The five hottest developments in neuroimmunology: clinical sciences

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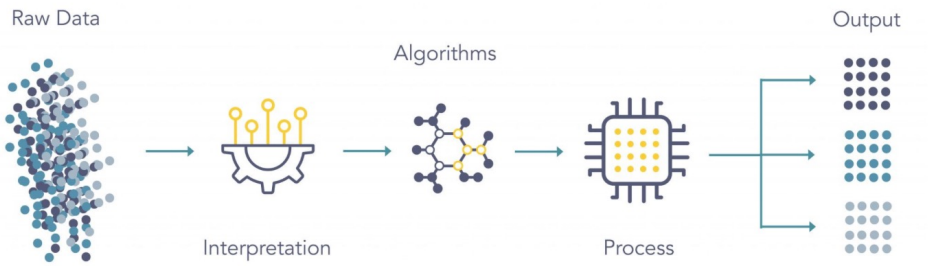
University of Münster, Germany

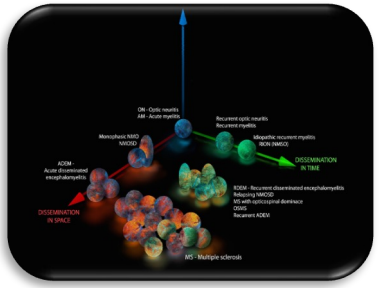
Brain&Mind Institute, University of Sydney

- **Thousands of papers / posters / presentations – 15 minutes highlight digest!**

hitlist of individual highlight picks



Clusters of trends and megatrends, future directions, unmet needs



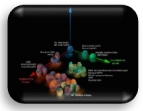
- Deconstructing and/or refining MS

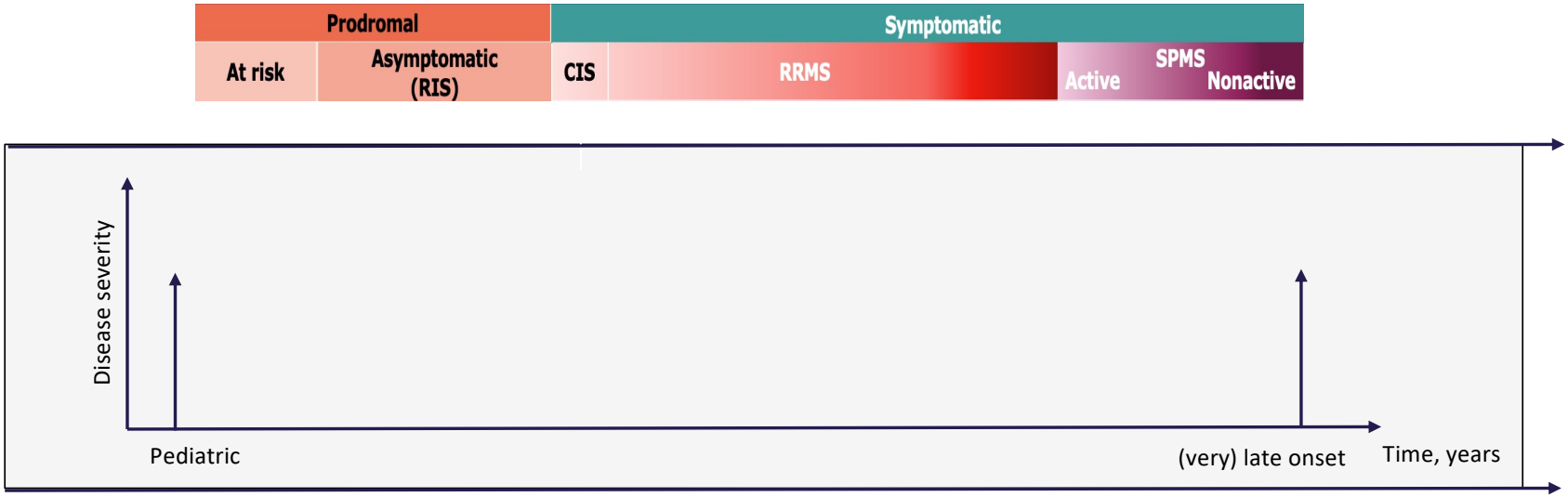
- Understanding disease progression

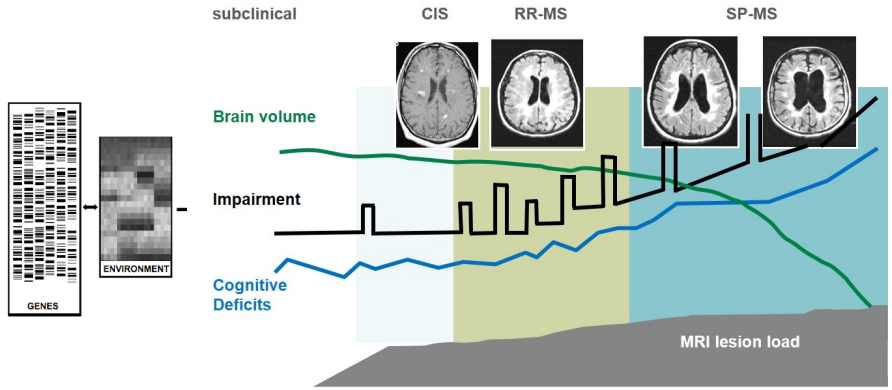
- Understanding (and targeting) lifestyle and environment

- Diagnostic, prognostic and therapeutic markers

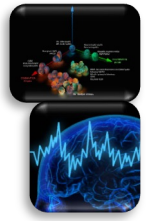
MS is occuring in all phases of life, starts earlier than diagnostic criteria currently pick, and is a whole brain disease





