



Weill Cornell Medical College in Qatar



Corneal Confocal Microscopy: Ready for Prime Time?

R A Malik
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Doha/New York

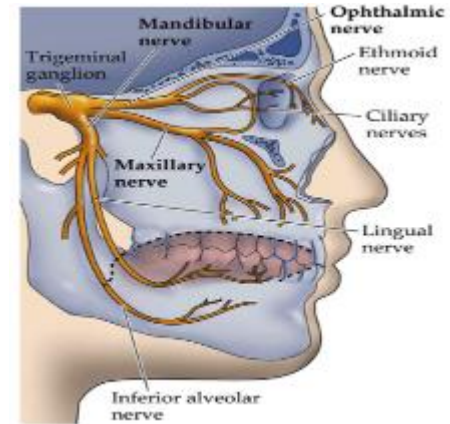
Corneal Confocal Microscopy

- Rapid (5 min)
- Non-invasive (in vivo)
- Reiterative
- Images Corneal Nerves.

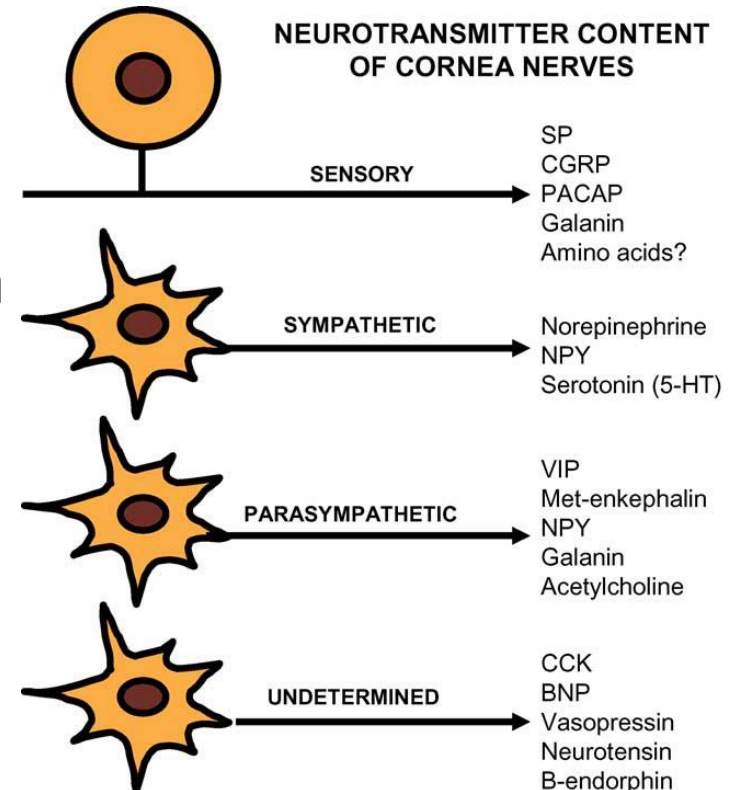


Corneal Nerves

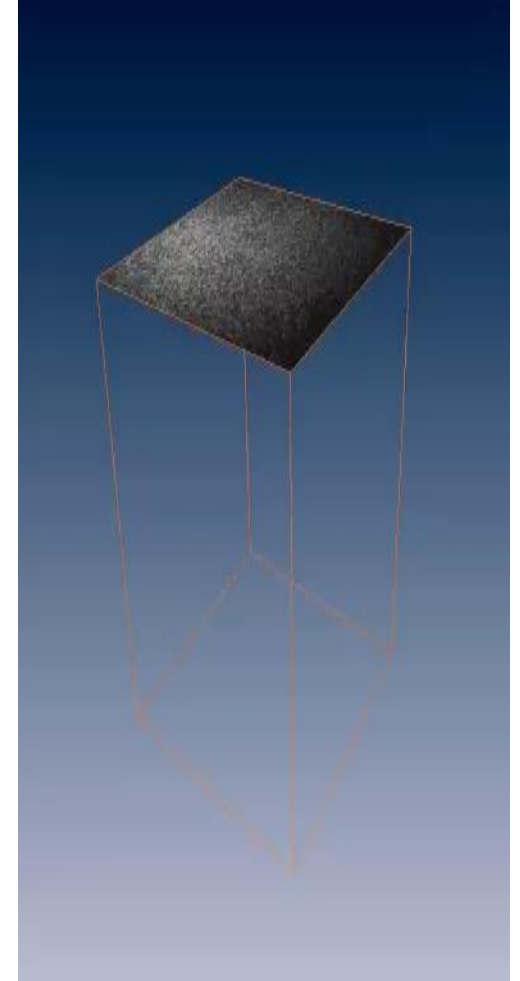
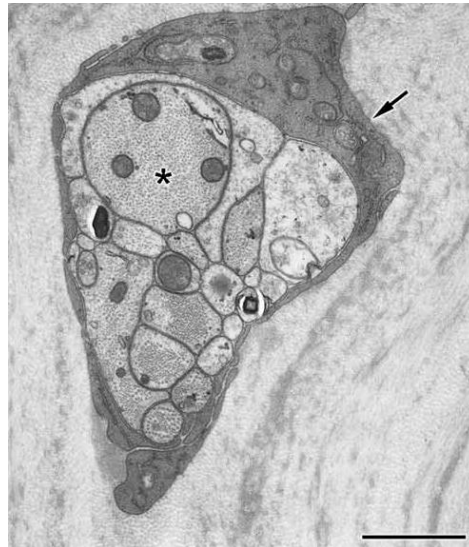
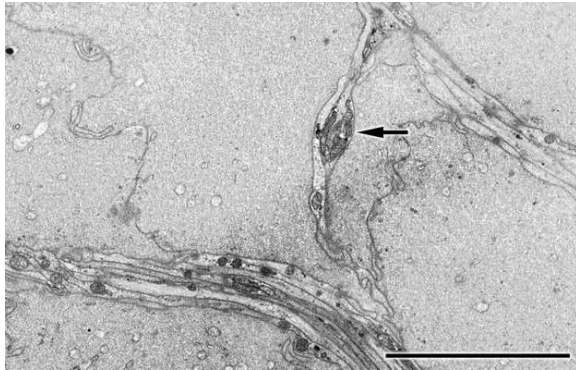
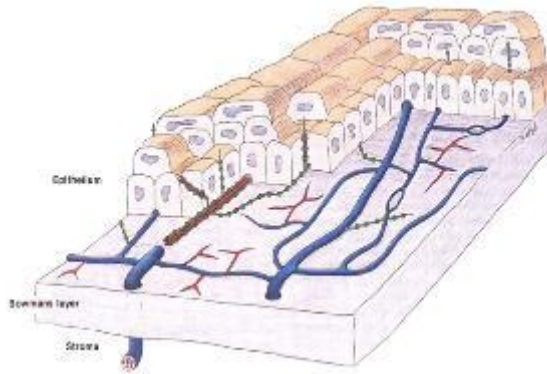
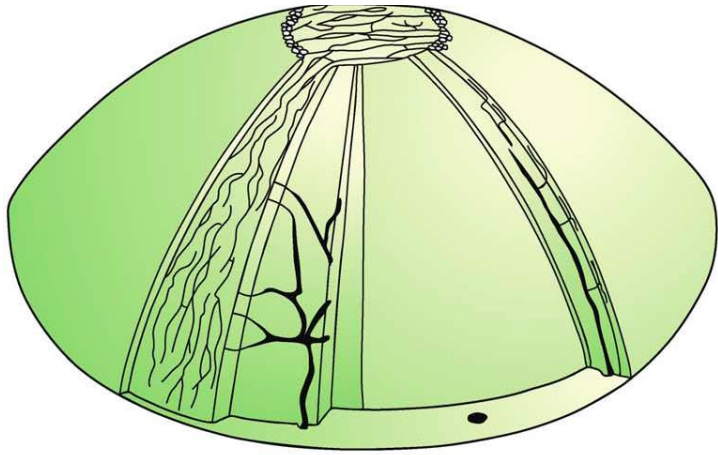
- Derived from the Ophthalmic division of the Trigeminal nerve.



- Skin 200 nociceptors/mm².
- Cornea most dense innervation in body 7000 nociceptors/mm².



Corneal Nerves



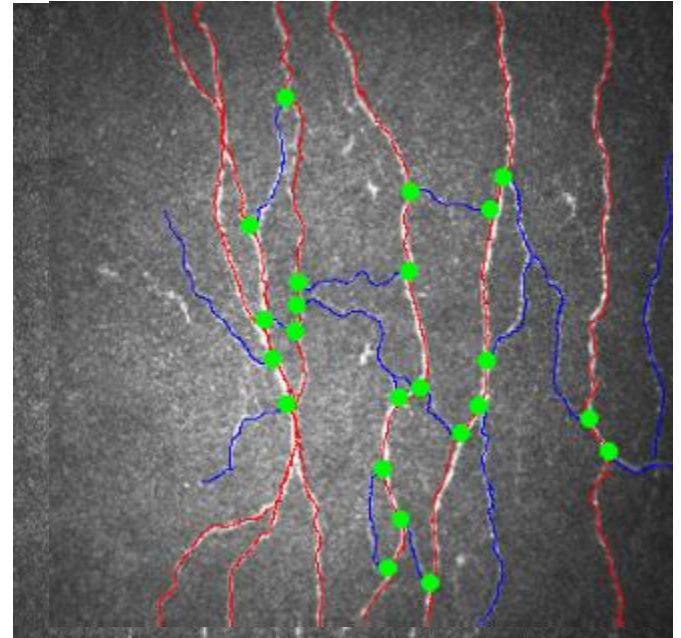
Corneal Nerve Quantification

CCM (6 images/patient)

CNFD (no./mm²) + TC (Red)

CNFL (mm/mm²) (Red + Blue)

CNBD (no./mm²) (Green)

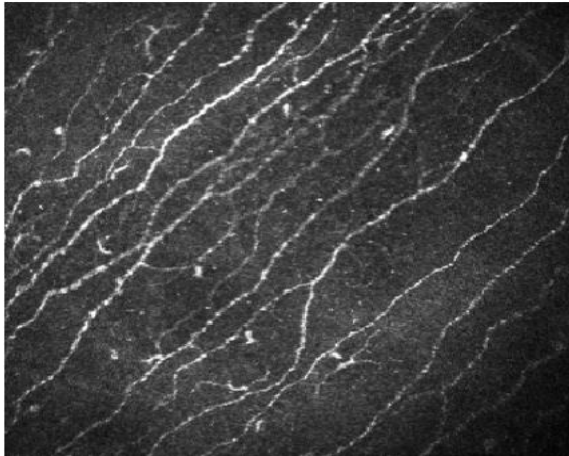


CCMetrics®, M. A. Dabbah, University of Manchester, Imaging Science and Biomedical Engineering, School of Cancer and Enabling Sciences.

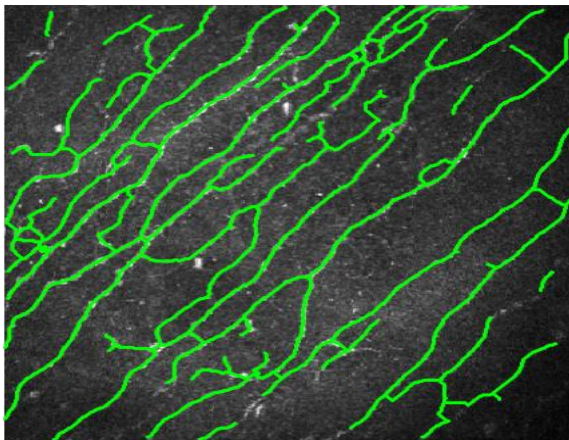
Malik et al. Diabetologia 2003; 46: 683-688

Kallinikos et al. IOVS 2004; 45: 418-422

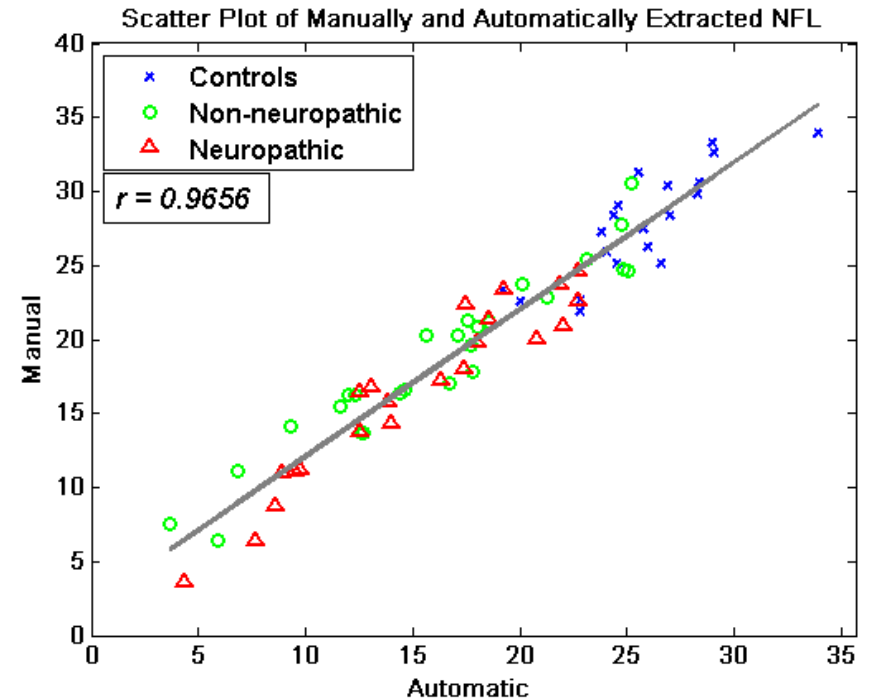
Automated Analysis (CCMetrics/ACCMetrics)



30 min



25 sec



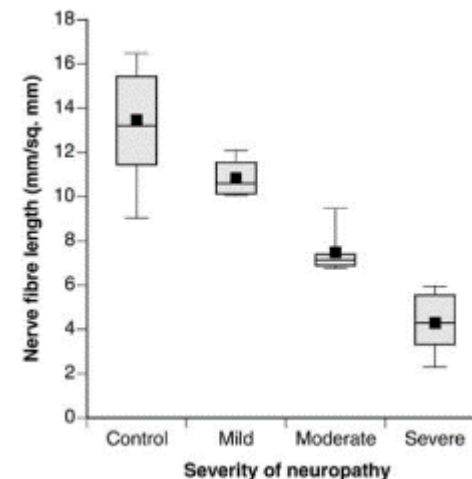
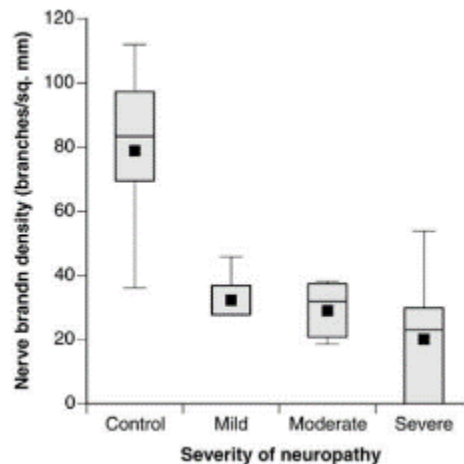
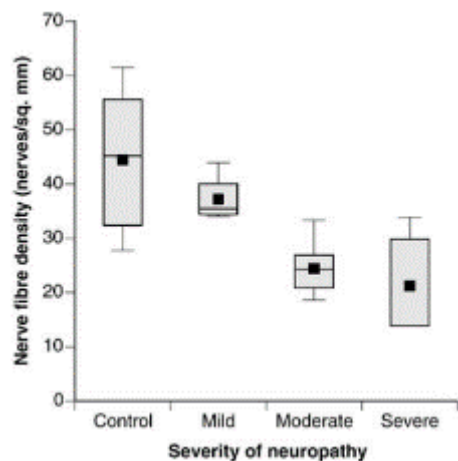
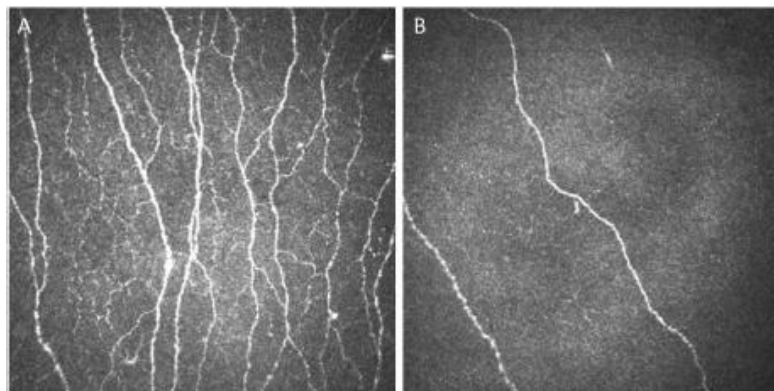
FDA End Point?

