Medical Device Regulation US vs EU
Establishing Safety and Efficacy
Growth Modulation of the Spine for Treating Pediatric Spine Deformity

Brian Snyder MD/PhD

Co-Chair POSNA-SRS Pediatric Device Task Force

NO RELEVANT CONFLICTS

SRS
Scoliosis Research Society

POSNA
The Pediatric Orthopaedic Society of North America

Medical Device Regulation
US vs. EU

- Medical device regulation controversial US and EU
  - ✓ FDA criticized for delays in approval
  - ✓ EU criticized lax device approval and inability to gather meaningful data
- FDA mandates device proved efficacious compared to a control or equivalent to predicate device
- EU mandates that device perform intended function
- Stringent, peer-reviewed safety data has not been consistently reported (post-market surveillance)
- Recent high-profile device failures = political pressure US and EU for more restrictive approval

FDA Approval Process

FDA regulation of devices motivated by patient safety concerns
(The Medical Device Amendments of 1976)

- Devices that have no predicate (device used before 1976) and are new device type are automatically classified as class III
- Class III devices are high-risk devices that require stringent safety and efficacy data for FDA approval unless they can be proved to be substantially equivalent to a predicate device or similar device with proved safety and efficacy (510k)
- Class III devices require premarket authorization (PMA)
  - requires investigational new device (IND) application and safety trial
  - key aspect IND application is prospective clinical trial - IND compared with standard of care
  - Randomized trials cost millions of dollars, require several years to complete
- FDA mandates post-market surveillance
  - Reporting system is voluntary for healthcare providers and consumers - adverse events substantially underreported

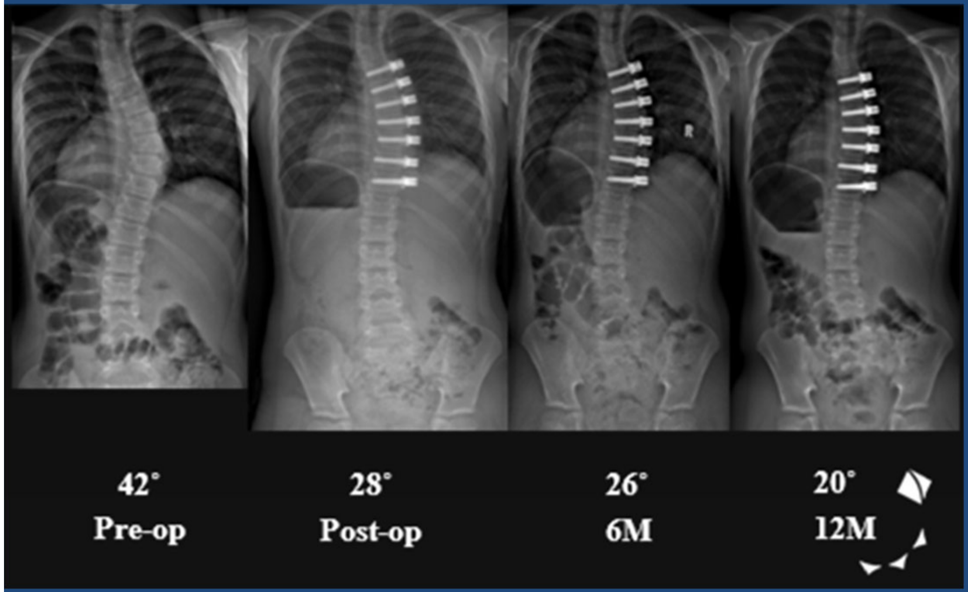
European Union Approval Process

Medical Device Directives motivated by unification EU market, aim to strengthen innovation and industrial process across Europe

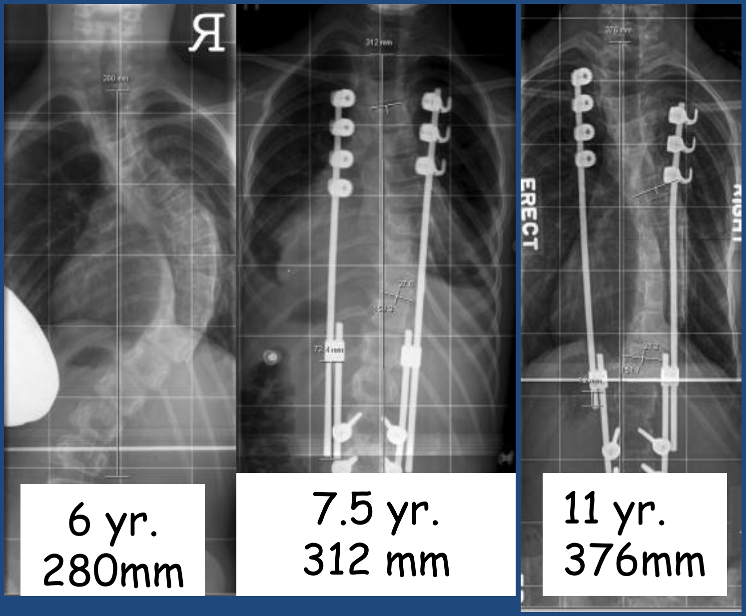
- Class IIb, (most orthopaedic devices) and class III require submission to notified body
- Notified Body: *for-profit companies* that contract with device companies regulate device approval
  - grant Conformité Européenne (CE) mark- allows device to be marketed in all EU countries
- Specific notified body contracted by device manufacturer within approving country determines specific requirements
- Submissions include clinical and preclinical evidence supporting device safety and performance.
  - includes literature review of similar approved devices
  - clinical data supporting safety and performance of device
  - clinical studies typically nonrandomized single-arm case series with historic control subjects
- Since 2011, all post-market adverse events must be reported to the European Databank on Medical Devices (Eudamed)

Modulating Spine Growth

Anteriorly based tether



Posteriorly based distraction

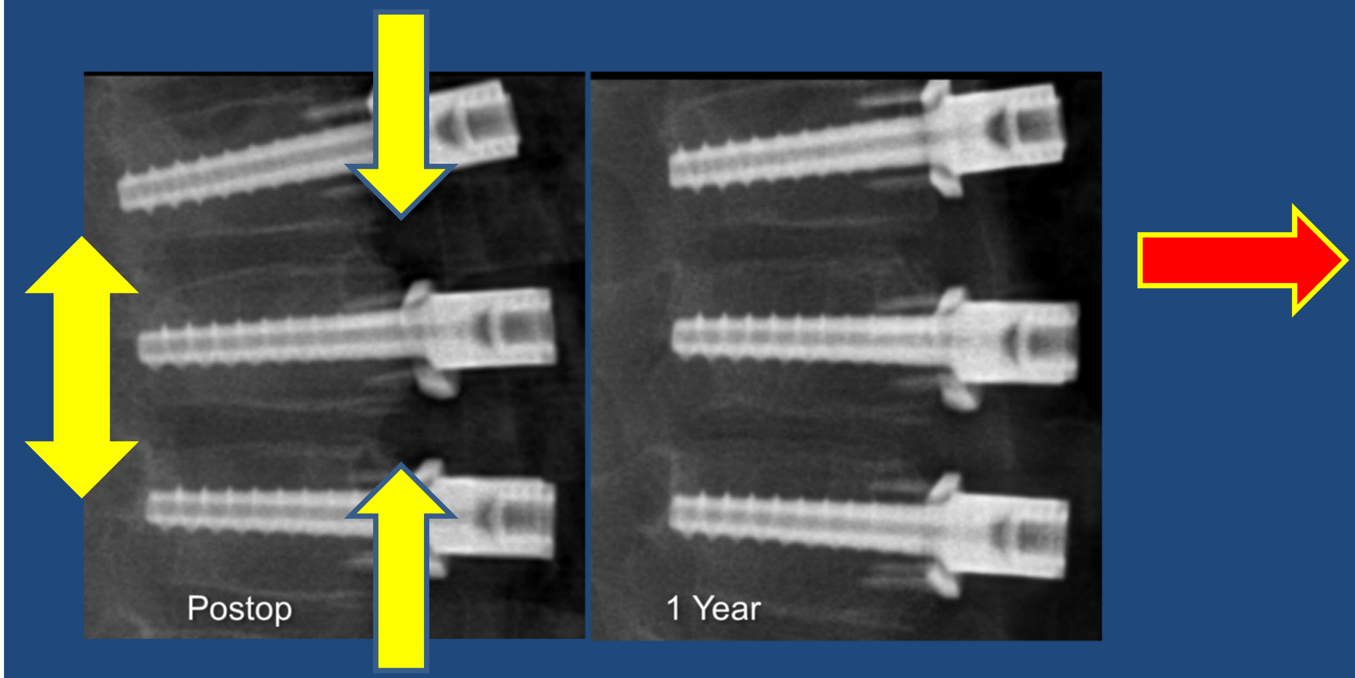


- **Goal: Modulate asymmetrical spinal growth**
  - Maintain motion of spine units
  - Maintain disc physiology
  - Allow growth and development of lung/thorax

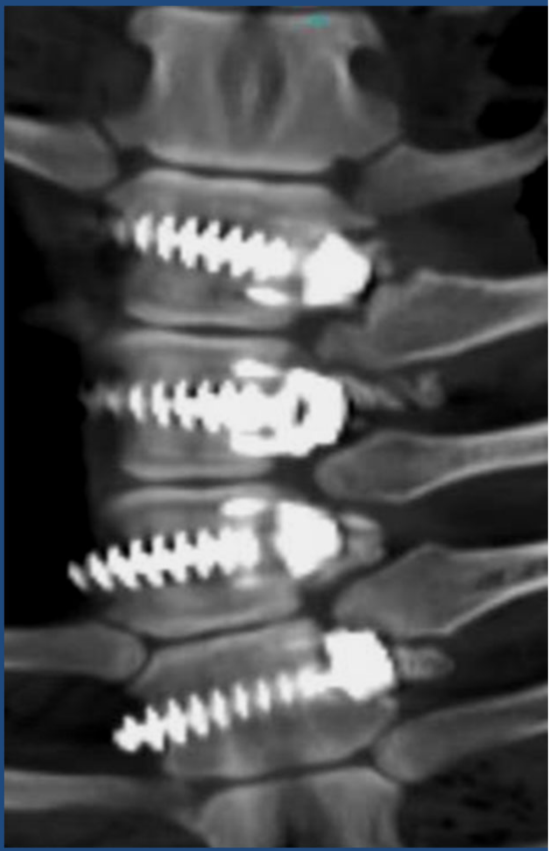
Growth Modulation

Based on Heuter-Volkman principal:

- Depends on loading mode and magnitude applied @ physis or apophysis
  - Tensile force (stress) stimulates growth
  - Compressive force inhibits growth



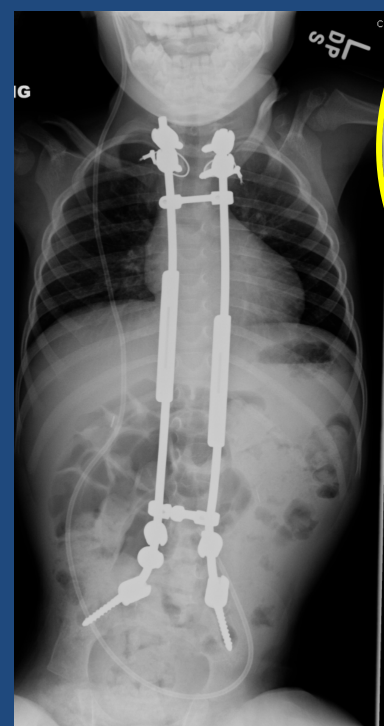
Asymmetric growth

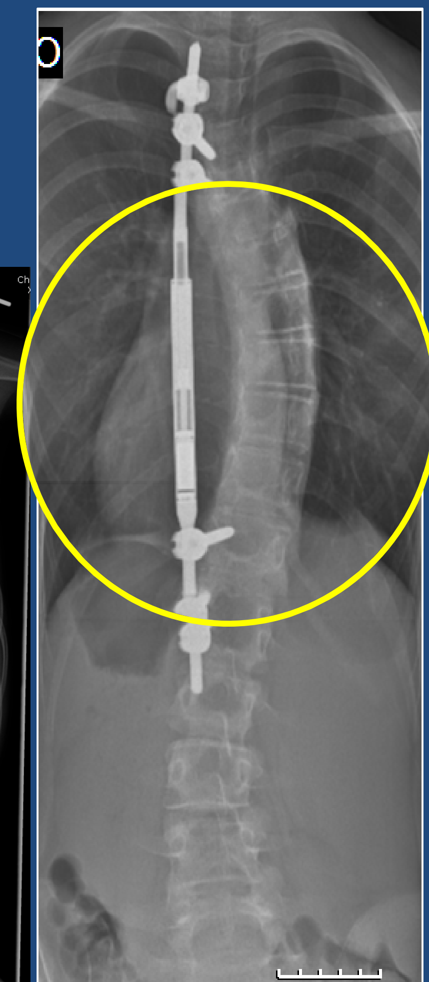


Growth Modulation Systems

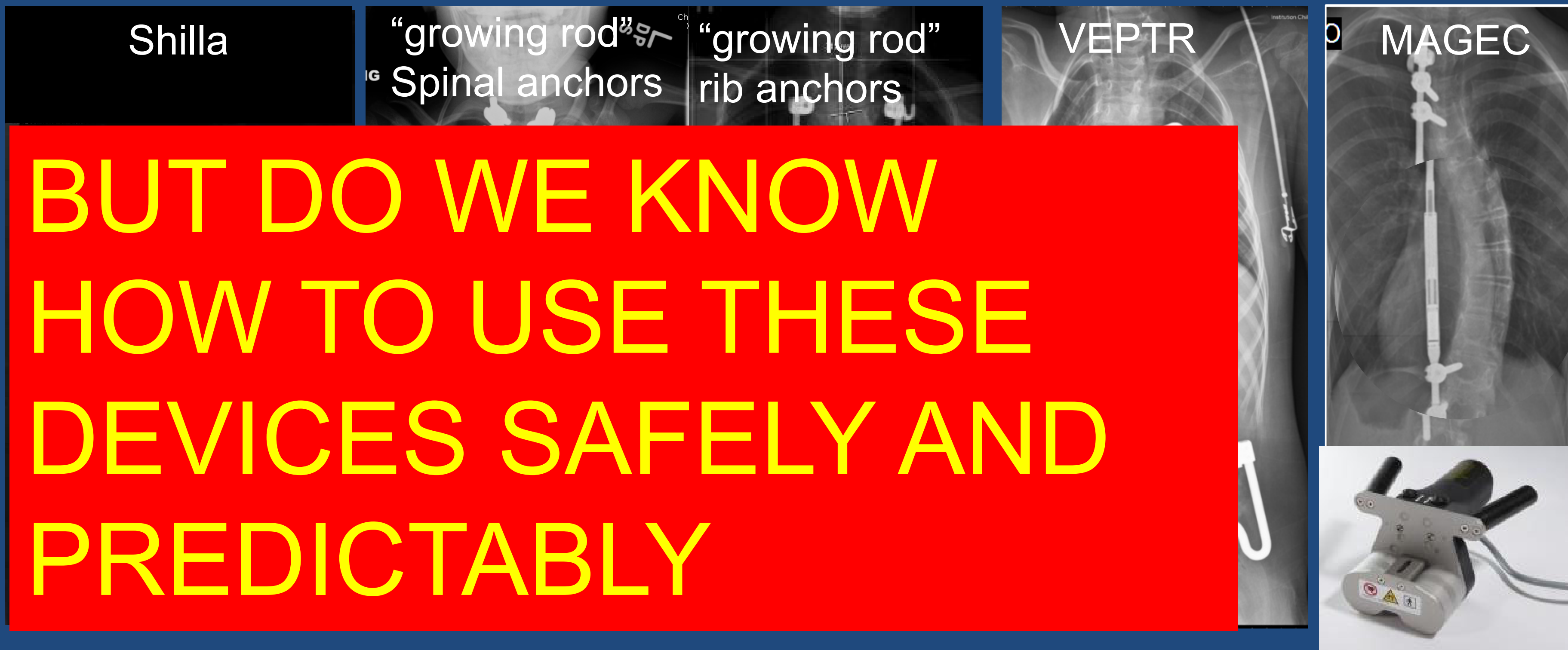
Devices Classified based on:

– Placement
  - anterior vs. posterior
– Loading mode
  - tension vs compression
  - static (staples, tethers) vs. dynamic (MAGEC)





FDA “approved” devices for growth modulation



BUT DO WE KNOW HOW TO USE THESE DEVICES SAFELY AND PREDICTABLY

2013 - Pre-amendment status established Harrington rods for specific pt. populations (EOS, TIS)

2014 - 510(k) clearance using pre-amendments Harrington rods as predicate for growing rods, Shilla, MAGEC, VEPTR

Devices cleared through this pathway **Unclassified -** subject to risk assessment

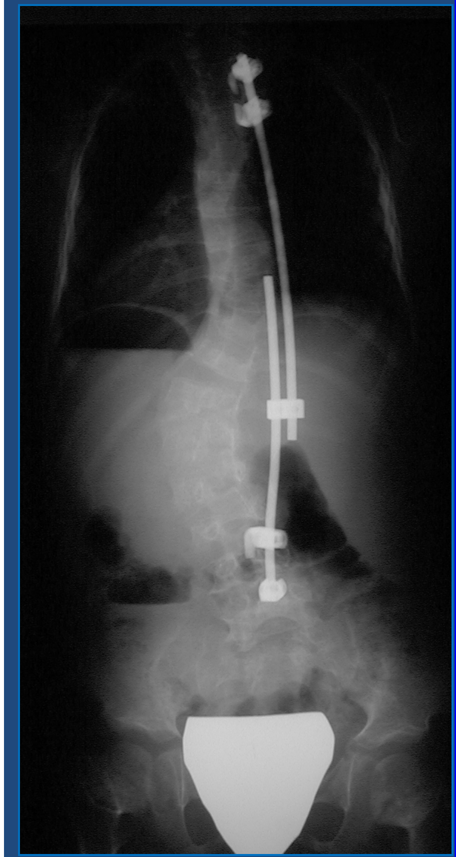
Medical Device Approval MUST establish Safety and Efficacy

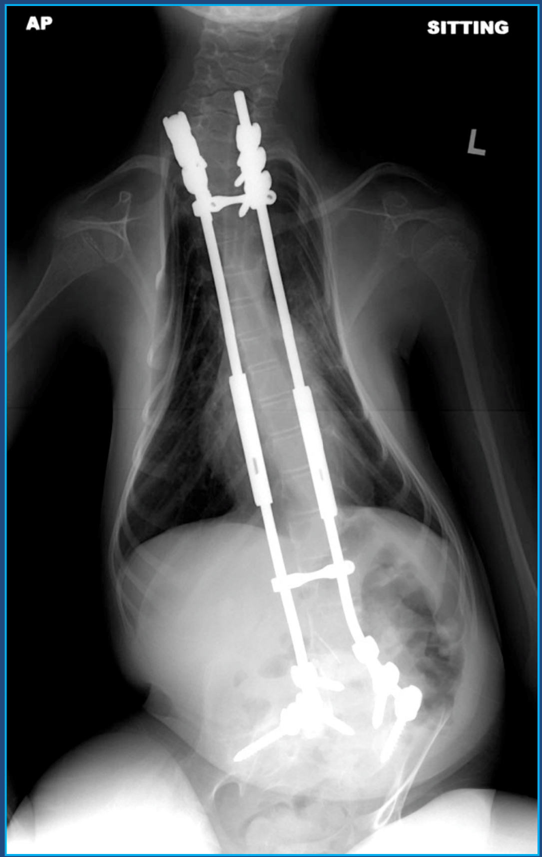
- Analysis predicated on ability of these systems to *predictably* modulate spine growth over time interval required to achieve desired clinical effect
- Necessitates specification of defined performance criteria for each device type *a priori* for pre-clinical and clinical evaluations

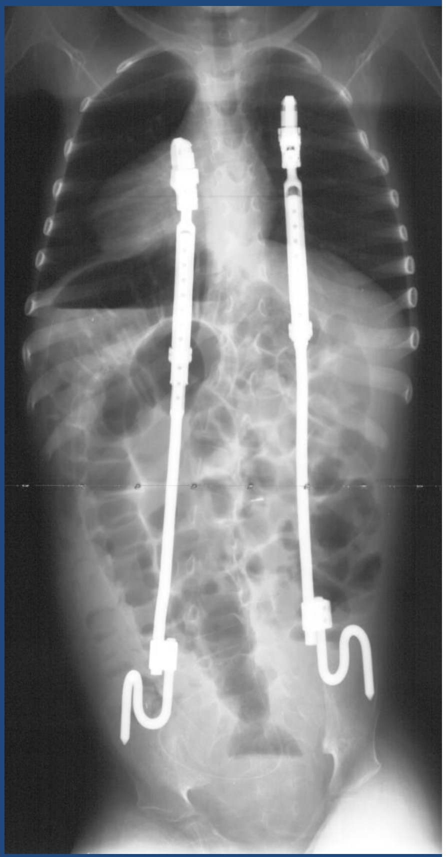
Unique Considerations in Children

- Multiple sizes of device required to accommodate children over range of heights and weights which change over time with growth
  - performance goals change with child's age
    - reflects evolving physical activity demands in same child over time
  - Device must serve dual function for indeterminate number of years without failing
    - maintain correction of spinal deformity
    - modulate growth of spine without inhibiting growth

<u>SAFETY</u> = Avoidance of Device Complication (Failure)

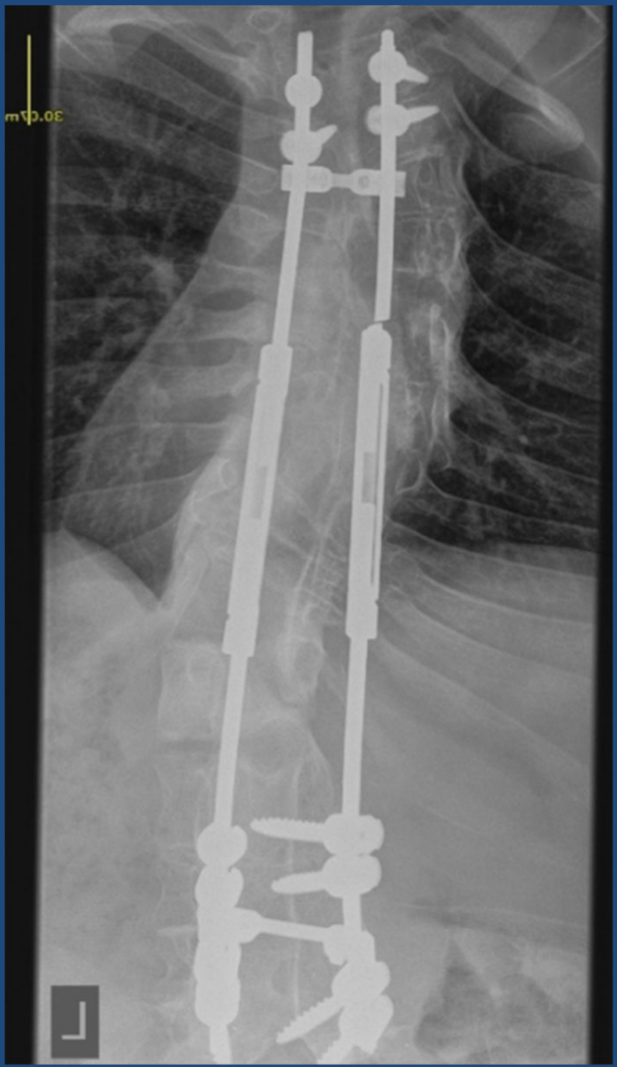






Safety Performance Criteria

- Performance criteria MUST reflect how devices function in growing children
- No standardized test protocols or established performance criteria for Non-Fusion spinal instrumentation
- No predicate adult device for similar indication



