Evaluating the impact of REiNS on clinical trials for NF2 and SWN: 2011 – 2019

REiNS Winter Meeting 2019

Scott Plotkin, MD, PhD

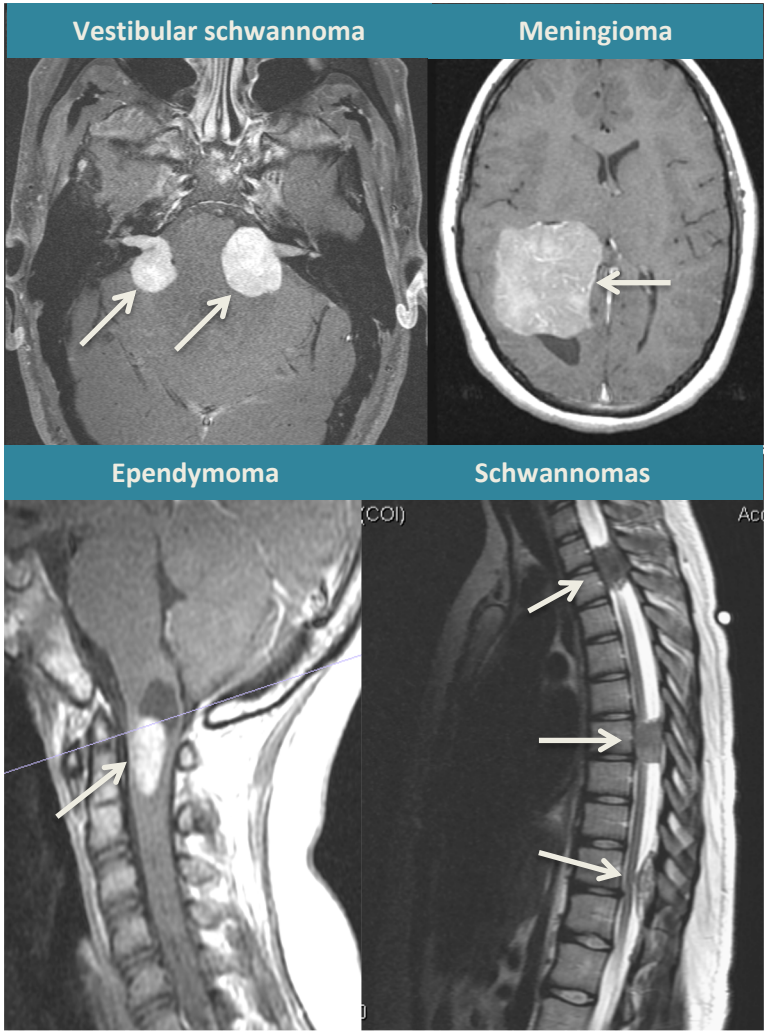
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Disclosures

- Co-founder of NFlection Therapeutics and NF2 Therapeutics, Inc
- Consulting with AstraZeneca
- None of the drugs in this presentation have been approved for use in NF2 patients by the FDA

