Effect of EOS Severity and Treatment on Pulmonary Function Relative to Stature (as Represented by Pelvic Width) in Children with SMA

Michael Troy BS, Patricia Miller MS, Jared Snyder
Robert Graham MD, Brian Snyder MD/PhD

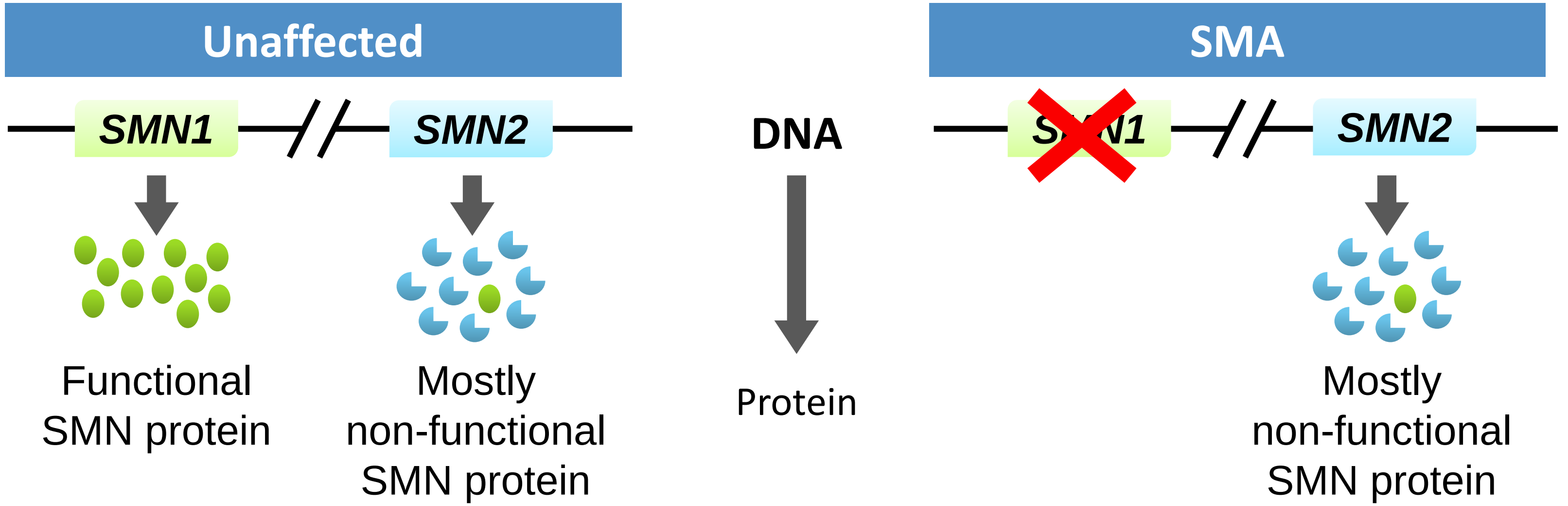
Boston Children's Hospital Orthopedic Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
MARIAN UNIVERSITY Indianapolis College of Osteopathic Medicine

Disclosures

- **Brian Snyder and Robert Graham are on the Board of CURESMA**
- **Brian Snyder and Robert Graham are consultants to BioGen**

SMA: Most Common Monogenic Cause of Infant Death

- Progressive debilitating neuromuscular disease characterized by degeneration spinal motor neurons → atrophy of skeletal muscle
- **Mutations or deletions *SMN1* gene (exon 7 and/or 8) chromosome 5q**
- **Extent of clinical involvement depends on copies of SMN2:**
  - **≤ 2 copies more severe disease; 3-4 copies milder disease**



Incidence:
~1 in 11,000 live births

Carrier frequency:
~1 in 40

SMA, spinal muscular atrophy;
SMN1, survival motor neuron 1.

Crawford TO, Pardo CA. Neurobiol Dis. 1996;3:97-110. D'Amico A, et al. Orphanet J Rare Dis. 2011;6:71. Kolb SJ, Kissel JT. Neurol Clin. 2015;33:831-46. Lefebvre S, et al. Cell. 1995;80:155-65. Lunn MR, Wang CH. Lancet. 2008;371:2120-33. Monani UR, et al. Hum Mol Genet. 1999;8:1177-83. Sugarman EA, et al. Eur J Hum Genet. 2012;20:27-32. Wang CH, et al. J Child Neurol. 2007;22:1027-49.

