The Taxonomy of Generalized Diabetic Polyneuropathy

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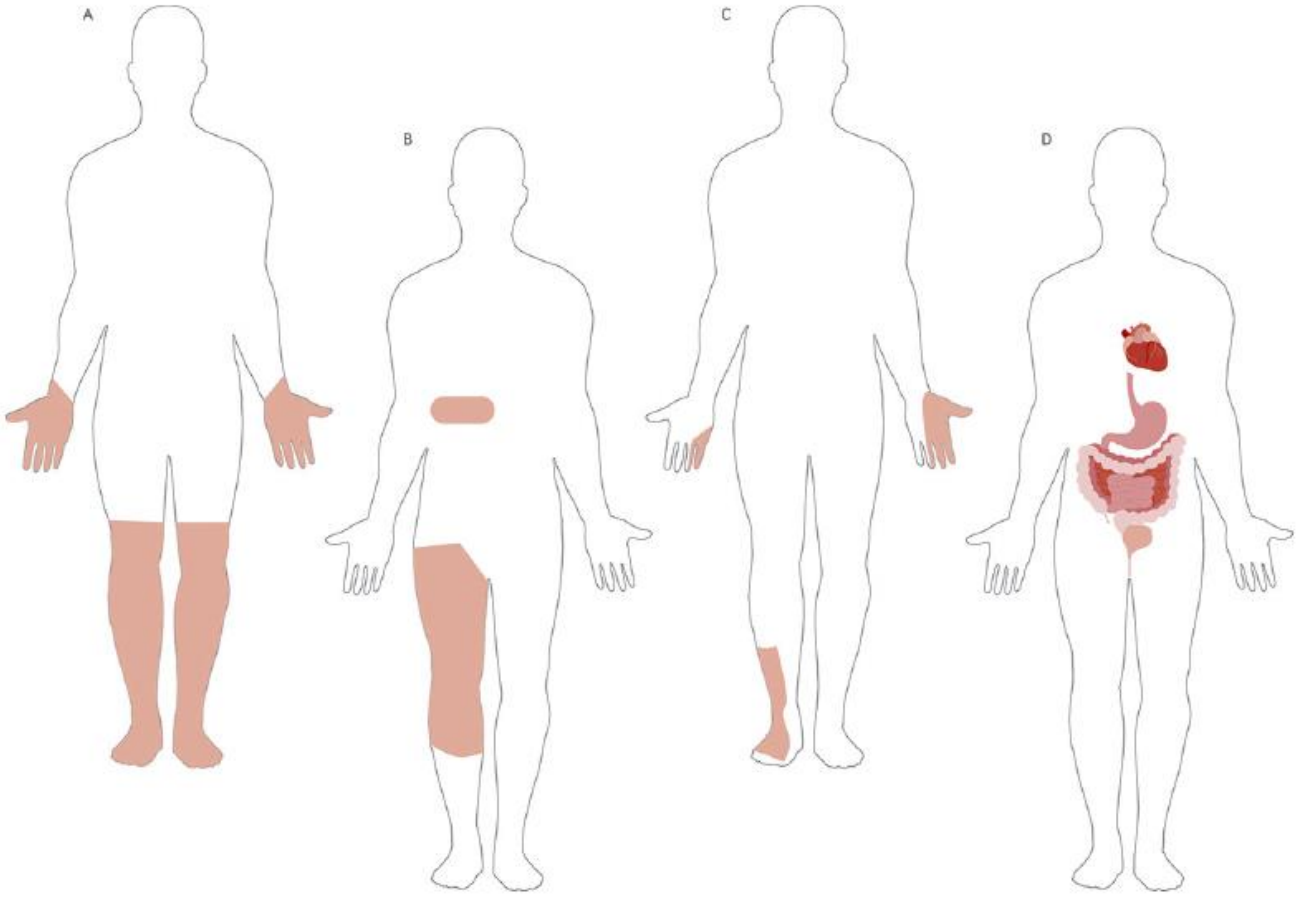
ACTTION – American Pain Society Taxonomy

Table 3. The Dimensions Comprising the AAPT

Dimension	Description
Dimension 1: Core diagnostic criteria	Includes symptoms and signs required for diagnosis of the disorder (eg, periauricular pain, palpation sensitivity, joint sounds in the case of TMD). Also includes diagnostic tests and differential diagnosis considerations.
Dimension 2: Common features	Provides additional information regarding the disorder, including common pain characteristics (eg, location, temporal qualities, descriptors), nonpain features (numbness, fatigue), and the epidemiology of the disorder. These features are helpful in describing the disorder but are not used as part of the diagnosis.
Dimension 3: Common medical comorbidities	Includes medical diagnoses that co-occur with high frequency with the pain disorder. For example, diabetes mellitus is often comorbid with osteoarthritis, and major depression is comorbid with many chronic pain disorders.
Dimension 4: Neurobiological, psychosocial, and functional consequences	Includes information regarding neurobiological and psychosocial consequences of chronic pain, as well as the functional impact of the pain disorder. Examples include allostatic load, sleep quality, mood/affect, coping resources, physical function, and pain-related interference with daily activities
Dimension 5: Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors	Includes putative neurobiological and psychosocial mechanisms contributing to the pain disorder, including potential risk factors and protective factors.

Fillingim, R. B., et al. (2014). The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. The journal of pain : official journal of the American Pain Society, Elsevier. **15:** 241-249.

The Diabetic *Neuropathies*



Peltier, A., et al. (2014). "Painful diabetic neuropathy." BMJ **348**(may06 1): g1799-g1799.

Core Diagnostic Criteria (Dimension 1)

Table 1. Characteristics of an Ideal Diagnostic System

Characteristic	Description
Biologically plausible	The diagnostic system must be consistent with the biological processes underlying the signs and symptoms that characterize the disorders of interest.
Exhaustive	The diagnostic system must encompass all clinical disorders within the domain of interest.
Mutually exclusive	The diagnostic system must encode each disorder once and only once.
Reliable	The diagnostic system must be applicable with a high degree of consistency across time and between diagnosticians.
Clinically useful	The diagnostic system must be useful in the clinical setting, guiding prognosis and therapy.
Simple	The diagnostic system must be both straightforward and efficient enough for practical use.

Fillingim, R. B., Bruehl, S., Dworkin, R. H., Dworkin, S. F., Loeser, J. D., Turk, D. C., et al. (2014). The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. (Vol. 15, pp. 241–249). Presented at the The journal of pain : official journal of the American Pain Society, Elsevier. http://doi.org/10.1016/j.jpain.2014.01.004

Core Diagnostic Criteria (Dimension 1)

Diabetes	Definition
Type 1	Autoimmune, GAD Ab +, Young onset, Insulin deficiency/requiring
Type 2	Insulin resistant (hyperinsulinemia), obesity, later onset (adolescent to adult),
Type 3	Other disorders of the exocrine pancreas (CF, drug induced)
Type 4	Gestational

TABLE 3-1 **Diagnostic Criteria for Diabetes and Prediabetes**

Diagnosis	Fasting Plasma Glucose	2-Hour Oral Glucose Tolerance Test	Hemoglobin A_{1C}
Normal	< 100 mg/dL (5.6 mmol/L)	< 140 mg/dL (7.8 mmol/L)	< 5.7%
Prediabetes	100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L)	140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L)	5.7% to 6.4%
Diabetes	≥ 126 mg/dL (7.0 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)	≥ 6.5%

Smith AG. Continuum Lifelong Learning Neurol. 2012

Core Diagnostic Criteria (Dimension 1)

T1D versus T2D

1. Is DPN associated with T1D the same disease as that associated withT2D?
2. Is DPN associated with T2D the same as DPN associated with Prediabetes/Obesity/Metabolic Syndrome?

Enrollment criteria for painful DPN trials

Duloxetine (Raskin 2005)

- ✓ T1 or T2D
- ✓ Symmetric onset of foot pain.
- ✓ 6 months or more
- ✓ MNSI >2
- ✓ ≥4 Likert

Pregabalin (Lesser 2005)

- ✓ T1 or T2D
- ✓ DSP 1-5 years
- ✓ Average daily pain ≥4 on at least 4 daily pain diaries.
- ✓ VAS ≥4

Raskin, J., et al F. (2005). A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med, 6(5), 346–356.

Lesser, H., Sharma, U., LaMoreaux, L., & Poole, R. M. (2004). Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology, 63(11), 2104–2110.

Kessler, J. A.et al. (2015). Double-blind, placebo-controlled study of HGF gene therapy in diabetic neuropathy. Annals of Clinical and Translational Neurology, n/a–n/a. http://doi.org/10.1002/acn3.186

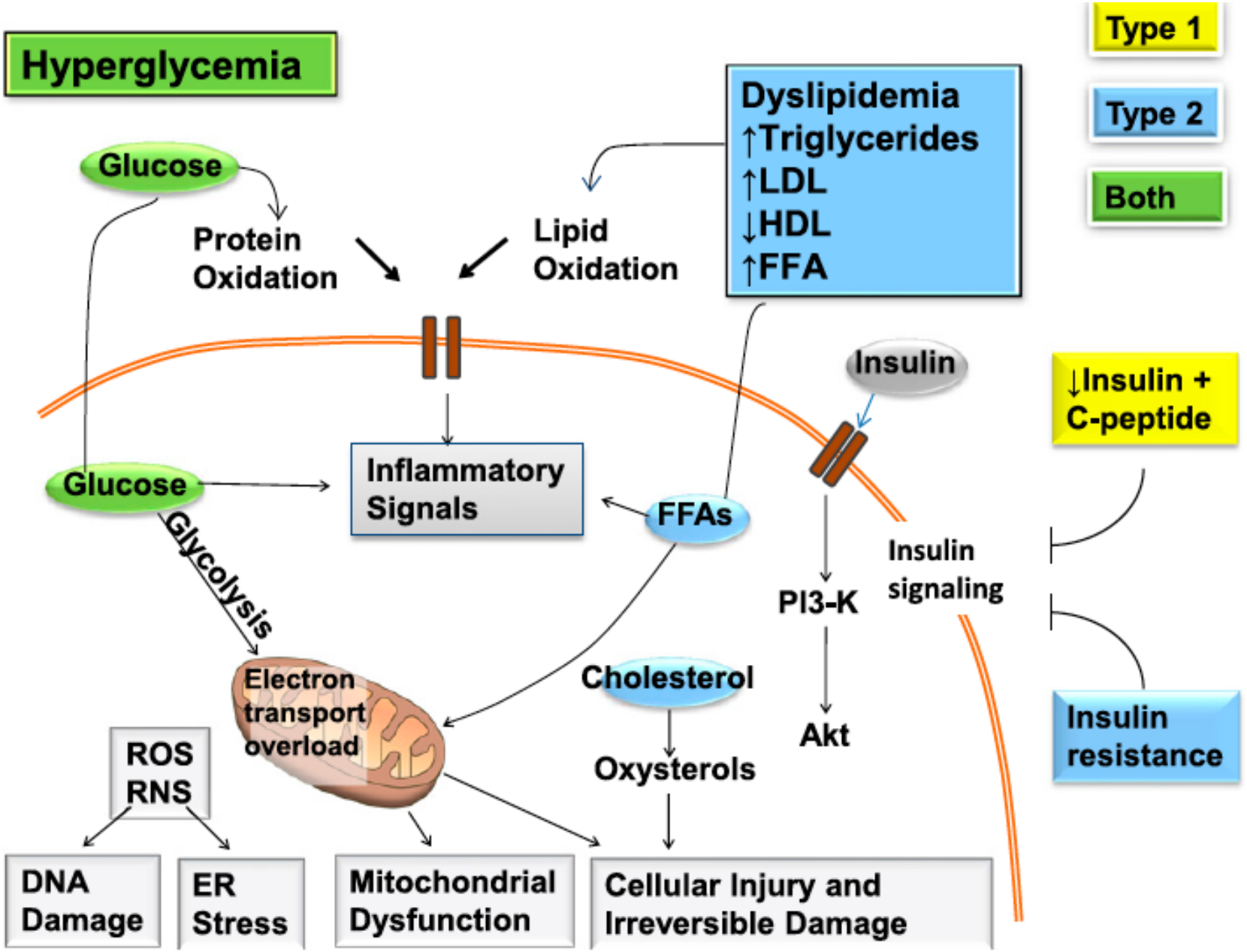
VM202 (Kessler 2015)

- ✓ T1 or T2D
- ✓ LE Pain of 6 months or more
- ✓ MNSI >2
- ✓ ≥4 VAS. Confirmed with 7 day Daily Pain and Sleep Interference Diary.

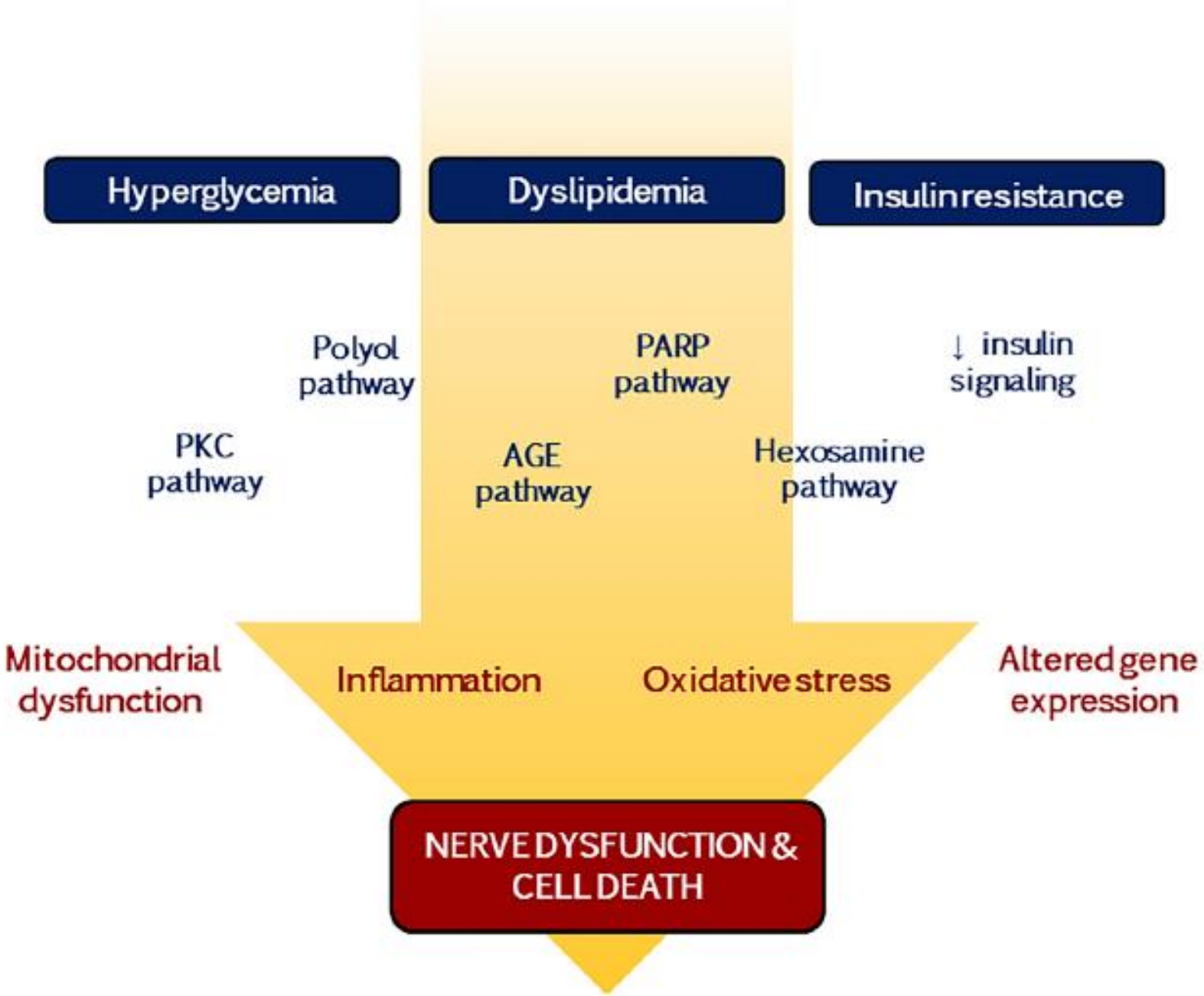
Pregabalin +/- Duloxetine (Tesfaye 2013)

- ✓ T1 or T2D
- ✓ Relatively symmetric onset of foot pain.
- ✓ 3 months or more
- ✓ MNSI >2
- ✓ ≥4 Likert

Tesfaye, S.., et al. (2013). Duloxetine and pregabalin: high-dose monotherapy or their combination? The “COMBO-DN study--”a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain, 154(12), 2616–2625. http://doi.org/10.1016/j.pain.2013.05.043



Pop-Busui, R., et al. (2017). "Diabetic Neuropathy: A Position Statement by the American Diabetes Association." Diabetes Care **40**(1): 136-154.