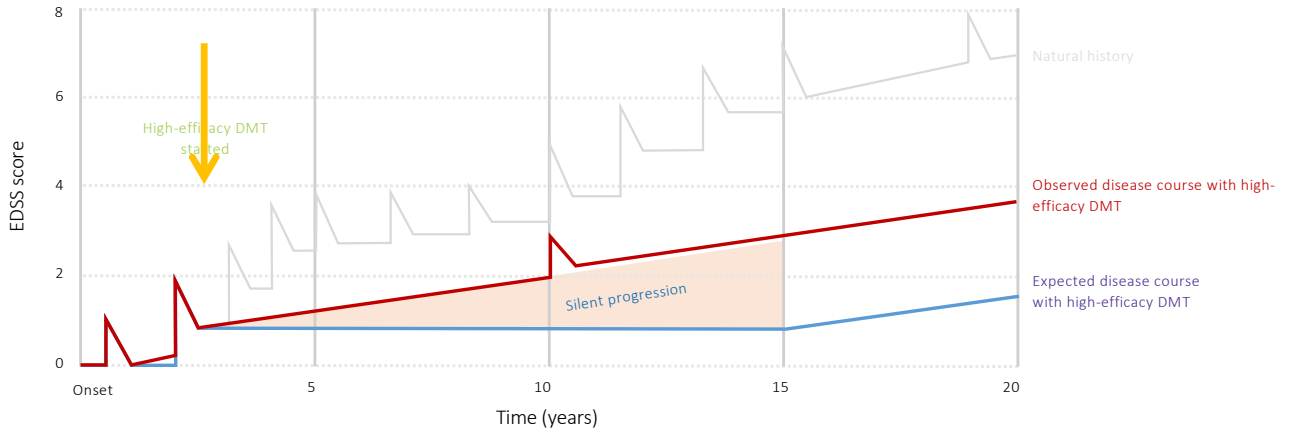


The "new" natural history of MS in the current treatment era:



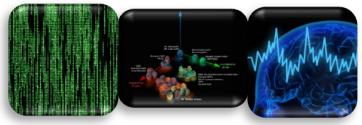
the notion of silent progression, smouldering disease, compartmentalized neuroinflammation, progression independent of relapse activity (PIRA)…

With use of highly effective therapies, attacks are abolished in most patients, but insidious progression independent of relapse activity, termed "silent progression", is now evident early during the relapsing phase.



Mod. from Hauser SL, Cree BAC. Am J Med 2020;133:1380–90

The notion of progression independent of relapse activity (PIRA) has major implications



- PIRA accounts for a major part of disability accrual, data however are mainly derived from clinical study cohorts
- MS is a continuum with an underlying progressive disease nature
- Assessment tools and detection of PIRA, especially early in the disease course, and especially in routine settings are difficult
- **Biomarkers** and/or digital tools may help to identify patients early/ier, decipher underlying mechanisms, homogenize „patients at risk“
- High efficacy therapy cohorts will help to understand this phenomenon

1. Integration of new diagnostic criteria for MS

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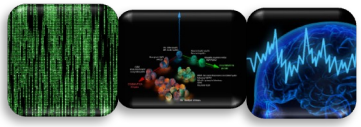
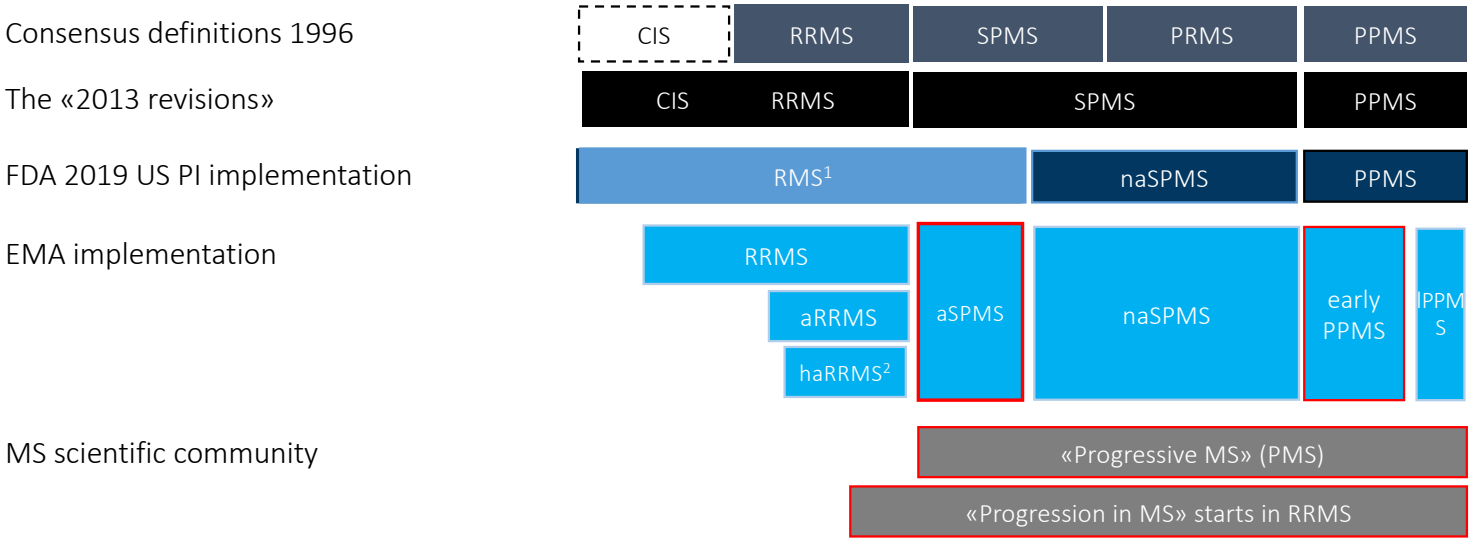
- 4th revision the diagnostic criteria
- Consensus-based revision
- Proposed changes to the 2017 criteria

