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Prospective Evaluation of Skeletal Disease Manifestations in NF1

REiNS Summer Meeting

June 23, 2023

Response Evaluation In Neurofibromatosis & Schwannomatosis

REiNS

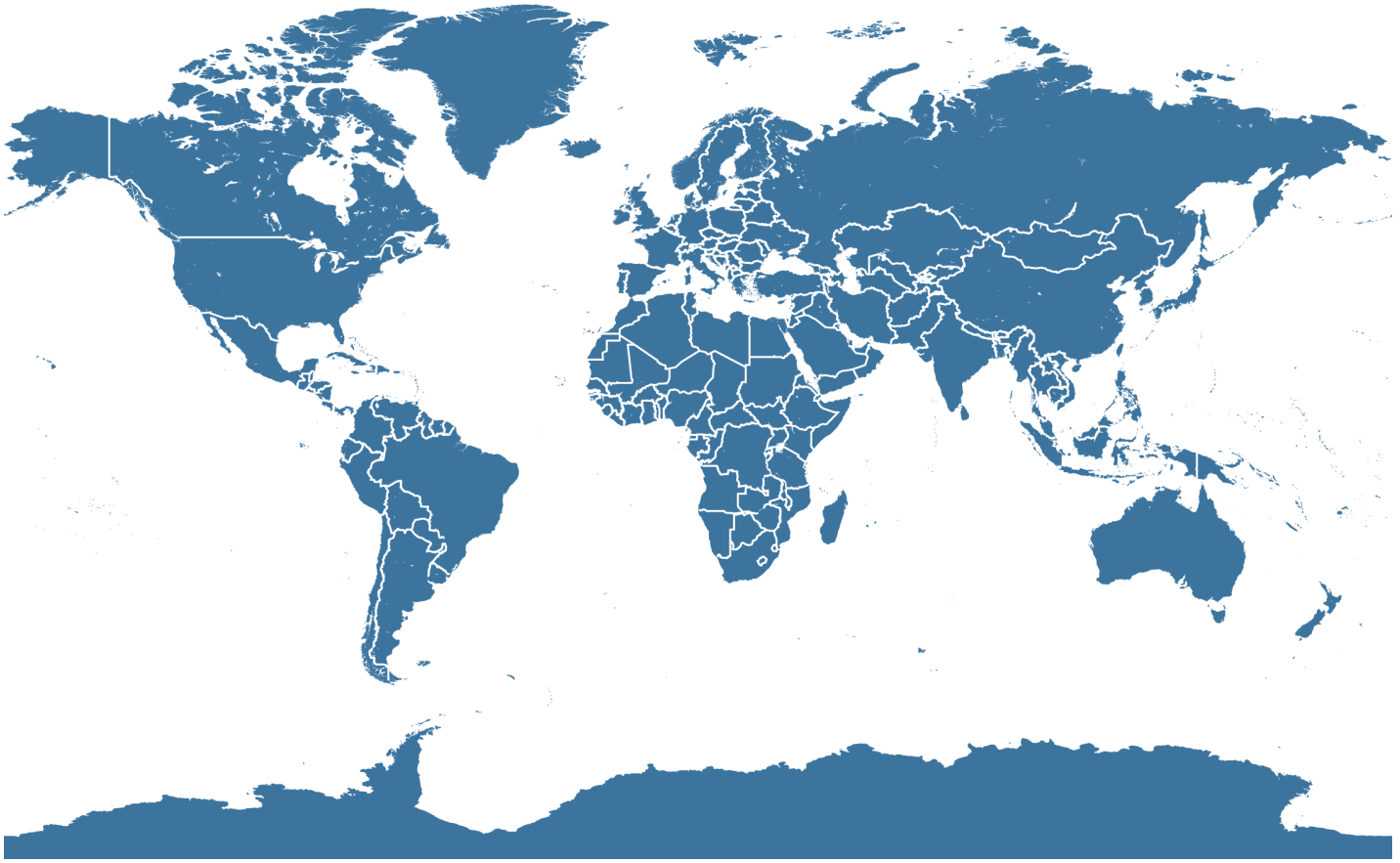
Response Evaluation In Neurofibromatosis Schwannomatosis

INTERNATIONAL COLLABORATION

Poll Question #1

For ALL REiNS Attendees

- Where do you live?



