Current and Future Genetic and Other NonOperative Management of Early Onset Scoliosis

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Disclosures

- Consultant: Depuy-Synthes , Biomet Spineguard, Nuvasive
- Royalties: VEPTR 2 Device
- Board Member: Children’s Spine Foundation

Why would Laurel give me this topic?
A bit of history about Utah…

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scoliosis

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The “promise” of genetics….

Imagine a simple little test that would tell you if you needed to treat your scoliosis…

The “promise” of genetics....

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Will Scoliscore genetic testing change future of scoliosis treatment?

Is the future of scoliosis treatment here? Could a cure for scoliosis be just around the corner? Possibly. Just look at this statement by George H. Thompson (past president of the SRS)

Future of Scoliosis Treatment

George H. Thompson, MD Past President, Scoliosis Research Society

The treatment of idiopathic scoliosis, particularly conservative treatment, has been controversial. It has been difficult to determine which patients were going to progress, and who would benefit from conservative treatment (physical therapy, bracing, etc.) or require surgery.

Genetic testing will soon be available, that will help answer some of the questions. An analysis of 51 DNA markers associated with scoliosis has allowed determination of three specific groups of patients: no risk for progression, moderate risk, and those that will progress to 45 degrees or more and probably require surgery. When this testing is available, it may change the entire paradigm of management of scoliosis. Those that will not require treatment will need to be followed only periodically for confirmation. Those that are in-between will still require periodic evaluation and may benefit by conservative methods of treatment, such as physical therapy and bracing. Those in the high risk category for curve progression, may have earlier surgical intervention involving fusionless techniques.

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The Genetics of Scoliosis

By John T. Smith, MD

Despite a tremendous amount of scientific research, the causes of some types of scoliosis remain largely unknown. Adolescent idiopathic scoliosis may be a disease that is inherited as a genetic trait, much like some other diseases, such as sickle cell anemia. The gene that causes scoliosis remains undiscovered, but scientists are trying to find this gene using new techniques for analyzing genetic inheritance. Defining the role of genetics in scoliosis is currently the focus of intense research at a number of academic centers throughout the world.

There is strong evidence that an abnormal gene is partially responsible for some forms of scoliosis. It is possible that genetic factors may influence important aspects of scoliosis such as the pattern of curvature (left versus right curves), the shape of the curve, and the risk of progression. The tendency for scoliosis to appear in people who are closely related, such as mothers and their daughters, identical twins, and first degree relatives, suggests that scoliosis can be inherited. For example, several studies have shown that the incidence of scoliosis in first degree relatives (such as parents, siblings, and children) ranges from 7-11%. In contrast, the incidence in second-degree relatives drops to less than 4%. The exact pattern of inheritance remains unknown, and the gene that is responsible for scoliosis has yet to be identified.

The “promise” of genetics…

The future of the understanding of idiopathic scoliosis will clearly be guided by human genome analysis. [86] The characterization of the structure and function of specific gene loci and eventual ability to regulate their expression will undoubtedly form the basis of scoliosis treatments of the future*. Someday, clinicians may look back upon present mechanically based treatments of scoliosis and wonder how patients ever benefited.*

With Genetics, even Chiropractors can now ‘cure’ scoliosis

Local teens given another option to treat their scoliosis

ALEX WENGER, 18, Freestyle Staff Writer Sep 30, 2011 (0)

eronline.com/content/tncms/live/#1

“Cure isn’t a word that you throw around lightly..”

"It turns out that there is a unique sequence of genetics that is common in all patients with severe scoliosis," Stitzel said.

Anna underwent the genetic testing. "He had a little cup and he was like, 'Anna, you have to spit in the cup.' That took a while," she laughed. This sample was sent to a lab and analyzed. Surprisingly for Stitzel and Anna's family, her test results revealed that she was at a low risk for developing scoliosis. However, because of a family history of scoliosis, her parents decided it was better to be safe than sorry.

Coupled with his therapy, Stitzel believes the genetic testing can lead to a huge breakthrough in scoliosis treatment. If patients with severe scoliosis can be diagnosed and begin therapy before symptoms of the disease appear, the spinal curvature can be prevented from occurring.

"'Cure' isn't a word you throw around lightly," Stitzel said. "So I'm not saying we have a cure, I'm saying we have an effective treatment that may be able to head the condition off particularly in its early stages, when we're not playing catch-up."

