Weill Cornell Medical College in Qatar

Qatar Foundation

Diabetic Neuropathy: Early Diagnosis and Prevention

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Qatar Foundation

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Rayaz A Malik

I DO NOT have a financial interest in commercial products or services referred to in this lecture.

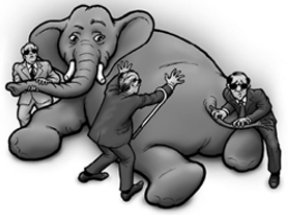
Conflict of Interest

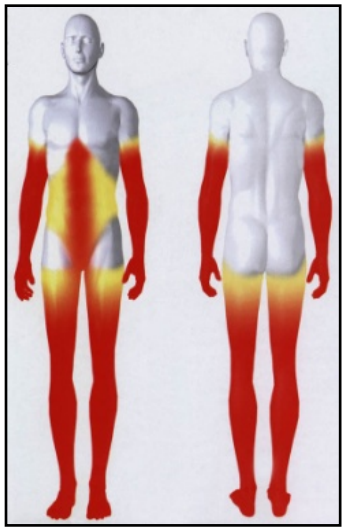
City		United
45	**Wins**	67
50	**Draws**	50
6-1 (2011)	**Biggest win**	5-0 (1994)
3	**League titles**	**20**
5	**FA Cups**	11
0	**European Cups**	3
2	**League Cups**	4

Overview

- Current Issues with Diabetic Neuropathy.
- Need for a Biomarker for DPN.
- Development of a Biomarker DPN
- Development of a Surrogate End Point for DPN.

Problem





"Progress in the development of disease modifying agents in diabetic neuropathy has completely stalled"
FDA (Feb 2013)

"Diabetic neuropathy is a nightmare
No clear endpoints, so we focus on nephropathy"
Head of late complications
Big Pharma (Sep 2012)

Failure after failure…2015

Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolr		ithdrawn (marginal effects)
	Zenare		ithdrawn (AE)
	Lidores		ithdrawn (AE)
	Fidares		ffective in phase II trials (studies halted)
	Ranires		ffective in phase II trial
	Epalres		arketed in Japan
myo-inositol ↑	*Myo*-inosi		quivocal
GLA synthesis ↓	γ-Linolen		ithdrawn (effective: deficits)
Oxidative stress ↑	α-Lipoic		ffective in RCTs (studies ongoing)
	Vitamin E		ffective in 1 RCT
Nerve hypoxia ↑	Vasodilat		
	ACE in		ffective in phase II trial
	Prostag		ffective in phase II trial
	PhVEG		ase III trial ongoing
Protein kinase C ↑	PKC-β in		ase III trial ongoing
C-peptide ↓	C-peptide		ffective in phase II trials
Neurotrophism ↓	Nerve gro		effective
	BDNF		effective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
NEG ↑	Aminoguanidine	AGE accumulation ↓	Withdrawn

PKC-B inhibitors
Alpha-lipoic acid
VEGF
Benfotiamine
……

NEG = non-enzymatic glycation; AGE = advanced glycation end products; EFA = essential fatty acids; LCFA = long-chain fatty acids; AE = adverse events; NBF = nerve blood flow; RCTs = randomized clinical trials; BDNF = brain-derived neurotrophic factor.

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.

Reviews/Commentaries/ADA Statements
REVIEW ARTICLE

Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

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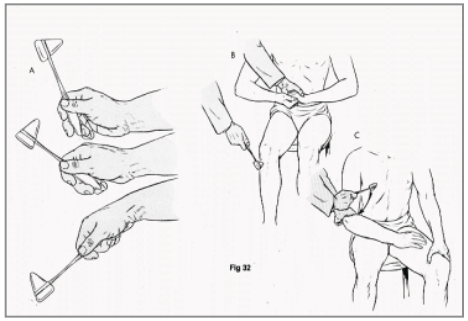
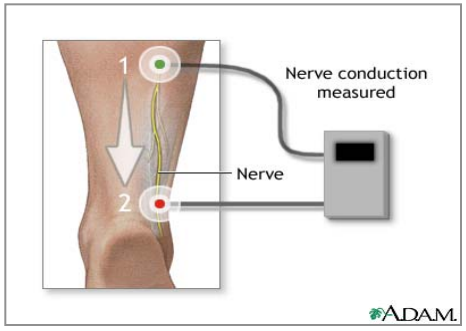
ROY FREEMAN, MD[4]
MICHAEL HOROWITZ, MD, PHD[5]
PETER KEMPLER, MD, PHD[6]
GIUSEPPE LAURIA, MD[7]
RAYAZ A. MALIK, MD[2]
VINCENZA SPALLONE, MD, PHD[8]
AARON VINIK, MD, PHD[9]
LUCIANO BERNARDI, MD[10]
PAUL VALENSI, MD[11]
ON BEHALF OF THE TORONTO DIABETIC NEUROPATHY EXPERT GROUP*

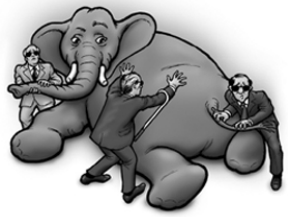
- Possible- Symptoms or Signs (⇓ sensation, reflexes).
- Probable- Symptoms & Signs.
- Confirmed- Abnormal NC + symptom(s) or sign(s).

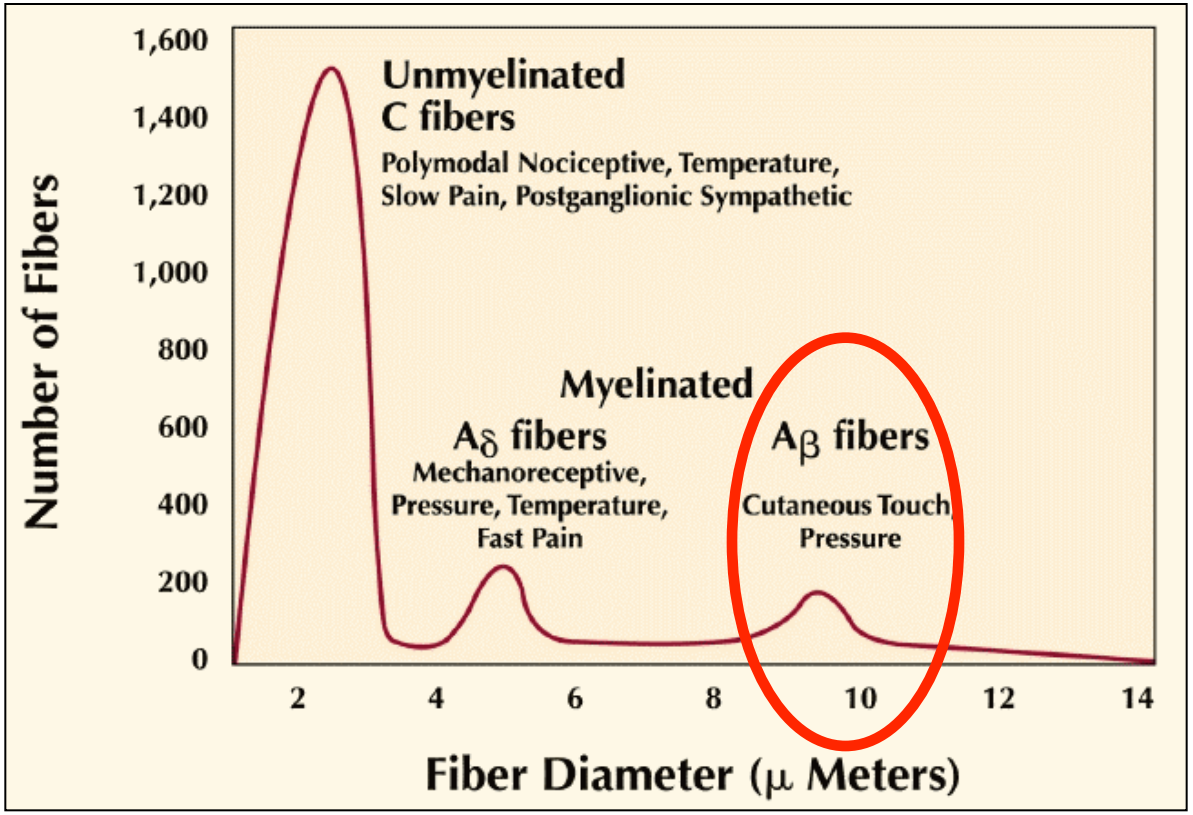


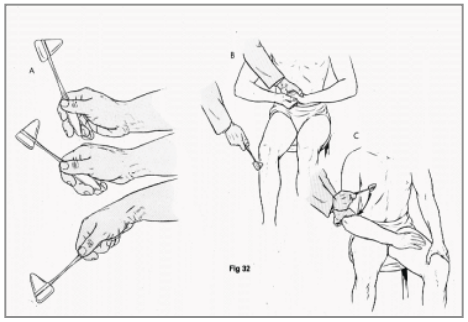


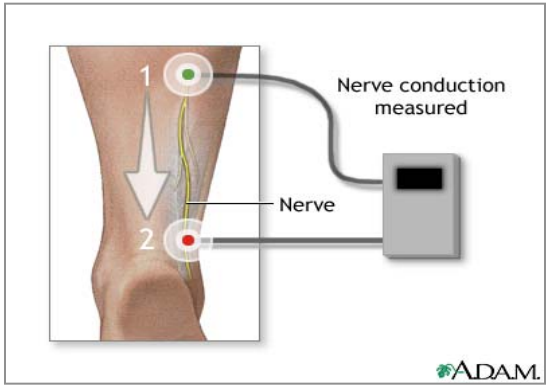
Tesfaye et al. Diabetes Care 2010; 33: 2285-2293

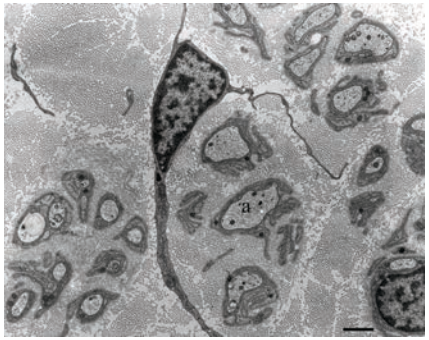
FDA: Pathological Relevance

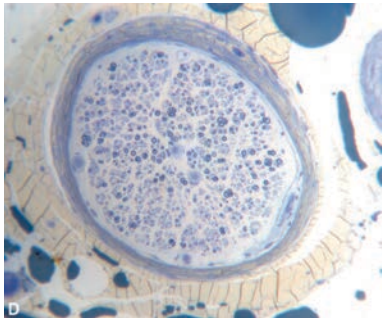




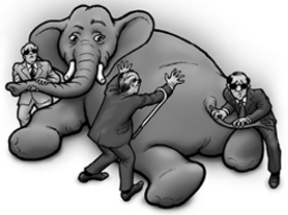






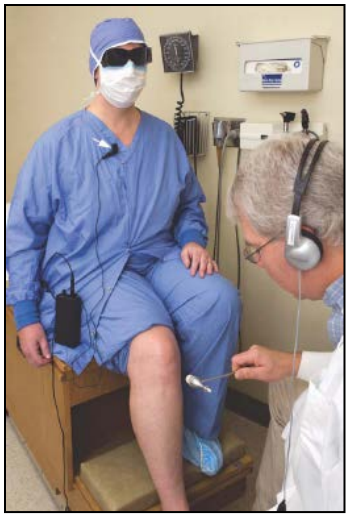


FDA: Diagnostic Utility?



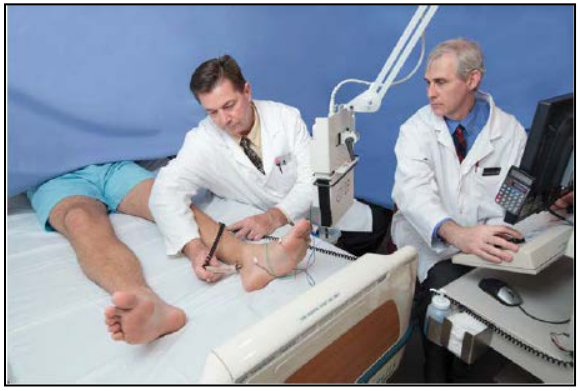
12 'experts' assessed 24 diabetic patients on consecutive days, physical features and voice disguised for symptoms and signs.

Study physician dx from signs and symptoms were excessively variable, often overestimating DSPN. Specific approaches to improving clinical proficiency should be tested.



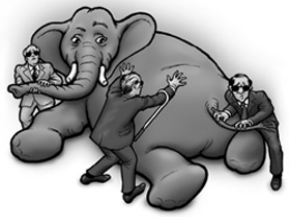
A TRIAL OF PROFICIENCY OF NERVE CONDUCTION: GREATER STANDARDIZATION STILL NEEDED

4 Expert clinical neurophysiologists, assessed NCV in 24 patients with diabetes on consecutive days. Significant inter-observer differences were seen

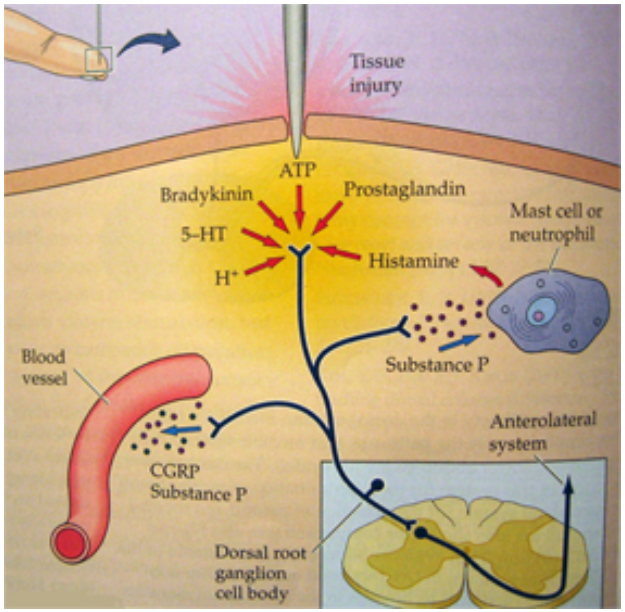


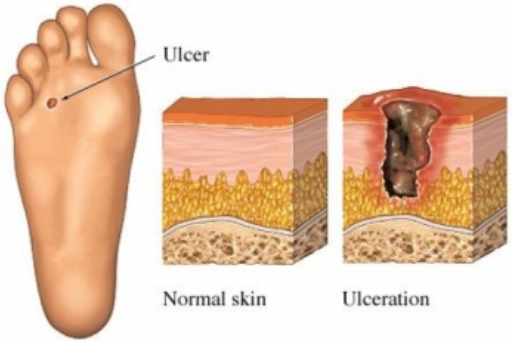
Dyck et al. Muscle Nerve 2010; 42:157–164.
Dyck et al. Muscle & Nerve 2013; 48: 369-374.

FDA: Clinical End Point



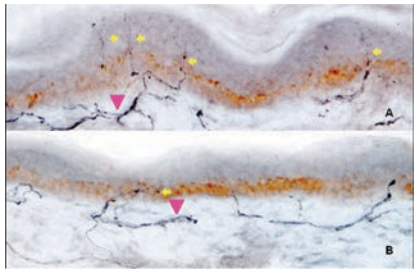
Pain, Skin Blood flow, Inflammation, Ulceration



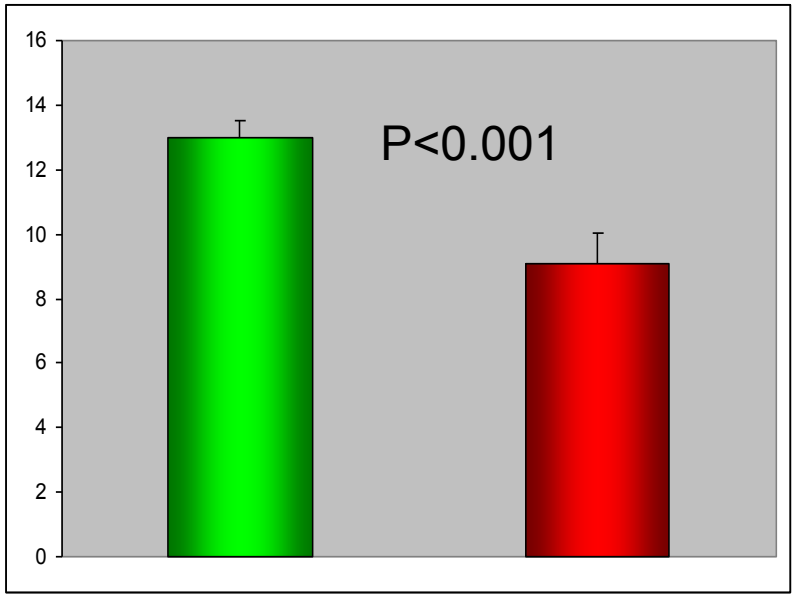


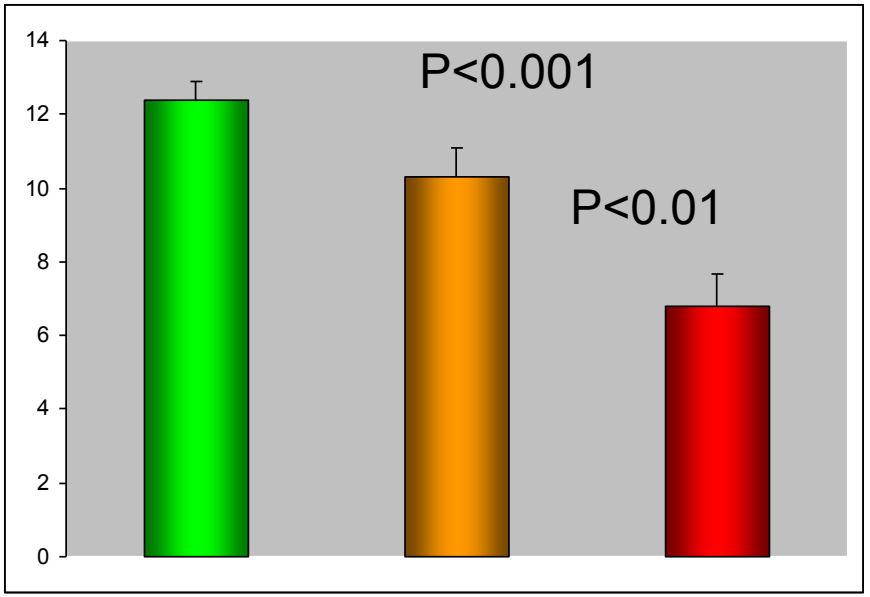
FDA: Diagnostic Utility

Normal NCS



Normal NCS





Umapathi et al. Muscle Nerve 2007 **35:** 591–598
Loseth et al. J Neurol. 2008 **255**:1197-202

Ignore Small Fibres!

As the doctors say of a wasting disease, to start with it is easy to cure but difficult to diagnose; after a time, unless it has been diagnosed and treated at the outset, it becomes easy to diagnose but difficult to cure.

