



Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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Developing Endpoints for Skeletal Manifestations in NF1

Jonathan J Rios

Scottish Rite for Children



Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

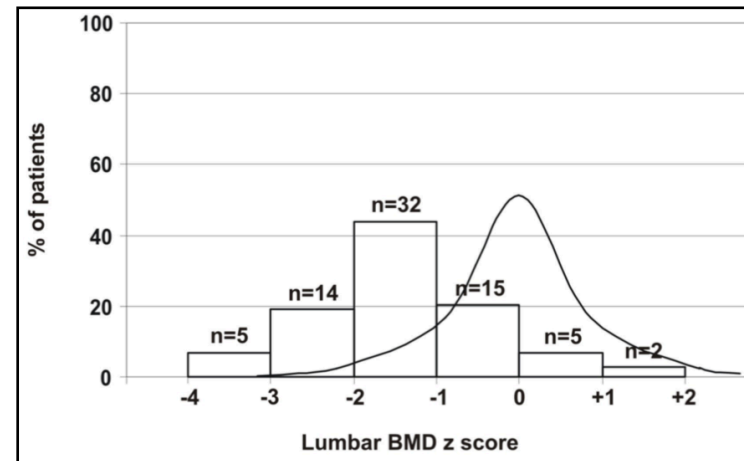
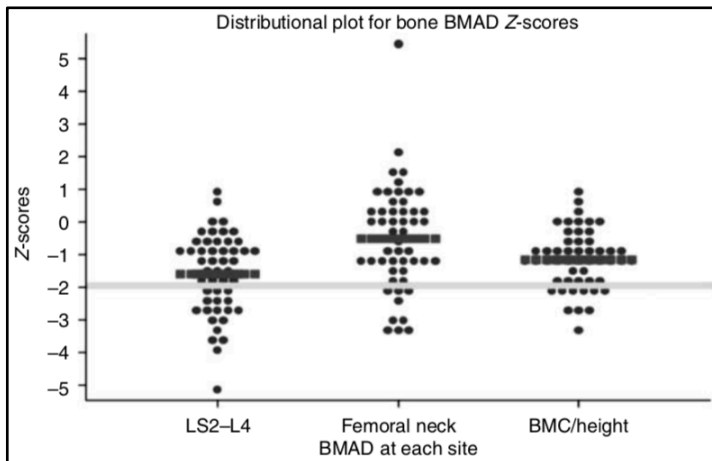
Skeletal Manifestations in NF1

- Osteopenia
 - Systemic and localized
- Scoliosis
 - With and without paraspinal neurofibroma
- Dysplasia and pseudarthrosis



Systemic Osteopenia & DEXA Imaging

Reduced Lumbar Spine BMD in NF1



Phase 2 Trial of Vitamin D

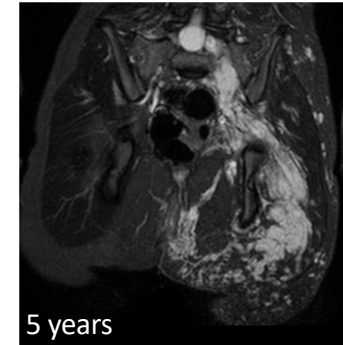
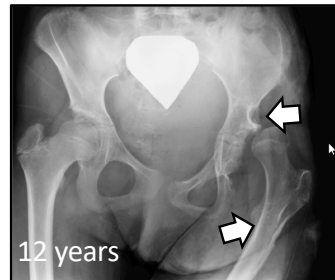
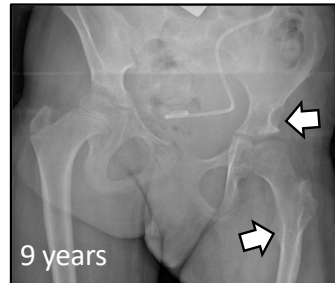
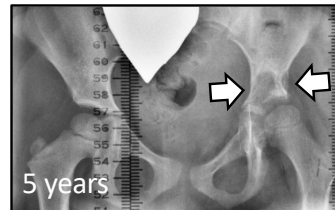
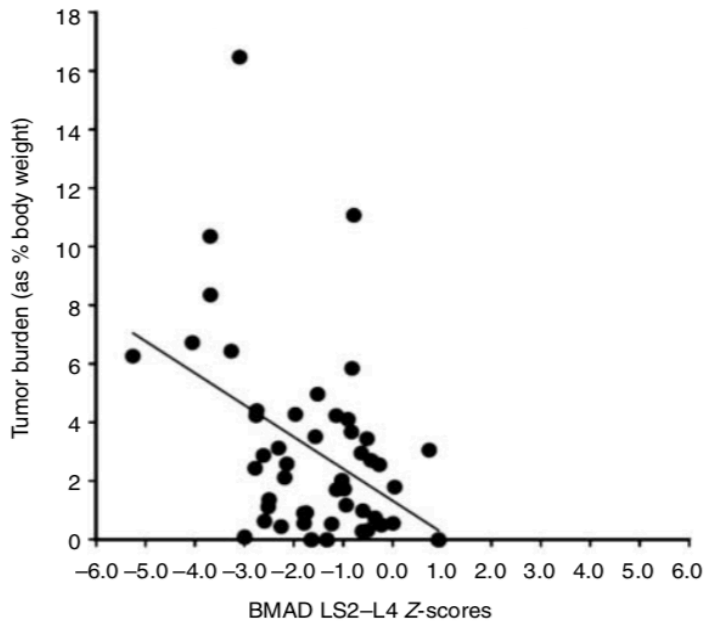
- Led by Dave Viskochil (U of Utah) and Betty Schorry (Cincinnati Children's)
- Young adults with Vitamin D insufficiency
 - 600 IU vs 4,000 IU (both +400mg Calcium)
- Bone density measured by DEXA
- 32 screened, 25 enrolled – target enrollment is 320
 - No safety concerns
 - Efficacy not yet evaluated
- Recruitment has been challenging.