2023 McDonald Diagnostic Criteria Review Meeting
Barcelona, Spain

  - DIT is not longer needed for diagnosis
  - Need for paraclinical evidence to diagnose MS
  - Optic nerve may serve as a fifth topography
  - Updated DIS criteria
  - CVS and PRLs are optional paraclinical tools in certain situations
  - Radiological isolated syndrome is MS in specific situations
  - Guidance for confirming diagnosis in individuals over 50 years, or with headache disorders (including migraine), or with vascular disorders
  - Laboratory tests (anti-MOG ab) should be used for confirming diagnosis in children and adolescents
  - Additional imaging features for PPMS diagnosis
  - kFLCs can support diagnosis

MS has more than 2 (relapses, disability) dimensions and there is a need for a more data derived, uniform view



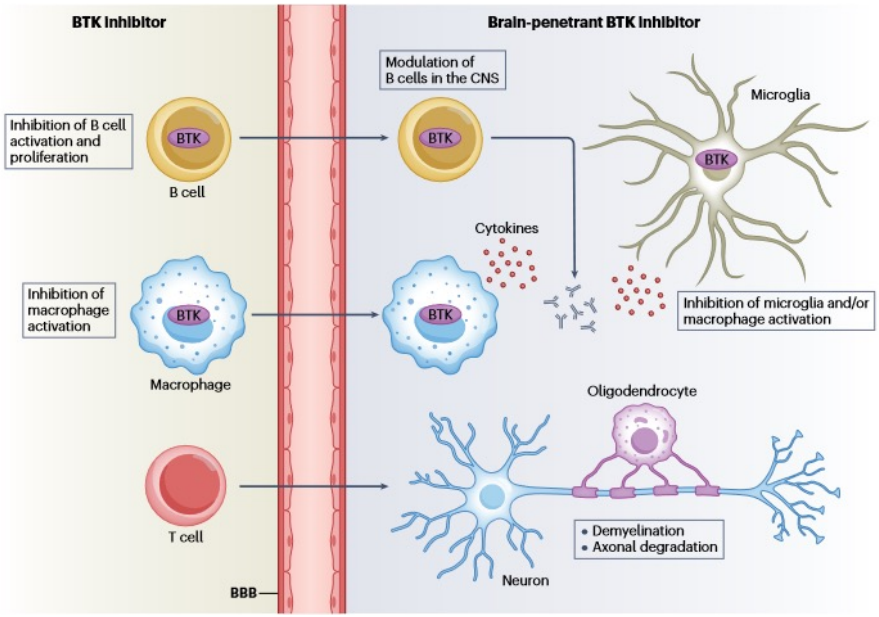


Characterization and definition of MS disease states using agnostic approaches and unsupervised learning models?!

Mod. from D. Häring, with permission

2: bruton tyrosin kinase inhibitors (BTKi) for the treatment of MS

Study	Phase	Setting	Treatment duration	Treatment groups[a]
Evobrutinib				
NCT02975349 (ref. 185)	II	RRMS (*n*=261)	24–48 weeks	Evobrutinib (*n*=154), dimethyl fumarate (*n*=54), placebo (*n*=53)
NCT04338061	III	RRMS (*n*=1,124)	≤156 weeks	Evobrutinib, teriflunomide
NCT04338022	III	RRMS (*n*=1,124)	≤156 weeks	Evobrutinib, teriflunomide
Tolebrutinib				
NCT03889639 (ref. 186)	IIb	RMS (*n*=130)	12 weeks	Tolebrutinib (*n*=129)
NCT04458051	III	PPMS (*n*=990)	24–48 months	Tolebrutinib (*n*=660), placebo (*n*=330)
NCT04411641	III	Non-relapsing SPMS (*n*=1,290)	24–48 months	Tolebrutinib (*n*=860), placebo (*n*=430)
NCT04410991	III	RMS (*n*=900)	18–36 months	Tolebrutinib (*n*=450), teriflunomide (*n*=450)
NCT04410978	III	RMS (*n*=900)	18–36 months	Tolebrutinib (*n*=450), teriflunomide (*n*=450)
NCT04742400	II	MS (*n*=10)	≥96 weeks	Tolebrutinib (*n*=10)
NCT03996291	II	RMS (*n*=125)	62 months	Tolebrutinib
Fenebrutinib				
NCT05119569	II	RMS (*n*=109)	12 weeks	Fenebrutinib, placebo
NCT04586023	III	RMS (*n*=736)	96 weeks	Fenebrutinib, teriflunomide
NCT04586010	III	RMS (*n*=736)	96 weeks	Fenebrutinib, teriflunomide
NCT04544449	III	PPMS (*n*=946)	120 weeks	Fenebrutinib, ocrelizumab
Remibrutinib				
NCT05147220	III	RMS (*n*=800)	≤30 months	Remibrutinib (*n*=400), teriflunomide (*n*=400)
NCT05156281	III	RMS (*n*=800)	≤30 months	Remibrutinib (*n*=400), teriflunomide (n=400)
Orelabrutinib				
NCT04711148	II	RRMS (*n*=160)	120 weeks	Orelabrutinib (*n*=120)[b], placebo (*n*=40)



