Diagnosis and Management of spinal muscular atrophy

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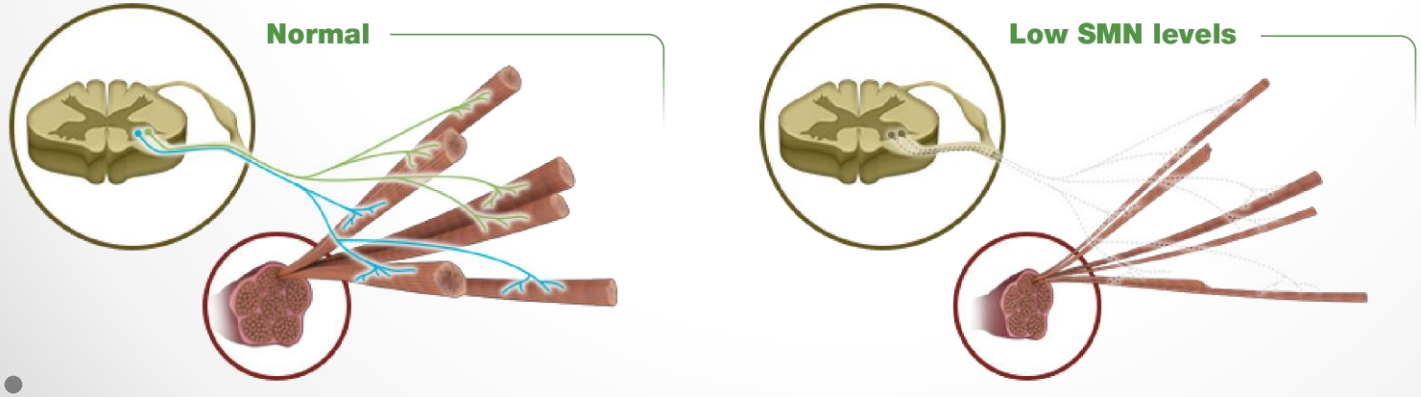
Spinal Muscular Atrophy (SMA)

- Neurodegenerative disease with degeneration of alpha motor neurons in the spinal cord resulting in progressive muscle weakness
- Homozygous deletions or mutation in exon 7 of the Survival Motor Neuron 1 (SMN1) genes located on chromosome 5q

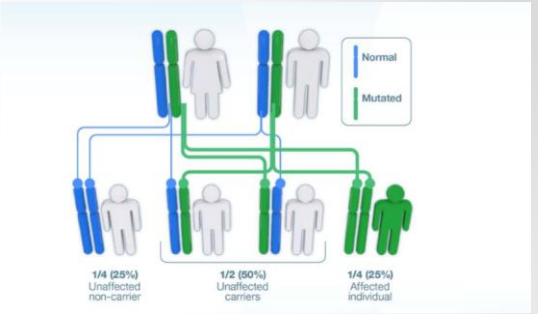
Lee et al, 2004

- Symmetric, proximal > distal, progressive, can involve brainstem motor nuclei
- The phenotypic spectrum is broad and ranges in age and severity

Lally et al, 2017



Spinal Muscular Atrophy (SMA)



- **Autosomal recessive disease**
- **1 in 6,000-10,000 live birth , with a carrier frequency of 1/40-60**
- **1/8,496, with a carrier frequency of 1/47 in Korea**

Ogino et al, 2002, Lee et al, 2004

- **SMA carrier generally has no symptoms but the faulty gene can be passed on to their children. Need for genetic counseling on inheritance**

	Adjusted carrier and disease frequencies					
	1 *SMN1* copy carriers		2 *SMN1* copies carriers		Disease Frequency	
Ethnicity	Frequency	95% CI	Frequency	95% CI	Frequency	95% CI
Asian	0.022	0.021–0.023	0.0014	0.0012–0.0015	1.3E-04	1.2E-04-1.4E-04
Asian Indian[a]	0.020	0.012–0.030	0.0021	0.0014–0.0030	1.0E-04	4.0E-05-2.4E-04
Black (Sub-Saharan ancestry)	0.014	0.011–0.018	0.0042	0.0034–0.0052	5.3E-05	3.4E-05-8.1E-05
Caucasian	0.022	0.021–0.024	0.0013	0.0011–0.0014	1.3E-04	1.1E-04-1.5E-04
Hispanic	0.014	0.011–0.017	0.0015	0.0013–0.0018	5.0E-05	3.5E-05-7.0E-05
Jewish	0.020	0.018–0.022	0.0016	0.0014–0.0018	1.0E-04	8.3E-05-1.2E-04

verhaart et al, 2017

SMA phenotypes

Phenotype	Age of onset	Life Span	Motor Milestone	Other Findings
SMA 0	Prenatal	< 6 months	None achieved	Severe neonatal hypotonia Severe weakness Early respiratory failure Facial diplegia
SMA I	<6 months	< 2 years, but may live longer	Sit w/support	Mild joint contractures Normal or minimal facial weakness Variable suck & swallow difficulties
SAM II	<6-18 months	70% alive at age 25	Independent sitting	Postural tremor of fingers
SMA III	> 18 months	Normal	Independent ambulation	
SMA IV	Adulthood	Normal	Normal	

SMA 0 (congenital SMA)

- 0SMN1/1SMN2 genotype

- Onset of symptoms occurred before birth
- Prenatal imaging may reveal fetal akinesia, increased abnormal amniotic fluid volume, congenital heart defects, joint contracture

- Cranial nerve involvement
  - severe weakness including bulbar, facial muscle
  → poor sucking, respiratory distress, external veniltation

- Prenatal demise can occur
- Life expectancy median 15 days (range 6-33 days)

Grotto et al, 2016

SMA I (infantile, Werdnig-Hoffmann disease)

- Symptom occurs after birth (differentiating from type 0)
- Weakness is invariable present by 6 months
- Progress to global hypotonia, poor head control
- Failure to sit upright without assistance
- “Frog leg posture”

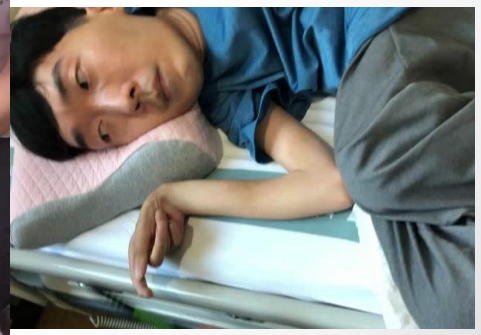
- Mismatch between more rapid progression of weakness in the intercostal muscle, diaphragm →“bell shaped” chest,
- Paradoxical breathing when accessory muscles compensates
- Sparing of the muscles served by the cranial nerves
- Median survival 13.6 months

Tizzano et al, 2017

SMA II (late-onset, Dubowitz disease)

- Approximately 32% of SMA
- First symptoms between 7 and 18 months
- Sit without support but not ambulatory
- Scoliosis is common
- Proximal > Distal, Lex. > Uex.
- Progressive respiratory muscle weakness leads to restrictive lung disease
- Median survival for was 59.9 years

Belter et al, 2017

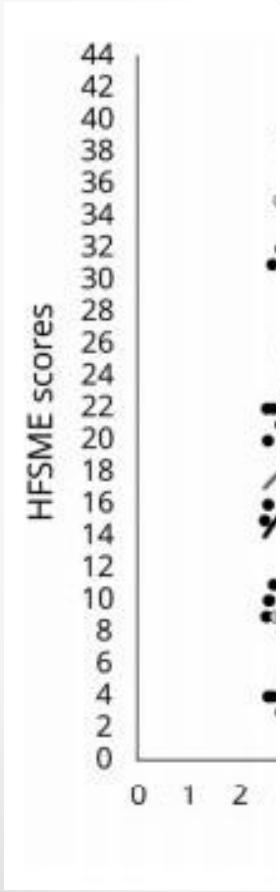


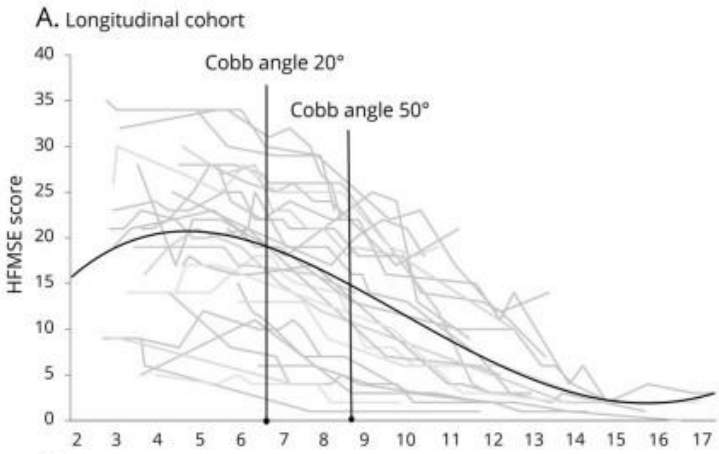
Neurology. 2019 Sep 24;93(13):e1241-e1247. doi: 10.1212/WNL.0000000000008166. Epub 2019 Aug 26.