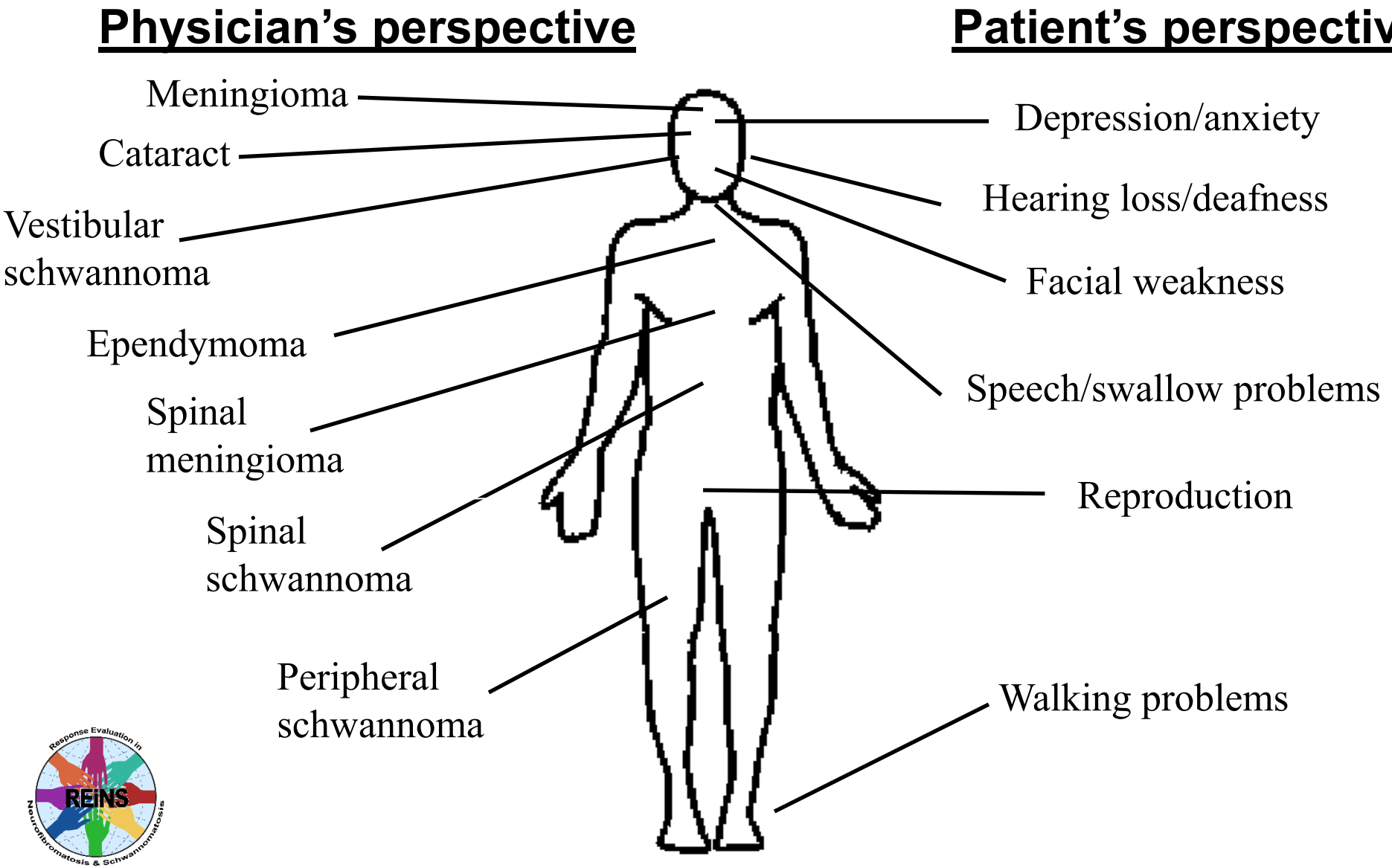
NF2 tumor suppressor syndrome

- Live birth incidence:1:25,000
  - about 12,000 Americans
- Caused by germline mutations in the *NF2* gene
- Diagnostic criteria:
  - Bilateral VS OR
  - Unilateral VS + 2 other tumors, cataracts
- Age at diagnosis: 22 years
- Multiple tumors and tumor types
- Benign histology but not benign clinical course



Evans et al., Q J Med, 304, 603-618, 1992.

