Neurofibromatosis Type 1: Clinical features and management

Nicole Ullrich, MD, PhD, MMsci

Multidisciplinary Neurofibromatosis Program and
Department of Neurology, Boston Children's Hospital
Pediatric Brain Tumor Program, Dana-Farber Cancer Institute

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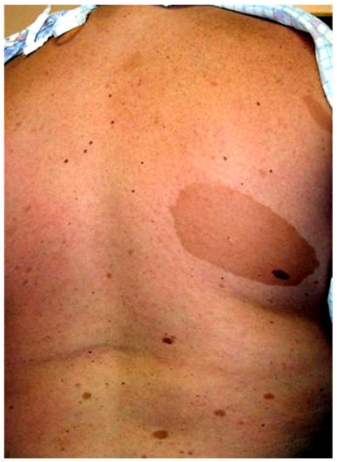
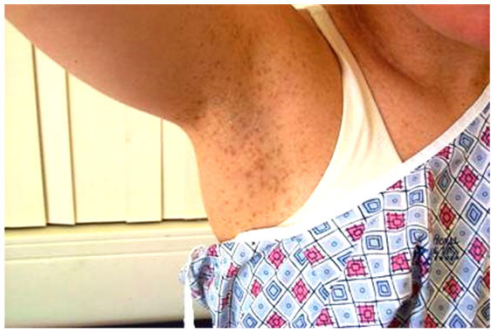
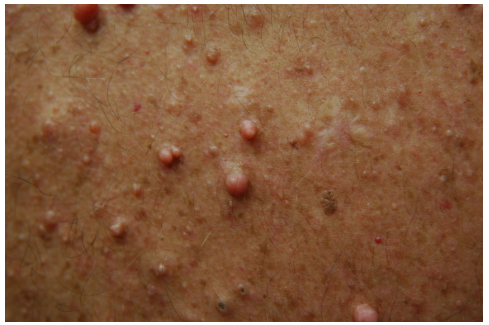
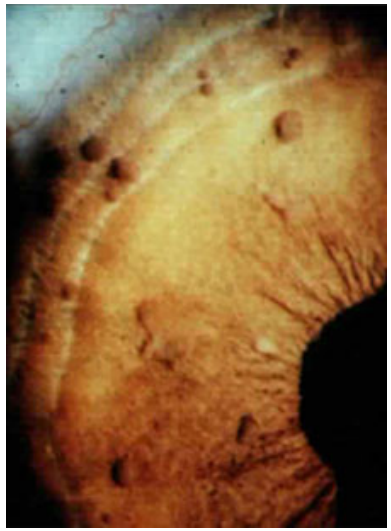
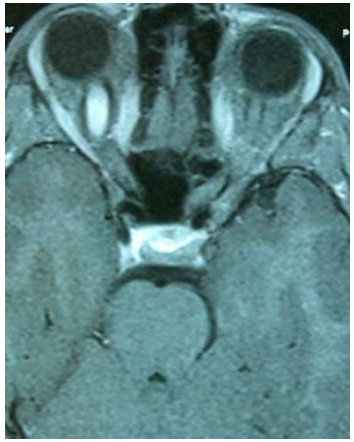
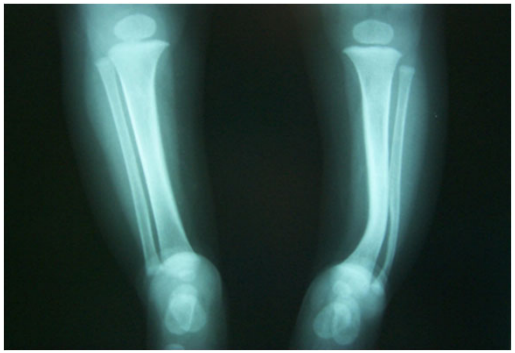
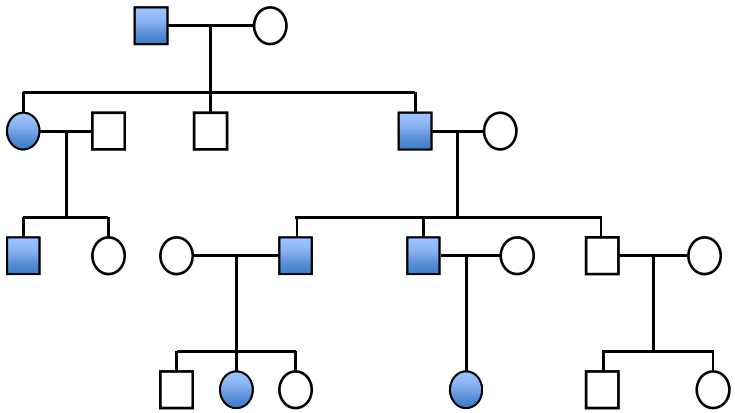
Neurofibromatosis 1 (von Recklinghausen's Disease)

- Autosomal dominant
- Diverse clinical manifestations
- Estimated incidence: 1/3000-1/4000
  - More common than CF, Huntington's, Muscular Dystrophy and Tay Sachs combined
- NF is worldwide in distribution and affects both sexes equally; no particular racial, geographic or ethnic distribution
- 100% penetrance; variable expression
- Mutation rate for the NF1 gene is among highest known for any gene in humans