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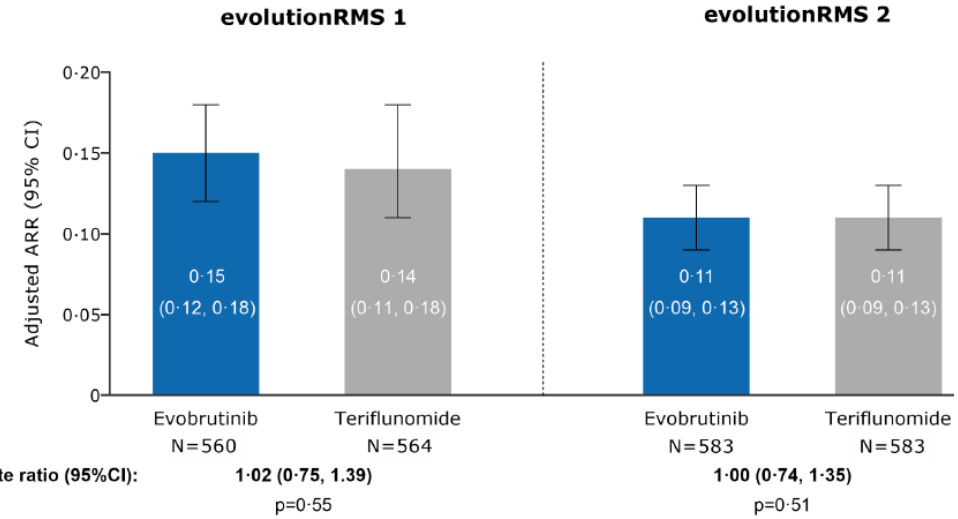
Krämer et al. Nat Rev Neurol. 2024

Negative Results of Evolution RMS 1 and 2

- Randomised, double-blind, double-dummy phase III trials of evobrutinib (45 mg twice daily [BID] + placebo once daily [QD]) versus teriflunomide (14 mg QD + placebo BID) in RMS
- RMS1: 1,124 participants (evobrutinib, n=560; teriflunomide, n=564).
- RMS2: 1,166 participants (evobrutinib, n=583; teriflunomide, n=583).
- **Superiority of evobrutinib over teriflunomide on ARR was not demonstrated**
- No evidence of clinical or imaging effects on CNS-compartmentalised inflammation

Figure 2. ARR up to 156 weeks

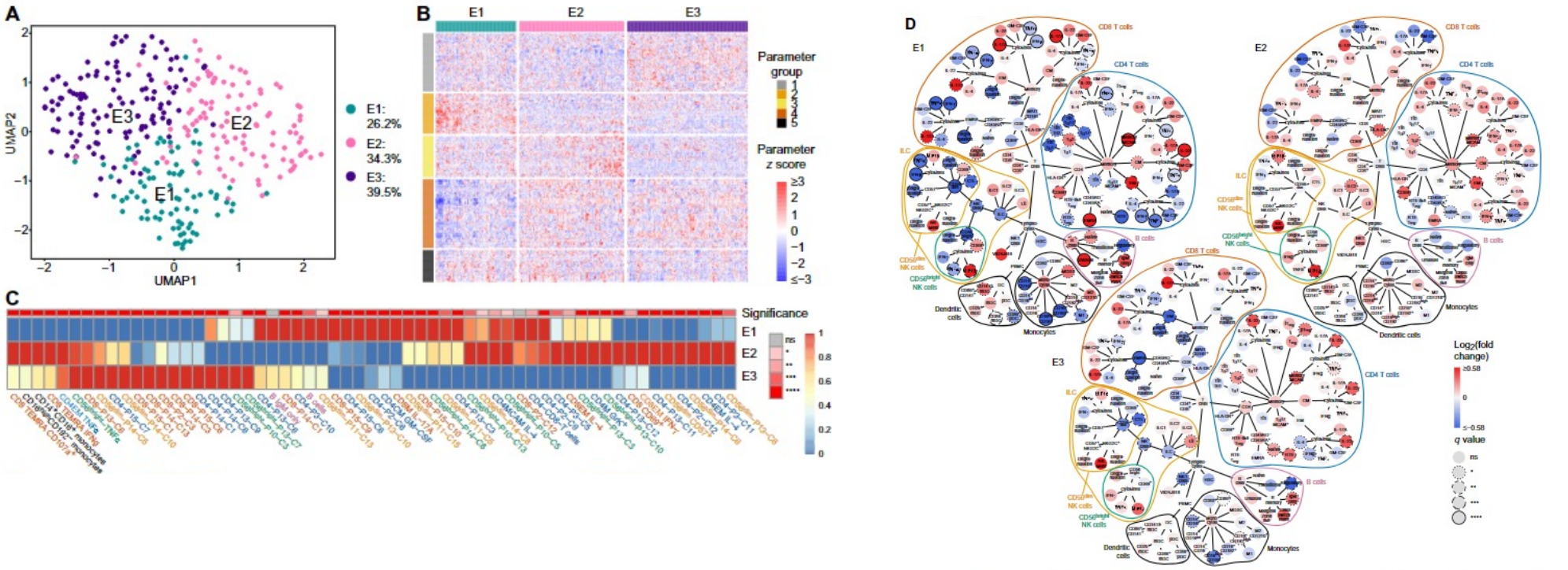


- Incidence of liver enzyme elevations ≥5x upper limit of normal was higher with evobrutinib than teriflunomide, particularly in the first 12 weeks (evobrutinib, 5.0%; teriflunomide, 0.8%)
- Evobrutinib was **not** superior to teriflunomide on any primary or secondary endpoints.
- The markedly-lower-than-expected teriflunomide ARR does not explain the overall outcomes of these trials.