- 1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.**
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. Surrogate Endpoint: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of therapeutic intervention.



Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients

R. A. Malik¹, P. Kallinikos², C.A. Abbott¹, C.H.M. van Schie¹, P. Morgan², N. Efron², A. J. M. Boulton¹



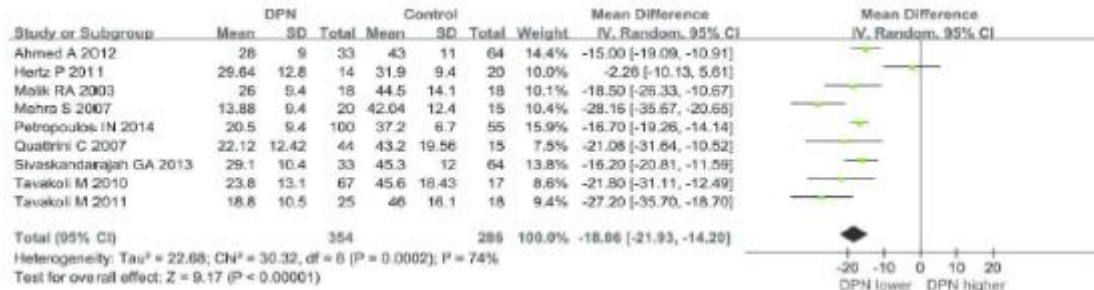
**JDRF Innovative grant
\$53K**

Diabetologia (2003) 46:683–688

Corneal Confocal Microscopy for Assessment of Diabetic Peripheral Neuropathy: A Meta-analysis

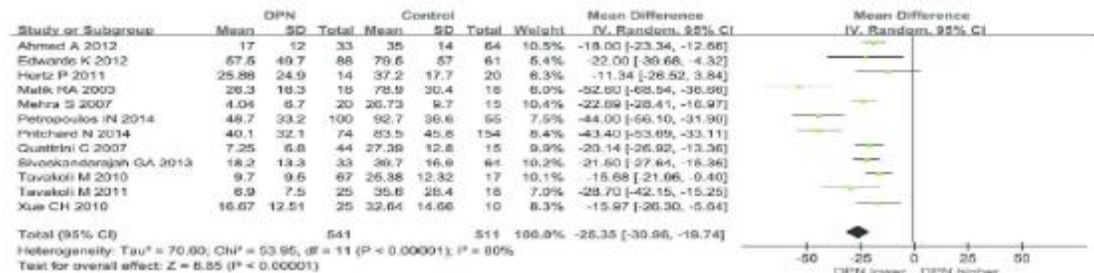
N=1680 (DPN-559, no DPN-592, Controls 529)

CNFD



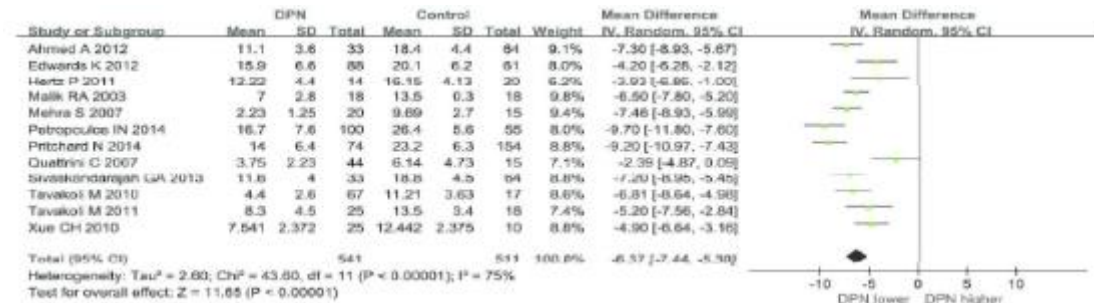
C v DPN P<0.00001
DPN v no-DPN, P<0.00001
C v no-DPN P<0.02

CNBD



C v DPN P<0.00001
DPN v no-DPN, P<0.00001
C v no-DPN P<0.02

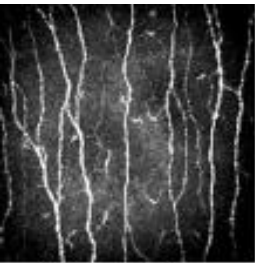
CNFL



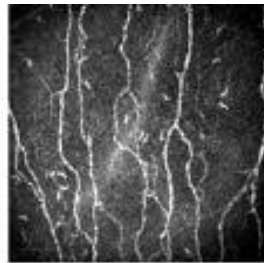
C v DPN P<0.00001
DPN v no-DPN, P<0.00001
C v no-DPN P<0.004

Normative Values for Corneal Nerve Morphology Assessed Using Corneal Confocal Microscopy: A Multinational Normative Data Set

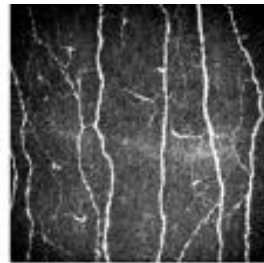
N=343



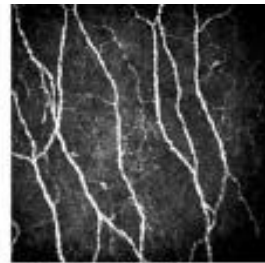
Age Group 5-15yrs



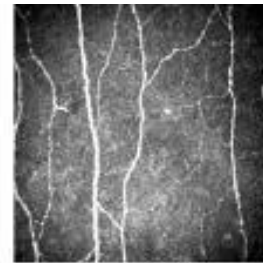
Age Group 16-25yrs



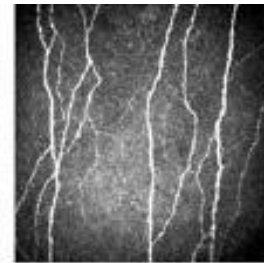
Age Group 26-35yrs



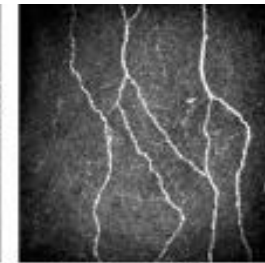
Age Group 36-45yrs



Age Group 46-55yrs

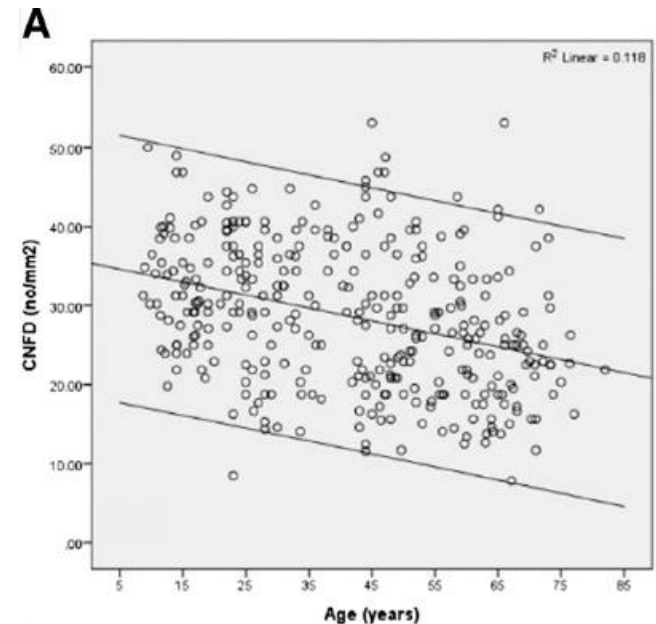


Age Group 56-65yrs



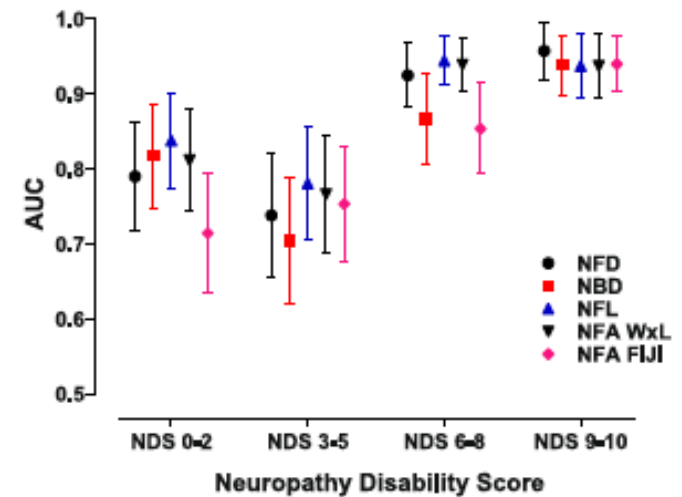
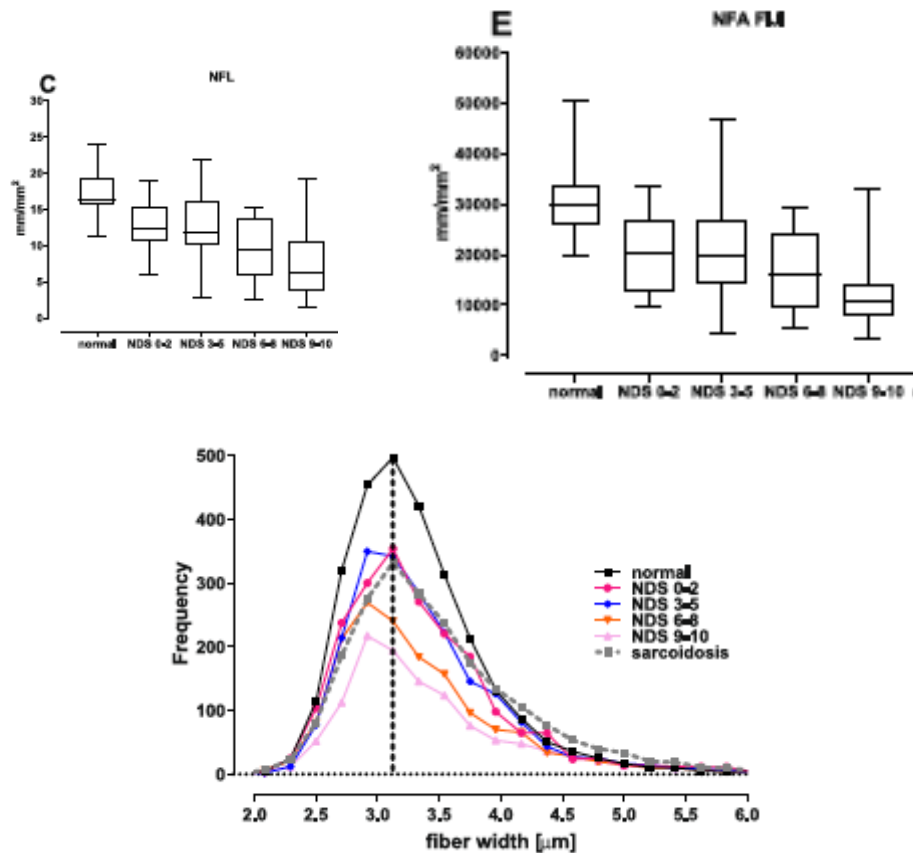
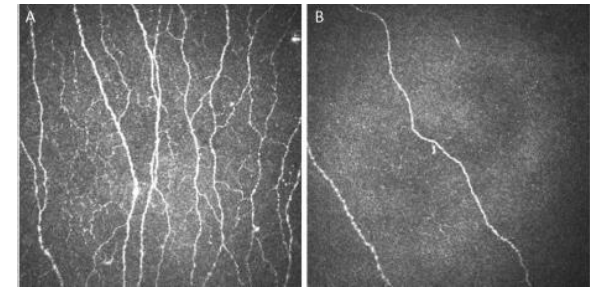
Age Group 66-85yrs

Age (years)	No. of subjects	Median CNFD (no./mm ²)	Median CNBD (no./mm ²)	Median CNFL (mm/mm ²)
<16	19	33.33	87.60	26.43
16-25	28	31.85	77.01	25.45
26-35	26	30.20	68.46	24.37
36-45	26	28.56	63.27	23.28
46-55	34	26.91	61.46	22.20
56-65	22	25.27	63.02	21.11
>65	16	23.54	68.28	19.97



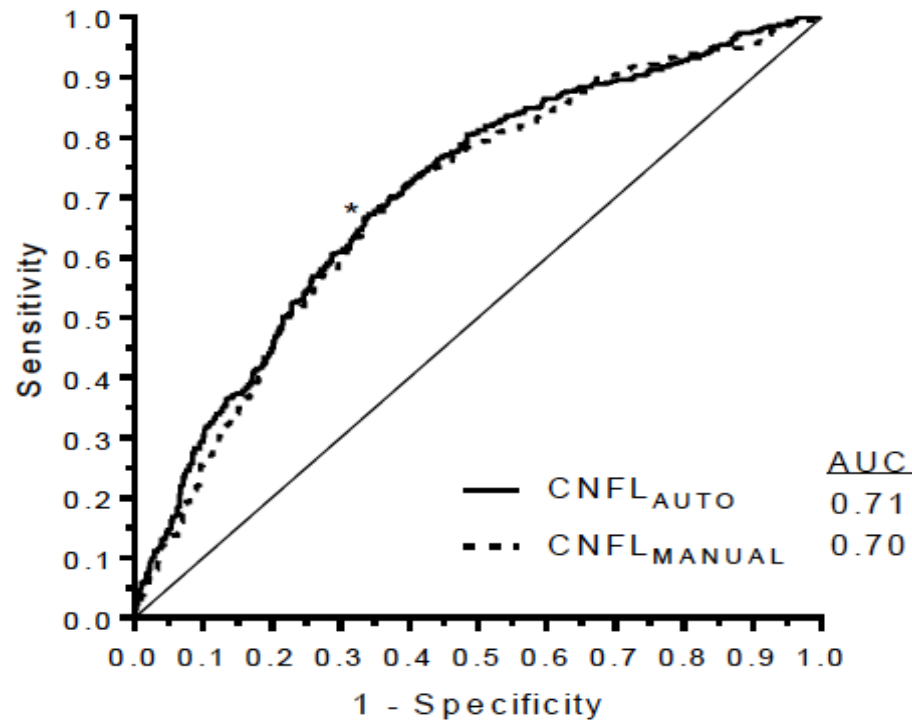
Corneal nerve fiber size adds utility to the diagnosis and assessment of therapeutic response in patients with small fiber neuropathy

