress of the World Muscle Society (WMS-23); October 6, 2018; Mendoza, Argentina.

Diagnosis: 2018 SMA Care Group Recommendations

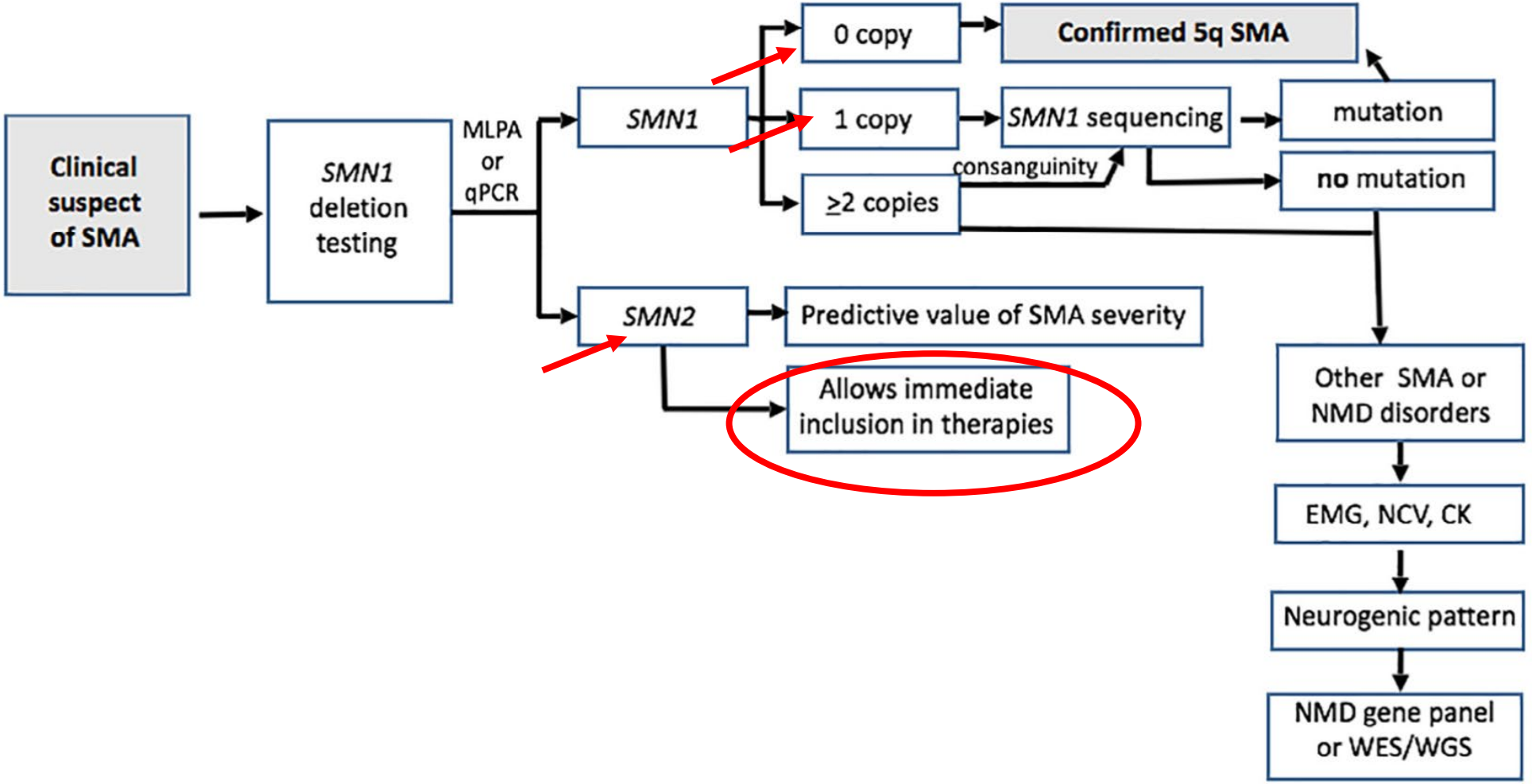
- Gold standard for genetic testing: “quantitative analysis of both *SMN1* and *SMN2* using MLPA, qPCR, or ddPCR”*
- Absence of both *SMN1* copies is diagnostic
- If 1 *SMN1* copy + strong clinical suspicion: perform *SMN1* sequence analysis
- Routinely assess *SMN2* copy number (criterion for clinical trial enrollment)

*PCR with restriction digest can also identify homozygous *SMN1* deletions. While this method is quicker, less expensive, and often readily available in any lab, it does not allow quantification of *SMN1* or *SMN2* copy number.

MLPA = multiplex ligation dependent probe amplification; qPCR = quantitative polymerase chain reaction; ddPCR = digital drop PCR

Mercuri E, et al. *Neuromusc Disorders*. 2018;28:103-115

Diagnosis and Genetics



Mercuri E, et al. *Neuromusc Disorders*. 2018;28:103-115.

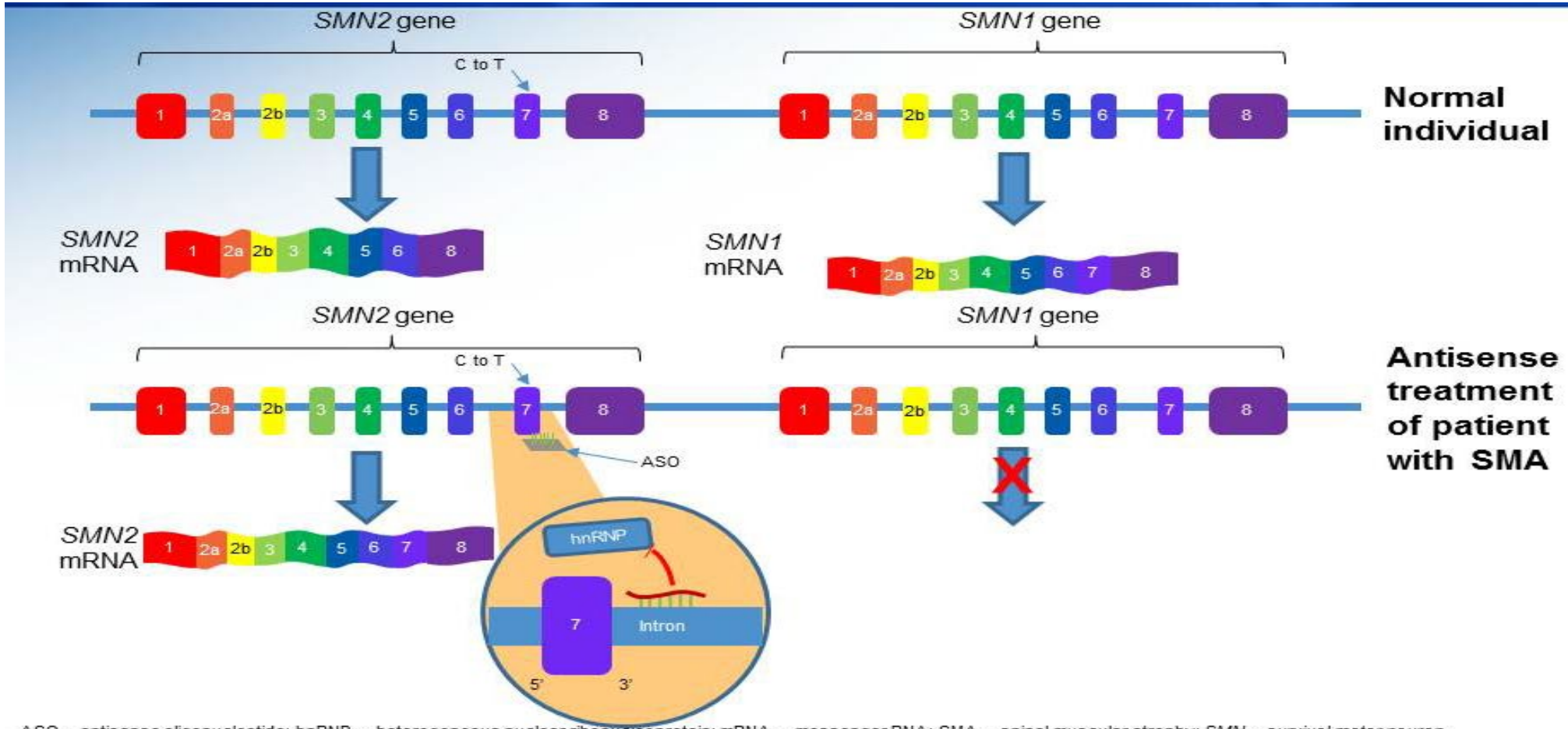
Conclusions

- 5q SMA is the most common genetic cause of death in infants and children
- Usually caused by bi-allelic mutations (deletions) in the *SMN1* gene
- Reduced SMN protein levels leads to death of motor neurons and other effects
- Severity and phenotype varies depends primarily on the number of *SMN2* gene copies
- Early diagnosis is critical particularly for the severe phenotype variants

Treatment strategies in SMA

Nusinersen: antisense oligonucleotide

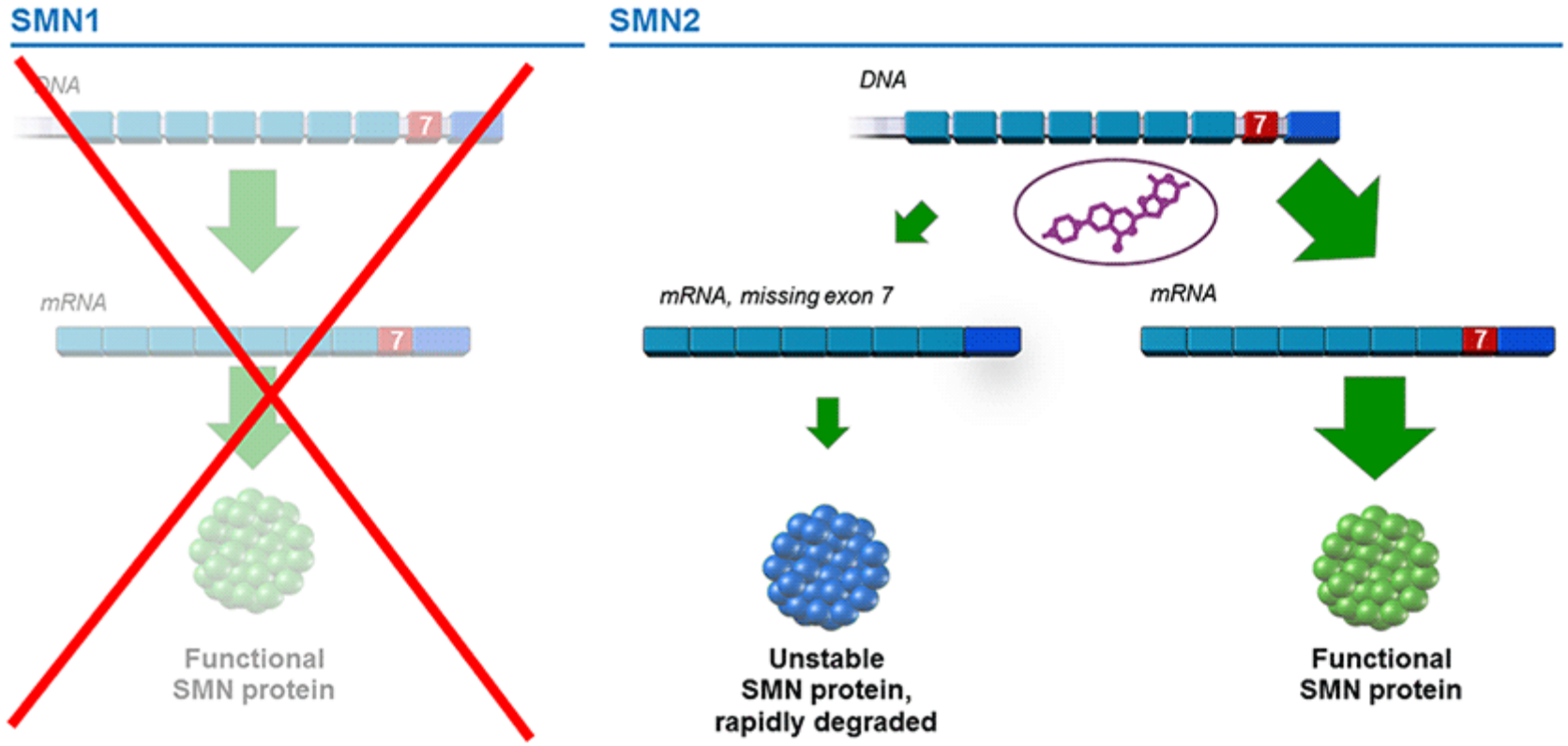
Modify the splicing of the mRNA homologous precursor SMN2 leads to an increase in SMN protein production at full length



ASO = antisense oligonucleotide; hnRNP = heterogeneous nuclear ribonucleoprotein; mRNA = messenger RNA; SMA = spinal muscular atrophy; *SMN* = *survival motor neuron*

1. Chiriboga CA, *et al. Neurology.* 2016;86(10):890-897.
Darras BT, Chiriboga CA, Montes J, et al. Nusinersen in Treatment-Naïve Patients With Later-Onset Spinal Muscular Atrophy (SMA): Efficacy Results From a Phase 1b/2a Multicentre Study (CS2) and Its Open-label Extension (CS12). October 4-8, 2016. Granada, Spain.

