ResponseEvaluationInNeurofibromatosisSchwannomatosis
INTERNATIONAL COLLABORATION

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Techniques and Endpoints for Osteoporosis in NF1

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Response Evaluation In Neurofibromatosis Schwannomatosis
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Terminology

<u>Bone Mineral Density (BMD):</u> amount of bone mineral in bone tissue

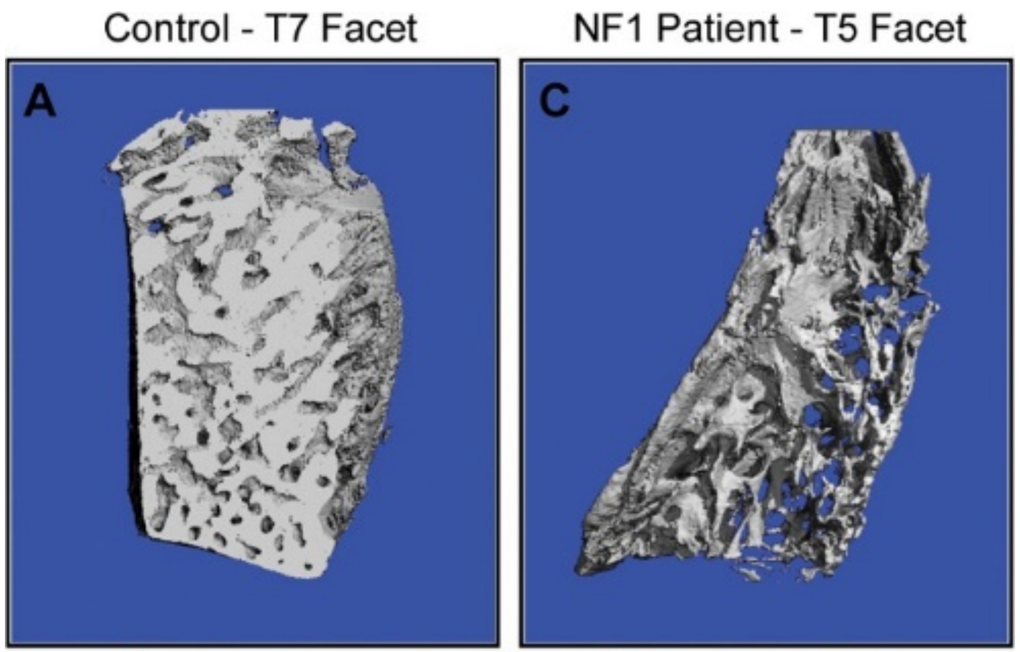
<u>Osteoporosis:</u>

adults: BMD T-score <-2.5 at hip or spine*

children: BMD Z-score ≤-2 and a clinically significant fracture history

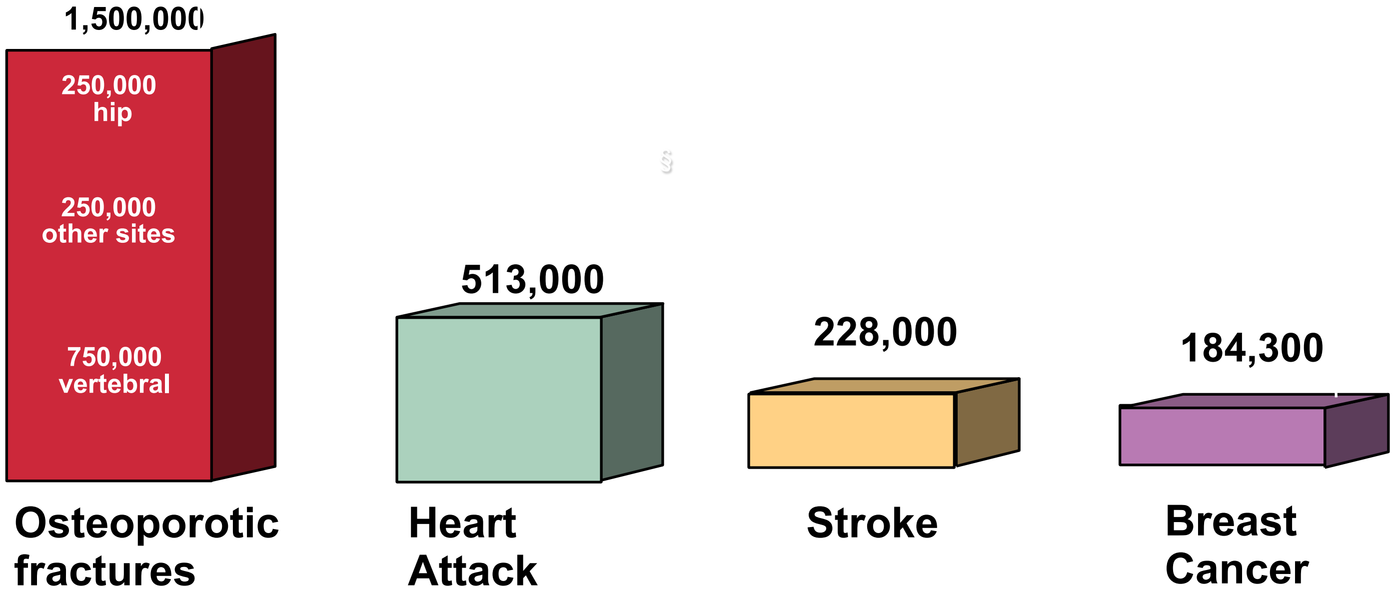
<u>Osteopenia:</u> Lower than normal BMD (controversy on terminology)