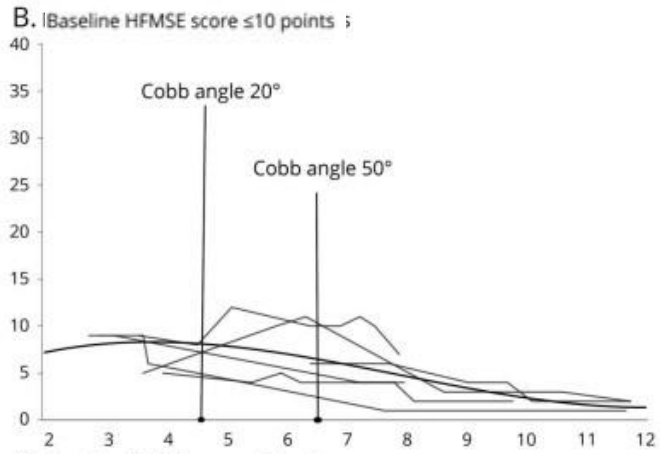
Long-term progression in type II spinal muscular atrophy: A retrospective observational study.

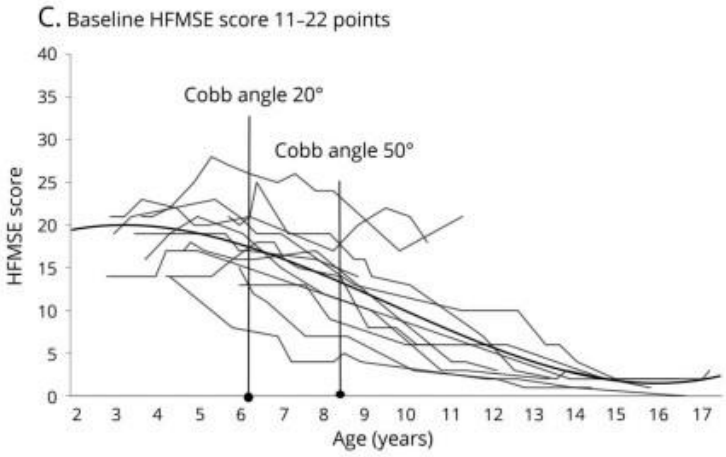
Mercuri E[1], Lucibello S[2], Pera MC[2], Carnicella S[2], Coratti G[2], de Sanctis R[2], Messina S[2], Mazzone E[2], Forcina N[2], Fanelli L[2], Norcia G[2], Antonaci L[2], Frongia AL[2], Pane M[2].

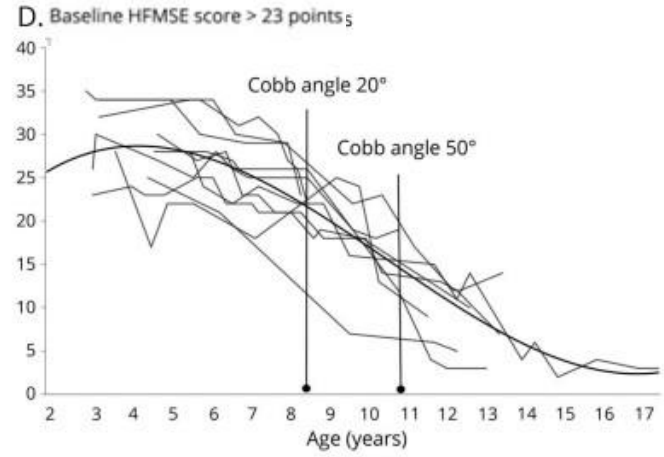
- **Total 73 patie**
- **SMN2 copy nu**
- **Mean follow u**











	A	D	C	B
Annual loss (5–13 years)	−2.15	−2.84	−2.02	−1.23
Cobb angle 20°	6.8 years	8.2 years	6.1 years	4.7 years
Cobb angle 50°	8.8 years	10.8 years	8.4 years	6.6 years
BiPAP	5/28 (53%) at 10.4 years	3/10 (30%) at 12.4 years	8/12 (66%) at 11.6 years	4/6 (66%) at 7.1 years

SMA III (Kugelberg-Welander disease)

- Typically manifest after 18 months
- Clumsy walking, new onset falling
- Scoliosis is common
- Onset before 3 years (3A) the probability of walking 10 years after 70%,
  onset after 3 years maintained (3B) nearly 60% ambulatory 40 years after onset
- Mortality before adulthood due to the sequelae is rare

Chabanon et al, 2018

Available online at www.sciencedirect.com

ScienceDirect

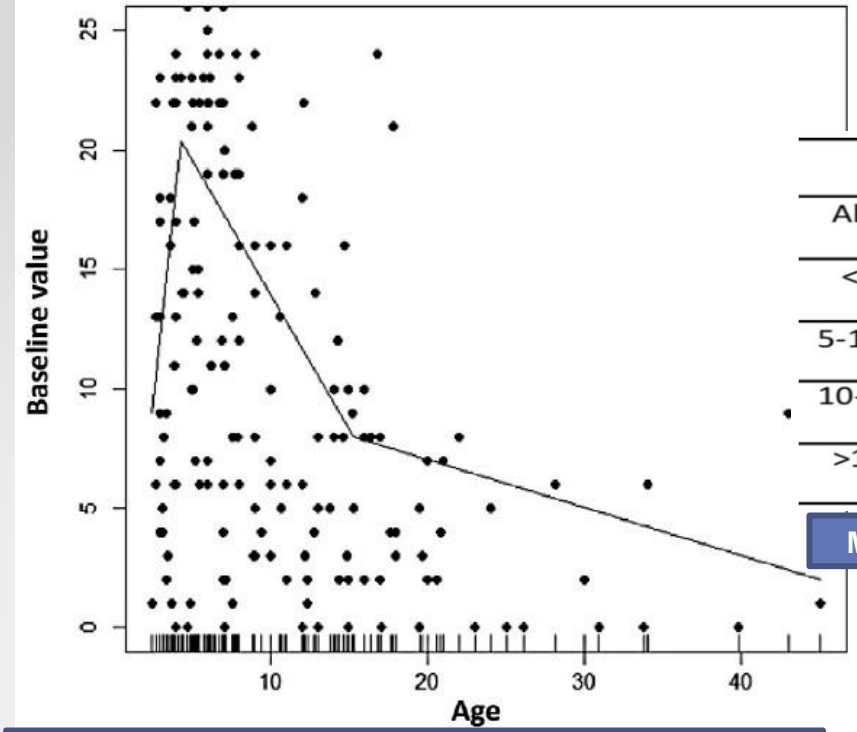
Neuromuscular Disorders 26 (2016) 126–131

www.elsevier.com/locate/nmd

Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials

Eugenio Mercuri [a,1,*], Richard Finkel [b,1], Jacqueline Montes [c], Elena S. Mazzone [a], Maria Pia Sormani [d], Marion Main [e], Danielle Ramsey [e], Anna Mayhew [f], Allan M. Glanzman [g], Sally Dunaway [c], Rachel Salazar [c], Amy Pasternak [h], Janet Quigley [h], Marika Pane [a], Maria Carmela Pera [a], Mariacristina Scoto [e], Sonia Messina [i], Maria Sframeli [i], Gian Luca Vita [i], Adele D'Amico [j], Marleen van den Hauwe [k], Serena Sivo [a], Nathalie Goemans [k], Petra Kaufmann [c], Basil T. Darras [h], Enrico Bertini [j], Francesco Muntoni [e,2], Darryl C. De Vivo [c,2]

- **Largest database with longitudinal using the same measure in SMA 2,3**
- **268 with longitudinal assessments (12 months)**
- **Age 2.5-55.5yrs at baseline (mean 10.65yrs)**
- **68 were ambulant and 200 non ambulant**



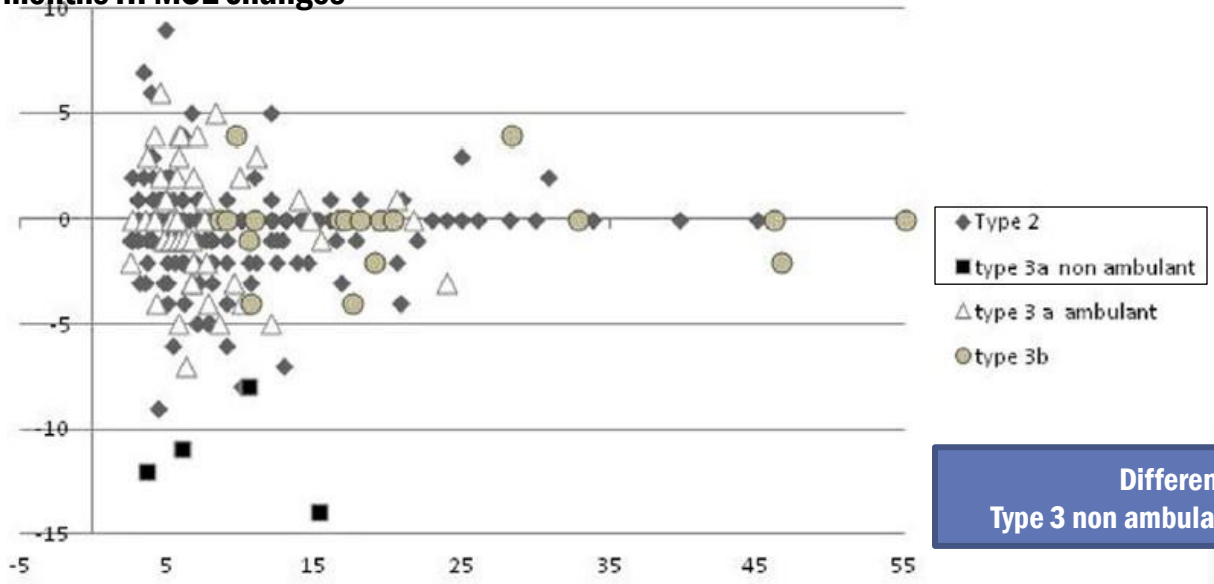
Different patterns of progression according to age