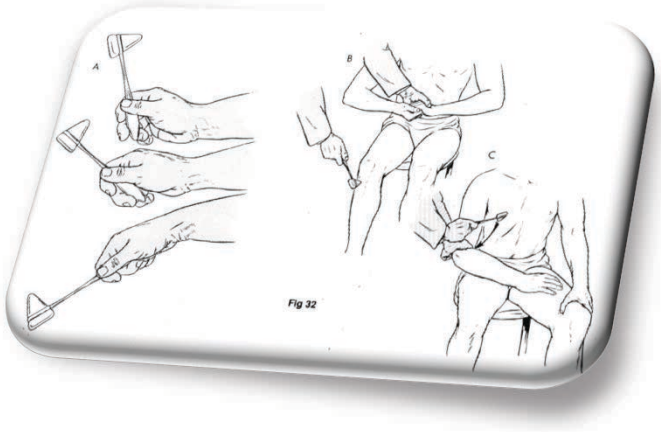
Niccolo Machiavelli
The Prince

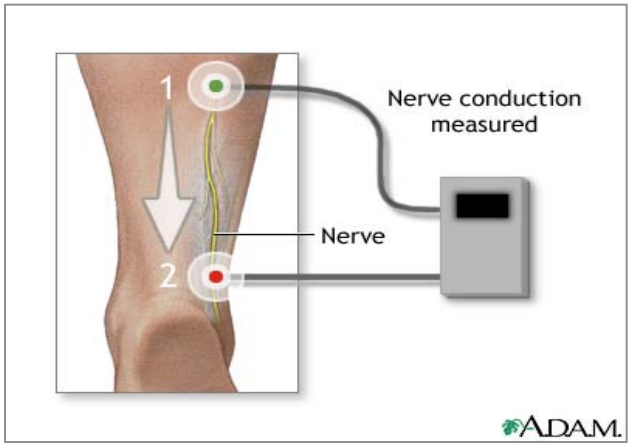
"We need to learn to measure what we value, not value what we can easily measure"

Roman Emperor & Philosopher

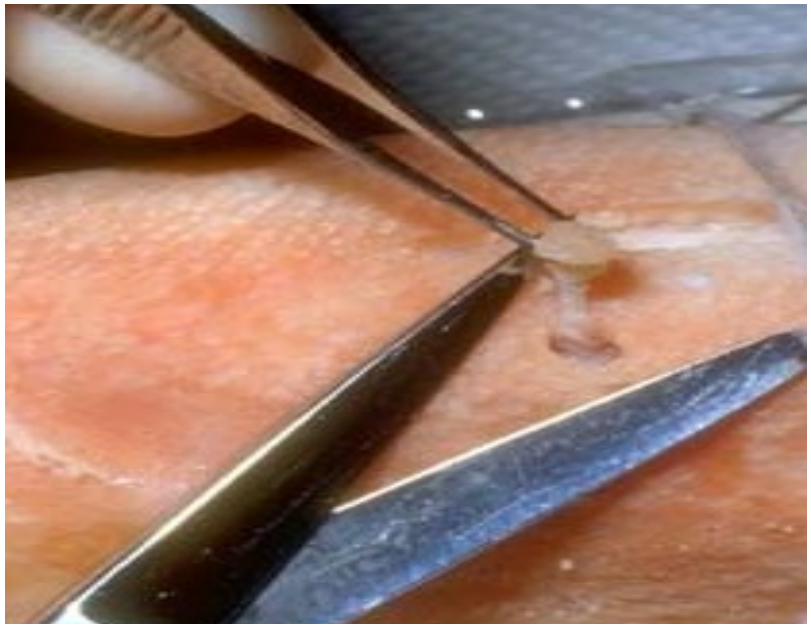
Marcus Aurelius AD 120

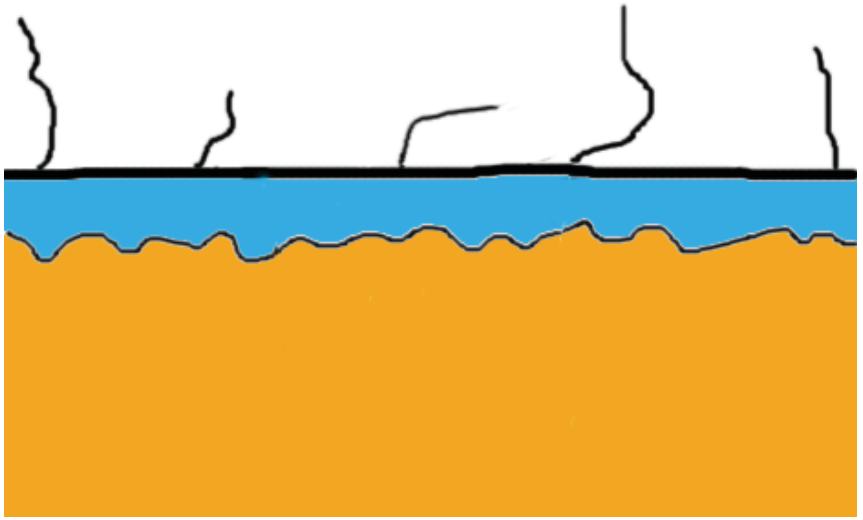
"Open mind and the courage to throw out yesterday's ideas when they don't appear to be working"



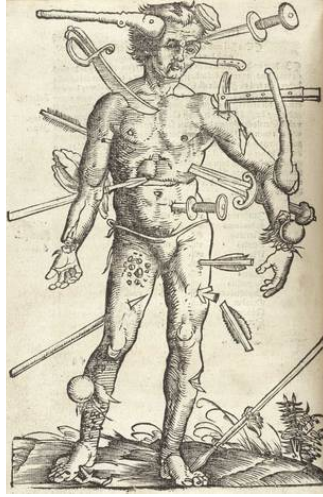


Skin Biopsy for all?





Infection/bleeding: 1.9/1000



14:00
21/05/2013

16:00
21/05/2013

20:00
22/05/2013

17:00
23/05/2013

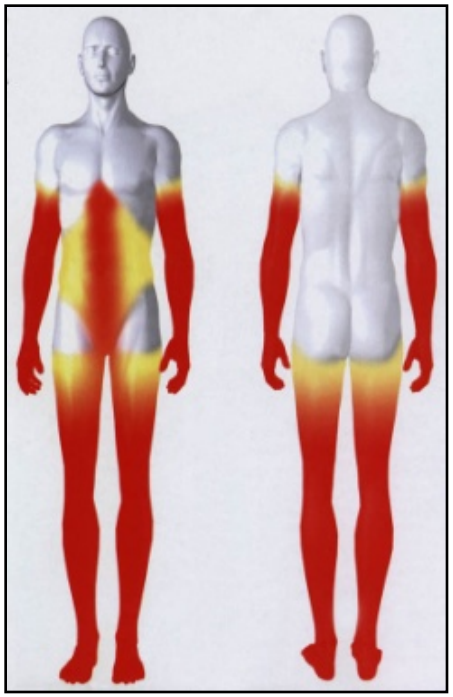
06:30
24/05/2013

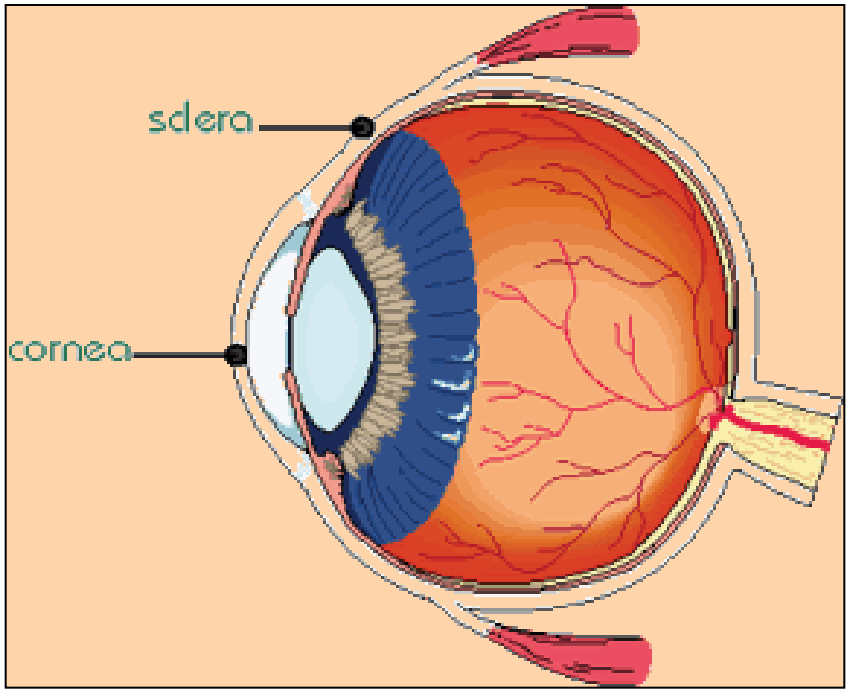
Perhaps not

Conversation with a Prof of Optometry about a Corneal confocal microscope!

Oliveira Soto & Efron: Morphology of Corneal Nerves Cornea 2001; 20: 374-384

Conventional Wisdom

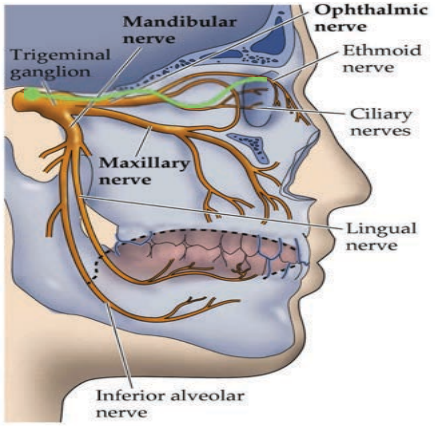




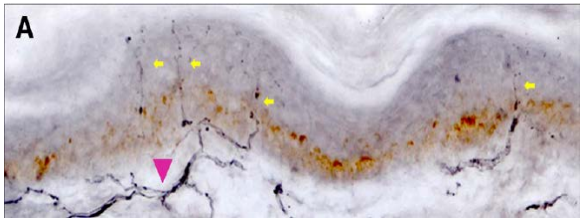
"How we think determines what we measure"
A Einstein

Anatomy

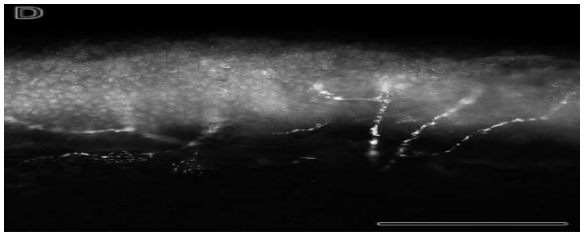
- Derived from the ophthalmic division of the Trigeminal nerve.



- Skin 200 nociceptors/mm^2.



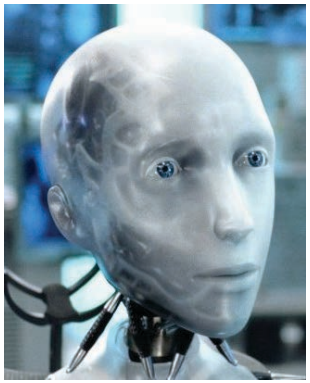
- Cornea most dense innervation in body 7000 nociceptors/mm^2.

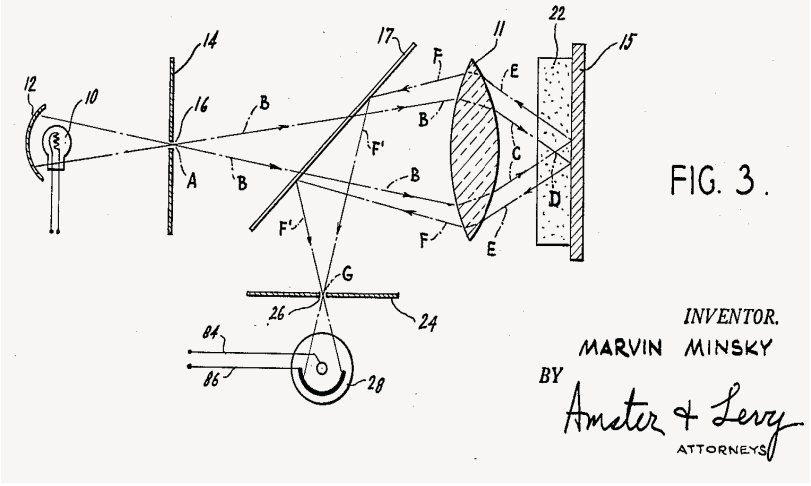


- Biopsy the Cornea!

Corneal Confocal Microscopy

- **Utilises CONFOCAL principle increases resolution (Minsky 1957).**
- **Scanning gives a wide field of view (Thomas & Christoph Cremer 1978).**
- **Cornea transparent use white light/lasers and no stains.**
- **10 um optical sectioning at x760.**



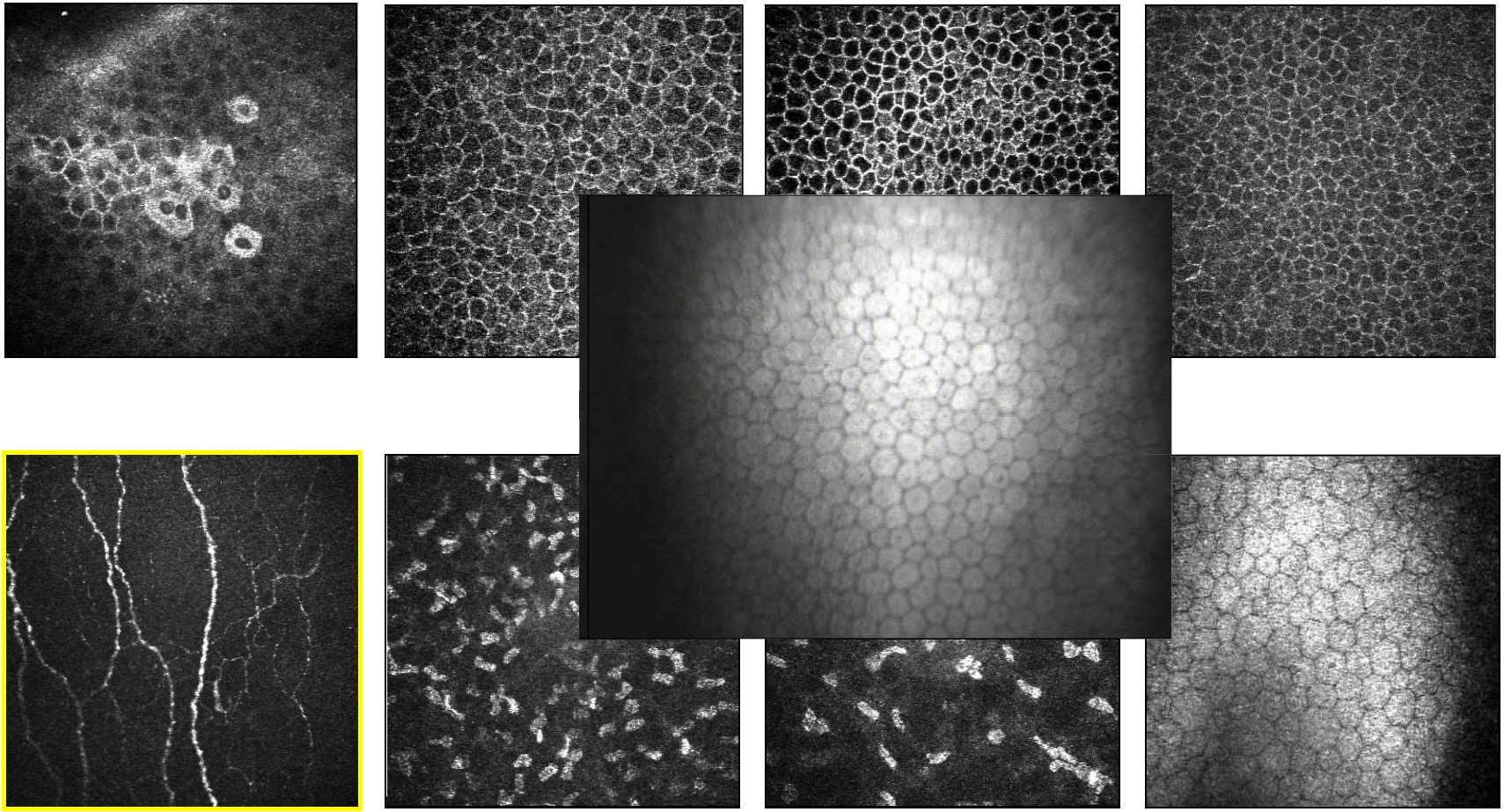


Corneal Confocal Microscopy

- Rapid (2 min)
- Non-invasive (in vivo)
- Reiterative

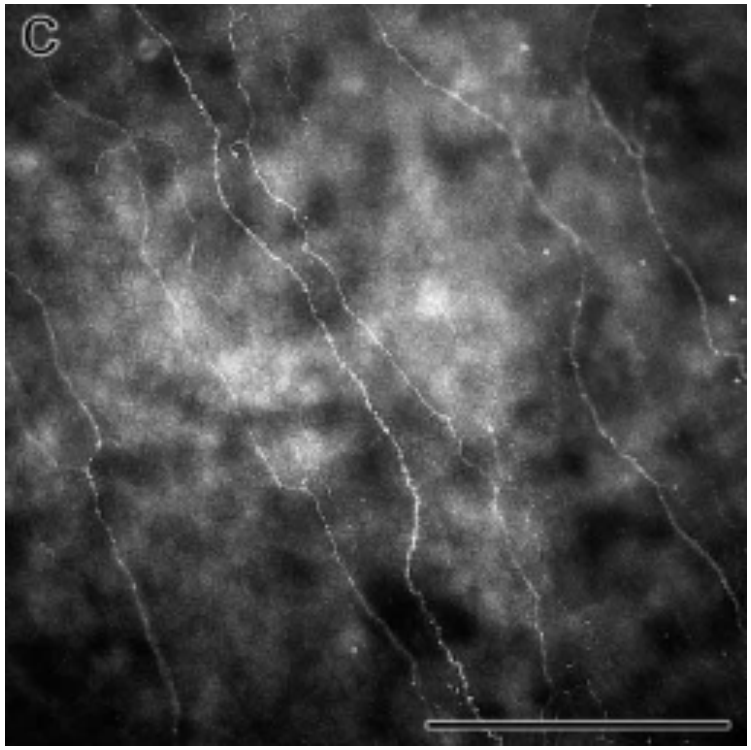
- Images Corneal Structure.

Corneal tomography



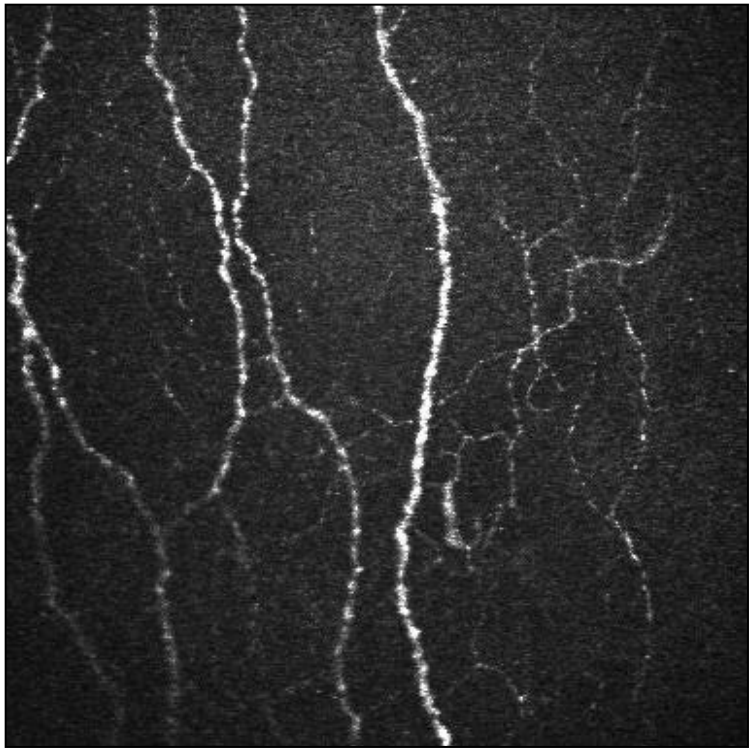
Corneal nerves

In vitro



CGRP whole mount

In vivo

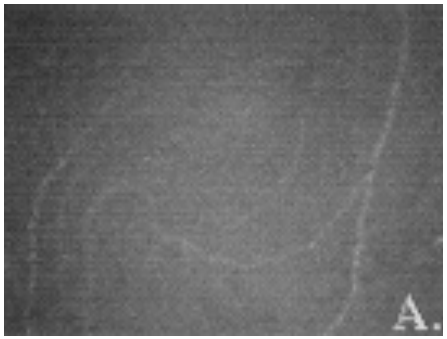


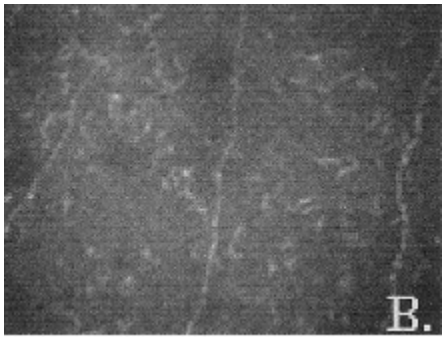
CCM

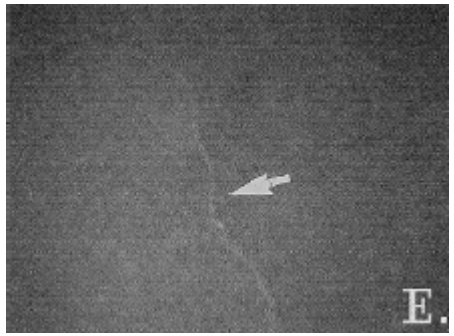
Corneal Structure and Sensitivity in Type 1 Diabetes Mellitus

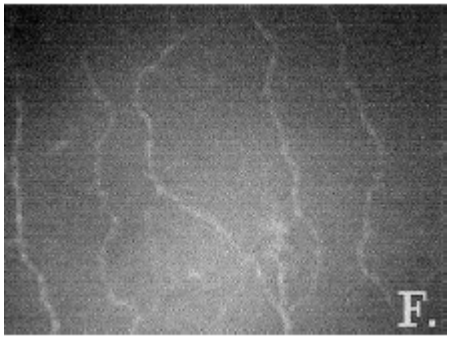
Maria E. Rosenberg,[1] Timo M. T. Tervo,[1] Ilkka J. Immonen,[1] Linda J. Müller,[2] Carola Grönhagen-Riska,[3] and Minna H. Vesaluoma[1]

From the [1]Department of Ophthalmology, University of Helsinki, Finland; [2]The Netherlands Ophthalmic Research Institute, Amsterdam, The Netherlands; and the [3]Department of Internal Medicine, Division of Nephrology, University of Helsinki, Finland.