Design Variables

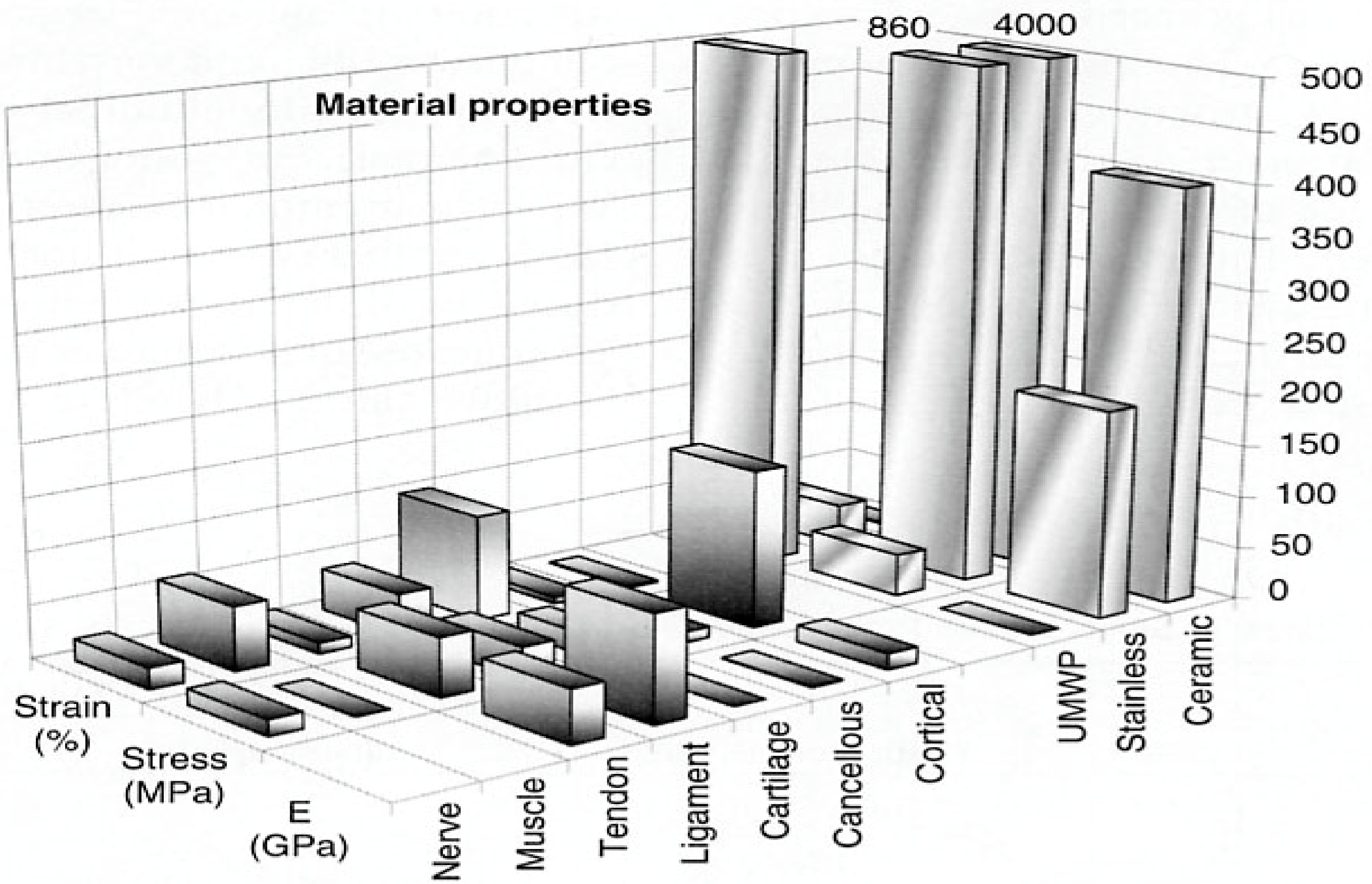
Properties of the device

- Material Properties
- Structural Geometry

➢**Controlled by manufacturer**

Comparison of Material Properties

Intrinsic Stiffness and Strength

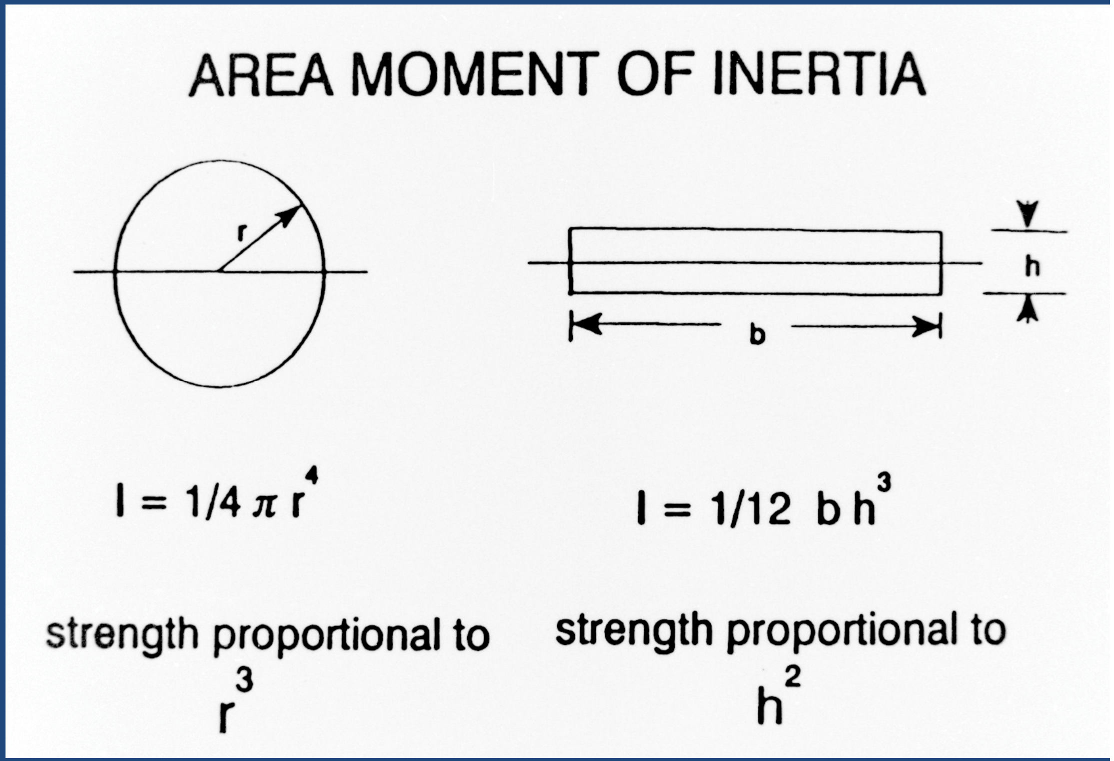


Geometry: Moment of Inertia

Determines Resistance to Bending

- Varies as 4th power of the distance from bending axis

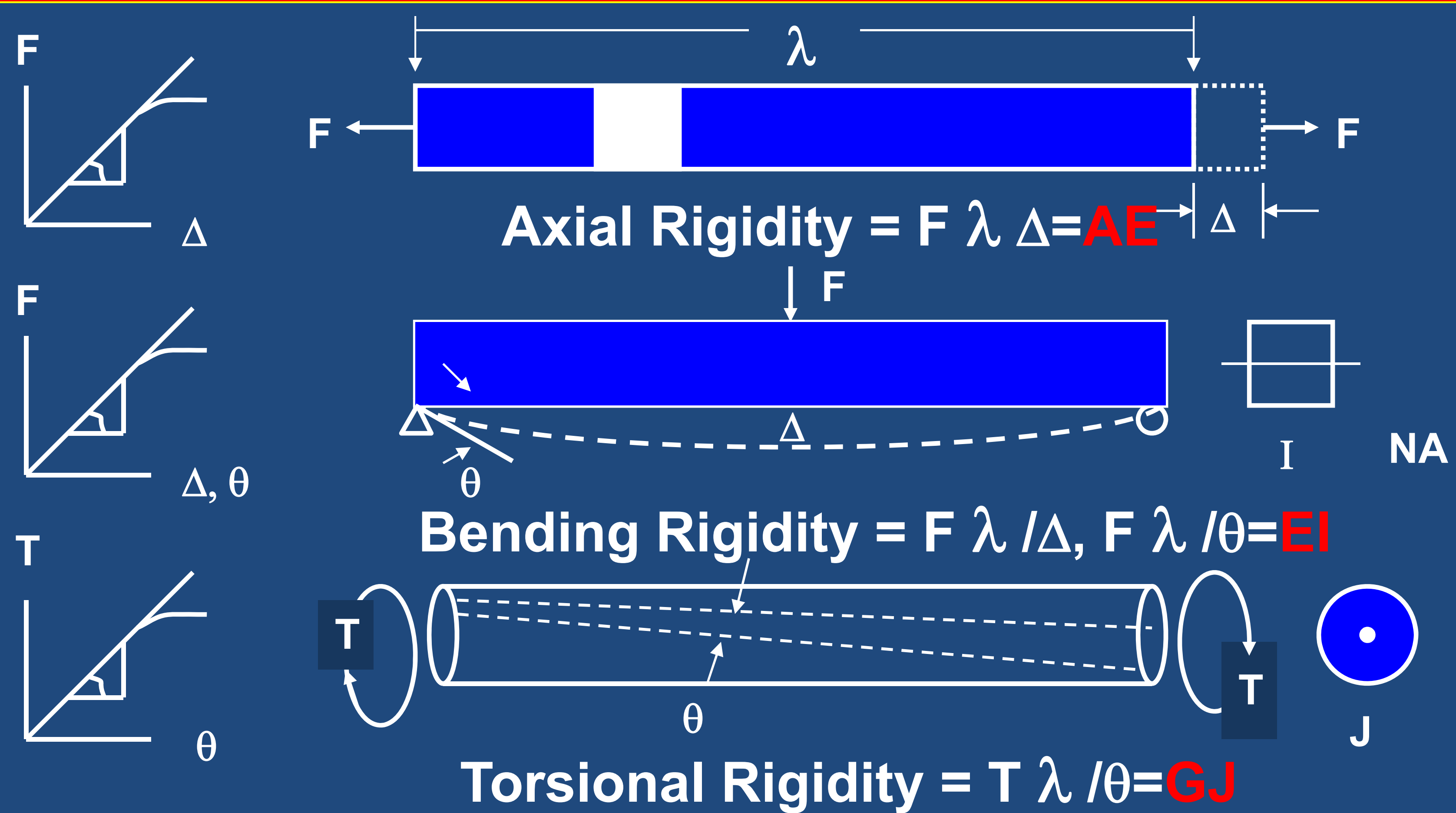
➢ **5mm diam rod 1.5x stiffer than 4.5 mm rod**



STRUCTURAL RIGIDITY

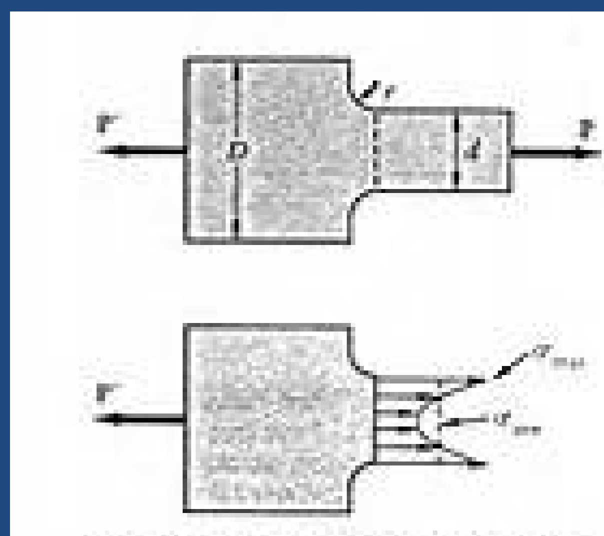
Product of Material Modulus x Geometric Property

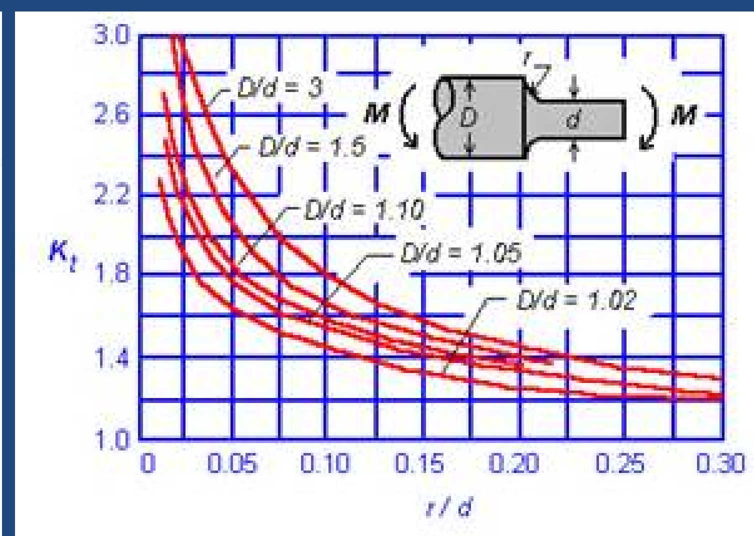
Determines Load Capacity of Rods



AVOID Stress Concentration

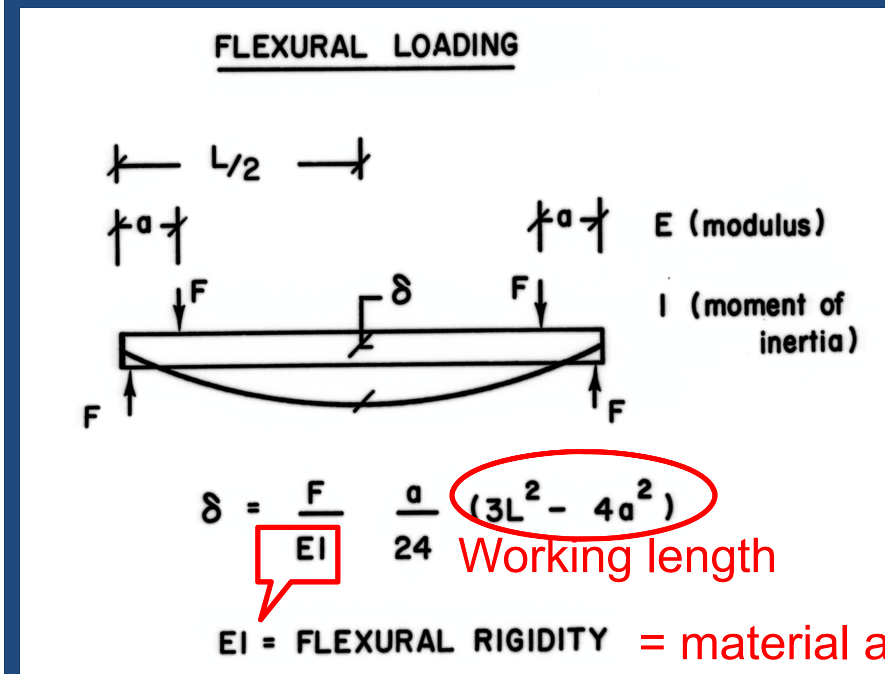
- **Abrupt change in geometry or material induces localized stress peak in structure that predispose fatigue failure**
- Discontinuities causes stress to be concentrated
  - Highest for small radius
- Mechanically assisted crevice corrosion @ couplings

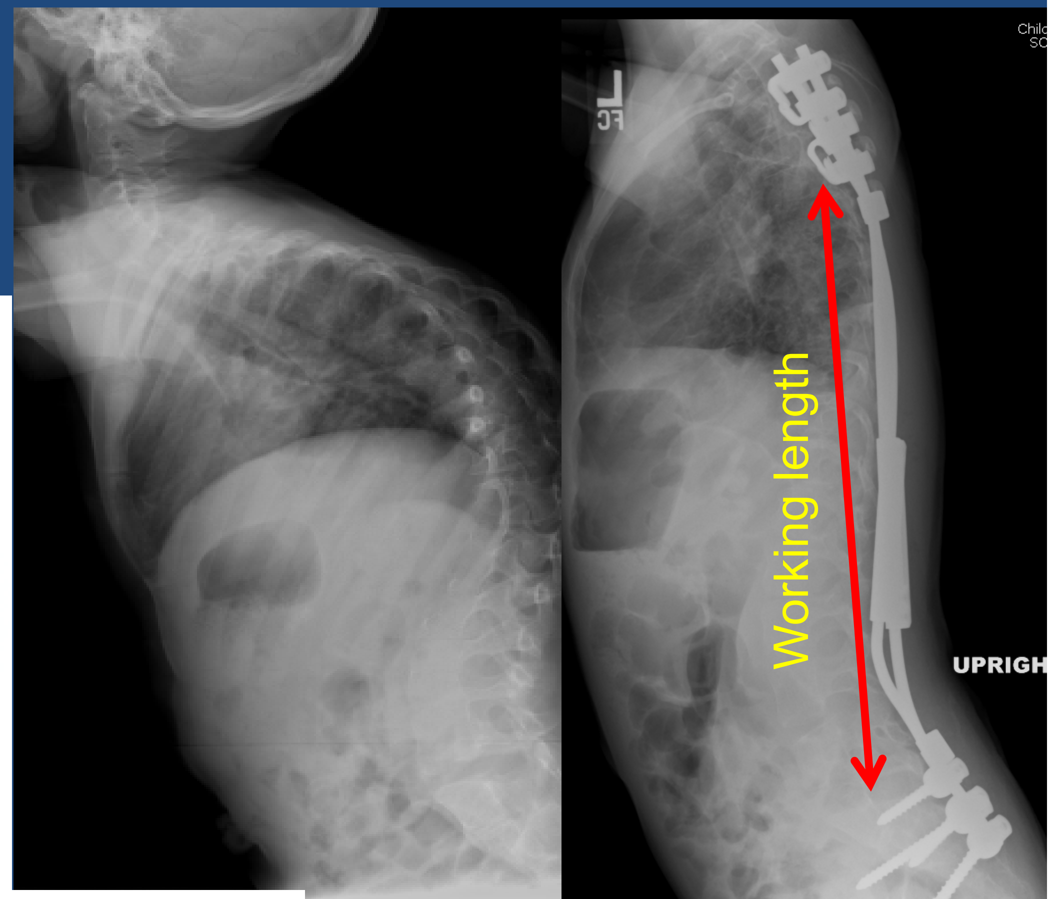




Other Factors Affecting Construct Stability

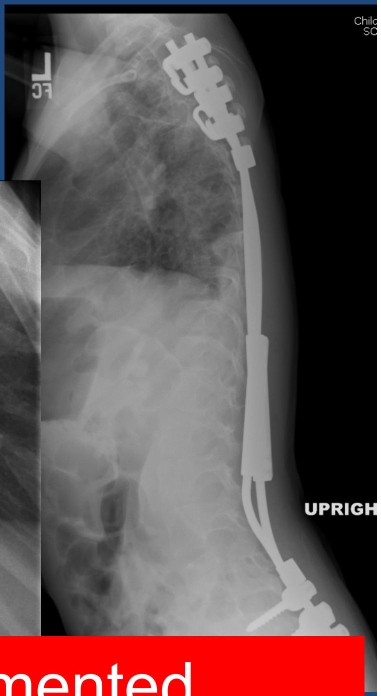
- Rod deflection (δ) varies as (working length)^2 **Working length = unsupported length**
- Working length and applied load/moment increase w/ lengthening

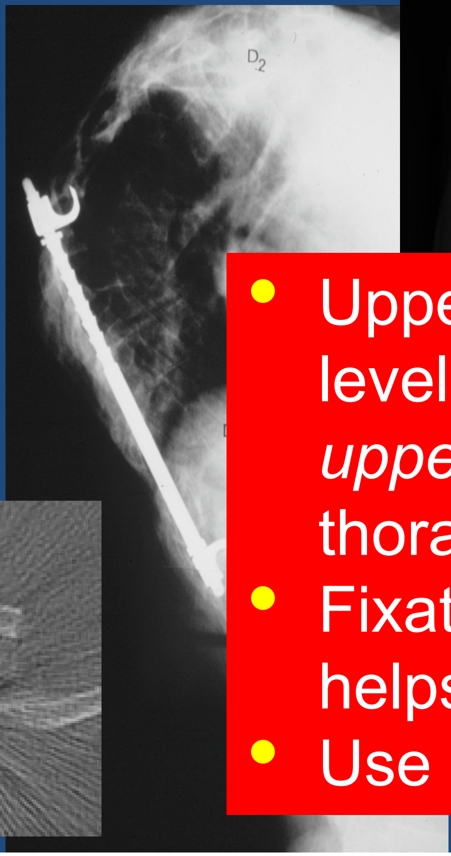


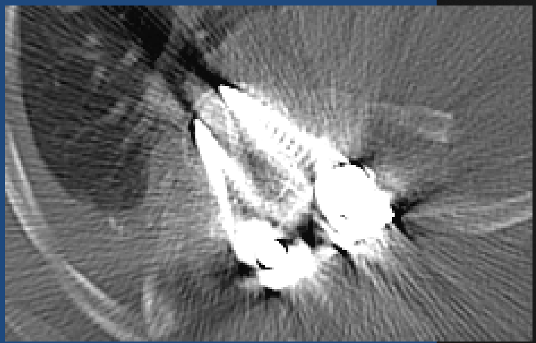


Properties of bone-anchor interface

- Screws (rigid) vs. hooks (semi-constrained)
  - Hook allows motion @ bone interface
  - relieves stress/energy similar to airplane wing
- Bone quality affects stability
  - Bone stiffness and strength vary with (density)^2



