GUTHY JACKSON®
Charitable Foundation

2024 NMO Roundtable Conference Proceedings



UCLA Luskin Conference Center

August 2-4, 2024

GUTHY JACKSON® Charitable Foundation

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Dear GJCF NMO Roundtable Conference Attendee,

Thank You! We are so appreciative of your time and effort in joining us recently for the 15th NMO Roundtable Conference in Los Angeles.

The Guthy-Jackson Charitable Foundation (GJCF) was established to drive breakthroughs to understand, prevent, treat and ultimately cure NMO and related diseases. Through tremendous collaborative effort, the field has seen an astounding rate of progress, including the first approved therapeutics. These are indeed great strides—and there is more to do to address patient burden and find life-saving cures.

To this end, The GJCF encourages all NMOSD stakeholders to think in innovative ways that unify knowledge to identify and accelerate therapeutics that save & improve lives. Attached are the Proceedings of the 15th NMO Roundtable Conference. Included in this summary are presentations as well as pre-conference and real-time surveys of world experts in response to high priority issues.

We are delighted to report that over 100 world experts and key opinion leaders from more than 25 worldwide countries contributed to advances discussed during the conference. A complete summary of the high priority topics discussed is provided in the Proceedings program. To access recorded presentations and other resources from the meeting, please click here to visit the special GJCF 2024 Roundtable Conference webpage.

On behalf of patients and families facing NMOSD, please accept our deepest thanks for your dedication to our collective mission on the journey to cures. For more information on the GJCF mission, please click here to visit our new ***Research Radar ®*** website tool.

Sincerely,

GJCF Team

GUTHY JACKSON®
Charitable Foundation

"Thank you very much to the foundation for organizing such a remarkable Roundtable event in LA. I thoroughly enjoyed every aspect of it—from the highly insightful content at every single presentation to the engaging and most relevant attendees from all over the world. It was undoubtedly a huge success."

-Shervin Gholizadeh, MD
Genentech



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2024 NMO Roundtable Conference: *Beyond*

UCLA Luskin Conference Center

August 2-4, 2024

FRIDAY, AUGUST 2

4:00 PM	**GJCF International Clinical Consortium Meeting** (*ICC Members*) *Illumination Room*
6:00 PM	**Registration & Reception** *Centennial Ballroom Registration & Pre-Function Area*
7:00 PM	**Welcome: *Beyond* – *Victoria Jackson*** *Centennial Ballroom AB*
7:10 PM	**Next Era Vision – *Michael Yeaman*** *Centennial Ballroom AB*
7:30 PM	**Dinner** *Centennial Ballroom CD*

THANK YOU TO OUR INDUSTRY SPONSORS

ALEXION® AstraZeneca Rare Disease

AMGEN Rare Disease

Roche Genentech

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2024 NMO Roundtable Conference: *Beyond*

UCLA Luskin Conference Center

August 2-4, 2024

SATURDAY, AUGUST 3

Breakfast & Headshots — **7:00 AM** — *Centennial Ballroom CD*

Session I — Optimizing the Impact of Approved Therapies – *Centennial Ballroom AB*

8:00 AM — **Industry Updates on Approved Therapeutics**

- **Amgen** – ***Kristina Patterson***
- **AstraZeneca / Alexion** – ***Lokesh Jha***
- **Genentech / Roche** – ***Shervin Gholizadeh***

8:45 AM — **Therapeutic Transition: Rationale & Actuation** – ***Jeffrey Bennett***

9:05 AM — **Minimizing Therapy-Associated AEs & SAEs** – ***Hesham Abboud***

9:25 AM — **Therapeutic Issues in Autoimmune Comorbidities** – ***Nasrin Asgari***

9:45 AM — **Digital Survey & Consensus Forum**

Recognition — **10:00 AM** — ***GJCF Rising Star Scholars***

Break & Headshots — **10:05 AM** — *Centennial Pre-Function Area*

Session II — Latest Insights into NMOSD Laboratory & Clinical Sciences – *Centennial Ballroom AB*

10:25 AM — **Pearls in Pathogenesis: NMO, MOGAD & SND** – ***Tanuja Chitnis***

10:45 AM — **Comparative Assay Platforms for Serodiagnosis** – ***Paddy Waters***

11:05 AM — **IPND-2025 Diagnostic Criteria: Goals & Progress** – ***Dean Wingerchuk***

11:25 AM — **Global Epidemiology: NMO, MOGAD & SND** – ***Kazuo Fujihara***

11:45 AM — **Digital Survey & Consensus Forum**

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2024 NMO Roundtable Conference: *Beyond*