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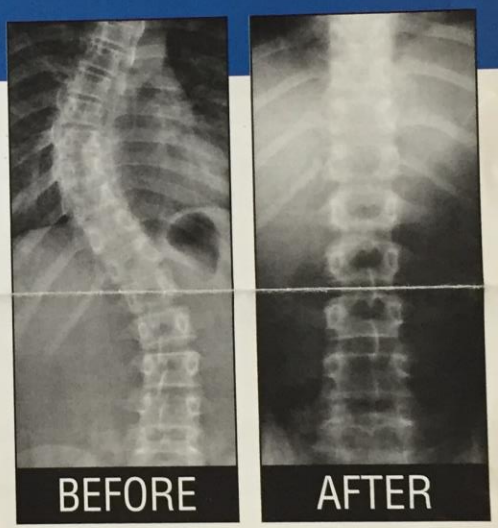

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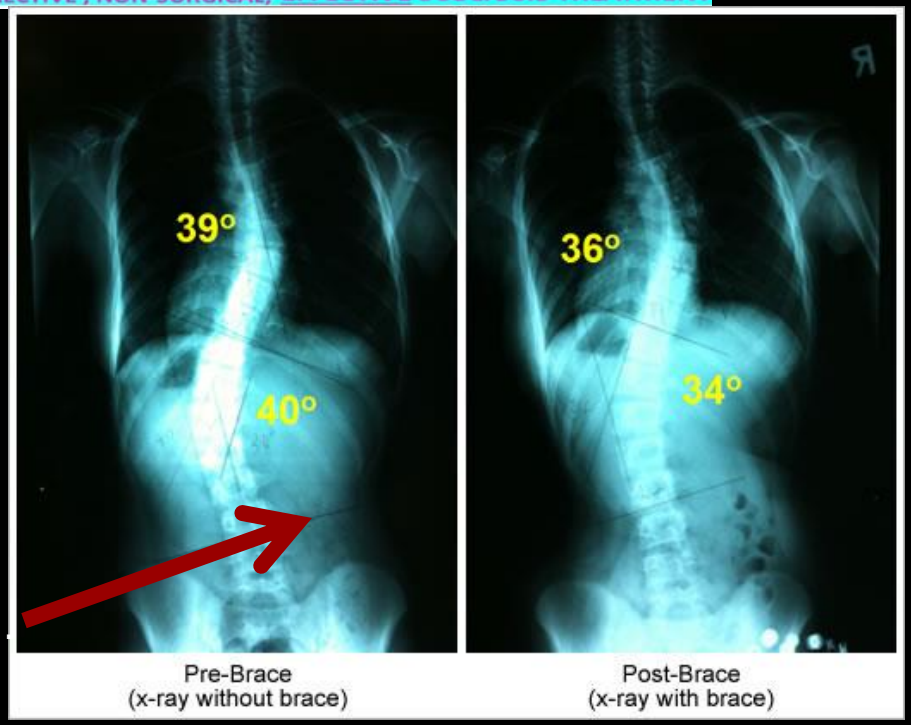


But...opps!

J Bone Joint Surg Am. 2015 Dec 16;97(24):1994-8. doi: 10.2106/JBJS.O.00217.

An Independent Evaluation of the Validity of a DNA-Based Prognostic Test for Adolescent Idiopathic Scoliosis.

Roye BD[1], Wright ML[1], Matsumoto H[1], Yorgova P[2], McCalla D[1], Hyman JE[1], Roye DP[1], Shah SA[2], Vitale MG[1].

Author information

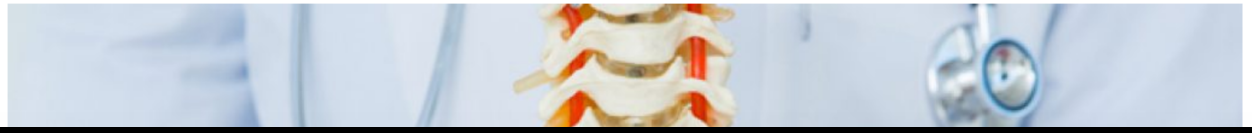
- No difference between mean Scoliscore between patients with progression vs. no progression (p=0.706)
- No difference in progression in pts with high risk scores (26%) and low risk scores (12%)
- Conclusion: Scoliscore did not differ in patients with and without curve progression.