Small Molecules for SMA



Risdiplam clinical trials for SMA

FIREFISH[1]

Type 1 SMA
1–7 months old

SUNFISH[2]

Type 2 or 3 SMA
2–25 years old

JEWELFISH[3]

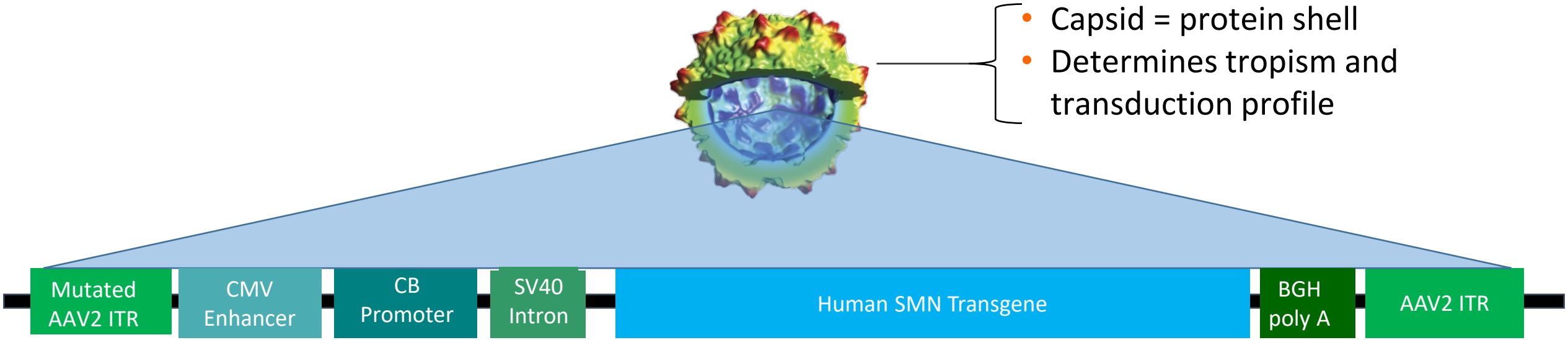
Type 2 or 3 SMA
12–60 years old
Previously received other *SMN2* splicing agents

RAINBOWFISH

Planned study in pre-symptomatic SMA
Birth–6 weeks old

SMN, survival of motor neuron.
1. NCT02913482; 2. NCT02908685; 3. NCT03032172, clinicaltrials.gov (Accessed June 2018).

Onesemnogene Abeparvovec-xioi: Key Components



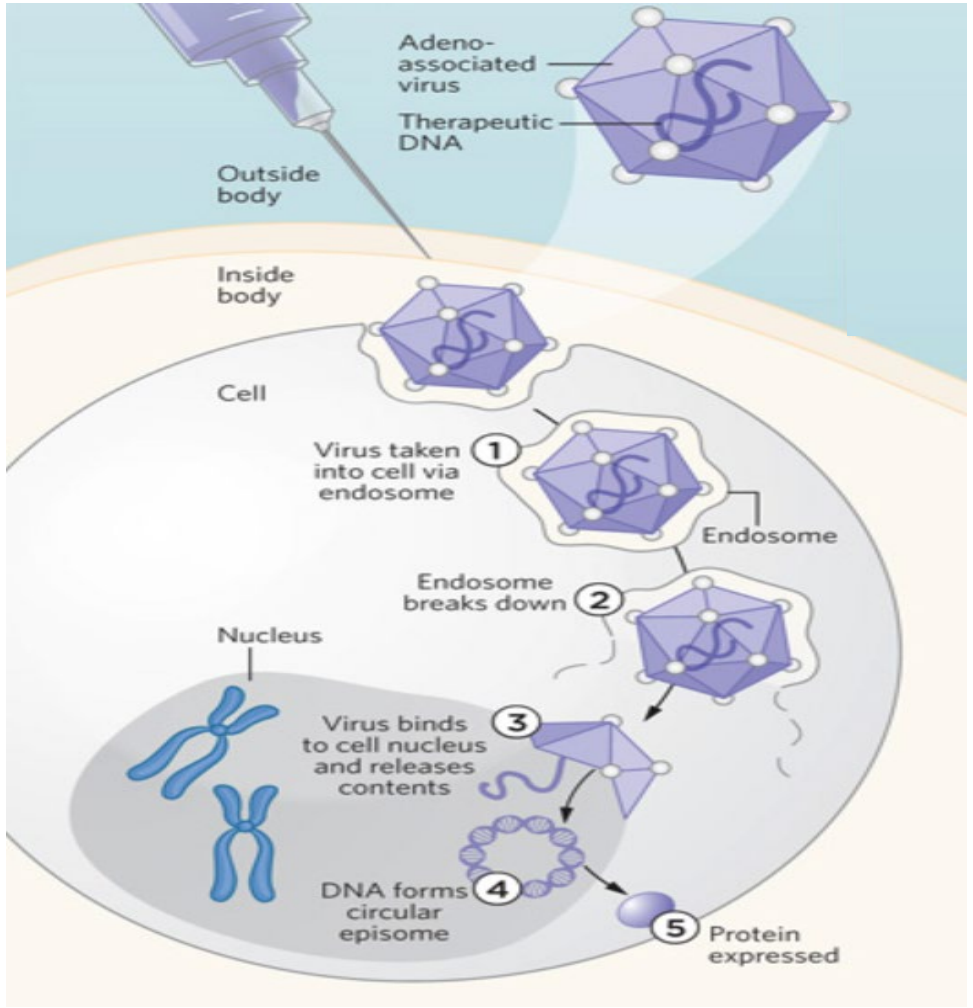
- Adeno-associated viral vector 9 (AAV9)
- Crosses the blood-brain barrier; targets neurons
- Non-integrating, nonpathogenic
- Rapid, sustained SMN expression
- Remains stable within the nucleus

CMV = cytomegalovirus; CB = chicken beta-actin; SV = simian vacuolating virus.

Adapted from DiMattia MA, et al. *J Virol.* 2012;86:6947; Day JW, et al. Poster 6-058. Presented at American Academy of Neurology Annual Meeting; May 5, 2019; Philadelphia, PA; Wang D, Gao G. *Discov Med.* 2014;18:67-77.

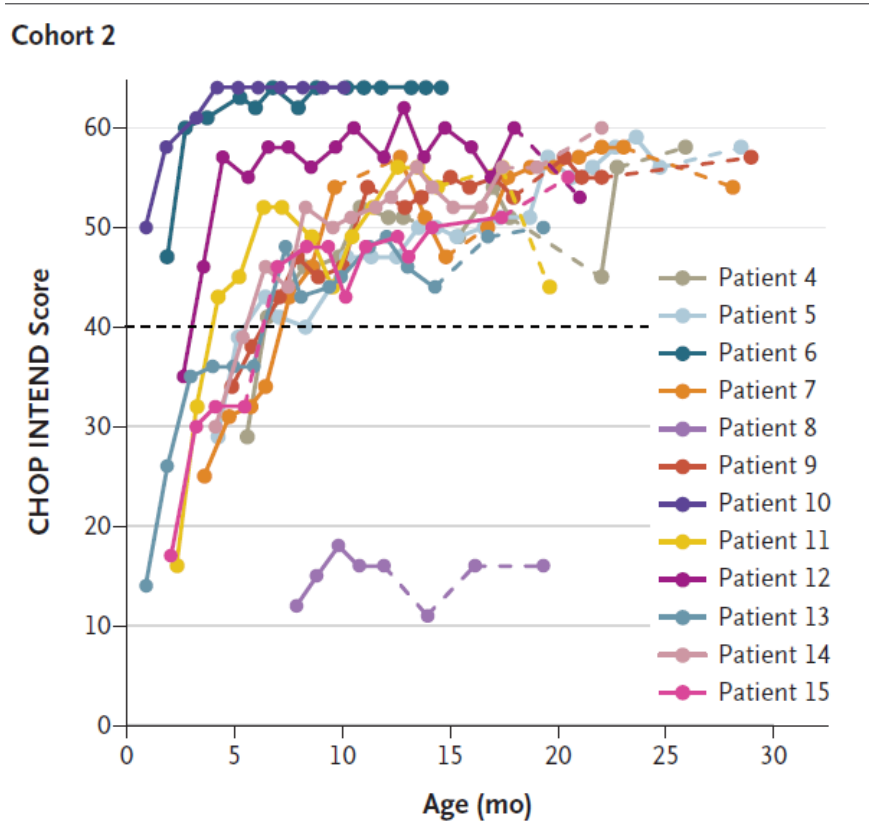
Gene Therapy for SMA: Cell/Nuclear Entry and Gene Expression

- Intravenous infusion
- Vector incorporated into target cells via endosomes
- Therapeutic DNA enters the nucleus, forms an episome ready for transcription
  - mRNA is transcribed, leaves the nucleus
  - Translated into SMN protein in the cytoplasm
- Sustained SMN synthesis prevents loss of further motor neurons



Adapted from Akst J. *The Scientist.* June 2012. https://www.the-scientist.com/features/targeting-dna-40937. Accessed July 2, 2020.

CHOP INTEND

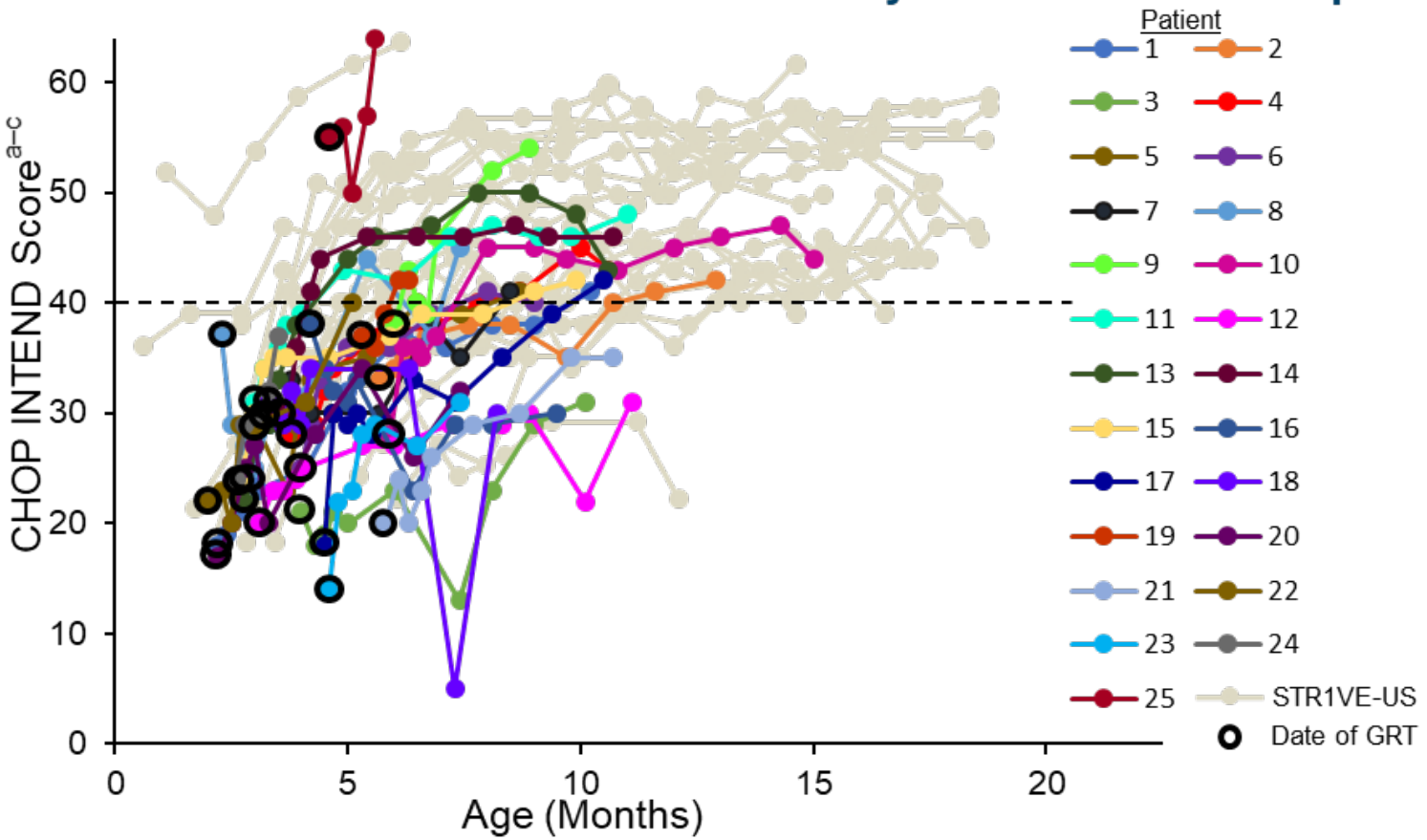


Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

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

Onasemnogene Abeparvovec

Patients in STR1VE-EU showed an early CHOP INTEND response as in STR1VE-US



Mean Increase in CHOP INTEND Score From Baseline		
Month	STR1VE-US (N=22)[c,d]	STR1VE-EU (N=33)[c,e]
1	6.9	6.4
3	11.7	10.6
5	14.3	12.3

[d]One patient in STR1VE-US was not assessed at Month 5, therefore n=21.
[e]As STRIVE-EU is newly enrolled, not all patients have been assessed at all visits yet: Month 1 (n=25), Month 3 (n=22), Month 5 (n=19).