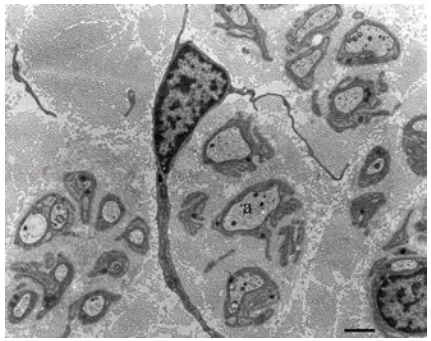


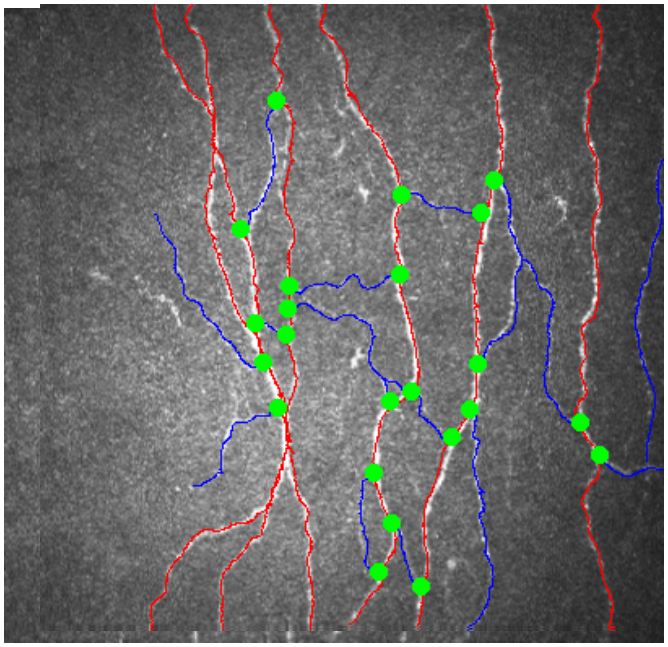
	Corneal Sensitivity (mm)	Number of Long NFBs per Image
No diabetes (n = 9)	ND	4.9 ± 1.1
No neuropathy (n = 11)	57.8 ± 4.9	4.0 ± 1.2 P = 0.067, M–W*
Mild to moderate neuropathy (n = 7)	56.9 ± 7.5 P = 0.72, M–W†	2.6 ± 1.4 P = 0.002, t-test* P = 0.035, M–W†
Severe neuropathy (n = 5)	26.0 ± 27.9 P = 0.027, M–W† P = 0.048, M–W‡	1.8 ± 0.8 P < 0.0001, t-test* P = 0.002, M–W† P = 0.30, t-test‡

Corneal Nerve Quantification

CCM (6 images/patient)

- CNFD (no./mm^2) + TC (Red)
- CNFL (mm/mm^2) (Red + Blue)
- CNBD (no./mm^2) (Green)





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

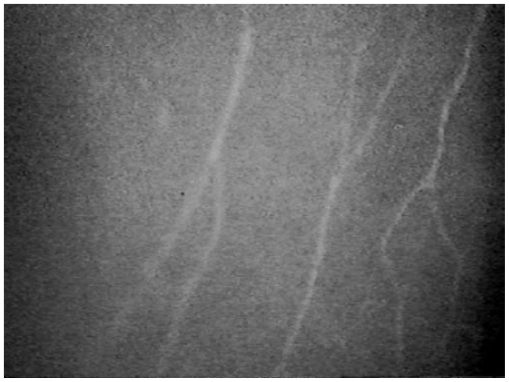
Malik et al. Diabetologia 2003; 46: 683-688
Kallinikos et al. IOVS 2004; 45: 418-422

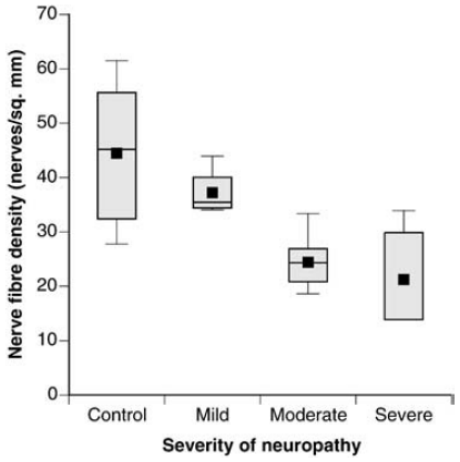
FDA End Point?

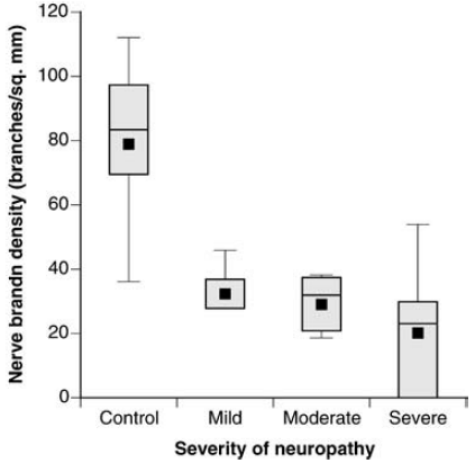
1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. Surrogate Endpoint: Biomarker intended to substitute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

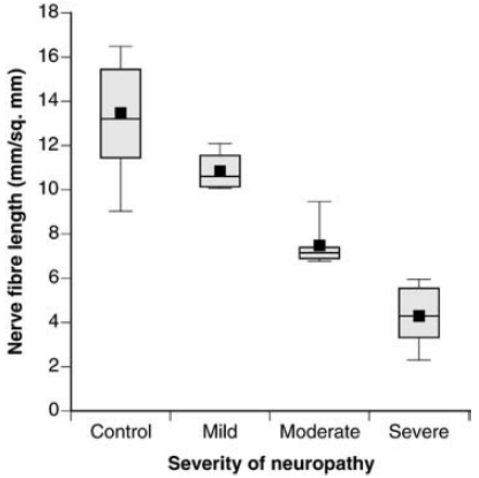
Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients

R. A. Malik[1], P. Kallinikos[2], C.A. Abbott[1], C.H.M. van Schie[1], P. Morgan[2], N. Efron[2], A. J. M. Boulton[1]



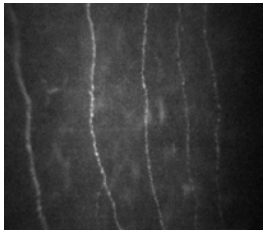


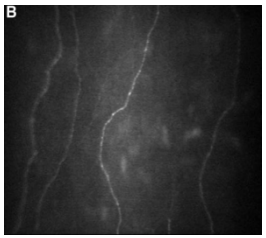


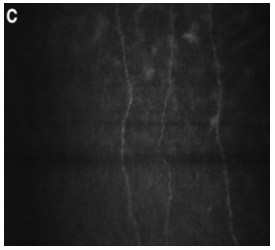


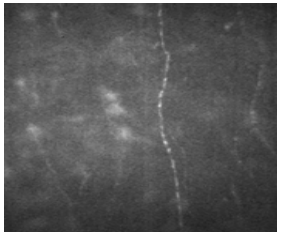
Diabetologia (2003) 46:683–688

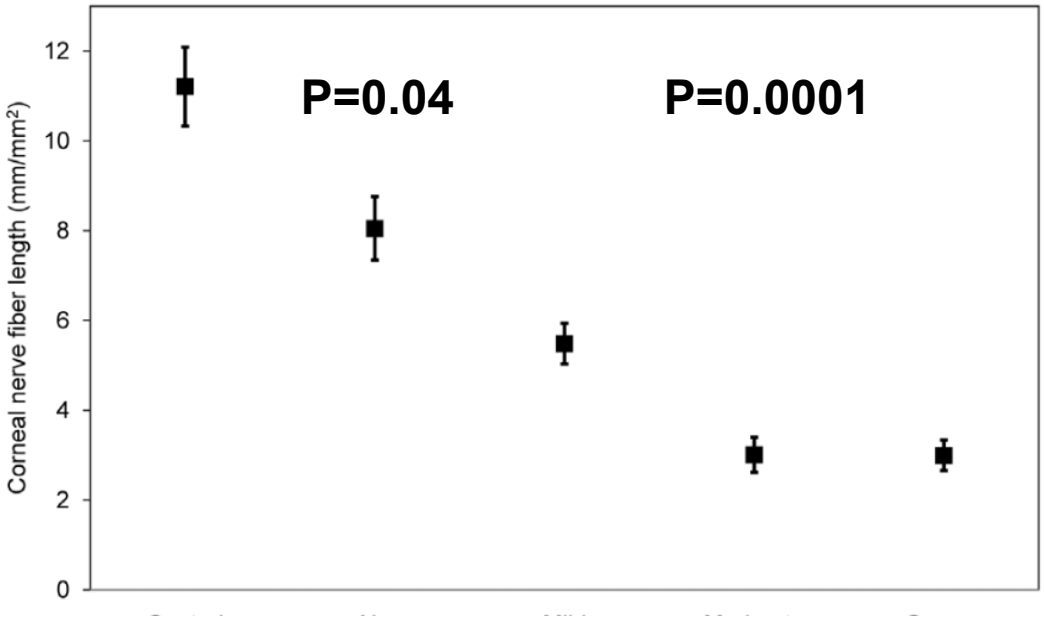
Diabetic Neuropathy









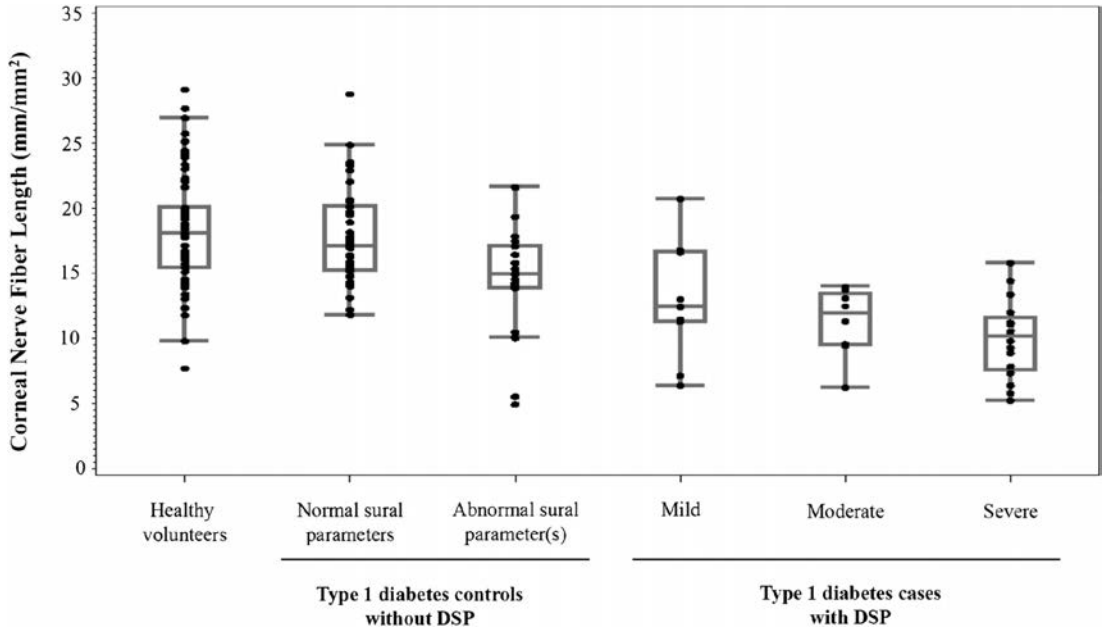


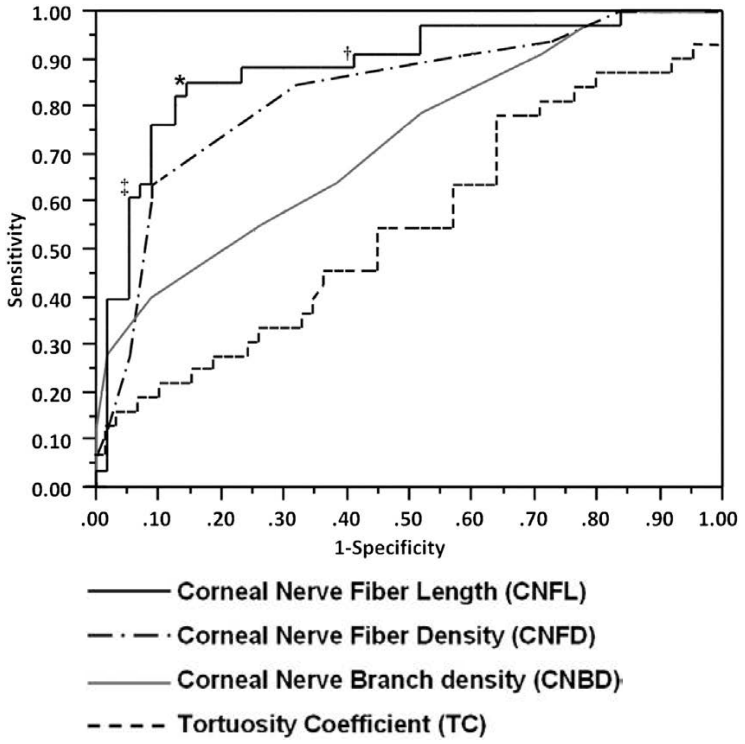
Diagnostic efficiency of corneal nerve parameters against the NDS > 5 (101 diabetic patients & 17 controls)

	NCCA(>1.01)	NFD (<31.5)	NBD (<17.5)	NFL (<8.30)
Sensitivity	70%	90%	96%	100
Specificity	51%	54%	63%	62

Tavakoli et al. Diabetes Care 2010; 33: 1792-97

Detection of Diabetic Sensorimotor Polyneuropathy by Corneal Confocal Microscopy in Type 1 Diabetes

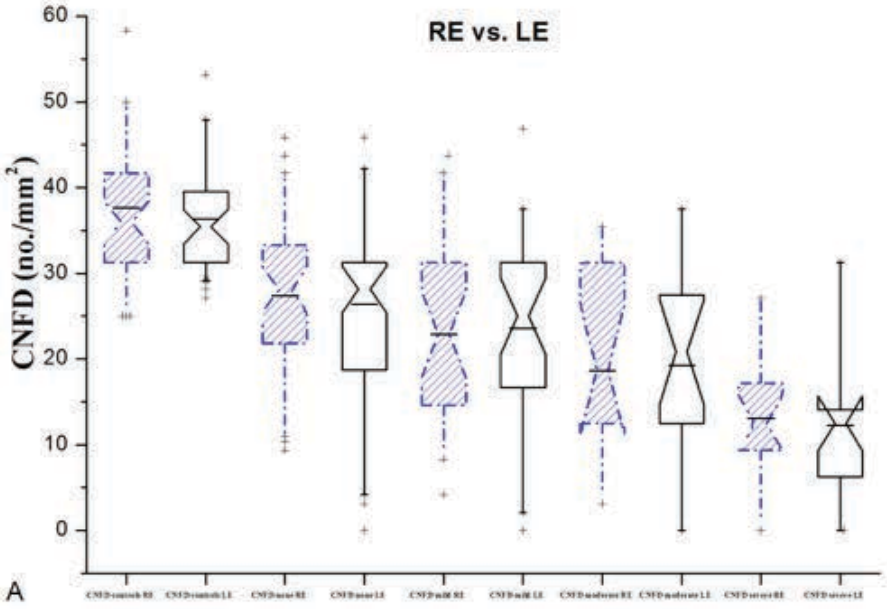


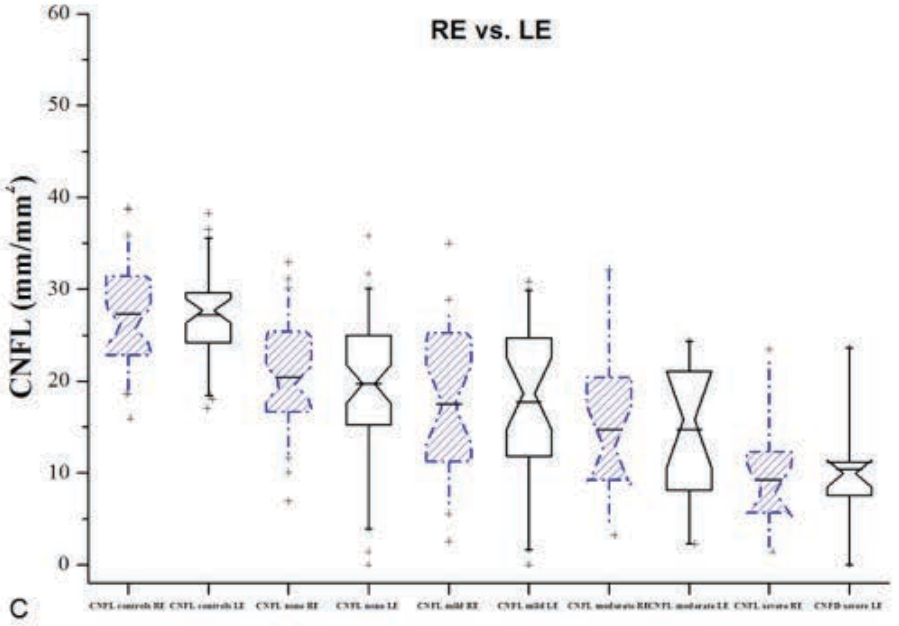


CNFL: AUC-0.88, Sensitivity-85%, Specificity-84% for DPN

Ahmed et al. Diabetes Care 2012; 35:821-828

Corneal Nerve Loss Detected With Corneal Confocal Microscopy Is Symmetrical and Related to the Severity of Diabetic Polyneuropathy



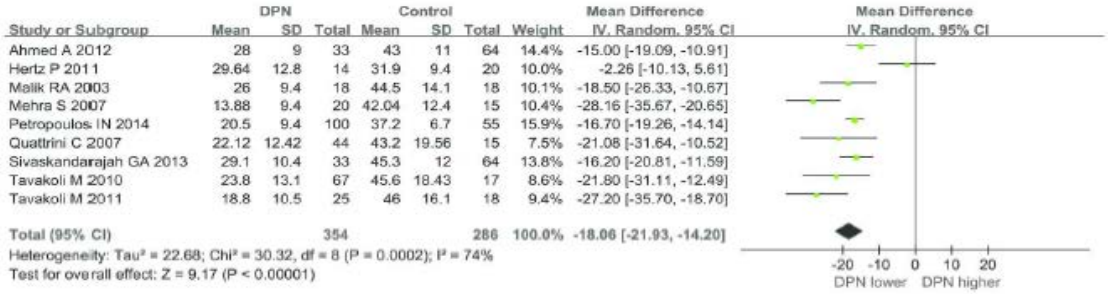


Petropoulos et al. Diabetes Care 2013; 36: 3636-3651

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

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

CNFD



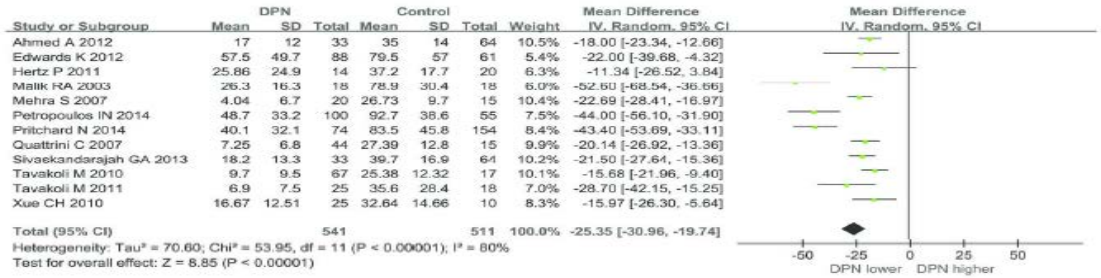
Study or Subgroup	DPN Mean	DPN SD	DPN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahmed A 2012	28	9	33	43	11	64	14.4%	-15.00 [-19.09, -10.91]
Hertz P 2011	29.64	12.8	14	31.9	9.4	20	10.0%	-2.26 [-10.13, 5.61]
Malik RA 2003	26	9.4	18	44.5	14.1	18	10.1%	-18.50 [-26.33, -10.67]
Mehra S 2007	13.88	9.4	20	42.04	12.4	15	10.4%	-28.16 [-35.67, -20.65]
Petropoulos IN 2014	20.5	9.4	100	37.2	6.7	55	15.9%	-16.70 [-19.26, -14.14]
Quattrini C 2007	22.12	12.42	44	43.2	19.56	15	7.5%	-21.08 [-31.64, -10.52]
Sivaskandarajah GA 2013	29.1	10.4	33	45.3	12	64	13.8%	-16.20 [-20.81, -11.59]
Tavakoli M 2010	23.8	13.1	67	45.6	18.43	17	8.6%	-21.80 [-31.11, -12.49]
Tavakoli M 2011	18.8	10.5	25	46	16.1	18	9.4%	-27.20 [-35.70, -18.70]
Total (95% CI)			354			286	100.0%	-18.06 [-21.93, -14.20]

Heterogeneity: Tau² = 22.68; Chi² = 30.32, df = 8 (P = 0.0002); I² = 74%
Test for overall effect: Z = 9.17 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-20 -10 0 10 20
DPN lower DPN higher