Outline of talk

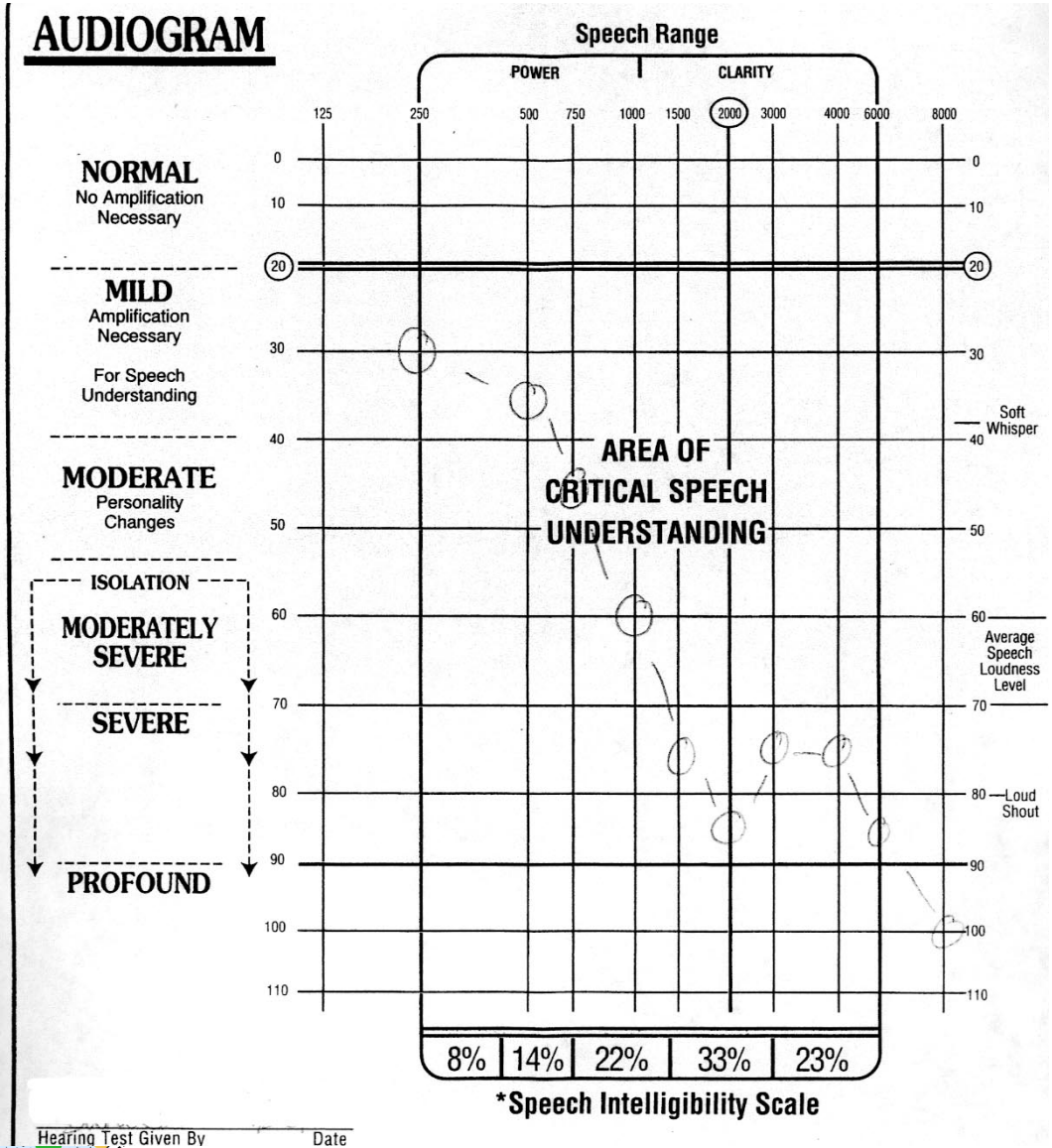


NF2 has many effects on patients

- Difficulty with communication
  - Hearing loss
  - Difficulty with speech
  - Facial weakness (reduced facial expressions)
- Mobility challenges
  - Weakness
  - Balance problems
  - Vision problems
- Psychological disorder
  - Isolation
  - Depression
  - Anxiety

Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS

Understanding hearing tests (audiology)



