Disease specific examination in the diabetic neuropathies

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Overview

- Review the details examination development
- Review the current status of diabetic neuropathy examinations
- Summarize the examination types
- Review the relationship between examinations and neurologic complications of diabetes
- Conduct an exercise in examination criteria
- Implications for the taxonomy of diabetic neuropathy

Historical Perspective

- Grading of strength, reflexes and sensation developed over the 19th and 20th century with contributions from Mitchell, Lewis, Plumer, and the Mayo brothers
  - Ordinal grading introduced
  - Lovett introduces a 6 point grade, later converted into the MRC scale
- The MRC scale came to prominence during WWII
  - The scale became widely used and highly relevant as a way to determine the severity of nerve injuries ranging from paralysis to full strength

Dyck P.J. History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. JPNS 2005

Diabetic Neuropathy Scales

- A total of 16 different scoring systems have been published in reports of diabetic neuropathy
- The scales differ widely in the scope of assessment, the weighting of different systems and the use of adjunctive testing
- Many of the scales are based on the MRC scoring systems, which are primarily used for the pattern recognition for diagnosis of a problem

Neuropathy Examinations

	Vibration	Reflex	Pin-prick	Muscle strength	Touch pressure	Joint Position	Temp Detection	Allodynia	Two-point discrimination	PRO or CRO-Symptoms	Nerve Conduction
DNE	✓	✓	✓	✓	✓	✓					
ENS	✓	✓	✓		✓		✓				
INCAT	✓		✓						✓		
MDNS	✓	✓	✓	✓	✓						✓
MNSI	✓	✓								✓	
NIS/NDS	✓	✓	✓	✓	✓	✓					✓
NIS-LL	✓	✓	✓	✓	✓	✓					
NIS-LL+7	✓	✓	✓	✓	✓	✓					✓
mNIS-LL+7		✓		✓							✓
PNS	✓	✓	✓	✓	✓	✓				✓	✓
PNP	✓	✓		✓						✓	
Reduced TNS	✓	✓	✓	✓						✓	✓
TNS	✓	✓	✓	✓						✓	✓
TNSc	✓	✓	✓	✓						✓	
TNSr-SF	✓	✓								✓	
TCNS	✓	✓	✓		✓	✓	✓			✓	
mTCNS	✓		✓		✓	✓	✓			✓	
UENS	✓	✓	✓	✓		✓		✓			

	Muscle Strength		Reflex	Vibration		Touch Pressure		Joint Position		Pin Prick		Percent of max score			
	Lower	Upper		Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Motor	Reflex	Large Fiber	Small Fiber
Diabetic Neuropathy Examination Score[R]	■		▭	▭		▭		▭		▭	▭	25	13	39	25
Early Neuropathy Score[B]			▭	▭ RS		▭				▭		0	20	40	40
INCAT[M]				■ RS	■					■	■	0	0	60	40
MDNS[B]	▬	▭	■	▭ 128		▭				▭		39	35	18	9
MNSI[B^]			▬	▭								0	25	25	0
NIS/NDS[B]	■	■	■	▭ 128/165	▭	▭	▭	▭	▭	▭	▭	71	11	12	4
NIS-LL[B]	■		▬	▭ 165		▭		▭		▭		73	9	15	5
NIS-LL+7[B]	■		▬	▭		▭		▭		▭		73	9	15	5
Modified NIS-LL+7[B]	■		▬									91	9	0	0
Peripheral Neurology Score[B^^]	■	■	■	■	■	■	■	■	■	■	■	38	31	18	6
Peripheral Neuropathy Score[B]	▭	▭	■	■ RS	▭							N/A	N/A	N/A	N/A
Reduced TNS[M]	■	■	■	■ 128	■					■	■	25	25	25	25
TNS[M]	■	■	■	■ 128	■					■	■	25	25	25	25
TNSc[M]	■	■	■	■ 128	■					■	■	25	25	25	25
TNSr-SF[M]			■	■ 128	■							0	50	50	0
Toronto Clinical Neuropathy Score**				▭		▭		▭		▭		0	62	24	16
Modified Toronto Clinical Neuropathy Score[N]				■		■		■		■		0	0	60	40
UENS[B]	▬		▭	▭ 128				▭		■		10	10	20	62
Key	▭ Toes or fingers ■ Toes/ankle or fingers/wrist ▬ More than toes/ankle or fingers/wrist		▭ Ankle ■ Ankle/knee ▬ More than ankle/knee	▭ Toes or fingers ■ Toes/ankle or fingers/wrist ▬ More than toes/ankle or fingers/wrist		▭ Toes or fingers ■ Toes/ankle or fingers/wrist ▬ More than toes/ankle or fingers/wrist		▭ Toes or fingers ■ Toes/ankle or fingers/wrist ▬ More than toes/ankle or fingers/wrist		▭ Toes or fingers ■ Toes/ankle or fingers/wrist ▬ More than toes/ankle or fingers/wrist					

Examination selection

- Why is this relevant?
- If a drug works to prevent diabetic neuropathy progression, or reverse an existing diabetic neuropathy, does it matter what examination criteria we select?

The natural history of diabetic neuropathy

- In a cohort of 62 individuals with well-controlled diabetes (HbA1C 7.2±1.3) were followed longitudinally for 3 years with detailed examination and neurophysiologic testing
- Associated risk factors (blood pressure, tobacco use, cholesterol, triglycerides) were all well controlled

Gibbons CH, Freeman R, Tecilazich F, Dinh T, Lyons TE, Gnardellis C, Veves A. The evolving natural history of neurophysiologic function in patients with well-controlled diabetes. J Peripher Nerv Syst. 2013 Jun;18(2):153-61.

