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Neuritis optica met speciale aandacht voor NMO-SD en MOG neuritis

Neuro-ophthalmologie lesmiddag
LVAO, 05-OCT-2023

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Disclosures

NIHR UK, UCSF
Stichting MS Research NL
Novartis, Heidelberg Academy

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Structure of this presentation

- Background
- Cases
- What to ask in clinic
- ICON 2022 Diagnostic Criteria
- ICON 2022 Classification
- NMO-ON & MOG-ON
- Summary

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The ICON 2022 story

THE LANCET Neurology

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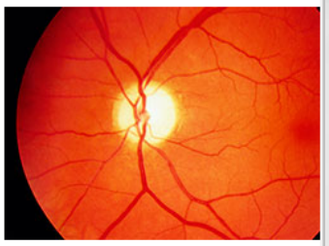
Optic Neuropathies

Published: September 22, 2022

Executive Summary

Optic neuropathies can reflect a wide range of pathophysiologies, both acquired and inherited. This Series provides an update on the clinical, imaging, and laboratory findings that differentiate these disorders, allowing clinicians to focus their diagnostic studies and optimise treatments. Multimodality optic nerve imaging—including fundus photography, optical coherence tomography, and MRI—has greatly advanced the diagnosis and follow-up of patients with optic neuropathies. Also reviewed in this Series, new evidence shows that optic neuritis can frequently indicate autoimmune neurological disorders, including multiple sclerosis and the recently recognised disease categories of aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder and myelin-oligodendrocyte glycoprotein antibody-associated disease. Early clinical recognition of optic neuritis is, therefore, important for prognosis and treatment. Also reviewed in the Series, a unifying feature in the pathophysiology of hereditary disorders of the optic nerve is mitochondrial dysfunction. Treatments are emerging for optic neuropathies, including immunotherapies and genetic therapies.



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The Lancet Neurology, Vol. 20, No. 9

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The Lancet Neurology, Vol. 20, No. 7

Published: July, 2021

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1st Case

- 34 year old Caucasian female patient
- 7 day history of pain in the right eye which worsens on eye movements
- Reduced colour vision
- VA RE: 6/9, left eye LE: 6/5
- Right RAPD
- Reports: fatigue, cognitive problems, urinary incontinence, depression
- PmHx: right sided numbness lasting 1m, 3y ago

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1st Case

- Bloods all normal except for low Vitamin D at 22 nmol/L (normal 50-200 nmol/L)
- MRI: DIS & DIT
three Gd+ non-symptomatic lesions
- CSF not done

What is the most likely diagnosis?

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2nd Case

- 28 year old, Afrocaribbean male
- Painless loss of vision LE (6/38)
- Dyschromatopsia
- L RAPD
- Several steroid responsive episodes over ~20 y fup
- OCT: pRNFL atrophy LE (IEPD >5%)
- MRI a swollen, Gd+, left optic nerve. No lesions elsewhere
- AQP4 seropositive

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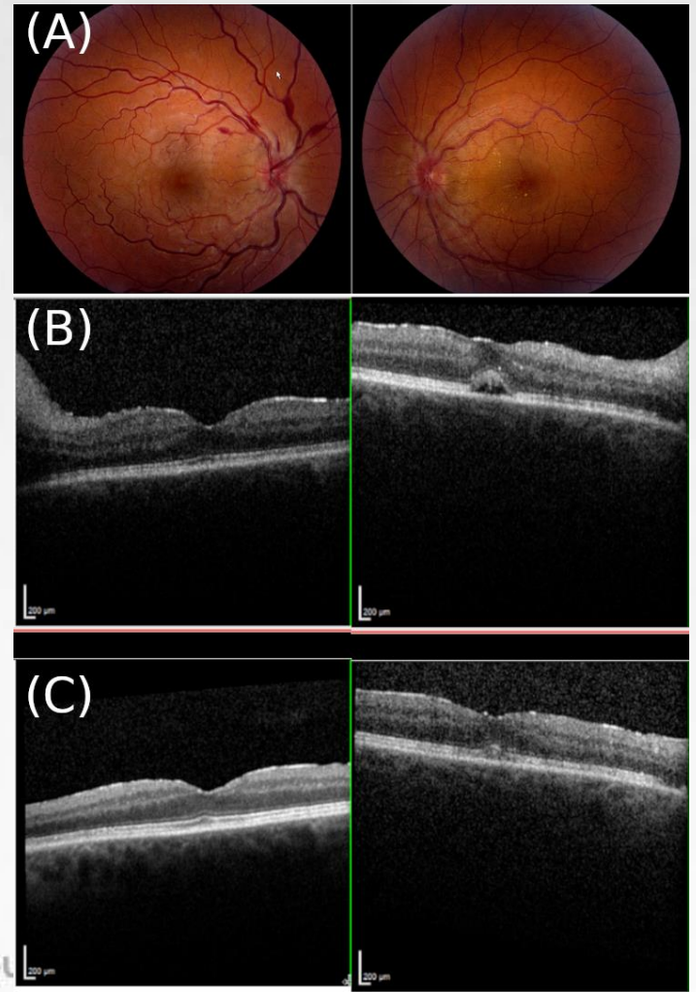
3rd Case

- 72 year old male develops febrile illness in Vietnam
- 2-3 weeks later bilateral, sequential, painless loss of vision (PL)
- no RAPD (but both pupils constrict with accomodation)
- Fundus (next slide):
  - Bilateral disc edema
  - RE hemorrhages
  - LE macular scar, CMO
- No recovery @ 6m fup (IVMP given ~6w after onset)



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Cases summary

- Case 1: is this MS ?

Scenario A: painful, monocular, subacute LOV, dyschromatopsia, RAPD

- Case 2: is this NMO ?

Scenario B: no pain, monocular, subacute LOV, dyschromatopsia, RAPD

- Case 3: what is this ?

Scenario C: binocular, subacute LOV, dyschromatopsia, no pain, no RAPD

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Is this quote still up to date?

"I can't see anything,
we can't see anything"

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“You & I don’t see anything”

- Key elements from Hx: Scenarios A-C
- Ethnicity is important:
  - MOG and AQP4 seropositivity more prevalent in African, Afrocaribbean and Asian background
- Examination: if you cannot demonstrate an afferent deficit, test the efferent pupil response
- Do an OCT if you cannot see anything

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Clinically alone

Acute unilateral optic neuritis:

- Loss of vision
- Pain worsening on eye movement
- Relative afferent pupillary defect

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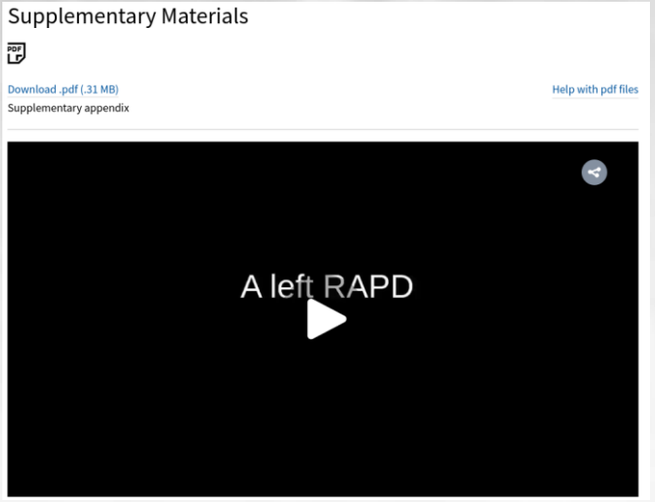
RAPD videos

CORRESPONDENCE | VOLUME 22, ISSUE 5, P376-377, MAY 2023 Download Full Issue

Application of diagnostic criteria for optic neuritis – Authors' reply

Axel Petzold • Yaou Liu • on behalf of the International Consortium on Optic Neuritis (ICON)

Published: May, 2023 • DOI: https://doi.org/10.1016/S1474-4422(23)00110-2



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What to ask in clinic

Panel 3: Signs and symptoms aiding the clinical classification of optic neuritis and exclusion of alternative pathologies

Clinical presentation*:

- Sequence of symptoms over time
- Preceding infection or vaccination
- Ethnic background or location
- Progression of pain or visual loss (>2 weeks)
- Absence of pain
- Associated epilepsy†
- Simultaneous bilateral ON
- Evidence of retinitis or retinal dysfunction from OCT or electrophysiology
- Presence of severe optic disc oedema
- Absence of optic disc oedema
- Unexplained optic atrophy in either eye at onset
- Fever or other systemic symptoms and signs‡
- Other focal neurological signs

Disease course§:

- Progressive loss of vision
- Progressive retinal layer atrophy for more than 12 months
- Sequential bilateral optic neuritis
- Absence of spontaneous recovery (>3 months)
- Corticosteroid dependence

Medical history:

- Medical history of cancer or diseases listed in panel 4
- Family history of a suspected hereditary optic neuropathy
- Family history of other mitochondrial cytopathy

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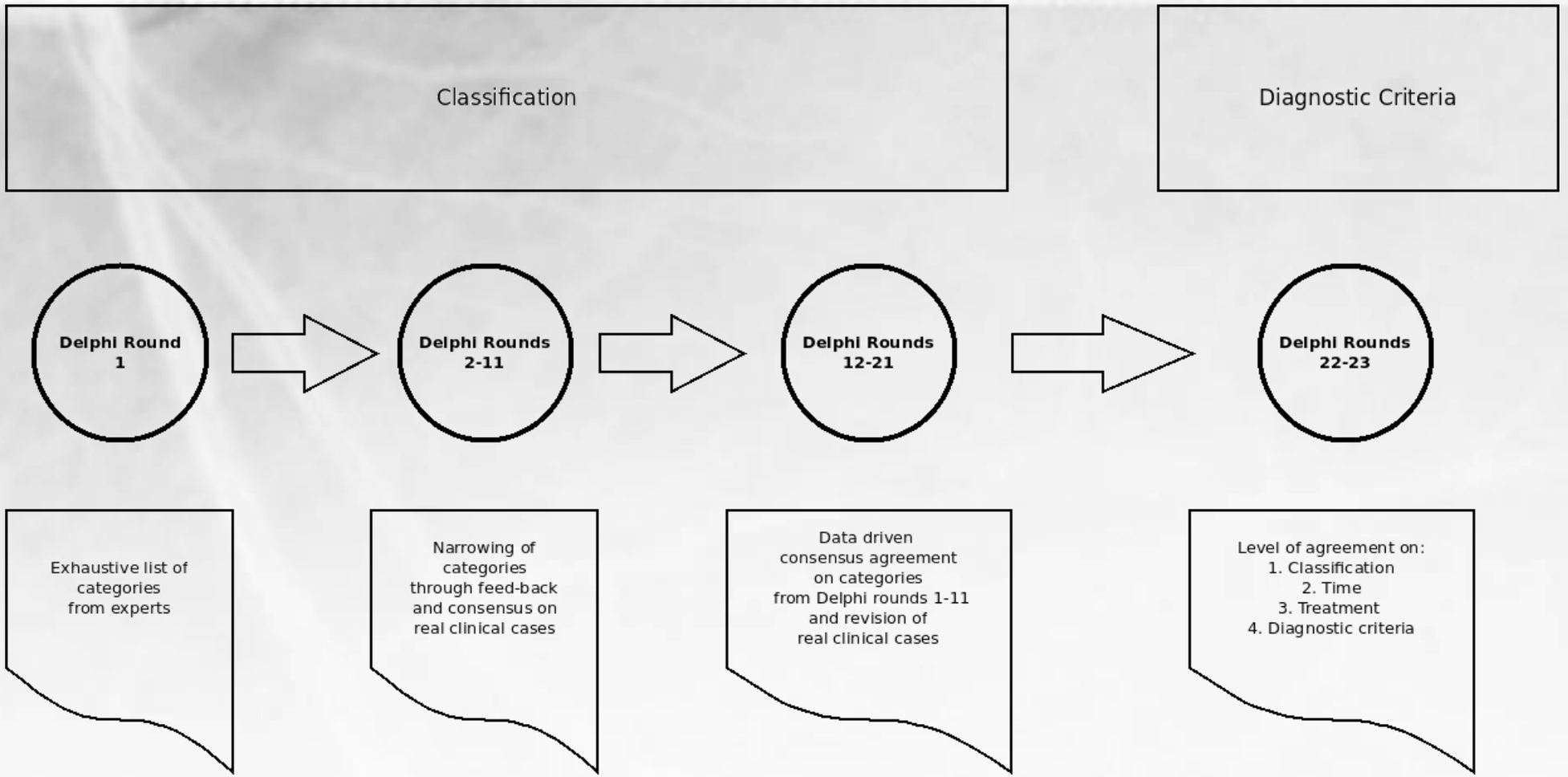
Delphi Process