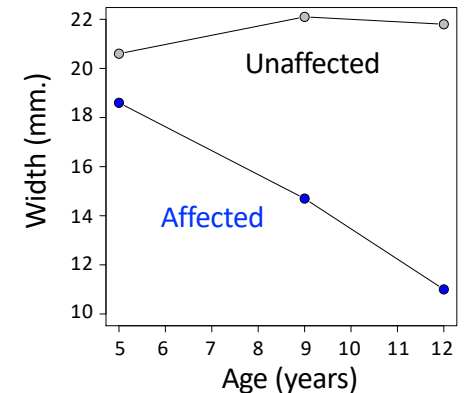
Localized osteopenia with PN

Patient with PN-associated bone loss

Reduced BMD correlates with tumor burden

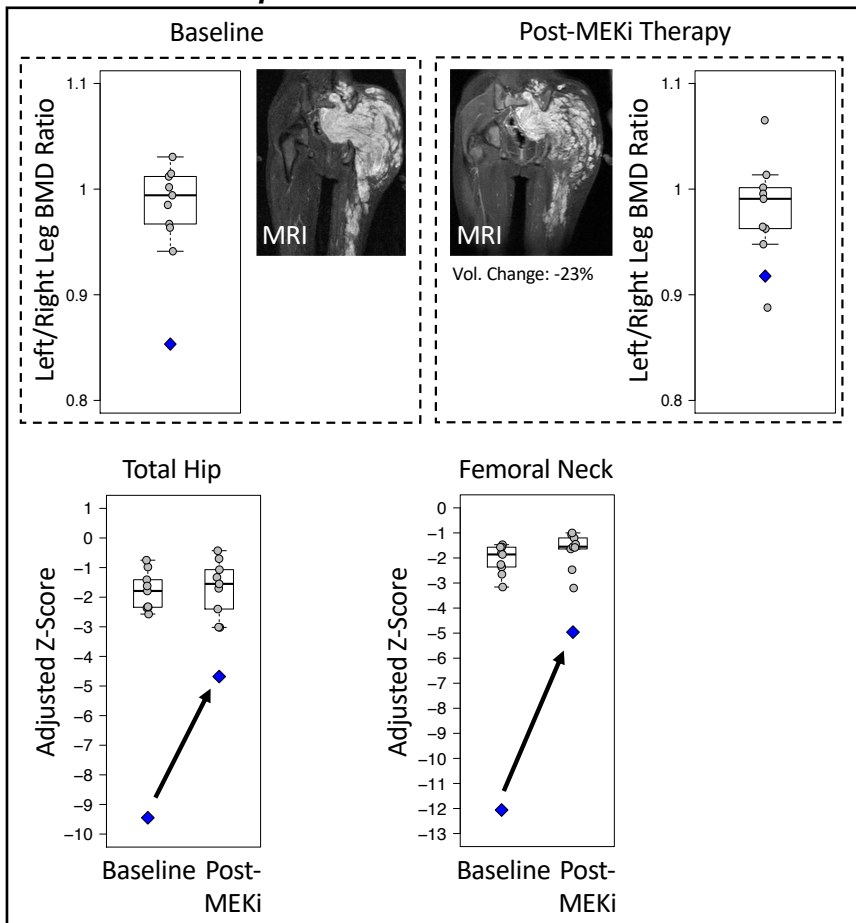


Sub-Troch. Femoral Diameter

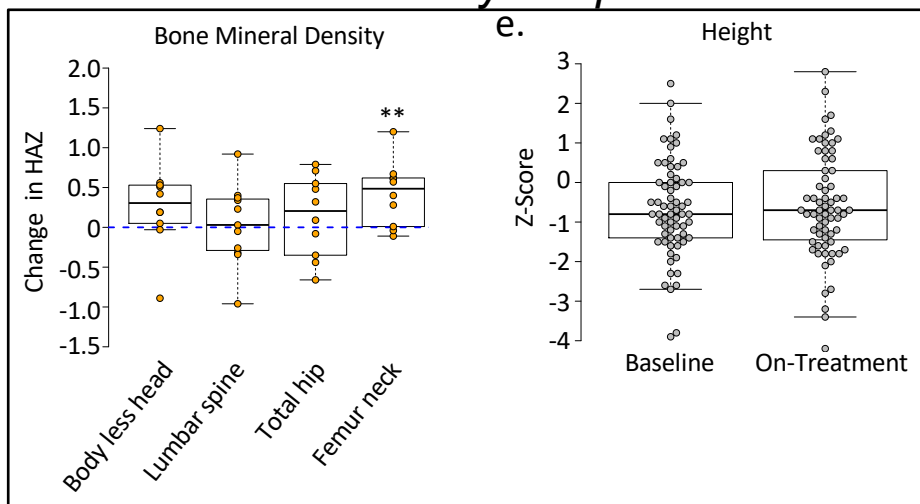


Measuring skeletal impact of MEKi

Potential for skeletal improvement with MEKi



Potential for DEXA/X-ray as secondary endpoints



How do we measure localized bone density?



Scoliosis

Somatic NF1 mutations in scoliosis

Journal of Molecular Neuroscience (2019) 68:11–18
