MDA 2023 Engage Symposium

Orthopedic Aspects of Spinal Muscular Atrophy: Evolving Treatments in the Age of Disease Modifying Therapies

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NEMOURS CHILDREN'S HEALTH

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Alfred I. duPont Hospital for Children

Disclosures

2022 ACCEL-CTR-DE Research Grant

- "Quantification of muscle stiffness in spastic hemiplegic cerebral palsy using magnetic resonance elastography

2020 POSNA Basic Science Research Grant

- "Muscle Stiffness in Cerebral Palsy: The Effect of Botulinum Toxin"

Consultancy:

- None

Acknowledgement, Nemours Muscle Clinic:

- Drs. **Mena Scavina** (Neurology), **Robert Heinle** (Pulmonology), **Eileen Shieh** (Rehab Medicine)
- **Amanda Erb** PT, **Jen Hultberg** (Coordinator)

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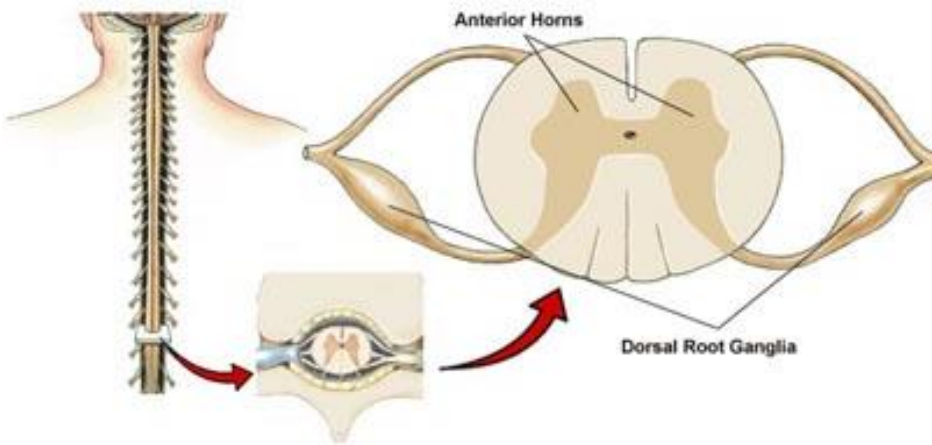
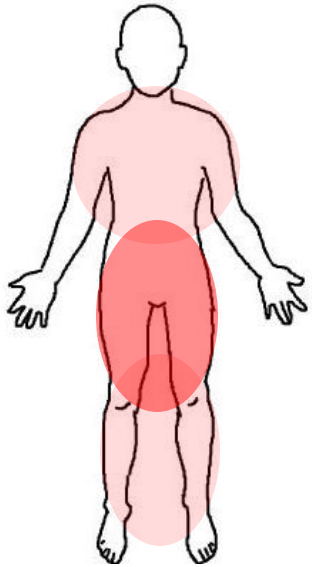
Spinal muscular atrophy



- **Relatively common**
  - 1/6000-1/10,000
- **Autosomal recessive**
- **Progressive neuromuscular disorder**
  - Spectrum of functional impairment, age of onset
- **Spinal cord anterior horn cells affected**
  - Low muscle tone, no reflexes
  - Proximal weakness, lower > upper extremity
  - Respiratory muscles involved



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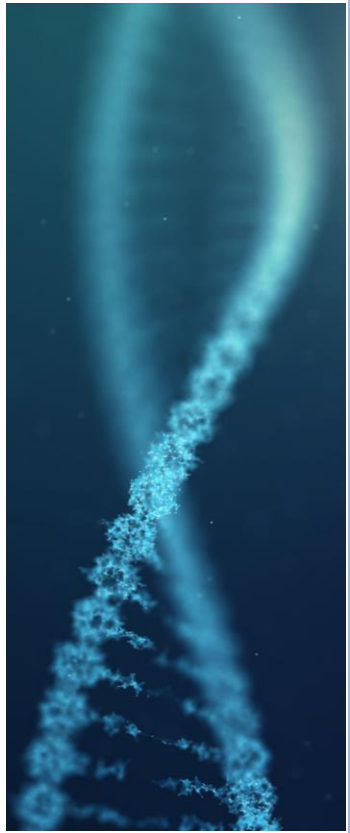
Survival motor neuron (SMN) protein

- **Important for neuronal development**
- **SMN1 gene involvement**
  - SMN protein affected
  - Anterior horn cell degeneration
- **SMN2 gene**
  - Much less viable SMN protein (5-10% of normal)
  - SMN2 Copy number important, more protein
  - **Generally, Type I: <2 copies, Type II,III: ≥3 copies**
- **Disease-modifying agents target these genes**
  - Nusinersen, Risdiplam, Onasemnogene abeparvovec



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TYPE I - Acute Infantile

Onset: birth - 6mos

- Floppy baby
- Severe motor delay
- Can't sit independently
- Improved respiratory function with gene Rx

TYPE II - Chronic Infantile

Onset: 6-18mos

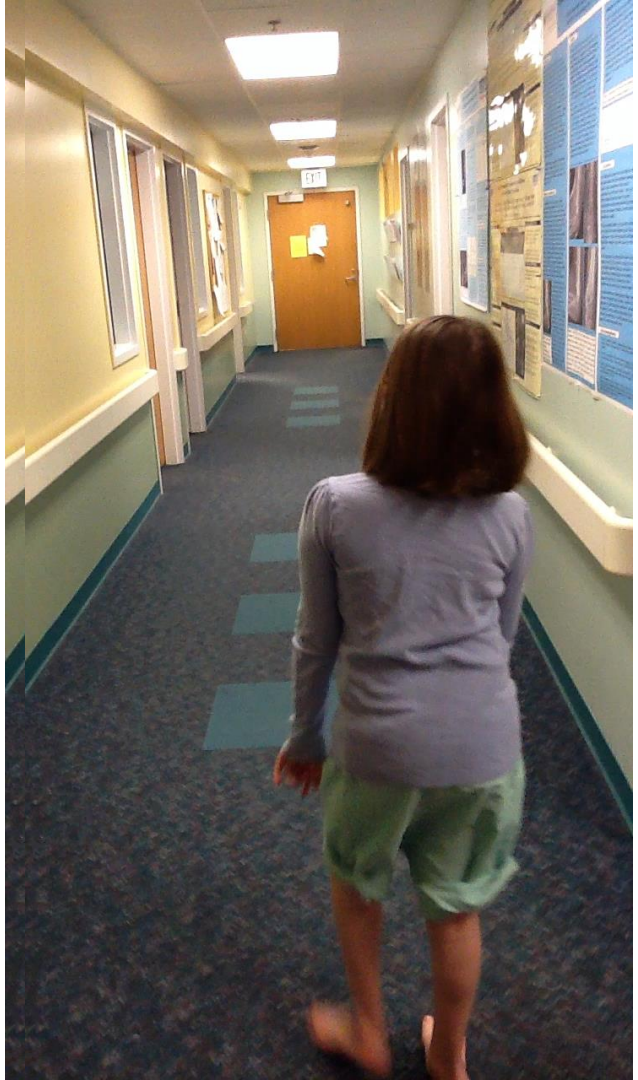
- Head control / sitting ok
- Wheelchair mobility
- Improved ambulatory function with gene Rx

Type III Kugelberg-Welander

Onset: 2 - 15yrs

- Hip extensor weakness
- Trendelenburg gait
- Lumbar lordosis
- Crouch/Knee hyperextension (quads weakness)
- Wheelchair as adults
- Near normal lifespan

Orthopedic Rx non-controversial



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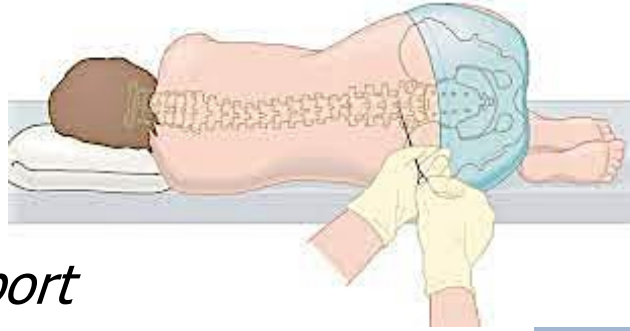
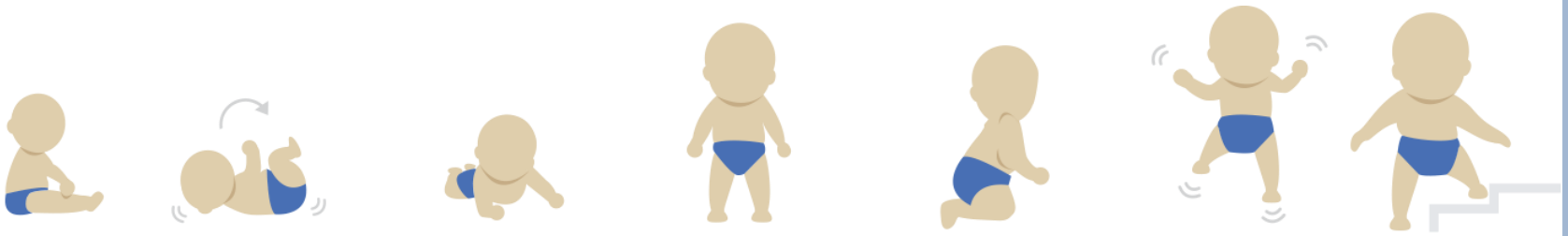
Disease-modifying agents (DMAs)



- **Nusinersen (Spinraza™)**
  - Delivered by lumbar puncture or *tunnelled port*
  - Modifies **SMN2** gene splicing
  - More SMN2 = more SMN protein
  - Improved survival and motor development
  - *Risdiplam* (oral)
- **Onasemnogene abeparsovec (Zolgensma™)**
  - Replaces the defective **SMN1** gene
  - Similar improvements in function

These agents have changed the way Orthopedists think about SMA

Hammersmith Functional Motor Scale



SITTING	ROLLING	TRANSITIONS/ CRAWLING	STANDING/ STEPPING	TRANSITIONS/ KNEELING	SQUAT/JUMP	STAIRS
ITEMS 1-4	ITEMS 5-9	ITEMS 10-17	ITEMS 18-20	ITEMS 21-27	ITEMS 28-29	ITEMS 30-33

HAMMERSMITH FUNCTIONAL MOTOR SCALE-EXPANDED (HFMSE) EXAM

- **Validity and reliability confirmed for SMA, developed primarily for Types II, III**
- **66 max total score**
- **Has been correlated with SMN2 copy #, FVC, muscle strength**
- **Used to document functional change after DMA Rx**

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Orthopedic Aspects of SMA

- **Scoliosis**
  - Seating imbalance
  - Standing/walking impairment
  - Respiratory dysfunction(?)
- **Hip instability**
  - Painful arthritis
  - Standing/walking impairment
- **Fractures**
  - Bone fragility
  - Tibia/femur most common