Definition of consensus >80%

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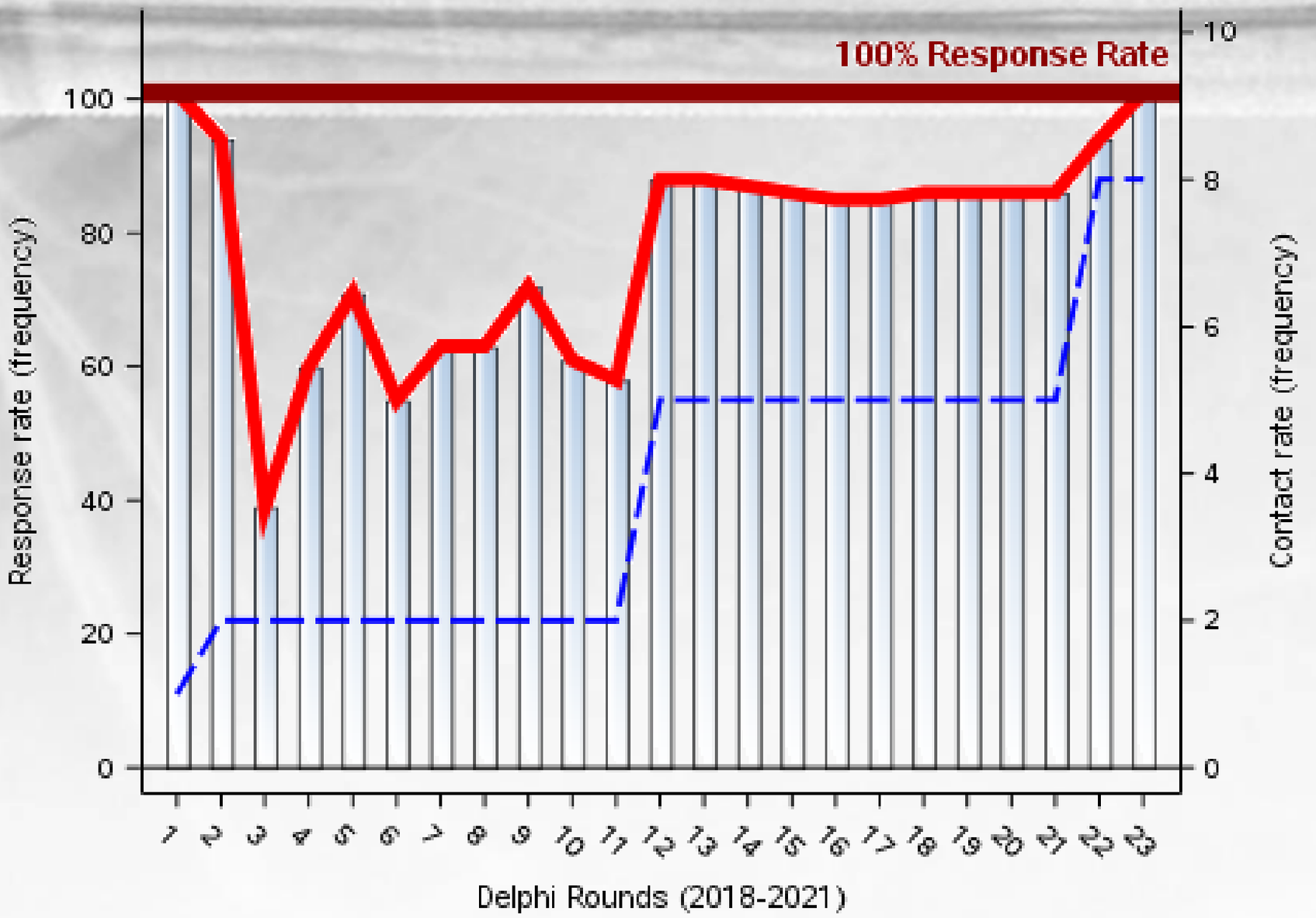
Delphi (2018-2021)



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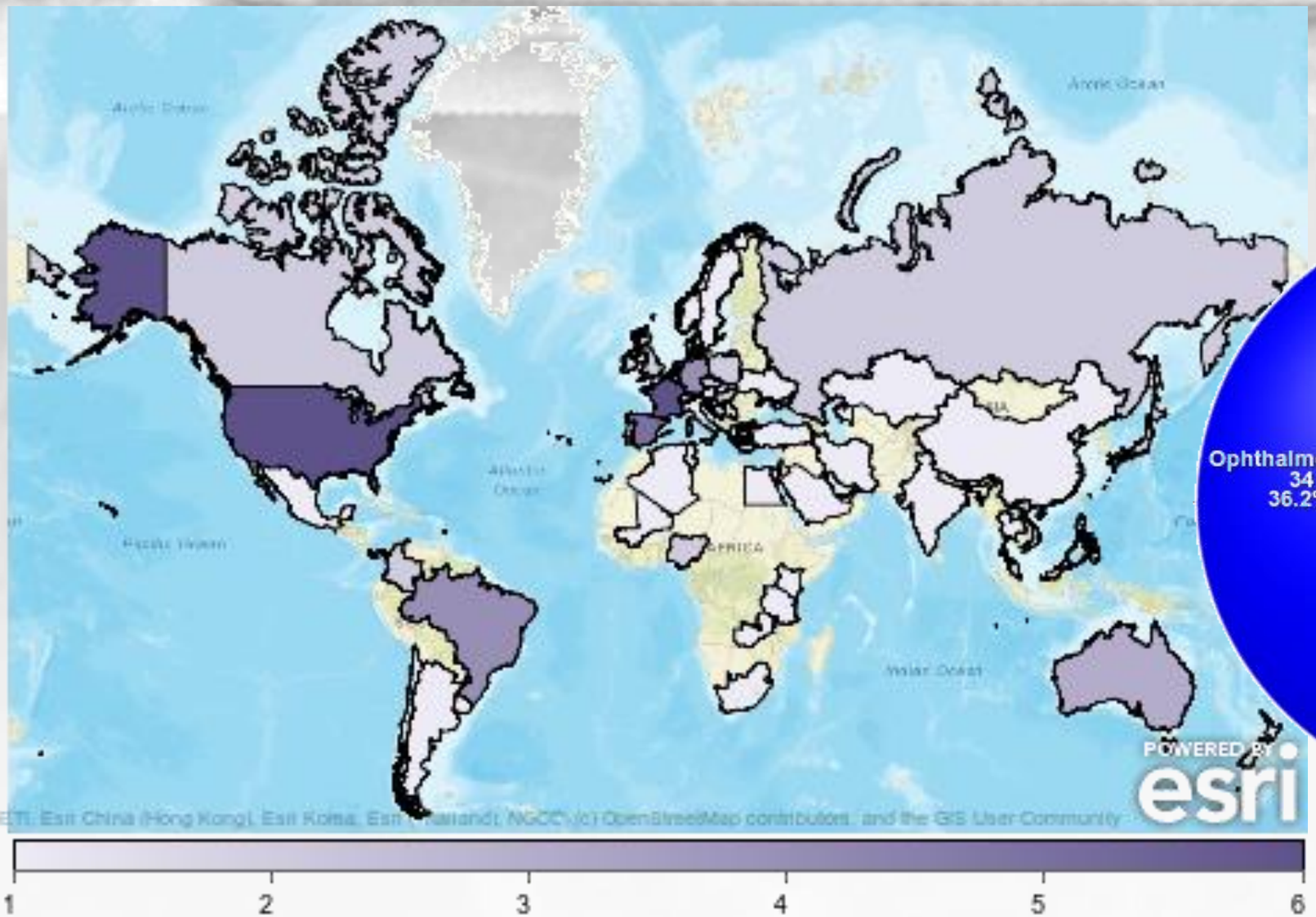
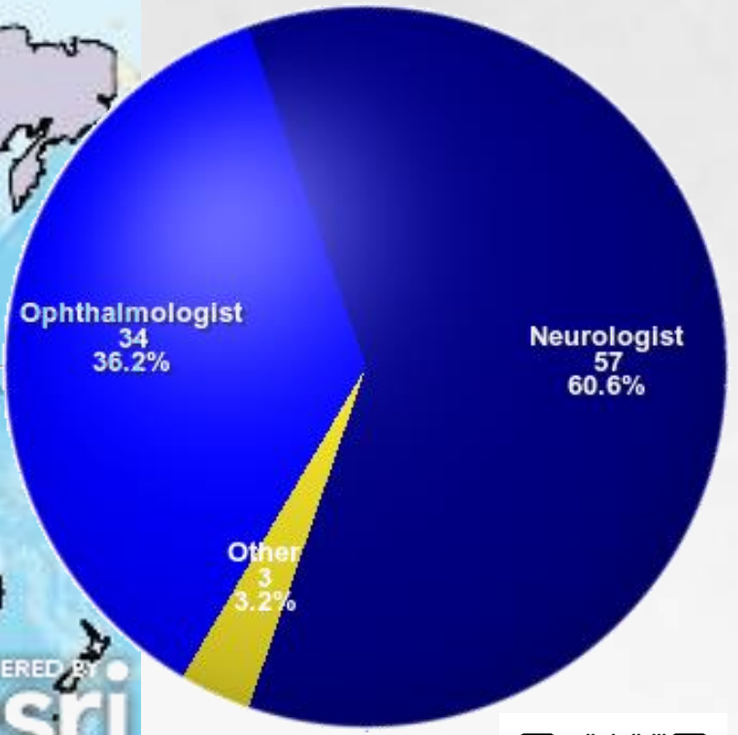
The Panel





World wide distribution of number of experts

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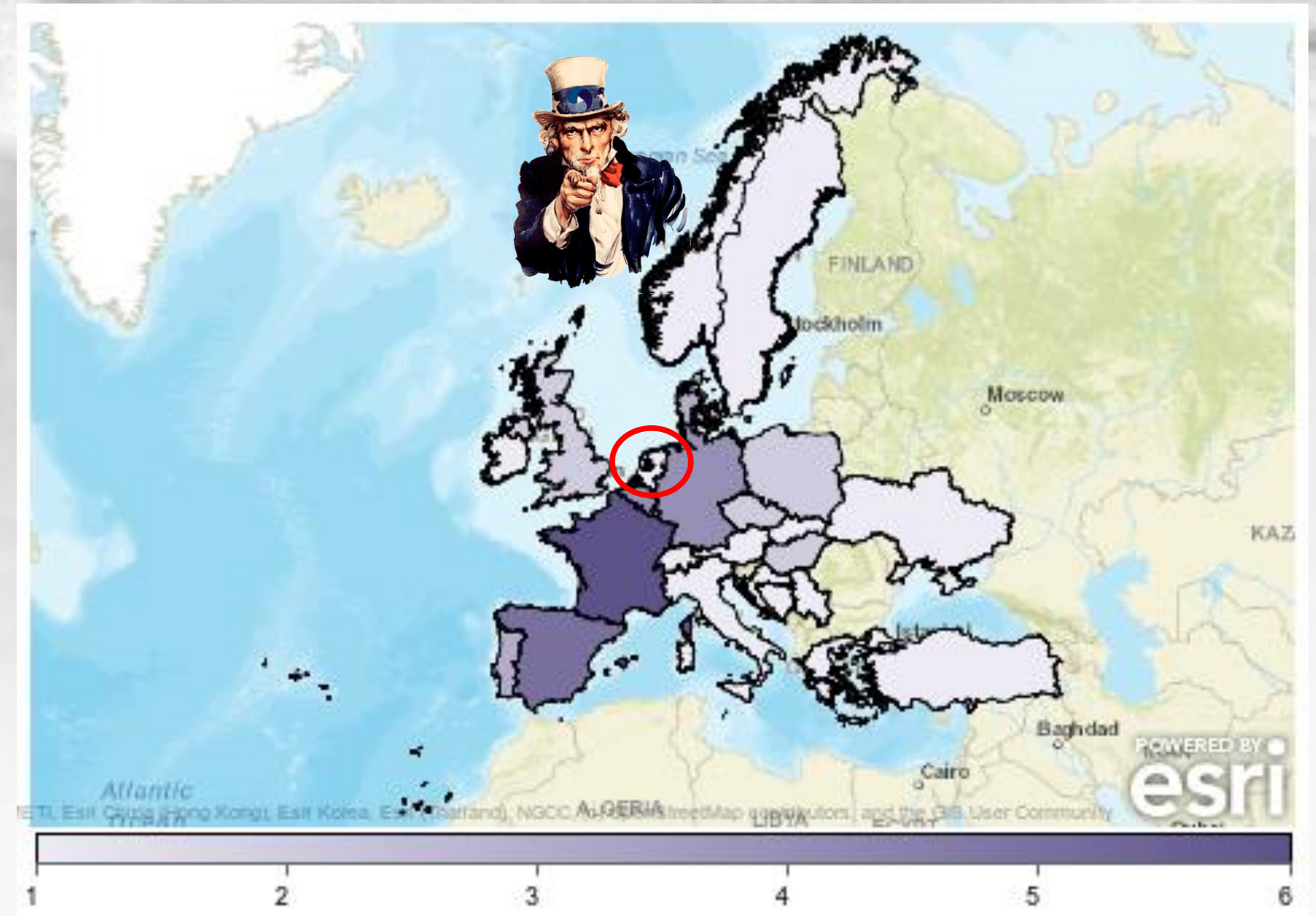
Oranje heef jouw nodig