Poll Question #2

For ALL REiNS Attendees

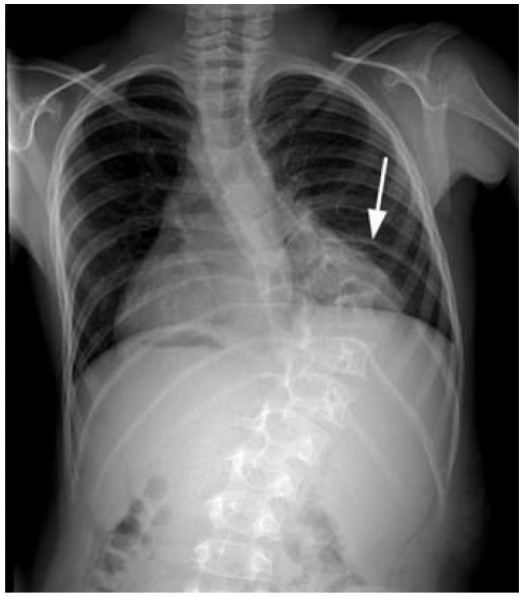
What words do you think of when you think of bone related issues and NF1?

Poll Question #3 (slide 1 of 7)

For Patient Representatives only

Rank the following NF1 bone-related issues that you worry about the most **for you or the person in your life with NF1** (top = most worried; bottom = least worried)?

- ❑ Scoliosis and other spine related problems

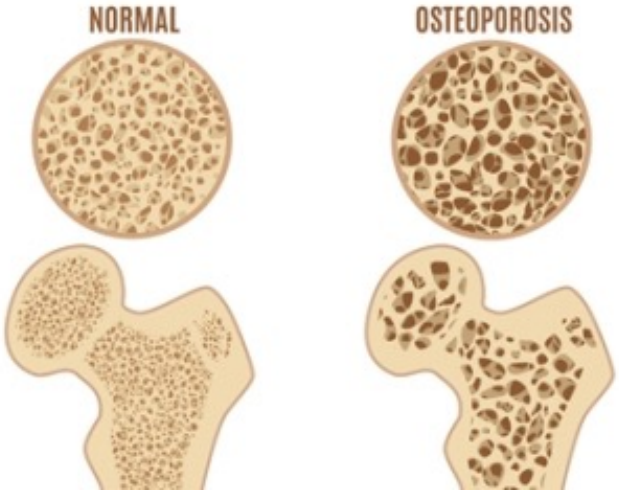


Poll Question #3 (slide 2 of 7)

For Patient Representatives only

Rank the following NF1 bone-related issues that you worry about the most **for you or the person in your life with NF1** (top = most worried; bottom = least worried)?

- ❑ Scoliosis and other spine related problems
- ❑ Low bone mineral density or increased risk of broken bones (fractures)



