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Spinal Muscular Atrophy: Clinical Aspects, Diagnostics and Follow-Up

Thursday, June 7, 2018

Dial in: 866.740.1260

(passcode 4852701#)

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Agenda

Moderator: Patricia Hunt, Texas Department of State Health Services

Speaker: Jennifer Kwon, MD, MPH, University of Rochester Medical Center

1:00 - 1:05	Welcome and Introduction
1:05 - 1:20	Overview of SMA, Clinical Manifestations
1:20 - 1:35	Diagnostic Issues
1:35 - 1:50	Treatment and Follow-Up
1:50 - 2:00	Q&A and Closing

APHL Webinar
Spinal Muscular Atrophy: Clinical Aspects, Diagnostics, and Follow-up

Jennifer Kwon, MD
University of Rochester Medical Center
Rochester, NY

June 2018

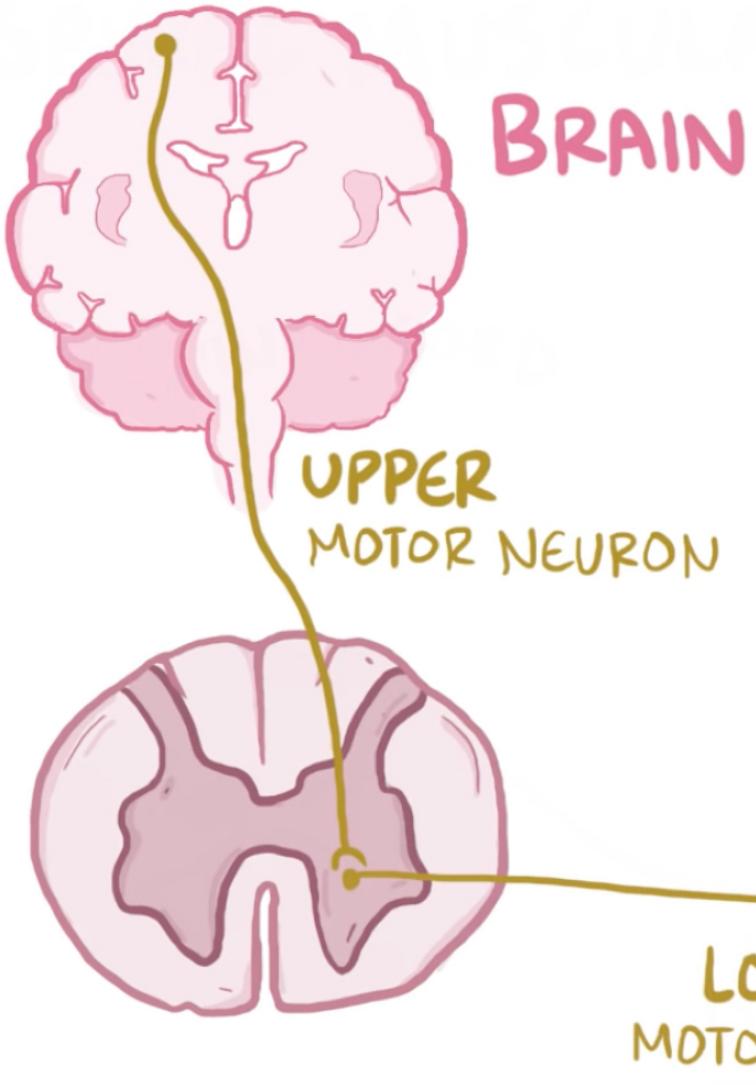
Disclosures

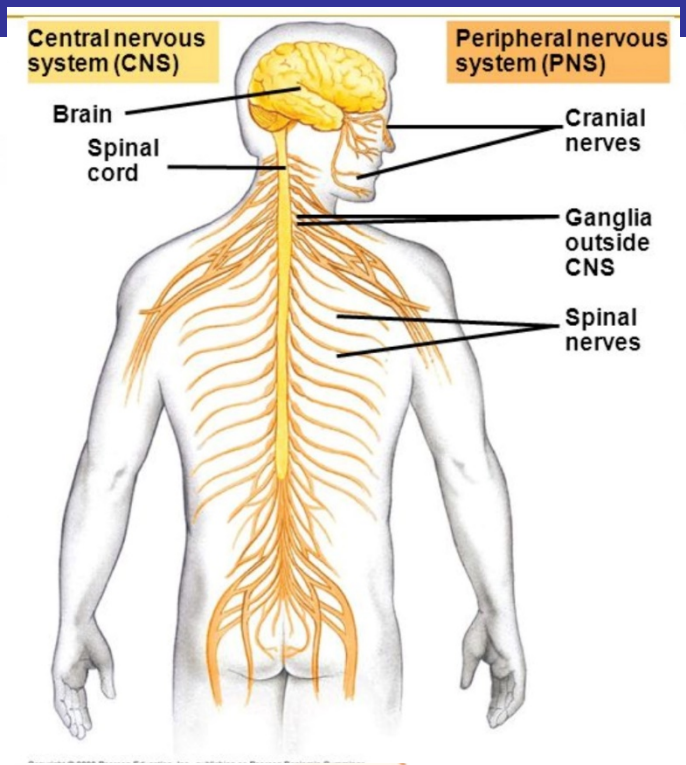
- Sanofi-Genzyme-site PI, Genzyme Registry; travel
- Biomarin – consultant fees, travel
- Evidence Review Group (Kemper, PI)

*My comments are my own should not be taken to reflect the views of any federally sponsored agency, including the ERG

Spinal Muscular Atrophy (SMA)

- Autosomal recessive disease affecting the (lower) motor neurons in the spinal cord and brainstem, resulting in progressive motor weakness and atrophy
- Broad phenotype spectrum ranging in age of onset (birth to adulthood), severity, and clinical course
  - Types of SMA are primarily distinguished by the severity of muscle weakness and age of symptom onset
  - Types 1 & 2 are most severe


BRAIN
UPPER
MOTOR NEURON
LOWER
MOTOR NEURON


Central nervous system (CNS)
Peripheral nervous system (PNS)
Brain
Spinal cord
Cranial nerves
Ganglia outside CNS
Spinal nerves

Spinal Muscular Atrophy (SMA)

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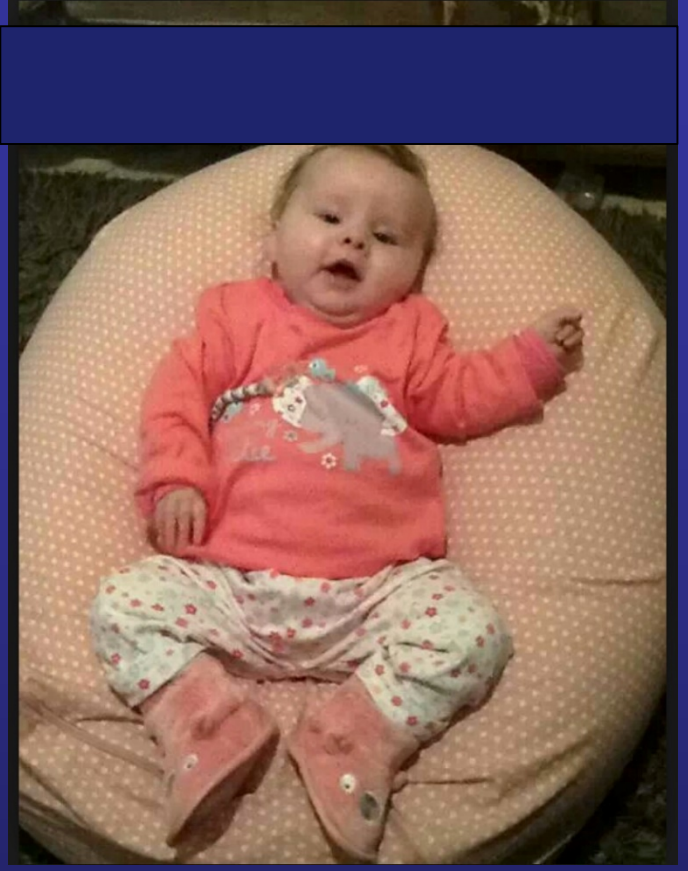
Maria



- 2nd child, normal pregnancy & delivery
- Admitted at age 3 months for viral respiratory infection (“a cold”) requiring intubation
- Exam: social smile, tracks well. Persistent head lag, unable to lift legs off bed. Could not lift arms at shoulders but could lift her forearms and grasp.
- Able to be extubated after 2 days
- By 6 months she was unable to feed well. Parents agreed to G-tube but did not want artificial airway.
- She received palliative care and died at 10 months of age.

