



**2018**

**28-30 JUNE**  
**VIENNA, AUSTRIA**

**SUPPORTIVE CARE  
MAKES EXCELLENT  
CANCER CARE POSSIBLE**

# **Chemotherapy-Induced Peripheral Neuropathy (CIPN) Measurement Approaches**

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VIENNA

**MASCC/ISOO**  
ANNUAL MEETING  
SUPPORTIVE CARE IN CANCER



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<input type="checkbox"/>	No, nothing to disclose
<input checked="" type="checkbox"/>	Yes, please specify:

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**CIPN has been a difficult side effect  
to measure.**



# Measurement Challenges

- Don't tell, don't ask
- Lack skills
- No standardized approach
- Lack access to best measures
- Hardwired use of unreliable grading scales
  - Under-estimate severity
  - Measurement error in clinical trials



Hershman, et al., 2014; Gewandter, et al., 2017; Postma, et al., 1998; Griffith, et al., 2010; Cavaletti, et al., 2010; Smith, et al., 2013; Albers, et al., 2011



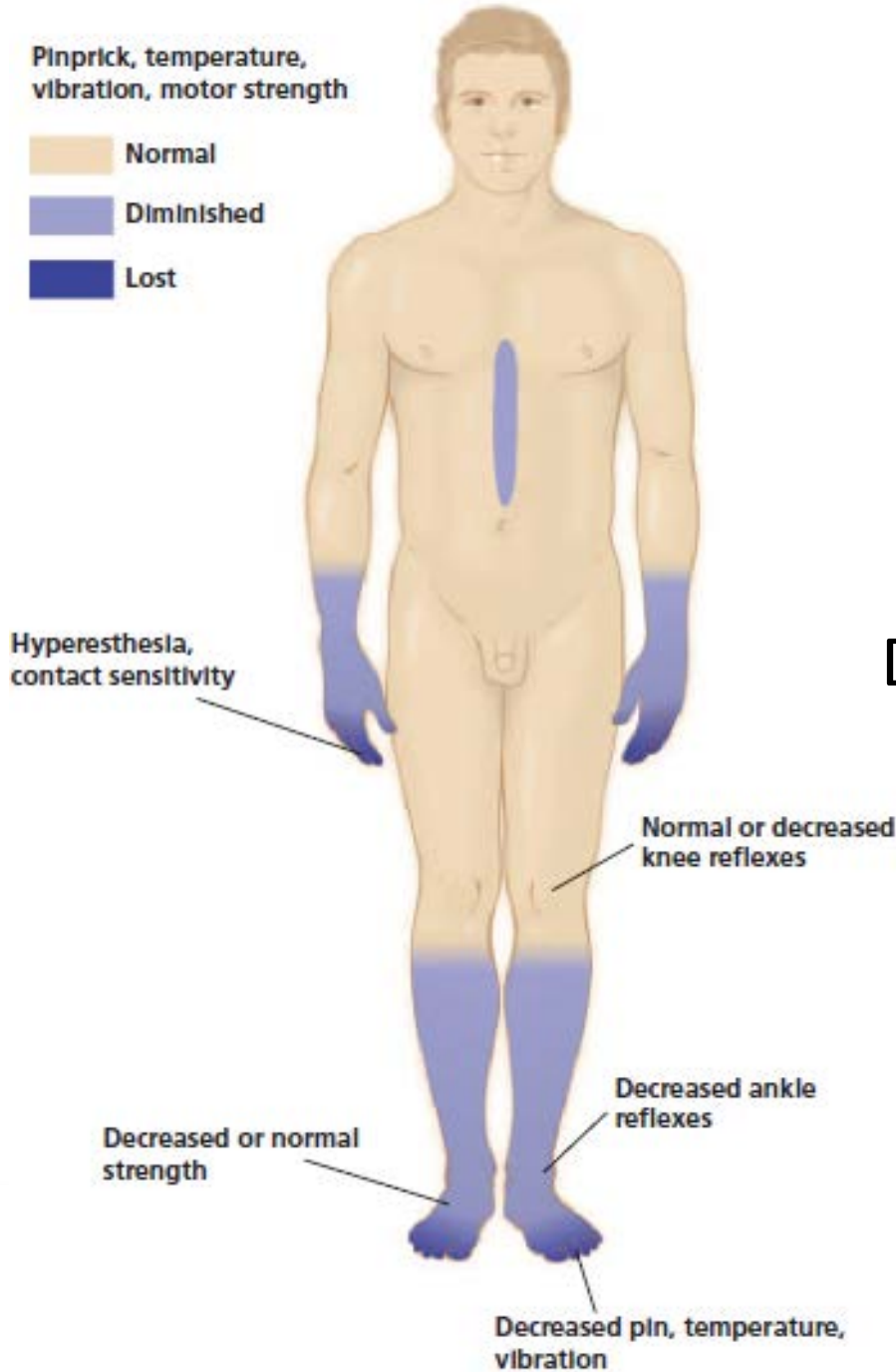




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Pinprick, temperature,  
vibration, motor strength

- Normal
- Diminished
- Lost



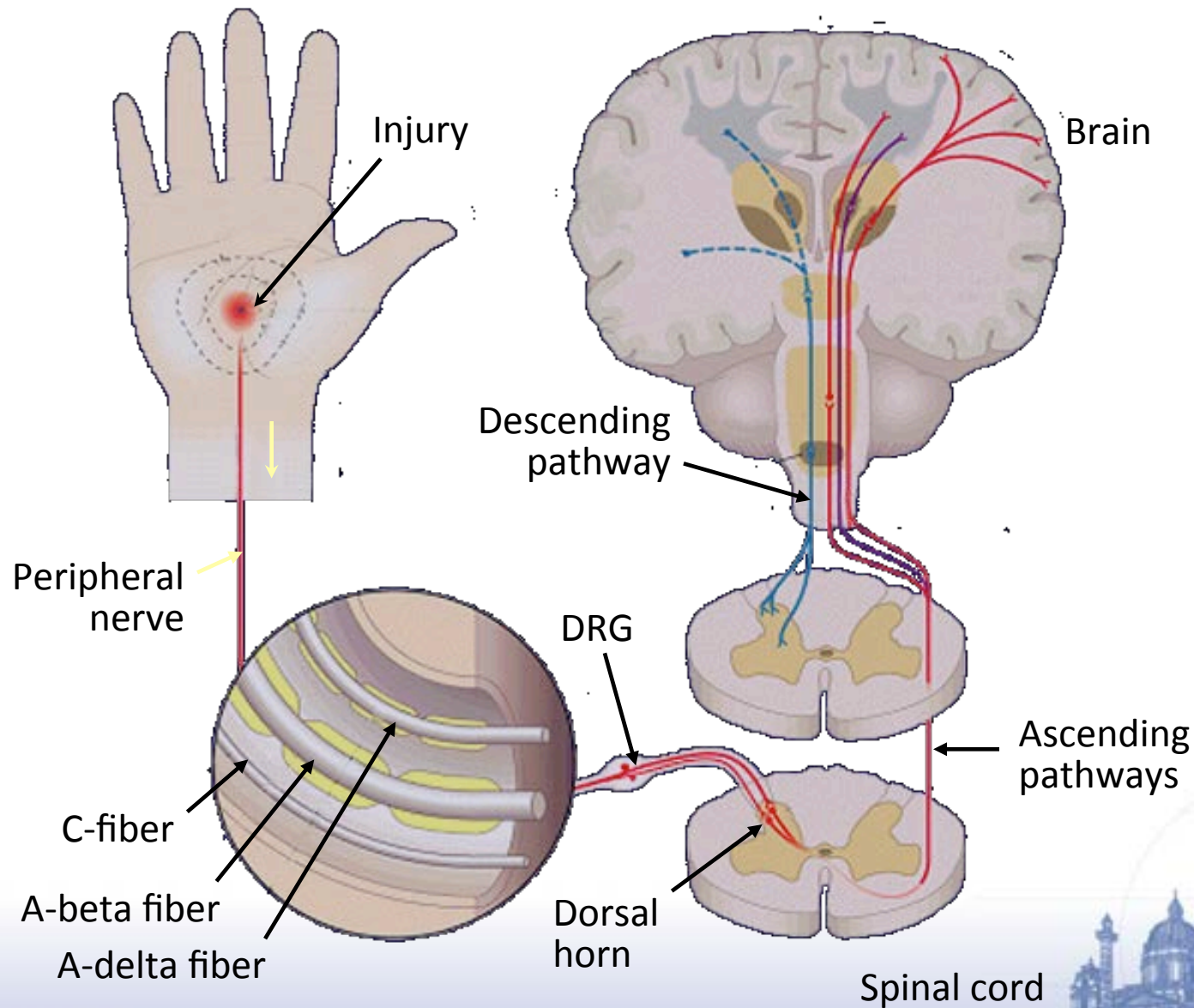
# Symmetrical Distal to Proximal Extension of Signs and Symptoms