<u>Bone Macro- and Micro-architecture:</u> shape, structure and size



*Treatment based on clinical risk factors (FRAX tool)

Osteoporosis Fracture Incidence > Heart Attack + Stroke + Breast Cancer



Decreased Bone Density in NF1

Multiple reports in NF1 (few examples below):

1. Illes et al., 2001 (Decrease in BMD of lumbar spine in 12 NF1 patients with scoliosis; DXA).
2. Kuorilehto et al., 2005 (Decreased BMD in 26 NF1 adults; DXA. **All** postmenopausal NF1 women had either osteoporosis or osteopenia)
3. Lammert et al., 2005 (Calcaneal values decreased in 104 NF1 adults; QUS)
4. Stevenson et al., 2007 (84 NF1 children; DXA)
5. Dulai et al., 2007 (23 NF1 children; DXA and QUS)
6. Yilmaz et al., 2007 (31 NF1 children; DXA)
7. Lodish et all, 2012 (69 NF1 children, DXA)

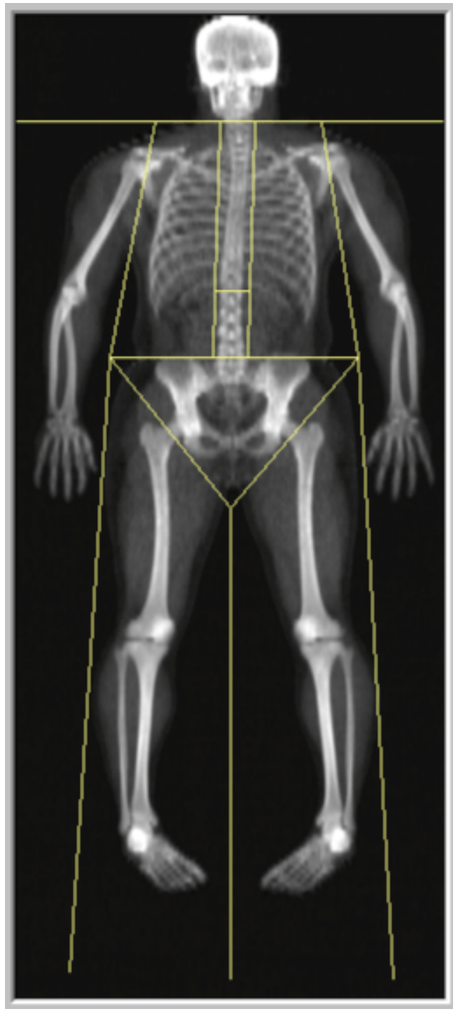
Impact of Low BMD in NF1

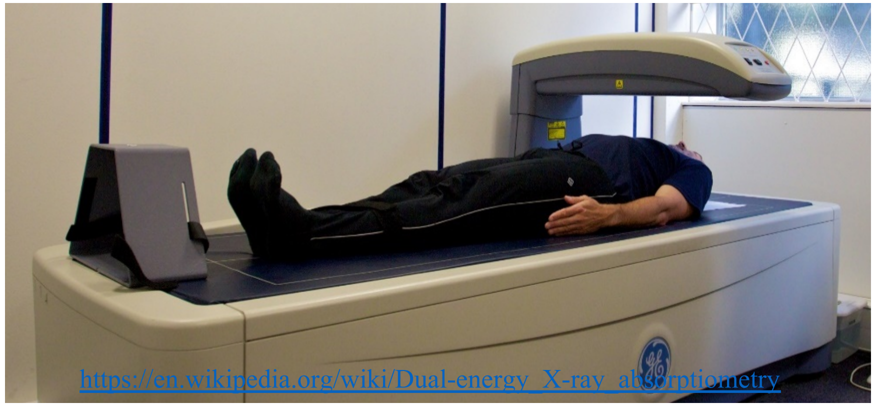
- Consequences of decreased BMD in NF1
  - Several studies show increased fractures (Tucker et al., 2009; Heerva et al., 2012)

- Peak accrual of bone mass is in early adulthood.