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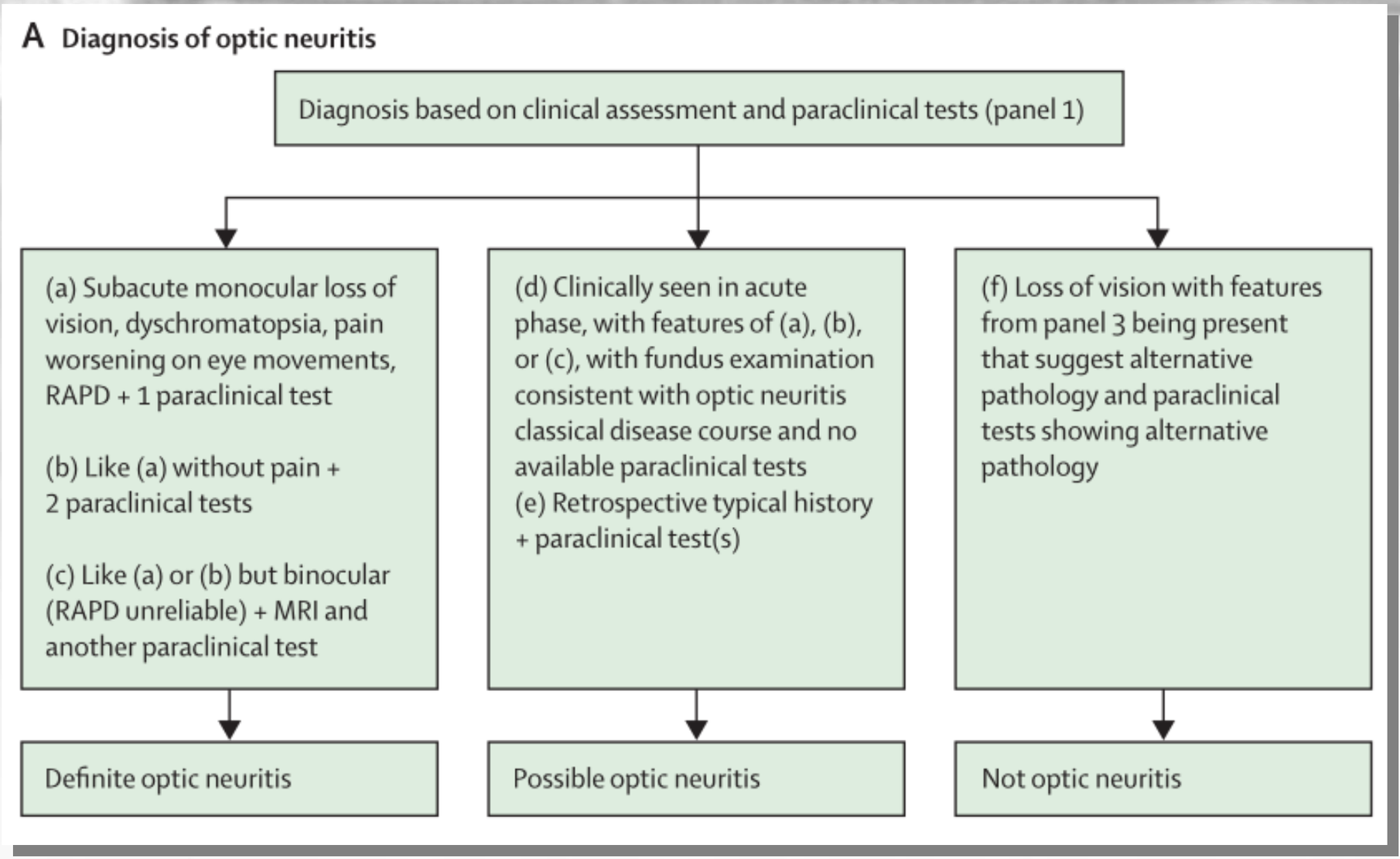
Diagnosis



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Panel 1: Diagnostic criteria for optic neuritis

Clinical criteria

- A: Monocular, subacute loss of vision associated with orbital pain worsening on eye movements, reduced contrast and colour vision, and relative afferent pupillary deficit
- B: Painless with all other features of (A).
- C: Binocular loss of vision with all features of (A) or (B).

Paraclinical criteria

- OCT: Corresponding optic disc swelling acutely or an inter-eye difference in the mGCIPL of >4% or >4 µm or in the pRNFL of >5% or >5 µm within 3 months after onset.
- MRI: Contrast enhancement of the symptomatic optic nerve and sheaths acutely or an intrinsic signal (looking brighter) increase within 3 months.
- Biomarker: AQP4, MOG, or CRMP5 antibody seropositive, or intrathecal CSF IgG (oligoclonal bands).

Application of the clinical and paraclinical criteria

Definite optic neuritis

- (A) and one paraclinical test
- (B) and two paraclinical tests of different modality
- (C) and two different paraclinical tests of which one is MRI

Possible optic neuritis

- (A), (B), or (C) if seen acutely but in absence of paraclinical tests, with fundus examination typical for optic neuritis and consistent with the natural history during follow-up
- Positive paraclinical test or tests, with a medical history suggestive of optic neuritis

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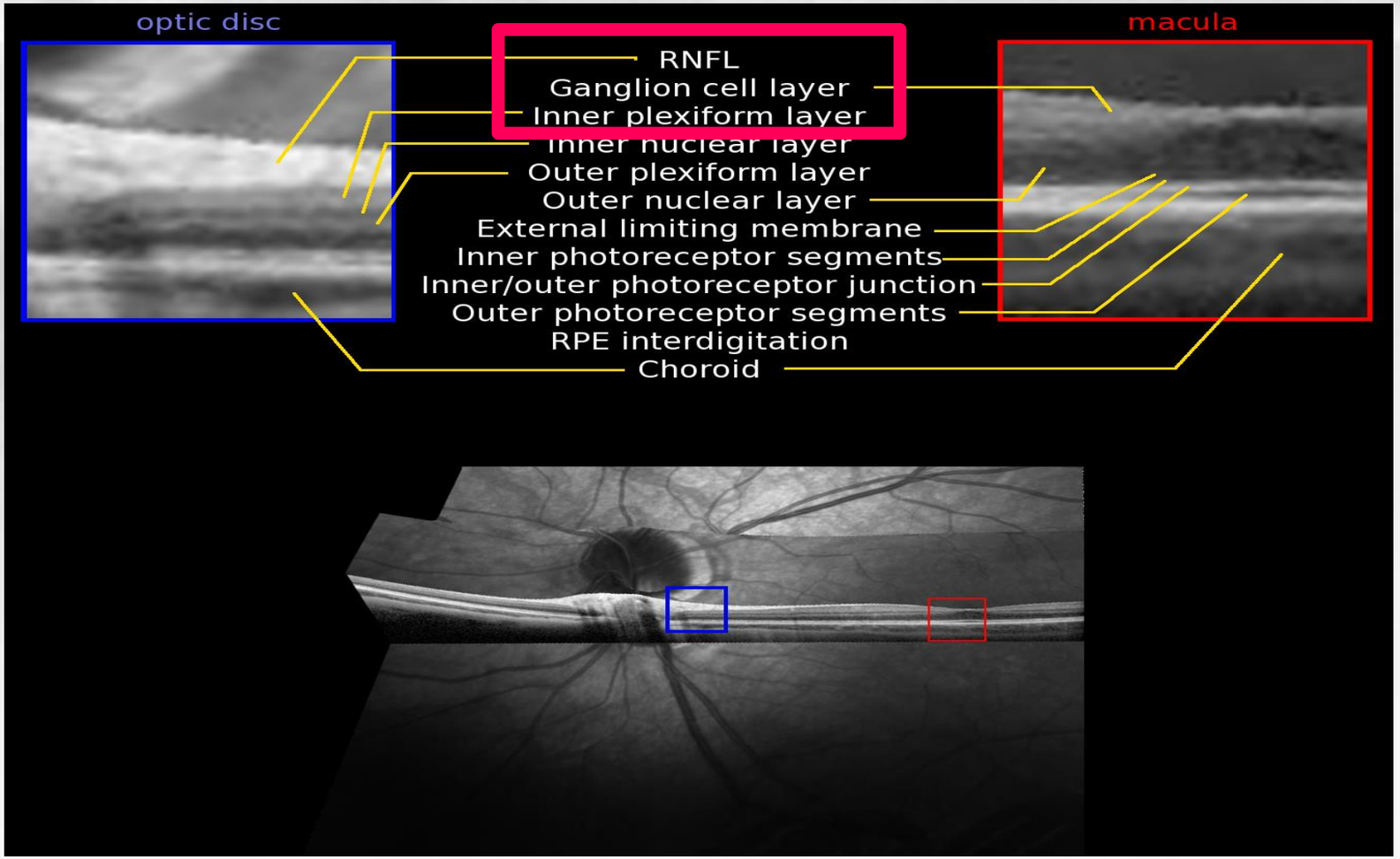
OCT



Petzold *et al.* TLN 2010

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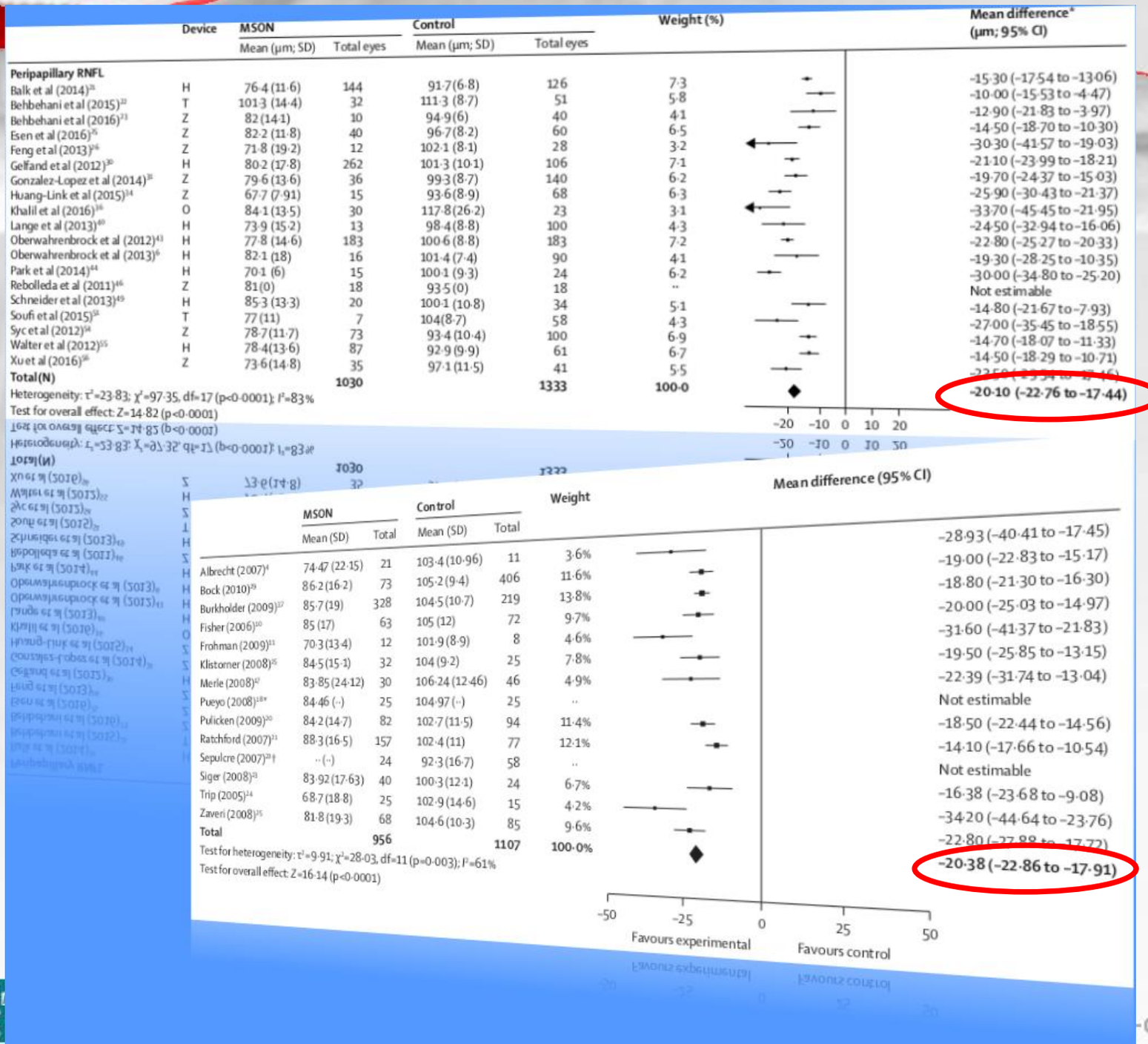
OCT in MS-ON



