Session 3: Mini Symposium: Spinal Muscular Atrophy (SMA) : **Spine**

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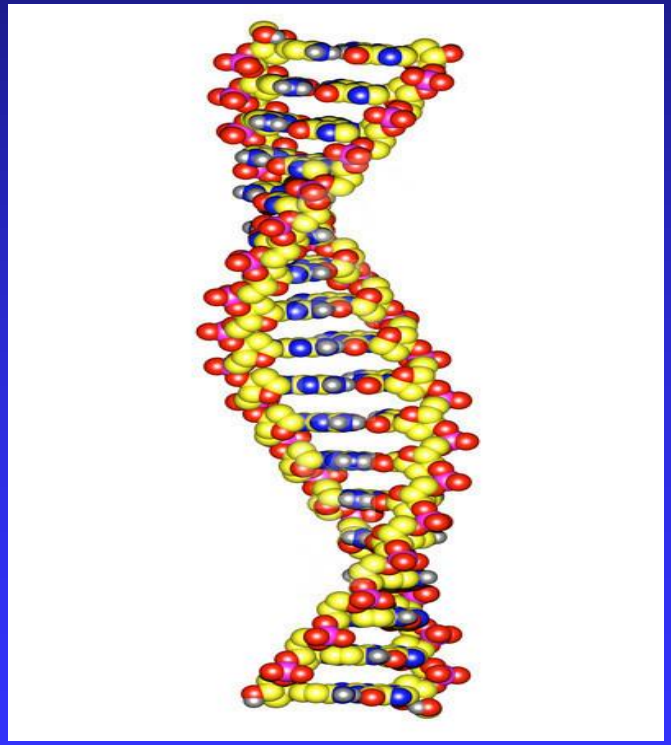
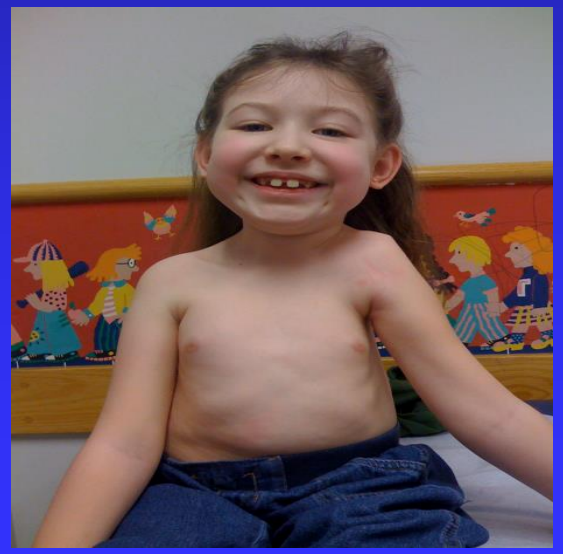
-Disclosures-

Warning: Science Coming !



What is Spinal Muscular Atrophy (SMA)?

- **Incidence: ~ 1 / 10,000 live births; 30,000 Worldwide**
- **Leading causes of genetic mortality in infants and toddlers, though manifestations highly variable**

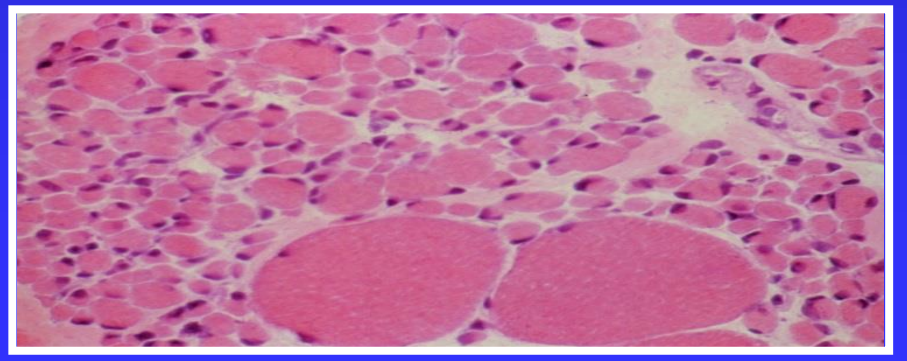


Pathophysiology

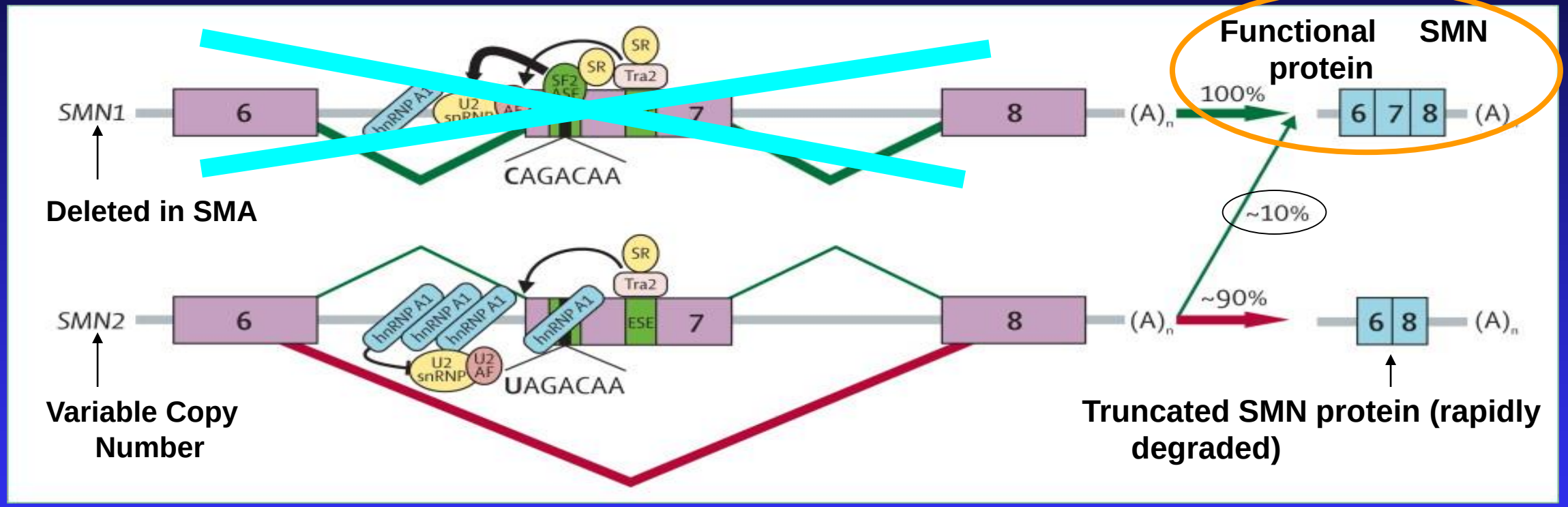
- Progressive degeneration of alpha lower motor neurons in anterior horn cells of spinal cord
- Sensation and intelligence normal
- Proximal muscles affected first
- Diaphragm, GI muscles, and heart spared

Genetics of SMA

- Autosomal recessive
- Chromosome 5q13 locus
  - One copy of *SMN1*
  - Variable number of copies of *SMN2*
- SMN involved in controlling apoptosis; keeps neurons alive
- Carrier frequency: 1/50



Multiple, but variable numbers of, copies of SMN gene in the human genome



~10% of SMN2 pre-mRNA is properly spliced and subsequently translated into full-length SMN protein

Lunn et al. Lancet 2008; 371: 2120-2133

Types of Spinal Muscular Atrophy

Type 1 (Werdnig-Hoffmann, Infantile SMA)

Most severe; little spontaneous extremity movement

Type 2 (Intermediate SMA)

Can often sit without support, but can rarely stand

Type 3 (Kugelberg-Walander, Juvenile SMA)

Ambulatory, but have weakness of the hip muscles

Type IV - Adult SMA; ambulatory

Sucato DJ. JBJS 2007; 89: 148-54

Scoliosis in SMA

- The severity and onset of scoliosis are directly related to the severity of SMA
- Type 1: 100% develop scoliosis

