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# Application of X-ray, MRI, pQCT, and DXA in a Natural History Study of Scoliosis Progression in Children with NF1

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# Objectives

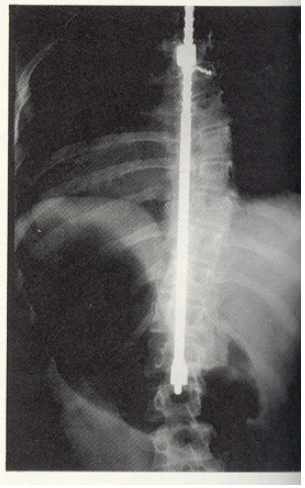
- Share our rationale leading to a natural history study of progressive scoliosis in NF1
- Review results of the natural history study with respect to scoliosis progression (Xray) and association with paraspinal plexiform neurofibroma (MRI)
- Review techniques available to assess bone in children as endpoints for clinical trials

# Spinal Deformities in Neurofibromatosis

Boy with kyphoscoliosis. Foreshortening of trunk secondary to kyphosis gives appearance of longer upper limbs


Girl with moderate scoliosis and café au lait spots

Radiograph shows severe scoliosis with characteristi short-segmented, sharply angulated curve



Relatively mild curve largely corrected and stabilized with fusion and Harrington rod

# Scoliosis in NF1

- Incidence ~10-33% in NF1 population
- 1-2% of individuals with scoliosis have NF1
- Classified as “dystrophic” (progressive) or “non-dystrophic”
- More rapid progression in NF1 and more complications than in non-NF1 population (ie. more surgeries and more aggressive management)

# Scoliosis in NF1: Xray findings

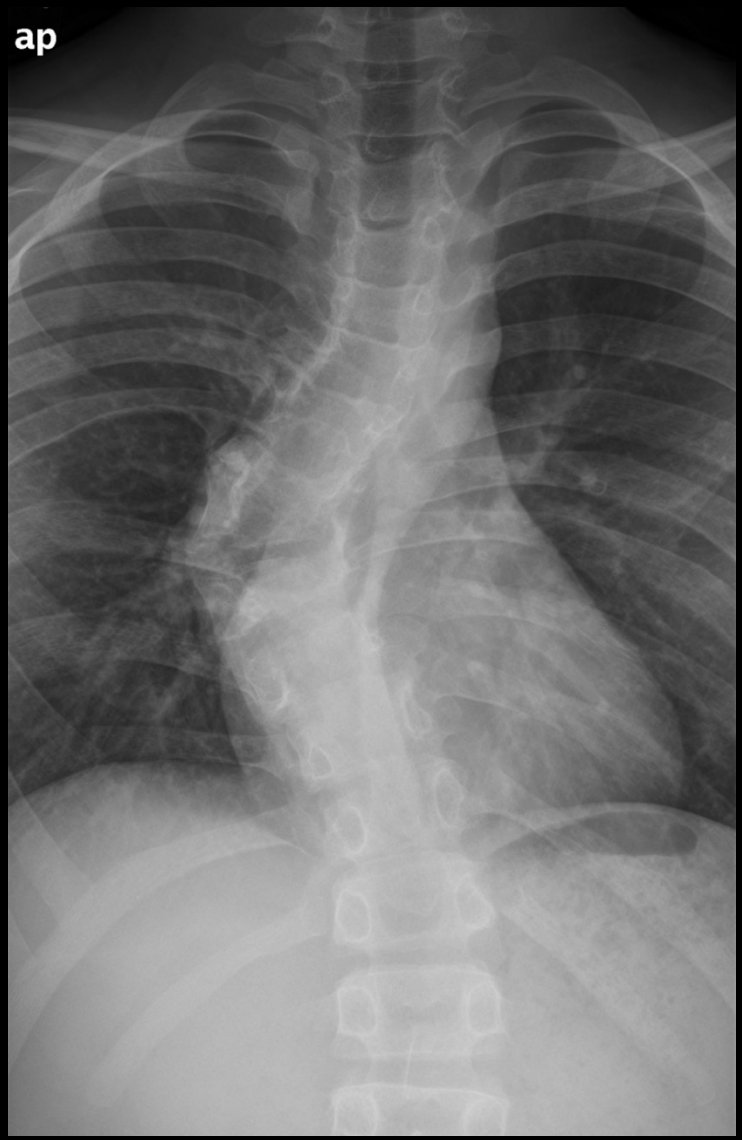
- 71/108 NF1 patients with scoliosis had dystrophic features (Funaski et al, 1994)

- Xray findings of rib-penciling and vertebral scalloping, and early age of onset found to be risk factors for curve progression (Funaski et al, 1994)

- Non-dystrophic scoliosis can “modulate” to dystrophic scoliosis (Durrani et al, 2000)

## Non-dystrophic


## Dystrophic

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# Scoliosis in NF1: MRI findings

- Spinal abnormalities detected by MRI in NF1 include spinal neurofibromas, dural ectasias, and meningoceles

- Of 62 children with NF1 who underwent prospective MRI of spine:
  - Age: Mean is 9.6 years old (range of 11 months to 18 years)
  - 7 had spine-related neurofibroma (13%)
  - 5/7 had scoliosis (71%); 16/55 no tumor with scoliosis (30%)
  - 2-fold increased risk for scoliosis (Khong, P-L et al., 2003)