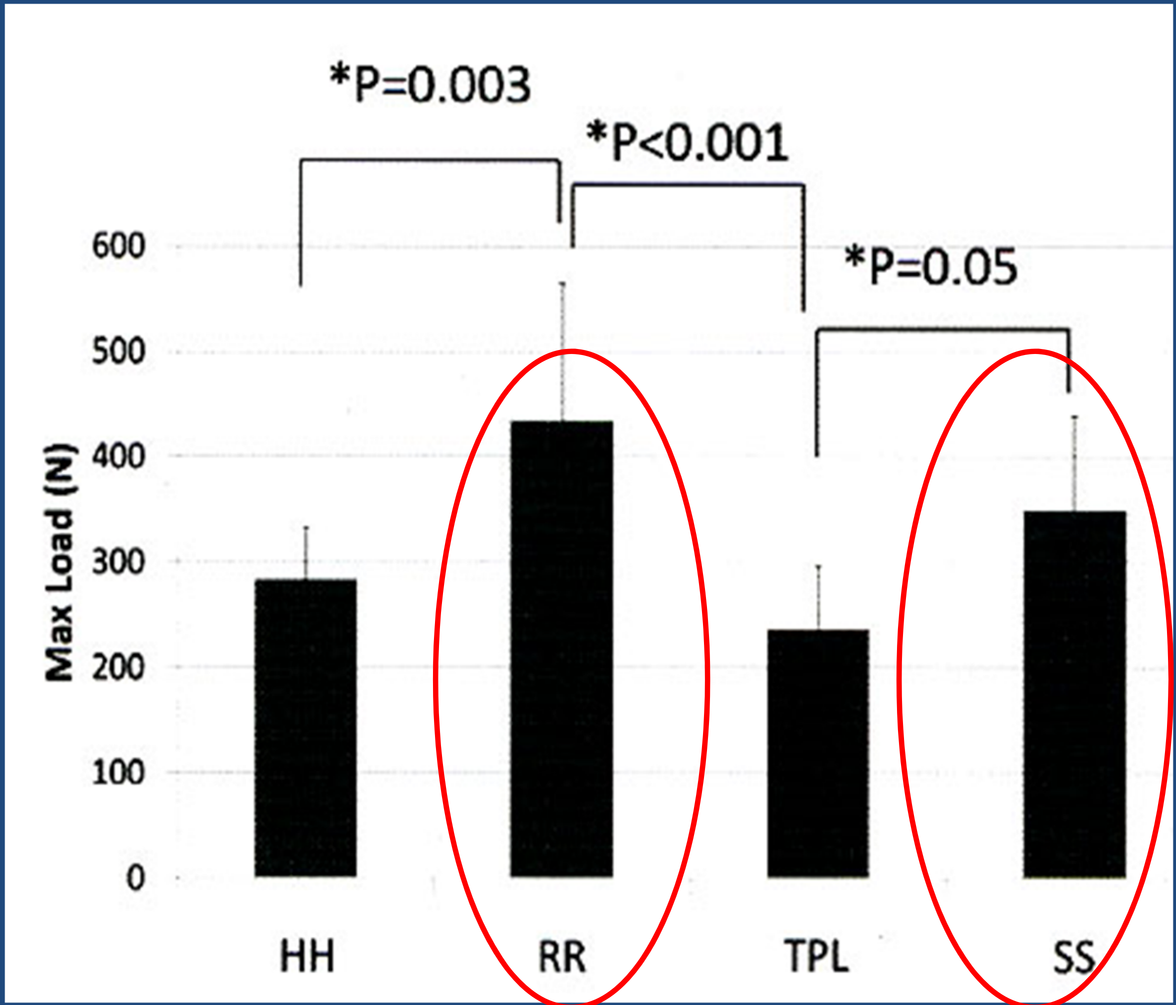




- Upper instrumented level should be *above upper end vertebra* of thoracic kyphosis
- Fixation ***proximal*** to T4 helps avoid PJK
- Use ≥ 5 anchors

Comparison of anchor construct strength
(Akbarnia et al. Spine Deformity 2:437-43; 2014)

- Rib based (RR) and Pedicle Screw (SS)
  - ✓ highest ultimate strength, but variable performance
- Laminar hook (HH) and transverse process hook (TPL)
  - ✓ lower ultimate strength but less variable performance

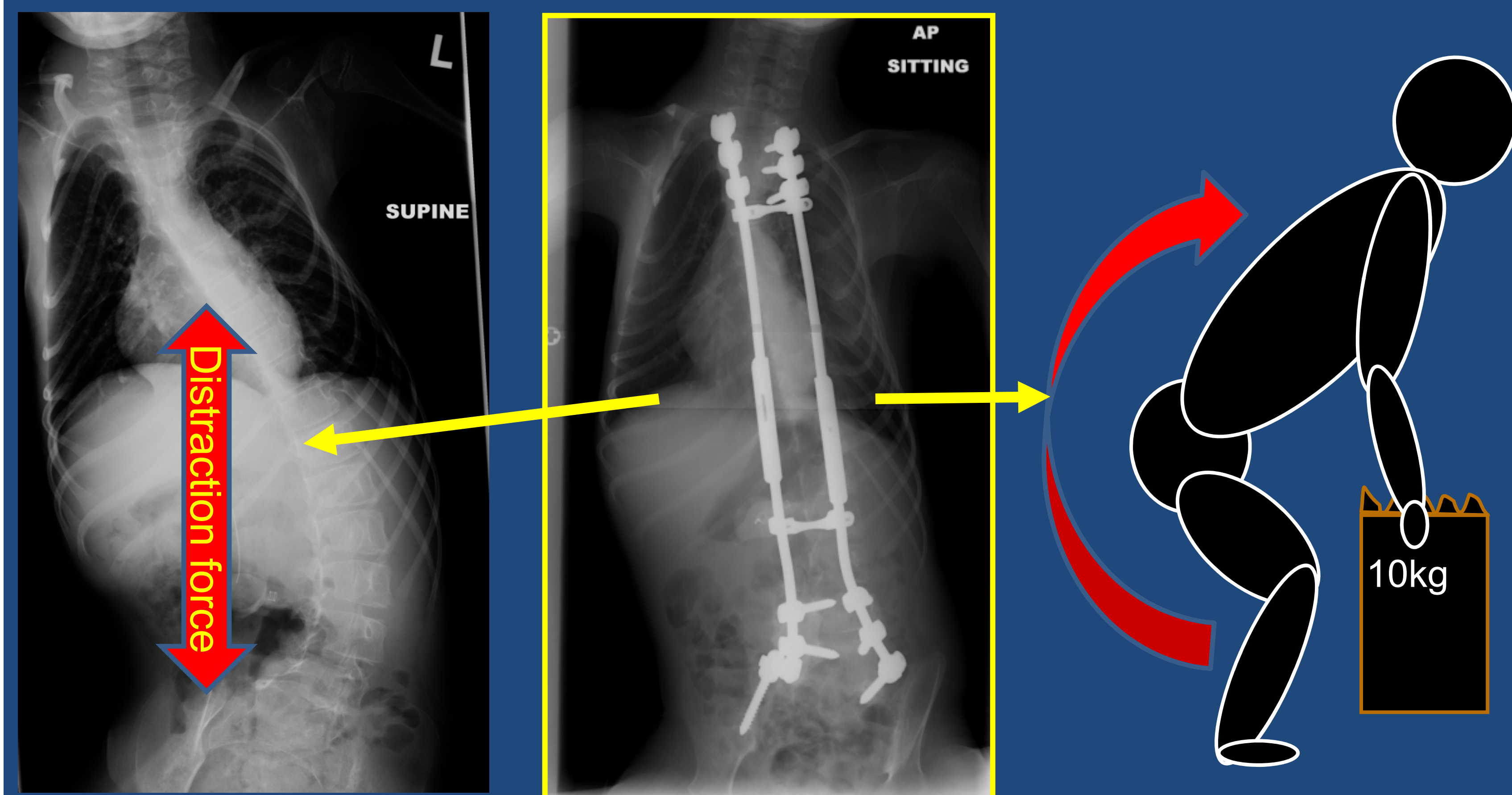


Applied Loads

- Mode of loading
- Magnitude of loads
- Number of cycles

➢ **Controlled by the patient**

Instrumentation must sustain forces & moments required to correct spinal deformity + those generated during activities of living



Cyclic Compression + Flexion + Torque

World Journal of
Orthopedics

How much distraction force ?

Measurement of forces generated during distraction of growing-rods in early onset scoliosis

Marco Teli, Giuseppe Grava, Victor Solomon, Giuseppe Andreoletti, Emanuele Grismondi, Jay Meswania

RESULTS: Twenty measurements were obtained showing a linear increase of the load with increasing distraction, with a mean peak force of 485 N at 12 mm distraction and a single reading over 500 N. We did not observe bone fractures or ligament disruptions during or after rod elongations. There was one case of superficial wound infection in the cohort.

CONCLUSION: The safe peak force carrying capacity of a motorized device for distraction of growing-rods is 500N.

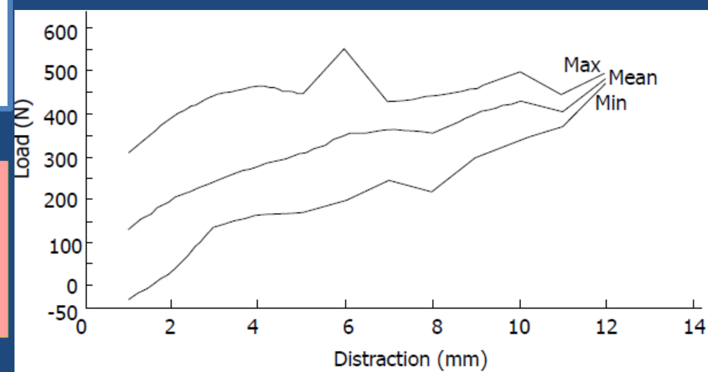


Figure 3 Force/distraction plot: maximum (top curve), mean (middle curve) and minimum (bottom curve) values.

Spine

SPINE Volume 36, Number 26, pp 2299–2303

DEFORMITY

The "Law" of Diminishing Growth

In Vivo Distraction Force and Length Measurements of Growing Rods

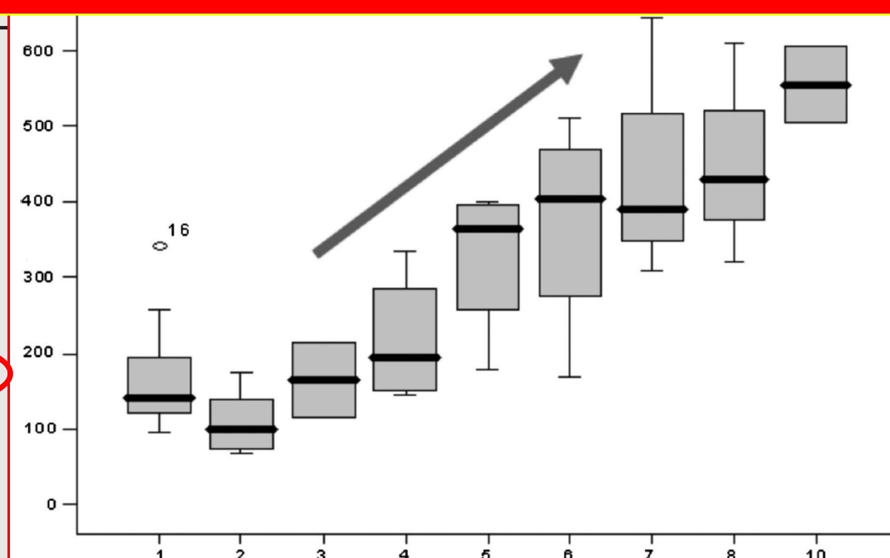
Which Factors Influence the Ability to Lengthen?

Hilali M. Noordeen, FRCS (Orth),* Suken A. Shah, MD,† Hazem B. Elsebaie, FRCS, MD,‡ Enrique Garrido,

IMPLIES THAT MORE FORCE REQUIRED OVER TIME TO MAINTAIN CONSISTENT INCREMENTAL LENGTH

MAY BE LIMITED BY STRENGTH OF MAGNETIC ACTUATOR

- There is a significant increase in distraction forces in growing-rod constructs with subsequent lengthening.
- Apical fusion increases the force needed to distract the rods significantly.
- The amount of length gained with each distraction decreases with time and with serial distractions.
- Instrumentation design must accommodate the forces generated and the trends observed in this study to minimize failure.



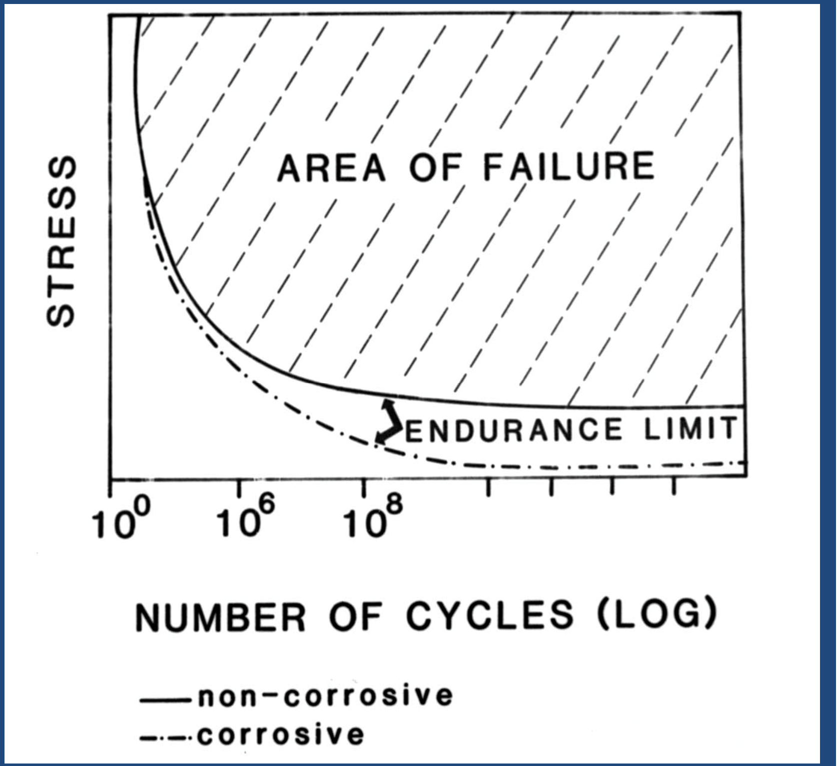
Fatigue

How many loading cycles must the implant withstand over 5-10 year course for growing child ?

- 6 mos of walking = 900,000 – 1,350,000 cycles

Is 5 million cycles (current ASTM guideline) enough ?