SMA TYPE 1

SMA TYPE 2

SMA TYPE 3

SMA: clinical variability

- All (*nearly*) types of SMA are caused by bi-allelic (*often homozygous*) deletions of SMN1
  - These mutations are inactivating
  - Absence of SMN protein is lethal
- Aberrant processing of SMN2 pre-mRNA leads an SMN1 transcript (*"two wrongs make a right"*)

SMA: genetic mechanism

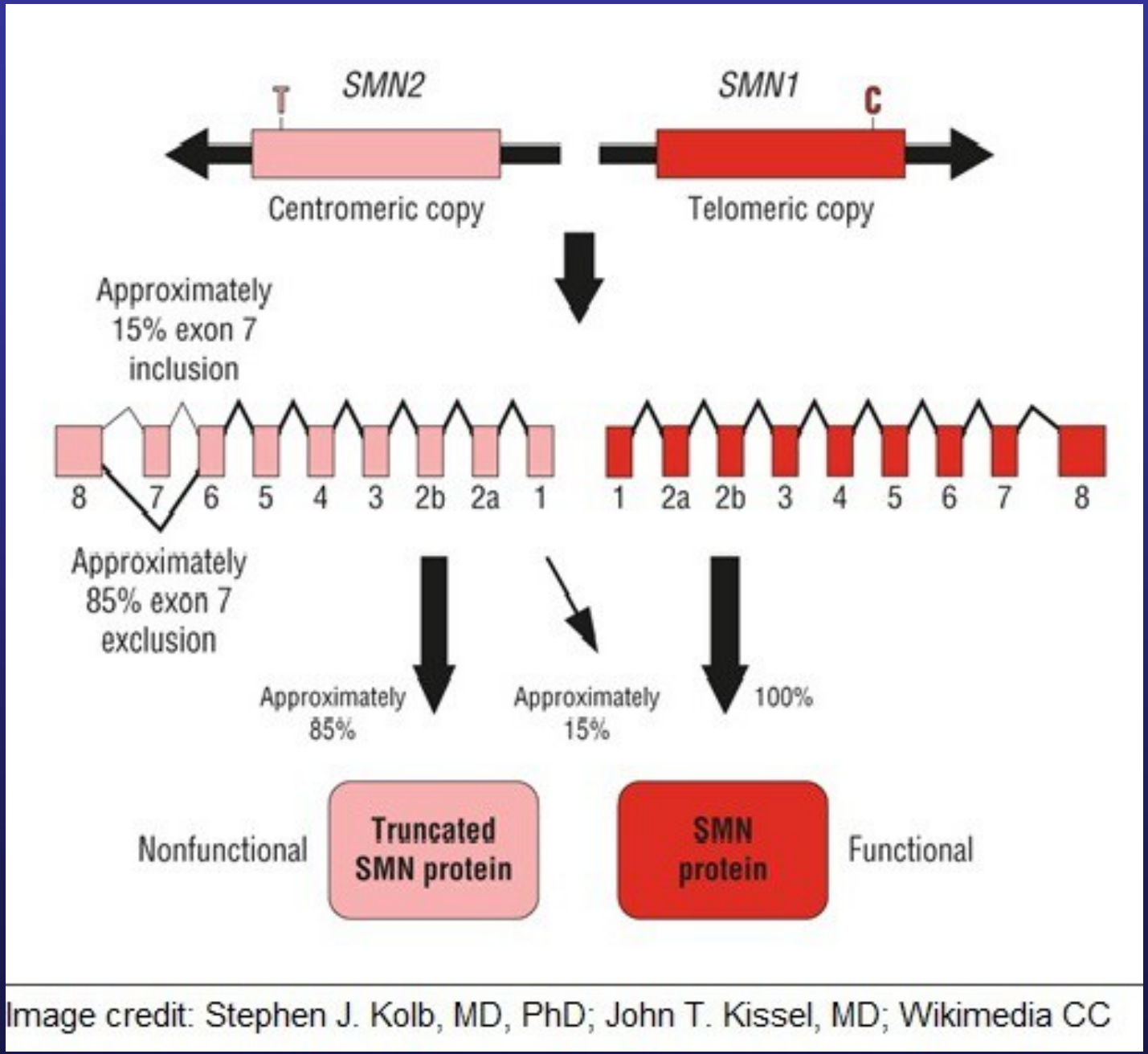
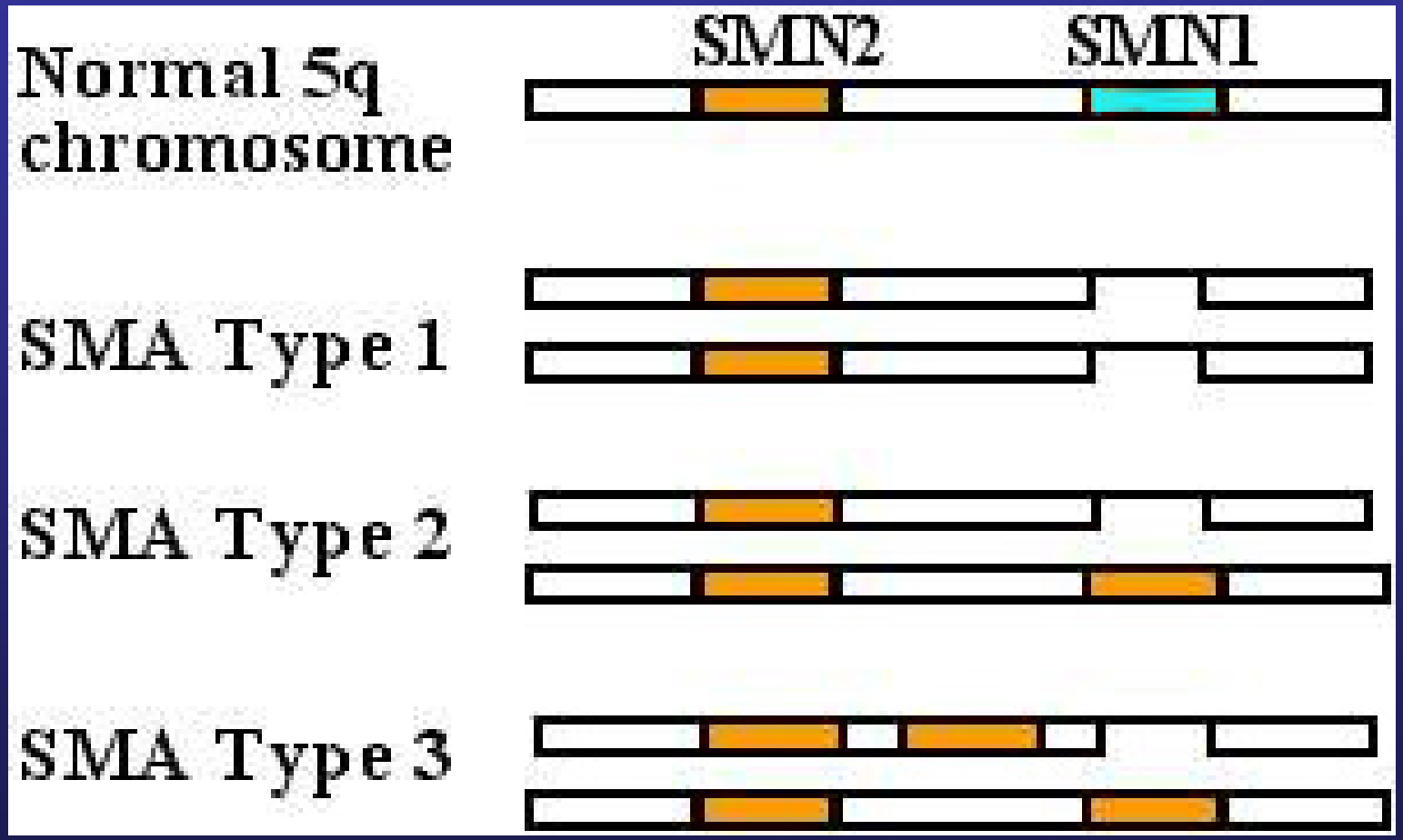