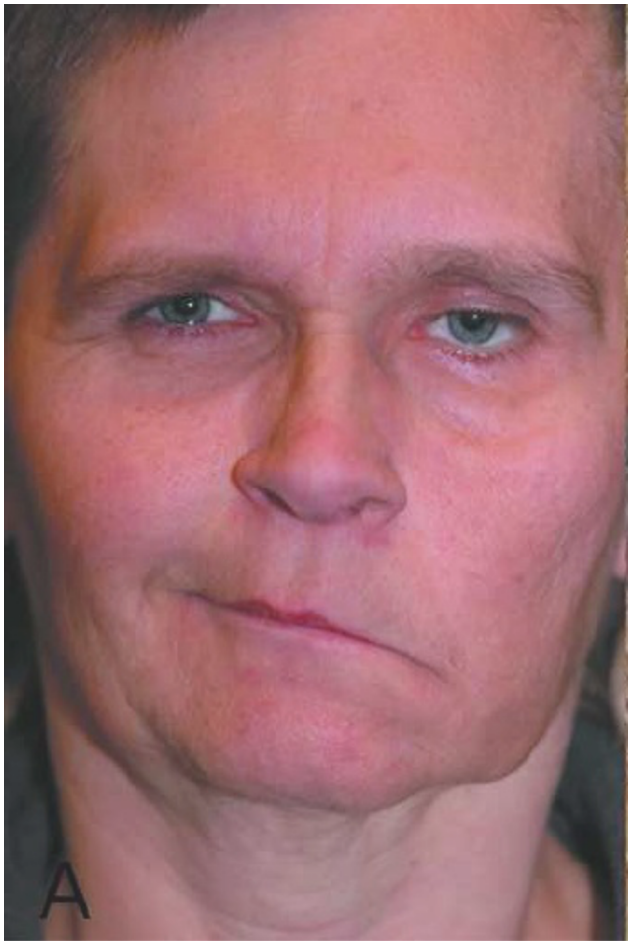
Pure tone average
Measures of how loud a sound has to be in order to be heard (**sensitivity**)

Word recognition score
Measures ability to correctly identify words presented at sufficient "loudness" (**intelligibility**)