→ **The efficacy and liver-related safety findings do not support the use of evobrutinib to treat RMS.**

Montalban et al., under revision

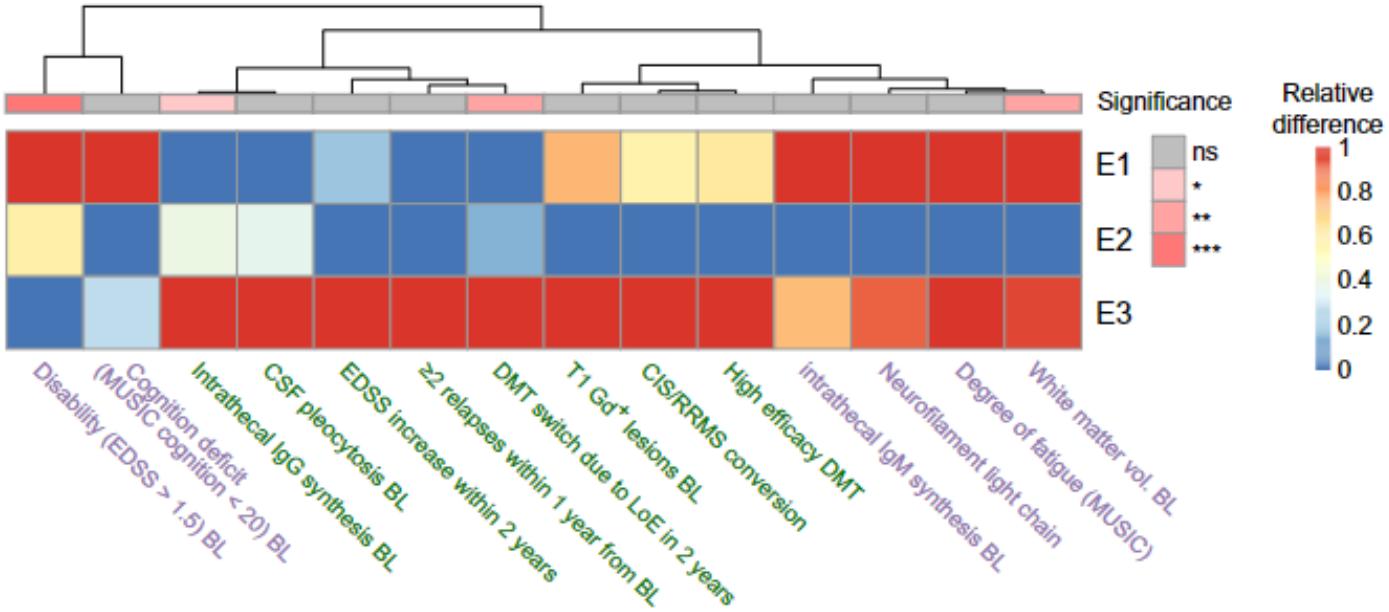
3: Early MS consists of 3 distinct immunological endophenotypes



Differences between MS - HD, differences within MS patients

Gross CC, et al. Sci Transl Med. 2024 Mar 27;16(740):eade8560.

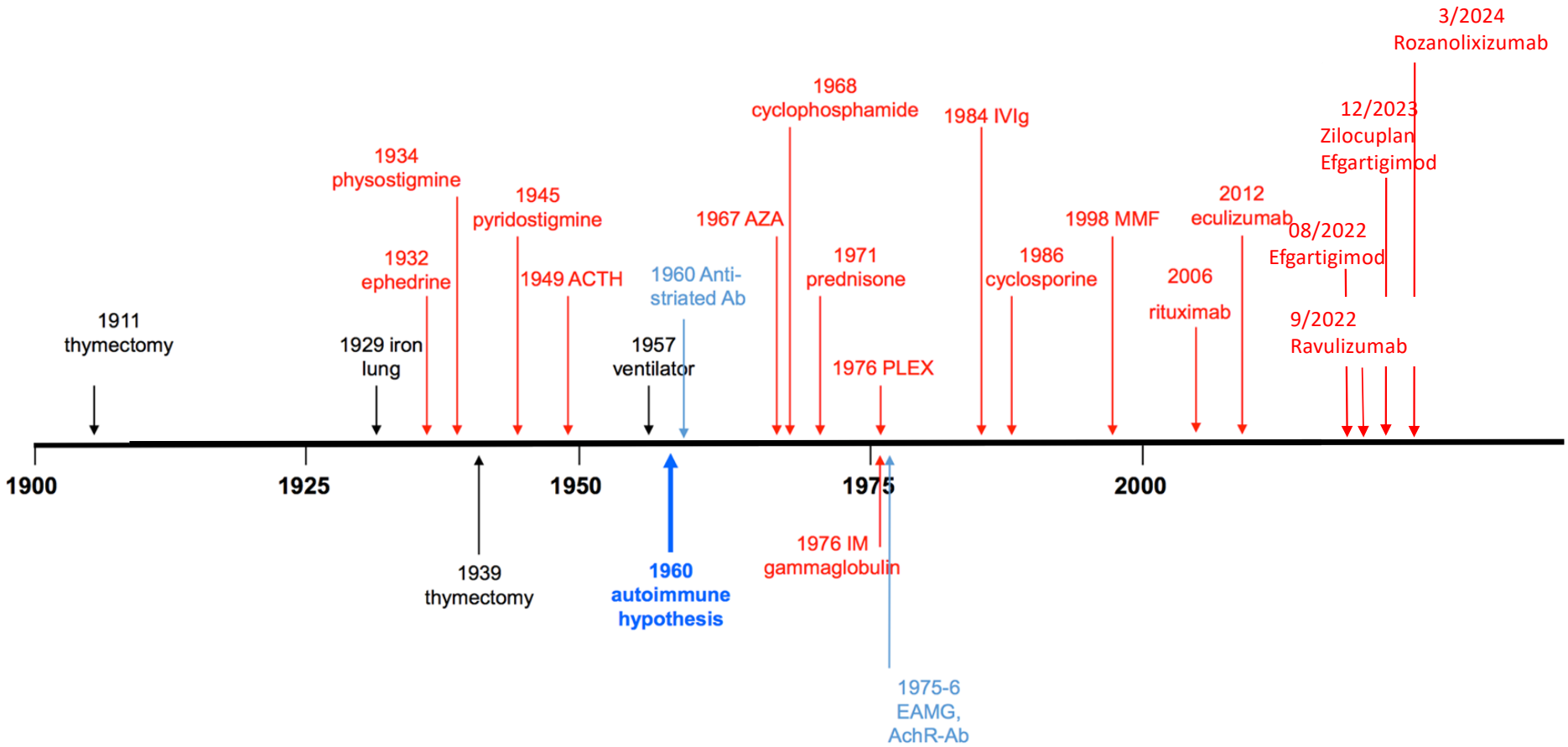
MS Endophenotypes are associated with different clinical trajectories and responses to immune therapy



