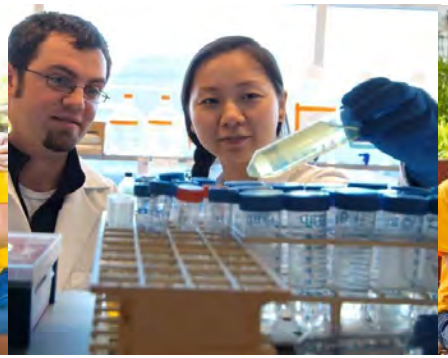
Paul & Sheila Wellstone
Muscular Dystrophy Center

UNIVERSITY OF MINNESOTA
Driven to Discover℠

Early diagnosis of neuromuscular disorder – why it is important.

Peter Karachunski, MD






Making the MD Community Stronger!

Therapeutic advances in treatment of neuromuscular disorders.

	ALS	DMD	SMA	Pompe	LES	MG	PPP	FA	hATTR
2023	Tofersen	Elevidys				Rystiggo		Skyclaris	
2022	Relyvrio								Amvuttra
2021		Casimersen		Nexviazyme		Vyvgart			
2020		Viltorasen	Risdiplam						
2019		Golodirsen							
2018	Nuedexta		Zolgensma		Firdapse	Ultomiris			Tegsedi, Onpattro
2017	Radicava	Emflaza				Eculizimab			
2016		Eteplersen	Nusinersen						
2006 - 15				Myozyme, Lumizyme, Nexviazyme			Keveyis		
1995	Rilutek								

Making the MD Community Stronger!

One of the latest news

August 10th, 2023: Today, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHNDC or "the Committee") voted to move the nomination of Duchenne muscular dystrophy for the Recommended Uniform Screening Panel (RUSP) onto the next stage of review. The nomination now moves on to the "Evidence-based Review" stage (also known as "full evidence review") in which the Committee examines the nomination further and ensures it is ready for recommendation to the RUSP.

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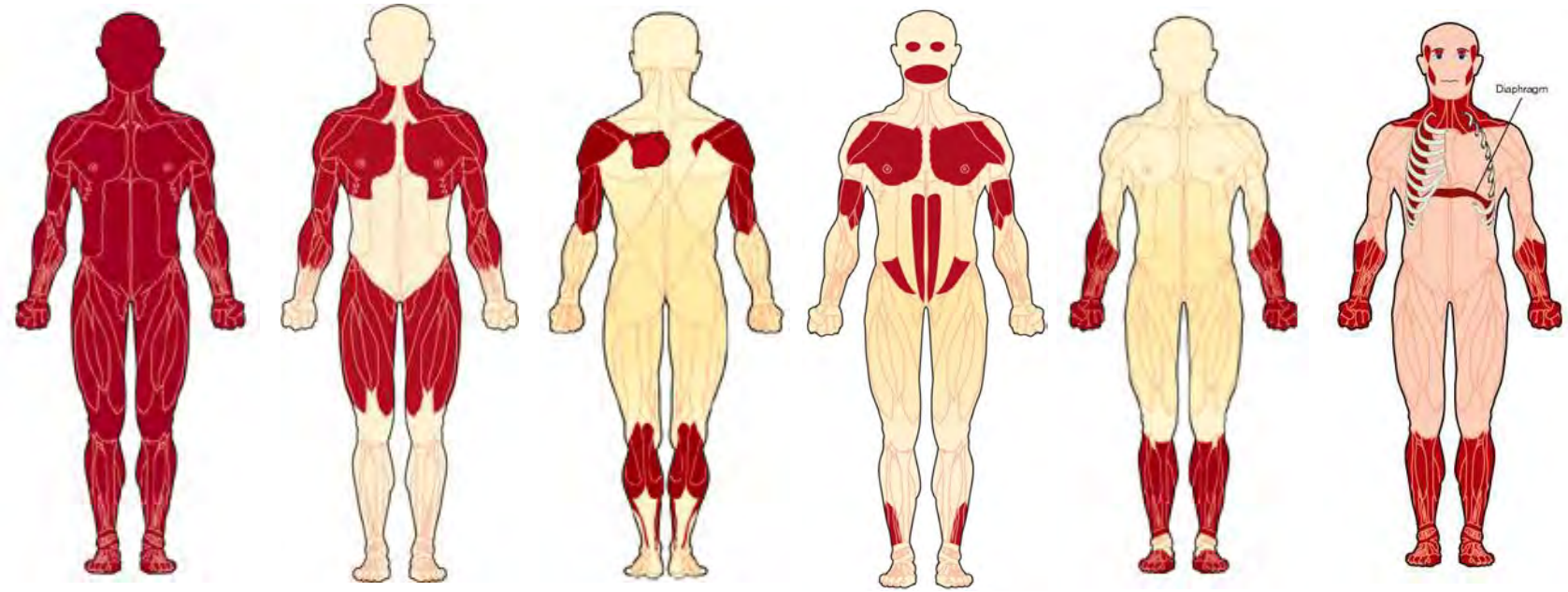
How are neuromuscular disorders diagnosed?

- Clinical evaluation - patient presents with symptoms – weakness, fatigue, developmental delay etc.
- Family history
- Incidental findings (abnormal lab values)
- Screening procedures:
  - Prenatal screening
  - Newborn screening
  - Screening for a carrier status
  - Screening biomarkers when individuals are at risk

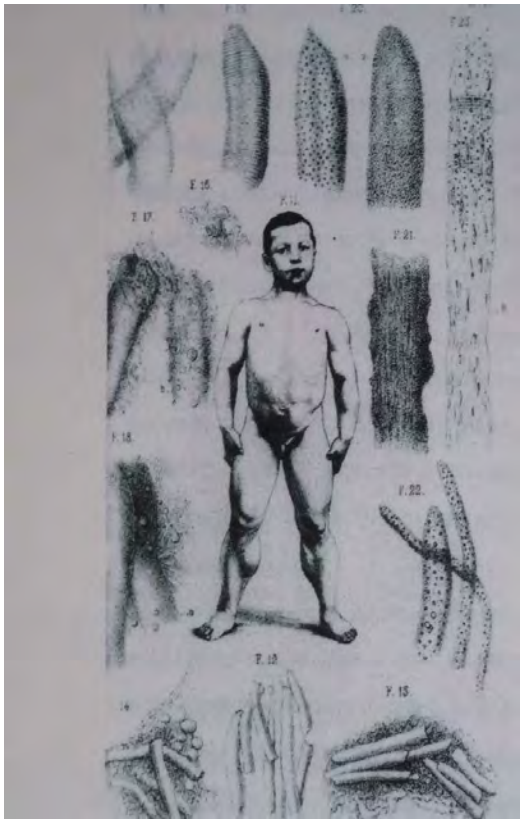
Pattern recognition -Phenotypic classification of common muscle disorders



Ancillary testing – electromyography, muscle and nerve imaging - MRI and ultrasound, measurement of biomarkers, such as CK level.

Duchenne Muscular Dystrophy

Guilliame Benjamin Amand Duchenne de Boulogne



- The French neurologist described progressive muscular atrophy with degeneration in 1858.
- Described key clinical features and pathological findings in “Pseudo-hypertrophic muscular paralysis” in 1868

Archiv für Psychiatrie und Zeitschrift Neurologie, Bd. 193, S. 427—448 (1955).

Eine neue x-chromosomale Muskeldystrophie.

Von
P. E. Becker und F. Kiener.

Mit 8 Textabbildungen.

(Eingegangen am 22. März 1955.)