- Will traditional medications for osteoporosis in the general population translate to NF1 population?

Dual Energy X-ray Absorptiometry (DXA)



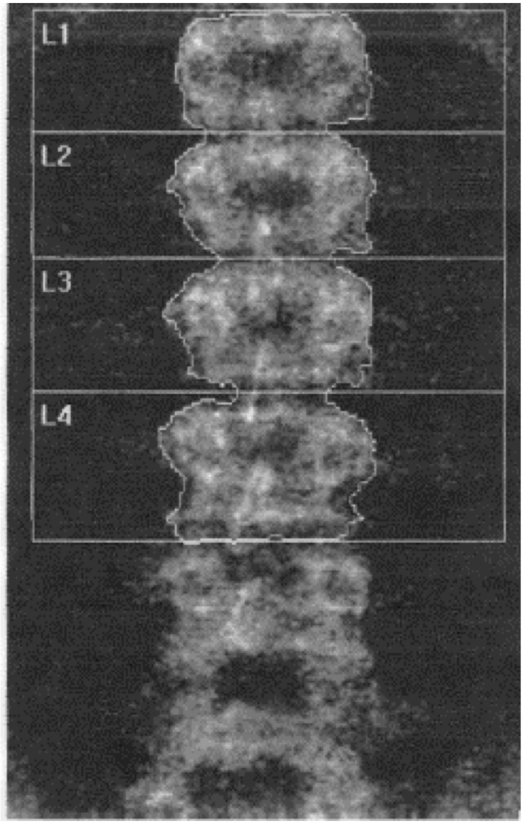


https://en.wikipedia.org/wiki/Dual-energy_X-ray_absorptiometry

Body Regions:

- **Whole body subtotal**
- **Hip**
- **Femoral Neck**
- **Lumbar Spine**

-Bone Mineral Content (BMC)
-Areal Bone Mineral Density (aBMD)



DEXA Results

- Report absolute values for individual regions (gm/cm^2)
- Not volumetric (areal scores)
- T-scores used for adults
- In children can generate normalized Z-score to compare to other patients with similar age, race and sex
- For pediatrics, need to adjust for height as well (“Height Adjusted Z-score”)
- Results vary with machine
- Other variables are being studies (e.g. trabecular bone score)

DXA Statistical Analysis (NF1 with and without osseous dysplasia, versus Controls)*

Variable	adjusted mean			equality of adjusted means (p-value)		
	Controls	NF1 (no osseous dysplasia)	NF1 (osseous dysplasia)	Controls vs. NF1 (no osseous dysplasia)	NF1 (no osseous dysplasia vs. osseous dysplasia)	overall p-value
Hip						
BMC (gm)	21.48	18.41	15.55	p<0.0001	p=0.0099	p<0.0001
aBMD (gm/cm^2)	0.779	0.711	0.668	p<0.0001	p=0.0513	p<0.0001
Femoral Neck						
BMC (gm)	3.16	2.88	2.66	p=0.0004	p=0.0647	p<0.0001
aBMD (gm/cm^2)	0.720	0.658	0.621	p<0.0001	p=0.0823	p<0.0001
Lumbar Spine						
BMC (gm)	34.3	32.1	30	p=0.0381	p=0.2598	p=0.0074
aBMD (gm/cm^2)	0.711	0.677	0.665	p=0.0152	p=0.0253	p=0.0092
Whole Body Subtotal						
BMC (gm)	1021	935	865	p=0.0003	p=0.1946	p<0.0001
aBMD (gm/cm^2)	0.777	0.735	0.720	p<0.0001	p=0.3171	p<0.0001

*Comparison adjusted for gender, Tanner stage, weight, height, and age using analysis-of-covariance with a fixed set of covariates. The column labeled "overall p-value" is the test for overall equality of adjusted means in the three groups from analysis of variance. [Controls (N= 290); NF1 without osseous dysplasia (N=60); NF1 with osseous dysplasia (N=24)].