12 months HFMSE changes

	< - 2	+/- 2	> + 2
All (n=268)	41 (15.29%)	206 (76.86%)	21 (7.83%)
<5 (n=61)	6 (9.83%)	47 (77.04%)	8 (13.13%)
5-10 (n=102)	21 (20.58%)	72 (70.58%)	9 (8.84%)
10-15 (n=47)	9 (19.14%)	36 (76.59%)	2 (4.27%)
>15 (n=58)	5 (8.62%)	51 (87.93%)	2 (3.45%)

Most of negative changes occurred in patients before puberty in whole cohort

12 months HFMSE changes



Different patterns in type 2 and 3
Type 3 non ambulant had results more similar to type 2

	< - 2	+/- 2	> + 2
NON AMBULANT (n=200)	26 (13%)	164 (82%)	10 (5%)
<5 (n=49)	5 (10.20%)	[illegible]	5 (10.20%)
5-10 (n=73)	14 (19.17%)	56 (76.73%)	3 (4.10%)
10-15 (n=38)	5 (13.15%)	32 (84.21%)	1 (2.64%)
>15 (n=40)	2 (5%)	37 (92.5%)	1 (2.5%)

	< - 2	+/- 2	> + 2
AMBULANT (n=68)	15 (22.05%)	42 (61.78%)	11 (16.17%)
<5 (n=12)	1 (8.3%)	8 (66.70%)	3 (25%)
5-10 (n=29)	7 (24.14%)	[illegible]	6 (20.69%)
10-15 (n=9)	4 (44.44%)	4 (44.44%)	1 (11.12%)
>15 (n=18)	3 (16.66%)	14 (77.77%)	1 (5.57%)

Positive changes in ambulant occur at 5 to 10 yrs, later than in non ambulant

	< - 2	+/- 2	> + 2
NON AMBULANT (n=200)	26 (13%)	164 (82%)	10 (5%)
<5 (n=49)	5 (10.20%)	39 (79.6%)	5 (10.20%)
5-10 (n=73)	14 (19.17%)	56	3 (4.10%)
10-15 (n=38)	5 (13.15%)	32 (84.21%)	1 (2.64%)
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Most negative changes in ambulant patients occur at 10 to 15 yrs, later than in non ambulant

Patterns of disease progression in type II,III

- Variable progression of the disease
- Ambulant and non ambulant patients have different trajectories
- Age effect different in the two groups

- In non ambulant patients
  - Some improvement cane be observed in younger children (below 5yr)
  - Faster decline more frequent from of 5

- In ambulant patients
  - Improvement can also be noted after the age or 5
  - More marked decline is observed art the time of reaching puberty

SMA IV (late adolescence/adulthood)

- Onset age: 18-21 years
- Less than 1% of all identified cases
- Physical symptoms are similar to type III
- Proximal limb mild weakness and fatiguability
- Mortality has not been reported

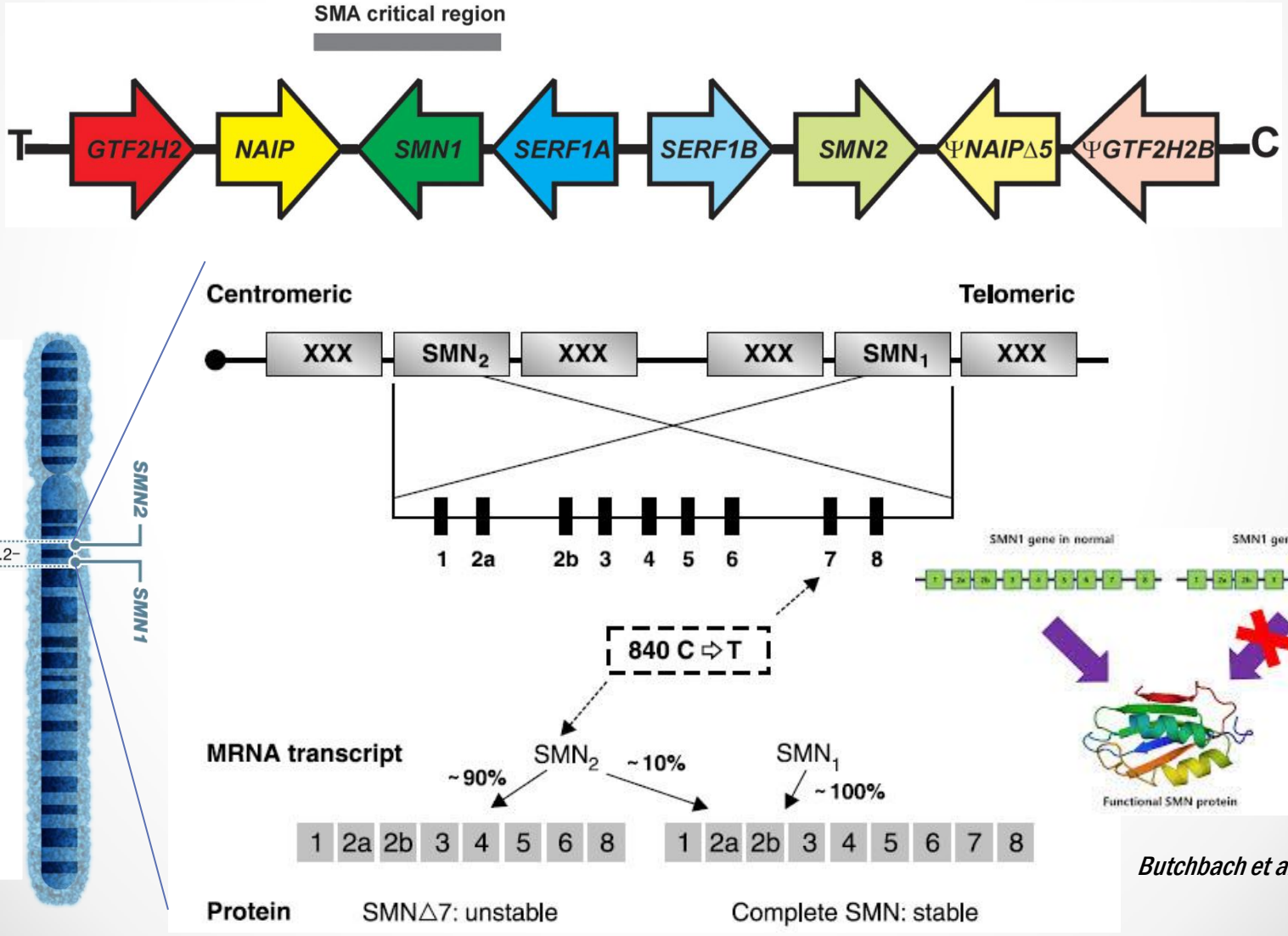
Wadman et al, 2018

Rev Neurol (Paris). 2017 May;173(5):308-319. doi: 10.1016/j.neurol.2017.03.015. Epub 2017 Apr 26.

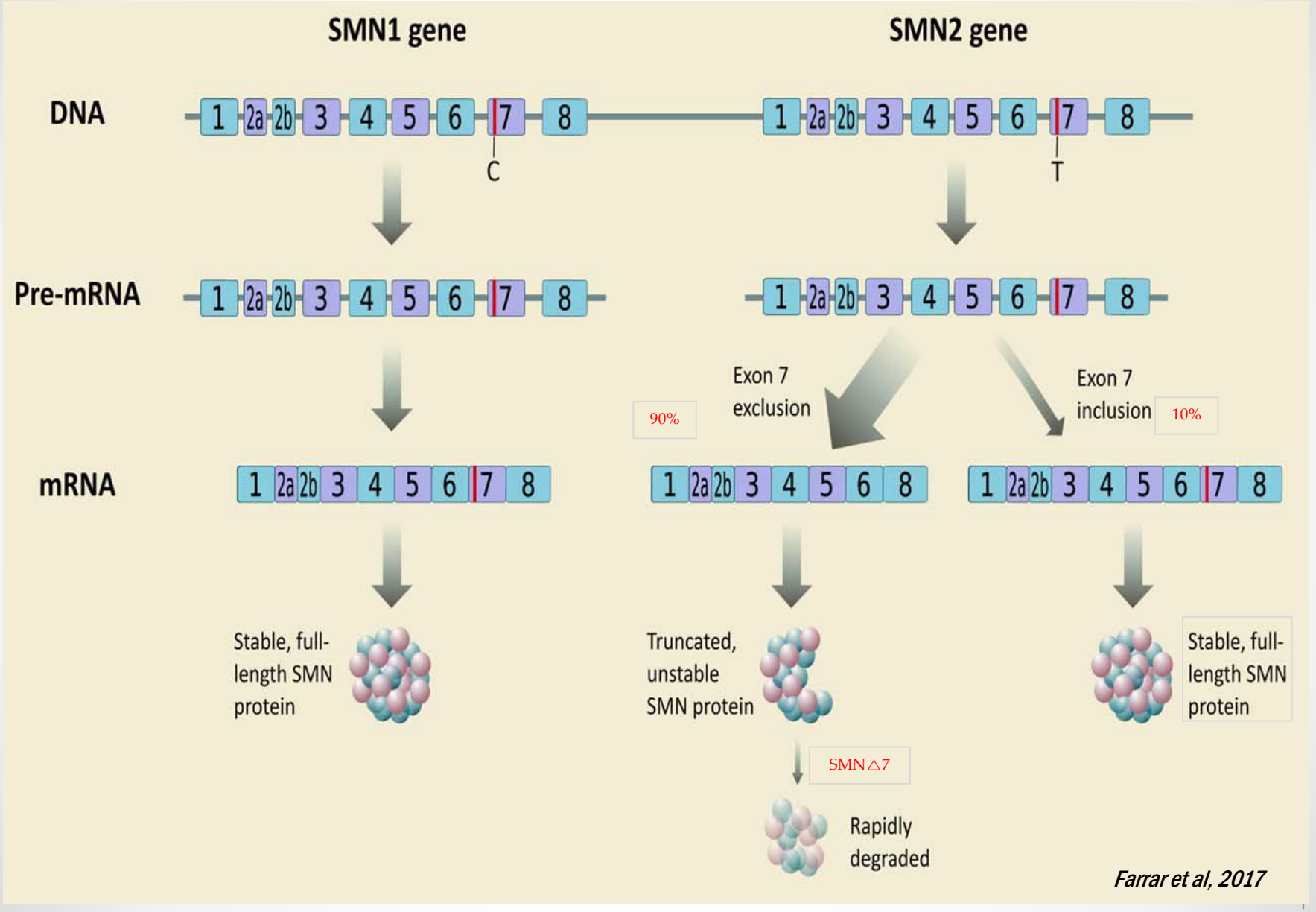
Adult-onset spinal muscular atrophy: An update.

