The unusual case of a rare disease, Spinal Muscular Atrophy

Rafael Yanez
Prof of Advanced Therapy, Royal Holloway University of London

Chaired by Sarah Hanson
Senior Paediatric Research Nurse, Leeds General Infirmary

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Who are LAT and the ATTCs?

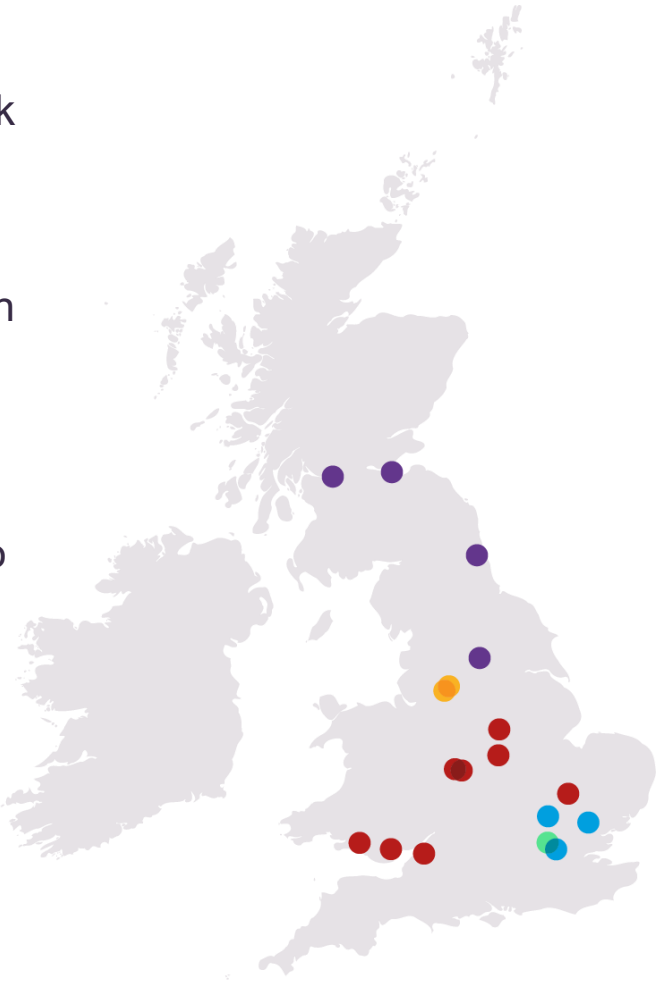
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



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The unusual case of a rare disease, spinal muscular atrophy

Rafael Yáñez, rafael.yanez@royalholloway.ac.uk

09.03.2021, ATTC/LAT webinar series

What is he talking about???

- What is a rare disease?
- Why are rare diseases important?
- Genes and rare diseases
- Gene therapy products
- The need for treatments
- Spinal muscular atrophy
- Treatments for spinal muscular atrophy
- The genomic medicine revolution

Why are Rare Diseases important?

In Europe, a disease is rare if fewer than 1 in 2,000 people are affected…

…more than 9,600 rare diseases, up to 6-7% of people, 20% of Health budget…

…most rare diseases affect children and 30% of people affected will die before their 5th birthday…

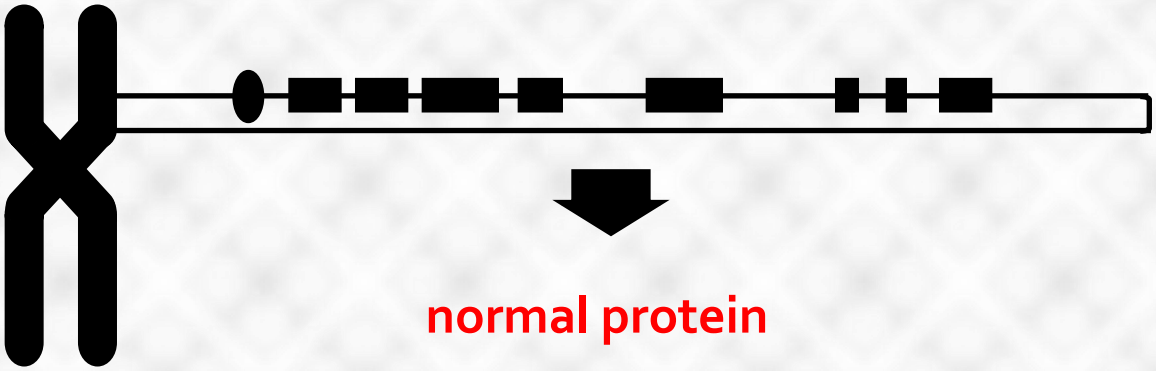
… 40-72% of rare diseases are inherited (genetic).

Why are Rare Diseases important?

In many monogenic genetic diseases the therapeutic target has been defined and validated.

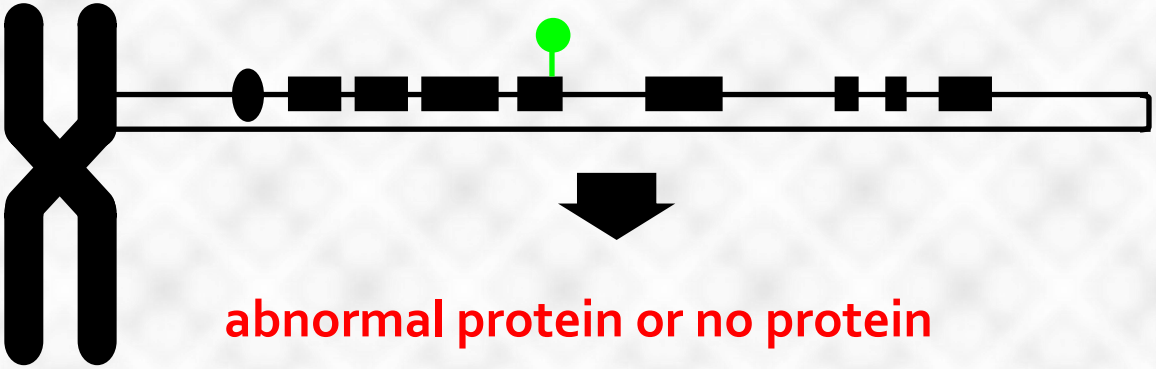
Most gene therapy technology has been developed and tested on rare diseases, but will also be applied to common diseases.