(Stevenson et al., J Peds, 2007)

Dual Energy X-ray Absorptiometry (DXA)

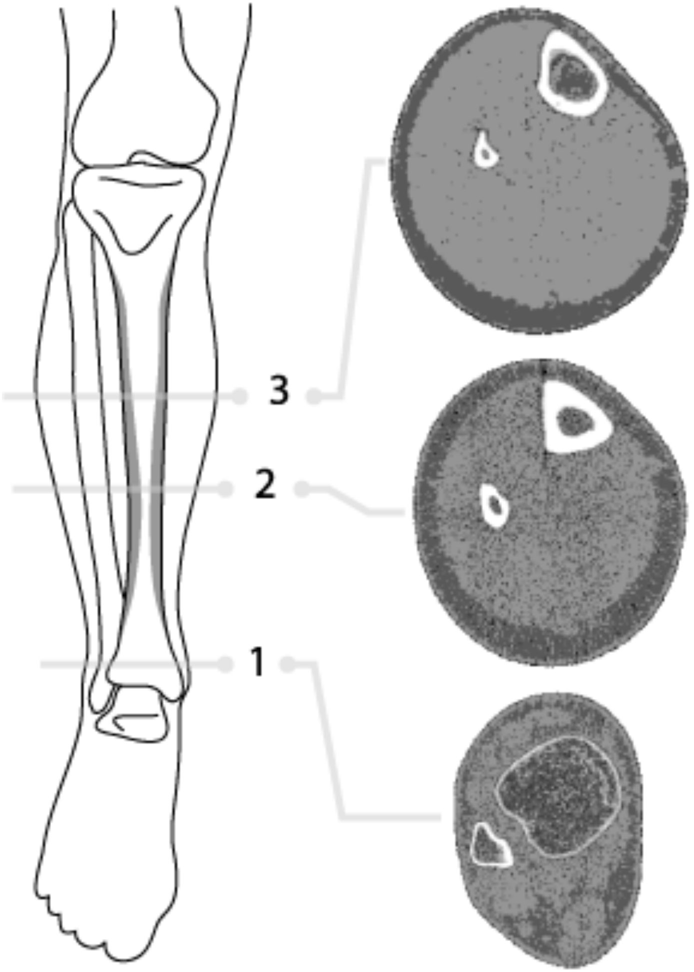
Pros

- Most clinically used
- Global assessment
- Data in NF1

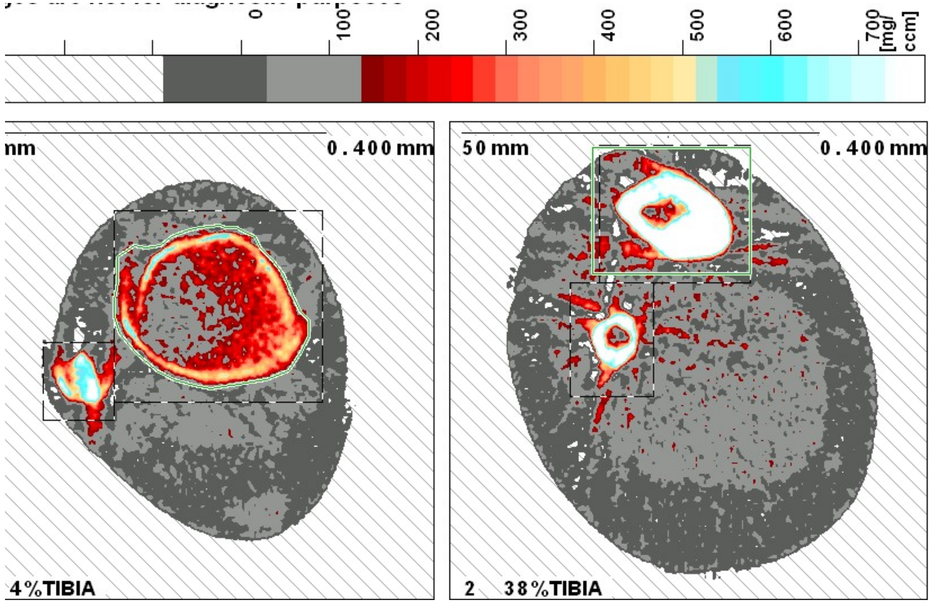
Cons

