

# Clinician-reported Sign Outcome Measures of CIPN

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# Examination/Sign Outcome Measures for CIPN: Outline

1. What has been done
2. What are current trials using
3. What should we be doing – a patient perspective
4. What should we be doing – an investigator's perspective.
5. Review of existing scales (brief)
6. Aspirational attributes of physician reported “sign” outcome measures.

# Research design characteristics and reporting adequacy in trials of chemotherapy-induced peripheral neuropathy (CIPN) treatments initiated during chemotherapy: ACTION systematic review

*Jennifer Gewandter et al. 2017 (submitted)*

- Systematic review of randomized controlled trials (preventative or symptomatic)
- 38 articles
- 95% initiated treatment before CIPN started

# CIPN Outcome Measures

- 22 (58%) specified primary outcome measure
- 20 (53%) specified primary endpoint
- 12 (32%) identified primary analysis.
- Primary outcomes:
  - NCI-CTCAE 4 (18%)
  - TNS (all versions) 3 (14%)
  - Vibration test 3 (14%)
  - EORTC-CIPN20 2 (9%)
  - Other PRO 6 (27%)
  - Pain 1 (4.5%)

*6 (28%) used sign or composite sign/symptom score as primary outcome measure*

# All outcomes

- 36 reported non-primary outcomes
    - NCI-CTCAE (13, 36%)
  - Among all outcome measures
    - 15 (40%) reported only symptom measures
    - 6 (16%) both symptom and signs
    - 5 (13%) symptoms and electrophysiology
    - 2 (5%) only signs
    - 2 (5%) functional measures (e.g. pegboard)
    - 2 (5%) signs, symptoms, and electrophysiology
- Only 26% reported signs, 5% functional measures.*

# Planned Trials (personal experience)

1. Gene therapy approach to CIPN prevention:
  - Primary: change in sural sensory amplitude from baseline to 3 months after oxaliplatin completion.
  - Secondary
    - Prevalence of clinically evident CIPN
    - Prevalence of confirmed (clinical + EDX)
    - Change in TNS
2. Unknown intervention: Sign score will be UENS

# Ongoing/Upcoming Trials on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

- 34 studies either enrolling or not yet enrolling
- 7 use a sign measure as primary outcome
- 15 identify a sign measure as a secondary outcome
- 17 (50%) are using a sign measure

Examination Categories		Primary	Secondary
<i>Sensory Exam</i>	10 g monofilament	0	3
	Thermal sensatiopn	0	1
	128 Hertz tuning fork	0	1
	Rydel-Seiffer	0	1
	Deep tendon reflexes	0	1
	Joint position	0	1
	Light tactile touch	0	1
	<i>Total</i>	0	9
<i>Balance and Gait</i>	2 foot and single foot balance with eyes open and closed	0	1
	Leg function and balance tests suh as walking or standing on 1 leg	0	1
	Center of pressure during upright static and dynamic stance	0	1
	Gait speed change	1	0
	Balance measured by body sway	1	0
	5 Times Sit to Stand	0	1
	<i>Total</i>	2	4
<i>QST</i>	Mechanical Pain Threshold	1	0
	QST	1	1
	Vibration testing	0	1
	Vibrometer	0	1
	Thermal sensation using thermode	1	0
	Thermal pain using thermode	0	1
	Vibration using thermode	0	1
	QST (pain)	1	0
	Thermal hypersensitviity assessed by VAS	0	1
	Gait and Balance	1	0
Gait Accuracy	0	1	
	<i>Total</i>	5	7
<i>Examination Scales</i>	Toronto case definition	1	0
	Toronto Clinical Scoring System	0	1
	TNS	0	1
	MNSI	0	1
	TNSc	0	1
	<i>Total</i>	1	4
<i>Other</i>	Grooved pegboard	0	1
	Heart rate variability	0	1
	BP variability	0	1
	Visual contrast sensitivity	0	1



# A Patient's Perspective



# Phases of chemo life: personal perspective

## Relevant to measuring, prioritizing CIPN (QOL)

1. Throes of treatment
  - Goals: survive treatments, hope for cure; manage daily symptoms
2. Early *post*-chemo (e.g. first ~ 6 months after)
  - Goals: managing chemo-related symptoms, including fatigue, chemo fog, pain
  - Manage feelings of “lost in the wilderness” and worries of cancer return
3. Intermediate *post*-chemo phase (e.g. 6 - 12 months)
  - Shift in goals: from “at least I’m alive” to thoughts about quality of life
4. Late *post*-chemo phase (year 2)
  - Attempts to return to normal: exercise, recreation with kids, etc; remove meds (eg want to be viewed by others as normal, and want to act the role)

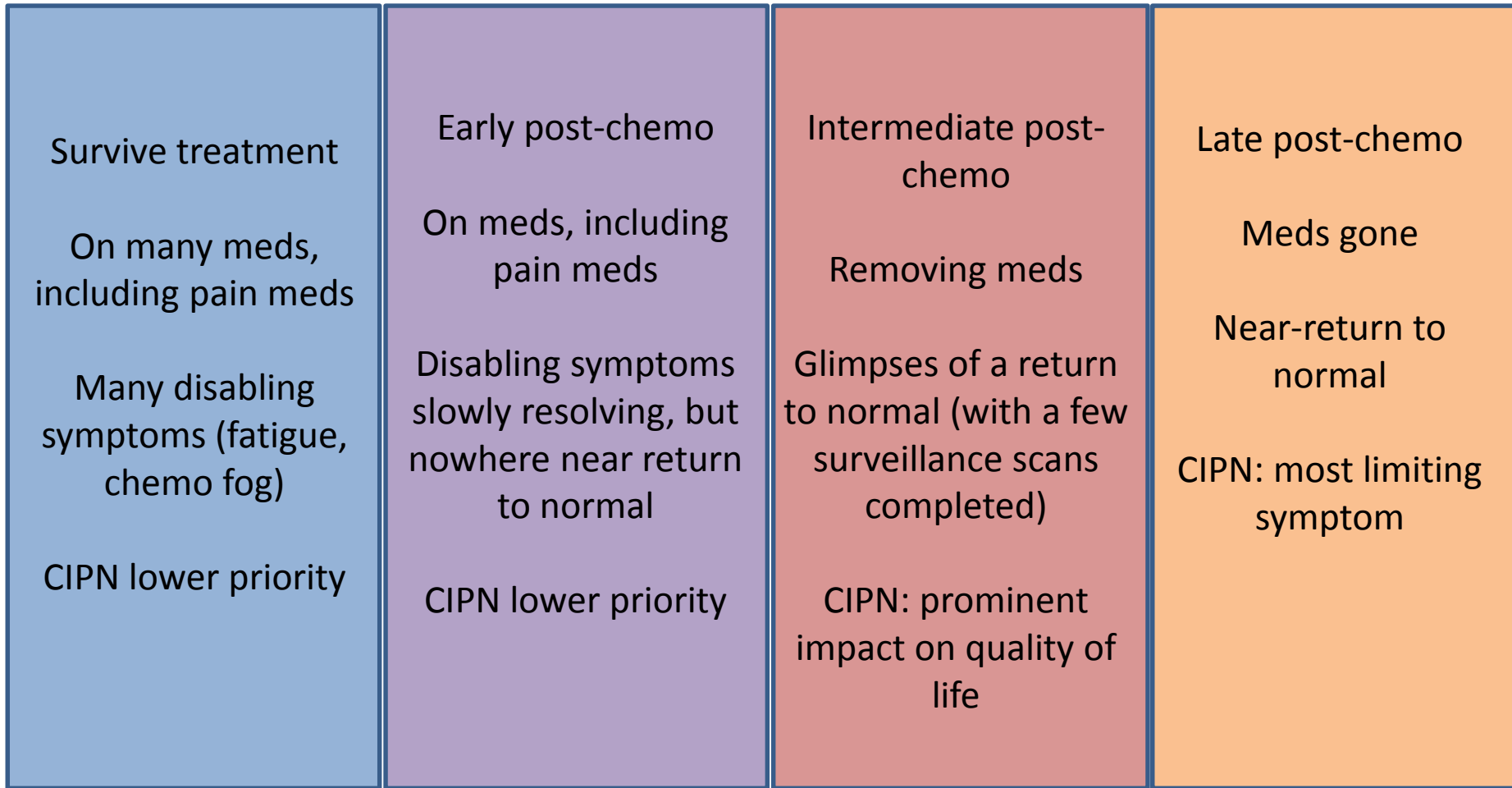
# If others are like me, then:

1. It's *not* only whether or not you get CIPN (not yes/no question)
2. It's:
  1. Whether you recover from it (e.g. year 2)
  2. And, of course, whether you can avoid complications (e.g. falls) when recovering from CIPN

“I never felt like complaining to my doctor about my CIPN; Furthermore, at no point did I find any meaningful value in the status of my ankle reflexes, toe flexion or extension, or sural sensory amplitude; nor did the 0 to 10 pain scale seem useful in expressing how CIPN was affecting me. My struggle expressed itself clearest in my CAP-PRI responses...”

Neurology 2016;87:1-2

# Personal phases with CIPN



-----chemo-----

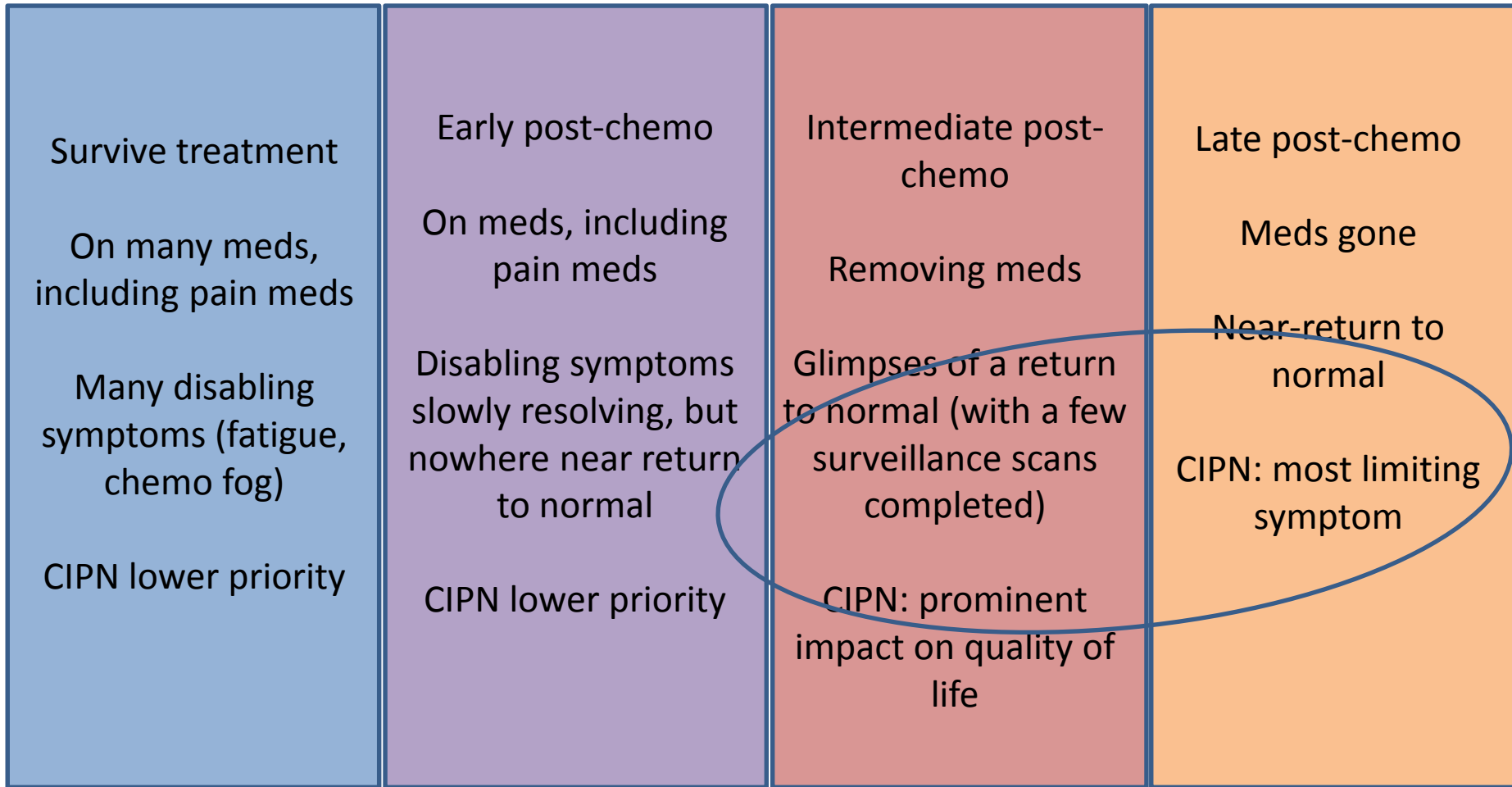
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-----One year post-chemo-----

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# Personal phases with CIPN

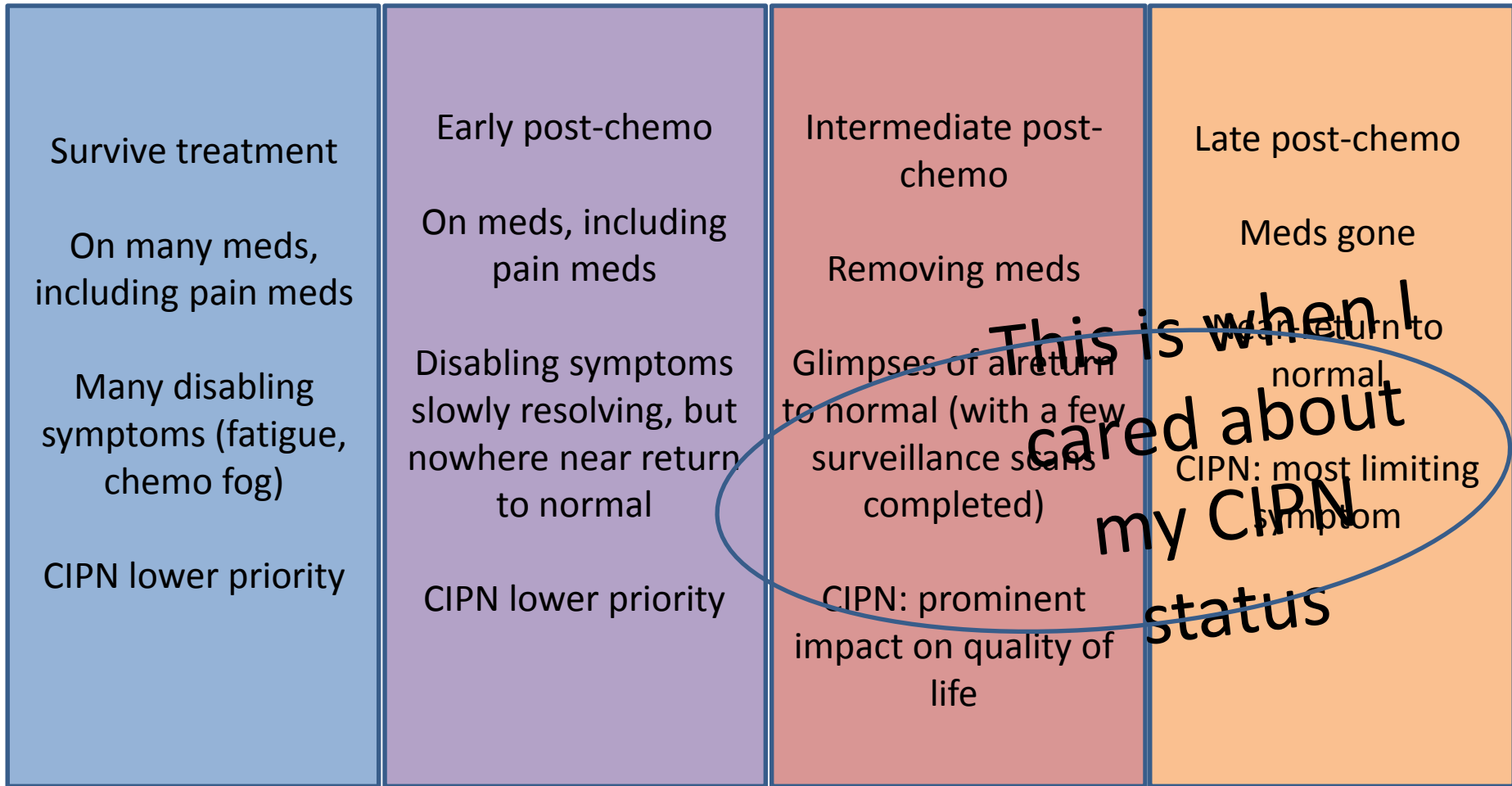


-----chemo-----  
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-----One year post-chemo-----  
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# Personal phases with CIPN



-----chemo-----  
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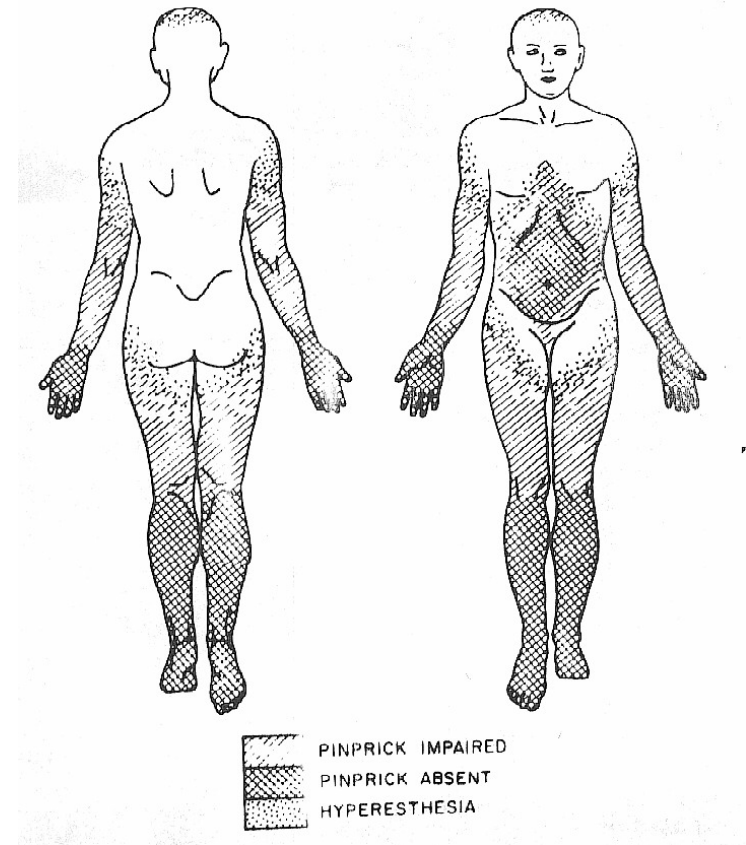
-----One year post-chemo-----  
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# Benefits of Sign Scales

*(an investigator's perspective)*

- Multimodal approach
- Impairment specific data
- Precise topographical localization and distribution
- Less influenced by stage bias

*Unique information (e.g. potentially divergent with symptoms in positive trials)*





# Cons of Sign Scales

- Are they clinically meaningful to patients?
- “Frequently perceived by oncologists as being too complicated and time-consuming”

Cavaletti, G., Cornblath, D. R., Merkies, I. S. J., Postma, T. J., Rossi, E., Frigeni, B., et al. (2013). The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 24(2), 454–462. <http://doi.org/10.1093/annonc/mds329>



Dyck, P. J., Overland, C. J., Low, P. A., Litchy, W. J., Davies, J. L., O'Brien, P. C., et al. (2010). Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: CI vs. NPhys trial. *Muscle & Nerve*, 42(2), 157–164. <http://doi.org/10.1002/mus.21661>


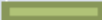






































## Diabetic Peripheral Neuropathy

- NIS, NIS-LL, NIS-LL +7
- NDS (Neurological Disability Score)
- Toronto
- Modified Toronto
- TNS (total neuropathy score)
- VEGF neuropathy scale
- DNS (Diabetic Neuropathy Score)
- DNI (Diabetic Neuropathy Index)
- MNSI (Michigan Neuropathy Screening Instrument)
- MDNS (Michigan Diabetic Neuropathy Score)
- Pancreatic Transplant Scale
- DNE (Diabetic Neuropathy examination)
- UENS (Utah Early Neuropathy Scale)
- NDS (Neuropathy Disability Score)
- Modified NDS

## Source

- Dyck P (multiple references)
- Dyck P (Ann Neurol 1980)
- Bril V (Diab Care 2002)
- Bril V (Diab Med 2009)
- Chaudhry V (Brain 1996)
- Simovic D (Arch Neur 2001)
- Fedele D (Diabetes Care 1997)
- Fedele D (Diabetes Care 1997)
- Feldman E (Diabetes Care 1994)
- Feldman E (Diabetes Care 1994)
- Kennedy W (NEJM 1990)
- Meijer J (Diab Care 2000)
- Singleton JR (JPNS 2008)
- Young MJ (Diabetologia 1993)
- Veves A (Diabetologia 1992)



DPN	Sensory	Motor	Reflexes	Cranial Nerves	General Function	Scoring	Scale
NIS-LL	✓ 	✓ 	✓ 			Motor 0-4 (with 0.25 increments on 3-4), Sensory 0-2, Reflexes 0-2	0-88 (64 motor, 16 sensory, 8 reflex)
NDS <sup>1</sup> (neurological disability score)	✓ 	✓ 	✓ 	✓ 		Scoring 0-4 all modalities	0-280 (128 motor, 40 reflexes, 48 cranial nerve weakness/abnormality, 64 sensory)
Toronto	✓ 		✓ 			0-1 symptoms and sensory, 0-2 reflexes	0-19 (8 reflexes, 5 sensory, 6 symptoms)
Modified Toronto	✓ 		✓ 			0-3 symptoms, 0-3 sensory, 0-2 reflexes	0-38 (8 reflexes, 15 sensory, 18 symptoms)
TNS	✓ 	✓ 	✓ 			0-4 sensation, 0-4 strength, 0-4 reflexes	0-40 (8 symptoms, 8 sensation, 4 motor, 4 reflexes, 8 QST, 8 NCS)
VEGF Neuropathy scale	✓ 	✓ 	✓ 			0-4 sensory, 0-4 motor, 0-4 reflexes (has a symptom score component)	0-64 (32 sensory, 16 reflexes, 16 motor - many combined muscle groups)
Diabetic Neuropathy Score	✓ 	✓ 	✓ 			0-2 sensory, 0-3 motor, 0-2 reflexes	0-46 (18 motor, 12 sensory, 16 reflex)
(DNI) Diabetic Neuropathy Index	✓ 		✓ 		✓ 	0-1 appearance of feet, 0-1 ankle reflexes, 0-1 vibration at great toe)	0-8 (4 appearance, 2 reflex, 2 vibration)
MNSI	✓ 		✓ 		✓ 	0-1 appearance, 0-1 reflex, 0-1 vibration, 0-1 ulceration	0-8 (4 appearance, 2 reflex, 2 vibration)
MDNS	✓ 	✓ 	✓ 			0-2 sensory, 0-3 motor, 0-2 reflexes	0-46 (12 sensory, 18 motor, 16 reflex)
Pancreatic Tx scale	✓ 	✓ 	✓ 			0-4 sensory, 0-4 motor, 0-4 reflexes	0 to -84 (24 motor, 12 reflex, 40 sensory)
DNE (diabetic neuropathy examination)	✓ 	✓ 	✓ 			0-2 Sensory, 0-2 motor, 0-2 reflexes	0-16 (2 reflexes, 4 motor, 10 sensation)
UENS	✓ 	✓ 	✓ 			0-4 motor, 0-34 sensory, 0-2 reflexes	0-42 (4 motor, 34 sensory, 4 reflex)
NDS <sup>NP</sup> (Neuropathy disability score)	✓ 		✓ 			0-1 sensory, 0-2 reflexes (also included a separate symptom score assessment)	0-10 (6 sensory, 4 reflexes)
Modified NDS <sup>NP</sup>	✓ 		✓ 			0-2 sensory, 0-2 reflexes	0-10 (4 reflexes, 6 sensory each foot - averaged sensory)

**Table 1.** Scoring used by the NIS-LL to grade motor activity (muscle power) in the lower limbs of patients with neurological deficits [14–16]

NIS-LL score	Muscle power grading
0	normal
1	25% weak
2	50% weak
3	75% weak
3.25	movement against gravity
3.50	movement with gravity eliminated
3.75	muscle flicker, no movement
4	paralysis

**Table 2.** Muscle groups evaluated by the NIS-LL to assess motor activity in the lower limbs of patients with neurological deficits

*Muscle groups tested*

Hip flexion  
 Hip extension  
 Knee flexion  
 Knee extension  
 Ankle dorsiflexion  
 Ankle plantar flexion  
 Toe extension  
 Toe flexion

*Scoring methodology*

0–4 points per side per muscle group; total of 64 points if paraplegic

The power of each muscle group is evaluated bilaterally [14–16].

**Table 3.** Scoring used by the NIS-LL to grade sensory and reflex activity in the lower limbs of patients with neurological deficits

NIS-LL score	Sensory/reflex activity grading
0	normal
1	decreased
2	absent

Sensory stimuli are applied to each side of the dorsal surface of the great toe at the terminal phalanx [14–16].

**Table 4.** Modalities and reflexes tested by the NIS-LL

*Reflexes tested*

Quadriceps  
 Ankle

*Modalities tested*

Touch pressure  
 Pinprick  
 Vibration (165 Hz) tuning fork  
 Joint position

*Scoring methodology*

0–2 points per side per reflex;  
 total of 8 possible points if  
 areflexic

Age-adjusted scoring: decreased ankle reflexes are considered normal for patients aged 50–69 years and scored as 0 and absent reflexes for patients >70 years are considered normal and scored as 0

0–2 points per side per modality;  
 total of 16 points if lacking all  
 sensation at the great toe

For reflexes, stimuli are applied to the quadriceps and ankle tendons bilaterally [14–16].

Patient Name:		
Study Number:		
Visit:		
Date:		
<b>Motor Examination</b>	Left	Right
0 normal		
2 weak		
<b>Great Toe Extension</b>	<input type="text"/>	<input type="text"/>
<b>Total Both Sides (out of 4)</b>	<input type="text"/>	

## The Utah Early Neuropathy Scale

<b>Pin Sensation:</b>	L	R
0 normal		
1 for each segment with reduced sensation	<input type="text"/>	<input type="text"/>
2 for each segment with absent sensation	<input type="text"/>	<input type="text"/>
<b>Total both sides (out of 24)</b>	<input type="text"/>	

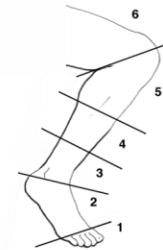
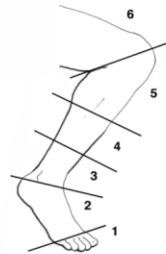
<b>Allodynia/Hyperesthesia</b>	L	R
0 normal		
1 if present in toes or foot	<input type="text"/>	<input type="text"/>
<b>Total both sides (out of 2)</b>	<input type="text"/>	

<b>Large Fiber Sensation</b>	L	R
0 normal		
1 diminished		
2 absent		
Great toe vibration time	<input type="text"/>	<input type="text"/>
	S	S
Great toe joint position	<input type="text"/>	<input type="text"/>
<b>Total both sides (out of 8)</b>	<input type="text"/>	

Segments for pin sensation reporting

Left Leg

Right Leg



<b>Deep Tendon Reflexes</b>	L	R
0 normal		
1 diminished		
2 absent		
Ankle	<input type="text"/>	<input type="text"/>
<b>Total both sides (out of 4)</b>	<input type="text"/>	

Left Leg Score (out of 21)

Right Leg Score (out of 21)

Total Score (out of 42)

# CIPN Disease Specific Scales

- Brief peripheral neuropathy screen (BPNS)
  - Ankle Reflex
  - Vibration at the great toe
- Total neuropathy score (TNS)

# Total Neuropathy Score

**Table 9 – Total Neuropathy Score (TNS) and related reduced versions.**

Parameter	SCORE				
	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger or toes	Symptoms extends to ankle or wrist	Symptoms extends to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomics symptoms	0	1	2	3	4 or 5
<i>Pin sensibility</i>	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
<i>Vibration sensibility</i>	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
<i>Vibration sensation (QST vibration)</i>	Normal to 125% of ULN	126-150% of ULN	151-200% of ULN	201-300% of ULN	>300% of ULN
<u><i>Sural amplitude</i></u>	Normal/reduced to <5% of LLN	76-95% of LLN	51-75% of LLN	26-50% of LLN	0-25% of LLN
<u><i>Peroneal amplitude</i></u>	Normal/reduced to <5% of LLN	76-95% of LLN	51-75% of LLN	26-50% of LLN	0-25% of LLN

QST = Quantitative Sensory Test; ULN = Upper Limit of Normal; LLN = Lower Limit of Normal

Note: In addition to the TNSc, parameters written in italics are used only in full-length TNS, underlined ones in TNSr.

Adapted from the original versions.<sup>10-14</sup>



		SCORE				
ITEM SCORE		0	1	2	3	4
	<b>SENSORY SYMPTOMS</b>	None	Limited to finger/toes	Extend to ankle or wrist	Extend to knee or elbow	Extend above knee or elbow or functionally disabling paralysis
	<b>MOTOR SYMPTOMS</b>	None	Slight difficulty	Moderate difficulty	Require help/assistance	paralysis
	<b>AUTONOMIC SYMPTOMS</b>	0	1	2	3	4 or 5
	<b>PIN SENSIBILITY</b>	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
	<b>VIBRATION SENSIBILITY</b>	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
	<b>STRENGTH</b>	Normal	MRC 4	MRC 3	MRC 2	MRC 0-1
	<b>DTR</b>	Normal	Ankle DTR reduced	Ankle DTR absent	Ankle DTR absent, others reduced	All DTR absent
	<b>TOTAL</b>					

MRC = Medical Research Council strength scale; DTR = deep tendon reflexes

# Efficacy and Safety of Antioxidant Treatment With $\alpha$ -Lipoic Acid Over 4 Years in Diabetic Polyneuropathy

The NATHAN 1 trial

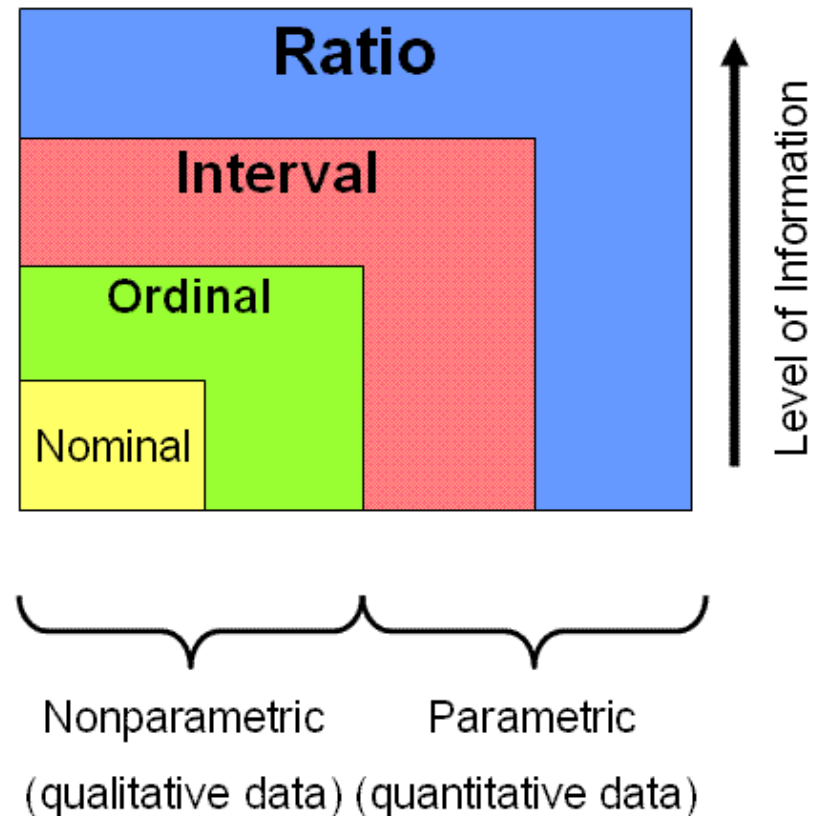
Diabetes Care 34:2054–2060, 2011

	ALA	Placebo
n	215	207
Composite score		
NIS-LL+7 (nds)	-0.37 ± 5.59*	0.29 ± 5.37
NIS and subscores		
NIS	-0.68 ± 6.44†	0.61 ± 6.61
NIS pinprick	-0.07 ± 1.60‡	0.05 ± 1.43
NIS-LL	-0.34 ± 4.48§	0.43 ± 4.49
NIS-LL sensory function	-0.12 ± 3.01	0.10 ± 2.89
NIS-LL muscular weakness	-0.21 ± 1.57†	0.17 ± 2.12
NIS-LL reflexes	0.03 ± 1.75	0.16 ± 1.80
NIS responders	41.1†	30.0
NIS unchanged	29.7†	31.9
NIS progressors	29.2†	38.1
NIS-LL responders	35.6†	29.0
NIS-LL unchanged	40.2†	36.2
NIS-LL progressors	24.2†	34.8
Nerve function tests		
Peroneal MNCV (m/s)	-0.35 ± 4.23	-0.06 ± 4.07
Sural SNAP ( $\mu$ V)	-0.20 ± 2.34	-0.15 ± 2.43
Foot VPT (JND)	0.87 ± 2.35	0.76 ± 2.38
Cold detection threshold (JND)	1.12 ± 3.96	1.28 ± 3.43
Heart rate deep breathing (bpm)	-0.67 ± 4.44¶	-1.35 ± 3.72
Neuropathic symptoms		
NSC weakness (number)	-0.04 ± 0.26†	0.04 ± 0.42
NSC weakness (severity)	-0.05 ± 0.39†	0.04 ± 0.50
TSS	-0.22 ± 2.42	-0.21 ± 2.45

\* $P = 0.105$ . † $P < 0.05$ . ‡ $P = 0.074$ . § $P = 0.0505$ . ¶ $P = 0.087$

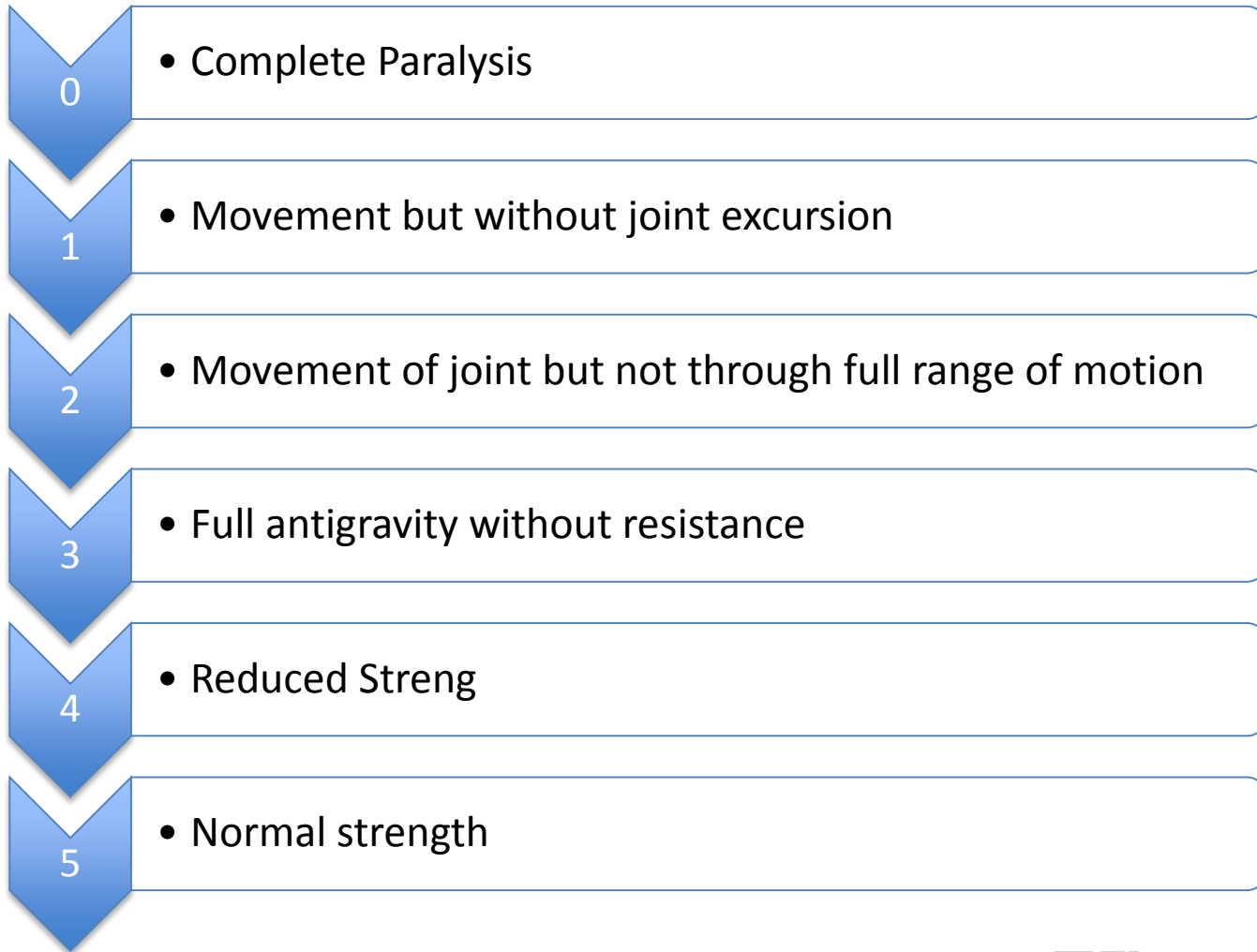
# Types of data

- **Nominal**
  - Religion, ethnicity
  - Not amenable to numerical values outside of sorting
- **Ordinal**
  - 0,1,2,3,4,5 (like MRC scale)
  - **Do not assume linearity!!**
- **Interval**
  - Continuous value (temp, ht)
  - Attempt to move in this direction with item response theory
- **Ratio**
  - There is an absolute zero (e.g, weight)