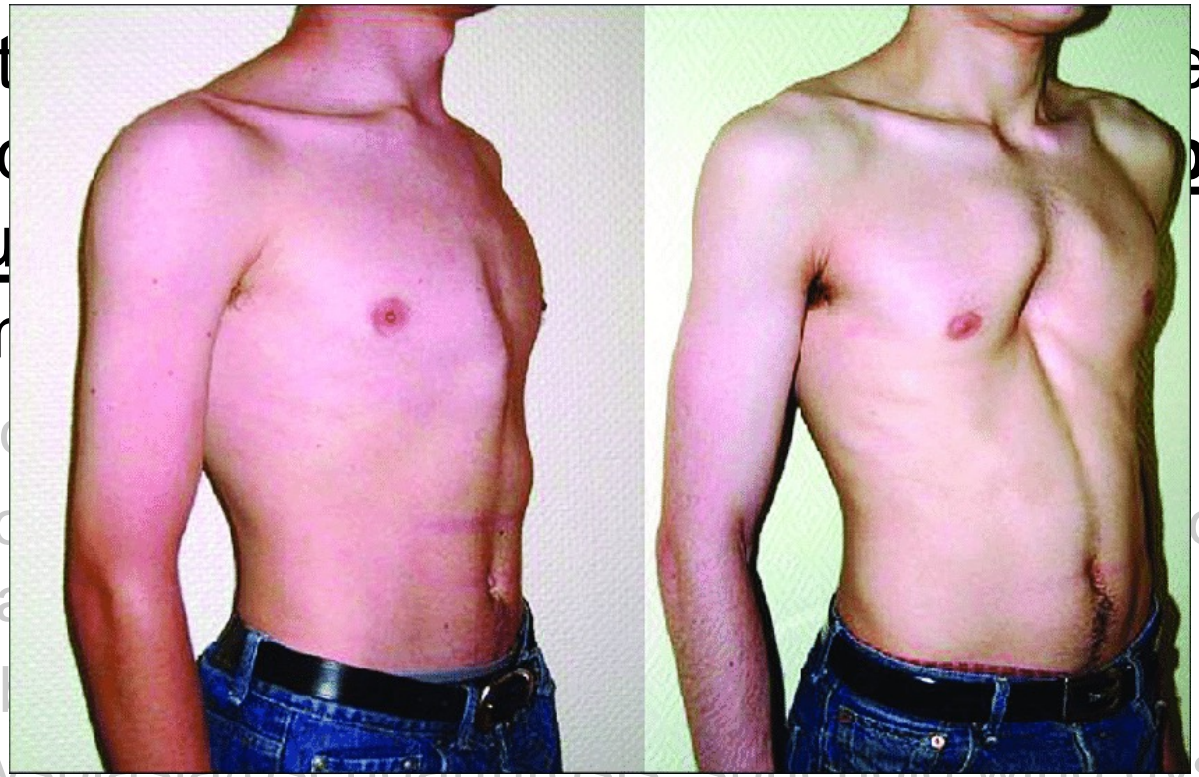
Poll Question #3 (slide 3 of 7)

- Abnormal bone formation (tibial dysplasia/pseudarthrosis, sphenoid wing dysplasia)

Poll Question #3 (slide 4 of 7)

For Patient Representatives only

Rank t…es that you wo…**person in you…** bottom…



- ❑ S…
- ❑ L…of fra…
- ❑ A… dysplasia/pseudarthrosis, sphenoid wing dysplasia)
- ❑ Pectus Excavatum (Sunken Chest) or Pectus Carinatum (Chest bone sticking out)

Poll Question #3 (slide 5 of 7)

For Patient Representatives only

Rank the following NF1 bone-related issues that you worry about the most **for you or the person in your life with NF1** (top = most worried; bottom = least worried)?

- ❑ Scoliosis and other spine related problems
- ❑ Low bone mineral density or increased risk of fractures
- ❑ Abnormal bone formation (tibial dysplasia/pseudarthrosis, sphenoid wing dysplasia)
- ❑ Pectus Excavatum (Sunken Chest) or Pectus Carinatum (Chest bone sticking out)
- ❑ Short Stature

Poll Question #3 (slide 6 of 7)

For Patient Representatives only

Rank the following NF1 bone-related issues that you worry about the most **for you or the person in your life with NF1** (top = most worried; bottom = least worried)?

- ❑ Scoliosis and other spine relate
- ❑ Low bone mineral density or in fractures
- ❑ Abnormal bone formation (tibia dysplasia/pseudarthrosis, sphe asia)
- ❑ Pectus Excavatum (Sunken Ch Carinatum (Chest bone sticking
- ❑ Short Stature
- ❑ Leg Length Discrepancy

Poll Question #3 (slide 7 of 7)

For Patient Representatives only

Rank the following NF1 bone-related issues that you worry about the most **for you or the person in your life with NF1** (top = most worried; bottom = least worried)?