	Device	MSON		Control		Weight (%)	Mean difference* (µm; 95% CI)
		Mean (µm; SD)	Total eyes	Mean (µm; SD)	Total eyes		
Peripapillary RNFL							
Balk et al (2014)[35]	H	76·4 (11·6)	144	91·7 (6·8)	126	7·3	−15·30 (−17·54 to −13·06)
Behbehani et al (2015)[22]	T	101·3 (14·4)	32	111·3 (8·7)	51	5·8	−10·00 (−15·53 to −4·47)
Behbehani et al (2016)[23]	Z	82 (14·1)	10	94·9 (6)	40	4·1	−12·90 (−21·83 to −3·97)
Esen et al (2016)[25]	Z	82·2 (11·8)	40	96·7 (8·2)	60	6·5	−14·50 (−18·70 to −10·30)
Feng et al (2013)[26]	Z	71·8 (19·2)	12	102·1 (8·1)	28	3·2	−30·30 (−41·57 to −19·03)
Gelfand et al (2012)[30]	H	80·2 (17·8)	262	101·3 (10·1)	106	7·1	−21·10 (−23·99 to −18·21)
Gonzalez-Lopez et al (2014)[31]	Z	79·6 (13·6)	36	99·3 (8·7)	140	6·2	−19·70 (−24·37 to −15·03)
Huang-Link et al (2015)[34]	Z	67·7 (7·91)	15	93·6 (8·9)	68	6·3	−25·90 (−30·43 to −21·37)
Khalil et al (2016)[36]	O	84·1 (13·5)	30	117·8 (26·2)	23	3·1	−33·70 (−45·45 to −21·95)
Lange et al (2013)[40]	H	73·9 (15·2)	13	98·4 (8·8)	100	4·3	−24·50 (−32·94 to −16·06)
Oberwahrenbrock et al (2012)[43]	H	77·8 (14·6)	183	100·6 (8·8)	183	7·2	−22·80 (−25·27 to −20·33)
Oberwahrenbrock et al (2013)[6]	H	82·1 (18)	16	101·4 (7·4)	90	4·1	−19·30 (−28·25 to −10·35)
Park et al (2014)[44]	H	70·1 (6)	15	100·1 (9·3)	24	6·2	−30·00 (−34·80 to −25·20)
Rebolleda et al (2011)[46]	Z	81 (0)	18	93·5 (0)	18	..	Not estimable
Schneider et al (2013)[49]	H	85·3 (13·3)	20	100·1 (10·8)	34	5·1	−14·80 (−21·67 to −7·93)
Soufi et al (2015)[52]	T	77 (11)	7	104 (8·7)	58	4·3	−27·00 (−35·45 to −18·55)
Syc et al (2012)[54]	Z	78·7 (11·7)	73	93·4 (10·4)	100	6·9	−14·70 (−18·07 to −11·33)
Walter et al (2012)[55]	H	78·4 (13·6)	87	92·9 (9·9)	61	6·7	−14·50 (−18·29 to −10·71)
Xu et al (2016)[56]	Z	73·6 (14·8)	35	97·1 (11·5)	41	5·5	−23·50 (−29·94 to −17·06)
Total(N)			**1030**		**1333**	**100·0**	**−20·10 (−22·76 to −17·44)**

Heterogeneity: τ^2=23·83; χ^2=97·35, df=17 (p<0·0001); I^2=83%

Test for overall effect: Z=14·82 (p<0·0001)

−20 −10 0 10 20

	MSON		Control		Weight	Mean difference (95% CI)
	Mean (SD)	Total	Mean (SD)	Total		
Albrecht (2007)[4]	74·47 (22·15)	21	103·4 (10·96)	11	3·6%	−28·93 (−40·41 to −17·45)
Bock (2010)[29]	86·2 (16·2)	73	105·2 (9·4)	406	11·6%	−19·00 (−22·83 to −15·17)
Burkholder (2009)[32]	85·7 (19)	328	104·5 (10·7)	219	13·8%	−18·80 (−21·30 to −16·30)
Fisher (2006)[10]	85 (17)	63	105 (12)	72	9·7%	−20·00 (−25·03 to −14·97)
Frohman (2009)[11]	70·3 (13·4)	12	101·9 (8·9)	8	4·6%	−31·60 (−41·37 to −21·83)
Klistorner (2008)[35]	84·5 (15·1)	32	104 (9·2)	25	7·8%	−19·50 (−25·85 to −13·15)
Merle (2008)[42]	83·85 (24·12)	30	106·24 (12·46)	46	4·9%	−22·39 (−31·74 to −13·04)
Pueyo (2008)[18*]	84·46 (··)	25	104·97 (··)	25	..	Not estimable
Pulicken (2009)[20]	84·2 (14·7)	82	102·7 (11·5)	94	11·4%	−18·50 (−22·44 to −14·56)
Ratchford (2007)[21]	88·3 (16·5)	157	102·4 (11)	77	12·1%	−14·10 (−17·66 to −10·54)
Sepulcre (2007)[28†]	·· (··)	24	92·3 (16·7)	58	..	Not estimable
Siger (2008)[33]	83·92 (17·63)	40	100·3 (12·1)	24	6·7%	−16·38 (−23·68 to −9·08)
Trip (2005)[24]	68·7 (18·8)	25	102·9 (14·6)	15	4·2%	−34·20 (−44·64 to −23·76)
Zaveri (2008)[25]	81·8 (19·3)	68	104·6 (10·3)	85	9·6%	−22·80 (−27·88 to −17·72)
Total		**956**		**1107**	**100·0%**	**−20·38 (−22·86 to −17·91)**

Test for heterogeneity: τ^2=9·91; χ^2=28·03, df=11 (p=0·003); I^2=61%

Test for overall effect: Z=16·14 (p<0·0001)

−50 −25 0 25 50

Favours experimental Favours control

pRNFL atrophy

TLN 2010

20.10 (17.44-22.76) µm

TLN 2017

20.38 (17.91-22.86) µm

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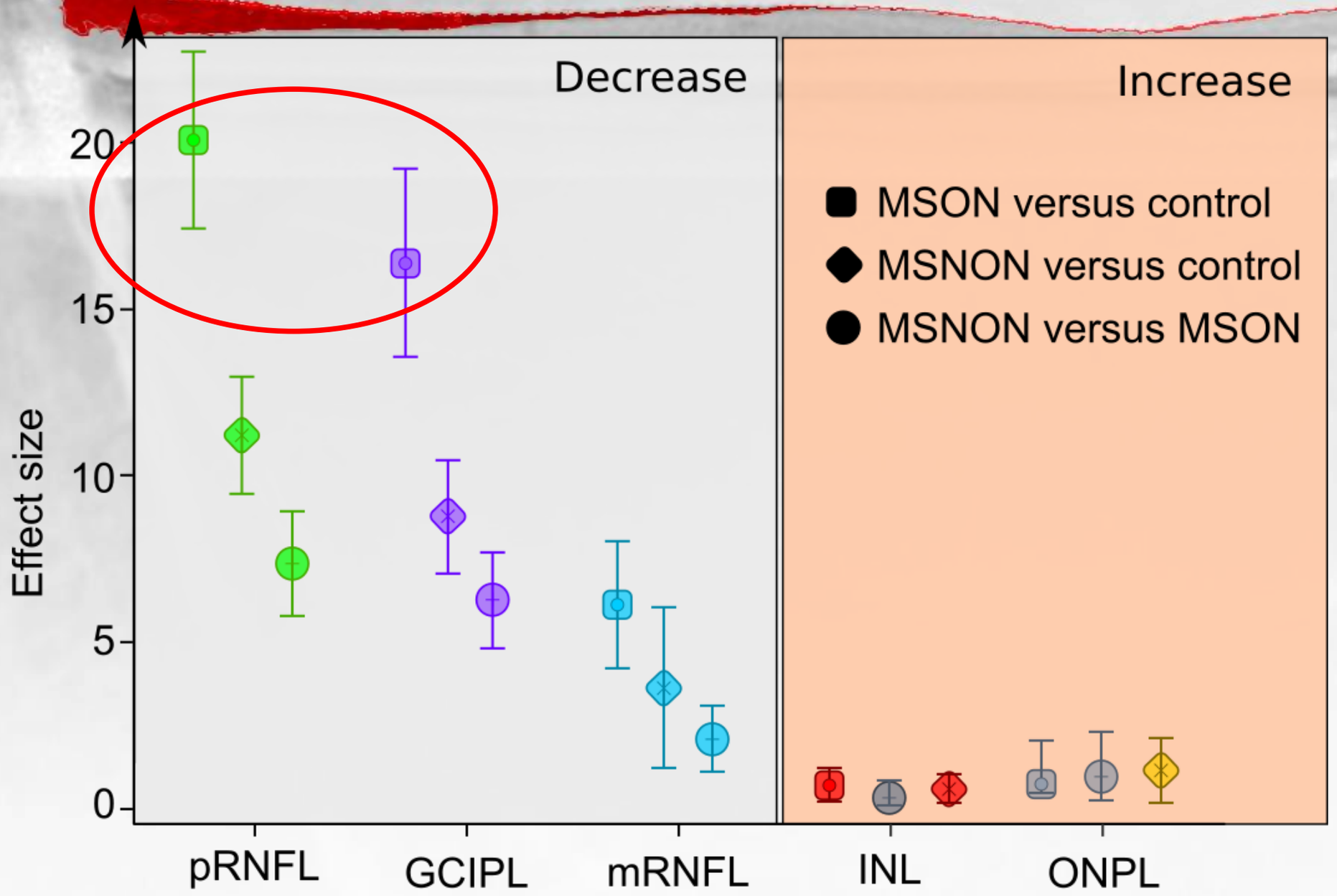
What is relevant ?



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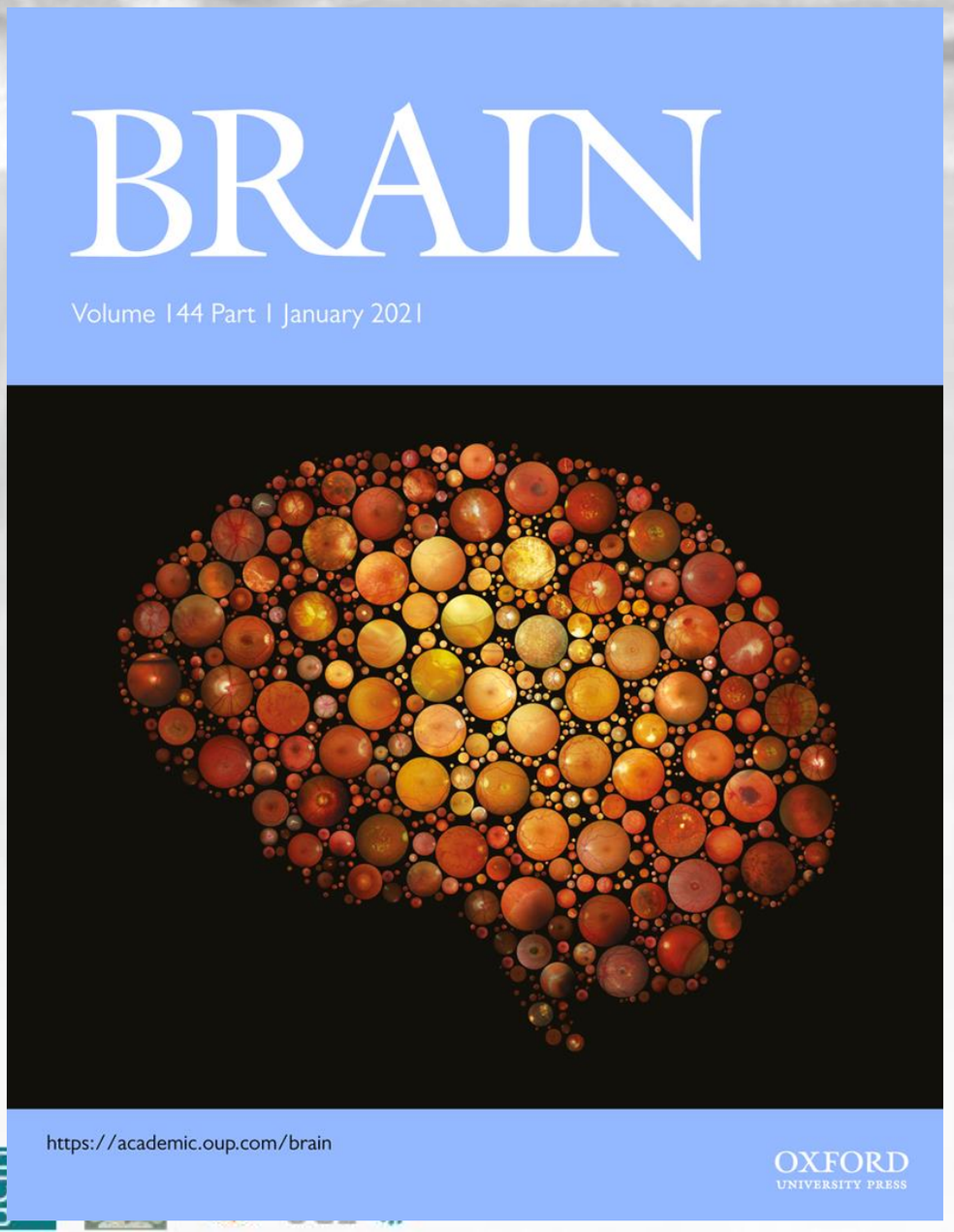
Retinal asymmetry



Inter-eye difference:

Percentage difference (IEPD): %

Absolute difference (IEAD): µm

Petzold *et al.* BRAIN 2021

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High diagnostic accuracy

OCT measure	Optimized cut-off	Reference	Group comparison	Specificity	Sensitivity
IEPD mGCiPL	5 %	Coric et al. 2017	Symptomatic bilateral MSON vs. healthy controls	97 %	86 %
IEPD mGCIPL	6 %	Coric et al. 2017	Symptomatic unilateral MSON vs. healthy controls	97 %	70 %
IEAD mGCIPL	4.0 µm	Nolan-Kenney 2019	Symptomatic unilateral MSON vs. non-MSON	77 %	68 %
IEAD mGCIPL	3.5 µm	Behbehani 2020	Unilateral optic neuritis vs. healthy controls	98%	100 %
IEAD mGCIPL	2.83 µm	Davion 2020	Symptomatic unilateral or bilateral MSON vs. non-MSON[a]	67.4 %	67.3 %
IEPD/IEAD	4% / 4 µm	Petzold 2020	MS without MSON vs controls (n=72,120)	82.8% / 86.8%	51.7% / 43.5%
IEAD mGCIPL	1.42 µm	Outteryck 2020	CIS patients with vs. without an asymptomatic optic nerve lesion on 3D-DIR MRI	72.6 %	89.3 %
IEPD mGCIPL	2 %	Outteryck 2020	CIS patients with vs. without an asymptomatic optic nerve lesion on 3D-DIR MRI	69.4 %	89.3 %