The search for the scoliosis gene continues…

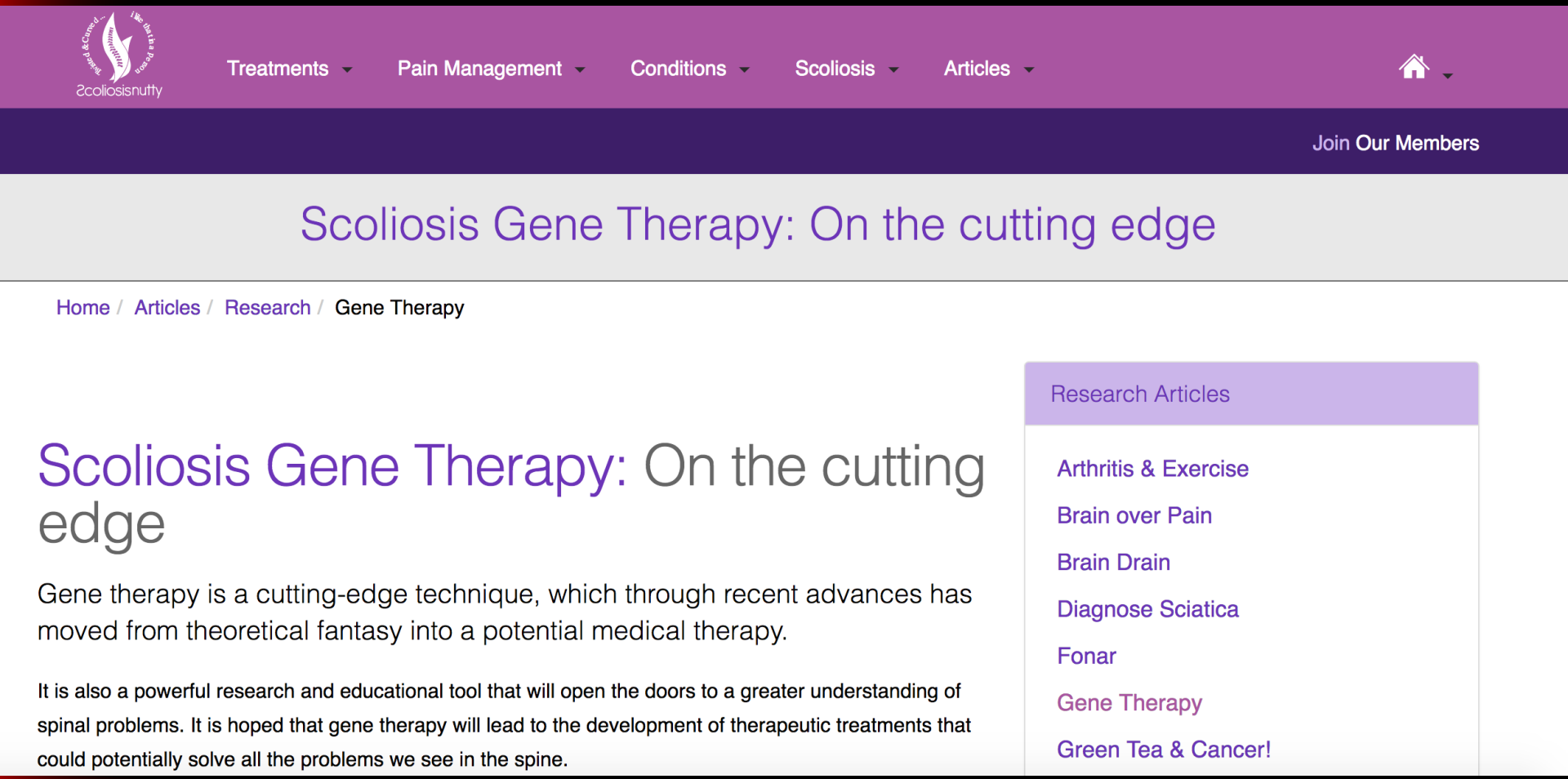
Researchers Identify Gene That Kickstarts Scoliosis

An overactive gene, called ladybird homeobox 1, was found to be the start of a genetic chain reaction that causes the spine to grow abnormally.

E



What about Gene Therapy?



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.