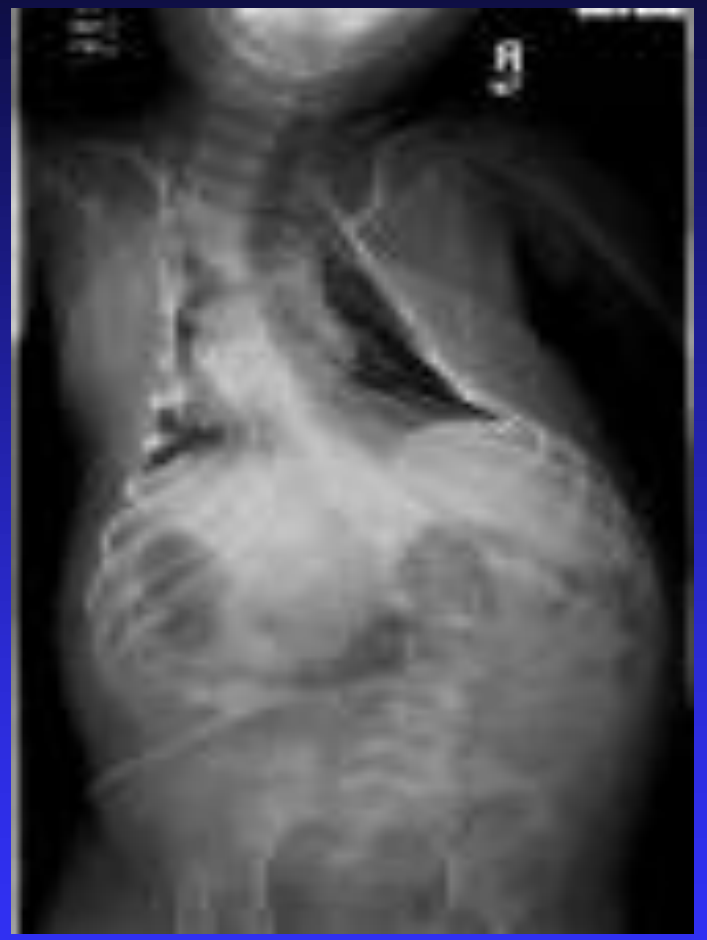
  ≤ 2 years of age
- Type 2: 100% develop scoliosis

  1-7 years of age
- Type 3: 50% develop scoliosis

  4-14 years of age

Scoliosis in SMA

- Can exacerbate pulmonary demise
- ? Role of Parasol
- Can lead to issues with seating, UE use, and comfort
- Can result or hasten hip dislocation



Mogul Using $100 Million in Race to Cure Daughter Lures Novartis

By Robert Langreth and Alex Nussbaum | Sep 7, 2011 12:01 AM ET | 2 Comments | Email | Print

Goldman Sachs Group Inc. (GS) partner **Dinakar Singh** discovered in 2001 that his 19-month-old daughter, Arya, had a crippling genetic disease called spinal muscular atrophy.

The malady makes the nerve cells that control muscles gradually deteriorate. There are no treatments, let alone a cure, Bloomberg Markets magazine reports in its October issue. Worse still, while the gene causing the ailment had recently been discovered, nobody in the drug industry was doing much about it, he says.

"I was fearful and anxious that treatments would be developed, but far too late to save Arya," says Singh, 42, who founded and runs New York hedge fund TPG-Axon Capital Management LP, which has $8.1 billion in assets. "We didn't want to find out 25 years later that the science was really there but there isn't a drug because nobody focused on it."

Singh, who left Goldman in 2004, has spent almost $100 million of his own money to create and fund

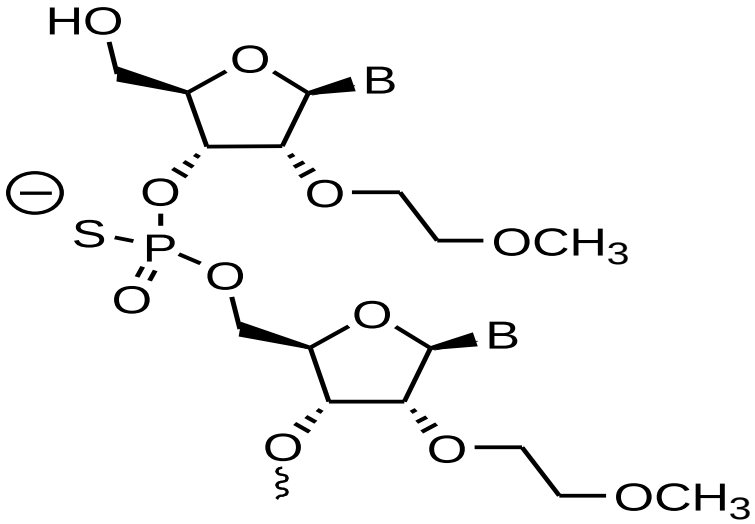
Related

Hedge-Fund Manager Looks to Cure Daughter of SMA

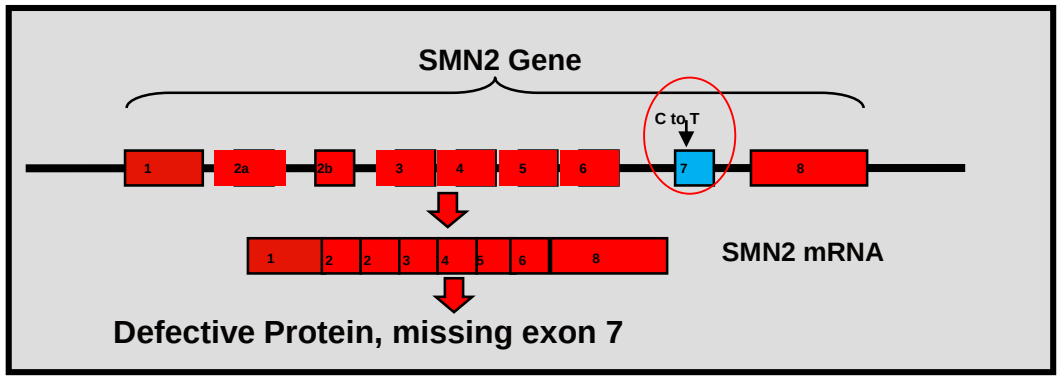
Emerging Drug Treatments for SMA

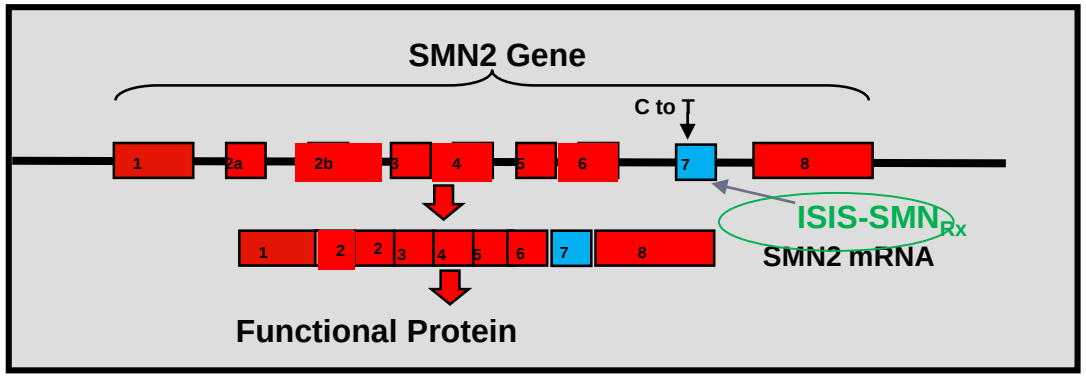
Courtesy of Dr Richard Finkel

ISIS-SMN$_{RX}$: MODULATING SPLICING OF SMN2 TO INCREASE NORMAL SMN PROTEIN



Must Be Given Intrathecally !