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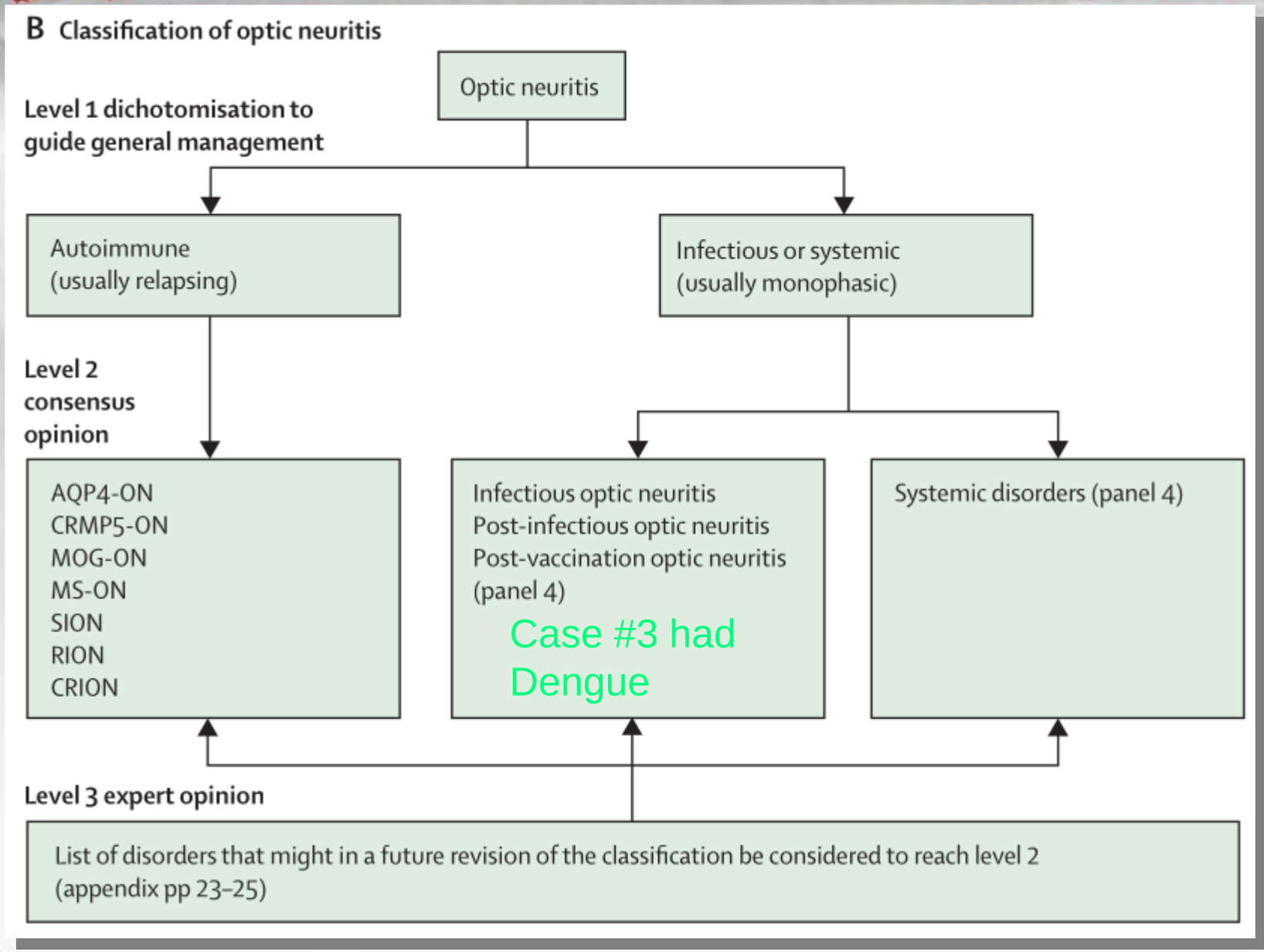
Classification



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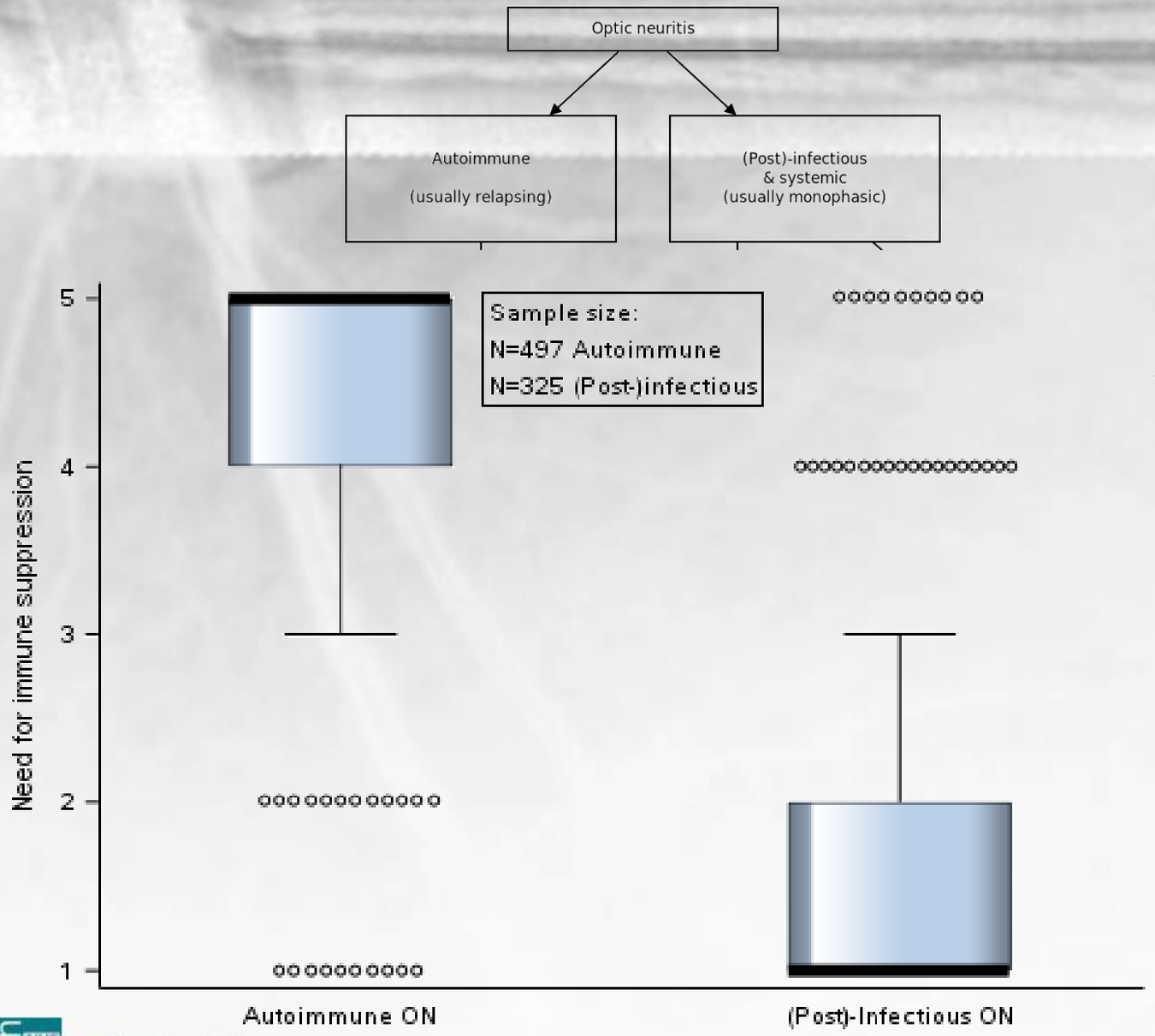
How did we get there?



Level 1: 95% agreement

Based on iterative assessments from Delphi rounds 2-21

Relevant for patient management

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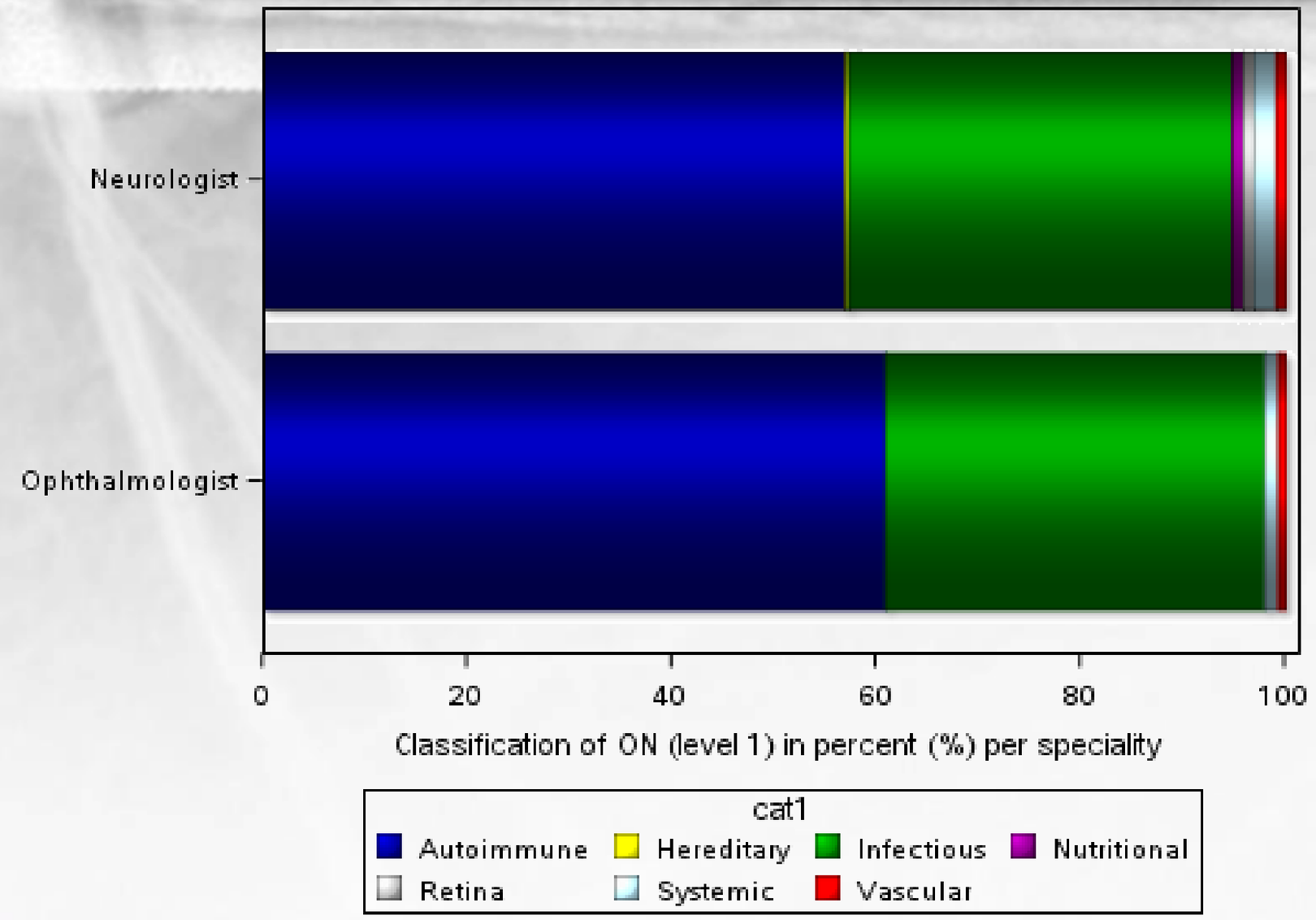
Agreement: Speciality