CHOP INTEND, n (%)	STR1VE-EU (N=33)[c]
Achieved score ≥40	18 (55)
Achieved score ≥50	3 (9)
Achieved score ≥60	0

Black dashed line: According to natural history, SMA1 children do not achieve/maintain CHOP INTEND scores >40 points.[1]
[a]Scores on the CHOP INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. [b]Only patients with at least one month of CHOP INTEND data are shown on the graph (n=25). [c]At last data cut (May 31, 2019).
CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; GRT, gene-replacement therapy; SD, standard deviation; SMA1, spinal muscular atrophy type 1.
1. Finkel RS, et al. *Neurology*. 2014;83:810–817.
Onasemnogene abeparvovec is not approved outside of the United States and has been submitted to EMA

Nusinersen Effect in Presymptomatic SMA Infants: 4.9 Year Interim of the NURTURE Study

Kirschner J,[1,2] Crawford TO,[3] Ryan MM,[4] Finkel RS,[5] Swoboda KJ,[6] De Vivo DC,[7] Bertini E,[8] Hwu W-L,[9] Sansone V,[10] Pechmann A,[2] Foster R,[11] Lago T,[12] Chin R,[12] Berger Z [12] on behalf of NURTURE study Group

[1]University Hospital Bonn, Bonn, Germany; [2]Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Royal Children's Hospital and Murdoch Children's Research Institute and University of Melbourne, Parkville, Victoria, Australia; [5]St. Jude Children's Research Hospital, Memphis, TN, USA; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Columbia University Irving Medical Center, New York, NY, USA; [8]Post-Graduate Bambino Gesù Children's Research Hospital, Rome, Italy; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Neuromuscular Omniservice Clinical Center, Milan, Italy; [11]Biogen, Maidenhead, Berkshire, UK; [12]Biogen, Cambridge, MA, USA

SMA-EU (2022) SMA Europe – 3rd International Scientific Congress on Spinal Muscular Atrophy | February 9-11, 2022 | Barcelona, Spain

Baseline Characteristics[1]

Characteristic	2 *SMN2* Copies (n = 15)[a]	3 *SMN2* Copies (n = 10)	Total (N = 25)
Median (range) age at first dose, d	19.0 (8–41)	23.0 (3–42)	22.0 (3–42)
Median (range) CHOP INTEND total score	45.0 (25–60)	53.5 (40–60)	50.0 (25–60)
Median (range) HINE-2 total motor milestones	3.0 (0–5)	3.0 (0–7)	3.0 (0–7)
Median (range) ulnar CMAP amplitude, mV	2.30 (1.0–6.7) n = 14	2.90 (1.8–4.9) n = 10	2.65 (1.0–6.7) n = 24
Median (range) peroneal CMAP amplitude, mV	3.20 (1.1–9.7) n = 12	4.00 (0.2–7.0) n = 10	3.30 (0.2–9.7) n = 22

Primary Endpoint: Time to Death or Respiratory Intervention[a]

All patients were alive and none required permanent ventilation, including tracheostomy[b]
Median age at last visit: 4.9 (range, 3.8–5.5) years

Nusinersen-Treated Infants, n (%)	2 *SMN2* Copies n = 15	3 *SMN2* Copies n = 10	Total N = 25
Alive	15 (100)	10 (100)	25 (100)
Required respiratory intervention	4 (27)	0	4 (16)
≥ 6 h/d continuously for ≥ 7 d, or tracheostomy	4 (27)	0	4 (16)
≥ 16 h/d continuously for > 21 day in the absence of an acute reversible event, or tracheostomy (permanent ventilation)	0	0	0

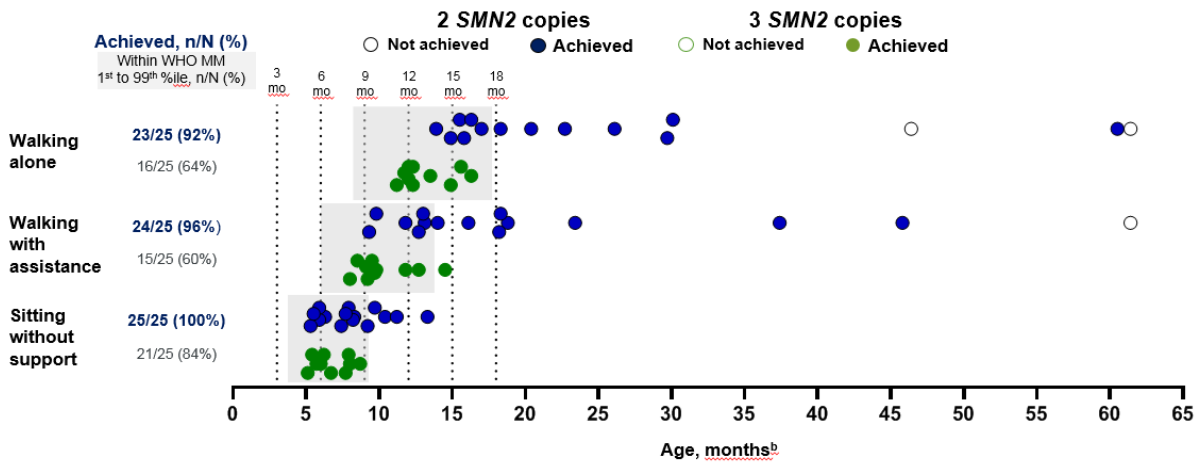
SMA Type I natural history

Median age at death or requiring ventilation support for ≥ 16 h/d for > 14 d was 13.5 (IQR, 8.1–22.0) mo[1]

- Median time to death or respiratory intervention (≥ 6 hours/day continuously for ≥ 7 days, or tracheostomy; primary endpoint) could not be estimated due to too few events
  - 4/25 patients (all with 2 *SMN2* copies) required respiratory intervention over the course of the study; all initiated respiratory support during an acute reversible illness

Clinical Scales

Children Achieved WHO Motor Milestones Inconsistent With SMA Type I and II,[1] Many in Timeframes Consistent With Normal Development[a,2]

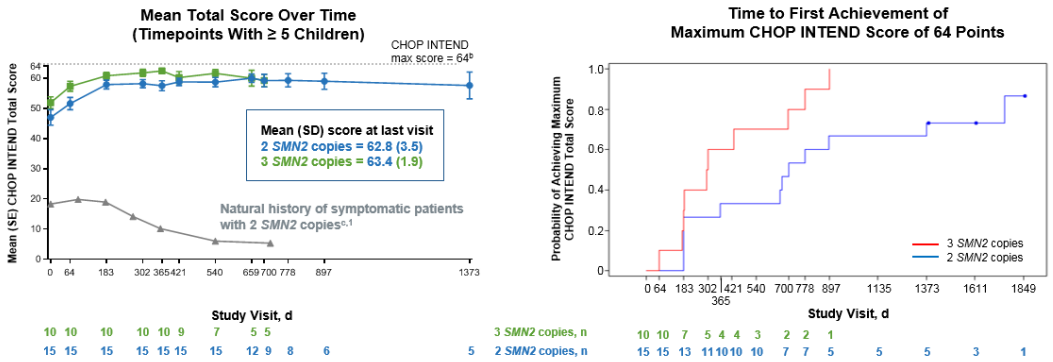


- One additional child achieved walking alone between the 19 February 2020 and 15 February 2021 data cuts.

22/25 (88%) Children Have Achieved a Maximum Score on the CHOP INTEND[a]

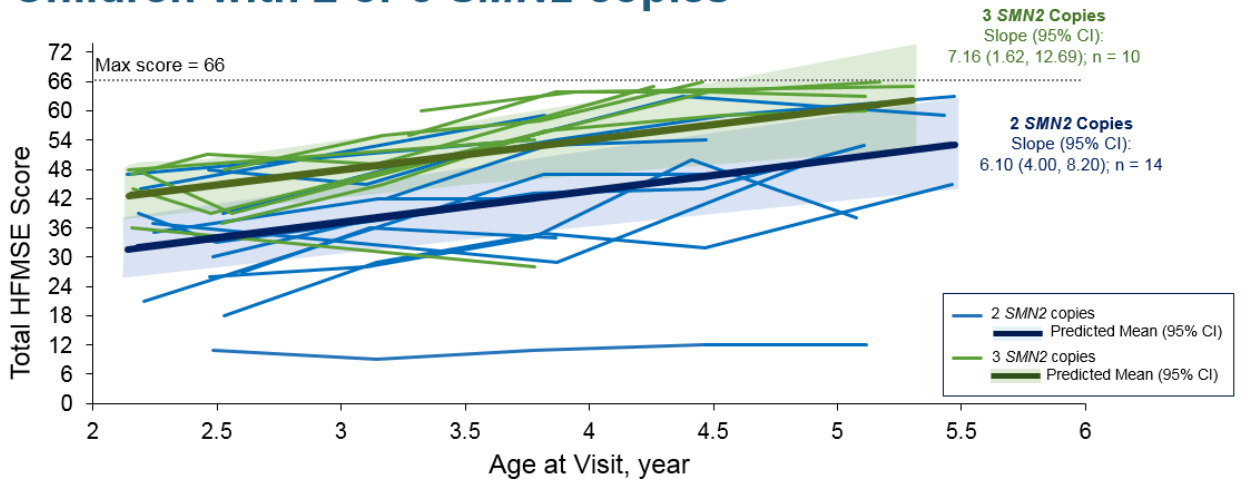
Mean score increased steadily from baseline before stabilizing around the maximum score of 64

- Mean (SD) change in CHOP INTEND from baseline to last visit was 13.9 (8.7)



CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; max = maximum; *SMN* = survival motor neuron. NURTURE study interim analysis data cutoff date: 15 February 2021. Only study visits with n ≥ 5 are included in the mean total score graph (left side). The Kaplan-Meier plot (right side) includes study visits with n ≥1 at the time of the data cutoff date. [c]Three participants, all 2 *SMN2* copies, had not yet achieved the maximum score by their last interim visit. [b]Per Version 6 of the study protocol, CHOP INTEND is assessed in participants until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed. [a]Infants were aged ≤ 6 months at enrollment, born between 36–42 weeks' gestation, and had genetically confirmed SMA; infants were excluded if they required noninvasive ventilatory support for > 12 hours/day, had a comorbid illness, or were enrolled in an SMA clinical trial. Data are plotted by study visit, which are linked to an infant's age. 1. Kolb SJ, et al; NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. *Ann Neurol*. 2017;82(6):883-891.