Michael Brines¹, Daniel A. Culver², Maryam Ferdousi³, Martijn R. Tannemaat⁴, Monique van Velzen⁵, Albert Dahan⁵ & Rayaz A. Malik⁶

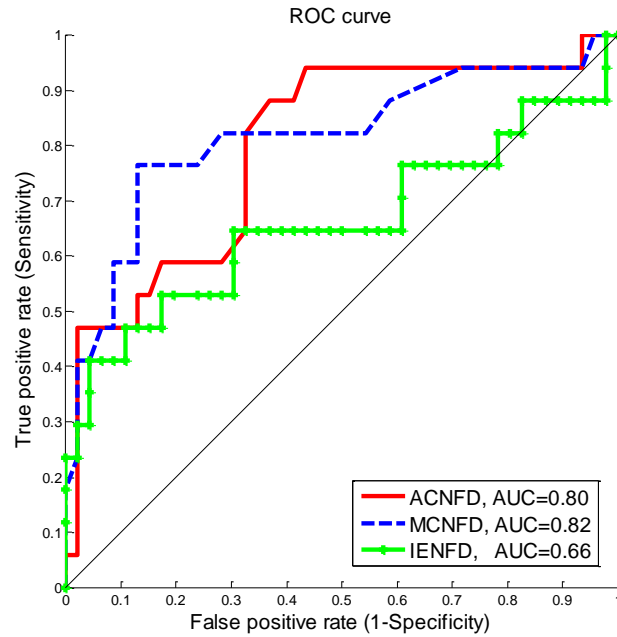
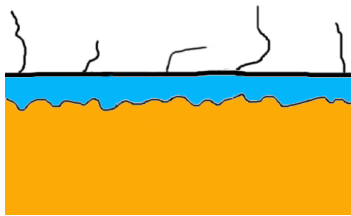


Corneal Confocal Microscopy for Identification of Diabetic Neuropathy: A Pooled Multinational Consortium Study

998 participants from 5 centres - 516 with type 1 and 484 with type 2 diabetes



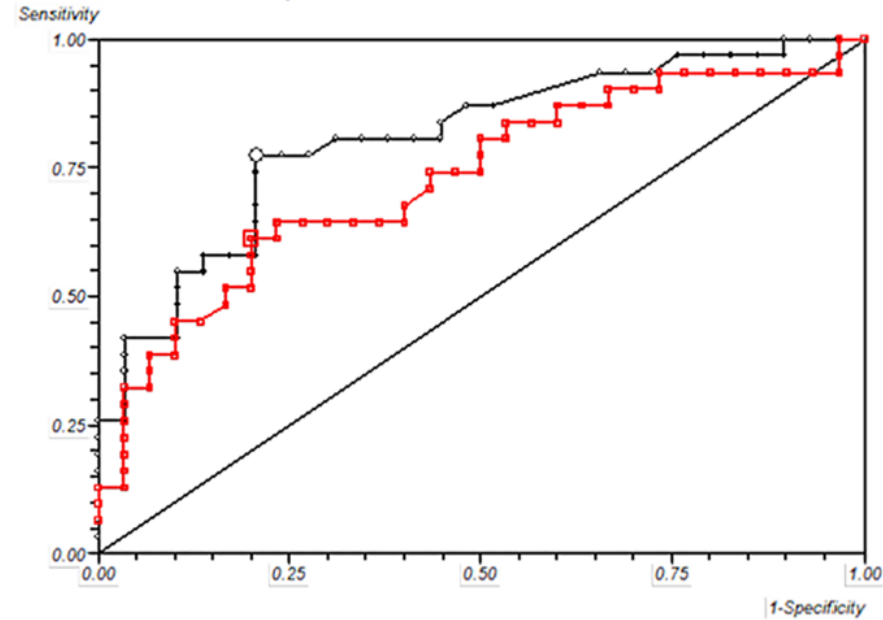
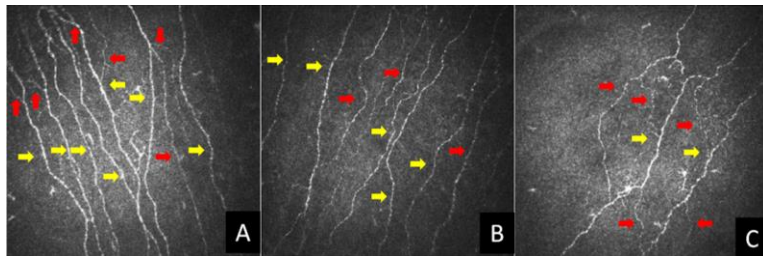
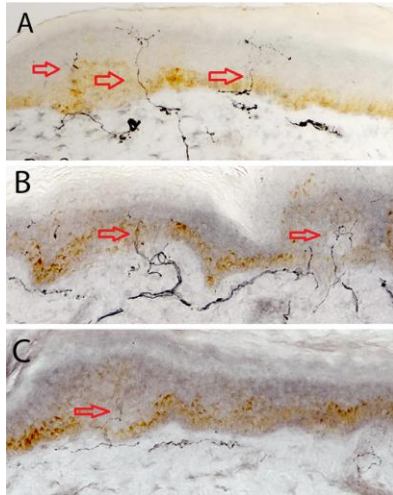
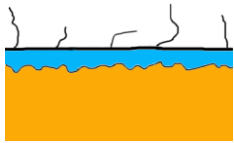
CCM v IENFD



	Sensitivity	Specificity
CNFD	0.79	0.71
IENFD	0.53	0.77

Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy

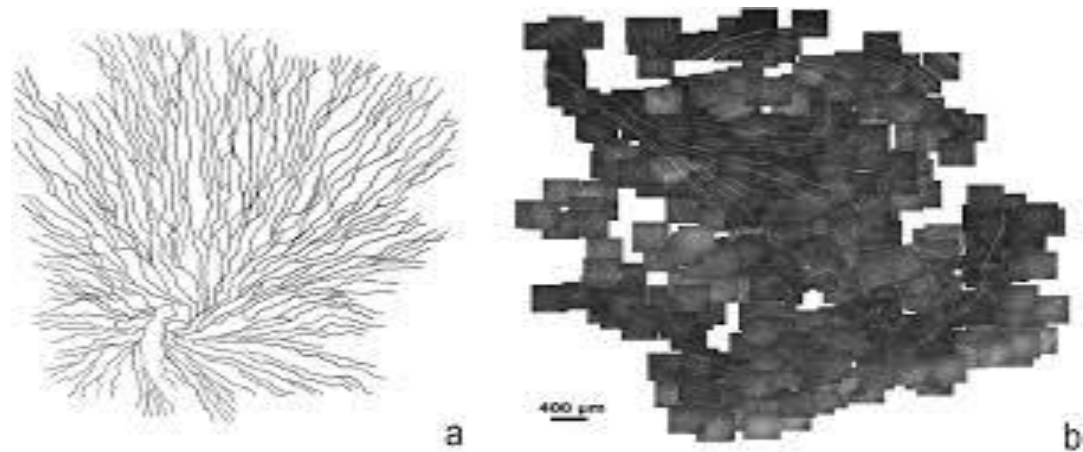
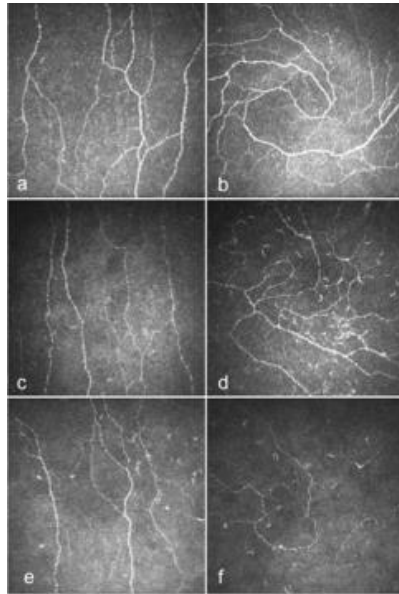
Uazman Alam^{1,2}, Maria Jeziorska², Ioannis N. Petropoulos², Omar Asghar², Hassan Fadavi², Georgios Ponirakis³, Andrew Marshall², Mitra Tavakoli^{2,4}, Andrew J. M. Boulton², Nathan Efron⁵, Rayaz A. Malik^{2,3*}



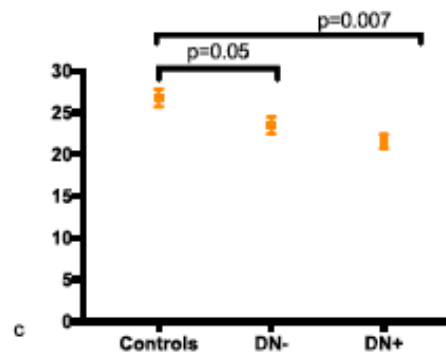
	Optimal Cut off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CNFD (no/mm ²)	25.0	• 0.81 • (0.47–1.0)	• 0.77 • (0.59–0.90)	• 0.79 • (0.60–0.92)
IENFD (no/mm)	4.5	• 0.73 • (0.46–1.0)	• 0.61 • (0.42–0.78)	• 0.80 • (0.61–0.92)

Greater corneal nerve loss at the inferior whorl is related to the presence of diabetic neuropathy and painful diabetic neuropathy

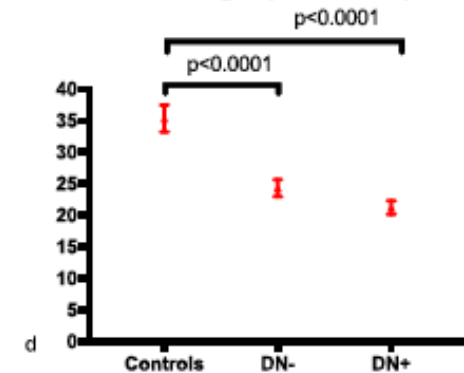
Alise Kalteniece¹, Maryam Ferdousi², Ioannis Petropoulos², Shazli Azmi¹, Safwan Adam², Hassan Fadavi², Andrew Marshall², Andrew J. M. Boulton², Nathan Efron³, Catharina G. Faber^{4,5}, Giuseppe Lauria^{6,7}, Handrean Sorin² & Rayaz A. Malik^{4,7}



Corneal nerve fibre length (mm/mm²) (Mean ± SE)



Inferior whorl length (mm/mm²) (Mean ± SE)

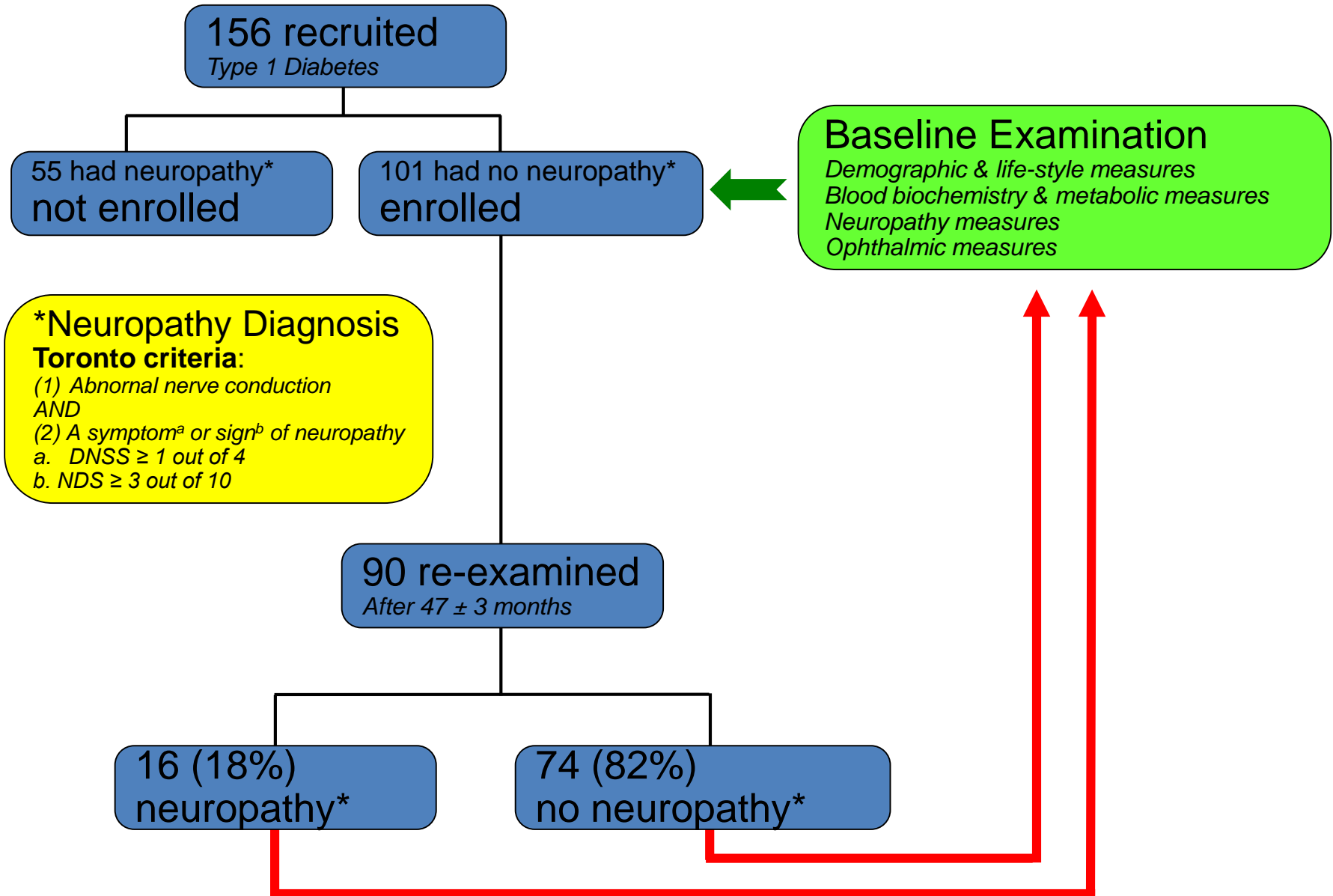


FDA End Point?

1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or **prognostic utility**.
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. Surrogate Endpoint: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of therapeutic intervention.