Image credit: Stephen J. Kolb, MD, PhD; John T. Kissel, MD; Wikimedia CC

SMA: genetic mechanism



Diagnosing SMA

- SMA is typically diagnosed DNA testing, and all commercial labs provide SMN1 deletion results and SMN2 copy number
- SMN2 copy number is associated with motor function but it is not sufficient to predict SMA type in presymptomatic children

Diagnosing SMA

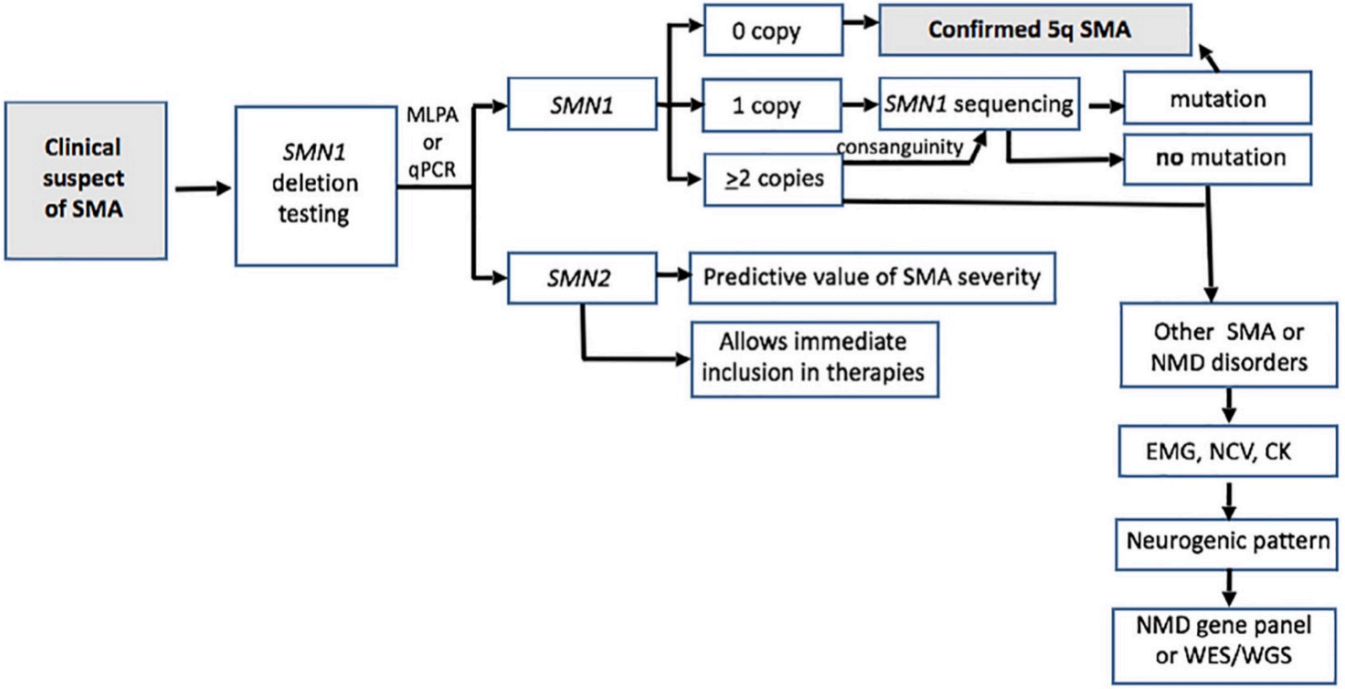


Fig. 1. Diagnostic algorithm for spinal muscular atrophy (SMA: spinal muscular atrophy; SMN1: survival motor neuronon 1; SMN2: survival motor neuron 2; NMD: neuromuscular disorders; EMG: electromyography; NCV: nerve conduction velocity; CK: creatine kinase levels; WES: whole exom sequencing; WGS: whole genome sequencing).

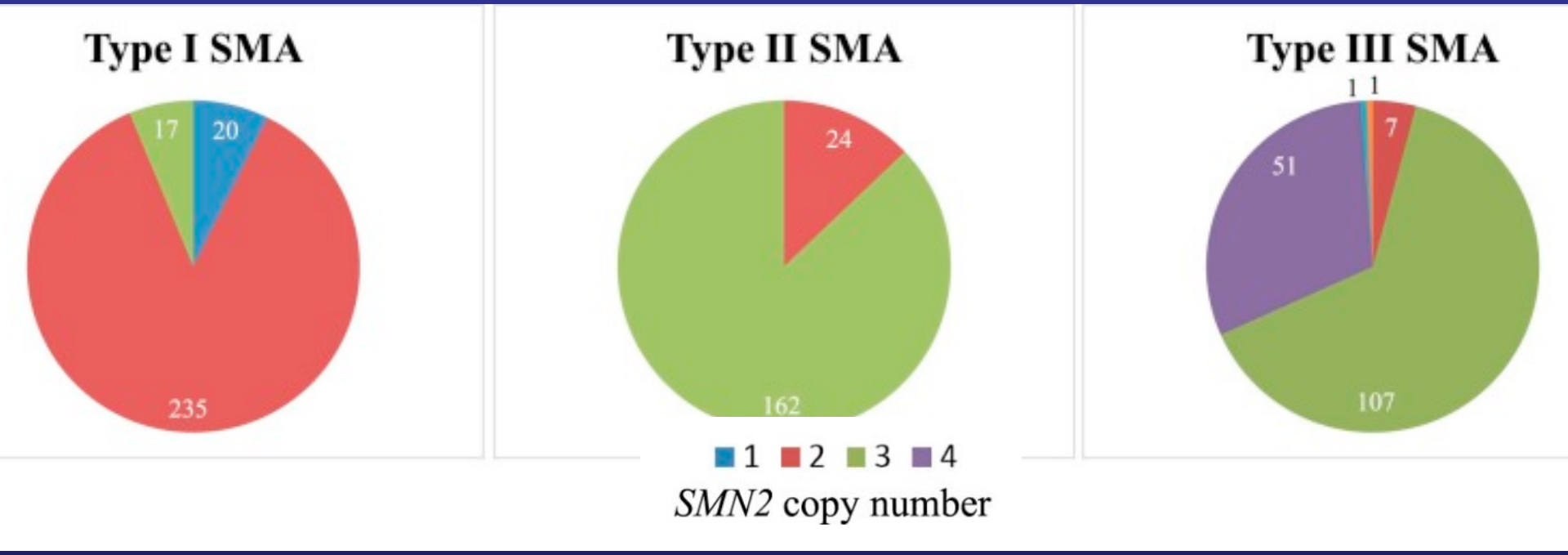
Eugenio Mercuri, Richard S. Finkel, Francesco Muntoni, Brunhilde Wirth, Jacqueline Montes, Marion Main, et al. 2018 Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care, Neuromuscular Disorders,28:103-115,

SMA Classifications & SMN2 Copy Number

SMA Type	Age Onset	Best Motor	SMN2 copies	Relative Freq	Life Span
1	0-6 months	Never sits	1*, 2, 3	0.54	< 2 years
2	6-15 months	Sits w/o support	2, 3, 4	0.18	> 2 years to early adult
3	> 18 mo	Walks	3, 4	0.25	Adult
4	>21 year	Walks	4, 5	0.03	Adult