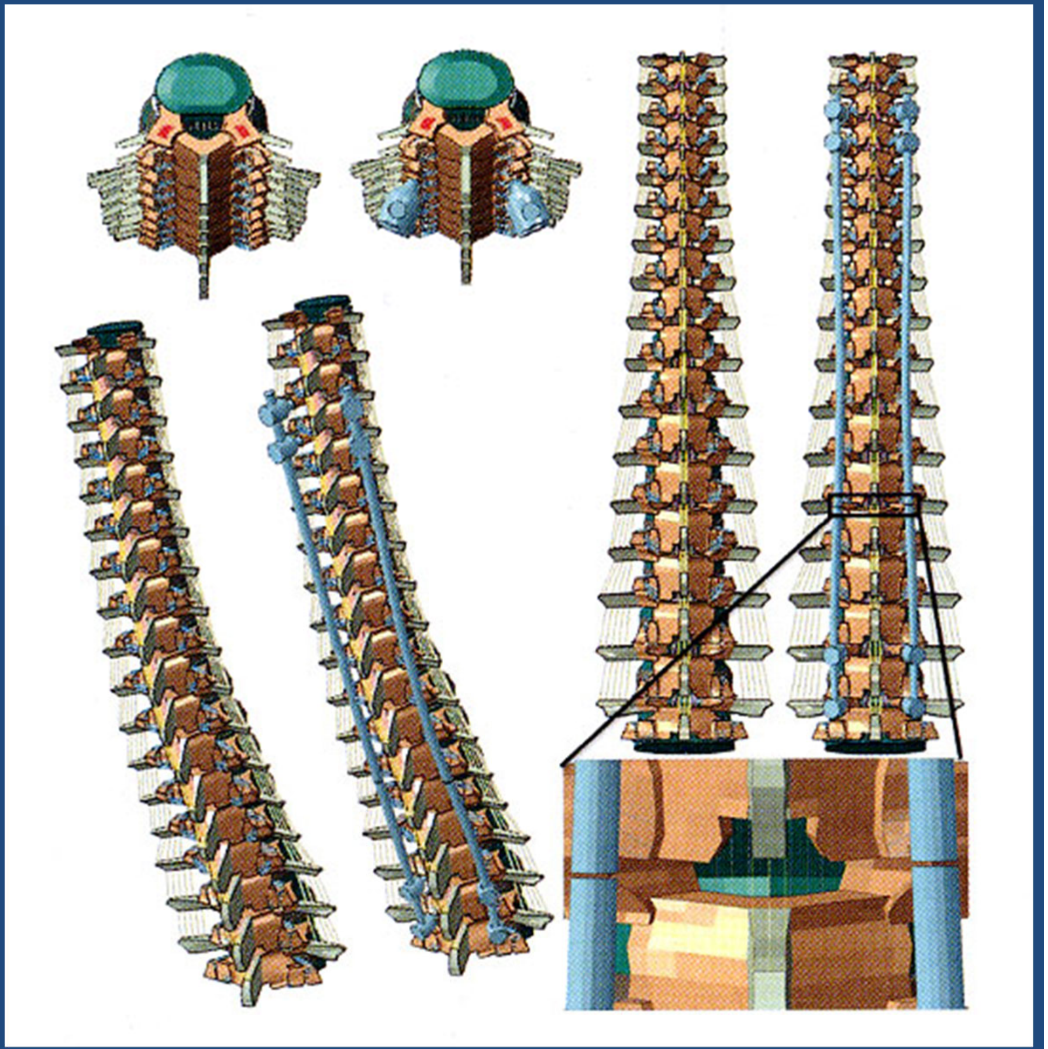
- <u>σ-N curve:</u> Number of loading cycles N required to fail specimen vs max stress attained during cyclic testing
- **<u>Endurance Limit:</u>** stress below which cyclic fatigue of material does not occur (even at infinite N)



Finite Element Models to determine optimal construct configurations, materials/geometry and lengthening intervals to minimize rod failure

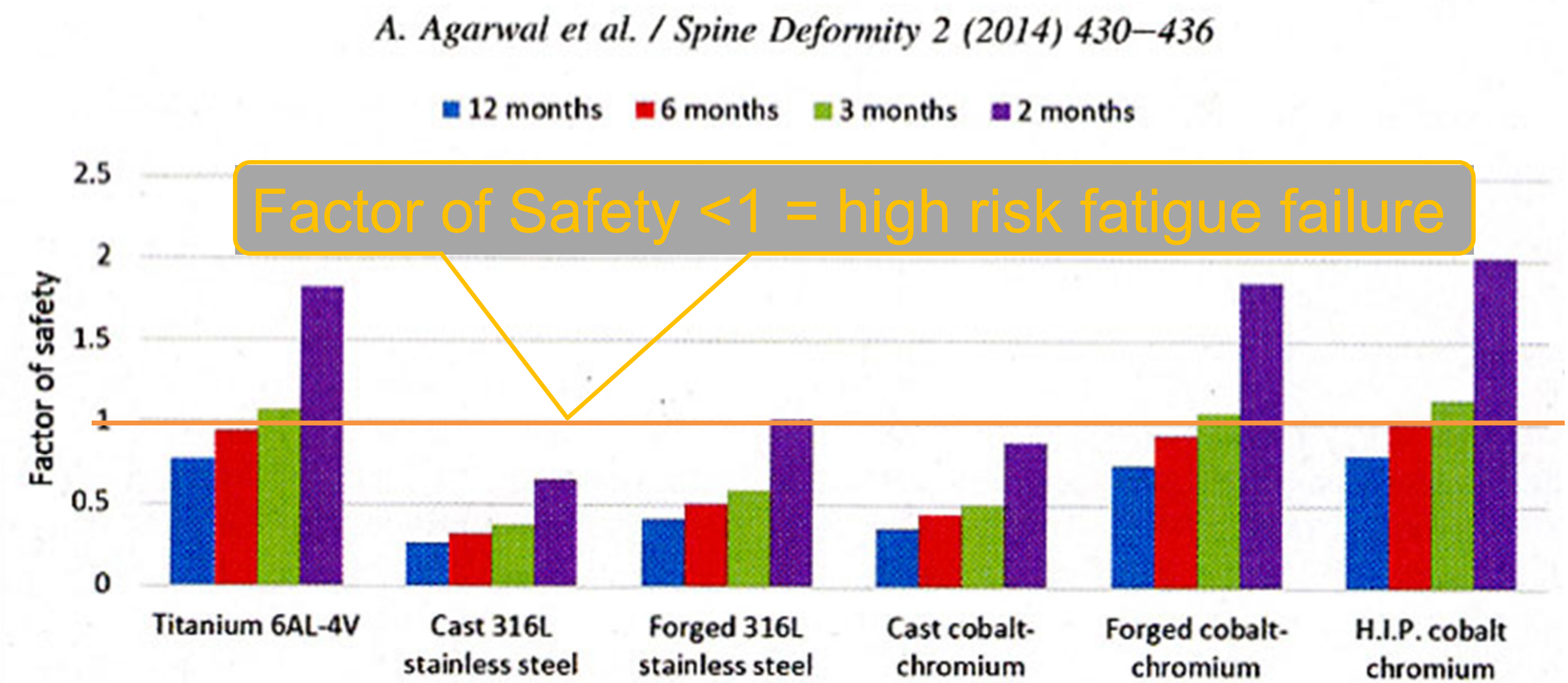
- FEM juvenile spine instrumented with dual growing rods
  - Appropriate material properties for bone, connective tissues
    - Elastic and Viscoelastic
  - Applied appropriate distraction to mimic growth over time interval
- Compared composite stress (Von Mises) on rods for different time intervals between distractions

➢ 12 mo, 6 mo, 3 mo, 2 mo



Agarwal et al. Spine Deformity 2:430-36; 2014

Factor of Safety (Fatigue strength / Max Von Mises Stress) for rod over 24 mos of sequential lengthening for different materials and lengthening intervals



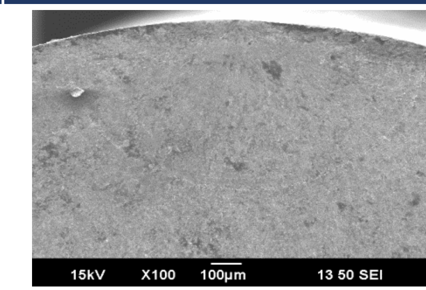
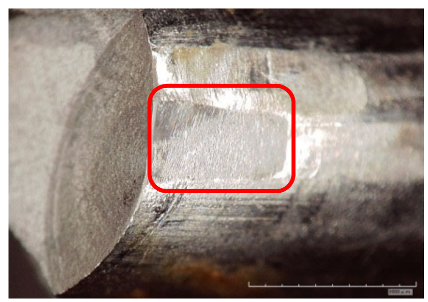
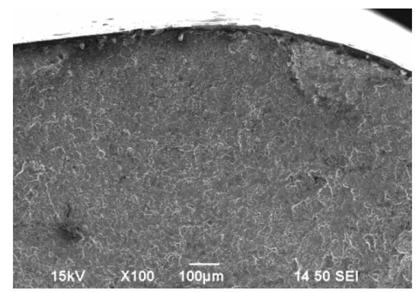
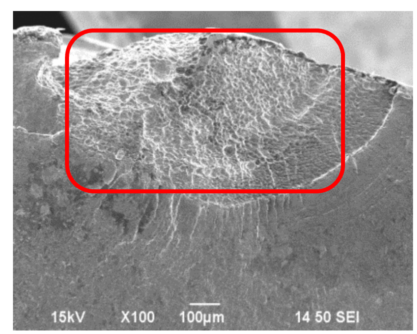
- Lengthening intervals > 2 mos, result in rod stresses approaching fatigue limit
- Ti & Cobalt chrome rod fail after 7 yrs walking (10 million cycles)
- Stainless steel and cast cobalt chrome fail in less time

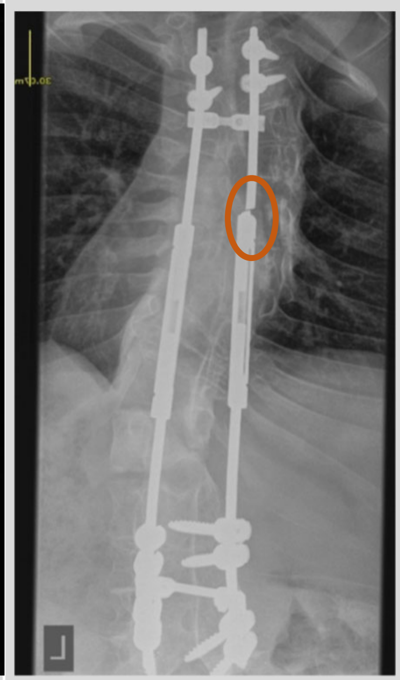
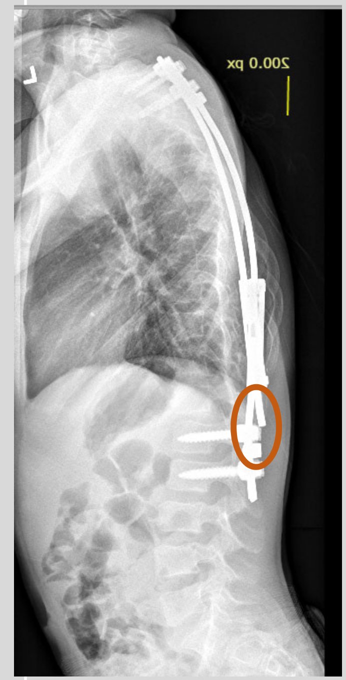
Genevieve Hill Ph.D.
Office of Device Evaluation Division of Orthopedic Devices

- Collaborated with CSSG, GSSG – Retrieval analysis, Registry review
- 40 retrieved constructs from 36 patients
  - ✓16 intact
  - ✓18 failed
  - ✓6 incomplete
- Registry provided supplementary clinical data
  - ✓Demographics, patient characteristics pre-operatively and implant removal, serial spine radiographs
- Retrieval analysis:
  - ✓Failure modes (metallurgical evaluation)
  - ✓Radiographic assessment
  - ✓Statistics

Failure Mechanisms (Root Cause)

All failed rods exhibited bending fatigue due to flexion

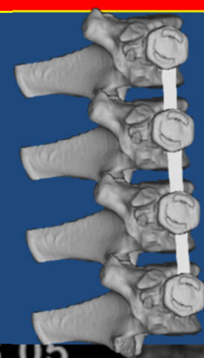
Failure Mechanism	Angled View of Fracture Initiation Site	Fracture Surface
Pure Fatigue **37% (9/24 rods)**		
Fatigue with Stress Riser **42% (10/24 rods)**		
Fatigue with Stress Riser and Local Overload **21% (5/24 rods)**		

Failure Location	Mid-Construct	Adjacent Tandem Connector	Anchor Foundation
Radiographic Characteristics			
Biomechanical Hypotheses	Long, unsupported lengths result large bending moments on rods	Differences in stiffness (geometry & material) between rod and tandem connector create stress concentration	Clustered components create rigid distal anchor Cantilever flexion cause high stress on rod “near” anchor

Risk Factors from Registry Data

- Failed constructs were associated significantly with:
  - ✓Syndromic scoliosis
  - ✓Prior surgeries for rod fracture
  - ✓Presence of crosslinks
  - ✓Use of tandem connectors
  - ✓Change in sagittal alignment
  - ✓Ambulation

Anterior Tether Systems Safety Considerations



- Fraying / failure of polyester braid
  - Fatigue
  - CREEP
- Decoupling of tether from bone anchor
- Failure bone-screw interface – ploughing of screw in vertebral body
- Fibrous adhesions of parietal pleura to tether
- Generation of wear debris

Next Step – Develop Appropriate Bench Tests
ASTM subcommittee F04.25

- Establish appropriate pre-clinical bench tests and performance criteria to evaluate non-fusion spinal systems that reflect *in-vivo* conditions
- Must account for different load configurations and applications posterior distraction rods vs. anterior tethers
  - **Expert consensus** - (Surveymonkey) practicing spine surgeons who use growth modulation systems as to perceived factors contributing to device failure
  - **Objective data** based on forensic analysis of existing registries of non-fusion constructs for EOS, Juvenile and Adolescent Scoliosis

<u>Efficacy of Growth Modulation</u>:
Success = Reliable Prediction Spine Morphology @ Maturity

..*“1.4 deg per year per level” – BUT* patient went on to over correction on further follow-up

Crawford and. Lenke; JBJS 2009

We Need Green-Anderson Growth Remaining Graph for Spine Growth

Need to understand

- Spinal growth of normal spine vs. deformed spine
- Mechanical transduction *signal* (magnitude stress, strain, # cycles) that modulates spine growth in normal vs. deformed

Successful Modulation of Spine Morphology @ Maturity Requires Understanding Mechanism of Mechanicotransduction

- What is interplay between mechanics and biology?
- Must understand how manipulation of stress state predictably affects biology
  - What is the stress/strain stimulus that Hueter Volkman Principal is operative)

Predicting Remaining Spine Growth

Jim Sanders, MD University of Rochester

T. Wingate Todd, MD

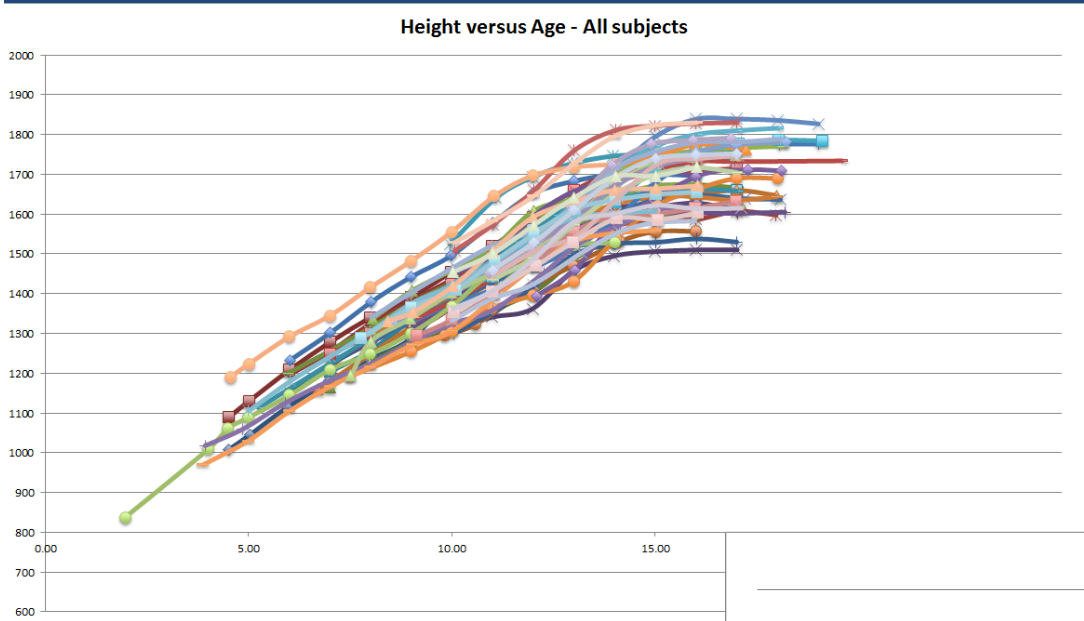
Brush Foundation Study of Child Growth and Development