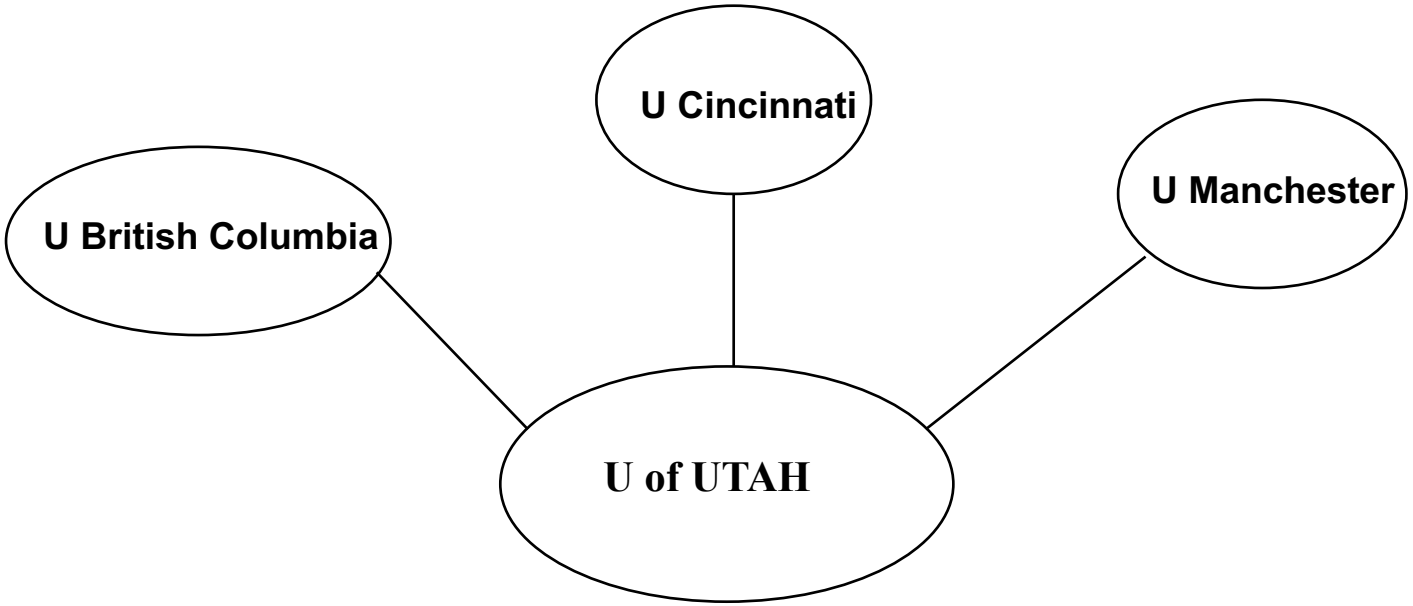
- More recent study (Nguyen, R et al., 2015) of 97 with NF1:
  - Referral center for anticipated treatment
  - Age: Median is 14.2 (range of 2.7 years to 48.2 years)
  - 50 had spine curvature (51%)
  - 6-fold increased risk to have tumor if have spinal curve

# Scoliosis in NF1

- Who will develop scoliosis?
- What is best management?
- What is the underlying biology?
- Can we prevent progression?

- HOW TO FIND OUT THE ANSWER TO THESE QUESTIONS?

# Spinal Abnormalities in NF1




## Multi-Center Collaboration

UBC - J Friedman, L Armstrong, P Birch
CIN - E Schorry, A Crawford, M Walker
MAN - Z Mughal, S Huson, G Evans, J Eelloo
UTA - D Viskochil, D Stevenson, H Hanson
Central Radiologist: Kathleen Murray

R01 NS050509

# Spine Abnormalities in NF1: Specific Aims

- Aim 1: Identify associations of spinal cord dural ectasias, spinal neurofibromas, and meningoceles with *dysplastic* osseous abnormalities and *dystrophic* scoliosis.

- Aim 2: Define the *clinical* history and short-term outcome of dystrophic scoliosis and describe a cohort of individuals with NF1 with respect to various radiologic indices *associated with dystrophic scoliosis*.

- Aim 3: Determine the differences in bone-health variables between NF1 individuals and individuals without NF1, and between NF1 individuals without dystrophic scoliosis versus NF1 individuals who develop dystrophic scoliosis.

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# Spine Abnormalities in NF1: Study

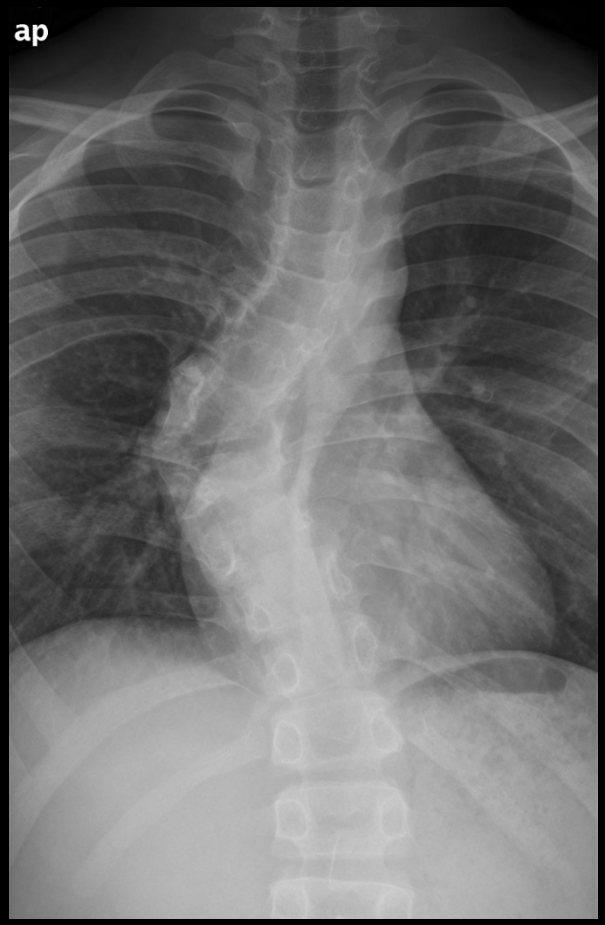
- Primary Outcome: Determine how many pre-pubertal children with NF1 develop scoliosis over a 4 year observation period

- Based on literature review we anticipate 10-33% of the children to develop scoliosis during observation period, and a smaller proportion will develop dystrophic scoliosis