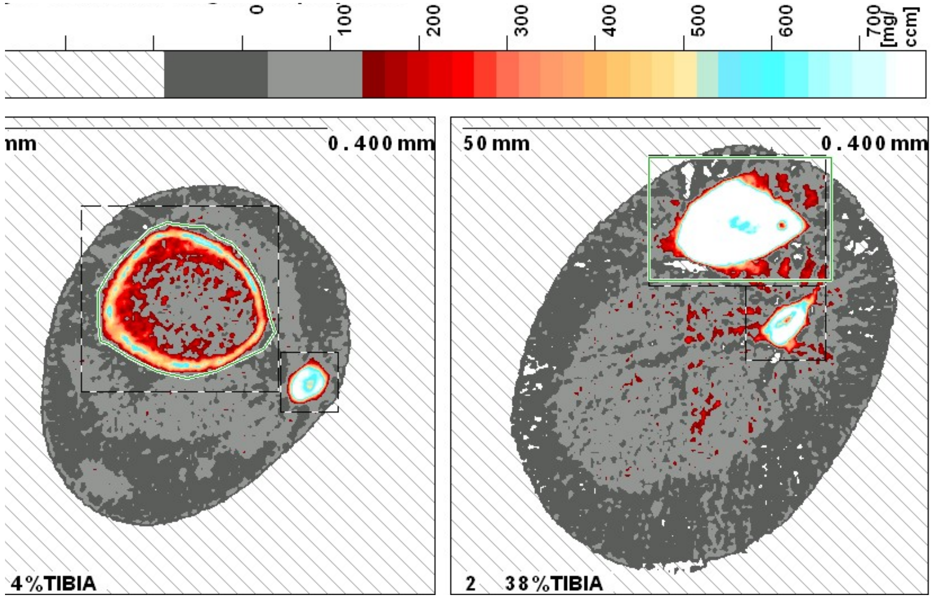
- Radiation (minimal)
- Areal measurement (not volumetric)

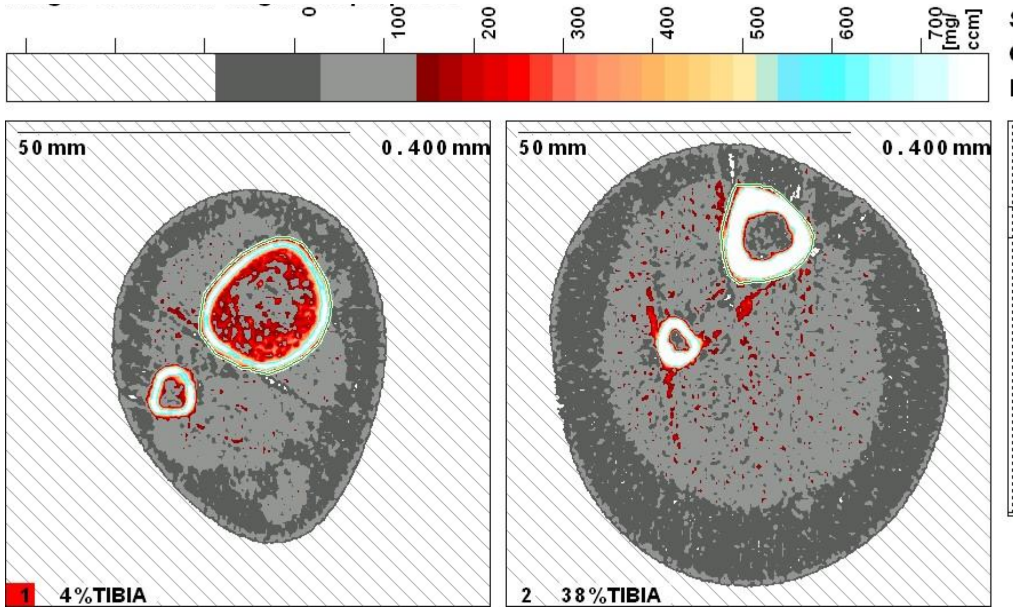
Quantitative Computed Tomography (pQCT)



Different sites available (spine; peripheral QCT = tibia, radius)