- ❑ Scoliosis and other spine related problems
- ❑ Low bone mineral density or increased risk of fractures
- ❑ Abnormal bone formation (tibial dysplasia/pseudarthrosis, sphenoid wing dysplasia)
- ❑ Pectus Excavatum (Sunken Chest) or Pectus Carinatum (Chest bone sticking out)
- ❑ Short Stature
- ❑ Leg Length Discrepancy

Poll Question #4

For ALL REiNS Attendees

Rank the following NF1 bone-related issues from in order of potential impact on life and daily activities **for people with NF1**? (**top = most potential impact; bottom = least impact**)

- ❑ Scoliosis (spine curvature) or other spine related issues
- ❑ Low bone mineral density or increased risk of fractures
- ❑ Abnormal bone formation (tibial dysplasia/pseudarthrosis, sphenoid wing dysplasia)
- ❑ Pectus Excavatum (Sunken Chest) or Pectus Carinatum (Chest bone sticking out)
- ❑ Short Stature
- ❑ Leg Length Discrepancy

Poll Question #5

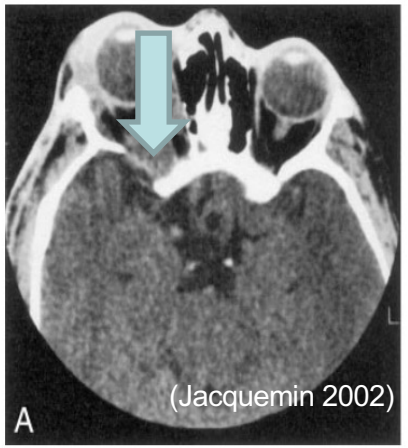
For ALL REiNS Attendees

If the bone-related issue you are most worried about or you feel has the most potential impact for people with NF1 was not listed, please enter it here.

Neurofibromatosis 1 (NF1) & Bone

What do we know?

- Spinal Deformities
  - Scoliosis
  - Dystrophic features (e.g. vertebral scalloping/wedging, dural ectasia)
- Bone Dysplasias (Long bones and sphenoid wing)
- Metabolic Bone Disease; Decreased bone mineral density
- Other Bone-Related Issues:
  - Pectus excavatum/carinatum
  - Non-ossifying fibromas
  - Short stature?