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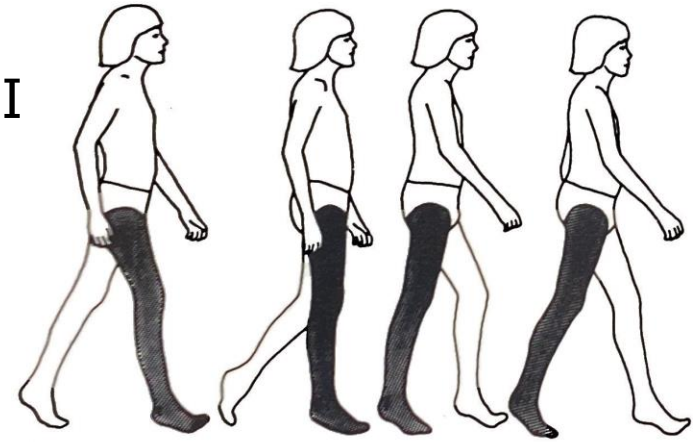
Orthopedic Aspects of SMA

- **Gait abnormalities**
  - Traditionally Type III
  - With Disease modifying agents, Type II
  - Lower extremity muscle contractures
  - Hip instability
- **Standing impairment**
  - Types I and II
  - Lower extremity muscle contractures
  - Hip instability/scoliosis



Type III SMA
Tight heel cords, toe-walker

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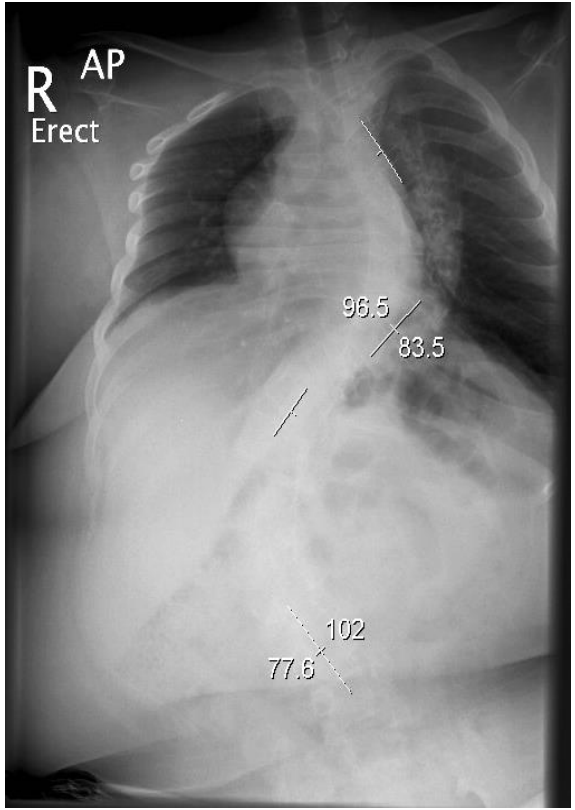
DMA Rx is changing attitudes…focus on function

Scoliosis in SMA

- **Very common**
  - 60-90% Type I/II
- **Earlier onset than idiopathic cause**
  - 7-8 years-old
- **Proportional to functional level**
  - DMAs likely having an impact
- **Seating problems**
- **Difficult with care giving**
- **Respiratory decline concurrent**



Double-major curve
Type II SMA

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Bracing for Scoliosis in SMA

- Seating support
- Does not improve scoliosis
- Can exacerbate respiratory dysfunction
- Abdominal cutout for G-tube, breathing
- Semi-rigid best

Curves > 50-60° indicated for surgery

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Image from: https://nationalscoliosiscenter.com/blog/scoliosis-insights/how-bracing-can-help-childhood-spinal-muscular-atrophy/

Goals of Scoliosis Surgery in SMA

- Comfortable SEATING
- EASE OF CARE-GIVING
- SOCIAL INTERACTION
- Decrease pain
- Benefits > Risks

DMAs improving function, decreasing risk

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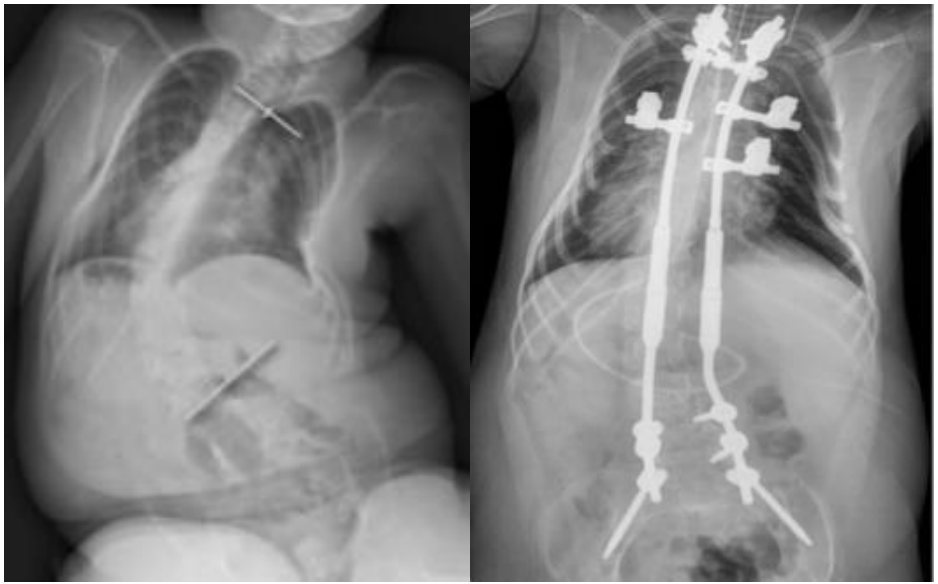
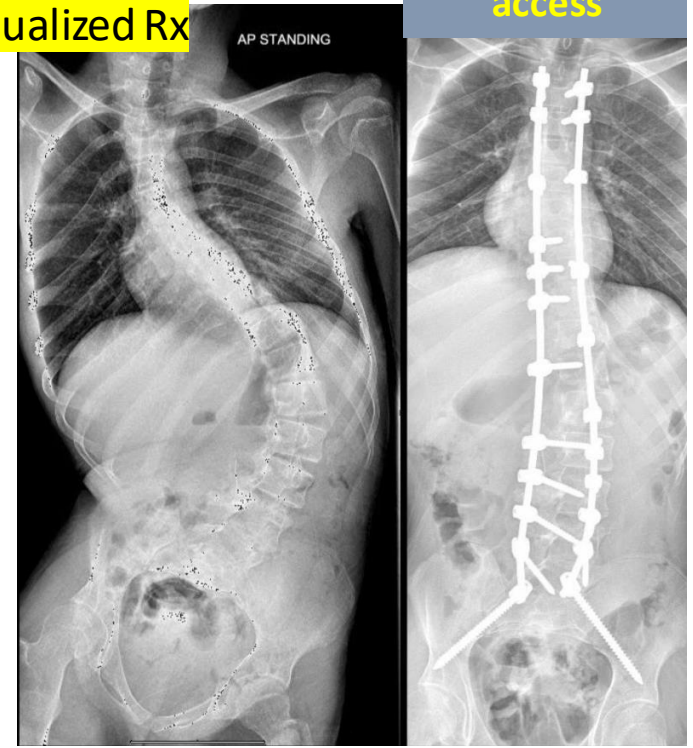
Types of scoliosis surgery

Leave a window for intrathecal access

8-10: individualized Rx



Growth-friendly < 8 years-old



Definitive fusion > 10 years old

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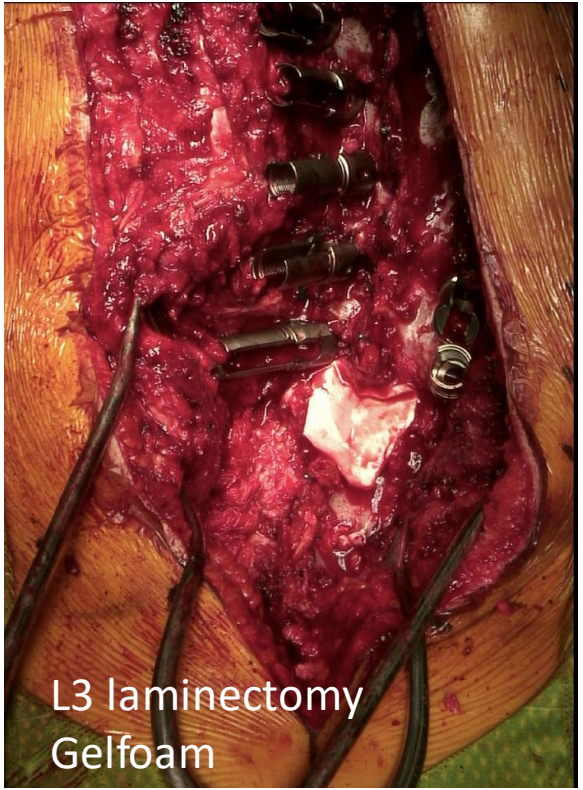
Nusinersen access after spinal fusion: Options

- **Laminectomy (L3) for intrathecal access**
  - Clips at spinous process of L2/L4 for IR easy visualization for intrathecal access
- **Convert to oral Risdiplam (Evrsdi®)**
- **Intrathecal catheter port**



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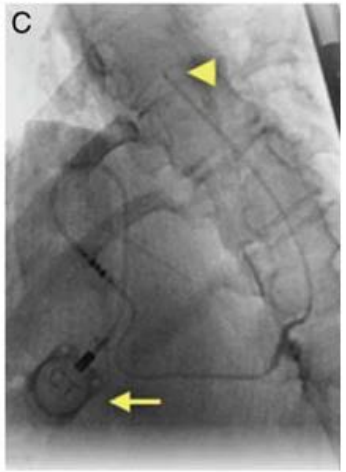
Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy

Kevin A. Strauss, MD, Vincent J. Carson, MD,* Karlla W. Brigatti, MS, LCGC,* Millie Young, RNC,* Donna L. Robinson, CRNP,* Christine Hendrickson, RNC,* Michael D. Fox, MD,†‡ Robert M. Reed, MD,§ Erik G. Puffenberger, PhD,* William Mackenzie, MD,†‖ and Freeman Miller, MD†‖*