en.wikipedia.org/wiki/Friedrich_Daniel_von_Recklinghausen

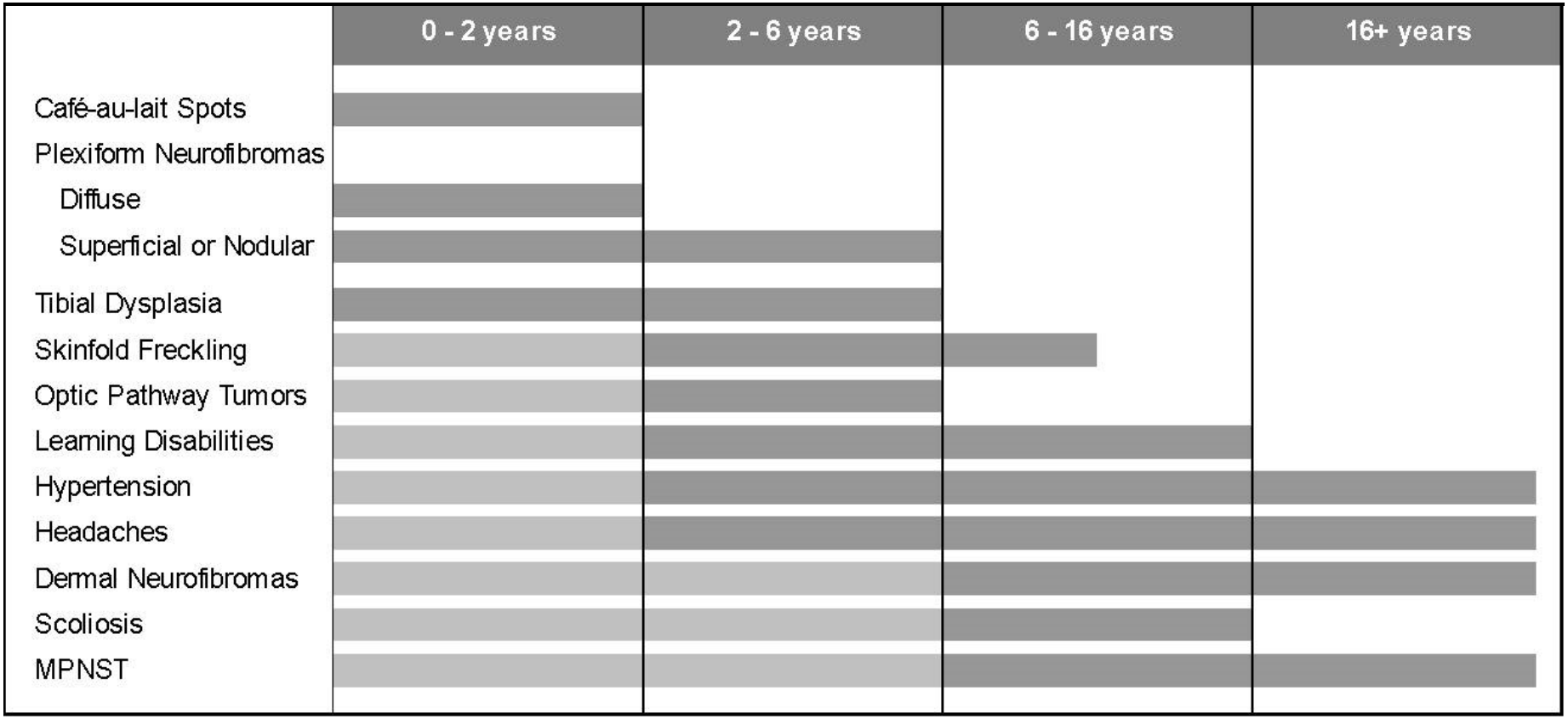
NF1 Diagnostic Criteria

Clinical manifestations

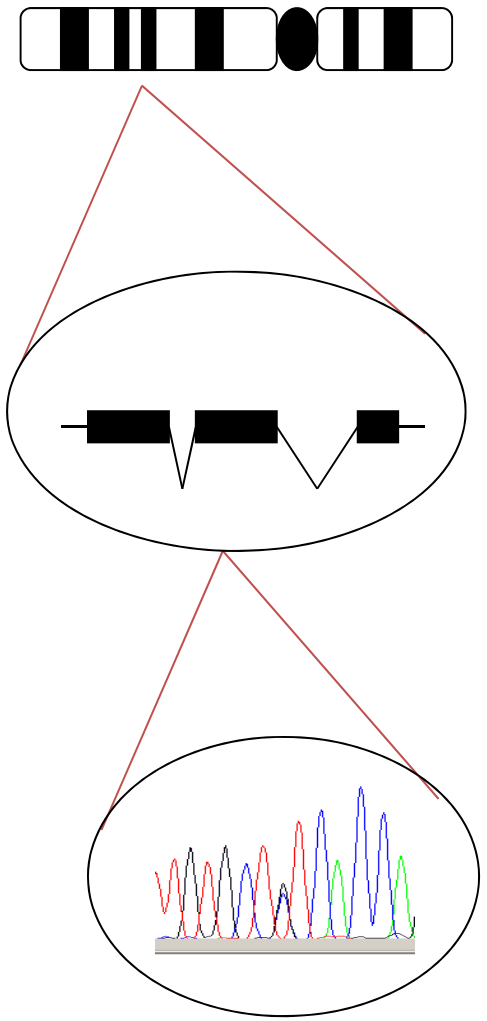
- Skin
  - Café au lait macules
  - Intertriginous freckling
  - Neurofibromas
  - Plexiform neurofibromas ~25%
- Ocular
  - Lisch nodules
  - Optic gliomas ~15-20%
- Skeletal
  - Scoliosis 12-20%
  - Vertebral dysplasia
  - Tibial or ulnar pseudoarthrosis
- Other
  - Vasculopathy (renal artery stenosis, coarctation, moyamoya)
  - Hypertension
  - Intracranial tumors 1-2%
  - MPNST (10%)
  - Macrocephaly
  - Short stature 25-35%
  - Learning disability (60%)
  - ADHD (50%)
  - Headache (20-40%)
  - Hydrocephalus 2%

