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Identifying Clinical, Genetic, and Radiologic Features Associated with Increased Risk for MPNST

Strategies to prevent MPNST

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JOHNS HOPKINS MEDICINE

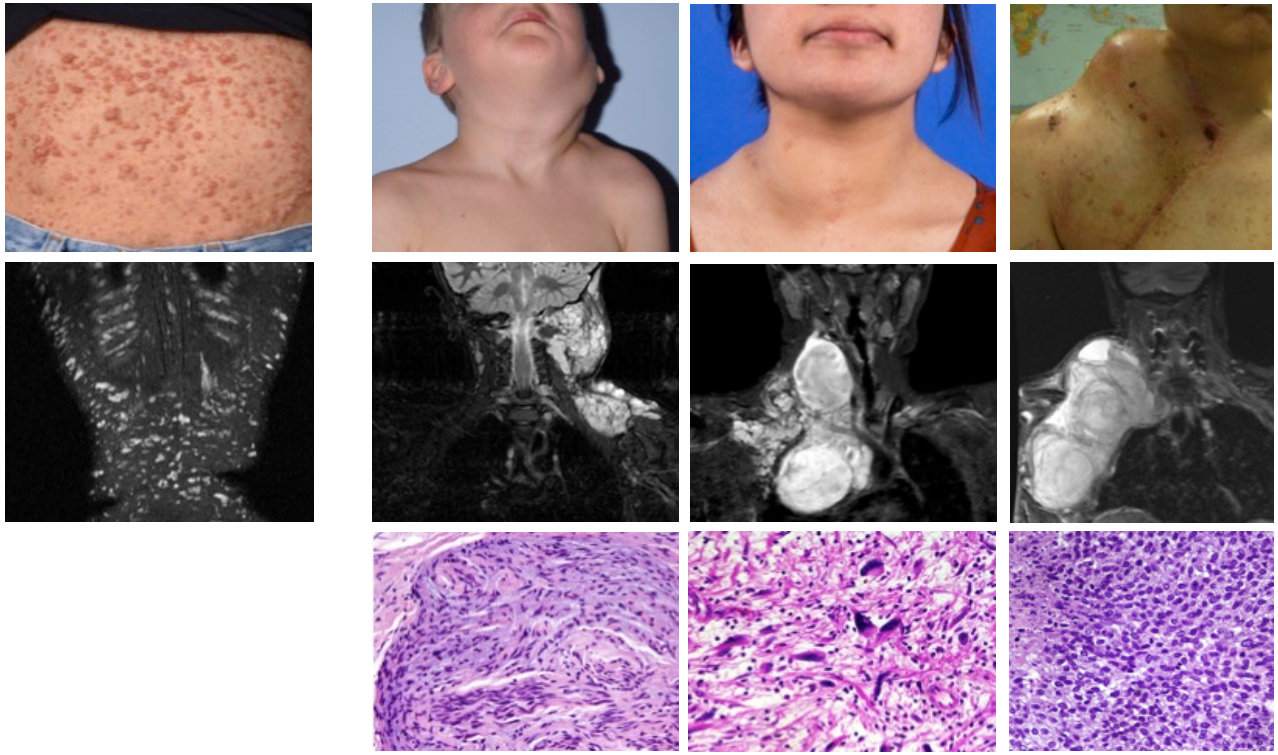
NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

REiNS
Response Evaluation In Neurofibromatosis & Schwannomatosis

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

NF1 Peripheral Nerve Sheath Tumors

Cutaneous ≥ 95%	Plexiform 25-40%	Atypical Unknown ?	MPNST 15.8%



Appearance, pruritus

Biallelic loss of *NF1*

Appearance, pain, function loss ➔ Malignant transformation

Biallelic loss of *NF1* + loss of *CDKN2A/B* + loss of PRC2, p53, (and others)

FDA Approval of Selumetinib (Koselugo™) – April 2020

FDA approves selumetinib for neurofibromatosis type 1 with symptomatic, inoperable plexiform neurofibromas

---------- INDICATIONS AND USAGE ----------

KOSELUGO is a kinase inhibitor indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). (1)

On 31 July 2018, orphan designation (EU/3/18/2050) was granted by the European Commission to AstraZeneca AB, Sweden, for selumetinib for the treatment of neurofibromatosis type 1.

Malignant Peripheral Nerve Sheath Tumor (MPNST)

- Aggressive soft tissue sarcoma (STS)
- 4% of all STS, 50% in neurofibromatosis type 1 (NF1)
- Lifetime incidence of MPNST in NF1 15.8%
- Risk factors:
  - Whole gene deletion, prior radiation therapy, ANF, large PN tumor burden
- Development in preexisting PN and ANF in NF1
  - LOF somatic alterations in PRC2 core components: *EED* and *SUZ12*
    - 92% of Sporadic MPNSTs
    - 70% NF1-associated MPNSTs
    - 90% Radiotherapy-associated MPNSTs
- Clinical signs and symptoms of PN and MPNST overlap
- Complete surgical resection with negative margins required for cure
- Response to standard chemotherapy in NF1: 8-30%
- No improvements in outcome

Lack of Progress in MPNST

Phase II Trials with Targeted Agents for Refractory MPNST

Target	Agent	Patients (N)	Age (yr)	Outcome
Erlotinib	EGFR	20 (10 NF1)	≥18	No PR, 18/20 PD after 2 cycles
Sorafenib	Raf, VEGFR, PDGFR, C-KIT	12	≥18	No PR, PFS 1.7 mo, SD n= 3
Imatinib	C-KIT, PDGFR VEGFR	7	≥10	No PR or SD
Dasatinib	C-KIT, SRC	14	≥13	No PR, no SD at 4 cycles
Bevacizumab Everolimus	Angiogenesis mTOR	25 (17 NF1)	≥18	No PR, 3 pts. SD at cycle 4
MLN8237 (Alisertib)	Aurora Kinase A	10	≥18	No PR, 12 week PFS 60%
Ganetespib Sirolimus	HSP90 mTOR	10 (5 NF1)	≥16	No PR, 1 SD at cycle 4 (RECIST)

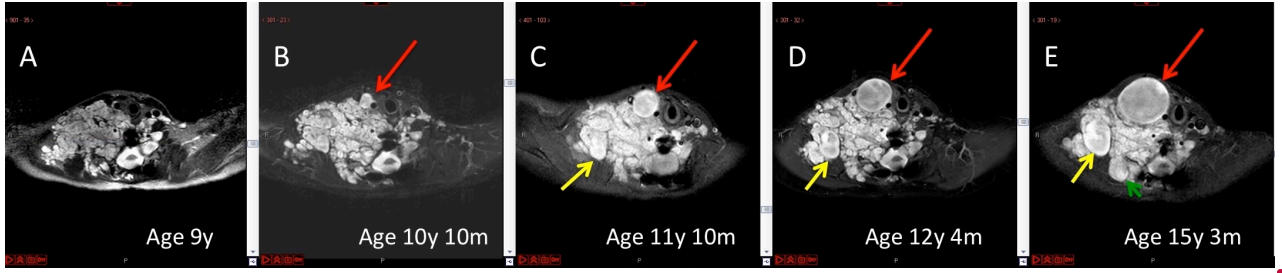
Clinical benefit in MPNST: **Complete response, partial response, stable disease at 4 cycles**

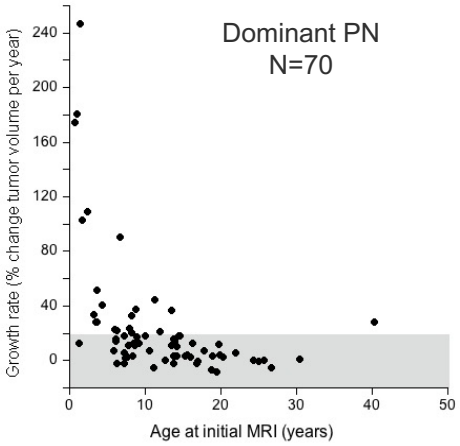
Characterization of Atypical Neurofibromas (AN)

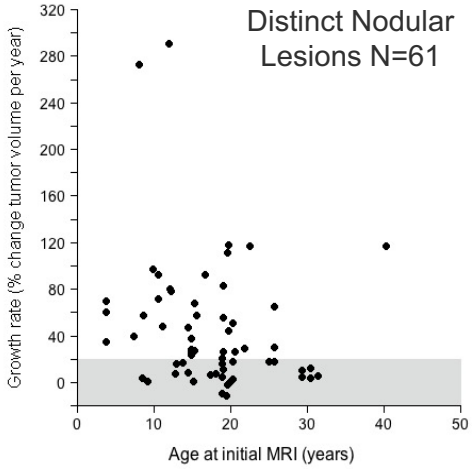
State of the Science Meeting

- Distinct imaging, clinical, and genomic (*CDKN2A* loss) characteristics

Distinct nodular lesion







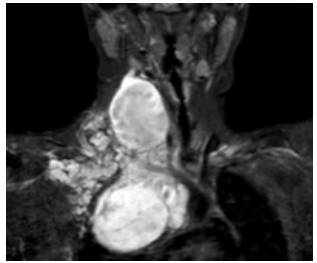
Pathology:

- Atypia,
- Loss of neurofibroma architecture
- Mitosis
- Increased cellularity
- ANNUBP:

  Atypical **N**eurofibromatous **N**eoplasm of **U**ncertain **B**iologic **P**otential

Akshintala S…Widemann B: Neuro Oncol 2020
Reilly K…Stewart D: JNCI 2017
Miettinen M…Perry A: Humpath 2017
Kim A…Widemann B: Sarcoma 2017