SMA Classified According to:
Age of Onset and Spectrum of Clinical Severity

Type I (severe - ≤ 2 copies SMN2)

- Most common
- Onset at < 6 months
- **Never sits**
- Areflexia = Classic 'floppy' infant
- Bulbar denervation, tongue fasciculation
- Swallowing and feeding difficulties
- Respiratory insufficiency

Type II (intermediate - > 2 copies SMN2)

- Onset at 6–18 months
- Can sit without support but progressive muscle atrophy (proximal > distal muscles)
- **Never stands**
- Tongue fasciculation
- Variable bulbar and respiratory weakness

Type III (mild - 3-4 copies SMN2)

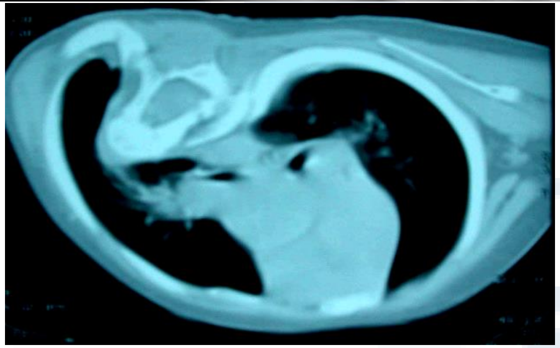
- Onset at > 18 months
- Proximal symmetrical weakness
- **Stands and walks,** but may need wheelchair or lose ambulation during adolescence
- Weak or absent tendon reflexes

This classification system does not reflect altered disease manifestations and trajectory observed with nusinersen treatment

D'Amico A, et al. Orphanet J Rare Dis. 2011;6:71. Darras BT. Pediatr Clin North Am. 2015;62:743-66.
Mercuri E, et al. Lancet Neurol. 2012;11:443-52. Munsat TL, Davies KE. Neuromuscul Disord. 1992;2:423-8.
Prior TW, Finanger E. GeneReviews®. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1352/.
Wang CH, et al. J Child Neurol. 2007;22:1027-49.

Early Onset Scoliosis → Thoracic Insufficiency

- Types 1 and 2 associated with progressive spine and thoracic (parasol rib) deformity
  - ➢ Contributes to Restrictive lung disease and respiratory dysfunction
- Cobb angle alone does not predict extent of respiratory deficiency
  - ➢ Fails to account for chest wall deformity and interference with pulmonary growth



Treatment of Scoliosis

(Cobb ≤ 50°)

- Bracing (TLSO) slows progression
  - ➢ does not decrease ultimate need for surgical correction

(Cobb > 50°)

