Correlation of Collagen X Biomarker (CXM) with Peak Height Velocity and Radiographic Measures of Growth in Idiopathic Scoliosis

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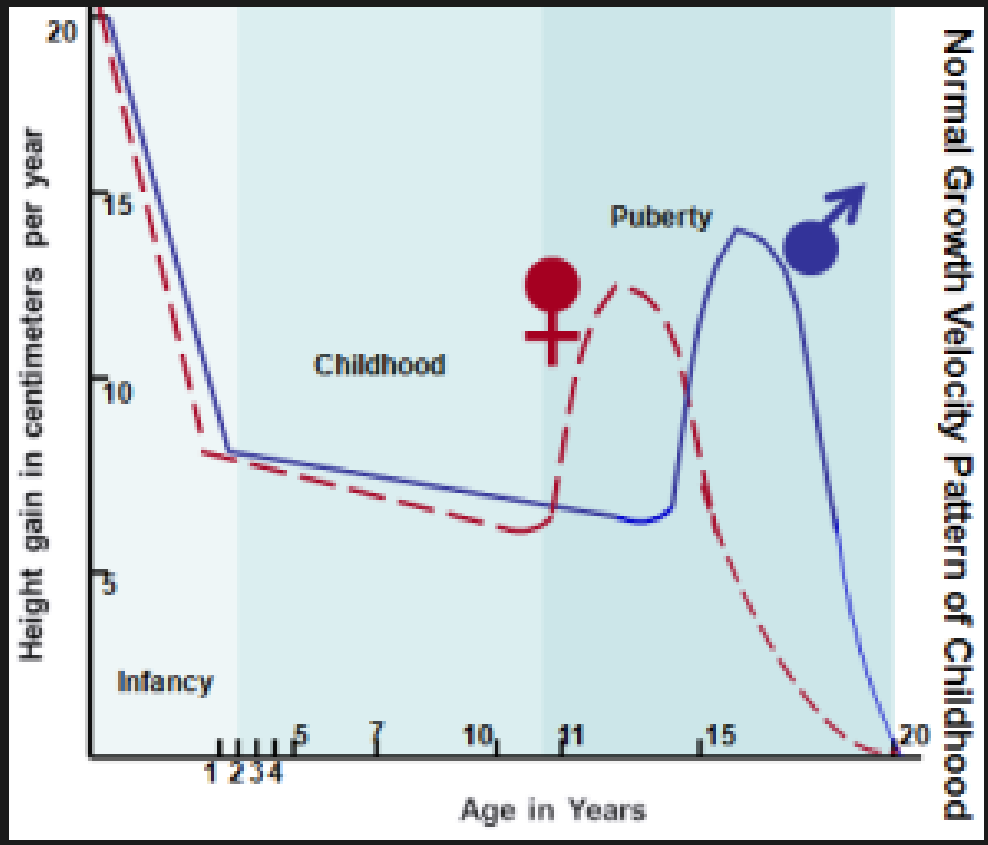
Prediction of Growth

- Growth velocity and the ability to predict remaining growth profoundly impacts all areas of pediatrics
  - Changes in growth velocity can be used as a surrogate for health status
  - Within spine deformity quantification of remaining growth and growth velocity can:
    - predict progression of spine deformity
    - Dictate treatment algorithm's including observation vs bracing vs growth friendly constructs vs guided growth vs fusion techniques