Corneal Confocal Microscopy Predicts 4-Year Incident Peripheral Neuropathy in Type 1 Diabetes



Corneal Confocal Microscopy Predicts 4-Year Incident Peripheral Neuropathy in Type 1 Diabetes

Baseline Characteristic	No DPN	DPN	p
Retinopathy status (ETDRS)	16±9	26±16	0.008
Corneal nerve fiber length (mm/mm ²)	16.2±3.5	14.0±4.1	0.041



In Vivo Corneal Confocal Microscopy and Prediction of Future-Incident Neuropathy in Type 1 Diabetes: A Preliminary Longitudinal Analysis

**65 Type 1DM
No DSP**

3.5 ± 0.9 yrs

54 (83%) No DSP

11 (17%) DSP

***Neuropathy Diagnosis Toronto criteria:**
 (1) Abnormal nerve conduction AND
 (2) A symptom^a or sign^b of neuropathy
 a. DNSS ≥ 1 out of 4
 b. NDS ≥ 3 out of 10

Characteristic	DSP controls (n=54)	New-onset DSP cases (n=11)	p value
Clinical characteristics			
Female sex, n (%)	27 (50%)	6 (55%)	0.78
Age (years)	34±15	38±16	0.33
Diabetes duration (years)	17±12	21±9	0.28
Smoking, n (%)	7 (13%)	4 (36%)	0.06
Height (m)	1.73±0.11	1.71±0.10	0.58
Weight (kg)	73.3±14.0	78.0±15.7	0.38
Body mass index (kg/m ²)	24.2±3.4	26.1±4.1	0.15
Systolic blood pressure (mm Hg)	123±13	129±17	0.21
Diastolic blood pressure (mm Hg)	69±8	71±6	0.58
Resting heart rate (bpm)	67±14	67±11	0.99
Biochemical characteristics			
A1C (%)	7.6±1.3	8.1±1.6	0.22
A1C (mmol/mol)	60±14.2	65±17.5	0.22
Total cholesterol (mmol/L)	4.58±0.76	4.70±0.84	0.67
LDL cholesterol (mmol/L)	2.55±0.66	2.76±0.82	0.43
HDL cholesterol (mmol/L)	1.62±0.41	1.45±0.34	0.26
Triglycerides (mmol/L)	0.89±0.58	1.09±0.65	0.39
TSH (mIU/L)	1.95 (1.18,2.93)	1.71 (1.59,2.97)	0.95
Creatinine (µmol/L)	75±14	70±11	0.28
Urine ACR (mg/mmol)	0.6 (0.3,1.1)	0.5 (0.4,0.7)	0.40
eGFR (mL/min/1.73m ²)	92±15	95±18	0.56

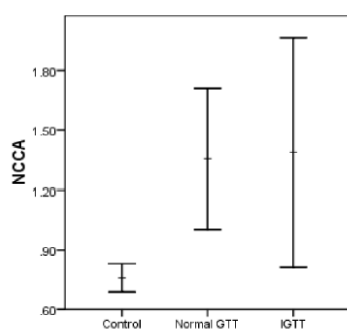
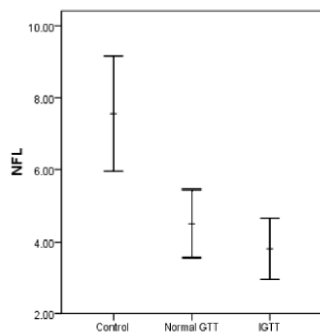
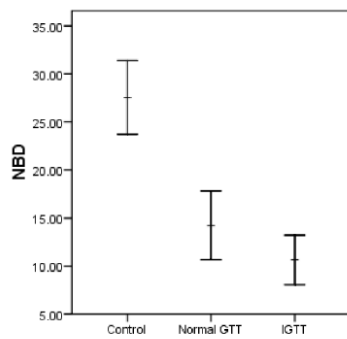
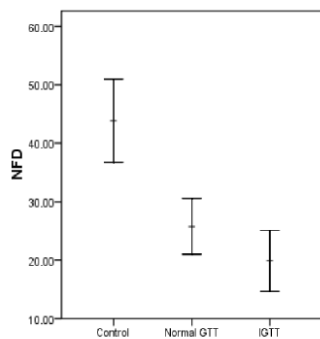
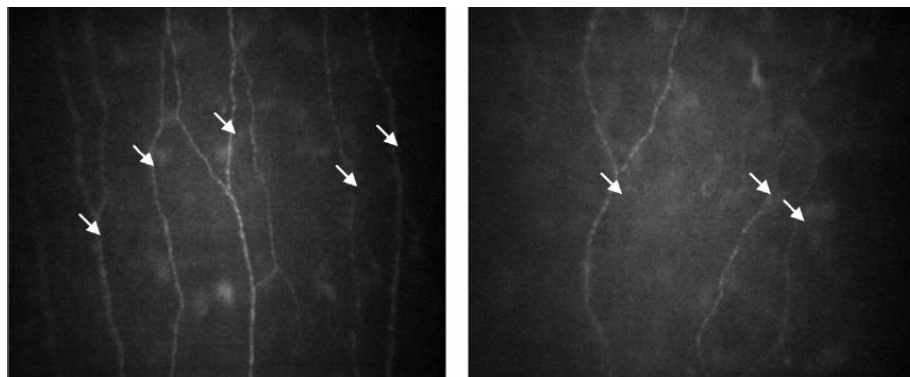
Neuropathy measure	DSP controls (n=54)	New-onset DSP cases (n=11)	p value
Clinical neuropathy measure			
TCNS	2 (0.4)	3 (0.7)	0.53
Nerve conduction studies			
Sural nerve amplitude potential (µV)	11.0 (9.1,16.0)	8.2(5.0,14.1)	0.20
Sural nerve conduction velocity (m/s)	46.7 (43.8,48.3)	43.2 (40.0,50.0)	0.37
Peroneal nerve amplitude potential (mV)	5.5 (4.4,6.8)	5.0 (3.5,6.1)	0.75
Peroneal nerve conduction velocity (m/s)	43.6 (42.1,46.0)	42.4 (41.1,44.4)	0.26
Peroneal nerve f-wave latency (ms)	51.6 (48.2,54.2)	52.9 (47.0,58.2)	0.36
Large-fibre function tests			
VPT upper (volts)	3.2 (2.5,4.3)	3.4 (2.9,5.1)	0.44
VPT lower (volts)	6.3 (5.3,9.6)	8.0 (5.0,12.3)	0.54
Small-fibre function tests			
Heart rate variability (%)	44 (28,54)	42 (23,48)	0.44
Cooling detection threshold (°C)	28.7 (27.0,29.8)	28.8 (27.4,30.2)	0.90
LDL _{small} area (cm ²)	2.16 (1.36,2.97)	1.83 (1.35,2.76)	0.91
Small fibre morphologic measure			
CNFL (mm/mm ²)	16.4±3.7	12.6±3.8	0.003
CNFT (tortuosity coefficient)	14.2±4.3	17.3±4.4	0.03
CNBD (branches/mm ²)	39.2±19.5	24.7±13.5	0.02
CNFD (fibres/mm ²)	44.7±10.8	39.4±12.3	0.16

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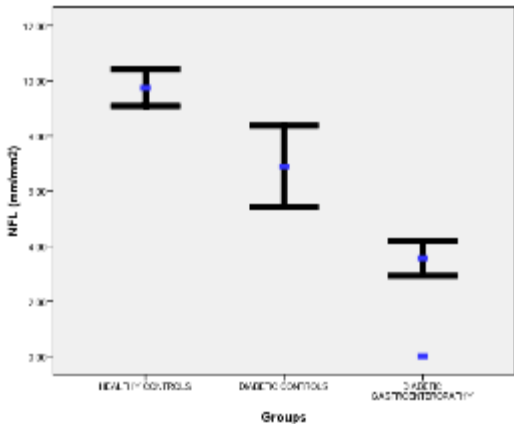
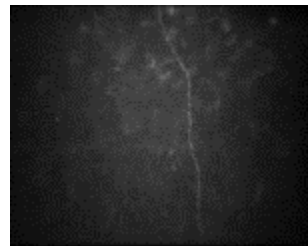
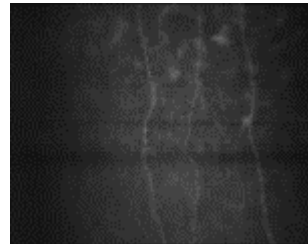
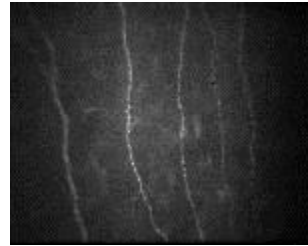
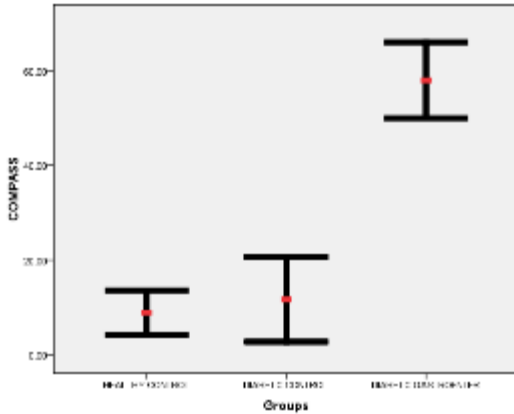
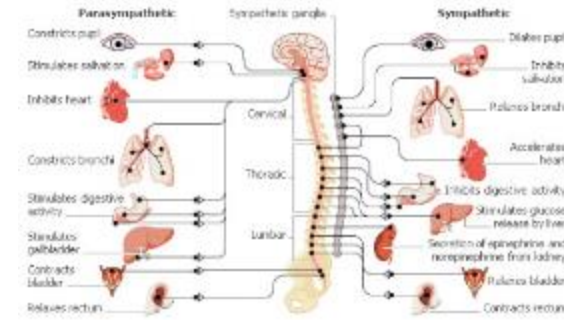


Corneal confocal microscopy: A novel means to detect nerve fibre damage in idiopathic small fibre neuropathy

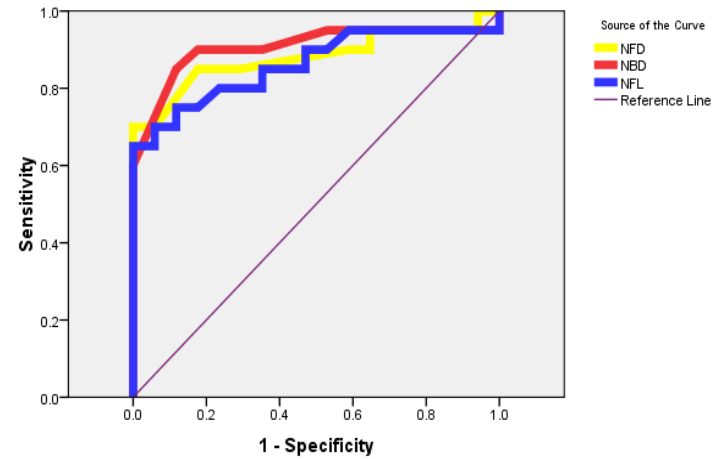


	NSP	NDS	Sural Vel.	WS
NFD	$r=-0.473^*$ P=0.03	$r=-.0504^*$ P= 0.02	$r=0.594^{**}$ P=0.007	$r=-0.375$ P=0.13
NBD	$r=-0.832^*$ P=0.01	$r=-.483^*$ P= 0.03	$r=0.631^{**}$ P=0.004	$r=-0.376$ P=0.13
NFL	$r=-0.462^*$ P=0.04	$r=-0.581^{**}$ P= 0.007	$r=0.549^*$ P=0.01	$r=-0.484^*$ P=0.04
NCCA	$r=0.657^{**}$ P=0.002	$r=0.598^{**}$ P= 0.007	$r=-0.381$ P=0.119	$r=0.205$ P=0.447

Autonomic Neuropathy



ROC Curve

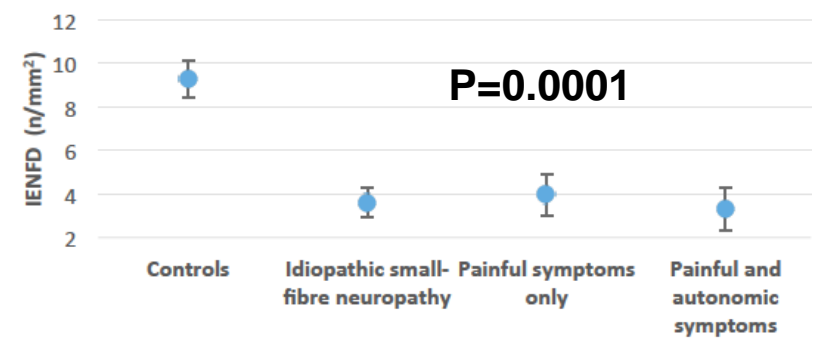
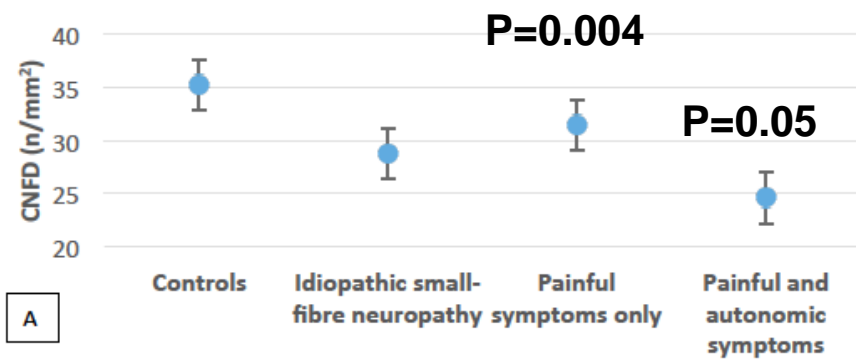
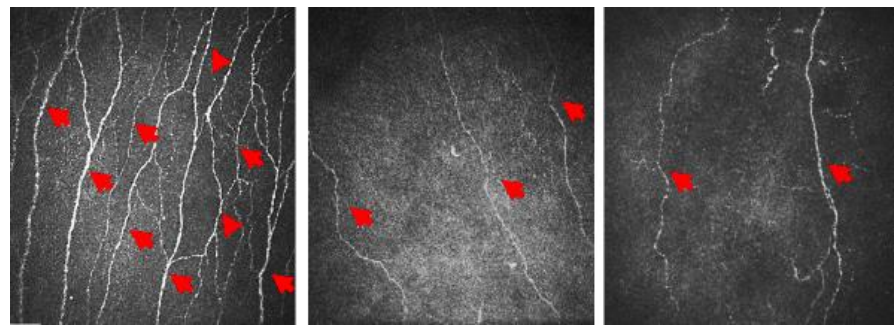
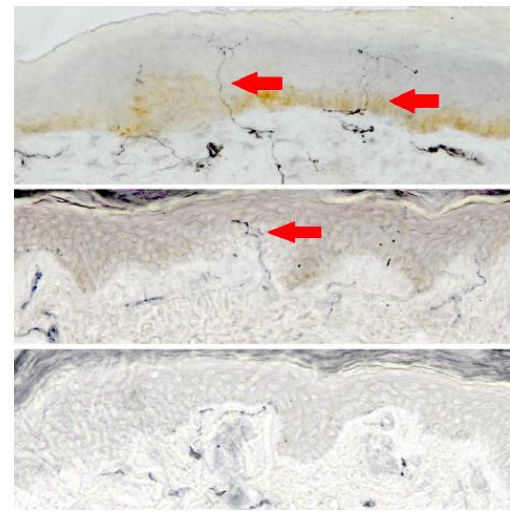


	AUC	Sensitivity	Specificity
NFD	0.915	86%	78%
NFL	0.907	86%	78%
NBD	0.889	100%	56%