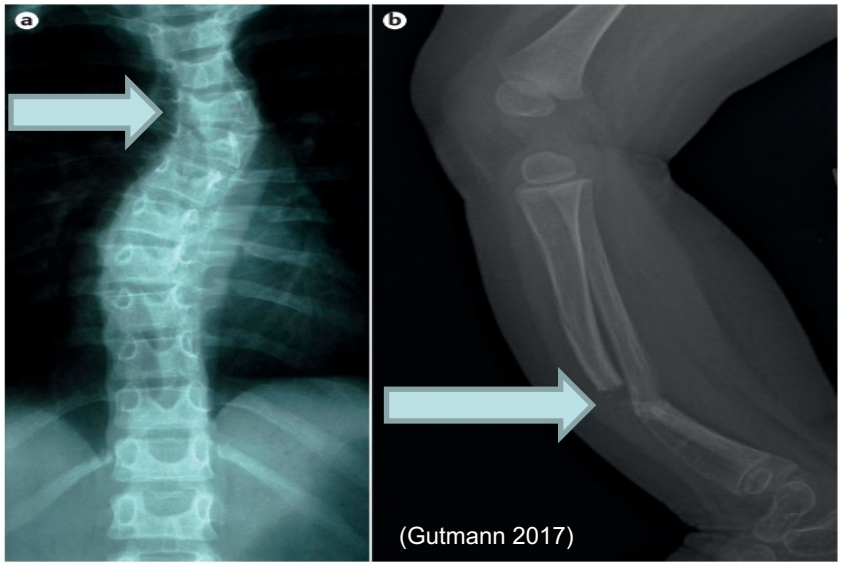
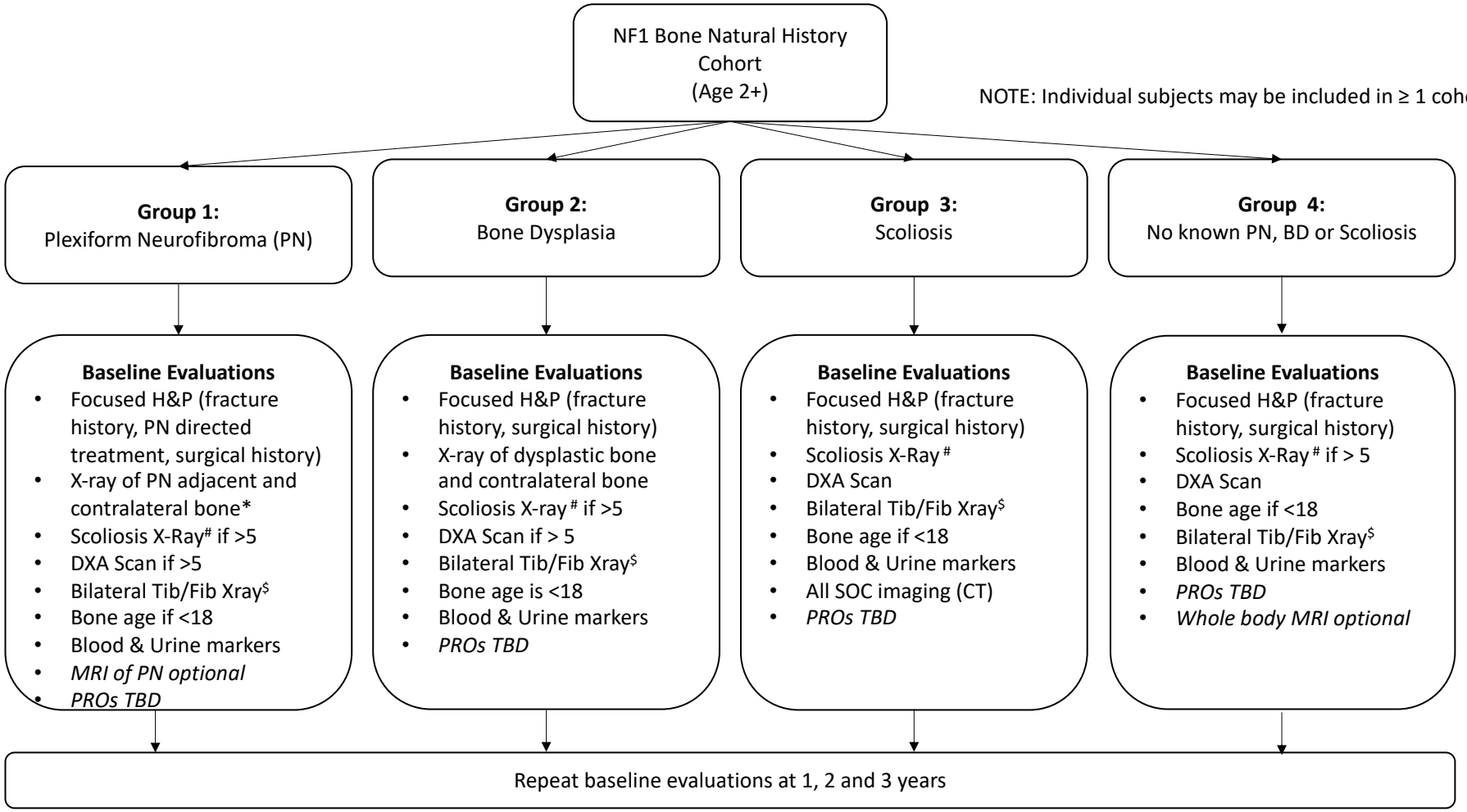


Figure 7 | **Skeletal defects in neurofibromatosis type 1.** Individuals with neurofibromatosis type 1 can present with a range of skeletal defects, including dystrophic scoliosis (part **a**) and tibial dysplasia (part **b**), which can be detected by radiographic imaging.