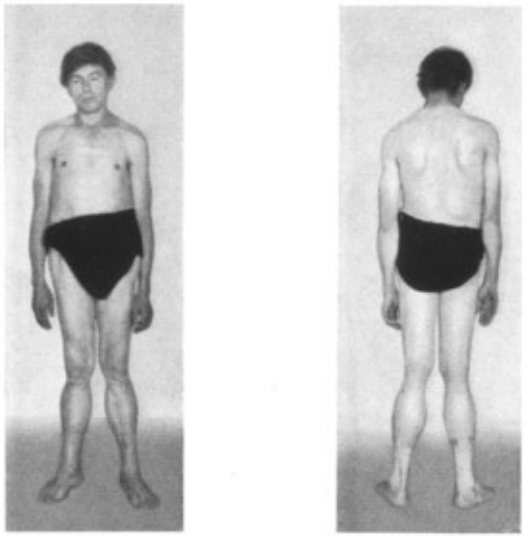
Die Dystrophia musculorum progressiva (Erb) ist heterogen. Bisher sind 3 verschiedene Arten von Muskeldystrophie bekannt, von denen die eine dominant autosomal, die andere recessiv autosomal und die dritte recessiv x-chromosomal erblich ist*. Die Klinik der 3 Arten ist verschieden hinsichtlich des Erkrankungsalters, der Lokalisation des dystrophischen Prozesses im Beginn, der Dauer des Verlaufs, des Ausprägungsgrades und des Vorliegens von Pseudohypertrophie. Sie unterscheiden sich außerdem im Vorkommen oder Fehlen von Knochen- und Fettdystrophie. Die klinischen Unterschiede waren in den vergangenen 70 Jahren bei der Benennung von „Unterformen" maßgebend. Diese Versuche einer Einteilung nach klinischen Symptomen haben heute, nachdem die Genetik der Muskeldystrophien weitgehend geklärt ist, nur noch historisches Interesse.

Die bisher bekannten Arten der Dystrophia musculorum progressiva.

Bei der dominanten autosomalen Art[1, 2, 3, 16] beginnt das Leiden zwischen dem 7. und 27. Lebensjahr, ein früheres oder späteres Erkrankungsalter ist sehr selten. Die Schultergürtel- oder die Gesichtsmuskulatur ist zuerst betroffen und der dystrophische Prozeß ergreift, wenn die Krankheit fortschreitet, die Arm-, Rumpf-, Beckengürtel- und Beinmuskulatur, wobei bestimmte Muskeln bevorzugt sind. Nicht selten ist die Muskeldystrophie asymmetrisch ausgeprägt. Pseudohypertrophie kommt vor. Der Verlauf ist, verglichen mit dem der anderen Arten, langsam und gutartig; langdauernde Stillstände werden häufig beobachtet, und die Kranken werden relativ selten gehunfähig. Viele sind bis ins späte Alter berufsfähig, und die Lebenserwartung ist durch das Leiden nicht erheblich herabgesetzt. Die durchschnittliche Kinderzahl der Kranken bleibt nur wenig hinter der der Bevölkerung zurück[4].

Bei der recessiven autosomalen Muskeldystrophie[1, 2, 3, 12] beginnt das Leiden zwischen dem 2. und 40. Lebensjahr; späteres Erkranken ist sehr

* Die periphere Form (Batten, Gowers), die neuerdings von Welander ausführlich beschrieben ist und die oculäre Form (Kiloh und Nevin) sollen hier außer Betracht bleiben.



a *b*

Abb. 3a und b. Kranker Nr. 11 aus der Oberpfälzer Sippe.

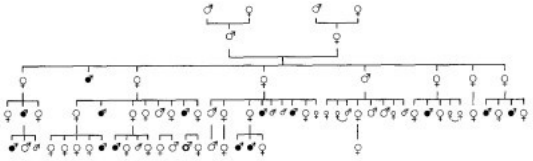


Abb. 4. Bonner Sippe (nach Derix).

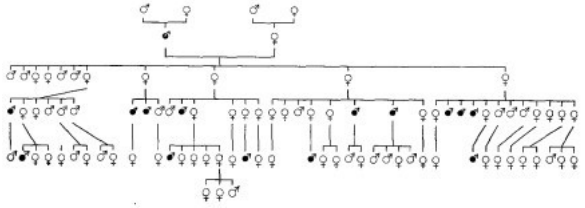


Abb. 5. Weseler Sippe (nach Gummersbach).

Family history

Pros:

- Patients can get early diagnosis
- Genetic counseling and family planning can result early diagnosis of a carrier status can prevent disease or lead to prenatal diagnosis.
- Severely affected individual can trigger diagnostic work up in other family members.

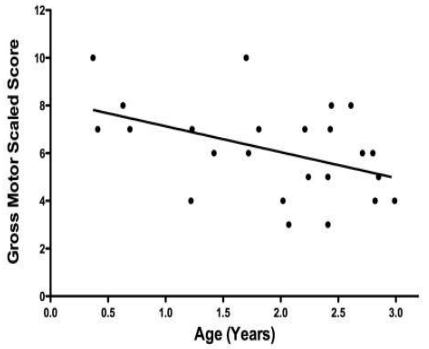
Cons:

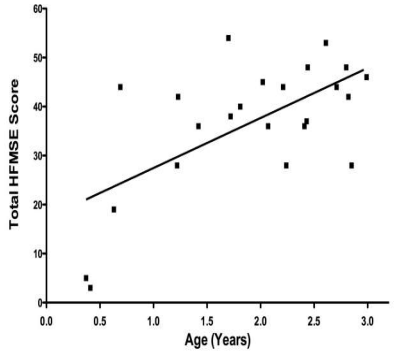
- Not all genetic disorders have family history, often presents in one individual in the family
- Only helpful for a fraction of patients.

Developmental delay - early symptoms of DMD

There is no good evidence about of motor and cognitive function in boys <5 years old.

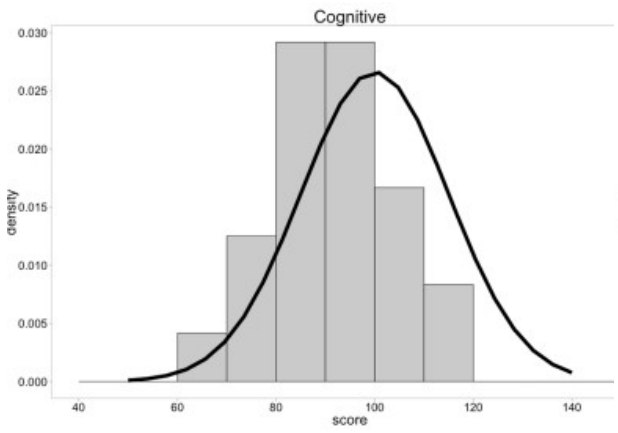
- Participants 24 boys - 1 m – 3 years old
- Family history – 13 , Incidental (CK level) – 3 and NBS – 3, other – 8
- Tools of assessment do not require cooperation:
  - Bayley III,
  - Hammersmith Functional motor,
  - North Star Ambulatory Assessment.

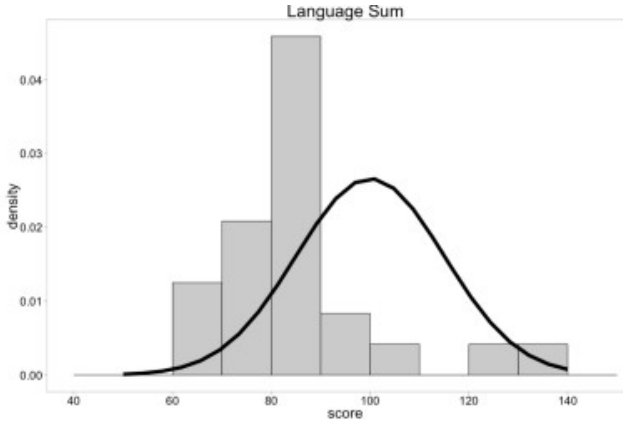


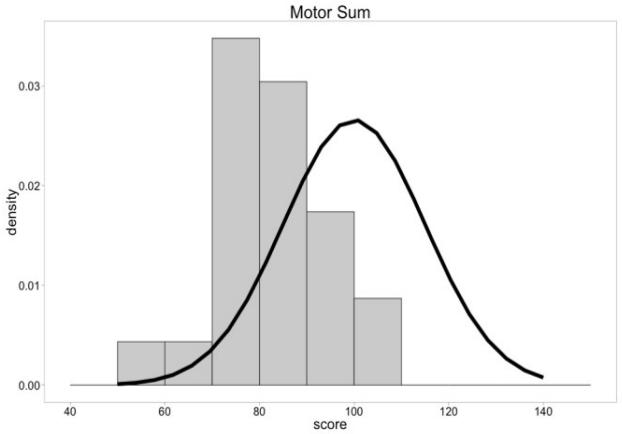


Motor and Cognitive Assessment of Infants and Young Boys with Duchenne Muscular Dystrophy; Results from the Muscular Dystrophy Association DMD Clinical Research Network. A. Connolly et al. Neuromuscul Disord. 2013