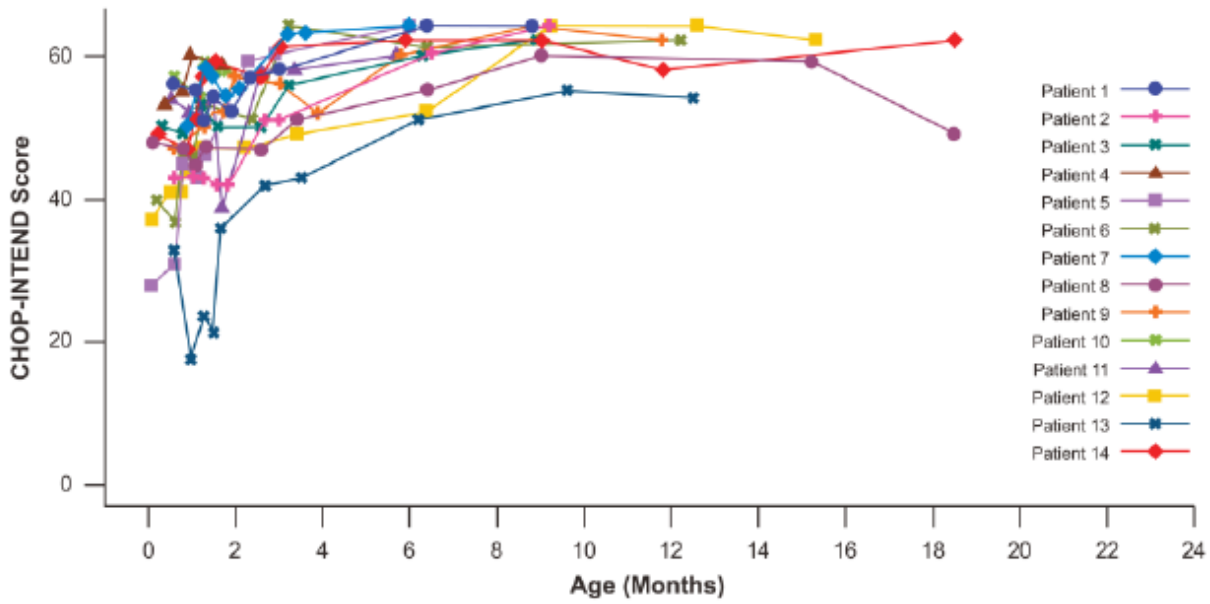
Mean HFMSE Total Scores Improved Over Time in Children with 2 or 3 *SMN2* copies



Mean (SD; range) HFMSE total score at first assessment: 2 *SMN2* copies: 33.1 (11.31; 11–48)
3 *SMN2* copies: 46.4 (7.441; 36–60)

SPR1NT: CHOP INTEND in children with 2 copies of *SMN2*

CHOP INTEND score increases from baseline in patients with two copies of *SMN2*[1]



	CHOP INTEND score
Mean baseline score (SD)	46.1 (8.77)
Increase at 1 month after dosing (n=14)	3.9 (8.28)
Increase at 3 months after dosing (n=7)	13.0 (10.97)
Increase at 6 months after dosing (n=12)	14.8 (8.08)
Increase at 8 months after dosing (n=7)	15.7 (6.47)

- All patients achieved CHOP INTEND scores of ≥50
- Thirteen patients (92.9%) achieved a CHOP INTEND score ≥58
- Untreated SMA Type 1 patients almost never achieve/maintain a CHOP INTEND score ≥40[1,2]

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMN, survival motor neuron.

1. Strauss et al. Poster presentation at the 2021 MDA Clinical and Scientific Conference (March 15–18 2021; 2 copies *SMN2*); 2. Finkel RS, et al. *Neurology* 2014;83:810–817.

Rainbowfish (Risdiplan)

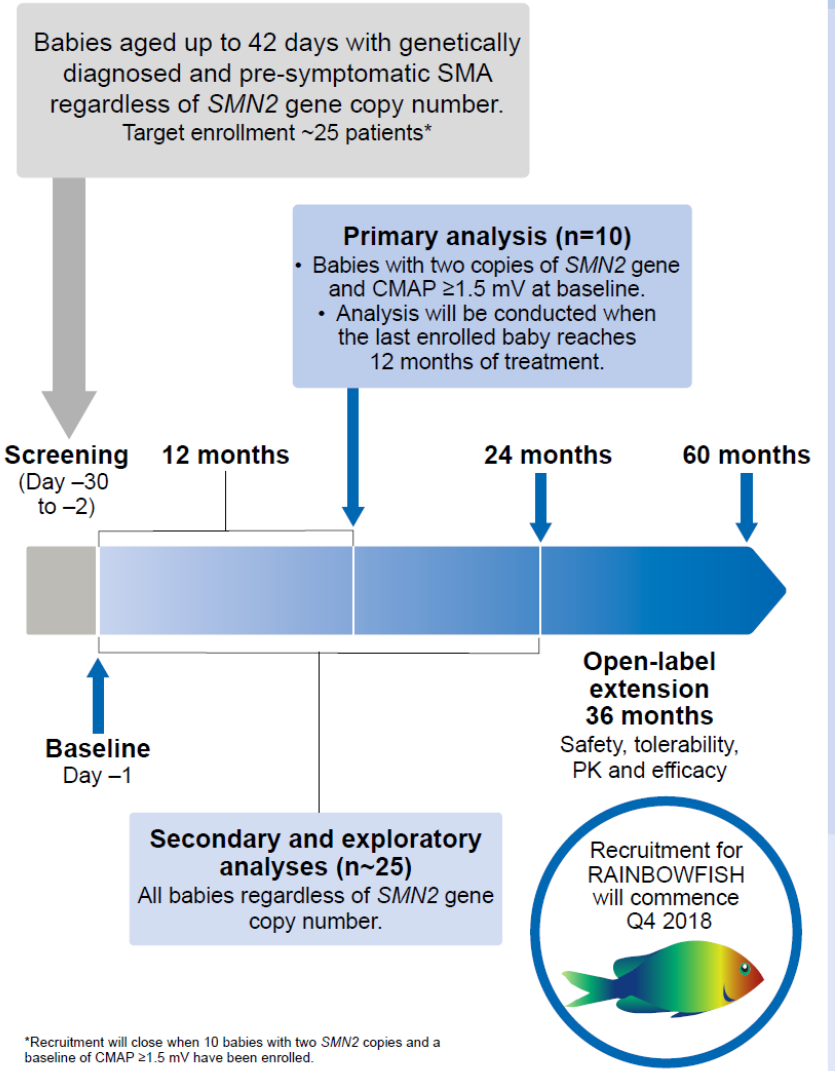
Study design

- RAINBOWFISH (BN40703) is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK, and PD of risdiplam in babies with genetically diagnosed SMA who are not yet presenting with symptoms.

RAINBOWFISH Birth–6 weeks old	Key inclusion criteria	• Genetic documentation of 5q *SMN1* homozygous gene deletion or mutation or compound heterozygous mutation (regardless of *SMN2* copy number). • Up to 6 weeks (42 days) of age at the time of first dose. • Adequately recovered from any acute illness at baseline. • Absence of clinical signs or symptoms prior to dosing that are strongly suggestive of SMA.
	Key exclusion criteria	• Concomitant or previous administration of an *SMN2*-targeting antisense oligonucleotide, *SMN2*-splicing modifier, or gene therapy. • Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation. • Presence of significant concurrent syndromes or diseases.

Study schema

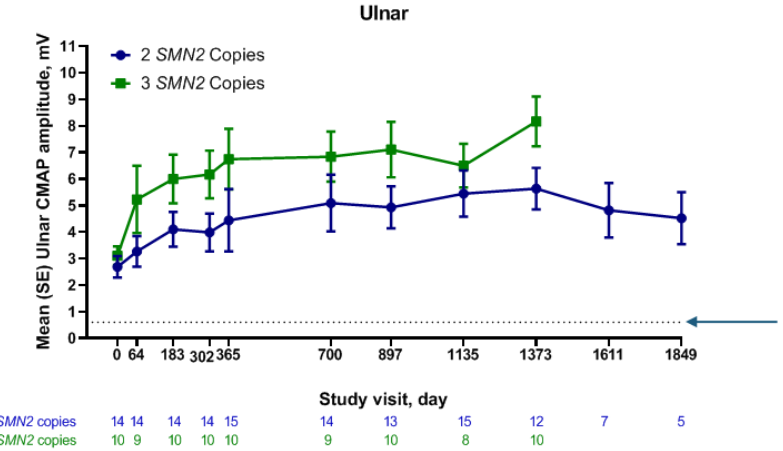
- Recruitment will be global.
- Enrolled babies will receive risdiplam orally once daily for 24 months, followed by an open-label extension phase of at least 36 months.



Neurophysiology (CMAP)

Mean Ulnar CMAP Amplitude Was Stable Over Time in NURTURE Infants With 2 or 3 *SMN2* Copies

- Similar results were observed for peroneal CMAP amplitude

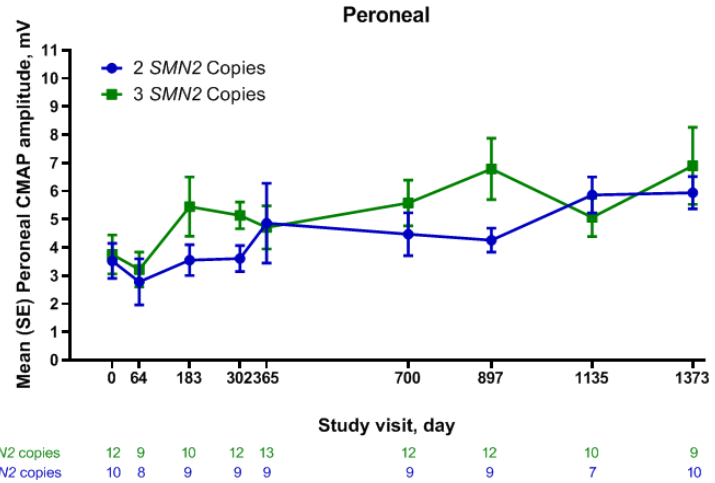


Range of normal values in healthy infants[1]

Age	Ulnar nerve CMAP amplitude, mV
Neonate	1.6–7.0
1–6 mo	2.5–7.4
7–12 mo	3.2–10.0

- In an SMA natural history cohort with 2 *SMN2* copies observed over 24 months[b,2]:
  - Maximum ulnar amplitude in infants aged ≥ 6 mo was 0.6 mV
  - Ulnar CMAP amplitude rapidly decreased and was often not detectable

Mean Peroneal CMAP Amplitude Was Stable Over Time in NURTURE Infants With 2 or 3 *SMN2* Copies

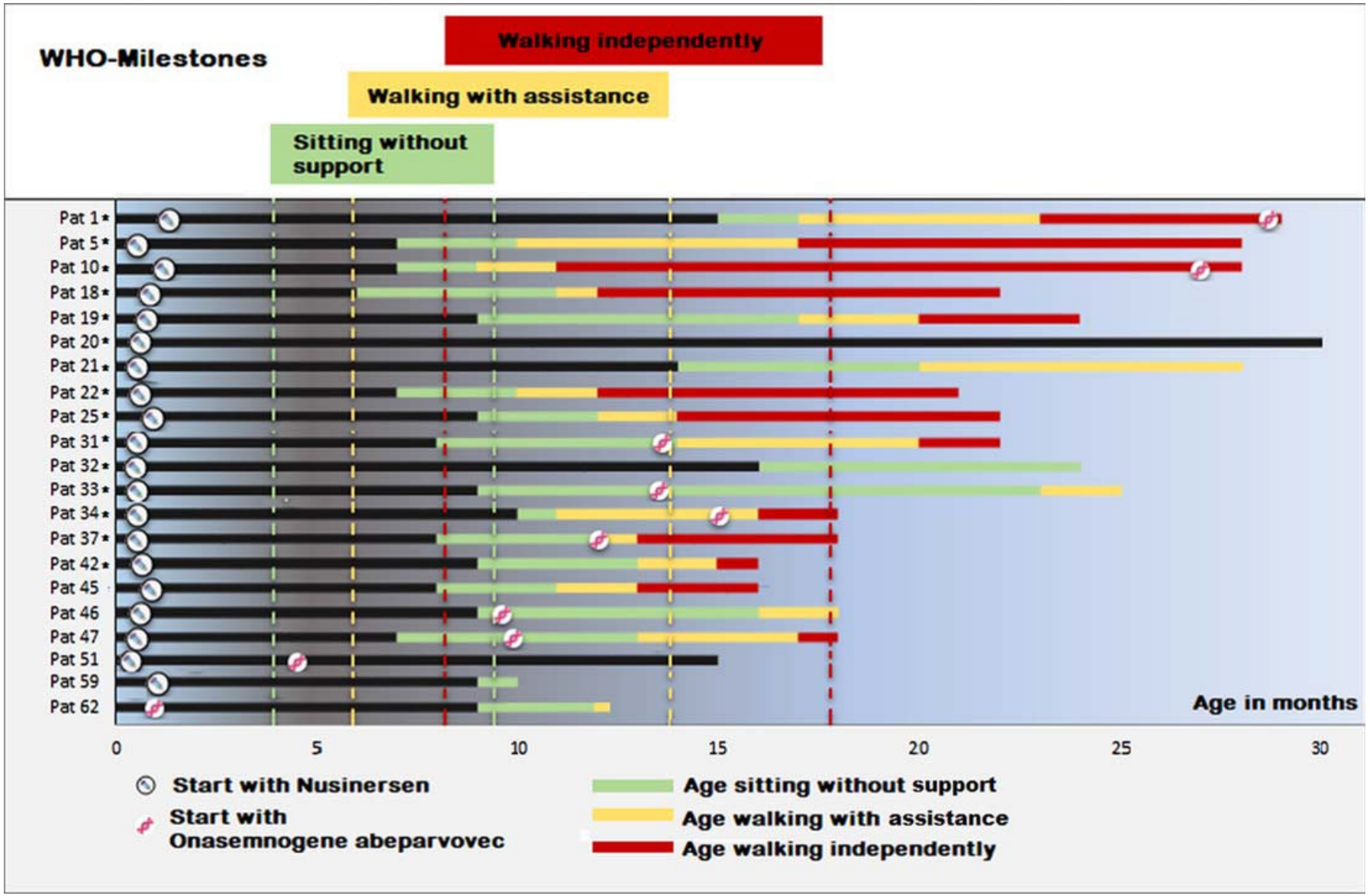


Clinical Trial	CMAP	SMN2	SMN3	SMN3+
Nurture	1 mVs	X	X	
Sprint	2 mVs	X	X	
Rainbowfish	1,5 mVs	X	X	X

Spinal Muscular Atrophy -Is Newborn Screening Too Late for Children with Two SMN2 Copies?