NF1 Bone: *Some* Unanswered Questions

- Spine Deformities & Scoliosis
  - What causes dystrophic changes in the spine?
  - How do you measure progression of dystrophic changes over time?
  - Is there a way to predict which scoliosis curves will progress from non-dystrophic to dystrophic?
  - What is the association of spinal PN with severity of dystrophic scoliosis?
- Bone Dysplasias:
  - What causes long bone dysplasia and/or sphenoid wing dysplasia?
  - What causes calvarial defects?
  - What causes benign osseus fibromas?
- 'Metabolic' Bone Disease/Low BMD:
  - What causes low BMD in NF1?
  - Is decreased BMD in NF1 associated with increased fracture risk? If so, what degree of low BMD?
  - Does low BMD in NF1 impact quality of life?
  - What predicts which patients with NF1 will have low BMD?
  - Does low BMD in NF1 get worse, stay the same or improve with age?
  - Are standard treatments effective for NF1 related low BMD (e.g. bisphosphonates, vitamin D, calcium)?
- Other:
  - What causes short stature?
  - What is the relationship of bone issues and neurofibromas (spinal or plexiform)?
  - What is the impact of tumor-directed therapy (e.g. MEK inhibitors) on bones in NF1?

…And many MANY more



*Where applicable $at baseline and end of study

EOS imaging maybe utilized if available

Poll Question #6

For Patient Representatives only

If ***distance and cost were not an issue***, would you (or the person in your life with NF1) be willing to participate in annual visits for at least 3 years for a Bone Natural History Study?

- ❑ Yes
- ❑ No - once a year is too often (prefer visits be spread out more)
- ❑ No - once a year is OK BUT three visits are too much
- ❑ No - once a year is too often AND three visits are too much

Poll Question #7 (slide 1 of 2)

For Patient Representatives only

If the study were open at all of the NFCTC sites (marked with green flags on map) would you or the person in your life with NF1 be willing to participate in annual visits for at least 3 years for a Bone Natural History Study?

Poll Question #7 (slide 2 of 2)

For Patient Representatives only

If the study were open at all of the NFCTC sites (marked with green flags on map) would you or the person in your life with NF1 be willing to participate in annual visits for at least 3 years for a Bone Natural History Study?