Hearing aids can only help makes sounds louder

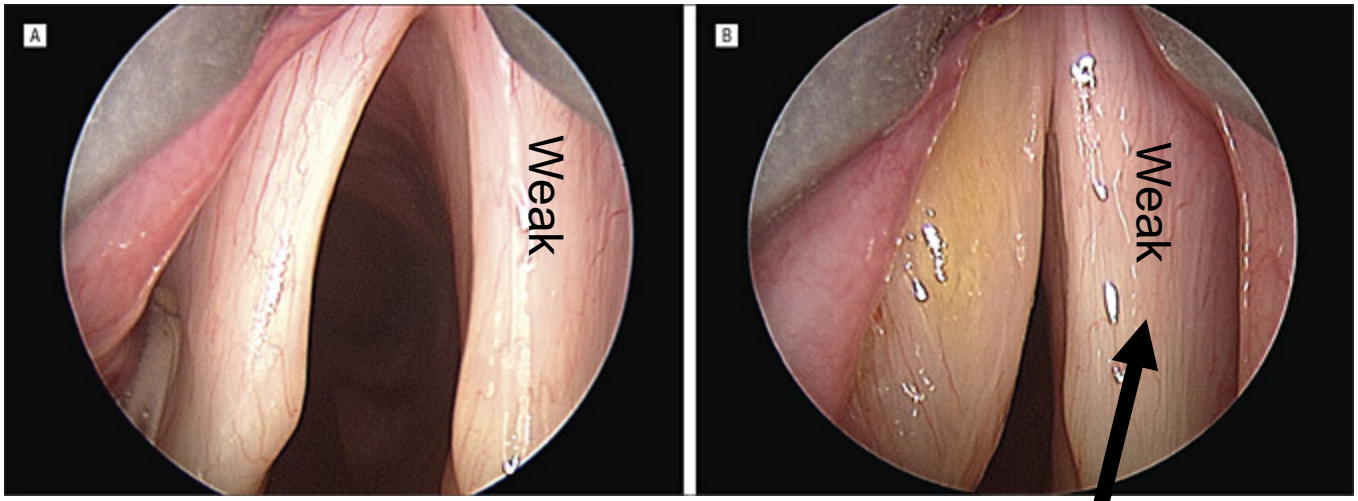
Facial weakness in NF2

- Causes
  - Late manifestation of vestibular schwannoma
  - Facial schwannomas
  - Surgery
- Effects
  - Dry eye → vision loss
  - Difficulty eating
  - Speech difficulty
  - Disfiguring/mood problems



Voice rehabilitation: injection laryngoplasty

- Office procedure
- Injection of filler into paralyzed focal fold (cord)
- Improved voice quality/volume
- Risk to breathing if overfilled



Before injection

After injection

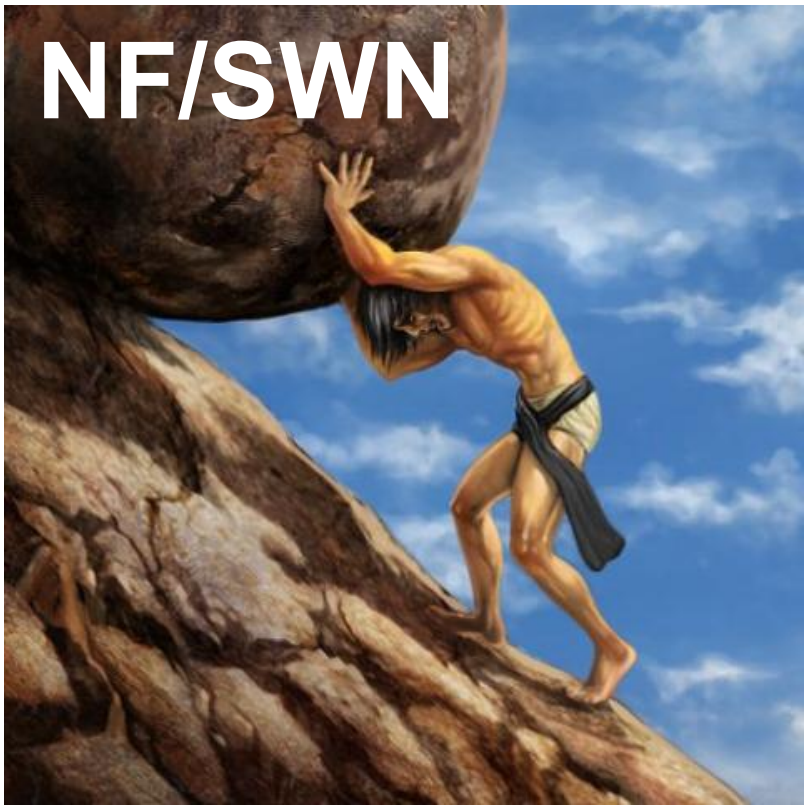
Courtesy of Dr. Philip Song, ME

Walking and physical exercise

- Walking problems related to balance problems (vertigo), vision loss, and foot drop
- Reduced activity can lead to bone loss which predisposes to fractures
- Recommendations:
  - Avoiding sedating medications
  - Maximize your exercise
  - Treat foot drop

Emotional functioning in NF patients

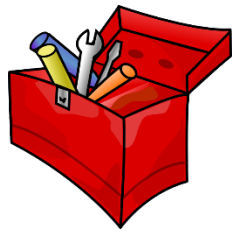
- ~40% of NF patients meet criteria for depression based on screening
- Higher rates of anxiety, perceived stress compared to general population
- Lower self-esteem compared to general population