Developmental delay - early symptoms of DMD







Motor and Cognitive Assessment of Infants and Young Boys with Duchenne Muscular Dystrophy; Results from the Muscular Dystrophy Association DMD Clinical Research Network. A. Connolly et al. Neuromuscul Disord. 2013

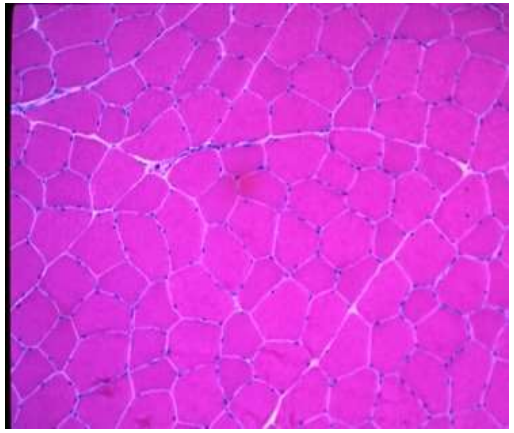
Table 1 Overview of the diagnostic pathway in Duchenne muscular dystrophy (DMD) for boys diagnosed in Newcastle

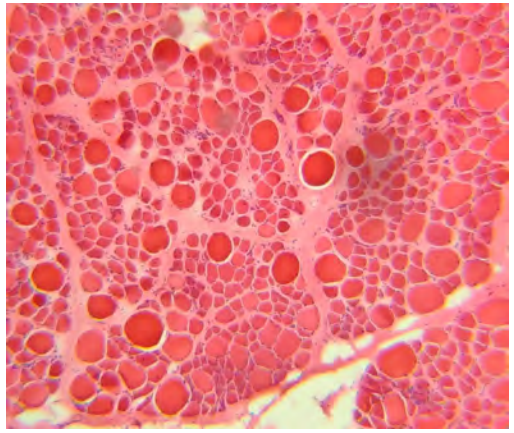
(n=20)	First symptoms	First presentation to a health professional	CK test	Diagnosis DMD
Mean age in months (years)	32.5 (2.7)	42.9 (3.6)	50.1 (4.2)	51.7 (4.3)
Range in months	8–72	10–90	14–91	10–91

Mean age (in months and years) at each step in the pathway for boys with DMD without a family history of the condition.
CK, creatine kinase.