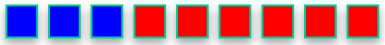
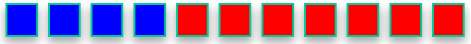
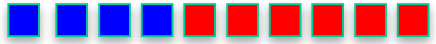
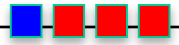
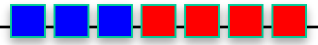
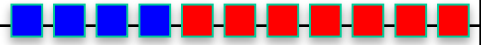
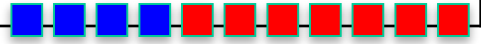




*(Hua et al., Genes Dev., 2010; Passini et al., Sci Transl Med, 2011; Hua et al., Nature, 2011)

ACHIEVEMENT OF MOTOR MILESTONES IN SOME INFANTS

BLUE—6 MG, RED—12 MG

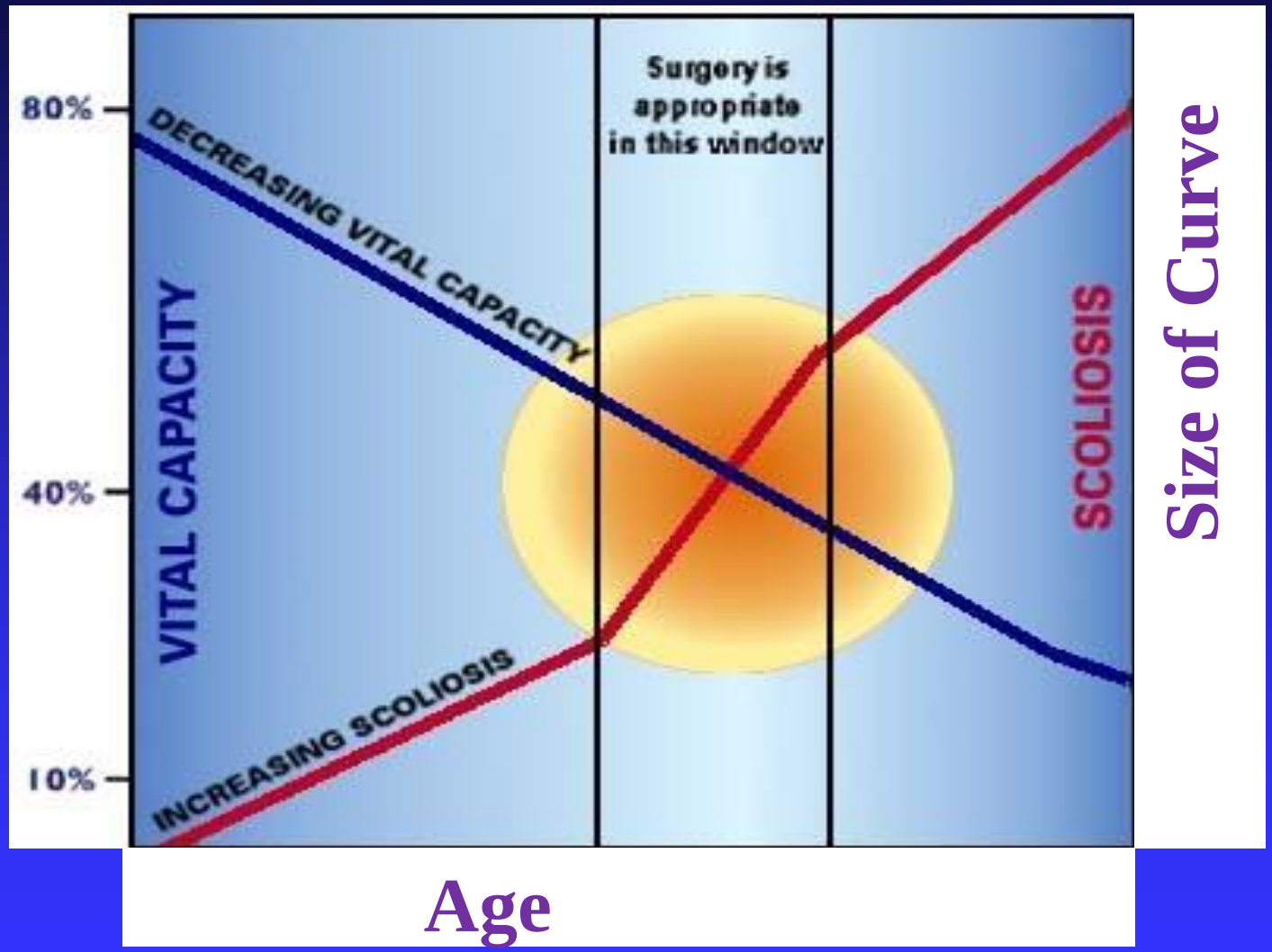
Head control	Unable to maintain upright 	Wobbles 	All the time upright		
Sitting	Cannot sit 	Sit with support at hips	Props	Stable sit	Pivots (rotates)
Voluntary grasp	No grasp 	Uses whole hand 	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking 	Kicks horizontally; legs do not lift 	Upward (vertically)	Touches leg	Touches toes
Rolling	No rolling 	Rolling to side	Prone to supine	Supine to prone	
Crawling	Does not lift head 	On elbow	On outstretched hand	Crawling flat on abdomen	On hands and knees
Standing	Does not support weight 	Supports weight	Stands with support	Stands unaided	
Walking	No walking 	Bouncing	Cruising (holding on)	Walking independently	

Consider Surgical Stabilization for Progressive Curves Before They Get Too Large

Etiology	Cobb Angle (Major Curve)	Maximum Total Kyphosis	Progression Modifier (optional)
Congenital/Structural	1: <20°	(-) <20º	P0: <10°/ yr
Neuromuscular	2: 20-49°	N: 21-49°	P1:10-19°/ yr
Syndromic	3: 50-89°	(+): ≥50°	P2: ≥20°/ yr
Idiopathic	4: ≥90°		

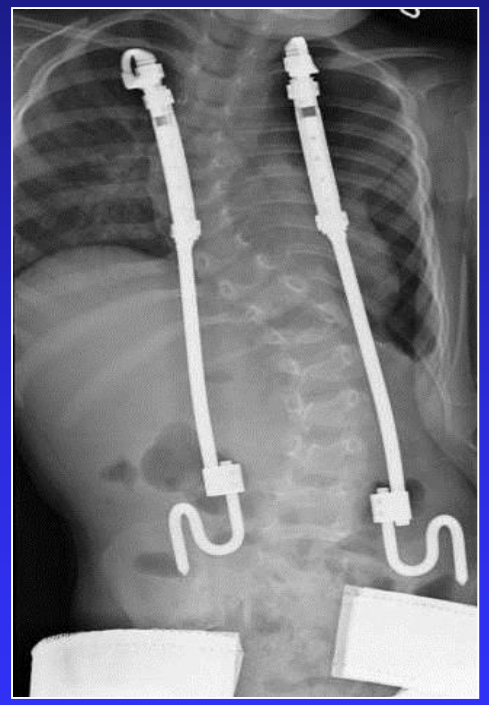
C-EOS Vitale et al.

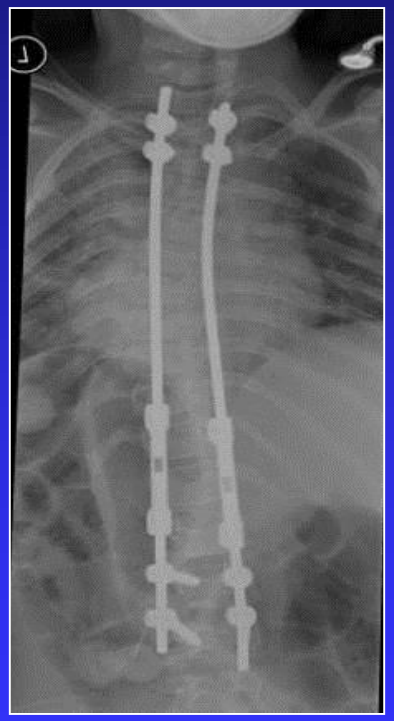
Optimal Window for Timing of Surgery?