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

CNBD



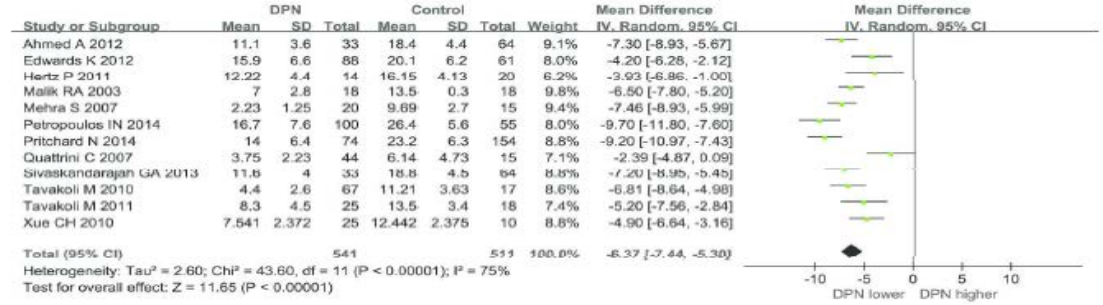
Study or Subgroup	DPN Mean	DPN SD	DPN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahmed A 2012	17	12	33	35	14	64	10.5%	-18.00 [-23.34, -12.66]
Edwards K 2012	57.5	49.7	88	79.5	57	61	5.4%	-22.00 [-39.68, -4.32]
Hertz P 2011	25.86	24.9	14	37.2	17.7	20	6.3%	-11.34 [-26.52, 3.84]
Malik RA 2003	26.3	16.3	18	78.9	30.4	18	6.0%	-52.60 [-68.54, -36.66]
Mehra S 2007	4.04	6.7	20	26.73	9.7	15	10.4%	-22.69 [-28.41, -16.97]
Petropoulos IN 2014	48.7	33.2	100	92.7	38.6	55	7.5%	-44.00 [-56.10, -31.90]
Pritchard N 2014	40.1	32.1	74	83.5	45.8	154	8.4%	-43.40 [-53.69, -33.11]
Quattrini C 2007	7.25	6.8	44	27.39	12.8	15	9.9%	-20.14 [-26.92, -13.36]
Sivaskandarajah GA 2013	18.2	13.3	33	39.7	16.9	64	10.2%	-21.50 [-27.64, -15.36]
Tavakoli M 2010	9.7	9.5	67	25.38	12.32	17	10.1%	-15.68 [-21.96, -9.40]
Tavakoli M 2011	6.9	7.5	25	35.6	28.4	18	7.0%	-28.70 [-42.15, -15.25]
Xue CH 2010	16.67	12.51	25	32.64	14.66	10	8.3%	-15.97 [-26.30, -5.64]
Total (95% CI)			541			511	100.0%	-25.35 [-30.96, -19.74]

Heterogeneity: Tau² = 70.60; Chi² = 53.95, df = 11 (P < 0.00001); I² = 80%
Test for overall effect: Z = 8.85 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-50 -25 0 25 50
DPN lower DPN higher

C v DPN P<0.00001
DPN v no-DPN, P<0.0001
C v no-DPN P<0.02

CNFL



Study or Subgroup	DPN Mean	DPN SD	DPN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahmed A 2012	11.1	3.6	33	18.4	4.4	64	9.1%	-7.30 [-8.93, -5.67]
Edwards K 2012	15.9	6.6	88	20.1	6.2	61	8.0%	-4.20 [-6.28, -2.12]
Hertz P 2011	12.22	4.4	14	16.15	4.13	20	6.2%	-3.93 [-6.86, -1.00]
Malik RA 2003	7	2.8	18	13.5	0.3	18	9.8%	-6.50 [-7.80, -5.20]
Mehra S 2007	2.23	1.25	20	9.69	2.7	15	9.4%	-7.46 [-8.93, -5.99]
Petropoulos IN 2014	16.7	7.6	100	26.4	5.6	55	8.0%	-9.70 [-11.80, -7.60]
Pritchard N 2014	14	6.4	74	23.2	6.3	154	8.8%	-9.20 [-10.97, -7.43]
Quattrini C 2007	3.75	2.23	44	6.14	4.73	15	7.1%	-2.39 [-4.87, 0.09]
Sivaskandarajah GA 2013	11.6	4	33	18.8	4.5	64	8.8%	-7.20 [-8.96, -5.45]
Tavakoli M 2010	4.4	2.6	67	11.21	3.63	17	8.6%	-6.81 [-8.64, -4.98]
Tavakoli M 2011	8.3	4.5	25	13.5	3.4	18	7.4%	-5.20 [-7.56, -2.84]
Xue CH 2010	7.541	2.372	25	12.442	2.375	10	8.8%	-4.90 [-6.64, -3.16]
Total (95% CI)			541			511	100.0%	-6.37 [-7.44, -5.30]

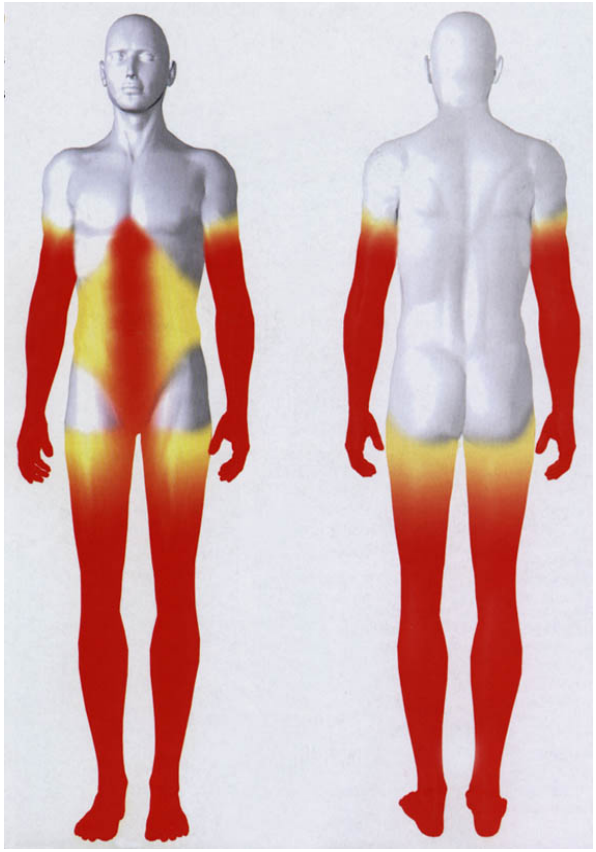
Heterogeneity: Tau² = 2.60; Chi² = 43.60, df = 11 (P < 0.00001); I² = 75%
Test for overall effect: Z = 11.65 (P < 0.00001)

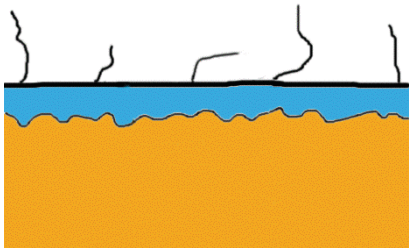
Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
DPN lower DPN higher

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

NIH: $750k

Prove that CCM is as good as Skin Biopsies!

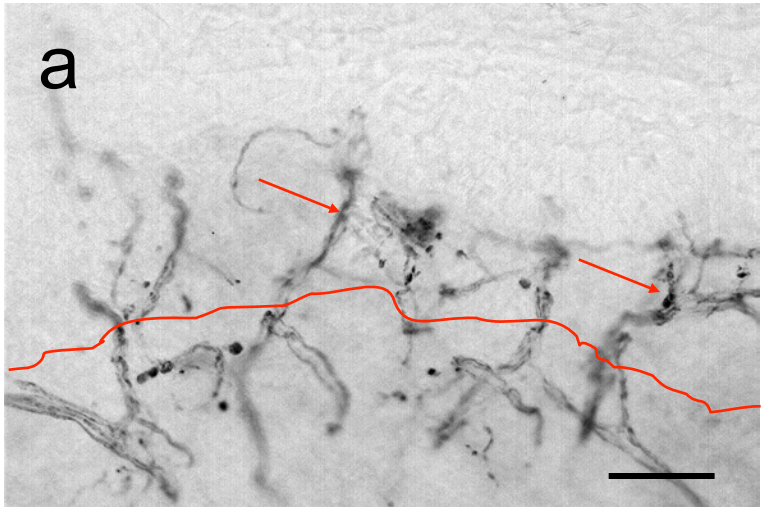


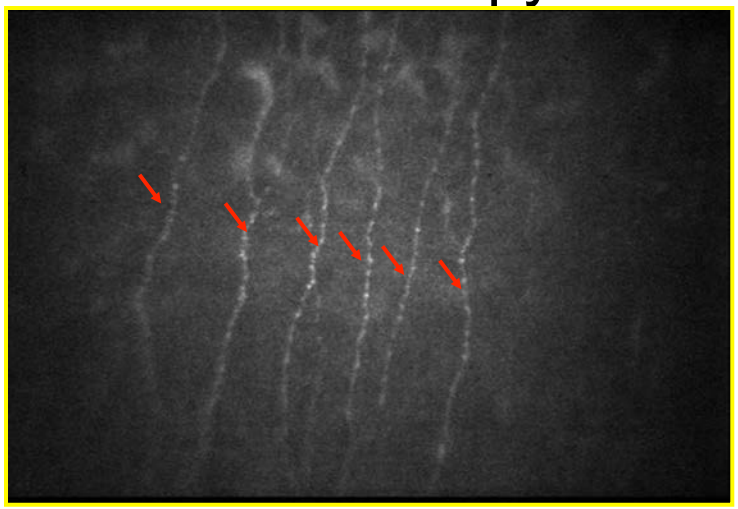


Skin biopsy v CCM

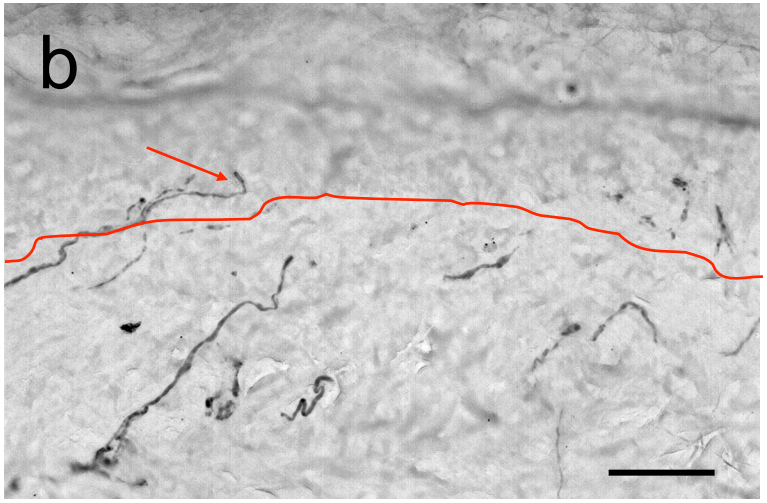
Corneal confocal microscopy

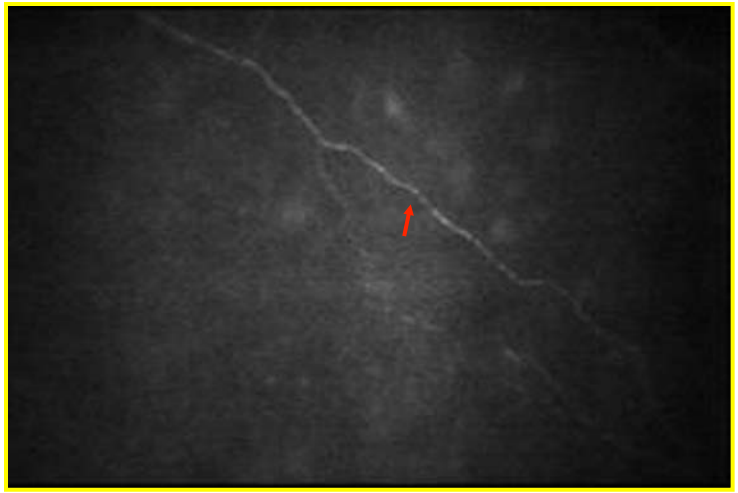
Control





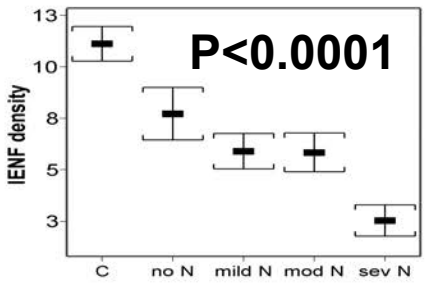
Diabetic

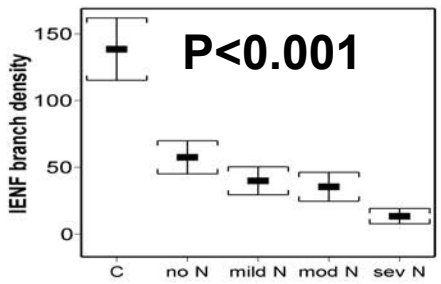


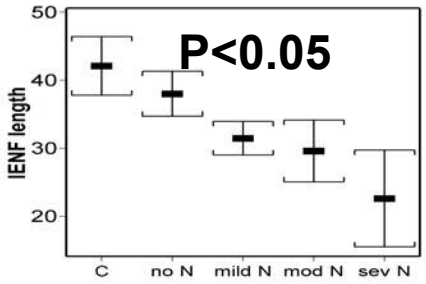


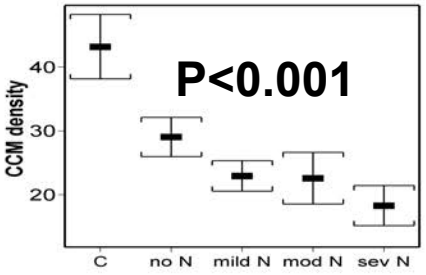
Quattrini *et al*. Diabetes 56(8):2148-54, 2007

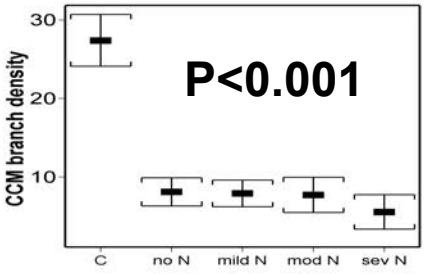
Skin biopsy v CCM

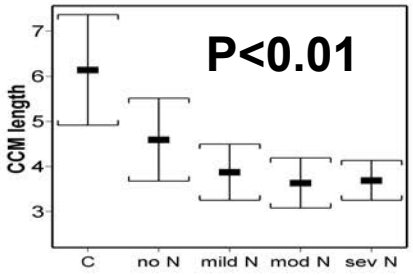






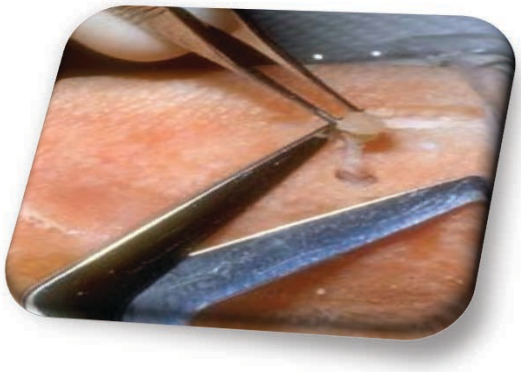


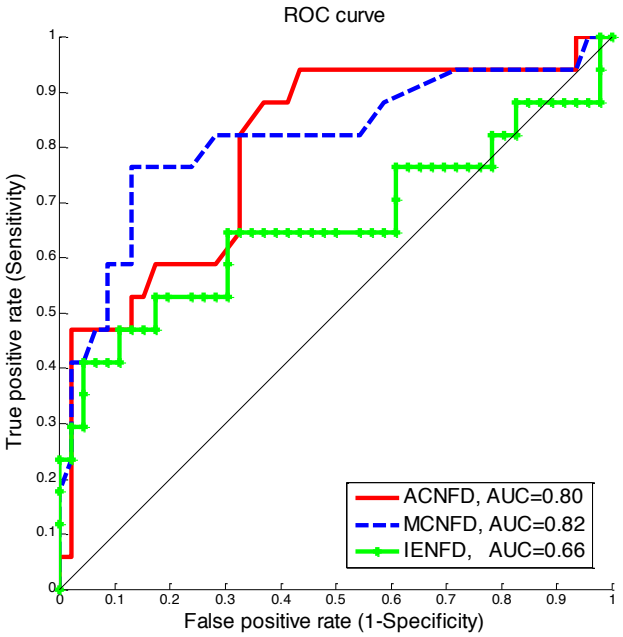




Quattrini *et al*. Diabetes 56(8):2148-54, 2007

Skin biopsy v CCM for DPN





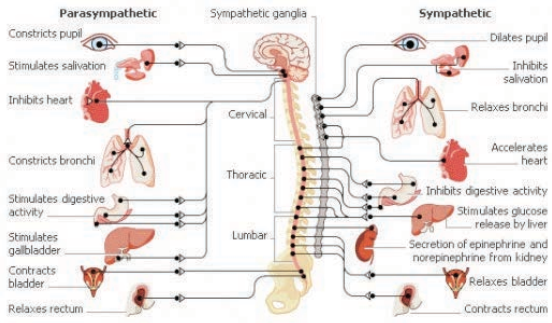
	Sensitivity	Specificity
Auto CNFD	0.64	0.79
Manual CNFD	0.79	0.71
IENFD	0.53	0.77

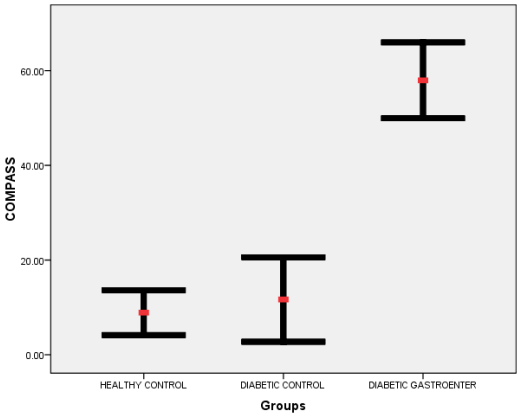
Chen et al. Diabetes Care (Positive review)

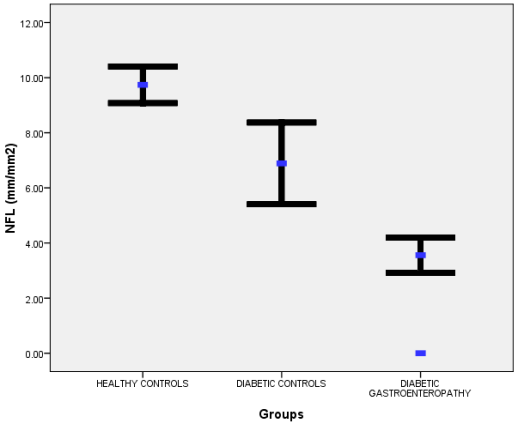
FDA End Point?