Risk of severe disease is different in different subtypes

Gross CC, et al. Sci Transl Med. 2024 Mar 27;16(740):eade8560.

4: Myasthenia gravis is the new MS?!



Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group*

Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension

Andreas Meisel[1] · Djillali Annane[2] · Tuan Vu[3] · Renato Mantegazza[4] · Masahisa Katsuno[5] · Rasha Aguzzi[6] · Glen Frick[6] · Laura Gault[6] · James F. Howard Jr.[7] on behalf of the CHAMPION MG Study Group

Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial

James F Howard Jr, Vera Bril, Tuan Vu, Chafic Karam, Stojan Peric, Temur Margania, Hiroyuki Murai, Malgorzata Bilinska, Roman Shakarishvili, Marek Smilowski, Antonio Guglietta, Peter Ulrichts, Tony Vangeneugden, Kimiaki Utsugisawa, Jan Verschuuren, Renato Mantegazza, and the ADAPT Investigator Study Group*

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Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study

Vera Bril, Artur Drużdż, Julian Grosskreutz, Ali A Habib, Renato Mantegazza, Sabrina Sacconi, Kimiaki Utsugisawa, John Vissing, Tuan Vu, Marion Boehnlein, Ali Bozorg, Maryam Gayfieva, Bernhard Greve, Franz Woltering, Henry J Kaminski, on behalf of the MG0003 study team*

Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study

James F Howard Jr, Saskia Bresch, Angela Genge, Channa Hewamadduma, John Hinton, Yessar Hussain, Raul Juntas-Morales, Henry J Kaminski, Angelina Maniaol, Renato Mantegazza, Masayuki Masuda, Kumaraswamy Sivakumar, Marek Śmiłowski, Kimiaki Utsugisawa, Tuan Vu, Michael D Weiss, Małgorzata Zajda, Babak Boroojerdi, Melissa Brock, Guillemette de la Borderie, Petra W Duda, Romana Lowcock, Mark Vanderkelen, M Isabel Leite and the RAISE Study Team*

The landscape of immune selective therapies is evolving – and within this the therapeutic and disease management concepts!

Verlaufsmodifizierende Therapie	Ocular	Generalized			
		AChR-ab positive[&]		MuSK-ab positive	
			1. Choice	2. Choice	1. Choice	2. Choice
	• Glucocorticoids[a] **and/or** • Azathioprine • *Mycophenolat-Mofetil*[c] • *Ciclosporine A* • *Methotrexat*	Mild/moderate disease activity/ disease severity	• Glucocorticoids[a] **and/or** • Azathioprine • Thymectomy[b]	• Glucocorticoids[a] **and/or** • *Mycophenolat-Mofetil*[c] • *Ciclosporind A* • *Methotrexat* • *Tacrolimus*	• Glucocorticoids[a] **and/or** • Azathioprine	• Glucocorticoids[a] **and/or** • *Mycophenolat-Mofetil*[c] • *Ciclosporine A* • *Methotrexat* • *Tacrolimus*
	• Corrective surgery	High Disease activity/disease severity[#] (incl. Therapy frefractory)	**+/-** Glucocorticoids **and/or** A therapy option for mild/moderate disease activiy/ severity as addition			
			• Complement inhibitors (Eculizumab[d], Ravulizumab[d], Zilocuplan[d]) • FcRn modulators (Efgartigimod[e], Rozanolixizumab[e]) • *CD20-antibodies (i.e. Rituximab)* • Thymectomy[b]	• *IVIG*[f] • *Plasmapherese/ Immunadsorption* • *AHSCT, Bortezomib, Cyclophosphamid*[h]	• FcRn-modulator (Rozanolixizumab[e]) • *CD20-antibody (i.e. Rituximab)*	• *IVIG*[f] • *Plasmapheresis/ Immunoadsorption* • *AHSCT, Bortezomib, Cyclophosphamid*[h]
		Crisis/crisis-like exacerbation	• IVIG[f] • Plasmapheresis/Immunadsorption • Steroid pulse therapy[g]			

#: A (highly) active generalized MG (including 'therapy refractory' MG) may be defined as
a) moderate/high MGFA score (≥ MGFA IIb) and/or at least two recessive severe exacerbations/myasthenic crises requiring therapeutic intervention (IVIG, PLEX, and IA) within 1 year after first diagnosis and despite adequate disease-modifying and symptomatic treatment

or

b) persistent symptoms relevant to daily living (≥ MGFA IIa) and one severe exacerbation/myasthenic crisis within the last 12 months despite adequate disease-modifying and symptomatic treatment

or

c) persistent symptoms relevant to daily living (≥ MGFA IIa) present in MG of mild/moderate disease course despite adequate disease-modifying and symptomatic treatment for more than 2 years.