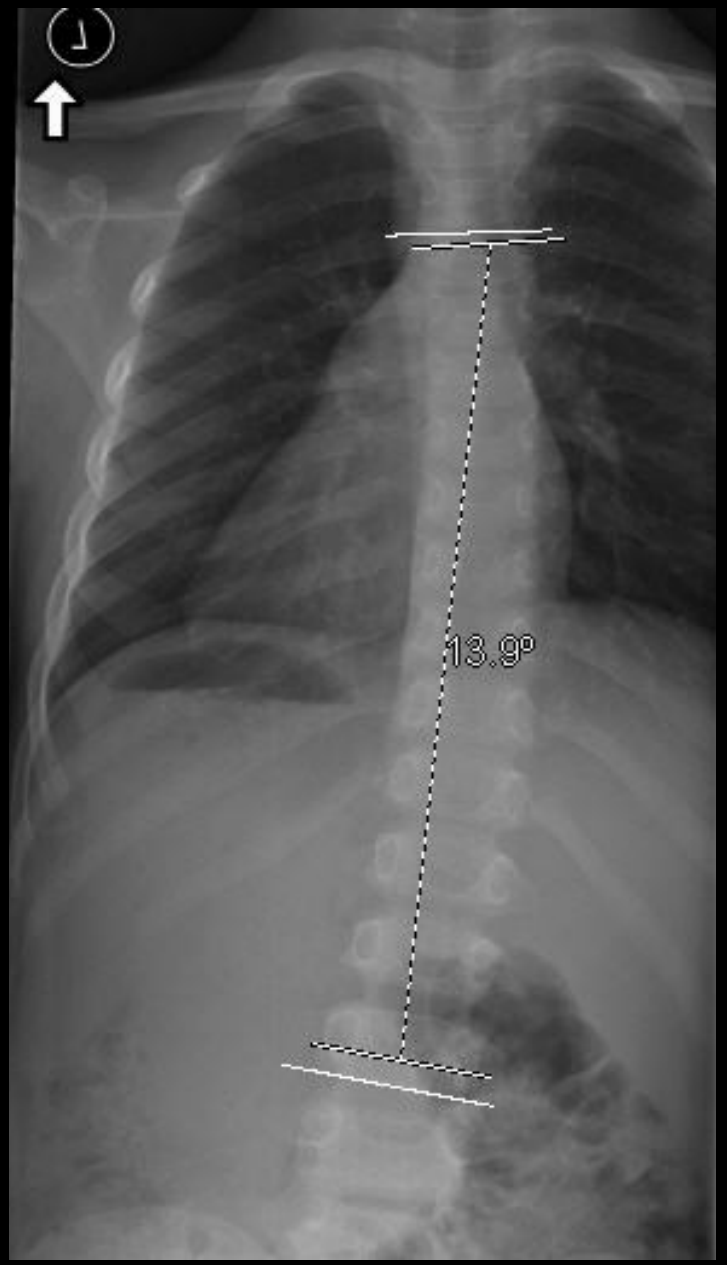
- Procedures:
  - Annual physical examination
  - Entry and exit radiographs of spine

Non-dystrophic


Dystrophic



# Technique of Cobb angle to estimate degree of scoliosis



# MAN025 PA spine

Research , Nf1
#1 21-Nov-2008 14:59
Ac: 0121200910
PA
Series: 1


- Scoliosis measurement

120 mm

W:2999 L:1663
Filter:None Fact:0

# Spine Abnormalities in NF1: Study

- Secondary Outcomes: Identify precursors that are predictive of scoliosis
  - Bone and MRI abnormalities of the spine:
    - sharp curve scoliosis
    - vertebral wedging and/or scalloping
    - defective pedicles
    - rib-penciling
    - paraspinal neurofibromas
    - widening of spinal canal
    - dural ectasia
  - DXA and pQCT
  - Urinary crosslinks, dietary intake, leisure activity
  - Associated clinical findings