Feldman, E. L., et al. (2017). "New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain." Neuron **93**(6): 1296-1313.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Variable	Group	DCCT Baseline	DCCT Closeout	EDIC Year 13-14
			No. (%)	
Clinical neuropathy	INT	57/600 (10)	57/533 (11) †	145/505 (29)
	CONV	48/581 (8)	96/526 (18)	154/448 (34)
Abnormal NCS	INT	185/601 (31)	73/410 (18) †	195/430 (45)
	CONV	196/582 (34)	137/382 (36)	151/290 (52)
Confirmed clinical neuropathy	INT	39/600 (7)	32/551 (6) †	117/541 (22)
	CONV	31/581 (5)	75/543 (14)	136/479 (28) ‡

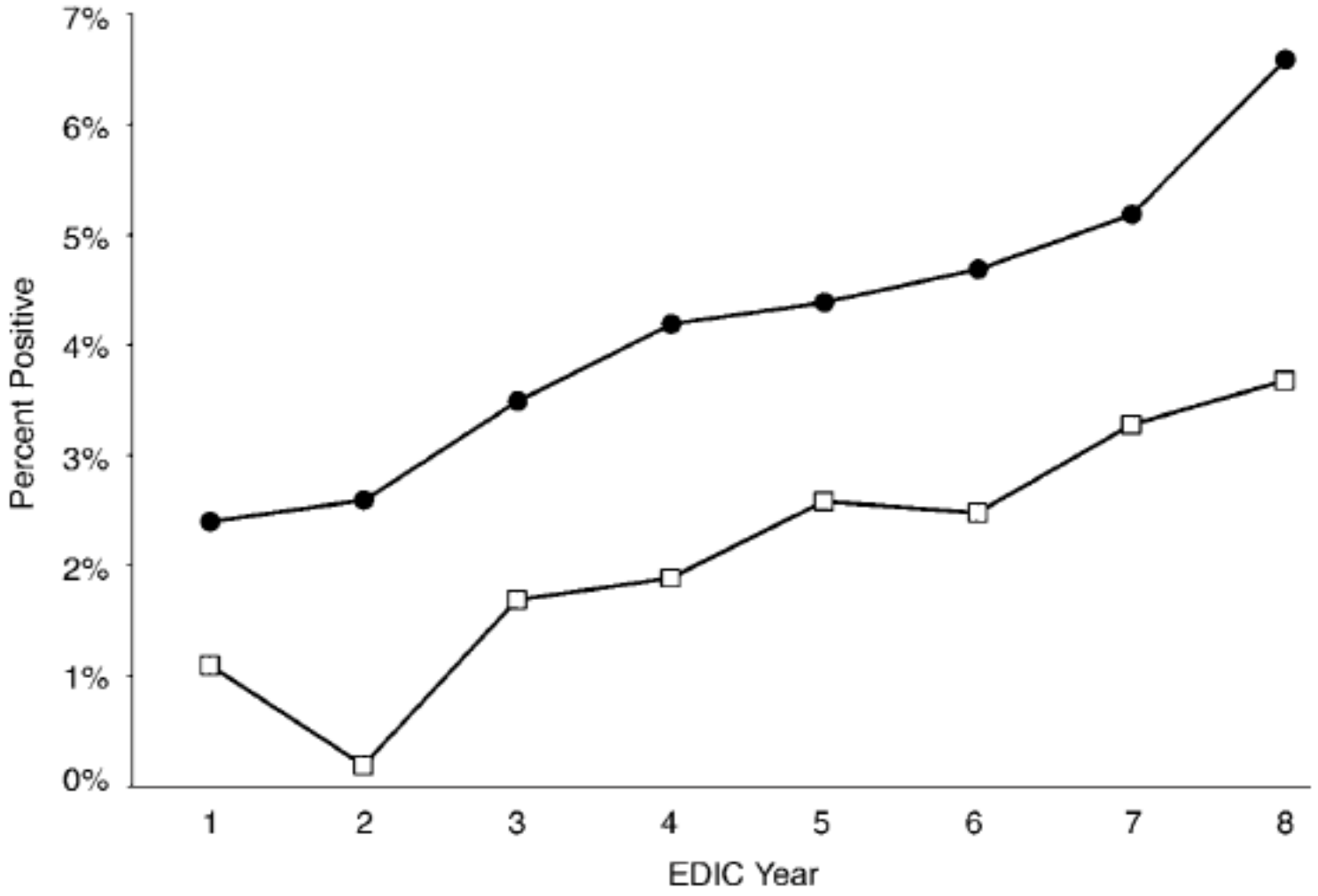
INT former intensive-treatment group, CONV former conventional-treatment group, NCS nerve conduction studies

* $p<0.01$ INT versus CONV

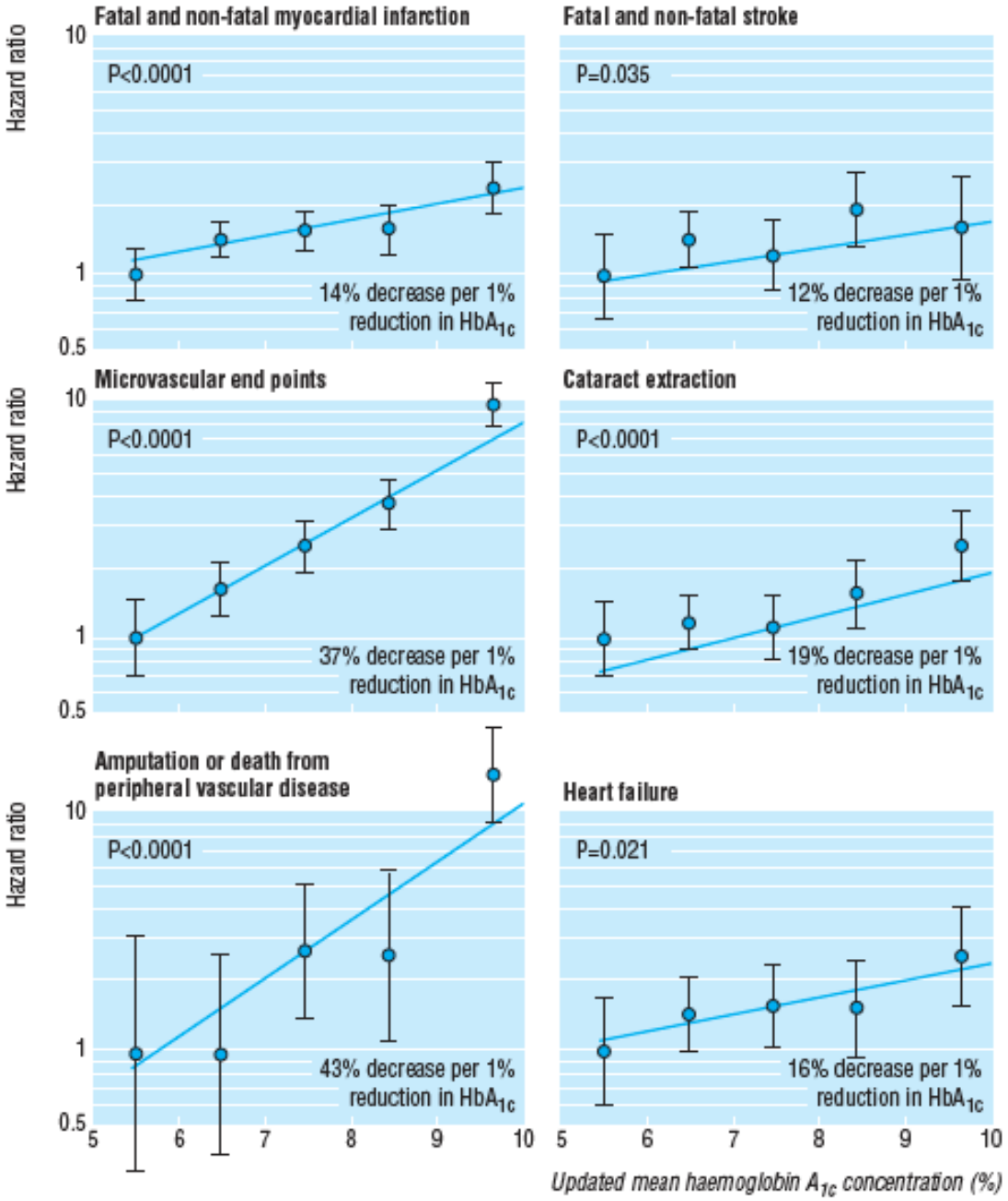
† $p<0.001$ INT versus CONV

‡ $p=0.0125$

Albers, J. W., et al. (2010). "Effect Of Prior Intensive Insulin Treatment During The Diabetes Control And Complications Trial (DCCT) On Peripheral Neuropathy In Type 1 Diabetes During The Epidemiology Of Diabetes Interventions, And Complications (EDIC) Study." Diabetes Care.



Martin, C. L., et al. (2006). "Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion." Diabetes Care **29**(2): 340-344.



Stratton, I., et al. (2000). "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study." BMJ **321**: 405-412.

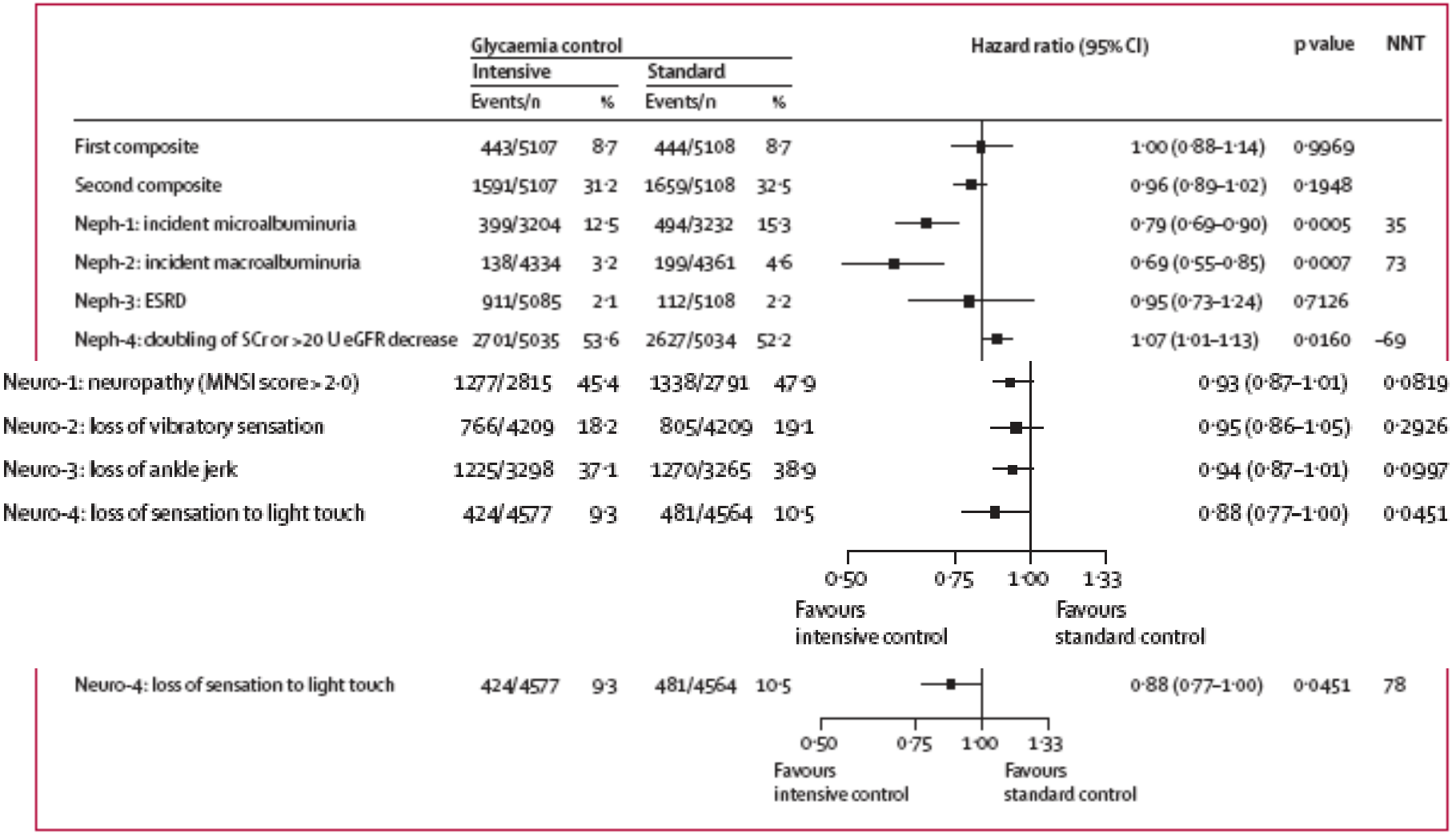


Figure 4: **Comparison of intensive and standard glycaemic therapy for all microvascular outcomes, until transition**
Intensive therapy was stopped before study end because of increased mortality, and patients were transitioned to standard therapy. Hazard ratios adjusted for baseline clinical cardiovascular disease history and second trial treatment group assignment. NNT=number needed to treat. ESRD=endstage renal disease (defined as requirement of dialysis or serum creatinine concentration of more than 291·72 µmol/L). SCr=serum creatinine. eGFR=estimated glomerular filtration rate. MNSI=Michigan neuropathy screening instrument score. *Defined as Snellen fraction <20/200.

Ismail-Beigi, F. et al. Lancet. 2010

THE COCHRANE COLLABORATION®

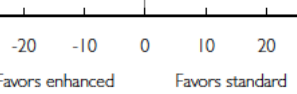
Analysis 1.1. Comparison 1 Type 1 diabetes: enhanced versus standard therapy, Outcome 1 Annualized risk difference (%).

Study or subgroup	Enhanced N	Control N	Annualized risk difference (%) (SE)	Annualized risk difference (%) IV,Fixed,95% CI	Weight	Annualized risk difference (%) IV,Fixed,95% CI
DCCT 1993a	252	292	-1.528 (0.518)		51.3 %	-1.53 [-2.54, -0.51]
DCCT 1993b	327	315	-1.974 (0.546)		46.1 %	-1.97 [-3.04, -0.90]
Linn 1996	23	19	-5.446 (2.296)		2.6 %	-5.45 [-9.95, -0.95]
Total (95% CI)					**100.0 %**	**-1.84 [-2.56, -1.11]**

Heterogeneity: Chi?? = 2.89, df = 2 (P = 0.24); I?? =31%

Test for overall effect: Z = 4.95 (P < 0.00001)

Test for subgroup differences: Not applicable



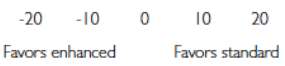
Analysis 2.1. Comparison 2 Type 2 diabetes: enhanced versus standard therapy, Outcome 1 Annualized risk difference (%).

Study or subgroup	Enhanced N	Control N	Annualized risk difference (%) (SE)	Annualized risk difference (%) IV,Fixed,95% CI	Weight	Annualized risk difference (%) IV,Fixed,95% CI
Accord 2010	2815	2791	-0.6973 (0.359459)		70.6 %	-0.70 [-1.40, 0.01]
Azad 1999	35	35	-1.43 (5.54)		0.3 %	-1.43 [-12.29, 9.43]
Duckworth 2009	464	498	-0.28571 (0.5625)		28.8 %	-0.29 [-1.39, 0.82]
Tovi 1998	16	15	0 (5.98)		0.3 %	0.0 [-11.72, 11.72]
Total (95% CI)					**100.0 %**	**-0.58 [-1.17, 0.01]**

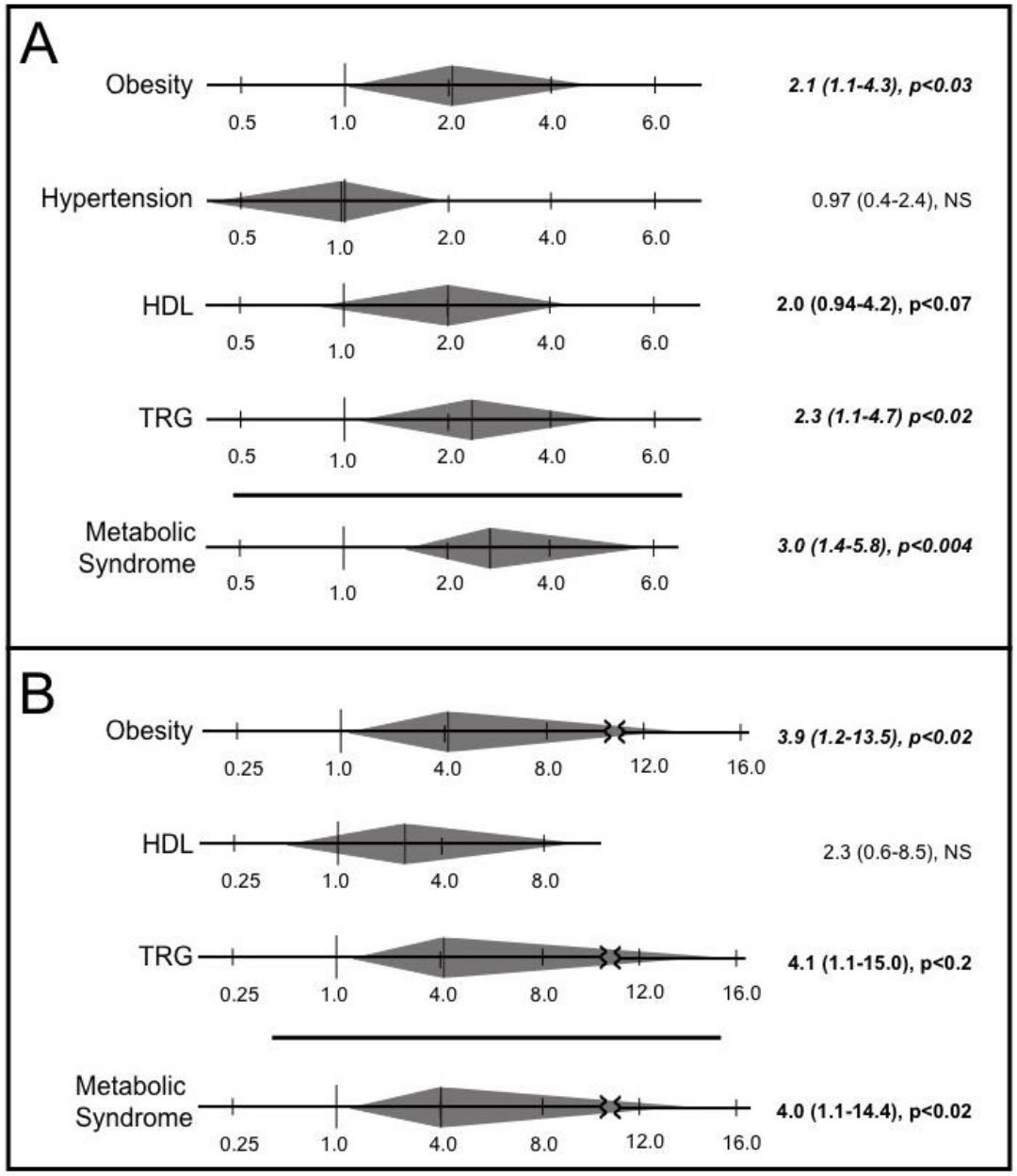
Heterogeneity: Chi?? = 0.41, df = 3 (P = 0.94); I?? =0.0%