Timeline of NF1 clinical features



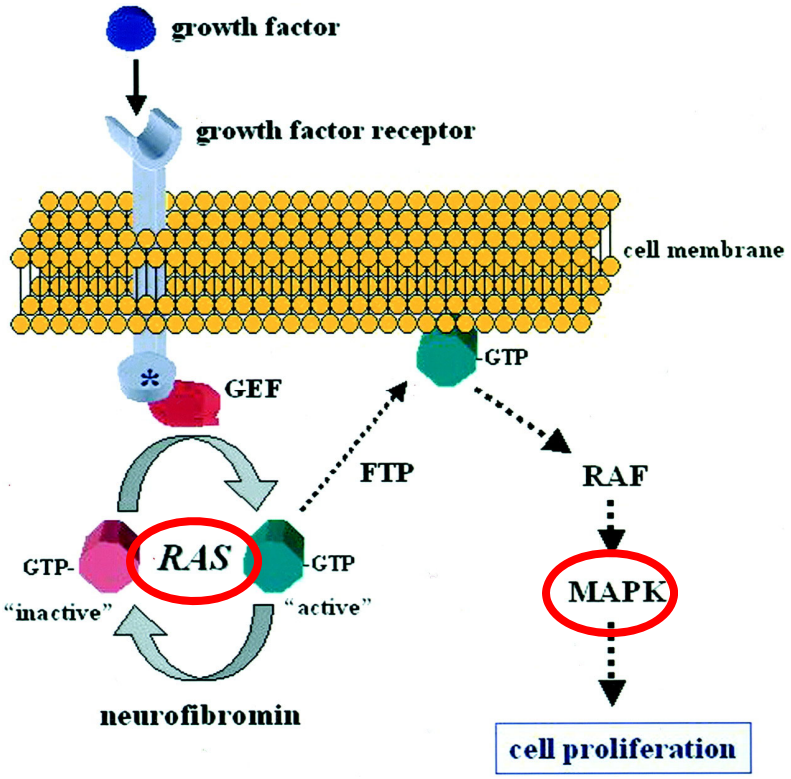
NF1 is caused by a functional loss of the *NF1* gene

- *NF1* is the only associated gene
  - 50% hereditary/50% sporadic
  - > 1000 different mutations (5% false negative rate)
- Each child of an affected parent has a 50% chance of inheriting the mutated gene
- Manifestations can vary in the same family
- Of the recurrent changes, none accounts for a large proportion of cases
- Most genetic changes causing NF result in a shortened protein (80%)
- No clear genotype-phenotype correlations exist for most patients
  - Except large NF1 gene deletions (5%, lots of dermal neurofibromas, developmental delay)
- Useful for: Confirmatory diagnostic testing and prenatal diagnosis



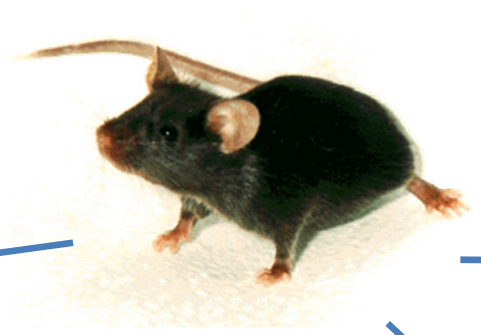
Neurofibromin: protein formed from NF1 gene

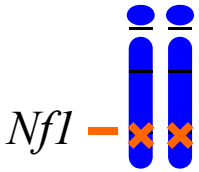
- Contains a GTP-activating protein that controls **Ras**
- **Ras** proteins – important for cell-cell signaling
- **MAPK/MEK** pathway also crucial
- Decreased levels of **neurofibromin** have been associated with a <u>continually activated ras-GTP</u> status



Packer, R. J. et al. Neurology 2002;58:1461-1470

Drug testing: Mouse models of NF1





Mouse Chromosome 17

LD/ADD

JMML

Neurofibroma

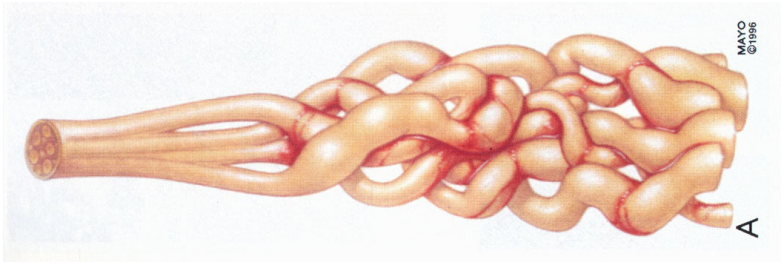
(dermal and plexiform)

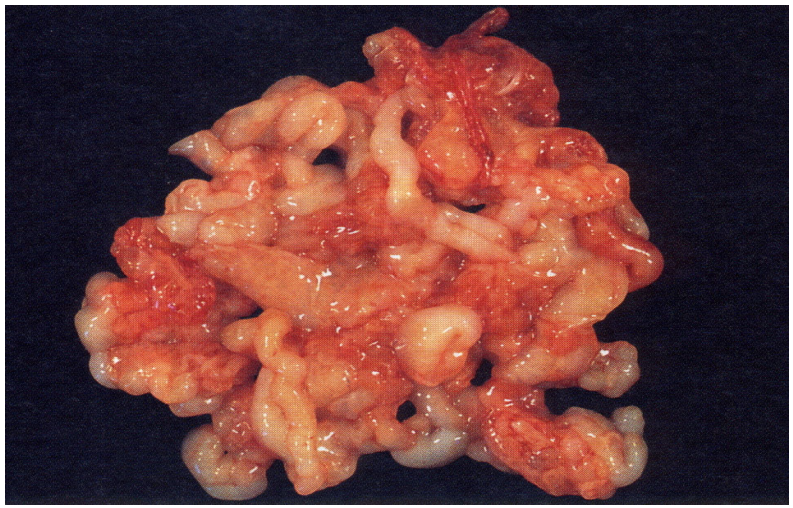
MPNST

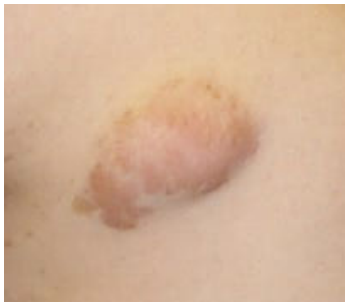
Optic Glioma

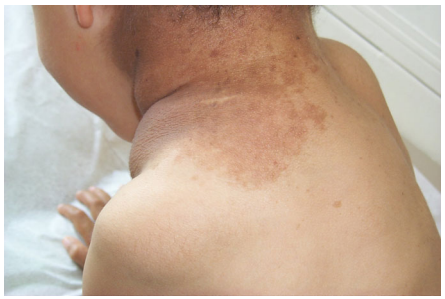
Plexiform Neurofibromas

- "Benign" nerve sheath tumors
- ~20-44% of NF1 patients
- Involve multiple nerves/fasicles; expanded by tumor cells, collagen
- Can grow to large size/disfigure
- **Associated skin and soft tissue hypertrophy**
- Impinge on normal structures
- Surgery difficult
    - 50% regrowth at original site
- Risk of progression high in early childhood and puberty
- Malignant transformation can occur – 10% lifetime risk of MPNST