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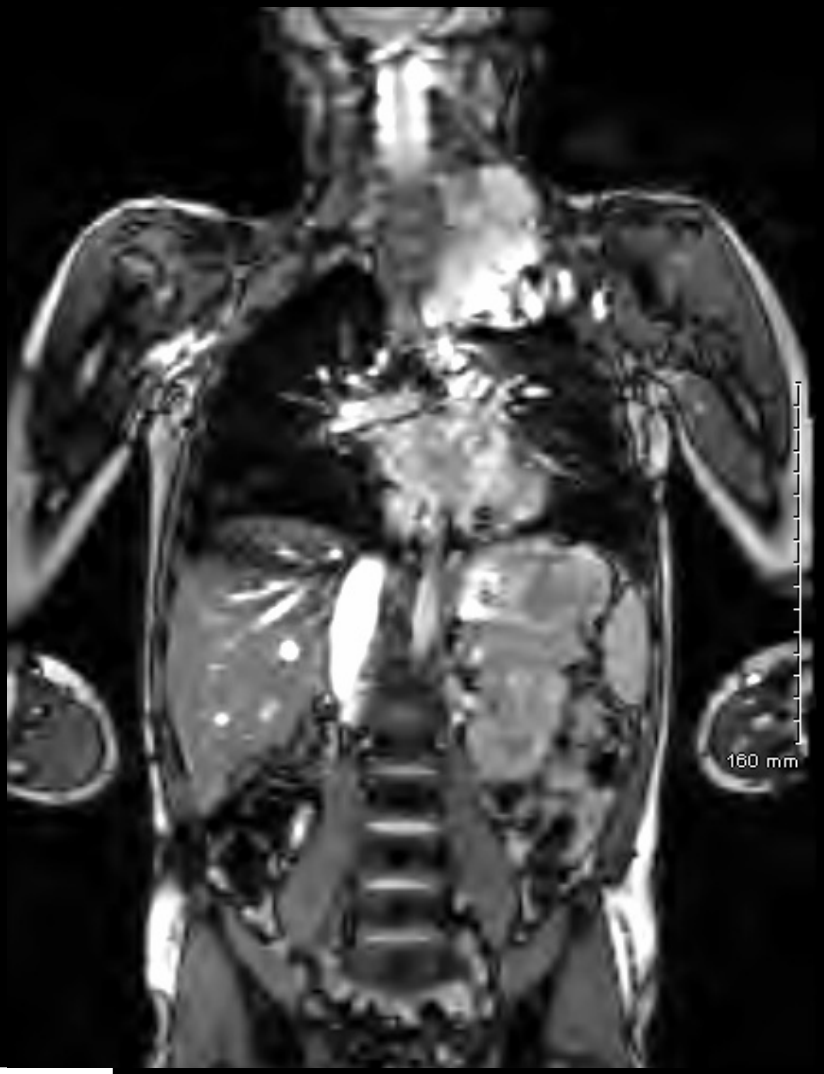
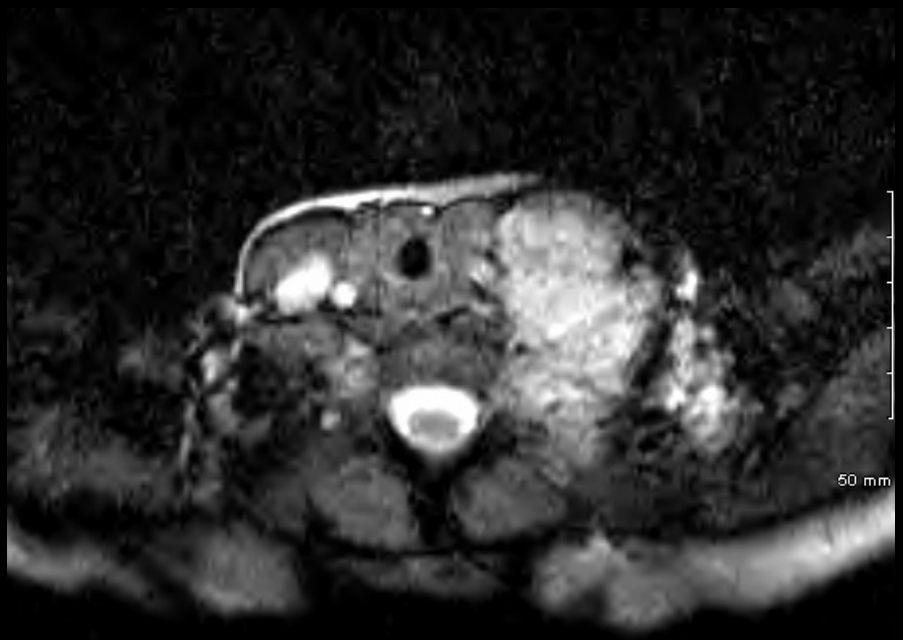
# UBC005 coronal T2-weighted




Axial image at C7

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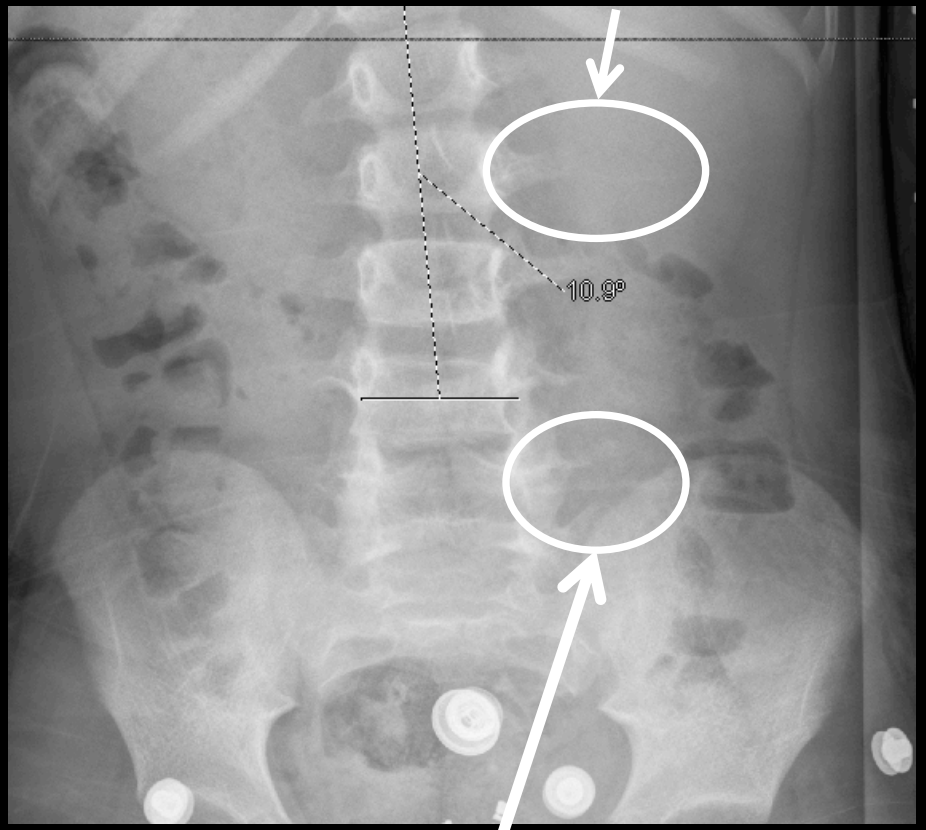
# CIN028 MRI sagital