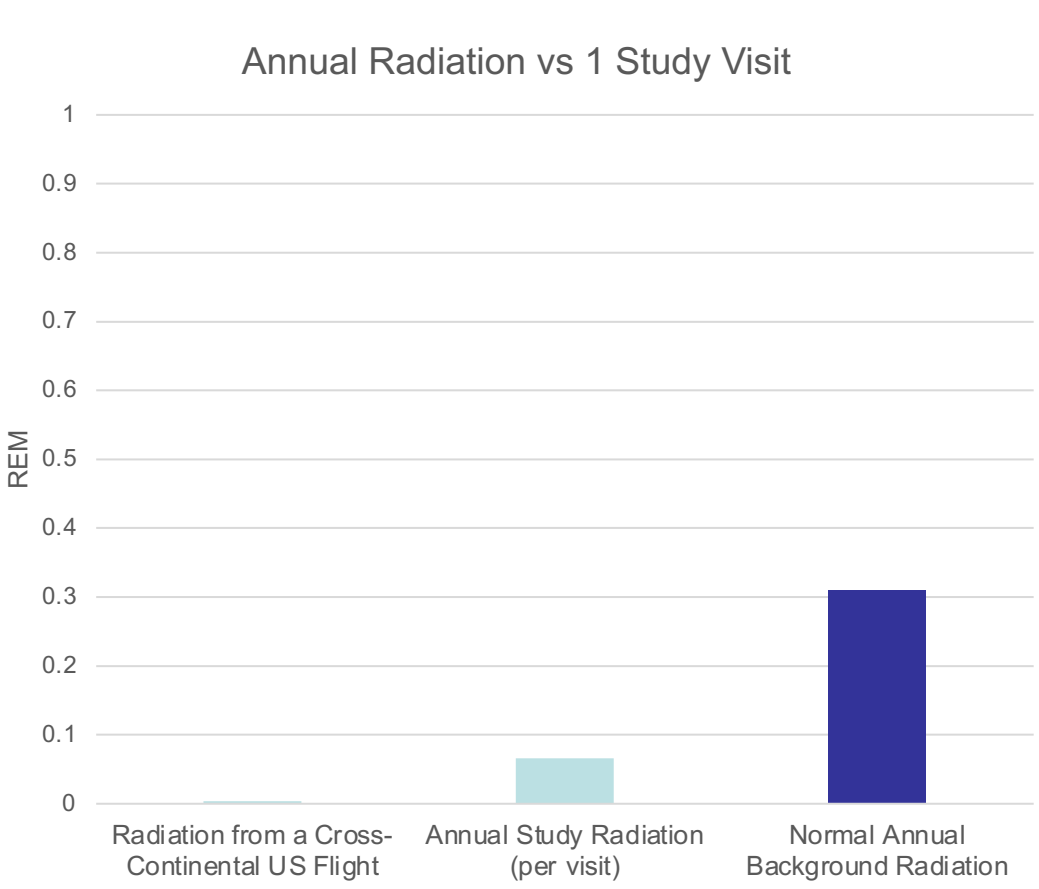
- ❑ Yes
- ❑ No - once a year is too often (prefer visits be spread out more)
- ❑ No - once a year is OK BUT three visits are too much
- ❑ No - once a year is too often AND three visits are too much

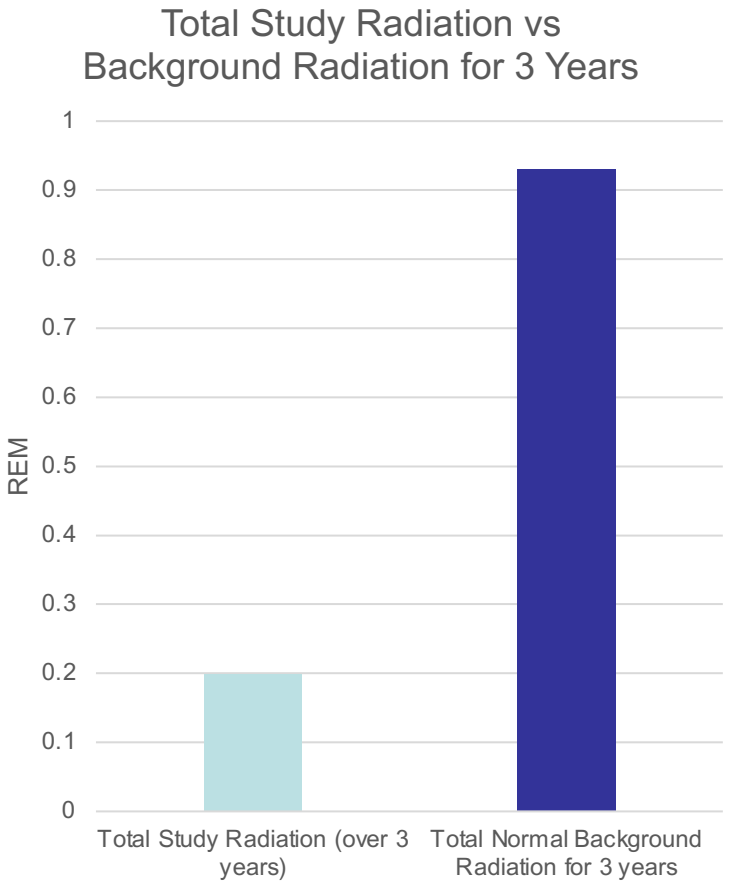
Radiation Exposure

Name of Procedure or Scan:	Number of Procedures in One Year:	Dose for Single Procedure (mrem):
Scoliosis Radiograph	1	0.0220
Radiograph PN affected limb	1	0.0010
Radiograph unaffected limb (contralateral)	1	0.0010
DXA Scan (>5 years old)	1	0.0001
Bone Age (<18 years old)	1	0.0000
Tibias/Fibulas (bilateral)	1	0.0421
	TOTAL Radiation per year	**0.0662**