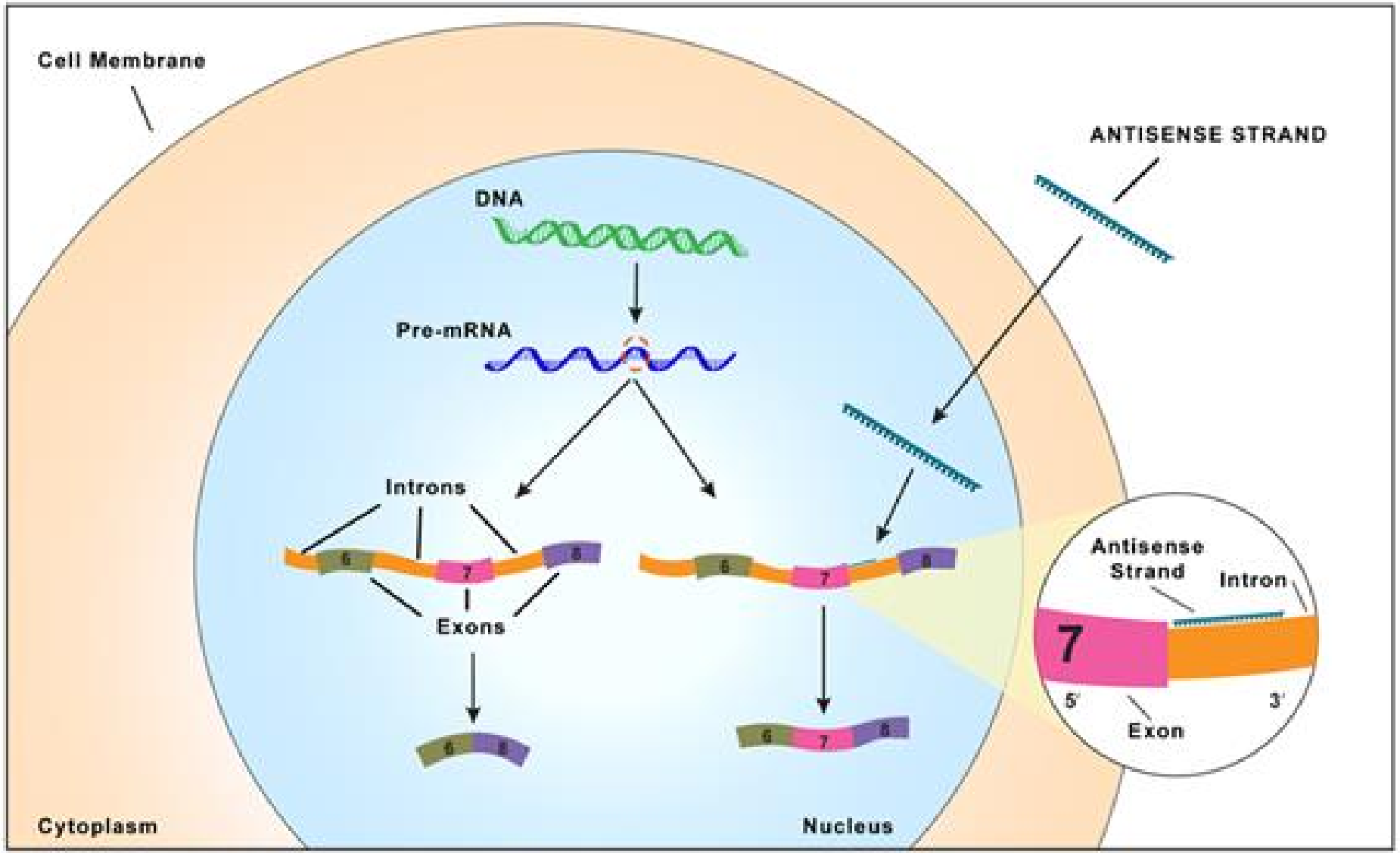
Adapted from Advisory Committee Presentation, February 2018

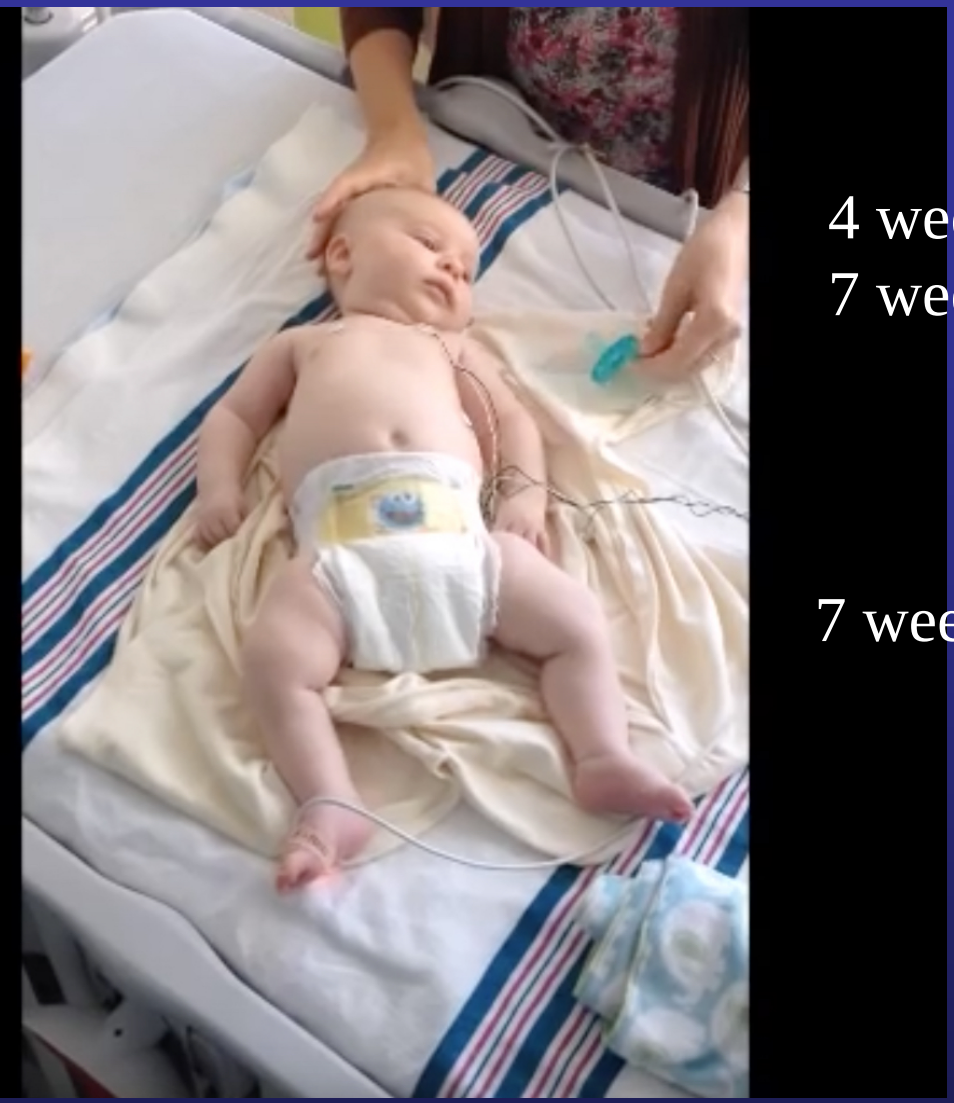
Distribution of SMN2 Copies



Calucho et al 2018, Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases

Nusinersen

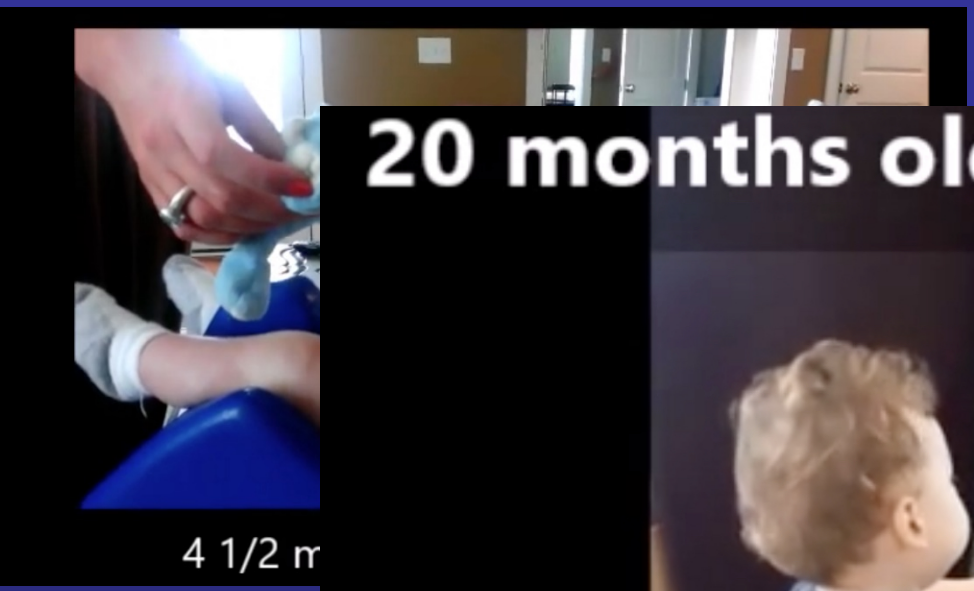

Cell Membrane
ANTISENSE STRAND
DNA
Pre-mRNA
Introns
Exons
Antisense Strand
Intron
7
5'
3'
Exon
Cytoplasm
Nucleus