https://doi.org/10.1007/s12031-019-01277-0



NF1 Somatic Mutation in Dystrophic Scoliosis

Rebecca L. Margraf¹ · Chad VanSant-Webb¹ · Rong Mao^{1,2} · David H. Viskochil^{3,4} · John Carey^{3,4} · Heather Hanson³ · Jacques D'Astous⁴ · Allie Grossmann² · David A. Stevenson⁵

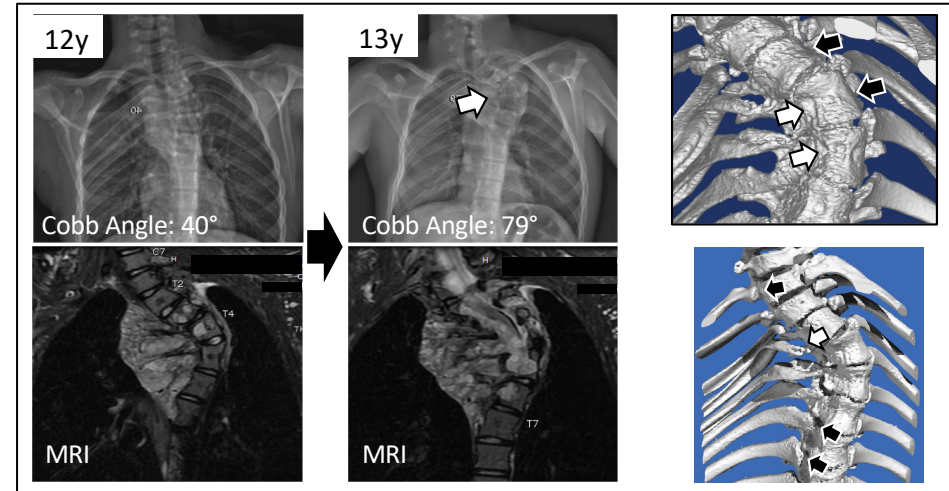
Somatic mutation in bone leads to MEK-dependent hypomineralization

nature
medicine

Asfotase- α improves bone growth, mineralization and strength in mouse models of neurofibromatosis type-1