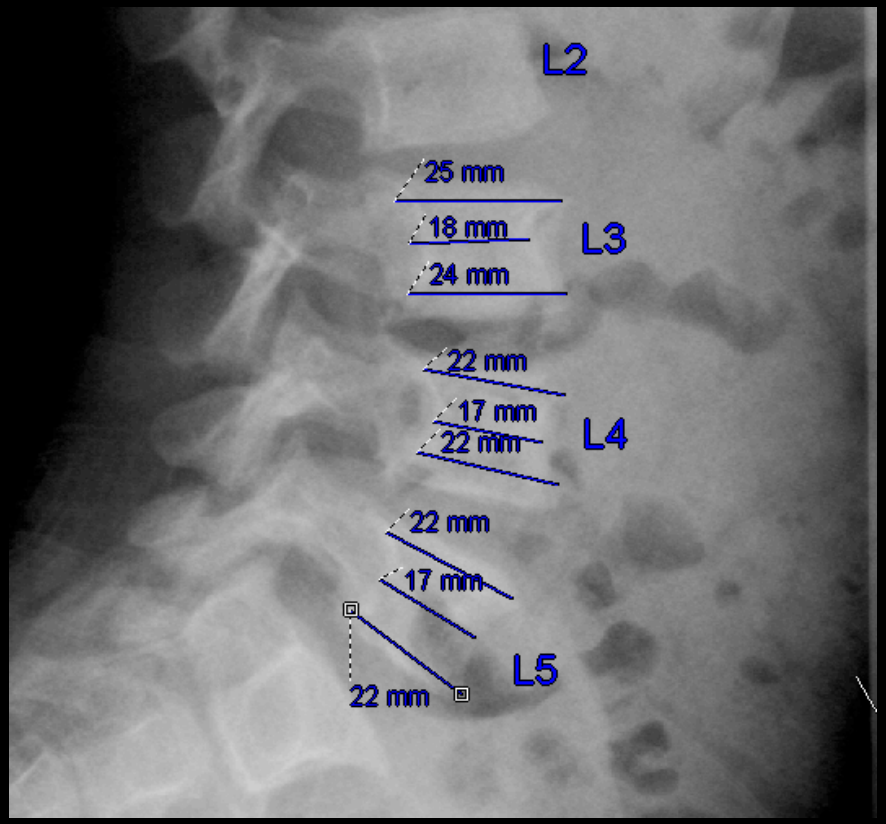
- Dural ectasia involving L3-L5


CIN028 –
mild scoliosis

normal

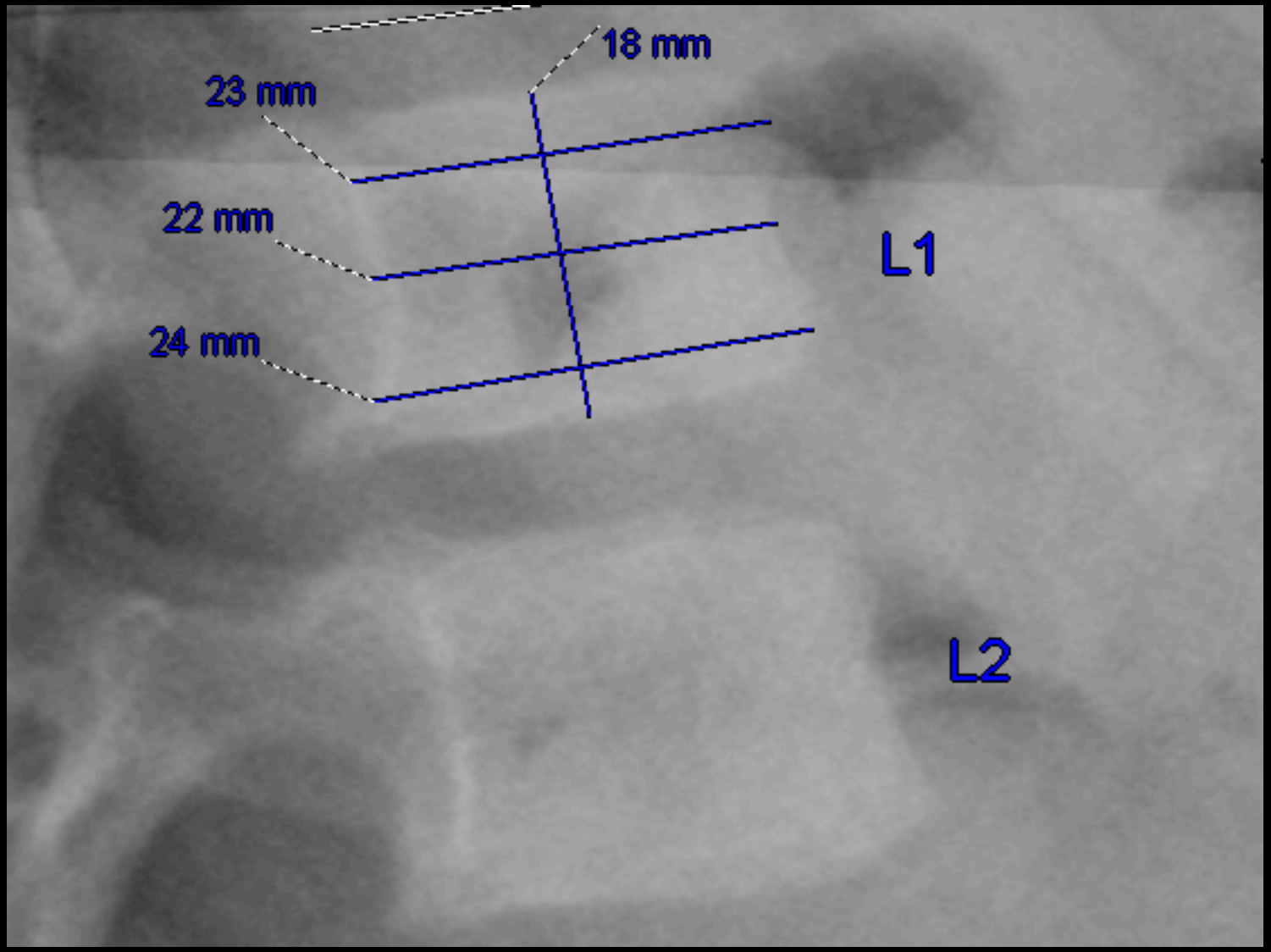



Spindling of transverse processes



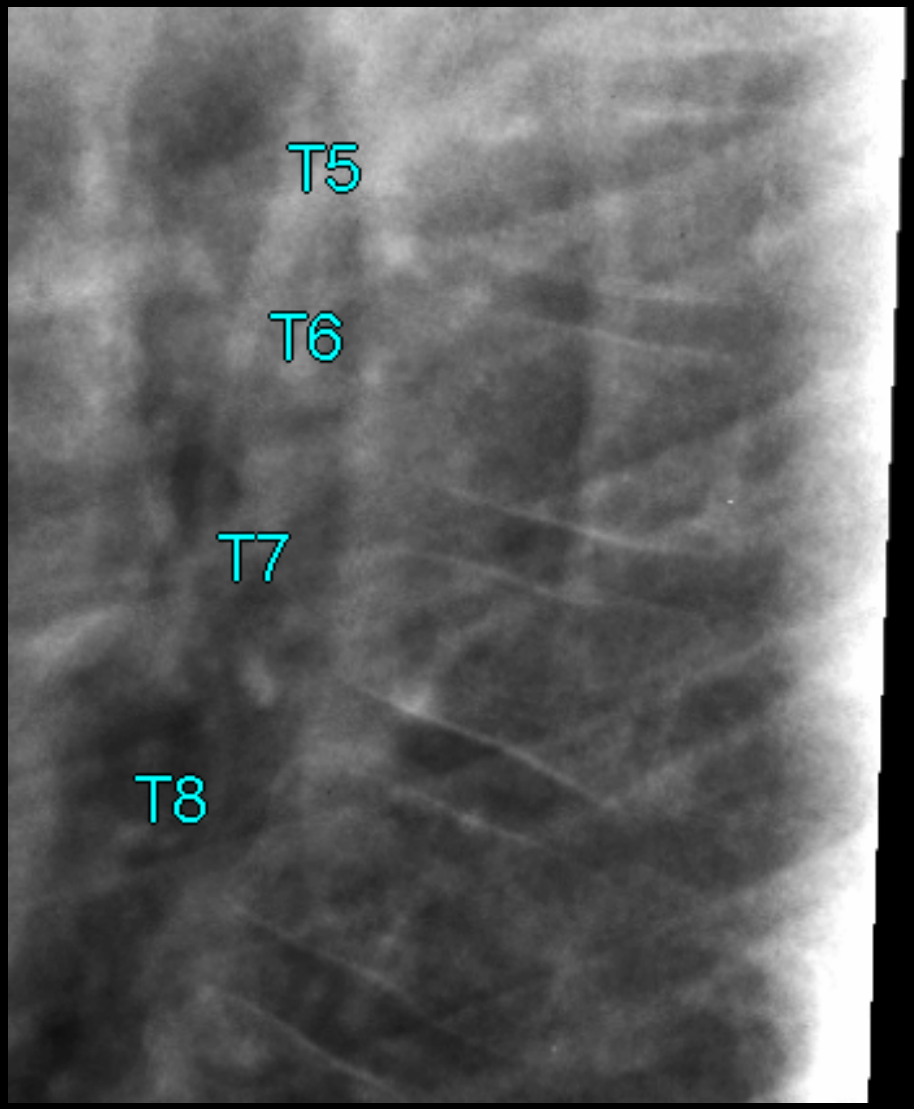

# CIN028 L3-L5 assessment of vertebral scalloping

# CIN028 L1 vertebral body measurements



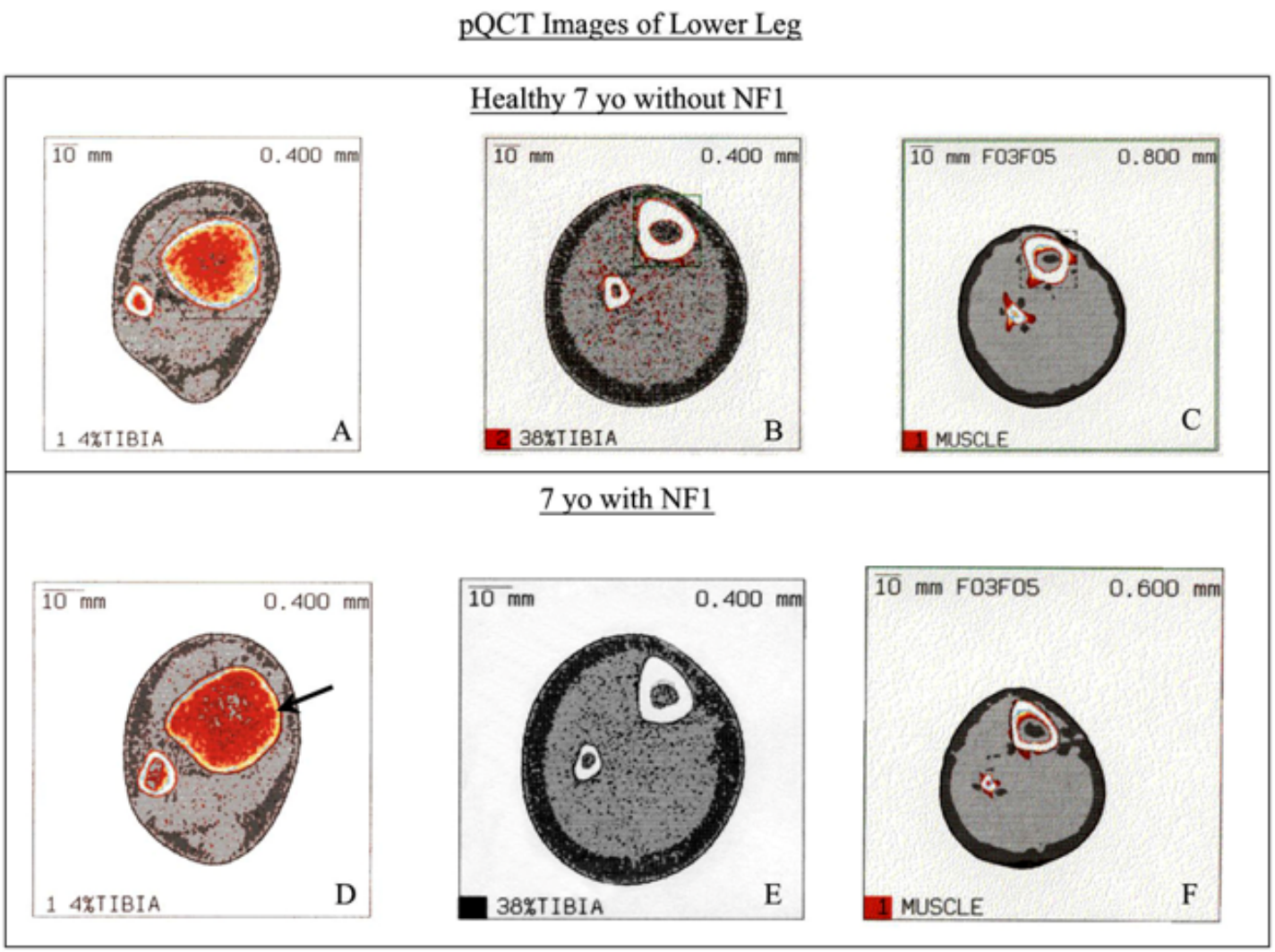
# UTA010 lateral spine


Lumbar Lordosis - 65 degrees




Vertebral Wedging at T7

**Figure 1** compares pQCT images from two 7-year-old patients with and without NF1.




pQCT can can assess general strength of bone in combination with DXA. Evaluate 4% and 38% site of the tibia for total bone mineral content, bone cortex, and muscle.

***Table I***

***DXA and pQCT Statistical Analysis (NF1 versus Controls)****

| Variable | NF1 (N=40) | | Healthy Controls | | | p-value |
|---|---|---|---|---|---|---|
| | Adjusted Mean | Adjusted SE | Adjusted Mean | Adjusted SE | N | |
| 4% Site Total BMD (mg/cm$^3$) | 256 | 5.9 | 299 | 1.9 | 376 | p<0.001 |
| **4% Tibial Site (Trabecular)** | | | | | | |
| BMC (mg/mm) | 83 | 4.7 | 119 | 1.5 | 376 | p<0.001 |
| Bone Area (cm$^2$) | 389 | 10.3 | 441 | 3.3 | 376 | p<0.001 |
| vBMD (mg/cm$^3$) | 202 | 7.6 | 271 | 2.4 | 376 | p<0.001 |
| **66% Tibial Site (Cortical)** | | | | | | |