Longitudinal cohort Healthy Cleveland Children 1929-1942 through growth –

- Radiographs: left hand, elbow, hip, shoulder, knee, foot
- Anthropometrics: height, weight, segment measurements

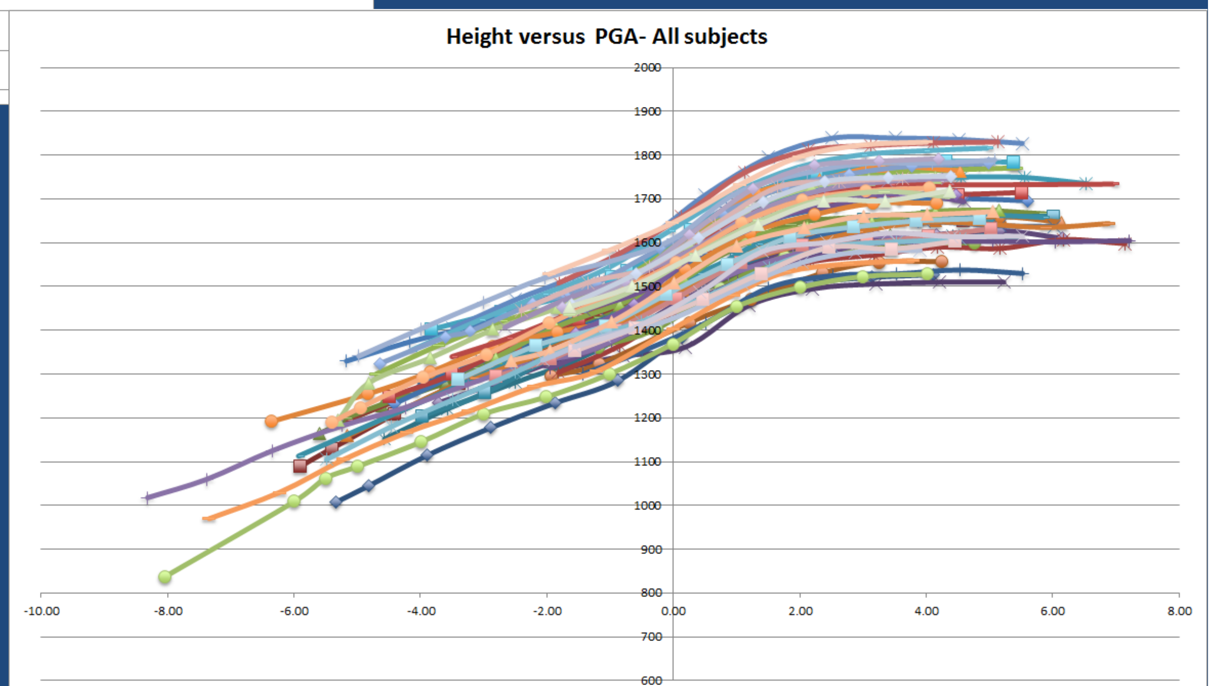
monthly until 1yr, every 6mo until 5yr, then annually

Height Relative to Peak Growth Age

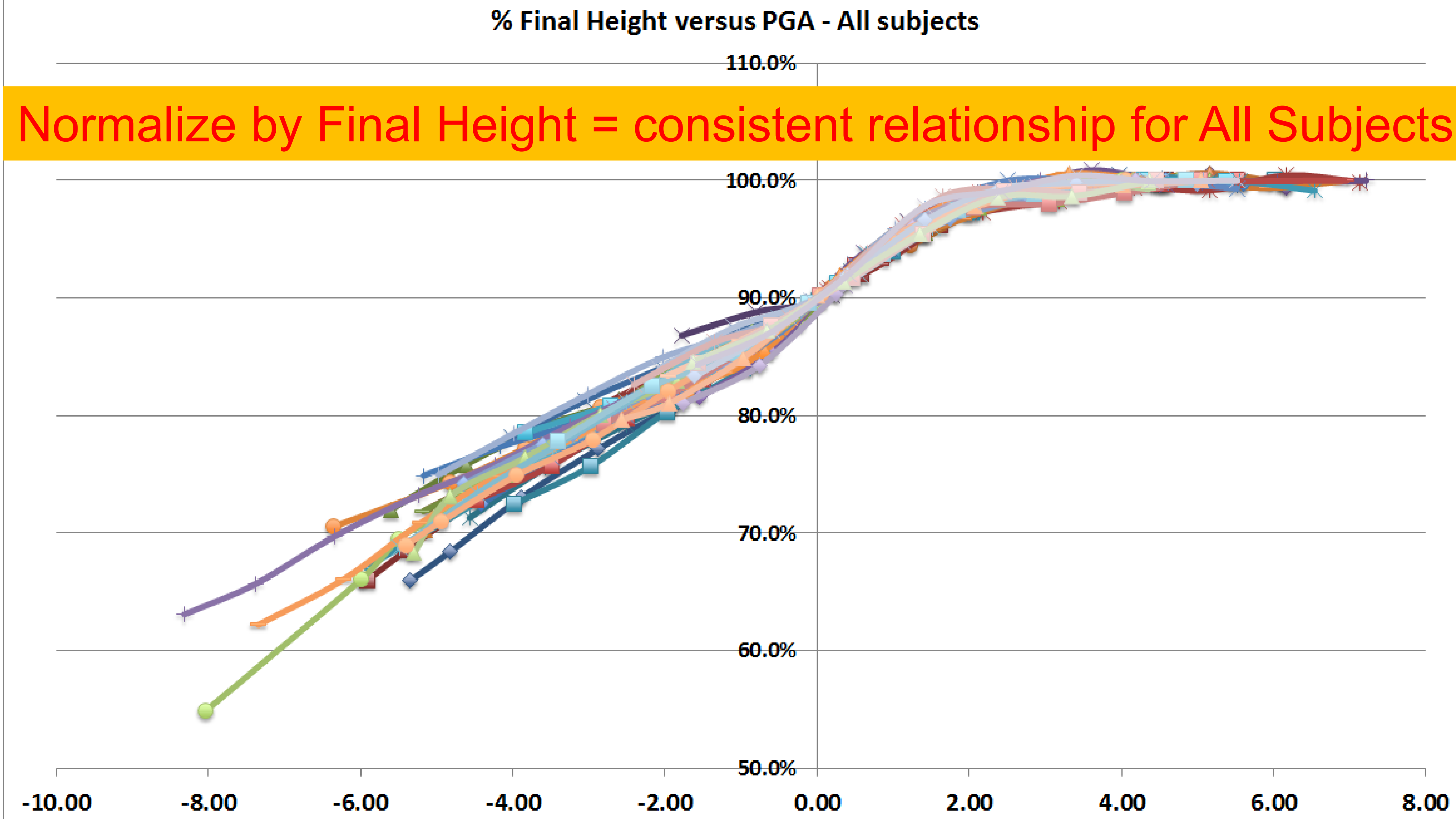


Shift spine height vs age curve to age at peak growth

- All growth curves can be "fit" to same relationship



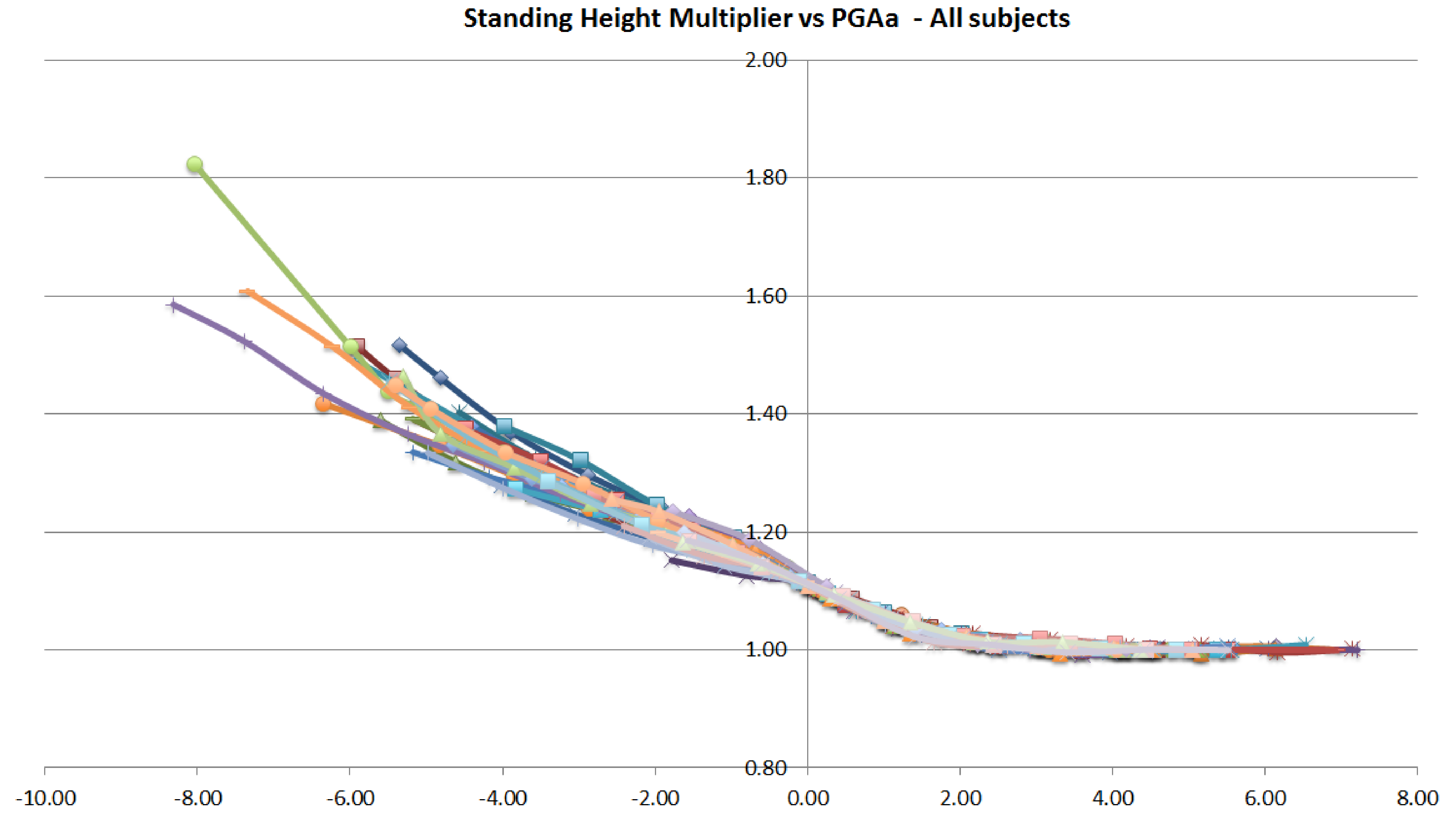
Height Plotted Relative to Final Height



Normalize by Final Height = consistent relationship for All Subjects

Reciprocal = relative growth remaining

Provides multiplier for predicting further growth of entire spine



Open Questions

- How well does this model modern cohort of children, racial diversity
- How well does this model spine growth for a child with scoliosis, syndrome, chronic disease
- Where is growth occurring – vertebra vs. IVD

Sriram Balasubramanian, PhD
Orthopedic Biomechanics Laboratory
Drexel University, Philadelphia, PA

Normal Spine Growth for EACH Vertebra
Data from CHOP Radiology Database

Evaluated Chest CT 100 normal male and female children ages 1-19 years

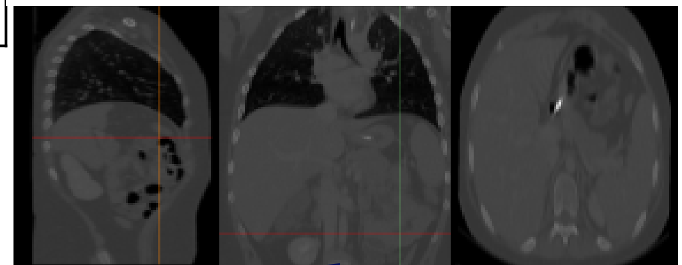
Methods

IRB Approval

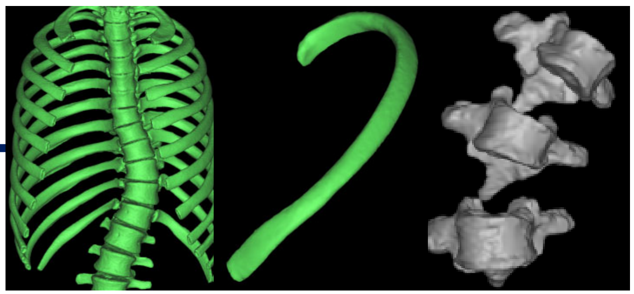
N = 13 AIS SUBJECTS		
Age (Yrs)	11-13	14-16
M	1	2
F	6	4

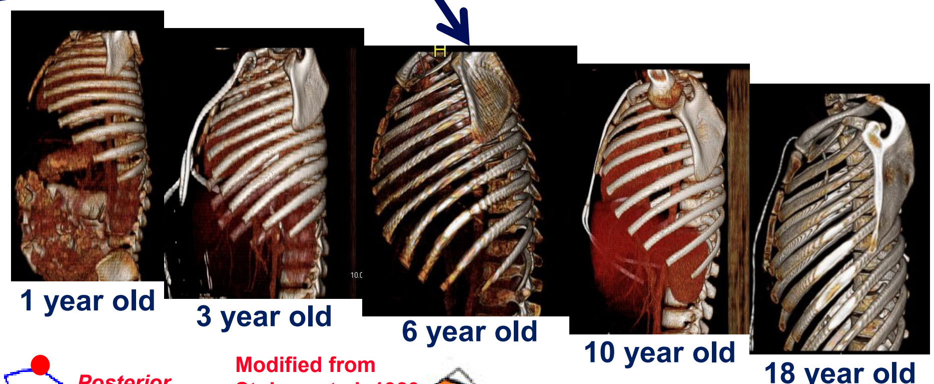
N=100 NORMATIVE SUBJECTS							
Age (Yrs)	1	3	6-9	10	12-14	15-16	18
M	7	5	6	6	7	8	6
F	9	5	7	5	7	11	5

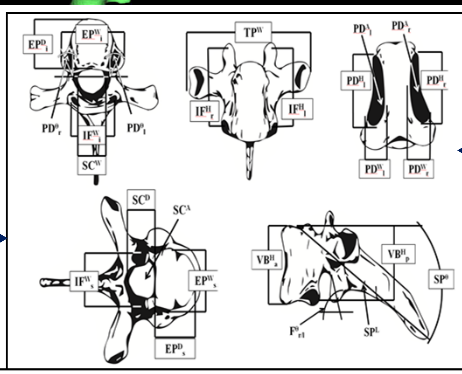
COMPUTED TOMOGRAPHY (CT) SCANS



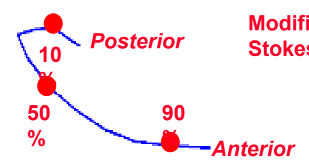
MIMCS BASED 3D RECONSTRUCTIONS







Thoracic vertebrae -- vertebral bodies (VB), spinous (SP) and transverse process (TP), and inter-facet (IF) dimensions. Height (H), width (W), depth (D), length (L), area (A), angle (θ), anterior (a), posterior (p), superior (s), inferior (i), right (r) and left (l)