- Triceps(lower cervical) >> Biceps
- Iliopsoas(upper lumbar) >> gluteus maximus
- Quadriceps femoris (upper lumbar) severely involved
- Ds. Duration was significantly correlated with glut max and triceps

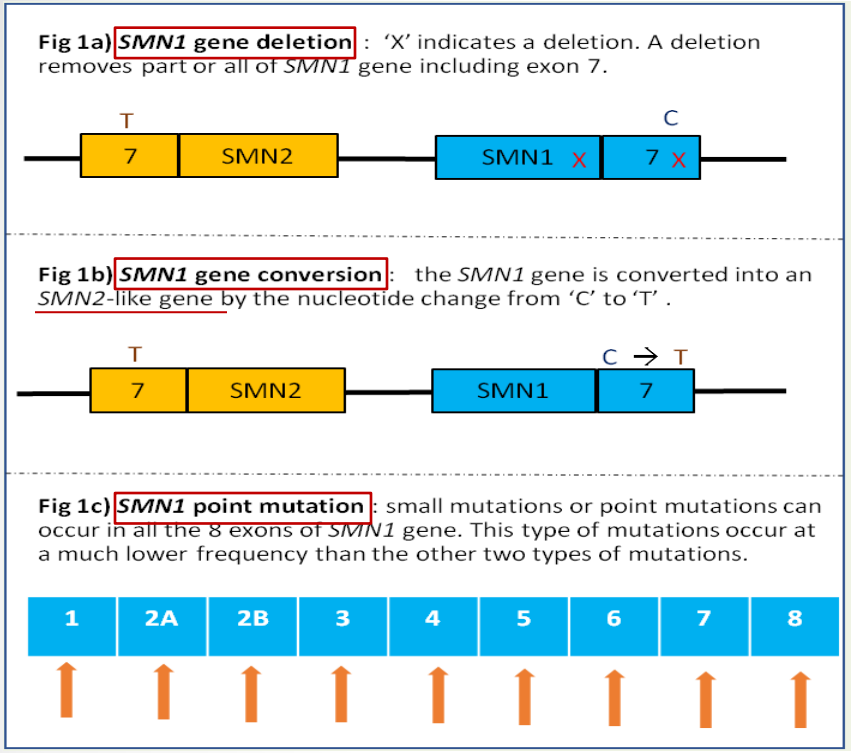
Structure of the SMN gene in chromosome 5

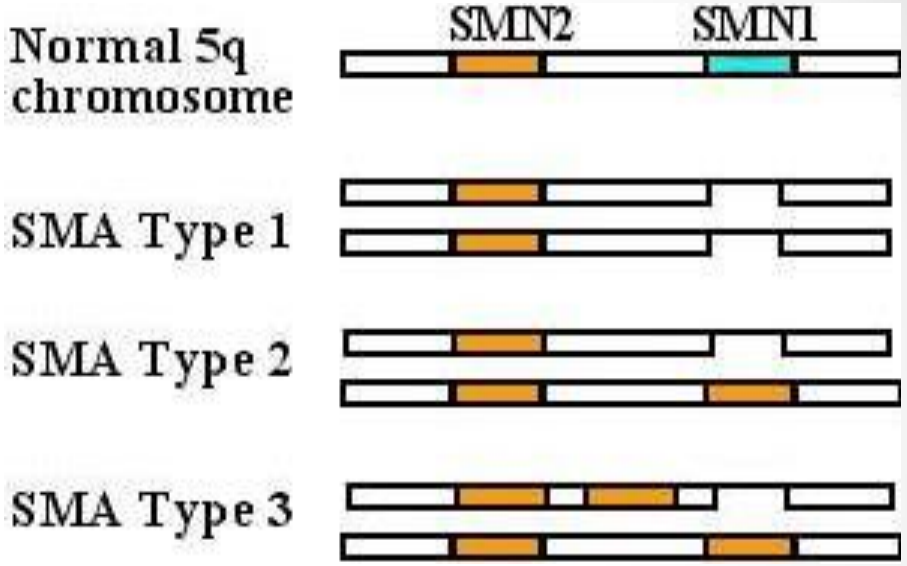


Butchbach et al, 2016


SMN1 gene
SMN2 gene
DNA
1 2a 2b 3 4 5 6 7 8
C
T
Pre-mRNA
Exon 7 exclusion
90%
Exon 7 inclusion
10%
mRNA
Stable, full-length SMN protein
Truncated, unstable SMN protein
SMN△7
Rapidly degraded
Stable, full-length SMN protein
Farrar et al, 2017

Typical SMN mutation in SMA





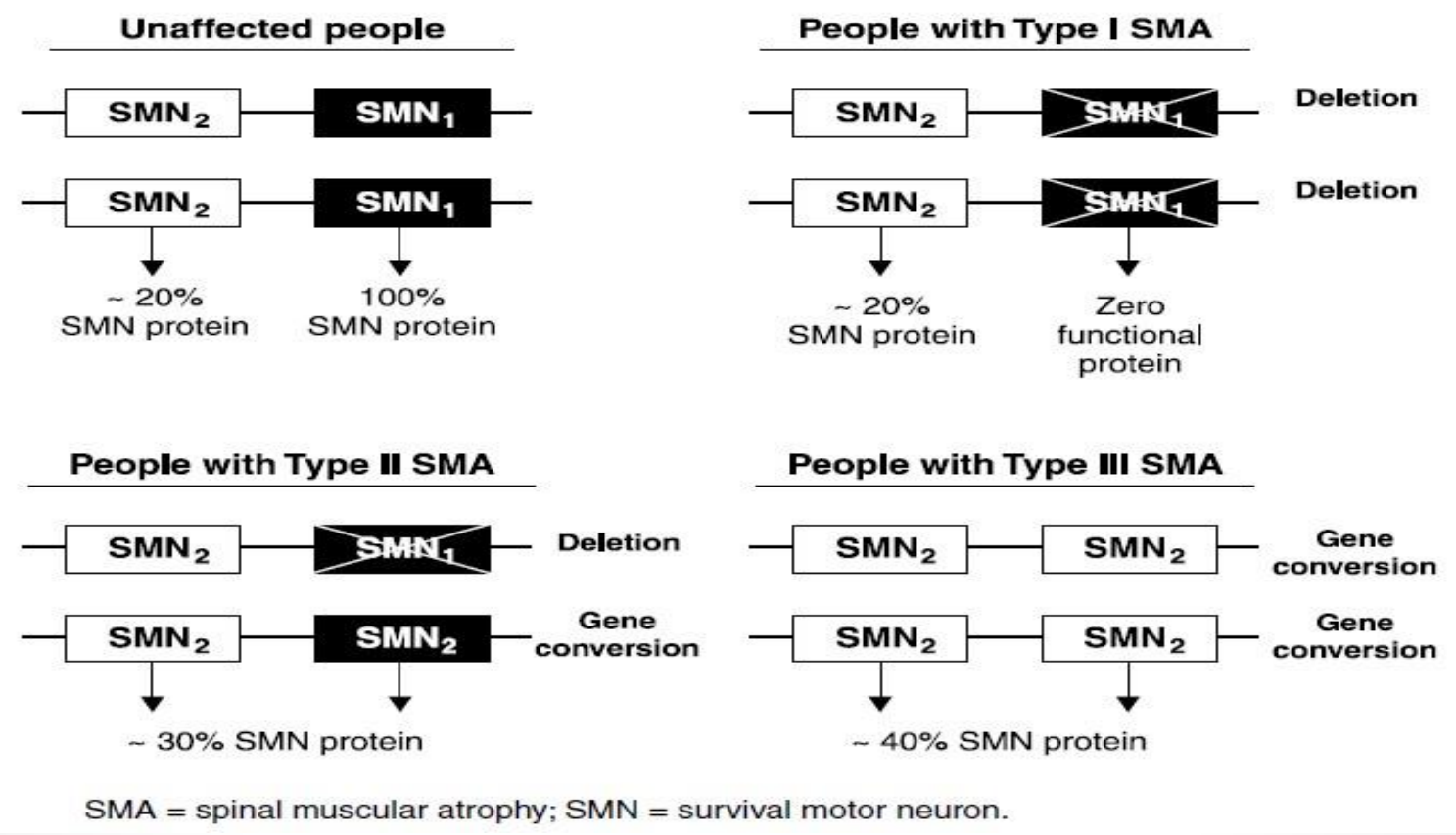
Homozygous loss of function of both SMN1 copies

- **95% SMN 1 deletion/conversion**
- **5% Compound heterozygotes with single SMN1 deletion and frameshift, nonsense, or missense mutation in the other SMN1 copy**

SMN1 Normal gene
SMN 1Mutation types
Deletion : more severe type
Conversion to SMN 2 gene : milder SMA
SMN2 gene : variations
More copies: correlate with milder SMA
SMN2 mutations alone: Don't produce SMA

Prior et al, 2016

Relationship between SMN2 copy number and disease severity



SMA = spinal muscular atrophy; SMN = survival motor neuron.