van Ruiten HJA, et al. Arch Dis Child 2014;99:1074–1077

Healthy control

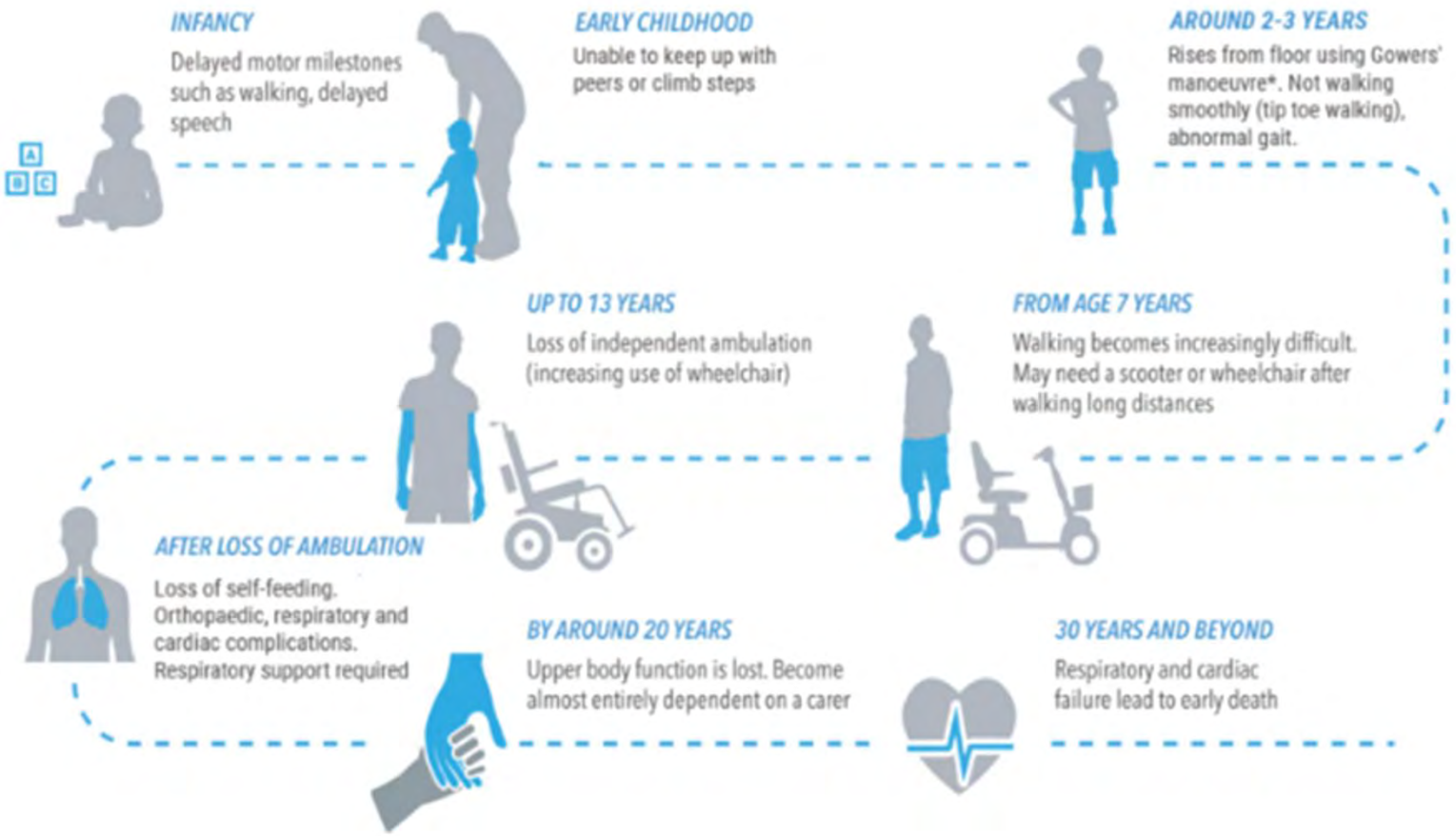




3 yo DMD patient

Majority of newborns with DMD mutation had CK level 2,000

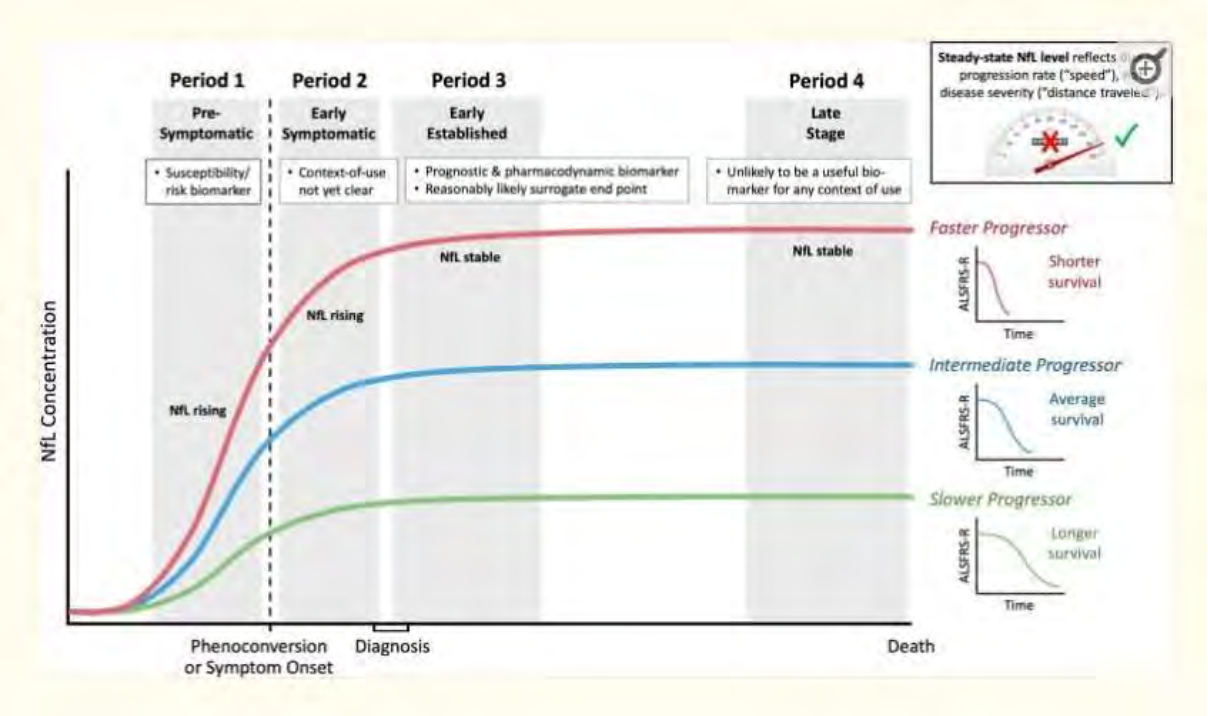
J.Mendell. Ann. Neurol. 2012



https://duchenneandyou.eu

Biomarkers in early diagnosis

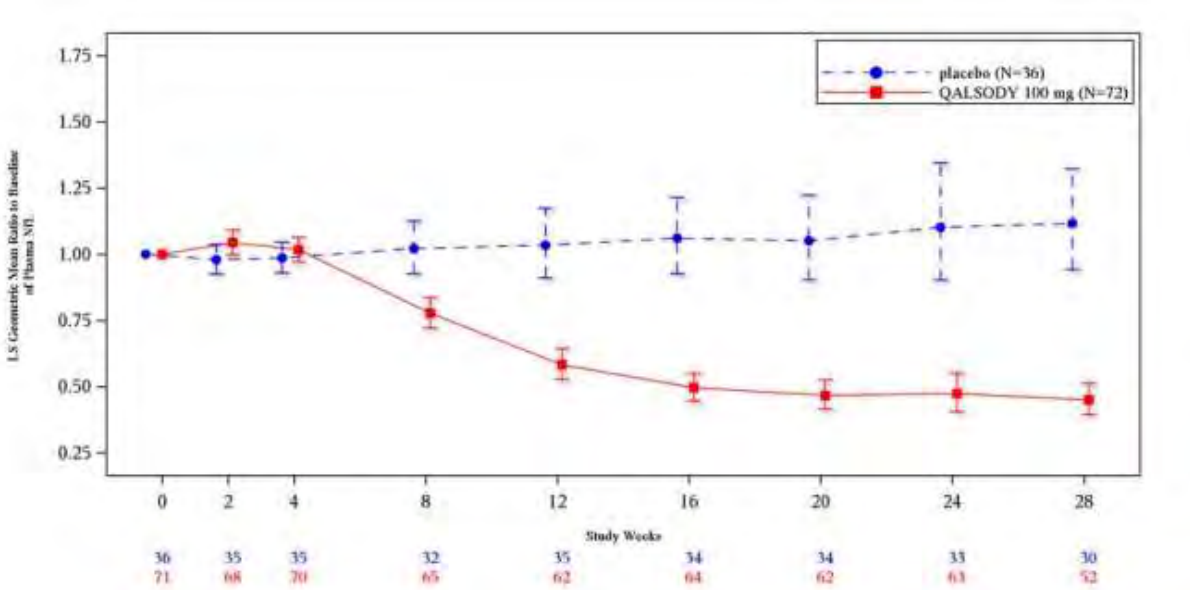
Neurofilament light chain and ALS



Neurofilament light chain in drug development for amyotrophic lateral sclerosis: a critical appraisal
Michael Benatar et al. Brain. 2023 Jul; 146(7): 2711–2716.

Making the MD Community Stronger!

Clinical trial to prevent or delay onset of ALS

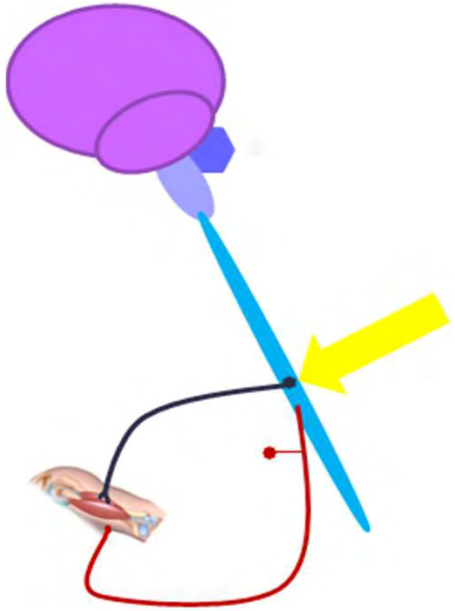


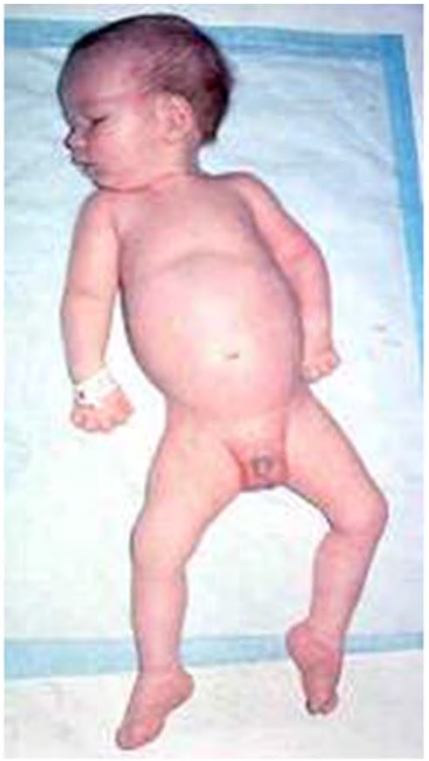
- 2% of ALS patient have SOD1 mutation
- Increasing levels of Nfl associated with conversion from asymptomatic phase to symptomatic
- Onset of symptoms begins within 6-12 months of elevated Nfl
- Clinical trial is designed to start treatment with Tofersen before onset of symptoms of ALS

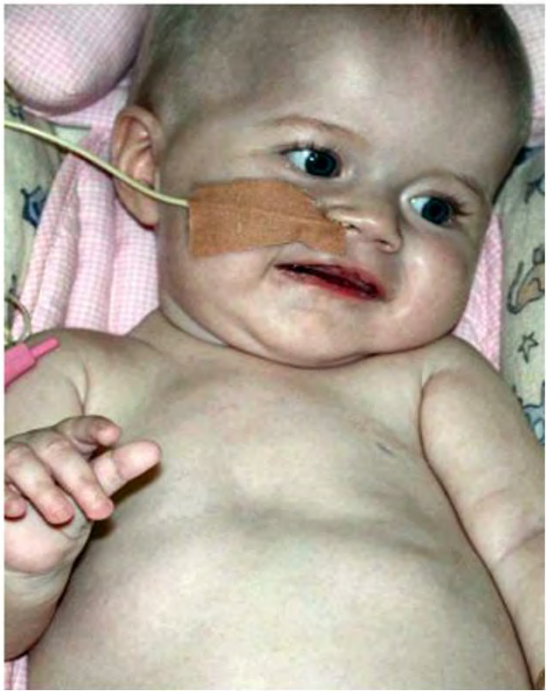
Screening approaches

- Newborn screening
- Parental screening
- Prenatal screening
- Familial screening
- Biomarker screening – Nfl, CK, others