- Estimated amount from a trans-continental US airplane trip is 0.0035 rem
- Estimated *NORMAL* background radiation per year is 0.3 rem
- Radiation from this study would be 22% (about 1/5) of annual radiation exposure

Radiation Exposure





- Estimated amount from a trans-continental US airplane trip is 0.0035 rem
- Estimated *NORMAL* background radiation per year is 0.3 rem
- Radiation from this study would be 22% (about 1/5) of annual radiation exposure

Poll Question #8

For Patient Representatives only

Would you or the person in your life with NF1 be willing to participate in a bone natural history study with 0.0662 rem of radiation per year (equal to about 1/5 of annual background radiation)?

- ❑ Yes
- ❑ No, this is too much radiation at any time point
- ❑ No, this amount of radiation would be OK once, but not for 3 annual visits
- ❑ I'm not sure

Poll Question #9

For Patient Representatives only

What would be the most helpful thing (or things) the study team could do or provide for participants to increase involvement in this natural history trial?

Objectives

- **Primary Objective**
  - To longitudinally assess the bone health in patients with neurofibromatosis type 1 (NF1)
- **Secondary Objectives**
  - Collect cross sectional and longitudinal bone health data in patients with NF1
  - Describe the impact of PN on local bone mineralization including BMD and cortical width
  - Describe the impact of PN on systemic bone mineralization
  - Understand the natural history of scoliosis progression
  - Understand the fracture incidence in the NF1 population
  - Describe the natural history of bone dysplasia in NF1
  - Understand the impact of bone-related issues on quality of life in NF1

Objectives, continued

- **Exploratory Objectives**
  - To bank blood and tissue samples as a resource for future research
  - Explore the utility of serum inorganic pyrophosphate (PPi) as a measure of bone health
  - Explore the impact of age on bone-health in patients with NF1
  - Explore the impact of MEKi on duration of time required for fracture healing
  - Describe the impact of PN-directed therapies on bone health
  - Explore the relationship between fracture incidence and measures of bone-health including imaging and laboratory markers
  - Explore potential radiographic predictors of fracture risk

Poll Question #10

For Patient Representatives only

Rank the following areas impacted by NF1 bone issues that you think are important to measure using surveys (Patient Reported Outcome measures) (top = most important; bottom = least important)?

- ❑ Appearance
- ❑ Mood
- ❑ Mobility
- ❑ Pain
- ❑ Sleep
- ❑ Daily activities/work/school
- ❑ Need for surgeries/Use of assistive medical devices

Poll Question #11

For ALL REiNS Attendees

Rank the following NF1 bone-related issues that you think are most important to collect information on from people with NF1 using surveys (Patient Reported Outcome measures) in a bone natural history trial (top = most important; bottom = least important)?

- ❑ Appearance
- ❑ Mood
- ❑ Mobility
- ❑ Pain
- ❑ Sleep
- ❑ Daily activities/work/school
- ❑ Need for surgeries/Use of assistive medical devices

Poll Question #12

For Patient Representatives only

How long would you be willing to spend on surveys (Patient Reported Outcome Measures)?

- ❑ None – I would not want to complete any surveys
- ❑ 0-15 minutes
- ❑ 15-30 minutes
- ❑ 30-45 minutes
- ❑ 45-60 minutes
- ❑ I'm happy to spend as long as it might take, even if it is >60 minutes

What is your favorite part (or parts!) of REiNS?

If interested in participating or have other questions or thoughts about the study, please email us at:

Andrea.gross@nih.gov
Laura.Klesse@UTSouthwestern.edu