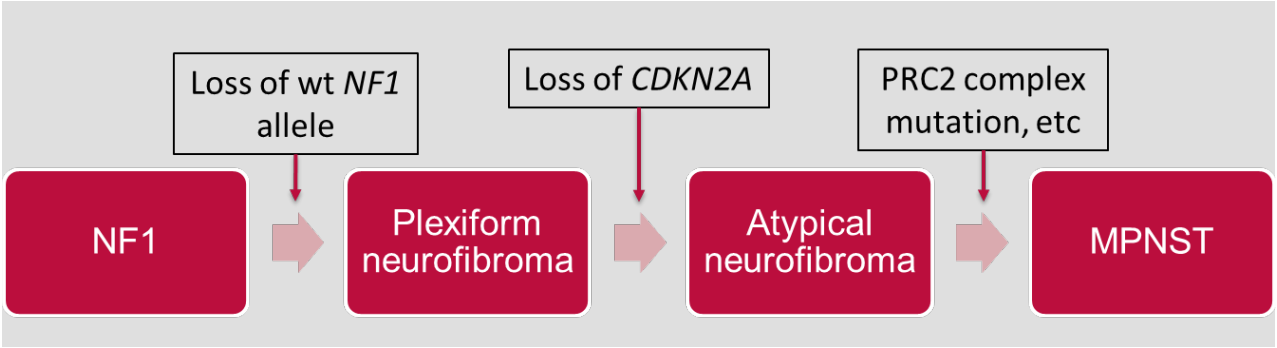
Atypical Neurofibromas Are MPNST Precursors



Atypical neurofibroma (AN) characterization:

- 63 patients (32 male, 31 female) with 76 AN
- Median age at diagnosis: 27.7 years (7.6-60)
- Most were FDG avid on FDG-PET (56/57)
- 21/63 (33%) of patients with AN had history of MPNST

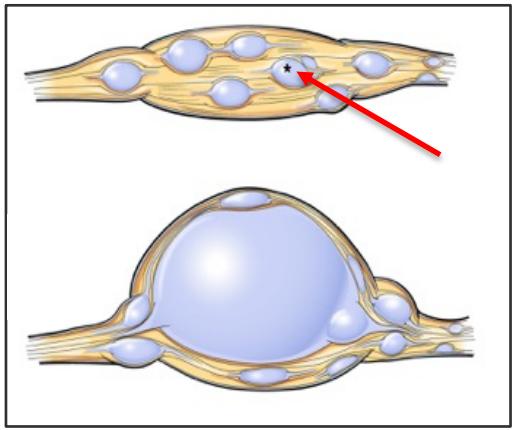
Hypothesis: Most MPNST arise from preexisting AN and not directly from PN



Clinical challenge: It is unknown if all and when AN transform to MPNST

Higham C,…Legius E, Widemann B*, Ferner R*: Neuro-Oncology 2018*

Strategies to Prevent MPNST



1) MPNST State of the Science Conference:

- Pathology consensus: **A**typical **N**eurofibromatous **N**eoplasm of **U**ncertain **B**iologic **P**otential (**ANNUBP**)
- Recommendation for surgical resection of AN
  - Marginal resection of AN: Safe and feasible
  - Low recurrence risk

2) Biomarkers for malignant transformation:

- Serial blood samples for detection of cell-free DNA
- Genomic dissection of tumor evolution, single cell sequencing

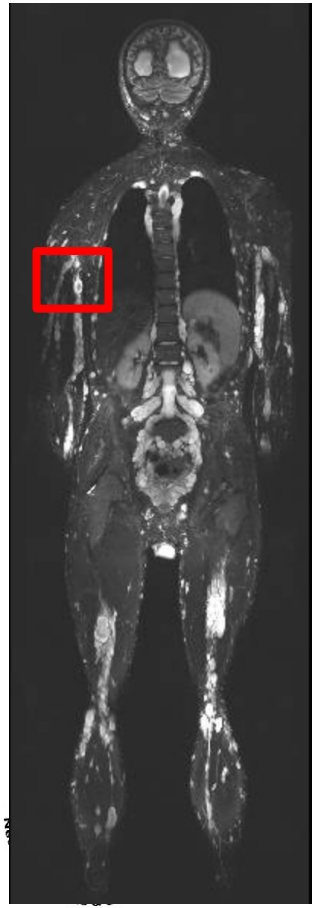
3) Clinical trials for atypical neurofibromas

- Phase I/II trial of CDK4/6 inhibitor abemaciclib
  Children and adults with unresectable pathology confirmed AN

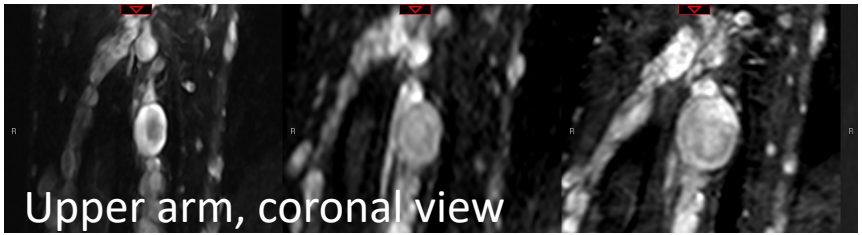
Miettinen M…Widemann B, Perry A: Humpath, 2017
Reilly K…Widemann B, Stewart D: JNCI, 2017
Nelson C…Widemann B, Chittiboina P., J Neurosurg, 2019

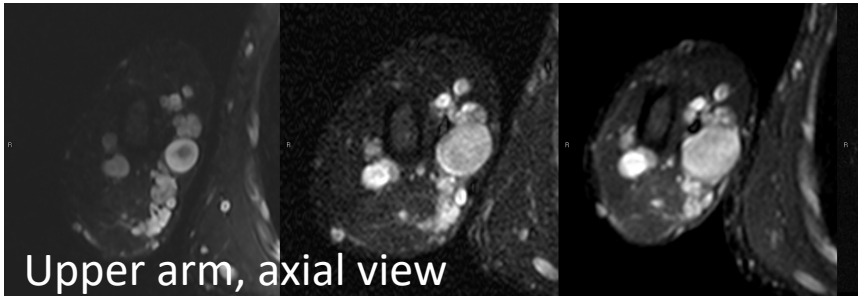
Development of MPNST in Atypical Neurofibroma