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable

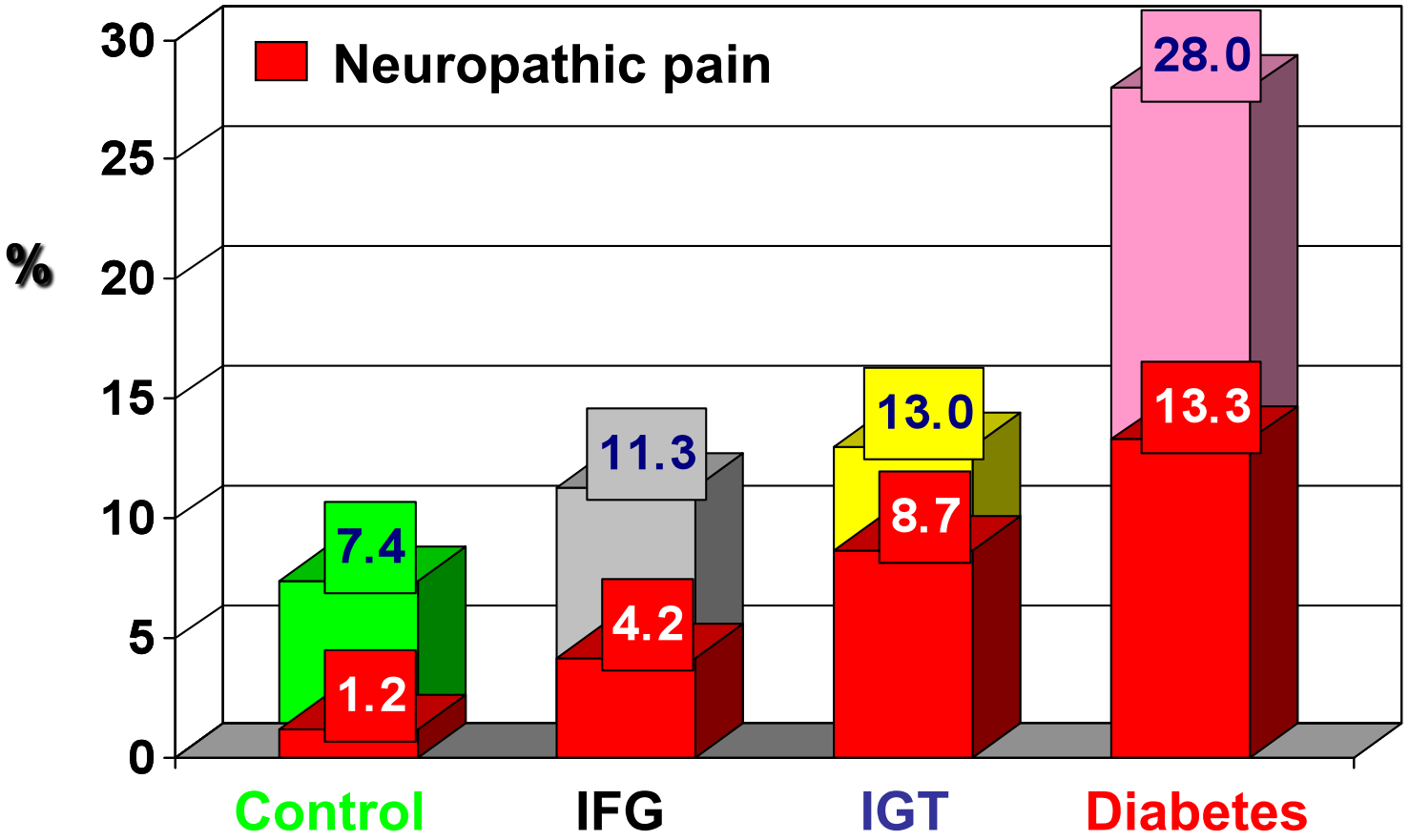


Callaghan, B. C., et al. (2012). "Enhanced glucose control for preventing and treating diabetic neuropathy." Cochrane Database Syst Rev **6**: CD007543.



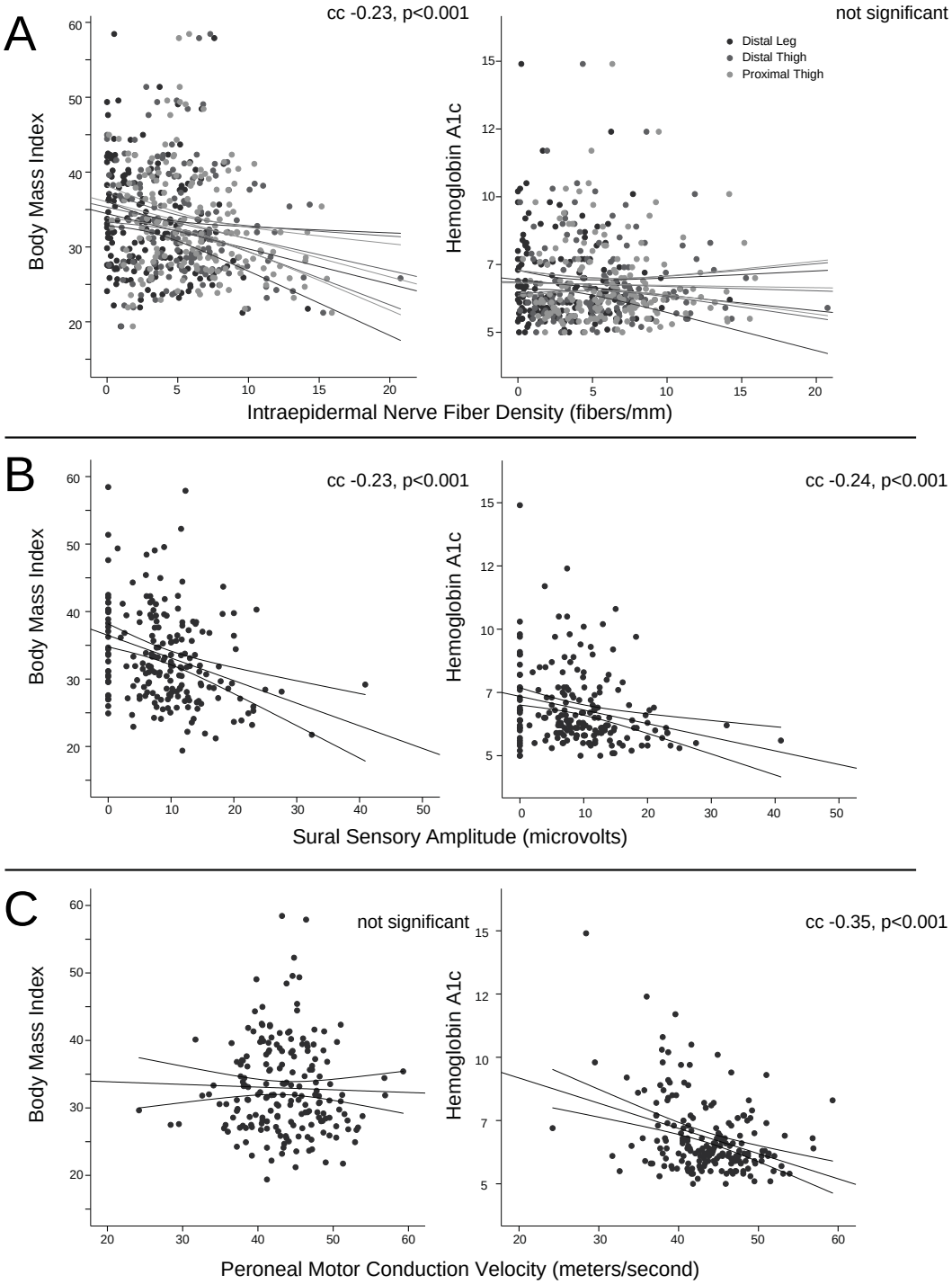
Smith, A. G. and J. R. Singleton (2013). "Obesity and hyperlipidemia are risk factors for early diabetic neuropathy." Journal of Diabetes and Its Complications.

Neuropathy (esp. painful) is more common in prediabetic patients than controls



IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Ziegler et al . Papanas, Vinik and Ziegler Nature reviews. Endocrinology 2011;7(11):682-90.



Smith, A. G. and J. R. Singleton (2013). "Obesity and hyperlipidemia are risk factors for early diabetic neuropathy." Journal of Diabetes and Its Complications.

Core Diagnostic Criteria (Dimension 1)
T1D versus T2D

1. Is DPN associated with T1D the same disease as T2D? *Probably not. Even if the mechanisms are the same, there are significant enough differences that trials of disease altering agents should focus on one type.*
2. Is DPN associated with T2D the same as DPN associated with IGT/Obesity/Metabolic Syndrome? *DPN and idiopathic neuropathy share risk factors and mechanisms. We will answer this question later today.*

Core Diagnostic Criteria for DPN (Dimension 1)

1. Is painful DPN a different different disorder?
2. What diagnostic criteria should be used?
3. Role of structured symptom and sign scales?
4. Role of confirmatory neurophysiological and/or pathologic testing?

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

Reliability of Clinical Diagnosis

Table 3. Agreement between diagnosis elicited from two evaluations of individual study physicians as compared to confirmed 75% clinical D_x Abnormality.*

	N (of 24)								
	Visit 1			Visit 2			Agreement Between Visits		
	Correct D_x	Under D_x	Over D_x	Correct D_x	Under D_x	Over D_x	Kappa	Z	*p*
Physician	Comparison of Individual Physician D_x to 75% D_x								
1	16	3	5	18	1	5	0.45	2.82	0.0024
2	16	1	7	18	0	6	0.41	2.22	0.0134
3	19	0	5	19	0	5	0.24	1.19	0.1178
4	20	0	4	15	0	9	0.50	2.83	0.0023
5	16	1	7	16	2	6	0.48	2.81	0.0025
6	16	1	7	20	0	4	0.37	2.12	0.0170
7	17	2	5	21	2	1	0.09	0.66	0.2560
8	18	5	1	20	1	3	0.08	0.58	0.2799
9	21	1	2	20	0	4	0.51	3.01	0.0013
10	13	0	11	11	0	13	0.83	4.15	<0.0001
11	12	2	10	16	0	8	0.37	2.12	0.0171
12	20	0	4	20	0	4	0.40	1.96	0.0250
Median	16.50	1.00	5.00	18.50	0.00	5.00	0.41	2.17	
SD	2.76	1.50	2.93	2.89	0.80	3.14	0.20	1.03	
Range	12 – 20	0 – 5	1 – 11	11 – 21	0 – 2	1 – 13	0.08 – 0.83	0.58 – 4.15	

**The full table with comparison of individual physician signs and individual physician symptoms to confirmed 75% group D_x is given in sumpplementary material.*

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

Consensus Statement

Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy

Report and recommendations of the San Antonio Conference on Diabetic Neuropathy. (1988). Consensus statement. Diabetes, 37, 1000–1004.

- Clinical criteria should include validated questionnaire or interview technique, and a neurological examination.
- Class 1: no signs or symptoms
  - A normal,
  - B EDX or AFT +QST,
  - C EDX and either AFT and/or QST.
- Class 2: Signs and/or symptoms:
  - A Symptoms +/- AFT or QST
  - B Signs +/- symptoms and EDX or AFT +QST
  - C Signs and/or Symptoms and EDX and either AFT or QST or both.

AMERICAN ACADEMY OF NEUROLOGY

Special Article

Distal symmetric polyneuropathy: A definition for clinical research

England, J. D. et al. (2005). Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology, 64(2), 199–207.

Formal consensus process with systematic literature review. "In the grading of studies, EDX studies were considered an objective outcome."

- Symptoms alone have poor accuracy
- Signs are better, particularly multiple signs
- Combination of symptoms, signs and EDX
- Rank ordered definitions
  - Highest: multiple symptoms, multiple signs, abnormal NCS (clinical trials)
  - Modest: multiple symptoms and signs without NCS available (epidemiology)
  - Lowest: discordant signs and NCS

Rochester Diabetic Neuropathy Study

- Of 64,573 inhabitants of Rochester, MN in 1986, 870 (1.3% had DM). 380 enrolled in RDNS (102 T1D, 278 T2D).
- 2/3 had some evidence of neuropathy, but only 13% symptoms. Using NSS, only 10% had DPN
- “Because symptoms are not constant but tend to come and go, for purposes of following course it is useful to have an overall measurement of severity of polyneuropathy excluding symptoms”.
- “…generally the frequency of abnormality was higher for attributes of NC than for individual clinical abnormalities.”
- Diagnostic performance base based on a gold standard of the NIS(LL)+7, a composite of clinical examination, NCS, QST, and HRDB.

Dyck, P. J., Davies, J. L., Litchy, W. J., O'Brien, P. C. (1997). Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. Neurology, 49(1), 229–239.

Toronto Criteria – Expert panel 2009

Diabetic sensorimotor polyneuropathy

- "Typical" Symmetric length dependent sensorimotor polyneuropathy with abnormal NCS.
- "Atypical DPNs" This term not clearly defined but has been used by some to encapsulate painful DPN:

Tesfaye, S., Boulton, A. J., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., et al. (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care, 33(10), 2285–2293. http://doi.org/10.2337/dc10-1303

Toronto Criteria for DSPN

1. **Possible DSPN:** symptoms such as decreased sensation, positive sensory symptoms in the toes feet or legs *or* signs such as symmetric decreased sensation or decreased or absent ankle jerks.
2. **Probable DSPN:** symptoms and signs including 2 ore more of the following: symptoms, decreased sensation, abnormal ankle DTRs.
3. **Confirmed DSPN:** Abnormal nerve conduction and a symptom or a sign. If NCS normal, must have abnormality of validated measure of small fiber function.
4. **Subclinical DSPN:** abnormal NCS or small fiber test in the absence of symptoms or signs.

Tesfaye, S., Boulton, A. J., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., et al. (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care, 33(10), 2285–2293. http://doi.org/10.2337/dc10-1303

Toronto Criteria Painful DPN

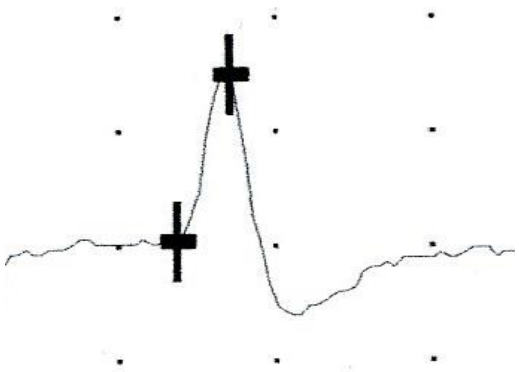
- IASP definition of pain
- Distal, symmetrical, nocturnal exacerbations
- Prickling, deep aching, sharp, electric shock, burning,
- Hyperalgesia and frequent allodynia.
- ***SFN Criteria:***
  - Possible: length dependent symptoms and/or signs
  - Probable: symptoms and signs with normal NCS
  - Definite: symptoms, signs, and abnormal IENFD or thermal QST

Tesfaye, S., Boulton, A. J., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., et al. (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care, 33(10), 2285–2293. http://doi.org/10.2337/dc10-1303

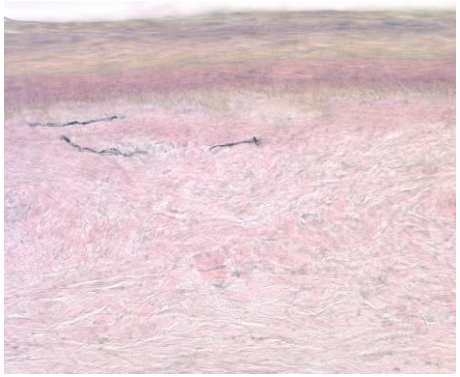
Assumptions of existing diagnostic criteria for DPN

1. Signs are more reliable than symptoms. Symptoms come and go, and are unreliable. *This assumption is based largely on non-painful DPN.*
2. Nerve conduction abnormalities are a very early (usually preclinical) and core feature of DPN.
3. Painful DPN is “atypical” and skin biopsy or other validated laboratory test must be used to confirm.