Genes store the info to make proteins



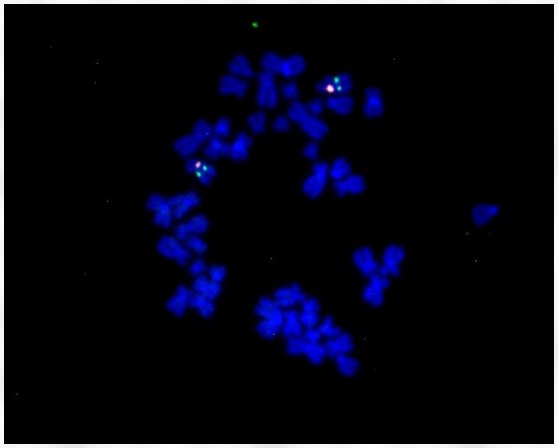
normal gene

normal protein



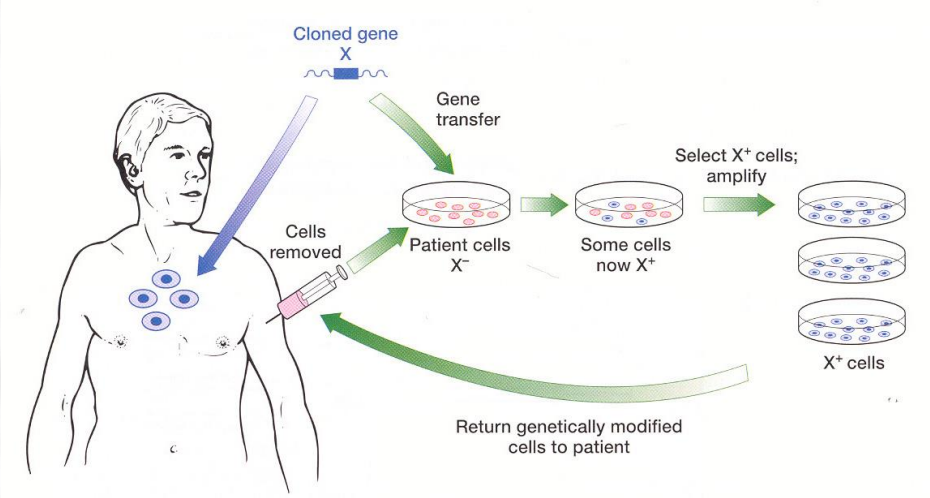
mutant gene

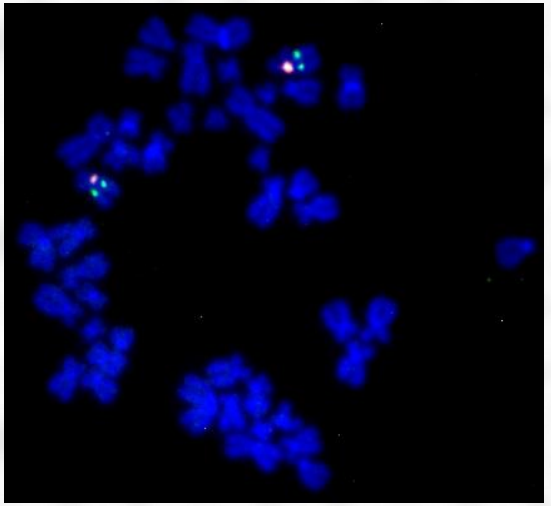
abnormal protein or no protein



What is gene therapy?

Deliberate alteration of the genome or its function to produce a therapeutic benefit. Sometimes cells are modified outside the body, resulting in gene cell therapy.

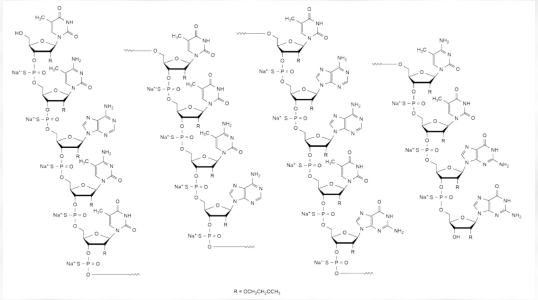




Approved gene therapy products

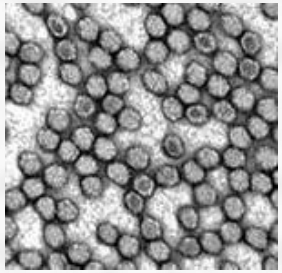
https://bit.ly/2Kf9OWo

[Antisense oligonucleotides:]



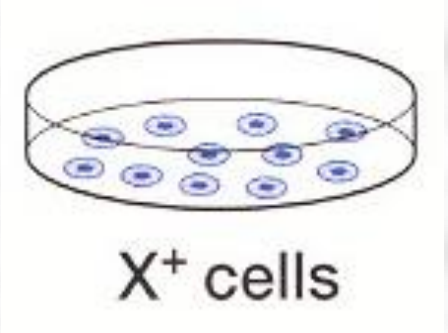
- Exondys 51 (antisense oligonucleotide, Duchenne muscular dystrophy, US)
- Spinraza (antisense oligonucleotide, Spinal muscular atrophy, US, EU…)
- Onpattro (siRNA in lipid nanoparticle, hereditary ATTR amyloidosis, US, EU)
- Tegsedi (antisense oligonucleotide, hereditary ATTR amyloidosis, EU)

Viral vectors:



- Gendicine (adenovirus vector, Cancer, China)
- [Glybera (adeno-associated virus vector, LPL deficiency, EU)]
- Imlygic (herpesvirus vector, Cancer, EU and US)
- Luxturna (adeno-associated virus vector, RPE65 deficiency, US, EU)
- Zolgensma (adeno-associated virus vector, Spinal muscular atrophy, US, EU)

Genetically modified cells:



- Strimvelis (ADA retrovirus vector-treated autologous HSCs, ADA deficiency, EU)
- Zalmoxis (HSV-TK retrovirus vector-treated allogeneic T-cells, HSCT, EU)
- Kymriah (CAR lentivirus vector-treated autologous T-cells, leukemia, US)
- Yescarta (CAR retrovirus vector-treated autologous T-cells, leukemia, US)
- Zynteglo (lentivector $\beta^{A\text{-}T87Q}$-globin-treated autologous $CD34^{+}$ cells, β-thalassemia, EU)

We need treatments, loads of them!

Limited therapeutics: Number of Rare Diseases *versus* Number of Diseases screened for in newborns

Newborn blood spot test

Every baby is offered newborn blood spot screening, also known as the heel prick test, ideally when they are five days old.

Newborn blood spot screening involves taking a blood sample to find out if your baby has one of nine rare but serious health conditions.

Most babies screened won't have any of these conditions but, for the few who do, the benefits of screening are enormous. Early treatment can improve their health and prevent severe disability, and even death.

What does the blood spot test involve?

When your baby is five days old, a health professional will prick their heel using a special device and collect four drops of blood on a special card. You can minimise any distress to your baby by cuddling and feeding them, and making sure they are warm and comfortable.

(http://www.nhs.uk/conditions/pregnancy-and-baby/pages/newborn-blood-spot-test.aspx)

Genomics leads …

Genomics england

About Us | 100,000 Genomes Project | Taking Part | For Healthcare Professionals | Research | Inc

Home > The 100,000 Genomes Project

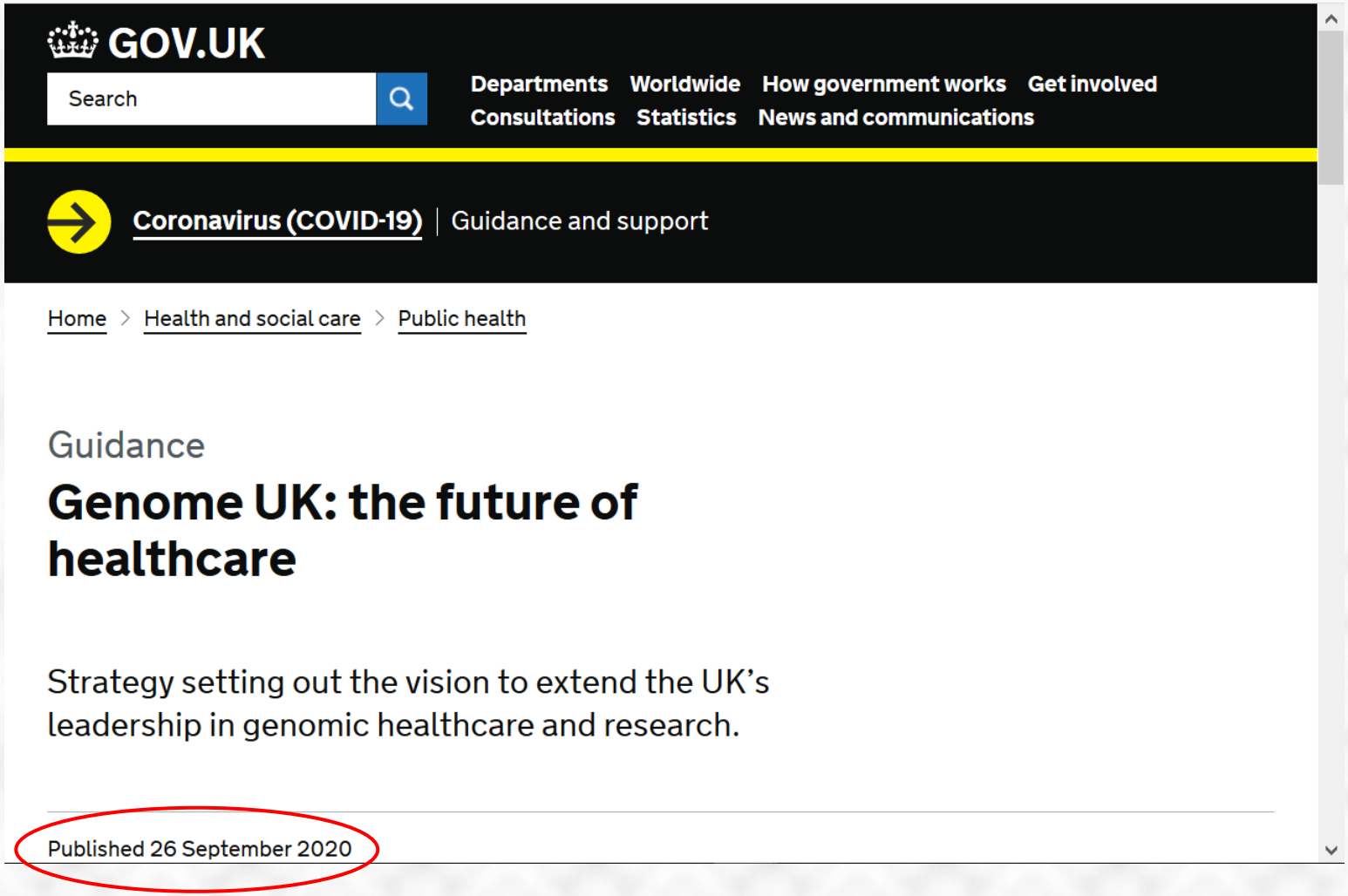
The 100,000 Genomes

The project will sequence 100,000 ger
people. Participants are NHS patients
their families, and patients with cance