Jean de la Croix Ndong^{1,2}, Alexander J Makowski^{1,3-5}, Sasidhar Uppuganti^{1,4}, Guillaume Vignaux^{1,2}, Koichiro Ono^{1,2,6}, Daniel S Perrien^{1,4,5,7}, Simon Joubert⁸, Serena R Baglio⁹, Donatella Granchi⁹, David A Stevenson¹⁰, Jonathan J Rios¹¹⁻¹⁴, Jeffrey S Nyman^{1,3-5} & Florent Elefteriou^{1,2,15,16}

PN-associated scoliosis



Considerations

1. X-rays for secondary endpoints in ongoing/future trials!!
2. Can we evaluate scoliosis with existing MRIs



Tibial Dysplasia



- 3-5% of children with NF1
- 2/3 progress to fracture

No current clinically-meaningful measure:

- 1. Quality of bone**
- 2. Degree of dysplasia**

Need to develop clinical endpoint:

- 1. Evaluate correction following treatment**
- 2. Predict fracture risk**



Potential Outcome Measures

Peripheral quantitative computed tomography

Contents lists available at ScienceDirect

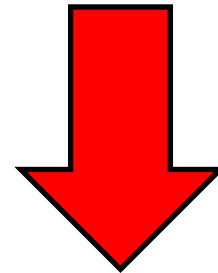
Bone

ELSEVIER journal homepage: www.elsevier.com/locate/bone

Tibial geometry in individuals with neurofibromatosis type 1 without anterolateral bowing of the lower leg using peripheral quantitative computed tomography

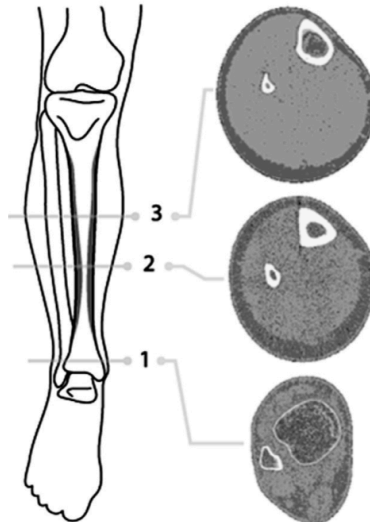
David A. Stevenson^{a,b,*}, David H. Viskochil^{a,b}, John C. Carey^{a,b}, Hillarie Slater^a, Mary Murray^a, Xiaoming Sheng^c, Jacques D'Astous^{b,d}, Heather Hanson^a, Elizabeth Schorry^e, Laurie J. Moyer-Mileur^a

Results comparing NF1 vs control



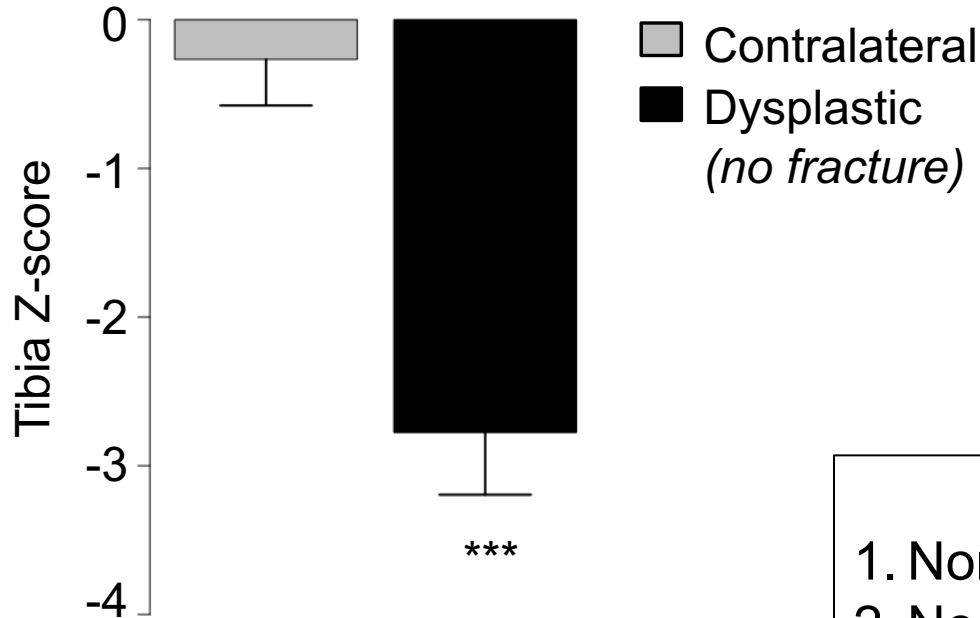
- Tibial area
- Cortical thickness
- Periosteal circumference
- Cortical area
- Strength strain index

Need to study dysplastic bone!