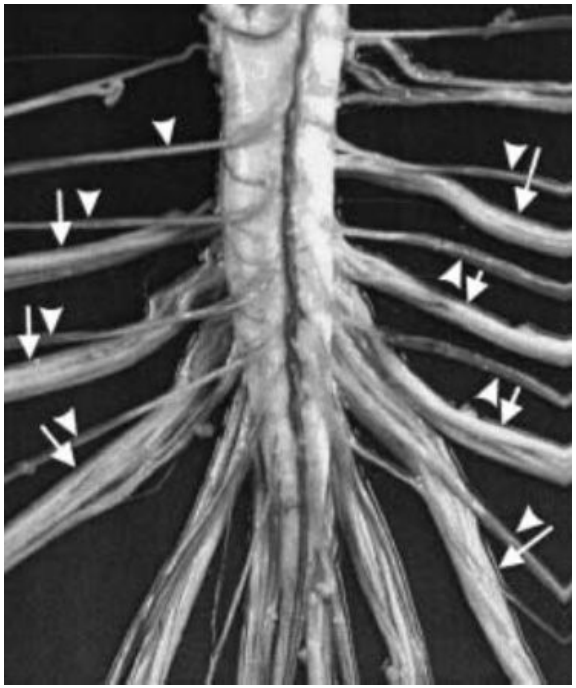
Spinal muscular atrophy

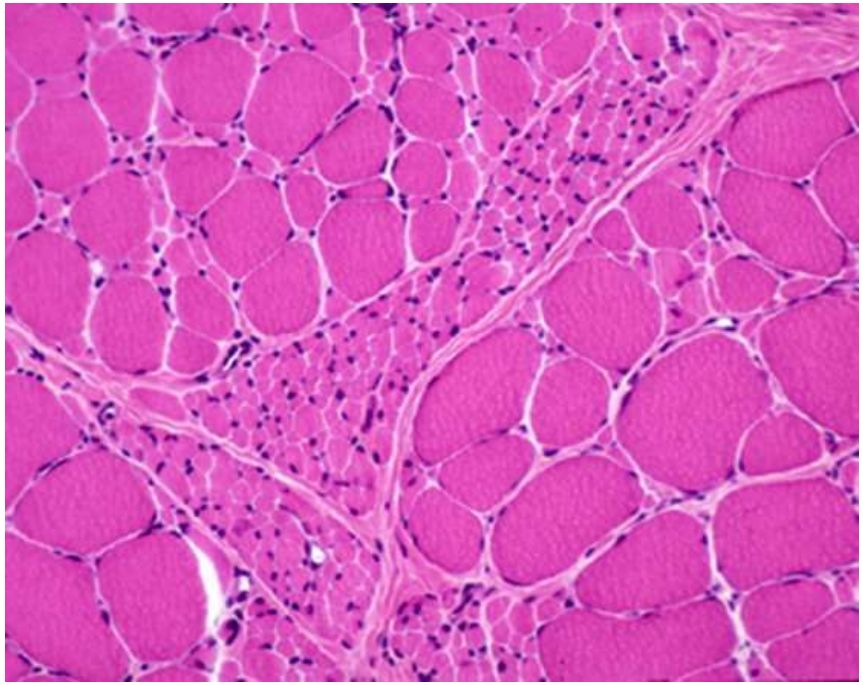






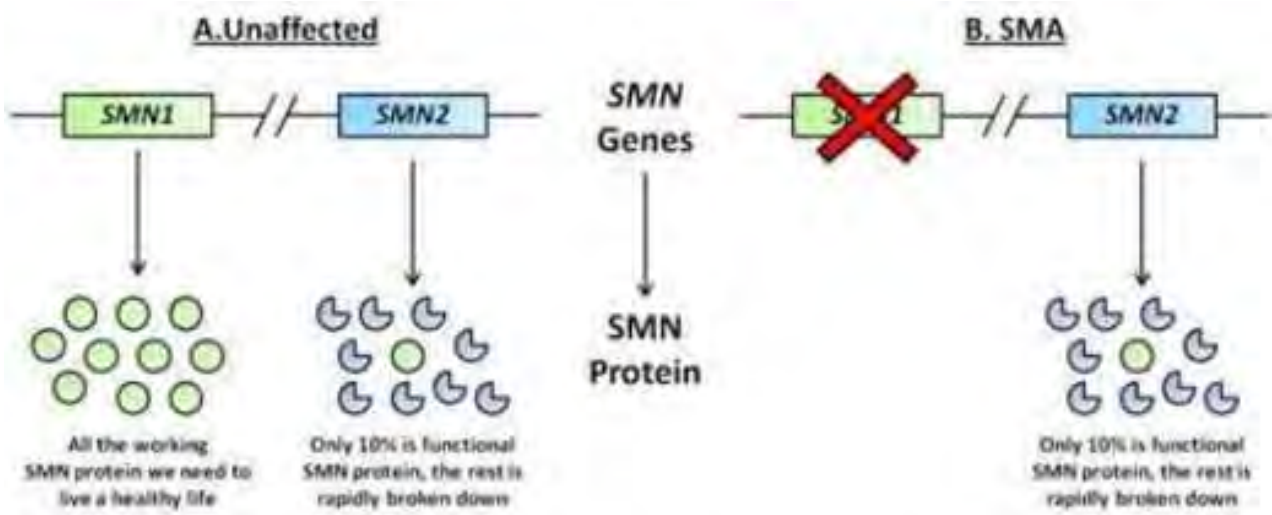
Disease process





Background

- The incidence 1:10,000
- SMN gene presents in 2 copies on each chromosome (SMN1 and SMN 2)
- Most patient have at least one copy of SMN2 gene
- > 2 SMN2 gene copies reduce severity
- Leading genetic cause of infant mortality before 2016
- Early diagnosis and novel disease modifying treatments changed outlook for patients with SMA



Spectrum of severity of SMA

SMA type		Clinical description
PS	Unknown	Presymptomatic identified at birth via newborn screening or prenatal screening
1	0/1a	Congenital onset with onset of symptoms at birth
	1b	Onset of symptoms within 3 months of life
	1c	Onset of symptoms after 3 months of life, able to control head but never achieve sitting
2	2a	Able to achieve sitting but never standing
	2b	Able to achieve sitting, able to stand up but never walk
3	3a	Onset before age 3 yo, short-term walkers
	3b	Onset after age of 3 yo, long-term walker
	4	Ambulatory with onset of weakness in adulthood

Modified from Ivon Cusc´o et al. Neurol Genet2020;6:e530

Newborn Screening

Newborn screening is a public health program in the United States that aims to identify newborns with certain serious and life-threatening genetic diseases that can be treated, and for which earlier treatment may contribute to better outcomes.