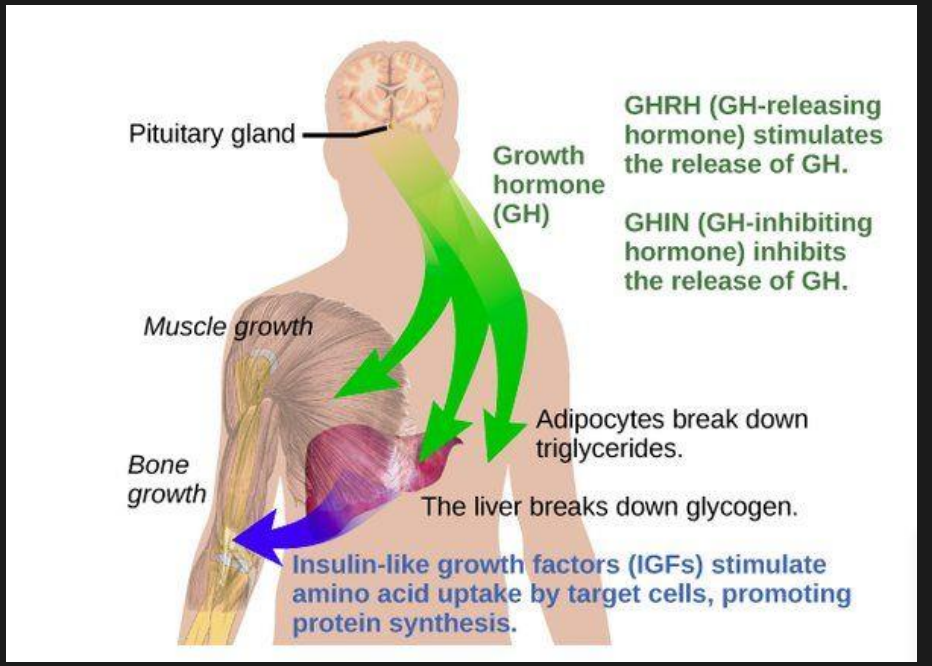


Current techniques for assessing growth:

- Current techniques are inadequate:
  - Anthropometric techniques are retrospective and have significant measurement error
  - Radiographic measures range from inaccurate (Risser score) to outdated (Greulich and Pyle) to overly complicated (TW3).
    - Risser score has been found to be less accurate than chronologic age
    - Sanders score is the most precise and accurate, but continues to have a large SE and is not accurate at assessing cessation of growth
      - **Accurate assessment of growth is critical. Compared to Sanders score, Risser score may result in the mistreatment of 1 in 4 AIS patients treated with bracing**
  - **The problem: scoring systems are based on population data and are not patient specific.**

So what about non-radiographic, patient specific methods?

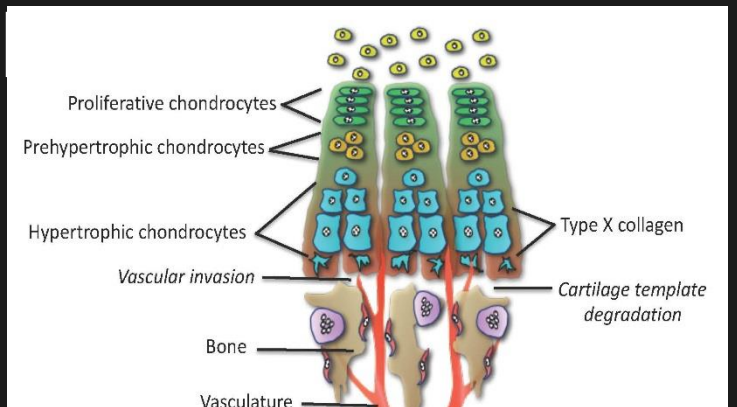
- Sanders et al, looked at numerous hormones and growth factors:
  - Growth factors:
    - insulin-like growth factor (IGF)-1
    - IGF binding protein-3
  - Hormones:
    - dehydroepiandrosterone sulfate
    - estradiol
  - Bone specific factors:
    - bone-specific alkaline phosphatase
    - osteocalcin levels
  - only estradiol and IGF-1 were found to be discriminatory and only if used in combination with Tanner stages and the appearance of the epiphyses on a skeletal age radiographs
  - **Problem: not specific for linear bone growth, high degree of variability,**