Surgical Treatment Options for Progressive Curves in SMA

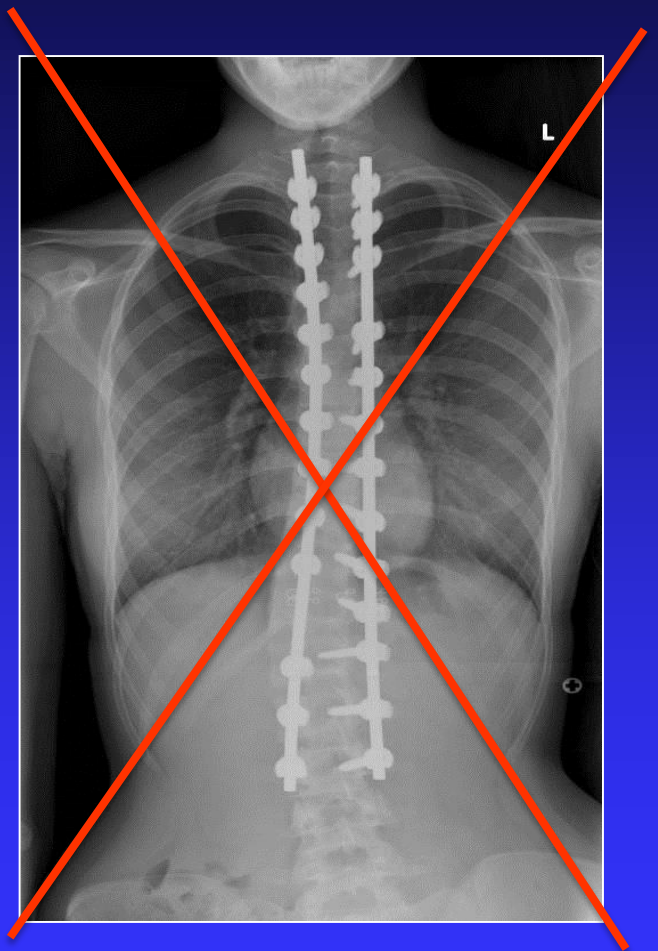
Growth Strategies
-MAGEC - TGR



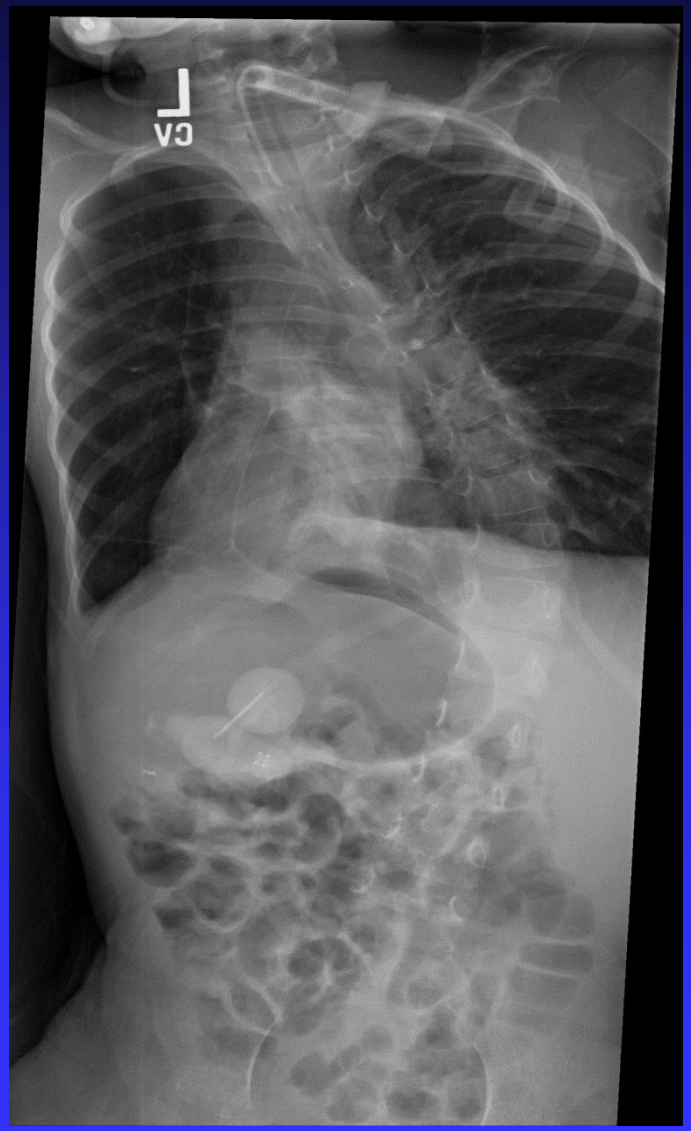


VS.