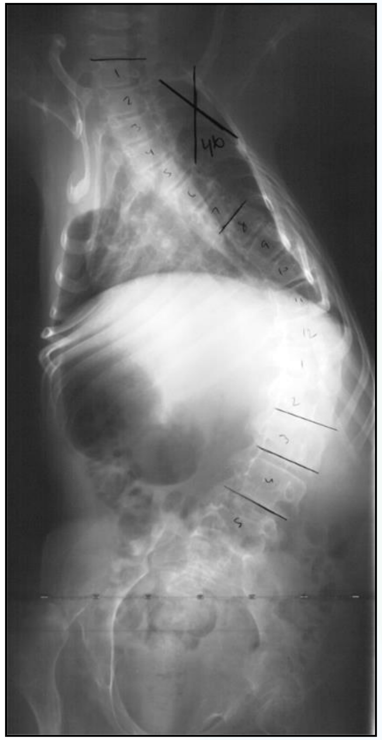
➢ <u>Skeletal age <8 y/o:</u>

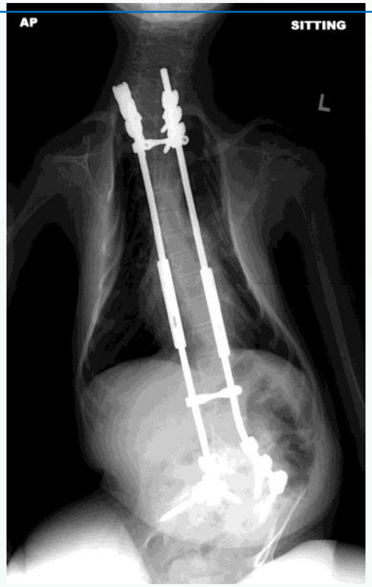
Posterior, Non-fusion "growing rods" (VEPTR, MAGEC, Luque Trolley)

➢ <u>Closed tri-radiate:</u>
Posterior multi-segmental instrumentation + spine fusion

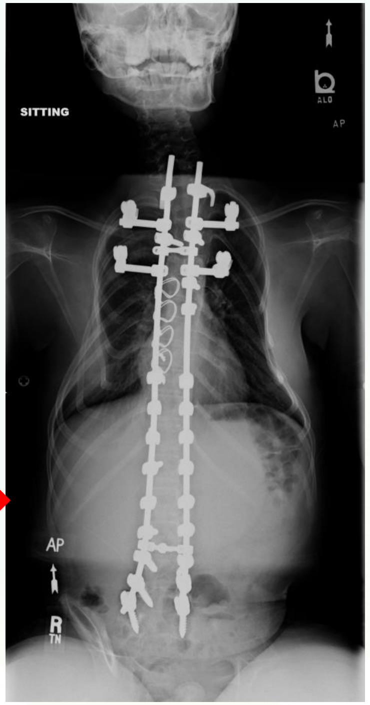
✓ Instrumentation to pelvis provides better control of "crank-shaft" & pelvic obliquity