Sysiphus

Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS

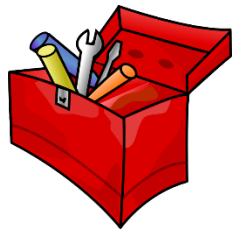
REiNS Clinical Trial Recommendations



- 2013 Neurology Supplement:

Clincial Trial Endpoint	Recommended Primary Outcome Measure(s)	Recommended Secondary Outcome Measure(s)
Pain	Numeric Rating Scale-11	
Visual Acuity	Teller Acuity Cards	HOTV; Visual Quality of Life PRO
Hearing	Maximum Word Recognition Score	Pure tone average
Facial Function	SMILE analysis	House-Brackmann Scale
Tumor Response	Volumetric MRI	

REiNS Clinical Trial Recommendations



- 2016 Neurology Supplement

Clincial Trial Endpoint	Recommended Primary Outcome Measure(s)	Recommended Secondary Outcome Measure(s)
Pain Interference	Pain Interference Index (Age 6-24) PROMIS-PI (Age ≥ 18)	
Physical Functioning	PROMIS-Physical Functioning (Self report/Parent Proxy	
Sleep	Apnea-Hypopnea Index	SpO_2, End Tidal CO_2, Arousal Index
Pulmonary	FEV_1 ($FEV_{0.75}$ for preschoolers) R_{10}	FVC, PEF, Forced Expiratory Flows R_5, R_{20}
Attention	Digit Span WISC-IV (performance-based) Conners Scale (observer-rated)	

*Additional publications on whole-body MRI and biomarkers also included in this supplement

NF2-associated vestibular schwannoma and meningioma trials

Drug	Phase	Target	N	Age (y)	Tumor/Endpoint	Results
Lapatinib[113] NCT00973739	2	EGFR/ErBb2	17	4-80	VS : 15% volume reduction	12% RR
RAD001 NCT01419639	2	mTORC1	10	≥3	VS: 15% volume reduction	0% RR
RAD001[112] NCT01490476	2	mTORC1	10	>15	VS : volume reduction	0% RR
Bevacizumab NCT01207687	2	VEGF	14	≥12	VS: hearing response as measured by word recognition score	43% RR 36% HR
Bevacizumab NCT01767792	2	VEGF	22	≥12	VS: hearing response as measured by word recognition score	38% RR 43% HR
RAD001 NCT01345136	2	mTORC1	4	16-65	VS : volume reduction	Ongoing
Axitinib NCT02129647	2	VEGFR2	12	≥18	VS : volume reduction	Ongoing
AZD2014 NCT02831257	2	mTORC1/2	18	≥18	M: 20% volume reduction VS: 20% volume reduction	6% RR 14% RR
Crizotinib	2	FAK	17	≥6	VS: 20% volume reduction	Anticipated 2020

Implementation of REiNS recommendations for trials of NF2

- Audiology has been integrated into VS studies
- Tumor response has been integrated in VS and meningioma studies
- No studies have integrated facial function
- No studies have integrated functional evaluations (like SPRINT)
- Multiple studies have integrated patient reported outcomes (PROs)

Patient reported outcomes

- NFTI-QOL (Neurofibromatosis 2 impact on quality of life)
  - Domains: Balance/dizziness; hearing; facial weakness; sight; mobility/walking function; pain; anxiety/depression
  - Under evaluation by REiNS PRO committee
  - Integrated into studies of bevacizumab, AZD2014, and crizotinib
- PAN-QOL
  - Assesses symptoms related to VS
  - Integrated into meningioma studies
  - No evaluation to date
- Tinnitus Reaction Questionnaire (TRQ)
  - Assesses response to tinnitus
  - Integrated into studies of bevacizumab and crizotinib
  - No evaluation planned

Holiday wish list for NF2 trials

- Functional measures
  - Strength
  - Balance/coordination
  - Walking
  - Swallowing
  - Speech
- Genetic severity scale