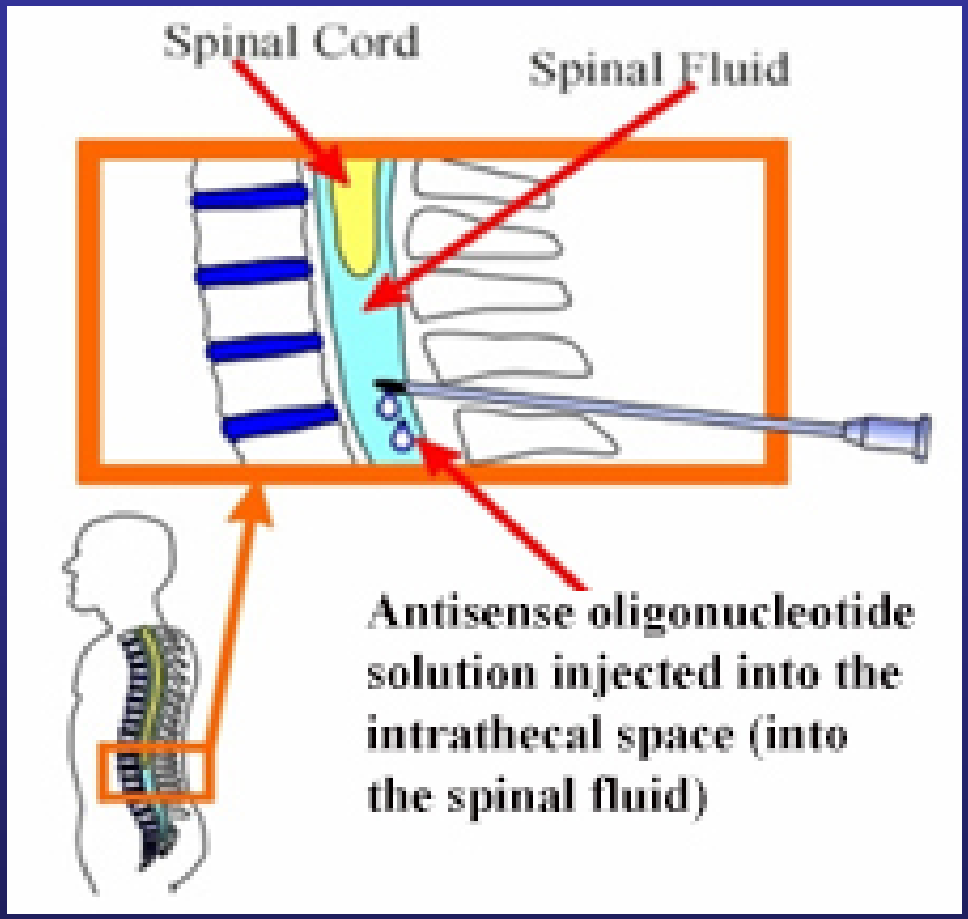
4 weeks Parents noted weakness
7 weeks Diagnosed with SMA

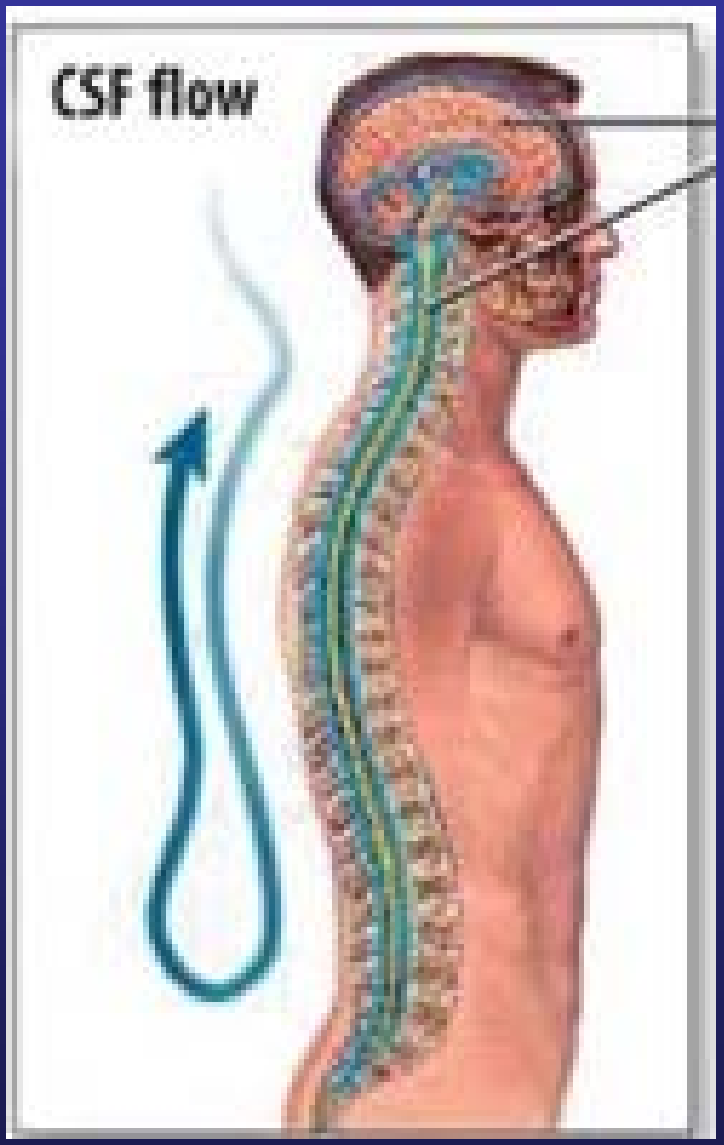
7 weeks Started receiving ISIS SMN_{RX}

Google: “Cameron” “SMA” “nusinersen”



play


Spinal Cord
Spinal Fluid
Antisense oligonucleotide solution injected into the intrathecal space (into the spinal fluid)


CSF flow

One difference between these boys...ISIS SMN$_{RX}$

Timeline

- 2015-2016 ISIS SMN_{RX} results
- December 2016 FDA approved nusinersen (Spinraza) for SMA , “all types, all ages”
- Announced the price: $750,000 in the first year, and $375,000 annually for life

Barriers

- High cost
- Managing the needs of SMA patients of “all ages and all types”
- Lack of information about optimal timing of treatment in milder forms of SMA.

SMA NBS Treatment Guidelines

(Glascock et al, 2018)

- The working unanimously recommended immediate treatment for infants likely to have SMA types I and II
  - Therefore, they recommended early nusinersen treatment in all infants with 2 or 3 SMN2 copies

SMA NBS Treatment Guidelines

(Glascock et al, 2018)