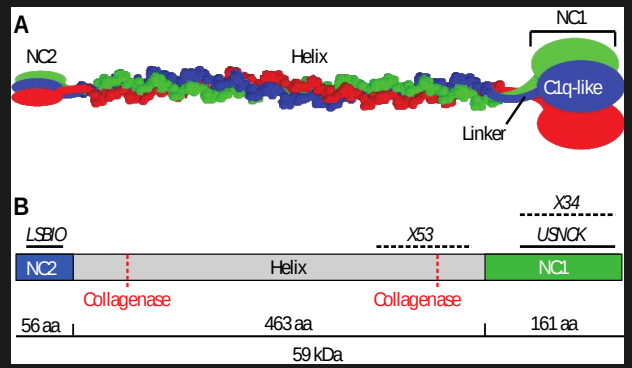
Developing a patient specific marker of bone growth: CXM

- Marker had to be specific for bone growth->
  - Collagen X (COLX) is produced in the physis during enchondral ossification
  - Enchondral ossification is the mechanism of **longitudinal bone growth** not appositional bone growth
- Had to be easily measureable
  - CXM is a stable degradation product of COLX found in serum measureable in dried blood spots

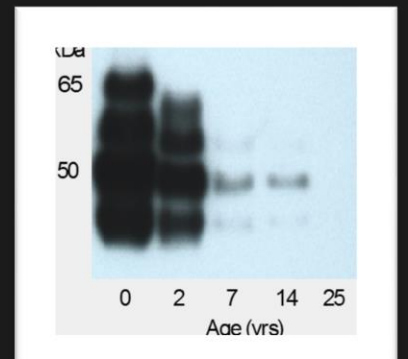
Location of COLX in the physis



Schematic of COLX structure antibody binding regions and collagenase sites- CXM is the NC1 terminal of COLX



CXM serum concentrations plotted against age and growth velocity



Purpose:

- Type X collagen is produced in the growing physis during enchondral ossification.
- CXM is a breakdown product from type X collagen that can be measured in serum.
- Theoretically higher levels of CXM would correlate with rapid longitudinal bone growth while lower CXM levels with growth cessation.
- The purpose of this study is to evaluate the correlation of CXM with growth and the radiographic measures of growth.

Methods

Criteria for Enrollment

Inclusion criteria:

- Idiopathic scoliosis Cobb >20 degrees
- Age 7-15 at start of

Exclusion criteria:

- Non-idiopathic scoliosis
- Prior surgery
- Pregnancy
- Significant medical comorbidities that may affect rate of growth

Research Protocol:

Clinical:

- Q 6mo visits
  - standing height, sitting height, arm span, ulnar length and weight
  - For female patients, the age at menarche will be recorded.

Radiographic

- standing PA and lateral EOS at initial visit
- standing PA EOS at subsequent visit
  - Risser score recorded
  - Hands positioned to obtain Sanders and TW3 scores
  - Major Cobb, T1-S1 height and spine length recorded

Biomarker

- DBS collected at home w/i 1 hour of waking three consecutive days every 1-2 months based on Sanders Score

Results:

- 32 patients were consecutively enrolled
  - Ave age 11.89 years (7.08-14.51)
  - 8 boys, 24 girls
  - 1396 samples collected
- Each sample measured in quadruplicate and assessed for internal reproducibility
  - Within plate ICC: 0.988-0.994
  - Between plate ICC: 0.932