Growing Rods < 8 y/o



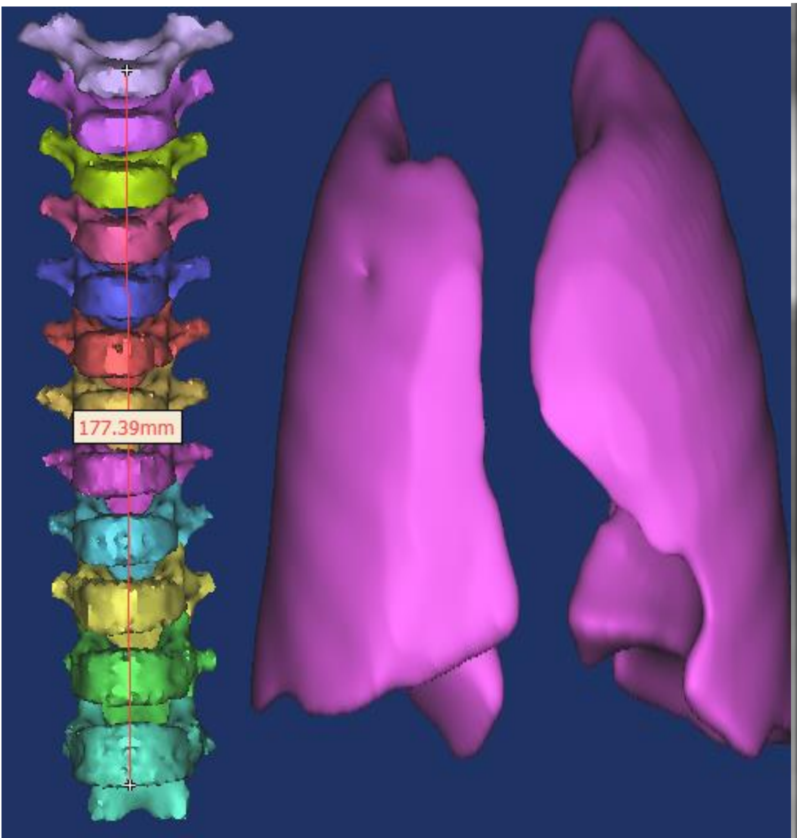


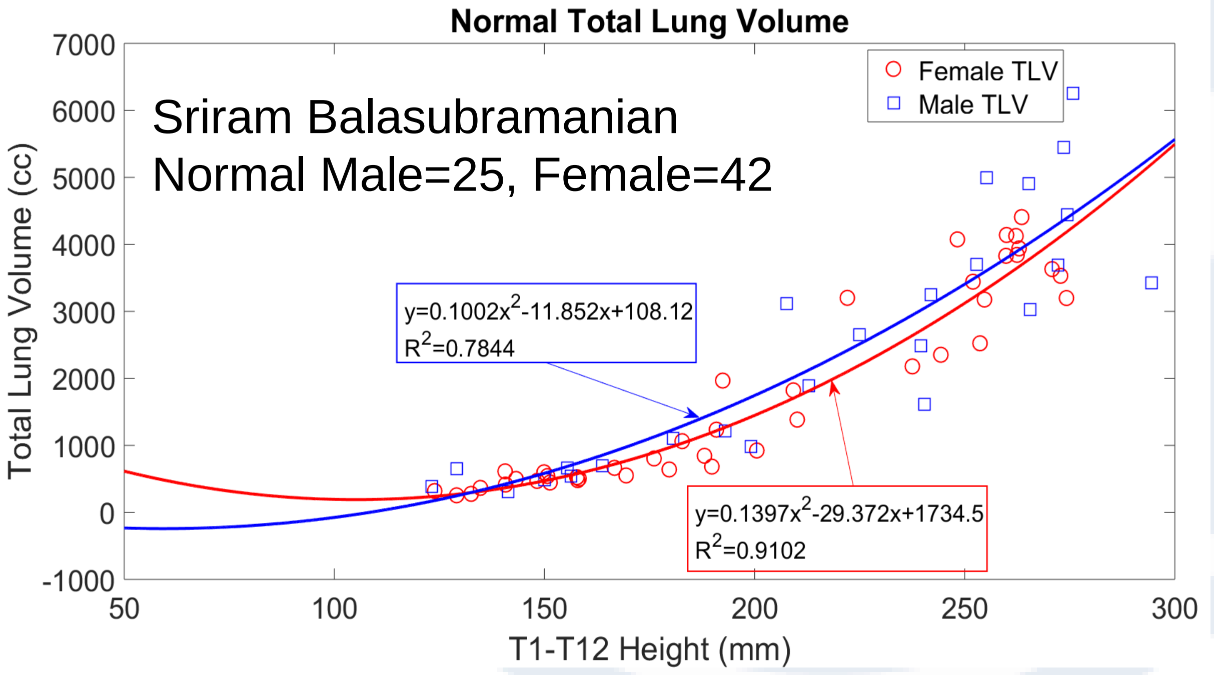
Instrumented Spine Fusion Closed tri-radiate



Pulmonary Function

- **PFTs reported as %tiles based on height (standing, sitting, spine)**
- **Traditional 2D measures of thoracic volume and spine length that predict pulmonary function are difficult to evaluate in SMA because of skeletal deformity (scoliosis, contractures)**