As the number of copies of SMN2 increases, functional SMN protein increases and the severity of the disease reduces

Gene conversion events are responsible for the milder phenotypes, while deletion of the SMN1 gene leads to more severe forms.

Baioni et al, 2016

Genotype-Phenotype Correlations

- **SMN1**
  - No correlation between type of SMN1 pathogenic variants and the severity of disease
- **SMN2**
  - The number of copies of SMN2 ranges from 0 to 5
  - The presence of 3 or more copies of SMN2 is correlated with a milder phenotype
  - Homozygous SMN1 deletion with 5 copies of SMN2, may compensate for the lack of SMN1 expression

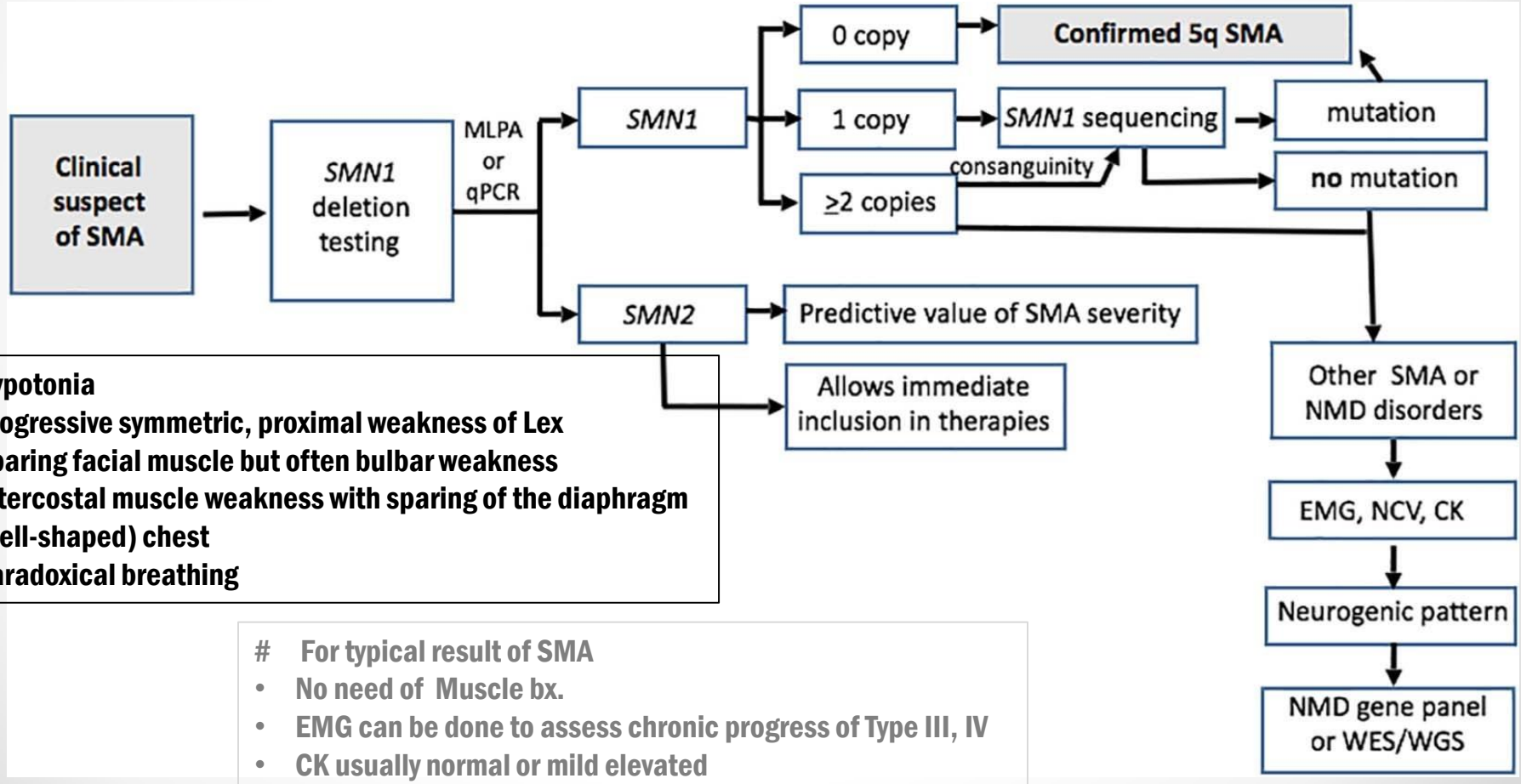
Prior et al, 2004

SMN2 Copy	Normal	SMA I	SMA III	Total
0	14.4%	0	0	
1	32%	7 (13.5%)	0 (0%)	7 (4.9%)
2	51%	43 (82.7%)	0 (0%)	43 (30.3%)
3	4%	2 (3.9%)	70 (77.8%)	72 (50.7%)
4		0 (0%)	20 (22.2%)	20 (14.1%)
Total		52	90	142

Mailman et al, 2002

Diagnostic process for SMA

Updated 2017 Diagnostic Algorithm for SMA Molecular Genetic Testing



Hypotonia
Progressive symmetric, proximal weakness of Lex
Sparing facial muscle but often bulbar weakness
Intercostal muscle weakness with sparing of the diaphragm (bell-shaped) chest
Paradoxical breathing

\# For typical result of SMA
- No need of Muscle bx.
- EMG can be done to assess chronic progress of Type III, IV
- CK usually normal or mild elevated

Diagnostic process for SMA

Updated 2017 Diagnostic Algorithm for SMA Molecular Genetic Testing

- **SMN1 copy number =0**
  - **Confirmed diagnosis of SMA**

- **SMN1 copy number =1**
  - **Look of point mutation in SMN1 gene through sequencing**
  - **Deletion in one SMN1 gene + point mutation in other SMN1 gene**
  - **If there is no point mutation, consider other differential diagnosis**

- **SMN1 copy number= 2**
  - **Consider other differential diagnosis through CK level, EMG-NCS, muscle Bx., multi-genes panel to look for other rare neuromuscular conditions with SMA-like presentation**

SMN1-negative variants resembling SMA

Gene/locus	Disease/phenotype, selected distinguishing features	Selected OMIM designations
DSMA/distal HMN		
Autosomal recessive		
IGHMBP2	SMA with respiratory distress or diaphragmatic SMA	SMARD1/HMN6 or DSMA1
9p21.1-p12	Distal HMN	DSMA2/HMNJ
11q13	Distal SMA	DSMA3/HMN3,4
PLEKHG5	Lower motor neuron syndrome with childhood onset	DSMA4
Autosomal dominant		
7q34-q36	Distal HMN/SMA, juvenile	HMN1
HSPB8	Distal adult HMN, Type IIA	HMN2A
HSPB1	Distal HMN, Type IIB	HMN2B
HSPB3	Distal HMN, Type IIC	HMN2C
GARS	Distal SMA with upper-limb predominance, Type VA	HMN5A[a]
	Charcot-Marie-Tooth disease 2D	CMT2D
BSCL2	Distal SMA with upper-limb predominance, Type VB	HMN5B[a]
	Silver syndrome/SPG17	
2q14	Distal HMN with vocal cord paralysis	HMN7A
Dynactin1	Distal HMN with vocal cord paralysis	HMN7B