The natural history of diabetic neuropathy

- There was no change in examination over 3 years

	Muscle Strength		Reflex	Vibration		Touch Pressure		Joint Position		Pin Prick		Percent of max score			
	Lower	Upper		Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Motor	Reflex	Large Fiber	Small Fiber
Diabetic Neuropathy Examination Score												25	13	39	25

- No change in symptom scores

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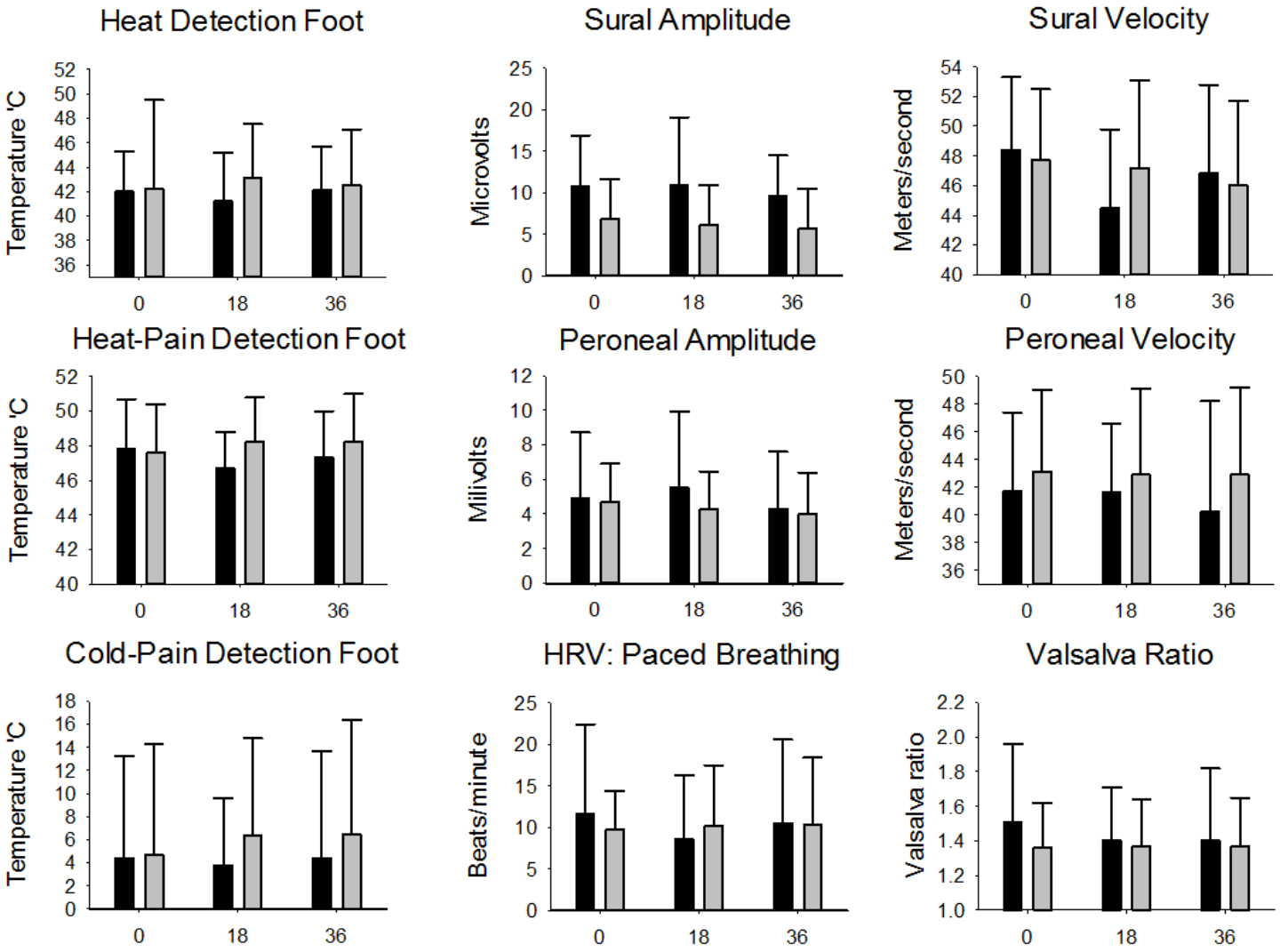
The natural history of diabetic neuropathy



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The natural history of diabetic neuropathy