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QCT/pQCT

Pros

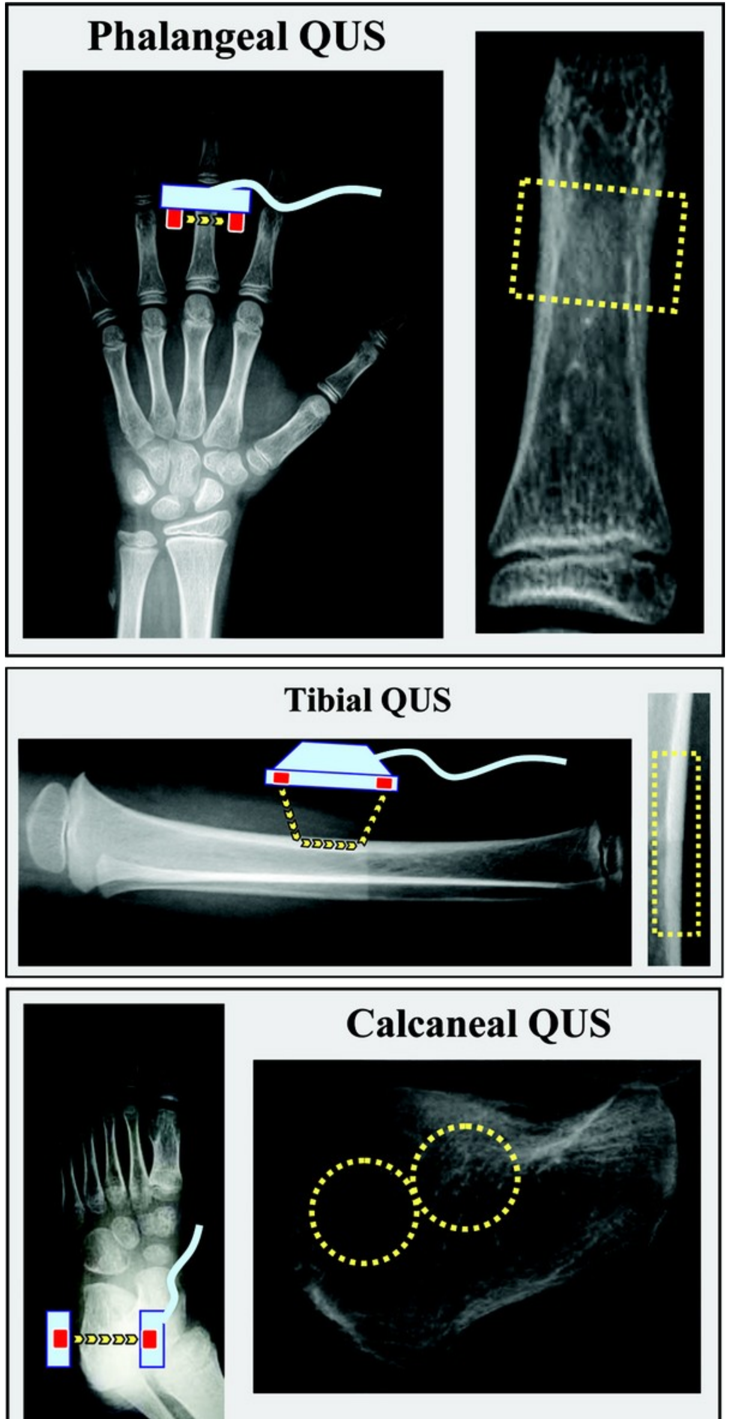
- Volumetric 3D measures
- More detailed (trabecular, cortical, strength strain index)
- Can model biomechanical strength
- Data in NF1
- Ability to use patient as control for localized manifestations

Cons

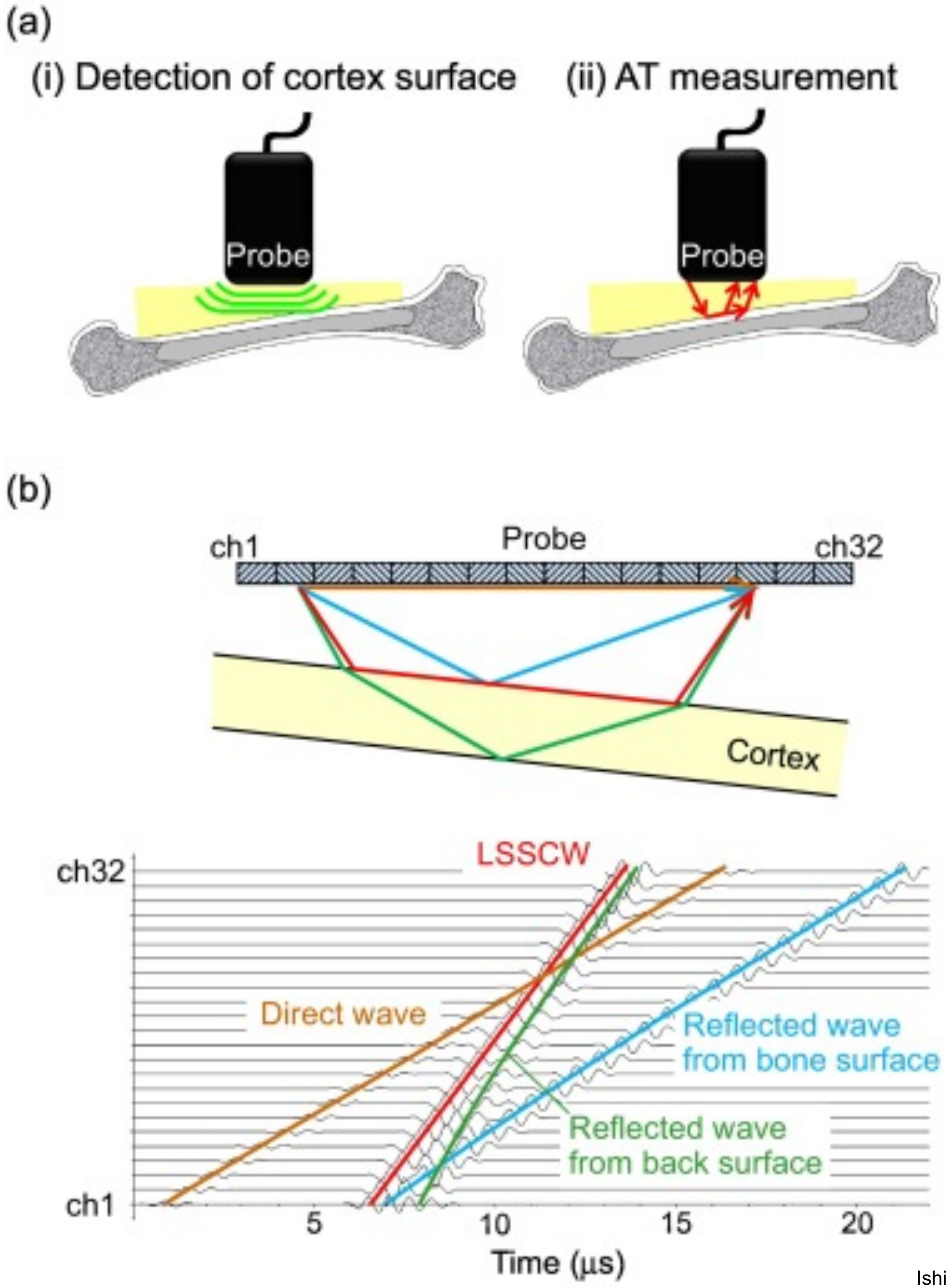
- Radiation (minimal if peripheral)
- Localized
- Age restrictions (pQCT)
- Can be more costly
- Complex with specialized software