Schwartz, O,Kölbel, H,Blaschek, A,Gläser, D,Burggraf, S,Röschinger, W, Schara, U,Müller-Felber, W,Vill, K. J Neuromuscul Dis. 2022 Apr 12. doi: 10.3233/JND-220789. Epub ahead of print. PMID: 35431259.

- 21 SMA patients identified in newborn screening projects in Germany
- Inclusion criteria were treatment at less than 6 weeks of age and a minimum clinical follow-up of 9 months
- Twelve patients (57%) developed completely normally, reaching the motor milestones without bulbar or respiratory problems
- Three children (14.5%) recovered after an initial delay in motor development
- Six patients (29%) developed proximal weakness despite early treatment:
    - 3 of them (14.5%) achieved the ability to walk with support
    - 3 others (14.5%) showed a type 2 SMA phenotype at the age of 16-30 months.
        - One patient (4.8%) had respiratory problems.
        - Three children (14.5%) had mild chewing problems
        - Two individuals (9.5%) required gastric tube feeding

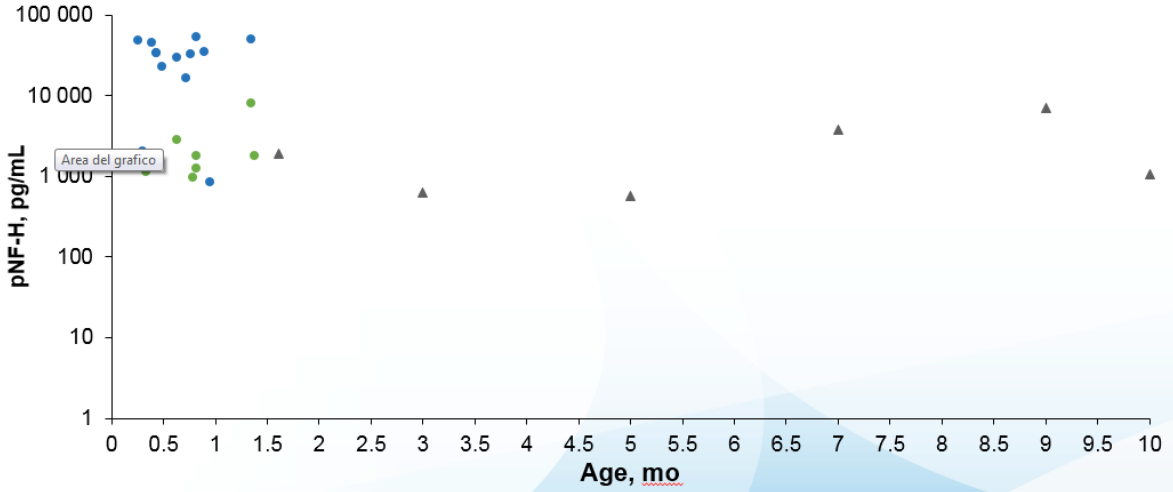


Schwartz et al., J Neuromuscul Dis. 2022 Apr 12

Neurofilaments

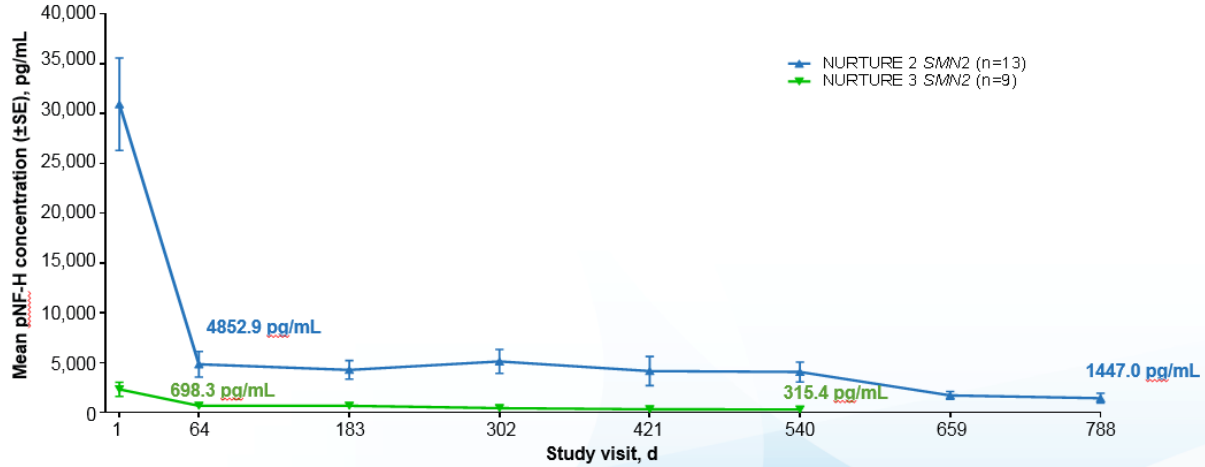
Baseline plasma pNF-H values[a] are highest in NURTURE infants with 2 *SMN2* copies

- Median (range) plasma pNF-H at baseline[b]: 3 *SMN2* copies, 1,770.0 pg/mL; 2 *SMN2* copies, 33,300.0 pg/mL
- Median (range) plasma pNF-H in children without SMA[c] aged <1 year: 1510 pg/mL (579-7030 pg/mL; n=6)



NURTURE study interim analysis data cutoff date: May 15, 2018. [a]Blood plasma pNF-H levels were evaluated using a pNF-H enzyme-linked lectin assay (ELLA) from ProteinSimple. 7.46 pg/mL used as the imputed value if the pNF-H concentration is below the limit of quantitation. [b]Baseline pNF-H values in NURTURE infants were obtained on Study Visit Day 1, either prior to nusinersen administration or 4 hours post-dose. [c]With thanks to Boston Children's Hospital and Analytical Biological Services Inc. for providing these samples.

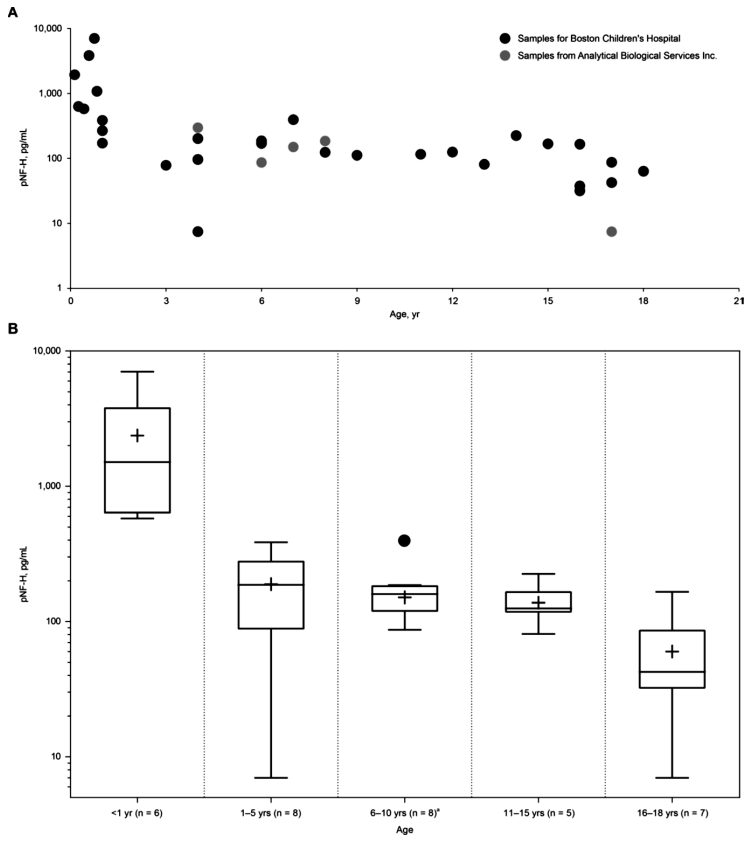
Plasma pNF-H Levels Decline Rapidly and Then Remain Relatively Stable

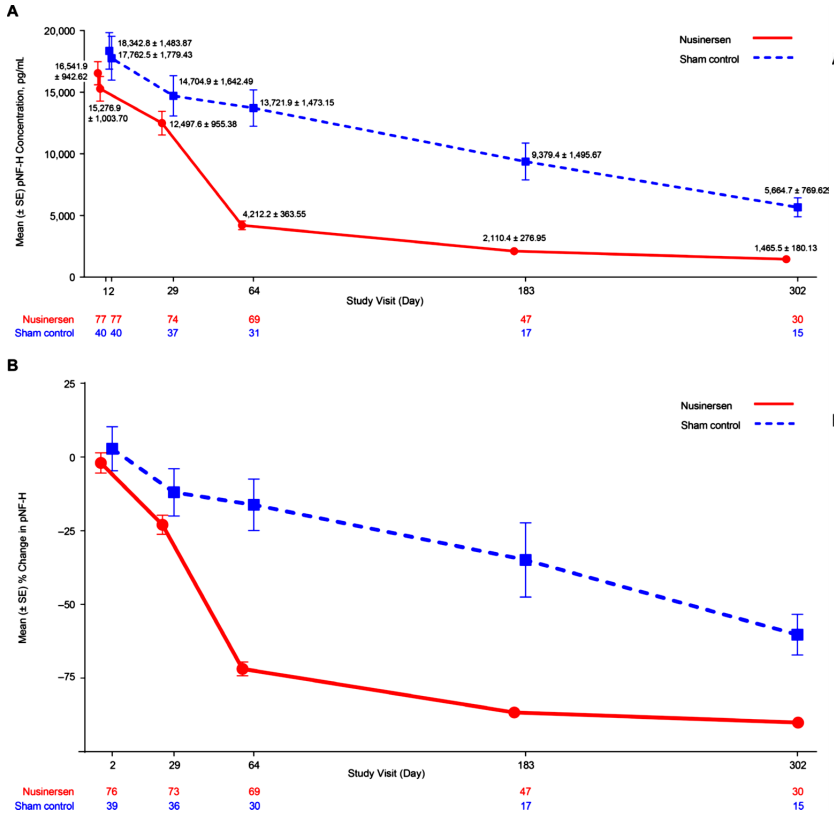


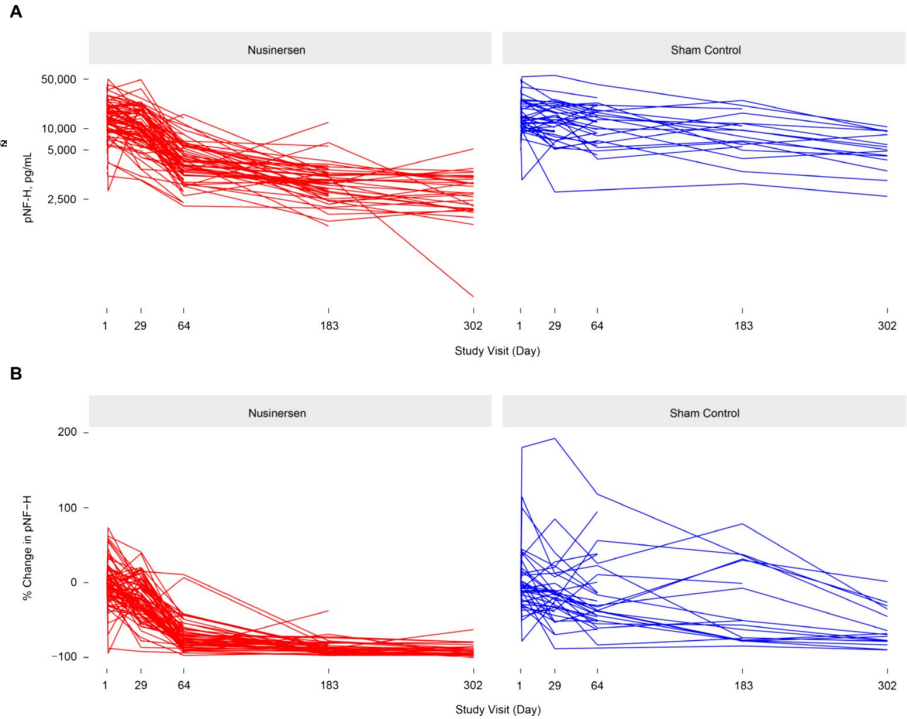
2 *SMN2*	13	14	13	12	12	11	8	6
3 *SMN2*	9	9	10	10	9	5		

NURTURE study interim analysis data cutoff date: May 15, 2018. Time points with n≥5 included.
Blood plasma pNF-H levels were evaluated using a pNF-H enzyme-linked lectin assay (ELLA) from ProteinSimple.