Potential Outcome Measures

Quantitative bone ultrasound

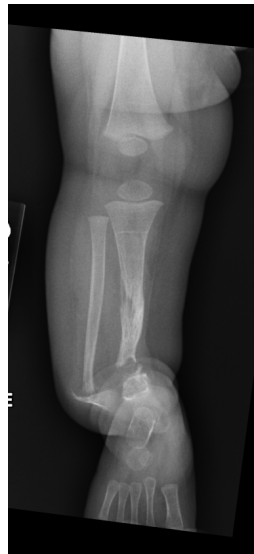
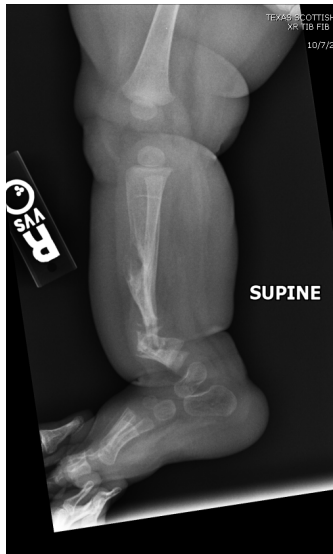


Advantages

1. Non-invasive
2. No radiation
3. Contralateral control
4. Age- and gender-matched Z-scores



Pseudarthrosis After Fracture



Modified RUST Score for NF1

A radiographic scoring system to assess healing in congenital pseudarthrosis of the tibia

B. Stephens Richards, David Wilkes, Molly Dempsey and Pamela Nurenberg

Orthop B 24:118-122 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Score per cortex ^a	Radiographic criteria	
	Callus	Fracture line
1	Absent	Visible
2	Present	Visible
3	Present	Invisible

RUST Score = Sum of scores for each of four cortices

- RUST developed Modified RUST Score without dysplastic bones

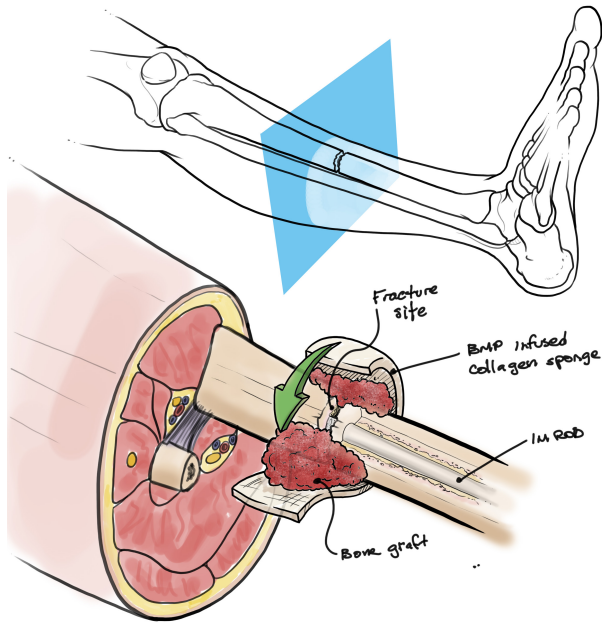
Score per cortex ^a	Radiographic criteria		
	Callus	Fracture line	
1	Absent	Visible	Eccentric rod location precludes visualization of cortex
2	Present	Visible	
3	Present	Invisible	Faint lucencies present in dysplastic bone, not representative of fracture line

*Union can be defined as at least 2 cortices scoring 3



INFUSE Clinical Trial

*Test the efficacy of rhBMP INFUSE graft (Medtronic)
to improve healing of NF1 pseudarthrosis*



- Closed due to lack of enrollment
- REiNS recommendations:
 - Better engage orthopaedists in NF1 clinics
 - Engage focus groups for patient perspectives
 - Consider registry studies
 - Recognize PN-associated bone manifestations
 - Further develop skeletal endpoints
 - Promote basic-translational research
 - Establish skeletal biorepository



Summary

- There are several skeletal manifestations amenable to clinical trials
- Important to consider recruitment strategies and difficulties
- Potential exists to include skeletal endpoints in *future* trials
 - Secondary endpoints
- Potential to evaluate skeletal endpoints from *completed* trials
 - MRI for spine deformity



Acknowledgements

- David Stevenson MD, *Stanford University*
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- Andrea Gross MD, *National Cancer Institute*
- Brigitte Wideman MD, *National Cancer Institute*

- B Stephens Richards MD, *Scottish Rite for Children*