Diagnostic performance

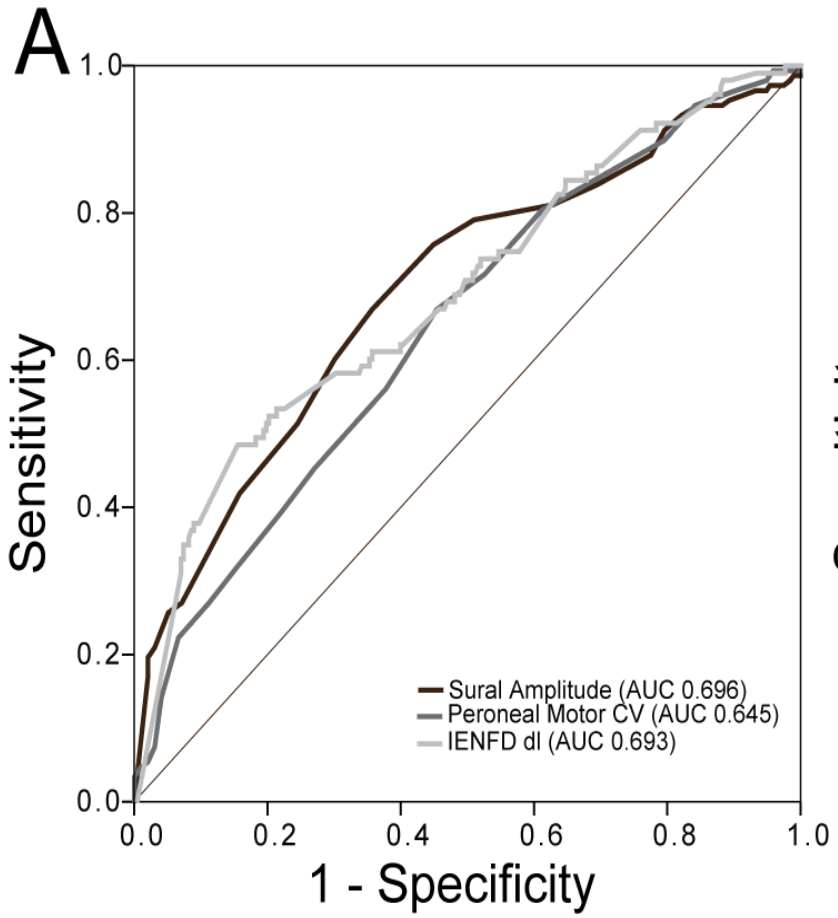


- NCS abnormal in approximately 70% of neuropathy patients.
- Frequently normal in those with burning feet/small fiber neuropathy (~40%).
- Specificity data are lacking



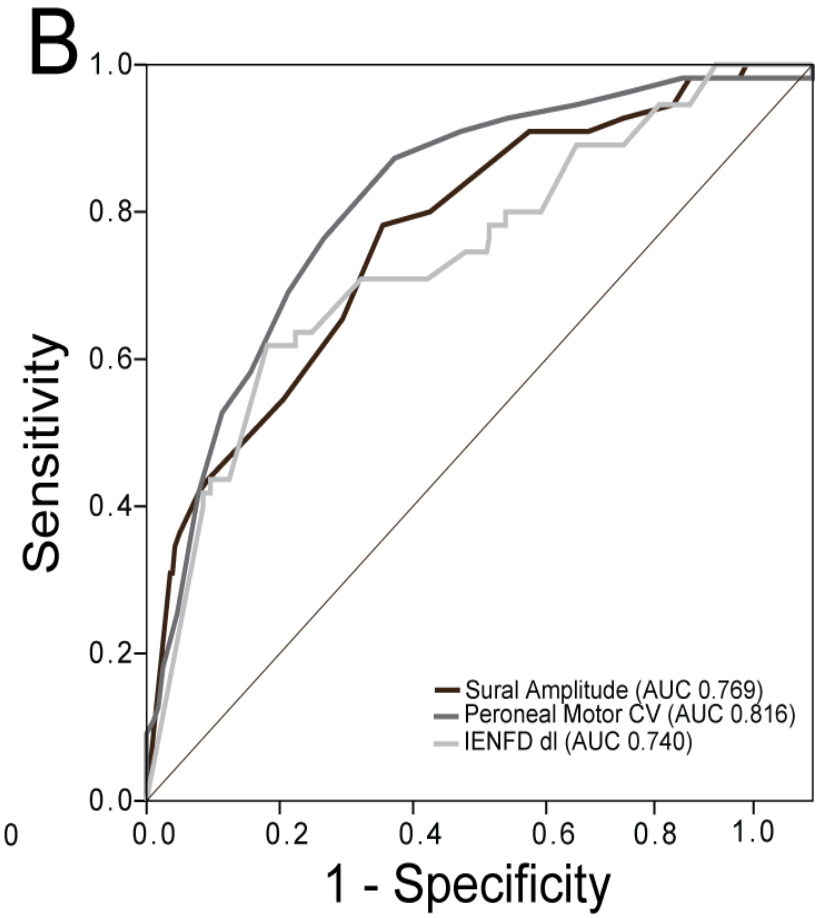
- Sensitivity and specificity reported to be 70-80%.
- Concerns regarding specificity in specific populations (diabetes).

Smith, A. G. (2014). Do all neuropathy patients need an EMG at least once? Continuum (Minneapolis, Minn.), 20(5 Peripheral Nervous System Disorders), 1430–1434. doi:10.1212/01.CON.0000455870.45685.c7



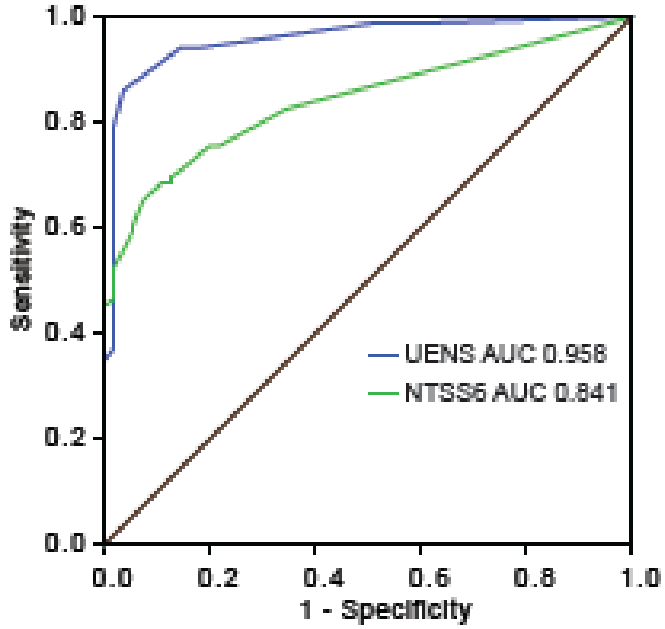
Signs/Symptoms + Confirmatory Test

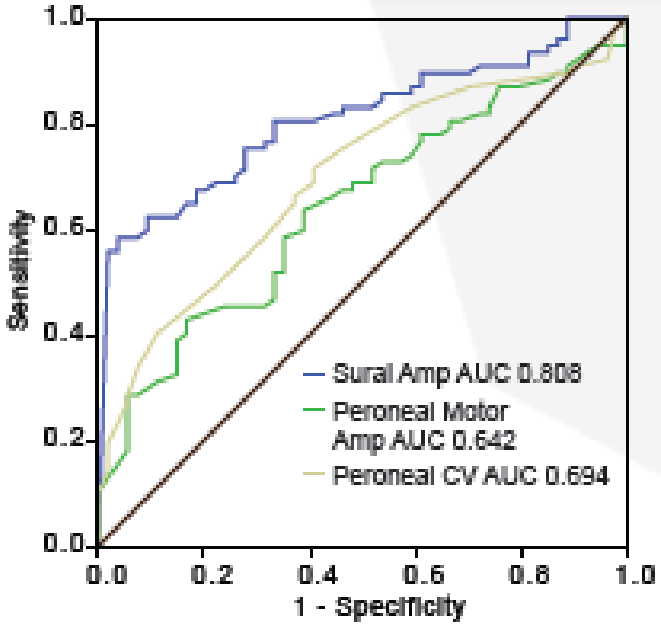
NCS: Sensitivity 75%, Specificity 66%, PPV 14%, NPV 97%



Signs and Symptoms

NCS: Sensitivity 71%, Specificity 76%, PPV 19%, NPV 97%





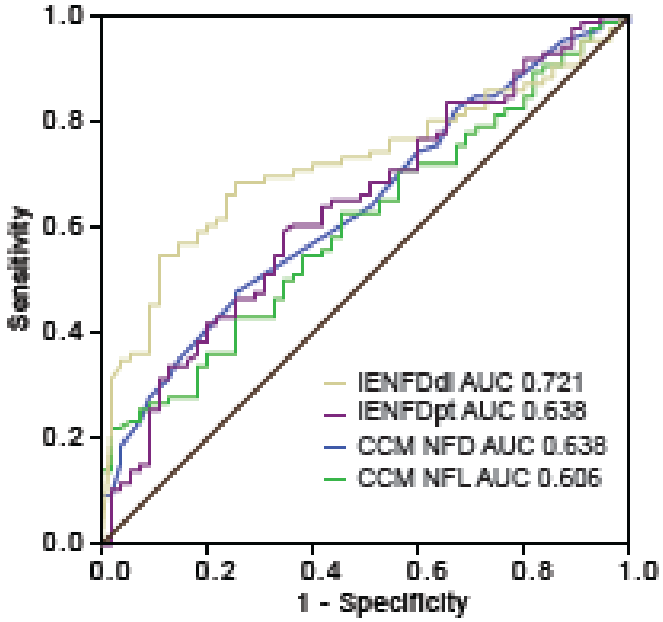
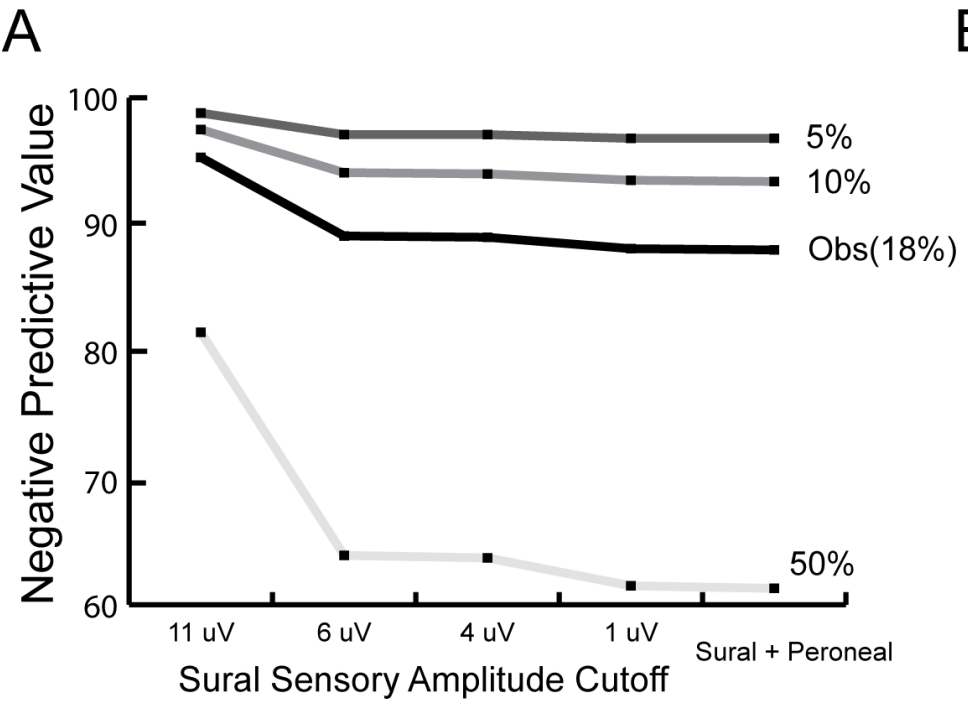
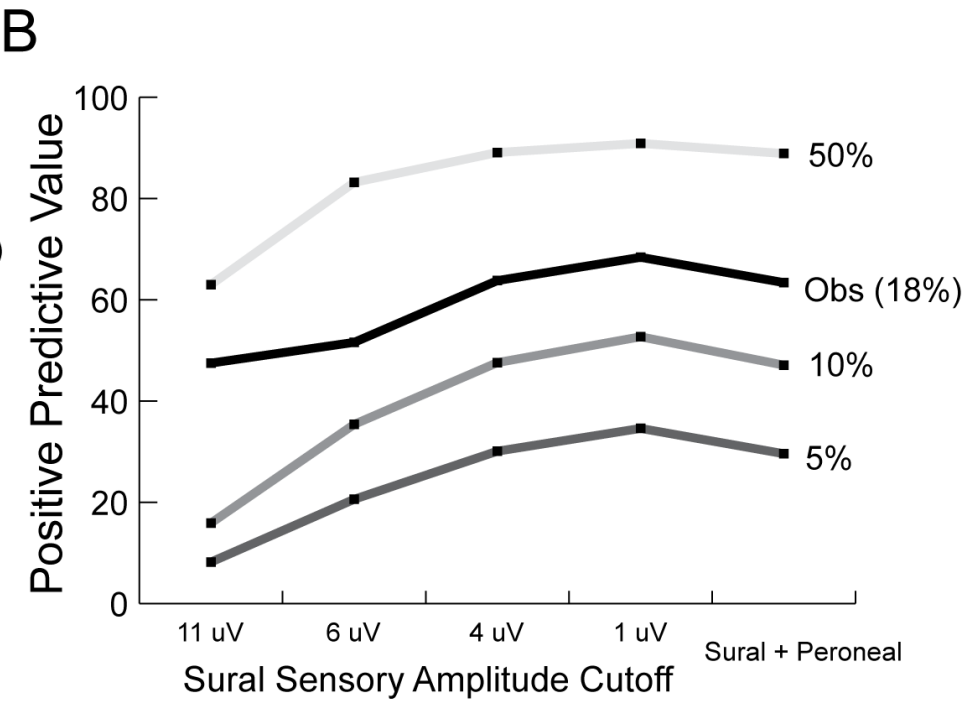


Figure 6. The UENS and NTSS-6 had superior diagnostic performance. Among DPN biomarkers, the sural sensory amplitude had the best performance (AUC 0.808), followed by IENFD at the distal leg (AUC 0.721). CCM paramenters (NFD and NFL) and peroneal motor amplitude and CV performed less well





Gold Standard: Signs plus symptoms										
Test criteria			Observed prevalence 17.8%		Prevalence 50%		Prevalence 10%		Prevalence 5%	
Sural Amplitude	Sensitivity	Specificity	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
11 uV	89.2	47.5	47.5	95.3	63	81.5	15.9	97.5	8.2	98.8
6 uV	49.2	90	51.6	89.1	83.2	63.9	35.4	94.1	20.6	97.1
4 uV	46.2	94.4	63.8	89	89.1	63.7	47.6	94	30.1	97.1
1 uV	40	96	68.4	88.1	90.9	61.5	52.7	93.5	34.6	96.8
Abnormal Sural Sensory and Peroneal Motor (amp. or CV)	40	95	63.4	88	88.9	61.3	47.1	93.4	29.6	96.8

"Unequivocally Abnormal" vs "Usual" Signs and Symptoms for Proficient Diagnosis of Diabetic Polyneuropathy

Cl vs N Phys Trial

Table 1. Test-Retest Reproducibility of Expert Neuromuscular Physicians' Judgments of Signs, Symptoms, and Diagnosis of DSPN Between Days 1 and 2 of Cl vs N Phys Trials 1 and 2[a]

Physician No.	Trial 1						Trial 2					
	Signs		Symptoms		Diagnosis		Signs		Symptoms		Diagnosis	
	κ	*P* Value	κ	*P* Value	κ	*P* Value	κ	*P* Value	κ	*P* Value	κ	*P* Value
1	0.41	.02	1.00	<.001	0.50	.006	0.57	.003	0.65	<.001	0.55	.004
2[b]	0.75	<.001	0.83	<.001	0.47	.01						
3	0.65	<.001	0.55	.003	0.49	.009	0.71	<.001	1.00	<.001	0.64	<.001
4	0.51	.002	0.73	<.001	0.57	.001	0.74	<.001	0.56	.003	0.81	<.001
5	1.00	<.001	0.68	<.001	0.49	.008	0.66	<.001	0.50	.006	0.66	<.001
6	0.42	.01	0.66	<.001	0.49	.008	0.65	<.001	0.28	.08	0.65	<.001
7	0.59	.002	0.71	<.001	0.33	.04	0.78	<.001	0.65	<.001	0.88	<.001
8	0.62	.001	0.22	.12	0.30	.04	0.71	<.001	0.78	<.001	0.80	<.001
9	0.48	.006	0.81	<.001	0.75	<.001	0.63	<.001	0.64	<.001	0.80	<.001
10	0.78	<.001	0.67	<.001	0.63	<.001	0.34	.04	0.58	<.001	0.58	.002
11	1.00	<.001	0.75	<.001	0.19	.17	0.49	.009	0.65	<.001	0.88	<.001
12	0.36	.04	0.88	<.001	0.66	<.001	0.58	.002	0.78	<.001	0.80	<.001
13[b]							0.64	<.001	1.00	<.001	0.81	<.001

Dyck, P. J., Overland, C. J., Low, P. A., Litchy, W. J., Davies, J. L., Dyck, P. J. B., et al. (2012). "Unequivocally Abnormal" vs "Usual" Signs and Symptoms for Proficient Diagnosis of Diabetic Polyneuropathy: Cl vs N Phys Trial. Arch Neurol, 1–6. http://doi.org/10.1001/archneurol.2012.1481

Core Diagnostic Criteria for DPN (Dimension 1)

1. How should painful DPN be defined? *Subject of another meeting, manuscript pending.*
2. What criteria should be used? *As a general construct, the Toronto criteria are the most logical.*
3. Role of structured symptom and sign scales? *Agreement on "unequivocal" abnormalities improves diagnostic performance, and simple tools such as the MNSI and UENS may have greater reproducibility and utility across the spectrum of disease severity.*
4. Role of confirmatory neurophysiological and/or pathologic testing? *The diagnostic performance of NCS, IENFD and CCM is modest, although given good NPV they may be used to exclude individuals with normal values (although there are concerns regarding pretest probability).*
5. Exclusion of other causes for neuropathy (or confounding risk factors).