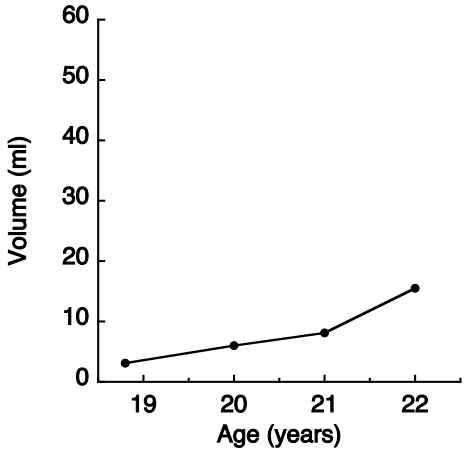
18Y 9M



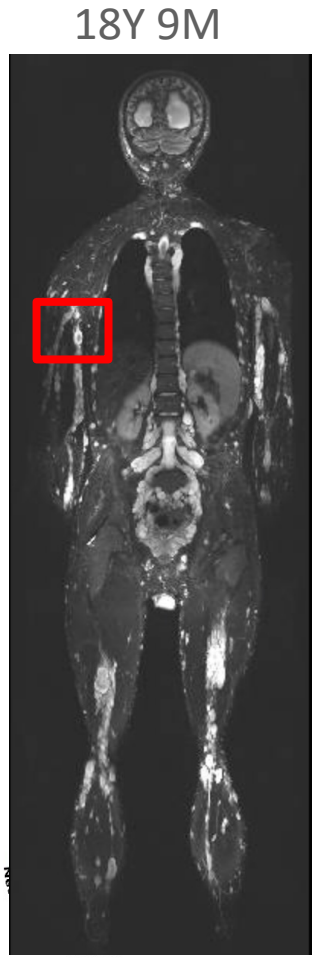
18Y 9M 21Y 0M 21Y 11M

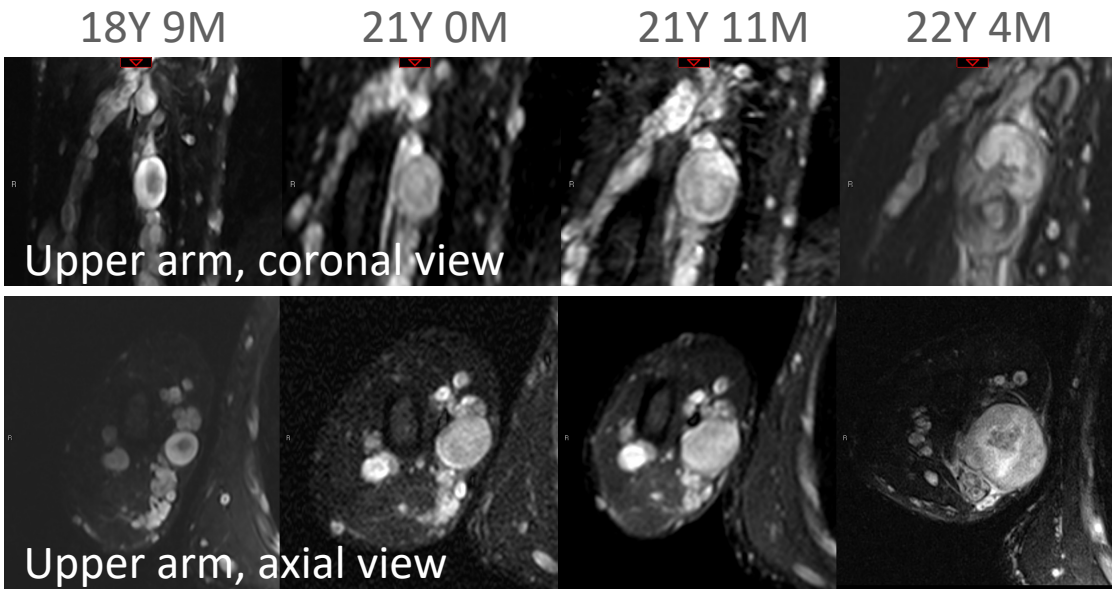


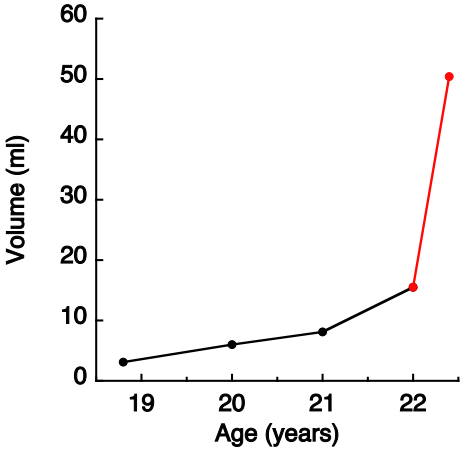




Development of MPNST in Atypical Neurofibroma







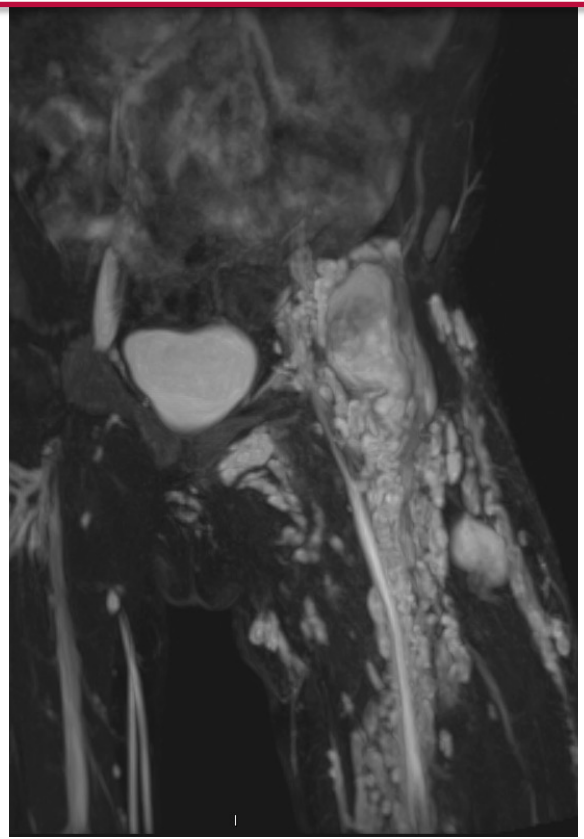
How can we predict malignant transformation?
When is the right time to intervene?

Factors identified in the literature that are associated with increased risk of MPNST

- Microdeletion on genetic testing
- Personal prior history of ANNUBP/ANF/MPNST
- Family history of ANNUBP/ANF/MPNST
- History of radiation treatment
- High burden of PN

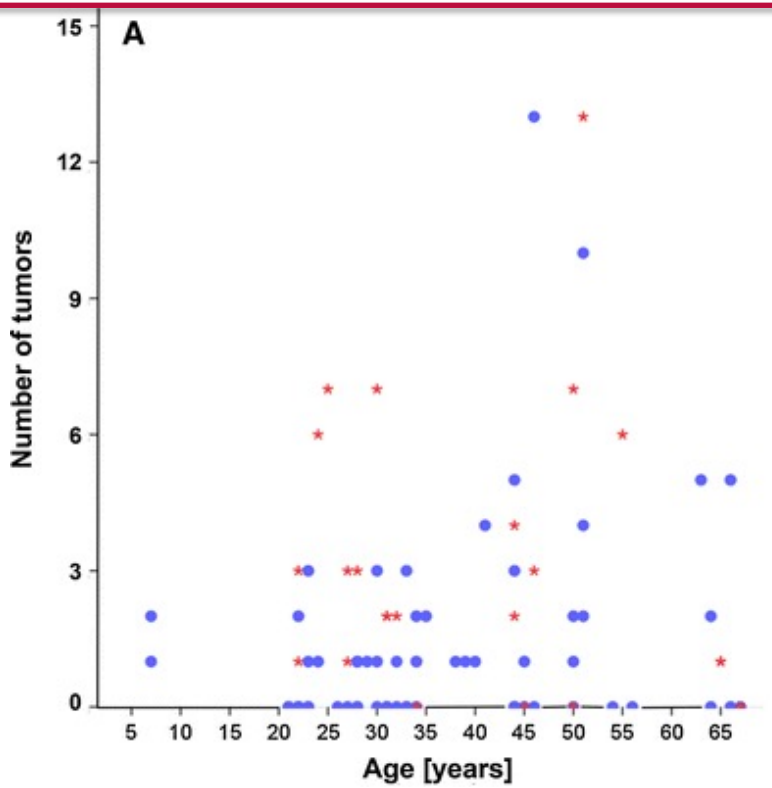
Radiologic factors identified in the literature that are associated with increased risk of MPNST

- **High internal PN burden**:
  - Number of PN
    - >1 PN?
    - Size threshold?
      - Whole body tumor volume?
- **Distinct nodular lesions (DNLs)**
  - Size threshold?



Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS

Number and volume of pNF in people with NF1 with and without MPNST



Nguyen, R., Jett, K., Harris, G.J. *et al.* Benign whole body tumor volume is a risk factor for malignant peripheral nerve sheath tumors in neurofibromatosis type 1. *J Neurooncol* **116,** 307–313 (2014).

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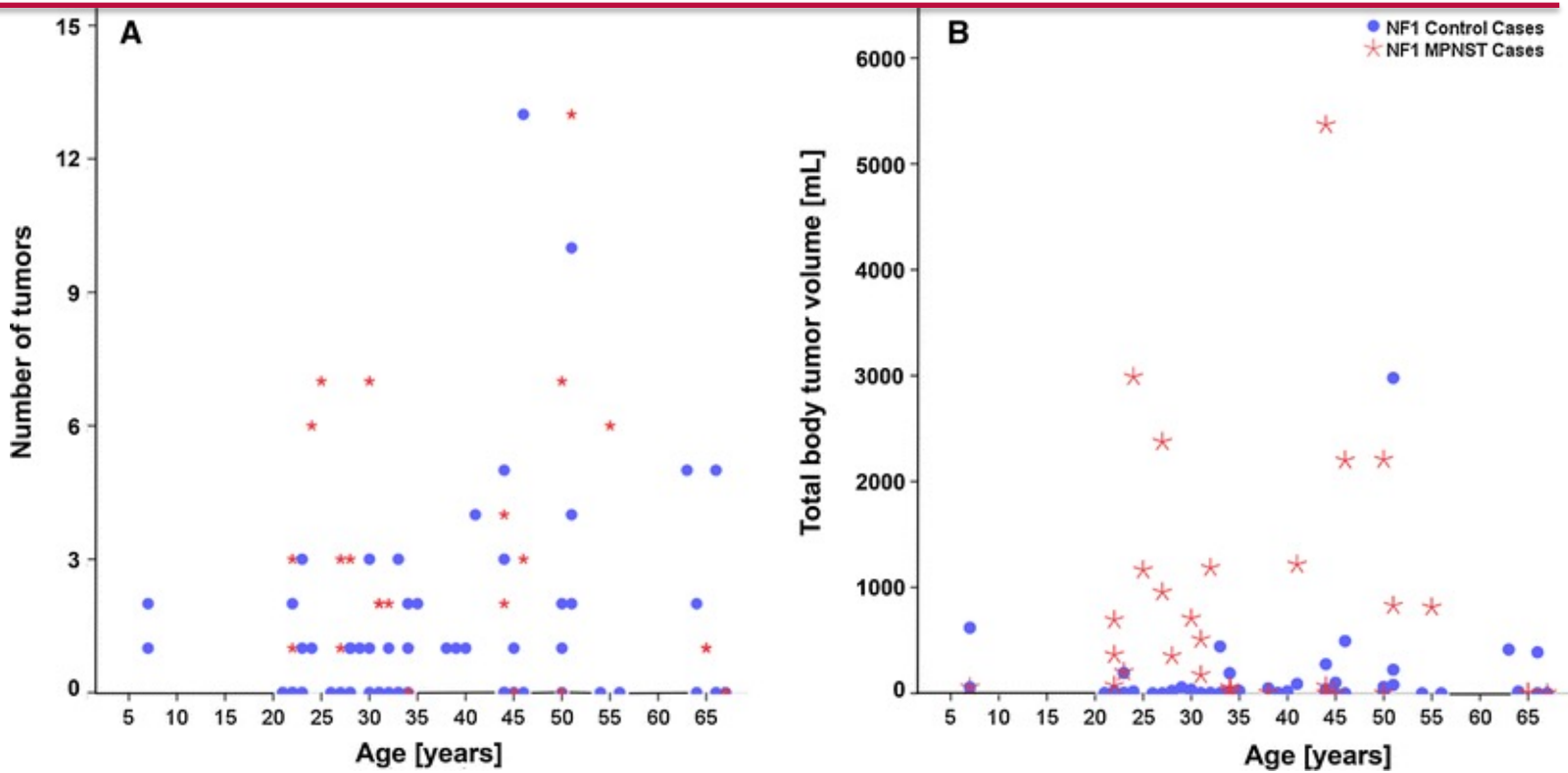