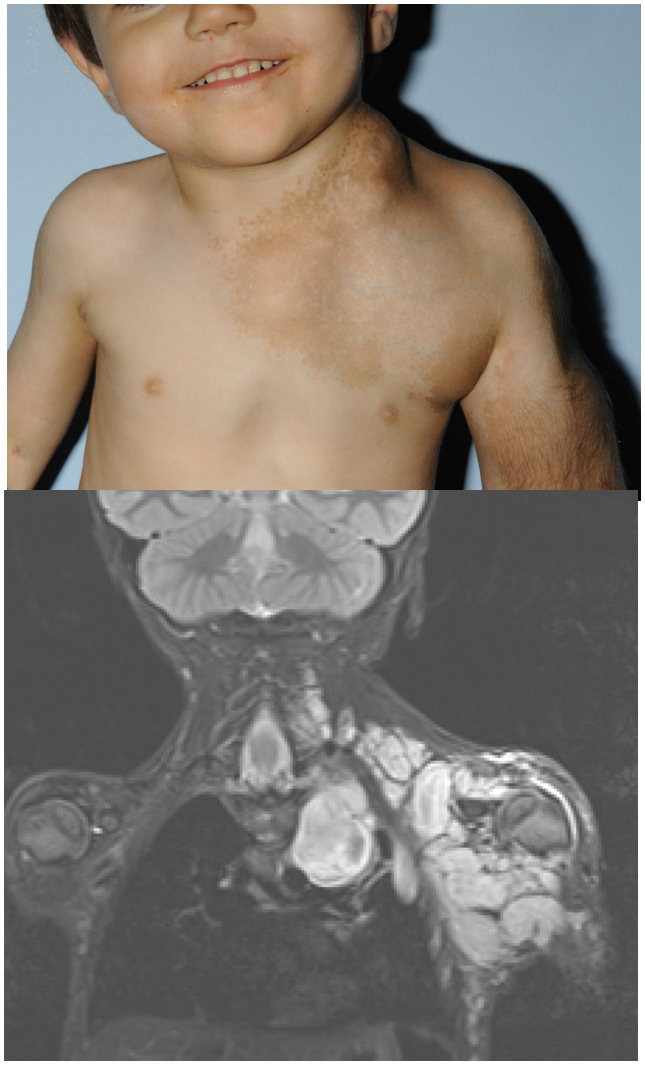




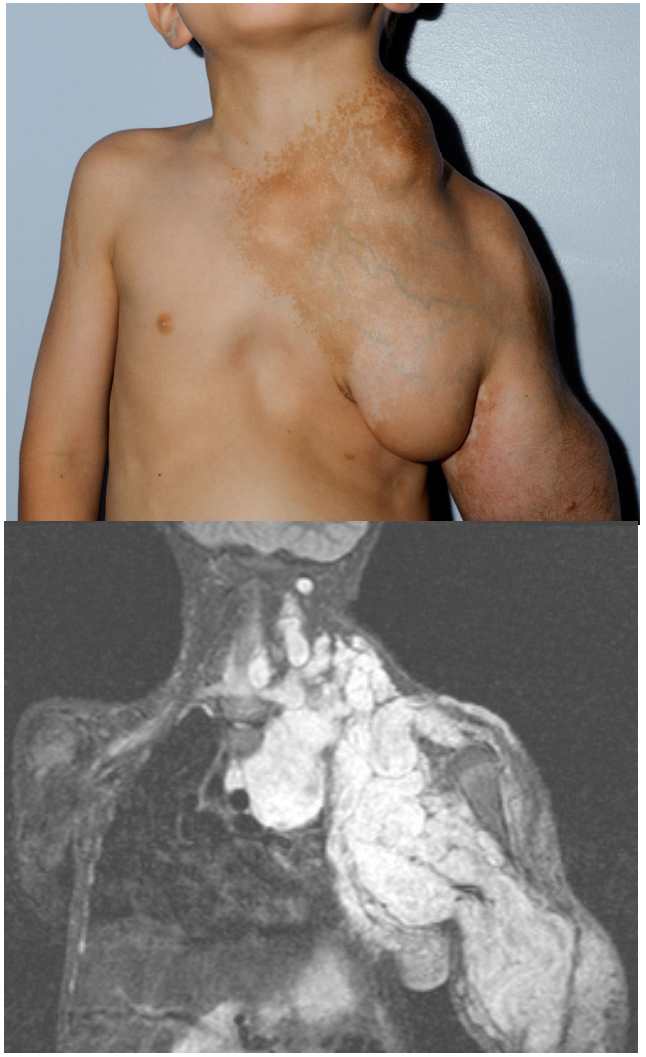


Plexiform Neurofibromas: Challenges

October 2008



October 2011



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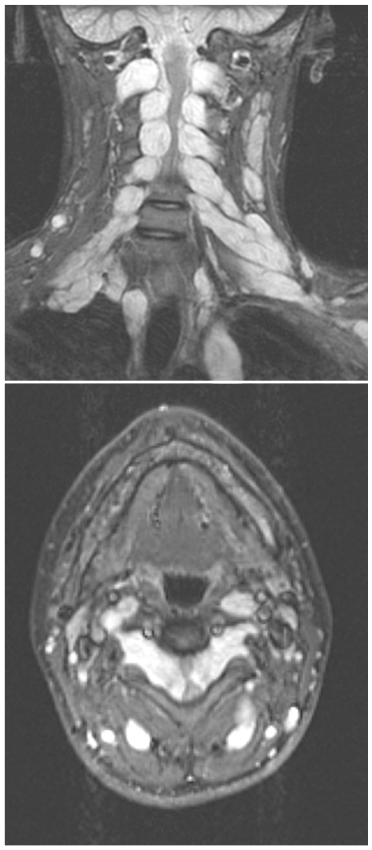
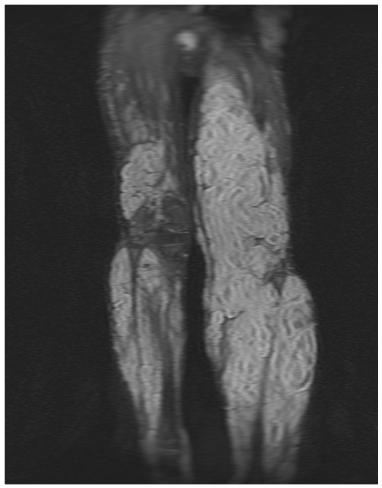
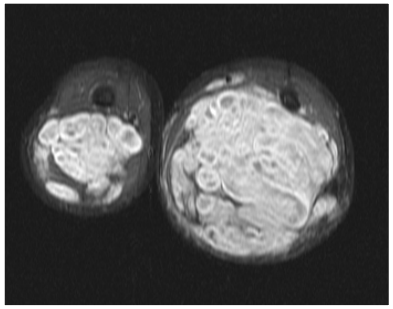
Plexiform Neurofibromas MRI