ORIGINAL ARTICLE

Genetic Severity Score predicts clinical phenotype in NF2

Dorothy Halliday,[1,2] Beatrice Emmanouil,[2] Pieter Pretorius,[3] Samuel MacKeith,[4] Sally Painter,[5] Helen Tomkins,[6] D Gareth Evans,[7] Allyson Parry[2,8]

Table 5 Tumour burden, presence of ocular features and hearing outcome according to genetic severity grade

Genetic severity			1 Tissue Mosaic	2A Mild	2B Moderate	3 Severe	Statistics
Tumour load	N (%)	Bilateral VS*	34 (54.0%)	24 (96.0%)	31 (88.6%)	19 (100.0%)	$\chi^2(1)=23.6$, p<0.001
		Unilateral VS*	22 (34.9%)	1 (4%)	3 (8.6%)	0 (0.0%)	$\chi2(1)=16.6$,p<0.001
		Intracranial meningioma*	36 (59.0%)	16 (64.0%)	28 (82.4%)	18 (94.7%)	$\chi^2(1)=11.5$, p=0.001
		Spinal meningioma*	9 (15.3%)	7 (29.2%)	13 (38.2%)	7 (36.8%)	$\chi^2(1)=6.4$, p=0.01
		Spinal schwannoma*	29 (48.3%)	19 (76.0%)	31 (94.7%)	18 (94.7%)	$\chi^2(1)=24.6$, p<0.001
		Spinal ependymoma *	7 (11.9%)	11 (44.0%)	11 (33.3%)	5 (26.3%)	$\chi^2(1)=3.8$, p=0.05
Ocular features	N (%)	Epiretinal membranes*	0 (0.0%)	2 (8.7%)	3 (8.8%)	5 (31.3%)	$\chi^2(1)=14.4$, p<0.001
		Cataract*	4 (6.6%)	9 (39.1%)	14 (41.2%)	11 (68.8%)	$\chi^2(1)=28.8$, p<0.001
		Combined hamartoma*	1 (1.6%)	5 (21.7%)	2 (5.9%)	6 (37.5%)	$\chi^2(1)=10.4$, p=0.001
		Optic nerve meningioma	1 (1.6%)	2 (9.0%)	0 (0.0%)	2 (10.5%)	$\chi^2(1)=1.2$, p=0.23
	Mean (SD)	Total eye features*	0.1 (0.35)	0.74 (0.81)	0.56 (0.61)	1.5 (1.16)	$r_s(132)=0.53$, p<0.001
Hearing outcomes	N (%)	Hearing grade* 1	53 (85.5%)	14 (56.0%)	19 (57.6%)	9 (50.0%)	$\chi^2(1)=13.4$, p<0.001
		2	3 (4.8%)	2 (8.0%)	3 (9.1%)	1 (5.6%)	
		3 or 4	3 (4.8%)	3 (12.0%)	3 (9.1%)	2 (11.1%)	
		5	1 (1.6%)	2 (8.0%)	3 (9.1%)	2 (11.1%)	
		6	2 (3.2%)	4 (16.0%)	5 (15.2%)	4 (22.2%)	
	Mean (SD)	Latest SDS*	86.78 (27.05)	58.95 (46.14)	64.56 (41.86)	53.19 (46.16)	$r_s(127)=-0.25$, p=0.004
		Age of loss of useful hearing*	58.2 (16.83)	28.38 (8.6)	29.2 (10.42)	23.14 (9.39)	$r_s(28)=-0.49$, p=0.006

Asterisk indicates statistical significance ($p<0.05$) in trends (χ^2) and correlations (r_s) of measures with genetic severity.
SDS, Speech Discrimination Score; VS, vestibular schwannoma.

Halliday et al, J Med Genet, 2017

What is NIH PROMIS?

- The **Patient-Reported Outcomes Measurement Information System** (PROMIS) is an NIH-funded initiative to develop and validate patient reported outcomes (PROs) for clinical research and practice.
- PROMIS was established in 2004 as a cooperative network that developed and validated PROs in global health, physical function, fatigue, pain, sleep/wake function, emotional distress, and social health.