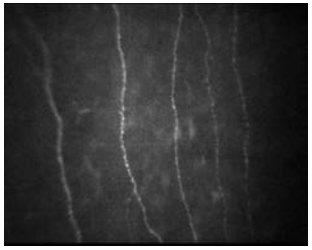
1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. Surrogate Endpoint: Biomarker intended to substitute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

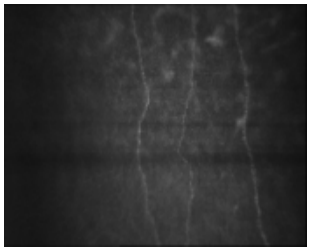
Autonomic Neuropathy

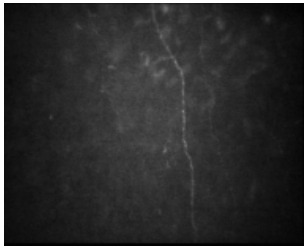


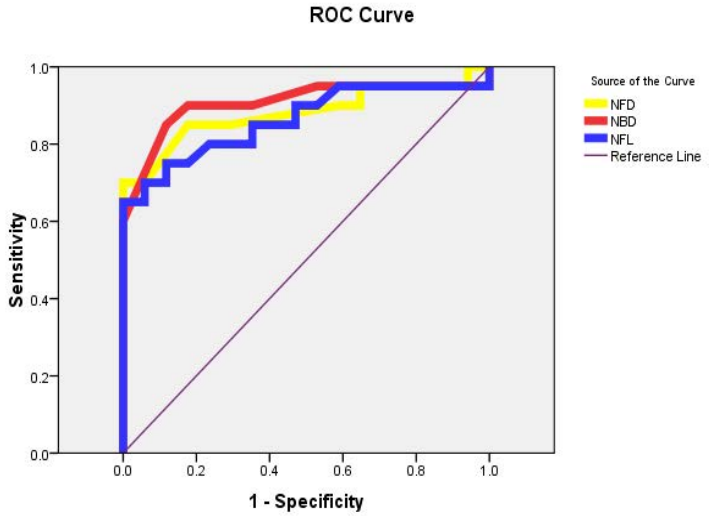










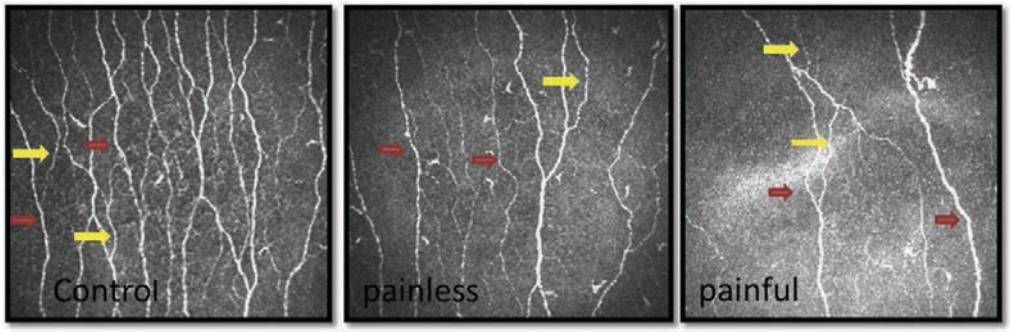


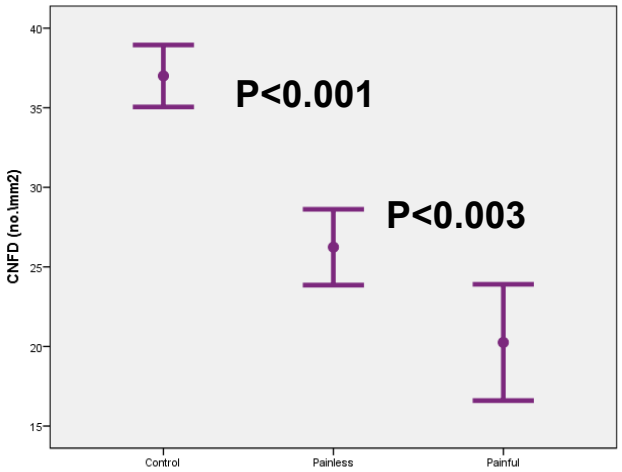
	AUC	Sensitivity	Specificity
NFD	0.915	86%	78%
NFL	0.907	86%	78%
NBD	0.889	100%	56%

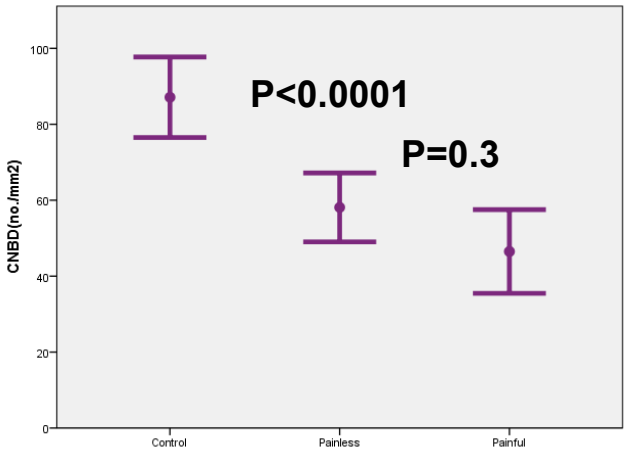
Tavakoli et al. Muscle and Nerve 2014 (In Press)

Painful v Painless

Parameters	Control (n=50)	Painless (n=50)	Painful (n=41)
CNFD (no./mm^2)	37.0±6.3	26.2±8.02*	20.2±10.7$^{\#}$
CNBD (no./mm^2)	87.1±34.4	58.1±30.5*	46.4±32.5
CNFL (mm/mm^2)	26.06±5.2	19.8±5.6*	15.7±7.8$^{\#}$







New Scientist

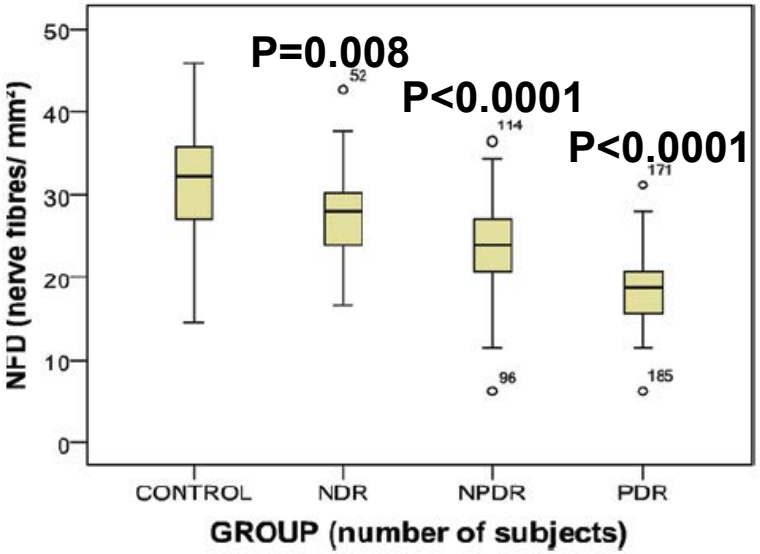
"Look into my eyes to predict my amputation risk"
March 2011

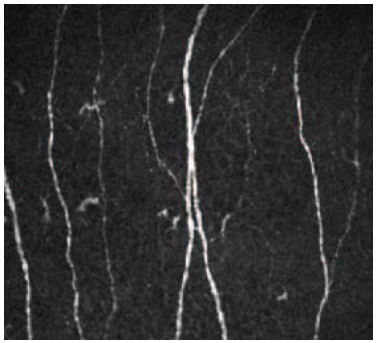
Conventional Wisdom

Retinopathy is the earliest Microvascular Complication

Correlation of Diabetic Retinopathy and Corneal Neuropathy Using Confocal Microscopy

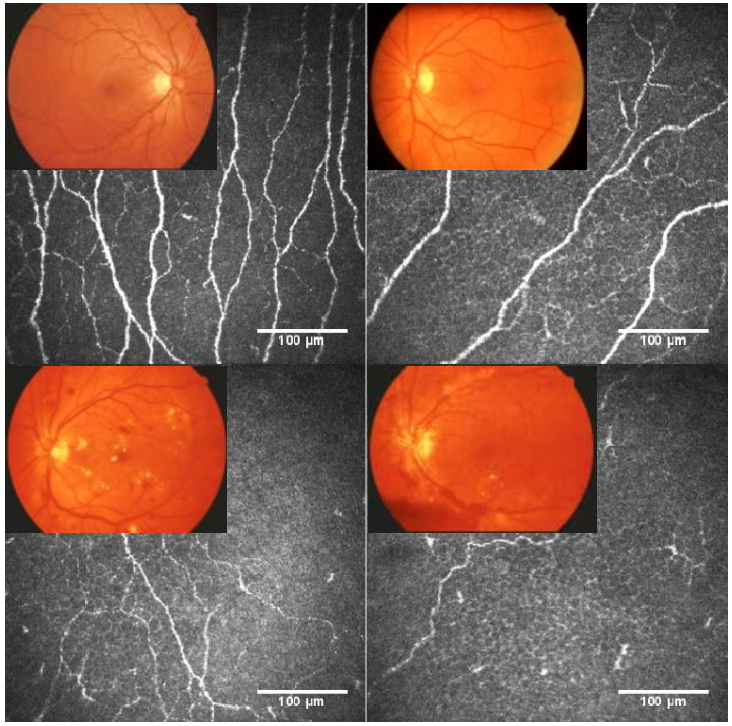
	Control ($n=47$)	NDR ($n=46$)	NPDR ($n=47$)	PDR ($n=46$)	ANCOVA Test statistic	
	Mean (*SE*)	Mean (*SE*)	Mean (*SE*)	Mean (*SE*)	$F(3, *)$	*p* value
NFD (fibers/mm^2)	31.3 (1)	27.4 (0.8)	23.7 (0.8)	18.8 (0.8)	35.5	<0.0001
NBD (branches/mm^2)	45.1 (2.8)	39.9 (3)	30.6 (2.7)	25.0 (2.1)	9.1	<0.0001
NFL (mm/mm^2)	16.6 (0.6)	14.8 (0.6)	12.3 (0.5)	10.4 (0.5)	23.7	<0.0001

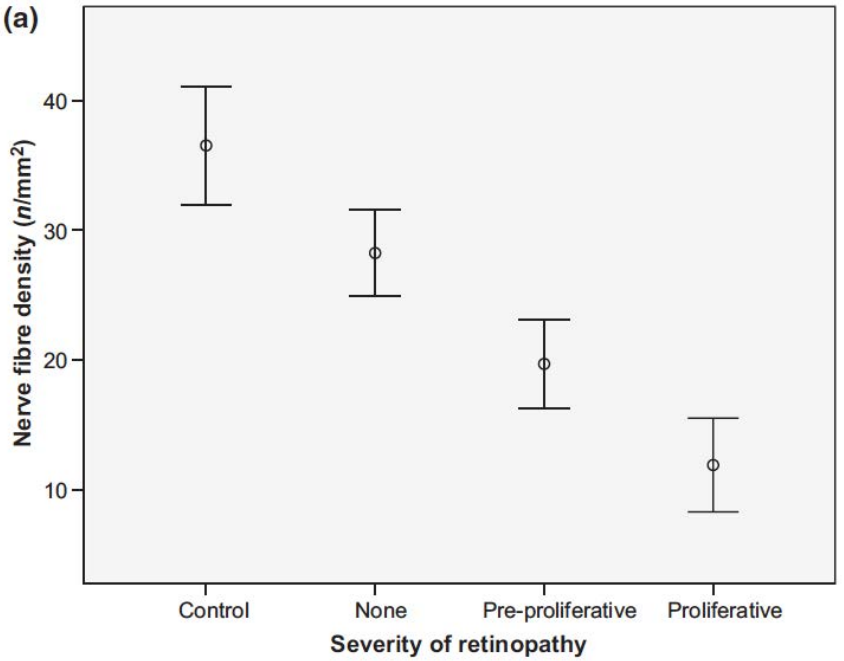




Nitoda et al. Curr eye Res 2012; 37: 898-906

Corneal nerve fibre damage precedes diabetic retinopathy in patients with Type 2 diabetes mellitus

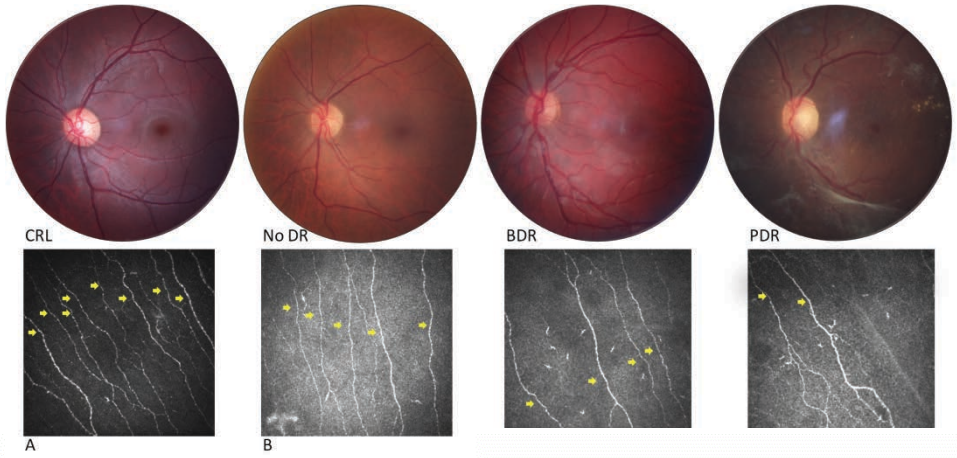


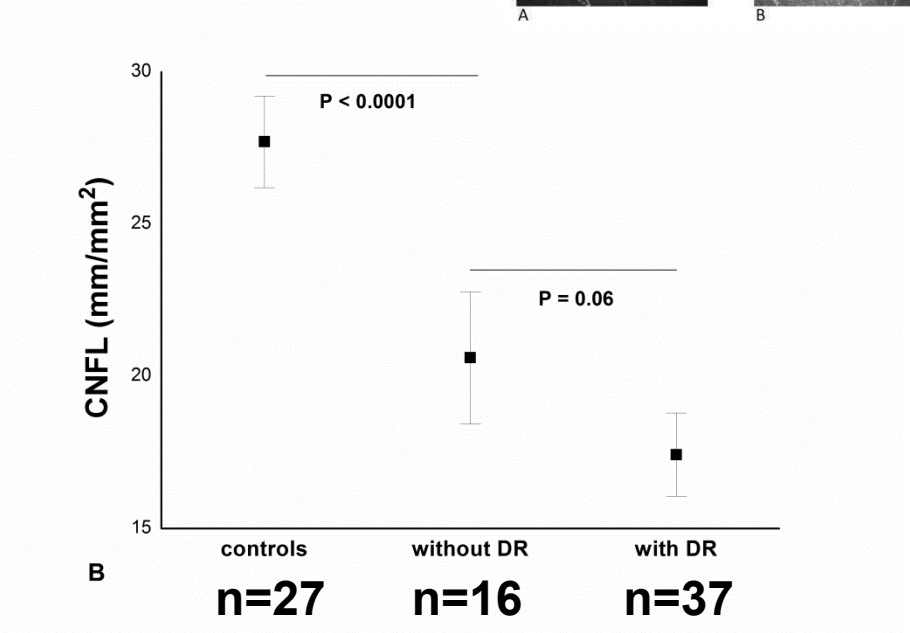


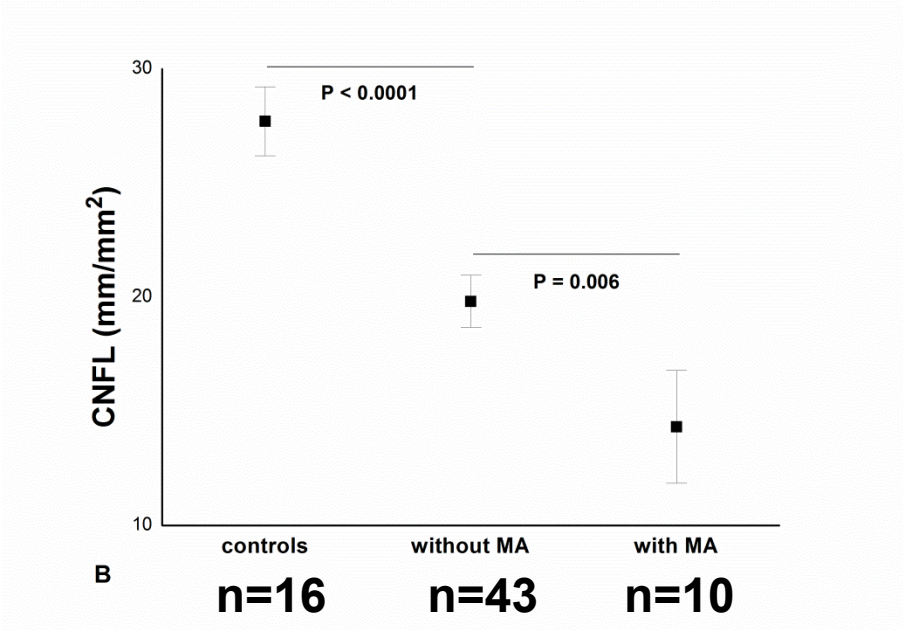
Bitirgen G et al. Diabetic Medicine 2014; 31: 431-8

Neuropathy precedes Retinopathy & Microalbuminuria

53 T1DM

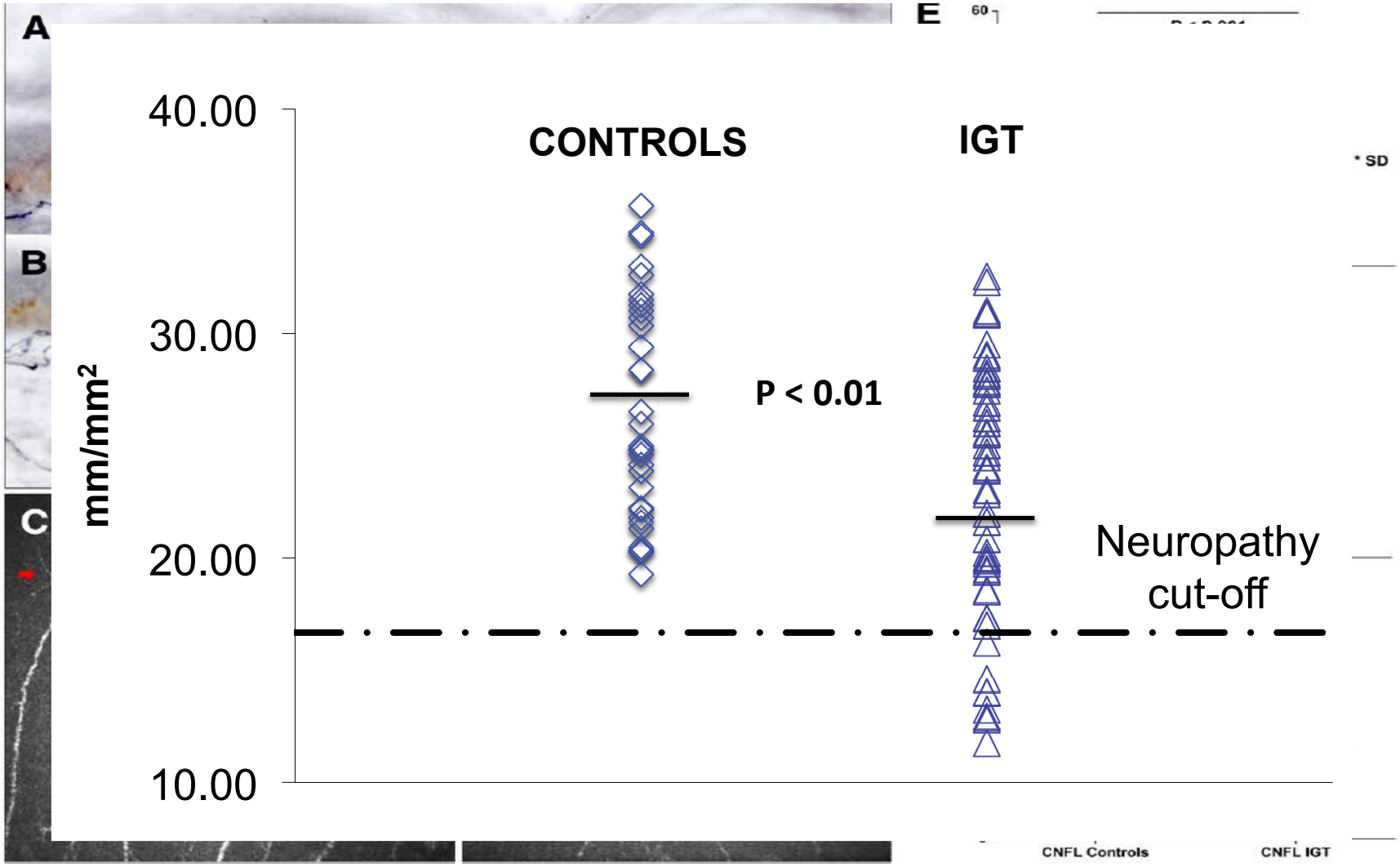






PloS 1 (positive review)

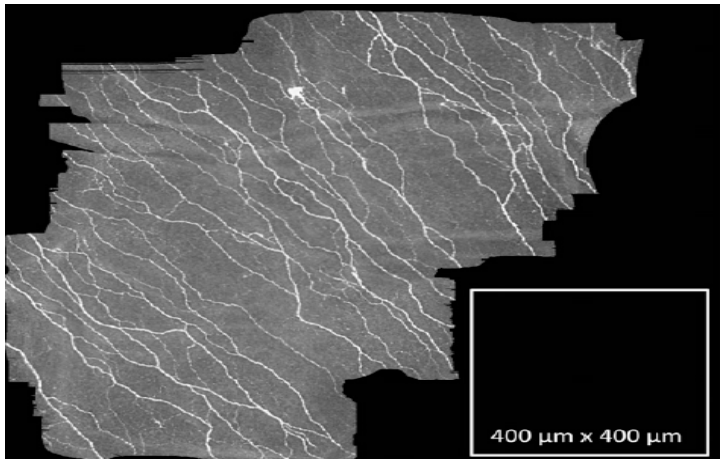
Corneal Confocal Microscopy Detects Neuropathy in Subjects With Impaired Glucose Tolerance

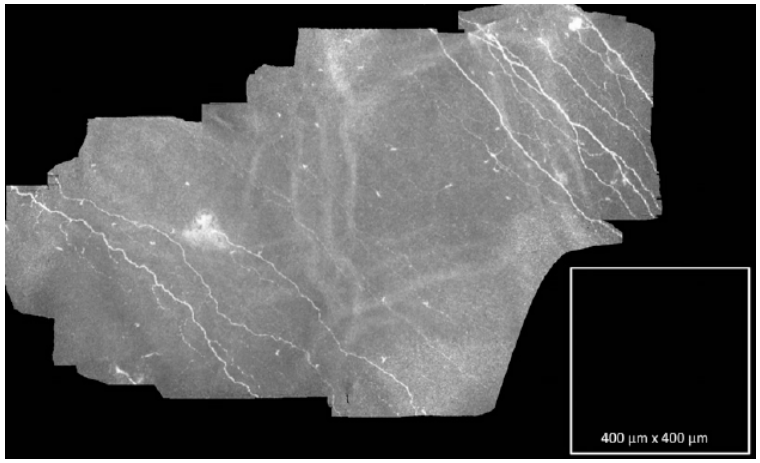


Asghar, Petropoulos et al. Diabetes Care 2014; 37: 2643-46

Early Detection of Nerve Fiber Loss by Corneal Confocal Microscopy and Skin Biopsy in Recently Diagnosed Type 2 Diabetes

Diabetes Duration- 2.1 yrs, HbA1c- 6.8%





	Diabetic group (n = 86)	Control group (n = 48)	P value
CNFL (mm/mm^2)	19.7 ± 7.5	24.9 ± 6.5	<0.001
CNFL-MNF (mm/mm^2)	9.8 ± 3.6	11.9 ± 2.9	0.001
CNFD (n/mm^2)	299.2 ± 152.8	397.3 ± 165.3	0.001
CNFD-MNF (n/mm^2)	58.2 ± 23.4	73.1 ± 17.9	<0.001
CNBD (n/mm^2)	165.2 ± 96.4	226.7 ± 103.1	0.001
IENFD (n/mm)	8.3 ± 3.0	10.6 ± 3.6	<0.001

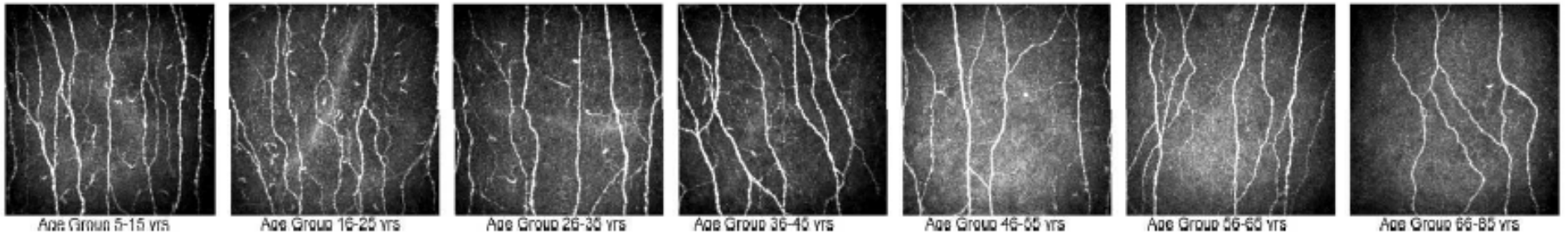
Ziegler et al. Diabetes 2014; 63: 2454-2463

FDA End Point?