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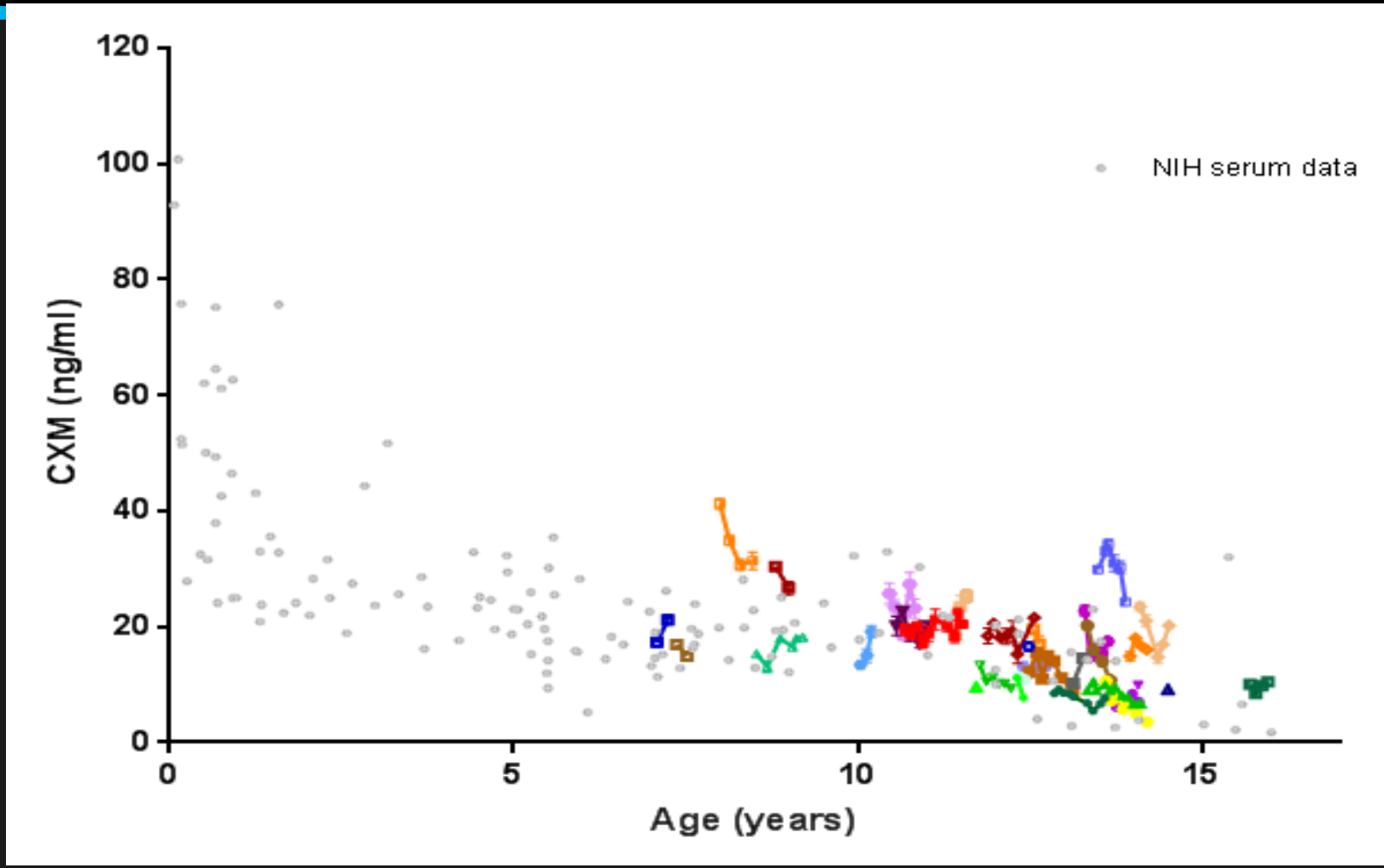
NIH serum data vs CXM data