Note: Disease severity is assessed according to MGFA classification. However, the MGFA status used here only takes into account the severity at the time of clinical assessment and not the highest score ever assessed in the course of disease.

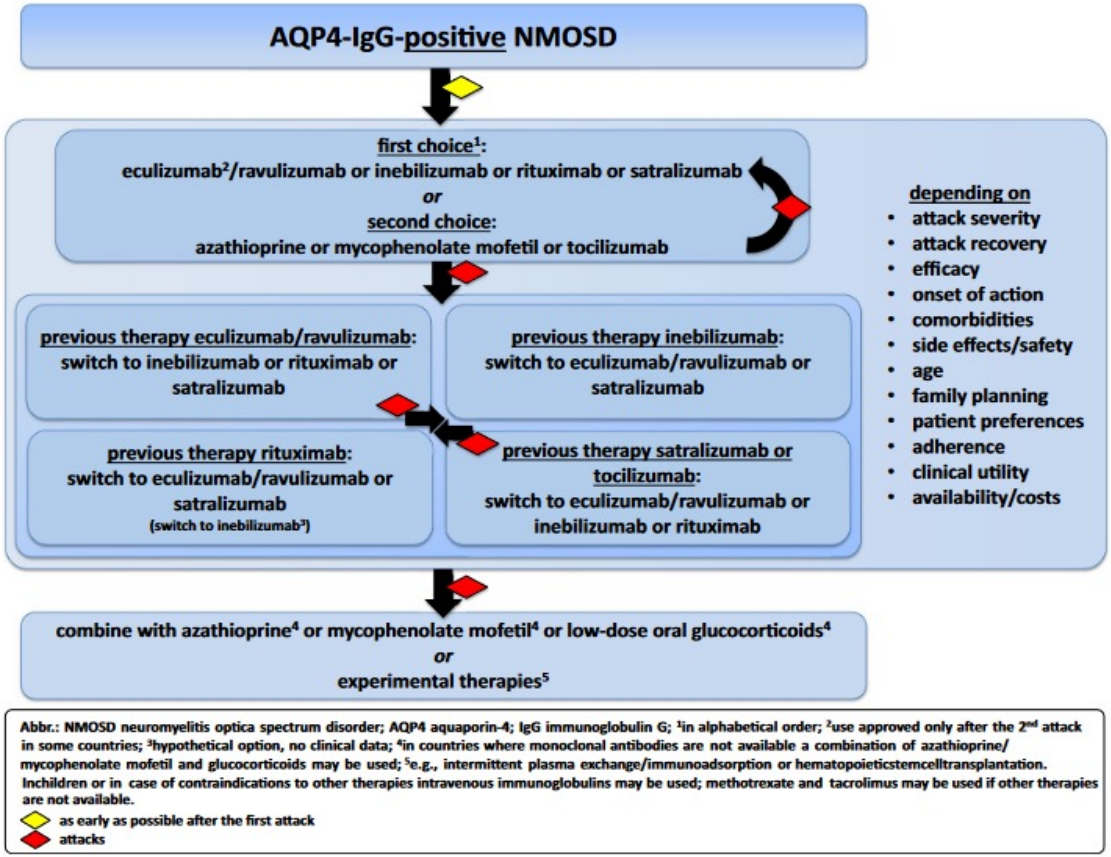
&: Seronegative and LRP4 antibody-positive MG are generally treated like AChR-Ab-positive MG.

In italics: *Off-label* therapies

a) Steroids are not indicated as long-term therapy (at least above Cushing's threshold, e.g. for prednisolone 7.5 mg/day); steroid-sparing strategies should be applied at an early stage.
b) Consider age (usually 18–65 years) and disease duration (usually <5 years); obligatory in case of suspected thymoma.
c) Off-label use of MMF is reimbursable as second choice therapy in Germany.
d) Eculizumab is on-label for the treatment of refractory AChR-Ab-positive gMG, ravulizumab is approved as add-on therapy for AChR-Ab-positive gMG.
e) Efgartigimod is approved as an add-on therapy for AChR-Ab-positive gMG.
f) IVIG is refundable when used as an off-label treatment for severe myasthenic exacerbations; SCIG can be used instead of IVIG in exceptional cases, but reimbursement is not regulated for this indication in Germany.
g) *Cave:* Steroid dip.
h) Justifiable as expanded access/compassionated use.

Wiendl et al., DGN guidlines of myasthenic syndromes, 2023, Wiendl et al., TAND 2023

5: NMOSD and MOGAD:
From “not a disease entity“ to 4 + X approved therapies!!



Precision medicine based on an understanding of pathophysiology

The standard of care for acute NMOSD attacks are:

- High-dose glucocorticoid therapy (Methylprednisolone + proton-pump inhibitor + thrombosis prophylaxis)
- Apheresis treatment (plasma exchange or immunadsorption)