Basil et al, 2011

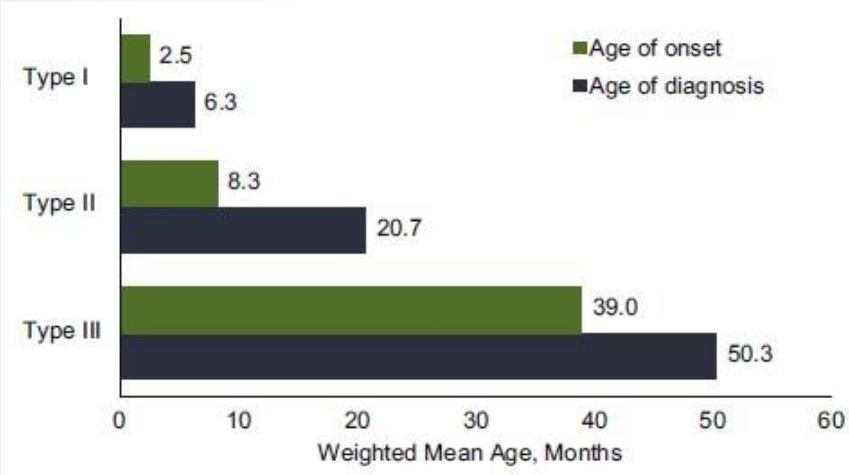
SMN1-negative variants resembling SMA

Proximal spinal muscular atrophy (± distal involvement)		
Autosomal dominant		
VAPB	SMA with late-onset, Finkel type/ALS8	
TRPV4	Congenital SMA with contractures/SMA, congenital, nonprogressive, with lower limb predominance	
	Scapuloperoneal SMA	SPSMA
	Charcot-Marie-Tooth, Type 2C	HMSN2C
14q32	SMA with lower extremity predominance (early onset)	SMALED
3q13.1	HMSN, proximal (Okinawa type)	HMSNP
Other non-5q spinal and bulbar muscular atrophies, SMA plus types		
Autosomal recessive		
GLE1	Lethal arthrogryposis with anterior horn cell disease or lethal congenital contracture syndrome	LAAHD
VRK1	Pontocerebellar hypoplasia with SMA	SMA-PCH1
RFT2 (C20ORF54)	Brown-Vialetto-Van Laere syndrome	BVVLS
	Fazio-Londe disease, bulbar palsy	
X-linked recessive		
Androgen receptor	Bulbo-SMA, Kennedy disease	SBMA/SMAX1
UBE1	Infantile SMA with arthrogryposis	SMAX2
ATP7A	Distal SMA, X-linked	SMAX3

Basil et al, 2011

Potential Delay in Diagnosis

Age of Onset and Diagnosis by Type of SMA



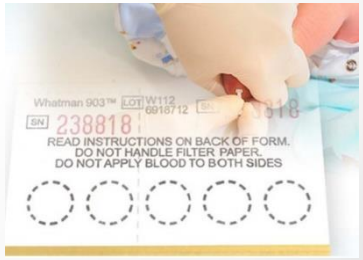
	Type I	Type II	Type III
Age of onset, months			
No. of studies	3	5	3
No. of patients	93	134	99
Range of reported median,	1.2-3.0	7.5-15.0	8.0-24.0
Age of diagnosis, months			
No. of studies	2	2	1
No. of patients	83	86	38
Range of reported median	2.3-6.0	11.5-13.2	42.0*

Abbreviations:
SD = Standard deviation
SMA = Spinal muscular atrophy
* Reported in only one study.

factor directly related to the length of delay in diagnosis was the type of SMA.

Cf) 1.4 months to 12.6 years in Pompe disease, 6 months to 4 years in DMD

Consider Genetic counseling, Prenatal diagnosis, Newborn screening



Lin et al, 2015

Methodology of the 2017 Standard of Care

Topics included in the 2017 Standard of Care update

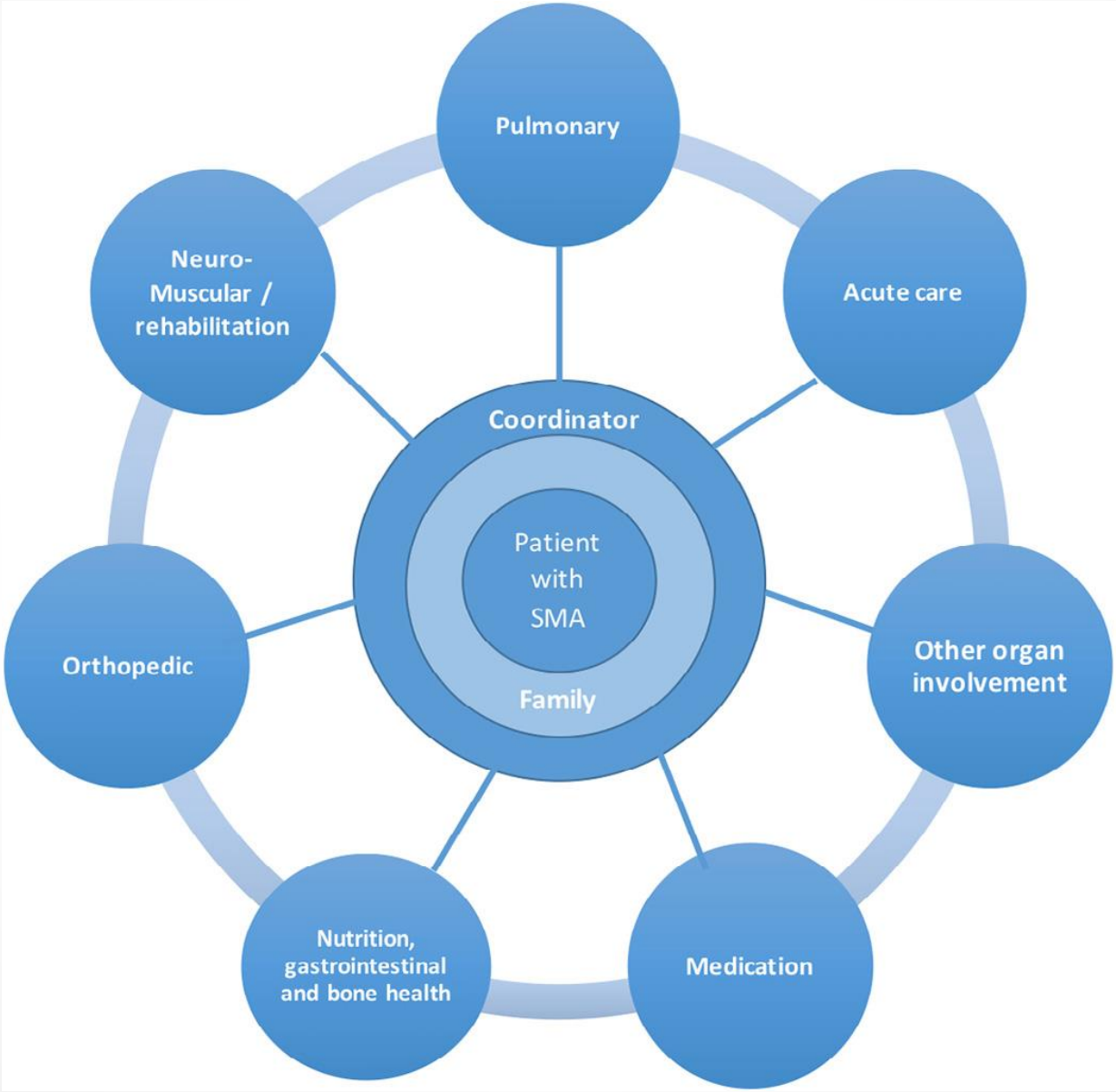
1. Diagnosis and genetics
2. Physical therapy and rehabilitation
3. Orthopedic care, growth and bone health care
4. Nutrition
5. Pulmonary care
6. Acute care
7. Other organ system involvement
8. Medication
9. Ethics and palliative care

Non-sitters	Sitters	Walkers
• Type I	• Type II • Type III with lost ambulation	• Type III • with still ambulant

In 2007 SoC, the committee decided that management for SMA patients should be tailored according to their current functional status

Basil et al, 2011

Multidisciplinary approach



Cochrane Database of Systematic Reviews

Drug treatment for spinal muscular atrophy type

Cochrane Systematic Review - Intervention | Version published: 07 December 2011 see what's new

https://doi.org/10.1002/14651858.CD006281.pub3

- 6 randomized placebo-controlled trials

- Creatine
- Phenylbutyrate
- Gabapentin
- Thyrotropin-releasing hormone
- Hydroxyurea
- Valproic acid + L-carnitine

→ Authors conclusion: No drug treatment for SMA

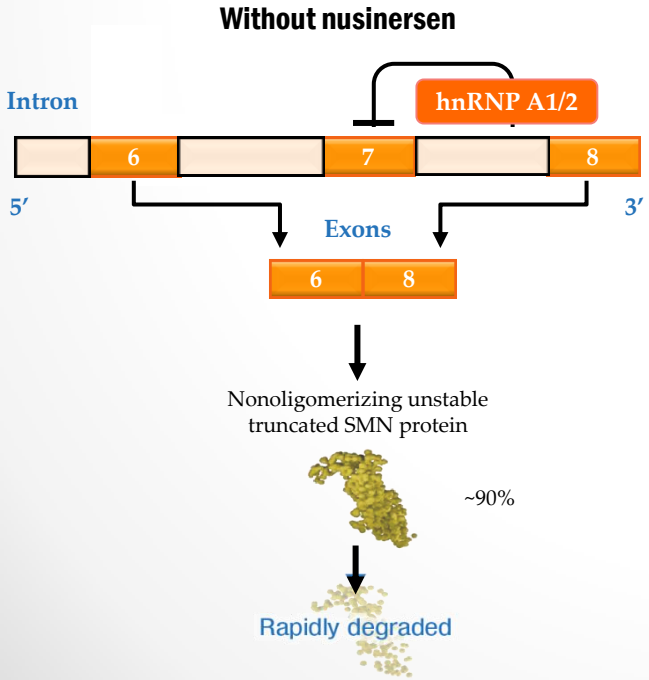
Current SMA trials and therapeutic target