**\*Nonparametric statistics may be used to analyze interval and ratio data measurements.**

# MRC Strength Scale

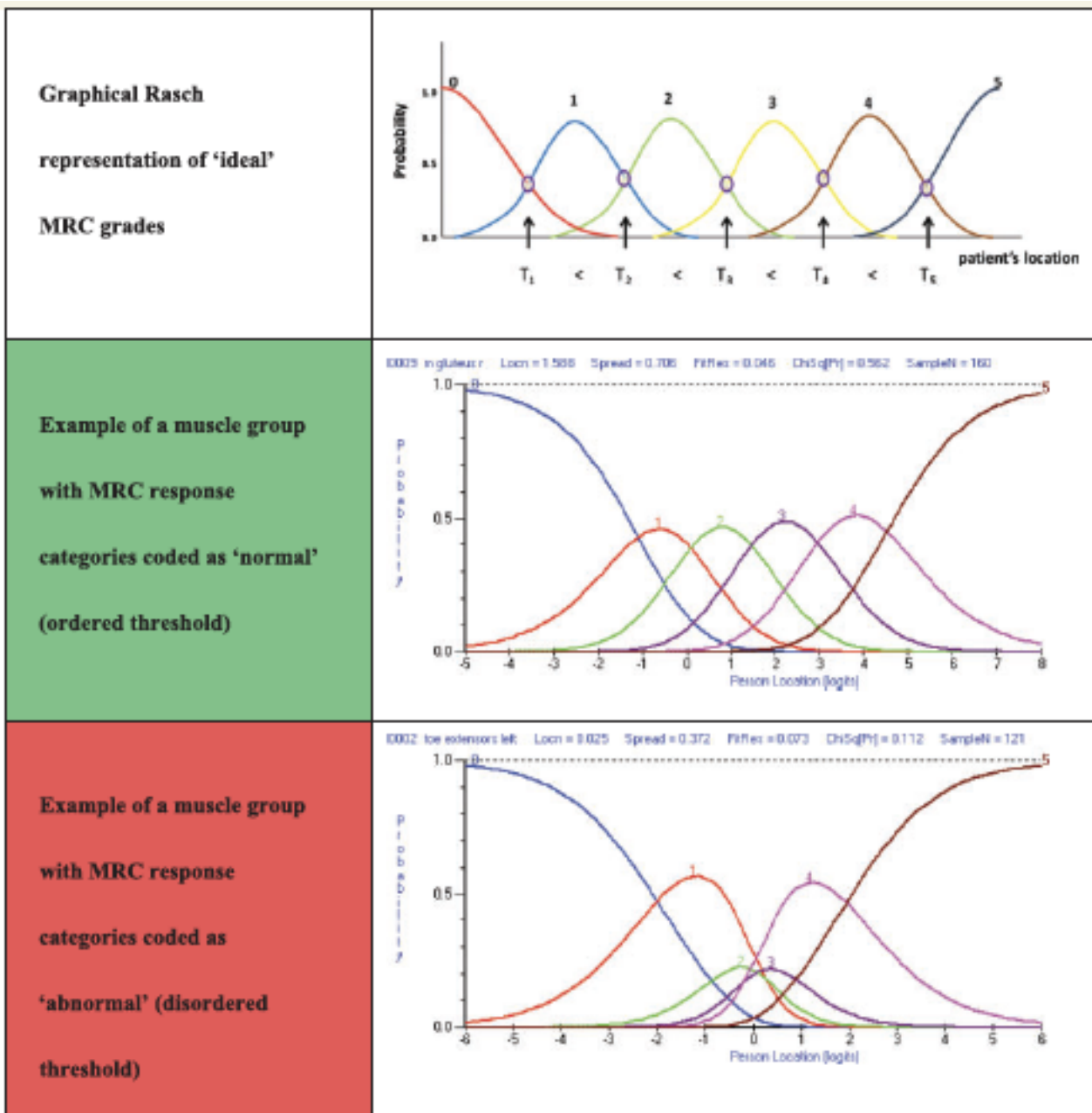


# Rasch Analysis (IRT)



**Georg Rasch (1901-1980)**

- Specific form of IRT
- Analyzes patient responses to individual questions (items) and ranks them based on difficulty and the ability of patients with differing degrees of disease severity to perform the task.
- General linear model is used to derive an interval scale



Thompson, A. G. B., Lowe, J., Fox, Z., Lukic, A., Porter, M.-C., Ford, L., et al. (2013). The Medical Research Council prion disease rating scale: a new outcome measure for prion disease therapeutic trials developed and validated using systematic observational studies. *Brain*, 136(Pt 4), 1116–1127. <http://doi.org/10.1093/brain/awt048>

# Rasch Transformed MRC Strength Scale



## RESEARCH REPORT

# Rasch-Transformed Total Neuropathy Score clinical version (RT-TNSc<sup>©</sup>) in patients with chemotherapy-induced peripheral neuropathy

Davide Binda<sup>1</sup>, Guido Cavaletti<sup>1</sup>, David R. Cornblath<sup>2</sup>, and Ingemar S. J. Merkies<sup>3,4</sup>  
on behalf of the CI-PeriNomS study group<sup>†</sup>

- TNSc 7 domains: sensory, motor, autonomic, pin, vibration, strength DTR.
- 281 patients with stable CIPN. Misfit statistics for strength and reflexes.
- Disordered thresholds for vibration and strength and item bias (cultural)

*Rasch built 5 domains (sensory, motor pin, vibration and strength).*





No widely used data standards in NINDS-funded clinical research

Researchers create data collection instruments for each new project

Meta-analyses across studies require extensive data re-formatting

Multitude of data formats creates barriers to data sharing

# Conclusions

- Sign scores provide unique information and are underutilized in CIPN trials.
- Score/sign selection is highly variable, and those selected often lack validation (generally or in CIPN)
- There is a need for consensus regarding score selection.
- Validation and consensus should prioritize proper clinimetric evaluation and characteristics