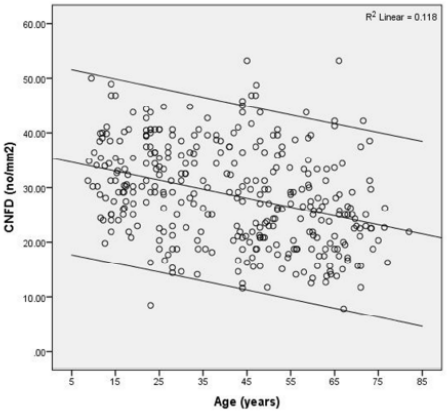
1. Biomarker: a physical sign or laboratory measurement that occurs in association with a pathological process and has diagnostic or prognostic utility.
2. Clinical endpoint: A clinically meaningful measure of how a patient feels, functions or survives.
3. Surrogate Endpoint: Biomarker intended to substitute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

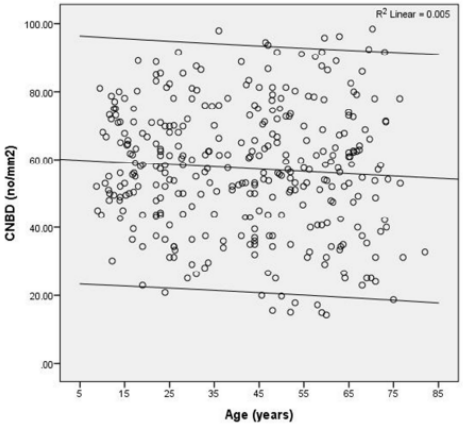
JDRF: $3.5M

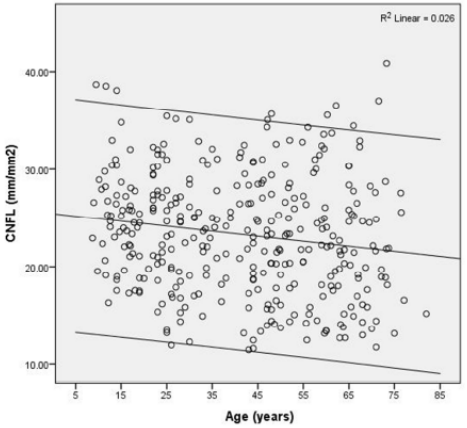
Normative Values (6 centre study: n=343)



CNBD ~+1.9/mm^2/decade, P=0.26





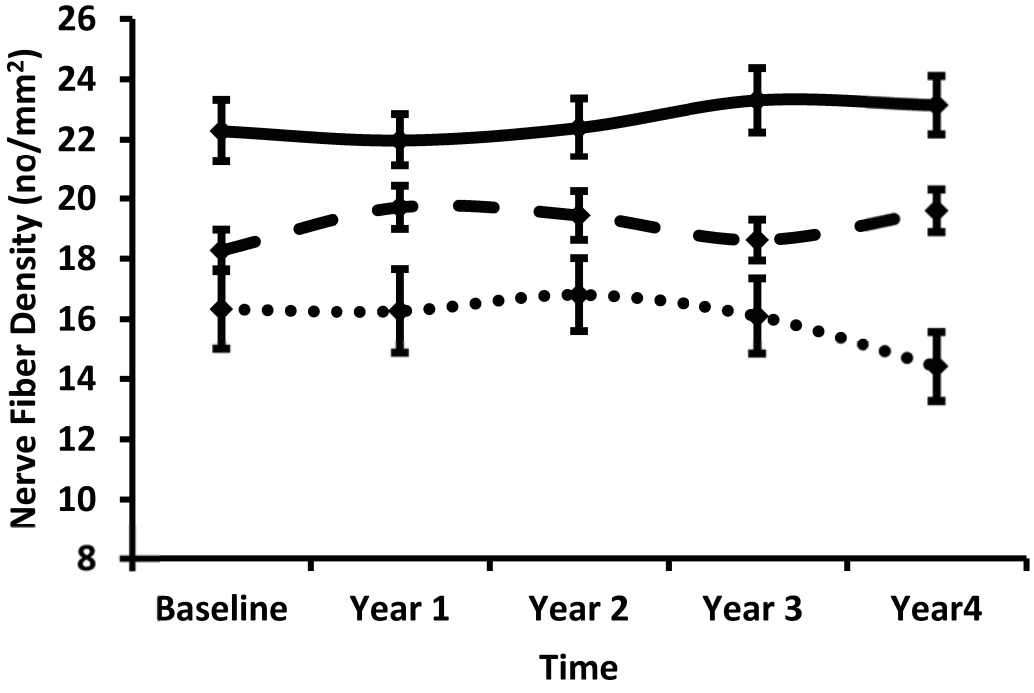


CNFD ~-1.6/mm^2/decade, P<0.01

CNFL ~-0.5/mm^2/decade, P<0.02

Tavakoli et al Diabetes Care (under review)

Natural History of Corneal Nerve Morphology in Mild Neuropathy Associated with Type 1 Diabetes: Development of a Potential Measure of Diabetic Peripheral Neuropathy



T1DM n=147
Control n=60

CNFD: -0.9/mm²/yrs, P<0.01
HbA1c: P=0.03
Duration of DM: P=0.01

Dehghani et al IOVS 2014; Nov 18. pii: IOVS-14-15605.

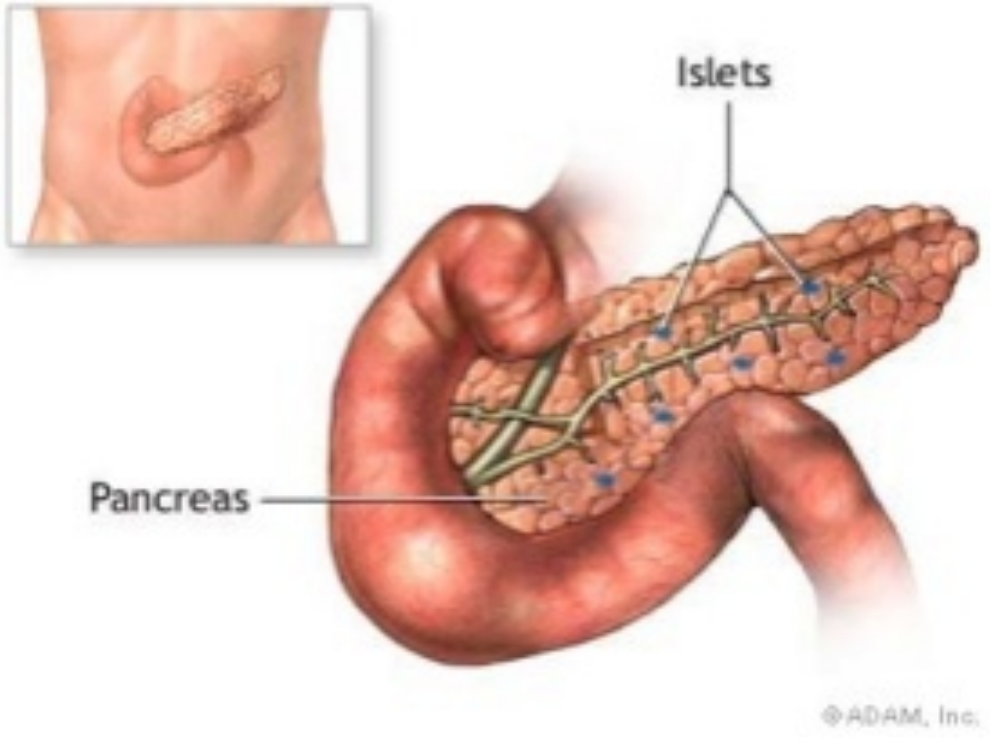
FDA End Point?

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.

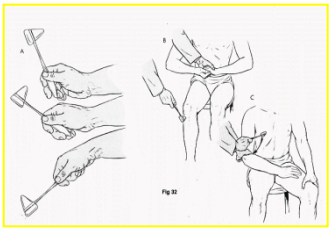
NIH- $1.5M

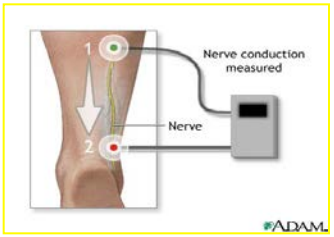
Prove that CCM improves with intervention!

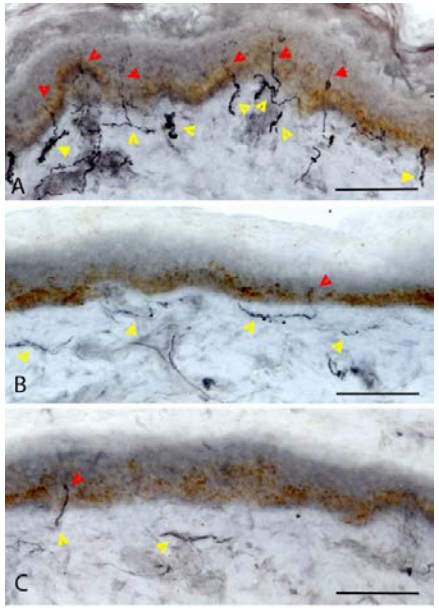
Conversation in the corridor with a friend and colleague: Transplant Surgeon

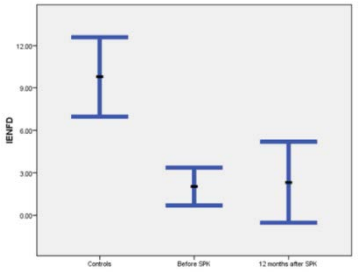


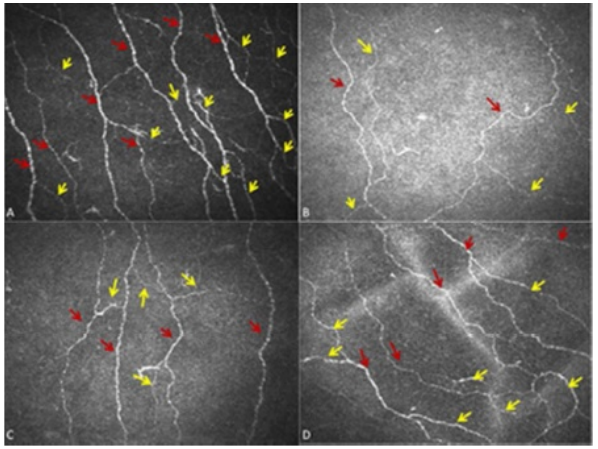
Pancreas Transplantation











Pathophysiology/Complications

ORIGINAL ARTICLE

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

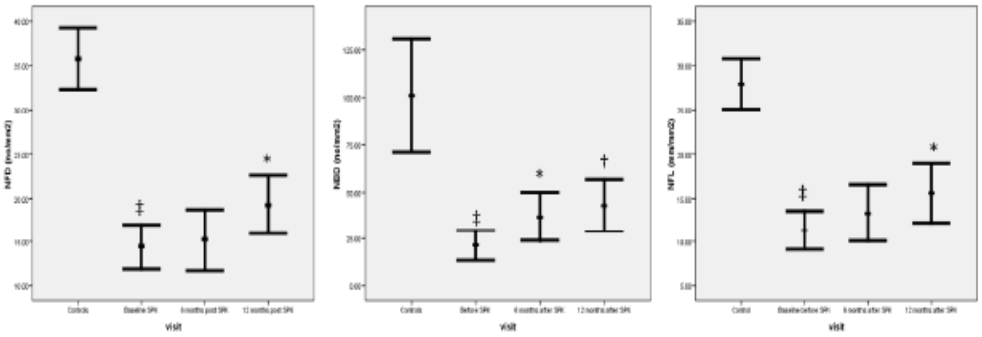
Sanjay Mehra, MD[1]
Mitra Tavakoli, MSc[2]
Panagiotis A. Kallinikos, PhD[2]
Nathan Efron, PhD[2]
Andrew J.M. Boulton, MD[2]
Titus Augustine, MD[1]
Rayaz A. Malik, MD[2]

tests 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 (3). Thus, nerve conduc-

ORIGINAL ARTICLE

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

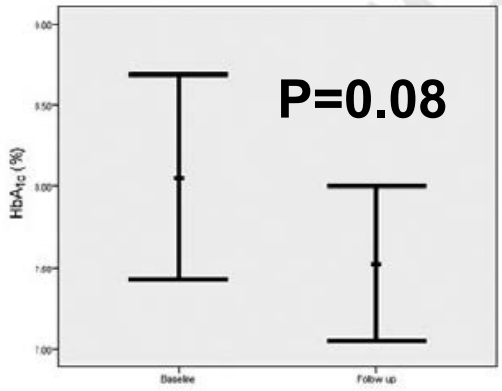
Mitra Tavakoli,[1] Maria Mitu-Pretorian,[2] Ioannis N. Petropoulos,[1] Hassan Fadavi,[1] Omar Asghar,[1] Uazman Alam,[1] Georgios Ponirakis,[1] Maria Jeziorska,[3] Andy Marshall,[4] Nathan Efron,[5] Andrew J. Boulton,[1] Titus Augustine,[2] and Rayaz A. Malik[1]

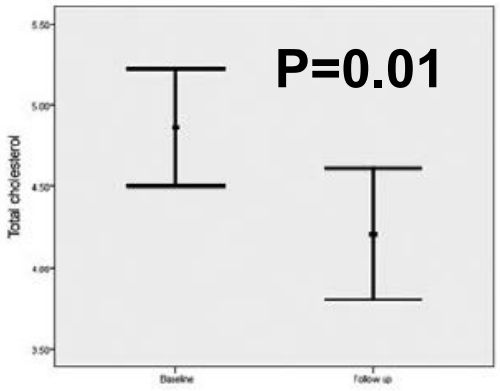


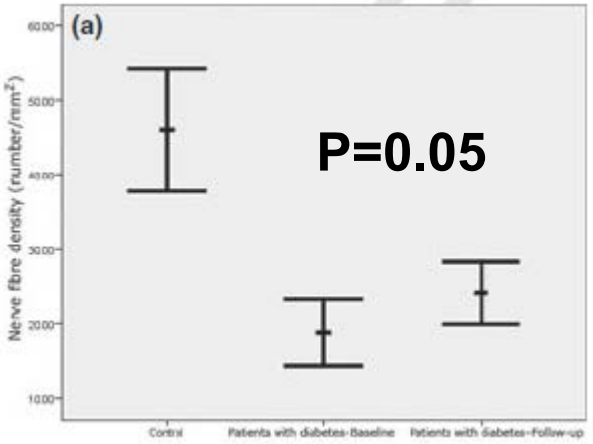
Corneal confocal microscopy detects improvement in corneal nerve morphology with an improvement in risk factors for diabetic neuropathy

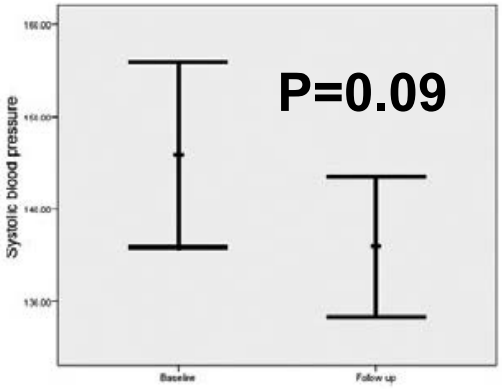
M. Tavakoli, P. Kallinikos, A. Iqbal, A. Herbert*, H. Fadavi, N. Efront, A. J. M. Boulton and R. A Malik

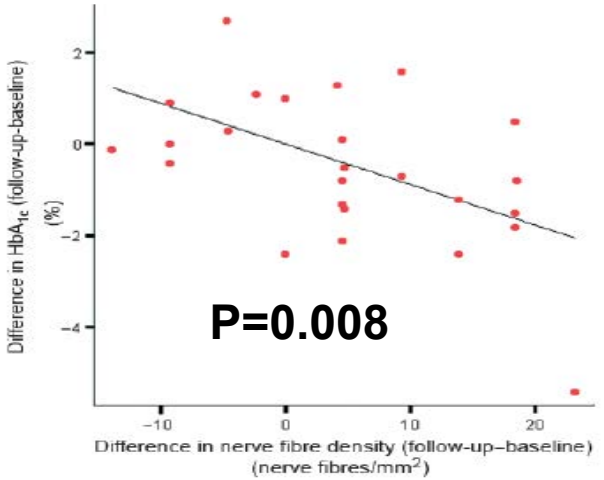
Multiple Risk Factor improvement











Tavakoli et al. Diabetic Medicine 2011; 28: 1261-7

Almost 2 years ago…

On 21 Feb 2013, at 12:17, "A Cerami" <acerami@araimpharma.com> wrote:

Dear Dr Malik-- Dr Duncan McGrouther of the Department of Surgery at Manchester with whom we collaborate suggested that I write you about a clinical program that we are pursuing. I have followed your work on CCM for a number of years and appreciate its potential for studying small fiber neuropathy, especially with regard to therapeutics. For a number of years we have been developing a new agent, ARA290, which has the ability to turn off inflammation and turn on repair in many tissues in a number of different animal models. During the last two years we have been studying patients with sarcoidosis and diabetes at the Leiden University Medical Center in the Netherlands. I have attached a paper which describes our first phase 2 study in sarcoidosis. We have recently completed another trial using a subcutaneous formulation in which we measured CCM at the beginning and after thirty days of daily administration and observe a difference between the treated and placebo groups. We would be most interested in discussing our results with you since we are planning to carry out a new trial in diabetes in the near future. Your insights would be gratefully received.
With best wishes,

Tony Cerami

The unexpected pathway to the creation of the HbA1c test and the discovery of AGE's

A. Cerami

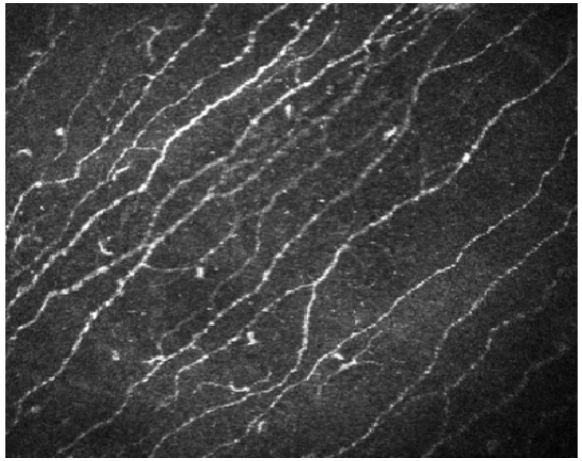
Derivatives of Erythropoietin That Are Tissue Protective But Not Erythropoietic