Corneal Confocal Microscopy and Skin Biopsy in Sensory and Autonomic

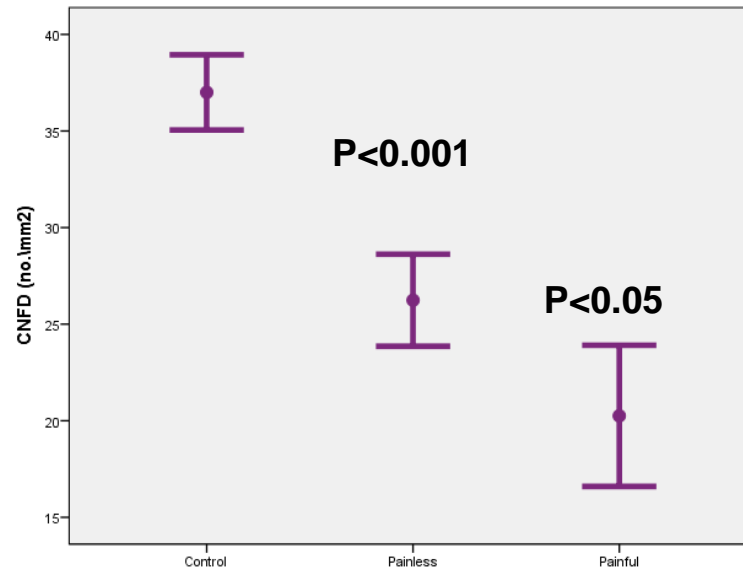
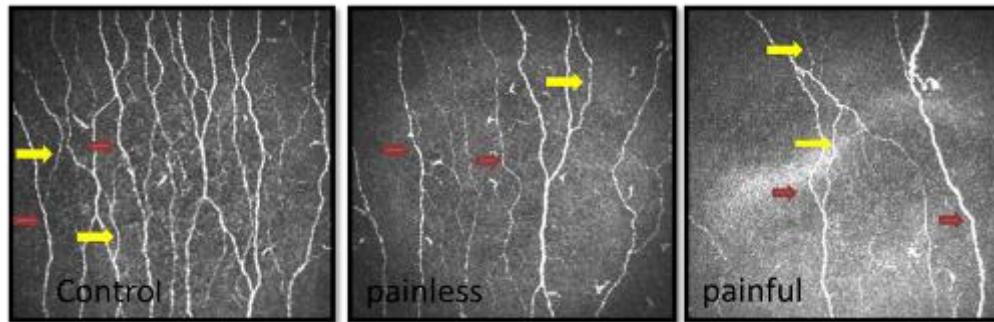
Idiopathic Small Fibre Neuropathy

	Controls	Idiopathic small-fibre neuropathy
Number	15	15
Age	51.5 ± 4.25	51.8 ± 1.78
Sex (female/male)	10/5	10/5
Painful symptoms	0	15
Autonomic symptoms	0	6
Normal nerve conduction studies	15	15



Painful v Painless DPN

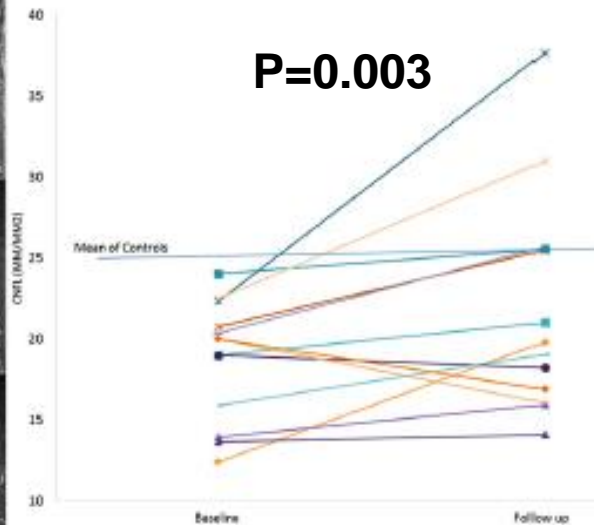
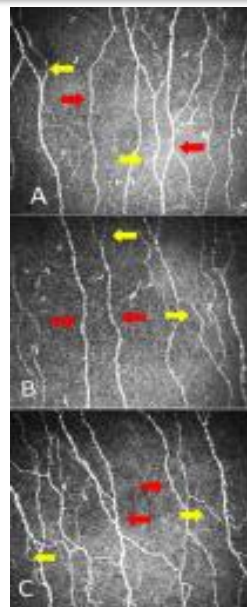
Parameters	Control (n=50)	Painless (n=50)	Painful (n=41)
CNFD (no./mm²)	37.0±6.3	26.2±8.02*	20.2±10.7 [#]
CNBD (no./mm²)	87.1±34.4	58.1±30.5*	46.4±32.5
CNFL (mm/mm²)	26.06±5.2	19.8±5.6*	15.7±7.8 [#]



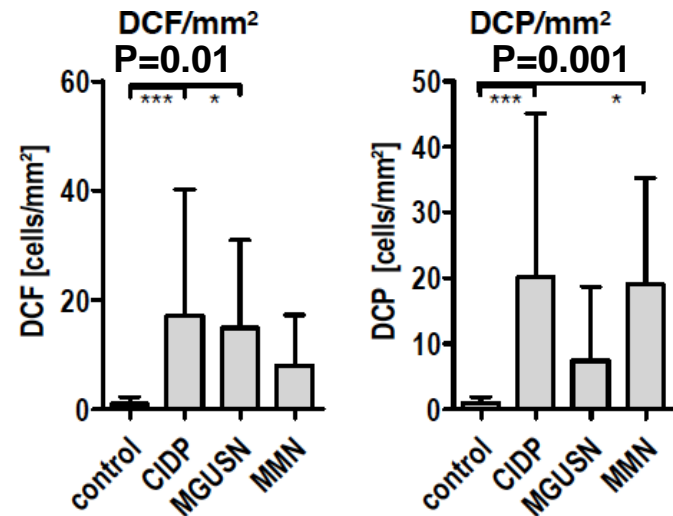
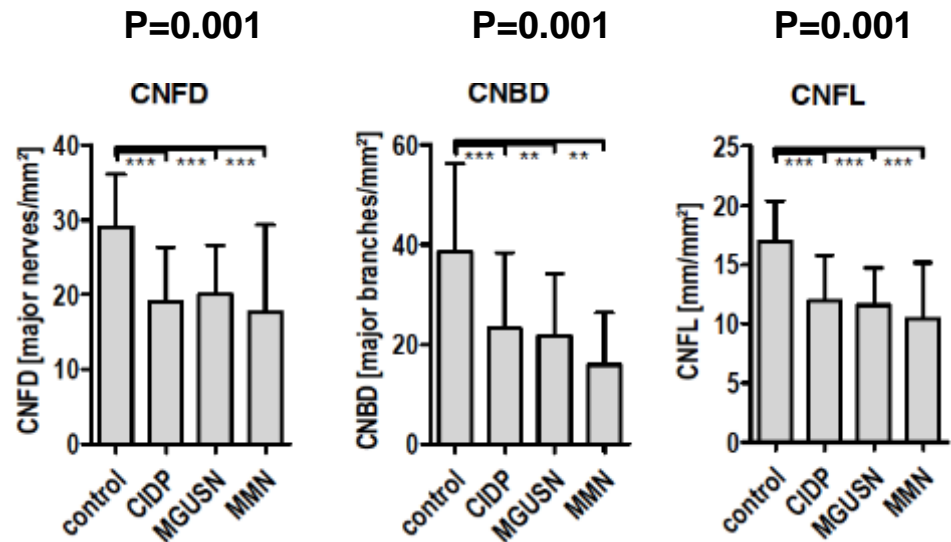
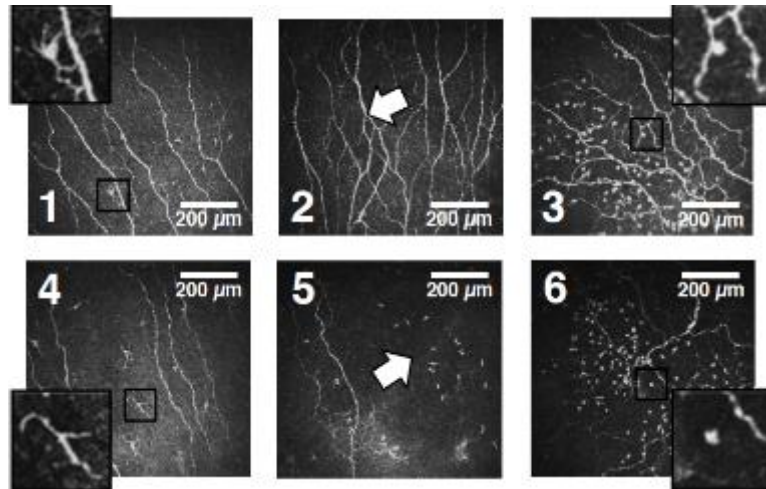
Chemotherapy Induced Peripheral Neuropathy

Parameters	Control	Patients
NSP (0-38)	0.67±1.06	0.83±1.7
McGill pain index (0-5)	0.29±0.96	0.12±0.5
NDS (0-10)	0.84±1.16	1.39±2.09
VPT (volts)	9.91±6.24	13.9±10.8
CST (°C)	27.99±2	26.8±2.1
WST (°C)	37.8±2.3	39.6±2.3#
CIP (°C)	13.01±8.72	10.1±8.1
HIP (°C)	43.39±10.33	46.8±2.8#
SSNCV (m/s)	48.14±3.12	44.1±6.3*
SSNamp (µA)	12.39±6.59	9.68±4.6
PMNCV (m/s)	46.04±3.62	42.7±3.8*
PMNamp (mV)	4.97±2.32	3.8±2.3
NCCA (mbars)	0.64±0.36	0.61±0.36
CNFD (no./mm ²)	37.13±6.28	25.34±4.85 [§]
CNBD (no./mm ²)	98.43±33.2	50.84±28.38 [§]
CNFL (mm/mm ²)	26.82±4.27	18.08±3.62 [§]

P<0.0001

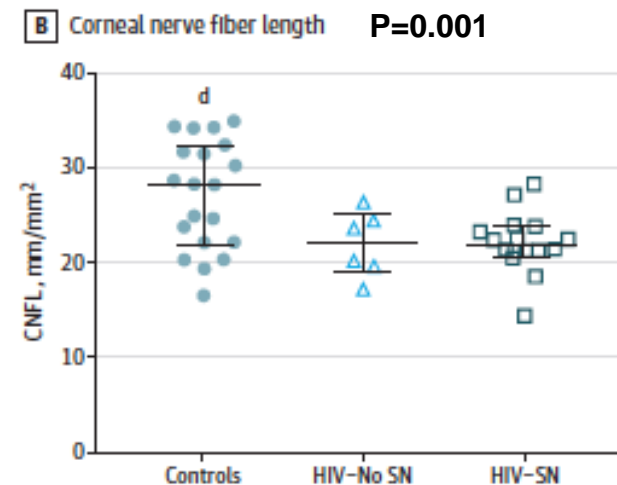
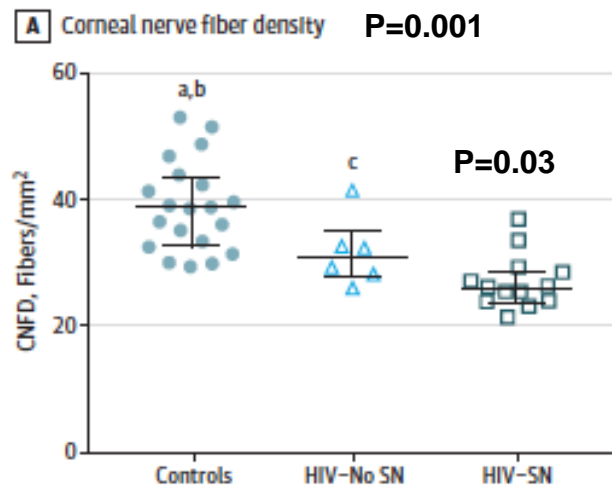
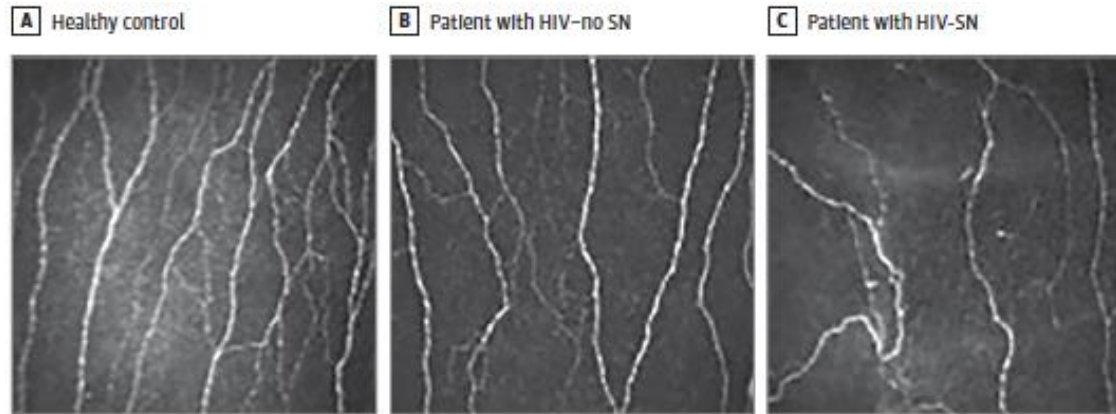


CIDP(n=82)/MGUSN (n=12)/MMN (n=6)

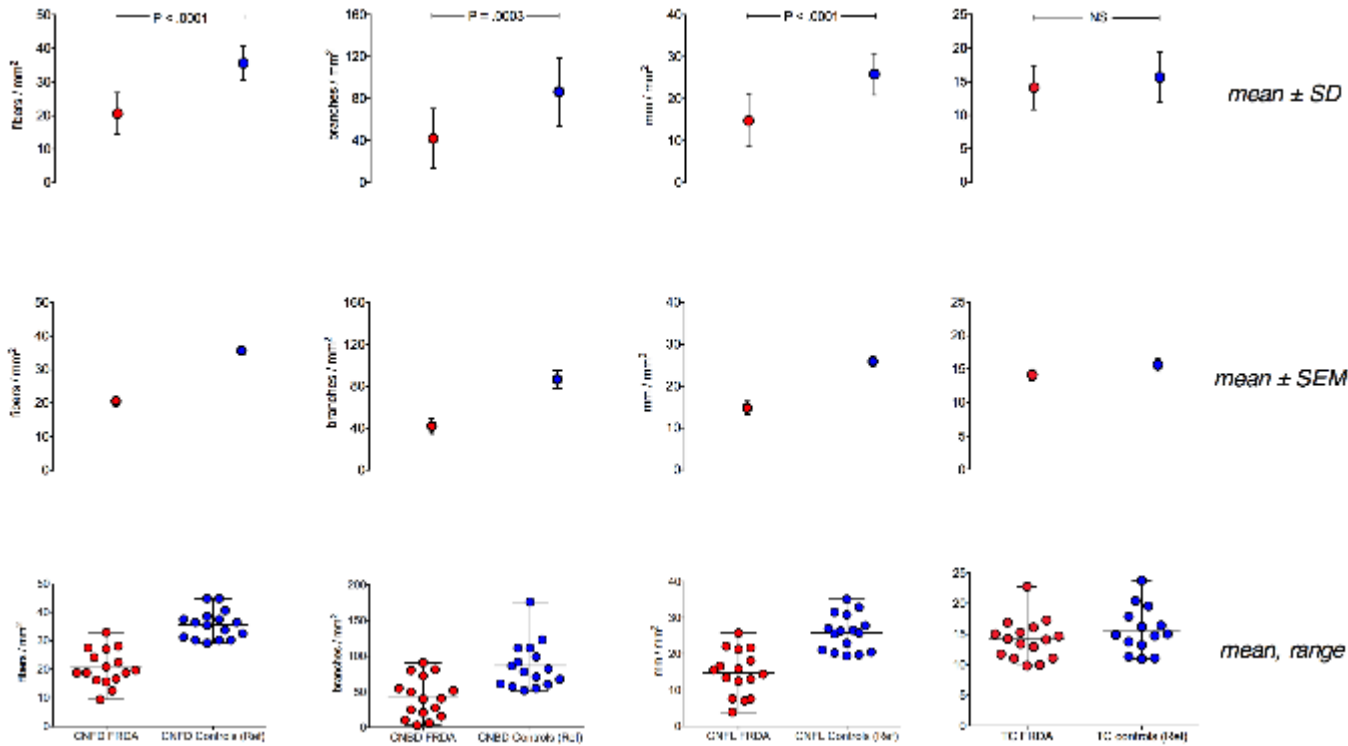
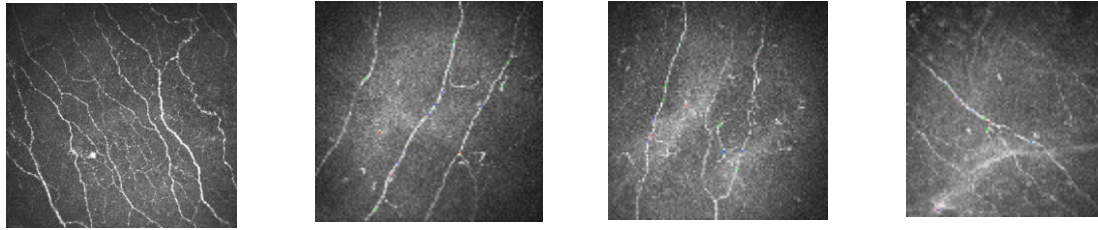


Use of Corneal Confocal Microscopy to Evaluate Small Nerve Fibers in Patients With Human Immunodeficiency Virus

Harriet I. Kemp, BM BCh, FRCA; Ioannis N. Petropoulos, PhD; Andrew S. C. Rice, MD, FRCP; Jan Vollert, MSc; Christoph Maier, MD; Dietrich Strum, MD; Marc Schargus, MD, FEBO; Tunde Peto, MD, PhD; Scott Hau, MSc, BSc; Reena Chopra, BSc; Rayaz A. Malik, MB ChB, PhD



Friedreich's Ataxia



**GAA triplet repeats
in the FXN gene
Correlates with CCM**



Other Peripheral Neuropathies

ISFN

Tavakoli et al. *Exp Neurol.* 2010;223(1):245-50.
Bucher et al. *Cornea.* 2015;34:1114-9.
Gemignani et al. *J Neurol Neurosurg Psychiatry.* 2010; 81:731-3.