(https://www.genomicsengland.co.uk)

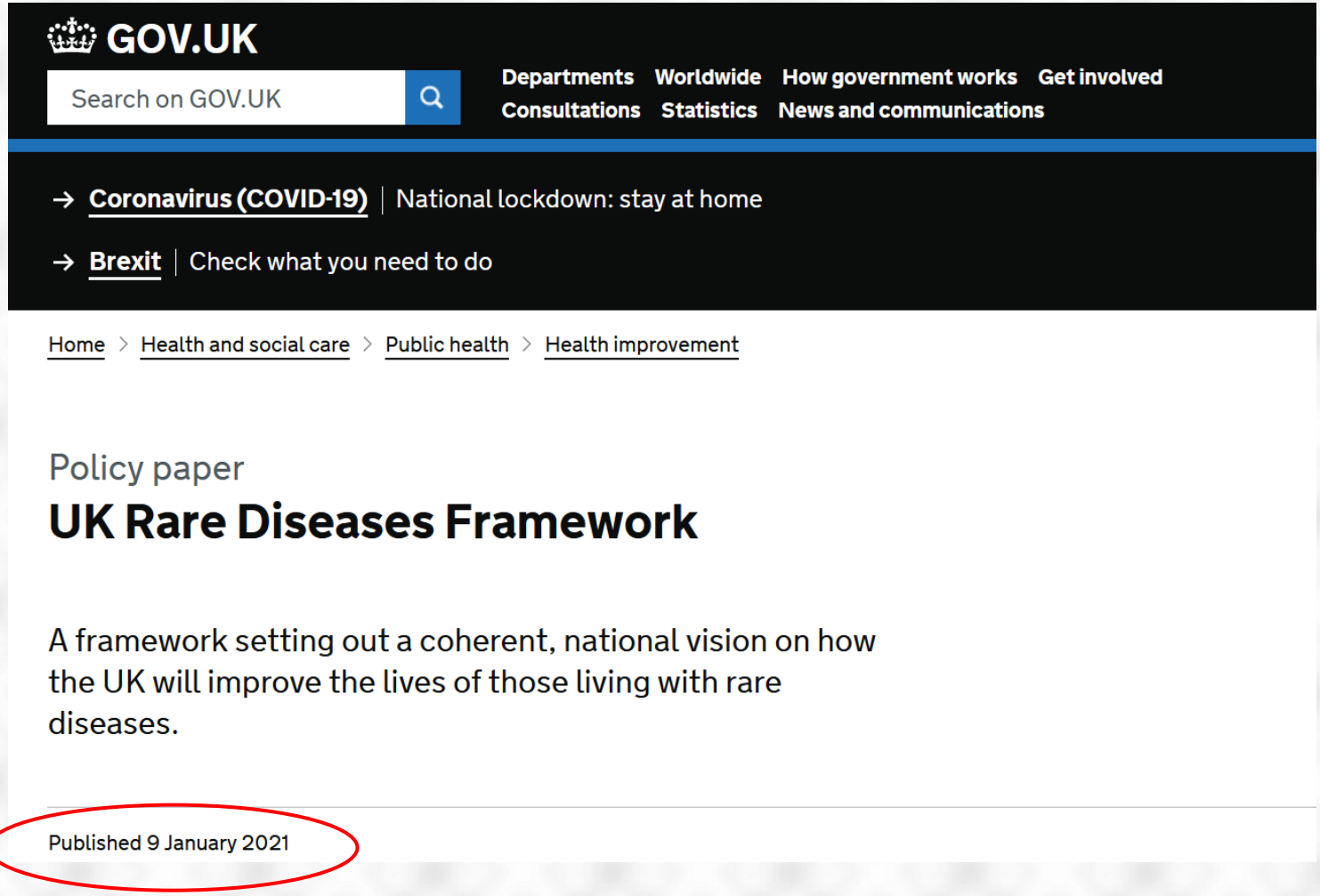
(Sanger Institute, Genome Research Limited)

The government 2020 strategy: Genome UK



(https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare)

The government 2021 Rare Diseases Framework



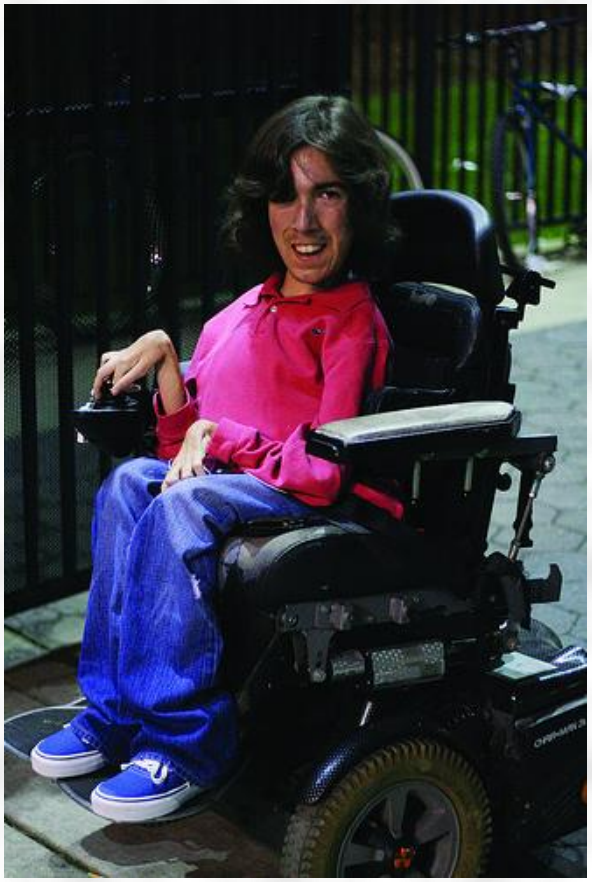
(https://www.gov.uk/government/publications/uk-rare-diseases-framework)

Spinal muscular atrophy

- Group of autosomal recessive neuromuscular disorders
- Motor neuron degeneration (but many tissues affected)
- Symmetrical muscular degeneration and atrophy
- Four types depending on age of onset, maximum muscular activity and survival
- Second to cystic fibrosis in Caucasians: 1:10,000 live births, 1:50 carriers
- Most common genetic cause of death in childhood

- Mutations in *SMN1*, 5q12.2-q13.3
- Modified by *SMN2* (and others)

- Widely expressed gene



SMA presents with varying severity

	OMIM number	Age at onset	Highest function achieved	Natural age of death
Type I (severe, Werdnig-Hoffmann disease)	253300	0–6 months	Never sit	<2 years
Type II (intermediate)	253550	7–18 months	Sit, never stand	>2 years
Type III (mild, Kugelberg-Welander disease)	253400	>18 months	Stand and walk	Adult
Type IV (adult)	271150	Second or third decade	Walk during adulthood	Adult

OMIM=Online Mendelian Inheritance in Man.