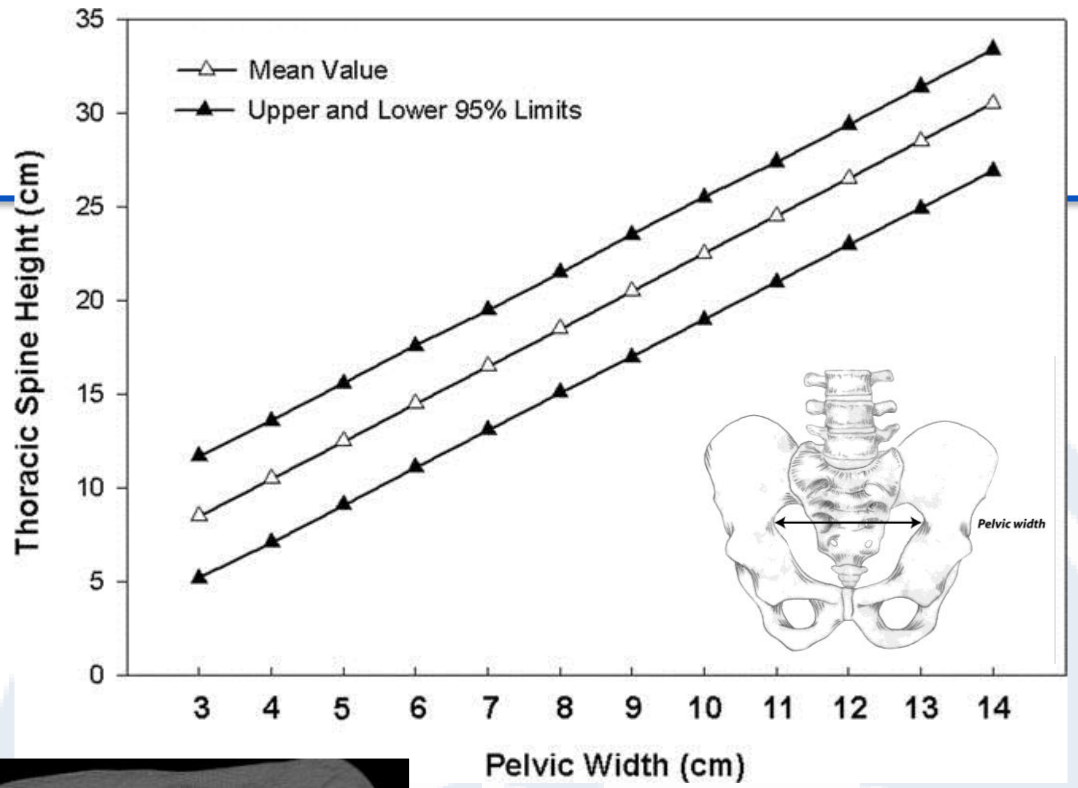


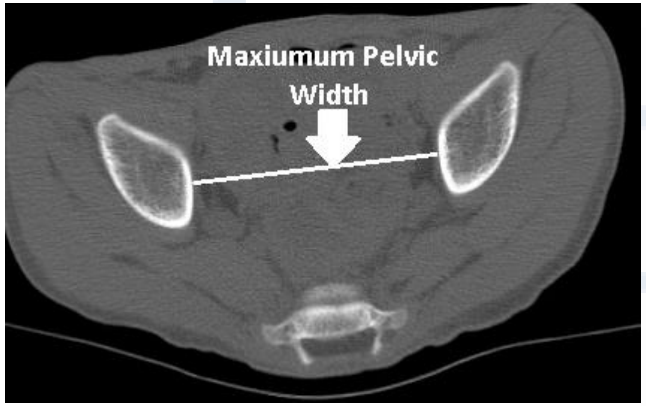


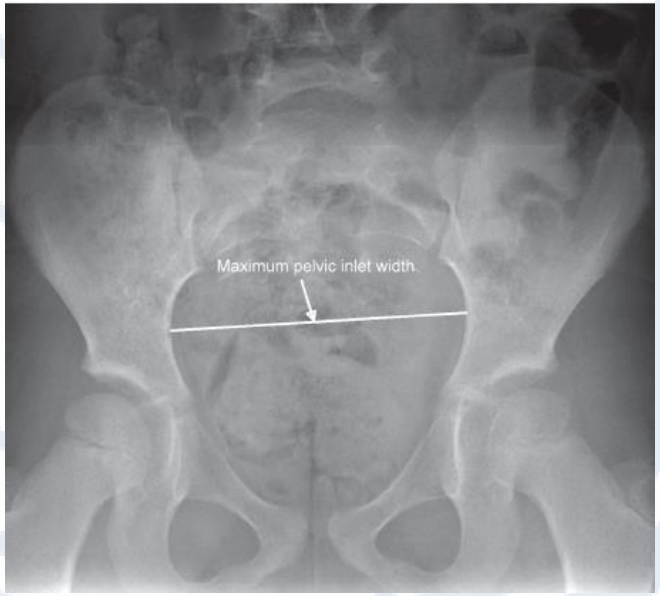
Pelvic Inlet Width (PIW)

- **PIW correlates with spine height and stature with growth**
  - independent of *disease* or *age*
  - PIW reliably measured on spine and/or hip X-rays

➢ ***Surrogate for thoracic height in EOS***







SPINE Volume 30, Number 24, pp 2824–2829
©2005, Lippincott Williams & Wilkins, Inc.