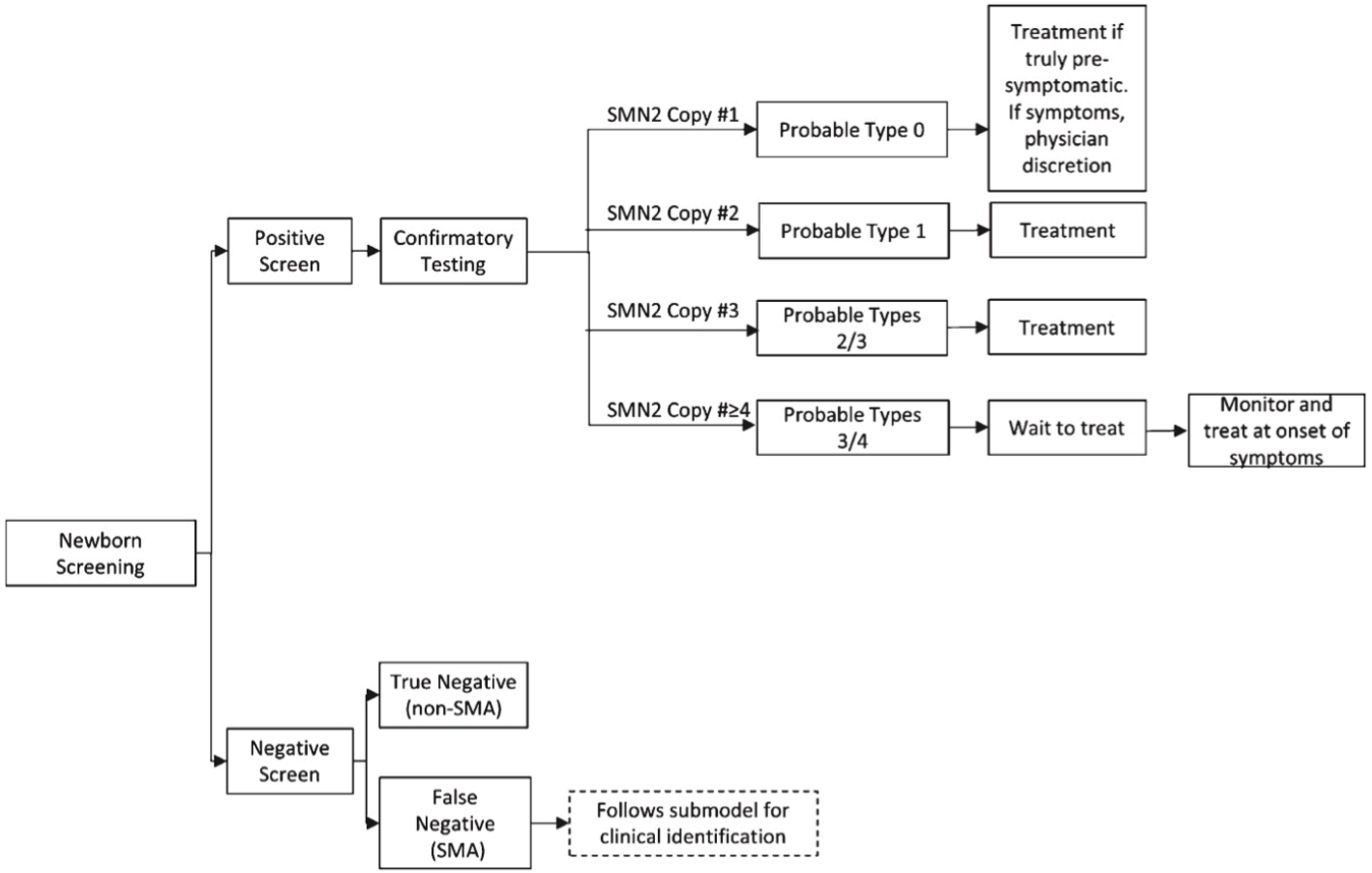
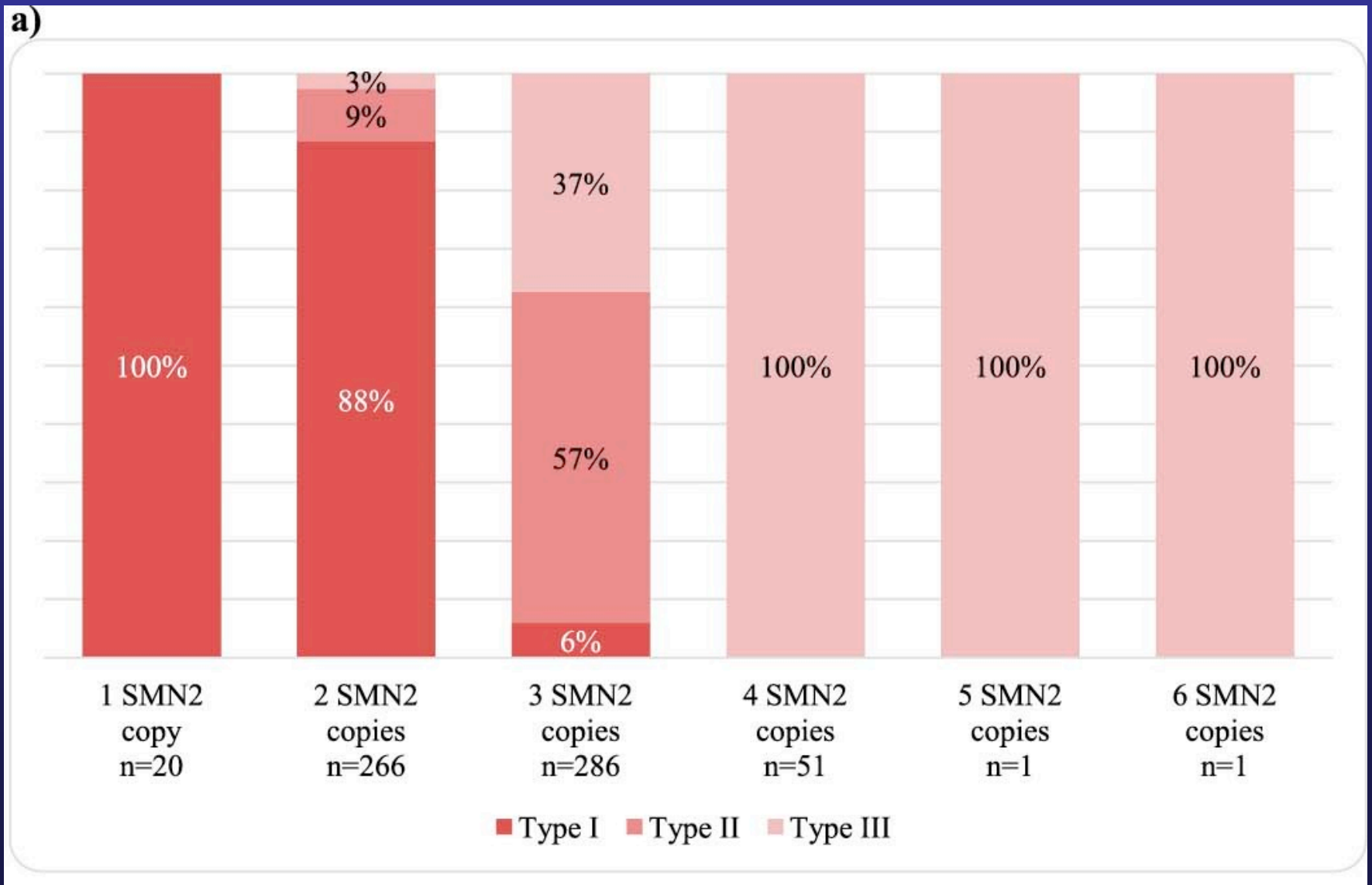


Fig. 1. SMA Newborn Screening Treatment Schematic for SMN-Up-Regulating Therapy. SMA=spinal muscular atrophy; SMN=survival motor neuron.

From Spanish cohort of 625 SMA patients, distribution of SMA types according to SMN2 copy number (Calucho et al 2018)