Table 1: **Classification criteria for spinal muscular atrophy**

Disease modifiers:

- **Number of *SMN2* copies**
- **Plastin 3 (stabilises filamentous actin)**
- **Others**

SMA presents with varying severity

Table 1. Clinical and molecular features of SMA sub-types

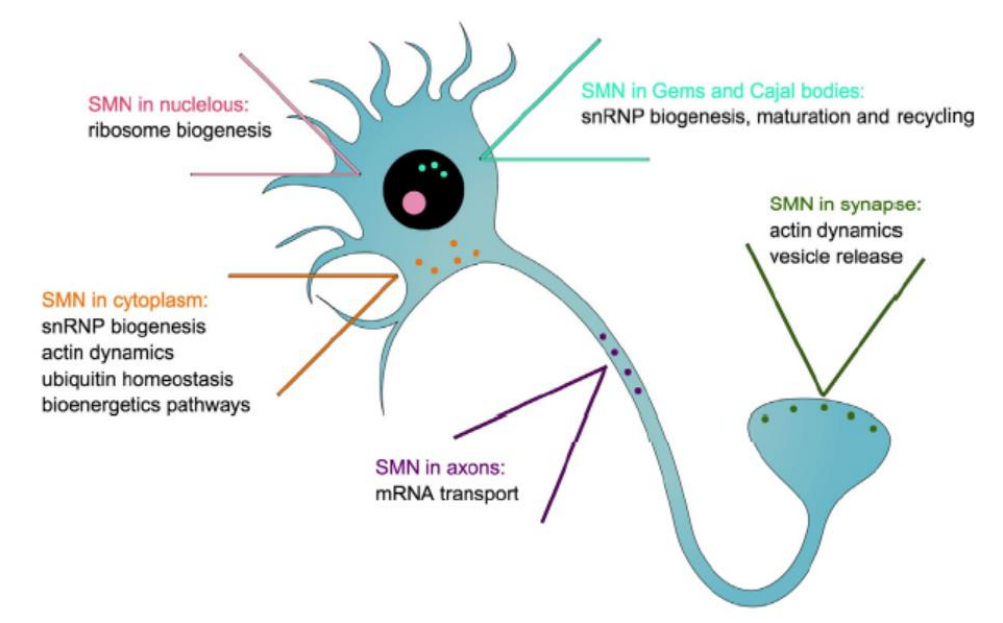
	Type of SMA				
	0	I	II	III	IV
SMN2* copy number	1	2	3	3-5	3-5
Age of onset	*In utero*	Majority by 6 months	6-12 months	After 18 months (IIIa: <3 years, IIIb: >3 years)	Adulthood
Key clinical features	Widespread motor and sensory neuronal loss Contractures High incidence of congenital cardiac defects	Neonatal hypotonia Poor feeding and head control Respiratory insufficiency Never develop ability to roll or sit unaided	Sit unsupported Never walk Respiratory muscle weakness	Walk unaided, even if briefly	Progressive proximal weakness Lower limb predominance
Natural history	Peri-natal death	50% death by 12 months 90% death by 24 months without invasive ventilation	Life expectancy 30-50 years depending on respiratory function	Loss of ambulation very variable (from childhood to late life) Respiratory involvement uncommon Life expectancy near normal	Slow progression Ambulation maintained Normal lifespan

*All SMA patients, regardless of type have no functional copies of *SMN1*; the number of *SMN2* copies in unaffected individuals (carriers or non-carriers) can range from 2 to 5.

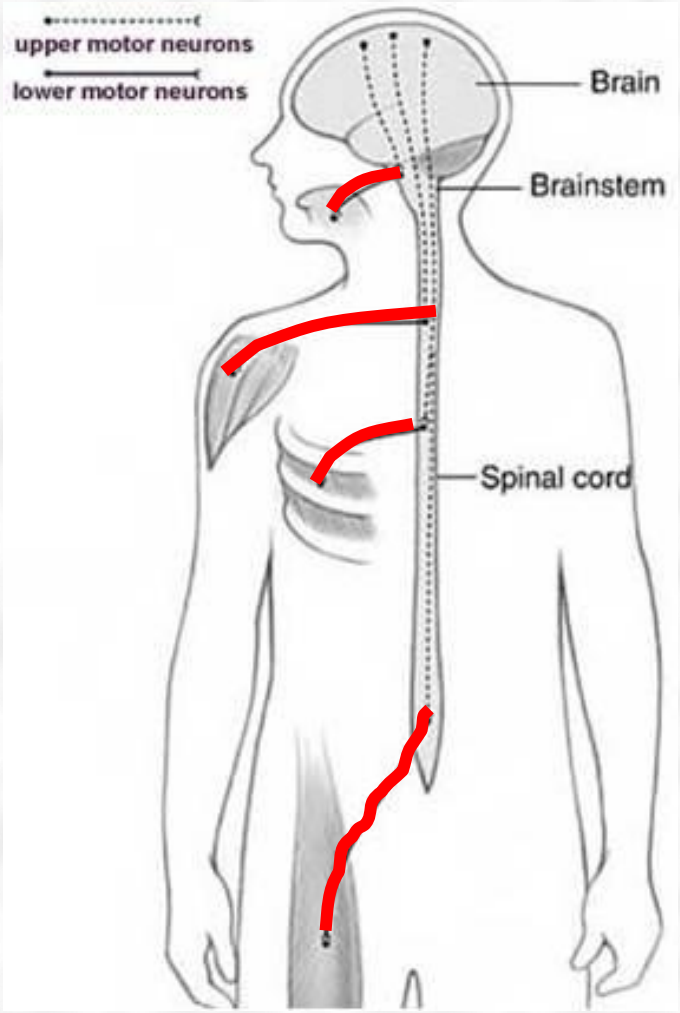
(Bowerman *et al*. Disease Models & Mechanisms (2017) 10, 943-954 doi:10.1242/dmm.030148)

Motor neuron degeneration in SMA

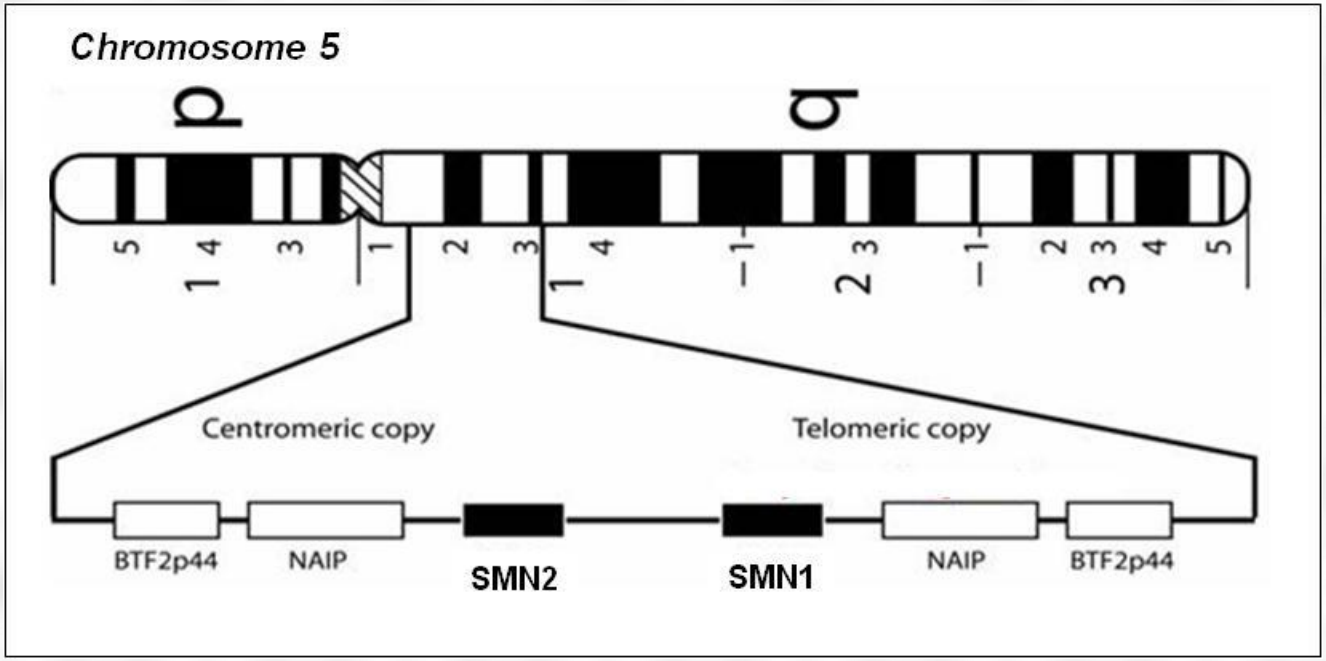
Loss of function of the ubiquitous protein SMN has major effect on α-motor neurons.