HSAN/CMT1A

Mimura et al. *Curr Eye Res.* 2008;33: 940-5.
Tavakoli et al. *Muscle & Nerve* 2012; 46: 698-704.

NGFB mutation

Perini et al *J Neurophysiol.* 2016;116:425-30.

CIDP/MGUSN/MMN

Stettner M et al. *Ann Clin Transl Neurol* 2015; 3: 88-100
Schnieder et al. *J Peripher Nerv Syst.* 2014; 19:322-7
Lalive et al *Arch Neurol.* 2009; 66: 403-5..

Migraine

Kinard et al *Headache.* 2015;5:543-9.

CIPN

Ferdousi et al. *PLoS One.* 2015; 10: e0139394
Camagnolo et al. *J Peripher Nerv Syst.* 2013; 3:269-71.
Ferrari et al *Arch Neurol.* 2010 Mar;67(3):364-5.

Fabry's Disease

Tavakoli et al. *Muscle Nerve.* 2009;40(6):976-84.



Wilson's Disease

Sturniolo et al *IOVS.* 2015; 56:1390-5

Graves Disease

Kokabyoglu et al. *Cornea.* 2015;34:745-9.

HIV neuropathy

Kemp et al *Acta Ophthalmol* 2017

Amyloid Neuropathy

Sturm et al. *Case Rep Neurol.* 2016;8: 134-9.
Rousseau et al. *JAMA Ophthalmol.* 2016; 134:983-9

Fibromyalgia

Ramirez et al. *Sem Arth Rheum.* 2015;45: 214-9.
Oudejans et al. *Sci Rep.* 2016; 6: 23573.

Keratoconus

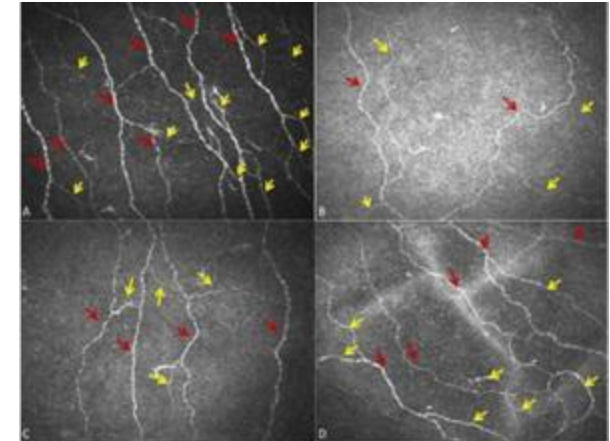
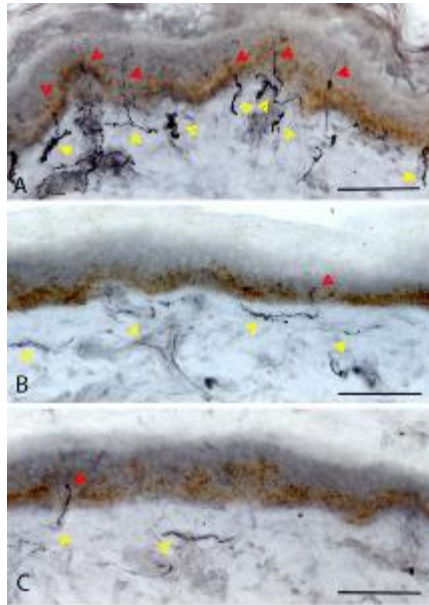
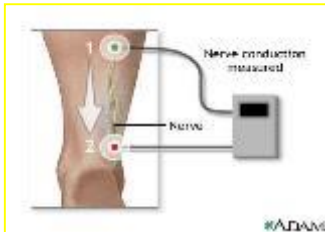
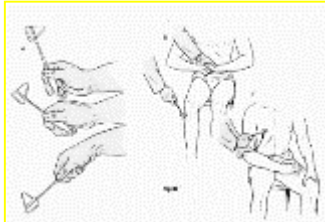
Bitirgen et al. *Int J Ophthalmol.* 2015;8:534-9.

FDA End Point?

1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. **Surrogate Endpoint: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of therapeutic intervention.**



Simultaneous Pancreas & Kidney Transplantation



Pathophysiology/Complications
ORIGINAL ARTICLE

Corneal Confocal Microscopy Detects Early Nerve Regeneration After Pancreas Transplantation in Patients With Type 1 Diabetes

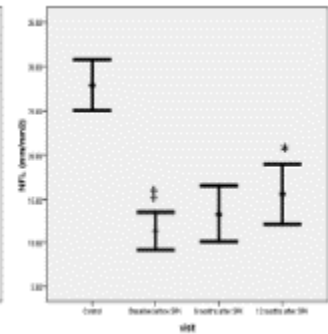
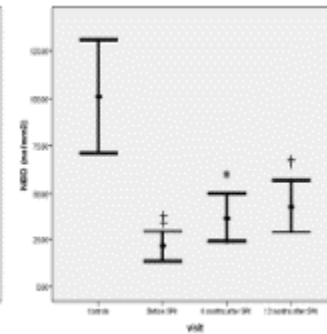
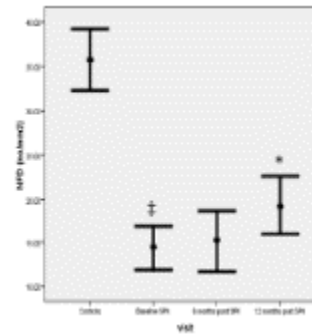
SARAY MEHRA, MD¹, MITRA TAVAKOLI, MD¹, GEORGIOS P. POURTAIBIS, MD², NATHAN EFRON, MD³, ANDREW J.M. BOULTON, MD⁴, TITUS ANGISSIMO, MD⁵, ROSE A. MALIK, MD⁶

tools that quantify predominantly large nerve fiber dysfunction, which were principally developed to aid diagnosis and not to assess nerve repair and hence a therapeutic response (1). Thus, nerve conduction

ORIGINAL ARTICLE

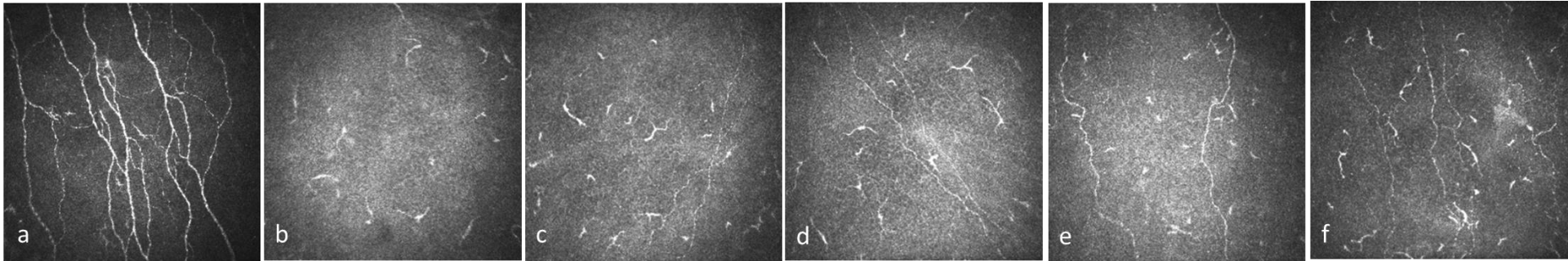
Corneal Confocal Microscopy Detects Early Nerve Regeneration in Diabetic Neuropathy After Simultaneous Pancreas and Kidney Transplantation

Mitra Tavakoli,¹ Maria Mita Petrotorian,² Ioannis N. Petropoulos,¹ Hassan Fadavi,¹ Omar Asghar,¹ Uzuman Alan,² Georgios Pourtaibis,² Maria Jezicic,³ Andy Marshall,¹ Nathan Efron,³ Andrew J. Boulton,⁴ Titus Angissimo,⁵ and Rose A. Malik⁶

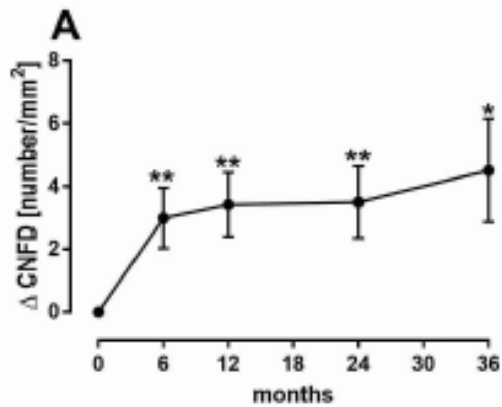


Mehra et al. Diabetes Care 2007; 30: 2608-12
Tavakoli et al. Diabetes 2013; 62: 254-60

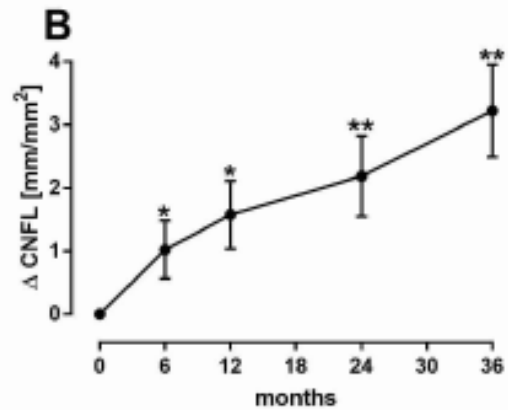
Post SPK Transplantation-3 yrs



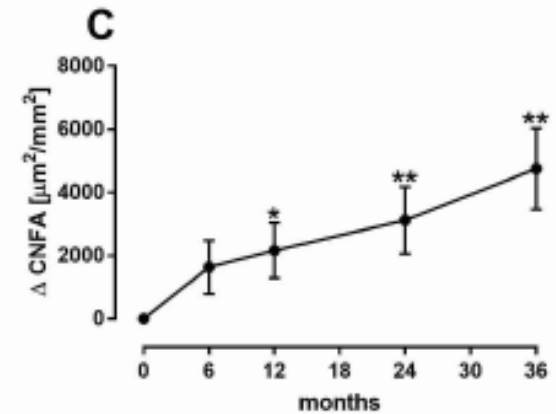
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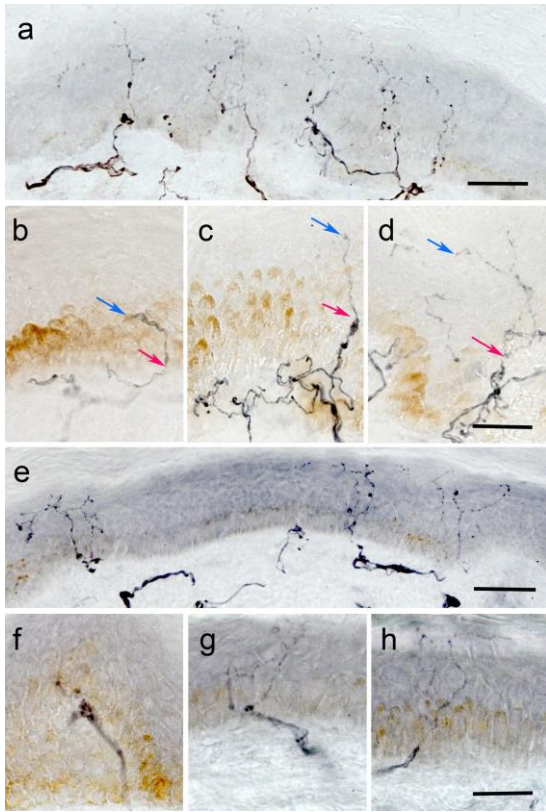


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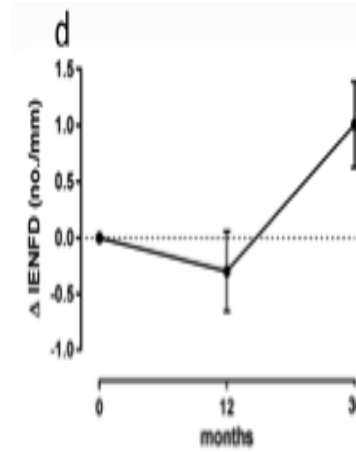