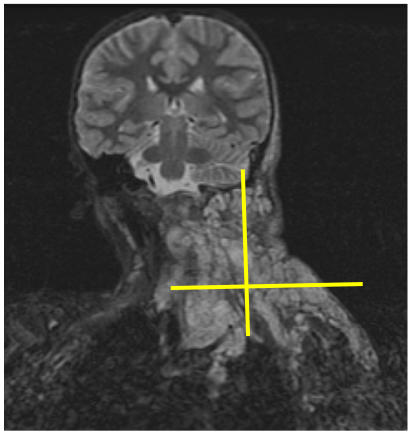
Cord compression

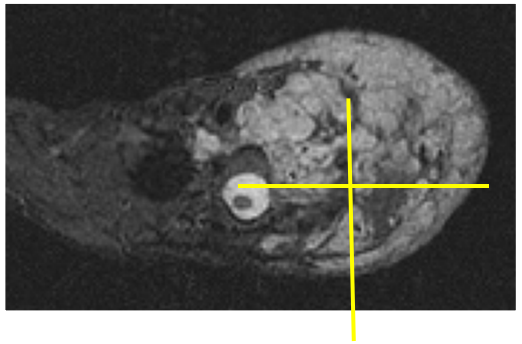


Pain, disfigurement, dysfunction









- **Difficulty measuring change in PN size (complexity, slow growth)**
- **Standard measurements for other tumors do not work**

MPNST

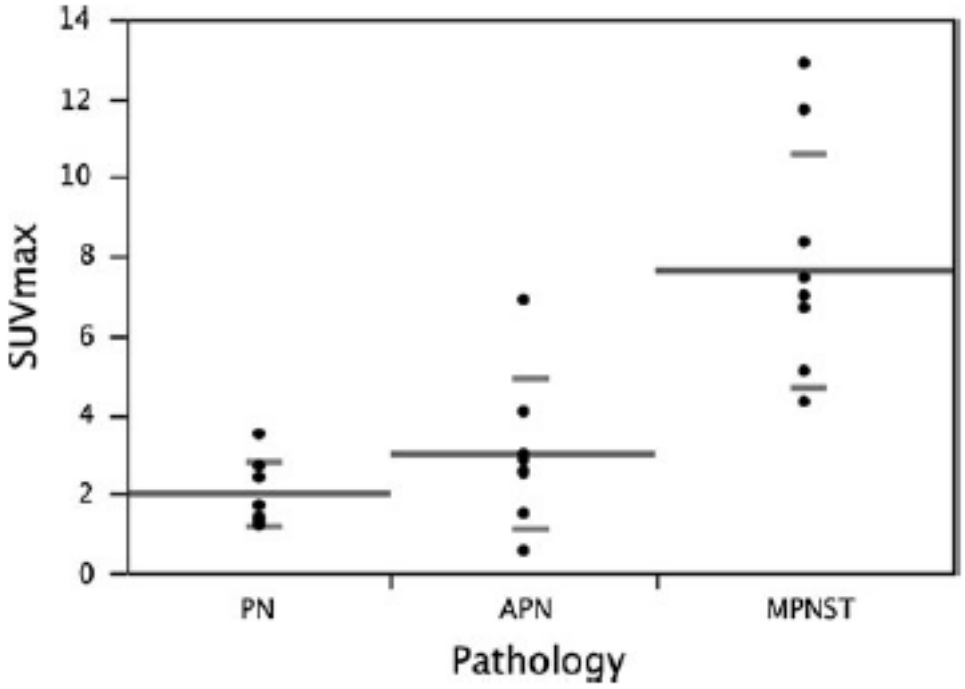
- MPNSTs are soft tissue sarcomas
  - Nerve sheath differentiation
  - High risk of local recurrence/hematogenous metastasis.
  - Account for 10% of all soft tissue sarcomas, and half arise in patients with NF1
- Lifetime risk of developing a MPNST in NF1 is 8-13%
- Majority arise in a previously clinically detectable plexiform neurofibroma, but they may develop in absence of known PN
  - Concerning features: Pain, rapid growth, change in consistency
- Early diagnosis of MPNSTs is crucial, as only complete surgical resection has been shown to be curative
  - Diagnosis is often difficult to establish, because clinical indicators of malignancy (mass and pain) may also be features of benign plexiform neurofibromas

J Neurooncol (2012) 108:469–475
DOI 10.1007/s11060-012-0840-5

CLINICAL STUDY

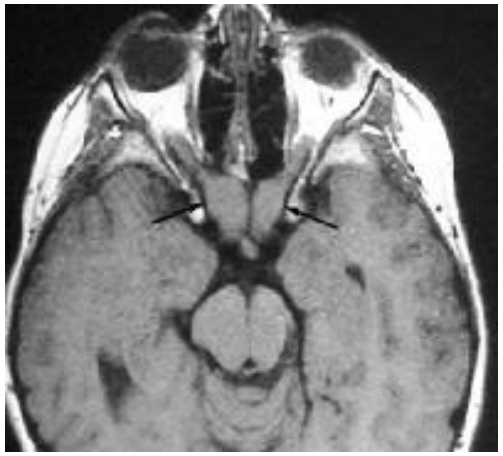
[18F]-Fluorodeoxyglucose positron emission tomography in children with neurofibromatosis type 1 and plexiform neurofibromas: correlation with malignant transformation