Neurofilaments



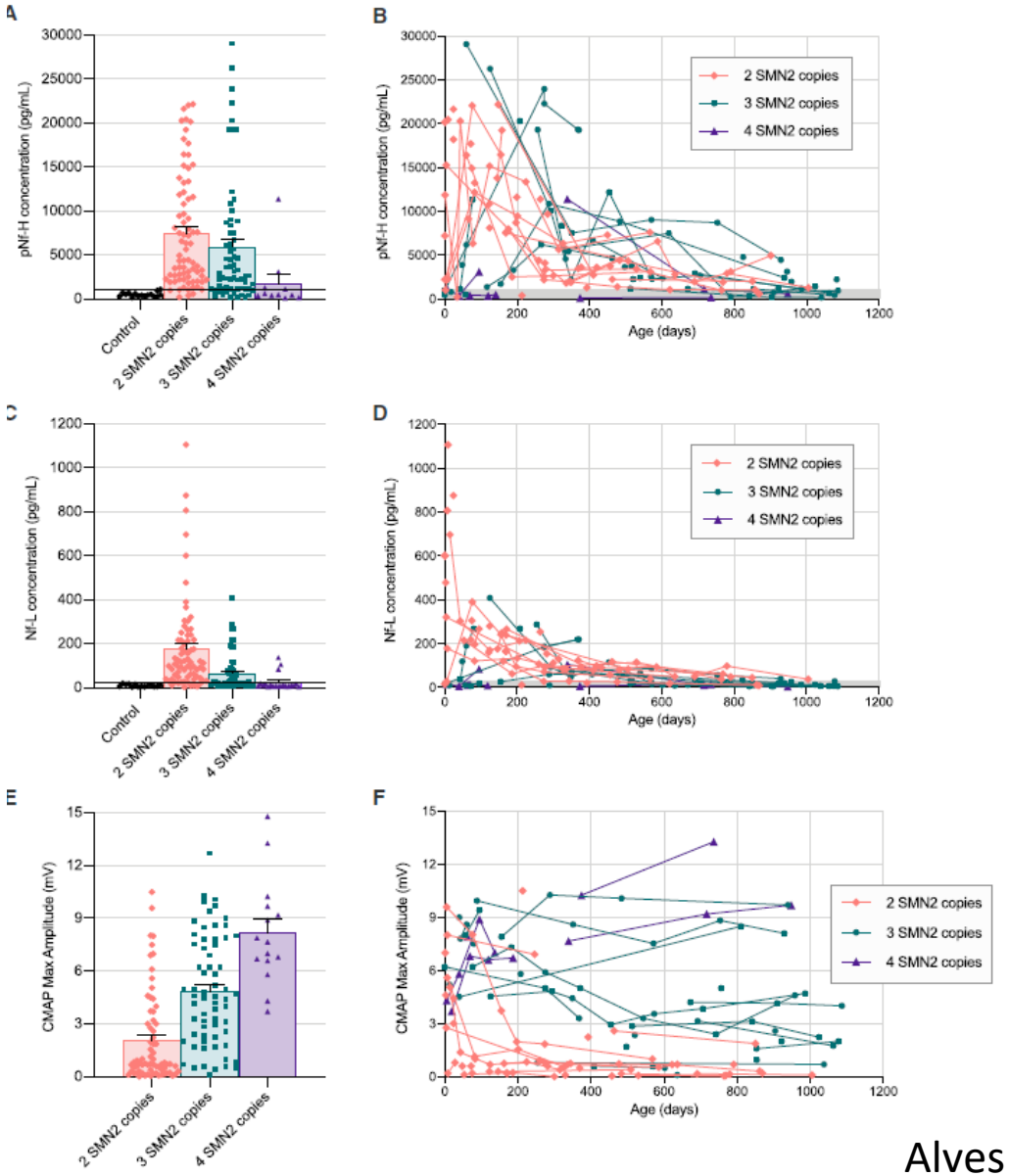




ENDEAR Trial (Spinraza)

Darras et al. Annals of Clinical and Translational Neurology 2019; 6(5): 932–944

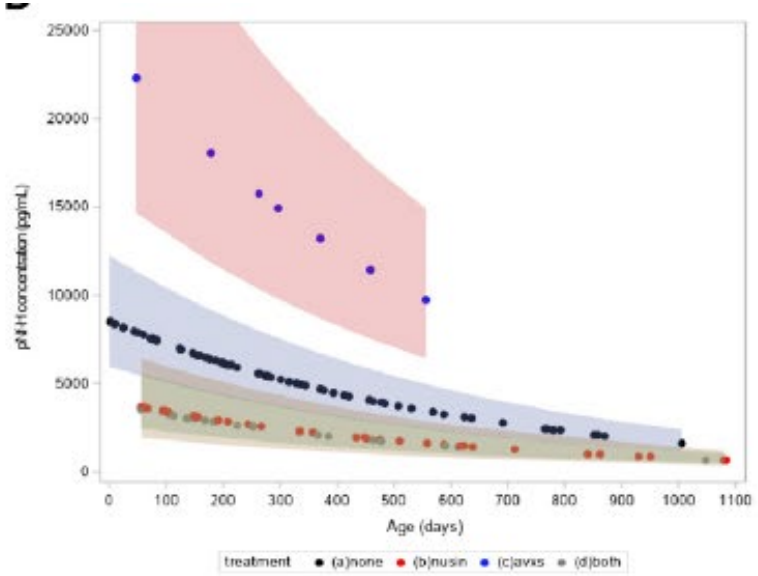
Neurofilaments

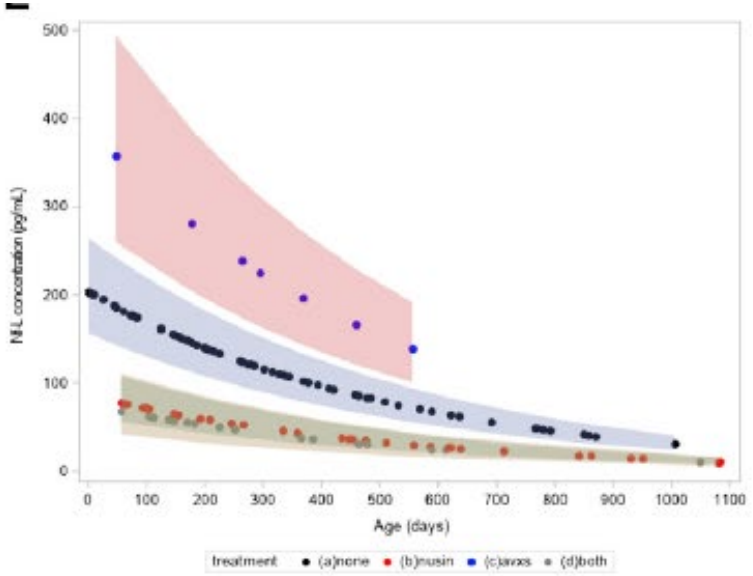


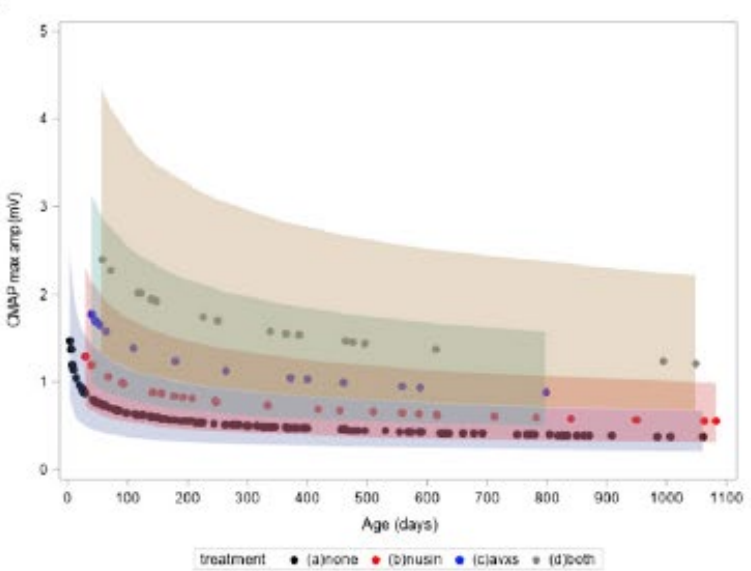
Alves et al., Molecular Therapy 23: 537, 2021