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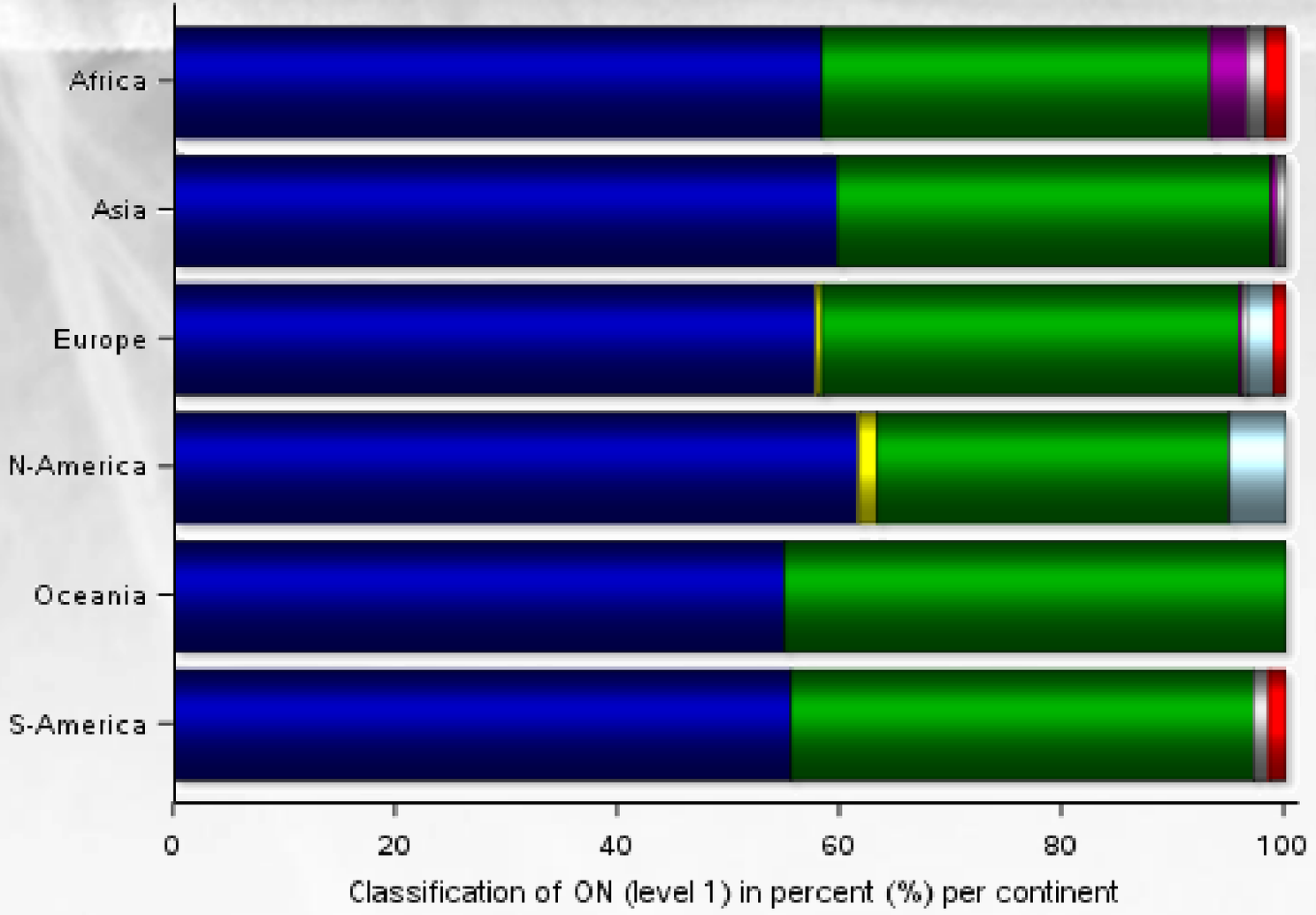
Agreement: Continent



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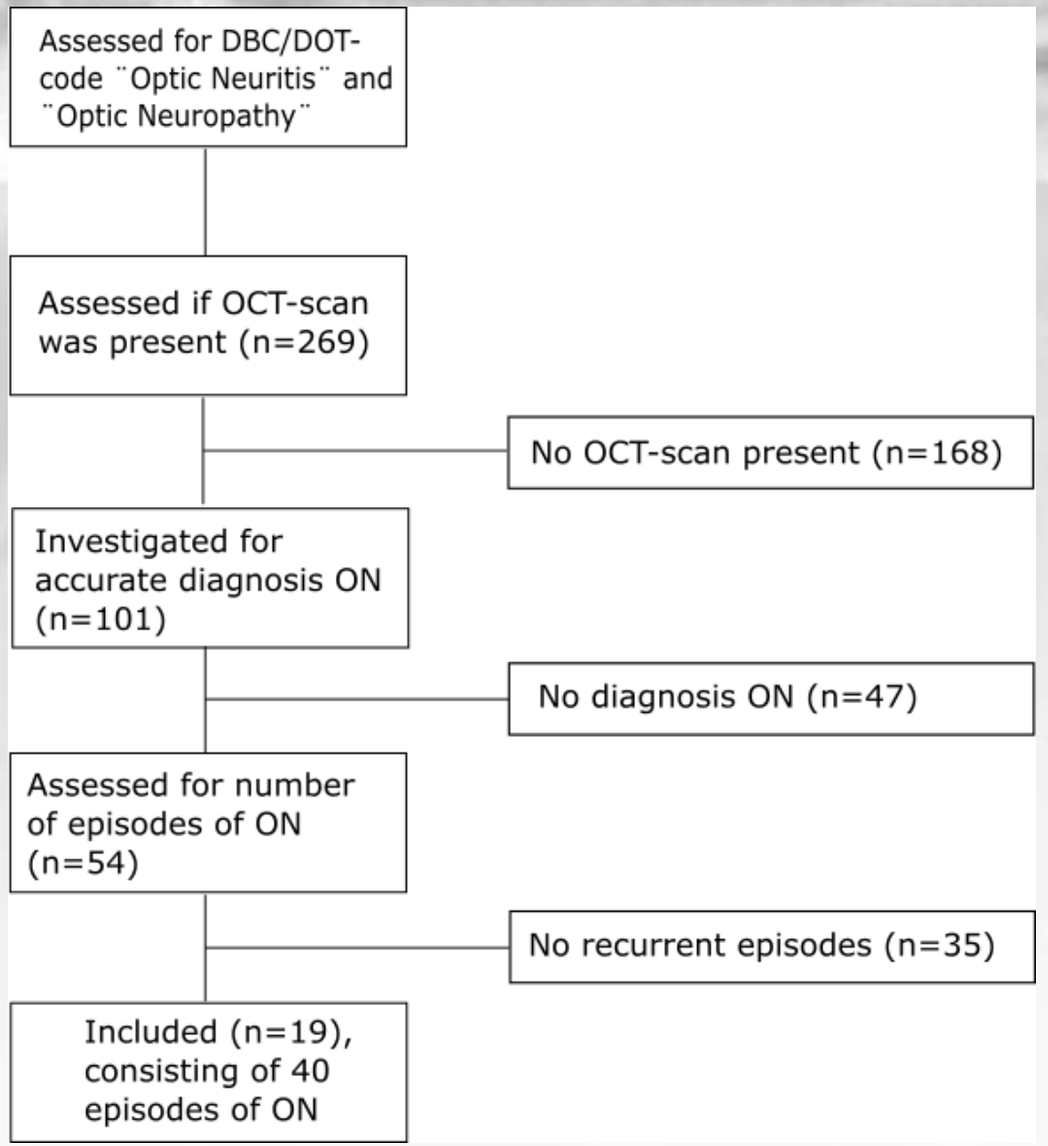
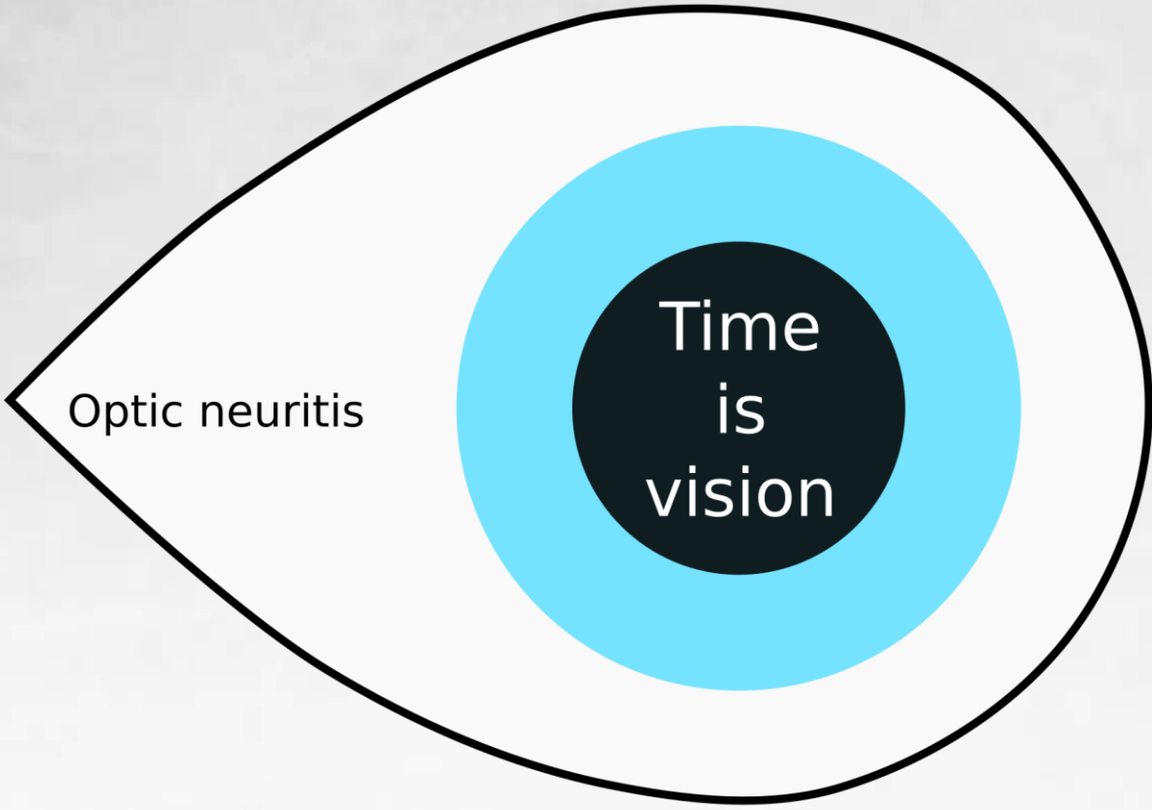
NMO-ON @Amsterdam UMC





Osinga *et al.* Brain Res 2017

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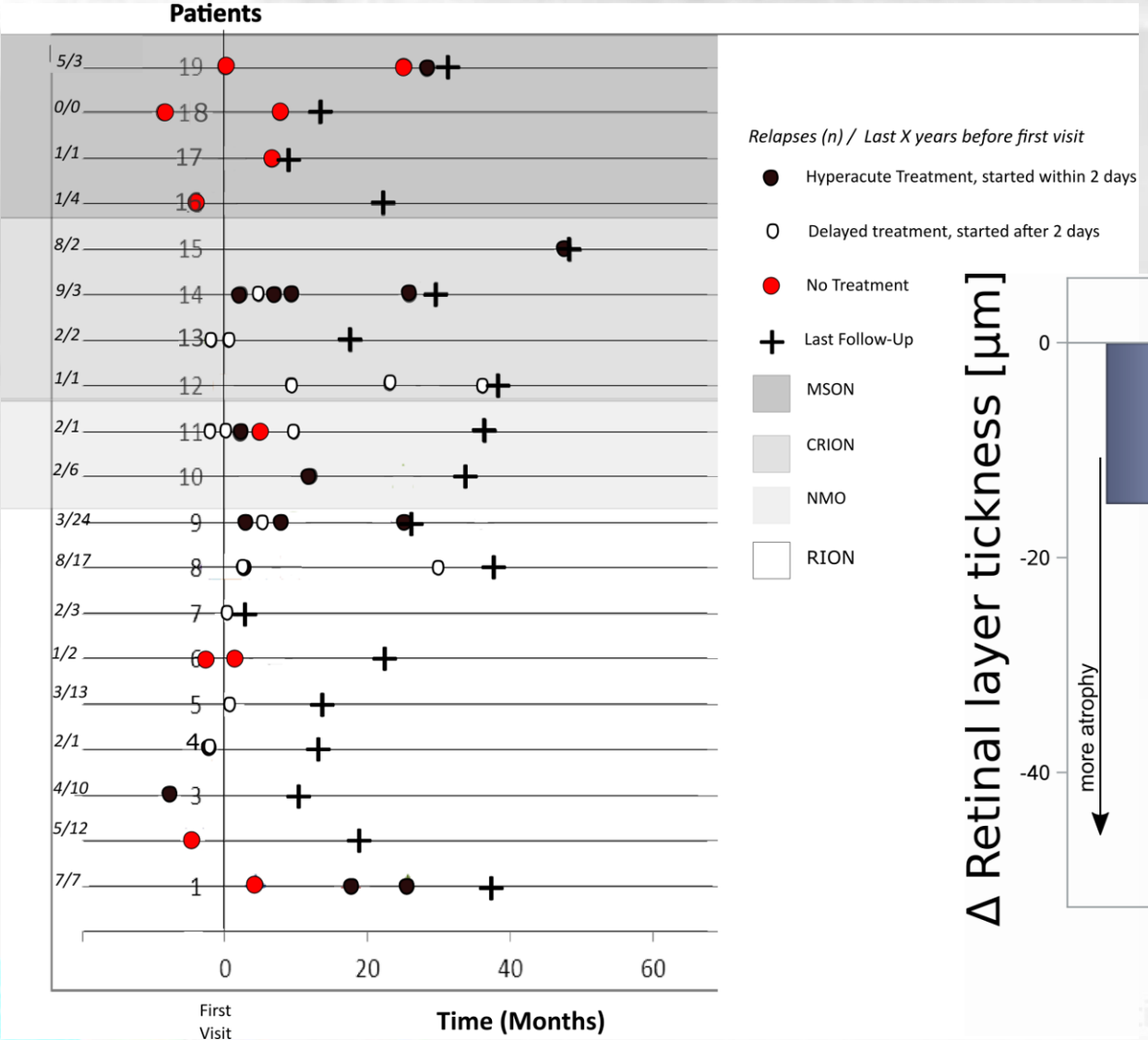
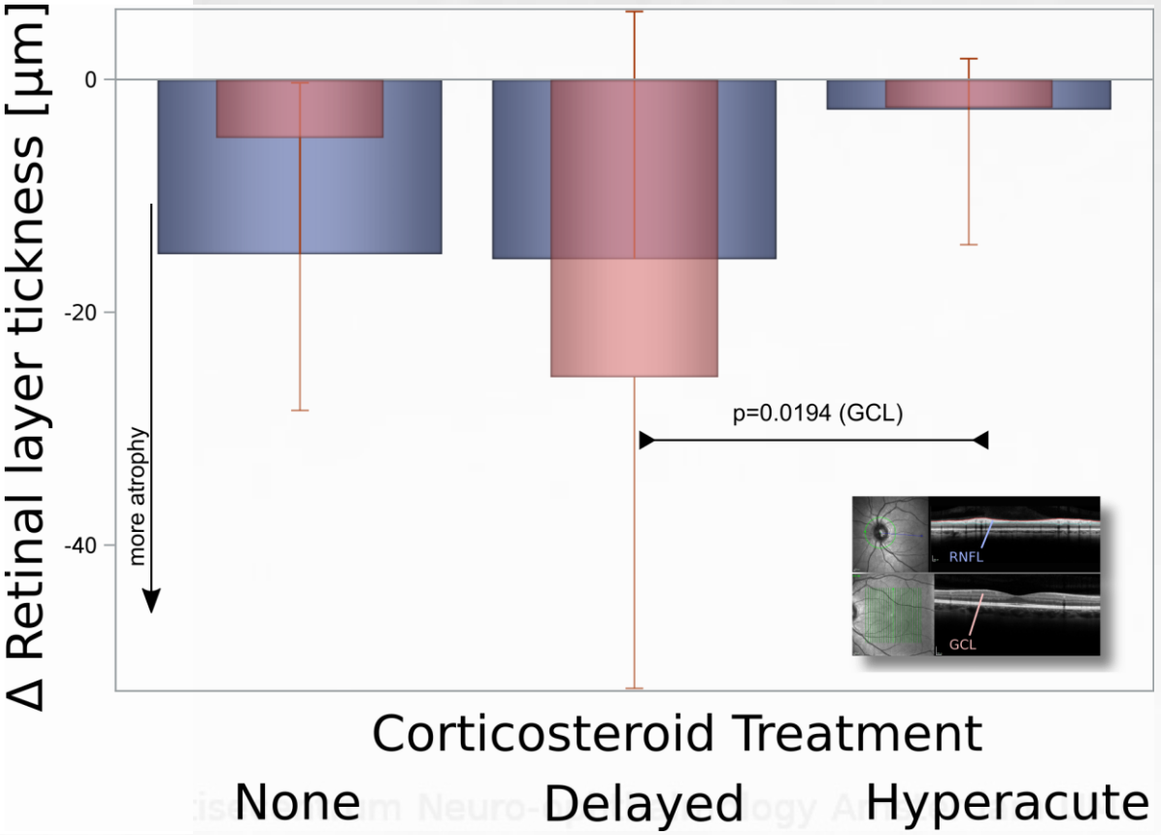
NMO-ON @Amsterdam UMC