Suggests that ~90% of newborns with SMA will have 2 or 3 SMN2 copies



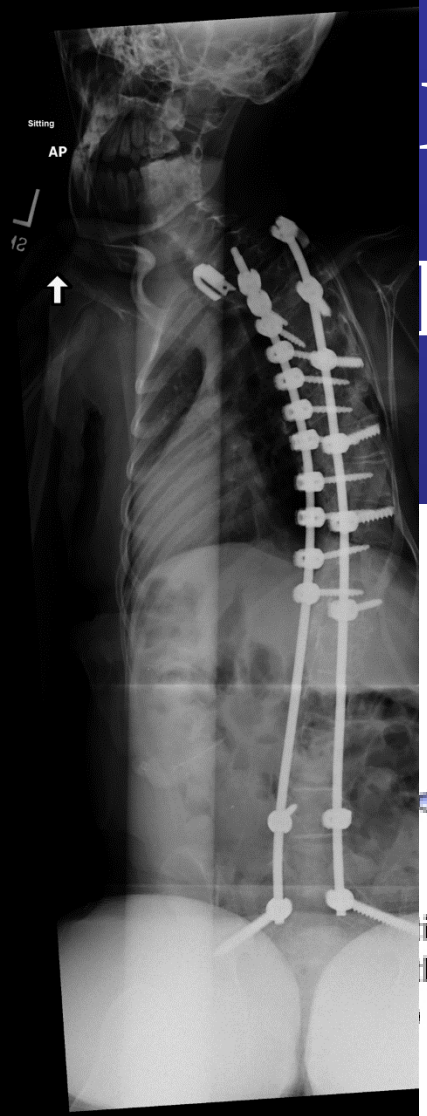
US Hospital Business 101

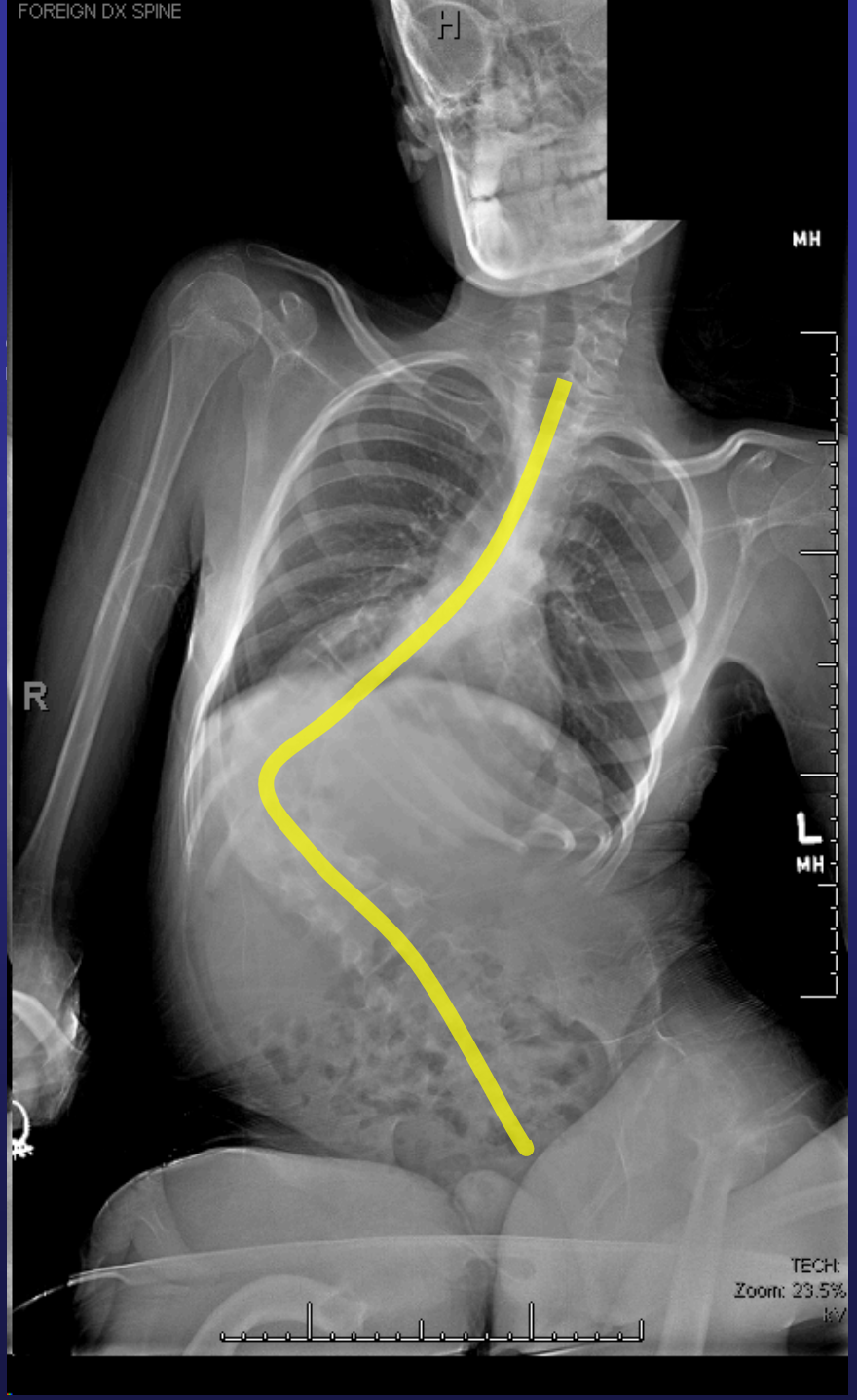
Part I. Expensive Drugs

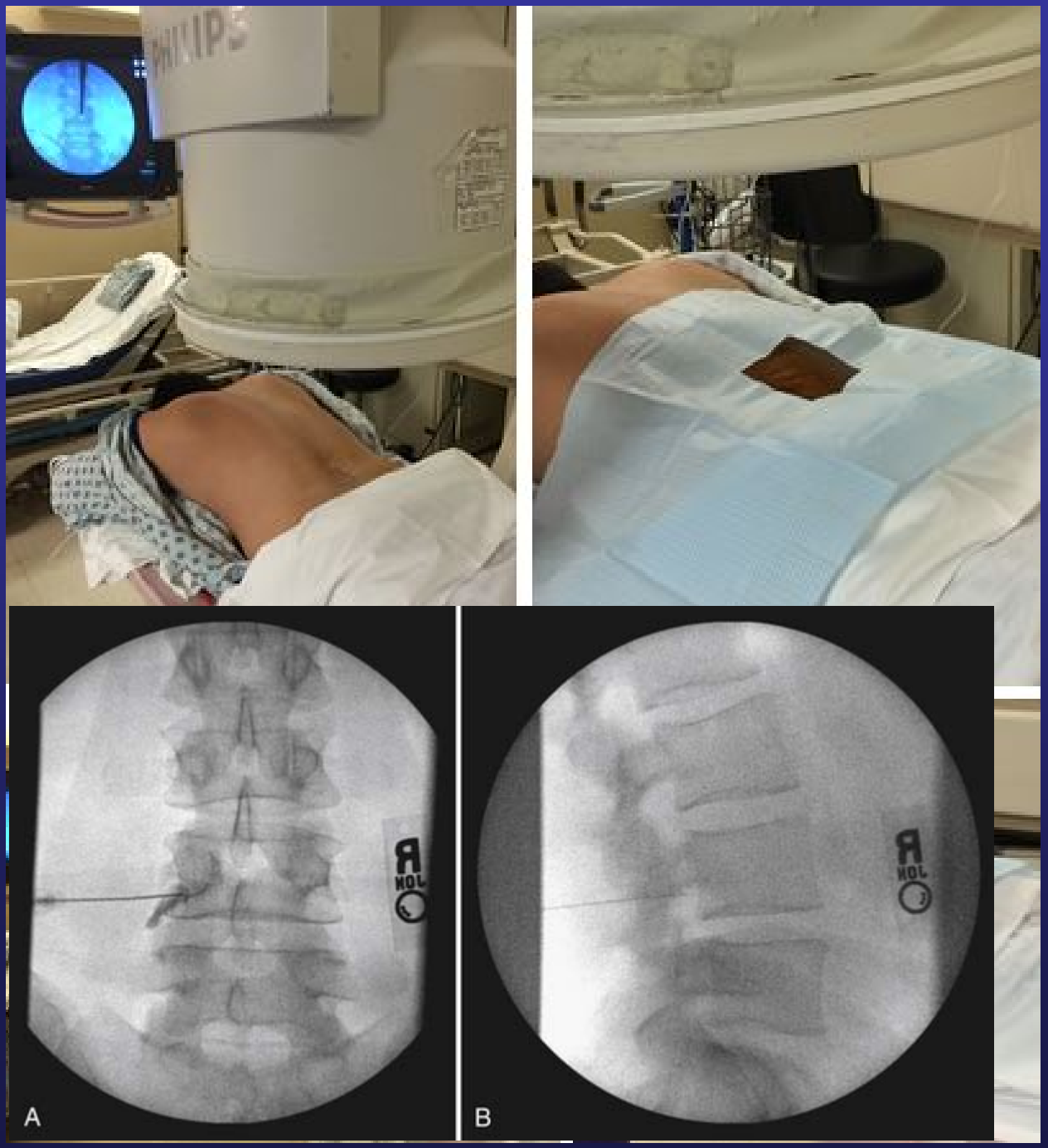
- Given in an outpatient setting
- Are never fully reimbursed by Medicaid
- Are financially risky to store in hospital pharmacies
- Are likely to cause deficits in pharmacy budgets because of the lag in payments