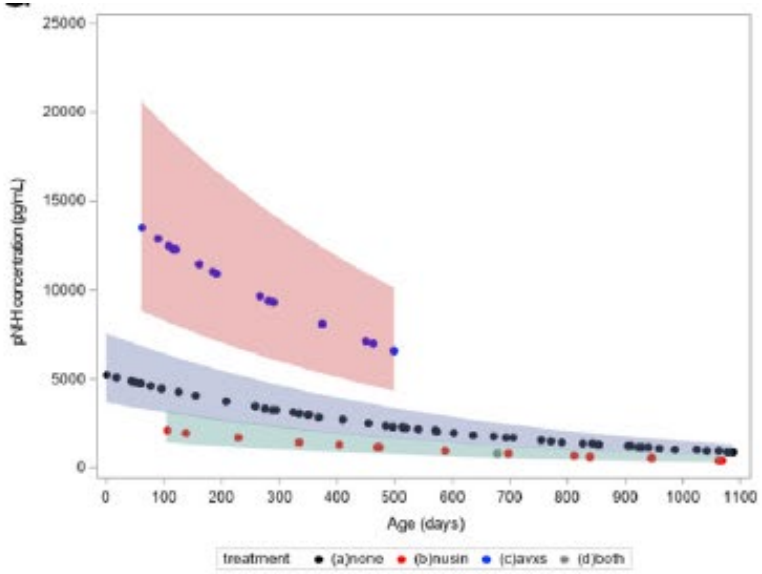
2 SMN2 copies

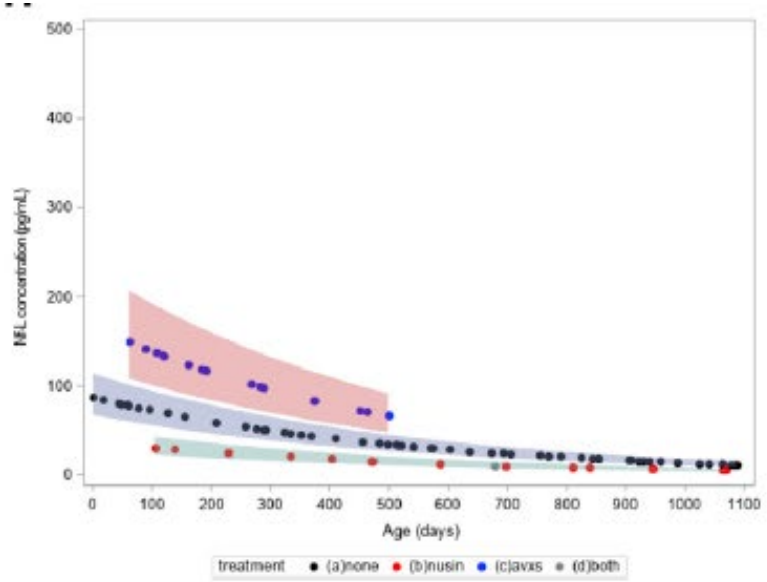
Neurofilaments - CMAP

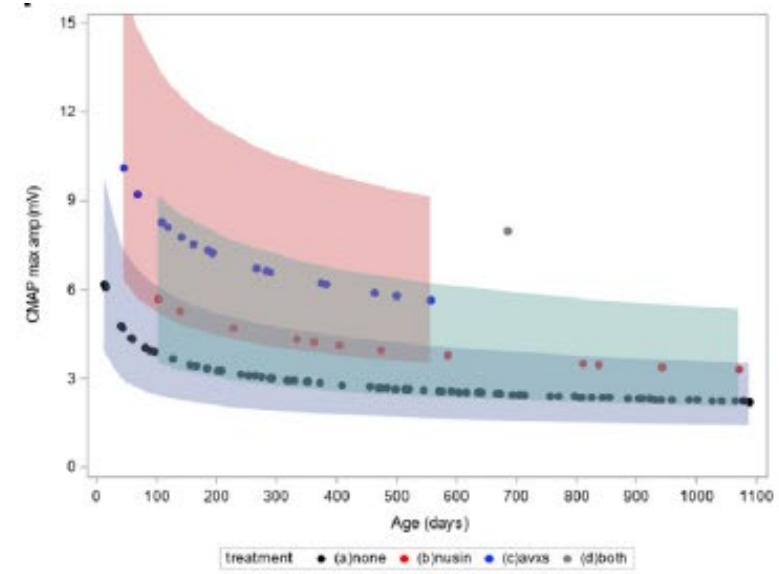








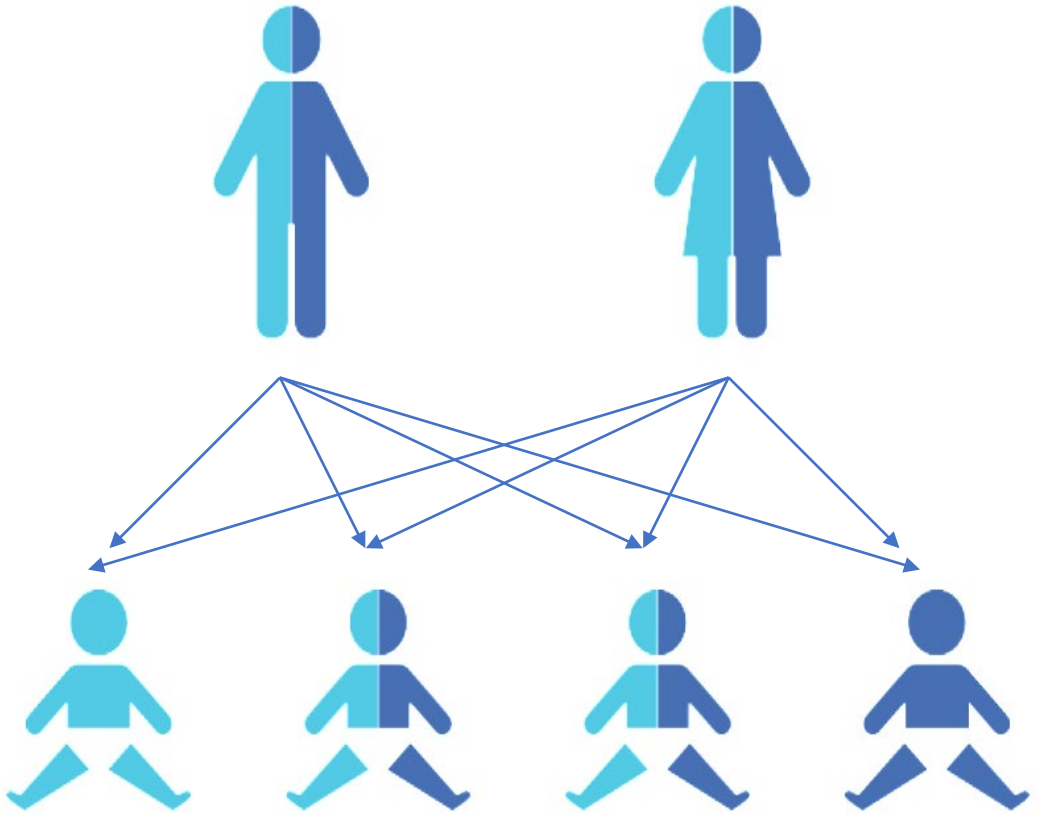




Alves et al., Molecular Therapy 23: 537, 2021

SMA Screening for early diagnosis

Carrier Screening



Aharoni S, et al. *Neuromusc. Disorders*. 2017;27:S137

Carrier Screening for SMA

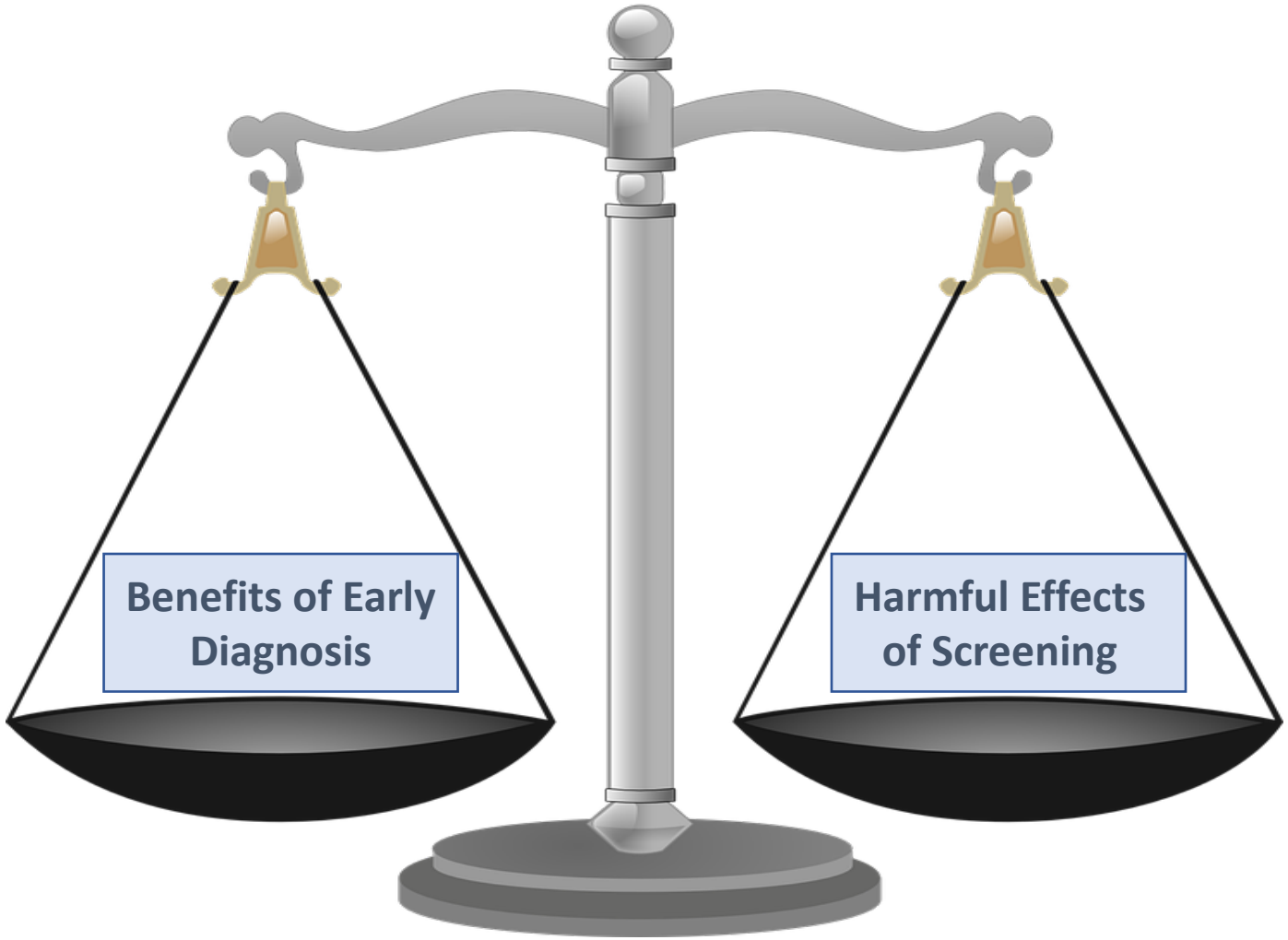
- Carrier frequency: Determined by quantitative analysis of *SMN1* copies (by MLPA)
- Limitations
  - Carrier testing identifies only 90% of carriers due to
    - *cis* configuration (2/0): 5%
    - Point mutation: 2-5%
    - De novo mutation (mostly paternal): 2%
  - Certain populations will not consent to carrier testing or therapeutic pregnancy termination

Ben-Shachar S, et a. *Genet Med*. 2011;13(2):110-114.

Prenatal/Pre-Implantation Testing

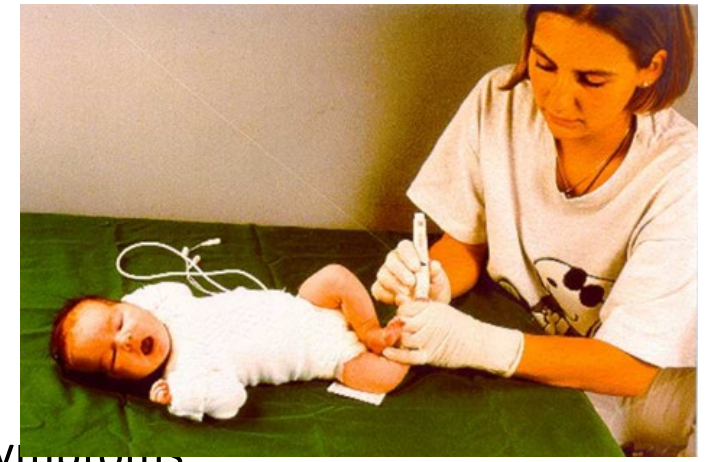
- Routinely available in some countries, but not in others
- Where available
  - Can be considered when the mother or her partner is a known carrier or has a family history of SMA
  - Determines whether the fetus has inherited 2 faulty *SMN1* copies
  - Testing involves chorionic villus sampling or amniocentesis

Newborn Screening (NBS)
Benefits vs Risks



Potentially Harmful Effects of NBS *(for Any Genetic Disease)*

- Direct side effects (eg, necessity of drawing blood)
- Potential for indirect harm
  - False postive test: Unnecessary test / psychological impact
  - False negative test: False reassurance → possible neglect or failure to recognize symptoms that occur later
  - Overdiagnosis
    - Detection of otherwise healthy persons carrying a pathogenic mutation
    - Impact on insurance, professional life
  - Overtreatment
    - Treatment for a disease that otherwise would not have caused symptoms



All NBS programs have the potential for harm

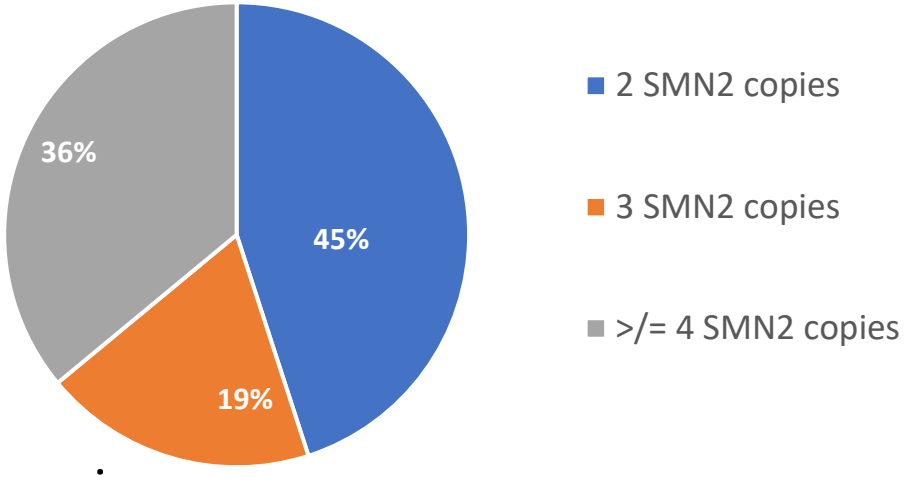
When to Establish a NBS Program?
Criteria for Screening

	SMA
The disease is life-threatening and treatable	✓
Early diagnosis improves outcome	✓
NBS is feasible	✓
NBS improves outcomes • Pilot studies	✓

Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. Geneva: WHO; 1968. https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17 Accessed July 2, 2020.

Implications of NBS: German Pilot Project, Year 1

- 165,525 newborns screened
  - 22 identified with SMA
    - 10 (45%) with 2 *SMN2* copies
    - 4 (19%) with 3 *SMN2* copies
    - 8 (36%) with ≥4 *SMN2* copies



- Recommendations
  - 2 or 3 SMN2 copies: immediate treatment with nusinersen
  - ≥ 4 *SMN2* copies: conservative, strict follow-up
- Patients treated before symptom onset showed no muscle weakness by age 1 year – consistent with nusinersen clinical trial findings
- ***Conclusion:*** NBS resulting in presymptomatic treatment improves outcomes for children with SMA

Vill K, et al. *J Neuromuscul Dis*. 2019;6(4):503-515.