Marcel Leist,[1]* Pietro Ghezzi,[2,3]* Giovanni Grasso,[3,4] Roberto Bianchi,[2] Pia Villa,[2,5] Maddalena Fratelli,[2] Costanza Savino,[2] Marina Bianchi,[2] Jacob Nielsen,[1] Jens Gerwien,[1] Pekka Kallunki,[1] Anna Kirstine Larsen,[1] Lone Helboe,[1] Søren Christensen,[1] Lars O. Pedersen,[1] Mette Nielsen,[1] Lars Torup,[1] Thomas Sager,[1] Alessandra Sfacteria,[3,4] Serhat Erbayraktar,[3,6] Zubeyde Erbayraktar,[3,6] Necati Gokmen,[6] Osman Yilmaz,[3,6] Carla Cerami-Hand,[3,7] Qiao-wen Xie,[3,7] Thomas Coleman,[3,7] Anthony Cerami,[3,7]† Michael Brines[3,7]

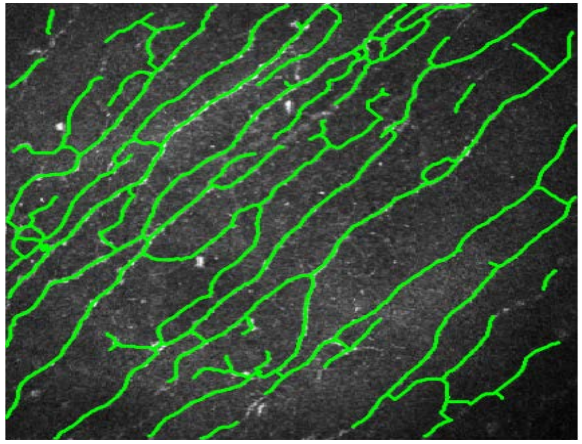
SCIENCE VOL 305 9 JULY 2004

Automated Analysis (CCMetrics/ACCMetrics)

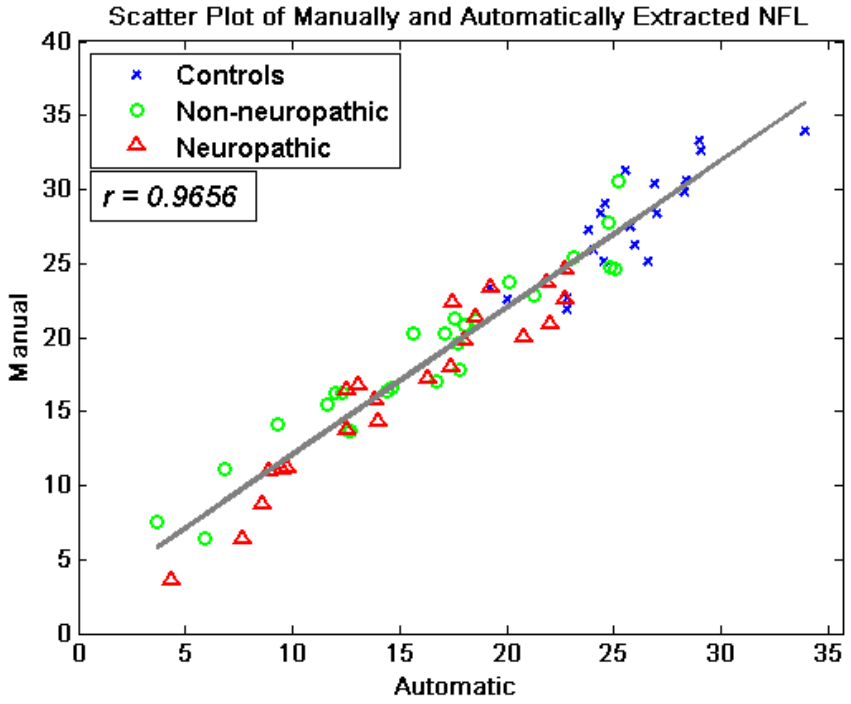
http://www.click2go.umip.com/i/software/Biomedical_Software/ccmetrics.html



30 min

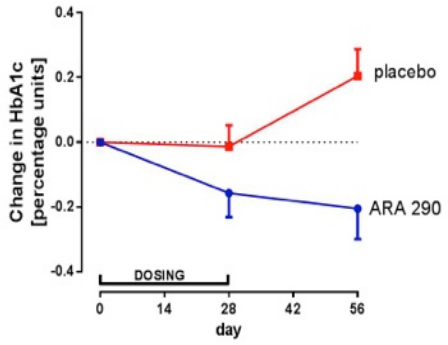


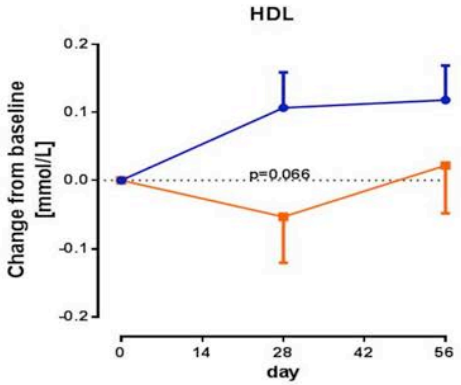
25 sec

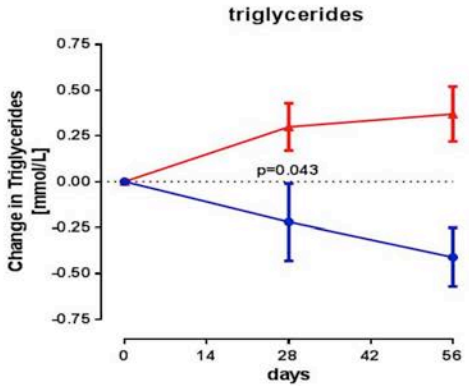


Dabbah et al. Med Image Anal. 2011; 15:738-47
Dabbah et al. Med Image Comput Assist Interv. 2010;13: 300-7

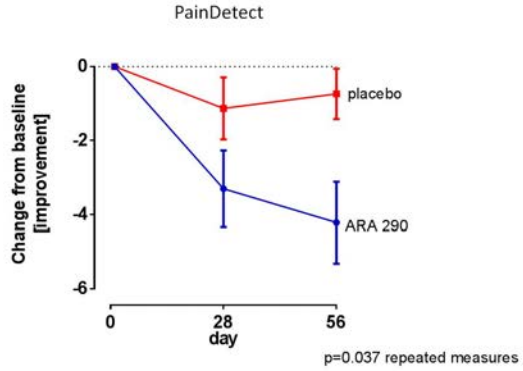
ARA 290, a non-erythropoietic peptide engineered from erythropoietin, improves metabolic control and neuropathic symptoms in patients with type 2 diabetes.

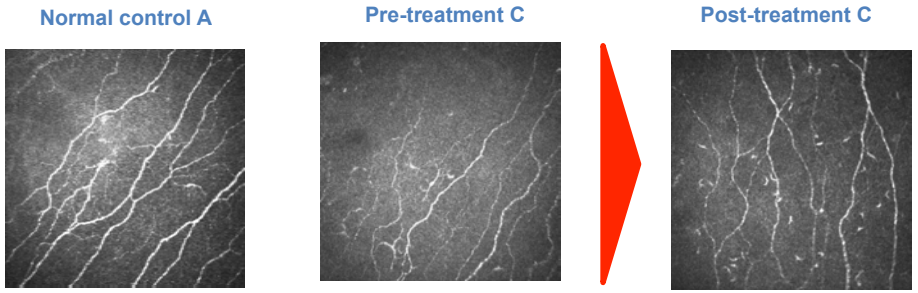






ARA-290: +2.6 ± 1.0 fibers/mm^2, P=0.02
Placebo: 0.7 ± 1.3 fibers/mm^2, P=ns





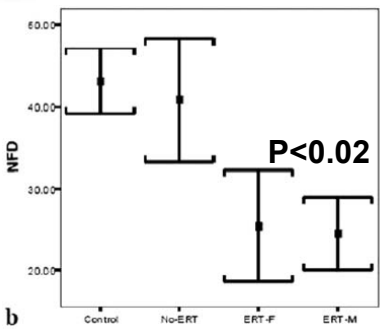
Brines et al. Mol Med. 2014 Nov 6. doi: 10.2119/molmed.2014.00215.

Other Peripheral Neuropathies

Muscle Nerve **40:** 976–984, 2009

CORNEAL CONFOCAL MICROSCOPY: A NOVEL NONINVASIVE MEANS TO DIAGNOSE NEUROPATHY IN PATIENTS WITH FABRY DISEASE

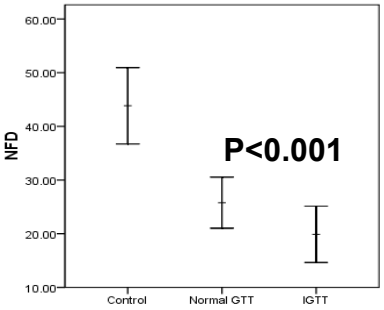
MITRA TAVAKOLI, PhD, MSc,[1] ANDREW MARSHALL, MRCP,[2]
LORRAINE THOMPSON, BSc,[3] MARGARET KENNY, BSc,[3] STEPHEN WALDEK, MD,[3]
NATHAN EFRON, PhD, DSc,[4] and RAYAZ A. MALIK, PhD, FRCP[1]



Contents lists available at ScienceDirect
Experimental Neurology
journal homepage: www.elsevier.com/locate/yexnr

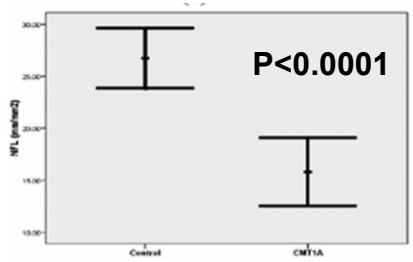
Corneal confocal microscopy: A novel means to detect nerve fibre damage in idiopathic small fibre neuropathy

Mitra Tavakoli [a], Andrew Marshall [b], Robert Pitceathly [c], Hassan Fadavi [a], David Gow [c], Mark E. Roberts [c], Nathan Efron [d], Andrew JM Boulton [a], Rayaz A. Malik [a,*]



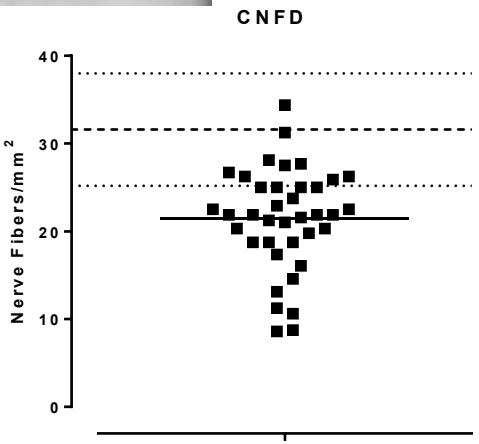
CORNEAL CONFOCAL MICROSCOPY DETECTS SMALL-FIBER NEUROPATHY IN CHARCOT–MARIE–TOOTH DISEASE TYPE 1A PATIENTS

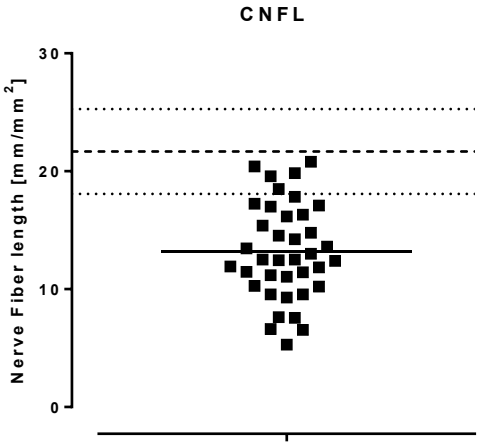
MITRA TAVAKOLI, MSc, PhD,[1] ANDY MARSHALL, MD, FRCP,[2] SIDDHARTH BANKA, MBBS, MRCPCh,[3]
IOANNIS N. PETROPOULOS, MSc,[1] HASSAN FADAVI, MD,[1] HELEN KINGSTON, MD, FRCP,[3] and RAYAZ A. MALIK, MBChB, PhD[1]

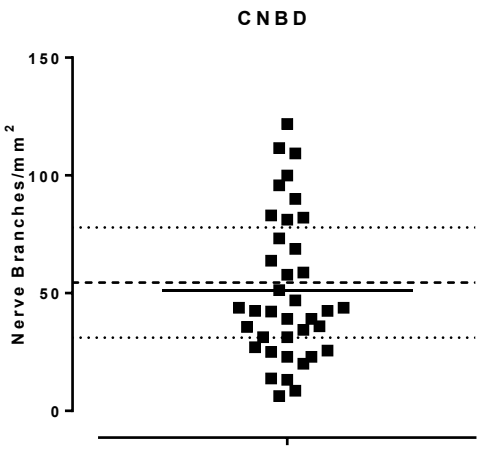


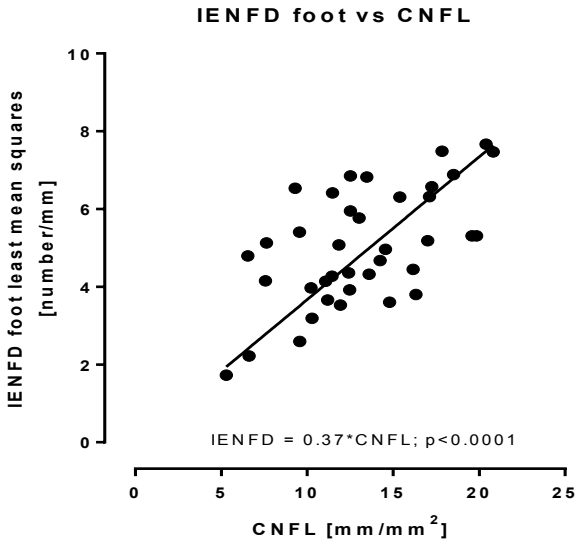
Tavakoli et al. Exp Neurol. 2010;223(1):245-50.
Tavakoli et al. Muscle Nerve. 2009;40(6):976-84.
Tavakoli et al. Muscle & Nerve 2012; 46: 698-704.

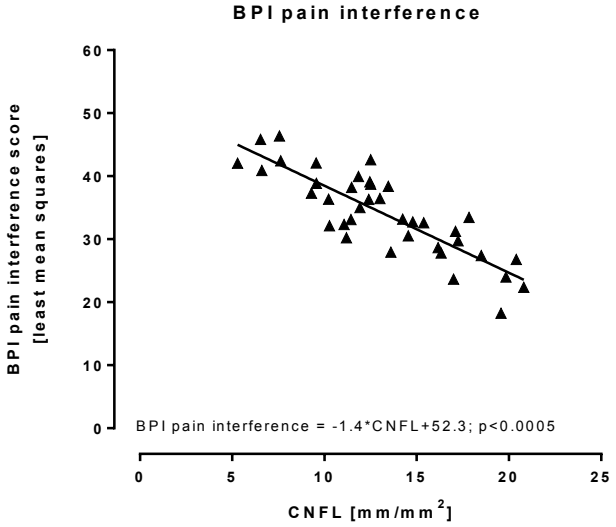
Sarcoid Neuropathy





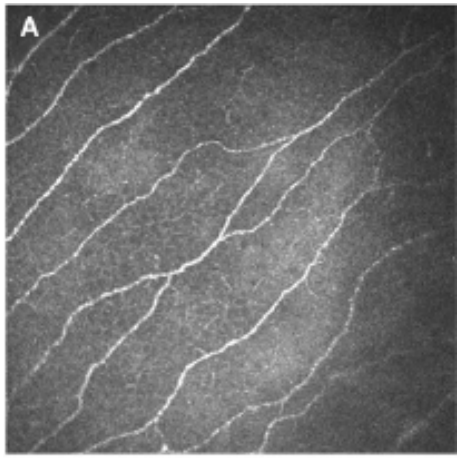


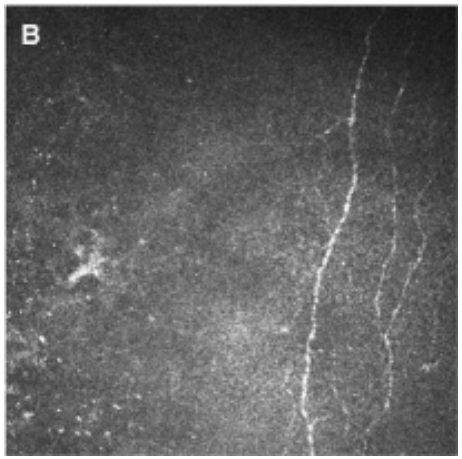


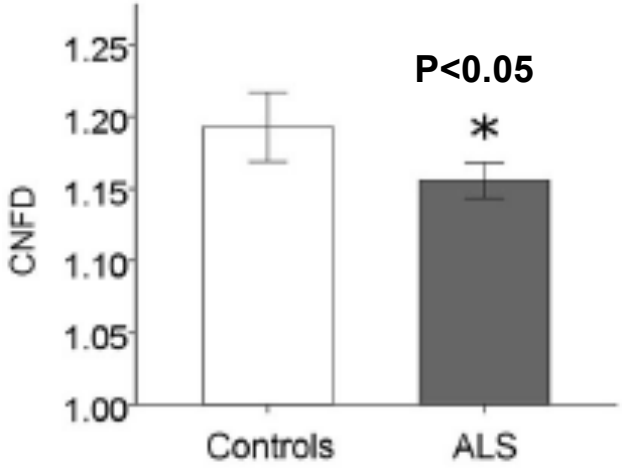


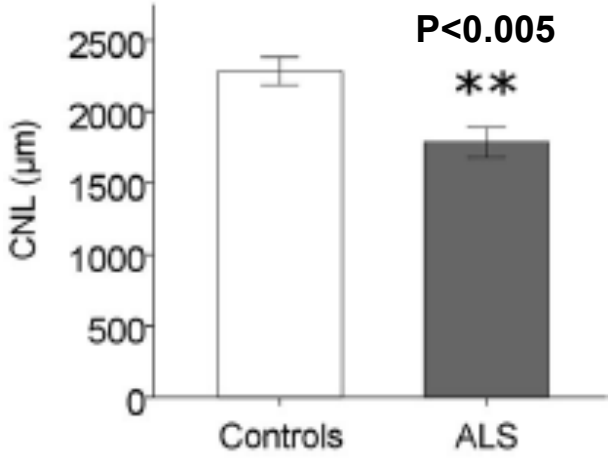
Central Neurological Conditions?