Related

Hedge-Fund Manager Looks to Cure Daughter of SMA

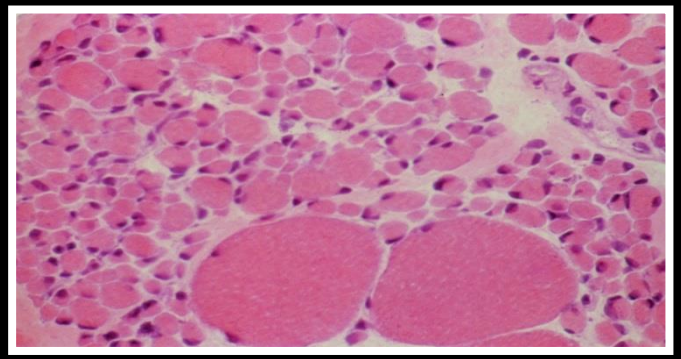
The malady makes the nerve cells that control muscles gradually deteriorate. There are no treatments, let alone a cure, Bloomberg Markets magazine reports in its October issue. Worse still, while the gene causing the ailment had recently been discovered, nobody in the drug industry was doing much about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

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



ISIS SMN-Rx

- Anti-sense drug designed by ISIS pharmaceuticals[1]
- ISIS SMN-Rx alters splicing of SMN2 gene → *increased production of functional SMN protein*[1]
- ISIS pharmaceuticals have also developed biomarker assay to measure level of SMN protein in CSF[1]

Must Be Given Intrathecally ! !

1. http://www.isispharm.com/Pipeline/Therapeutic-Areas/SevereandRare.htm#ISIS-SMNRx

The first drug had an unfortunate name:ISS-N1 (not to be confused with..)

Now FDA approved. Sounds better..

Scoliosis in SMA

Severity and onset are directly related to the severity of the disease

- **Type 1: 100% develop scoliosis**

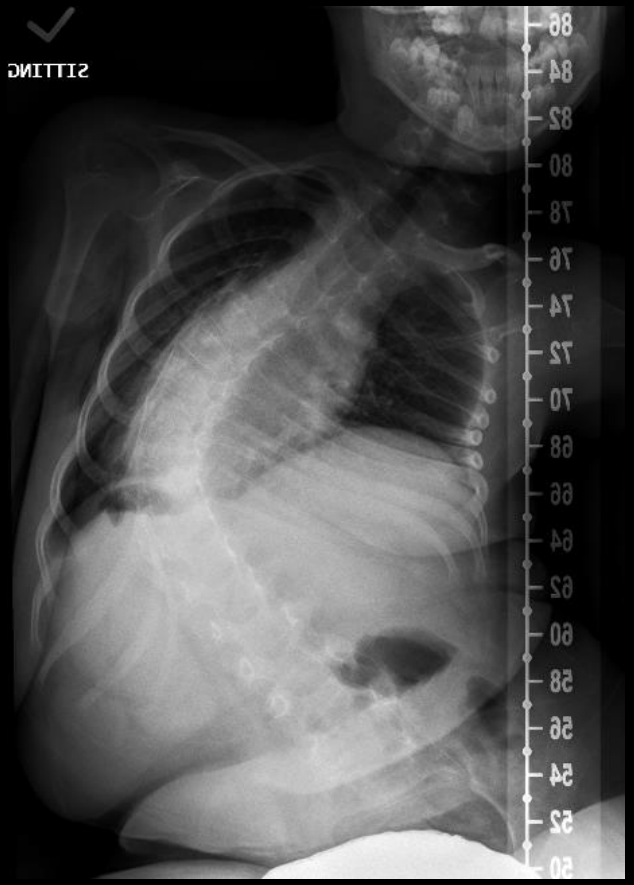
  ≤ 2 years of age

- **Type 2: 100% develop scoliosis**

  1-7 years of age

- **Type 3: 50% develop scoliosis**

  4-14 years of age



Phase 1 Trial

Neurology. 2016 Mar 8;86(10):890-7. doi: 10.1212/WNL.0000000000002445. Epub 2016 Feb 10.

Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy.

Chiriboga CA[1], Swoboda KJ[2], Darras BT[2], Iannaccone ST[2], Montes J[2], De Vivo DC[2], Norris DA[2], Bennett CF[2], Bishop KM[2].