Stubblefield, et al., 2009  
Adapted from: Simpson DA, Tagliati M, Gonzales-Duarte A, Mongello S. Neurologic manifestations. In: Mildvan D, ed. International Atlas of AIDS, 4th edition. Hoboken, NJ: Current Medicine Group LLC; 2007; with permission.

# Neurotoxic Drugs & Our Nervous Systems



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# Measurement Approaches

- There is no “gold standard” approach for clinical and research settings.
- A comprehensive approach improves validity.
  - Objective measurement of large and small fibers
  - Distal to proximal extension
  - Patient-reported outcomes (PRO)
  - Function assessment
- Must have strong psychometric properties



# Objective Measures

Clinical neurologic exam, quantitative sensory testing (QST), nerve conduction studies (NCS), electromyography (EMG), skin biopsy





# Total Neuropathy Score (TNS)

- The only comprehensive composite tool to be extensively tested in patients receiving neurotoxic chemotherapy
  - Reliable, valid, sensitive, & responsive
- Multidimensional
  - Symptoms - Proximal Extension Tingling, Numbness, Pain
  - Signs – e.g., Reflexes, Vibration & Pin Sensibility, Strength
  - NCS and QST - Optional
- Abbreviated versions can be used in clinical practice to assess adults and children.



# 5-item TNS Scoring



Item	0	1	2	3	4
Symptom extension (tingling)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (numbness)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (neuropathic pain)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent or others reduced	All reflexes absent
Vibration sensibility	Normal	Absent or decreased from toes to midfoot (not including heel)	Absent or decreased from midfoot to ankle	Absent or decreased above ankle to knee	Absent or decreased above knee or in lower and upper extremities concurrently

*Note.* Based on information from Chaudhry et al., 1994; Cornblath et al., 1999; Lavoie Smith et al., 2011; Smith et al., 2008, 2010.