Common features including clinical, epidemiologic and life span (Dimension 2)

Painful diabetic neuropathy
- 20%
- Often early in the disease course
- Small fiber predominant
- Normal nerve conduction studies in >40%. Skin biopsy abnormal in most.

Painless diabetic neuropathy
- Later in the course
- Slowed motor conduction velocities (but not in CIDP range)
- Risk for painless injury/ulceration

Asymptomatic neuropathy
- In some patients may be “laboratory based”
- Large fiber involvement
- Later, with risk for ulceration.

Painful DPN: Core Clinical Features

- Burning
- Electrical shock
- Stabbing or knife-like
- Tingling or “novocaine-like”
- Feet feel like they are wrapped tightly.
- Walking on marbles
- Walking on hot sand
- Worse at night, touch sensitivity to bedclothes.
- Comorbid conditions include (dimensions 3 and 4):
  - Sleep disturbance (>95%) (Gore 2011)
  - Depression and anxiety (67%) (Selvarajah 2014)

Selvarajah, D., Cash, T., Sankar, A., Thomas, L., Davies, J., Cachia, E., et al. (2014). The contributors of emotional distress in painful diabetic neuropathy. Diabetes & Vascular Disease Research, 11(4), 218–225. http://doi.org/10.1177/1479164114522135

Gore, M., et al. (2011). Clinical Characteristics, Pharmacotherapy, and Healthcare Resource Use among Patients with Diabetic Neuropathy Newly Prescribed Pregabalin or Gabapentin. Pain Pract. http://doi.org/10.1111/j.1533-2500.2011.00450.x

Screening tools for neuropathic pain

Table 1
Comparison of items within five neuropathic pain screening tools (*shaded boxes highlight features shared by two or more tools*)

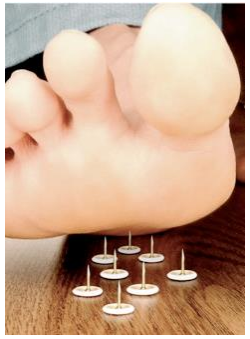
	LANSS[a]	DN4[a]	NPQ	pain*DETECT*	ID Pain
Symptoms					
Pricking, tingling, pins and needles	•	•	•	•	•
Electric shocks or shooting	•	•	•	•	•
Hot or burning	•	•	•	•	•
Numbness		•	•	•	•
Pain evoked by light touching	•		•	•	•
Painful cold or freezing pain		•	•		
Pain evoked by mild pressure				•	
Pain evoked by heat or cold				•	
Pain evoked by changes in weather			•		
Pain limited to joints[b]					○
Itching		•			
Temporal patterns				•	
Radiation of pain				•	
Autonomic changes	•				
Clinical examination					
Brush allodynia	•	•			
Raised soft touch threshold		•			
Raised pin prick threshold	•	•			

[a] Tools that involve clinical examination.
[b] Used to identify non-neuropathic pain.

Bennett, M. I., Attal, N., Backonja, M. M., Baron, R., Bouhassira, D., Freynhagen, R., et al. (2007). Using screening tools to identify neuropathic pain. Pain, 127(3), 199–203. http://doi.org/10.1016/j.pain.2006.10.034

DPN Phenotype Evolves Over Time

10-20% of patients have neuropathy at T2D diagnosis, often painful, small fiber predominant.

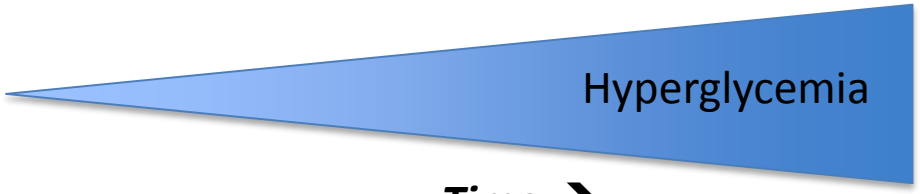


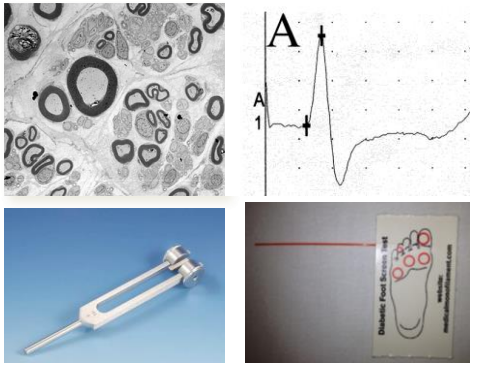
Another 30% develop neuropathy - often painless, with ulcer risk.

DPN is a spectrum of clinical disorders that evolve over time

T1D

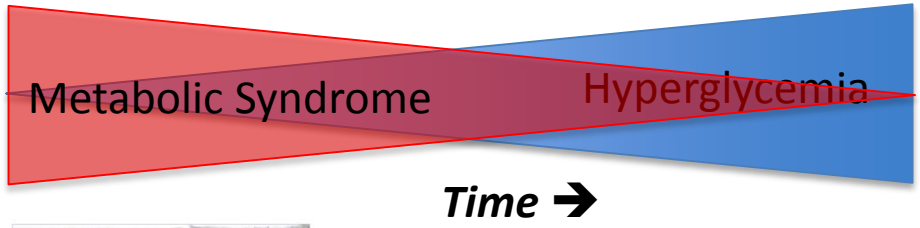
Neuropathy Risk

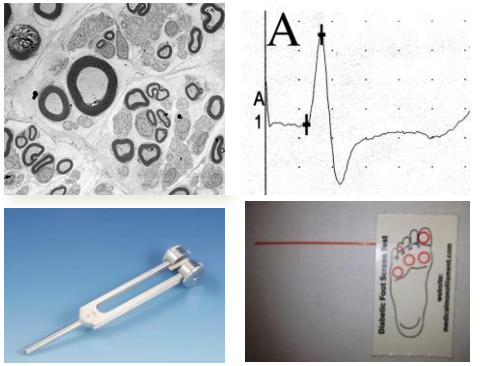


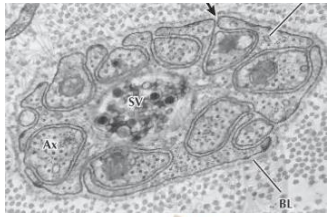


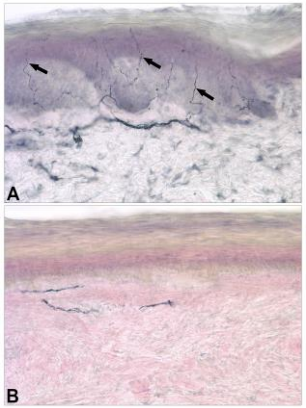
T2D

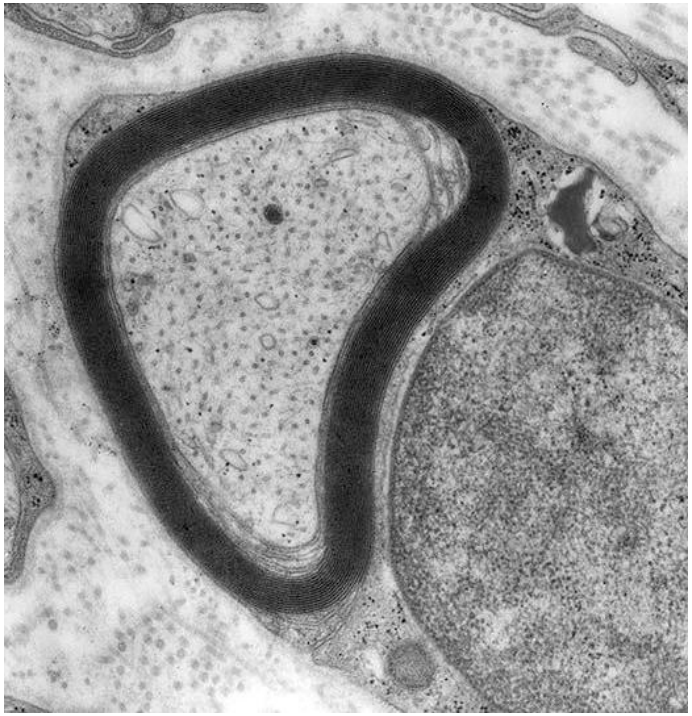
Neuropathy Risk

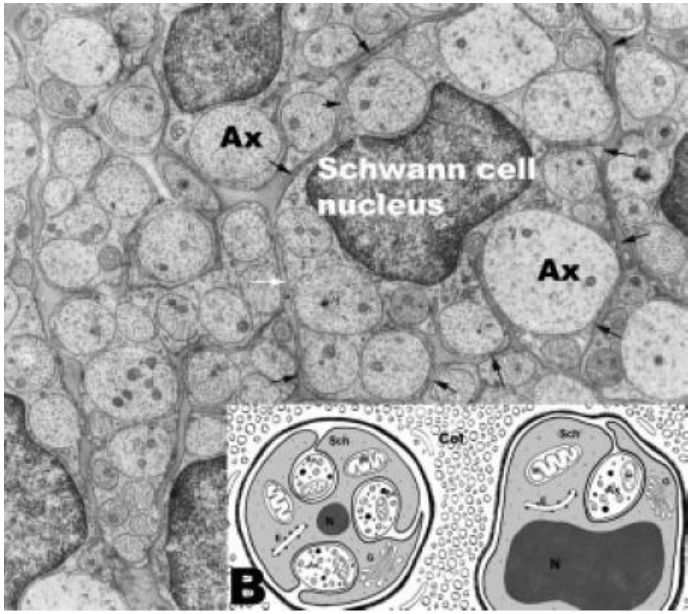








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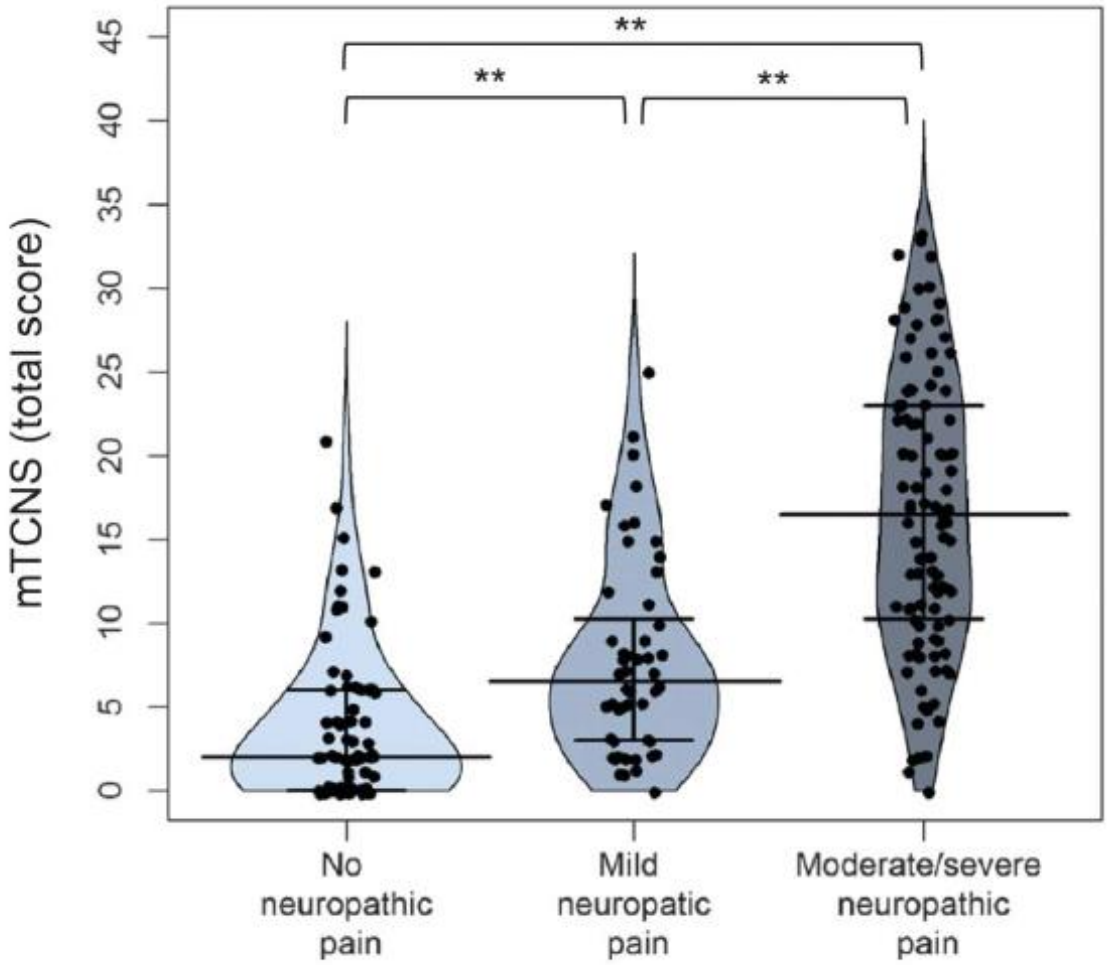
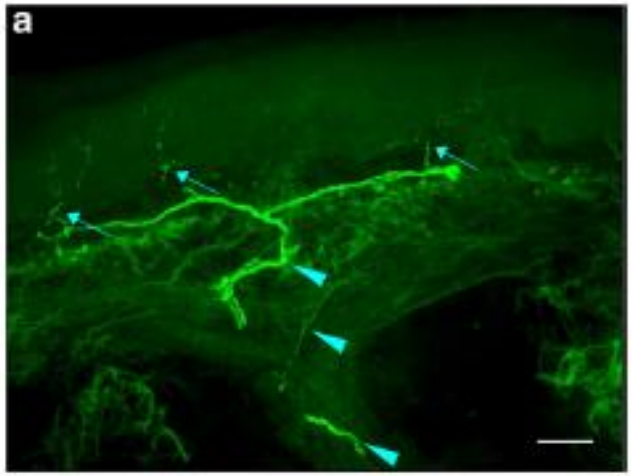
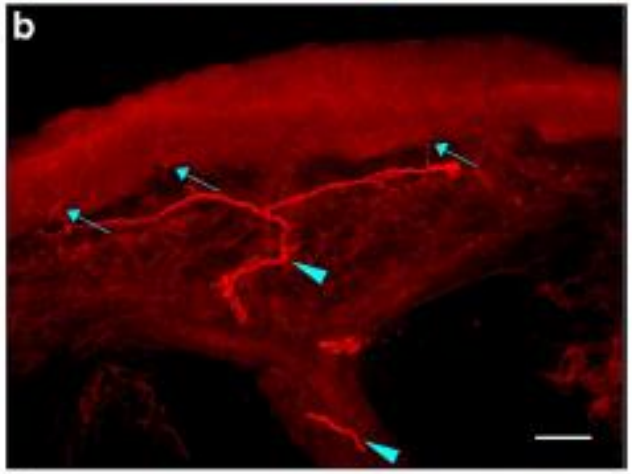
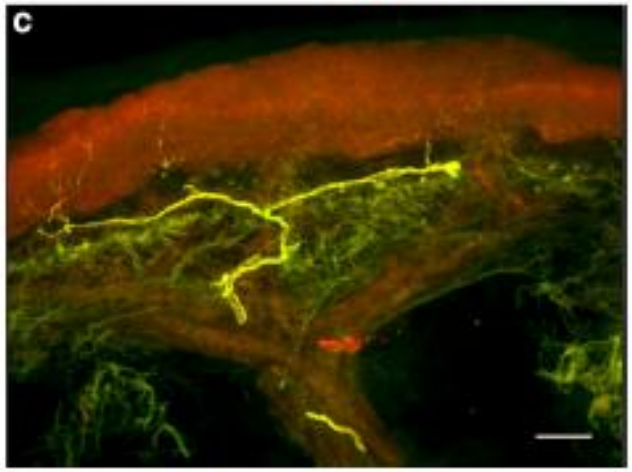


Figure 5. Median and interquartile ranges of modified Toronto Clinical Neuropathy Score (mTCNS) total score in patients with no neuropathic pain, mild and moderate/severe neuropathic pain. Kruskal–Wallis test, post hoc comparison: $^{*}P < 0.05$, $^{**}P < 0.01$.