Quantitative Bone Ultrasound

- Measures Speed of Sound (SOS) m/s
- Z-score generated using sex- and age-matched references
- Various sites available (calcaneus, tibia, forearm)



Baroncelli, Pediatric Research 2008



Ishimoto et al., Bone 2019

NF1 Tibial Bowing Study

<u>Quantitative Bone Ultrasound (QUS):</u>

Lower mean difference z-score for affected tibia (p=0.0001)

Participant	Age (years)	Sex	Tibia Affected	Z-score Unaffected Tibia	Z-score Bowed Tibia
Participant #1	1.4	M	Left	-0.7	-1.0
Participant #2	13.5	M	Left	-3.3	-2.4
Participant #3	22.3	F	Left	+1.3	-1.0
Participant #4	5.6	M	Right	-0.7	-3.7
Participant #5	12.6	F	Right	+0.3	-0.5
Participant #6	0.8	M	Right	-1.7	-4.2
Participant #7	7.5	M	Left	-0.3	-1.0
Participant #8	4.5	F	Left	-0.3	-3.9
Participant #9	5.3	F	Right	+0.5	-7.5
Participant #10	8.8	M	Right	-0.7	-4.5
Participant #11	7.1	F	Right	-2.4	-3.2
Participant #12	1.7	M	Left	+3.2	-5.2
Participant #14	2.1	F	Right	-0.2	-5.2
Participant #16	6.2	M	Left	-2.3	-3.9
Participant #17	2.4	F	Right	-0.5	-2.2
Participant #18	2.3	F	Left	+0.7	-2.8
Participant #19	3.8	M	Left	+0.9	-2.8
Participant #20	7.0	F	Right	-0.2	-0.4
Participant #21	19.3	F	Left	-0.5	-0.5
Participant #22	9.3	F	Right	+0.2	-1.0
Participant #23	16.3	F	Left	+1.1	-1.4

Bone Ultrasound

Pros

- No radiation
- Data in NF1
- Quick (all ages)
- Non-invasive
- Portable
- Ability to use patient as control for localized manifestations

Cons

- Localized
- Not used widely clinically
- Limited control data

MRI for Bone

- Not well studied
- Evaluation of bone marrow fat quantification (limited cortical bone assessment)
- Limited quantitative measurements (more qualitative)

MRI for Bone

Pros

- No radiation
- Potential for detailed evaluation of bone at microarchitechtural and molecular level
- MRI frequently performed in NF1