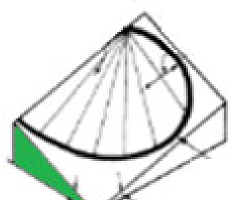


Rib apparent curvature

Modified from Stokes, et al. 1989

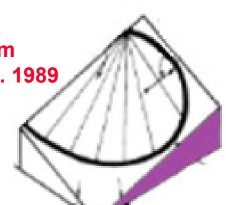
Enclosed Area

MATLAB CODE FOR GEOMETRIC QUANTIFICATION

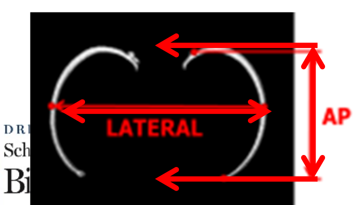


Frontal Angle

Modified from Stokes, et al. 1989



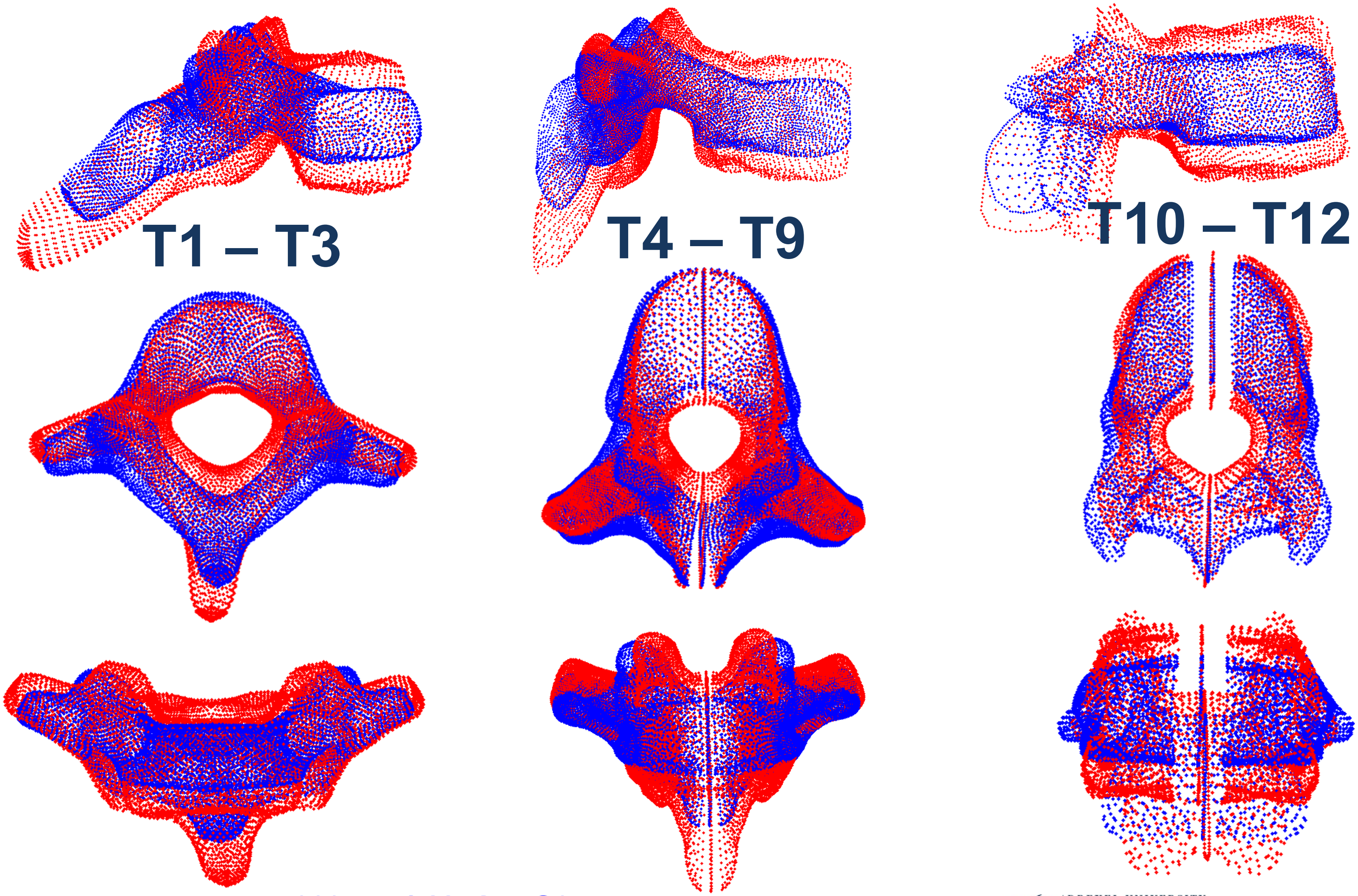
Lateral Angle



Thoracic Index

Science and Health Systems

Calculated Anatomic Growth Trajectory of Each Vertebrae



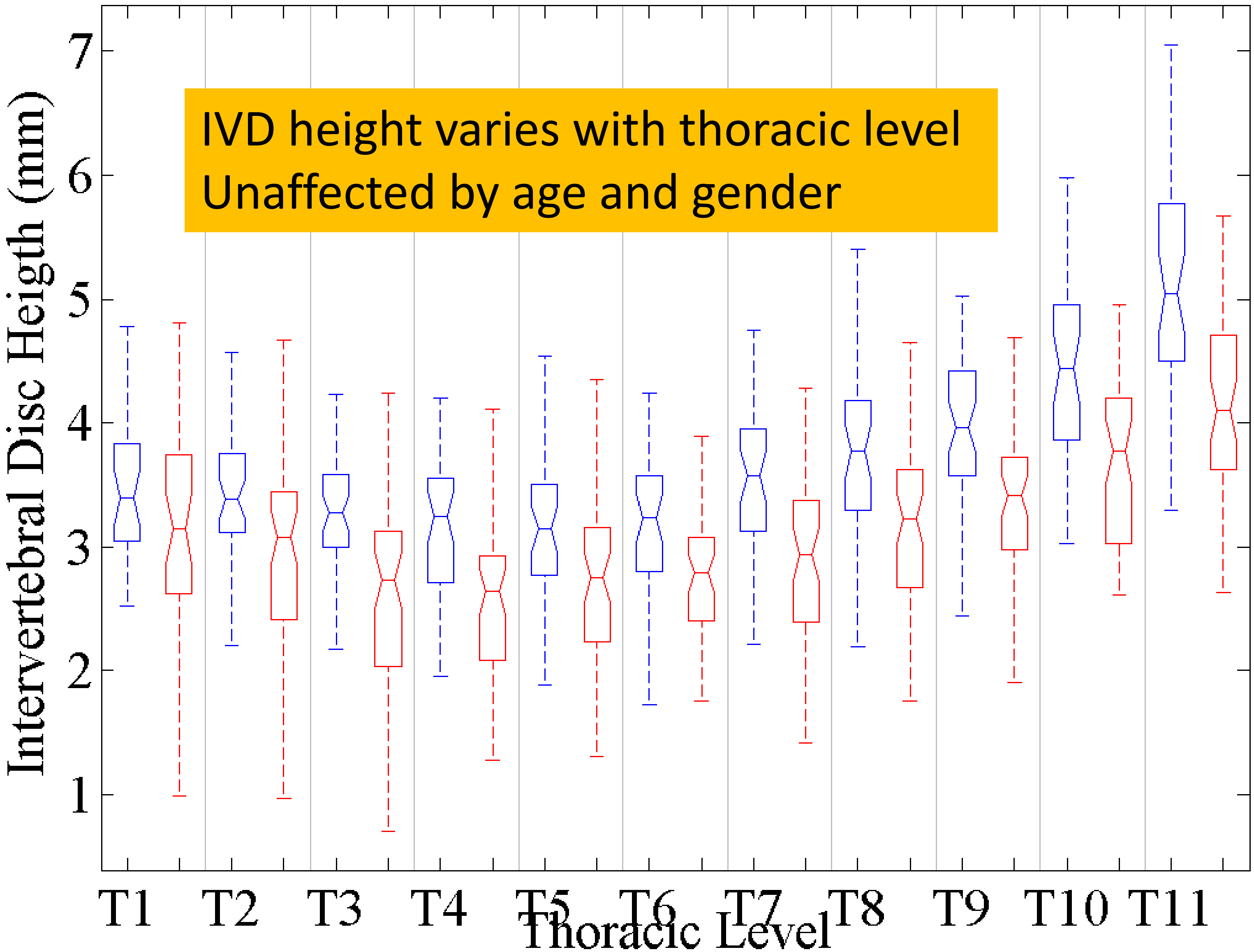
BLUE – 1 YEAR OLD

RED – 19 YEAR OLD

Vertebra Morphology

- Vertebral body, Pedicles, Facets, Transverse and Spinous process dimensions vary with age
- Spinal canal depth does not vary with age
- Pedicle width significantly varies with sex (T4 –12)
- No other vertebral geometry depend on sex
- Asymmetries observed in vertebral body heights, endplate width & depth, and facet widths

Male and Female Intervertebral Disc Height



Finite Element Model To Predict Scoliosis Progression and Correction

J. Clin PhD, C.E. Aubin *Ph.D., P.Eng.*, S. Parent *MD, PhD*

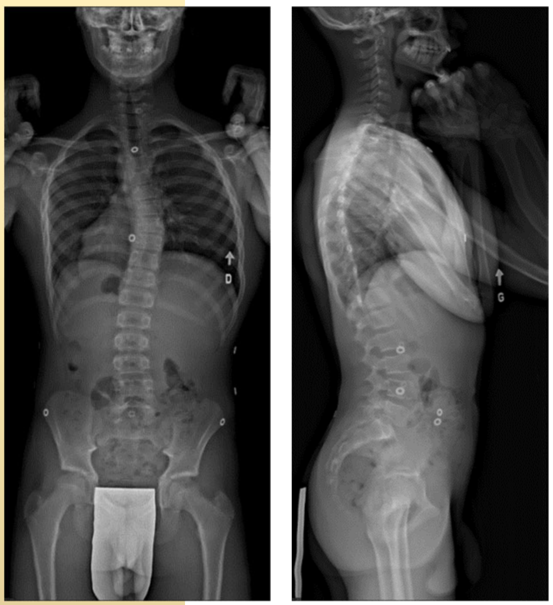
Spine
SPINE Volume 40, Number 6, pp 369-376

BIOMECHANICS

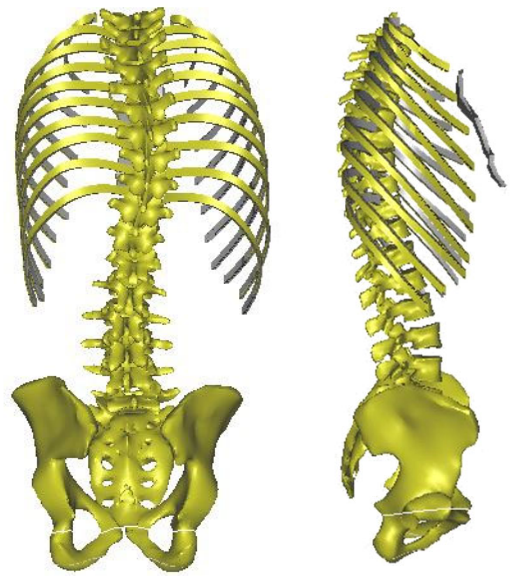
Biomechanical Simulation and Analysis of Scoliosis Correction Using a Fusionless Intravertebral Epiphyseal Device

Julien Clin, PhD,*† Carl-Éric Aubin, PhD, P.Eng.,*† and Stefan Parent, MD, PhD†

bi-planar calibrated radiographs



3D Reconstruction



Finite Element Model

Vertebrae, Discs; Articular joints; Ligaments; Rib cage; Soft tissues; Pelvis; Growth plates

POLYTECHNIQUE MONTRÉAL

NSERC-Medtronic Industrial Chair in Spine Biomechanics

Polytechnique Excellence Research Chair in Orthopedic Engineering

CHU Sainte-Justine
Mother and Child University Hospital Center
For the love of children

Université de Montréal

Analytic Model of Growth Dynamics

- Growth dynamics governed by the ***Hueter-Volkmann*** principle integrated in FEM
- Controlling equation:

  (based on Stokes 90 & Villemure 02):

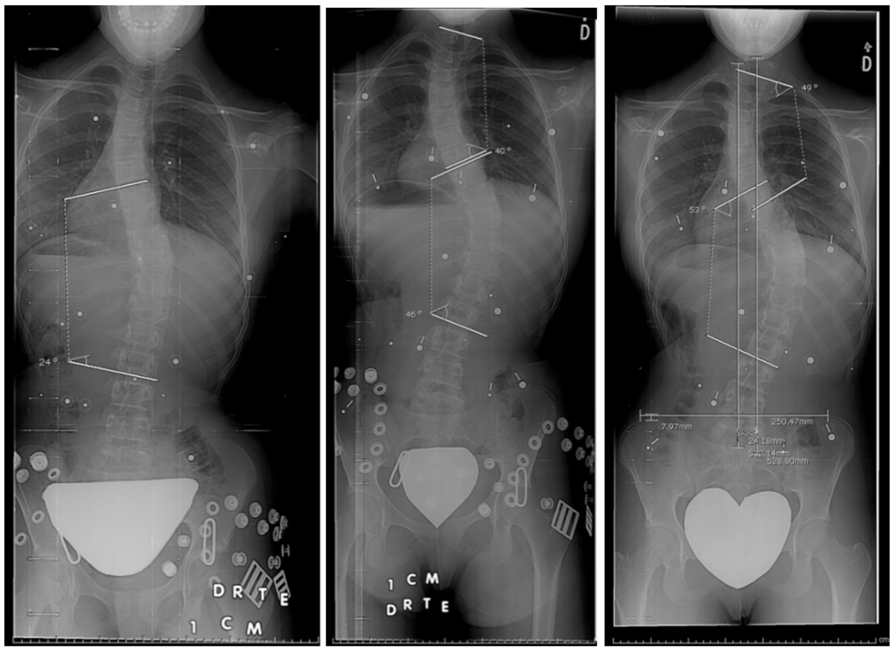
  $$\mathbf{G = G_m [1 - \beta (\sigma - \sigma_m)]}$$

  G_m= growth rate (0.8-1.1 mm/year)
  β = bone sensitive factor (1-3 MPa^{-1})
  σ = stress in pathologic spine
  σm = normal stress