Prediction of Thoracic Dimensions and Spine Length Based on Individual Pelvic Dimensions in Children and Adolescents

An Age-Independent, Individualized Standard for Evaluation of Outcome in Early Onset Spinal Deformity

John B. Emans, MD,* Michelle Ciarlo, BS,* Michael Callahan, MD,† and David Zurakowski, PhD*

Spine
DIAGNOSTICS
SPINE Volume 38, Number 00, pp 1-8
©2013, Lippincott Williams & Wilkins

Prediction of Thoracic Dimensions and Spine Length Based on Individual Pelvic Dimensions

Validation of the Use of Pelvic Inlet Width Obtained With Radiographs Compared to CT

Meryl Gold, BA, Michael Dombek, BS, Patricia E. Miller, MS, John B. Emans, MD, and Michael P. Glotzbecker, MD

Hypothesis

1. Pulmonary function as represented by FVC varies proportionately with stature (thoracic height).

   Scoliosis affects this relationship:

   - ✓ children with mild/moderate scoliosis (Cobb angle ≤50º) *follow* this relationship
   - ✓ children with more severe scoliosis (Cobb angle >50º) *do not*

2. Correction of scoliosis by spinal instrumentation partially restores this relationship

➢ Therefore, we evaluated whether FVC varies proportionately with stature, *as represented by PIW,* and whether this relationship was affected by EOS severity or treatment (TLSO, spinal instrumentation)

Methods

- **Cohort**
  - 53 SMA pts. types: Type 1 (2%), Type 2 (53%),Type 3 (45%)
  - Analyzed over 5.2 yrs. (SD 2.8; range 1.1-11.6 yrs).
  - Nearly all received Nusinersin via lumbar puncture
- **Treatment**
  - Cobb ≤ 50° Rx = TLSO
  - Cobb > 50° or unresponsive to TLSO, Rx = GR (age ≤10 yr) or PSF (closed tri-radiate)
- **Analysis (Bi-annual)**
  - Bedside Forced Vital Capacity
  - Sitting spine X-ray in/out of TLSO or after Growing Rod insertion/lengthening

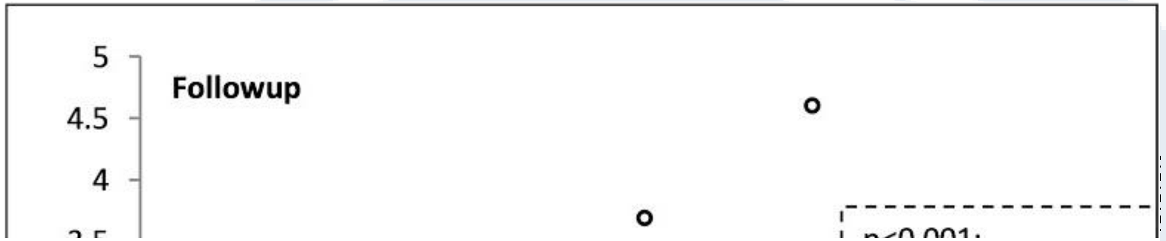
➢ **Cobb, PIW, FVC @ initiation treatment (TLSO, GR) compared to last follow-up**

Boston Children's Hospital
Orthopedic Center
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
MARIAN UNIVERSITY
Indianapolis
College of Osteopathic Medicine

Results: PIW vs FVC

- **At Presentation**
  - Cobb ≤50º: variability in PIW accounts for 74% variability in FVC

    (r = 0.86; $p<0.001$)
  - Cobb >50º: no correlation ($p=0.27$)