NBS for SMA
244th ENMC International Workshop

- ✓ Benefit of early treatment in patients with SMA type 1 has been suggested in published and ongoing studies
- ✓ SMA seems to fall within the Wilson and Jungner criteria
- ✓ Clear exceptions in prediction between correlation of *SMN2* copy number and SMA phenotype (search for modifying factors)
- ✓ Precise quantification of *SMN2* copy number may vary from one lab to another, especially for highest number of copies
- ✓ Main practical question in NBS context: is there a high probability for a given patient to develop a specific phenotype based on a specific number of *SMN2* copies? (relative frequency must be considered)
- ✓ Some variants found in the *SMN2* gene act as modifiers; can be tested at the DNA level (eg, *SMN2* c.859G>C)

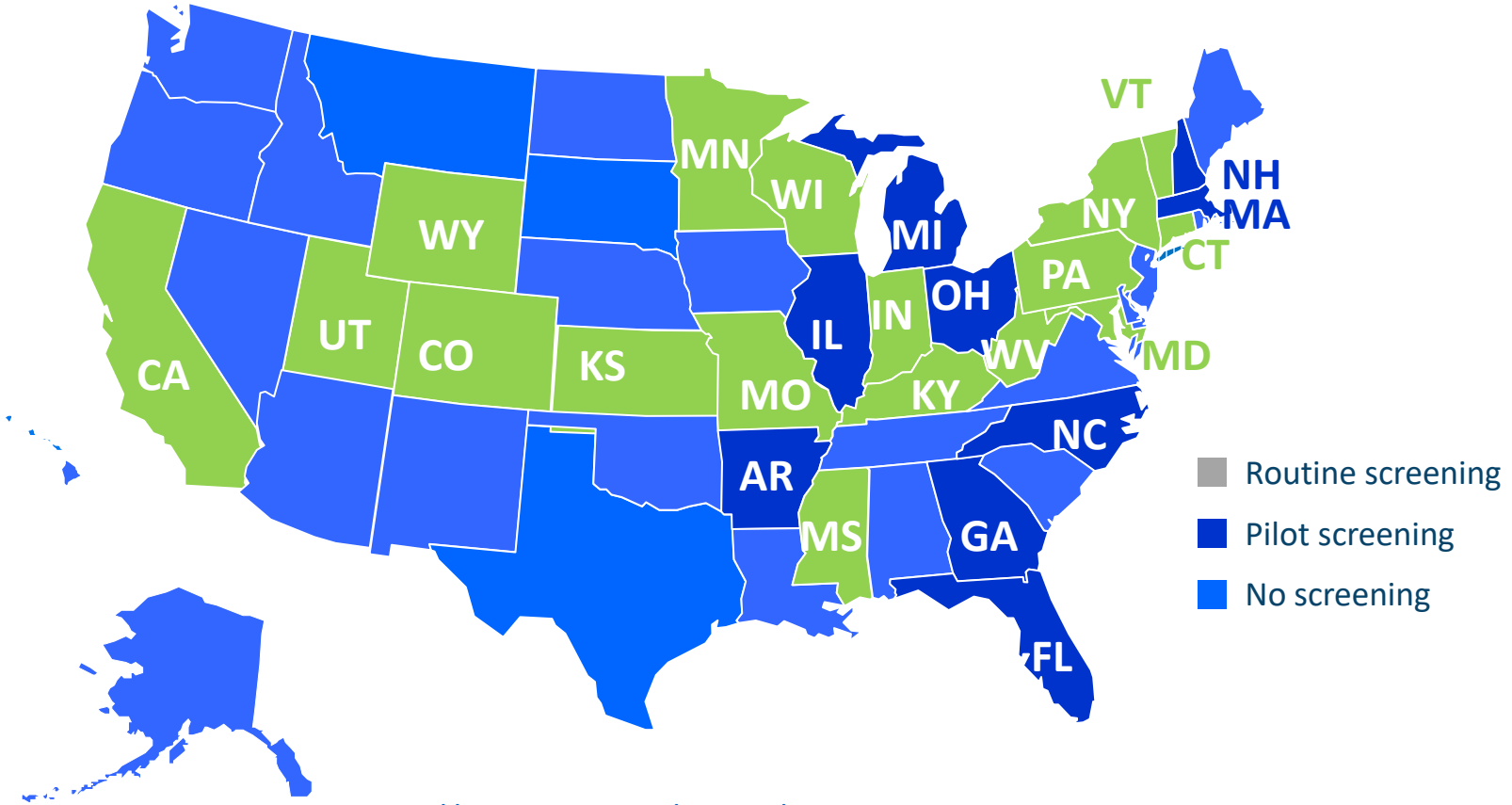
Dangouloff T, et al. *Neuromuscul Disord*. 2020;30(1):93-103.

244th ENMC international workshop:
Newborn screening in spinal muscular atrophy
May 10–12, 2019, Hoofdorp, The Netherlands

Tamara Dangouloff[a], Arthur Burghes[b], Eduardo F. Tizzano[c,*], Laurent Servais[a,d,**], on behalf of the NBS SMA Study Group[1]

[a] *Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, 4000 Belgium*
[b] *Department of Biological Chemistry and Pharmacology, The Ohio State University, Columbus, OH, USA*

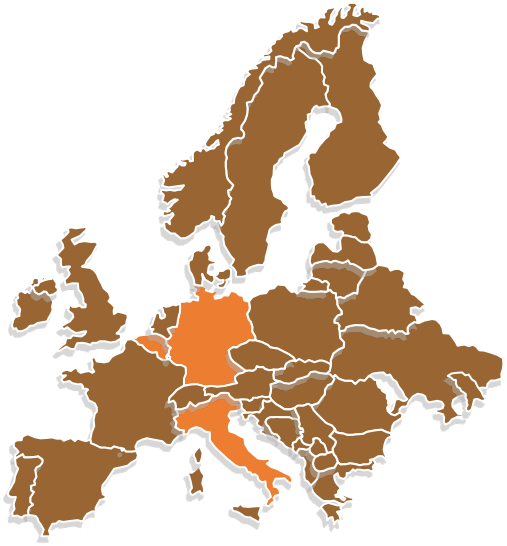
SMA Newborn Screening – United States



American Legislative Exchange Council. January 29, 2020. https://www.alec.org/article/many-states-now-screening-newborns-for-spinal-muscular-atrophy-others-considering-action-in-2020/.
Colorado Dept of Public Health and Environment. November 20, 2019. https://www.colorado.gov/pacific/cdphe/news/newborn-screenings-sma.
Frank G. SMA News Today. February 12, 2020. https://smanewstoday.com/2020/02/12/efforts-continue-require-newborn-screening-sma-more-states/. Accessed June 30, 2020

Newborn Screening Worldwide

Europe



No newborn screening

Ongoing clinical trials examining applicability of SMA screening in **Belgium,[1,2] Italy,[2] Germany[3]**

Middle east

No newborn screening

Prenatal carrier screening in Israel[4] and Qatar[5]

Africa

No newborn screening

South America

No newborn screening

Taiwan, Japan,[6] Australia[7]

No newborn screening

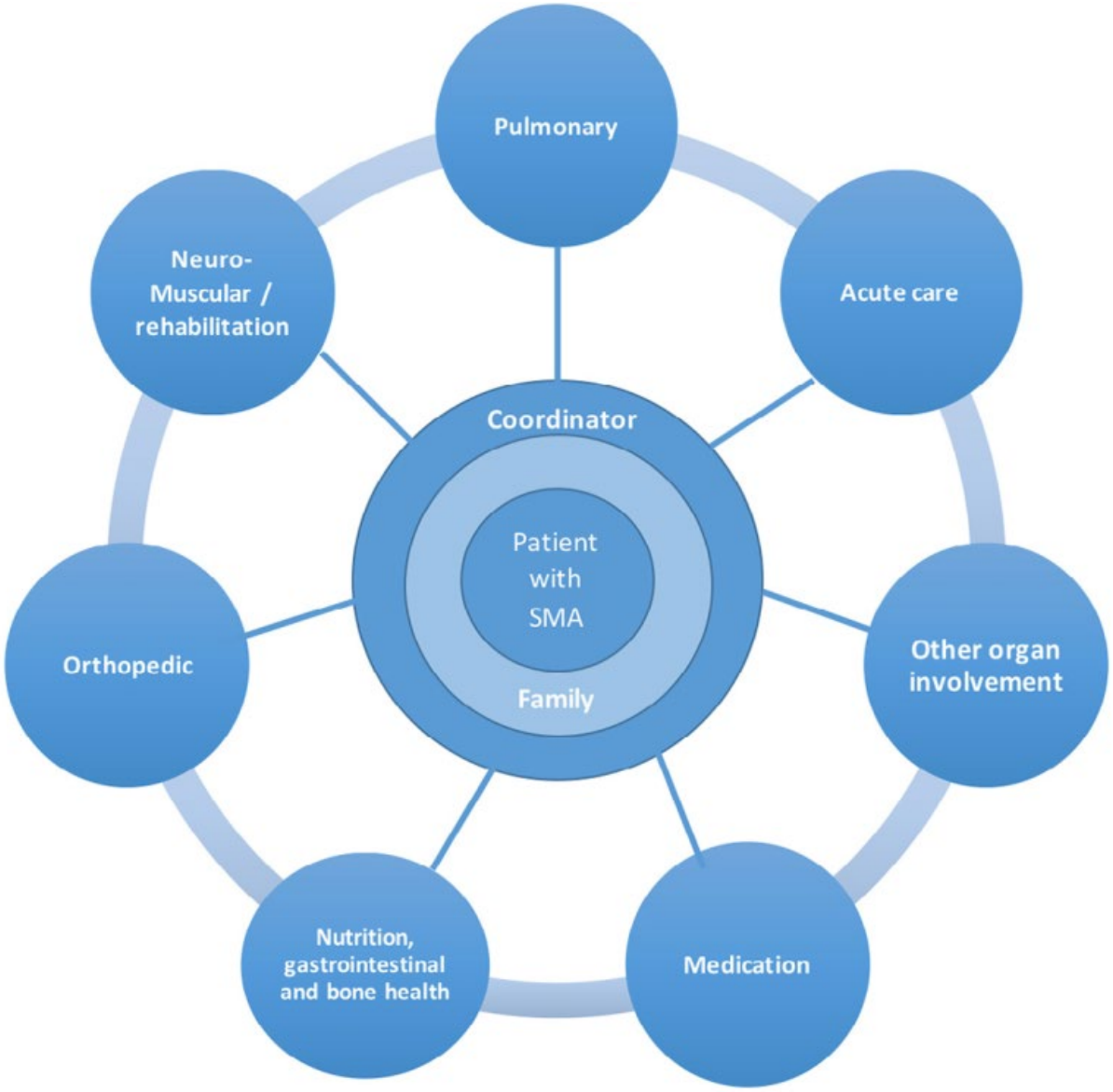
Ongoing studies examining strategies/applicability

1. Boemer et al. *Neuromusc Disorders*. 2019;29(5):343-349;2; **2**. Luxner L. SMA News Today. June 7, 2019. https://smanewstoday.com/2019/06/07/zolgensma-arrival-adds-urgency-sma-newborn-screening-efforts-us-europe/; Accessed June 30, 2020; **3.** Vill K, et al. *J Neuromuscul Dis*. 2019;6(4):503-515. **4**. Boardman FK, et al. *Mol Genet Genomic Med*. 2018;6:99-108. **5.** Aharoni S, et al. *Neuromusc Disord.* 2017;27(Suppl2):S137; **6.** Shinohara M, et al. *Int. J. Neonatal Screen.*2019;5(41):1-13; **7**. Kariyawasam DST, et al. *Genet Med*. 2020;22:557-565.

Conclusions

- Diagnosis of 5q SMA is based on detection of *SMN1* mutations/deletions plus *SMN2* copy number
- In patients with SMA, *SMN2* copy number is the main determinant of phenotype/disease severity, though other factors may contribute
- Early, presymptomatic treatment can dramatically change the SMA disease course; phenotypes are changing with treatment
- Newborn screening is crucial to early detection and early treatment (but in many countries, neither is available)
- Potential role of electrophysiology as a biomarker

Need for Ongoing Care and Support by a Multidisciplinary Team



Mercuri E, et al. *Neuromusc Disorders*. 2018;28:103-115.

Bambino Gesù
OSPEDALE PEDIATRICO

Adele D'Amico
Michela Catteruccia
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Daria Diodato
Michele Tosi
Irene Mizzoni
De Luca Giacomo
Adelina Carlesi
Giulia Colia
Fabiana Fattori

Molte grazie

Telethon
COMBATTI LA DISTROFIA MUSCOLARE E LE ALTRE MALATTIE GENETICHE

Famiglie SMA
Genitori per la Ricerca sull'Atrofia Muscolare Spinale