Fusion

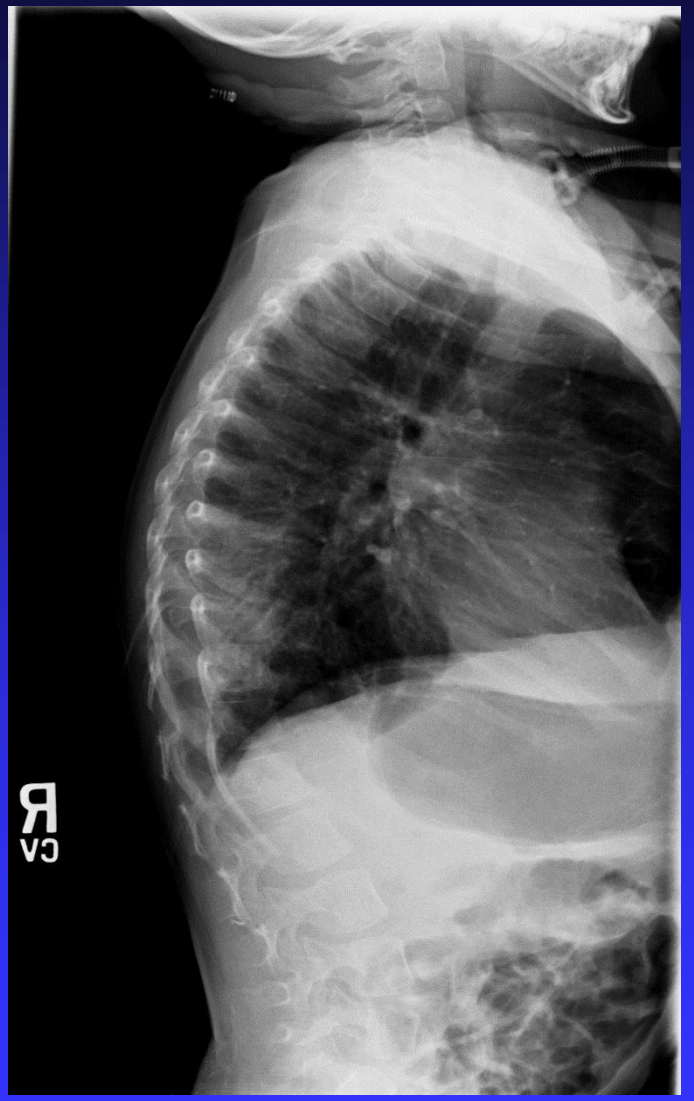


Patient TJ: 3 yo with Type I SMA

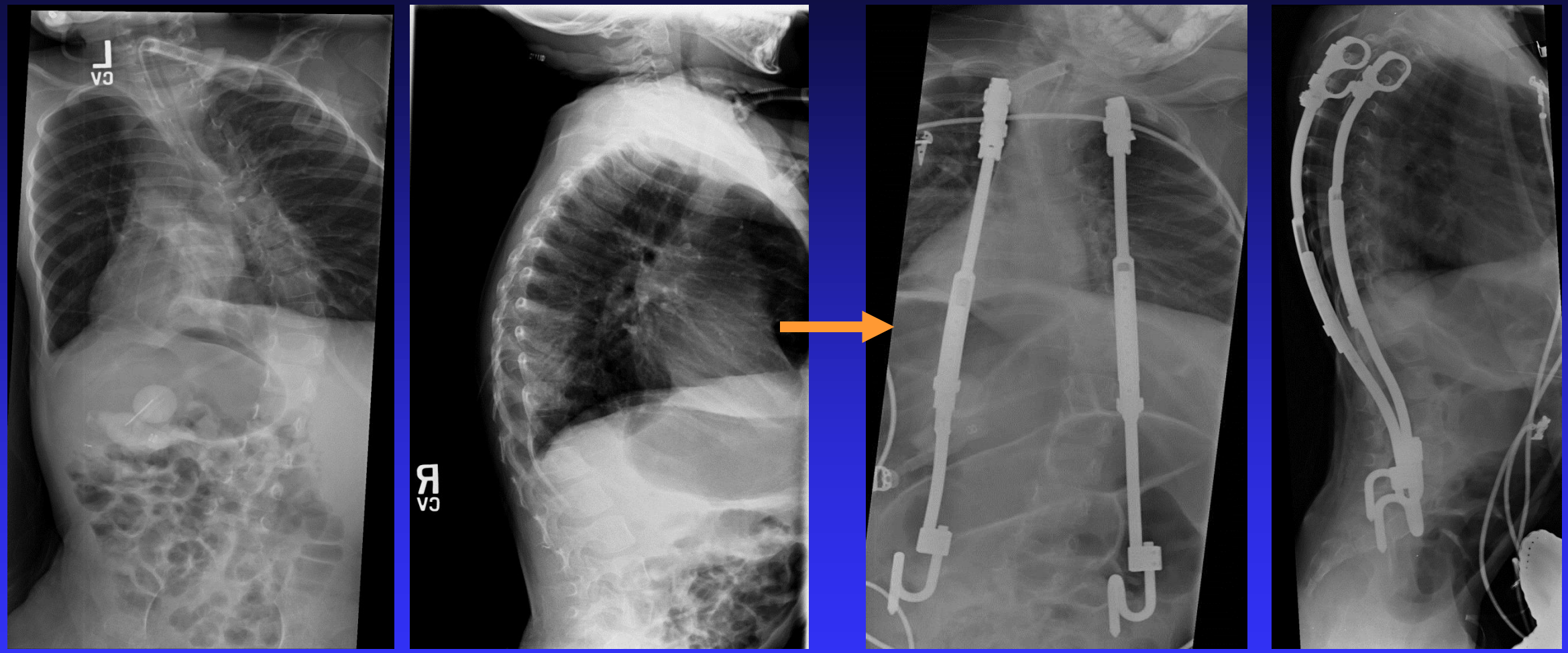


SMA Type 1

- 3 year old boy
- Gastrostomy Tube
- Ventilator dependent
- LE w/ decreased tone
- Arm Contractures
- Scoliosis Jacket 1 ½ y
- B/L VEPTRs to pelvis

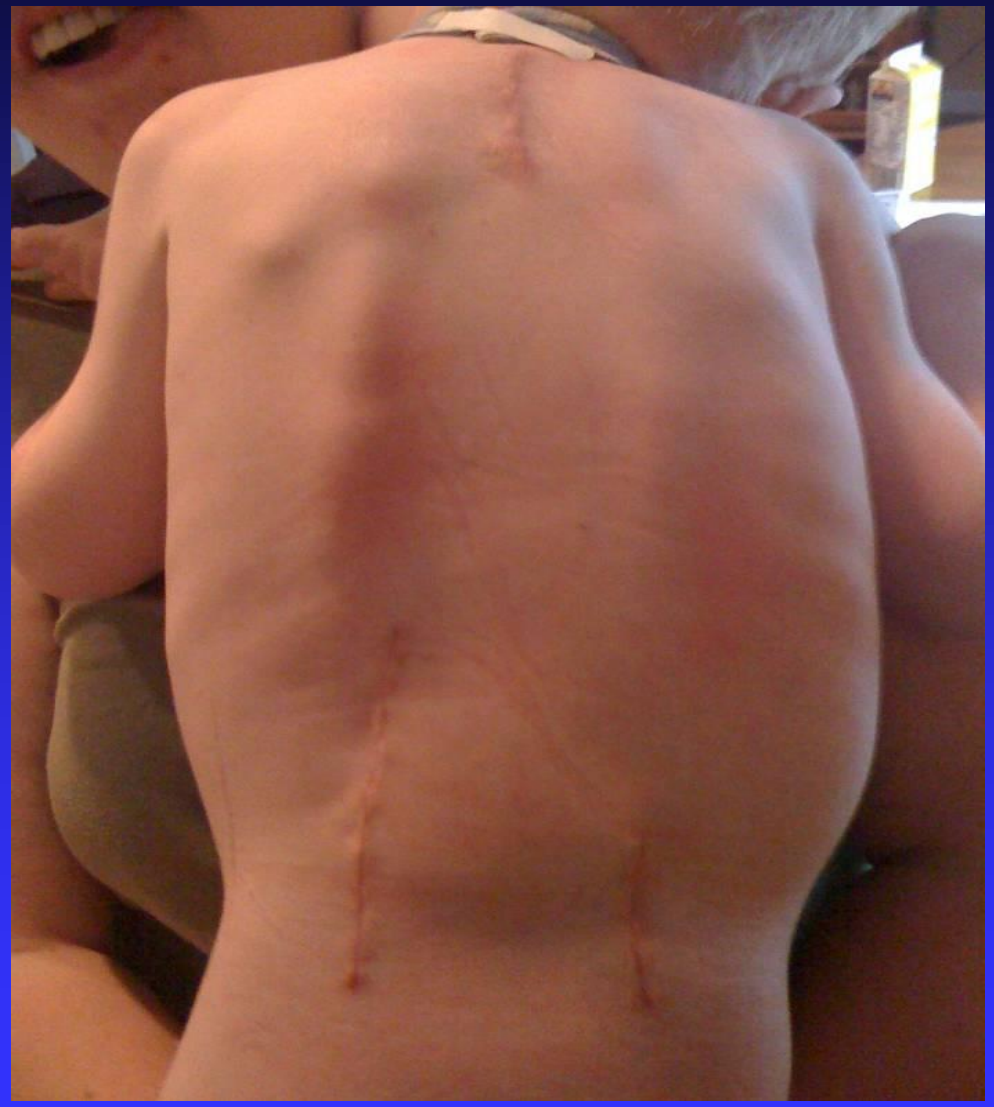


Patient TJ – s/p VEPTR



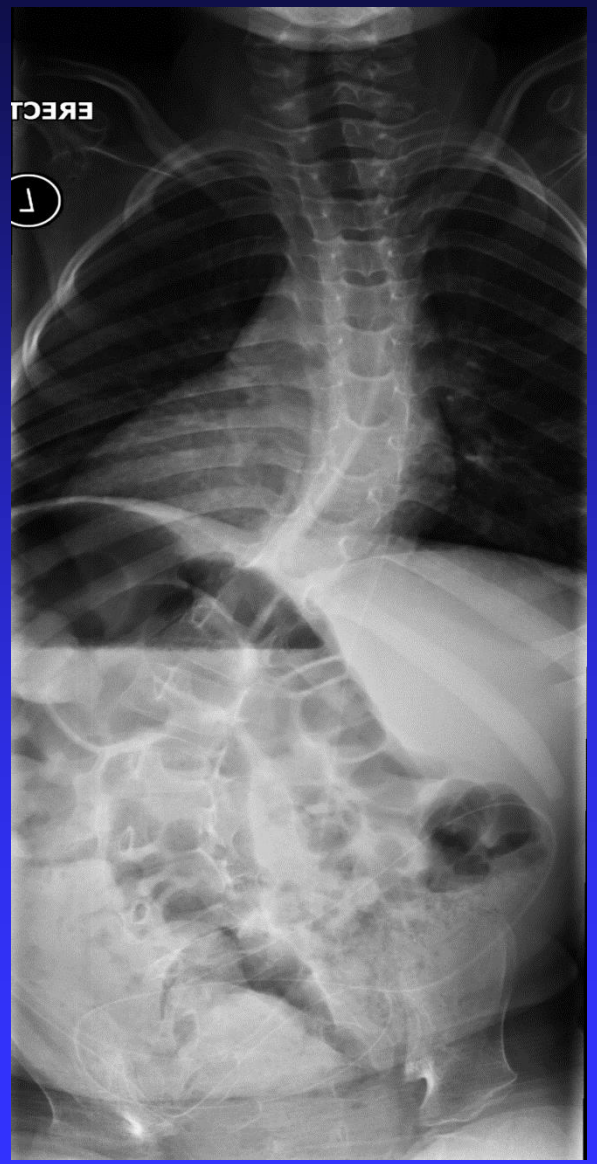
Limitation with Amount of Proximal Rib Fixation