| BMC (mg/mm) | 197 | 6.6 | 216 | 1.8 | 377 | p=0.001 |
| Bone Area (cm$^2$) | 190 | 5.2 | 209 | 1.6 | 377 | p=0.001 |
| vBMD (mg/cm$^3$) | 1028 | 5 | 1024 | 1.6 | 377 | NS |
| Thickness (mm) | 3.22 | 0.1 | 3.39 | 0.02 | 377 | p=0.025 |
| Strength Strain Index (mm$^3$) | 1176 | 50 | 1314 | 16 | 377 | p=0.010 |
| **Hip** | | | | | | |
| Bone Area (cm$^2$) | 24 | 0.55 | 26 | 0.23 | 210 | p=0.001 |
| BMC (gm) | 18 | 0.78 | 22 | 0.33 | 210 | p<0.001 |
| aBMD (gm/cm$^2$) | 0.69 | 0.02 | 0.79 | 0.01 | 210 | p<0.001 |
| **Femoral Neck** | | | | | | |
| Bone Area (cm$^2$) | 4.19 | 0.05 | 4.34 | 0.02 | 211 | p=0.009 |
| BMC (gm) | 2.82 | 0.09 | 3.29 | 0.04 | 211 | p<0.001 |
| aBMD (gm/cm$^2$) | 0.65 | 0.02 | 0.74 | 0.01 | 211 | p<0.001 |
| **Spine** | | | | | | |
| Bone Area (cm$^2$) | 30.7 | 5.5 | 50.2 | 2.2 | 110 | p<0.001 |
| BMC (gm) | 24.5 | 8 | 34.7 | 3.26 | 110 | p<0.001 |
| aBMD (gm/cm$^2$) | 0.522 | 0.091 | 0.714 | 0.037 | 110 | p<0.001 |
| **Whole Body Subtotal** | | | | | | |
| BMD (gm/cm$^2$) | 0.73 | 0.01 | 0.79 | 0.004 | 212 | p<0.001 |

**Comparison of the bone variables between groups was adjusted for gender, Tanner stage, height, and age using analysis-of-covariance with a fixed set of covariates. The strength of the statistical association between the covariates and bone variables are not presented in