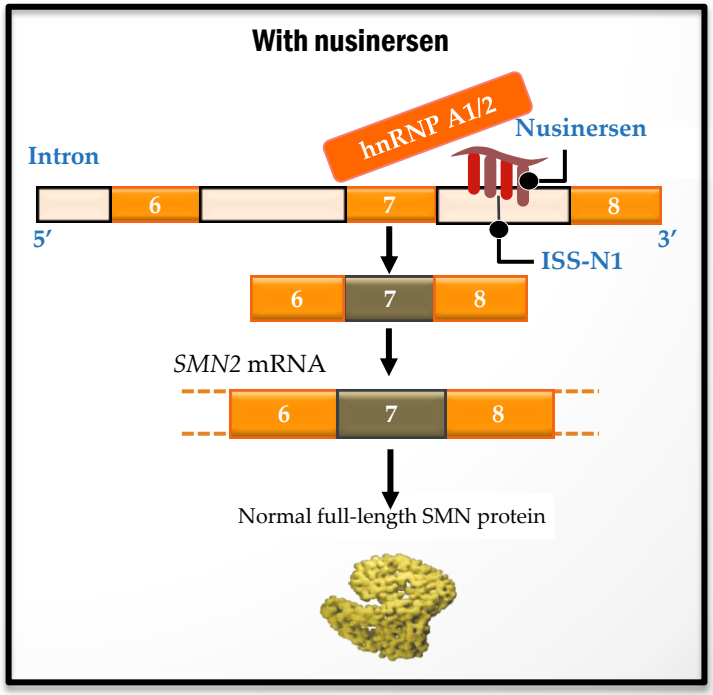
Drug[a]	Target	Associated trials	Stage	Sponsors
Spinraza [53, 54, 56]	*SMN2* splicing	NCT01494701, NCT02052791, NCT01703988, NCT01839656, NCT02462759 (EMBRACE), NCT02386553 (NURTURE), NCT02193074 (ENDEAR), NCT02292537 (CHERISH), NCT02594124 (SHINE), NCT02865109 (EAP)	I/II/III/EAP	Biogen, Ionis
AVXS-101 [64]	*SMN1* gene replacement	NCT02122952, phase II trial announced (STR1VE)	I/II/III	AveXis, Inc.
Branaplam (LMI070)	*SMN2* splicing	NCT02268552	I/II	Novartis Pharmaceuticals
RG7916	*SMN2* splicing	NCT02633709, NCT02908685 (SUNFISH), NCT02913482 (FIREFISH), NCT03032172 (JEWELFISH)	I/II	Hoffmann-La Roche
Valproic acid [71–76]	HDAC inhibitor	NCT00374075, NCT00227266 (CARNI-VAL part 1 and 2), NCT00481013 (VALIANT), NCT00661453 (CARNI-VAL Type I)	I/II	University of Utah
		NCT01033331	–	University of Sao Paulo General Hospital
Olesoxime [82]	Mitochondria	2006-006845-14, NCT01302600, NCT02628743	I/II	Hoffmann-La Roche, Trophos SA
CK-107	Troponin activator	NCT02644668	II	Cytokinetics, Astellas Pharma Global Development, Inc.
SRK-015	Myostatin inhibitor	Trial announced	Trial announced	Scholar Rock

Recent SMA drug pipeline – June/2019

Nusinersen (Spinraza™)

- Modified 18-mer ASO
- Binding to the ISS-NI regulatory motif in the intron downstream of exon 7 on SMN2 pre-mRNA
- Preventing binding of heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1)
- Promotes the inclusion of exon 7, increasing full-length SMN2 mRNA
- Increasing full-length SMN protein





The NEW ENGLAND JOURNAL of MEDICINE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

Richard S. Finkel, M.D., Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Anne M. Connolly, M.D., Nancy L. Kuntz, M.D., Janbernd Kirschner, M.D., Claudia A. Chiriboga, M.D., M.P.H., Kayoko Saito, M.D., Ph.D., Laurent Servais, M.D., Ph.D., Eduardo Tizzano, M.D., Ph.D., Haluk Topaloglu, M.D., Már Tulinius, M.D., Ph.D., et al., for the ENDEAR Study Group*

ENDEAR trial

- **Multinational, randomized, double-blind, sham-controlled121 patients under age of 7 months (80 Nusinersen: 41 Control)**
- **Safety and efficacy of Nusinersen**
- **51% responder compared to 0% of controls (HINE)**
- **Higher event-free survival (hazard ratio for death or used of permanent assisted ventilation, 0.53; p=0.005)**
- **The adverse events were respiratory infection, constipation which were similar in the 2 groups**

The NEW ENGLAND JOURNAL of MEDICINE

Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Claudia A. Chiriboga, M.D., M.P.H., John W. Day, M.D., Ph.D., Craig Campbell, M.D., Anne M. Connolly, M.D., Susan T. Iannaccone, M.D., Janbernd Kirschner, M.D., Nancy L. Kuntz, M.D., Kayoko Saito, M.D., Ph.D., Perry B. Shieh, M.D., Ph.D., Már Tulinius, M.D., Ph.D., et al., for the CHERISH Study Group*

CHERISH trial

- **Multinational, randomized, double-blind, sham-controlled 126 who had symptom onset after 6 months**
- **HFMSE score at 15 months**
- **57% Nusinersen group compared with 26% in the control group had an increase of HFMSE at least 3 points (p<0.001)**

Ongoing studies:

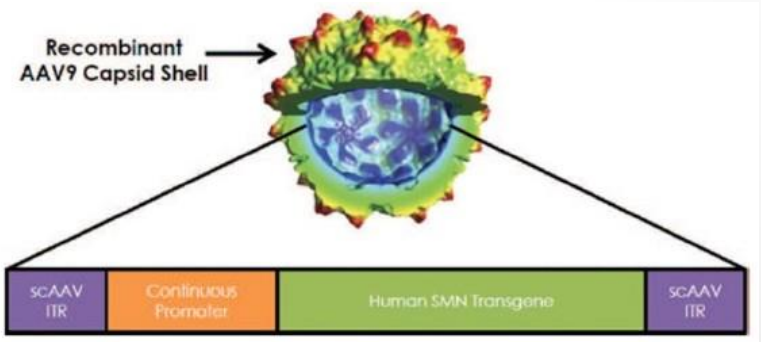
The Phase 2 NURTURE (CS5) study in infants with genetically diagnosed presymptomatic SMA (most likely to develop SMA Type I or II)

The SHINE (CS11) study, which is an open-label extension study of nusinersen for infants and children who previously completed CS3A, ENDEAR, CHERISH, CS12, or EMBRACE (CS7)

SMA
Inter-department conference
Yong Beom Shin, M.D.
Department of Rehabilitation Medicine
Pusan National University Hospital
Pusan National University School of Medicine
TG

AVXS-101 (Zolgensma®)

- Gene replacement therapy using a adeno-associated viral vector to deliver SMN1 gene to cells
- Phase 3 STR1VE data (ongoing, open-label, single-arm, single-dose, multi-center trial in the U.S.)
- 22 patients, rage 0.5 to 5.9 months, interim result when average of 13.8 months
- CHOP-INTEND scores increased by an average of 6.9 points one month, 11.7 points three months and 14.3 points five months after gene transfer,
- Twenty-one of 22 (95 percent) patients achieved a CHOP-INTEND >40
- U.S FDA approval 5/24/2019



Management of limb contractures and deformity

- **UE contracture**

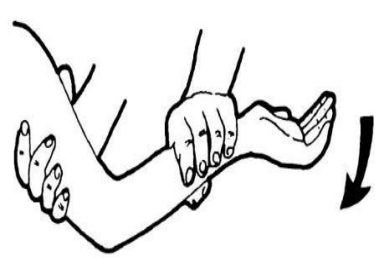
  Severe elbow flexion contracture > 60 degree

  forearm pronation tightness, wrist flexion-ulnar deviation

- Active-assistive and passive techniques stretching (proximal → distal)

- Splinting

- Positioning to promote extension and oppose joint flexion



Management of limb contractures and deformity

- **LE contracture**

  Prevention with early diagnosis

  Start stretching, splinting when contracture are mild

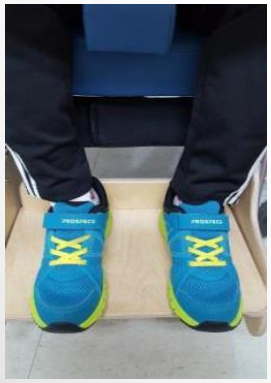
  Advanced contracture become fixed and show little response to stretching program

  - Supported standing

  - Active-assistive and passive stretching

  - Positioning of leg to promote extension

  - AFO, KAFO for knee, ankle extension



Physical therapy

- Regular session of physical therapy blunted the progression in most treated patients

- Lack of evidence which therapy regimen is most advantageous, or the optimal duration and frequency of treatments

- Muscles with antigravity strength cane be strengthened through resistance exercise
- Muscles less than antigravity strength should not be subjected to eccentric exercises
- Importantly resistance exercises should not be used on neck muscles

- Adjust most appropriate exercise regimen is necessary according to effect of Nusinersen (Spinraza) treatment

- Periodic evaluation is necessary for understanding performance status, constructing targeted treatment plan and tracking treatment success

Functional evaluation tests

- Hammersmith Infant Neurological examination (HINE) section 2
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Hammersmith Functional Motor Scale-Expended(HFMSE)
- Revised Upper Limb Module (RULM)
- 6 Minute Walk Test (6MWT)

척수근위축증을 위한 해머스미스

기능적 운동 평가 확대 지수(HFMSE) 메뉴얼

번역본(2019.10.28)

- 역자의 글

2003년 척수근위축증(Spinal Muscular Atrophy, SMA) 환아들의 운동기능을 평가하기 위한 도구가 해머스미스(Hammersmith) 병원에서 개발되어 보고되었다. 이후로 개선을 위한 여러번의 수정판이 제안되었고, 2007년 해머스미스 기능적 운동척도 확대 버전(Expanded version of Hammersmith Functional Motor Scale, HFMSE)이 제안된 이후 미국, 유럽 등지의 여러 나라에서 전문가들의 협의체(Pediatric Neuromuscular Clinical Research SMA Network, PNCR) 활동을 통하여 내용이 합의되고 세계적으로 이 HFMSE는 널리 활용되고 있다. 이제까지 몇 과정들을 통하여 약간의 업데이트가 이루어졌으며 2019년 3월 29일 최종본이 공개되었고, 우리나라에서도 대한소아재활발달의학회에서 이를 한국화하여 사용하고자 하는데 이르렀다.