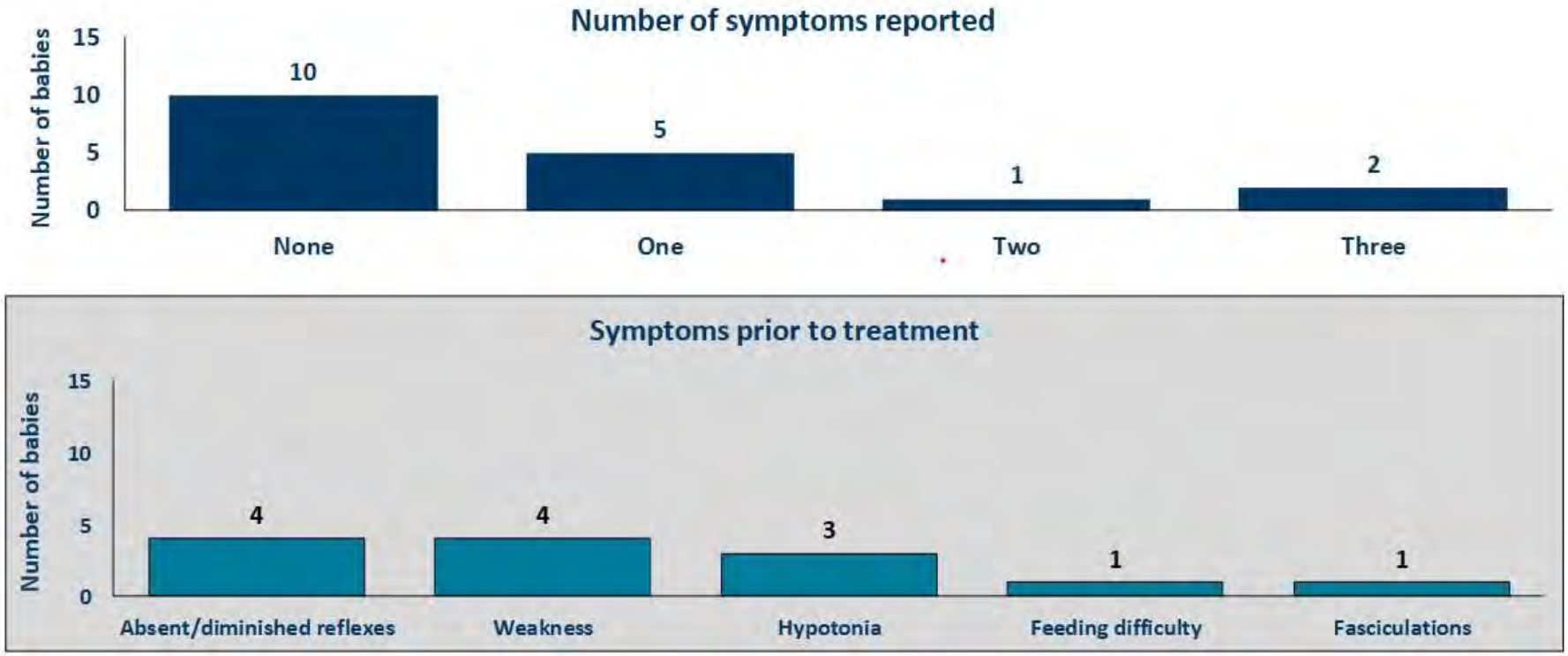
- Started in 1960s (1964 in Minnesota)
- The first newborn screening test in the United States was developed to detect phenylketonuria, a biochemical genetic disorder.
- NBS program screens >60 disorders
- Two neuromuscular disorders – Pompe and SMA
- Newborn screening for SMA began on March 1st , 2018
- As of 2023 99% of infants born in the United States are screened for SMA

Screening for SMA 100% specific Results from Minnesota program

Year	Newborns screened	True Positive	False Positive
2018	55,833	8	0
2019	64,811	6	0
2020	62,338	4	0
2021	63,162	6	0
Total	246,144	24	0

Incidence of SMA - 1 per 10,256 newborns

Most newborns are asymptomatic when diagnosed at birth.



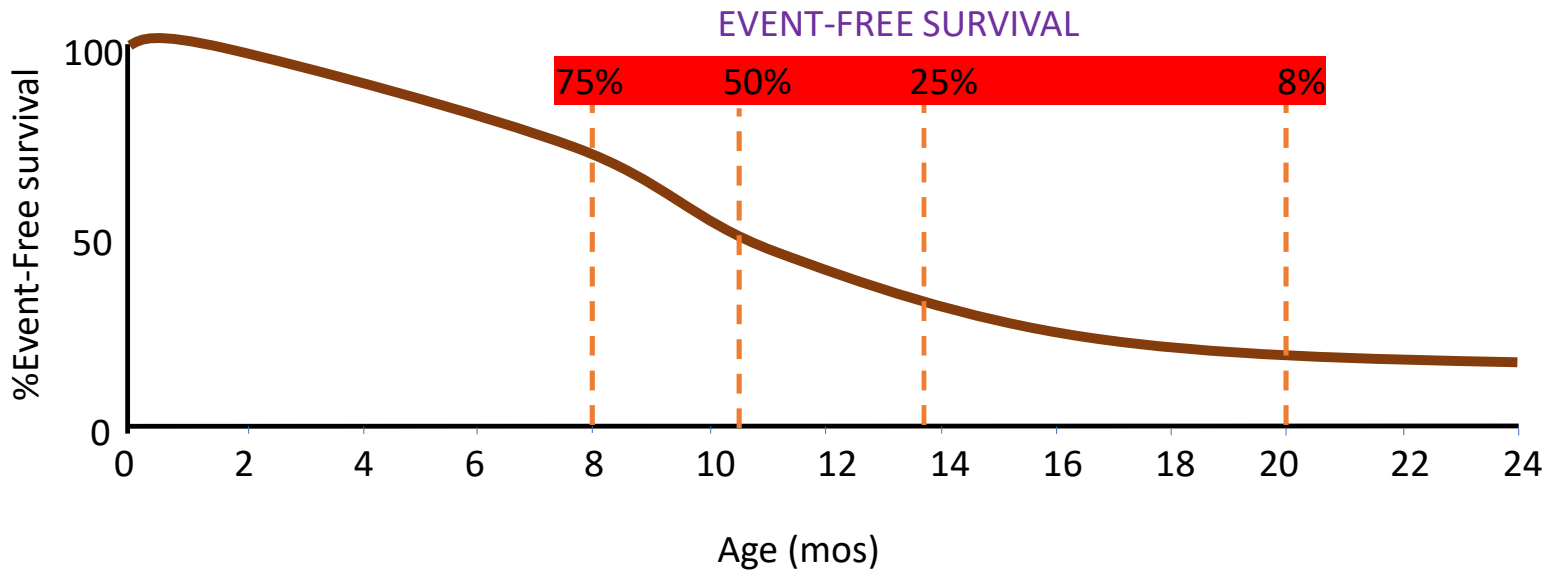
Disease modifying treatment for SMA

- Nusinersen – spinal injections
  - Given every 4 months
  - Very safe, but side effects are common from procedure
- Onasemnogene amoparvovec - gene transfer therapy
  - Children 0-2 years old
  - Single infusion
  - Clinical monitoring following infusion
  - Safety concerns
- Risdiplam – oral medication
  - Once a day
  - Generally safe but there some GI side effects