Author information

Abstract

- Safe
- Well tolerated
- CSF half-life of 4-6 months
- Improved motor scores at 3 months after dose
- Conclusion: Results support further development

Phase 2 Trial

Lancet. 2016 Dec 17;388(10063):3017-3026. doi: 10.1016/S0140-6736(16)31408-8. Epub 2016 Dec 7.

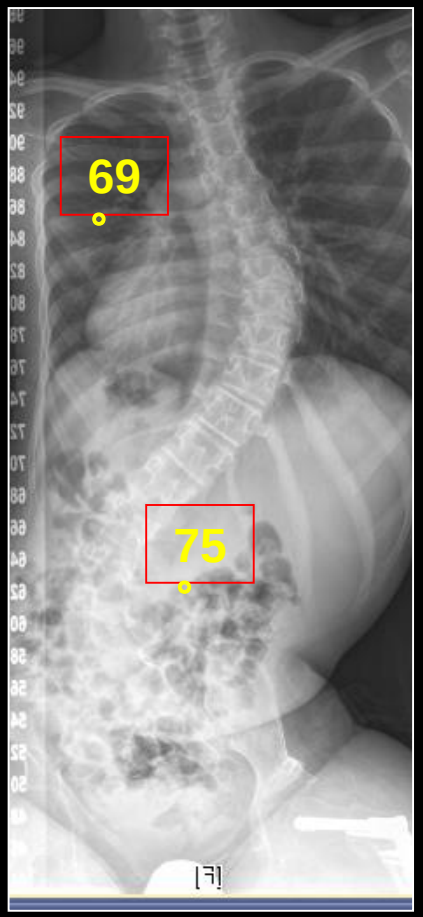
Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study.

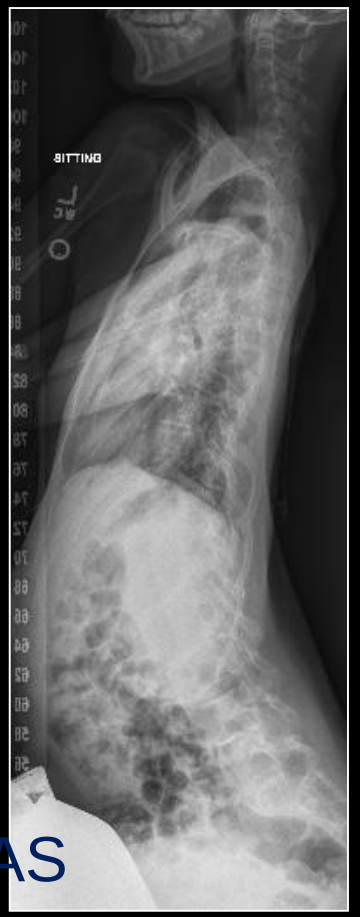
Finkel RS[1], Chiriboga CA[2], Vajsar J[3], Day JW[4], Montes J[2], De Vivo DC[2], Yamashita M[5], Rigo F[5], Hung G[5], Schneider E[5], Norris DA[5], Xia S[5], Bennett
Bishop KM[5].

- Incremental achievements in motor milestones
- Improved motor function scores
- Improved motor action potentials
- Conclusion: acceptable safety and tolerability

Treatment of SMA-scoliosis in the era of Spinraza

- 12yo girl
- Type 2 SMA
- No BiPAP
- Over 15 months:
  - T4-T12: 43 → 69
  - T12-L5: 24 → 75
- C-EOS: N3(-)P2