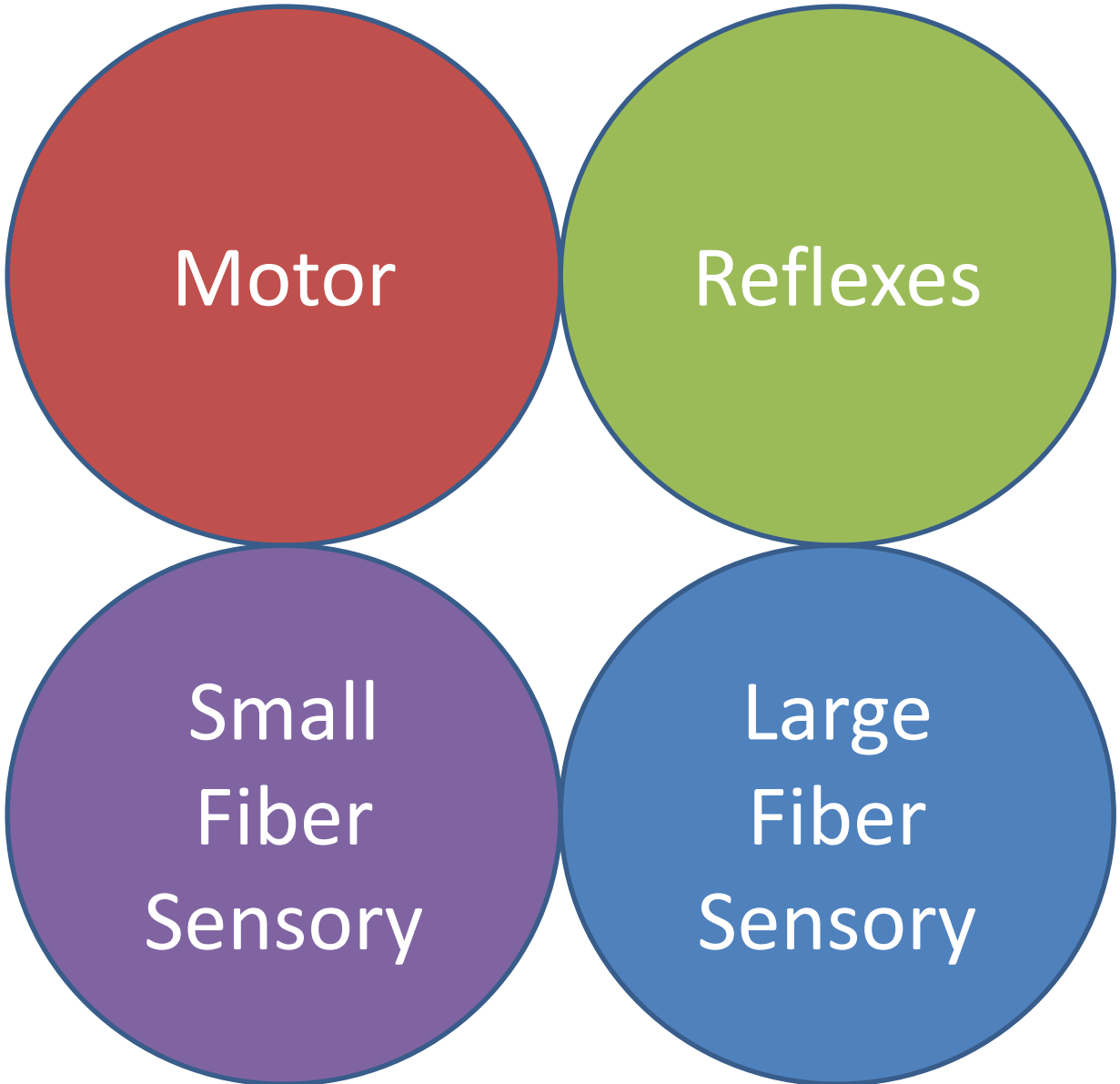
- So what is the point of measuring if nothing changes?

CONCEPPT/IDNC Meeting

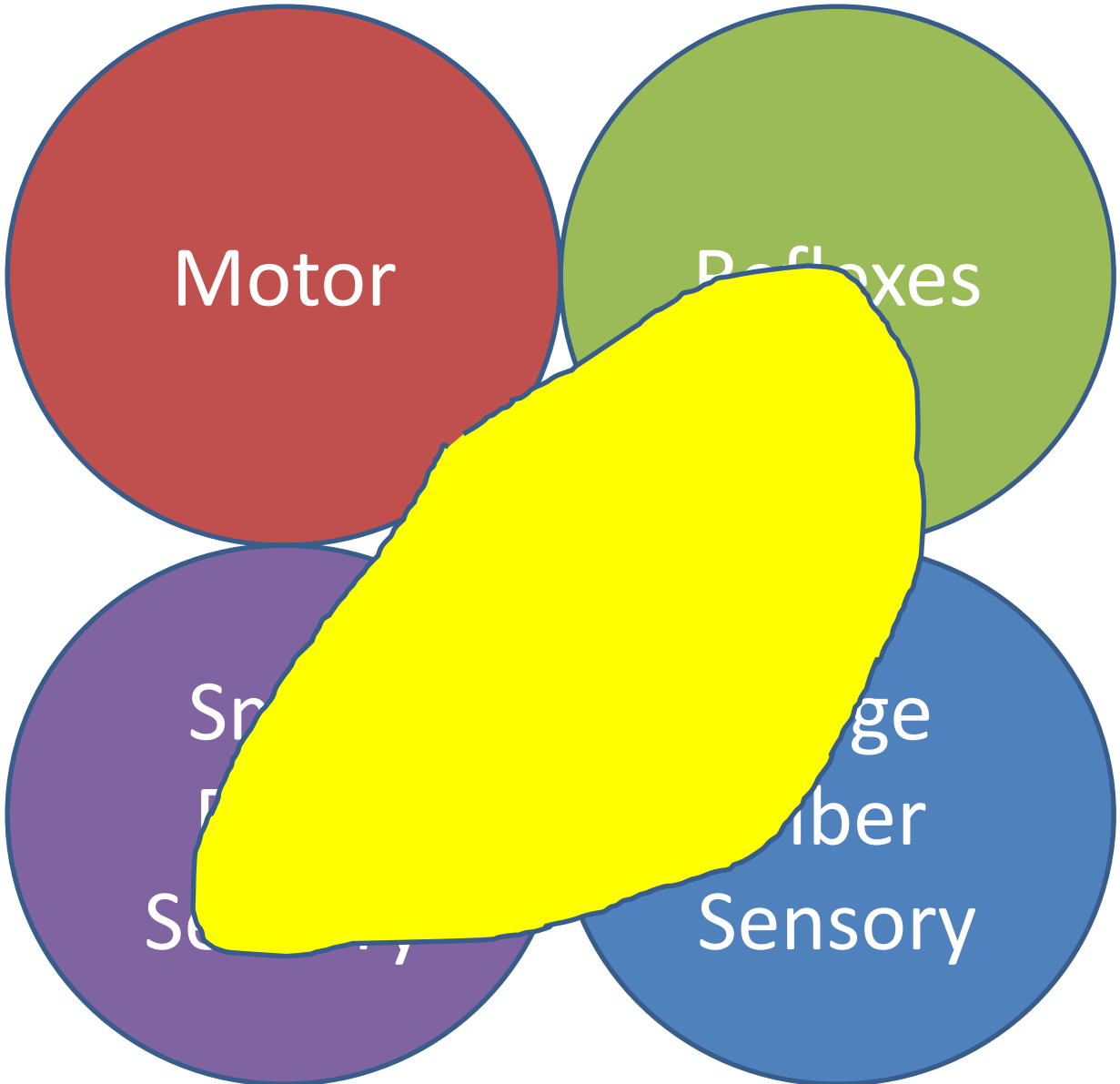
- Diabetic neuropathy
- Neuropathy of the pre-diabetic state
- Treatment induced neuropathy
- Lumbosacral radiculoplexus neuropathies
- Focal, entrapment neuropathies: carpal tunnel syndrome, ulnar neuropathy, peroneal neuropathy

