



# Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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# REiNS Functional Group Update

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Response Evaluation In Neurofibromatosis Schwannomatosis  
INTERNATIONAL COLLABORATION

# Functional Group Update

- Skeletal Manifestations of NF1
  - NF1 Bone Outcome Measurements Landscape
  - Development of Dystrophic Scoliosis Score
  - Ongoing Projects: Scoliosis in MRI vs Radiographs retrospective review
- Gastrointestinal Issues in NF1
- Future Plans for Functional Committee



# NF1 Skeletal Endpoints Landscape

## Manuscripts

- Potential Endpoints for Assessment of Bone Health in Persons with NF1
  - Submitted for REiNS supplement, currently under revision
  - Summarizes possible techniques for evaluating overall bone health in future NF1 trials
  - Includes suggestions for what should be included in a future NF1 Bone Natural History Study

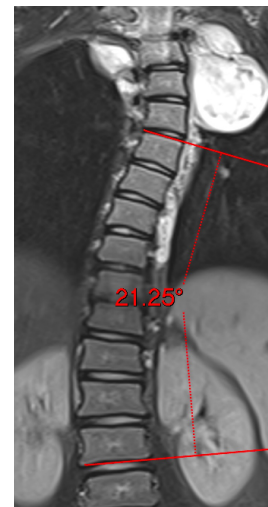
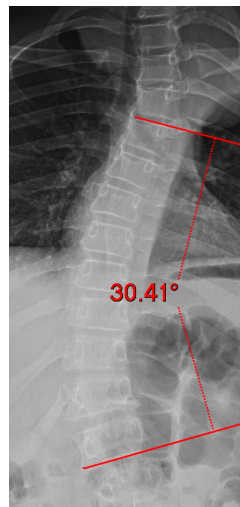


Technique	Possible Endpoint(s)	Advantages
<b>Dual-energy X-ray Absorptiometry (DXA)</b>	<ul style="list-style-type: none"> <li>· Areal Bone Mineral Density (aBMD) (g/cm<sup>2</sup>)</li> <li>· Bone Mineral Content (BMC) (g)</li> <li>· Bone mineral apparent density (BMAD)</li> <li>· Height-adjusted z-scores</li> <li>· Trabecular bone score (TBS)</li> </ul>	<ul style="list-style-type: none"> <li>· Available at most centers</li> <li>· Normal values available for children and adults at multiple body sites (lumbar spine, femoral neck, total hip, whole &amp; sub-total body)</li> </ul>
<b>Quantitative Ultrasound (QUS)</b>	<ul style="list-style-type: none"> <li>· Bone Transmission Time (BTT, <math>\mu</math>s)</li> <li>· Amplitude-dependent speed of sound (AD-SoS, m/s)</li> <li>· Ultrasound Bone Profile Index (UBPI)</li> <li>· Broadband ultrasonic attenuation (BUA)</li> </ul>	<ul style="list-style-type: none"> <li>· No radiation</li> <li>· portability of apparatus</li> <li>· Lower costs</li> <li>· Utilization in infants</li> </ul>
<b>Quantitative Computed Tomography (QCT); Multi-Detector Quantitative Computed Tomography (MDQCT) and Peripheral Quantitative Computed Tomography (pQCT)</b>	<ul style="list-style-type: none"> <li>· Total, trabecular and cortical area (cm<sup>2</sup>)</li> <li>· Total, trabecular and cortical volumetric bone mineral density (vBMD) (g/cm<sup>3</sup>)</li> <li>· Endosteal and periosteal circumference (cm)</li> <li>· Section modulus (mm<sup>3</sup>)</li> <li>· Bone strength index (BSI, mm<sup>3</sup>)</li> <li>· Strength strain Index (SSI)</li> <li>· Finite element analysis (FEA)</li> </ul>	<ul style="list-style-type: none"> <li>· Better ability for the measurement of bone size, geometry and strength with the separation of the bone and muscle compartments</li> <li>· Assessment of volumetric BMD</li> <li>· pQCT with low radiation exposure (&lt; 0.01 mSv<sup>30</sup>)</li> </ul>
<b>Radiographs</b>	<ul style="list-style-type: none"> <li>· Ratio of cortical width to total width</li> <li>· Ratio of cortical area to total cross-sectional area</li> <li>· Cortical Thickness Index (ratio of the outer diaphyseal diameter minus the intramedullary canal inner diameter to the diaphyseal diameter)</li> </ul>	<ul style="list-style-type: none"> <li>· Minimal radiation with limited inter- and intra-institutional variability</li> </ul>
<b>Magnetic Resonance Imaging Techniques</b>	<ul style="list-style-type: none"> <li>· High Resolution Trabecular imaging:</li> <li>· Ultrashort echo time imaging</li> <li>· Quantitative susceptibility mapping (QSM)</li> <li>· Magnetic resonance spectroscopy (MRS)</li> </ul>	<ul style="list-style-type: none"> <li>· No ionizing radiation</li> <li>· May be able to use sequences already obtained for evaluation of NF1 related tumors</li> </ul>
<b>Markers of bone formation</b>	<ul style="list-style-type: none"> <li>· N-propeptide of type 1 collagen (P1NP)</li> <li>· Alkaline phosphatase (ALP)</li> <li>· Bone-specific alkaline phosphatase (bone ALP)</li> <li>· Osteocalcin (OC)</li> </ul>	
<b>Markers of bone resorption</b>	<ul style="list-style-type: none"> <li>· C-terminal cross-linking Telopeptide of type I collagen (CTX)</li> <li>· N-terminal telopeptide of type 1 collagen (NTX)</li> <li>· Hydroxyproline</li> <li>· Urinary Pyridinium cross-links</li> <li>· Urinary calcium: creatinine ratio</li> </ul>	
<b>Markers of General Calcium-Phosphorous Metabolism</b>	<ul style="list-style-type: none"> <li>· Total calcium</li> <li>· Ionized calcium</li> <li>· Phosphorus</li> <li>· Magnesium</li> <li>· Parathyroid hormone (PTH)</li> <li>· 25-OH vitamin D (25OHD)</li> </ul>	