Cons

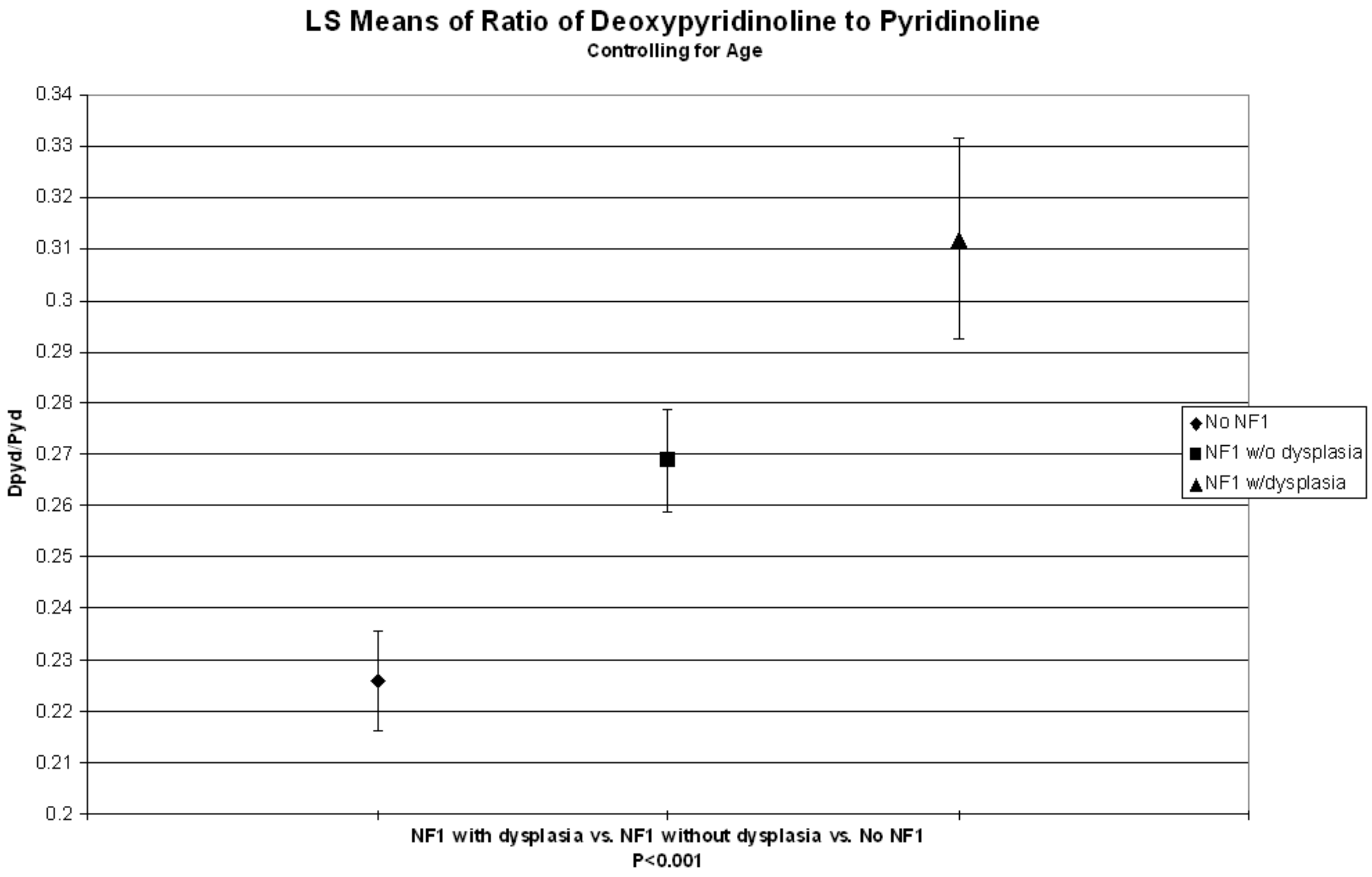
- Limited studies
- No data in NF1
- Expense
- More time consuming
- Not typically used clinically
- Lower spatial resolution than CT

Markers of Bone Turnover

(significant variability - day to day and hourly; meals etc.)

- Resorption
  - Urine pyridinium crosslinks (urine easy to obtain; data in NF1)
  - C-terminal telopeptide (CTX)
  - N-terminal telopeptide (NTX)

- Formation
  - Osteocalcin (need for prompt and special handling)
  - Bone specific alkaline phosphatase (some cross-reactivity with liver isoform)
  - Procollagen type 1 N propeptide (P1NP)



-Suggests effect primarily due to bone resorption

Different modalities measure different variables

DXA: (areal BMD)

pQCT: (volumetric BMD, trabecular and cortical indices, endosteal circ., etc.)

QUS: (speed of sound)

What variable should we measure?

Some state BMD may be the wrong measure (density is not synonymous with mass or structural strength).

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