(Bowerman *et al*. Disease Models & Mechanisms (2017) 10, 943-954 doi:10.1242/dmm.030148)



Chromosomal location of *SMN* genes

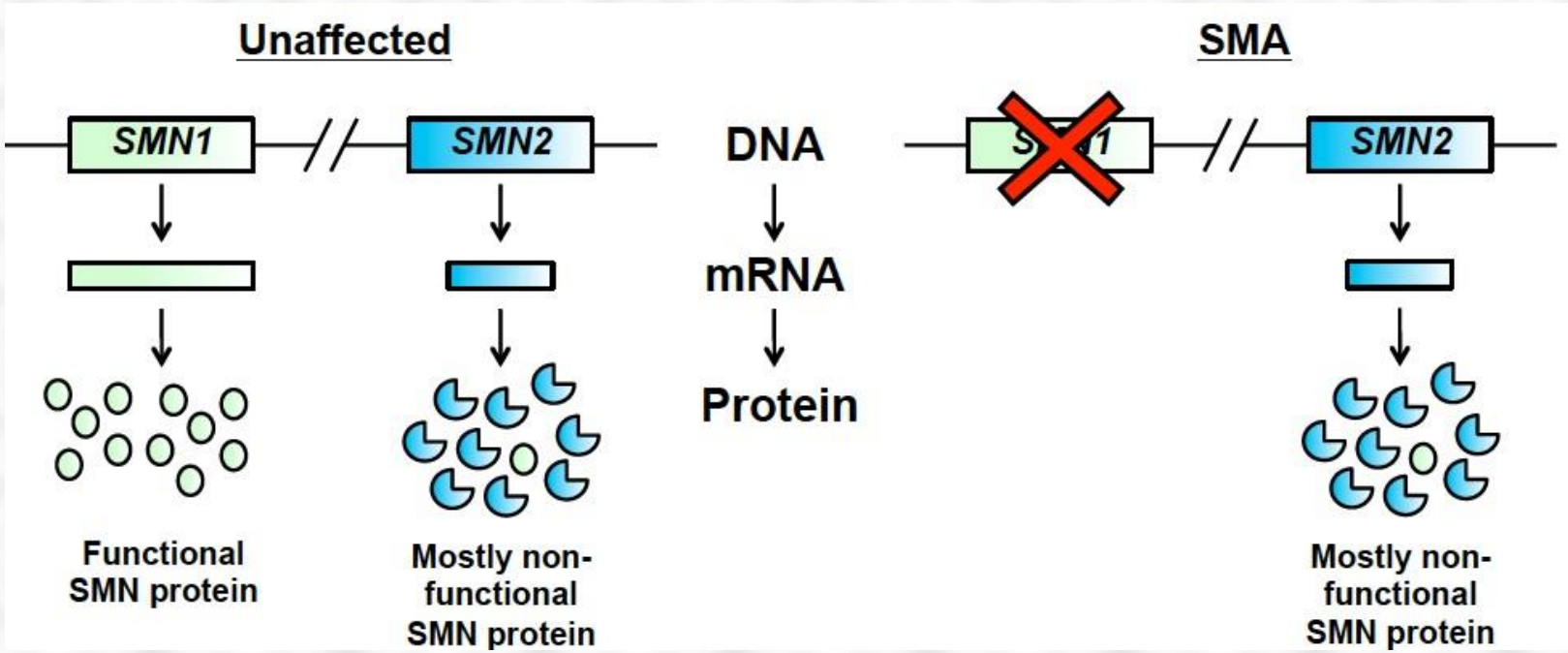


SMA is caused by loss of function of SMN protein (survival of motor neuron)

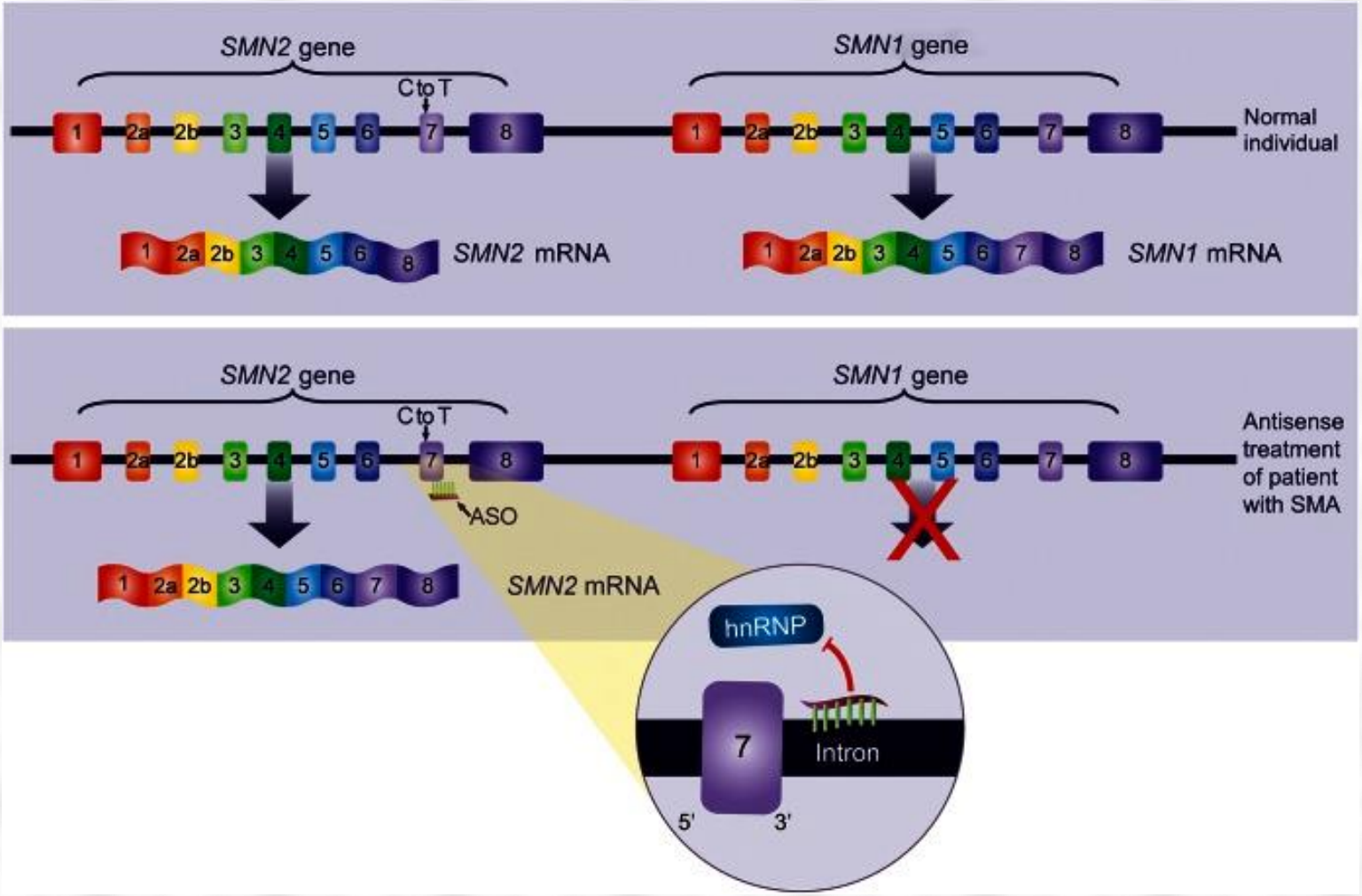
Two nearly identical genes produce SMN protein:

- ***SMN1*, telomeric copy**
- ***SMN2*, centromeric copy (inverted intrachromosomal duplication of *SMN1*)**