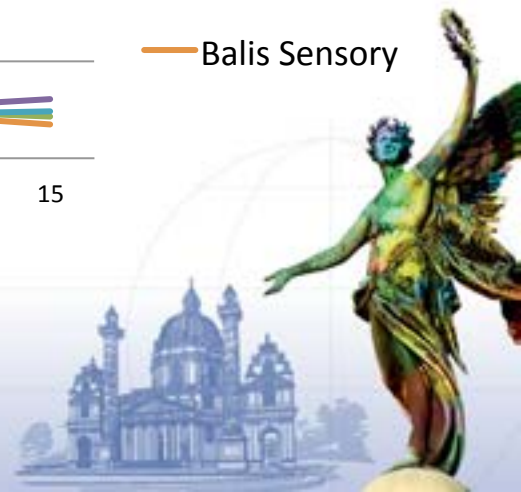
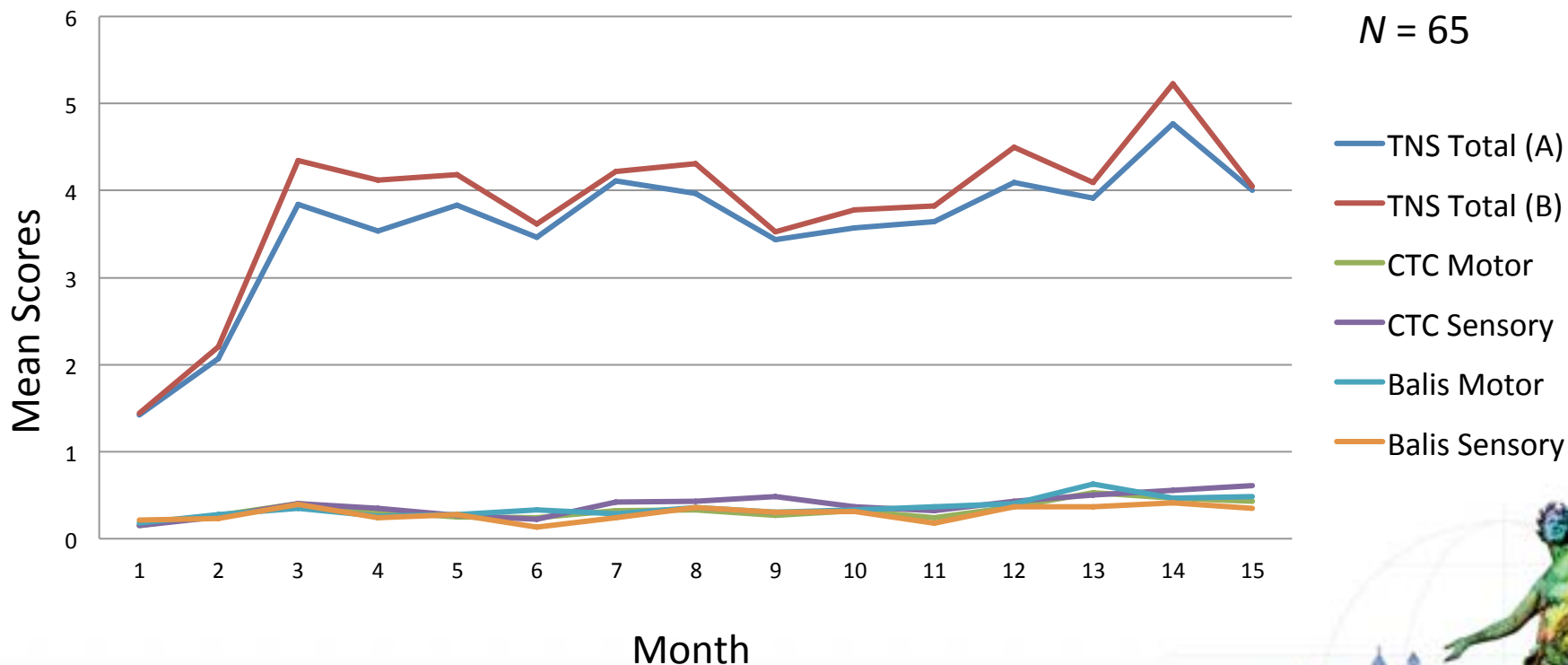


# TNS-PV Responsiveness

- Sample: Children ages 1-18 receiving vincristine for ALL



## TNS Versus Grading Scale Scores by Week



# Testing Vibration Sensibility

Feasible to perform in individuals  $\geq 6$  years of age



Use weighted 128Hz Tuning Fork





# Grading Scale Problems

- OK for screening but . . .
- Under-reports severity when compared to patient report
- Poor sensitivity & responsiveness
- No operational definitions, poor reliability
- Imprecisely captures progression
  - Preclinical and clinical signs/sx in same grade
  - Distal to proximal extension
  - What about pain?





# National Cancer Institute (NCI) CTCAE V. 4.0

## Mandated in all NCI-Sponsored Trials



### Sensory Neuropathy

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
No signs or symptoms	Asymptomatic: loss of deep tendon reflexes or paresthesia	Moderate symptoms: limiting instrumental ADL	Severe symptoms: limiting self care ADL	Life-threatening consequences: urgent intervention indicated	Death

# PRO Measures

Seven Measures: The most extensively tested are the FACT-GOG/  
NTX & EORTC QLQ-CIPN20.