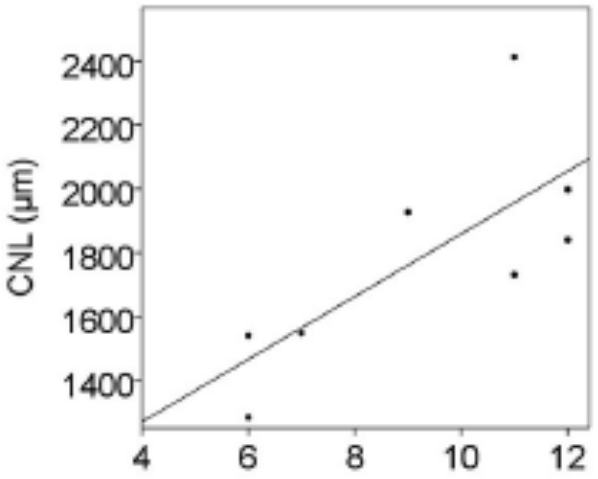
Corneal confocal microscopy reveals trigeminal small sensory fiber neuropathy in amyotrophic lateral sclerosis





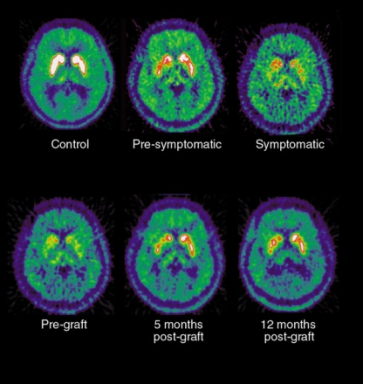




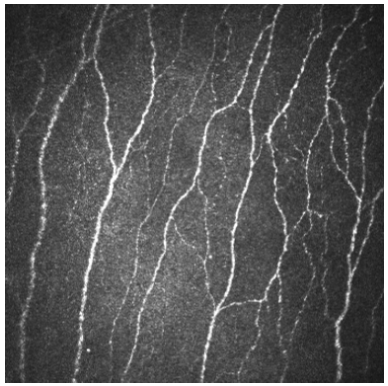


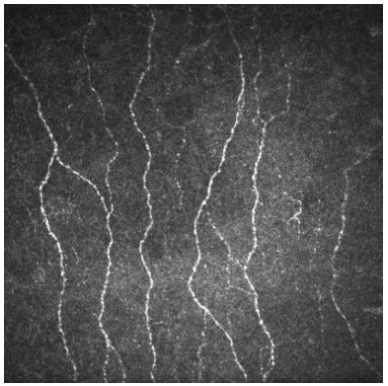
ALS-FRS Bulbar score
r=0.764, P<0.02

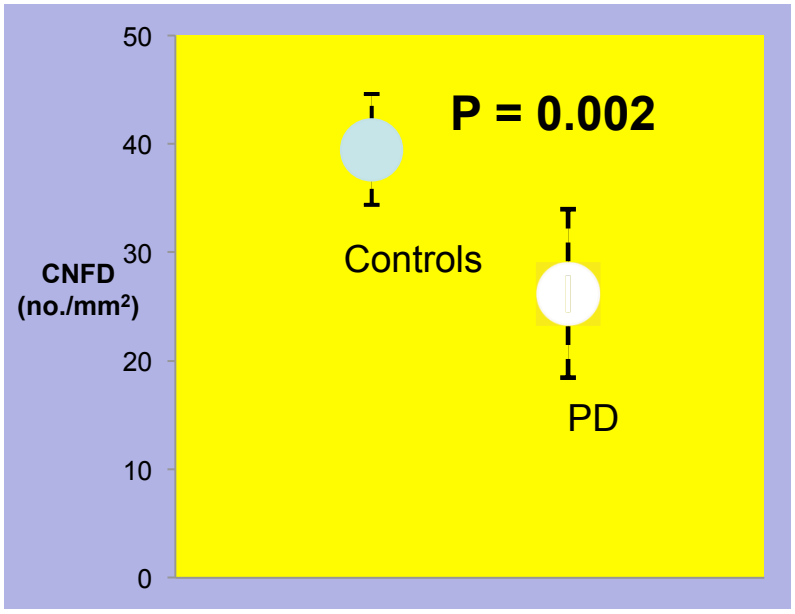
Ferrari et al. Front Age Neurosci 2014; 6: 1-4

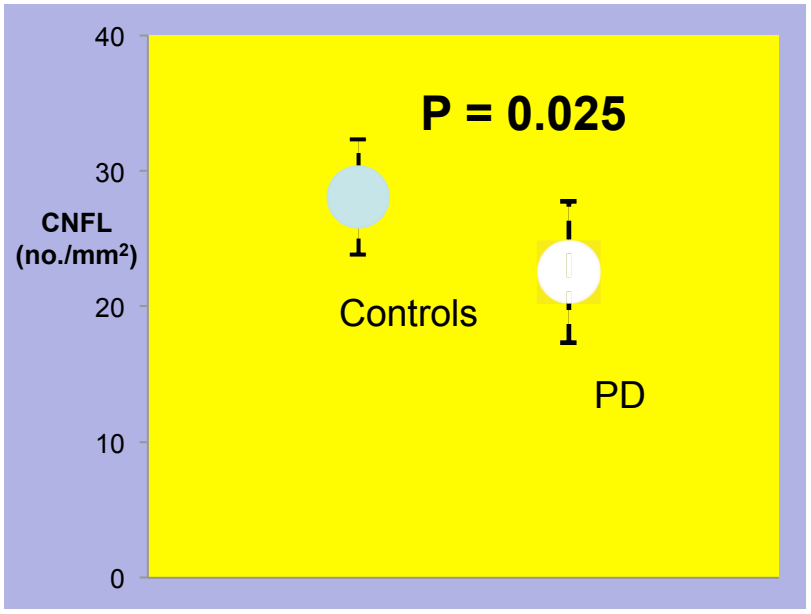


Parkinson's Disease



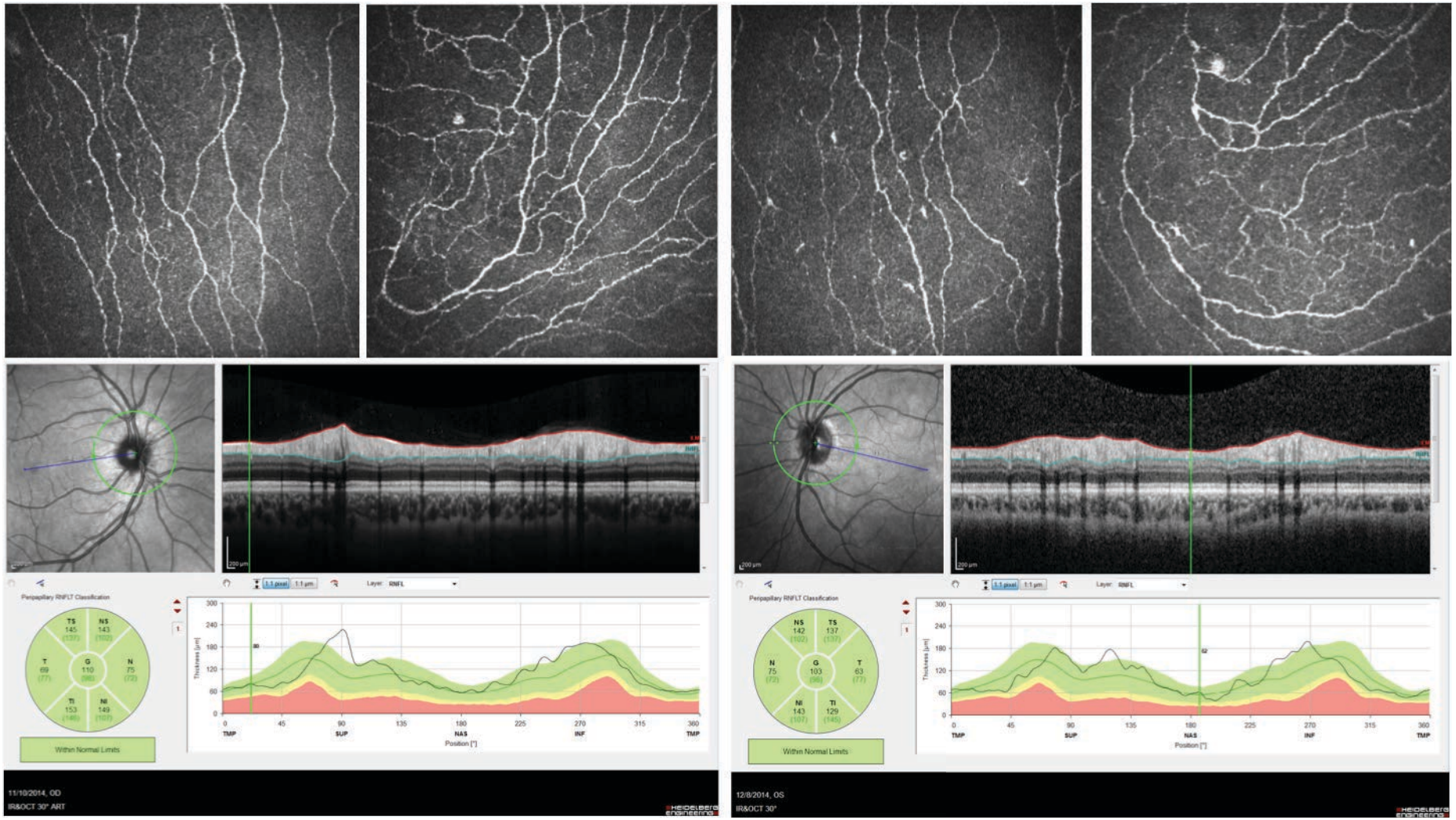






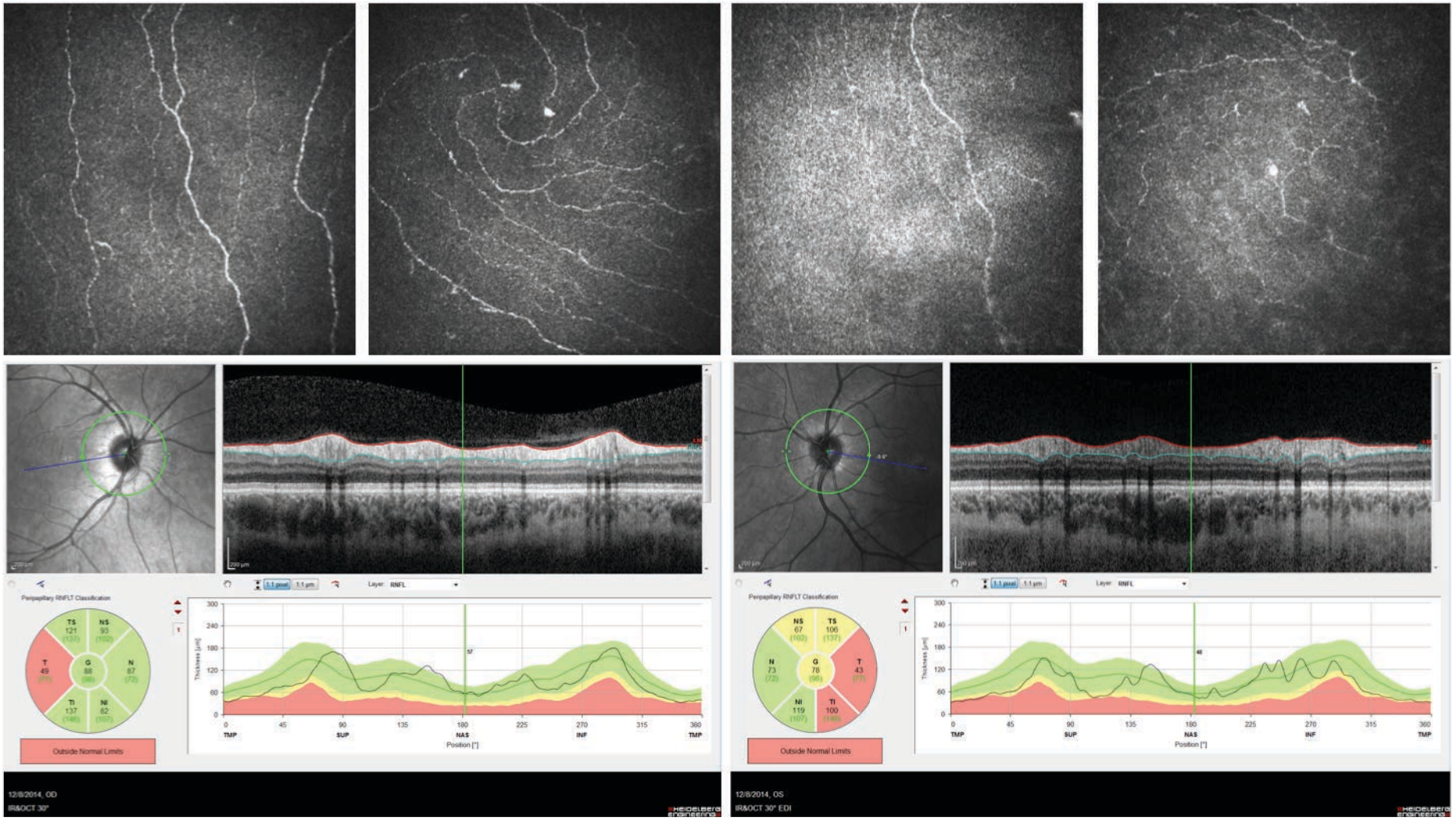
Control

MS with no optic neuritis



MS with no optic neuritis (RE)

MS with optic neuritis (LE)



Collaborations

Stockholm
Malmo
Maastricht

Dusseldorf
Heidelberg

Moscow

Helsinki

Calgary
Toronto
Winnipeg

Tokyo
Kobe
Hiroshima

Seoul

Harvard
Johns Hopkins
Ann Arbor
UCSD
Utah

Taipai

Brisbane
Sydney

Rio de Janeiro
San Paulo

Istanbul
Ankara
Konya

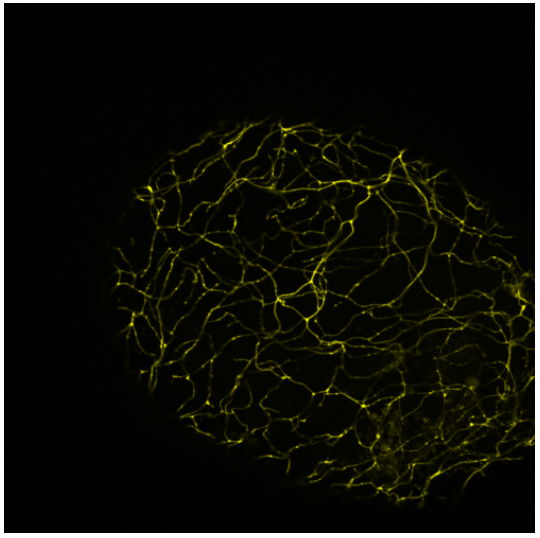
Madinah
Riyadh
Doha
Abu-Dhabi

Chandigarh
Delhi
Chennai

Singapore

Reverse Translation

Sprague Dawley rat



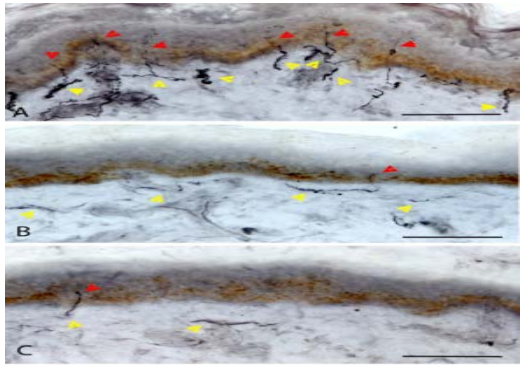
NOD mouse/ZDF rat

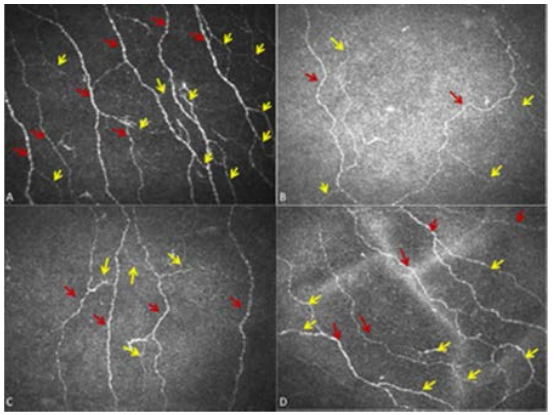
Chen DK et al. Neurodiab 2011, UCSD
Reichard et al EASD 2011, ARVO 2012
Davidson et al. IOVS 2012;53:1182-7.
Walker SL. PLoS One. 2012;7:e29916.

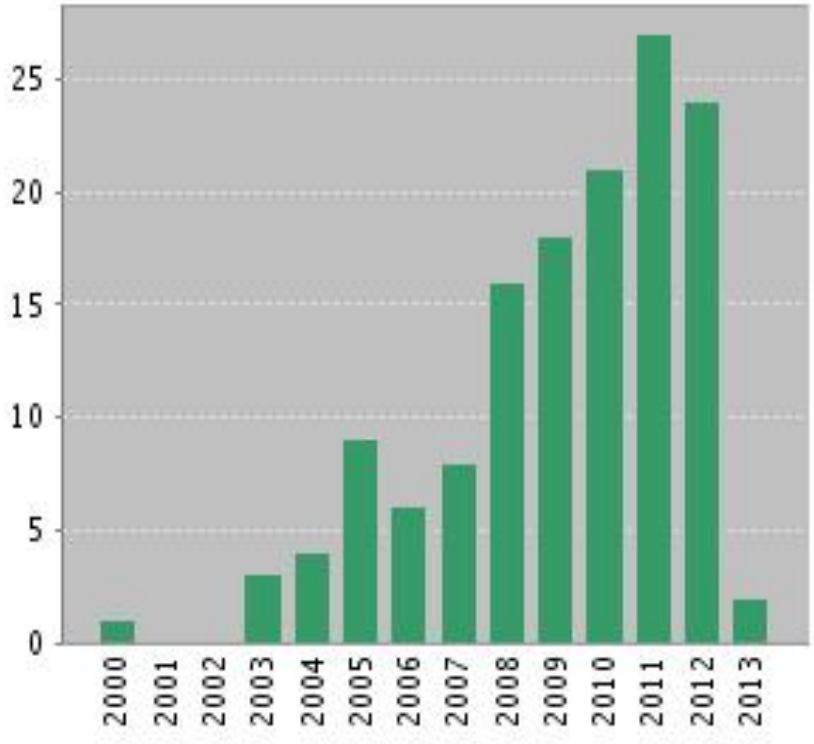
Future Projects

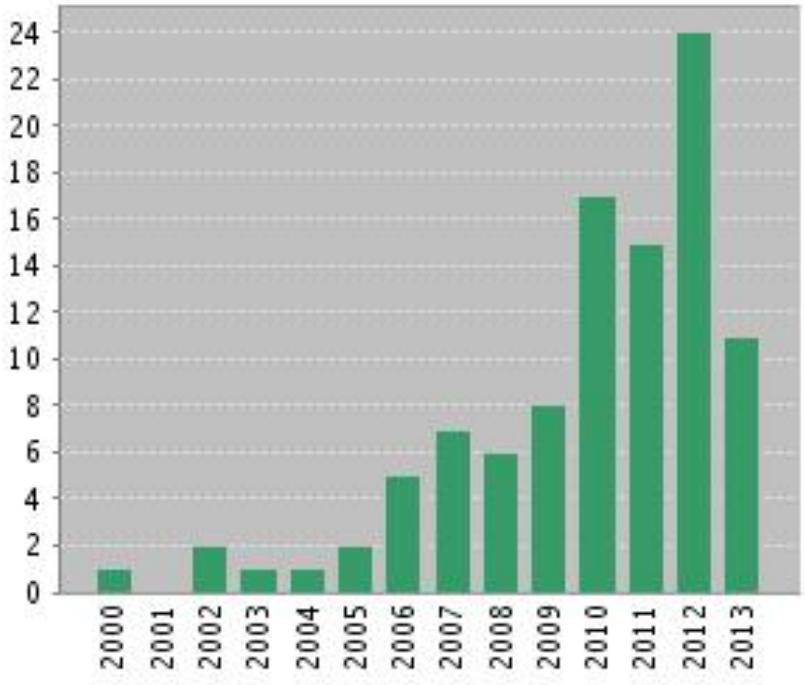
Chemotherapy Induced Neuropathy ✔
Sarcoidosis ✔
Parkinson's ✔
CIDP ✔
Obesity (Bariatric Surgery) ✔
Freidrich's Ataxia
Dementia
Stroke
MS
HIV neuropathy
ARA 290 Phase 2b
…….

Translational Impact







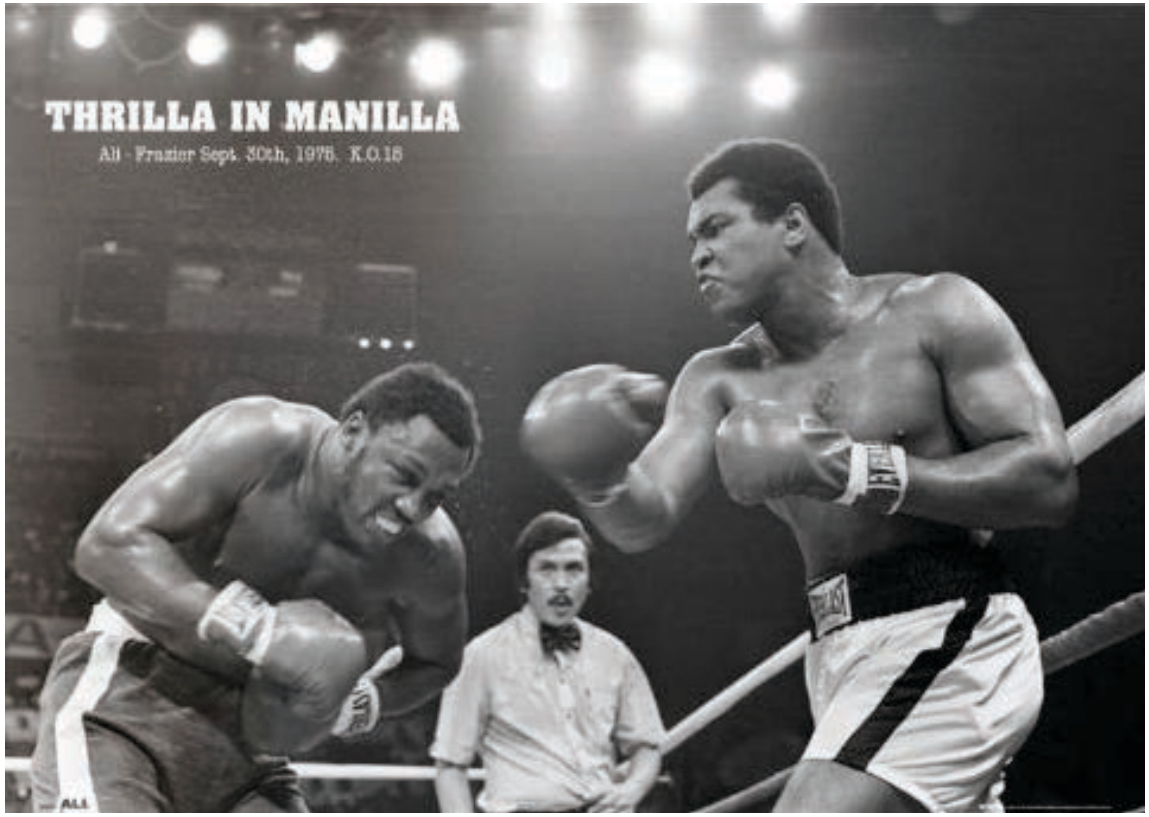


FDA End Point?

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.

"He who is not courageous enough to take risks will accomplish nothing in life"

Muhammad Ali



Thank you

JD Ward
AJM Boulton
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A Veves
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N Efron
M Jeziorska
J Graham

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

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