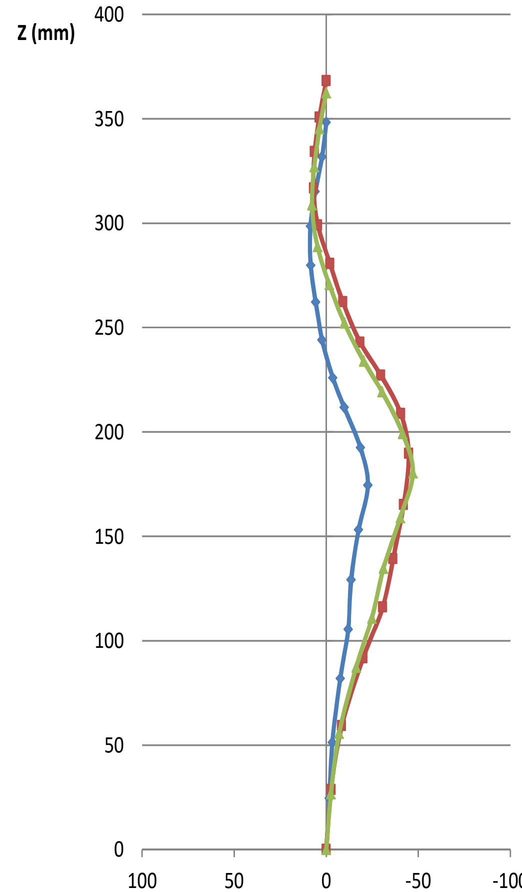
- Validated model to predict scoliotic progression (Villemure 2002, Stokes 2007, Lin 2011)

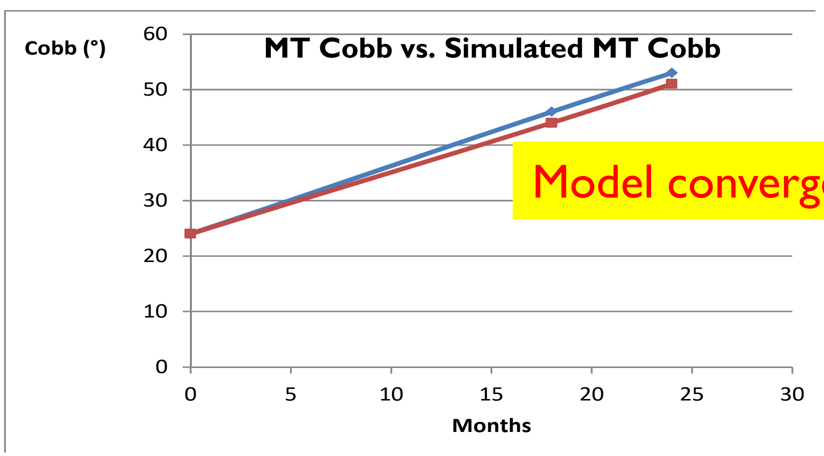
Model Validation

simulate evolution of scoliosis over 2 yrs of growth



Sept. 2004 | April 2006 | Sept. 2006





Model converges to Radiographic Cobb angle

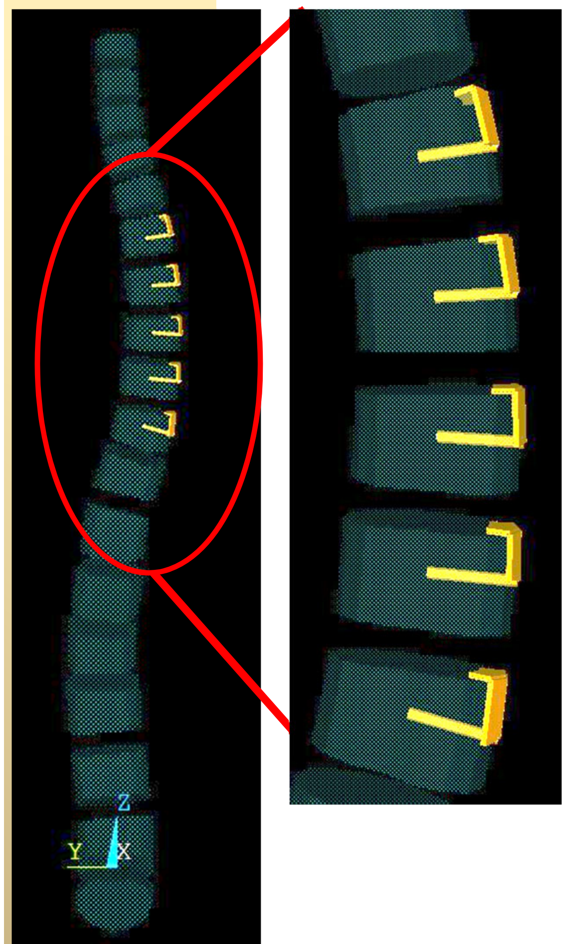
Predict Growth Modulation
For different configurations growth inhibition

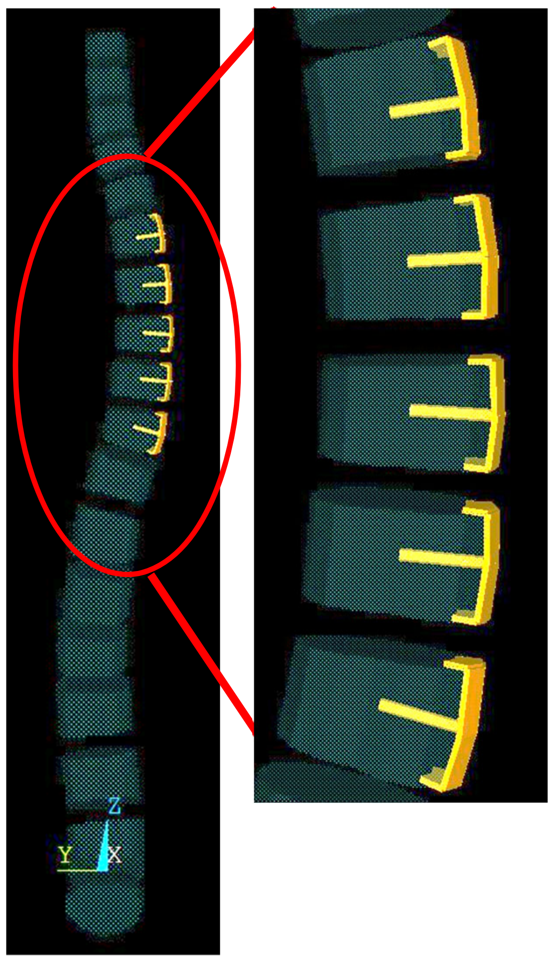
Config #1:
5 instrumented levels
(**MT** spine)
Single growth apophysis

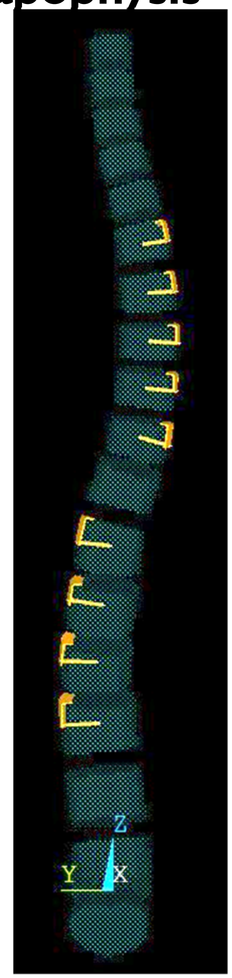
Config #2:
5 instrumented levels
(**MT** spine)
Both growth apophyses

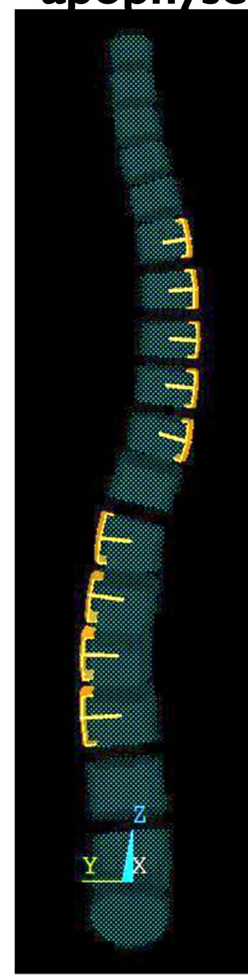
Config #3:
9 instr. levels
(**MT & TL/L** spine)
Single growth apophysis

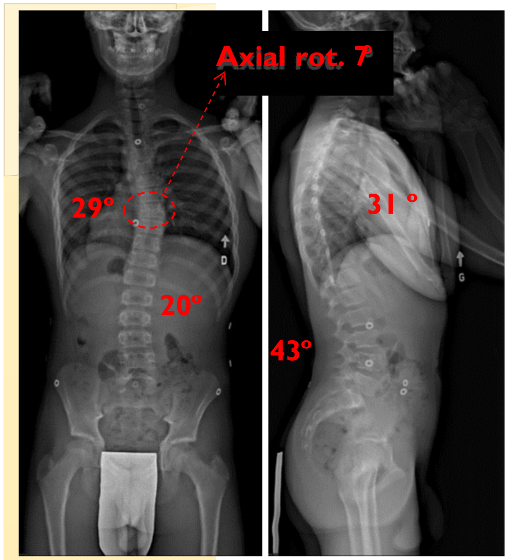
Config #4:
9 instr. levels
(**MT & TL/L** spine)
Both growth apophyses





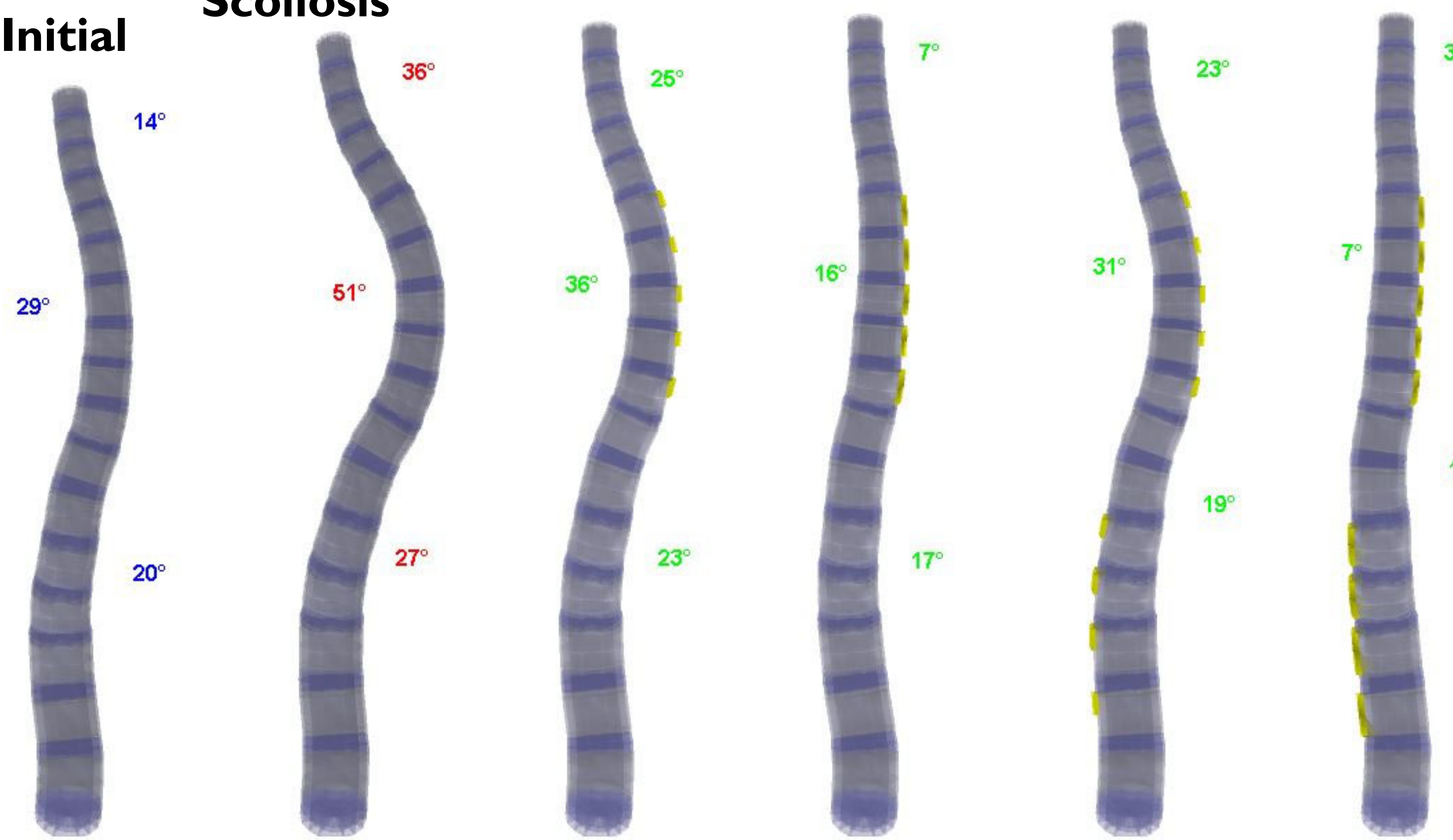






Predicted Spine Morphology Over 2 yrs of Modulated Growth for Each Configuration

Initial | **UNTREATED Predicted Scoliosis** | Conf #1 | Conf #2 | Conf #3 | Conf #4



Future Work

Identify benefits/risks of current devices

- Retrospective review current device failures
  - ✓ Material / mechanical failure
  - ✓ Infection, medical and neurological complications
  - ✓ Unintended result: over- vs. under-correction of deformity
- Develop "Growth Modulation" Registry
  - – Prospective analysis – consistent measures success/failure
    - **Clinician reported** - serial X-rays, PFT's, infection, failures
    - **Patient reported** - pain, function, HRQOL
  - – Compare *ALL* methods of spine growth modulation
    - Casting, bracing, posterior based systems, anterior based tethers
  - – What to do with "graduates" when growth completed
  - ➢ Are proposed benefits realized – preservation of growth, pulmonary function, mobility

Future Work
Identify benefits/risks of current devices

2016-2017 CDRH Priorities

Leveraging Real-World Knowledge to Enhance Device Evaluation Strategies

- **Strategic priorities:**
  - Increase the access and use of real-world evidence to support regulatory decision making
    - Examples: electronic health records, registries, and medical billing claims

- **Regulatory science priorities:**
  - Leverage big data and clinical experience for regulatory decision making
  - Develop computational modeling technologies to support regulatory decision making
  - Advance methods to predict clinical performance of medical devices and their materials

SRS/POSNA Sponsored Universal Spine Deformity IDE registry

- Develop normative data expected growth each spine segment T1-S1/Pelvis
  - Compare spine growth: AIS, EOS, congenital, syndromic, NM

  Hypotheses:
  - ✓ Spinal deformity reflects asymmetric inhibition of normal spine growth
  - ✓ Deformity can be predictably corrected by modulating remaining growth
- **Make accessible data from BrAIST, CSSG, GSSG, Harms in single site**
  - Provide "real world" cross-sectional and longitudinal data for FDA and device industry to reference and compare
  - ➢ ***Can Include ANTERIOR TETHER Data (without device IDE)***
  - Forensic analysis device failure to develop appropriate bench tests (generation particulate "wear" debris, mechanisms of device failure)
  - Provide longitudinal data to evaluate preservation thoracic volume, lung growth, trunk mobility, need (?) to remove instrumentation at maturity
- Compare Safety & Efficacy Anterior staple/tethers, Post Distraction, Brace, Fusion
  - prospective and retrospective data: complications (hardware vs. patient/disease related), clinician reported outcomes - radiographic, PFT's, functional tests; patient reported outcomes – QOL
  - **MUST be better or = to BRACE or FUSION**
- Develop Evidence Based Practice Guidelines for recommending most appropriate methods for modulating spine growth children and adolescent
  - based on patient age (spine + lung growth remaining), type + extent spine deformity (C-EOS, Lenke), co-morbidities

Thank You

SRS
Scoliosis Research Society

POSNA
The Pediatric Orthopaedic Society of North America