Genetic basis of spinal muscular atrophy

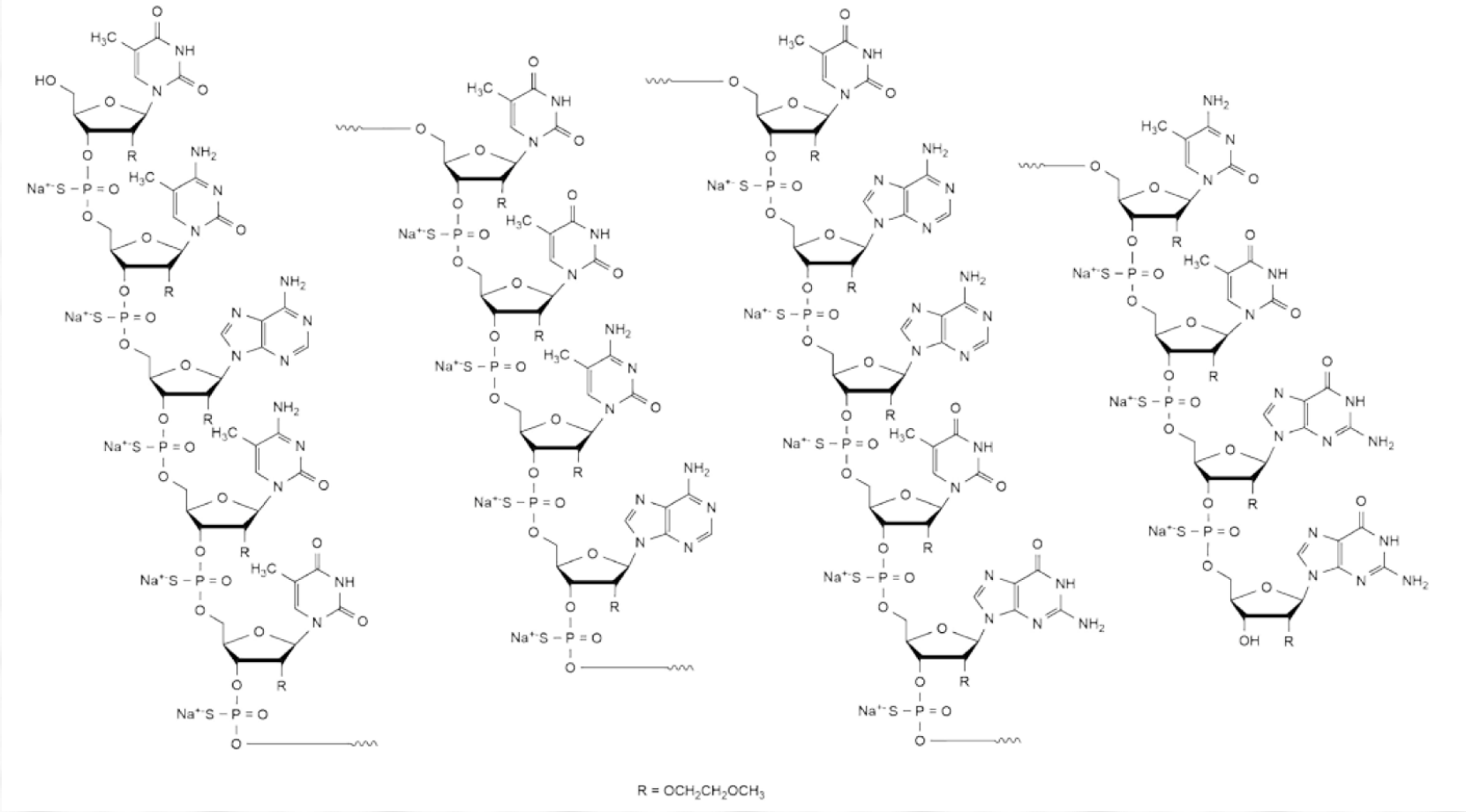


Nusinersen (Spinraza) and Spinal muscular atrophy



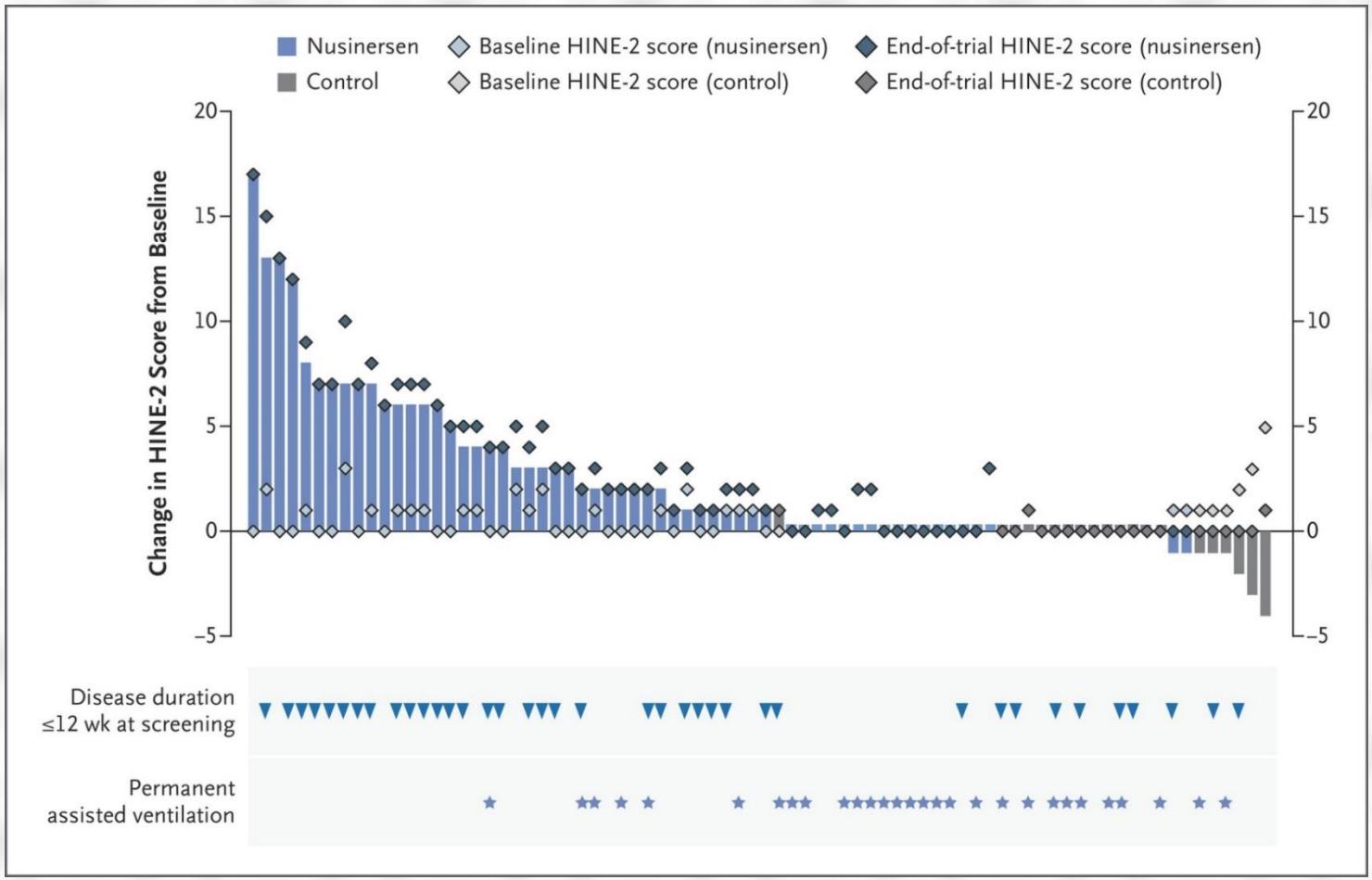
(Chiriboga *et al*. Neurology. 2016 Mar 8; 86(10): 890–897)

Nusinersen (Spinraza) antisense oligonucleotide for Spinal muscular atrophy



Nusinersen is a modified antisense oligonucleotide, where the 2'-hydroxy groups of the ribofuranosyl rings are replaced with 2'-O-2-methoxyethyl groups and the phosphate linkages are replaced with phosphorothioate linkages

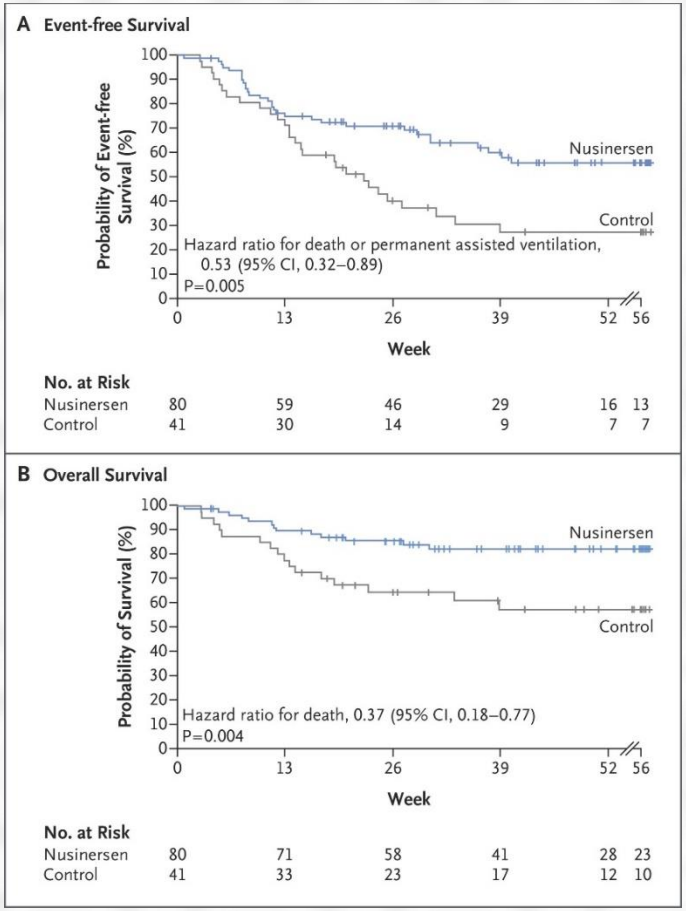
Effect of nusinersen (Spinraza™) in infantile-onset SMA