J Pediatr Orthop • Volume 38, Number 10, November/December 2018



Dr. Freeman Miller

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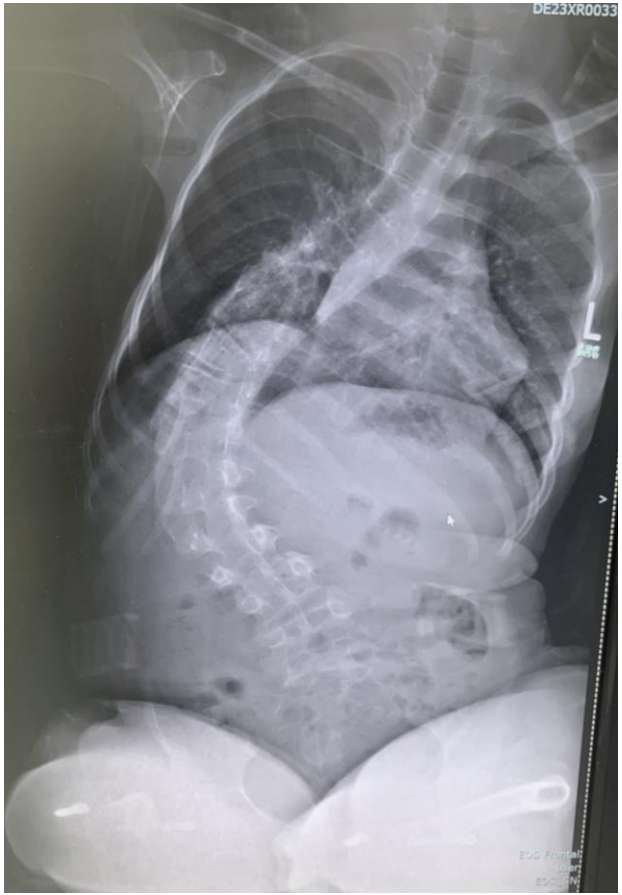
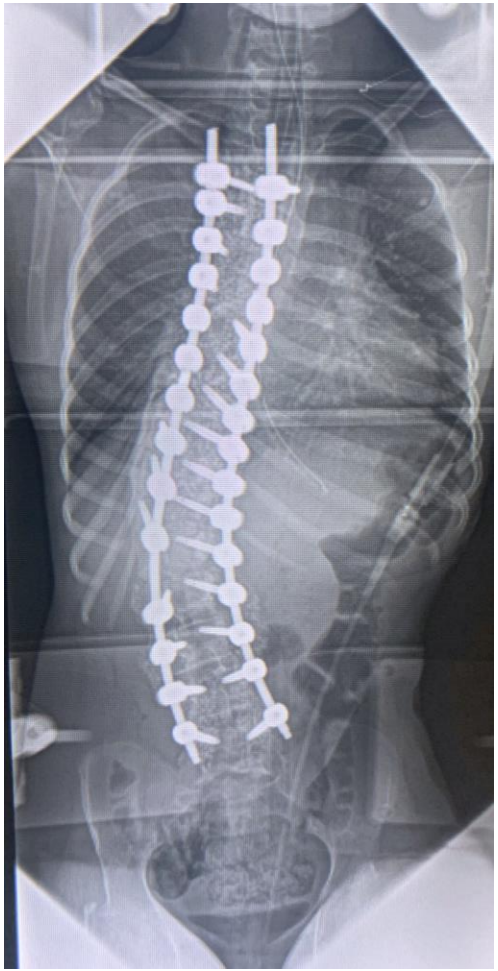


For children who walk: consider not fusing to the pelvis for pelvic motion preservation



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Chest deformity in SMA

- **Bell-shaped chest**
  - Intercostal muscle weakness
  - Relatively strong diaphragm
  - Ribs sag, lack of support
  - Respiratory decline over time
- **Does scoliosis surgery help?**
  - Not addressing the primary problem
  - Respiratory decline can vary with age
  - Prior studies not controlled

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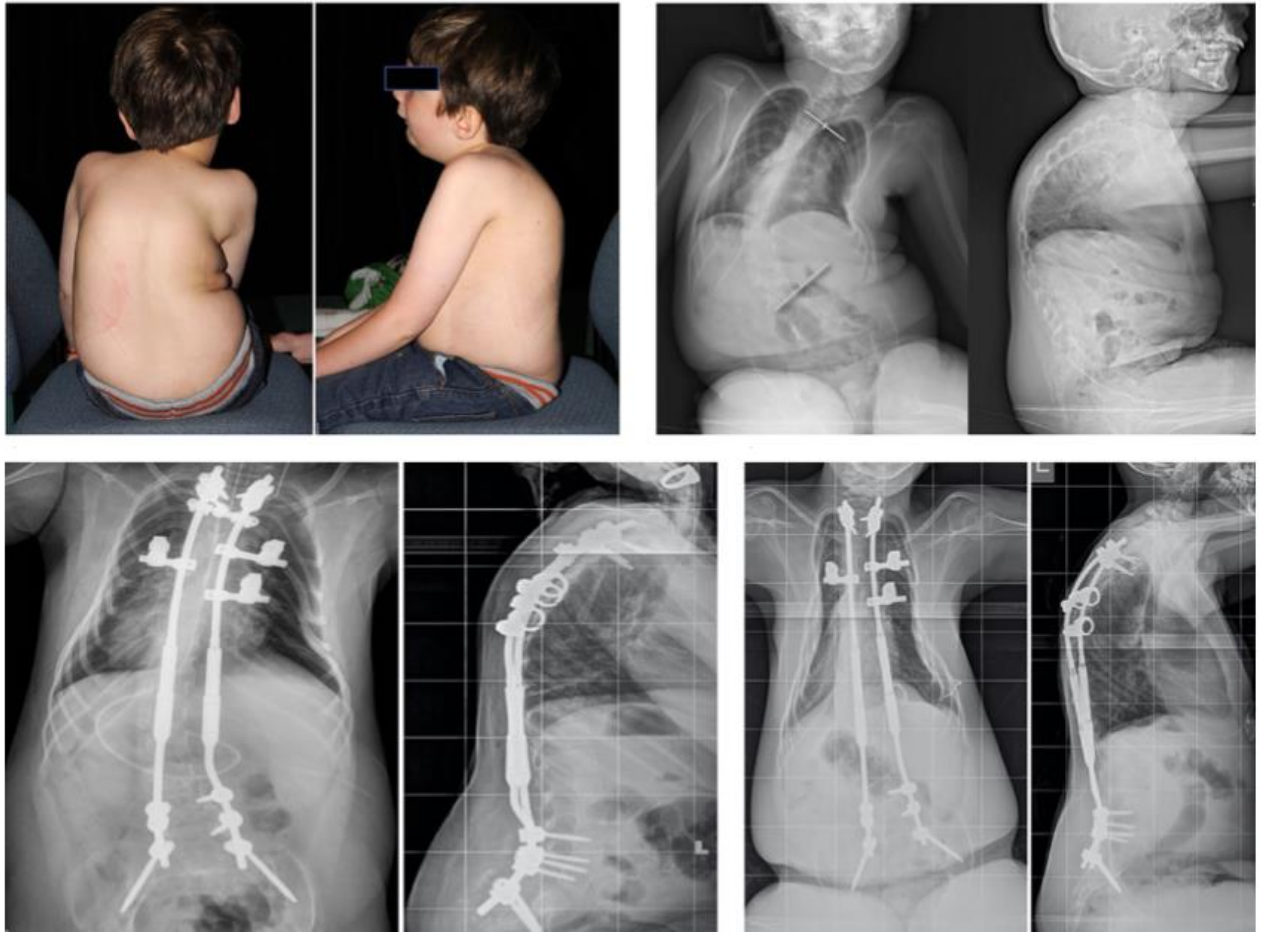
Chicken, egg, or two different chickens?



Chest gets worse despite early scoliosis surgery

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(Courtesy, Dr. Ron El-Hawary)

REVIEW ARTICLE

Pre-DMA Treatment era

The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review

Abduljabber Alhammoud[1,2] · Yahya Othman[3] · Ron El-Hawary[4] · William G. Mackenzie[5] · Jason J. Howard[5]

Evidence-based Statement	GRADE Recommendation
Surgery is most often associated with **decreases in pulmonary function**	C
The impact of surgery on pulmonary function is variable but **does not reliably improve over pre-operative baseline**	C
Surgery may result in a **decreased rate of decline** in pulmonary function post-operatively	C

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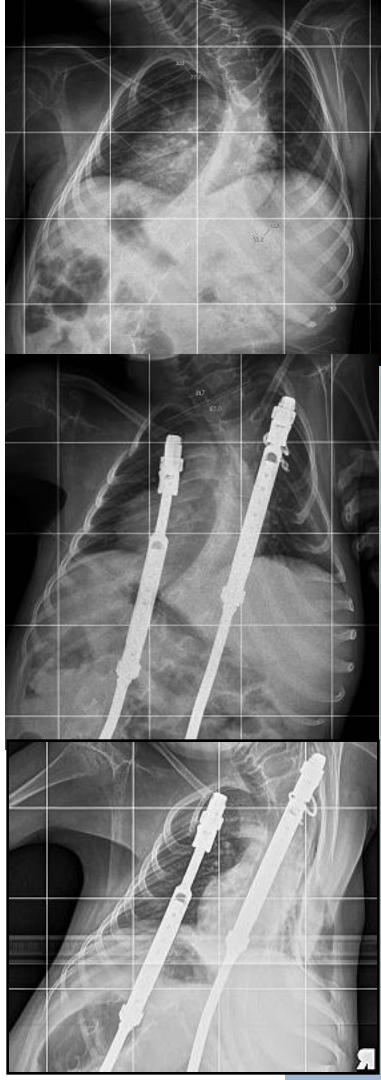
GRADE C – poor or conflicting evidence based on level IV/V evidence.