ital

Type



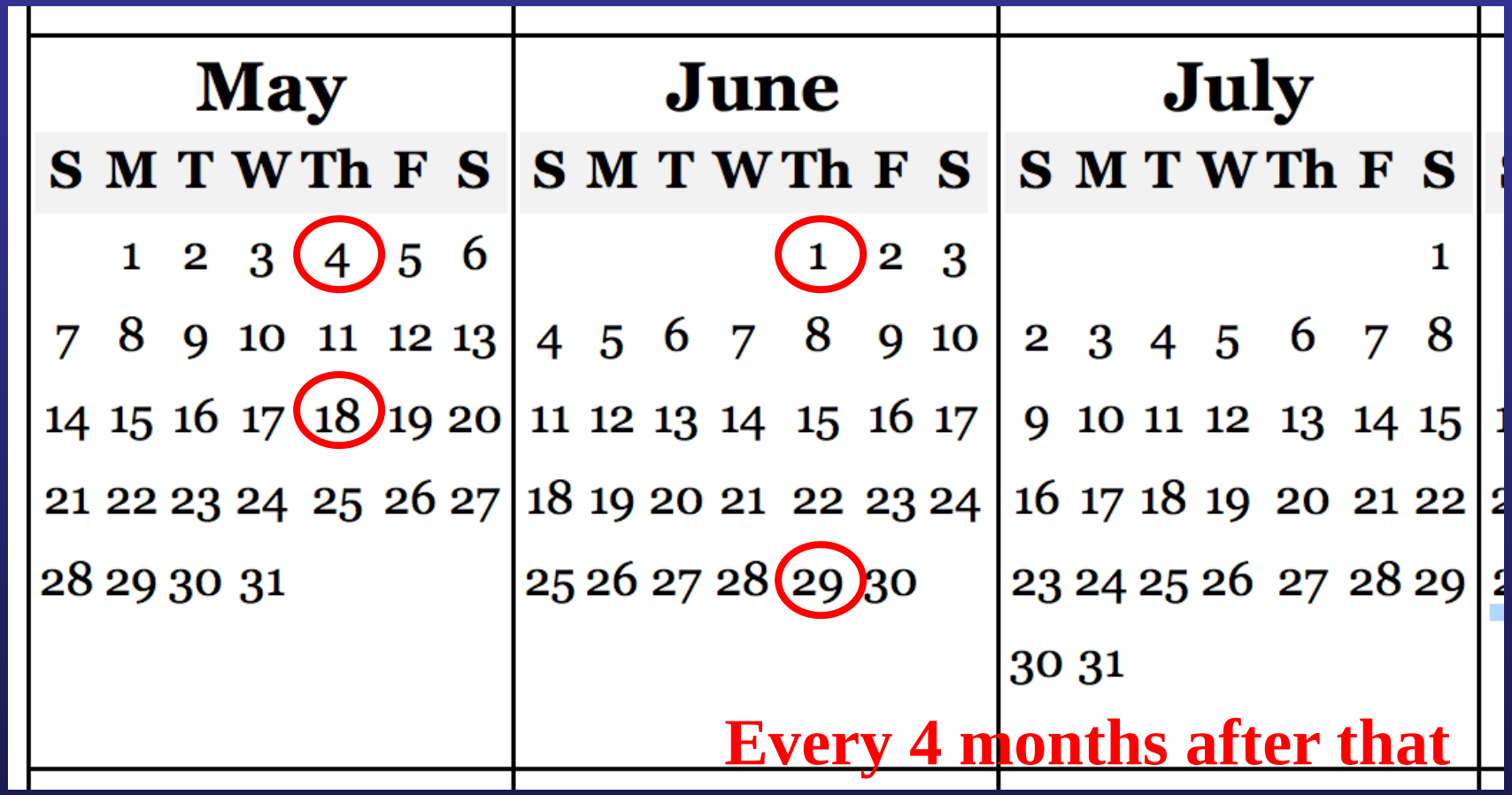



A
B

Challenges of Intrathecal Administration

- In modern hospitals, places to performing lumbar punctures (LPs) are limited
- The location of this procedure depends on whether sedation is required or not
- Issues of scheduling rooms and personnel over two months

Infusion Schedule



May

S	M	T	W	Th	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

June

S	M	T	W	Th	F	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

July

S	M	T	W	Th	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

Every 4 months after that

Who Will be Treated?

- A reasonable business plan for treating SMA longterm with nusinersen is unlikely to be equitable or just
- Guidelines for SMA care exist, but need to be modified now that we have NBS

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 103–115

www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Eugenio Mercuri [a,b,1,*], Richard S. Finkel [c,1], Francesco Muntoni [d], Brunhilde Wirth [e], Jacqueline Montes [f], Marion Main [d], Elena S. Mazzone [a,b], Michael Vitale [g], Brian Snyder [h], Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H. Meyer [m], Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Kirschner [q], Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thomas Sejersen [v] for the SMA Care Group

Feb, 2018

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 197–207

www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,1], Eugenio Mercuri [b,1,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group

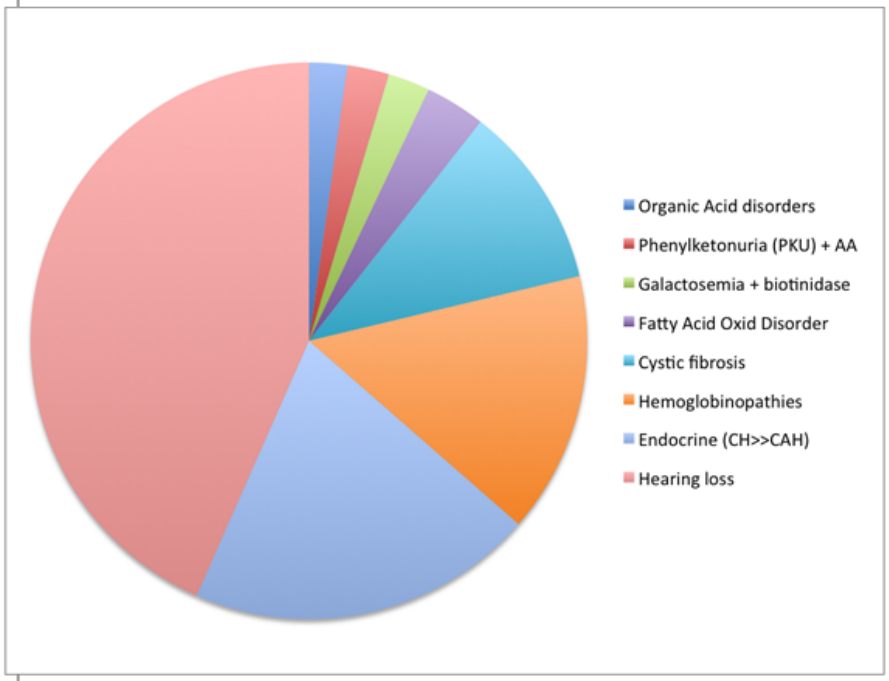
Mar, 2018

SMA Longterm Care Guidelines

- Premise that proactive and regularly scheduled PT, orthopedic, pulmonary, and nutritional care can lead to better outcomes
- Follow-up in the MDA (neuromuscular) clinics every 3-6 months for type 1 & 2 patients.

Annual # Infants Diagnosed by NBS in U.S.

MMWR, 2012



SMA n~ 400

X-ALD n~ 300

Pompe n~150

6000
5000
4000
3000
2000
1000
0

260
283
286
408
1,248
1,775
2,358
5,073

Organic Acid disorders
Phenylketonuria (PKU) + AA
Galactosemia + biotinidase
Fatty Acid Oxid Disorder
Cystic fibrosis
Hemoglobinopathies
Endocrine (CH>>CAH)
Hearing loss

Final Thoughts

- SMA is a disorder of lower motor neurons where the most patients have severe weakness and early death
- Nusinersen is a treatment offering great benefit to those with SMA type 1 and 2 when give presymptomatically (before irreversible lower motor neuron damage)
- Nusinersen is still a new drug and we still have much to learn about who should receive treatment, when treatment should start, and whether it should ever stop

Questions?

- Please press *7 to unmute, or type your question in the chat box.

Upcoming Webinar

- SMA: Overview of Available Screening Methods

  Thursday, June 28, 2018, 1:00 – 2:30 pm ET

* Webinar access information can be found on the Newborn Screening Training webpage at aphl.org and will be sent via the listserv

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