# NF1 and Scoliosis

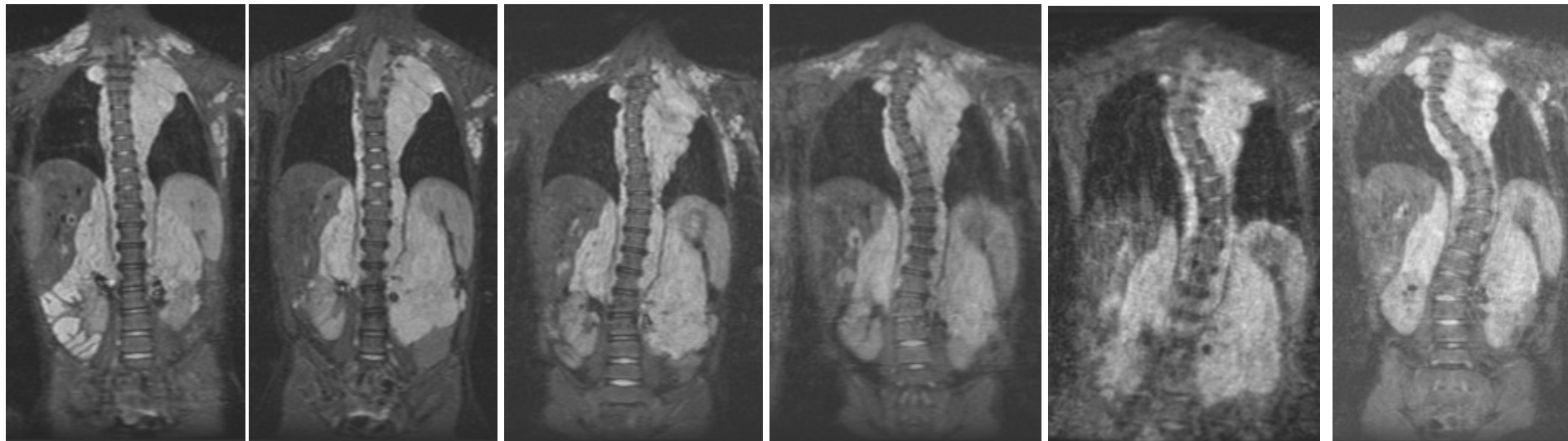
- **Ongoing:** Retrospective review of scoliosis radiographs vs MRIs

The degree of spinal curvature and changes in degree of curvature visualized on MRI can be directly correlated with the degree of spinal curvature seen in standard standing scoliosis radiographs (Cobb angle) obtained at the same time point