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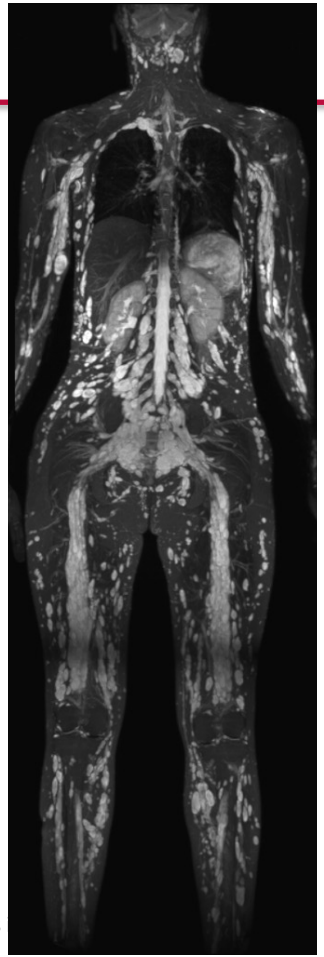
Number and volume of pNF in people with NF1 with and without MPNST

	NF1 + MPNST	NF1 - MPNST	P-value
n	31	62	
# of tumors	2.8 Range: 0–13 median: 2.0	1.4 Range: 0–13 Median: 1.0	0.0012



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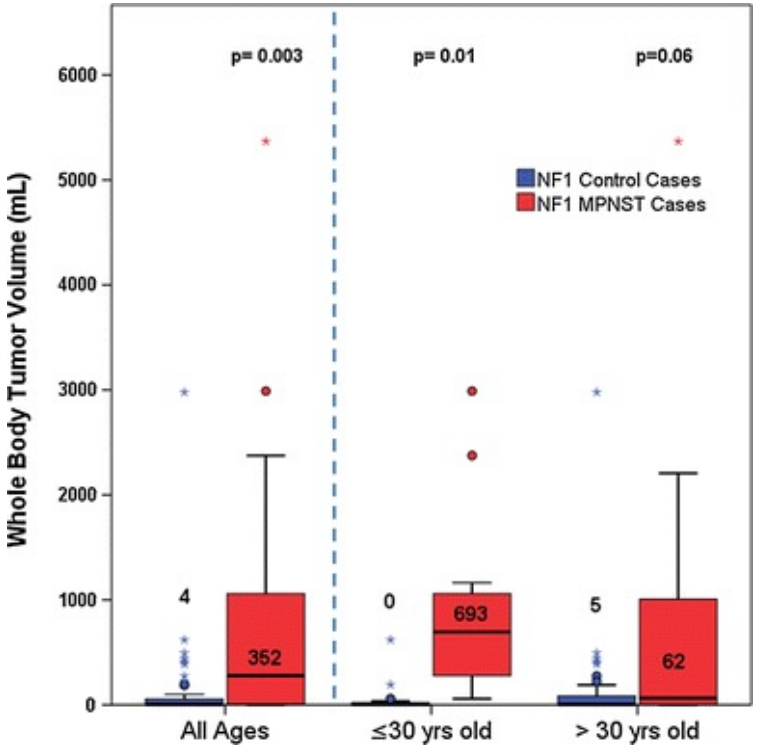
n	31	62	
# of tumors	2.8 Range: 0–13 median: 2.0	1.4 Range: 0–13 Median: 1.0	0.0012
Median **volume** (ml)	352.0 mL (Range: 0-5,368)	3.8 mL (range:0-2,978)	< 0.001



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Number and volume of pNF in people with NF1 with and without NF1 gene deletion (Microdeletion)

	Deletion	Non-deletion	P-value
n	30	90	
Incidence of internal tumors	21/30 (70%)	56/90 (62%)	0.5
# of tumors	2 (range: 1-5)	2 (range: 1-5)	0.22

Kluwe L, Nguyen R, Vogt J, Bengesser K, Mussotter T, Friedrich RE, Jett K, Kehrer-Sawatzki H, Mautner VF. Internal tumor burden in neurofibromatosis Type I patients with large NF1 deletions. Genes Chromosomes Cancer. 2012 May;51(5):447-51.

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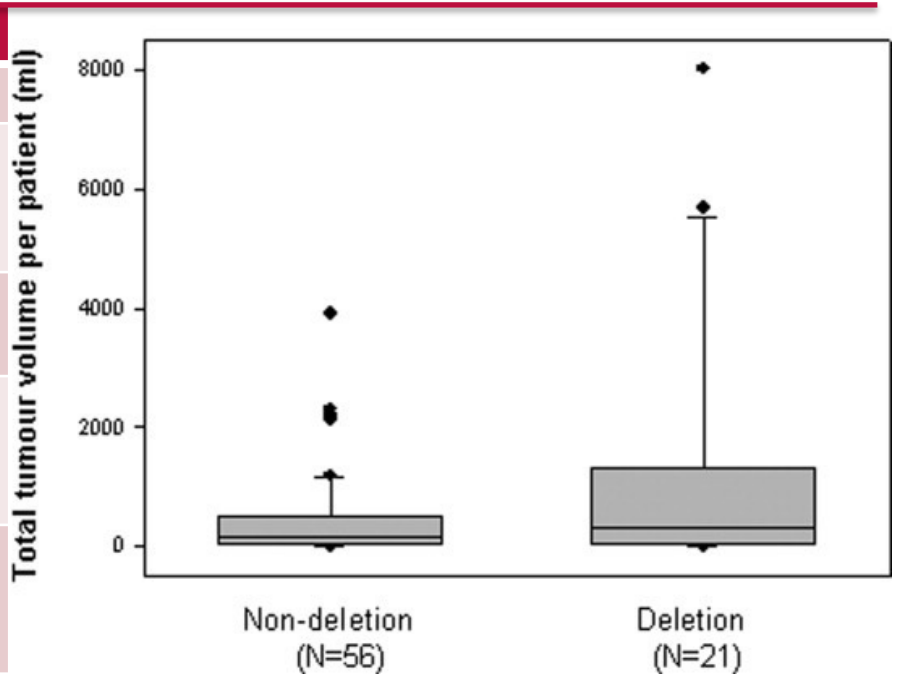
n	30	90	
Incidence of internal tumors	21/30 (70%)	56/90 (62%)	0.5
# of tumors	2 (range: 1-5)	2 (range: 1-5)	0.22
Median **volume** (ml)	321 (Range: 8-8018)	176 (range:2-3910)	0.19
High tumor burden (>3000 ml)	4/21 (19%)	1/56 (2%)	0.018



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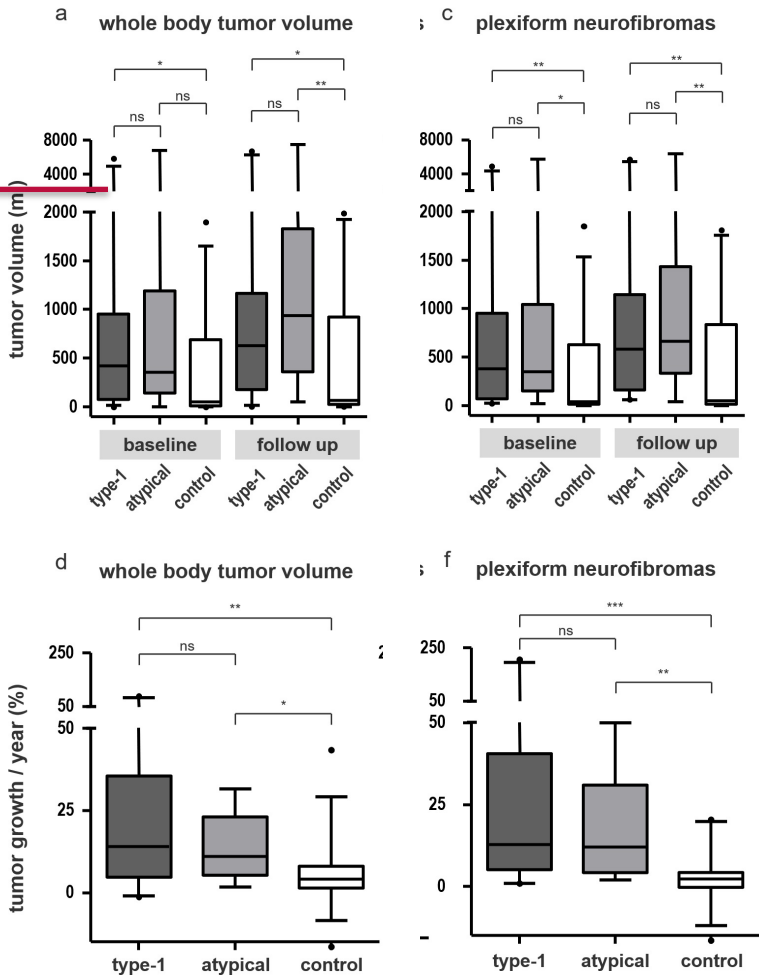
Number and volume of pNF in people with NF1 with and without NF1 gene deletion

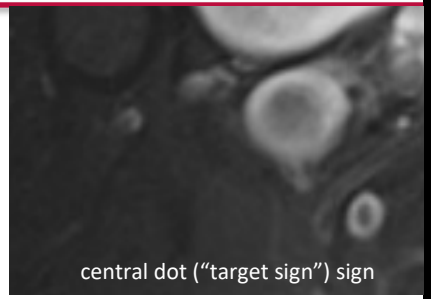
- *NF1* **whole gene deletions → more severe phenotype** of NF1 with higher tumor burden and higher growth-rates
  - 38 patients with *NF1* whole gene deletions
    - type-1 group: n = 27
    - atypical group: n = 11
    - an age- and sex matched control: n= 38