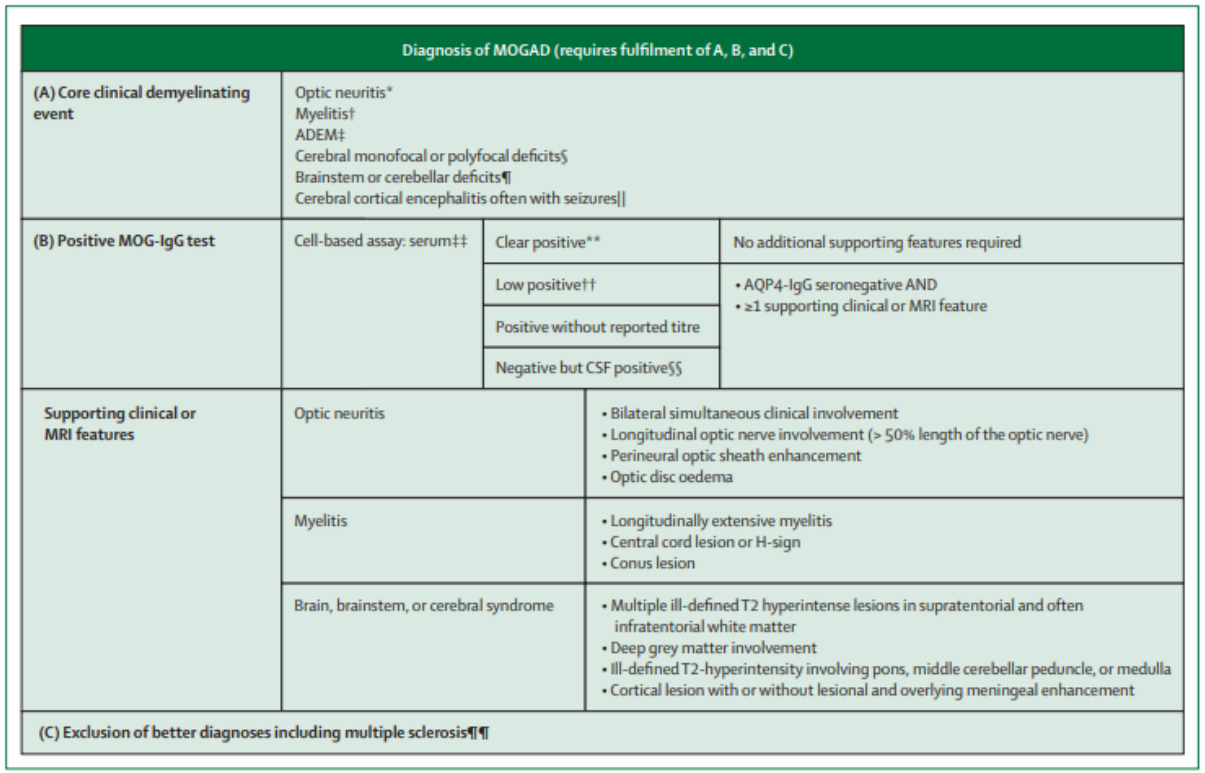
→Other experimental therapy approaches: IVIG, early anti-CD20 therapy, and early anti-complement therapy AQP4-IgG-positive NMOSD takes a relapsing course in almost all cases

→ Long-term therapy must be offered asap after diagnosis

- Immunosuppressants: Azathioprine*, mycophenolate mofetil**, low-dose glucocorticoids
- **Biologicals: Rituximab, eculizumab, ravulizumab, inebilizumab, satralizumab, tocilizumab****

but: order of preference for these therapies is yet unclear

MOGAD: proposed new diagnostic criteria



Diagnosis of MOGAD (requires fulfilment of A, B, and C)			
(A) Core clinical demyelinating event	Optic neuritis* Myelitis† ADEM‡ Cerebral monofocal or polyfocal deficits§ Brainstem or cerebellar deficits¶ Cerebral cortical encephalitis often with seizures‖		
(B) Positive MOG-IgG test	Cell-based assay: serum‡‡	Clear positive**	No additional supporting features required
		Low positive††	• AQP4-IgG seronegative AND • ≥1 supporting clinical or MRI feature
		Positive without reported titre	
		Negative but CSF positive§§	
Supporting clinical or MRI features	Optic neuritis		• Bilateral simultaneous clinical involvement • Longitudinal optic nerve involvement (> 50% length of the optic nerve) • Perineural optic sheath enhancement • Optic disc oedema
	Myelitis		• Longitudinally extensive myelitis • Central cord lesion or H-sign • Conus lesion
	Brain, brainstem, or cerebral syndrome		• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter • Deep grey matter involvement • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla • Cortical lesion with or without lesional and overlying meningeal enhancement
(C) Exclusion of better diagnoses including multiple sclerosis¶¶			

Figure 3: **Proposed diagnostic criteria for MOGAD**
ADEM=acute disseminated encephalomyelitis. AQP4=aquaporin-4. MOG=myelin oligodendrocyte glycoprotein. MOGAD=MOG antibody-associated disease.

- Not every pos. MOG-AK means MOGAD
- Low titres have poor predictive power
- Cell-based testing

Banwell et al. Lancet Neurol. 2023 Mar; 22 (3): 268-282.

Clinical Highlights:
Summary of trends, megatrends and future unmet needs

- Novel treatment concepts, especially high efficacy therapy approaches have changed and will continue to change the natural history of neuroimmunological diseases
- Multiple sclerosis, NMOSD, MOGAD, Myasthenia gravis etc.:
  - Need for better (individual) stratification and prognostication of early MS
  - Need for early identification, understanding and tackling of relapse independent "progression"
  - Usage of lower dimensionality (clinical) assessments in big cohorts/registries together with higher dimensionality approaches integrating imaging/biological data
  - Need for a more accurate, uniform characterization of MS (based on a data driven approach)
  - Integration of biological/immunological data into diagnosis, prognosis, treatment stratification, disease monitoring: best possible disease control
- E-health and digital medicine to improve **disease understanding** and care (digital tools, e-health, social media, Iwatch-like principles)
- Need for prevention strategies, repair strategies, tolerance induction strategies

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follow the developments on www.isniweb.org

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ISNI has put together groups that works on White Papers in:

- Animal models mimicking aspects of neuroimmunological diseases animal
- How to approach human clinical translation in neuroimmunology.
- MS Act: THE FUTURE OF MS TRIALS

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An innnovative resource designed for neurologists and healthcare professionals seeking the latest education in neuroimmunology

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CONGRESS CHAIR: TAKASHI YAMAMURA

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