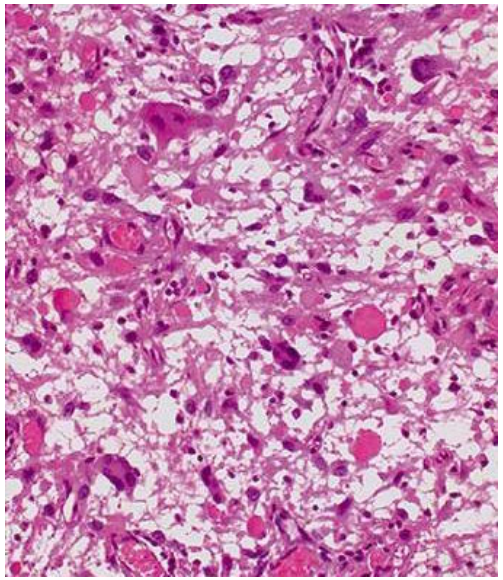
L. L. Tsai · L. Drubach · F. Fahey · M. Irons · S. Voss · N. J. Ullrich



Optic pathway gliomas

- Approximately 15-20% of NF1 patients
- Typically slow growing, most WHO grade 1
- Mainly in children
- Most do not require treatment (3-5%)
- Peak age 2-6 years (mean ~4.2yr)
- At Boston Children's Hospital routine MRI is not performed
  - NIH Optic Pathway Glioma Task force found that it did not affect outcome
  - Many of the tumors are asymptomatic
  - No treatment would occur if there are no symptoms – Observation alone
- How to determine if someone needs to begin treatment? → Change on MRI versus vision change?



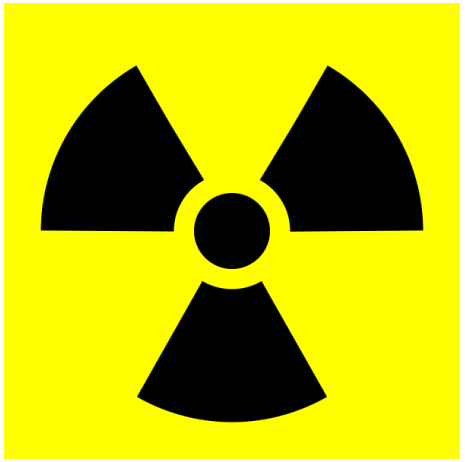


Why not take it out??
Surgery for optic pathway gliomas

- Tumor location often precludes surgery
- Not typically pursued because of other risks
  - Compromise in vision, endocrine changes, risk of stroke
- Indications:
  - Biopsy – if diagnosis unclear
  - Advanced degree of proptosis with poor vision
  - Removal of intraorbital optic nerve
    - Cosmetic or to treat corneal exposure
  - Unilateral tumor with blindness in that eye and impending chiasmal involvement
  - If there is hydrocephalus

Radiation for optic glioma → why not?

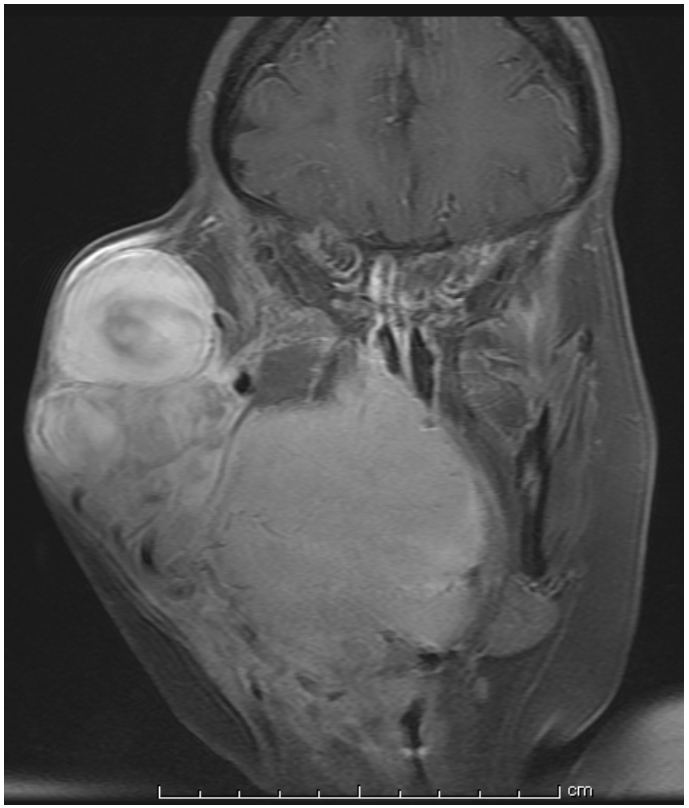
- At least 7 studies 1980s-1990s with follow-up 6-10 years
  - 10 year progression free survival 65-90%
  - Improvement in vision in 9-57%



- <u>Risks/significant toxicities:</u>
  - Secondary tumor formation
  - Neurocognitive deficits
    - Children with NF1 probably more sensitive/susceptible
  - Endocrine/hormonal dysfunction
  - Vasculopathy/moyamoya

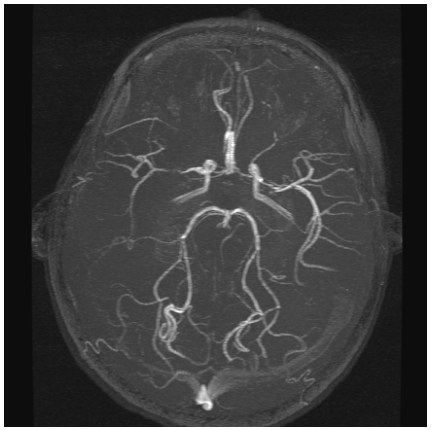
Secondary tumor formation after radiation