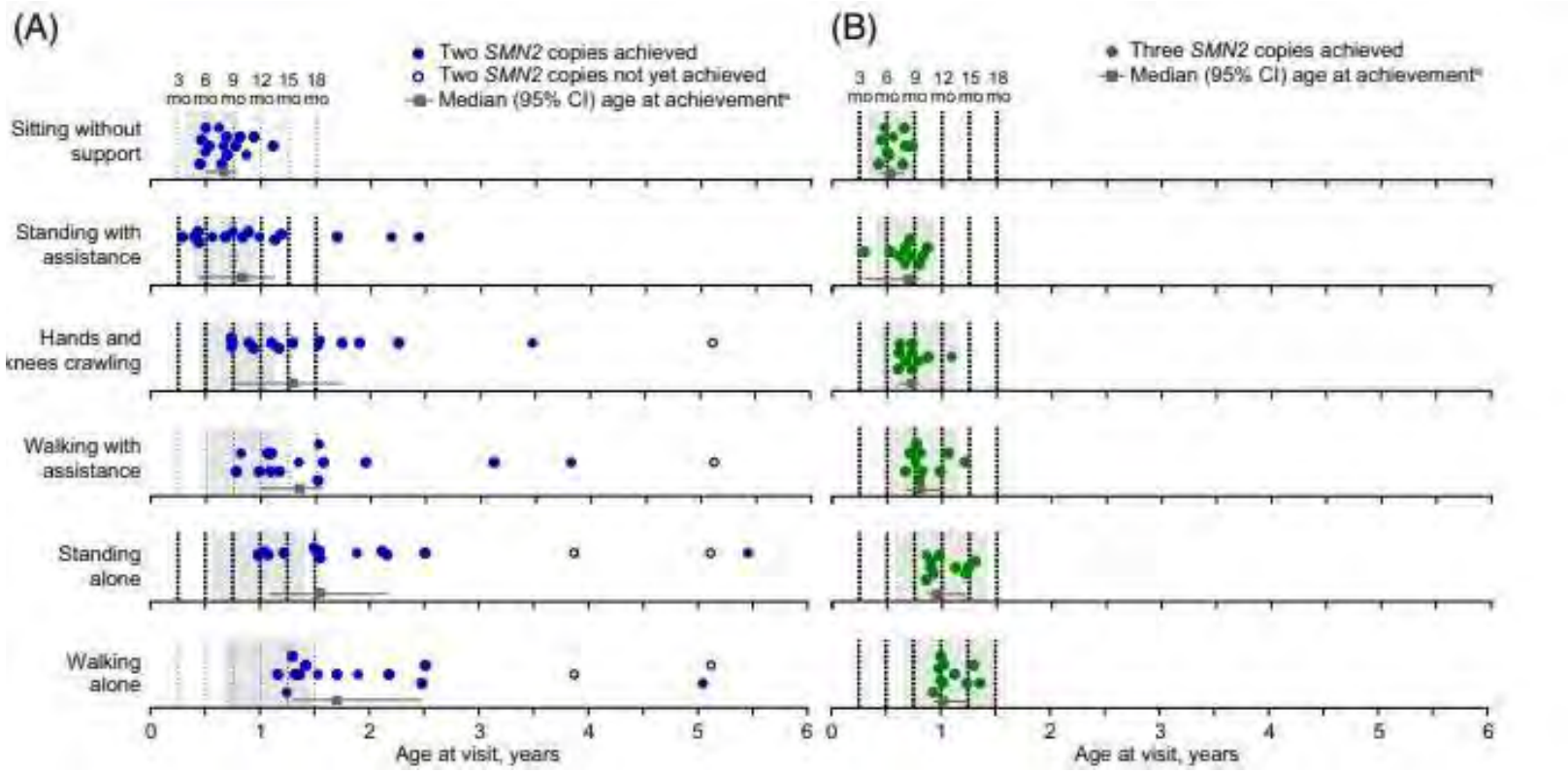
There were no comparative studies to understand which treatment is better

Discussions about concurrent combination therapy, but no specific guidelines as no clinical trials done to answer this question.

Event-Free Survival of SMA type 1 patients with 2 copies of SMN2 gene

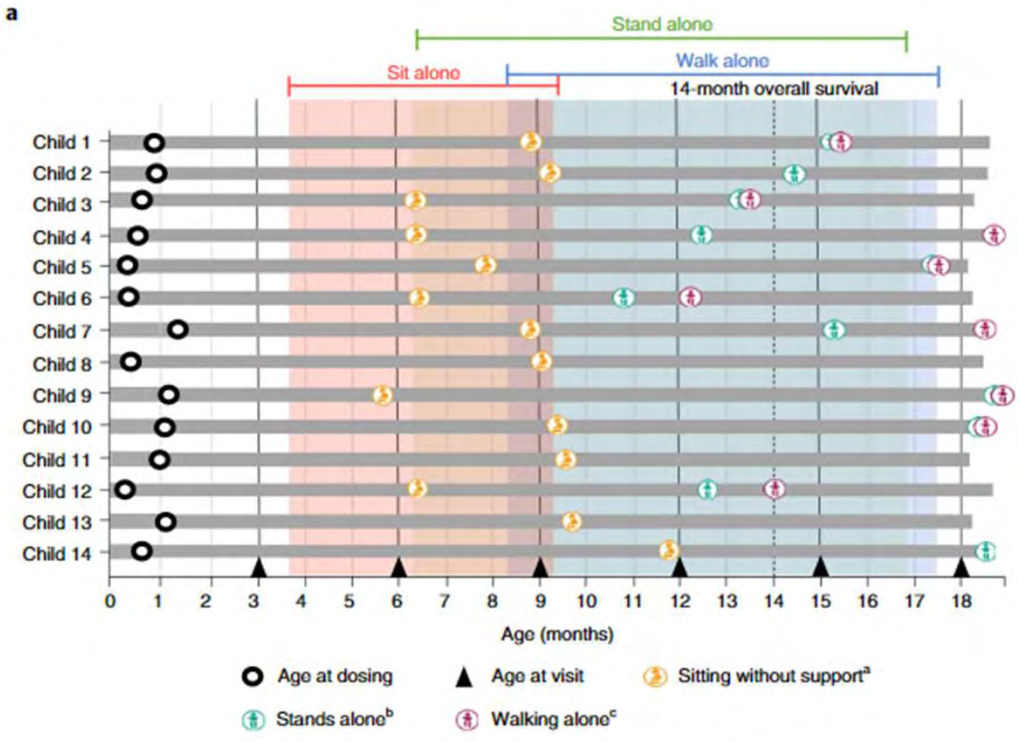


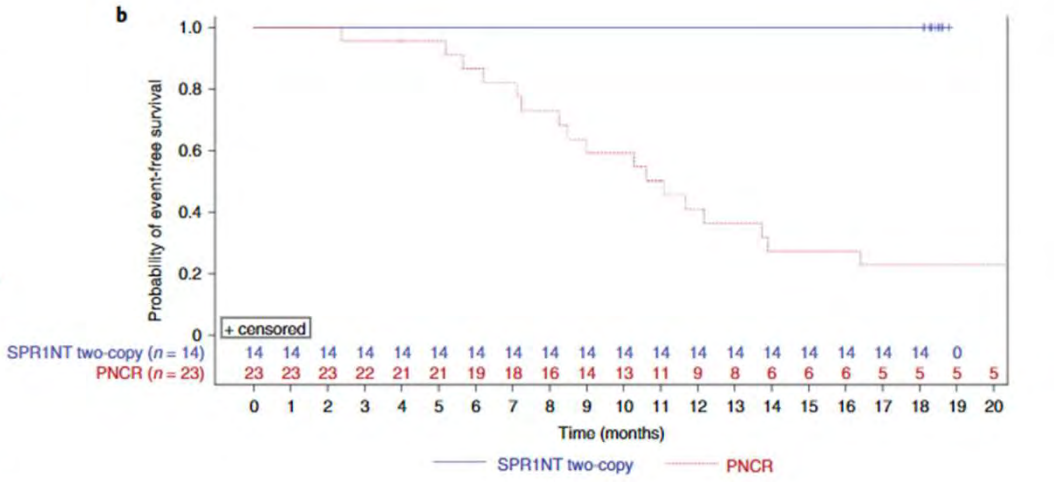
Five year follow up presymptomatic patients on treatment with Nusinersen (Nurture study)