UCLA Luskin Conference Center

August 2-4, 2024

Lunch & Headshots	**12:00 PM**	*Centennial Ballroom CD*
Session III	Emerging Molecular, Cellular & Imaging Biomarkers – *Centennial Ballroom AB*	
	1:00 PM	**Molecular & Cellular Biomarkers of CNS Injury** – ***Yang Mao-Draayer***
	1:20 PM	**Imaging Biomarkers of Disease Status & Relapse** – ***Frederike Oertel***
	1:40 PM	**Prognostic Biomarker Signatures of Relapse in NMOSD** – ***Alessandra Breschi***
	2:00 PM	**Digital Survey & Consensus Forum**
Session IV	Improving Rescue Interventions for Acute Relapse	
	2:15 PM	**Burdens of Disease: Disparities in Acute Healthcare** – ***Annette Langer-Gould***
	2:35 PM	**PLEX & IVIG in Acute Relapse Settings** – ***Jacqueline Palace***
	2:55 PM	**Novel Rescue Strategies for Relapse** – ***Michael Levy***
	3:15 PM	**Digital Survey & Consensus Forum**
Break & Headshots	**3:30 PM**	*Centennial Pre-Function Area*
Session V	Accelerating Toward Curative Therapeutics – *Centennial Ballroom AB*	
	3:50 PM	**Emerging Technologies for Immune Tolerization** – ***Michael Yeaman***
	4:10 PM	**Clinical Trial Ecosystem for Immune Tolerization** – ***Brian Weinshenker***
	4:30 PM	**Digital Survey & Consensus Forum**
Closing	**4:45 PM**	**Adjourn & Group Photo**
Reception	**5:15 PM**	*Centennial Pre-Function Area*
Dinner	**6:00 PM**	*Centennial Ballroom CD*



SUNDAY, AUGUST 4

Breakfast	**7:30 AM**	*Centennial Ballroom CD*
Session VI	**Consilience & Next Steps** – *Centennial Ballroom AB*	
	8:30 AM	**2024 Unifying Consensus**
	9:00 AM	**Emerging Unmet Needs**
	9:30 AM	**International Prospectus**
Closing	**10:00 AM**	**Adjourn**

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"Thank you for your kind invitation to participate in this years GJCF meeting. It is always invigorating. I truly appreciate the collaborative nature of the foundation as well as the clear thought and effort that has gone into the organisation of the meetings by your team."

- Patrick Waters, PhD
Oxford University



ATTENDEE ROSTER

THE GUTHY-JACKSON CHARITABLE FOUNDATION
2024 INTERNATIONAL NMO ROUNDTABLE CONFERENCE
UCLA LUSKIN CONFERENCE CENTER
AUGUST 2-4, 2024

THE GUTHY-JACKSON CHARITABLE FOUNDATION

Victoria Jackson, Founder
Bill Guthy, Founder
Terry Smith, MD, GJCF Advisor
Michael Yeaman, PhD, GJCF Advisor
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Jacinta Behne
Megan Behne
Kim Jackson-Matthews
Maoloude Toure
Megan Woolf

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Christine Rowe
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Bea McLucas
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Tanuja Chitnis, MD
Michael Levy, MD, PhD

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Brian Weinshenker, MD

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VERILY

Alessandra Breschi, PhD

YALE UNIVERSITY

Soumya Yandamuri, PhD

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"The sessions were fantastic and full of inspiring research ideas. Besides gaining new knowledge, I also had the opportunity to network for future collaborations. Thank you for the opportunity to attend this meeting."

-Nisa Vorasoot, MD
Mayo Clinic



2024 GJCF Rising Star Scholars



Monique Anderson, MD, PhD
Mass General Brigham
United States



Sara Carta, MD
University of Verona
Italy



Yuki Matsumoto, MD, PhD
Tohoku University
Japan



Andrea Savransky, MD
National Pediatric Hospital
Argentina



Carson Moseley, MD, PhD
UCSF
United States



Cristina Valencia-Sanchez, MD
Mayo Clinic Scottsdale
United States



Nisa Vorasoot, MD
Mayo Clinic Rochester
United States

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Next Era Vision

Michael Yeaman, PhD, MSc

Distinguished Professor of Medicine
Chief, Division of Molecular Medicine
Director, Institute for Infection & Immunity
Vice Chair, Department of Medicine
UCLA School of Medicine & Harbor-UCLA MC

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15th NMO International Roundtable Conference
Los Angeles / August 2, 2024