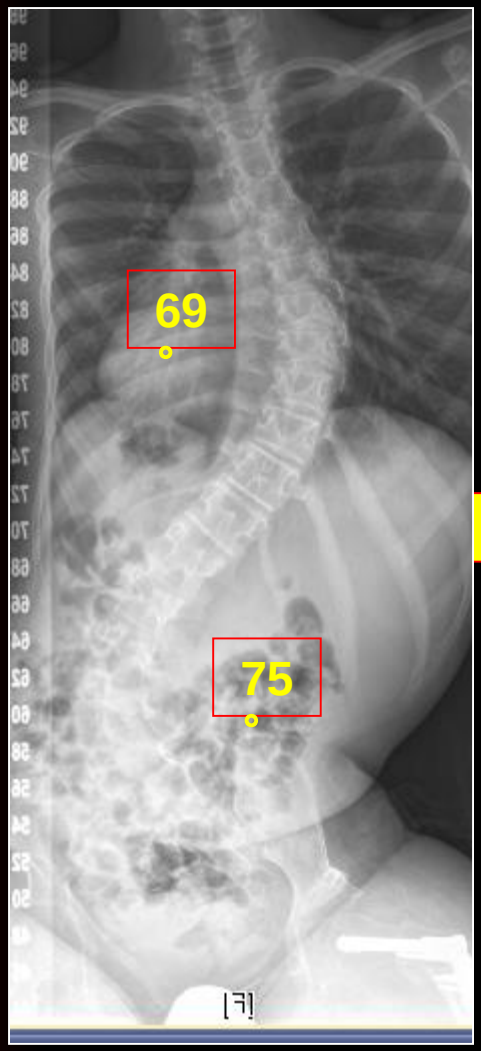


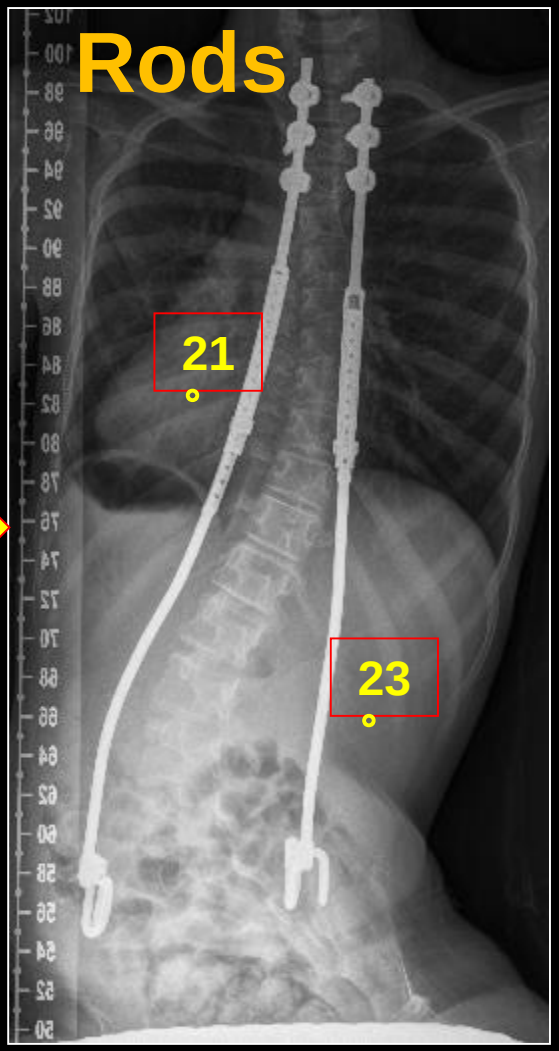


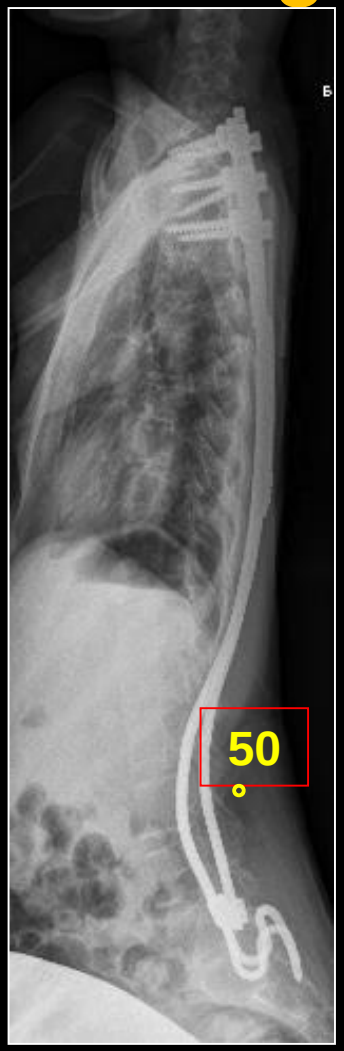
Courtesy of Michael Vitale, MD

Case Presentation: AS

Dual T2-T4 to Pelvis VEPTR Growing Rods





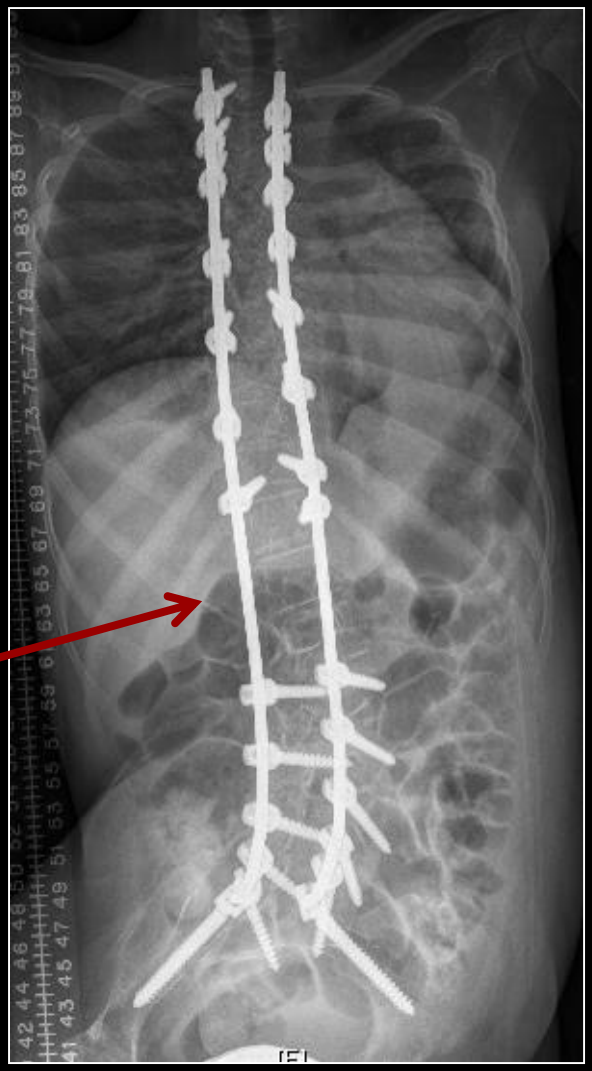


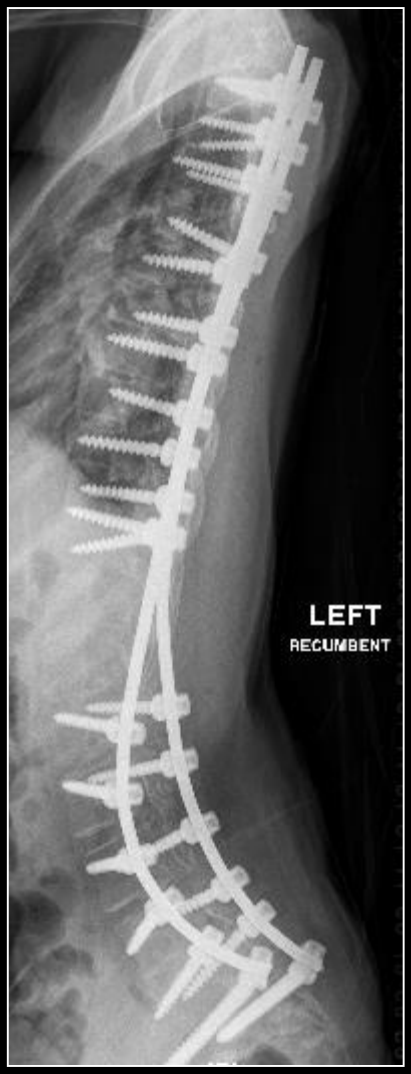
Courtesy of Michael Vitale, MD

10 days post-op

“SMA Construct”: AS

- Now 13yo
- S/P 1 Lengthening
  - Screws for Pelvic Control
- PSIF T2-Pelvis
- Pt enrolled in ISIS trial:
  - Requires intrathecal injections SMNRx via lumbar spine
  - Gap left: T12-L2 instrumented but unfused





Courtesy of Michael Vitale, MD

Scoliosis in SMA in the Era of Spinraza

- Medical treatments are here and also continuing come down the pipeline
- Perhaps a rationale to
  - Be more aggressive about treating SMA I
  - Use enough rib fixation and get balance early
  - Use an SMA (skipping) construct

So.. Genetic interventions *are possible*. More to come!

Thank You