Azmi et al 2018

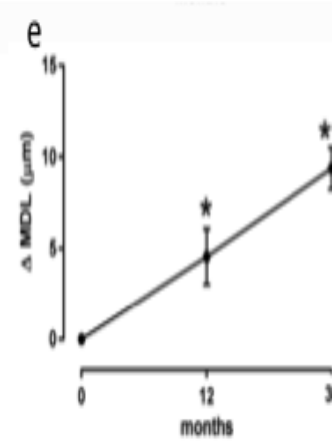
Skin Biopsy/Symptoms/Neurophysiology



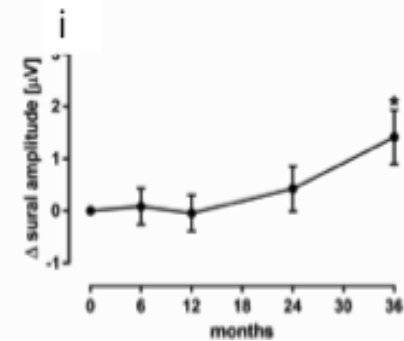
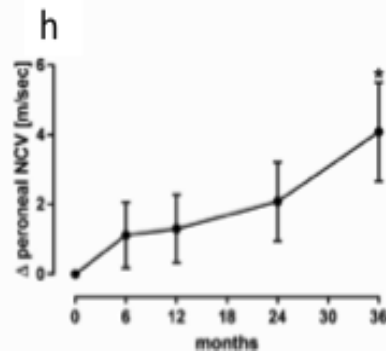
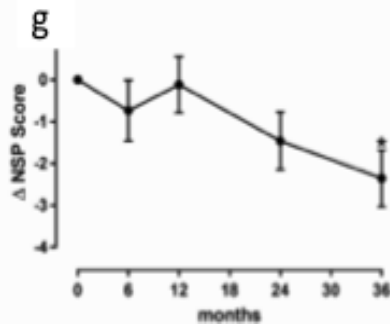
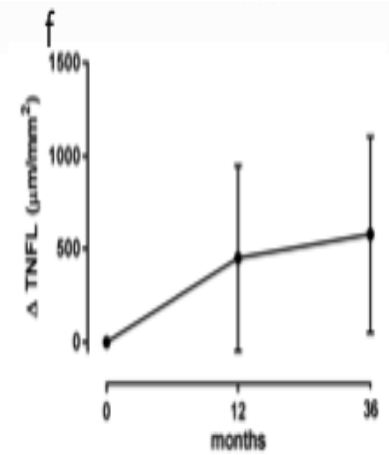
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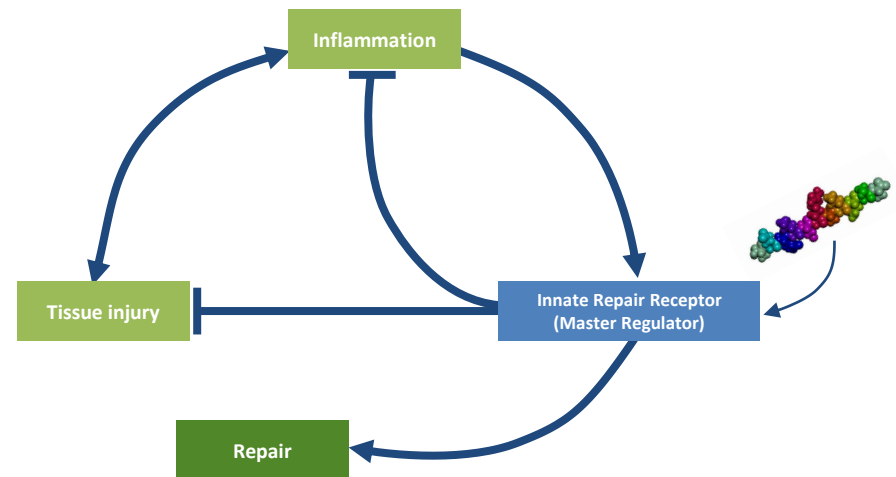
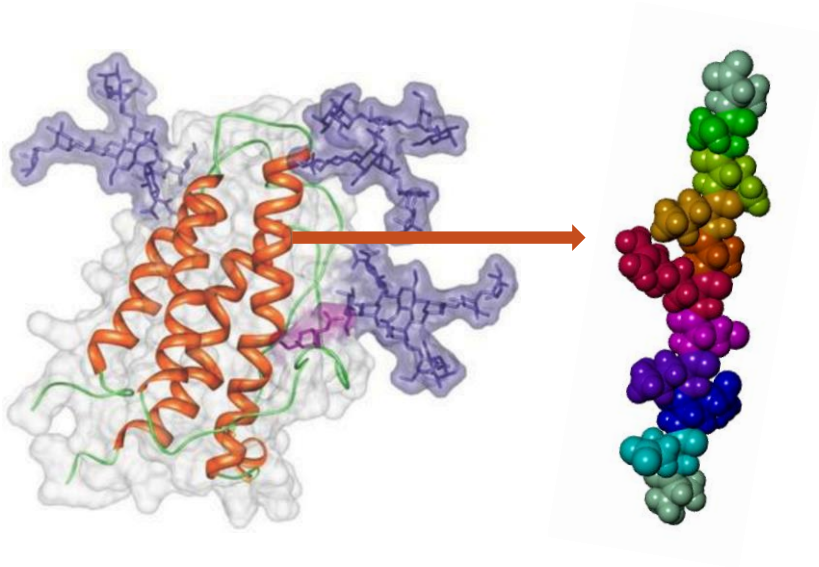
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P=0.05



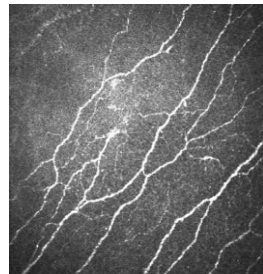
ARA 290



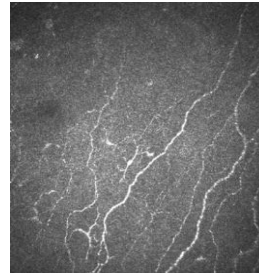
- ❑ Designed to selectively interact with the Innate Repair Receptor
- ❑ Blocks the pro-inflammatory response and activates the body's natural repair system
- ❑ Does not interact with other receptors
- ❑ Safe, with none of the thrombotic effects observed with EPO

ARA 290, a non-erythropoietic peptide engineered from erythropoietin, improves metabolic control and neuropathic symptoms in patients with type 2 diabetes.

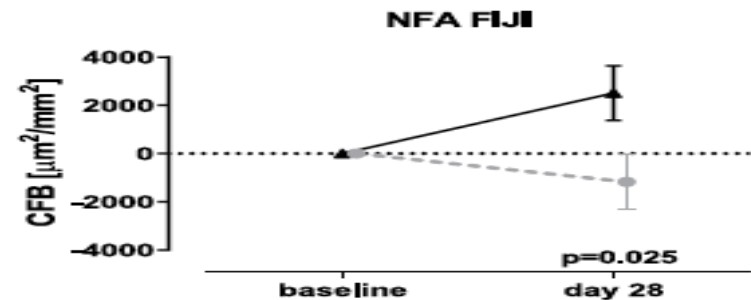
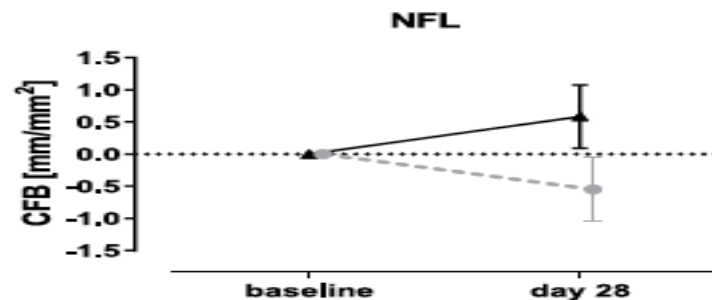
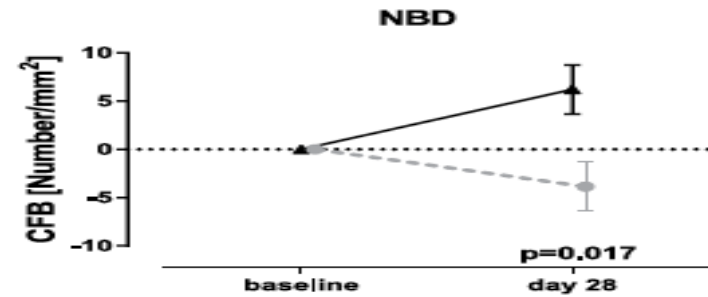
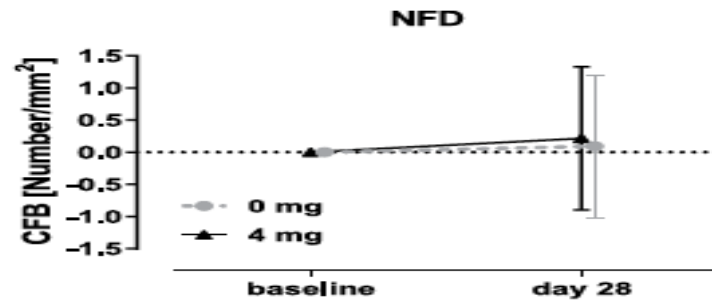
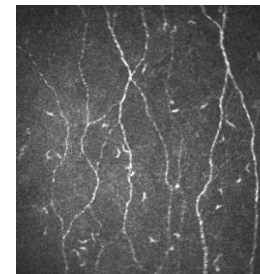
Normal control A



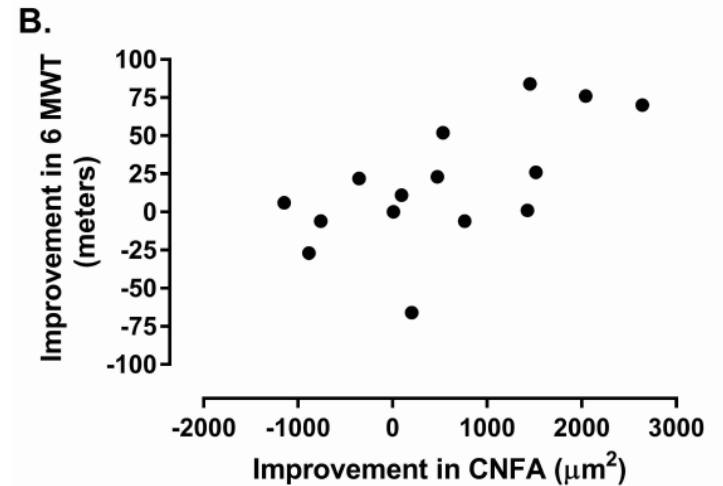
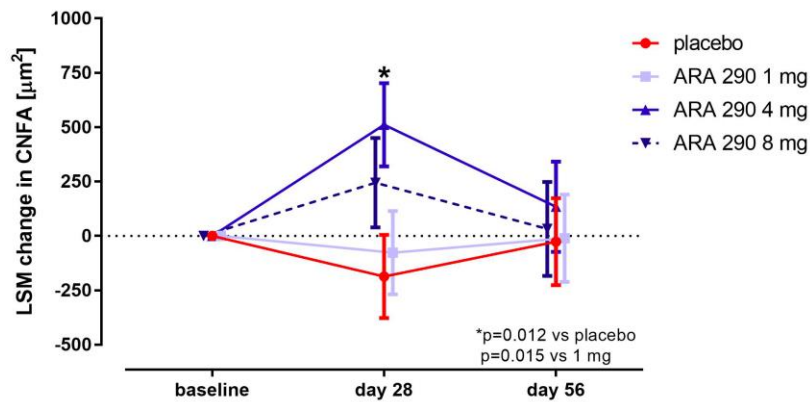
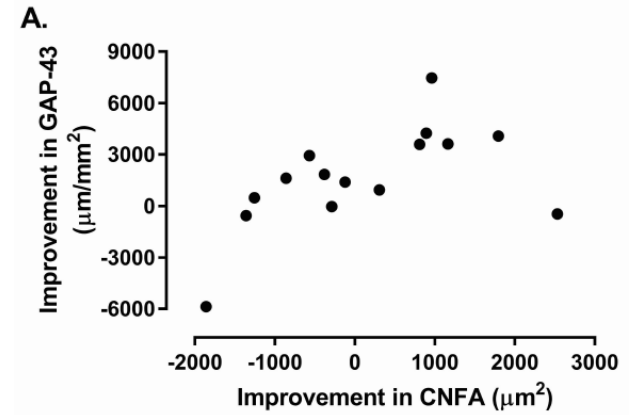
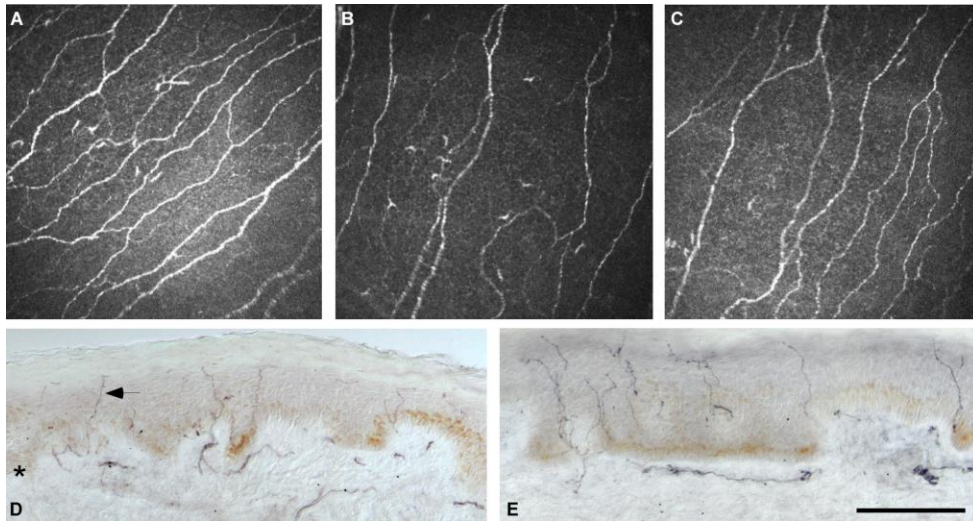
Pre-treatment C



Post-treatment C



Cibinetide improves corneal nerve fiber abundance in patients with sarcoidosis-associated small nerve fiber loss and neuropathic pain





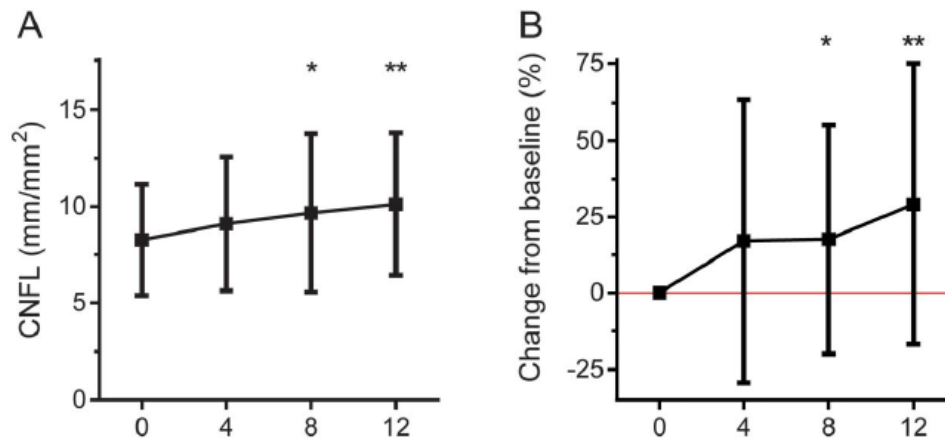
Effect of omega-3 supplementation on neuropathy in type 1 diabetes

Evan J.H. Lewis, PhD
Bruce A. Perkins, MD
Leif E. Lovblom, MSc
Richard P. Bazinet, PhD
Thomas M.S. Wolever,
DM, PhD
Vera Bril, MD