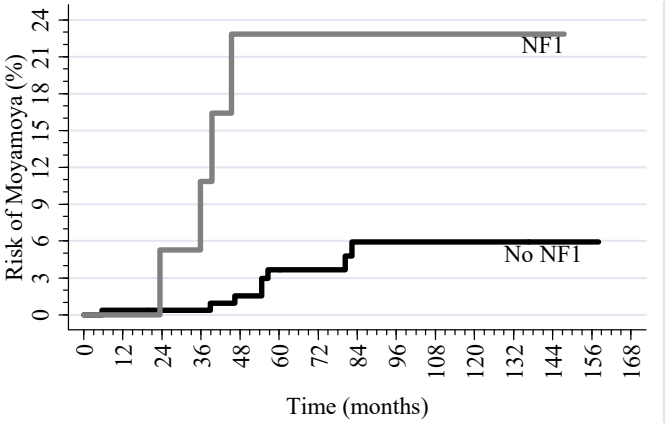
- Risk of RT-induced secondary tumors in persons with NF1 has been largely overlooked
- Sharif et al, J Clin Oncol 2006
  - Secondary tumors formed in 17 of 58 patients treated for an OPG
  - Increased risk of new gliomas in NF1 patients who were irradiated for optic glioma
  - 3-fold increase of malignant tumor/MPNST in RT field compared to patients who did not receive RT

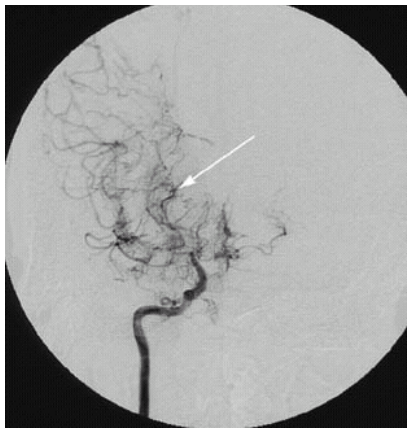


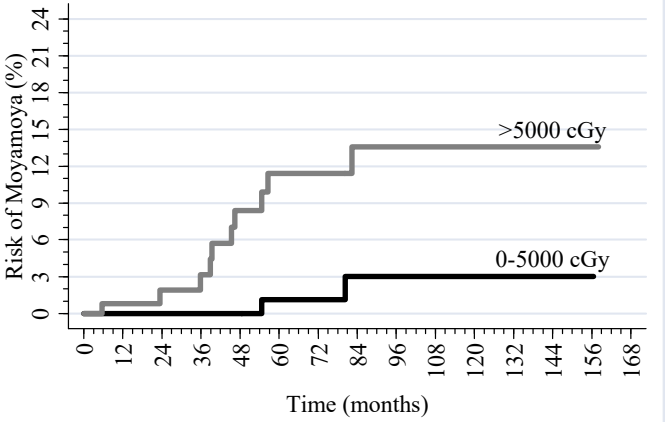
Radiation-induced vasculopathy

- Children with NF1 who receive radiation are at increased risk for moyamoya, more rapidly and at lower doses than children without NF1



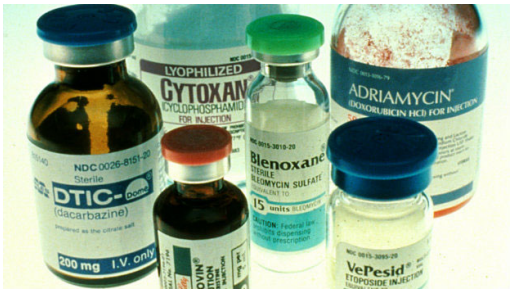




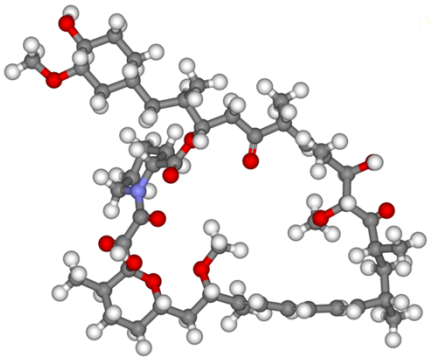


Ullrich et al, Neurology 2007; 68:932

Chemotherapy first



- Attempt to delay or eliminate need for radiation
- Front line therapy: Vincristine/carboplatin
  - Best progression-free survival
- Concerns with other regimens
  - Leukemia risk in patients with NF1 treated with alkylators
  - High frequency hearing loss
- There is no standard second-line therapy
  - Targeted treatments now available



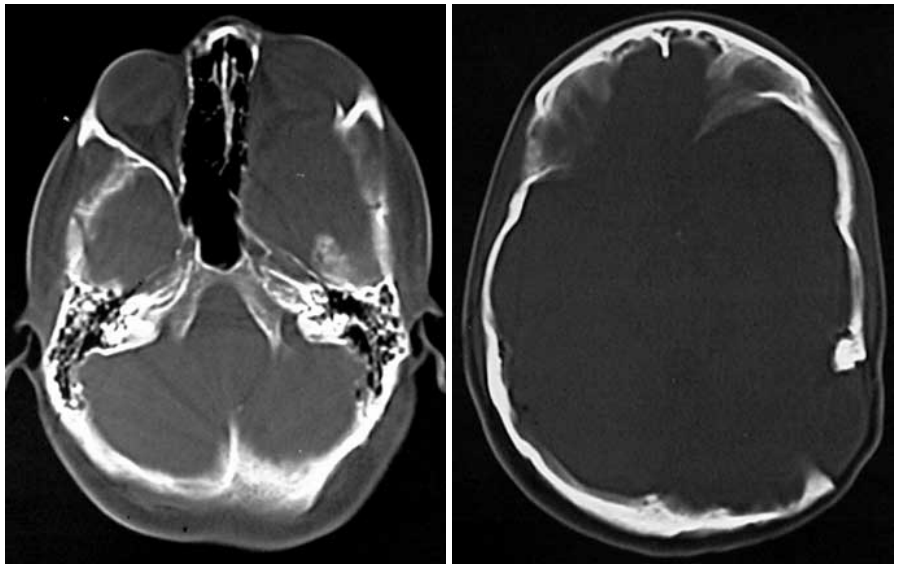
Learning disabilities in NF1

- Complex deficits in learning and memory are frequent and occur in 35-65% of children with NF1 (vs 5-17.5% in general population
- Common features are visual-spatial deficits and difficulties with complex motor tasks
- Slight decrease in IQ compared to siblings
- Impairments in written language, reading accuracy and comprehension, spelling, and mathematics also frequent
- Nearly half of all individuals with NF1 meet the clinical criteria for ADD
- Currently testing lovastatin, an HMG-CoA reductase inhibitor