# NF1 and Scoliosis

- **Next Project:** Developing Dystrophic Scoliosis score to be able to track changes over time
- **Challenge:** How to score evolution over time beyond the Cobb angle



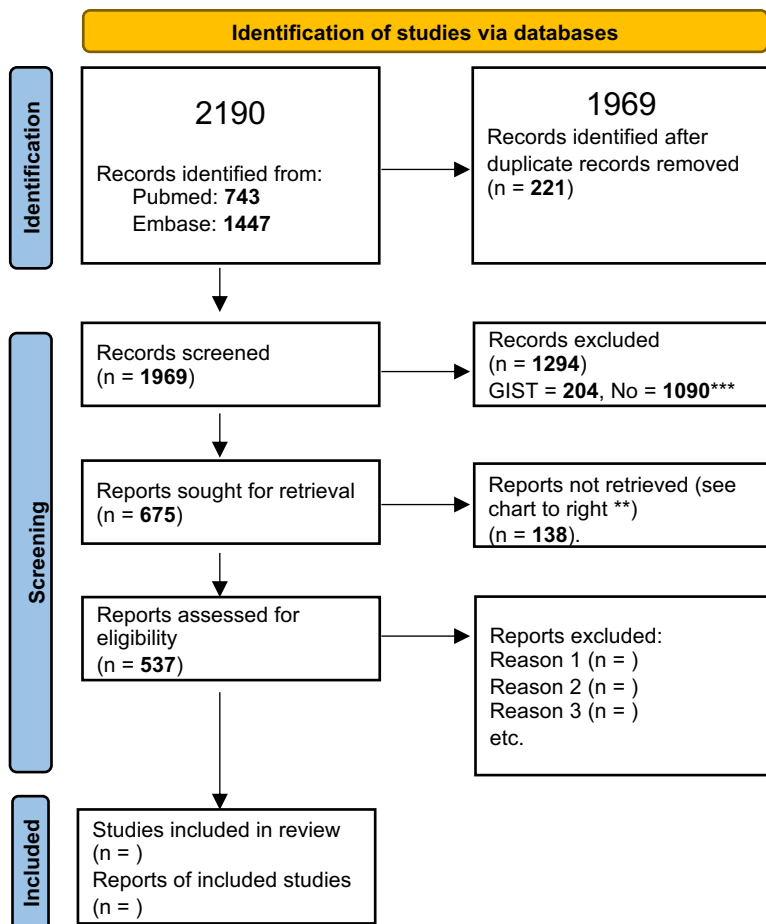
# NF1 and Gastrointestinal Issues AKA the “*Not Just GIST*” Project

- Project lead: **Andres Lessing**
- Currently performing a systematic review to assess the incidence of reported GI-related issues in NF1
- Considerations for developing survey for people with NF1 to get a sense of the prevalence of these issues





# Current PRISMA Diagram for NF1 and GI Systematic Review Analysis



## Inclusion\Exclusion Criteria:

- Must include NF1
- Exclude animal models
- Exclude if exclusively GIST
- Exclude when GI symptom is secondary to a non-GI cause
- Exclude somatic mutations
- Excluding if GI symptom is due to treatment
- Including oral cavity
- Including if GIST if something else GI related
- Include any tumor on GI track regardless of origin (other than GIST)
- No bladder unless directly impacting GI

\*\* Manuscript we could not retrieve

YEAR	Number of Articles that Could Not be Retrieved
<1980	47
1980-1989	31
1990-1999	27
2000-2009	11
2010-2019	15
2020	2
2021	2
2222	3

*Slide courtesy of Andres Lessing*

# Functional Committee Future Plans

- Completing MRI vs Radiograph study
- Developing Dystrophic Scoliosis Score
- Completing GI Systematic Review and potentially developing a survey for
- Revisiting/revising recommendations from previous publications
- Others??



# Thank you!!

- REiNS Functional Committee Members:
  - Andres Lessing
  - Bev Oberlander
  - Brigitte Widemann
  - Brittany Simpson
  - David Stevenson
  - David Viskochil
  - Gareth Evans
  - Heather Thompson
  - Herb Sarnoff
  - Jonathan Rios
  - Kelly Carpenter
  - Laura Klesse
  - Michael Fisher
  - Miranda McManus
  - Nicole Ullrich
  - Noelle Larson
  - Renie Moss
  - Scott Plotkin
  - Vandana Akshintala
  - ...and more!