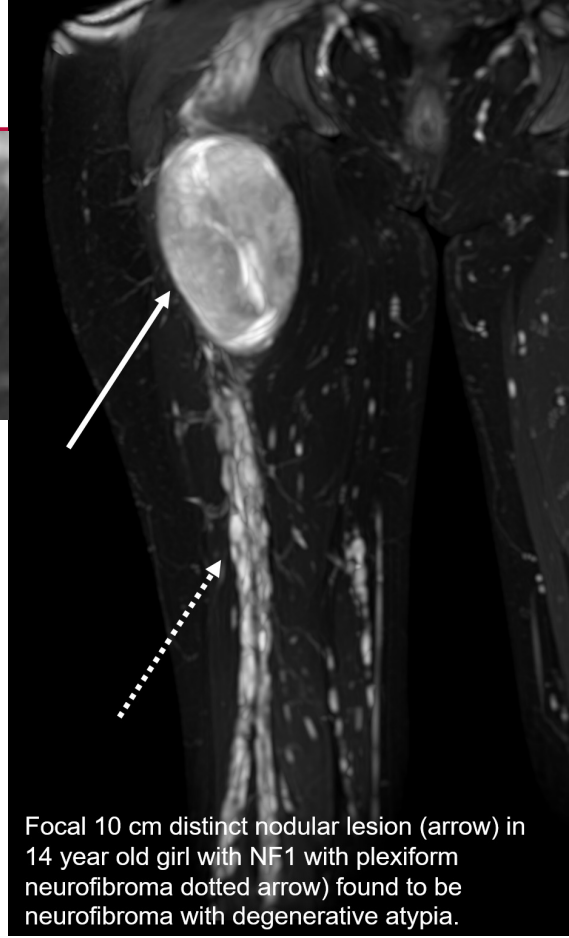
Well L, Döbel K, Kluwe L, Bannas P, Farschtschi S, Adam G, Mautner VF, Salamon J. Genotype-phenotype correlation in neurofibromatosis type-1: NF1 whole gene deletions lead to high tumor-burden and increased tumor-growth. PLoS Genet. 2021 May 5;17(5):e1009517.

DNLs in NF1

- Definition:
  - Well-demarcated
  - Encapsulated-appearing
  - Size ≥3 cm lesions
  - Lacking the central dot (“target sign”) sign characteristic of PNs
  - Present within or outside of a PN



central dot (“target sign”) sign

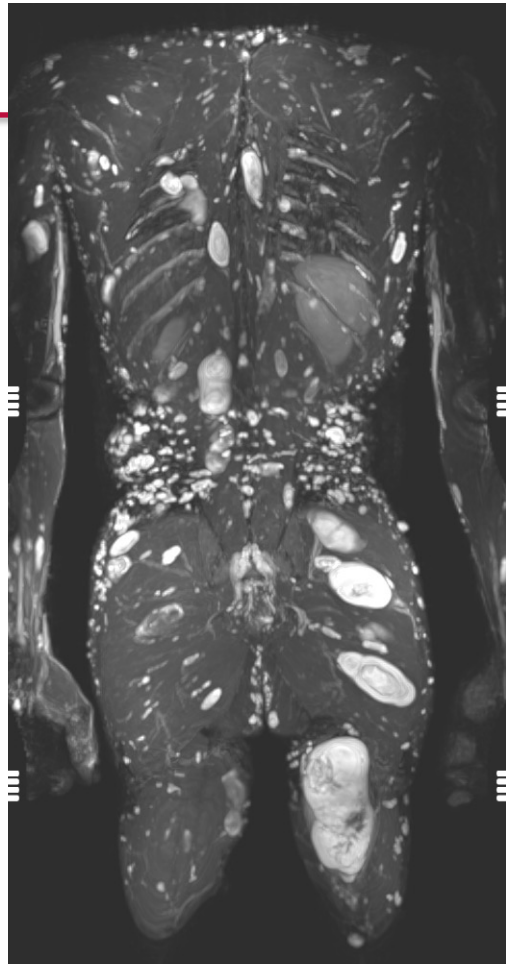


Focal 10 cm distinct nodular lesion (arrow) in 14 year old girl with NF1 with plexiform neurofibroma dotted arrow) found to be neurofibroma with degenerative atypia.

Akshintala S, Baldwin A, Liewehr DJ, Goodwin A, Blakeley JO, Gross AM, Steinberg SM, Dombi E, Widemann BC. Longitudinal evaluation of peripheral nerve sheath tumors in neurofibromatosis type 1: growth analysis of plexiform neurofibromas and distinct nodular lesions. Neuro Oncol. 2020 Sep 29;22(9):1368-1378.

DNLs on PET

- N= 103 enrolled in NF1 natural history study
  - 81 (79%) had PN on WB-MRI
    - 15 patients → nodular **target** lesion
      - History of prior MPNST
      - Occurred in absence of prior MPNST history, but were associated with new pain, growth of the nodular lesion exceeding the growth of the surrounding or adjacent PN
      - History of prior abnormal FDG-PET study
    - 46 patients with nodular non-target lesions + least 1 FDG-PET
  - Histology of **target** DNLs
    - Benign + No Bx: 10/15 (67%)
    - **Atypical NF: 2/15 (13%)**
    - MPNST/Sarcoma: 3/15 (20%)



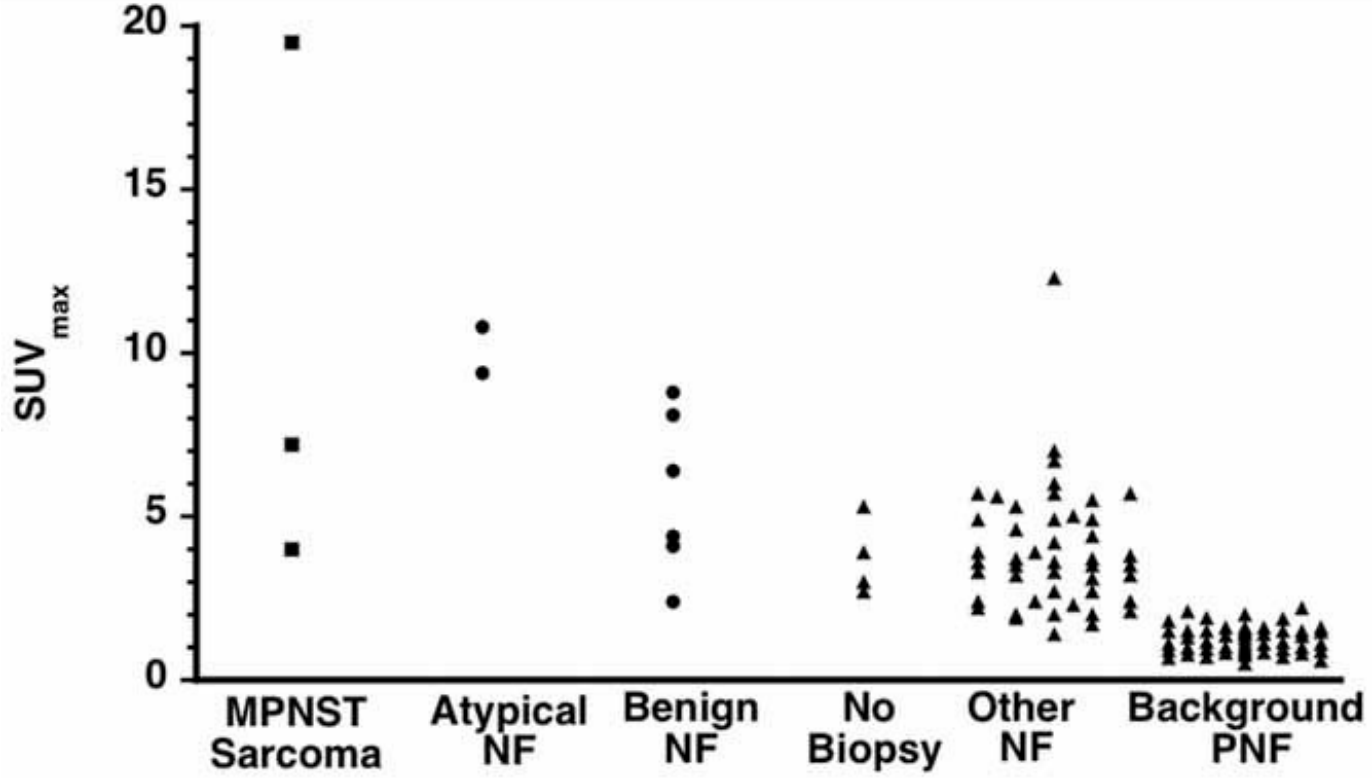
Meany H, Dombi E, Reynolds J, Whatley M, Kurwa A, Tsokos M, Salzer W, Gillespie A, Baldwin A, Derdak J, Widemann B. 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) evaluation of nodular lesions in patients with Neurofibromatosis type 1 and plexiform neurofibromas (PN) or malignant peripheral nerve sheath tumors (MPNST). Pediatr Blood Cancer. 2013 Jan;60(1):59-64.

DNLs on PET

	Nodular target lesion					Nodular non-target PET avid lesions		PN
	n	**SUVmax (g/ml)**	**Vol. (ml)**	**Vol. change (% per year)**	**Pathology**	**No. of lesions**	**SUVmax (g/ml)**	**TTV (ml):TTB vol./BSA**
History of MPNST	4	3.0–8.8	71–356		NF (n=1) No path (n=3)	0–10	2.1-12.3	1,859–6,800
Prior Abnormal PET Scan or a Growing, Painful DNL	11	2.4–19.5	11–372	10–538	NF (n=4) No path (n=2) **ANF (2)** MPNST (n=2) Angiosarcoma (n=1)	0–5	1.9-8.8	83–8,649

Meany H, Dombi E, Reynolds J, Whatley M, Kurwa A, Tsokos M, Salzer W, Gillespie A, Baldwin A, Derdak J, Widemann B. 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) evaluation of nodular lesions in patients with Neurofibromatosis type 1 and plexiform neurofibromas (PN) or malignant peripheral nerve sheath tumors (MPNST). Pediatr Blood Cancer. 2013 Jan;60(1):59-64.