현대의 의학의 발달이 근본적인 치료가 불가능하다고 인식되어 온 유전자질환의 하나인 SMA의 치료에 까지 이르게 된 시점에서 HFMSE는 더욱 중요한 의미를 가지게 되었으며, 본 역자들은 이 평가도구가 관련 전문가들에게 잘 활용되기를 바라는 마음이다.

대한소아재활발달의학회

2019. 10. 28

(역자: 국민건강보험 일산병원 재활치료실 강경이실장
차의과학대 분당차병원 재활의학과 김민영 교수
부산대학교 부산대병원 재활의학과 신용범교수
- 가 나 다 순)

Spine deformity management

- **Cervical Bracing**

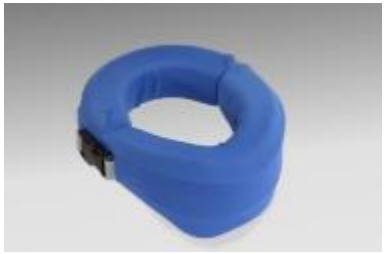
Head control is often absent of not fully developed

For non-sitters, and sitters,

need to use for head support

prevent neck injury during transportation

minimize risk of asphyxiation while upright and meat time



Spine deformity management

- **Thoracolumbar scoliosis**
  - **SMA 1-3 with incidence of 60-90%**
  - **Long C curve extends to pelvis**
  - **Thoracic kyphosis also develops in most patients**
  - **Coronal, sagittal plane radiography in upright position**
  - **Cobb angle > 20 deg. Should be monitored every 6 months**

Spine deformity management

- **Thoracic brace**
  - To support hypotonic trunk and treat scoliosis > 20 deg.
  - Bracing is palliative and unable to halt progression of spinal deformity
  - Indicated to preserve trunk balance in sitting, re-align the distorted thorax to facilitate respiratory function, and to improve QOL
  - Can interfere with pulmonary function: some controversy

- **Sitting system**
  - pelvic level correction with maintaining lumbar lordosis

Spine deformity management

- Surgical Ix.: Cobb angle > 50 deg., progression rage ≥ 10 deg/yr
- Surgical treatment should be delayed until 4 yr

- For age 8-10 yr, growth-friendly instrument allows spine growth should be considered

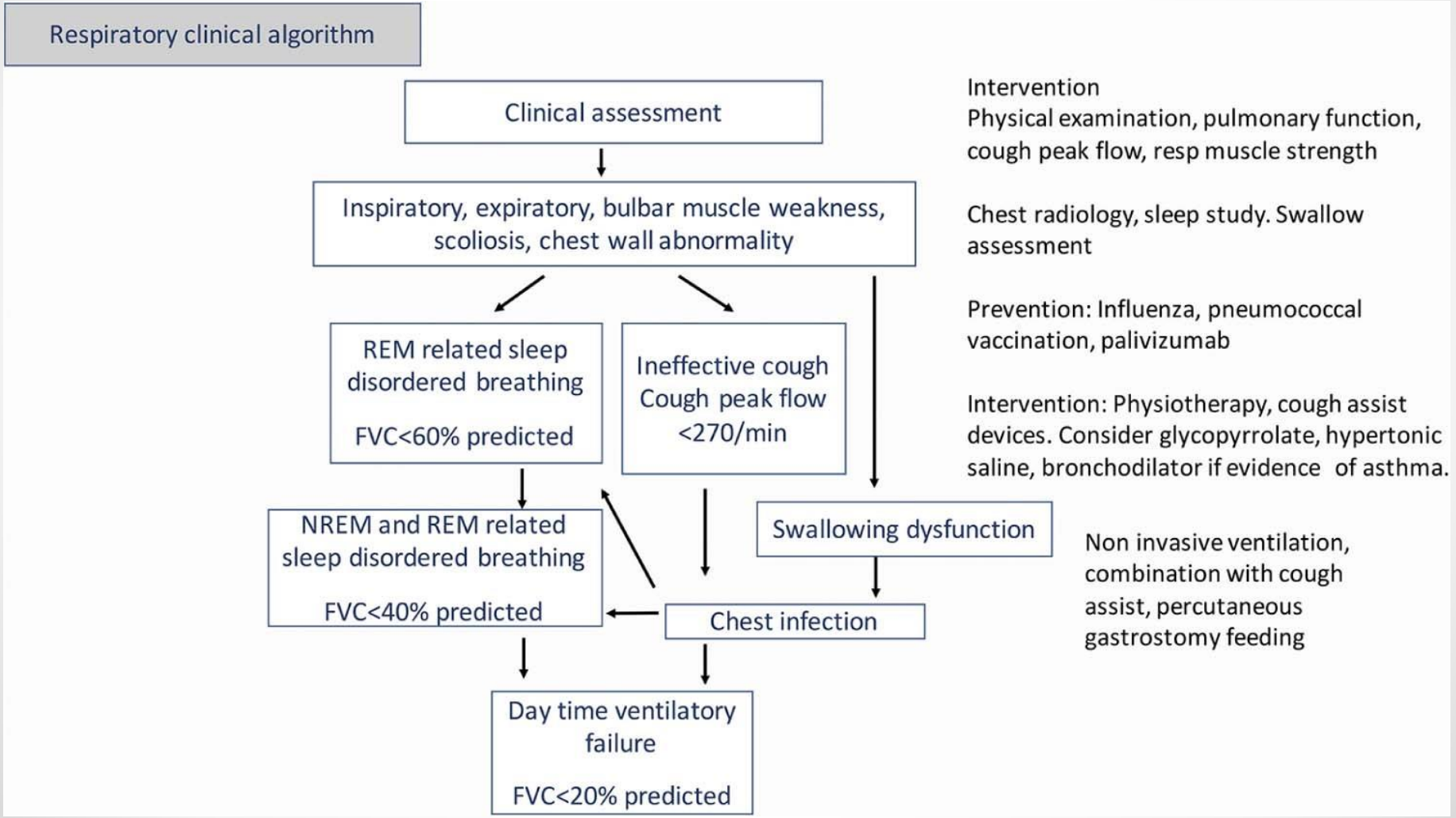
- For age > 12 yr, posterior spine fusion using dual rod, multi segmental constructs should be implemented

- On or two mid-lumbar levels shoulder be left unexposed in the midline to accommodate intrathecal access, for administration of Nusinersen

- Doctor should inform the patient and family decrease in UE function, difficulty in patient care secondary to a long, rigid trunk although sitting balance may improve following fusion

Pulmonary management

***Reactive → Proactive approach**



Pulmonary management

- **Key respiratory problems in SMA**
  - impaired coughing → poor clearance of secretion
  - hypoventilation, esp. during sleep
  - chest wall and lung underdevelopment
  - recurrent infection that exacerbate muscle weakness

- **Pulmonary compromise is caused by**
  - combination of inspiratory and expiratory muscle weakness
  - greater involvement of expiratory and intercostal muscle
  - diaphragm is relatively spared

Pulmonary management

- **Assessment of respiratory status**

- Every 3-6 months
- Physical examination : chest wall shape, skin color (cyanosis or pallor)
- Pulse oximetry and capnography ($EtCO_2$ or $TcCO_2$) when awake
- Sleep study or pneumograms in all symptomatic patients or to determine if a patient need to initiate NIV
- For sitters, spirometry (when possible depending on age and cooperation)

Pulmonary management – Airway clearance

- Manual chest physiotherapy combined with MIE for airway clearance therapy

- Insufflation and exsufflation pr. should be increase gradually to 30-40 cmH20
- No correlation between pressure used and either age or type of disease

- 2-4 sec inspiration and 4-5 sec expiration usual setting
- Asymmetric setting may be preferred with abdominal distention related to insufflation or problems with reflux or emesis related to exsufflation

- Oral suctioning with a mechanical suction pump and catheter is a critical part of airway clearance in patient with ineffective cough

- High frequency chest wall oscillation (Vest) therapy does not improve clearance of secretion in the setting of ineffective cough

Pulmonary management – Ventilation

- **NIV (BiPAP) apply**
  - initially, IPAP 10cmH2O → quickly increased to 20 cmH2O →25cmH2O
    EPAP 3cmH2O: to prevent excessive CO2 rebreathing
  - high span BiPAP and backup rate (higher than spontaneous rate): facilitate synchrony

- **CPAP may cause respiratory muscle fatigue**
  But may be used with caution temporarily to help maintain resting lung volume (FRC) who are unable to synchronize with ventilator and who are not markedly hypercapnic

- **At least two comfortable interfaces using a nasal interface initially**

- **Tracheostomy ventilation is an option in selected patients in whom NIV is insufficient or fails, or if there is no effective interface for providing ventilation**

Thank You