CONCEPPT/IDNC Meeting

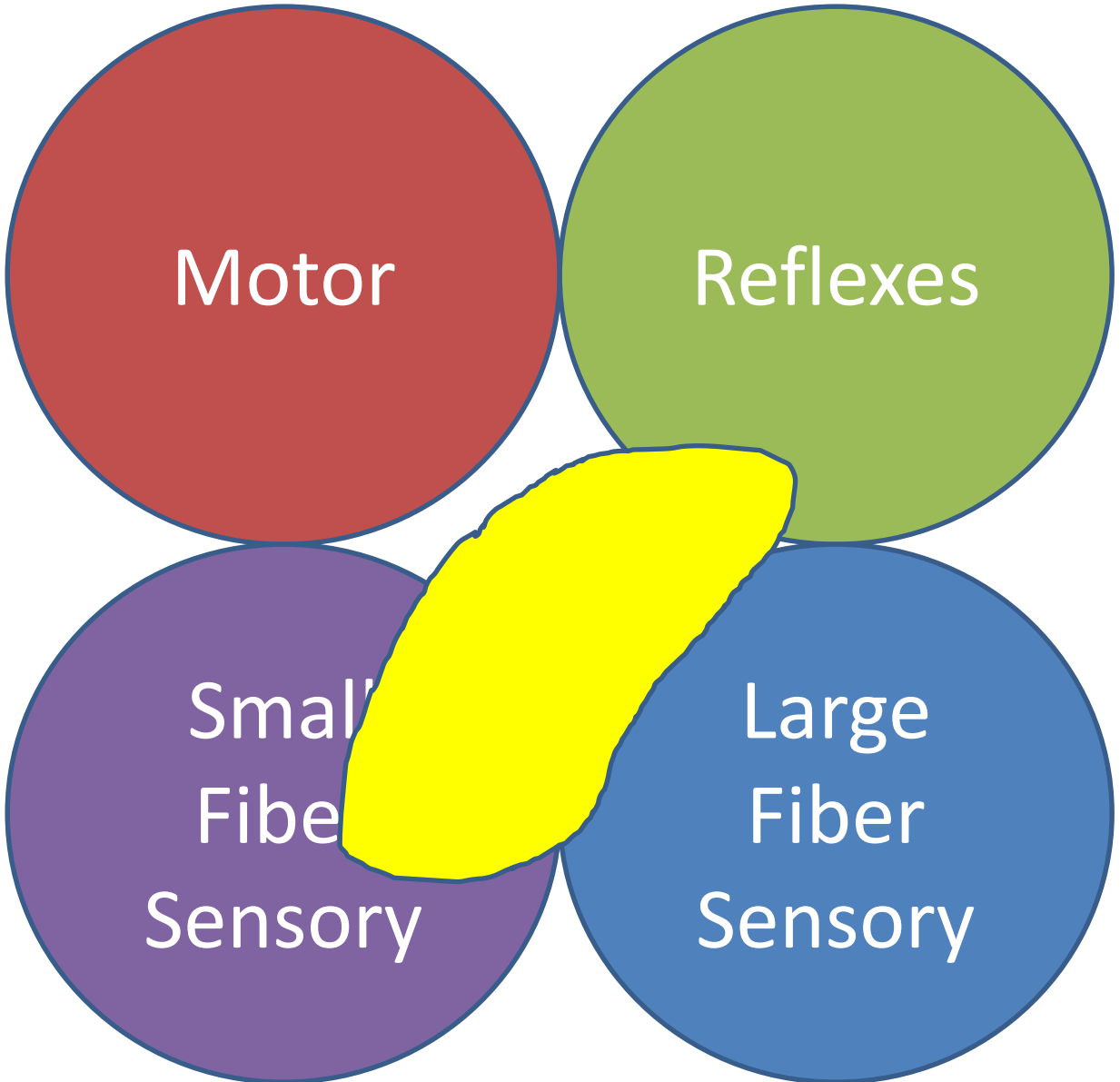
Neuropathy specific details



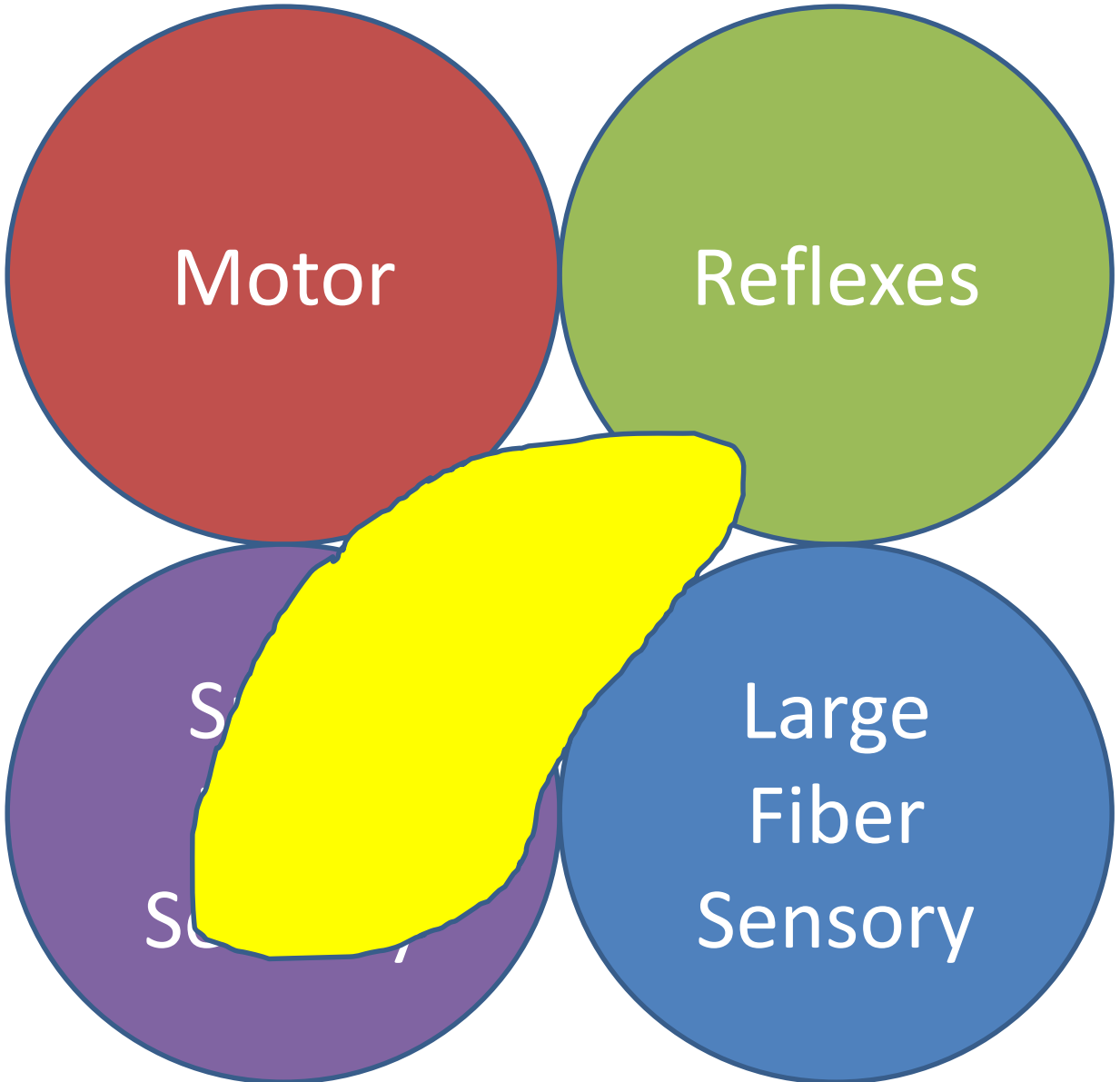
Diabetic Neuropathy



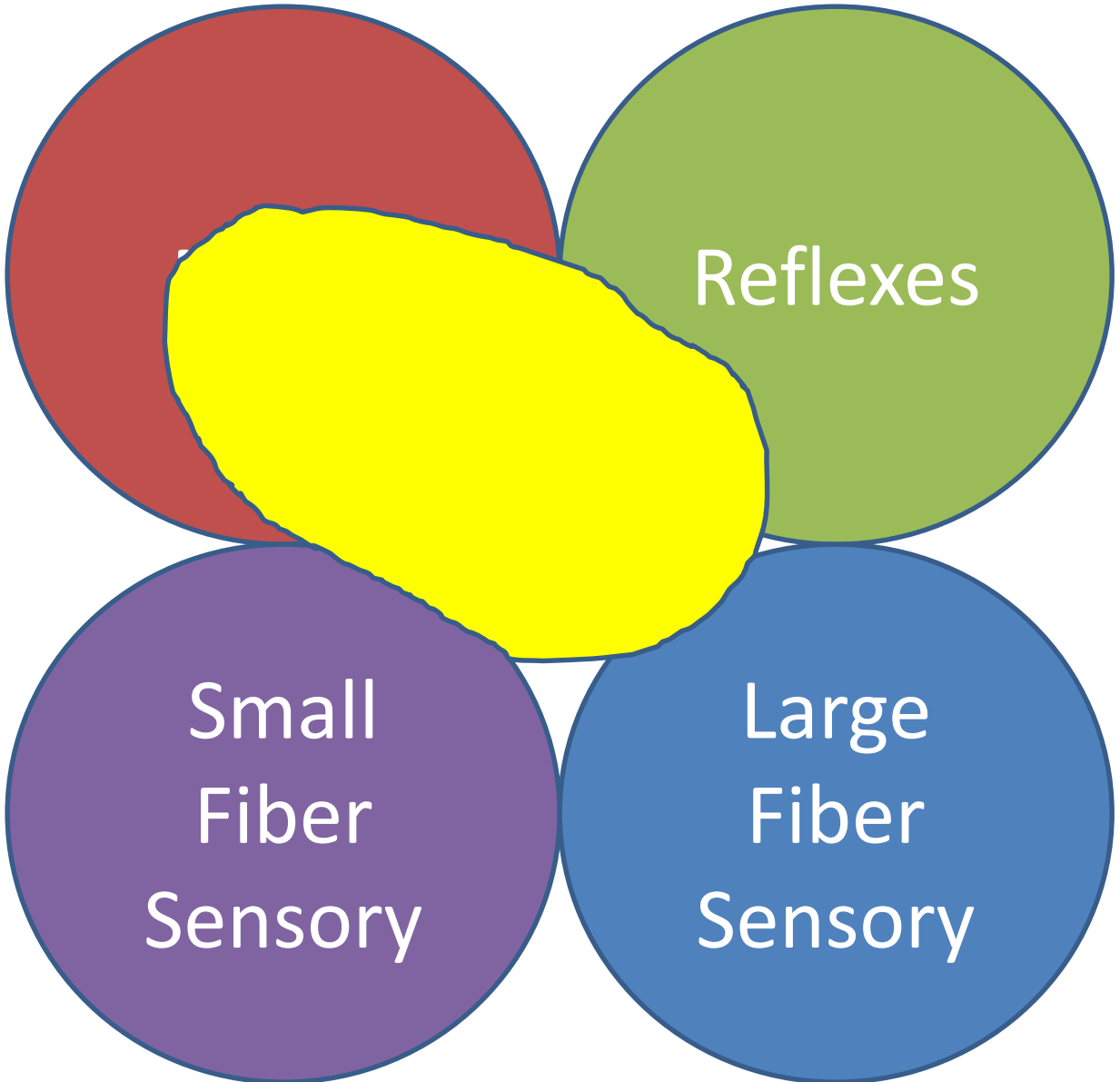
Neuropathy of the pre-diabetic state



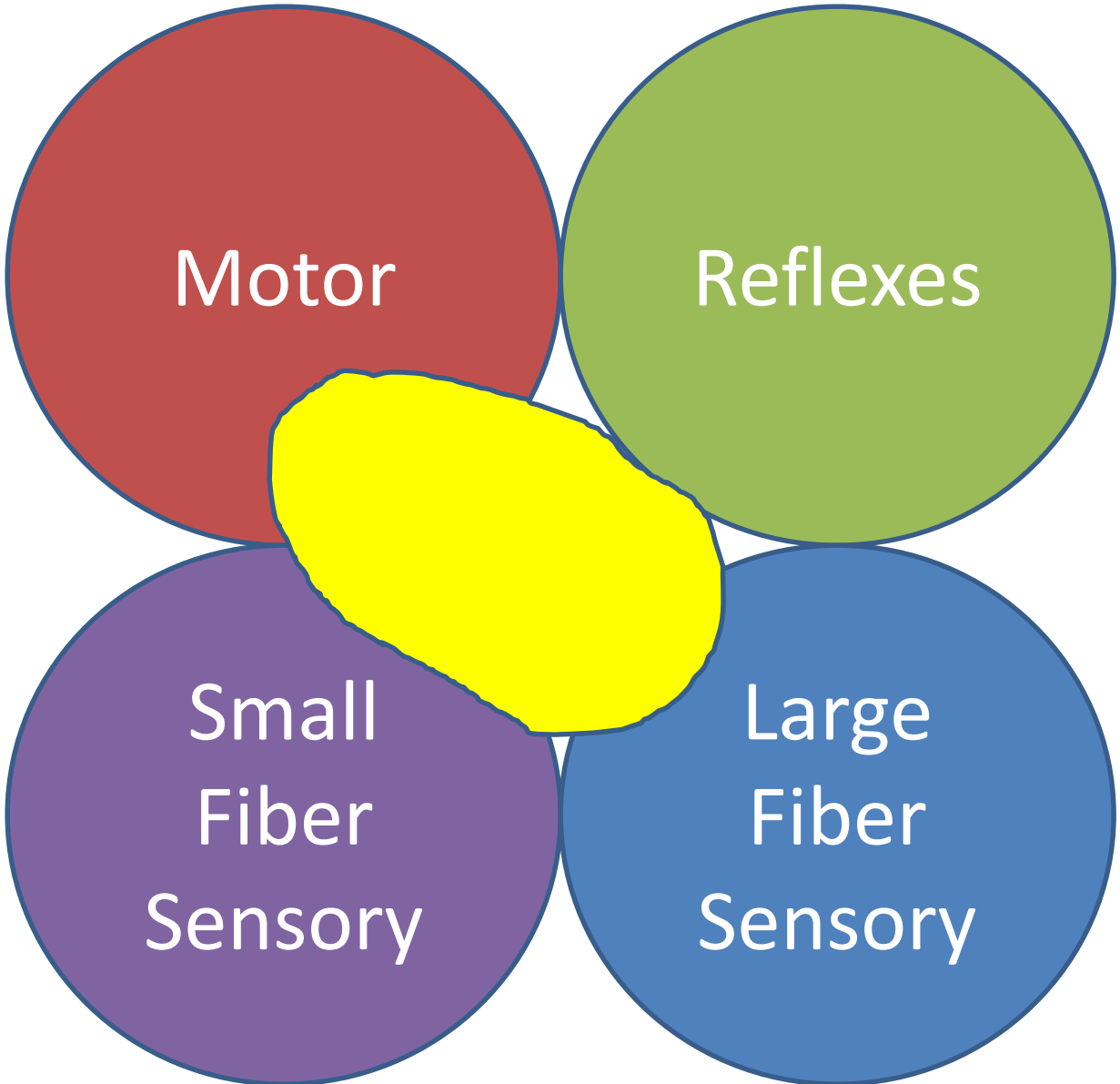
Treatment Induced Neuropathy



Lumbosacral Radiculoplexus Neuropathy