DNLs on PET



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DNLs: marker for ANF?

63 patients with76 pathologically confirmed ANF

- Pain (n=46)
- Motor weakness (n=19)
- Palpable or visible (45)
- No clinical signs (n=12)

Higham CS, Dombi E, Rogiers A, et al. The characteristics of 76 atypical neurofibromas as precursors to neurofibromatosis 1 associated malignant peripheral nerve sheath tumors. *Neuro Oncol*. 2018;20(6):818-825. doi:10.1093/neuonc/noy013

DNLs: marker for ANF?

63 patients with76 pathologically confirmed ANF

- Pain (n=46)
- Motor weakness (n=19)
- Palpable or visible (45)
- No clinical signs (n=12)

	MRI (*N* = 58)	Median	Range
Size on MRI (*N* = 58)	Longest diameter (cm)	5.5	1.7–18.2
	Calculated 3D volume (cm^3)	65.1	1.6–1647
Prior MRI (*N* = 22)	1D growth rate (%/y)	5.8	−42–43.9
	3D growth rate (%/y)	27.4	−51–379

Higham CS, Dombi E, Rogiers A, et al. The characteristics of 76 atypical neurofibromas as precursors to neurofibromatosis 1 associated malignant peripheral nerve sheath tumors. *Neuro Oncol*. 2018;20(6):818-825. doi:10.1093/neuonc/noy013

DNLs: marker for ANF?

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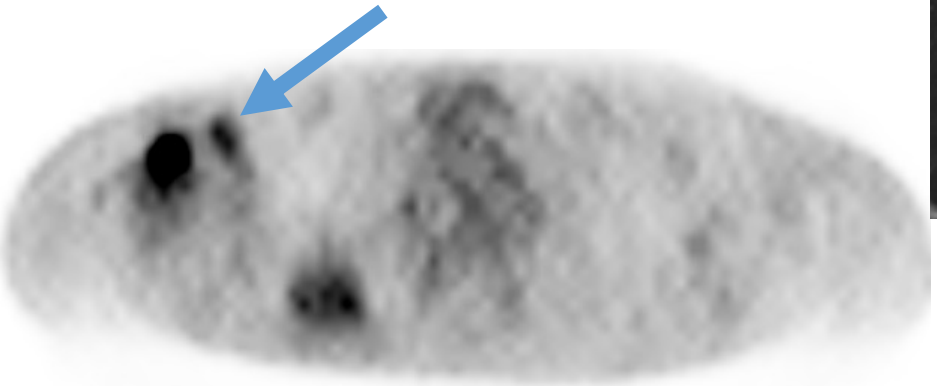
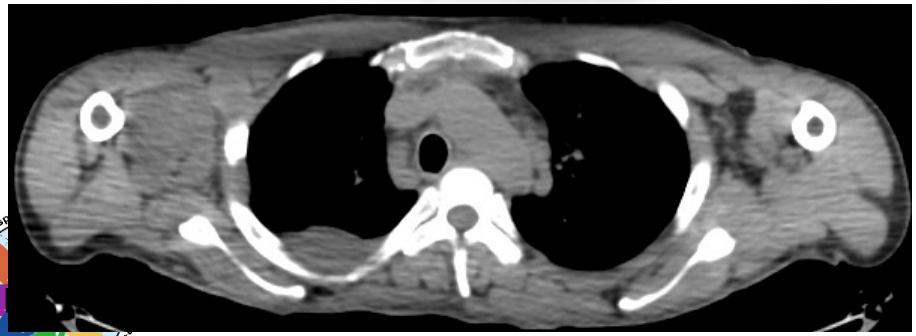
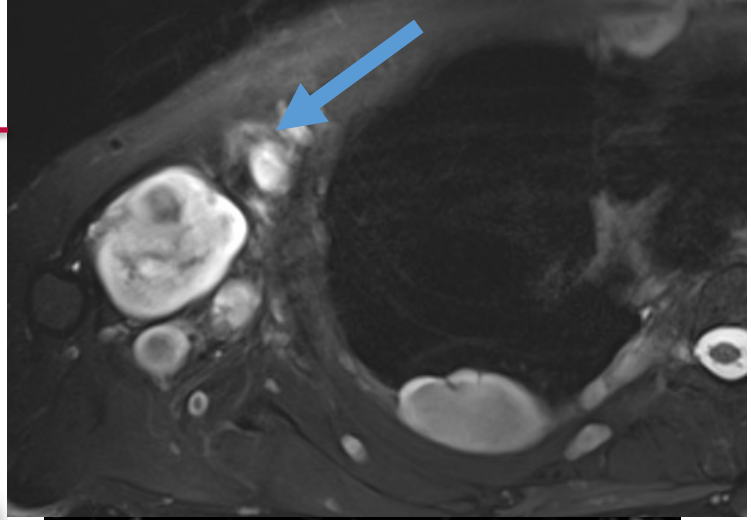
Size on MRI (*N* = 58)	Longest diameter (cm)	5.5	1.7–18.2
	Calculated 3D volume (cm^3)	65.1	1.6–1647
Prior MRI (*N* = 22)	1D growth rate (%/y)	5.8	−42–43.9
	3D growth rate (%/y)	27.4	−51–379
FDG-PET (*N* = 56)	PET avid lesions per patient	2	0–12
	Median SUV_{max}: 60–90min (*N*=50)	5.6	0–22.3
	Median SUV_{max}: 180–240min (*N*=26)	6.6	3.2–21.6
Prior FDG-PET (*N* = 18)	Increase in SUV_{max}	13	
	Decrease in SUV_{max}	3	
	No change	2	

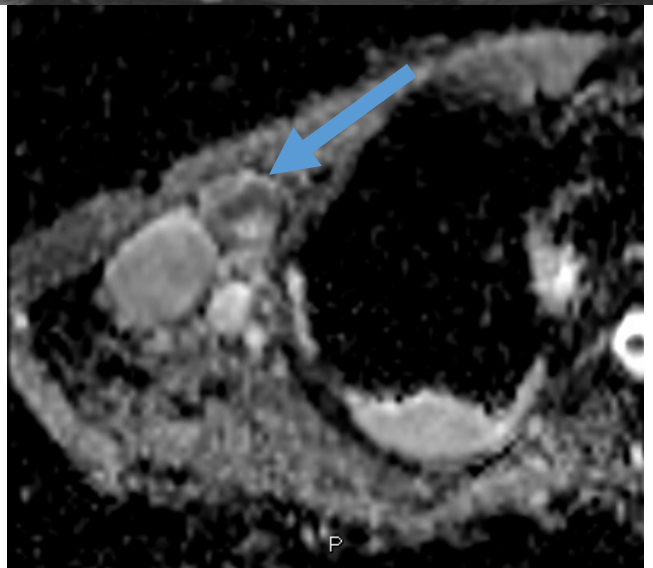
Higham CS, Dombi E, Rogiers A, et al. The characteristics of 76 atypical neurofibromas as precursors to neurofibromatosis 1 associated malignant peripheral nerve sheath tumors. *Neuro Oncol*. 2018;20(6):818-825. doi:10.1093/neuonc/noy013