TJ



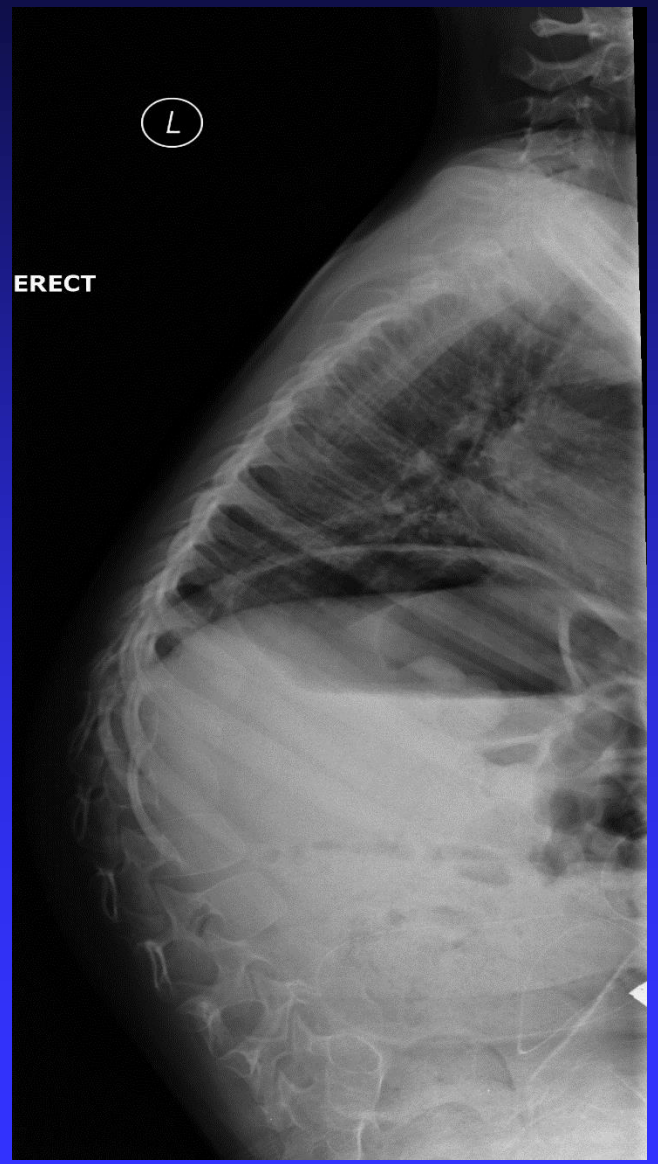
EOSQ 54 → 68

Patient JL



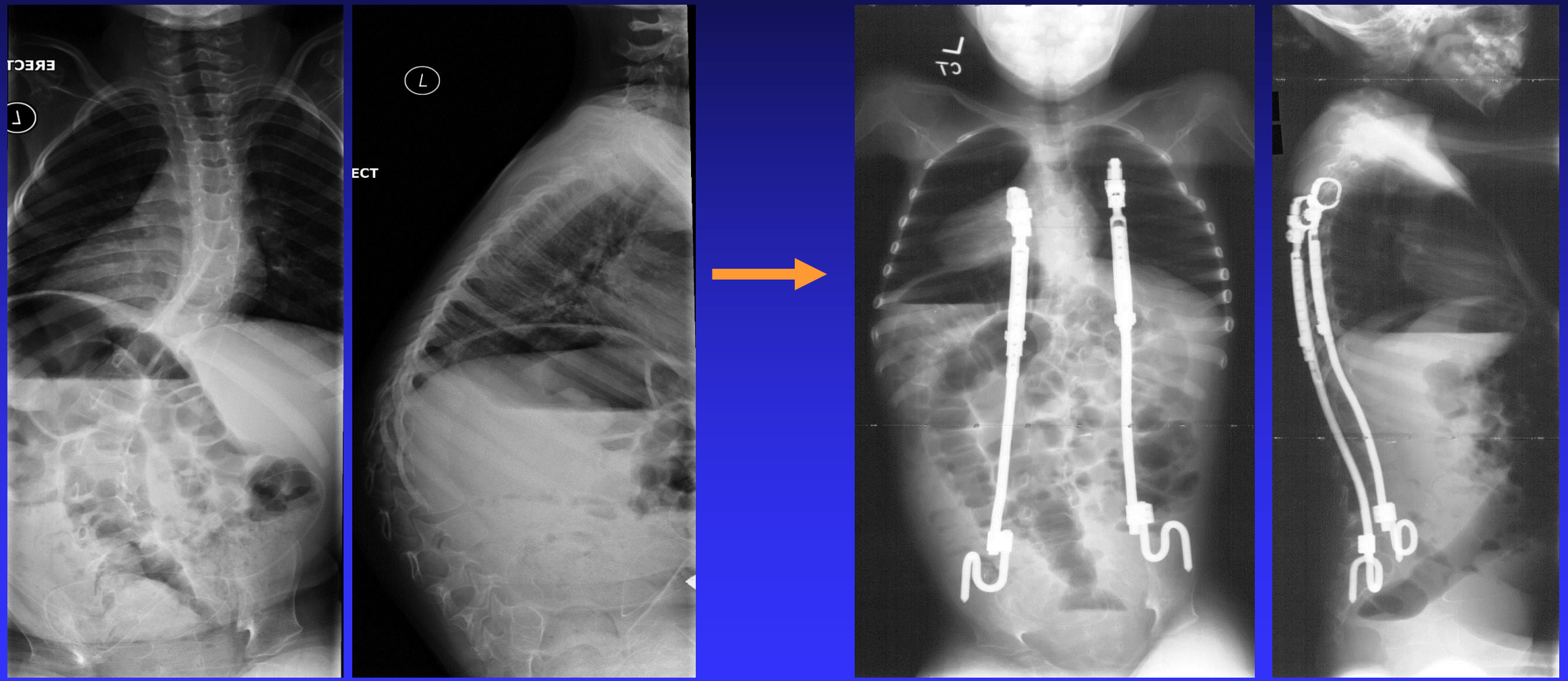
7 year old girl

SMA Type 2



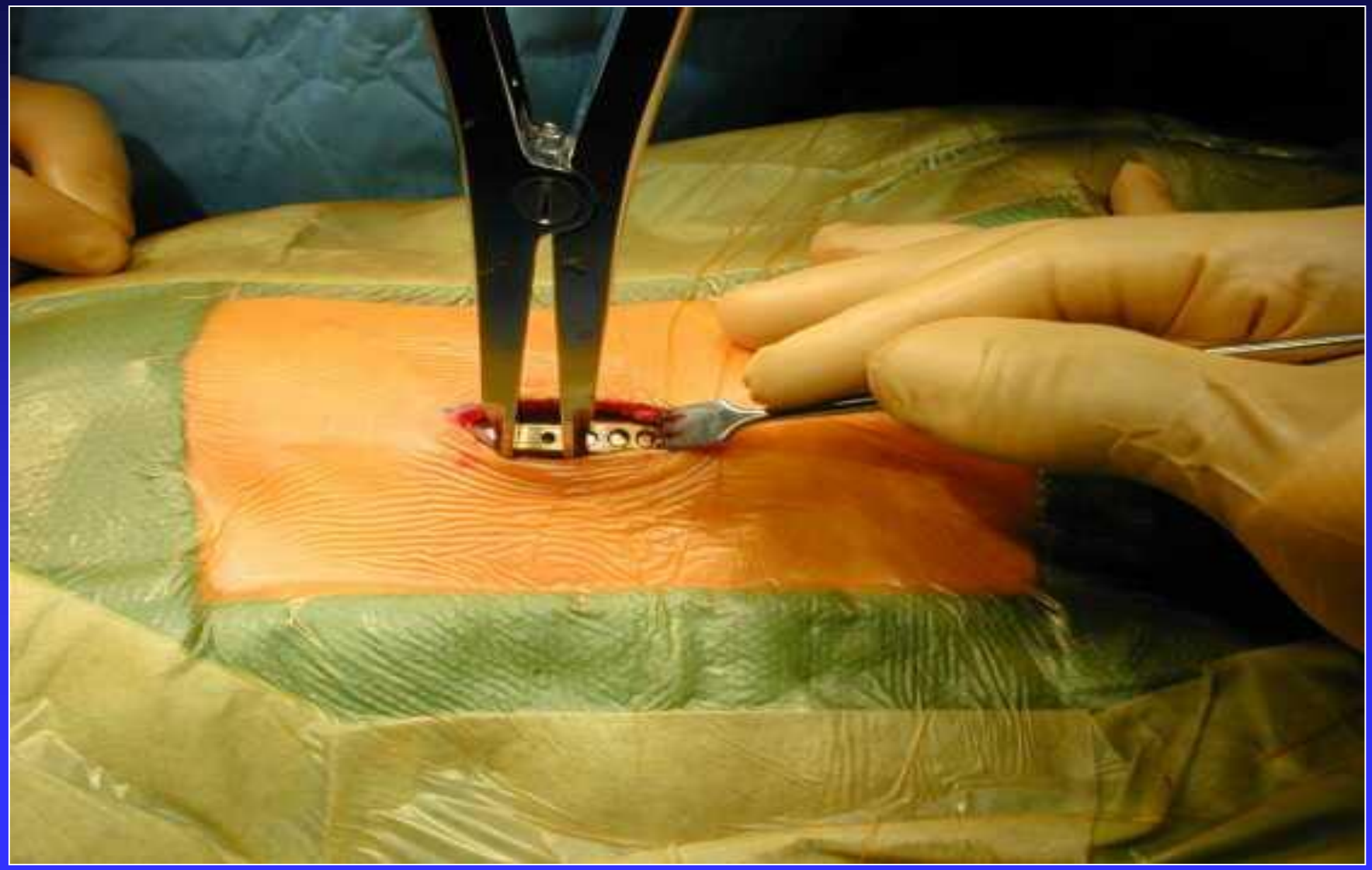
Patient JL

Improvement in need for daytime respiratory support

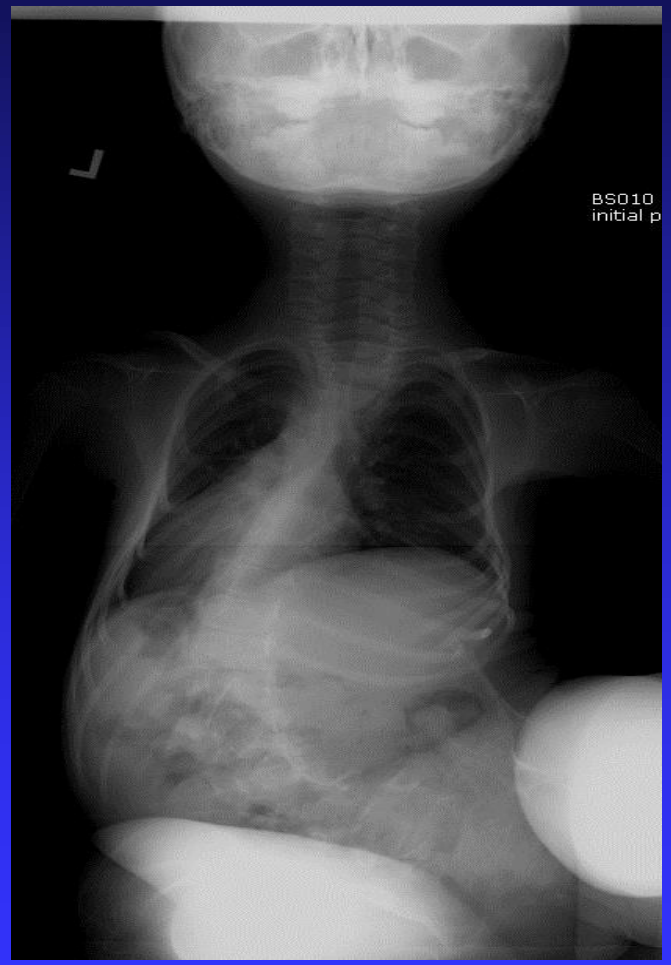