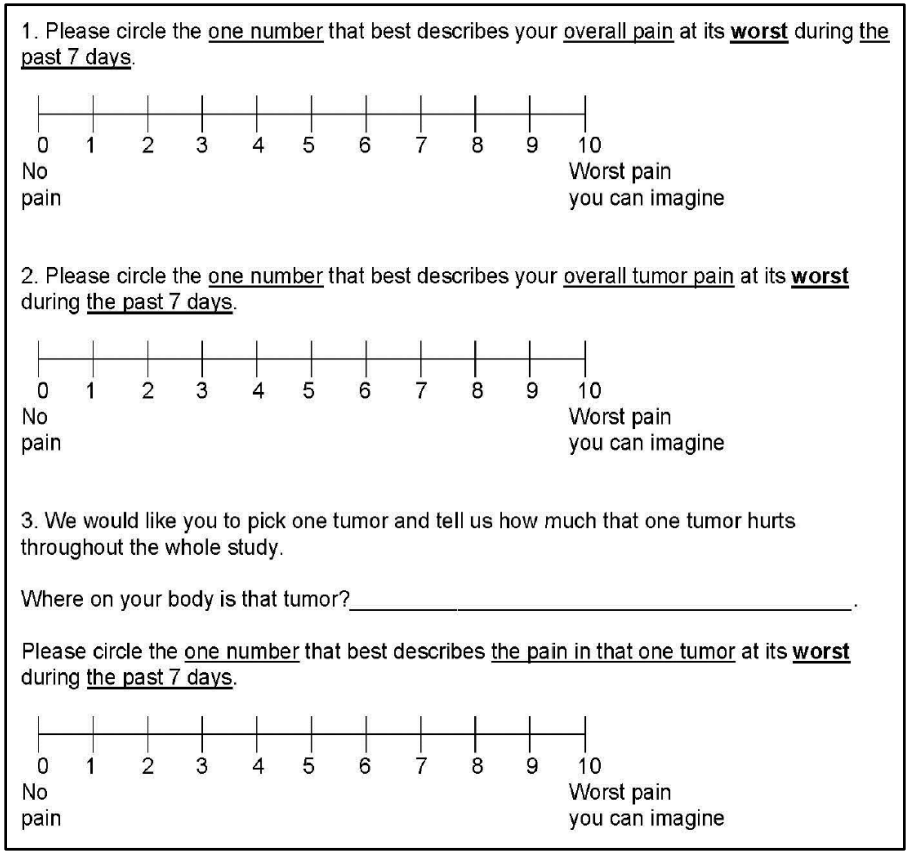
Implementation of REiNS recommendations for trials of SWN

- Upcoming trials of tanezumab for schwannomatosis patients with moderate to severe pain

- Pain intensity: NRS-11
- Pain interference: PROMIS
- Physical function: PROMIS
- Pain quality: PROMIS
- Anxiety: PROMIS
- Depression: PROMIS

NRS-11

- Rating pain on scale from 0-10
- REiNS Endorsed Measure



1. Please circle the one number that best describes your overall pain at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst pain you can imagine

2. Please circle the one number that best describes your overall tumor pain at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst pain you can imagine

3. We would like you to pick one tumor and tell us how much that one tumor hurts throughout the whole study.

Where on your body is that tumor?_____.

Please circle the one number that best describes the pain in that one tumor at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst pain you can imagine

- Ongoing focus groups during the study found that patients could differentiate between different tumor pains and some patients found it helpful to have the tumor selected for them to rate

Holiday wish list for SWN trials

- An active clinical trial for my patients

Key Conclusions

- REiNS toolbox = essential framework for evaluating functional and PRO endpoints in clinical trials
- PROMIS toolbox – helpful tools for many PRO domains including pain, physical function, anxiety, and depression
- We need more experience integrating endpoints in clinical trials in order to improve
- We need input from patients!