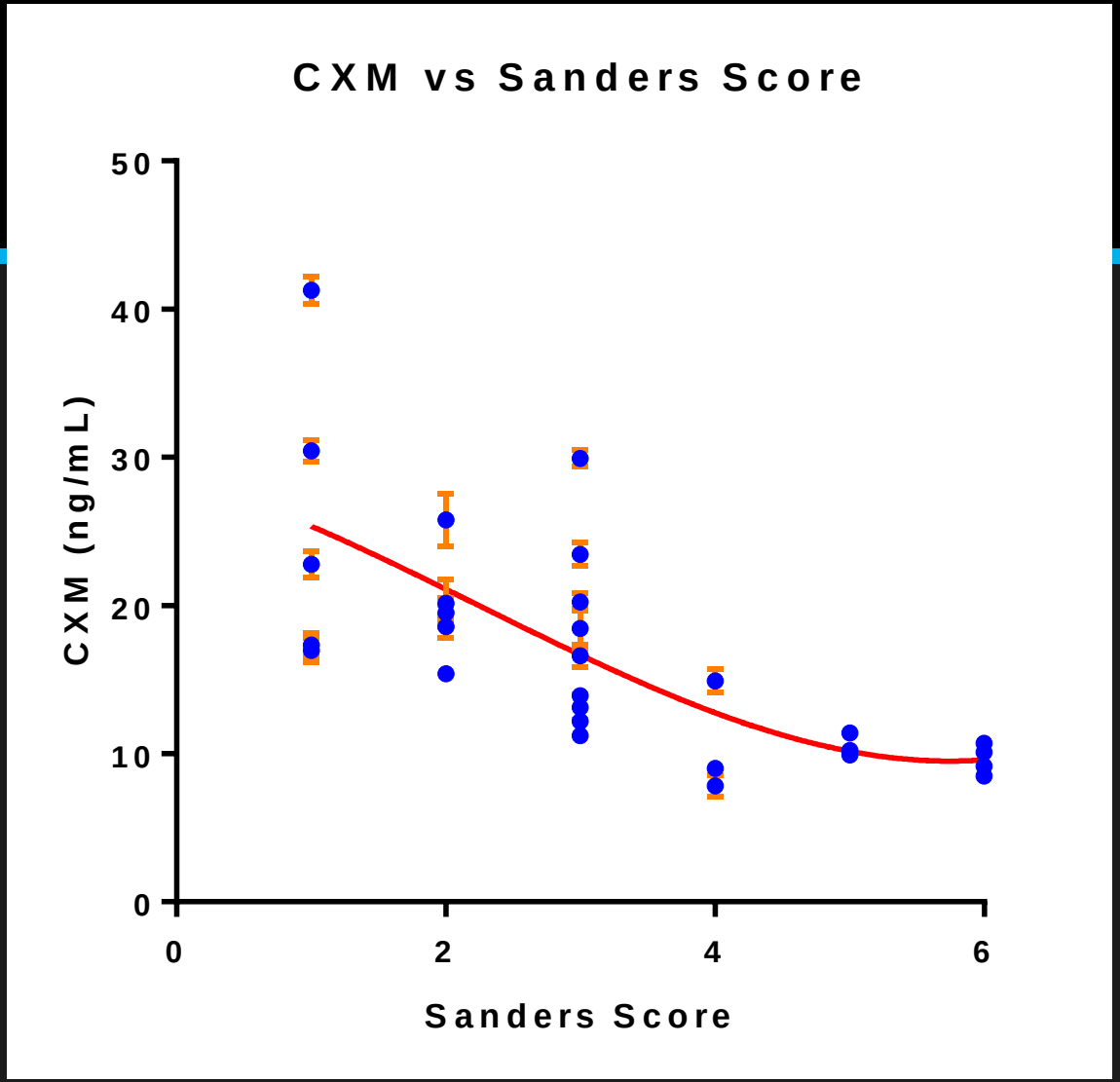
1396 DBS samples in 32 idiopathic scoliosis patients plotted against NIH population data demonstrating high degree of correlation within one patient and the high degree of variation between patients of the same age.
(Male patients were indicated in shades of blue)



CXM vs established markers of growth:

CXM levels were statistically significantly correlated with all established measures of growth P value <0.05

- Risser score p=0.009,
- TW3 p=0.000,
- Sanders Score p=0.000
- Change in height p=0.042,
- Change in arm span p=.026
- Change in ulnar length p=0.046.



CXM levels plotted against Sanders score: CXM levels obtained the week following radiographic measurement of Sanders score demonstrating the higher degree of variability of CXM at more rapid stages of growth vs Sanders Score

Conclusion

- Each patient follows their own growth curve, these curves are similar in pattern but have different rates and durations of growth and occur at different times. These individual patterns of growth profoundly impact the treatment of the growing patient
- CXM is a measure of enchondral ossification and thus has the potential to be a patient specific marker of longitudinal bone growth
  - Early results indicate that CXM is:
    - highly reproducible with a low standard error
    - statistically correlated to the established measures of growth

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