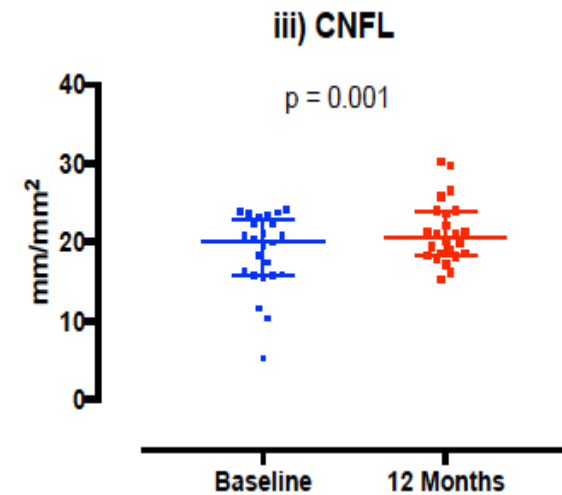
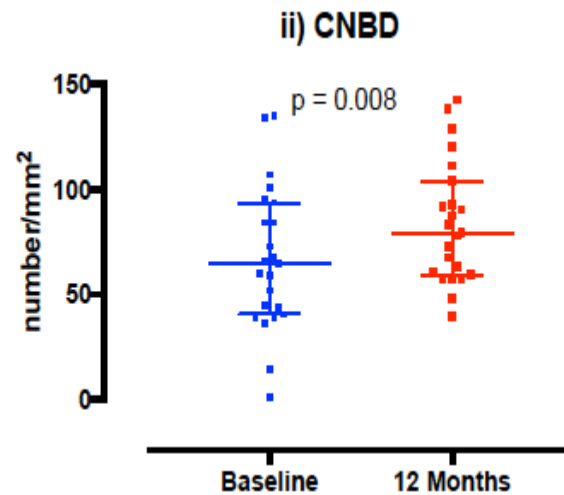
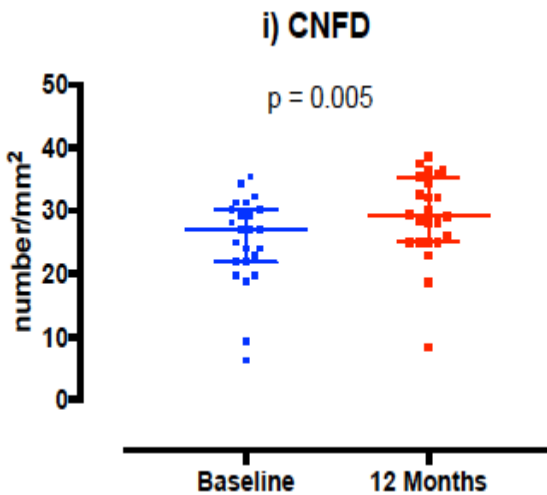
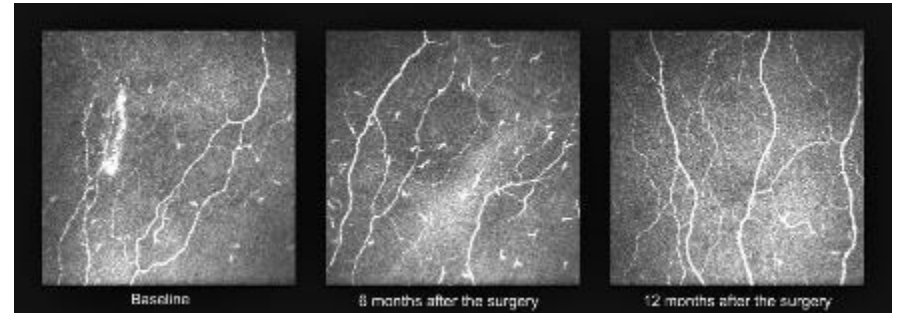
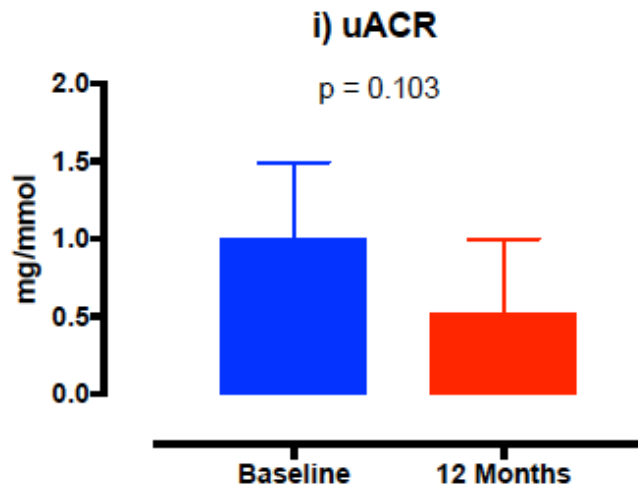
	0 months	12 months	p Value
Nerve conduction study			
Sural nerve amplitude, μV	2.7 ± 9.1	3.0 ± 6.7	0.4
Sural nerve conduction velocity, m/s	43.8 ± 11.0	44.0 ± 17.4	0.6
Peroneal nerve amplitude, ankle, mV	3.2 ± 4.6	3.4 ± 2.9	0.2
Peroneal nerve conduction velocity, fibular head, m/s+	38.8 ± 6.6	39.2 ± 6.2	0.2
Peroneal nerve F-wave, ms	55.5 ± 18.3	56.8 ± 9.9	0.06
Small and large nerve fiber function			
Cooling detection threshold, $^{\circ}\text{C}$	25.2 ± 4.7	25.4 ± 5.2	0.8
Vibration perception threshold-hand, V	4.5 ± 2.7	4.9 ± 2.2	0.06
Vibration perception threshold-toe, V	15.2 ± 8.9	16.1 ± 9.5	0.2
LDI _{FLARE} area, cm^2	1.9 ± 0.7	1.9 ± 0.6	0.6
Autonomic function			
Resting heart rate, beats/min	62 ± 7	64 ± 8	0.1
Resting heart rate, deep breathing, beats/min	62 ± 8	64 ± 9	0.4
Heart rate variability, %	16 ± 11	12 ± 8	0.01 ^a
Heart rate variability, deep breathing, %	24 ± 14	24 ± 13	0.9

Effect of omega-3 supplementation on neuropathy in type 1 diabetes

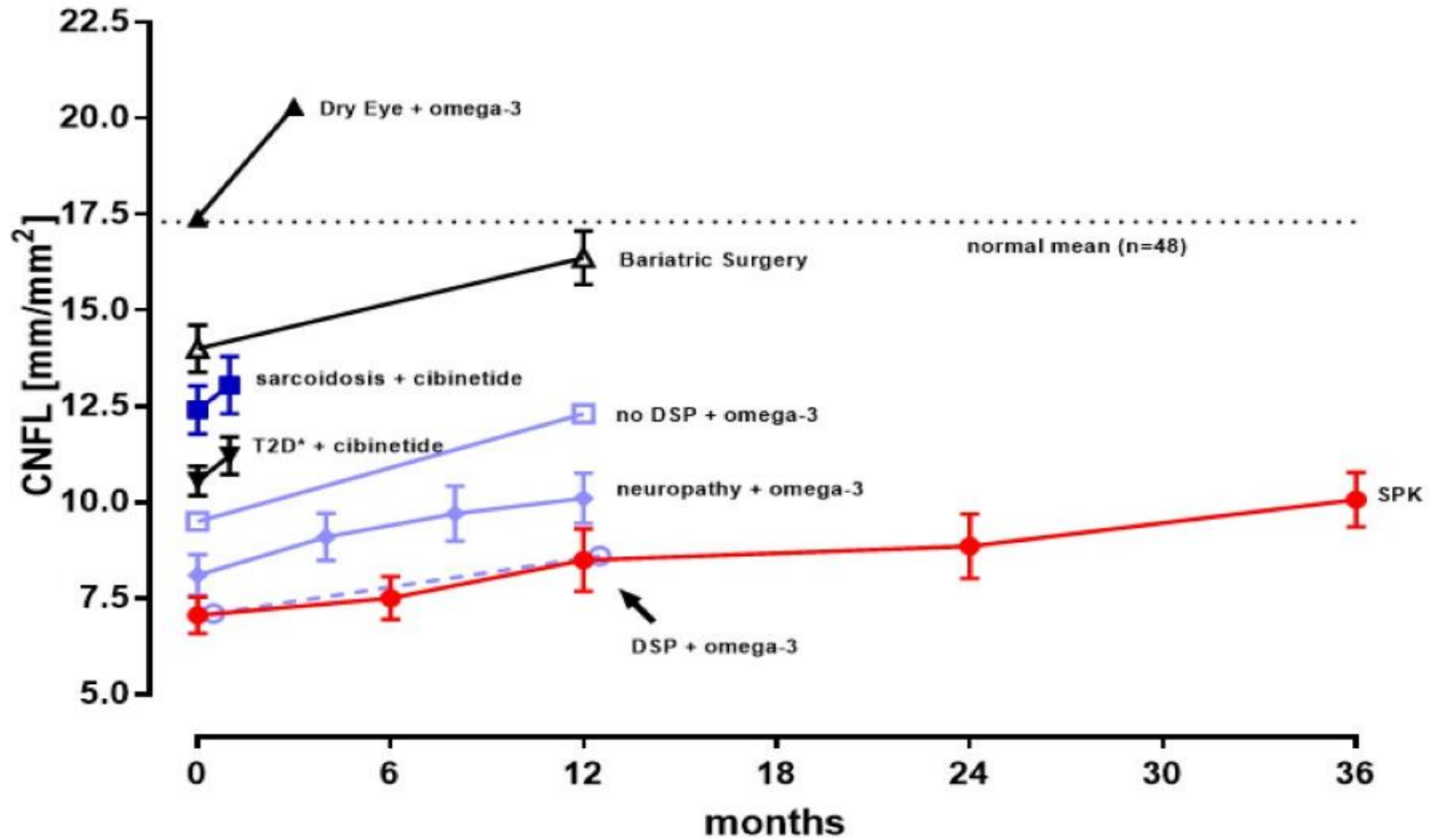
IVCCM measure	0 months	4 months	8 months	12 months	p Value
CNFL, mm/mm ²	8.1 ± 3.0	9.1 ± 3.5	9.7 ± 4.1	10.1 ± 3.7	0.002
CNBD, br/mm ²	10.6 ± 12.5	14.8 ± 17.2	16.7 ± 19.1	19.6 ± 19.7	0.03
CNFD, fib/mm ²	16.2 ± 10.7	18.8 ± 10.7	21.0 ± 12.8	23.1 ± 13.8	0.07
CNFA, mm ² /mm ²	0.0033 ± 0.0011	0.0037 ± 0.0016	0.0037 ± 0.0015	0.0039 ± 0.0015	0.07



Bariatric Surgery



8 Interventional Studies



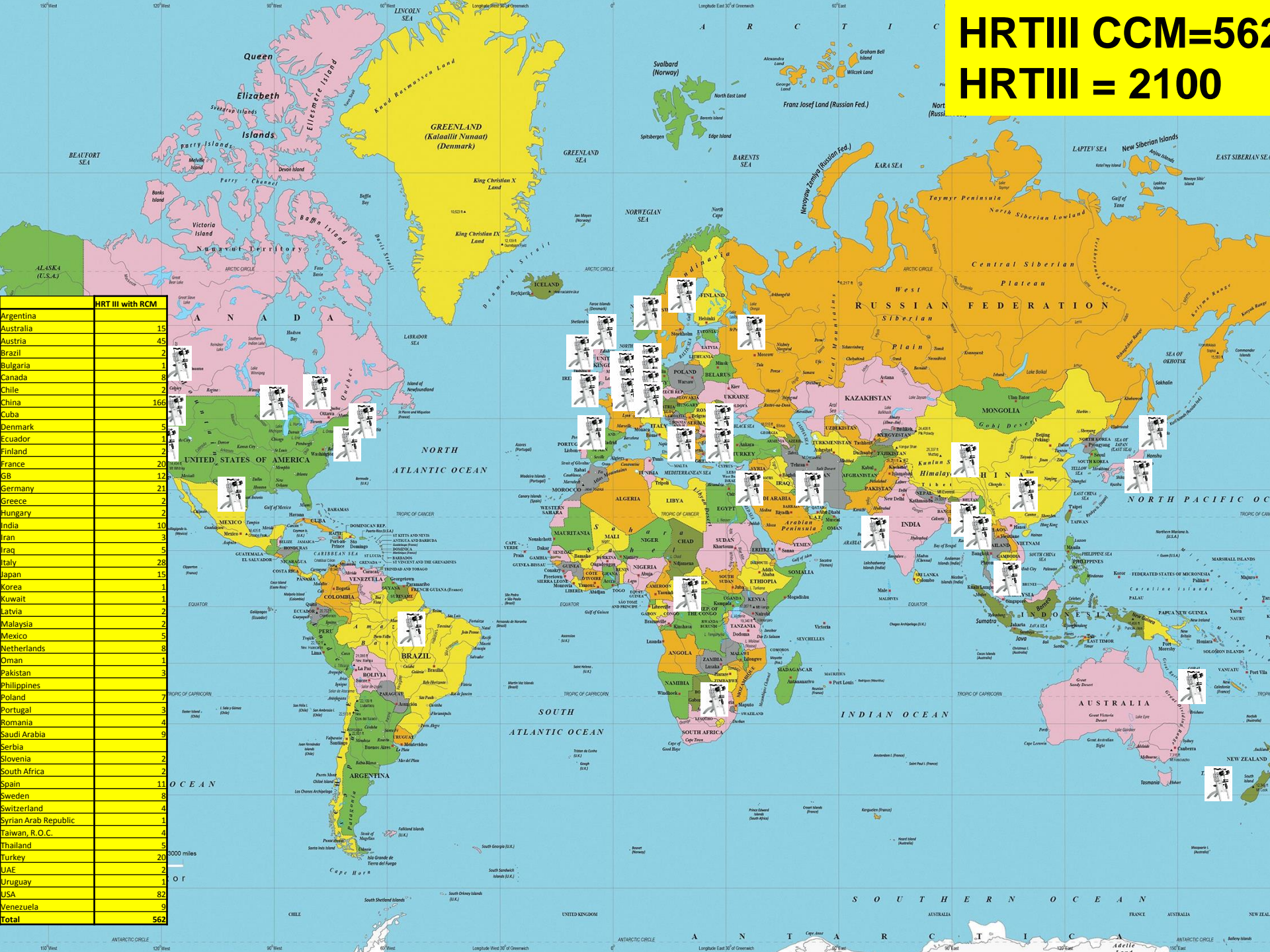
*subjects >1SD from normal

FDA End Point?

- 1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.**
- 2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.**
- 3. Surrogate Endpoint: Biomarker intended to substitute for a clinical endpoint and is expected to predict the effect of therapeutic intervention.**



HRTIII CCM=562
HRTIII = 2100



Country	HRT III with RCM
Argentina	1
Australia	15
Austria	45
Brazil	2
Bulgaria	1
Canada	8
Chile	2
China	166
Cuba	1
Denmark	5
Ecuador	1
Finland	20
France	2
GB	12
Germany	21
Greece	2
Hungary	2
India	10
Iran	3
Iraq	5
Italy	28
Japan	15
Korea	1
Kuwait	1
Latvia	2
Malaysia	2
Mexico	5
Netherlands	8
Oman	1
Pakistan	3
Philippines	1
Poland	7
Portugal	3
Romania	4
Saudi Arabia	9
Serbia	1
Slovenia	2
South Africa	1
Spain	11
Sweden	8
Switzerland	4
Syrian Arab Republic	1
Taiwan, R.O.C.	4
Thailand	5
Turkey	20
UAE	2
Uruguay	1
USA	82
Venezuela	9
Total	562

Thank you



<http://qatar-weill.cornell.edu>
<http://www.medicine.manchester.ac.uk/ena/>

P Kallinikos
M Tavakoli
C Quattrini
M Dabbah
M Mojaddidi
A Al-Sunni
U Alam
I Petropoulos
H Fadavi
O Asghar
G Ponirakis
S Ahmed
X Chen
M Ferdousi
S Azmi
M Al-Murdhi
A Kalteniece

JD Ward
AJM Boulton
PK Thomas
AK Sharma
S Tesfaye
A Veves
G Rayman
G Sundkvist
N Efron
M Jeziorska
J Graham
S Ashfaq
N Akhtar
S Kamran



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