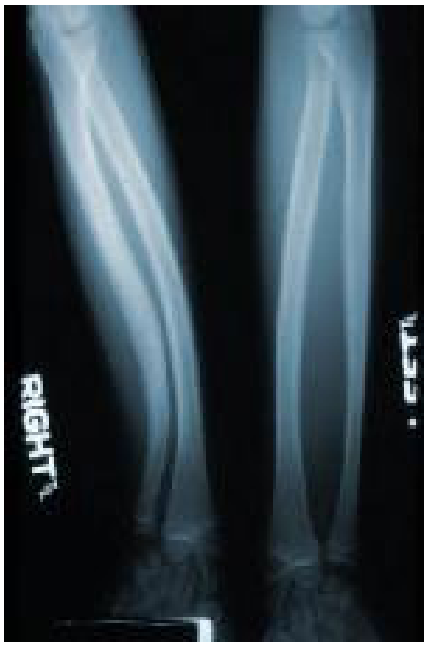
** <u>Cognitive and behavioral issues are NOT progressive – issues change as demands change</u>

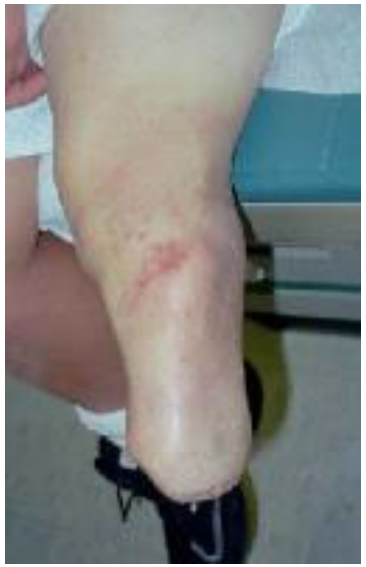
Non-scoliosis, NF1-associated Bone Lesions

- Dysplasia or absence of sphenoid wing



- Thinned cortical bone
- Pseudarthrosis



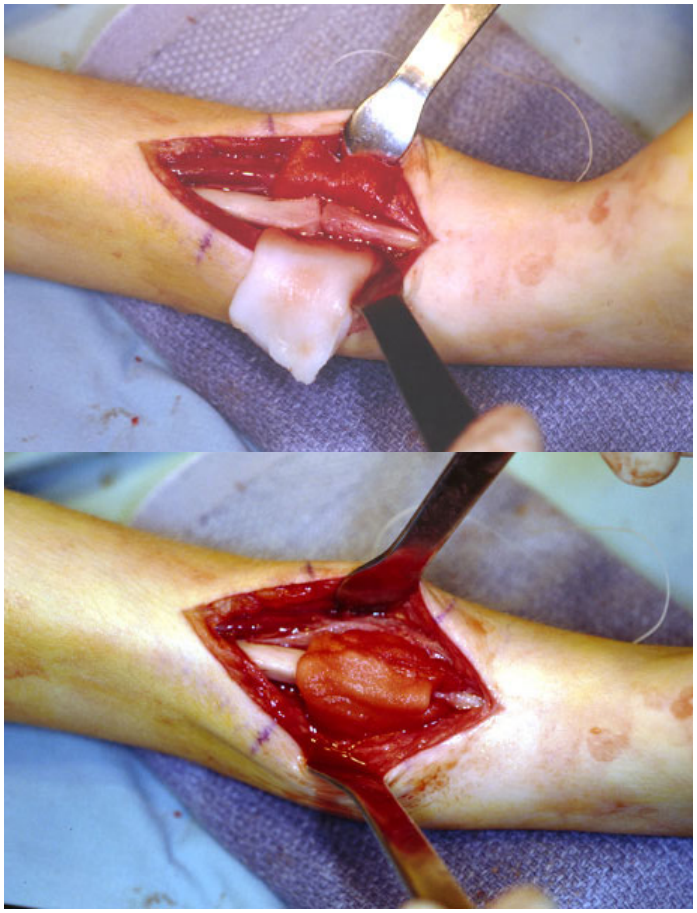


Bone healing in tibial pseudarthrosis

- Patients with tibial dysplasia are prone to fracture with poor healing
  - Up to 50% will refracture after initial surgery
- Bone morphogenic proteins come from the bone matrix
  - When applied to bone at the time of surgery, BMP's induce stem cells to infiltrate the fracture zone to form new bone
- Recombinant human bone morphogenetic protein-2 (rhBMP-2), as a collagen sponge device marketed as INFUSE , is currently approved by the FDA for use in adults for lumbar spine fusion and open tibial fractures
- In pilot studies, INFUSE improves the integrity of tibial bone union in children with NF1, and it was not associated with adverse events or long-term safety issues when applied locally to the osteotomy site

Primary Objectives

- To determine if rhBMP-2 applied locally at the time of surgical repair for fracture of dysplastic tibia in individuals with NF1:
  - Improves bone healing in NF1-related TD based on radiographic evidence of cortical bone union and callus formation.
  - Results in objective radiographic union sooner than historical controls treated by the same surgical procedure without use of rhBMP-2



BMP-soaked collagen sponge is placed around bone junction at the osteotomy site after bone graft

Thanks

- Our patients and families, without whom none of this work and progress would be possible
- Multidisciplinary NF program: Drs. David Miller, Mayra Martinez Ojeda, Gena Heidary, Caroline McGowan
- Dr. Mark Kieran, Christopher Weldon, Carlos Rodriguez-Galindo and the NeuroOncology and Solid Tumor Groups at DFCI
- Dr. Scott Plotkin and MGH collaborators
- Children's Tumor Foundation
- NF, Northeast