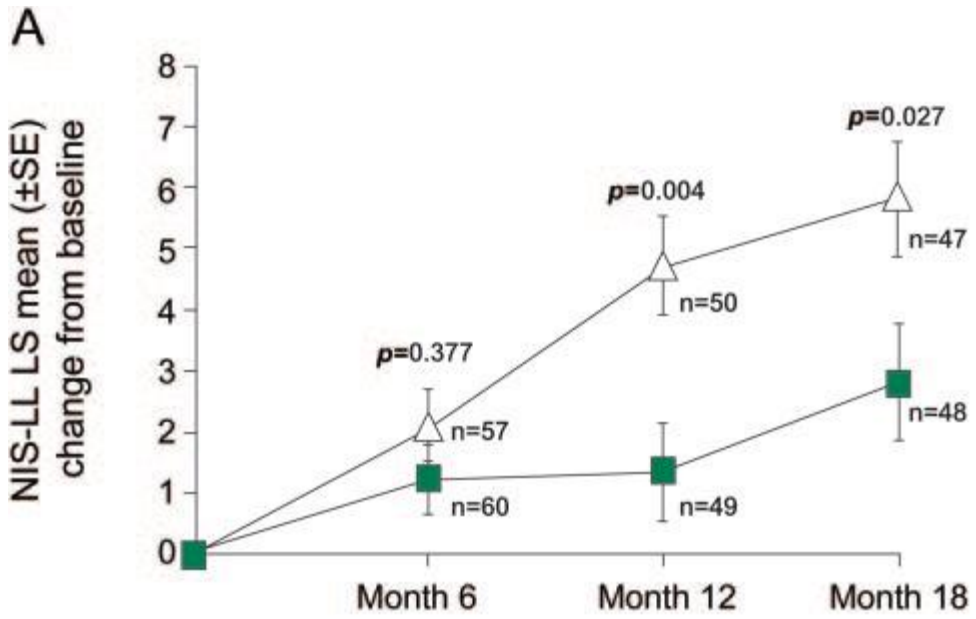


Entrapment Neuropathy



Why do examinations count?

- A randomized controlled trial of Tafamidis for FAP
- 18 months duration
- The primary outcome was a 2 point change in NIS-LL



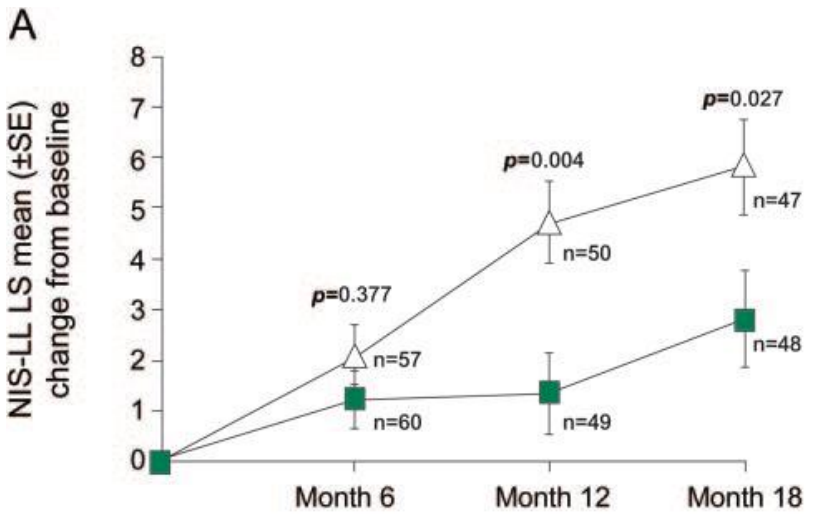
Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, Suhr OB, Campistol JM, Conceição IM, Schmidt HH, Trigo P, Kelly JW, Labaudinière R, Chan J, Packman J, Wilson A, Grogan DR. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012 Aug 21;79(8):785-92.

NIS-LL

NIS-LL Scores

- Tafamidis: 8.3±11.4 and increased to ~11.1±11.7
- Placebo: 11.4±13.5 and increased to ~17.2±12.8

- **Worsening in placebo group was primarily change in strength**



NIS-LL

NIS-LL Scores range 0-88

- Strength in the lower extremities (0,1,2,3,3.25,3.5,3.75,4)
  - Score range 0-64
- Reflexes in the lower extremities (0,1,2) with age adjustment
  - Score range 0-8 (except if >50 then 0-6, if >70 then 0-4)
- Sensory examination in the lower extremities (0,1,2)
  - Score range 0-16

Revisionist history….