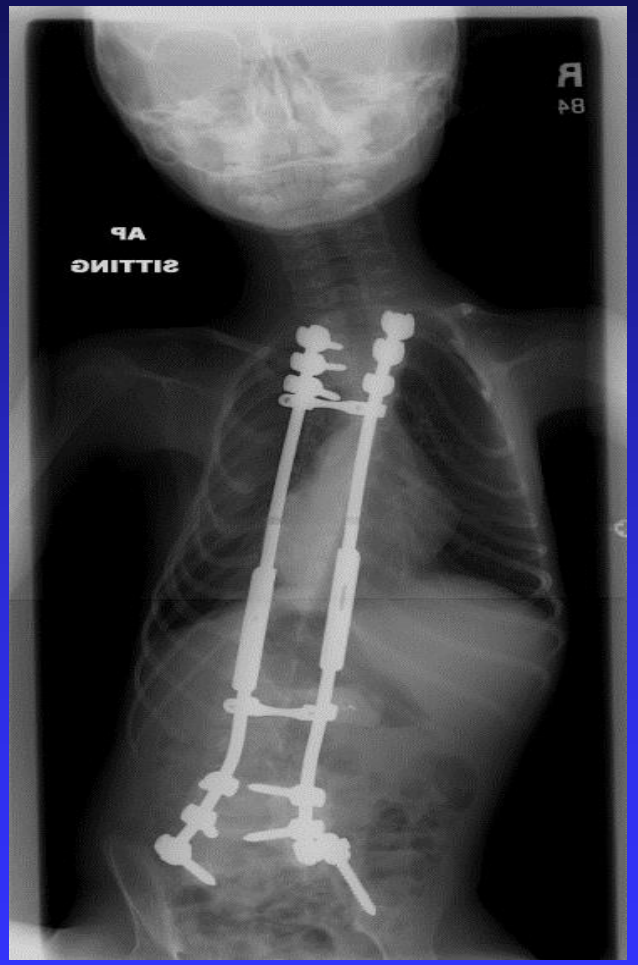
Improvement in Secondary TIS?

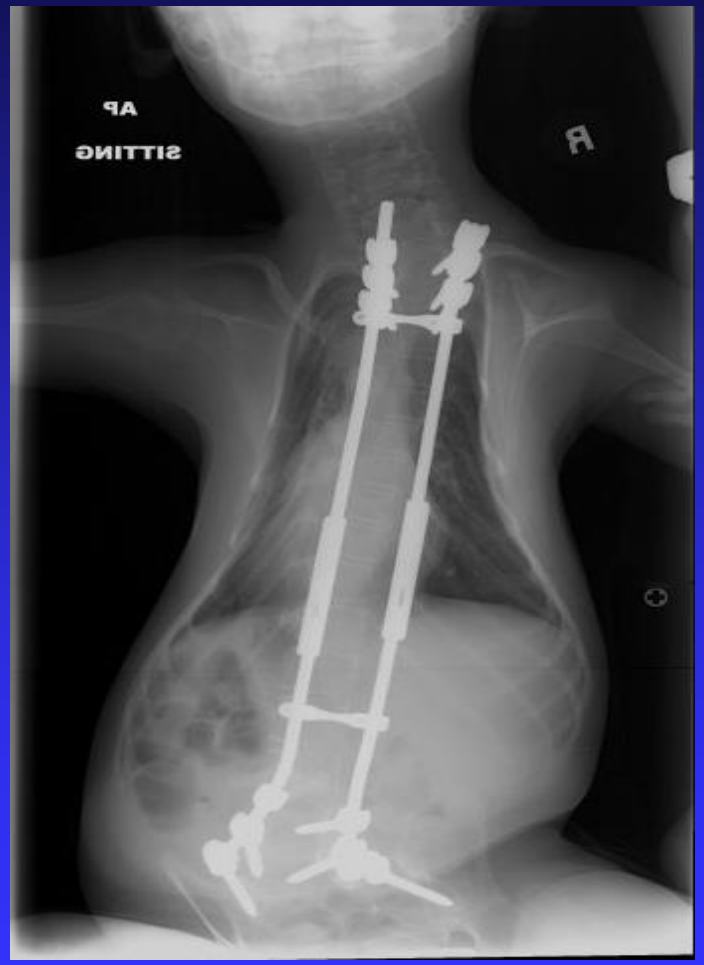
Lengthening Procedures every 4-6 months
Not ideal



Parasol seems to happen despite *traditional* growing rods and also despite *traditional* VEPTR