Raputova, J., et al. (2017). "Sensory phenotype and risk factors for painful diabetic neuropathy: a cross-sectional observational study." Pain **158**(12): 2340-2353.



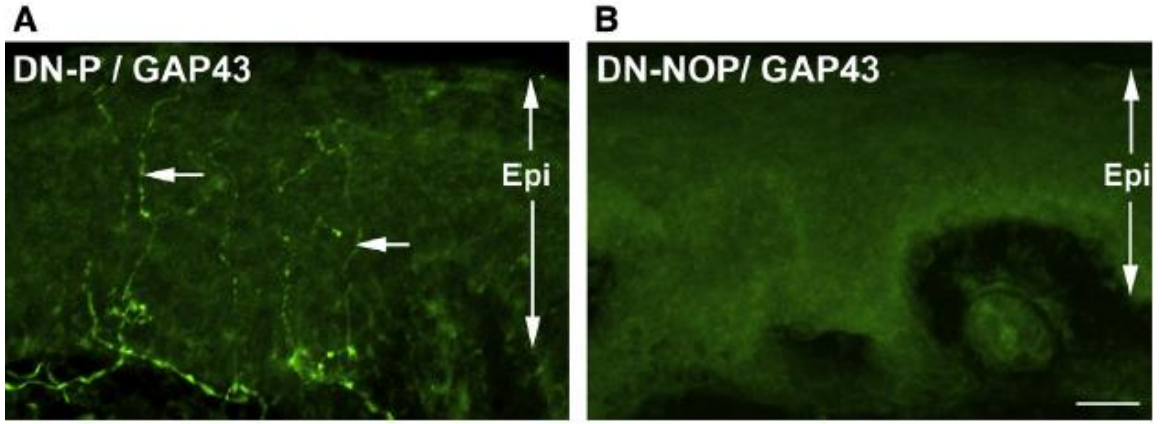




Patterns of cutaneous nerve fibre loss and regeneration in type 2 diabetes with painful and painless polyneuropathy

Gidon J. Bönhof[1] · Alexander Strom[1,2] · Sonja Püttgen[1] · Bernd Ringel[1] · Jutta Brüggemann[1] · Kálmán Bódis[1] · Karsten Müssig[1,2,3] · Julia Szendroedi[1,2,3] · Michael Roden[1,2,3] · Dan Ziegler[1,2,3]

Bonhof, G. J., et al. (2017). "Patterns of cutaneous nerve fibre loss and regeneration in type 2 diabetes with painful and painless polyneuropathy." Diabetologia **60**(12): 2495-2503.



Increased Axonal Regeneration and Swellings in Intraepidermal Nerve Fibers Characterize Painful Phenotypes of Diabetic Neuropathy

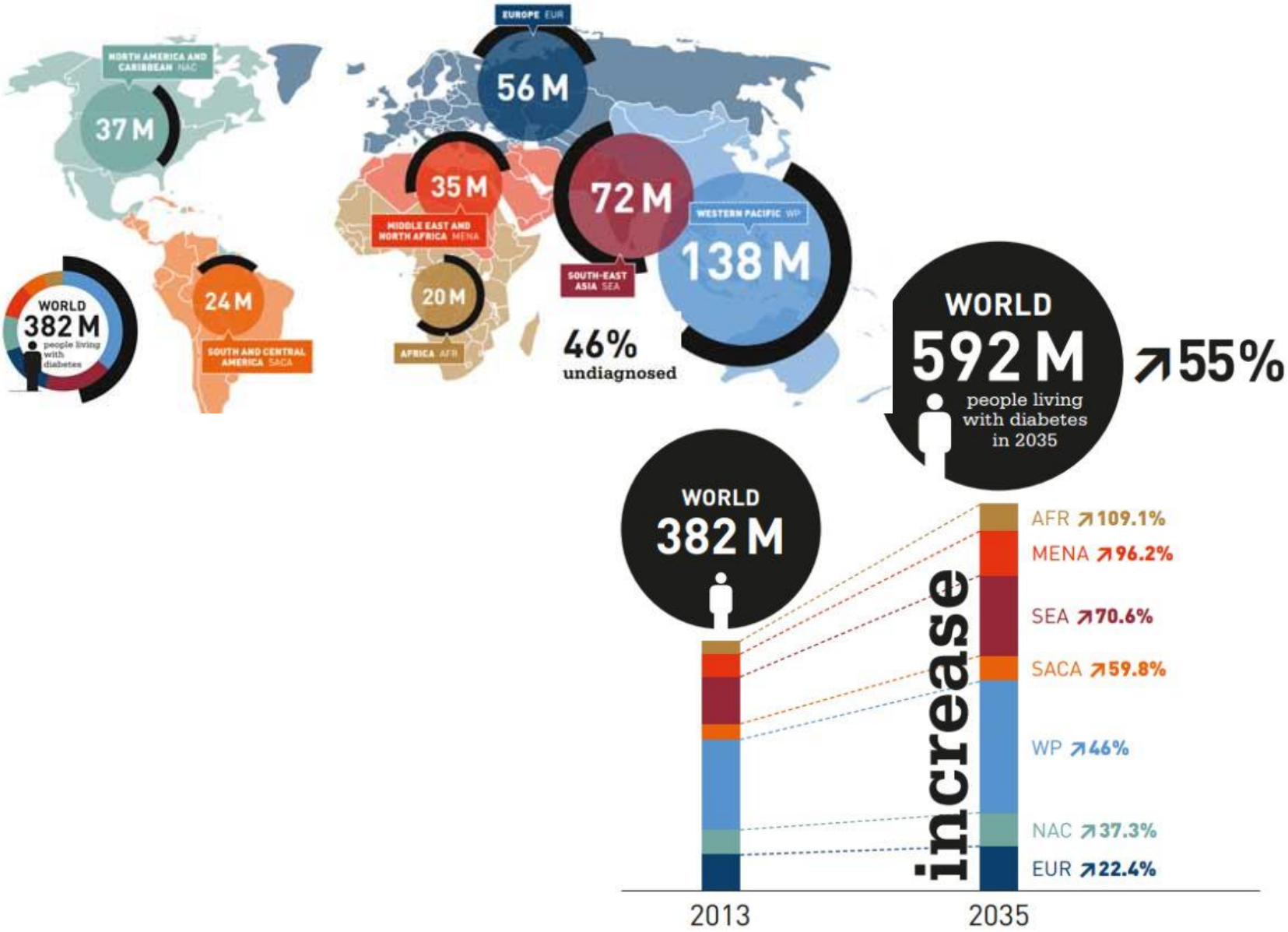
Hsinlin T. Cheng,* Jacqueline R. Dauch,* Michael T. Porzio,† Brandon M. Yanik,‡ Wilson Hsieh,‡ A. Gordon Smith,† J. Robinson Singleton,† and Eva L. Feldman*

*Department of Neurology, University of Michigan Medical Center, Ann Arbor, Michigan.
†Department of Neurology, University of Utah, Salt Lake City, Utah.
‡College of Literature, Science, and the Arts, University of Michigan, Ann Arbor, Michigan.

Cheng, H. T., et al. (2013). "Increased Axonal Regeneration and Swellings in Intraepidermal Nerve Fibers Characterize Painful Phenotypes of Diabetic Neuropathy." J Pain.

Epidemiology of DPN (Dimension 2).

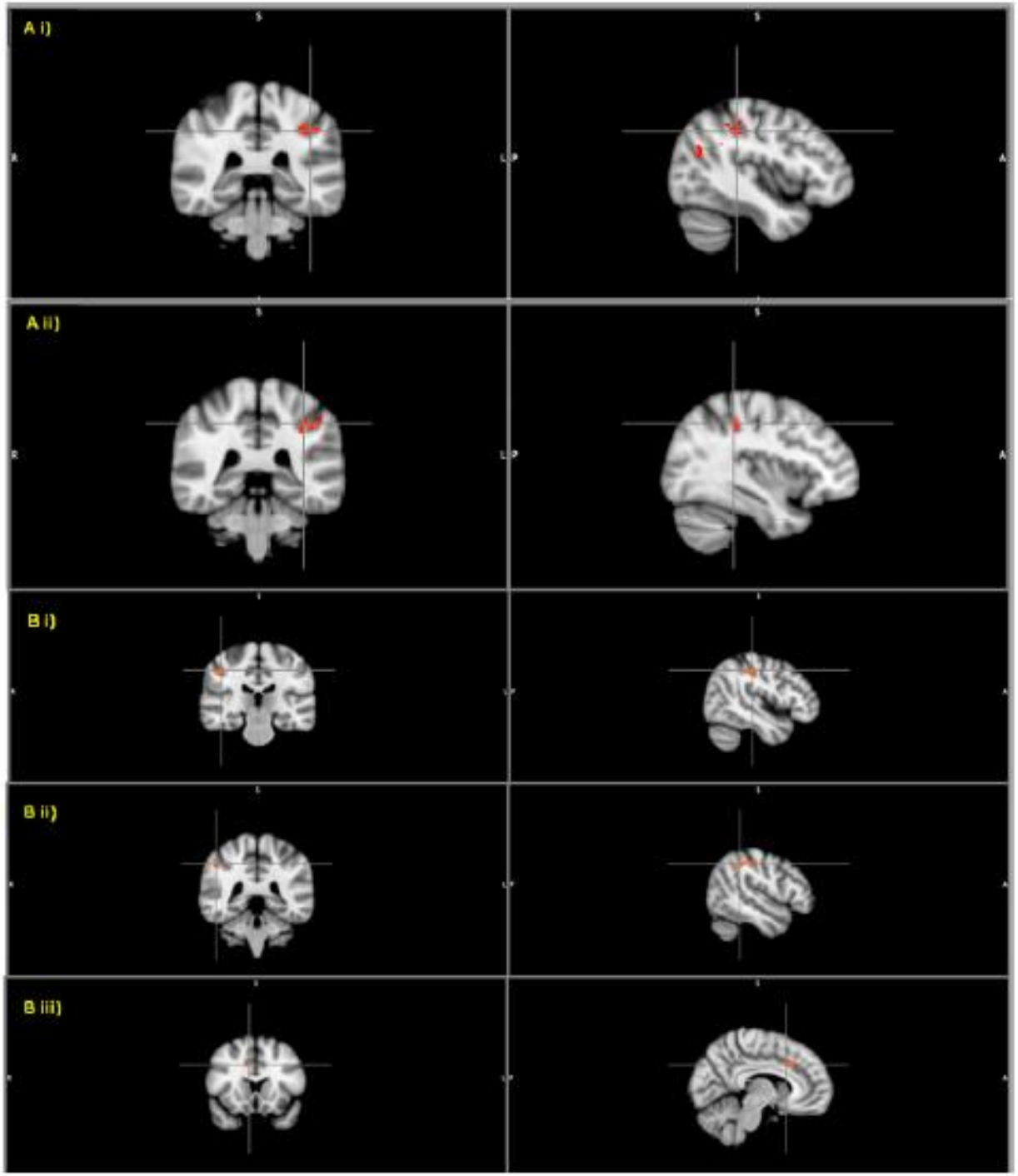
- Diabetes affects 8.5% of Americans and Europeans.
- Neuropathy occurs in up to 50%
- 10-20% of patients with T2D have neuropathy at diagnosis.
- 1/3rd of patients with neuropathy have painful DPN.
- ~ 50% of patients with idiopathic neuropathy have prediabetes. Most have painful neuropathy.



IDF Diabetes Atlas Sixth Edition, International Diabetes Federation 2013.

Common Medical Comorbidities (Dimension 3)

- Obesity, hypertension, hyperlipidemia and obesity.
- Other microvascular complications are more common in patients with DPN.
- Macrovascular disease
  - PAD
  - Cerebrovascular disease
- CNS Neurodegeneration
- Depression/anxiety
- Sleep disorders



Selvarajah, D., et al. (2014). "Magnetic Resonance Neuroimaging Study of Brain Structural Differences in Diabetic Peripheral Neuropathy." Diabetes Care **37**(6): 1681-1688.

Neurobiological, psychological risk factors and protective factors for DPN (Dimensions 4-5)

- Age
- BMI, glycemic control, metabolic syndrome
- Other diabetic complications.

Peltier, A., Goutman, S. A., & Callaghan, B. C. (2014). Painful diabetic neuropathy. Bmj, 348(may06 1), g1799–g1799. http://doi.org/10.1136/bmj.g1799

Table 1. Risk factors of distal symmetric sensorimotor polyneuropathy

Risk factor	Degree of association	References
Diabetes duration	+++	1, 11-18
Hyperglycemia	+++	1, 23-29
Glycemic variability	+	39, 42
Prediabetes	++	43-47
Age	+++	1, 10-12, 26, 27, 43-45, 50, 51
Height	++	11-14, 26
Hypertension	++	1, 12, 13, 24, 25, 51, 53
Dyslipidemia	+	11, 13, 25, 26, 55-57
Smoking	+	11, 13, 15, 48, 59
Obesity	++	43-45, 60, 61
Metabolic syndrome	++	60, 62, 63
Insulin resistance	+	58, 64
Alcohol consumption	+	1, 12, 50
Hypoinsulinemia	+	14, 15, 24
Oxidative stress	++	65-77
Platelet activation	+	78, 79, 81, 82
Vitamin D deficiency	++	83, 84, 86, 87
Genetic factors	++	95-100, 102-112
Subclin. inflammation	++	89-92
Low physical activity	++	43-45
Growth factor depletion	+	114-117

Legend: Moderate association (+), stronger association (++), very strong association (+++).

Papanas, N. and D. Ziegler (2015). "Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015." Rev Diabet Stud **12**(1-2): 48-62.

Genetic Risk Factors for DPN

Table 1 – Major genes described associated with susceptibility to diabetic neuropathy.

Gene	SNPs	Ethnicity	Cases with DPN (*n*)	Controls without DPN (*n*)	Effect of association	*P* value	References
ACE	I>D	Turkish	235	281	Risk	0.032	Inanir et al. [14]
		Egyptian	47	311	Risk	<0.001	Settin et al. [15]
		Caucasian	173	399	Risk	0.02	Stephens et al. [16]
		Asiatic	276	496	Risk	0.001	Mansoor et al. [17]
		Japanese	21	63	Protective	0.03	Ito et al. [18]
		North Catalonia	82	201	Risk	0.02	Jurado et al. [19]
		Asiatic/Caucasian	1720	1899	Risk	0.001	Wu et al. [20]
		Asiatic/Caucasian	1316	1617	Risk	0.006	Li et al. [21]
		Asiatic/Caucasian	1430	1873	Risk	0.01	Xu et al. [22]
MTHFR	rs1801133 C>T	Turkish	230	282	Risk	0.003	Serbulent et al. [29]
		Egyptian	47	311	Risk	<0.0001	Settin et al. [15]
		Asiatic/Caucasian	1720	1899	Risk	<0.001	Wu et al. [20]
GLO1	rs2736654 A>C	Caucasian	251	273	Risk	0.03	Groener et al. [41]
APOE	ε4/-	Greek	54	180	Risk	0.0001	Monastiriotis et al. [46]
VEGF	rs3025039 C>T	Han	204	240	Protective	0.004	Zhang et al. [60]
	rs25648 C>T	British-Caucasian	81	167	Risk	0.02	Tavakkoly-Bazzaz et al. [61]
	I>D	Romanian	84	90	Risk	<0.0001	Stoian et al. [62]
IL-4	VNTR (P1/P2 allele)	Turkish	227	241	Risk	0.0002	Basol et al. [72]
GPX1	rs1050450 C>T	Caucasian	211; 63	558; 319	Risk	0.01; 0.02	Tang et al. [75]
eNOS	27VNTR (a/b) rs270744 T>C	North and South Indian	139; 133	356; 342	Risk	0.006	Shah et al. [80]
ADRA2B	I>D	Greek	130	60	Risk	0.001	Papanas et al. [88]
MIR146A	rs2910164 G>C	Italian	61	69	Protective	0.032	Ciccacci et al. [94]
MIR128A	rs11888095 C>T	Italian	61	69	Risk	0.007	Ciccacci et al. [94]
GFRA2	rs7428041 T>C	UK	572	2491	Protective	1.77×10^{-7}	Meng et al. [96]
GSTT1	wild/null	Slovack	19	27	Risk	<0.05	Vojtková et al. [33]
TCF7L2	rs7903146 C>T	Italian	13	171	Risk	0.02	Ciccacci et al. [51]