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Retinal asymmetry in NMO-ON

Table 1 Demographic overview

	HC	NMOSD-NON	NMOSD-ON
Subjects (n)	62	45	28
Eyes (n)	124	90	56
Patients with a disease duration <10 years (n)	.	43	21
Patients with ON as first manifestation (n)	.	.	17
Age (year, mean±SD)	37.7±10.2	39.0±10.4	38.8±12.1
Sex (male, n (%))	20 (32)	2 (4)	3 (11)
Time since ON (year, median (min–max))	.	.	2.8 (0.7–19.5)
Time since onset (year, mean±SD)	.	3.8±4.0	6.5±5.6
pRNFL thickness (µm, mean±SD)	98.5±9.4	98.8±10.8	80.7±24.9
pRNFL IEPD (%, mean±SD)	2.7±2.3	3.7±4.4	28.6±19.9
pRNFL IEAD (µm, mean±SD)	2.7±2.2	3.8±4.5	27.0±19.8
GCIPL thickness (µm, mean±SD)	79.9±5.3	77.6±6.3	66.3±13.2
GCIPL IEPD (%, mean±SD)	1.3±1.1	2.7±3.5	19.0±14.3
GCIPL IEAD (µm, mean±SD)	1.0±0.9	2.1±2.9	14.1±10.9

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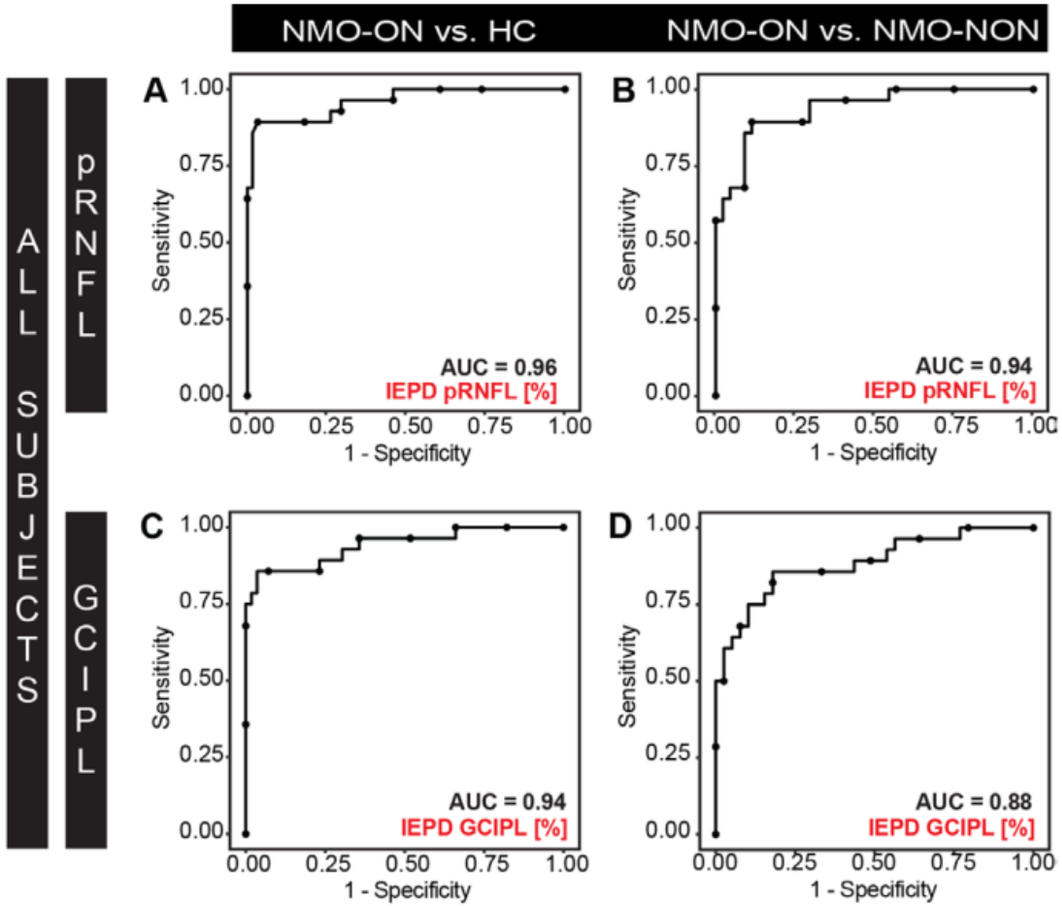
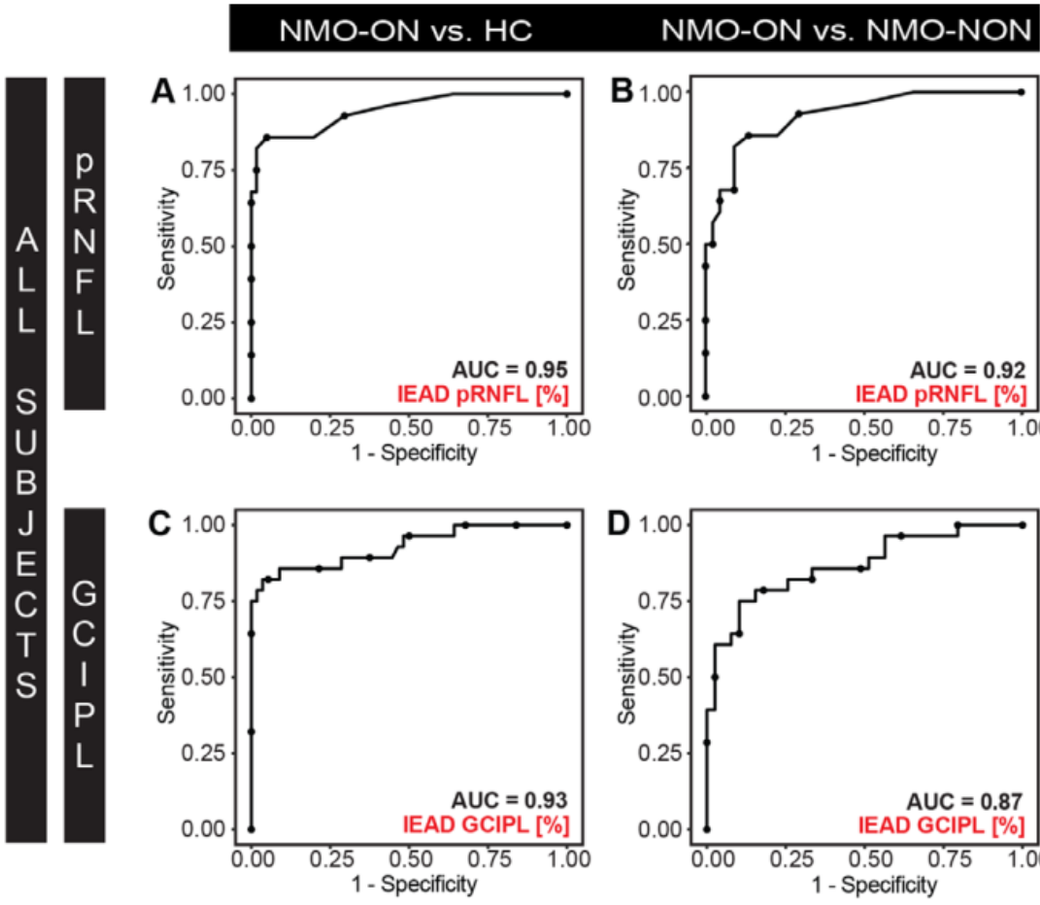
Retinal asymmetry in NMO-ON

IEPD



IEAD



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Retinal asymmetry in MOG-ON

Baseline (subjects)	HC	MOG
N	33	33
Center [N (%)]		
Berlin	28 (84.8)	7 (21.2)
Mangalore	5 (15.2)	4 (12.1)
UCL	0 (0.0)	22 (66.7)
Age [years, mean(SD)]	34.33 (11.33)	38.74 (14.75)
Sex [m, N(%)]	16 (48.5)	16 (48.5)
Time since ON [years, mean(SD)]	NaN (NA)	3.33 (4.07)
IEAD pRNFL [µm]	2.70 (2.49)	18.31 (23.29)
IEPD pRNFL [%]	2.77 (2.61)	20.43 (23.35)
IEAD GCIPL [µm]	2.61 (2.70)	15.88 (18.74)
IEPD GCIPL [%}	2.92 (2.88)	20.37 (20.66)

[a] MOGAD and HC were matched for age (p=0.178) and gender (p>0.99)

Giulio Volpe et al. (unpublished)

