



Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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REiNS functional working group

Reliability of measuring muscle strength using a hand-held dynamometer in NF

September 22, 2019



Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Objectives

To assess the reliability of hand held dynamometry (HHD) in measuring strength in children and adults with NF1 and NF2 and evaluate its utility as an outcome measure in clinical trials



Disclosures

None



Background and rationale

- Muscle weakness has been described in NF1* and NF2**
 - primary myopathy, central nervous system dysfunction, abnormalities of peripheral nerves, spinal tumors
- Clinical trials targeting PNs in children with NF1 have anecdotally shown to decrease functional impairments including muscle weakness
- Functional outcome measures are therefore needed to assess clinical benefit, in particular, muscle strength



*Souza et al 2009, Johnson et al 2011, Cornett et al 2015

** Evans 2009

Methods for strength testing

Manual Muscle Testing (MMT)
using 0-5 MRC scale



Handgrip testing



Isokinetic dynamometers



Handheld dynamometer



Image sources:
Biodex, Jamar Technologies website

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Concerns for poor reliability, ceiling
effect

HHD clinical studies

- Strength testing using a HHD has also been used as an efficacy measure in clinical trials for amyotrophic lateral sclerosis##
- Systematic review comparing HHD to isokinetic strength measurement concluded that HHD can be reliable and valid*
- Reliability of strength measurements using a HHD has been studied in many patient populations**
- Systematic review of intraobserver reliability using HHD concluded ~half studies had acceptable ICC (≥ 0.9)#

*Stark et al 2011, *Hedengren et al 2001, Douma et al 2014, van den Beld et al 2006, Macfarlane et al 2008, Hebert et al 2015, Brussock et al 1992, Berry et al 2006, Hebert et al 2011 #Schrama et al 2014, ##Shefner et al 2016



Study design

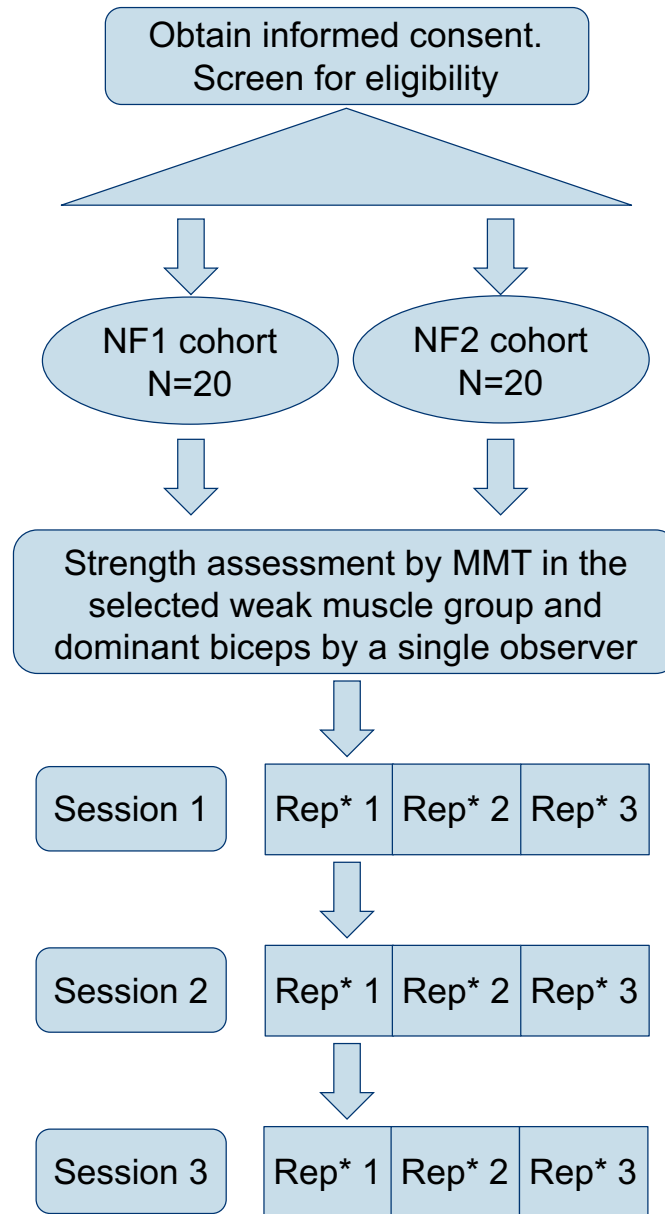
Patient Eligibility:

- Patients with clinically confirmed NF1 or NF2 or a known NF mutation
- at least 1 muscle group that is weak per MMT (<5/5 strength) out of a list of pre-selected potential muscle groups
- Age ≥ 5 years & able to follow instructions
- No orthopedic procedure or other major surgery that could influence extremity strength in past 6 months
- No tibial dysplasia



Study design

- Single observer tested one weak muscle (<5/5 by MMT) & dominant biceps
- Maximal isometric muscle strength using Ametek Chatillon® DFE2 HHD
- Standardized test protocol
- ICC calculated to assess reliability
- Standard error calculated to assess variability



Study design

- Potential muscle groups to evaluate

Muscle	Test	Muscle	Test
Gluteus maximus	Hip ext	Deltoid	Shoulder Abd
Iliopsoas	Hip flex	Shoulder external rotator	Shoulder external rotation
Gluteus medius	Hip Abd		
Hamstring	Knee flex	Biceps	Elbow flex
Quadriceps	Knee ext	Triceps	Elbow ext
Plantar flexors	Plantar flex	Wrist extensors	Wrist ext



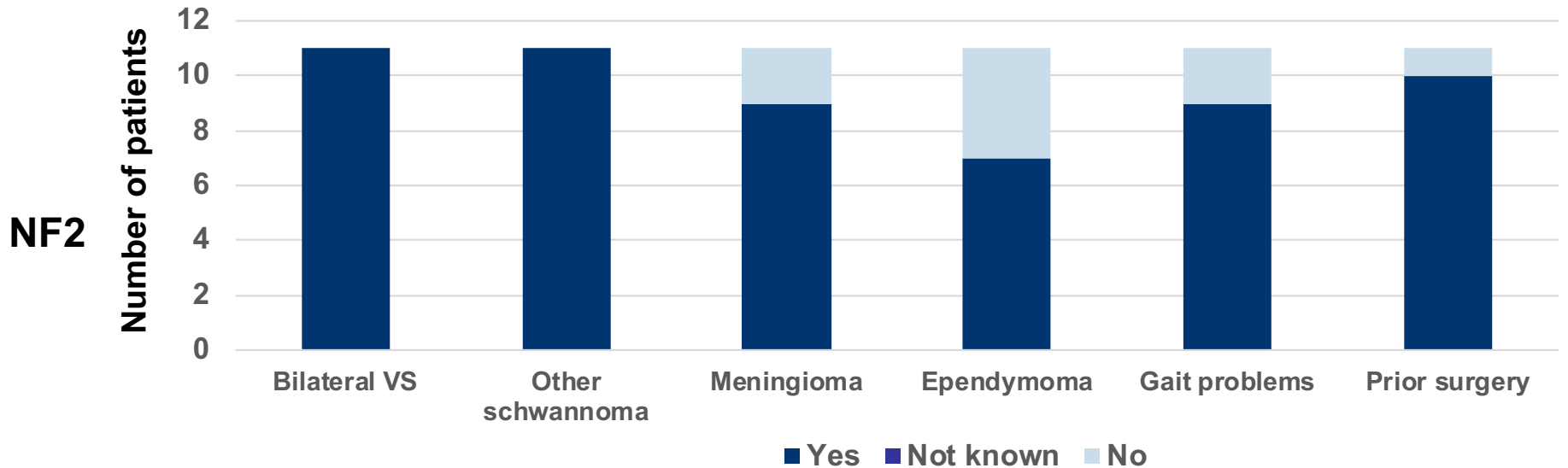
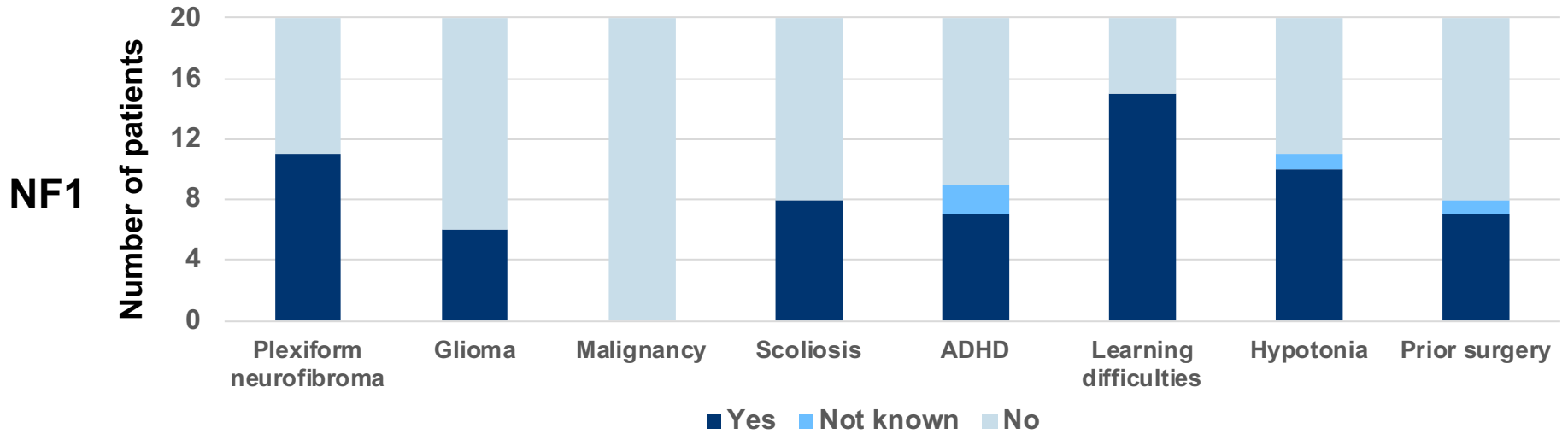
Results

Patient characteristics

	NF1 (N=20)	NF2 (N=11)	All (N=31)
Age (years) (min - max)	14 (9) (6 – 45)	33 (17) (15 – 75)	21 (15) (6 – 75)
Male/Female	15/5	4/7	19/12
Weight (Kg)	45.2 (18.6)	61.5 (9.9)	50.6 (17.9)
Height (cm)	145 (18)	168 (11)	153 (19)
Weak muscle: Strength by MMT	Range: 2/5 - 4+/5	Range: 2-/5 - 4+/5	Range: 2-/5 - 4+/5
Weak muscle: Strength by HHD**	74 (32)	100 (55)	83 (43)
Biceps: Strength by MMT**	All 5/5	All 5/5	All 5/5
Biceps: Strength by HHD**	96 (44)	126 (35)	107 (43)

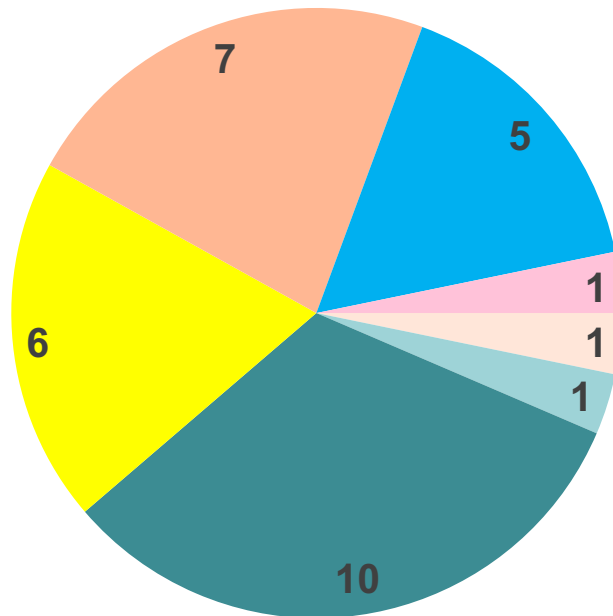
Results

Clinical manifestations



Results

Weak muscles tested on the study (N=31)



- Biceps (Elbow flexion)
- Deltoid (Shoulder Abduction)
- Gluteus medius (Hip abduction)
- Iliopsoas (Hip flexion)
- Quadriceps (Knee extension)
- Shoulder ER (Shoulder external rotation)
- Wrist extensors (Wrist extension)

Results

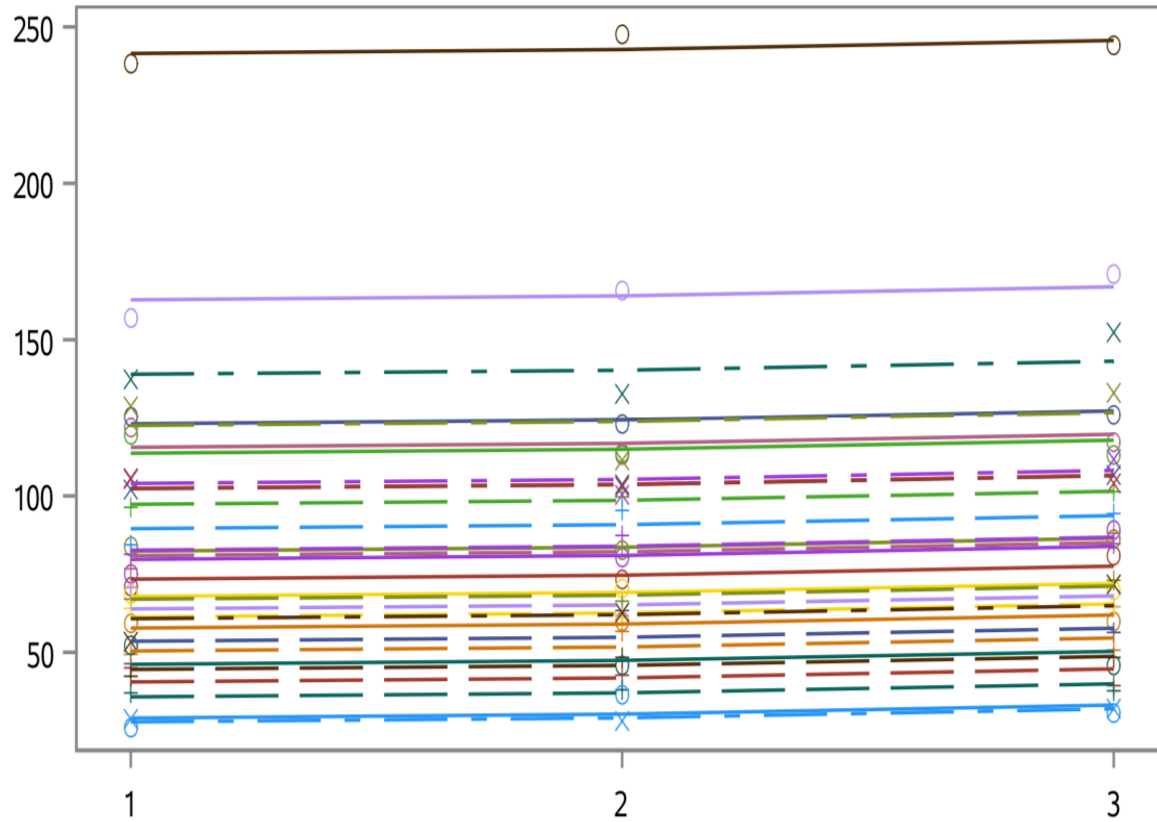
Intra-session and intersession ICCs

	Intrasession ICC	Intersession ICC
Weak muscle		
NF1 (N=20)	0.96 - 0.98	0.98
NF2 (N=11)	0.97 - 0.98	0.99
All (N=31)	0.97 - 0.98	0.99
Biceps*		
NF1 (N=19)	0.97 - 0.98	0.97
NF2 (N=11)	0.91 – 0.94	0.96
All (N=30)	0.96 - 0.97	0.97

* Biceps strength was unable to be tested in 1 patient with NF1, and was only tested for 1 session in 1 NF2 patient

Results

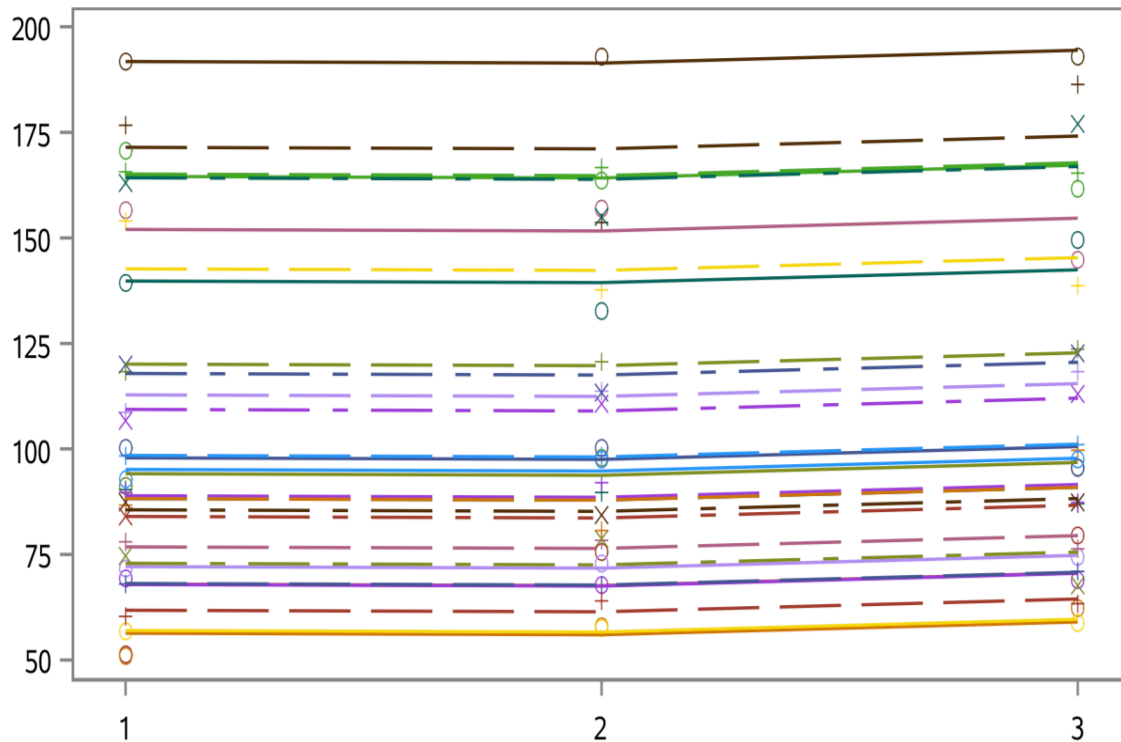
Interaction plots for measured muscle strength in the weak muscle



Session	Least squares mean	Std error
1	84.46	0.86
2	85.73	0.86
3	88.63	0.86

Results

Interaction plots for measured muscle strength in the biceps



Session	Least squares mean	Std error
1	105.78	1.12
2	105.40	1.16
3	108.44	1.16

Summary and questions for the group

- NF1 cohort testing complete. NF2 cohort enrollment ongoing
- High intra-observer intraclass correlations (ICC) and low measurement variability suggesting HHD is a reliable and can be useful as a functional endpoint in future clinical trials
- ? Need for testing inter-observer reliability
- ? Interest and feasibility of using muscle strength with HHD as an endpoint in future treatment trials
 - Correlate with imaging and patient reported outcomes

Acknowledgements

Patients and their families

Study team

Nashwa Khalil

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David Stevenson

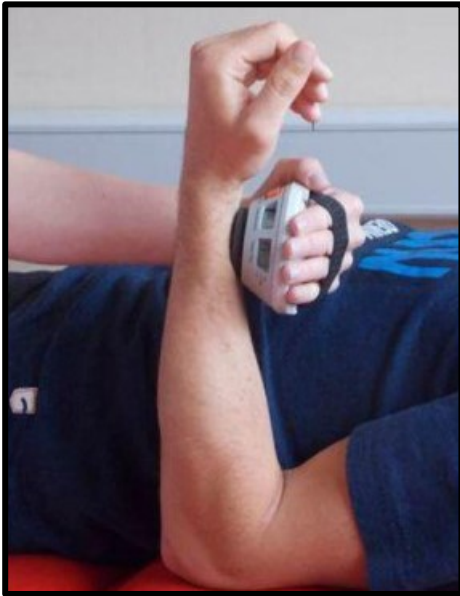
Scott Plotkin

REiNS functional group





HHD



Common muscle groups:
Shoulder: abduction, extension, external rotation
Elbow: flexion, extension
Wrist: extension
Hip: flexion, extension, abduction
Knee: extension, flexion
Ankle: dorsiflexion, plantar flexion

Douma et al 2014

Advantages

- Measure strength in various muscle groups
- Testing of each muscle group takes few min
- Can be performed in clinic setting
- Does not use testing till exhaustion

Limitations

- Ceiling effect for strong muscles (subject overcomes strength of examiner)



Study design

- Clinical data collected:
 - age, sex, weight, height, handedness, muscle strength by MRC scale
 - h/o NF manifestations including presence of spinal or peripheral nerve tumors, CNS manifestations, ADHD, skeletal deformities, prior surgeries
- All the weak muscles will be analyzed together
- Reliability of measuring biceps strength will be analyzed separately
- Sample size of 20 subjects with 3 observations per subject
 - 90% power to detect an intraclass correlation of 0.91 under the alternative hypothesis when the intraclass correlation under the null hypothesis is 0.75 using an F-test with a significance level of 0.05



Methods for strength testing

- Manual Muscle Testing (MMT) using 0-5 MRC scale
 - Concern not sensitive or reliable especially for muscles 4-5/5 in strength*
- Isokinetic dynamometers**
 - Computerized machines that measure multiple elements muscle strength: peak force, endurance, power, angle of maximal force, etc., and generate strength curves
 - Reliable and valid instrument for muscle force testing and is often used as a reference standard
 - Limitation: Cost and complex equipment
- Hand held dynamometry (HHD)**
 - Convenient device that provides a quantitative measurement of force generated by an individual muscle in newtons
- Handgrip strength
 - Measure strength of hand and forearm. General test of strength



* John 1984, **Stark et al 2011