the interest of brevity. (vBMD=volumetric bone mineral density; aBMD= areal bone mineral density; BMC=bone mineral content; SE = Standard Error)*

NF1 and non-NF1 bone is different as shown in this table comparing pQCT in the upper 2 rows and DXA in the lower 4 rows in a cohort of 40 Individuals with NF1 versus healthy controls.

# Surveys and Pyridinium Crosslinks

- Diet Records – difficult in memory and analyses
- Activity Records – difficult in memory and analyses
- Urine samples – easy

- Take-home message – these collections take a lot of time from coordinators and statisticians to break down every component. Might serve as start for intervention.

# Spine Abnormalities in NF1

- Inclusion Criteria
  - NF1 by NIH diagnostic criteria
  - Between 6 and 9 years of age on entry
  - Tanner stage not greater than 1
  - No scoliosis on physical examination
    - Visual inspection of back while standing
    - Adams bend-over test

# Spine Abnormalities in NF1

- Exclusion Criteria
  - Clinical evidence of scoliosis
- Radiographic evidence of scoliosis >20$^{o}$
  - Prior spine repair
  - Chronic steroid use
  - Hormone replacement therapy
  - Tibial dysplasia
  - Chronic medical problem associated with scoliosis (ie. cerebral palsy, diabetes mellitus…)

# Scoliosis in NF1


Not a candidate!