# FACT GOG-NTX

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

## ADDITIONAL CONCERNS

Not at all    A little bit    Some-what    Quite a bit    Very much

NTX 1	I have numbness or tingling in my hands.....	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet.....	0	1	2	3	4
NTX 3	I feel discomfort in my hands.....	0	1	2	3	4
NTX 4	I feel discomfort in my feet.....	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps.....	0	1	2	3	4
HII2	I feel weak all over.....	0	1	2	3	4
NTX 6	I have trouble hearing.....	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears.....	0	1	2	3	4
NTX 8	I have trouble buttoning buttons.....	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand.....	0	1	2	3	4
Att6	I have trouble walking.....	0	1	2	3	4

**During the past week :**

# QLQ CIPN20

**Not at  
All**

**A  
Little**

**Quite  
a Bit**

**Very  
Much**

31	Did you have tingling fingers or hands?	1	2	3	4
32	Did you have tingling toes or feet?	1	2	3	4
33	Did you have numbness in your fingers or hands?	1	2	3	4
34	Did you have numbness in your toes or feet?	1	2	3	4
35	Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36	Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37	Did you have cramps in your hands?	1	2	3	4
38	Did you have cramps in your feet?	1	2	3	4
39	Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40	Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41	Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42	Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43	Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44	Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

# QLQ CIPN20 (cont.)



**During the past week :**

	Not at All	A Little	Quite a Bit	Very Much
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4

46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
--	---	---	---	---

47 Did you have blurred vision?	1	2	3	4
---------------------------------	---	---	---	---

48 Did you have difficulty hearing?	1	2	3	4
-------------------------------------	---	---	---	---

**Please answer the following question only if you drive a car**

49 Did you have difficulty using the pedals?	1	2	3	4
--	---	---	---	---

**Please answer the following question only if you are a man**

50 Did you have difficulty getting or maintaining an erection?	1	2	3	4
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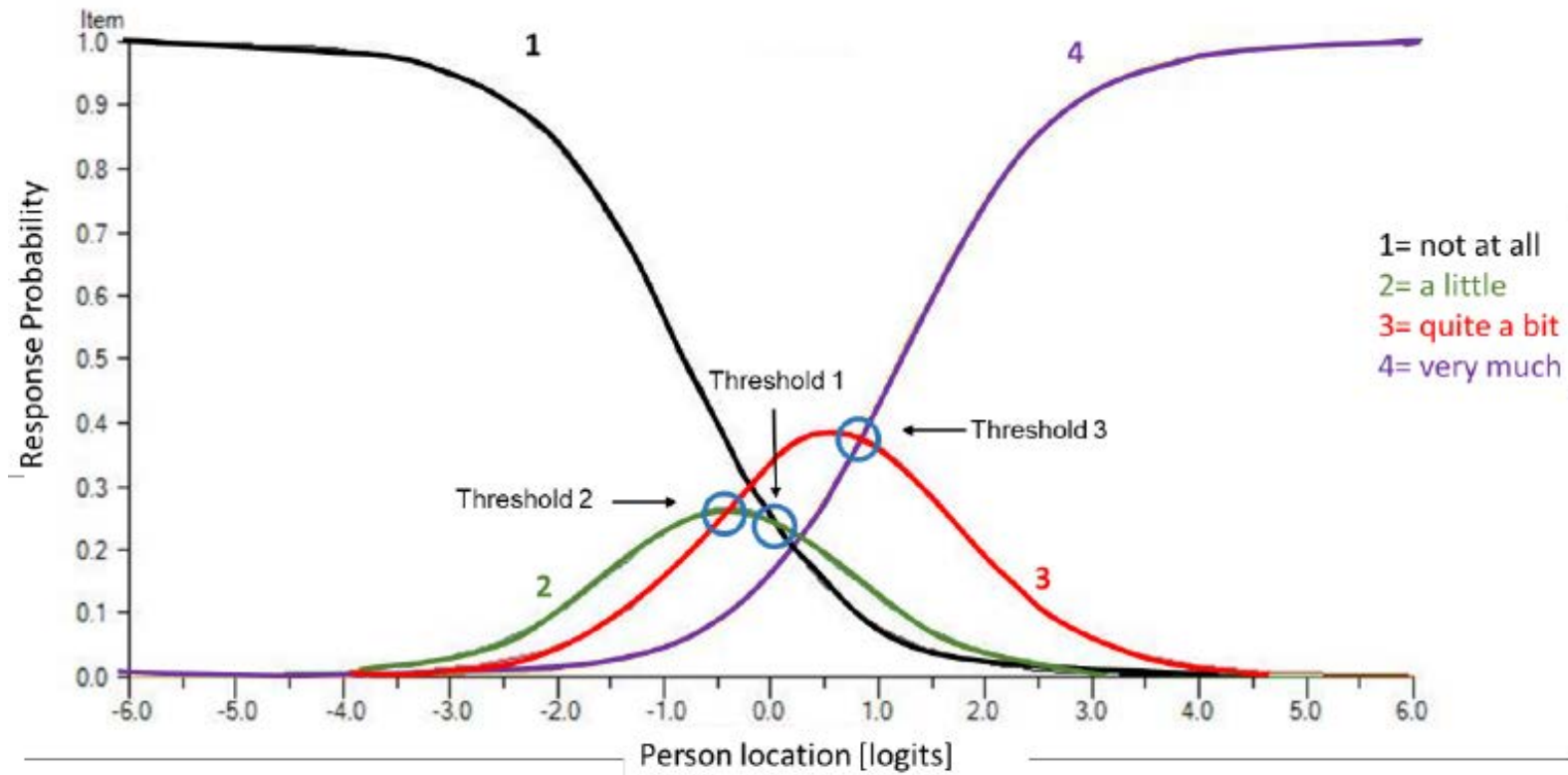