Hammersmith Infant Neurological Examination (HINE-2) scores

Finkel et al NEJM 2017 https://www.nejm.org/doi/10.1056/NEJMoa1702752

Effect of nusinersen (Spinraza™) in infantile-onset SMA



Event-free survival

Overall survival

Finkel et al NEJM 2017 https://www.nejm.org/doi/10.1056/NEJMoa1702752

Nusinersen-treated Spinal muscular atrophy

Comparison of viral vectors

		Adenovirus	Adeno-associated virus	Alphavirus	Herpesvirus	Retrovirus / Lentivirus	Vaccinia virus
Particle characteristics	Genome	dsDNA	ssDNA	ssRNA (+)	dsDNA	ssRNA (+)	dsDNA
	Capsid	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Complex
	Coat	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped
	Virion polymerase	Negative	Negative	Negative	Negative	Positive	Positive
	Virion diameter	70 - 90 nm	18 - 26 nm	60 - 70 nm	150 - 200nm	80 - 130 nm	170 - 200 X 300 - 450nm
	Genome size	39 - 38 kb	5 kb	12 kb	120 - 200 kb	3 - 9 kb	130 - 280 kb
							
	Family	*Adenoviridae*	*Parvoviridae*	*Togaviridae*	*Herpesviridae*	*Retroviridae*	*Poxviridae*
Gene Therapy Properties	Infection / tropism	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing (RV and LV) and non-dividing cells (LV)	Dividing and non-dividing cells
	Host genome interaction	Non-integrating	Non-integrating*	Non-integrating	Non-integrating	Integrating	Non-integrating
	Transgene expression	Transient	Potential long lasting	Transient	Potential long lasting	Long lasting	Transient
	Packaging capacity	7.5 kb	4.5 kb	7.5 kb	> 30 kb	8 kb	25 kb

http://www.genetherapynet.com/viral-vectors.html, with modifications

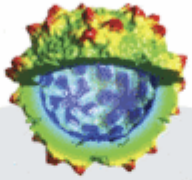
AAV9-CAG-hSMN1 (Zolgensma) for Spinal muscular atrophy

Our Solution: AVXS-101

An Innovative Treatment Approach for SMA

Gene therapy is the right approach for SMA: Monogenic mutation that drives the pathology

Recombinant AAV9 Capsid Shell



scAAV ITR	Continuous Promoter	Human SMN Transgene	scAAV ITR

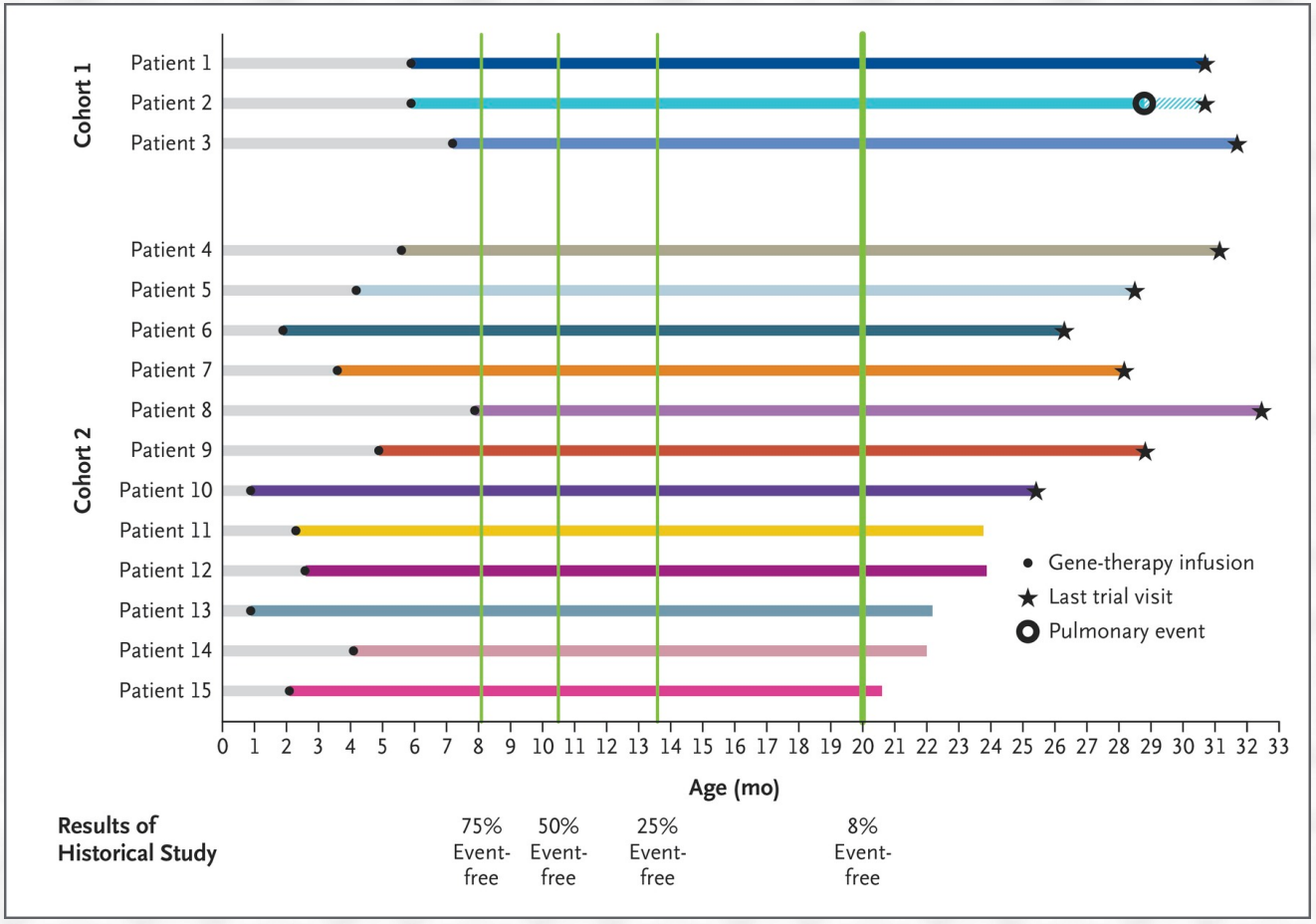
KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver across the blood brain barrier (BBB) and into the spinal cord - Avoids the need for intrathecal delivery when treating infants • Non-replicating virus does not modify the existing DNA of the patient.
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
Continuous Promoter	• Activates the transgene to allow for continuous and sustained SMN expression
Human SMN Transgene	• Full copy of a stable, functioning SMN gene that is introduced into the cell's nucleus

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J. Virol. June 2012.