T. Crawford et al. Muscle & Nerve. 2023;68:157–170.

Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial





K.A. Strauss et al. Nature Medicine vol 28, 2022,1381–1389

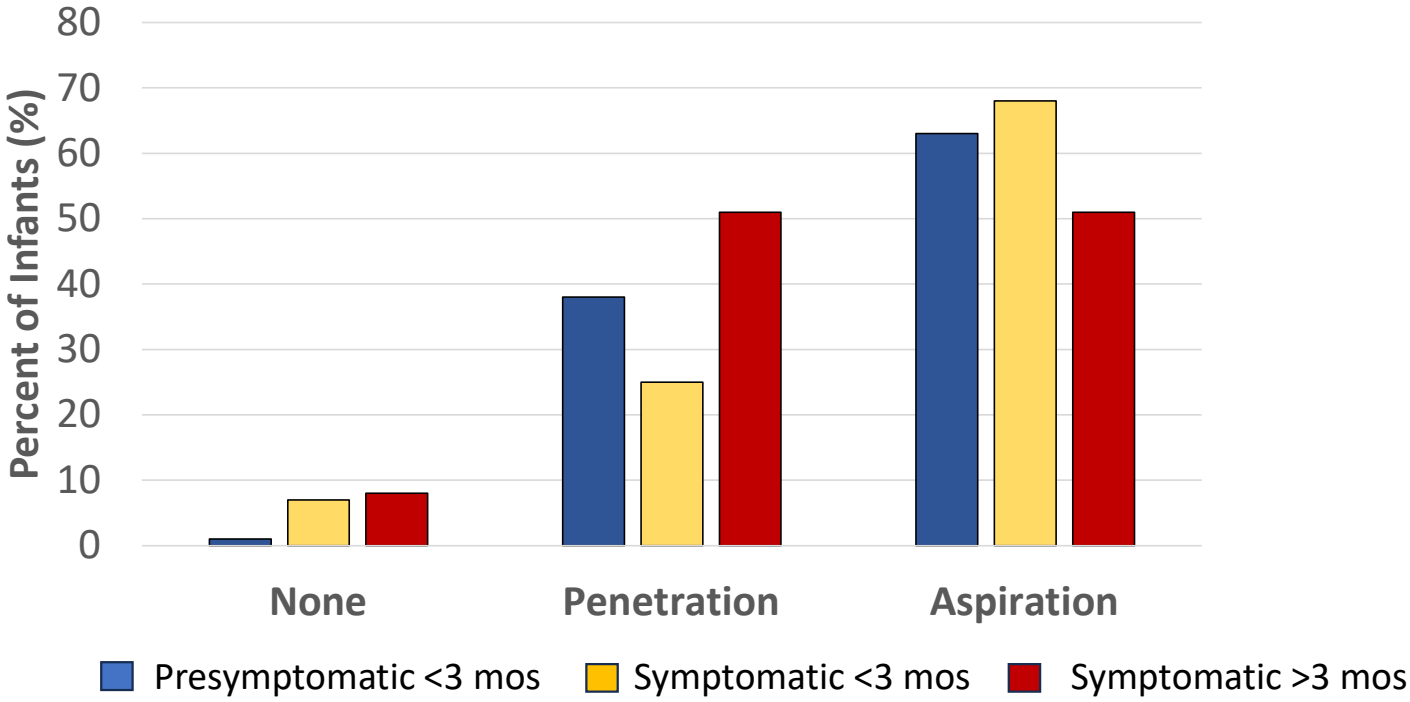
Wilson and Jungner criteria for screening

- Established natural history marked by significant burden of suffering and detectable preclinical phase
- Target population is clearly defined, including optimal timing of treatment
- Positive screening result triggers a consensus plan of action that includes a confirmatory testing algorithm, beneficial intervention with acceptable risk, and follow-up plan
- Screening platform is robust, reproducible, and affordable at a population scale.

Patient with 2 copies of SMN2

Siblings with 3 copies of SMN2

New understanding of swallow function in SMA type 1



- Early treatment does not make swallow better but prevents worsening
- Even presymptomatic patients have a swallow dysfunction but better outcomes

Katlyn McGrattan PhD et al.

Benefits of early diagnosis

- Early treatment
  - Disease modifying- leads to better outcomes
  - Symptomatic – improvement in quality of life
- Elimination of diagnostic odyssey
- Better understanding natural history
- Development of preclinical surrogate outcome measures biomarkers, imaging etc.
- Better understanding and discovery of pathophysiological mechanisms of the diseases

TRUNK OR TREAT OPEN HOUSE

Paul & Sheila Wellstone
Muscular Dystrophy Center

UNIVERSITY OF MINNESOTA
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Join us for a day of trick or treating with our team, labs, and partners!

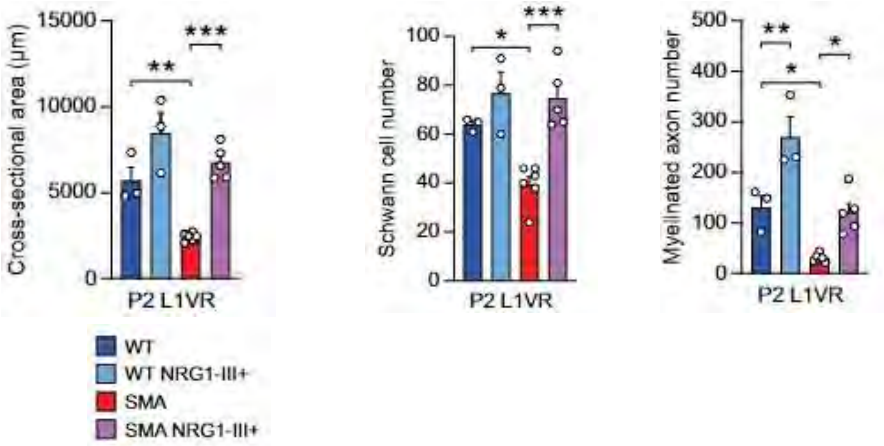
SUNDAY, OCT. 29th, 2023
10:30am-1pm
Cancer and Cardiovascular Research Building:
2231 6th St SE, Minneapolis, MN 55455

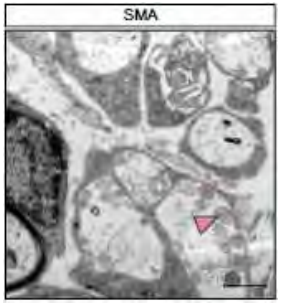
Lunch provided: Please RSVP to Jenny at marz0031@umn.edu
The building conference room is reserved for adult support group networking & conversation

www.mdcenter.umn.edu

Delayed nerve myelination in SMA type 1

- Intercellular communication between axons and Schwann cells is critical for attaining the complex morphological steps necessary for axon maturation.
- In the early onset SMA, many motor axons are not ensheathed by Schwann cells resulting in delayed myelination.
- These developmentally arrested motor axons are dysfunctional and vulnerable to rapid degeneration with possibility of limiting efficacy of current SMA therapeutics.
- Neuroregulin 1 type III is reduced in motor neurons and axons of the SMA patients





Kong et al. Acta Neuropathologica Communications (2023) 11:53

SMA patients with 4 and more copies of SMN2

University of Minnesota cohort

	Age (yo)	SMA type	Age of diagnosis/onset	Motor function	Loss of ambulation	Treatment
1	0.3	Unknown	newborn	Normal		Pending
2	1	Unknown	Newborn	Normal		Nusinersen
3	2	Unknown	Newborn	Normal		Nusinersen , gene transfer
4	**12**	**3**	**2**	**amb**		**Nusinersen**
5	**21**	**3**	**toddler**	**amb**		**Pending**
6	22	3	2nd decade	Amb		Nusinersen
7	28	3	2nd decade	amb		Nusinersen
8	**32**	**3**	**1st decade**	**Non-amb**	**12 yo**	**None**
9	33	3	2nd	Amb		None
10	**34**	**2**	**10 month**	**Non-amb**	**Not achieved**	**Nusinersen**
11	36	3	2nd	Amb		Nusinersen
12	40	3	toddler	Non-amb	5 yo	Nusinersen
13	49	3	2nd decade	Non-amb	45 yo	None- appeal for Risdiplam
14	50	3	2nd decade	Non-amb	36 yo	None
15	53	3	2nd decade	Amb		Nusinersen, Risdiplam
16	56	3	2nd decade	Non-amb	45 yo	Nusinersen, Risdiplam
17	62	3	1st decade	Non-amb	unknown	Nusinersen
18	63	3	2nd decade	Non-amb	unknown	Nusinersen
19	61	3	2nd decade	Non-amb	36 yo	None

Onset of symptoms

- **1st decade – 6 (31%)**
- 2nd decade – 13 (69%

SMA Types

- Type1 -0%
- ***Type 2 – 5%***
- Type3 – 95%