# Comparison of FACT GOG/NTX with CIPN20



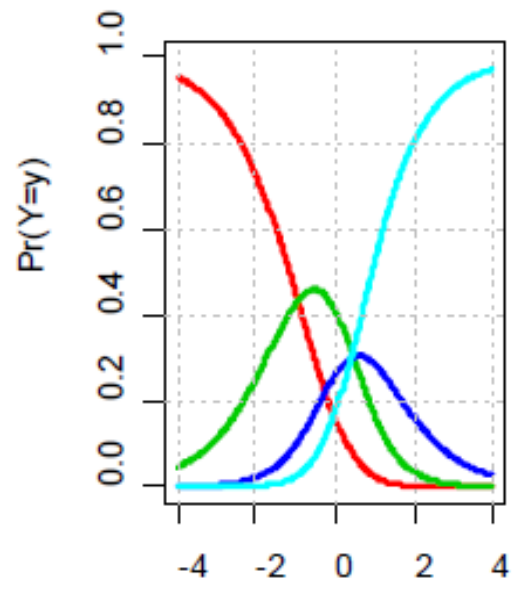
	FACT GOG/NTX/NTX12	QLQ-CIPN20
Number of Studies	10	9
Populations	N Range 20– 395 US, European, Asian, African Various Cancers	N Range 25 – 1155 US, European, Asian Various Cancers
Properties Tested	ICR, Contrasting Group, Content, Structural, Contrasting Groups, & Convergent Validity, Sensitivity & Specificity, Responsiveness	ICR & Test-Retest Reliability; Content, Structural, Contrasting Group, & Convergent Validity, Sensitivity, Responsiveness, Mode Equivalence, Item Response
Languages	Numerous	Numerous
Neuropathy Types	Taxanes, Platinums, Vinblastine, Bortezomib	Taxanes, Platinums, Vincas, Bortezomib
Strengths	Feasible for multisite trials Brief (11/12-items, 4-items)	Feasible for multisite trials Brief (20-items) but longer than FACT.
Weaknesses	Some items may not be neuropathy-specific	Lack of Consensus About Autonomic & Driving items; Disordered response thresholds