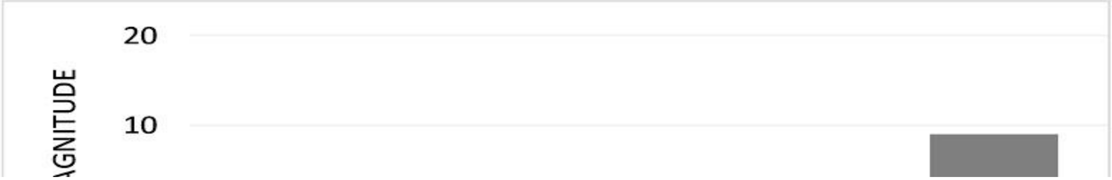
IMPLIES: SMA children with moderate spinal deformity, pulmonary function varies proportionately with change in stature (i.e. growth)

However for severe scoliosis, the change in pulmonary function is disproportionate relative to change in stature = *thoracic insufficiency*

Results: 2-way ANOVA comparing FVC normalized by PIW

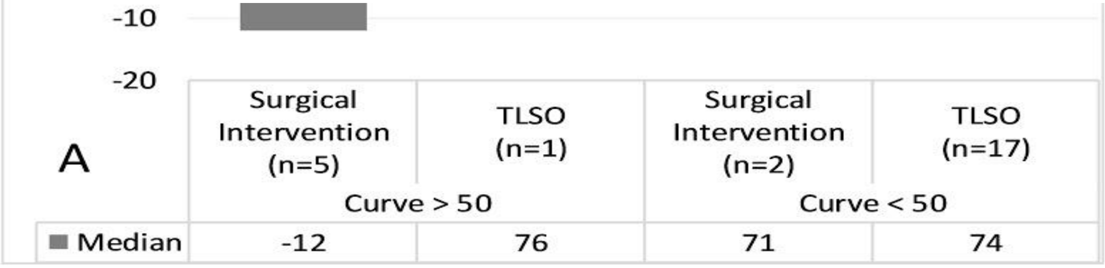
For treatment (TLSO vs GR) @ initiation vs last f/u, segregated by initial curve severity (Cobb >50º vs <50º)

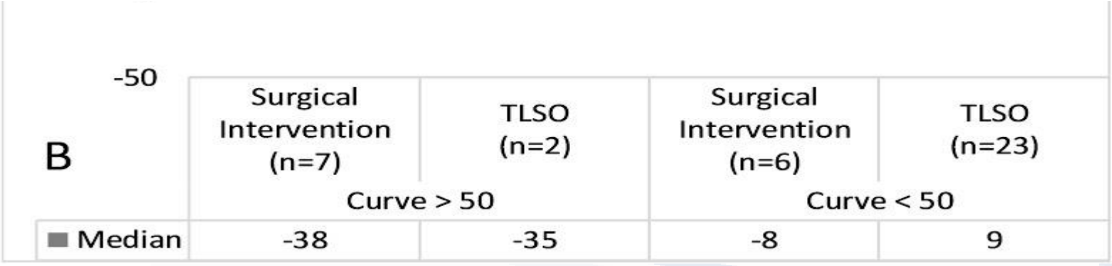
- Underpowered, and Biased cohort – more severe curves treated surgically, less severe curves treated by TLSO



Indicates that surgical treatment for Cobb >50º, while scoliosis corrects by ~40%, even if Cobb corrected to <50º, it did *not* restore the proportionality between PIW and FVC;

Whereas for less severe spinal deformity treated by TLSO, even though curve progressed 10%, the proportionality between PIW and FVC was preserved





Conclusions

- **The direct relationship between (PIW), a radiographic surrogate for thoracic height an acity (FVC), a measure of pulmonary function indicates th en, age <18 yrs, with moderate spinal deformity (Cobb ≤50º) pu is able to change proportionately with the change h).**
- ***However* for severe scoliosis (C nary function was unable to change in relative proportion to ture = *thoracic insufficiency.***
- **Surgical treatment did not modi relationship *because*-**
  - surgical intervention occurred t ic (and irreversible) changes to the thorax and lung parenchym
  - increased thoracic stiffness, a c ered ventilator mechanics induced by Parasol deformity o scarring, rigidity of surgical instrumentation, and/or failure o vention to improve the projected surface area and excursion of t

Thank You

Funding Sources: Department of Patient Services' Research Funding Program at Boston Children's Hospital

Boston Children's Hospital
Orthopedic Center

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

MARIAN UNIVERSITY
Indianapolis
College of Osteopathic Medicine