DNLs in NF1

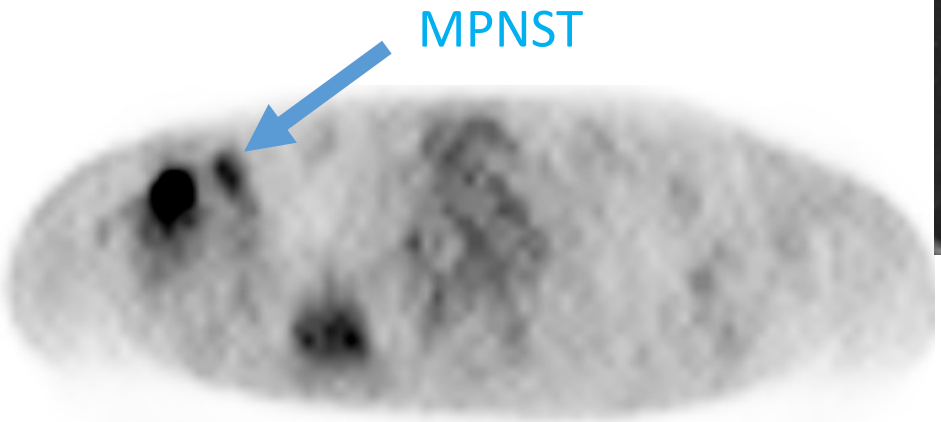


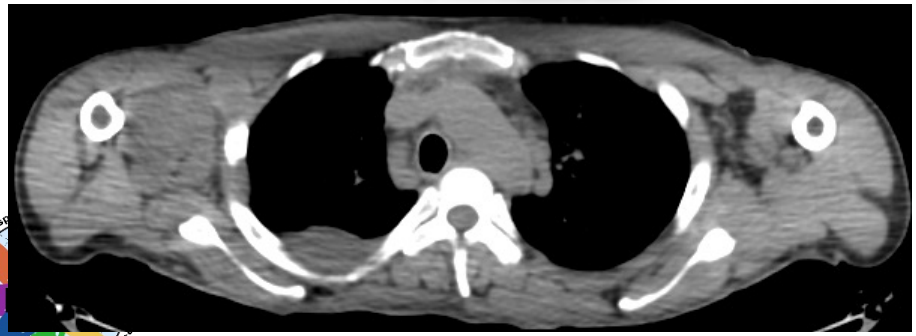


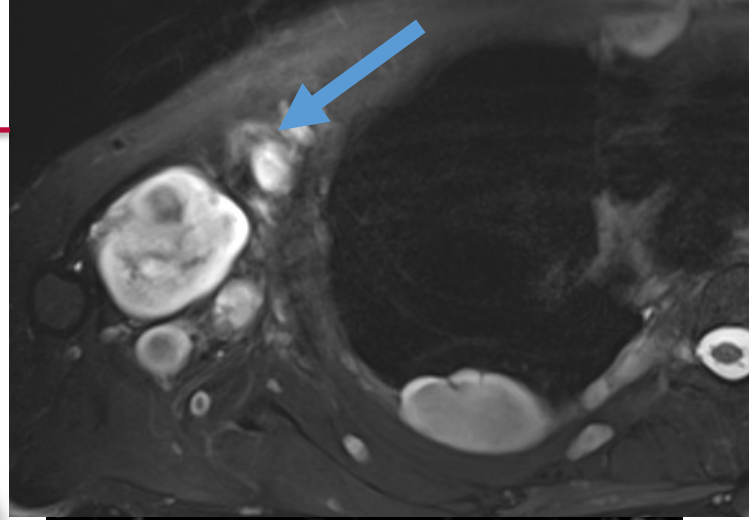


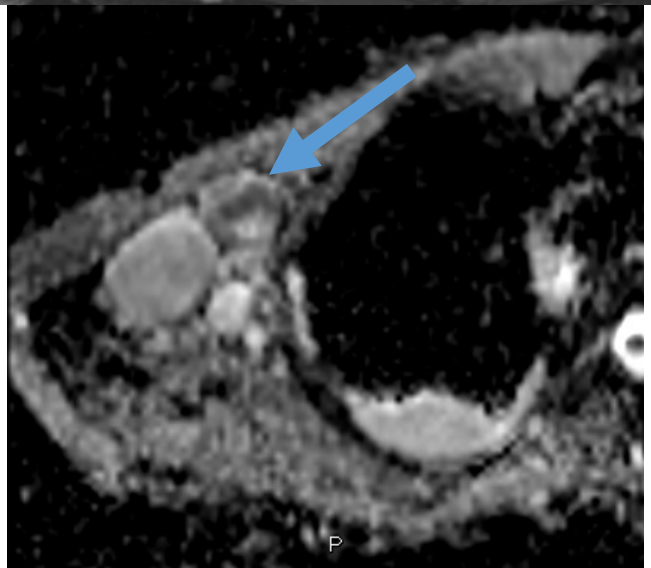


DNLs in NF1

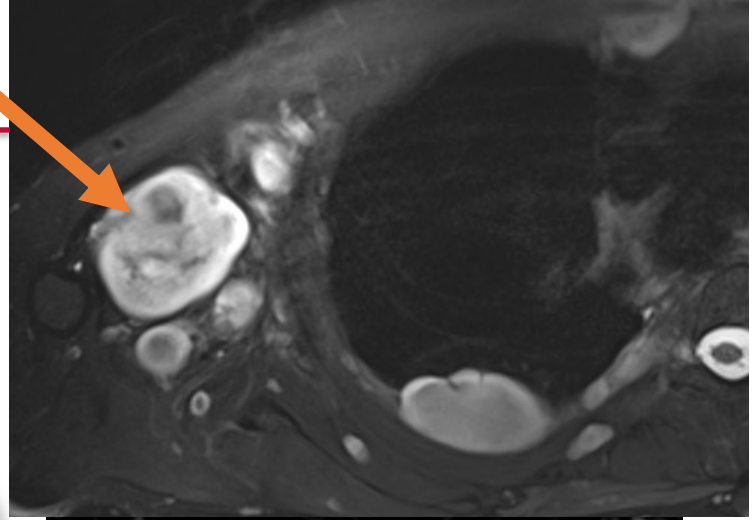


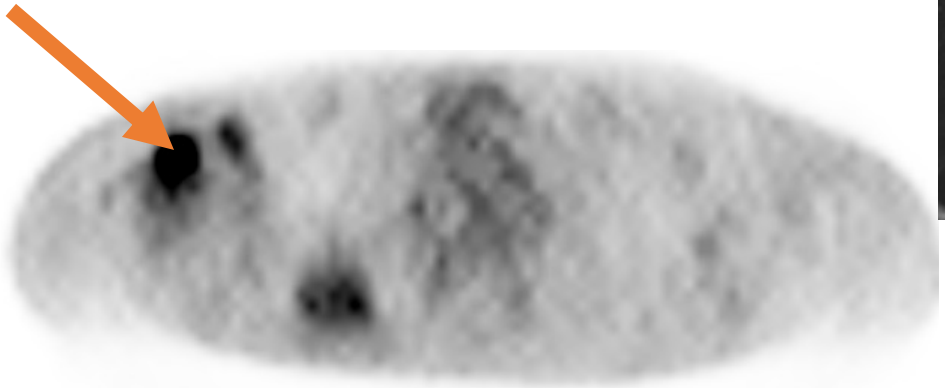


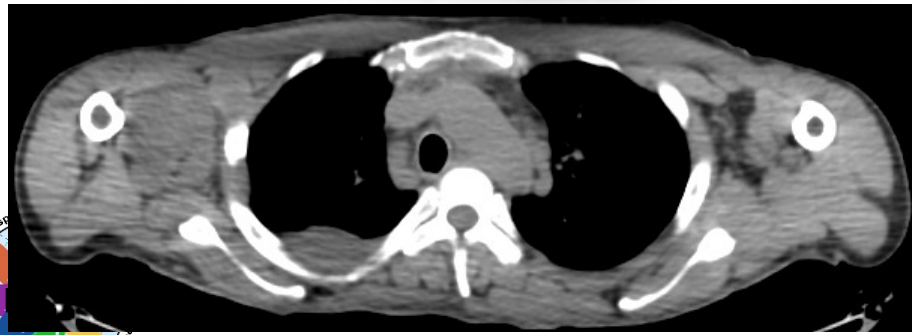


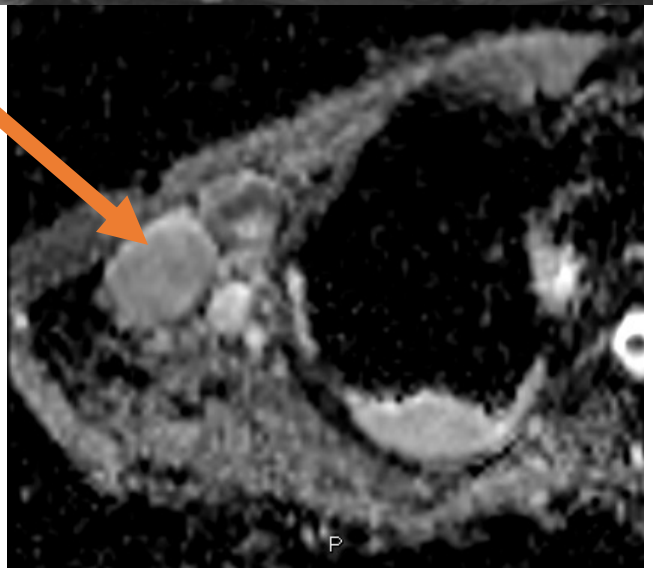


DNLs in NF1







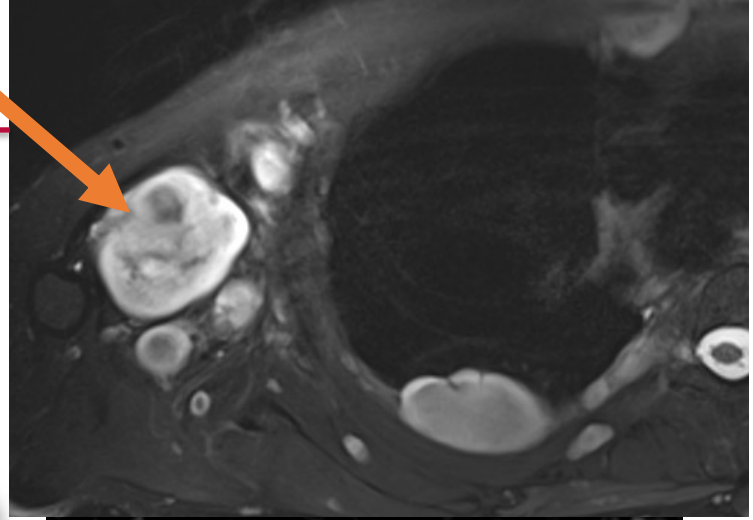


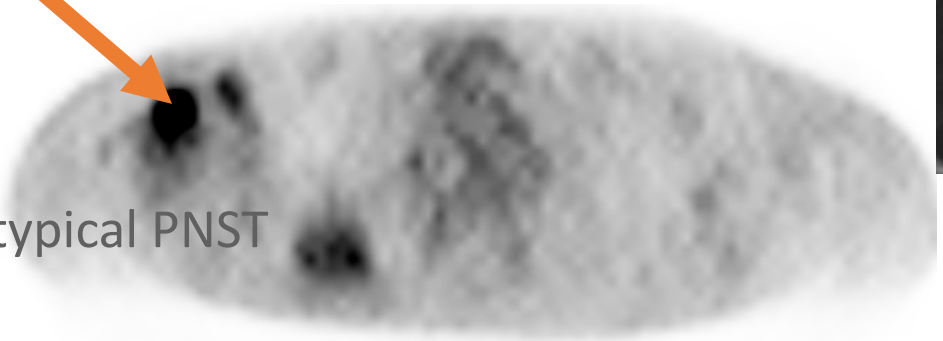
DNLs in NF1

Incidence: **58/122 (45.6%)** patients in NIH NHx study
Median 2 DNLs/patient

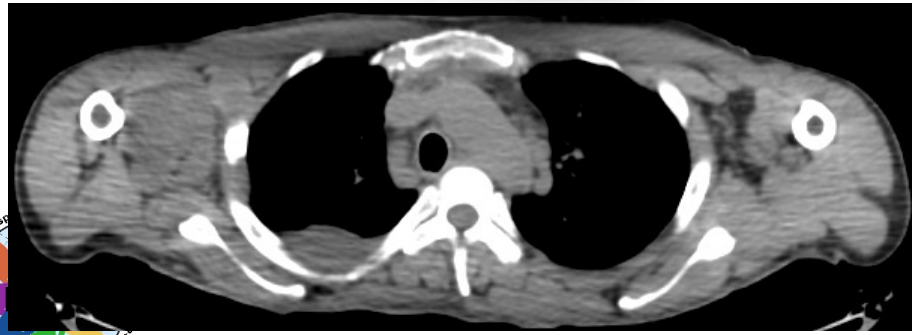
No histologic data

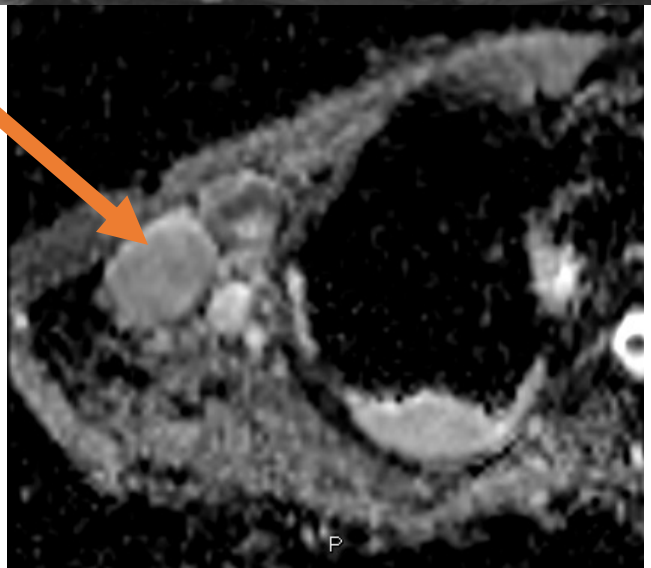
Akshintala S et al. Neuro Oncol. 2020 Sep 29;22(9):1368-1378.





Atypical PNST





Proposed Eligibility Criteria for Increased Risk of MPNST:

Eligibility Criteria: Diagnosis of NF1 AND at least one of the following:

- Microdeletion
  - Other Genotypes associated with increased risk of MPNST?
- Family/personal history of ANNUBP/ANF/MPNST
  - DNL (Number? Size Criteria?)
- Prior radiation therapy
- High internal tumor burden
  - Large PN burden (≥ 350 mL)?
  - PN ≥ 3 cm?
  - More than 1 PN, complex PN?
- Other (High subcutaneous tumor burden?)

For Discussion

Extra Slides

Imaging Concerning Features: Hopkins / NCI

Concerning Features" defined as at least one of the following:

- Clinical:
  - New symptoms, change in pain pattern
  - Concerns on physical exam
- Imaging MRI:
  - Rapid growth
  - ADC values $<1x10^3 mm^2/s$
  - Concerning change in imaging appearance
- Imaging FDG-PET:
  - Any tumor with SUV ≥ 3.5
  - Any individual DNL ≥ 5 cm diameter

For Discussion

Natural History Study: Focus on Increased Risk for MPNST

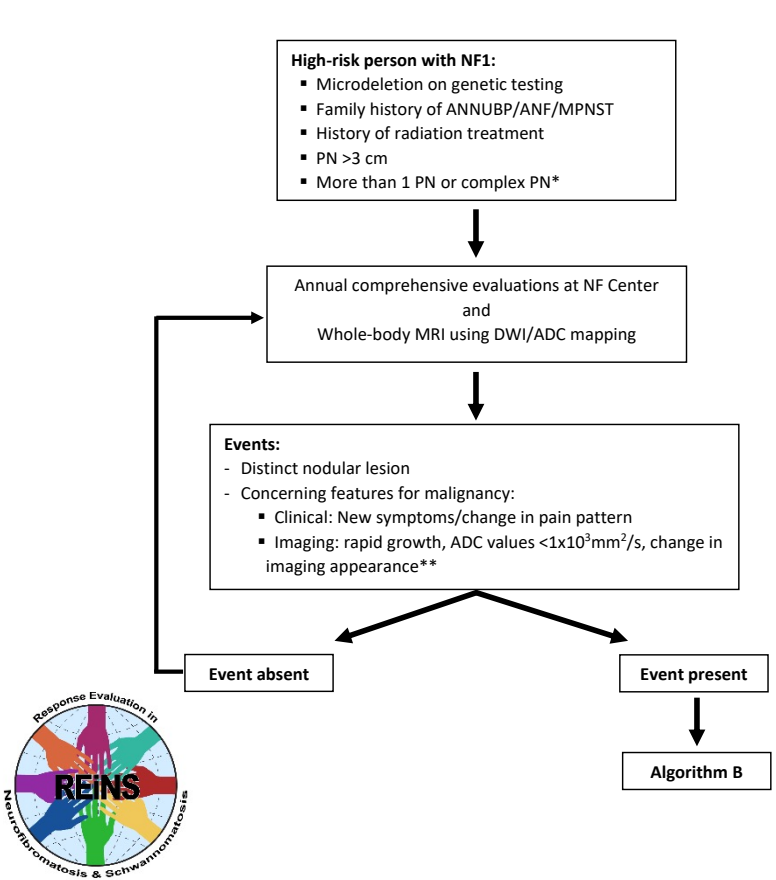
- Eligibility criteria: Need to identify criteria to enrich for at risk population
- Standardized longitudinal evaluations:
  - Clinical, genetic:
    - Family and medical history, physical exam
    - Germline NF1 sequencing
  - Imaging:
    - Whole body MRI
    - Regional MRI
    - FDG-PET-Imaging
- Identify and manage high risk lesions prior to transformation:
  - Biopsy
  - Marginal resection
  - Safety and tolerability of approach
  - Incidence of MPNST in spite of prevention efforts
  - Develop algorithms

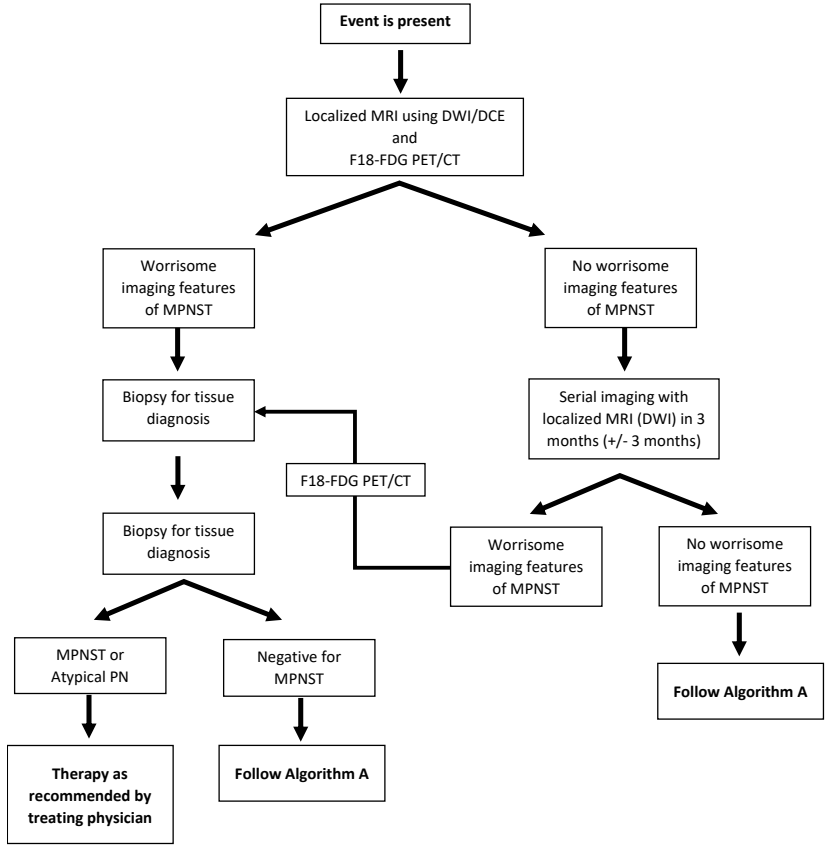
Multi-parametric Biomarker Development to Predict Malignant Conversion in Patients with Neurofibromatosis type 1

1. Determine the prevalence of DNL in high-risk people with NF1
    1. To describe the multi-parametric (qualitative and quantitative) MRI/PET features of DNL in NF1
    2. *For people with DNL on WB-MRI with serial exams:*
        a. Determine the growth rate
        b. Assess the incidence of new DNLs

2. To correlate the multi-parametric (qualitative and quantitative) MRI/PET features with histology to see which DNL turn out to be benign versus atypical versus malignant
1.Develop a predictive model for people with NF1 at risk for MPNST

Multi-parametric Biomarker Development to Predict Malignant Conversion in Patients with Neurofibromatosis type 1: Study Schema





Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS

New NCI NF1 Natural History Study for Patients at Higher Risk for MPNST

Eligibility Criteria: Patient with a diagnosis of NF1 AND at least one of the following:

- Microdeletion
- Family history of ANNUBP/MPNST or Personal history of ANNUBP/ANF/MPNST
- Prior radiation therapy
- Large PN burden (>350 mL)

Cohort 1: Tumors with Concerning Features

Cohort 2: Tumors with **NO** Concerning Features

"Concerning Features" defined as at least one of the following:

- Biopsy proven ANNUBP/ANF (if not fully resected)
- Any tumor with SUV ≥ 3.5
- DWI with ADC value < 1
- Any individual DNL ≥ 5 cm diameter

Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS