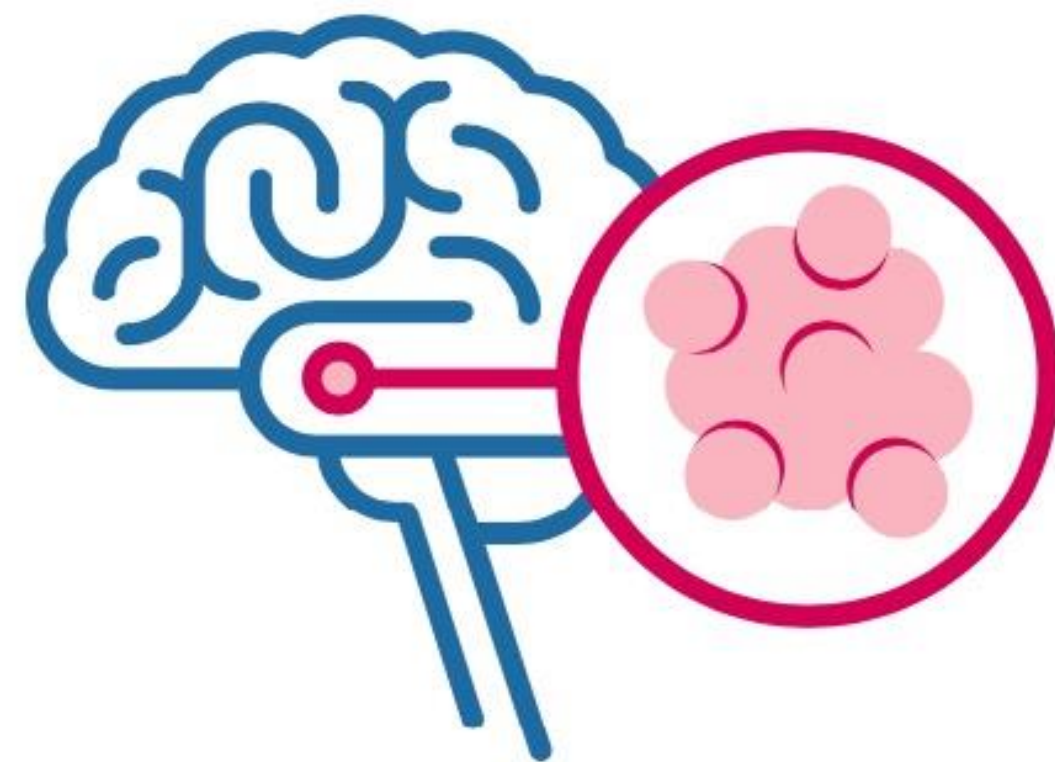


Response **E**valuation **I**n **N**eurofibromatosis **S**chwannomatosis
INTERNATIONAL COLLABORATION

- If sharing any data or information from these slides generated by the REiNS International Collaboration, please acknowledge the authors, group chairs, and specific working group.
- If using any information presented with a citation, please reference the primary source.

The natural history of Neurofibromatosis Type 2

National Institutes of Health Cohort



Prashant Chittiboina, MD, MPH
Neurosurgery Unit for Pituitary and Inheritable Diseases
Surgical Neurology Branch, NINDS, Bethesda, MD

National Institutes of Health, Bethesda, MD



RECRUITING 

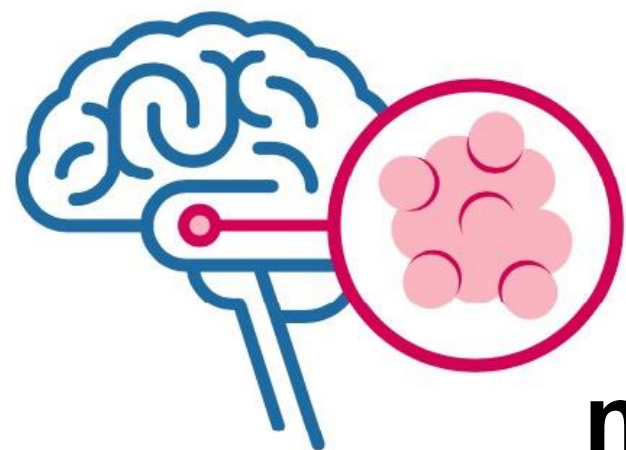
ClinicalTrials.gov Identifier: NCT00598351

Natural History Study of Patients With Neurofibromatosis Type 2

Information provided by National Institute of Neurological Disorders and Stroke (NINDS) (Responsible Party)

Last Updated: October 26, 2022

Original study: 168 subjects. Closed to recruitment.



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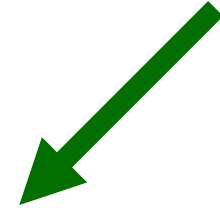
Ashok Asthagiri, MD



John D Heiss, MD

Updated study: Open for recruitment.

RECRUITING 

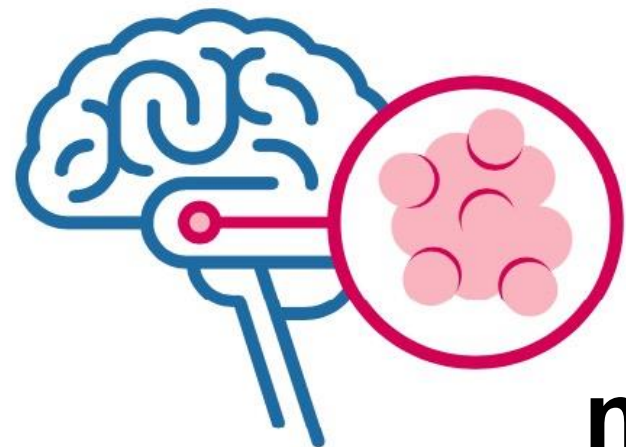


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nf2@nih.gov

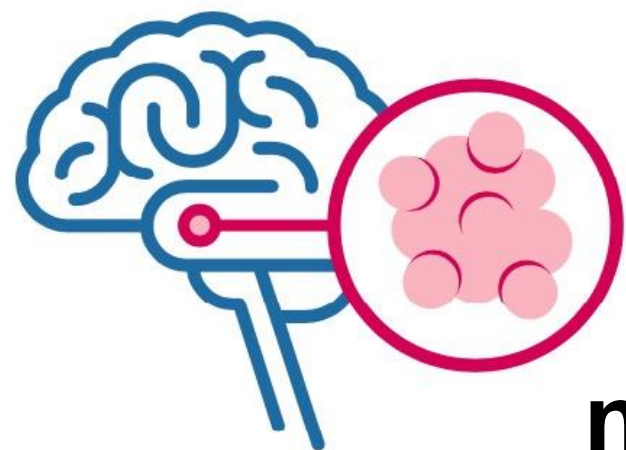
Original Study: Objectives

Primary Objective

To determine the natural history (clinical and radiographic) of nervous system tumors in NF2.

Secondary Objectives

1. To identify stochastic factors that underlie the growth of NF2-associated tumors.
2. To identify imaging and clinical changes that can predict tumor progression and ultimately the development of neurological signs and symptoms requiring treatment.
3. To determine if serum biomarkers (FSH, LH, testosterone, estradiol, GH, IGF-1, ACTH, cortisol, TSH, free T4, prolactin, progesterone) can be used to predict or correlate with growth of tumors.
4. To determine if germ-line mutations can be used to predict the severity and natural history of NF2.



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Original Study: Interventions

169 subjects
5 year follow up
Closed in 2013

Imaging

1. Volumetric MRI of Brain
2. Volumetric MRI of spine
3. Specialized exams: MRI FLAIR

Clinical

1. Neurosurgery clinical evaluation
2. Neurotology clinical evaluation
3. Karnofsky performance status
4. Ambulatory function
5. ASIA grading scale

Patient reported measures

1. Functional independence measure
2. SF36 evaluation
3. Speech and swallowing questionnaire

Audiovestibular

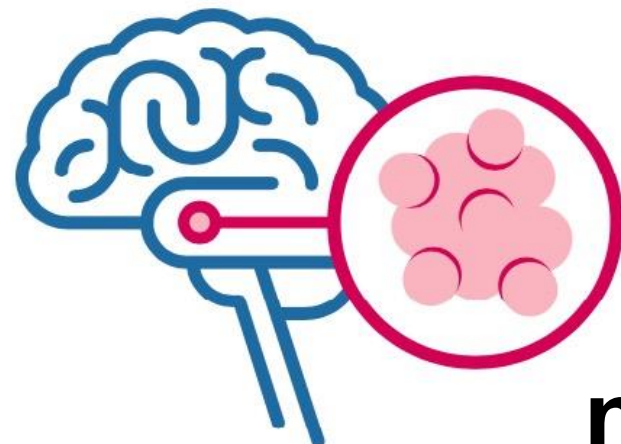
1. Audiometric evaluation
2. Vestibular evaluation

Speech Language Pathology

Rehab Medicine Evaluation

Laboratory

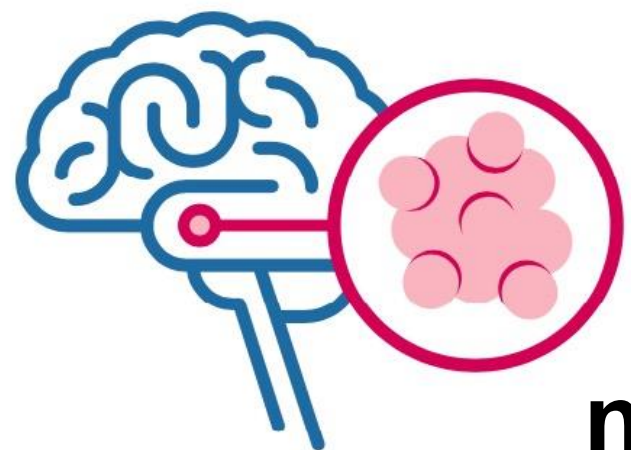
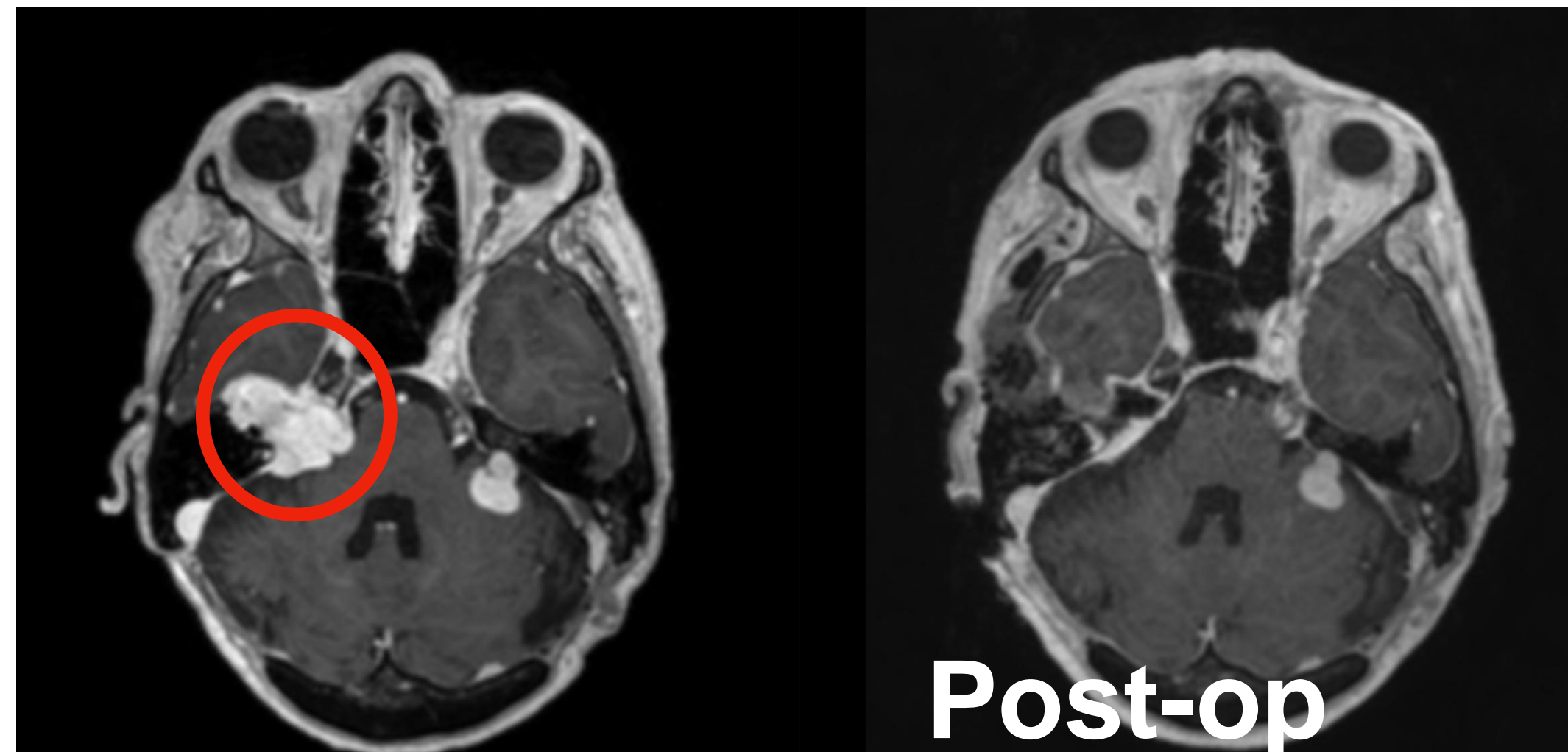
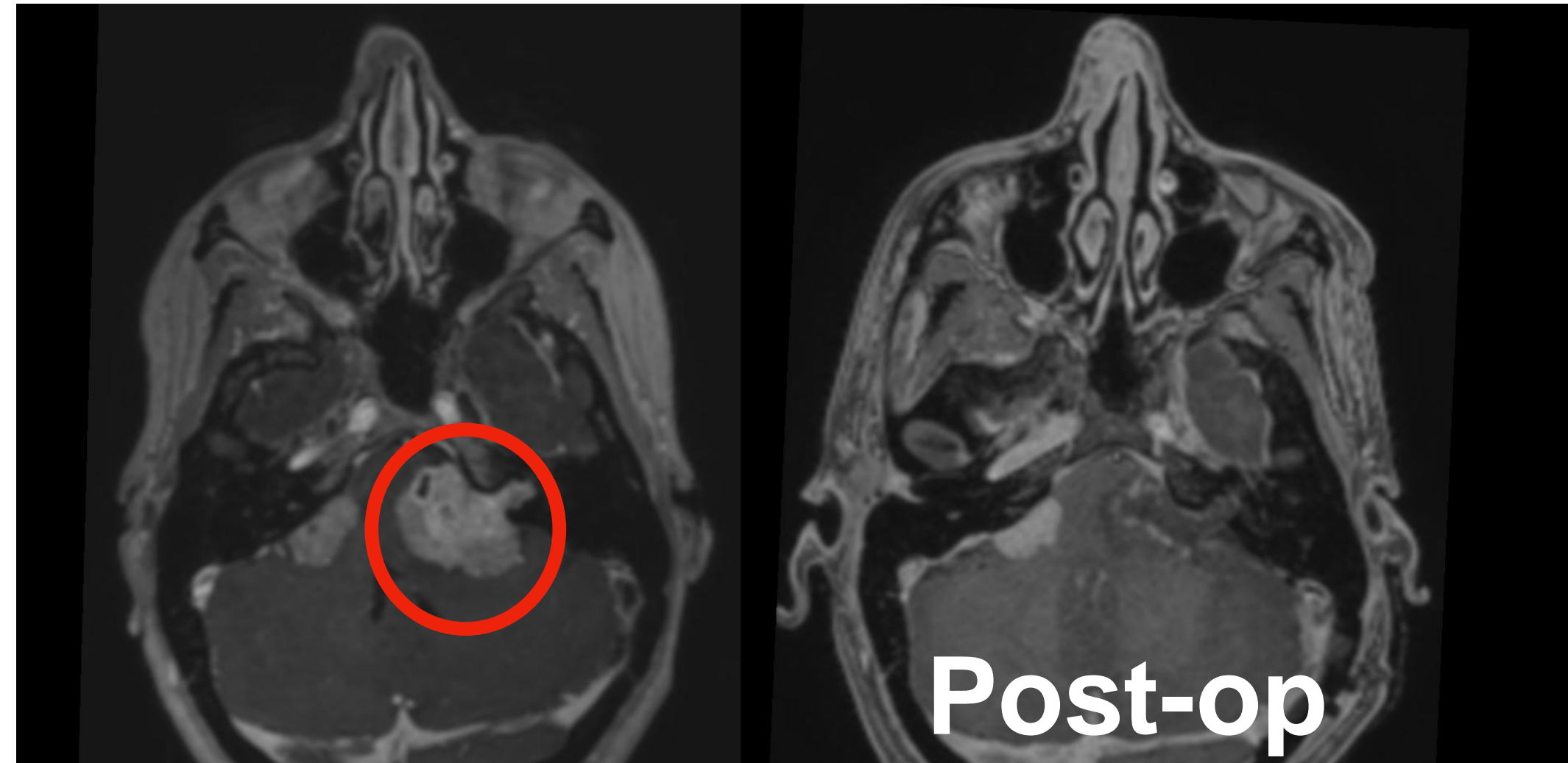
1. Routine labs
2. Blood/serum testing



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Clinical Care for NF2

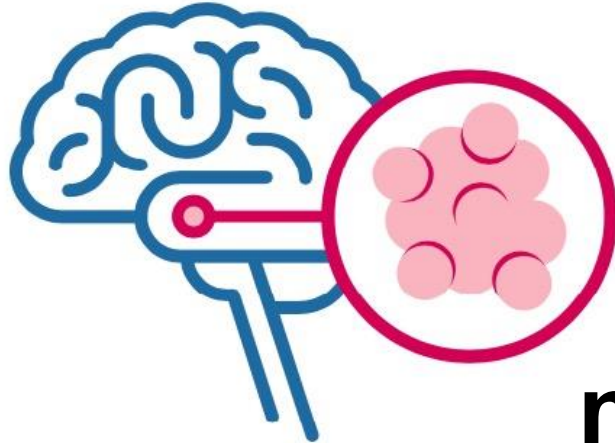
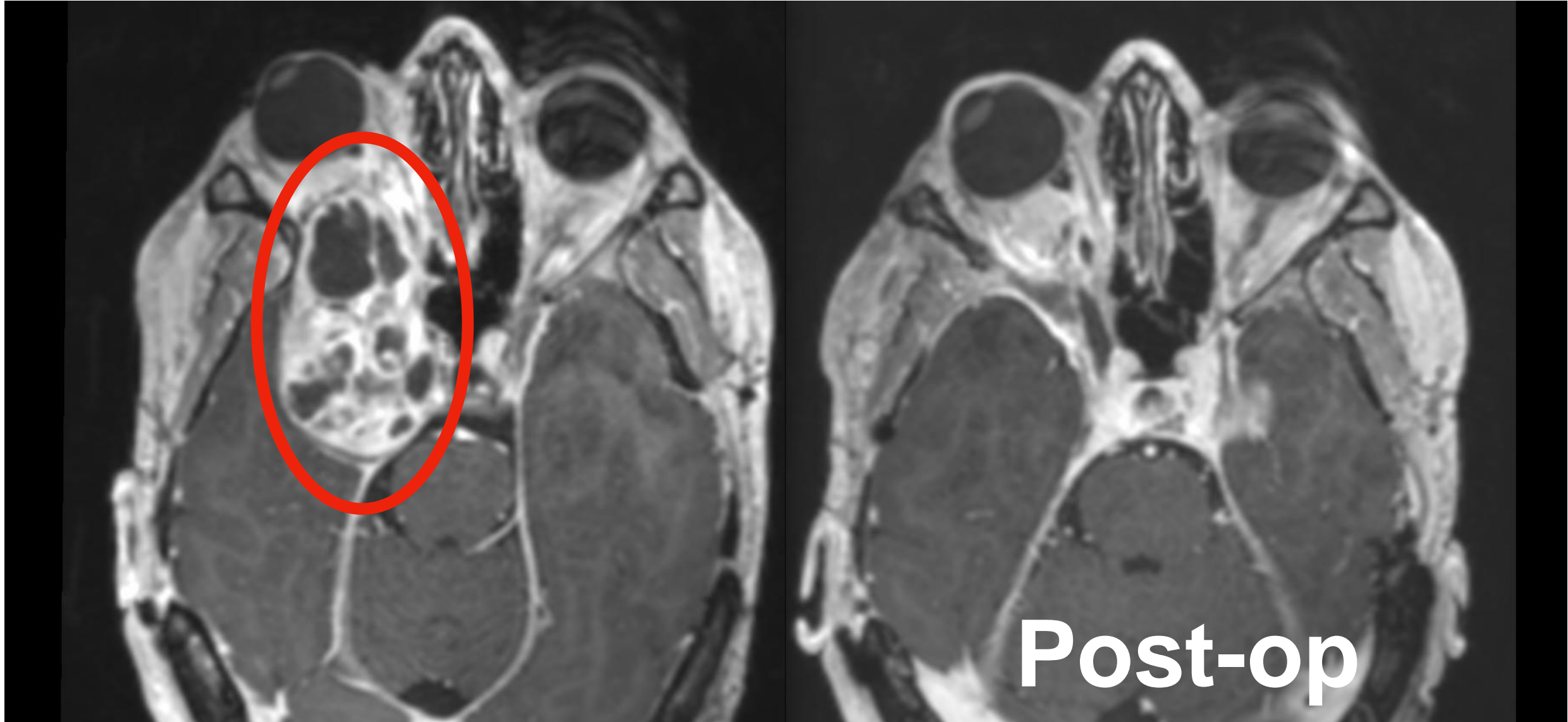
Vestibular schwannoma (Acoustic neuroma)



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Clinical Care for NF2

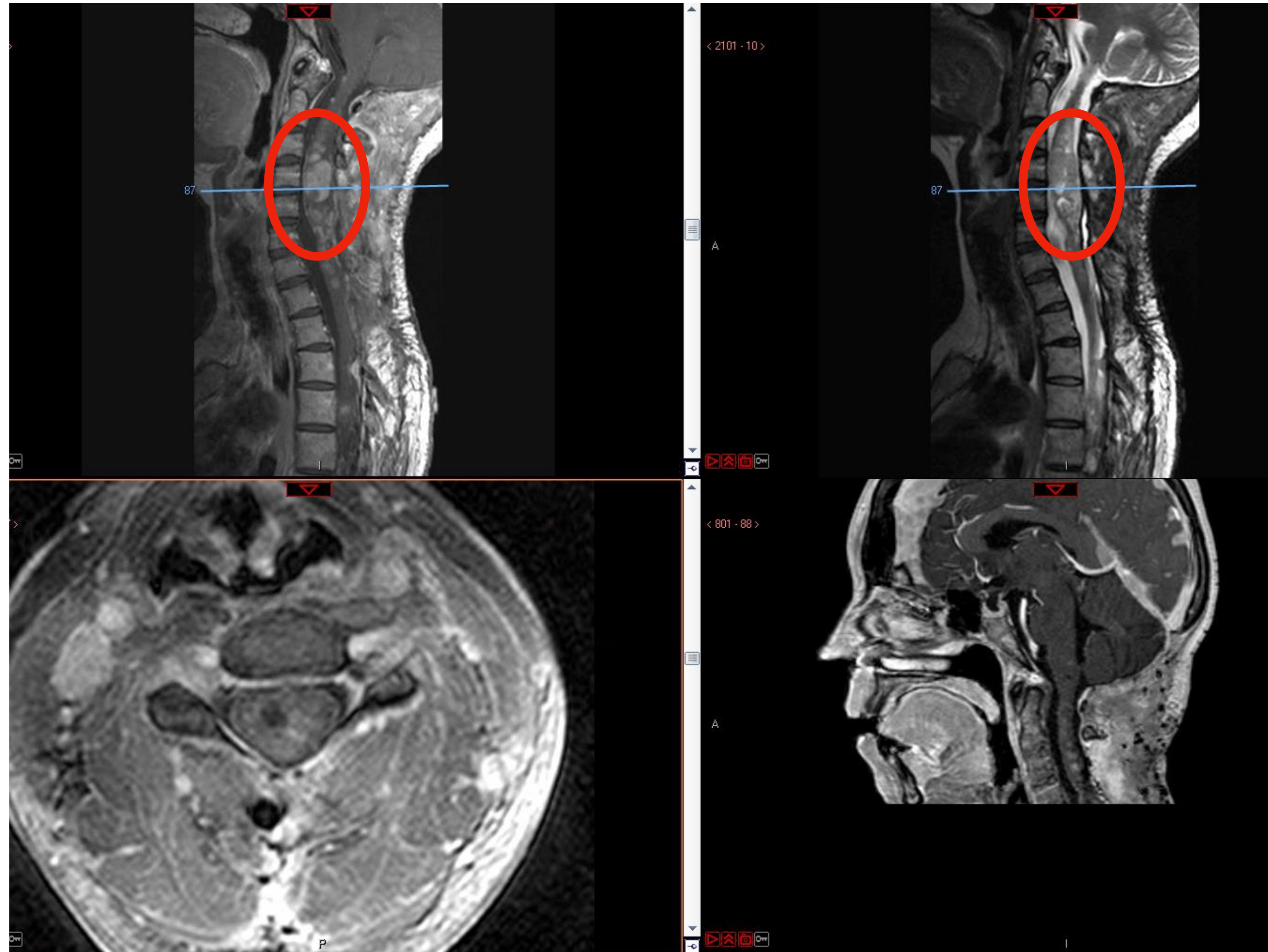
Other schwannomas



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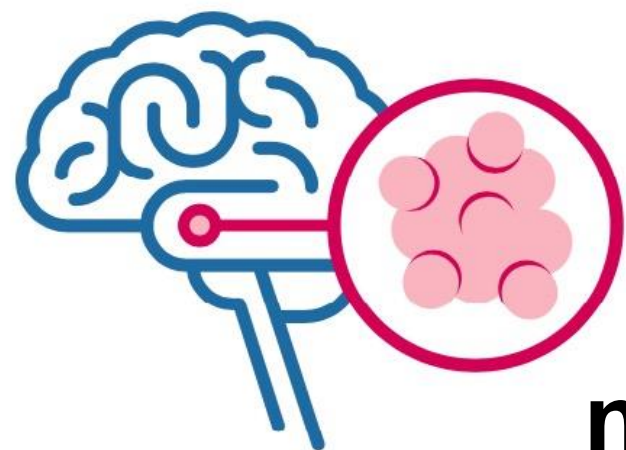
Clinical Care for NF2

**Spinal cord
ependymomas**



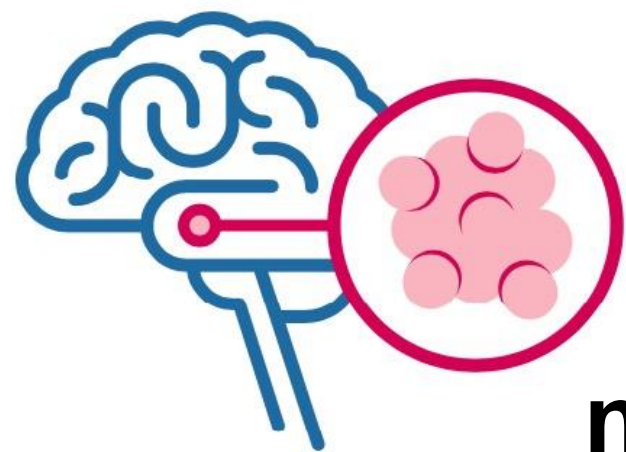
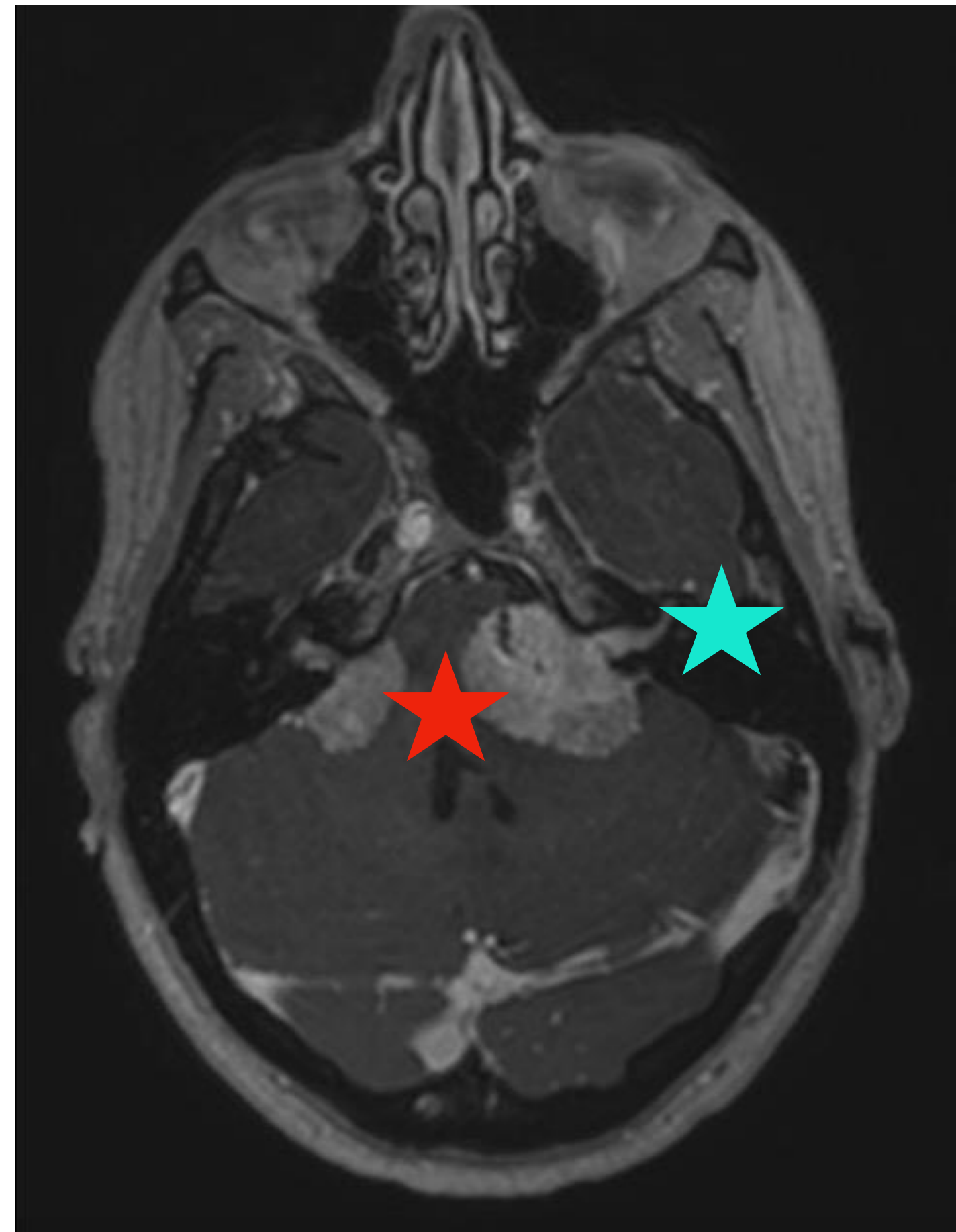
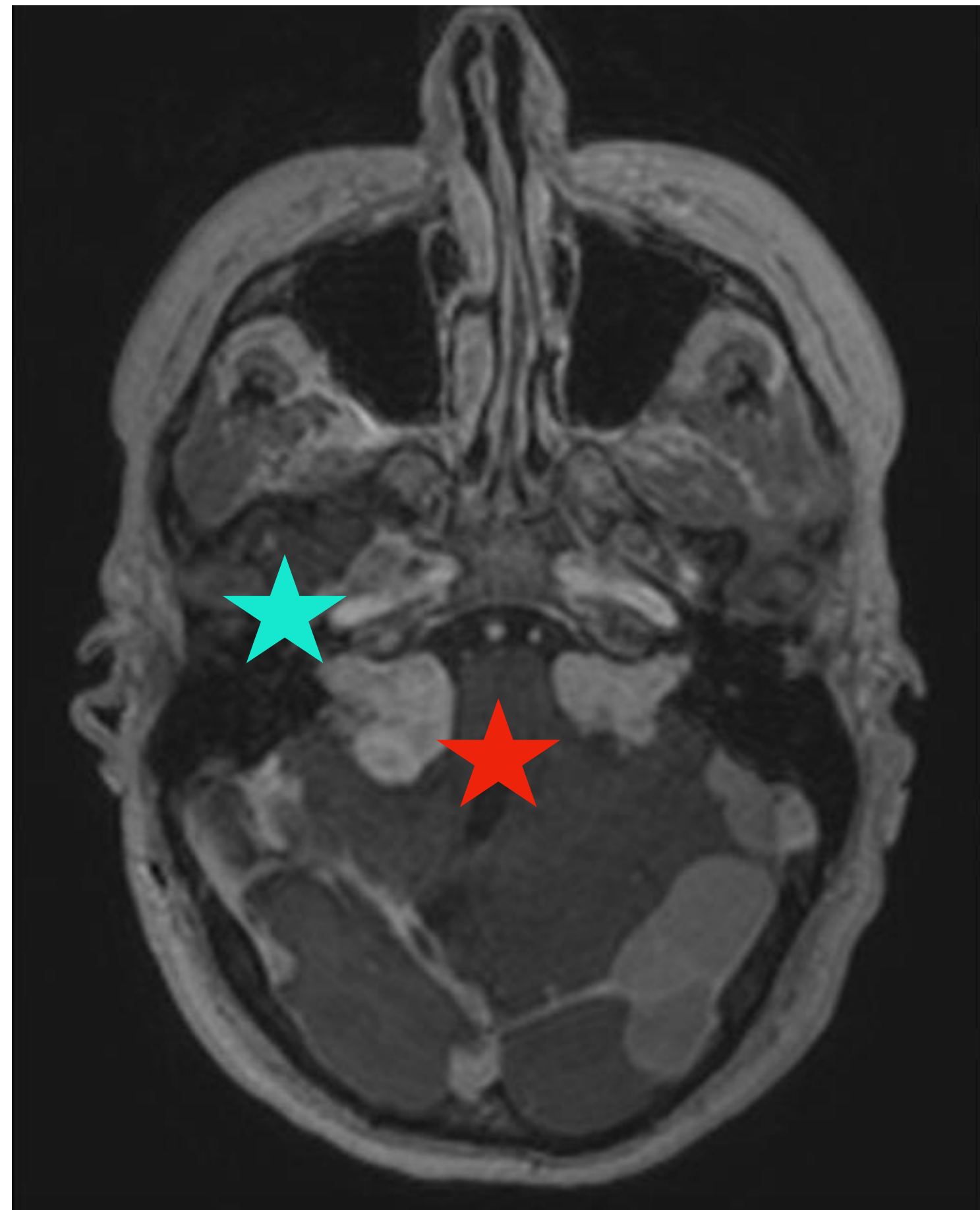
Presentation

Post-op



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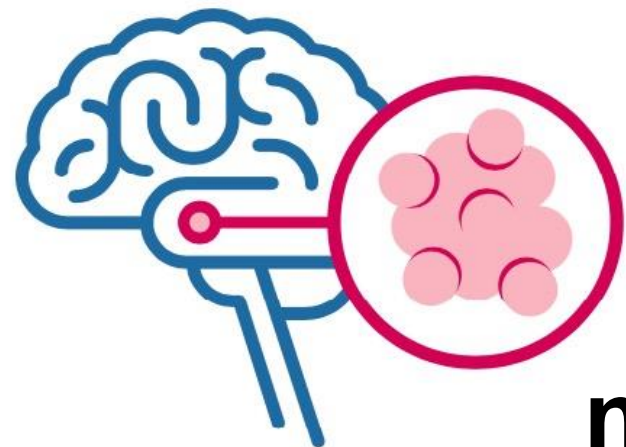
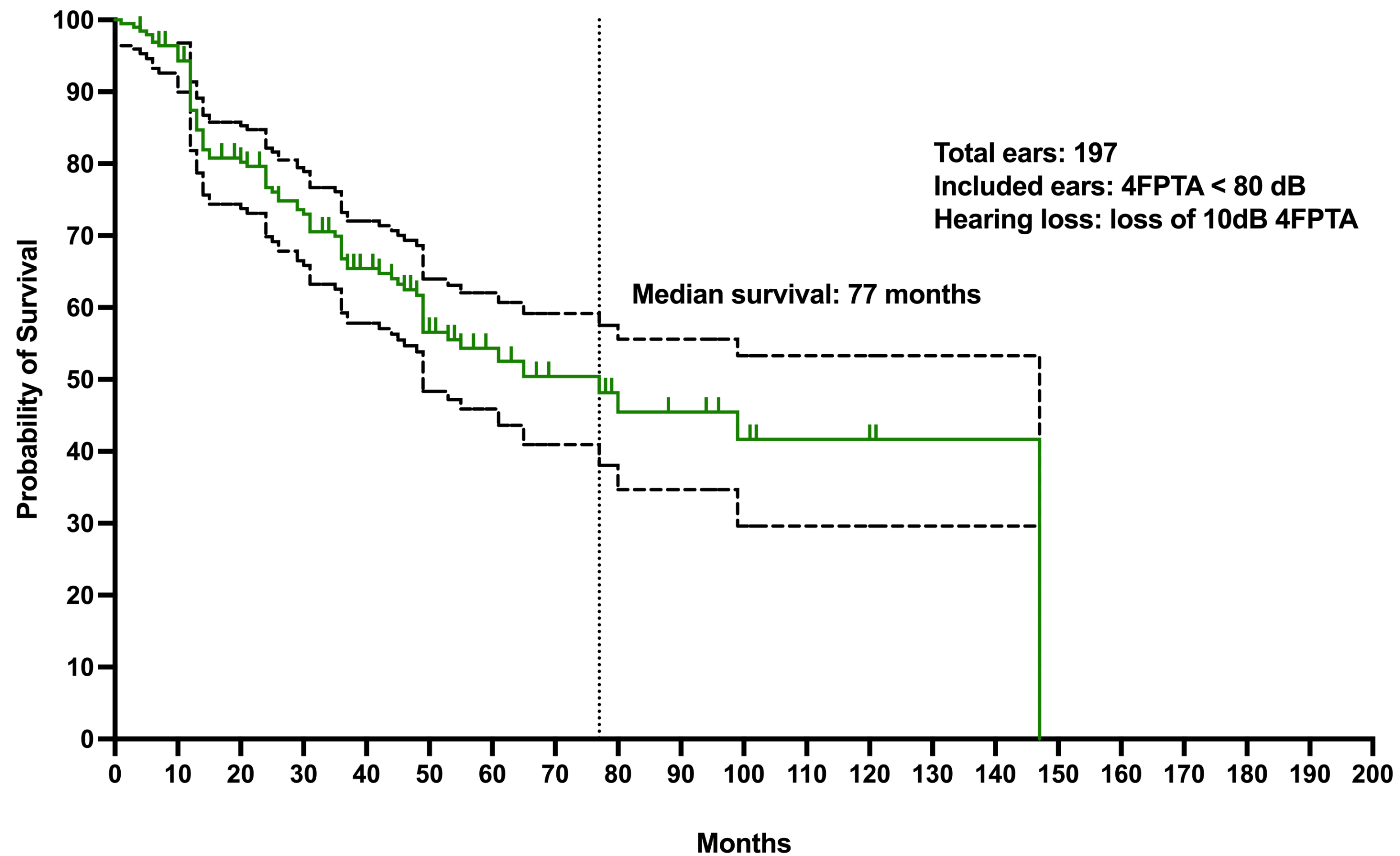
1: hearing loss can occur with small vestibular sch



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1: hearing loss can occur with small vestibular sch

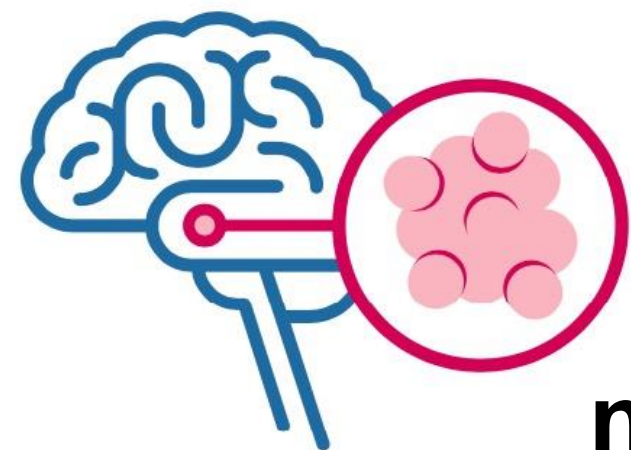
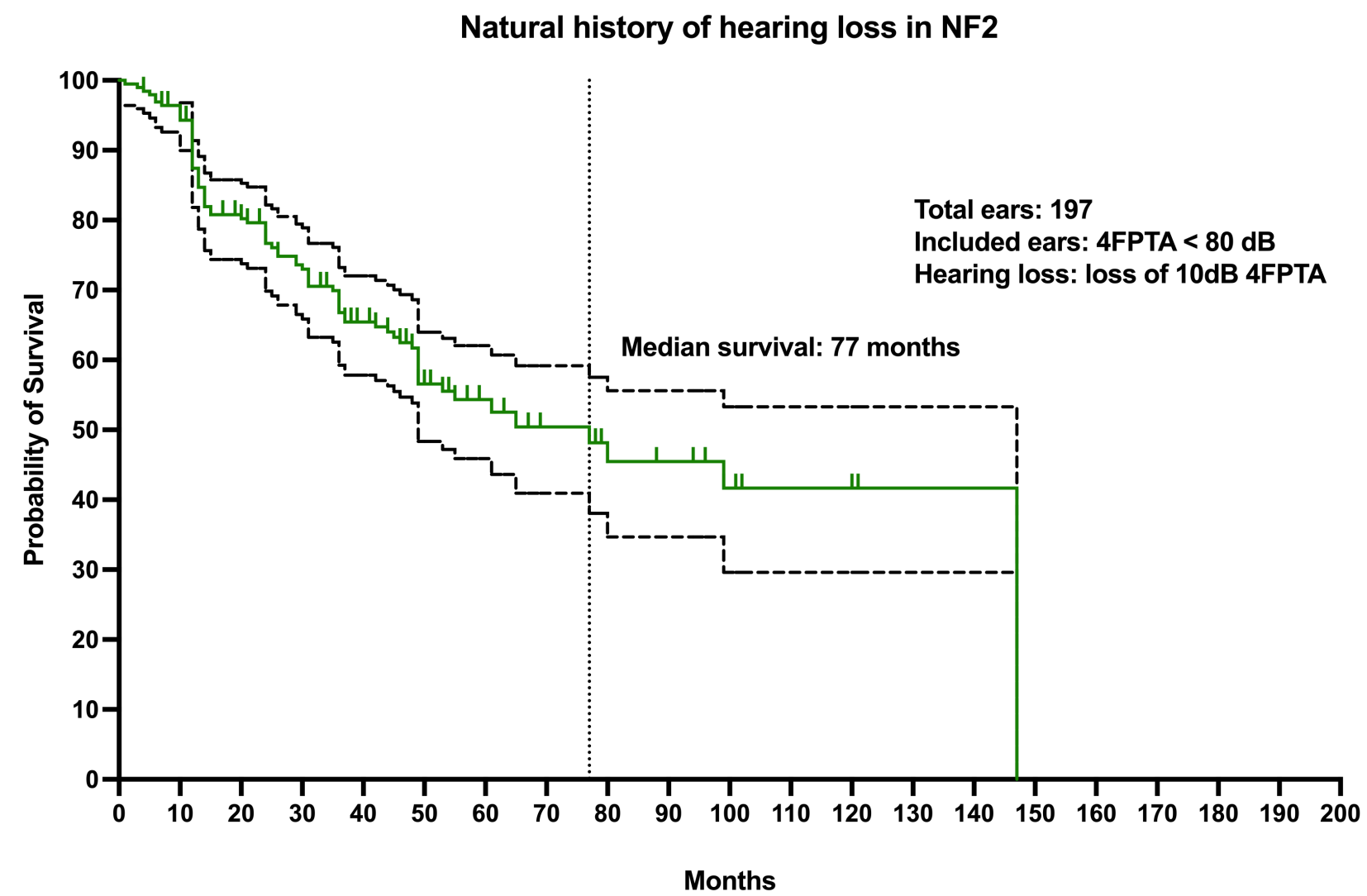
Natural history of hearing loss in NF2



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Unpublished

1: hearing loss can occur with small vestibular sch

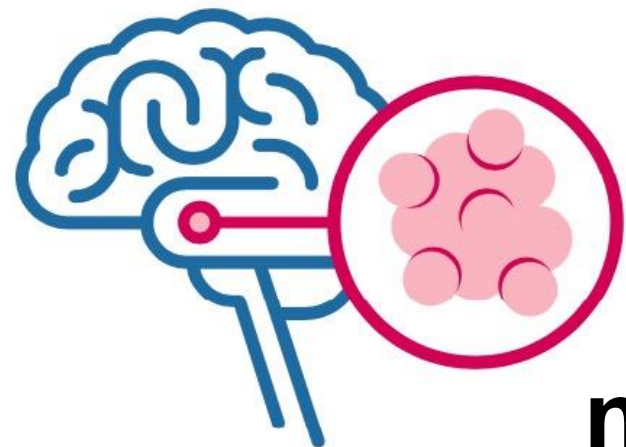
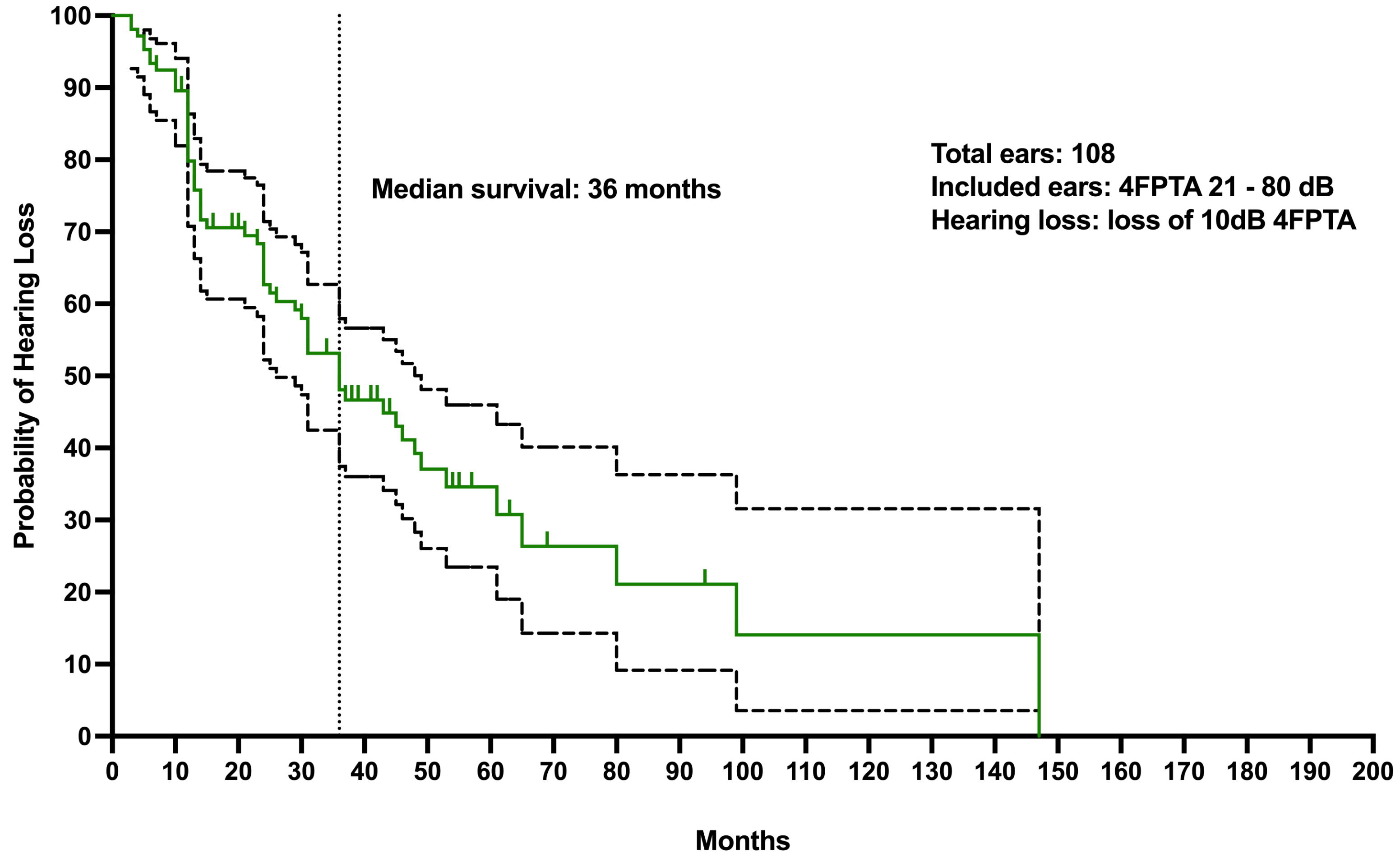
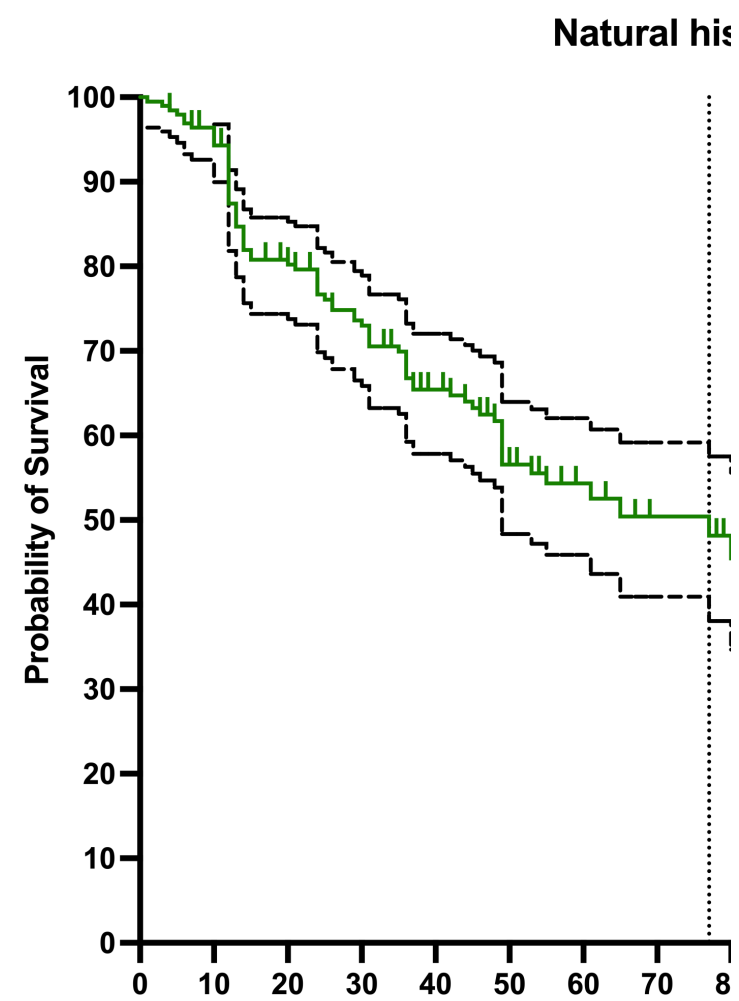


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Unpublished

hearing loss can occur with small vestibular sch

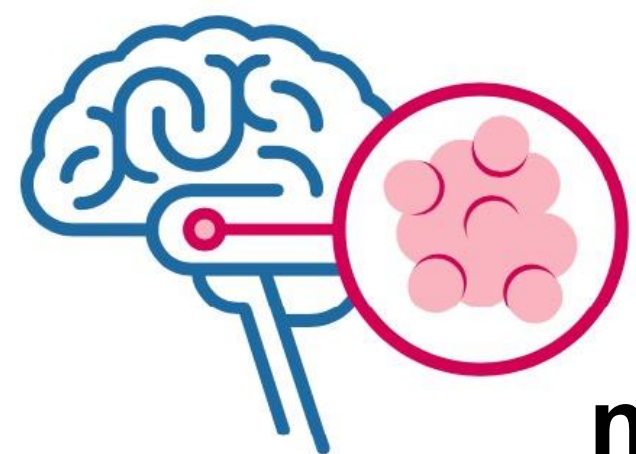
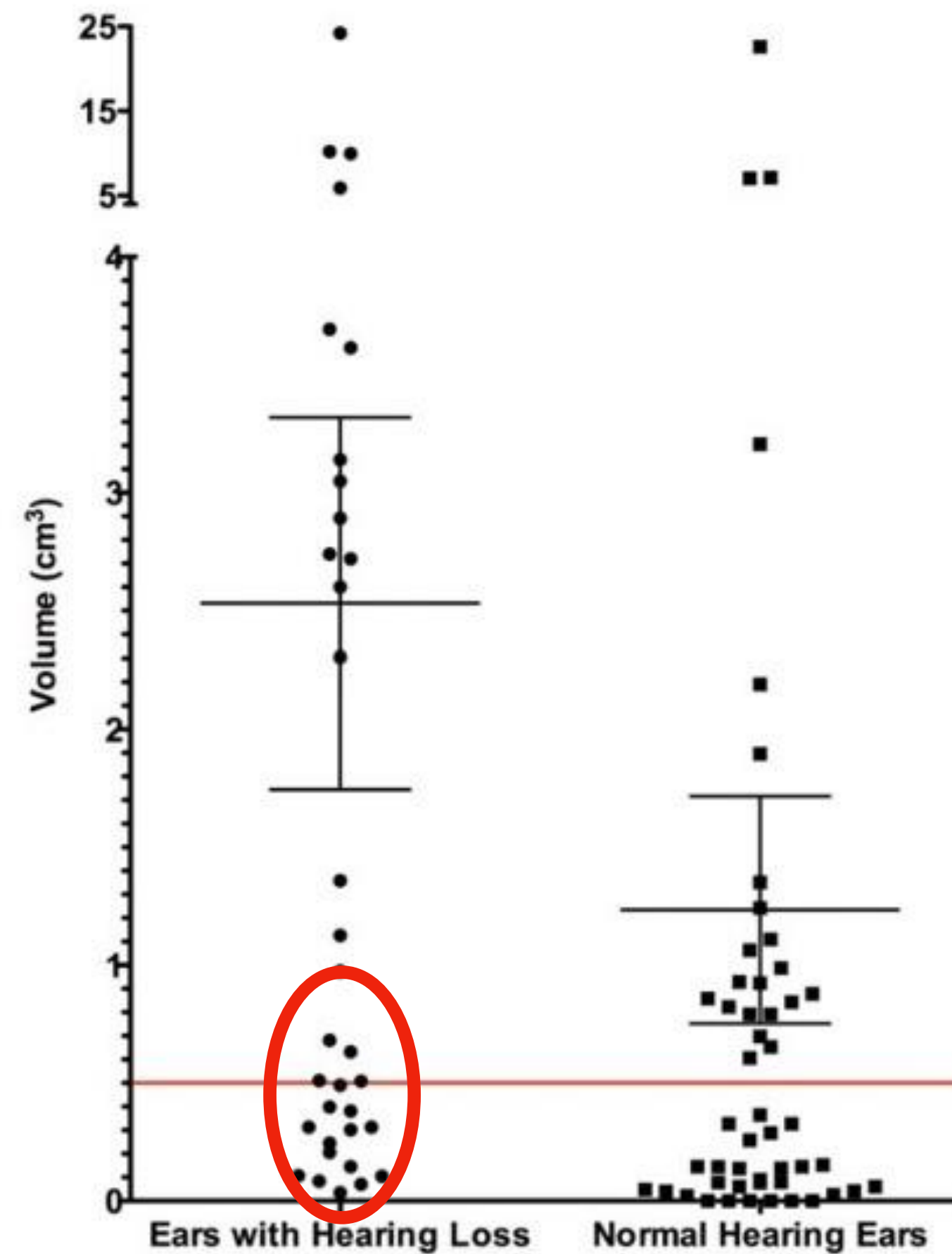
Natural history of hearing loss in NF2



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Unpublished

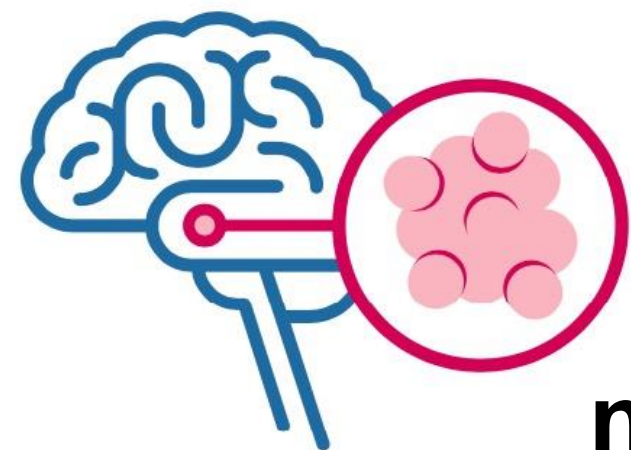
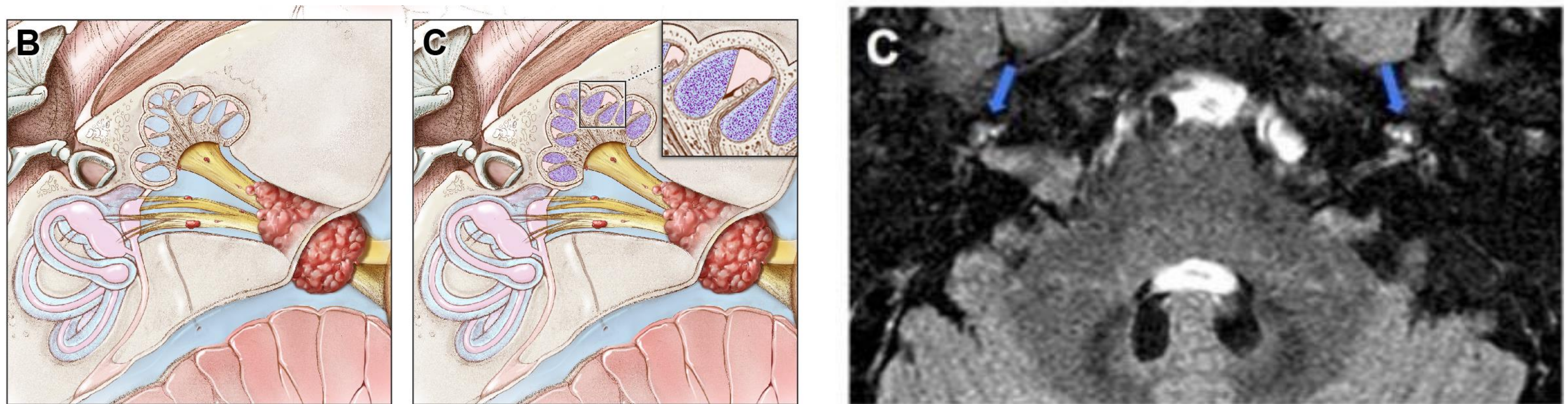
Small vestibular sch: hearing loss can occur with small vestibular sch



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Asthagiri et al. PlosOne 2012

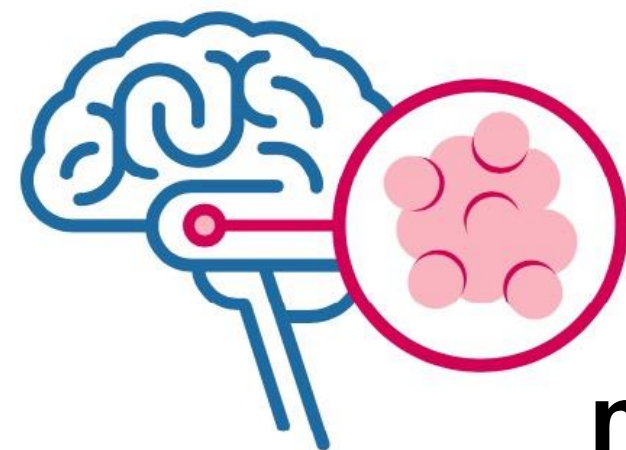
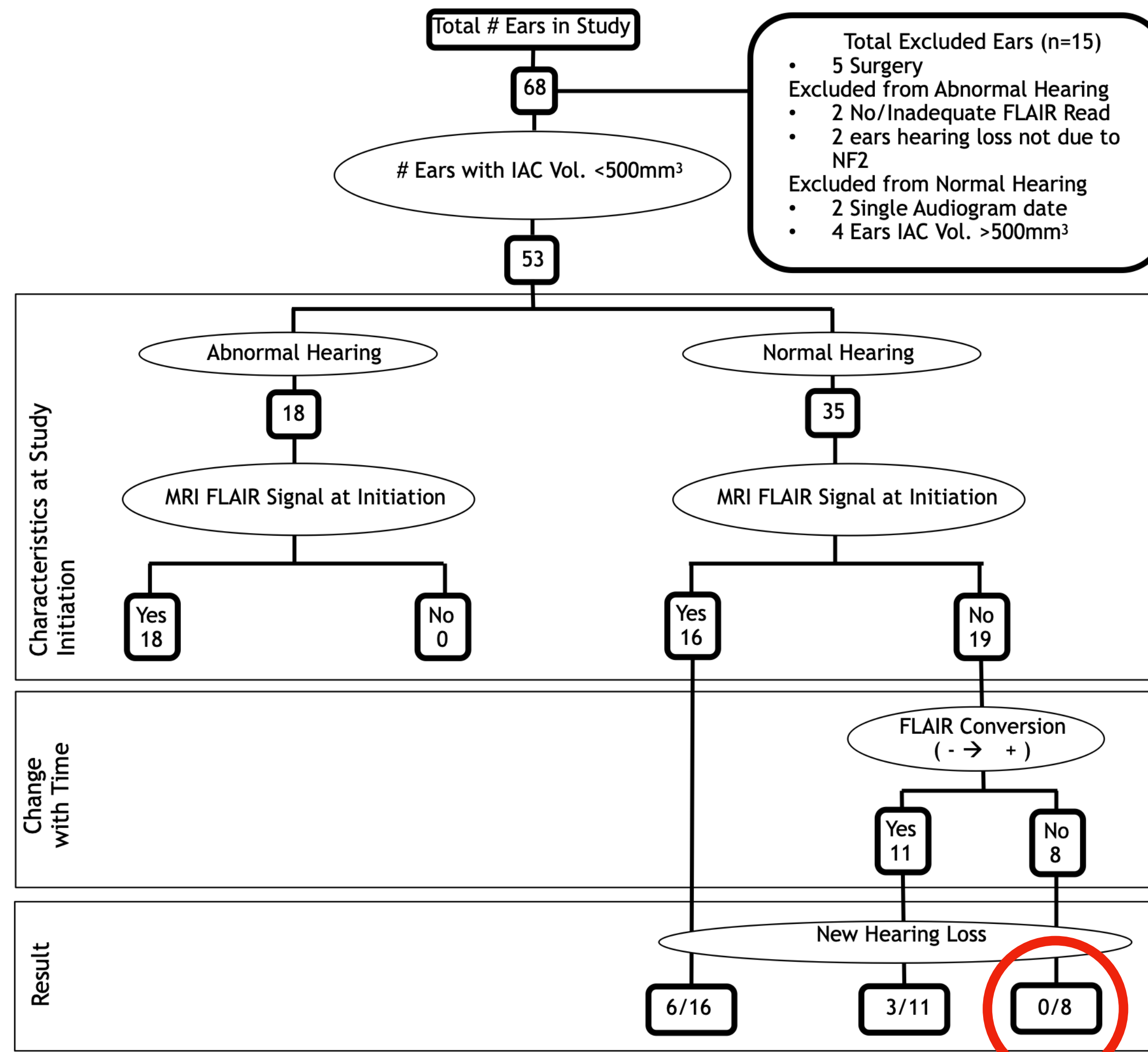
Lesson#1: hearing loss is preceded by MRI FLAIR si



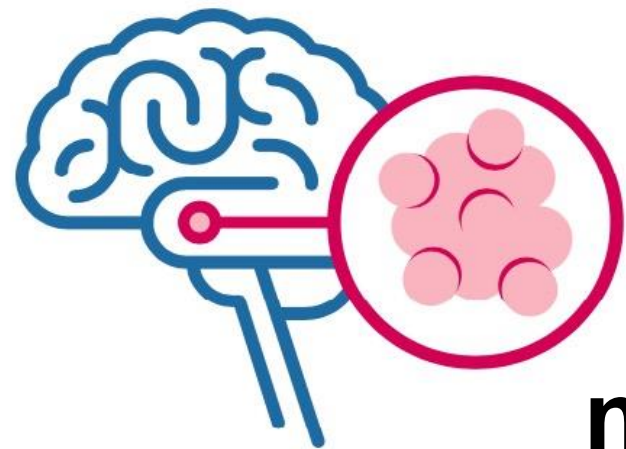
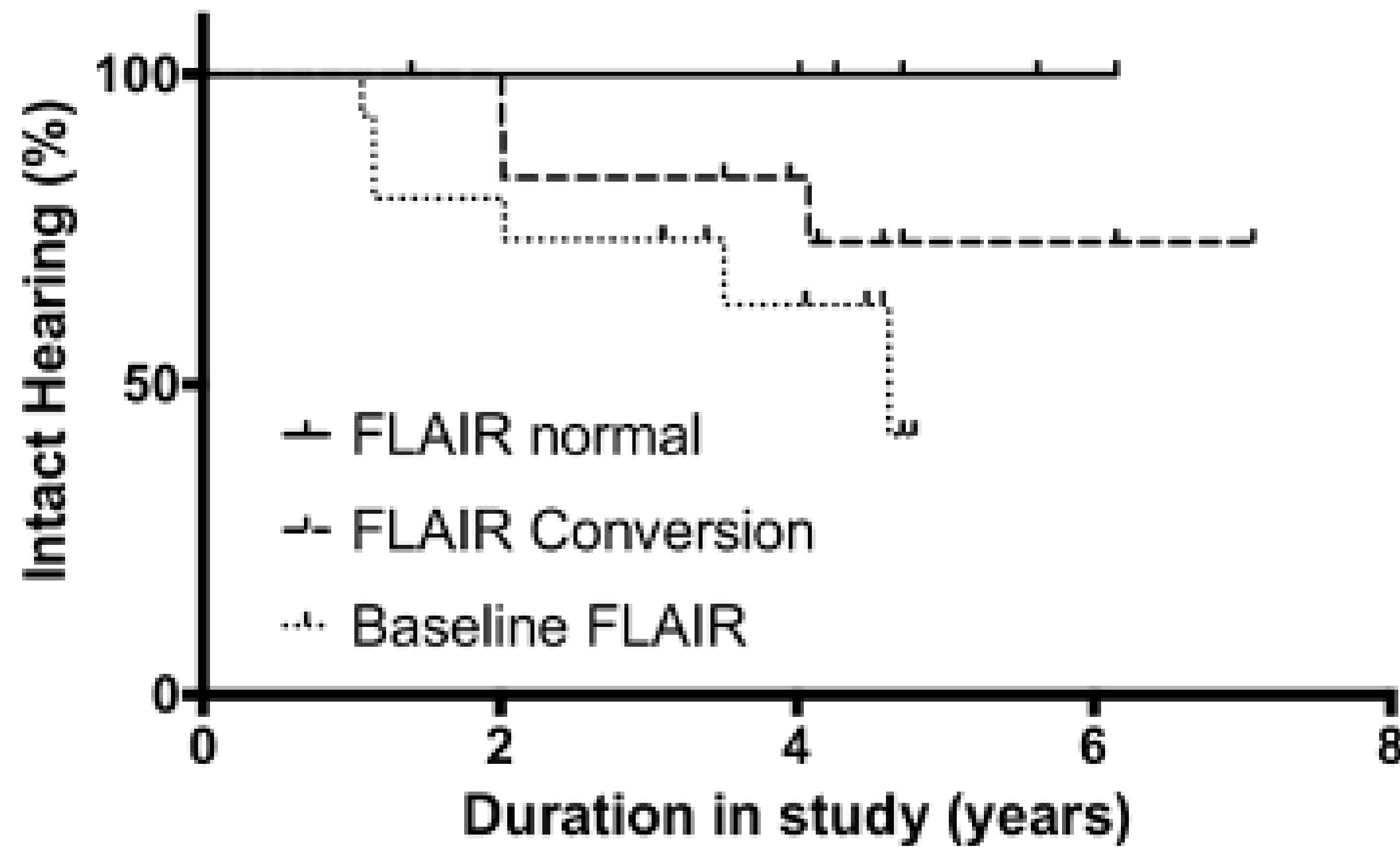
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Asthagiri et al. PlosOne 2012

#1: hearing loss does not occur if MRI FLAIR signal



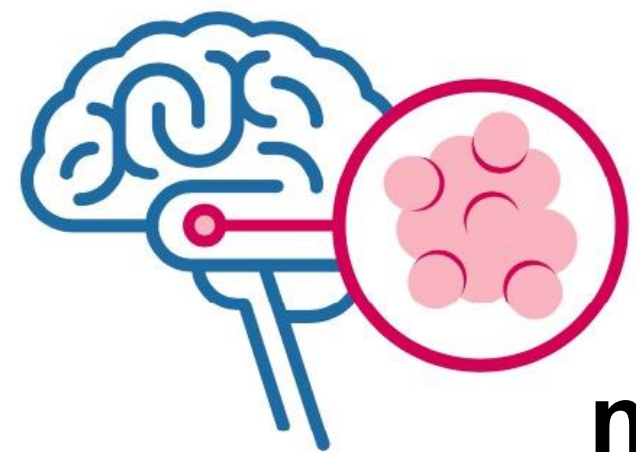
n#1: hearing loss can be predicted by MRI FLAIR s



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Unpublished

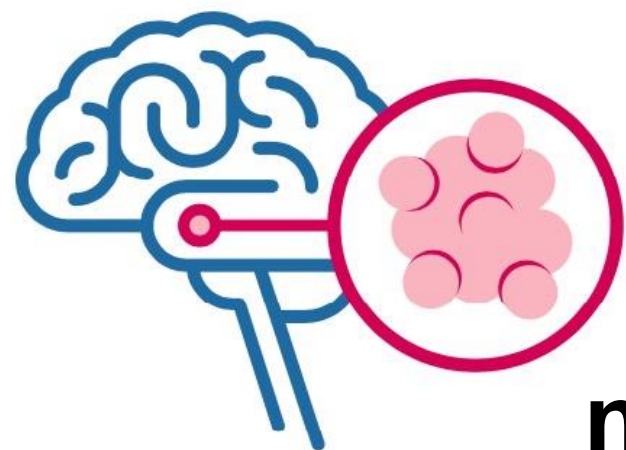
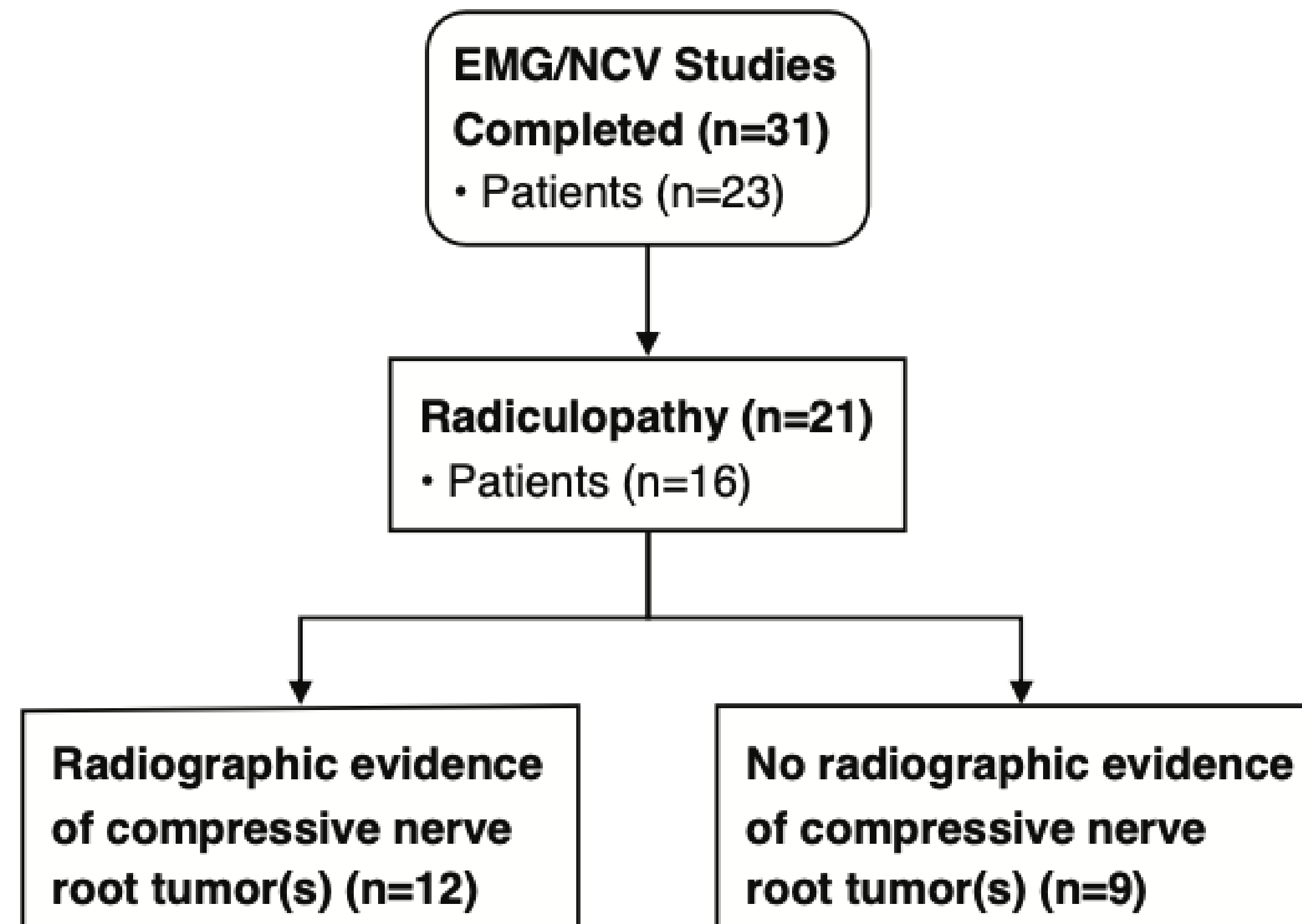
Speech and swallowing dysfunction in NF2 is unre



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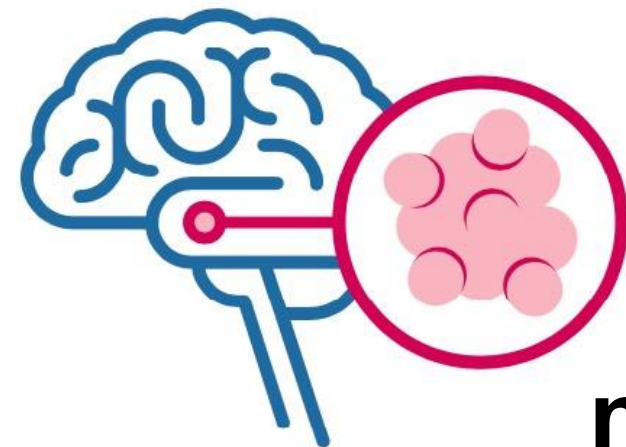
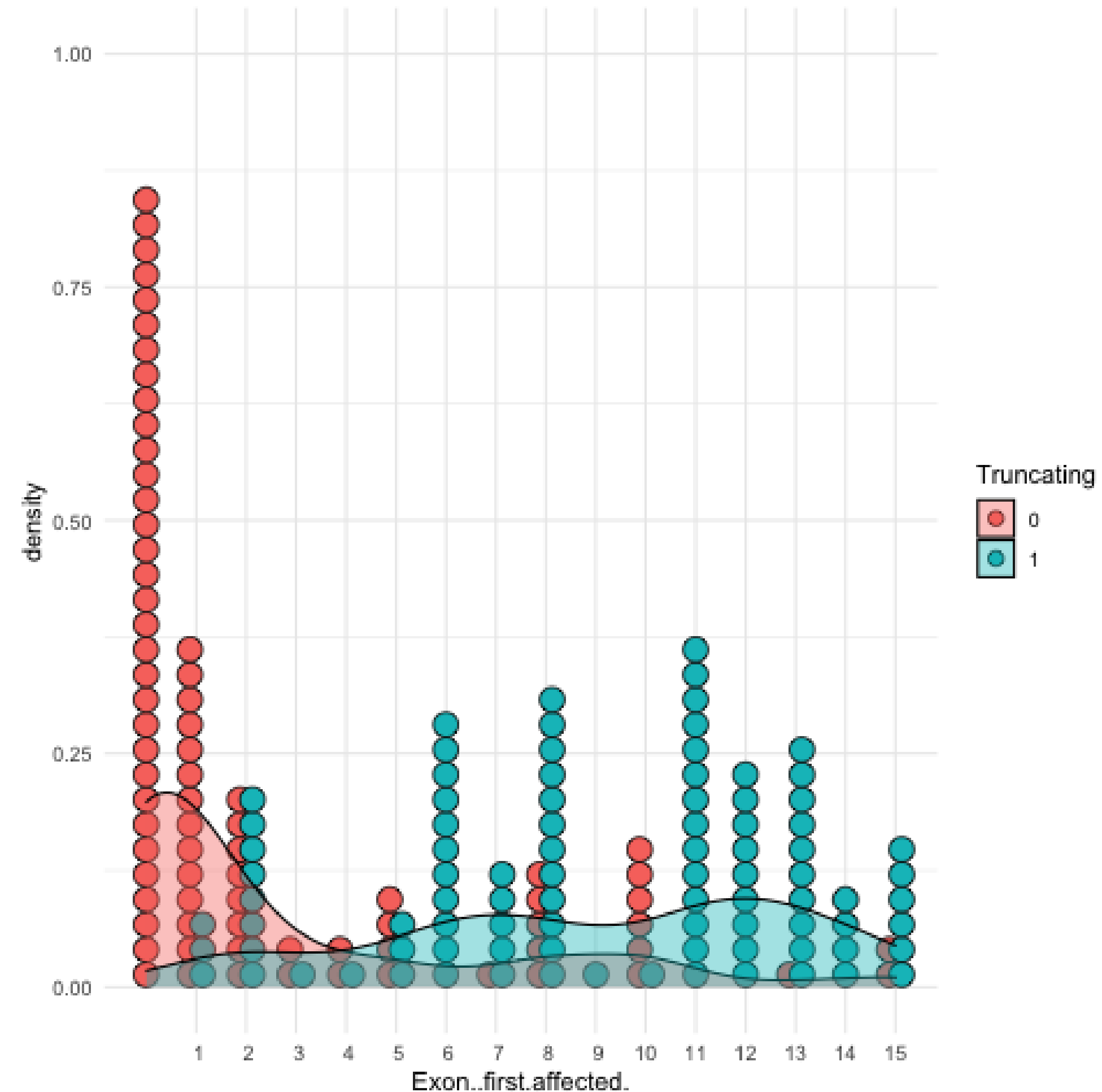
Rajendran et al. J Neurol Surg. 2021

Lesson #2: Neuropathy in NF2 is unrelated to tumor



Genotype-phenotype association in NF2

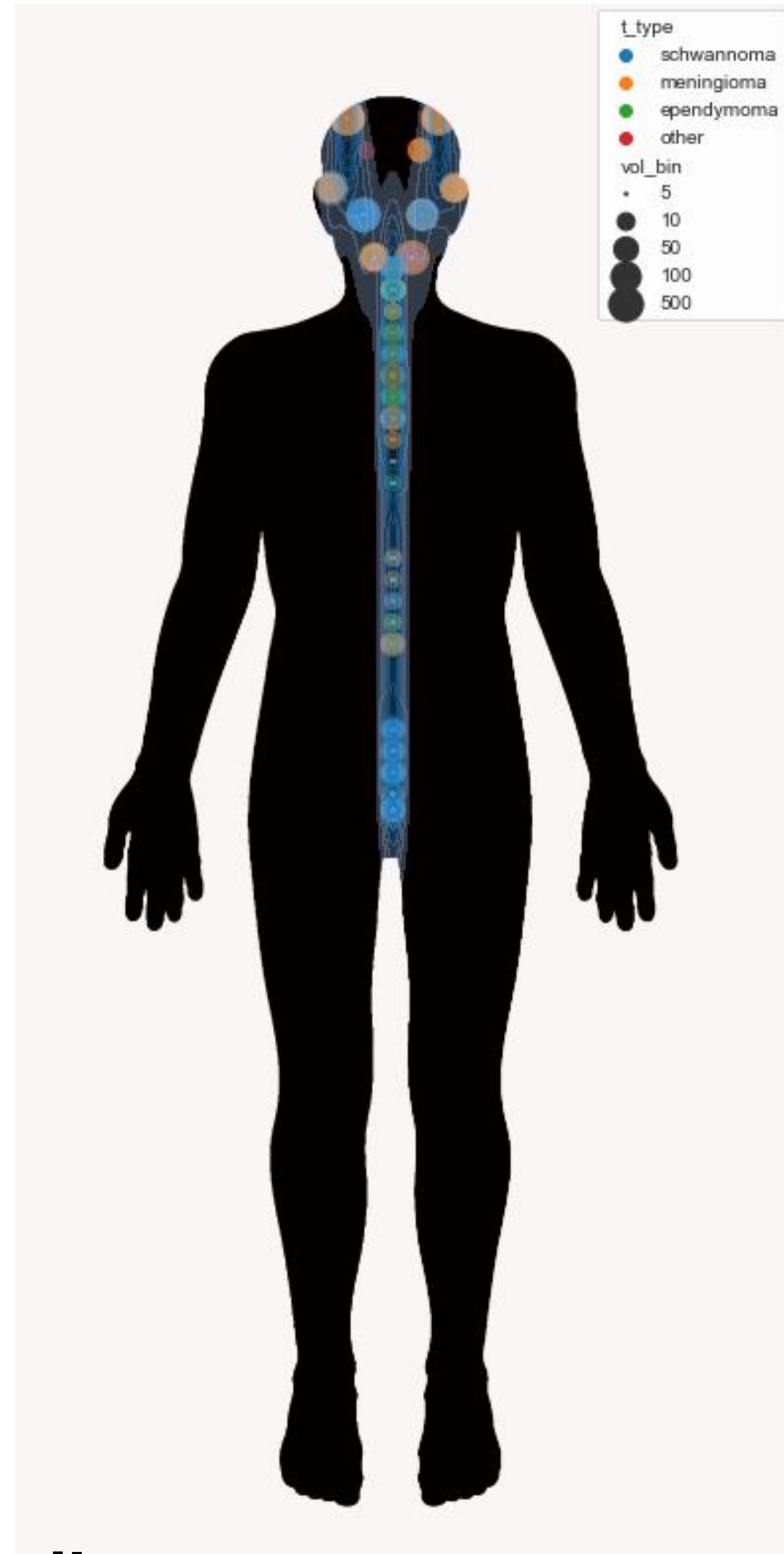
Mutation types	# of patients	% (n=166)
Deletion/Insertion - Large partial	26	16%
Deletion/Insertion - non-frameshift	2	1%
Deletion/Insertion - small frameshift	19	11%
Missense	1	1%
Nonsense	59	36%
Splice site	27	16%
Splice site - predicted truncating	11	7%
Splice site - predicted non-truncating	16	10%
Not found	32	19%
Truncating	89	54%
Non-truncating	77	46%
Truncating (non-mosaic)	68	41%
Non-truncating (non-mosaic)	44	27%
	54	33%



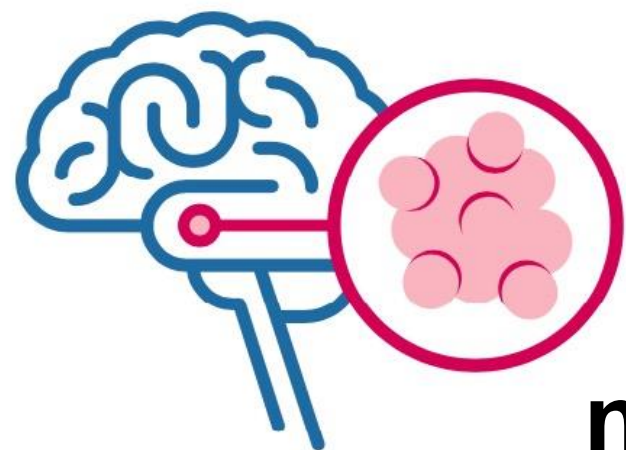
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Unpublished

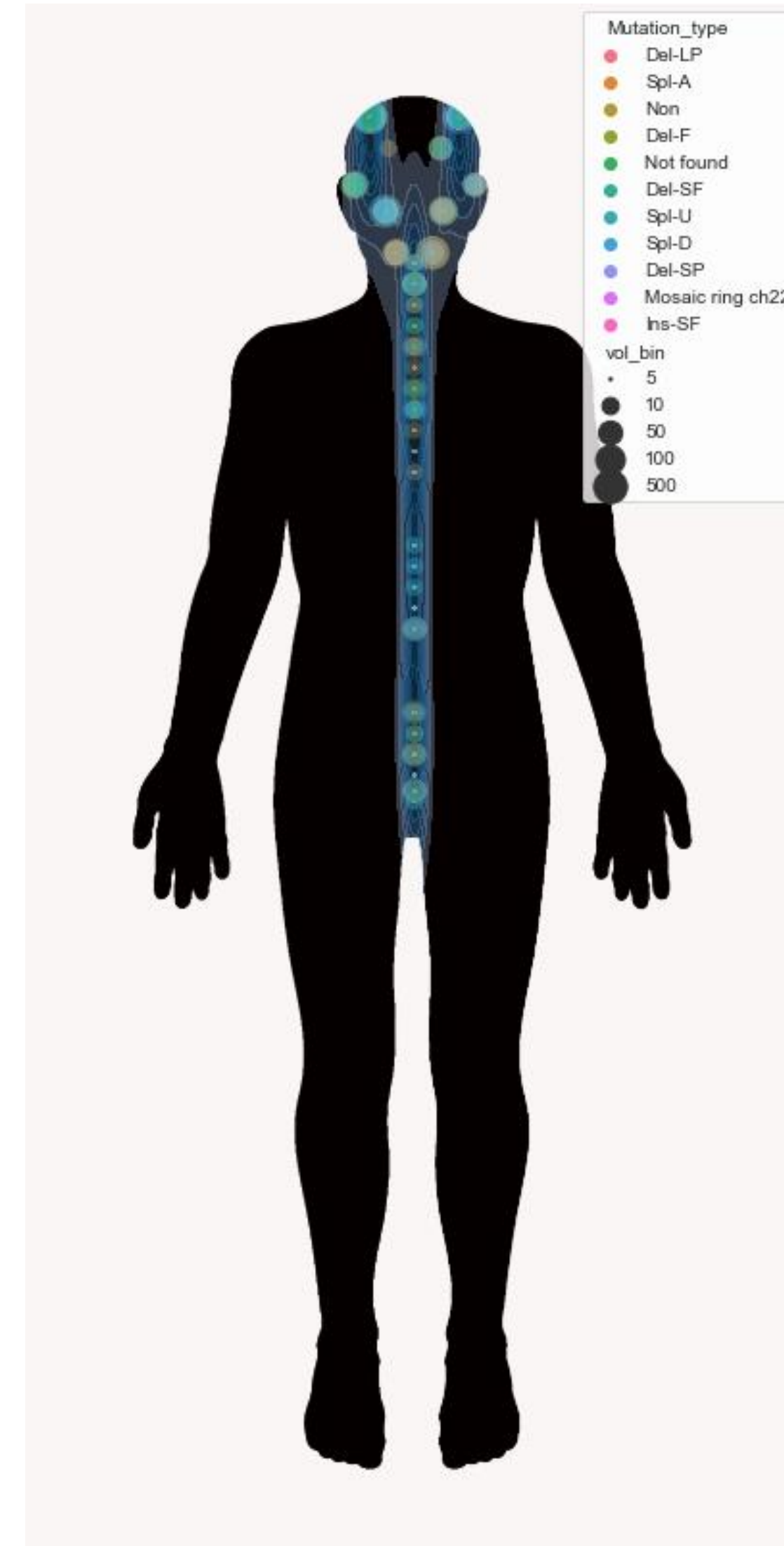
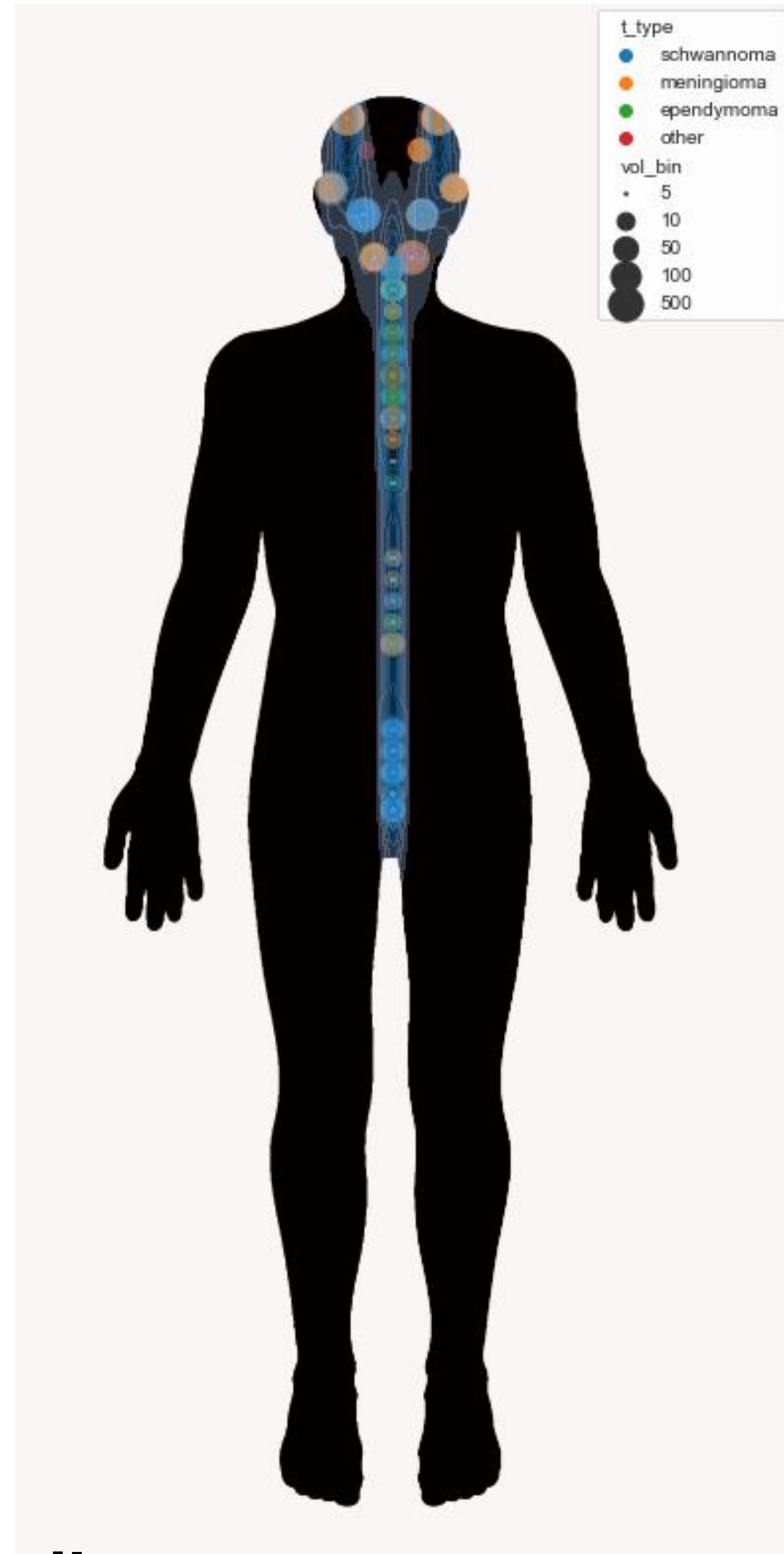
Genotype-phenotype association in NF2



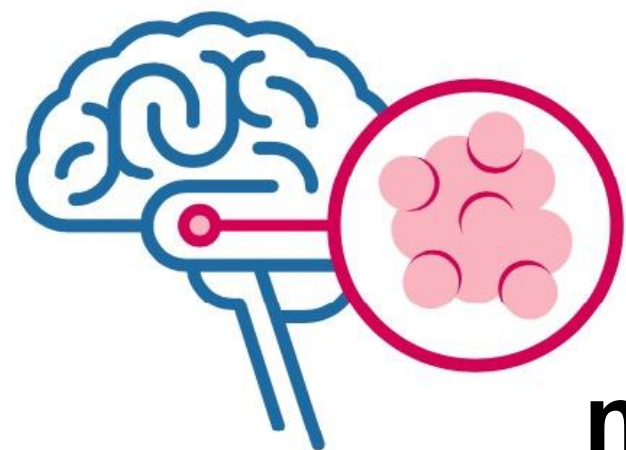
Distribution of ~5000 tumors by tumor type in 168 patients.



Genotype-phenotype association in NF2



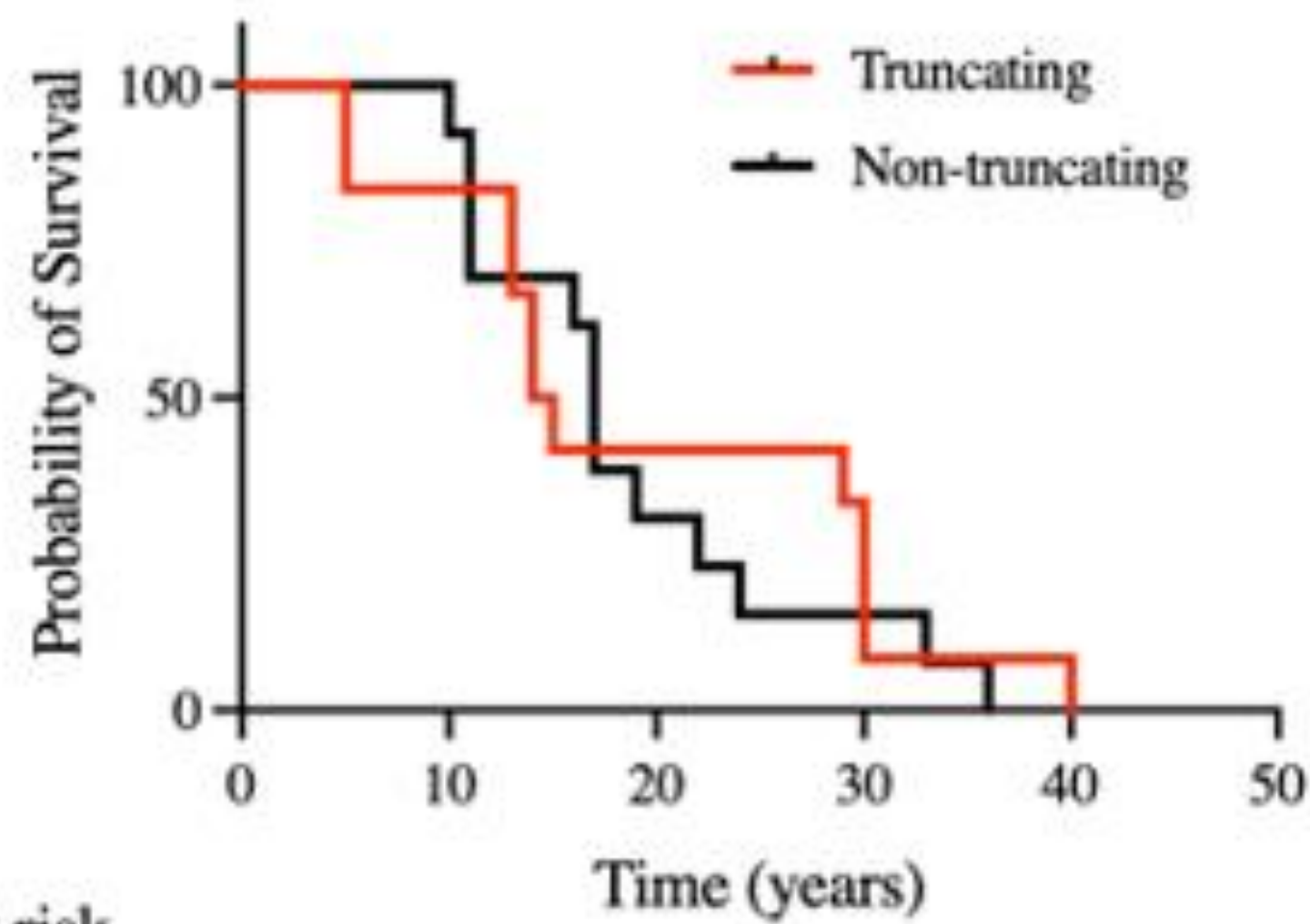
Distribution by mutation type



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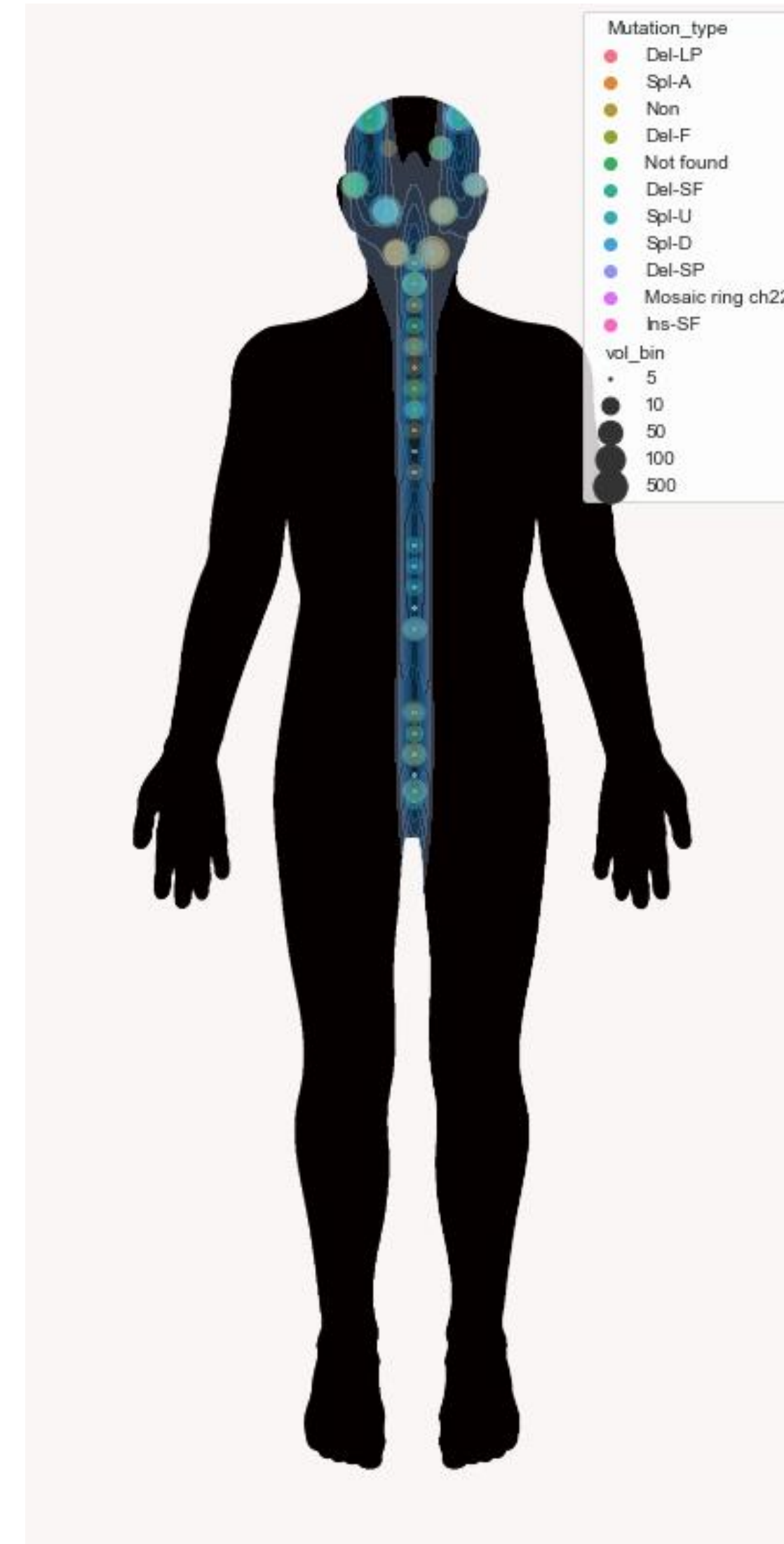
Unpublished

Genotype-phenotype association in NF2

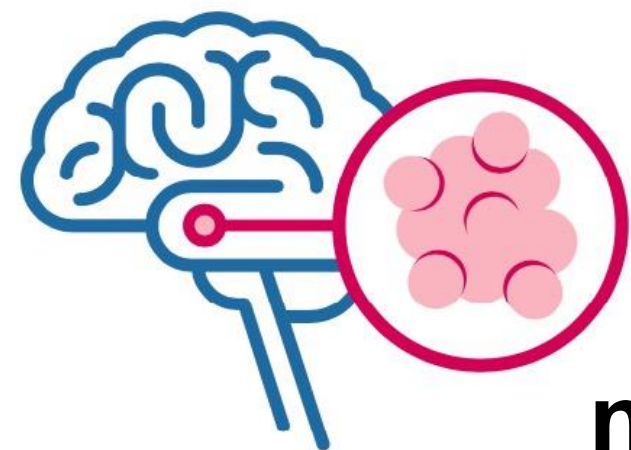


Number at risk

Truncating	13	13	4	2	0
Non-truncating	12	10	5	4	1



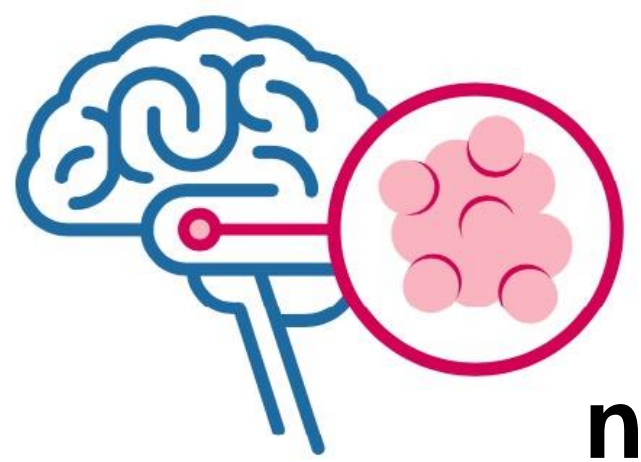
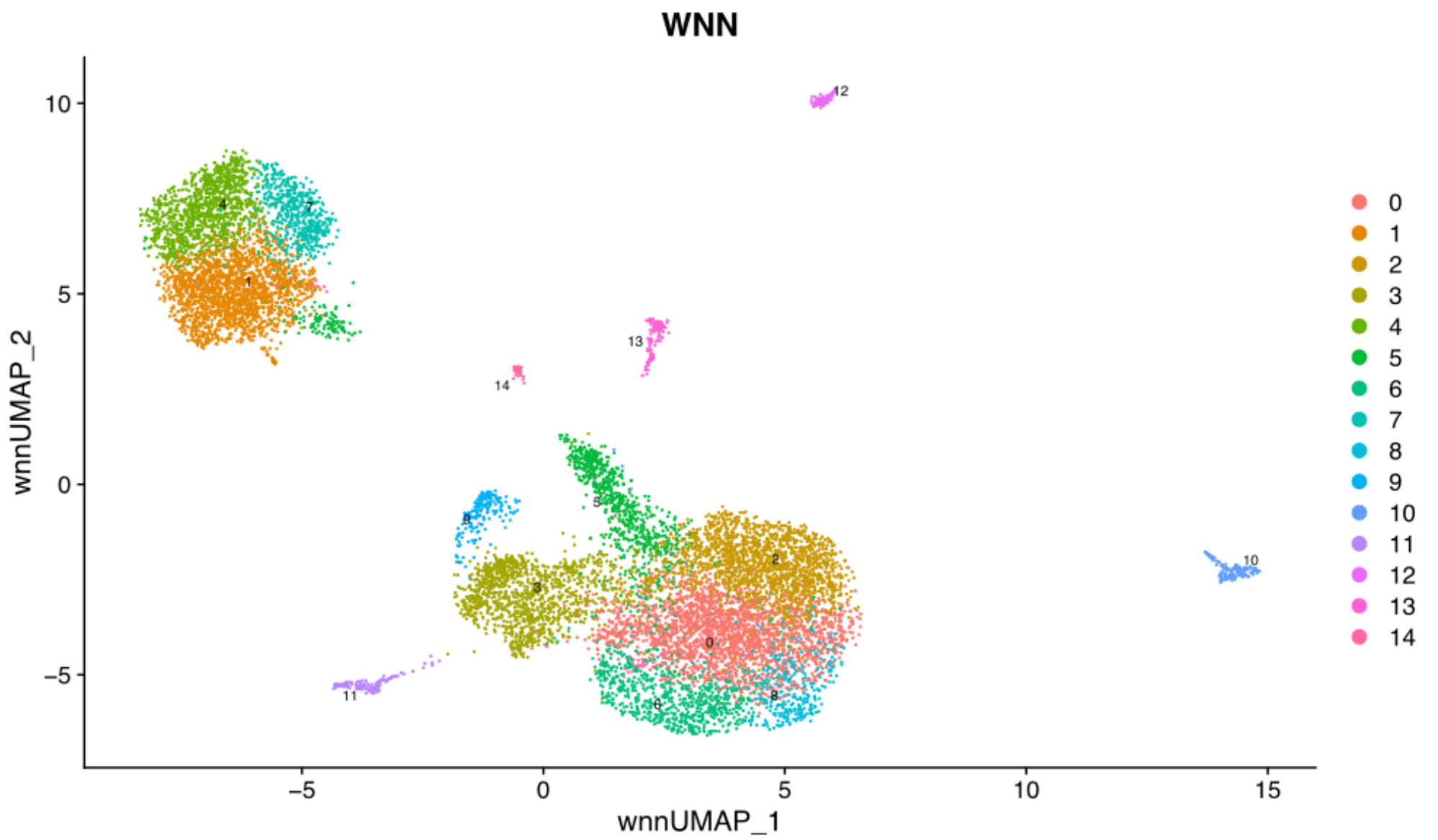
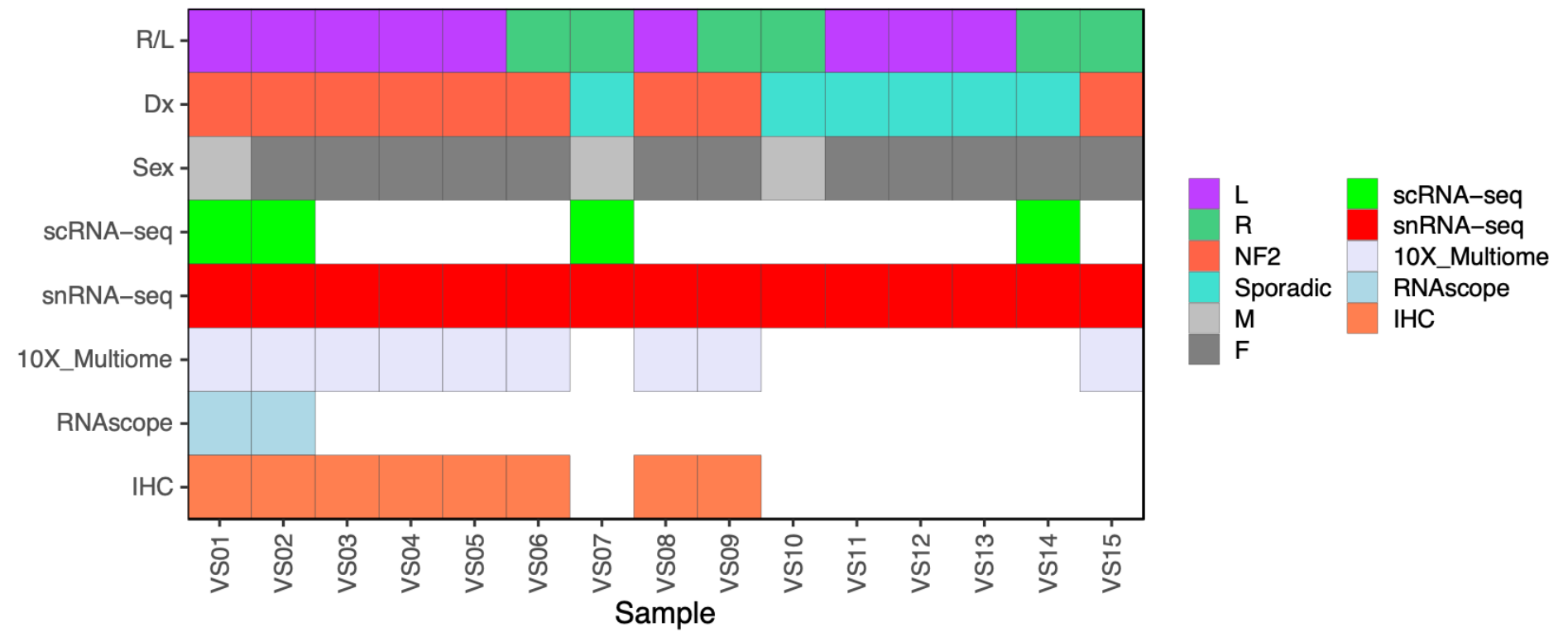
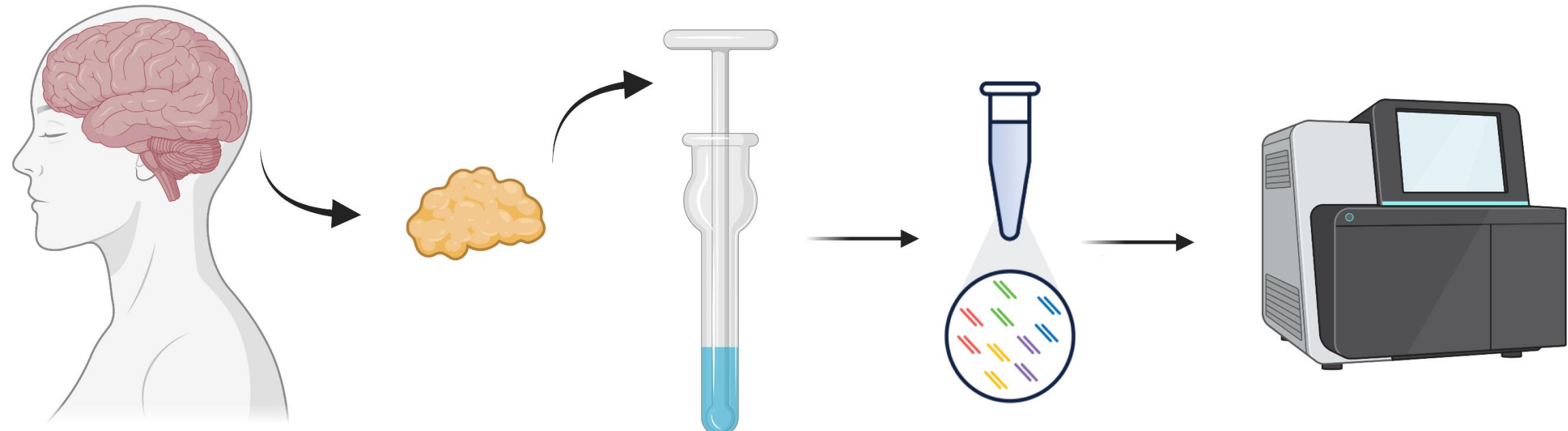
Distribution by mutation type



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Unpublished

Tumor drivers in NF2 vestibular schwannomas



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Unpublished

Collaborative data sharing

Clearinghouse for natural history 'control' cohorts

RECRUITING 

ClinicalTrials.gov Identifier: NCT04374305

Innovative Trial for Understanding the Impact of Targeted Therapies in NF2 (INTUITT-NF2)

Information provided by Scott R. Plotkin, MD, PhD, Massachusetts General Hospital (Responsible Party)

Last Updated: October 18, 2022

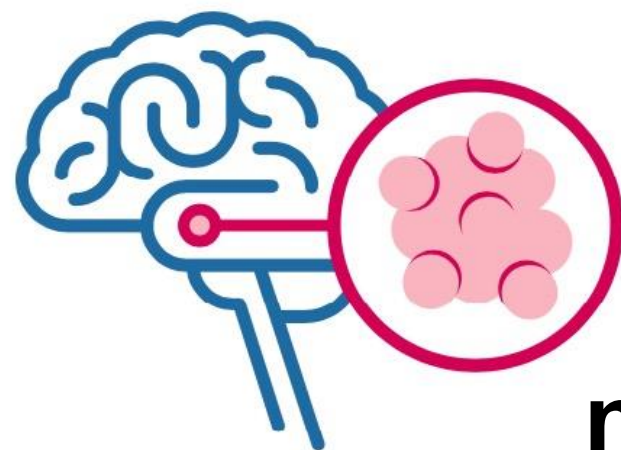
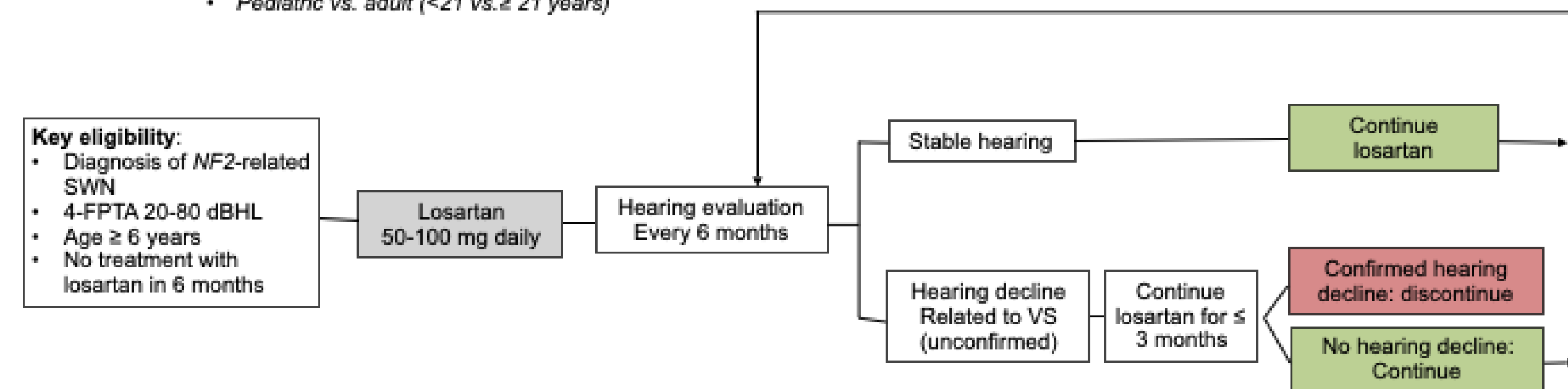


Scott Plotkin, MD

Study design: single arm study

Proposed Losartan study

- Stratified by
- monaural vs. binaural
 - Tumor size (≤ 1 cc vs. > 1 cc)
 - Pediatric vs. adult (< 21 vs. ≥ 21 years)



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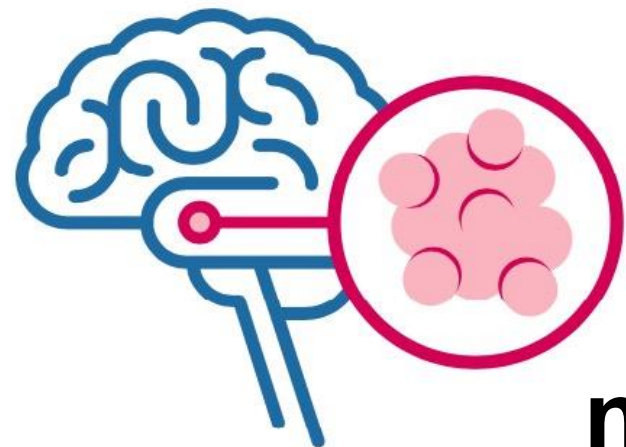
Updated Study: Objectives

Primary Objective

To determine the natural history (clinical and radiographic) of nervous system tumors in NF2.

Secondary Objectives

1. To identify the underlying causes, and patterns of progression of speech and swallowing problems in patients with NF2.
2. To identify imaging biomarkers of hearing loss in patients with NF2.
4. To identify the etiology of peripheral neuropathy in patients with NF2.
5. To identify serum biomarkers of NF2 disease progression.
6. To accurately map the epigenome of NF2 tumor related tumors.



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Updated study: Interventions

Target enrollment - 100 subjects
10 year follow up

Imaging

1. Volumetric MRI of Brain
2. Volumetric MRI of spine
3. Specialized exams: MRI FLAIR
4. Whole body MRI (No contrast)

Clinical

1. Neurosurgery clinical evaluation
2. Neurotology clinical evaluation
3. Pediatric oncology evaluation
4. Karnofsky performance status
5. Ambulatory function
6. ASIA grading scale

Patient reported measures

1. Functional independence measure
2. ~~SF36~~ evaluation **NFTI-QOL**
3. Speech and swallowing questionnaire

Neurology

1. EMG/NCV
2. Nerve ultrasound

Audiovestibular

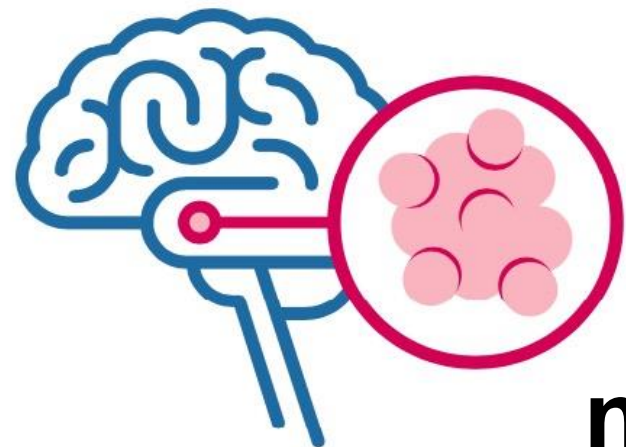
1. Audiometric evaluation
2. Vestibular evaluation

Speech Language Pathology

Rehab Medicine Evaluation

Laboratory

1. Routine labs
2. Blood/serum testing
3. **Non-CLIA custom genetic panel**



nf2@nih.gov

Michaela Cortes, BSN, RN, CCRN

Gretchen Scott, BSN, RN

Isac Kunnath, MS, CCRC

John D Heiss, MD

Christina Hayes, CRNP

Samantha Dill, CRNP



Surgical Neurology Branch,

National Institute of Neurological Disorders and Stroke

National Institutes of Health, Bethesda, MD

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