- Repeat the existing study and selecting different examinations

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FAP

- Of the 18 potential examination scores, 14 would have resulted in ‘no clinical effect’ and may have resulted in cessation of study
- The 4 potential effective scales were all variations of the NIS

- Thus, the selection of the appropriate examination score may play a significant role in the potential for a positive study outcome.

CONCEPPT/IDNC Meeting

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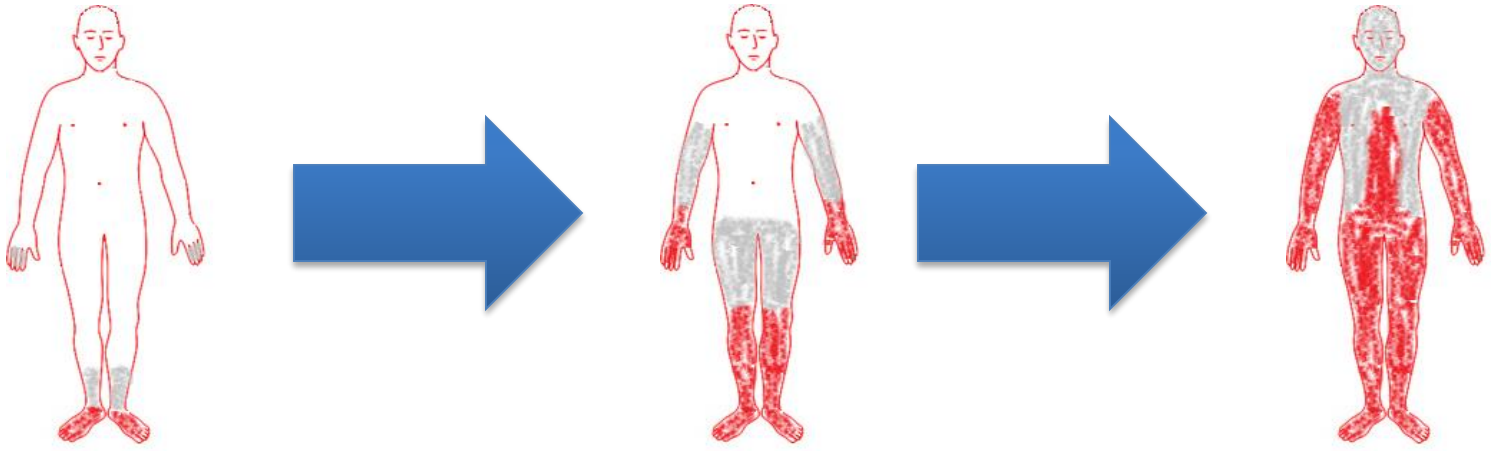
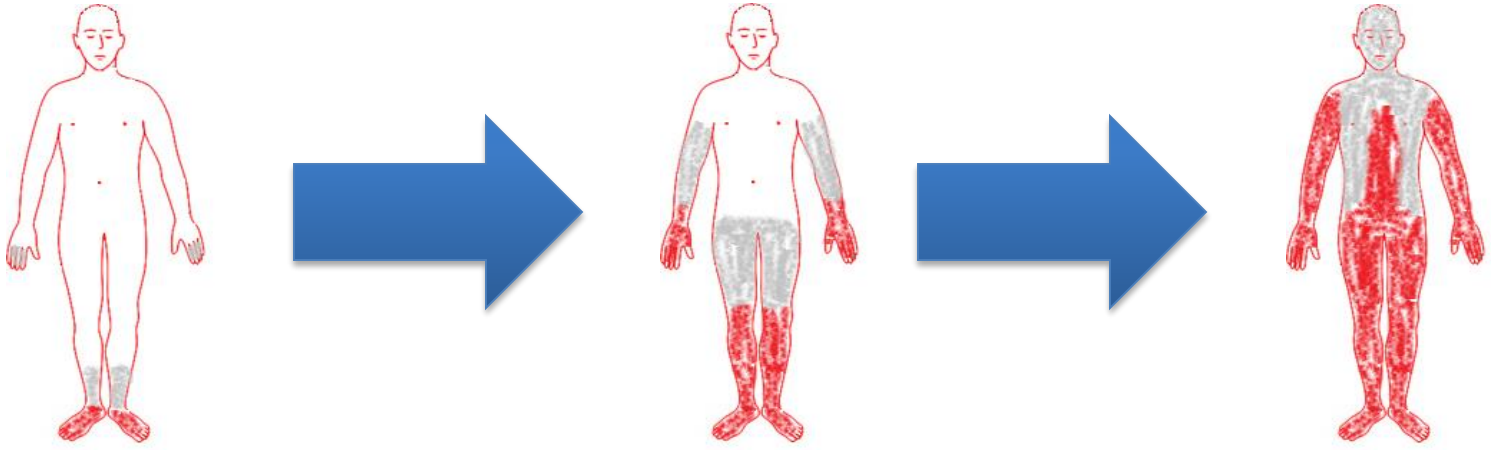
Treatment Induced Neuropathy of Diabetes

- What if NIS-LL was the exam score chosen?
- Examination worsens from:



Treatment Induced Neuropathy of Diabetes

- The NIS-LL score would be 4 in all cases
  - Loss of pain and temp in the great toes
    - No loss of vibration or proprioception
  - No loss of reflexes or strength



Choice of Outcome Measures Matter