# Enrollment in Spine Study

- Physical examination
- Routine scoliosis series – PA, Lat standing radiographs
- Modified MRI of thorax and lumbar regions - 30 minutes, non-sedated
  - Coronal, Axial T1/T2, Sagital T1/T2 (S.T.I.R. not included)
- DEXA – total body for bone area and bone mineral content
- pQCT - lower leg for bone density, size, and geometry
- Urine - pyridinium crosslinks (biomarker for bone resorption)
- Diet and Activity Questionnaires

# Spine Abnormalities in NF1

- Time lines
  - Initial enrollee - 1/07
  - Complete enrollment - 12/08
  - Complete enrollment studies - 3/09
  - Complete natural history observation - 4/12
  - Initial assessment of DXA, pQCT - 1/09
- Target of 120 subjects
  - 110 were enrolled from 4 centers
  - Spine radiographs (routine - PA, lateral)
    - Scoliosis, vertebral body structure, rib penciling
  - Spine MRI (modified sequence without sedation)
    - Paraspinal neurofibromas, dural ectasia, meningocoele

# Spine Abnormalities in NF1: At Enrollment

- **86** subjects assessed with both radiographs and MRI
- **48** - Normal spine radiographs and MRI
- **38** - At least 1 abnormal finding (44%)
  - 18 with scoliosis between 10-18 degrees
  - 24 with paraspinal tumors
  - 9 with wedging, beaking or scalloping of the vertebral bodies
  - 5 with dural ectasia or meningocoele

# Cohort of 108 prepubertal children with NF1

- 63 females and 45 males
- Age at time of enrollment
  - 4-5 yr: 1
  - 5-6 yr: 12
  - 6-7 yr: 36
  - 7-8 yr: 22
  - 8-9 yr: 25
  - 9-10 yr: 11
  - 10-11 yr: 1
- Of 108 enrolled
  - 96 had at least 1 follow-up exam and scoliosis study
  - 64 completed 4 years of exams and scoliosis studies

# 108 prepubertal children with NF1 over 4 years

- None developed dystrophic scoliosis
- None initially had scoliosis over 25 degrees

- No scoliosis and no signs of neurofibroma: 47 (42%)
- Scoliosis (≥10 degrees) in 38 (35%)
- Spine-related neurofibromas in 31 (29%)

- Scoliosis ≥10 degrees without neurofibroma: 26 (~2/3)
- Scoliosis ≥10 degrees with neurofibroma: 12 (~1/3)

- Neurofibroma without scoliosis: 19 (~60%)
- Neurofibroma with scoliosis: 12 (~40%)

# Data Analyses per NIH Study Protocol

- This is a longitudinal study in which findings on initial screening will be used to predict patients who will develop *dystrophic scoliosis* over the next 3 years.

- *Dystrophic scoliosis* – scoliosis that requires surgical treatment or short-segment (4-6 vertebrae) curve with a Cobb angle ≥45 degrees

- At time of screening, participants are placed in either high-risk or low-risk to develop dystrophic scoliosis on basis of scoliosis series and whole-spine MRI.

# Data Analyses per NIH Study Protocol

- This is a longitudinal study in which findings on initial screening will be used to predict patients who will develop *dystrophic scoliosis* over the next 3 years. – NONE !!

- *Dystrophic scoliosis* – scoliosis that requires surgical treatment or short-segment (4-6 vertebrae) curve with a Cobb angle ≥45 degrees

- At time of screening, participants are placed in either high-risk or low-risk to develop dystrophic scoliosis on basis of scoliosis series and whole-spine MRI. OF 66 evaluable: 24 high; 42 low

# Scoliosis in NF1: MRI findings

- Spinal abnormalities detected by MRI in NF1 include spinal neurofibromas, dural ectasias, and meningoceles

- Of 62 children with NF1 who underwent prospective MRI of spine:
  - Age: Mean is 9.6 years old (range of 11 months to 18 years)
  - 7 had spine-related neurofibroma (13%)
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    - 2-fold increased risk for scoliosis (Khong, P-L et al., 2003)

- More recent study (Nguyen, R et al., 2015) of 97 with NF1:
  - Referral center for anticipated treatment
  - Age: Median is 14.2 (range of 2.7 years to 48.2 years)
  - 50 had spine curvature (51%)
  - 6-fold increased risk to have tumor if have spinal curve

# Acknowledgments


## International NF1 Bone Study Group (INBSG)

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- General Clinical Research Center M01-RR00064
- NIH NINDS K23 NS052500 and **R01 NS050509**
- Shriners Research Foundation

# Examples from the Natural History Spine Study


# UTA010 MRI sagital spine


Vertebral wedging by MRI

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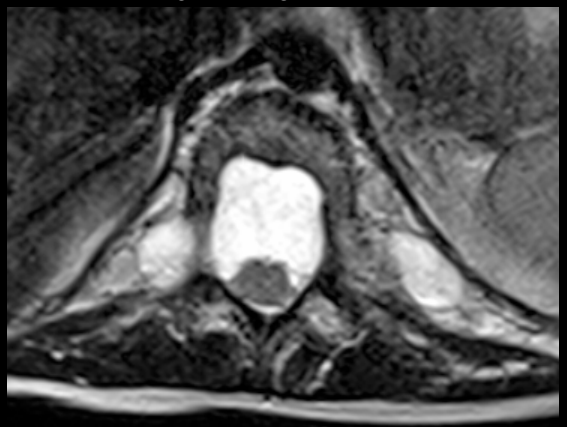
# MAN021 Spine

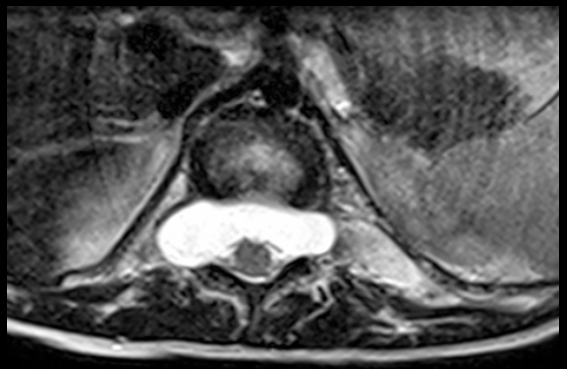
REiNS
Response Evaluation in Neurofibromatosis & Schwannomatosis

# MAN021 lat spine

MAN021 MRI sagital T2-weighted

MAN021 Axial T12





MAN021 Axial T12-L1