Growth Friendly

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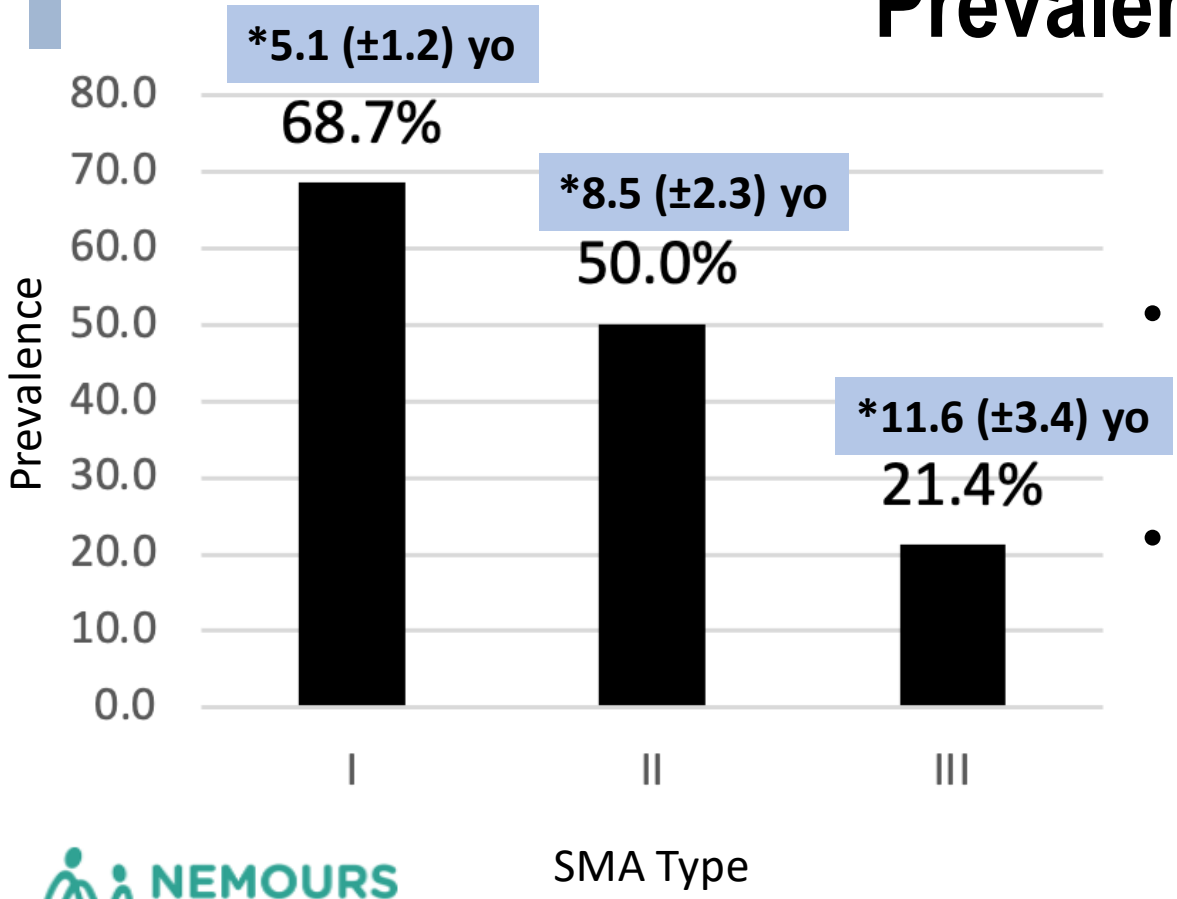
Prevalence of Scoliosis in SMA



- Overall prevalence
  - 52%
- *Age at scoliosis onset:
  - Overall: 7.1 (±2.3) y
  - Rises with SMA type

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(Ulusaloglu, Howard et al, POSNA 2023)

Risk factors for Scoliosis in SMA

- **Overall prevalence 52%**
  - Age of onset: 7.2 years-old
  - 34(SD:22)° to 48(SD:29)° over 7y FU

Proxies of disease severity (non-ambulatory)

DMA treatment did not prevent scoliosis

Risk Factor	Univariate p	Univariate Exp (B)	Multivariate p	Multivariate Exp(B)
SMN2 <3 copy	.029*	2.899		
SMA type 1	.006*	8.067	0.96	4.046
SMA type 2	.076	3.667	0.529	1.68
DMA treatment	.066	0.335		
Non-ambulatory, FMS_{50}=1	.039*	3.378		
Hip displacement	<0.001*	10.303	.003*	8.372

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(Ulusaloglu, Howard et al, POSNA 2023)

Hip instability in SMA

- **Hip instability is common in most neuromuscular disorders**
  - Cerebral palsy (CP) being the most studied
  - Also highly prevalent in SMA, linked to functional level
- **Hip abductor weakness, lack of functional weightbearing**
- **Leads to laterally directed growth of the proximal femur (ball), acetabulum (socket) dysplasia**
- **Eventual dislocation, osteoarthritis**
  - BUT variable outcomes in prior studies, small numbers.
  - Recent studies show higher pain prevalence than previously thought (58%)

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*(Xu et al, JPO 2022)

Hip Pain in SMA

- **Risk Factors**
  - Obesity
  - Prior scoliosis surgery with fusion to pelvis
  - Hip contractures
  - Hip dislocations
- **Higher pain with ↑SMN2 copies, Type II > Type I**
  - Better function, more strength
- **Impact of DMAs on hip pain unknown**
  - Higher function may lead to more pain (muscle force)

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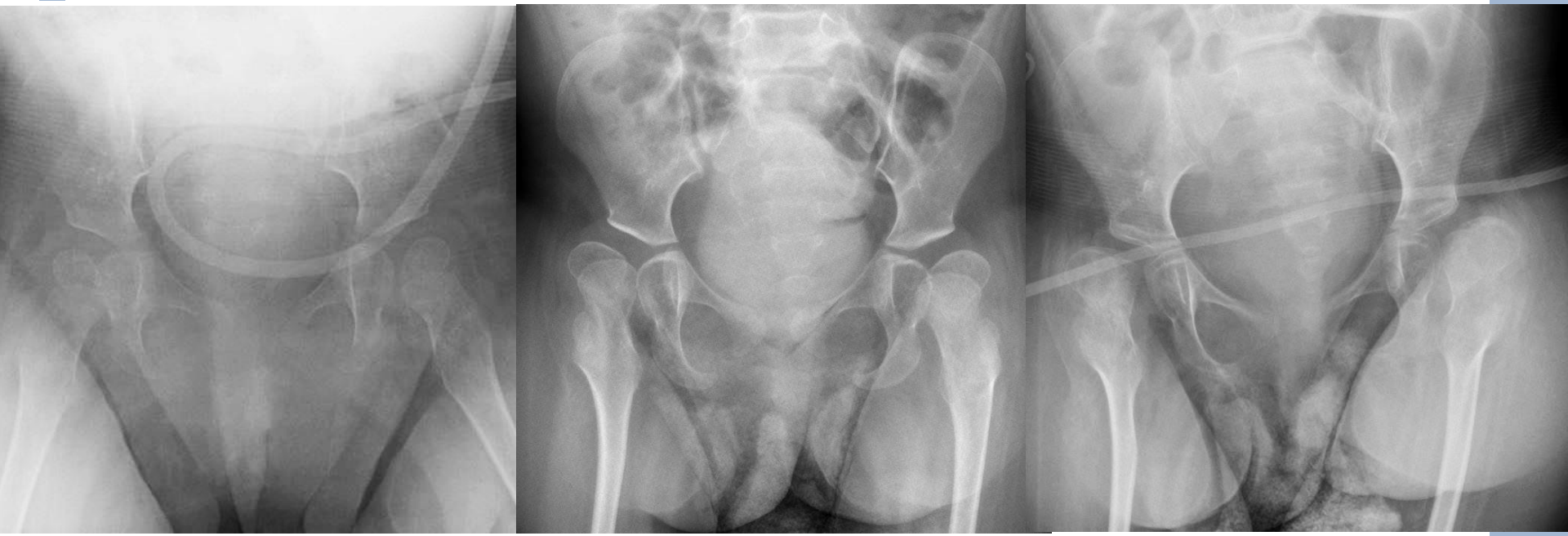
*(Hanna et al JBJS OA 2023; Xu et al, JPO 2022)

Type I SMA with progressive hip displacement



2 years-old

5 years-old

7 years-old

Usually painless until later, not all develop pain

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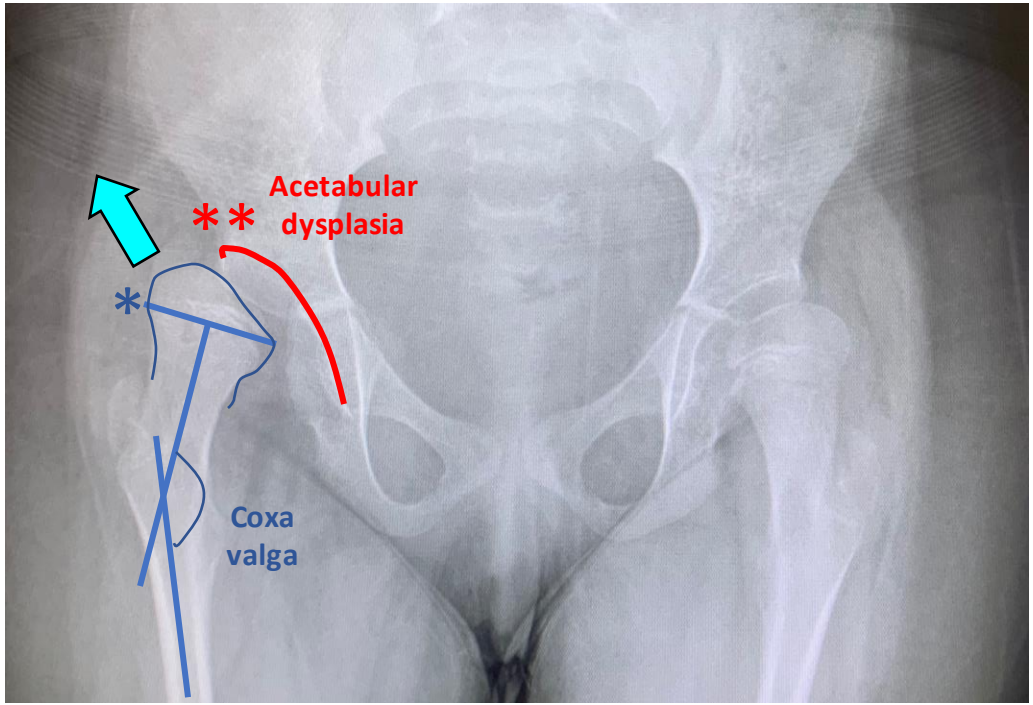
SMA hip instability: X-ray features



- **Growth plate tilt (*)**
  - Ball tilts laterally
  - 'Coxa valga'
  - Pressure on the socket (**)
- **Acetabular dysplasia**
  - Progressive
  - Lack of support (roof)
  - Dislocation

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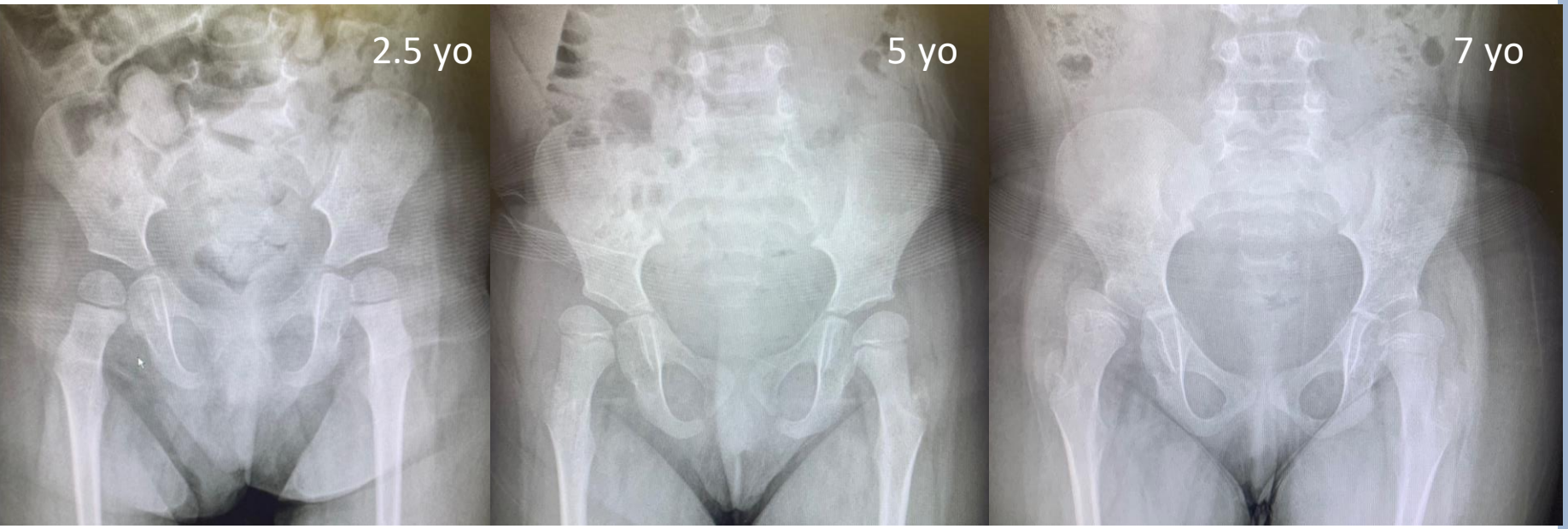
Type II SMA, Nusinersen, able to walk



<u>Indications for surgery</u>: Pain, walkers, DMA treatment?

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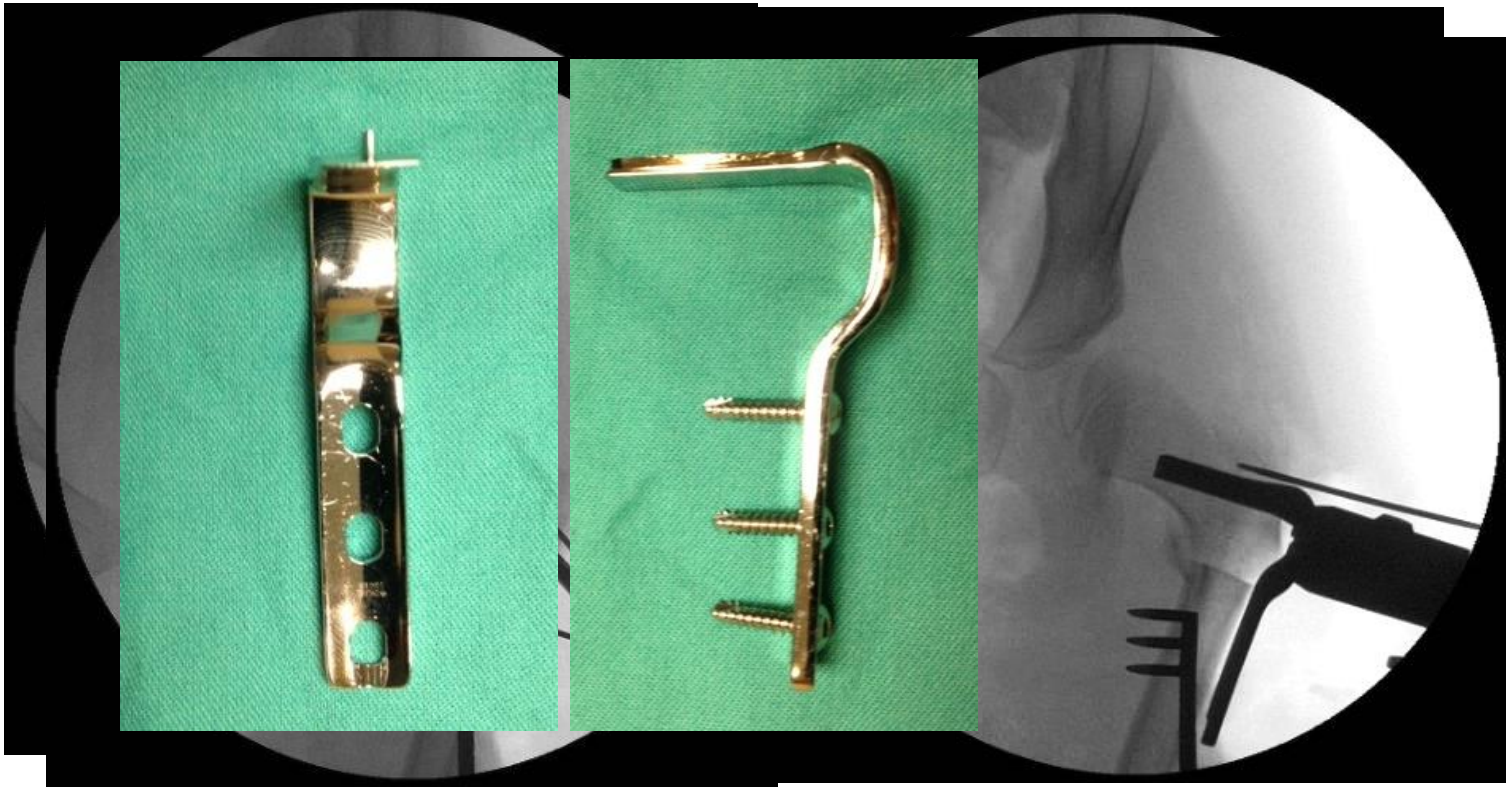
Direct the ‘ball’ into the socket



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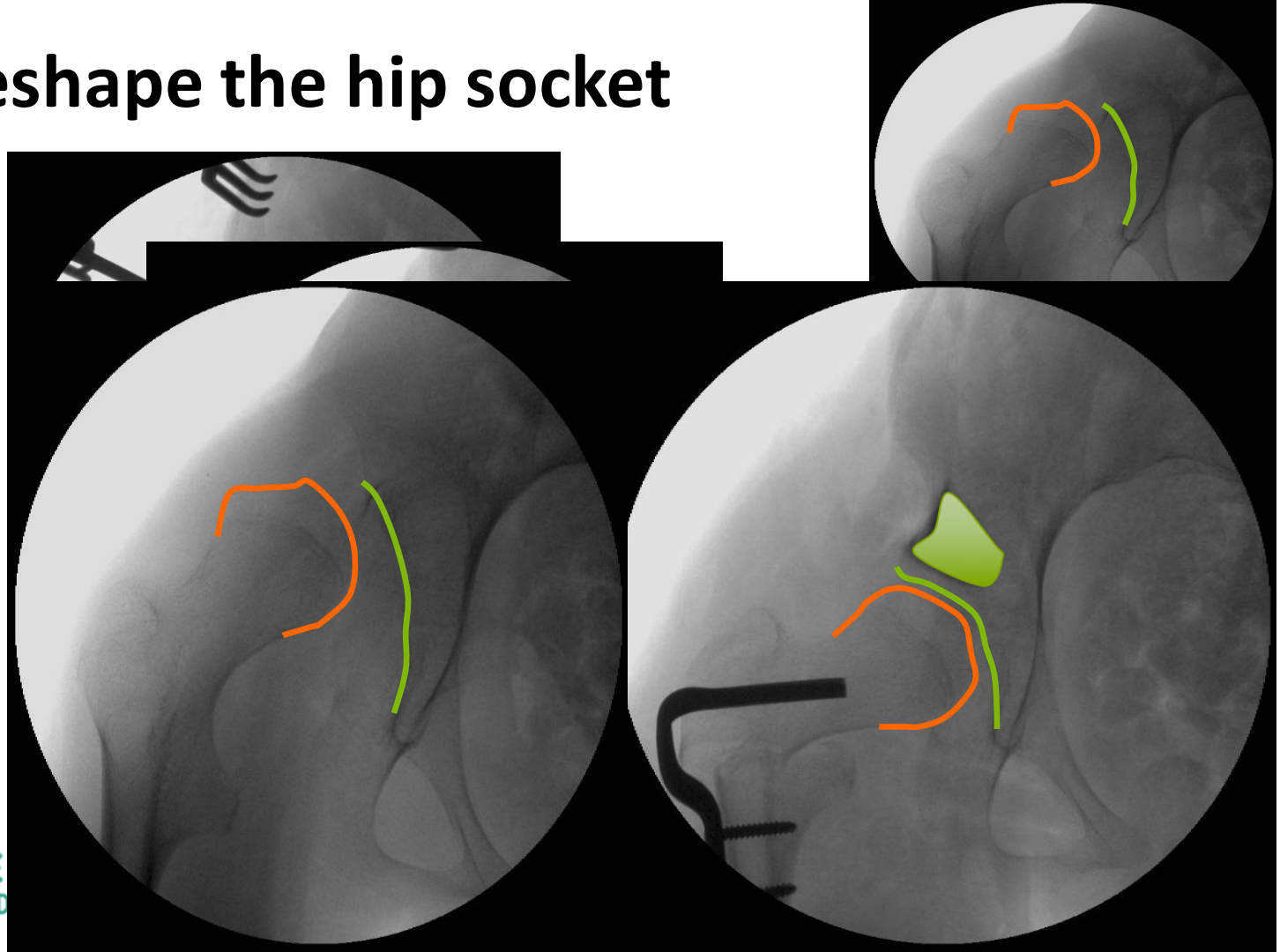
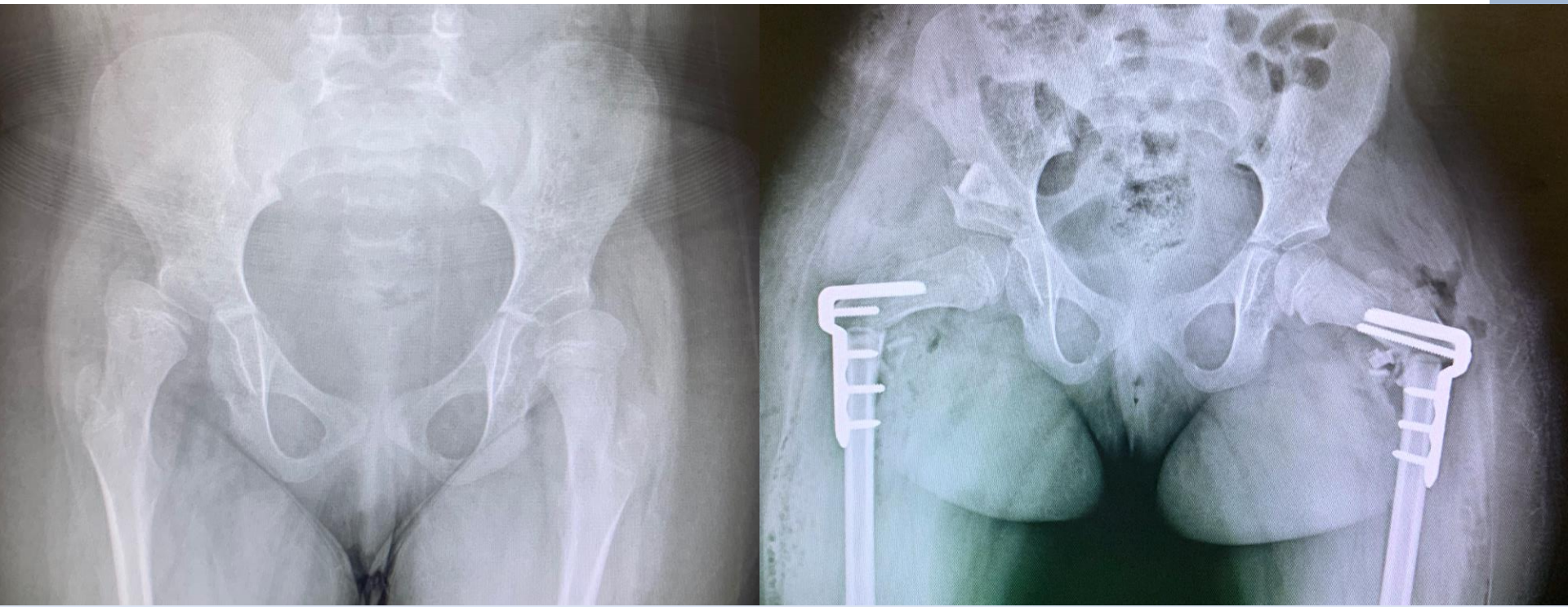
Reshape the hip socket



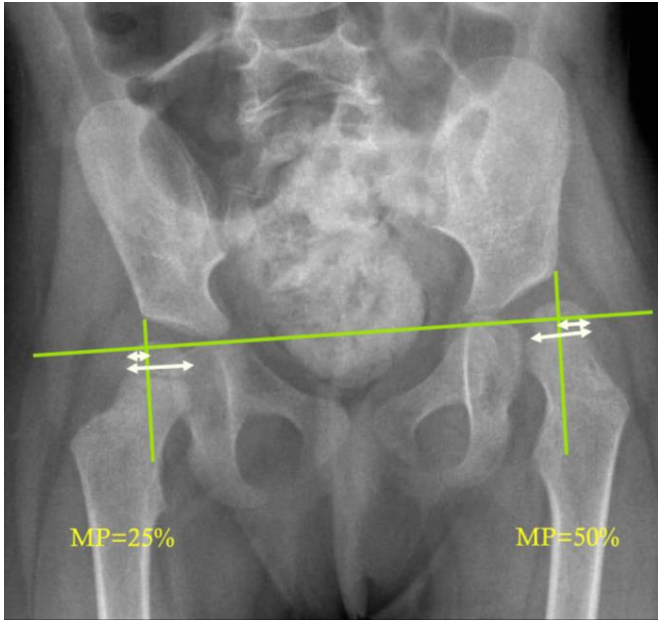
SMA hip instability: Surgical Treatment



Prevent arthritis, improve seating, improve positioning/perineal care

Risk factors for Hip Instability in SMA

- **82 patients with SMA, Nemours Muscle Clinic**
  - Type I: 39%, II: 44%, III: 17%
- **Hip surveillance X-rays**
- **Risk factors investigated**
  - Genetic severity (# of SMN2 copies)
  - SMA Type
  - DMA Treatment > 2 years (mostly Nusinersen)
  - Walking status
  - Hammersmith Motor Scale (66 max score)
  - Presence of Scoliosis (>40°)



Hip surveillance X-ray with MP measurement

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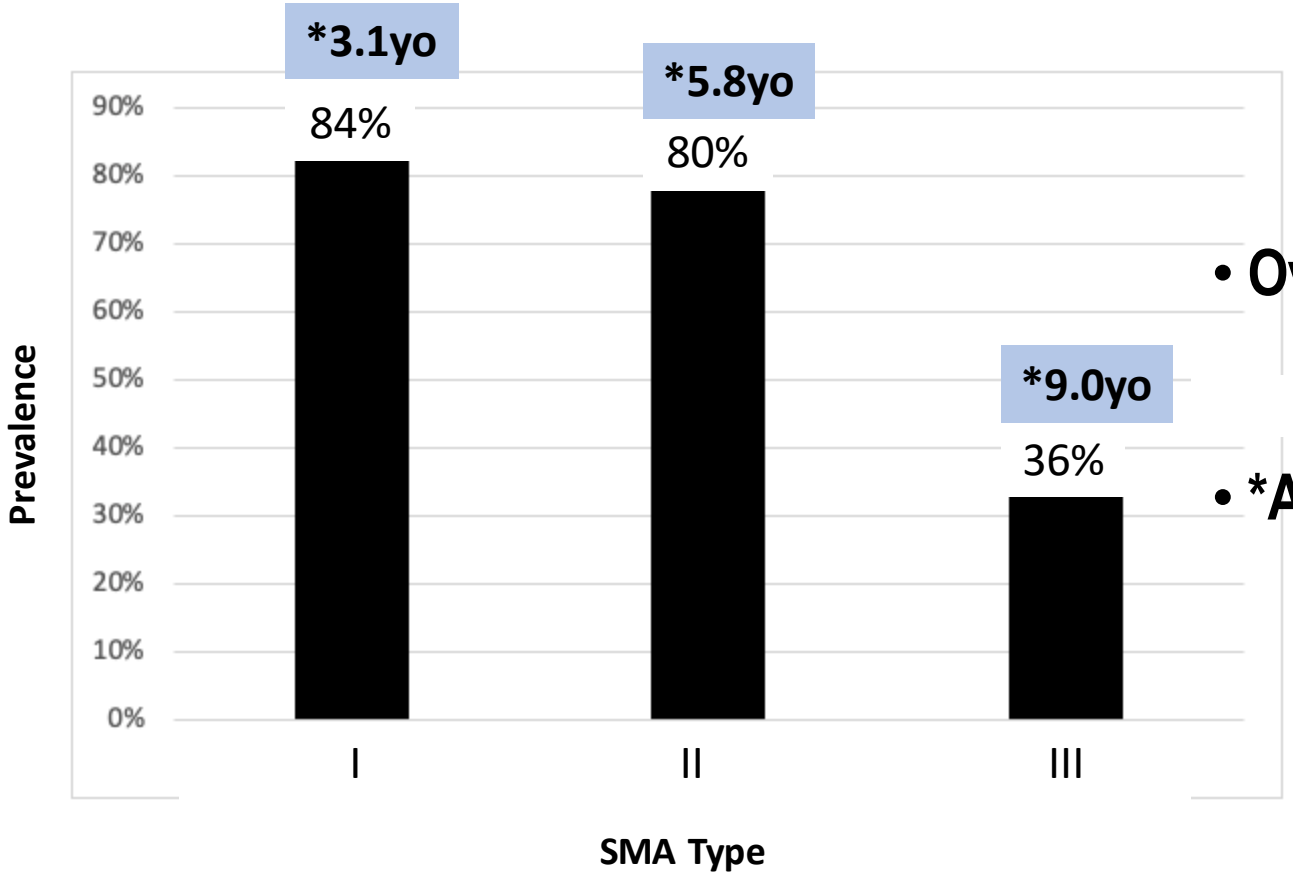
(Ulusaloglu, Howard et al, POSNA 2022)

Prevalence of hip displacement in SMA

(Ulusaloglu, Howard et al, AACPDM 2022)



- Overall prevalence
  - 75.6%
- *Age at HD onset:
  - 4.6 (SD: 2.7) years

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Risk Factors for Hip Displacement

	Univariate Analysis		Multivariate Analysis*	
	EXP (B) OR	Sig. P	EXP (B) OR	Sig. p
SMA Type 1	9.72	**0.002**	1.439	0.731
SMA Type 2	9	**0.002**	**6.185**	**0.038**
SMN2 Copy < 3	2.703	**0.107**	6.732	0.088
HFMS ≤23	9.8	**0.01**	-	-
Non-ambulatory (FMS_{50}=1)	7.636	**0.001**	-	-
Scoliosis	14	**0.014**	**9.698**	**0.039**
DMA Treatment	4.5	**0.011**	-	-

*Backward Multivariate Logistic Regression Analysis

- **Independant risk factors**
  - SMA Type II (OR: 6.2)
  - Scoliosis (OR: 9.7)
- **DMA Rx not protective**
  - 66 (80%) patients w/ DMA
  - 64% Nusinersen

Hammersmith Score > 23 was protective

DMA treatment did not prevent hip instability

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Should we treat hip Instability in SMA?

- **We know the risk factors**
- **Prior studies on SMA hips controversial (except Type III)**
  - No DMA Treatment
  - Poor outcome measures
  - Better medical management now
- **DMA treatment influential**
  - Patients are stronger
  - More ambulatory
  - Can better tolerate bigger surgeries

Although DMA treatment does not seem to prevent hip instability, increased function reported to lead to higher risk of moderate to severe pain*

Pre-op bisphosphonates, especially for Type I

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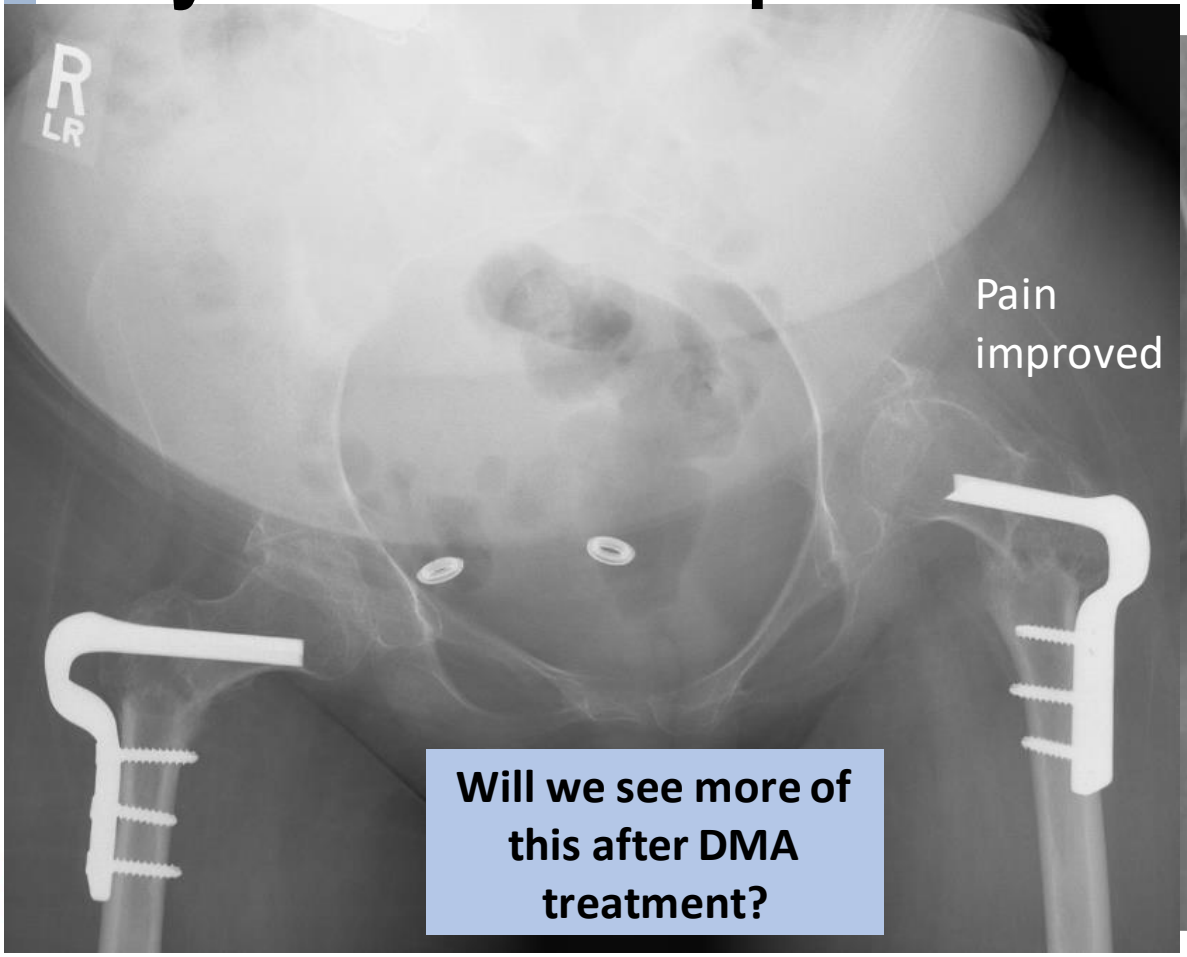
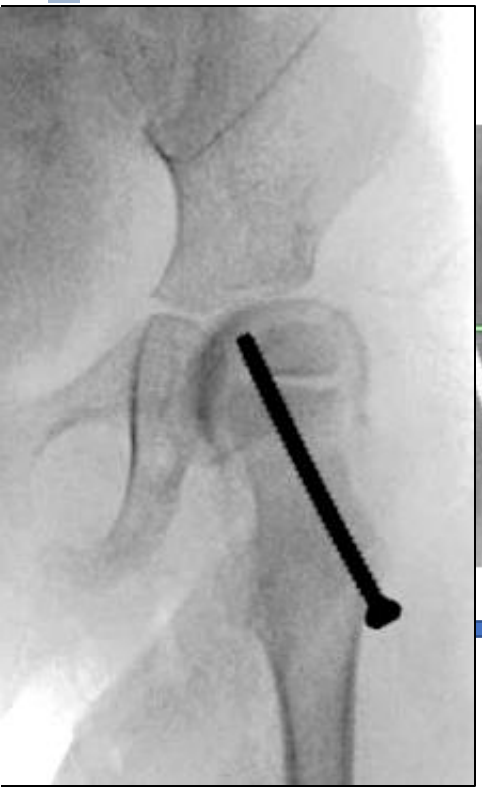
*(Hanna et al, JBJS OA 2023; Xu et al, JPO 2022)

16 year-old F with painful left hip (Type II)



Guided growth may provide a low-risk Hip Rx



4y8m old

32 MONTHS POSTOP

NEWER MINIMALLY INVASIVE OUTPATIENT R_X USED IN CEREBRAL PALSY

MAY HOLD PROMISE FOR SMA AS WELL

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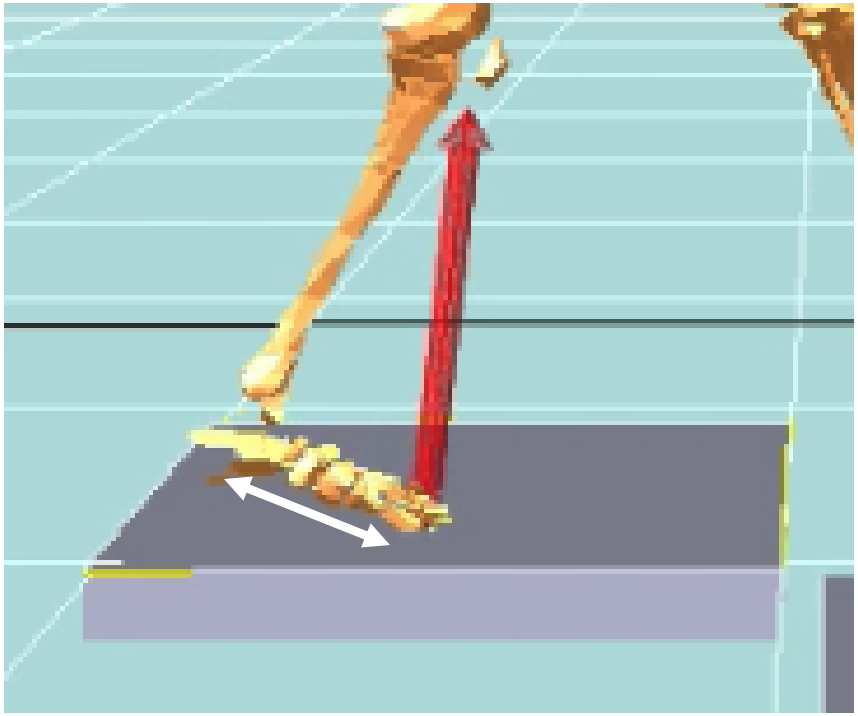
Muscle Contractures in SMA

- **Muscle imbalance**
- **Lower > upper limbs**
  - Tight heel cords (equinus)
  - Knee flexion contractures
  - Hip flexor/adductor>abductor contractures
- **Foot deformities**
  - Equinovarus (‘clubfoot’)
  - Planovalgus (‘flatfoot’)
  - Toe flexor contractures

Equinovarus foot
Affecting wheelchair footplate positioning/orthotic fitting

Contractures worsen by SMA Type and with age…braces may delay but not prevent

The Foot as a lever



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The right brace can turn a flexible foot deformity into a stable lever

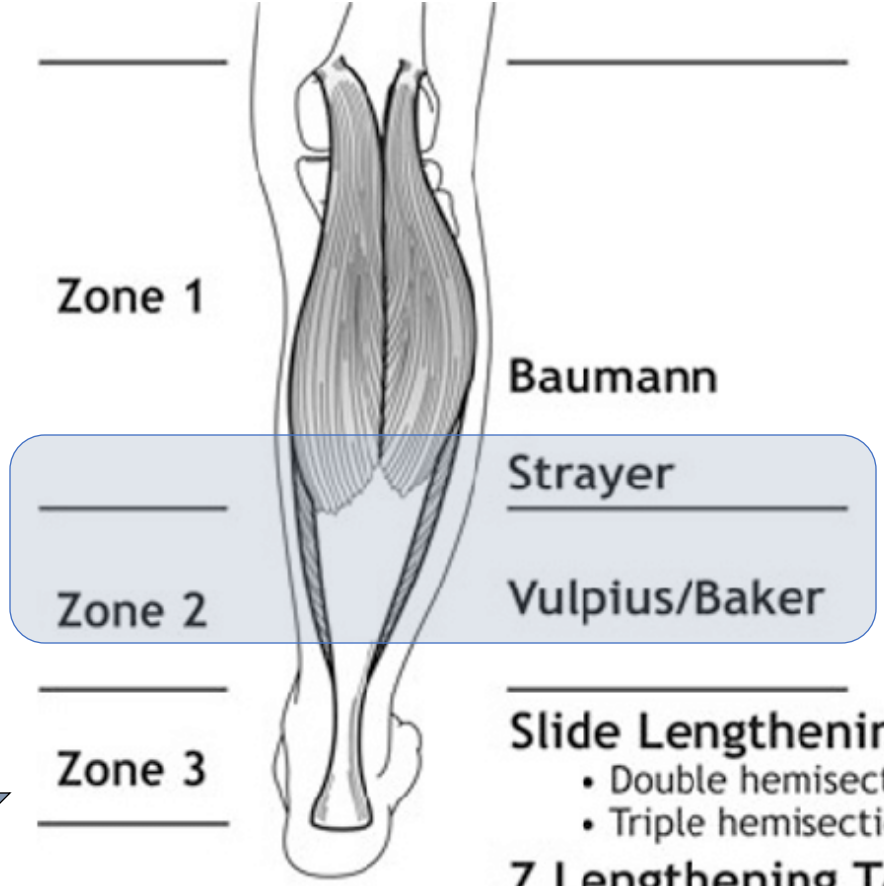
Goals of Muscle Contracture Surgery in SMA

- **Improve sitting**
  - Wheelchair seating
- **Improve standing**
  - Traditionally Type II
  - With Disease modifying agents, Type I
- **Improve walking**
  - Traditionally Type III
  - With Disease modifying agents, Type II
  - Orthotic/shoe fitting

Type II SMA (DMA Rx)
Knee flexion contracture
Affecting walking

DMA Rx is changing attitudes…<u>focus on function</u>

INCREASING SURGICAL DOSE



Baumann

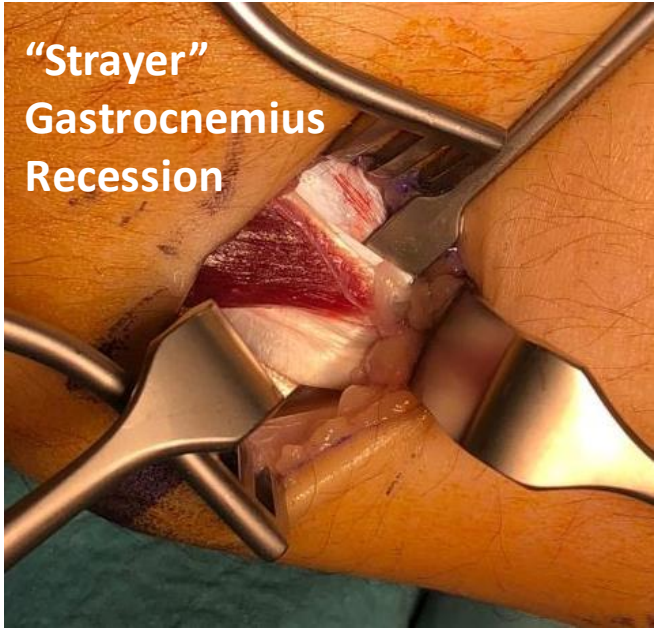
Strayer

Vulpius/Baker

Slide Lengthening TAL
- Double hemisections – White
- Triple hemisections – Hoke

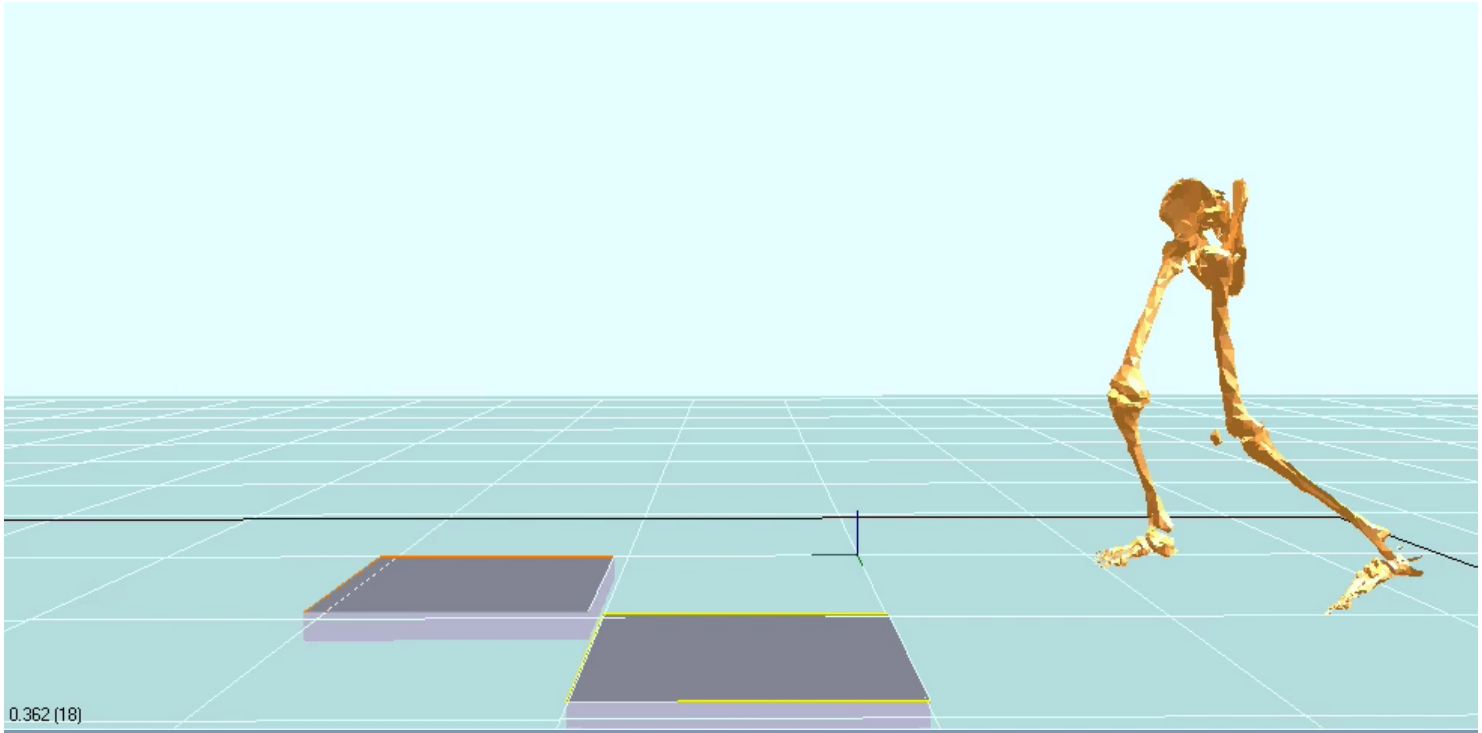
Z Lengthening TAL (Open)

Heel Cord Advancement (HCA)



Courtesy HK Graham
RCH Melbourne

Crouch gait after heel cord lengthening (CP)



Quads weakness in SMA, risk of losing walking ability

Needs to be “low dose” surgery

Knee flexion contractures limiting gait

10 year-old F Type II SMA, early Nusinersen trial, walking
Progressive knee flexion contractures

Nemours. Alfred I. duPont Hospital for Children

Physical Examination

	PASSIVE ROM				STRENGTH			
	Right		Left		Right		Left	
Hip Flex	125	140	125	120	2+	3+	2	3+
Hip Ext	-15	15	-15	15	2	3-	2	3-
Hip Abd	28	30	28	25	2	3-	2	3-
Hip Int Rot	45	45	48	55				
Hip Ext Rot	35	45	34	55				
Knee Ext	-23	-15	-25	-5	3+	3+	3+	3+
Knee Flex	WNL	145	WNL	145	3+	3+	3+	3+
Pop Angle	55 55	30 30	65 60	45 45				
Ely Test	120	145	120	145				
Dorsi (flex)	10	15	10	25	4	3+	4	3+
Dorsi (ext)	5	15	3	15				
Plantar	35	60	35	60	4	3+	4	3+
Ankle Inv	10	60	10	45	4	3+	4	3+
Ankle Ever	40	30	45	25	4+	3+	4+	3+
TMA	30 EXT	15 EXT	20 EXT	15 EXT				

5 years-old

10 years-old

Progression in muscle contractures

- Knee
- Hip

Some decrease in strength around the hip but otherwise preserved/improved

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Knee flexion contractures limiting gait (braces)

Better with braces but knee flexion requires quads activation = fatigue

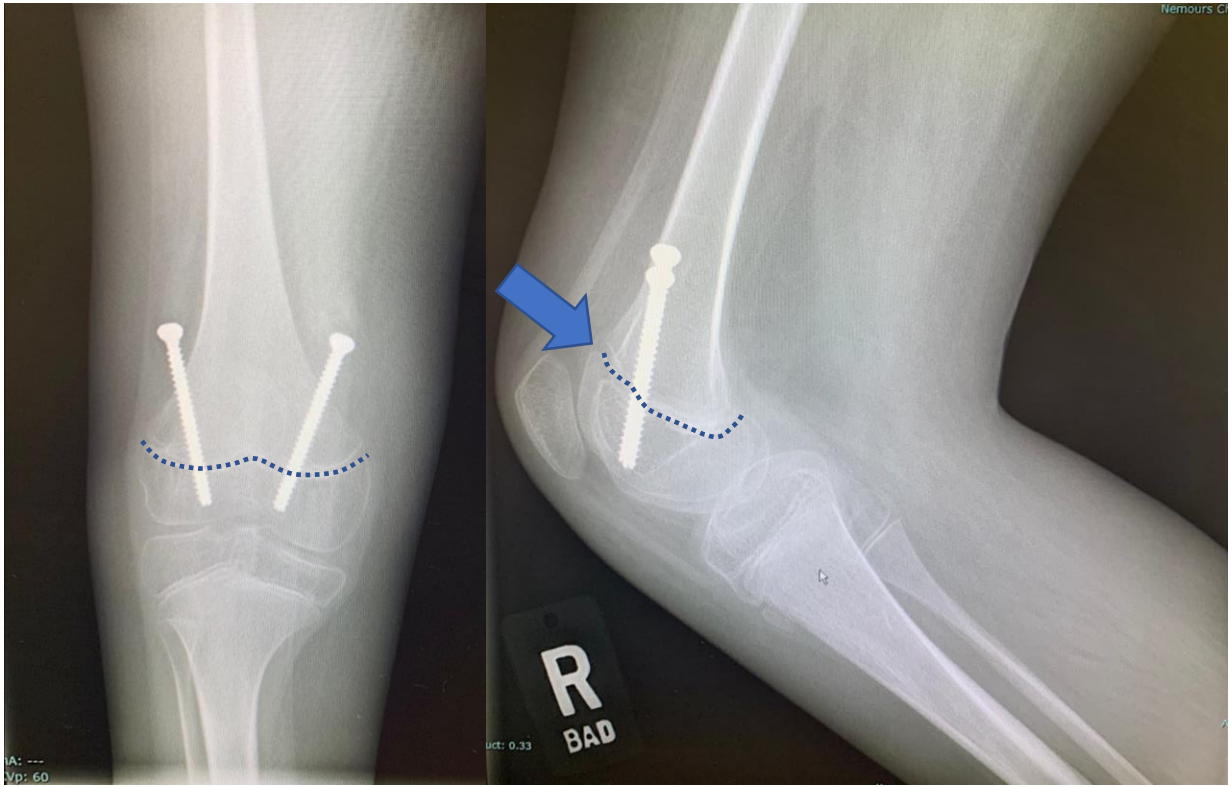
Guided growth: gradual correction, easier rehabilation

Growth plate tether

- Anterior (front)
- Untethered at the back

Gradual improvement over time

- 1° per month
- Weightbearing
- Easier rehab than bony osteotomy



Minimize immobilization, early weightbearing and ambulation are key after surgery

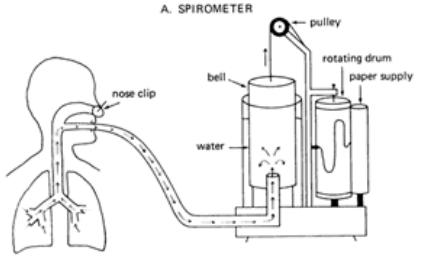
Case: 9yo M, MMC, Diastomatomyelia w/ 30° fixed knee contracture

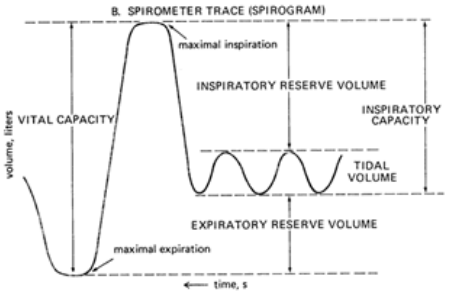
NEMOURS CHILDREN'S HEALTH

Time for screw removal WHEN DEFORMITY CORRECTED or when end of growth

Peri-operative considerations

- **Respiratory optimization**
  - Pulmonary function tests essential
  - Pneumonia/Resp failure risks
  - Related to SMA Type
- **Nutritional optimization**
  - Reduces infection risk
  - Improves wound healing
- **Bone health optimization**
  - Bone Density (DEXA) scan
  - Need strong bone to hold implants
  - Reduces risk of fracture
  - Consider bisphosphonates, especially for Type I





Type I SMA
DEXA scan distal femur

NEMOURS CHILDREN'S HEALTH

Solid Ankle-Foot Orthosis (SAFO)

- GRF: augmented, in front of knee
  - CROUCH, minimal knee FC
- Appropriate for SMA walkers when soleus/quads weak
- Corrects flexible foot deformity
- Requires ankle DF to at least 0 deg
- Stair climbing more difficult
- Better tolerated than GRAFO

Focus on function:
Different patients need different braces

NEMOURS CHILDREN'S HEALTH

Summary

- Disease-modifying agents (DMA) targeting SMN1 and SMN2 genes improve function in SMA
- Orthopedic problems seem to develop despite DMA treatment
- DMA treatment improves medical aspects of SMA, allowing safer surgeries
- Given improvements in strength with DMA treatment, hip arthritis may become a bigger problem
- Scoliosis surgery for functional goals and quality of life, not pulmonary function
- Surgical decision-making should focus on functional goals and surgical "dose"

Medical literature lagging behind advances in SMA gene Rx…
Need more studies to determine orthopedic outcomes in this new era

THANK YOU

NEMOURS
CHILDREN'S HEALTH