9

http://investors.avexis.com/phoenix.zhtml?c=254285&p=irol-SECText&TEXT=aHR0cDovL2FwaS50ZW5rd2l6YXJkLmNvbS9maWxpbmcueG1sP2lwYWdlPTExNTQzMzA2JkRTRVE9MCZTRVE9MCZTUURFU0M9U0VDVElPTI9FTlRJUkUmc3Vic2lkPTU3

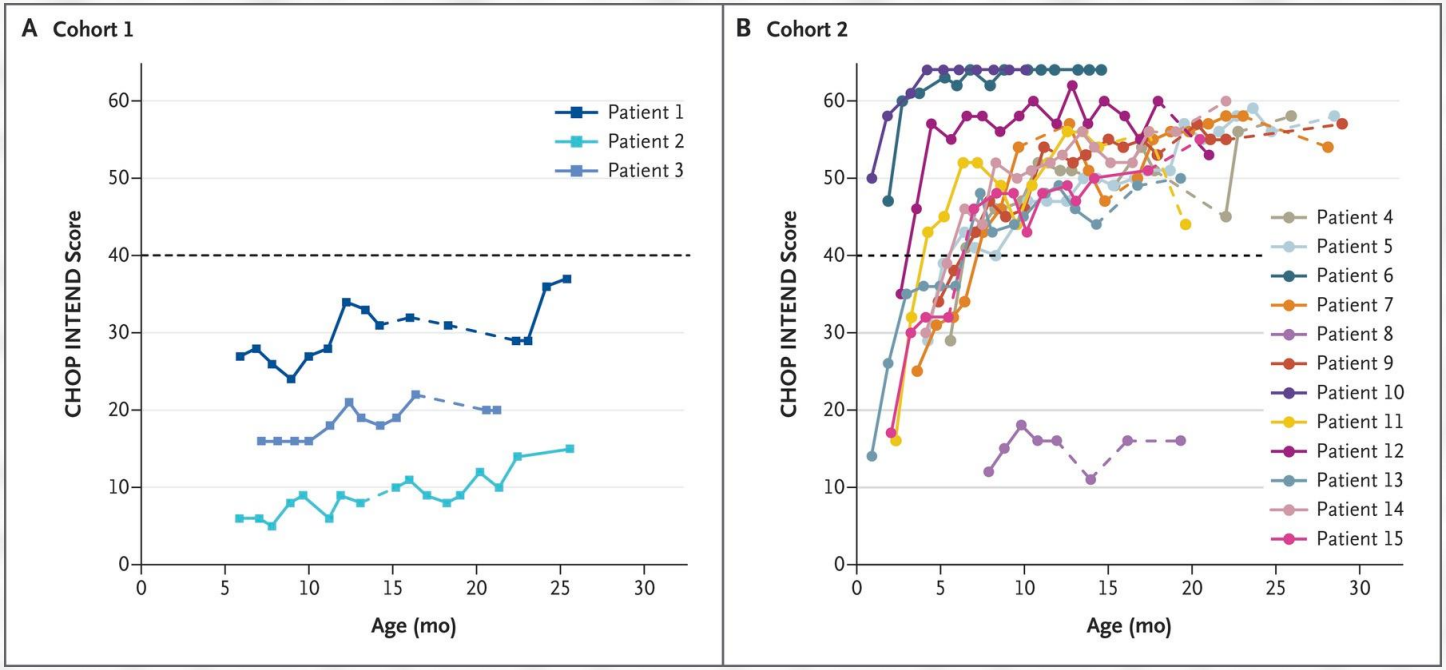
AAV9-CAG-hSMN1 (Zolgensma) for Spinal muscular atrophy



Survival Free from Permanent Ventilation in the 15 Study Patients. The 3 patients in cohort 1 received a single intravenous low dose of AAV vector containing DNA coding for SMN (6.7×10^{13} vg per kilogram), and the 12 patients in cohort 2 received a high dose (2.0×10^{14} vg per kilogram). Stars indicate the completion of the ongoing 2-year safety follow-up. Percentages of control patients who were event-free in a historical study are provided at the bottom of the, as indicated by the vertical green lines. At 20 months, only 8% of the patients with this disease typically survive without permanent ventilation.

Mendell et al., NEJM 377, 1713-1722 (2017) https://www.nejm.org/doi/full/10.1056/NEJMoa1706198

AAV9-CAG-hSMN1 (Zolgensma) for Spinal muscular atrophy



Motor Function after Gene Therapy. Changes in the score for motor function on the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale among the 3 patients in cohort 1 (Panel A) and the 12 patients in cohort 2 (Panel B). The scale ranges from 0 to 64, with higher scores indicating better motor function; historical controls with spinal muscular atrophy type 1 never reach 40 points (indicated by the black dashed line). The dashed lines on the individual patient curves indicate either a missed assessment or a partial assessment because of illness, lack of cooperation, or fatigue of the patient; such data were not included in the analyses.

Mendell et al., NEJM 377, 1713-1722 (2017) https://www.nejm.org/doi/full/10.1056/NEJMoa1706198

AAV9-CAG-hSMN1 (Zolgensma) for Spinal muscular atrophy

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‖

* At baseline, none of the patients in cohort 2 had achieved any of the listed motor milestones except for bringing a hand to the mouth. As of August 7, 2017, the majority of these patients had reached at least one major motor milestone. No patients in cohort 1 are listed, since none attained any motor milestones. NA denotes not available, and NIV noninvasive ventilation. Plus signs indicate achievement of milestone.

† Event-free survival (the primary efficacy outcome) was defined as the age at the last follow-up at which patients were free of ventilatory support, which was defined as the need for ventilation for at least 16 hours per day for at least 14 consecutive days.

‡ According to item 20 on the Bayley Scales of Infant and Toddler Development, rolling over is defined as movement of at least 180 degrees both left and right from a position of lying on the back.

§ Sitting unassisted for at least 5 seconds is in accordance with the criteria of item 22 on the Bayley Scales of Infant and Toddler Development gross motor subtest and surpasses the 3-second count that is used as a basis for sitting (test item 1) on the Hammersmith Functional Motor Scale–Expanded for Spinal Muscular Atrophy (SMA). Sitting unassisted for at least 10 seconds is in accordance with the criteria used in the World Health Organization Multicentre Growth Reference Study. Sitting unassisted for at least 30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 on the Bayley Scales of Infant and Toddler Development gross motor subtest.

¶ Nutritional support refers to the placement of either a gastrostomy tube or a nasogastric tube, as determined by the preference of the parents or the primary physician. Once enrolled in the study, all the patients who required nutritional support underwent gastrostomy-tube placement, and none were removed during the study.

‖ Data are from Finkel et al.[4]

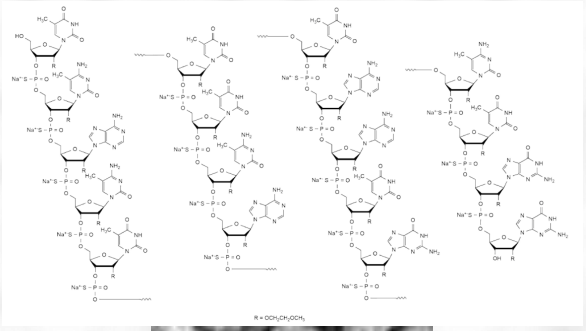
** Data are from De Sanctis et al.[6]

Mendell et al., NEJM 377, 1713-1722 (2017) https://www.nejm.org/doi/full/10.1056/NEJMoa1706198

The problems with access to the market

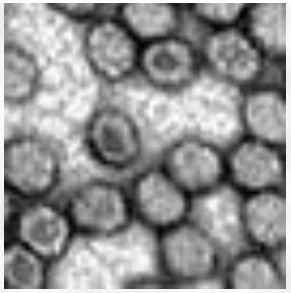
Spinraza: Intrathecal, £75,000/dose (£450,000 first year, £225,000 thereafter)

NICE: For people with pre-symptomatic SMA, or SMA types 1, 2 or 3 if the conditions in the managed access agreement are followed.



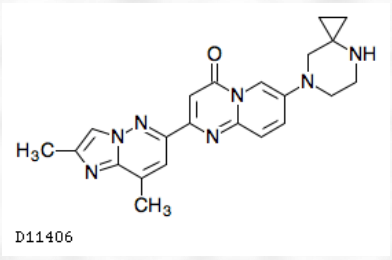
Zolgensma: Intravascular, £1,700,000 (one-off)
Most expensive medicine ever

NICE: For babies aged up to 12 months with type 1 SMA



Risdiplam (Evrysdi): Oral, $340,000 per year

Approved by FDA, Recommended for approval by EMA (EMA approval will apply to Northern Ireland)



Join the genomic medicine revolution!

Thank you !

Q&A

Advanced Therapy Treatment Centres

Please add any question you have into the Q&A box

Please fill in feedback survey, your input is really valuable to us

Upcoming webinars,

ATMPs on the horizon

4pm 22nd March, Joanne McEntee (Senior medicines information pharmacist, North West Medicines Information Centre)

Patient and public perspectives on advanced therapies

12pm, 24th March, Dr Lee Aiyegbusi, CPROR Deputy Director, University of Birmingham