# Rasch Analysis-Response Ordering



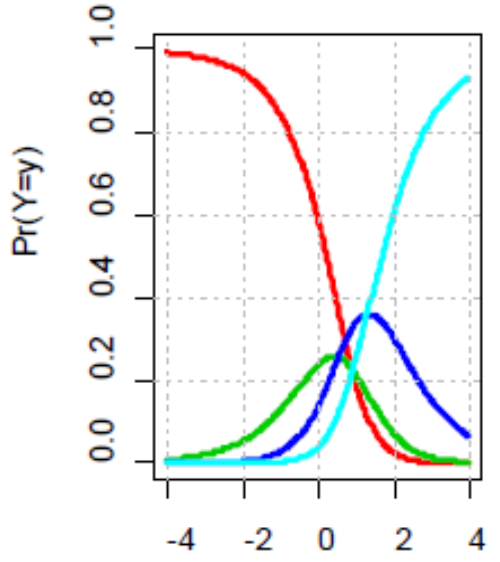
Small Objects

CIPN 12

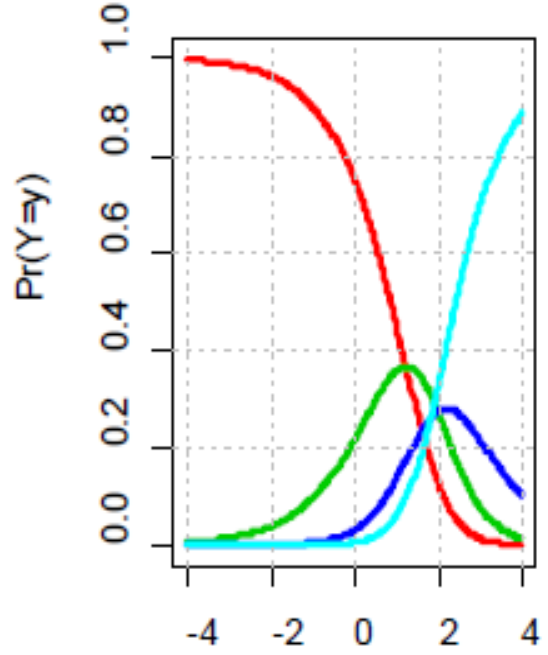


Foot Drop

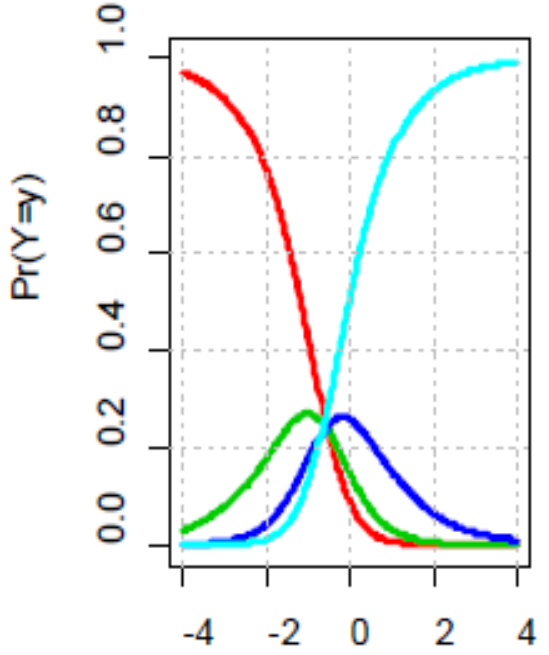
CIPN 14



Pedals CIPN 19



Erection CIPN 20



# PRO-CTCAE - Neuropathy



What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST in the past 7 days?

How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities in the past 7 days?



Concurrent validity when compared to QLQ CIPN20



# Function Measures



Examples: Timed Up-and-Go (TUG), 9-Hole Peg Test, Bumps Test

Advantages	Disadvantages
Assesses functional outcomes such as walking and balance, hand dexterity and sensory function.	Requires special training and equipment
Useful for research settings	Time-consuming
	Limited psychometric testing in CIPN





# Summary



## No Consensus About Measurement Approaches But Many Good Options

Assess:  
At Baseline,  
During Rx, &  
In Survivors

Practice Settings:  
CTCAE  
PRO-CTCAE  
★ 5-item TNS

Research Settings:  
Objective Measures  
FACT GOG/NTX or  
QLQ-CIPN20  
Functional Measures  
PRO-CTCAE



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**Thank you!**