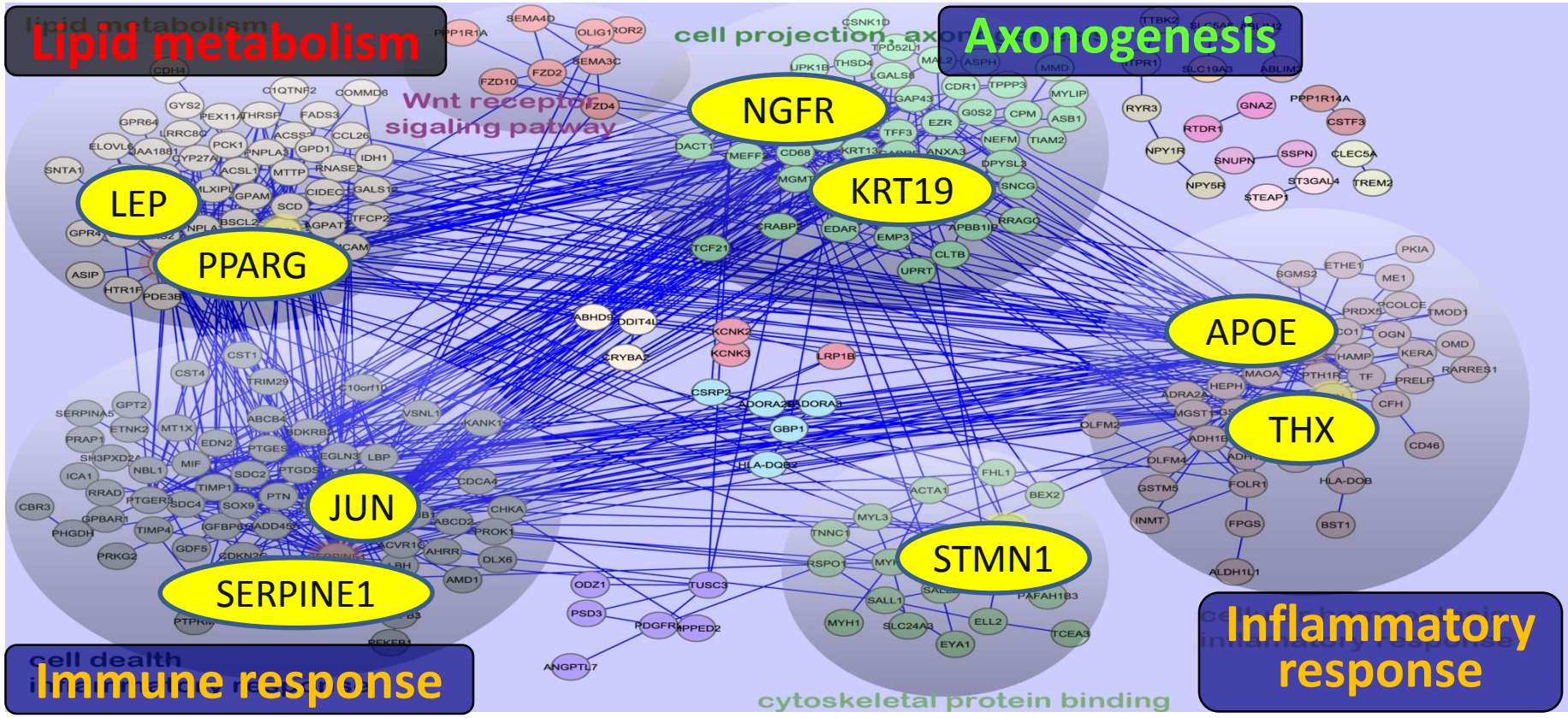
Politi, C., et al. (2016). "Recent advances in exploring the genetic susceptibility to diabetic neuropathy." Diabetes Res Clin Pract **120**: 198-208.

The identification of gene expression profiles associated with progression of human diabetic neuropathy

Junguk Hur,[1,2] Kelli A. Sullivan,[2] Manjusha Pande,[2,3] Yu Hong,[2] Anders A. F. Sima,[4,5] Hosagrahar V. Jagadish,[1,3,6] Matthias Kretzler[1,3,7] and Eva L. Feldman[1,2,3]

doi:10.1093/brain/awr228

532 differentially regulated genes



Clinical Trial/Experimental Study

Medicine®

OPEN

Identification of genes and signaling pathways associated with diabetic neuropathy using a weighted correlation network analysis

A consort study

Ya Li, MD[a,b,c], Weiguo Ma, MM[b], Chuanqing Xie, MM[b], Min Zhang, MM[b], Xiaohong Yin, MM[b], Fenfen Wang, MM[b], Jie Xu, MM[c], Bingyin Shi, MD[a,*]

Among 25 sural nerve samples (18 progressive 17 non- progressive):

PPARG

SCD

CD36

PCK1

AMPK pathway

PPAR pathway

Li, Y., et al. (2016). "Identification of genes and signaling pathways associated with diabetic neuropathy using a weighted correlation network analysis: A consort study." Medicine (Baltimore) **95**(47): e5443.

Research Article

Gene Expression Profiling Identifies Downregulation of the Neurotrophin-MAPK Signaling Pathway in Female Diabetic Peripheral Neuropathy Patients

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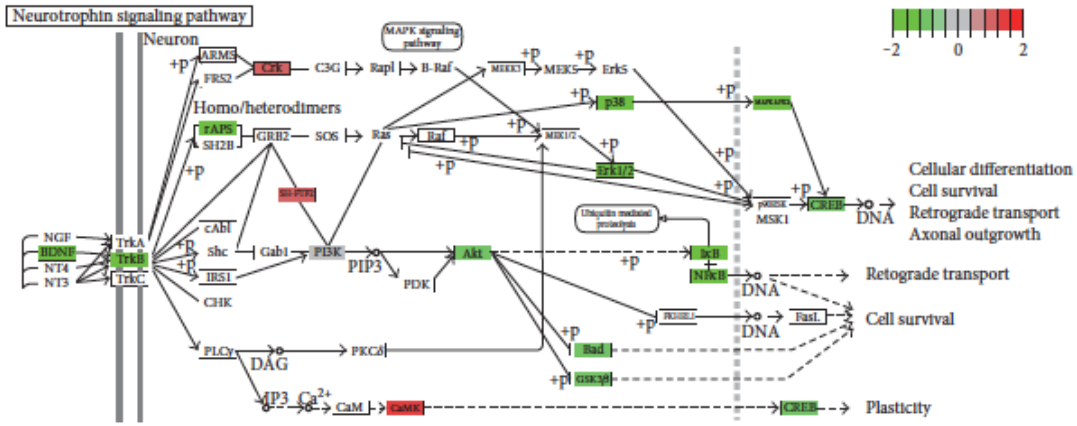

FIGURE 3: Downregulation of the neurotrophin-MAPK signaling pathway in DPN.

Luo, L., et al. (2017). "Gene Expression Profiling Identifies Downregulation of the Neurotrophin-MAPK Signaling Pathway in Female Diabetic Peripheral Neuropathy Patients." J Diabetes Res **2017**: 8103904.

Functional consequences (Dimensions 4-5)

- Diabetes costs are €77 Billion in the EU and $174 Billion in the US. Data suggest 25% of diabetes costs are attributable to neuropathy and its complications.

- Among diabetic complications, painful DPN is second only to amputations in reduction of QOL.

Peltier, A., Goutman, S. A., & Callaghan, B. C. (2014). Painful diabetic neuropathy. Bmj, 348(may06 1), g1799–g1799. http://doi.org/10.1136/bmj.g1799

DPN and gait disturbance

- DPN patients have a 3-5 times greater risk of falling.
- Contributors include sensory loss, reduced lower extremity strength, impaired joint range of motion and changes in CNS control.
- Abnormal gait is strongly correlated with depression (and mood and cognition impact gait).

Alam, U., et al. (2017). "Diabetic Neuropathy and Gait: A Review." Diabetes Ther **8**(6): 1253-1264.

Vileikyte, L., et al. (2005). "Diabetic peripheral neuropathy and depressive symptoms: the association revisited." Diabetes Care **28**(10): 2378-2383.

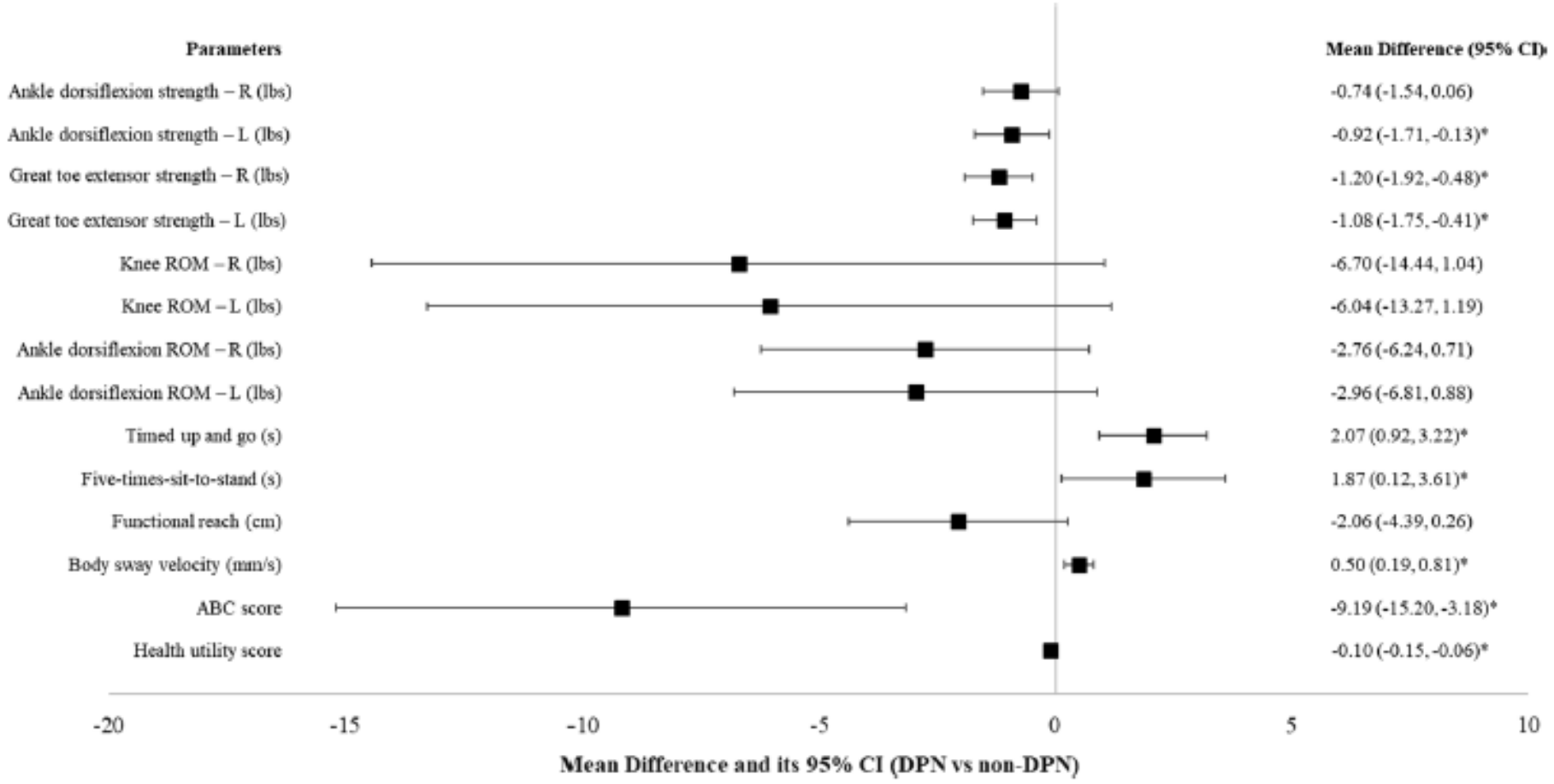

Fig. 1 Functional status and HRQoL differences between DPN and non-DPN groups. ***R* right, *L* left. *$p < 0.05$**

Riandini, T., et al. (2017). "Functional status mediates the association between peripheral neuropathy and health-related quality of life in individuals with diabetes." Acta Diabetol.

Timar, B., et al. (2016). "The Impact of Diabetic Neuropathy on Balance and on the Risk of Falls in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study." PLoS One **11**(4): e0154654.

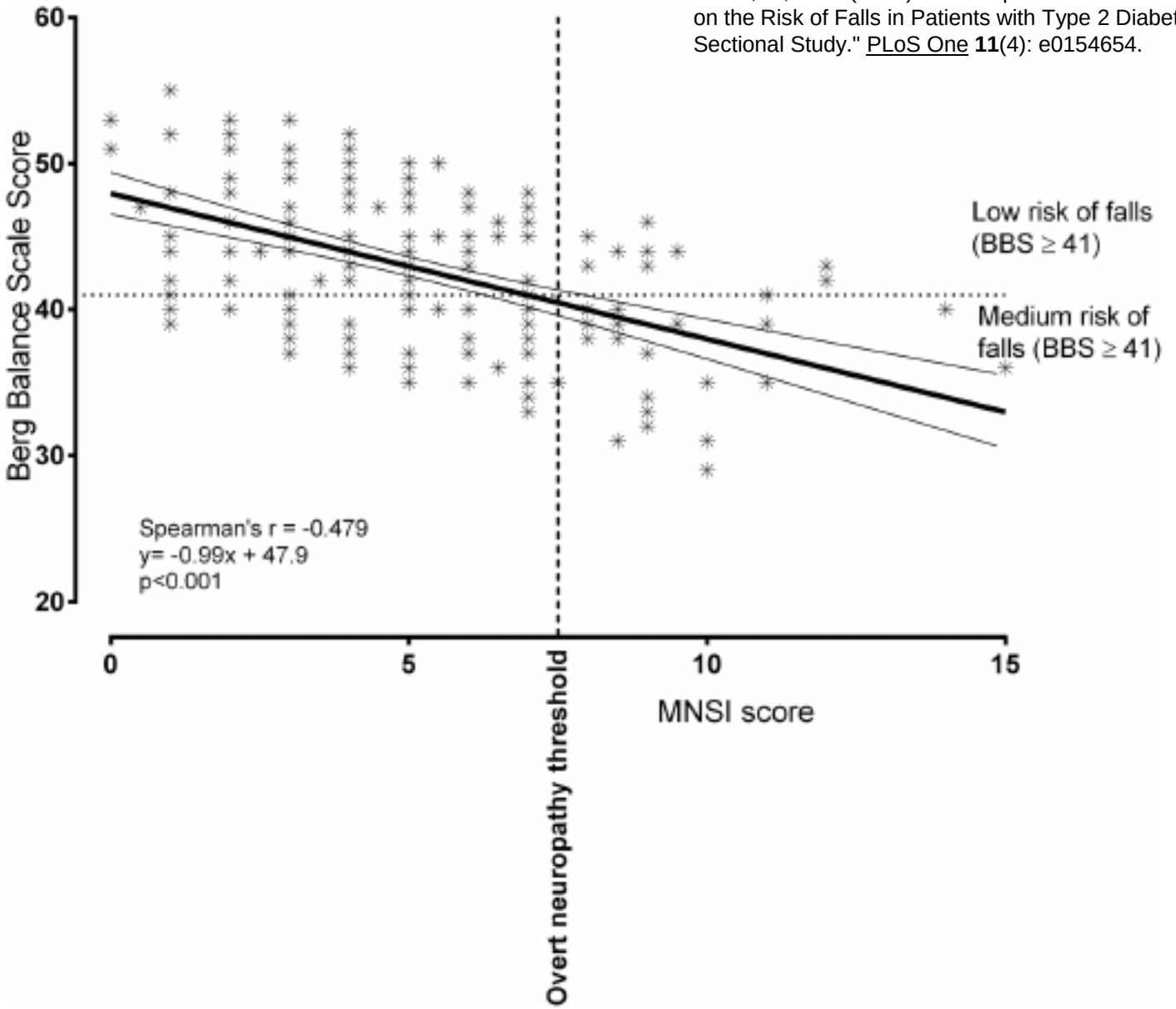

Fig 1. The correlation between MNSI and BBS score. MNSI—Michigan Neuropathy Screening Instrument; BBS—Berg Balance Scale.