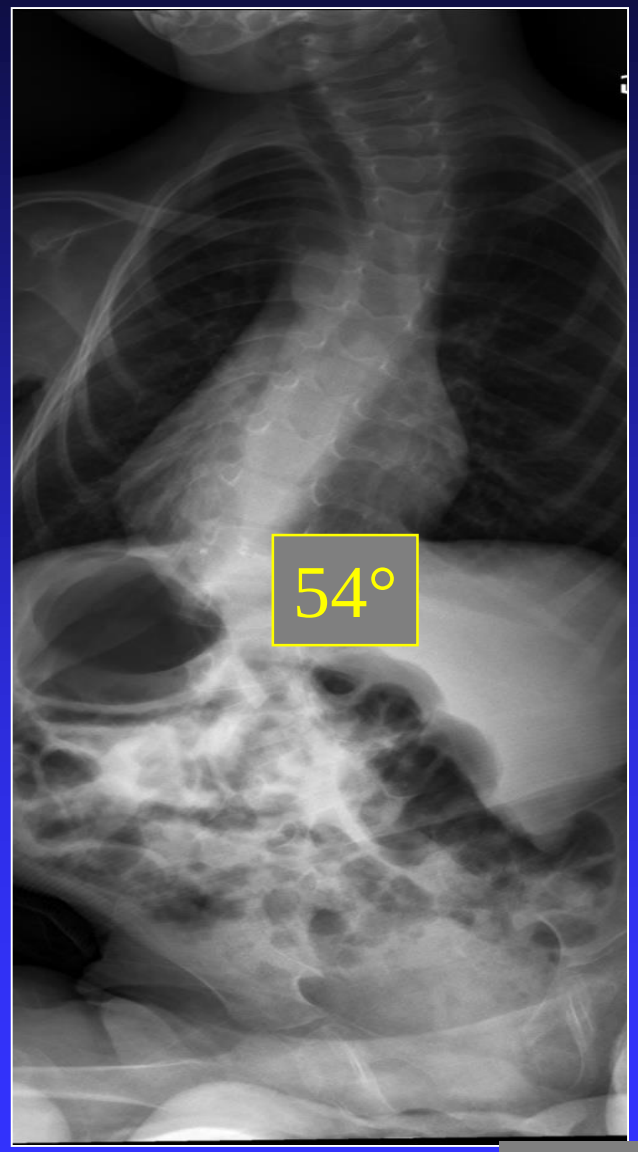


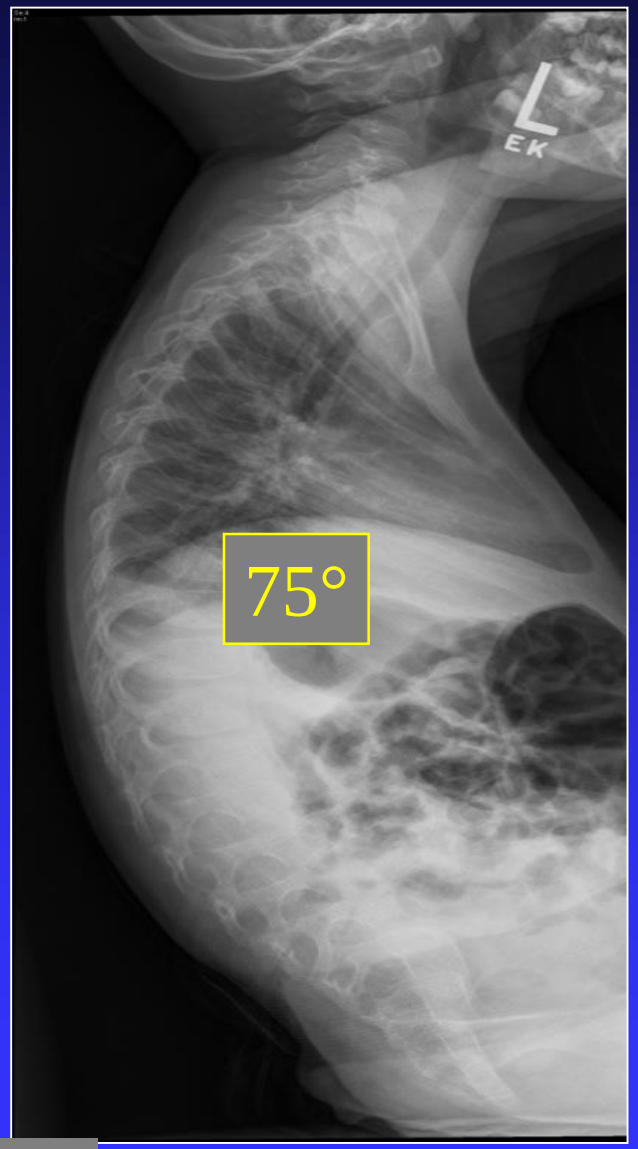




Courtesy Livingston, Zurakowski ,and Snyder, ICEOS 2014

3 yo Spinal Muscular Atrophy Type 1

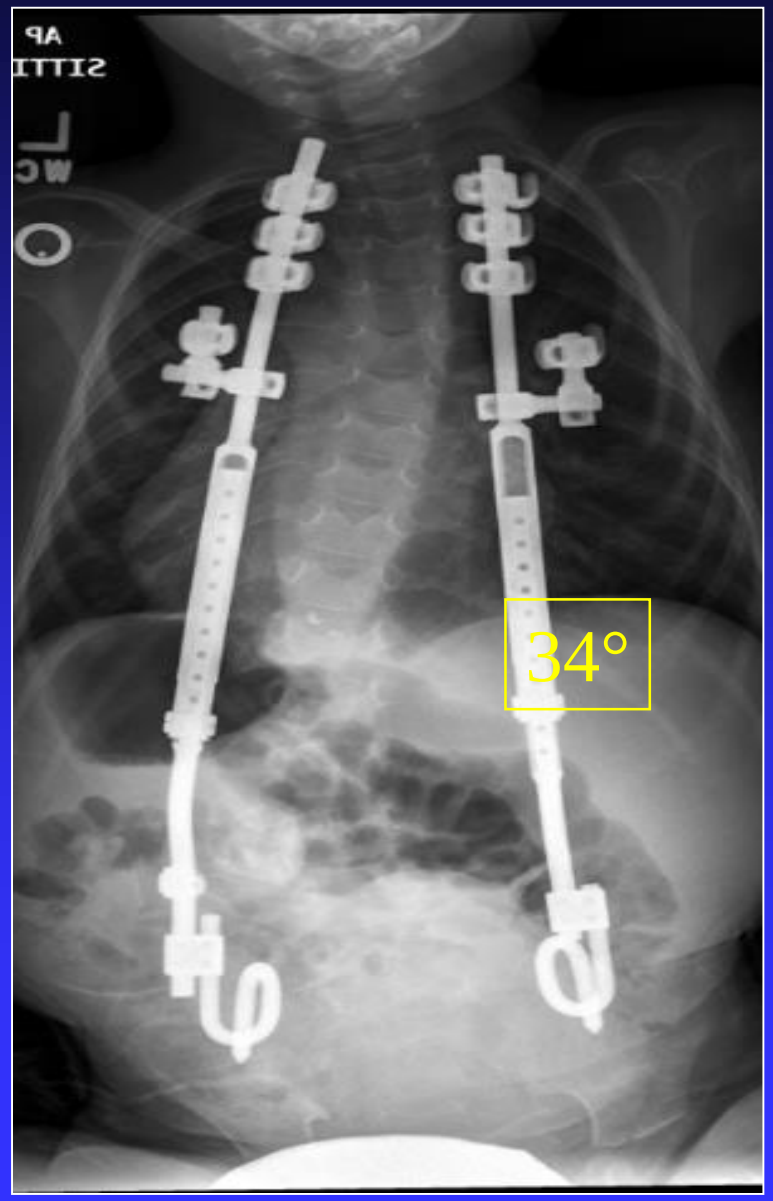




Patient OK:

- No BiPAP, but uses Cough Assist nightly
- G-tube
- Cobb 23º → 54º in 6 mo.
- C-EOS: N3+P2

Will More Rib Support Slow Parasol?



- **High Density Rib Fixation for SMA**

Confronting the Realities of EOS Treatment

- too much uncertainty in indications
- too many complications

Conclusion- Early Onset Scoliosis

- Significant Challenge and Unsolved Problem
- Be vigilant, prepare for “obstacles”, have stamina!
- Every tool in our disposal
- Significant opportunities to improve care through Clinical Research
  - GSSG and CSSG



THANK YOU

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