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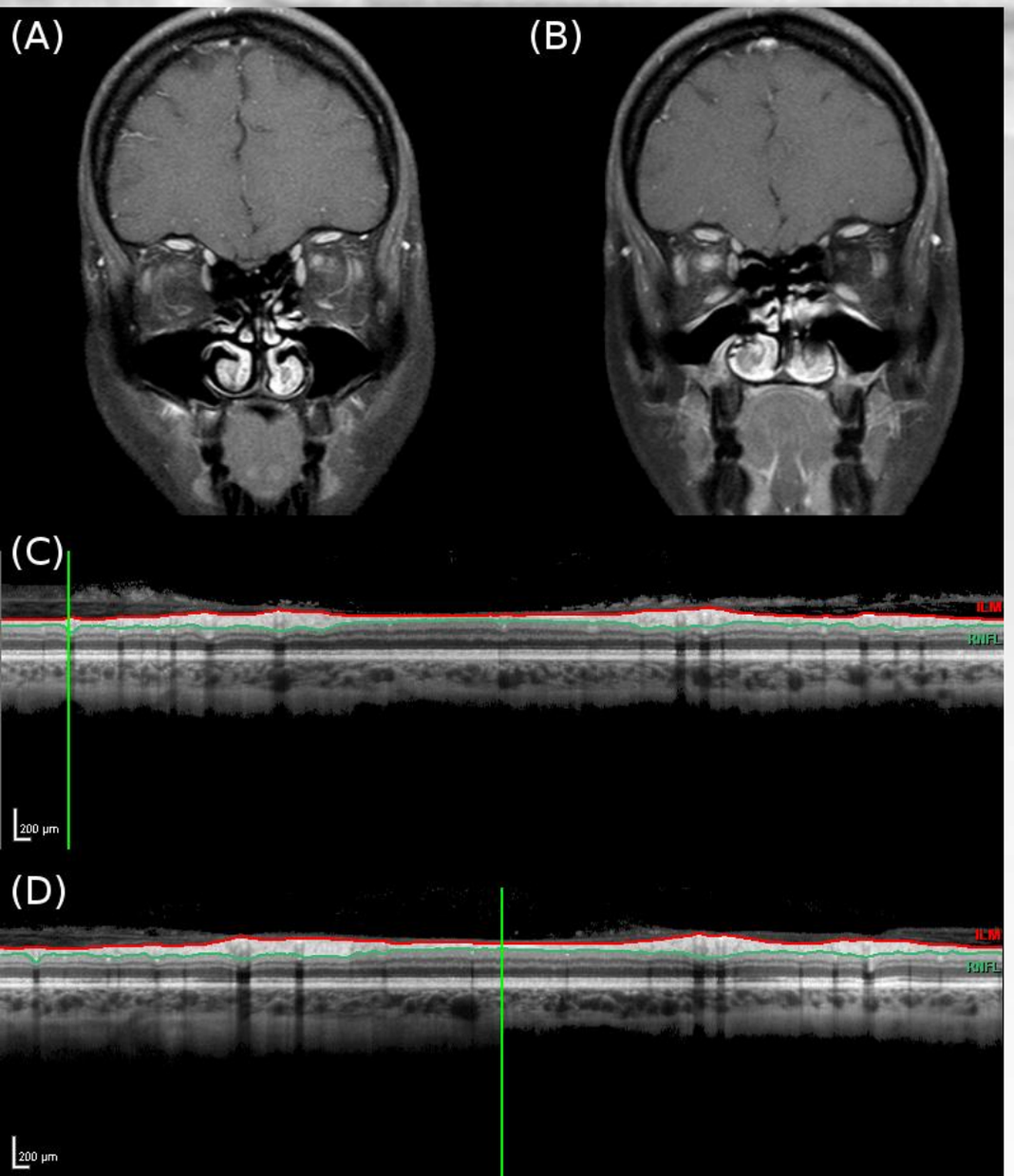
My 1st MOG-ON patient in NL



Hx: bilateral, simultaneous ON as child & < 3seg myelopathy

LOV RE was preceded by severe pain on eye–movements (VAS 6-8/10) & MRI (A)

During follow–up LE LOV preceded by pain on eye–movements, MRI (B)

Stabilised with immunosupression (corticosteroid taper & AZT)

pRNFL RE 59 µm (C)
PRNFL LE 64 µm (D)
IEPD = 9.2% (normal < 5%)

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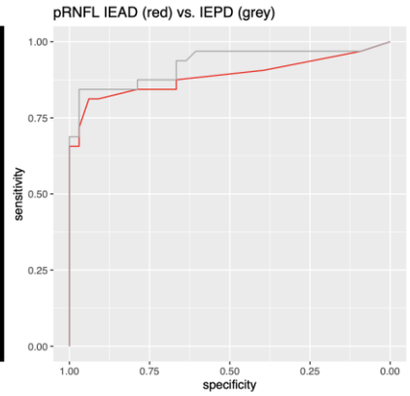
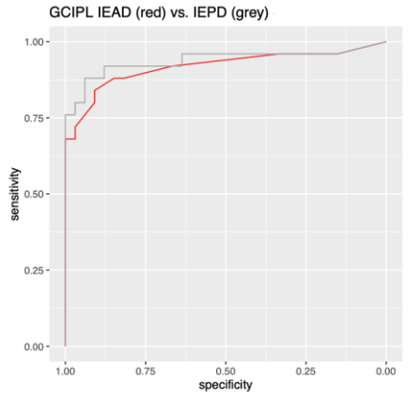
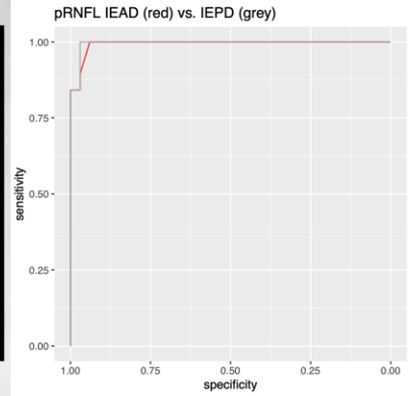
Retinal asymmetry in MOG-ON

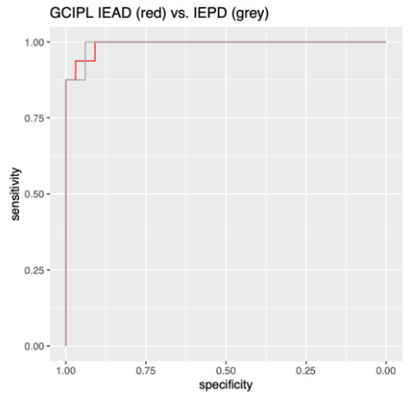
MOG vs HC



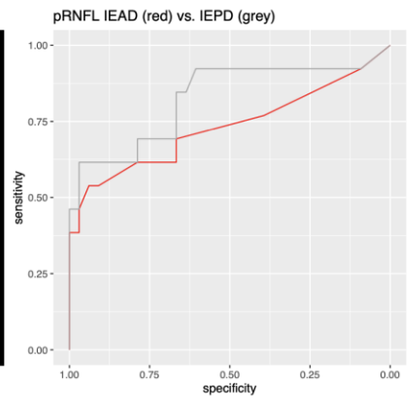


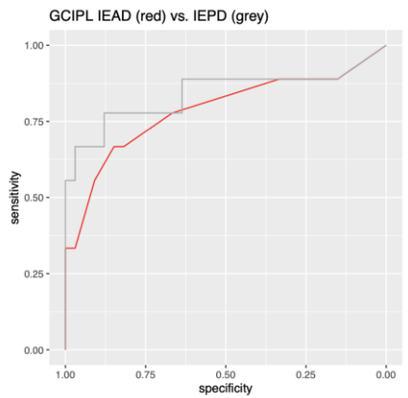
MOG unilat. vs HC





MOG bilat. vs HC





Baseline (eye)				
	HC	**MOG-ON**		
		pooled	**Unilateral**	**Bilateral**
N	**66**	**66**	**40**	**26**
pRNFL	95.98 (7.91)	71.03 (24.35)	78.26 (23.06)	60.46 (22.63)
mGCIP	86.48 (9.64)	67.32 (19.46)	75.88 (17.61)	51.61 (11.25)

Giulio Volpe *et al.* (unpublished)

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What else is new in ICON 2022

- Consensus on time & disease course
- Isolated ON as from fruste of MS, NMO, MOG
- PPON
- 4 Compartment model
- Pre-laminar ON

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Chronological Classification

- Acute <7 days
- Subacute 7 days to 3 months
- Chronic >3 months

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Disease course classification

- Monophasic
- Spontaneously relapsing
- Immune suppression dependent relapsing
- Progressive

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Isolated MS-ON

MS-ON

Multiple sclerosis associated optic neuritis as the first presentation of a clinical isolated syndrome with MRI or CSF findings compatible with multiple sclerosis; can also occur as a multiple sclerosis relapse. Isolated MS-ON is a forme fruste of multiple sclerosis.

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Primary progressive ON

PPON

Primary progressive optic neuritis. Diagnosis requires progressive atrophy or progressive visual loss, or both for >12 months. Diagnosis of PPON is based on time and applies to all subforms of ON that present with a progressive rather then a relapsing disease course.

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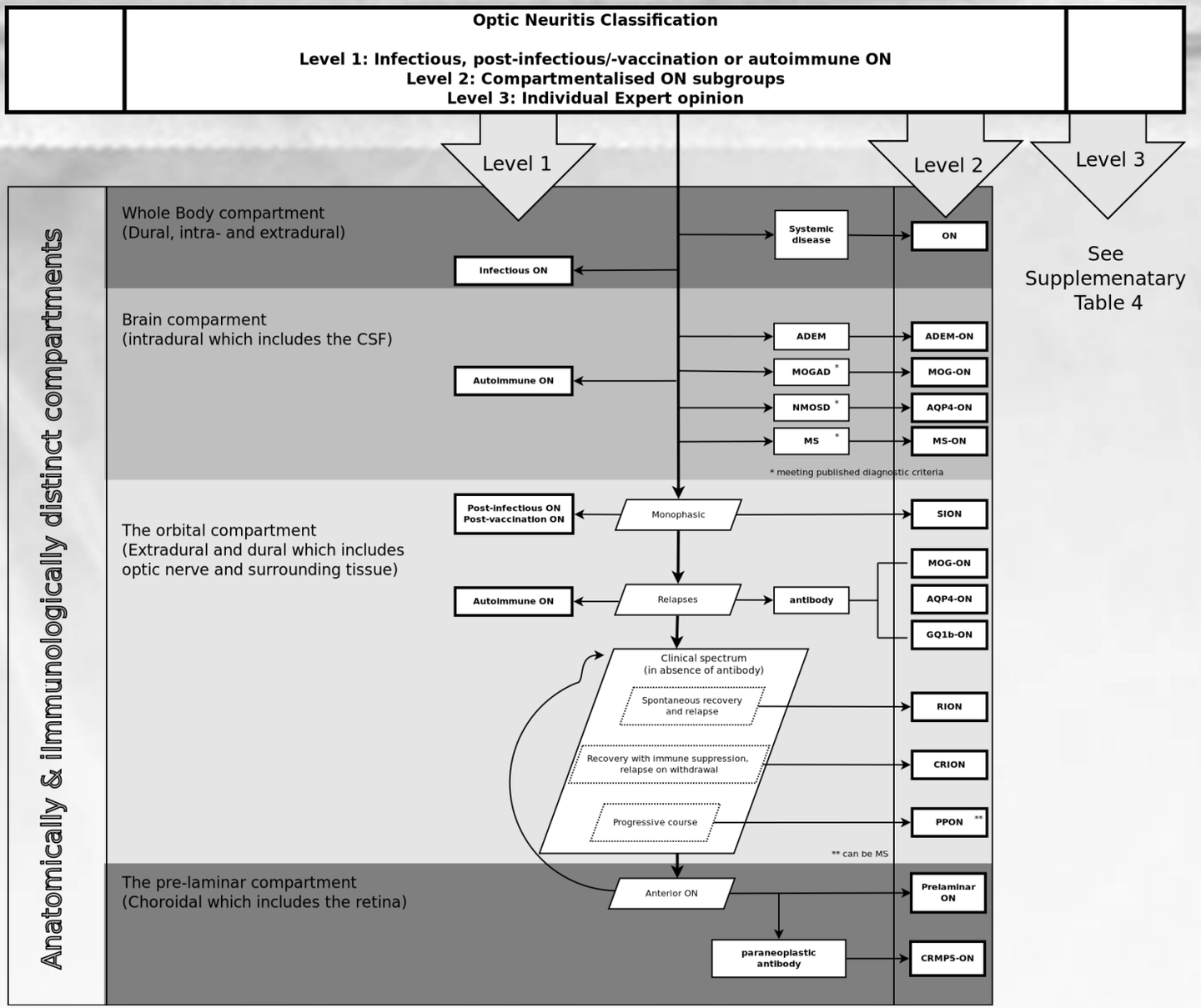
Compartment model



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4 compartments

Compartment

An anatomically and immunologically defined space as relevant to pathogenesis of optic neuritis:

- dural, intradural, and extradural (whole body)
- intradural (including CSF compartment)
- extradural and dural (includes optic nerve sheath and surrounding tissue)
- choroidal (includes retina and uveal tract)

Antibody production can be intradural, extradural, or choroidal, and the target antigen can be limited to one or more compartments.

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Pre-laminar ON

Prelaminar optic neuritis

The most anterior manifestation of optic neuritis, which involves the non-myelinated retinal axons and ganglion cell layer and which remains restricted to the prelaminar optic nerve. Acutely, the MRI of the retrobulbar optic nerve does not show an abnormality. Prelaminar optic neuritis is an anatomically based description that applies to all subforms of optic neuritis.

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Structure of this presentation

- Background
- Cases
- What to ask in clinic
- ICON 2022 Diagnostic Criteria
- ICON 2022 Classification
- NMO-ON, MOG-ON
- Summary

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Cases summary

- Case 1: **MS-ON**

Scenario A: painful, monocular, subacute LOV, dyschromatopsia, RAPD

- Case 2: **NMO-ON**

Scenario B: no pain, monocular, subacute LOV, dyschromatopsia, RAPD

- Case 3: **post-infectious ON**

Scenario C: binocular, subacute LOV, dyschromatopsia, no pain, no RAPD

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Overall summary

- Optic Neuritis: Clinical approach
- ICON 2022 Diagnostic Criteria incorporating OCT (sensitivity 61-100%), MRI (sensitivity 22-44%), biomarker (specificity >95%)
- ICON 2022 Classification prioritising the practical management
- Validation studies of the ICON 2022 criteria in NMO-ON, MOG-ON

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Dank u wel
voor uw aandacht