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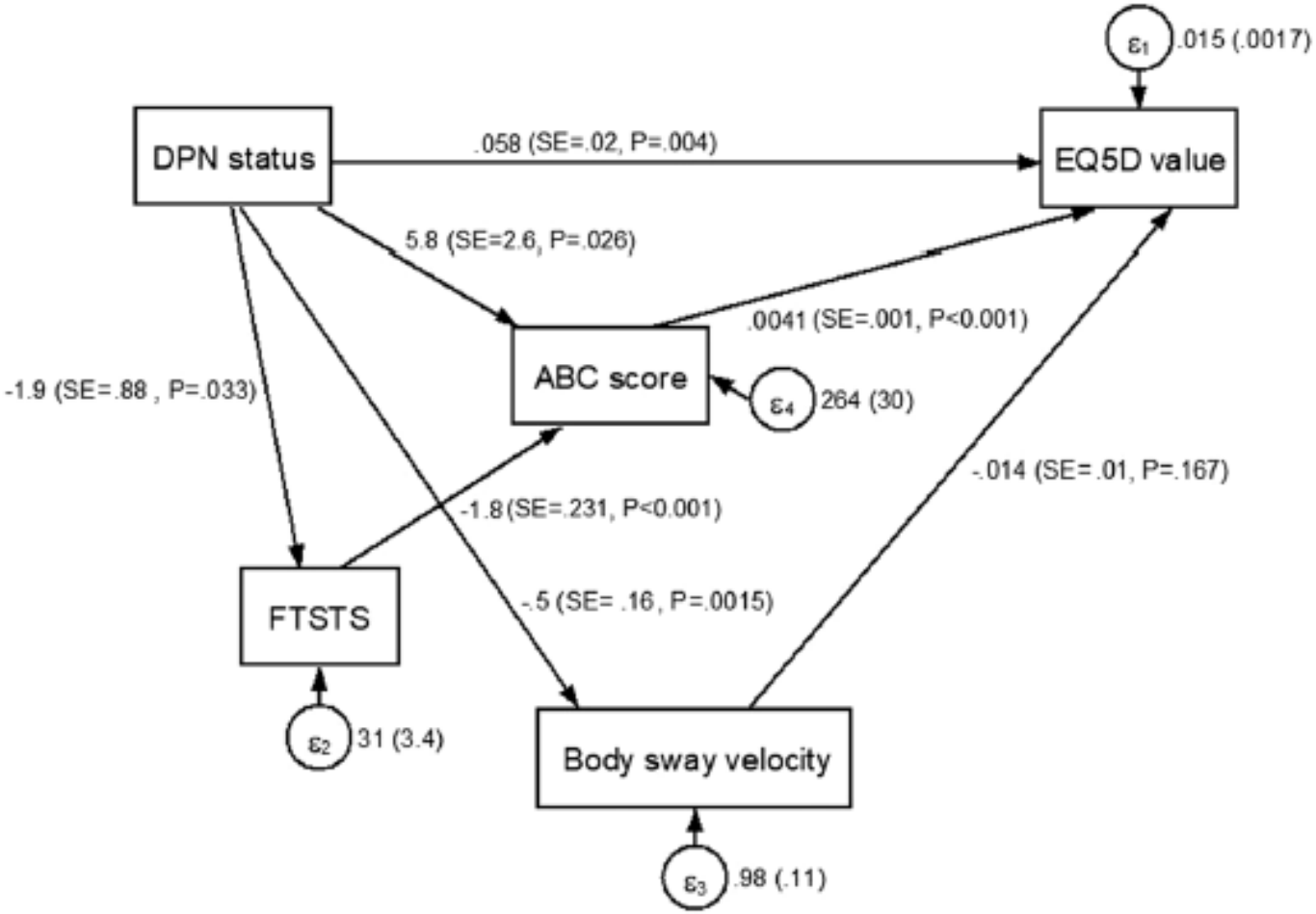
Reduced balance and gait function is correlated to lower QoL

Fig. 2 SEM analysis of HRQoL predictors. Path diagram showing inter-relationships between DPN status, functional status, and HRQoL. Boxes represent observed variables, single-headed arrows represent hypothesized causal relationships, and circles represent error terms/residuals. Reported values for each path: effect estimate (SE, p value); reported values for error terms ($\varepsilon_1 - \varepsilon_4$): raw variance (SE)



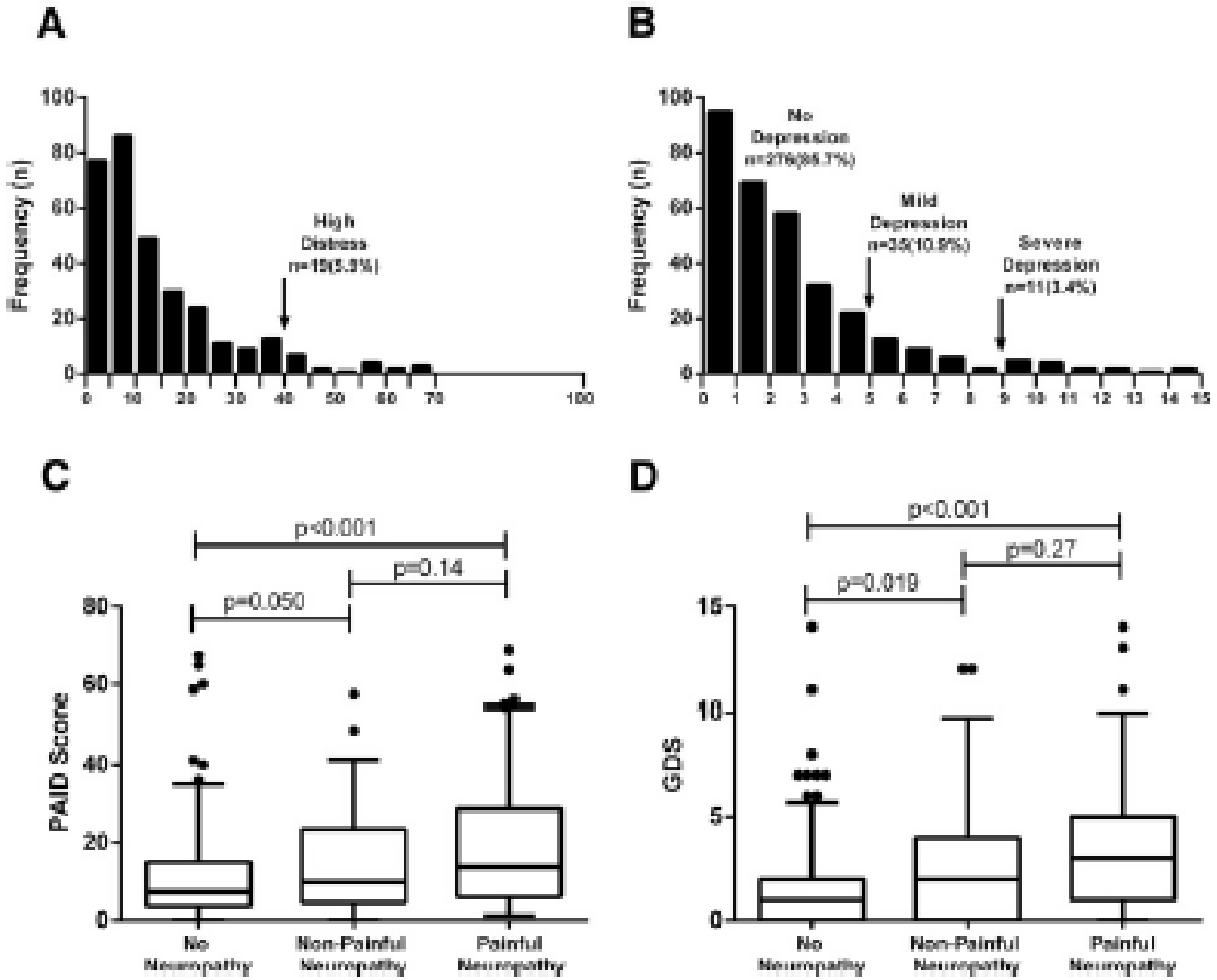
Riandini, T., et al. (2017). "Functional status mediates the association between peripheral neuropathy and health-related quality of life in individuals with diabetes." Acta Diabetol.

DPN is Associated with Increased Risk of Depression and Anxiety

- 50% relative increase in risk of depression in those with neuropathy (DPN and CSPN) compared to controls (23% vs. 15%, $p<0.001$).
- 50% with painful DPN have depression or anxiety and 26% have both.
- Pain and gait instability are most potent predictors of depression.

Callaghan, B., et al. (2015). "Longitudinal patient-oriented outcomes in neuropathy: Importance of early detection and falls." Neurology **85**(1): 71-79.

Selvarajah, D., et al. (2014). "The contributors of emotional distress in painful diabetic neuropathy." Diabetes & vascular disease research **11**(4): 218-225.



Bai, J. W., et al. (2017). "Neuropathy and presence of emotional distress and depression in longstanding diabetes: Results from the Canadian study of longevity in type 1 diabetes." J Diabetes Complications **31**(8): 1318-1324.

Personalized DPN Trials

- T1D vs. T2D
- DPN duration
- Ulceration
- Symptomatic vs. Asymptomatic
- Painful
- Depression/Anxiety
- CNS factors

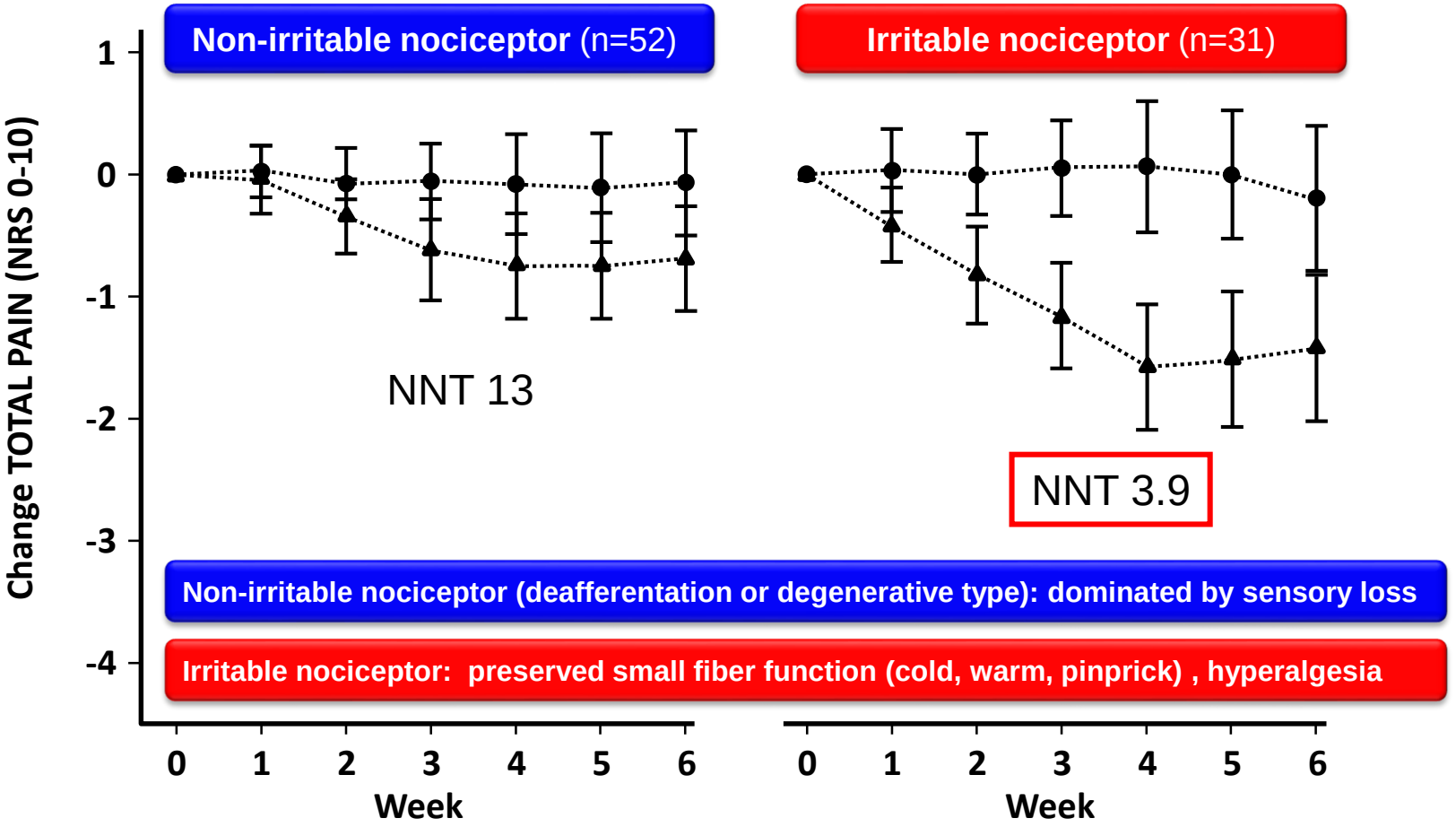
Toronto panel recommendations for clinical trial enrollment criteria for painful DPN

- Use rigorous selection criteria including neuropathic pain measures.
- Enrollment criteria
  - DPN > 6 months
  - Mean weekly pain 4-10 on an 11 point scale
  - Exclude other pain causes.

Tesfaye, S., Boulton, A. J., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., et al. (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care, 33(10), 2285–2293. http://doi.org/10.2337/dc10-1303

Effect of Oxcarbazepine in Peripheral Neuropathic Pain Depends on Pain Phenotype:

Placebo-controlled Phenotype-stratified (QST) Study



Demant, D. T., et al. (2014). "The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study." Pain **155**(11): 2263-2273.

COMBO-DN

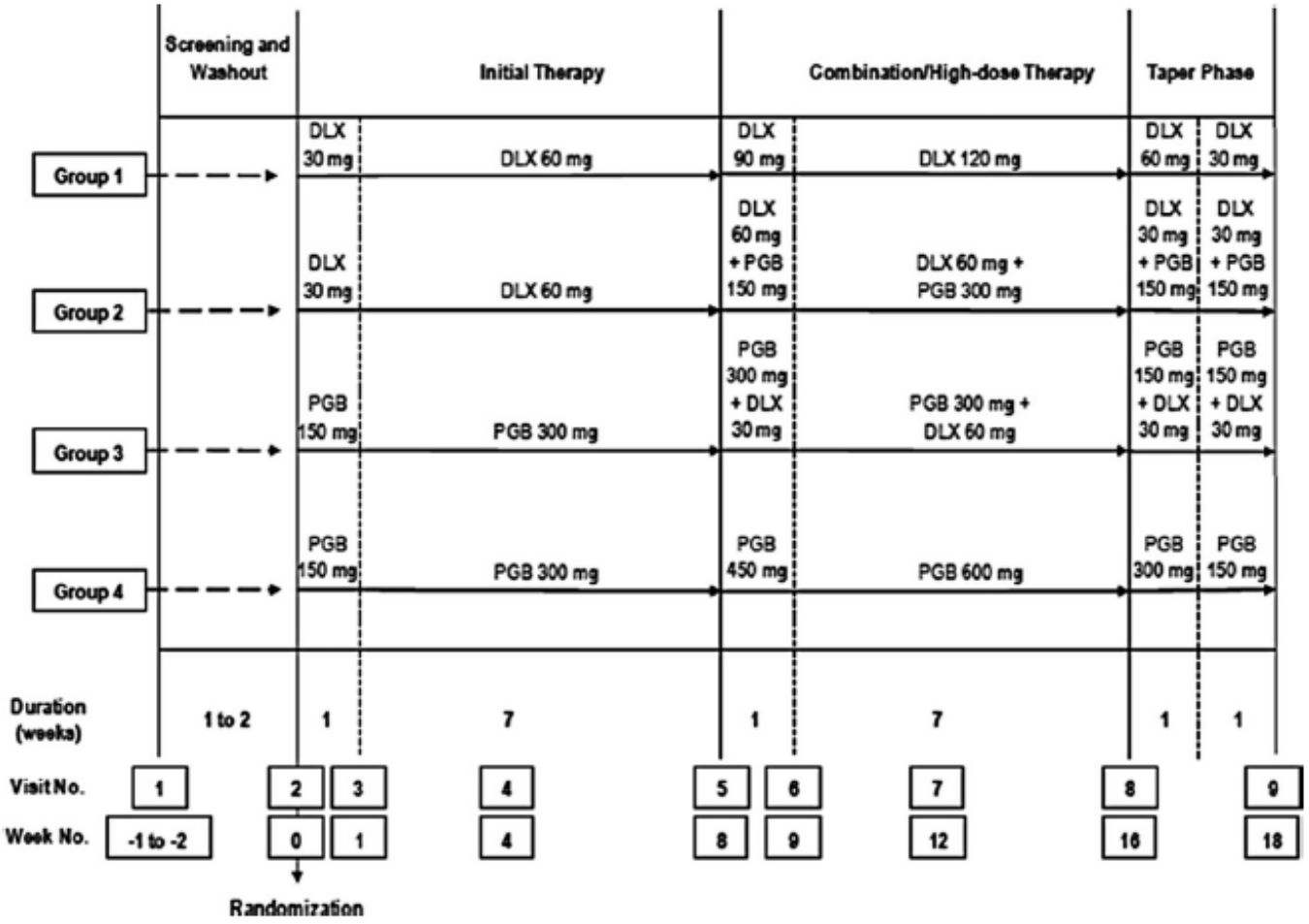


Fig. 1. Study design. DLX, duloxetine; PGB, pregabalin.

Tesfaye, S., et al. (2013). "Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain." Pain **154**(12): 2616-2625.

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Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: Data from the randomized, double-blind, COMBO-DN study

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Bouhassira, D., et al. (2014). "Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study." Pain **155**(10): 2171-2179.

Conclusions

- Toronto consensus criteria provide an appropriate framework, although there are some concerns regarding use of NCS and IENFD.
- Trials of disease altering agents should usually focus on T1D or T2D.
- More work needs to be done to understand disease risk factors (including genetics).
- Sensory phenotyping should be considered in painful DPN trials (and may eventually be useful as enrollment or stratification criteria).