Disclosures

- **Founder**: NovaDigm Therapeutics, Inc. (vaccines)
  Tegos Therapeutics, LLC (anti-infectives)
  ImmunoTx, LLC (immunotherapeutics)
  Metacin, Inc. (music neuroscience)

- **Grants**:

NIH U19 AI-172713	NIH R01 AI-139244
NIH U01 AI-124319	NIH COVID-19 SPARTA
NIH R01 AI-309241	DoD CDMRP JW-190421
NIH R01 AI-310380	DoD CDMRP JW-160125

- **Advisor**: Advisor, Guthy-Jackson Charitable Foundation
  AstraZeneca; Genentech–Roche; Amgen
  Vatican Council; US NIH; US DoD; XPrize

Perspectives



Revolution in NMOSD research and therapy landscape



Remaining unmet needs in NMOSD: burdens and risks



Completing our mission: end NMOSD once and for all



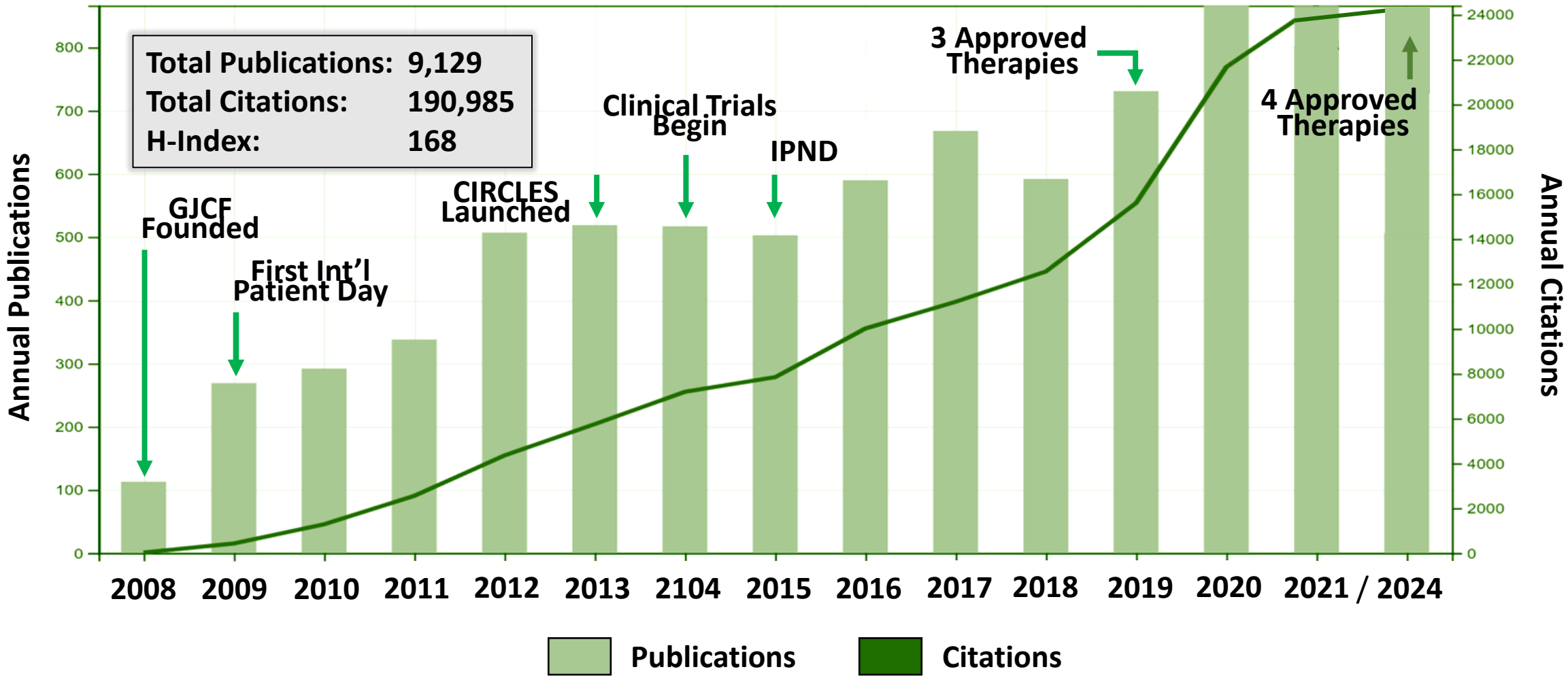
Update on new GJCF toolkit for providers and patients



NMO as a key to solve autoimmune disease & beyond

NMO Revolution

NMO: A Rare Disease Success Story



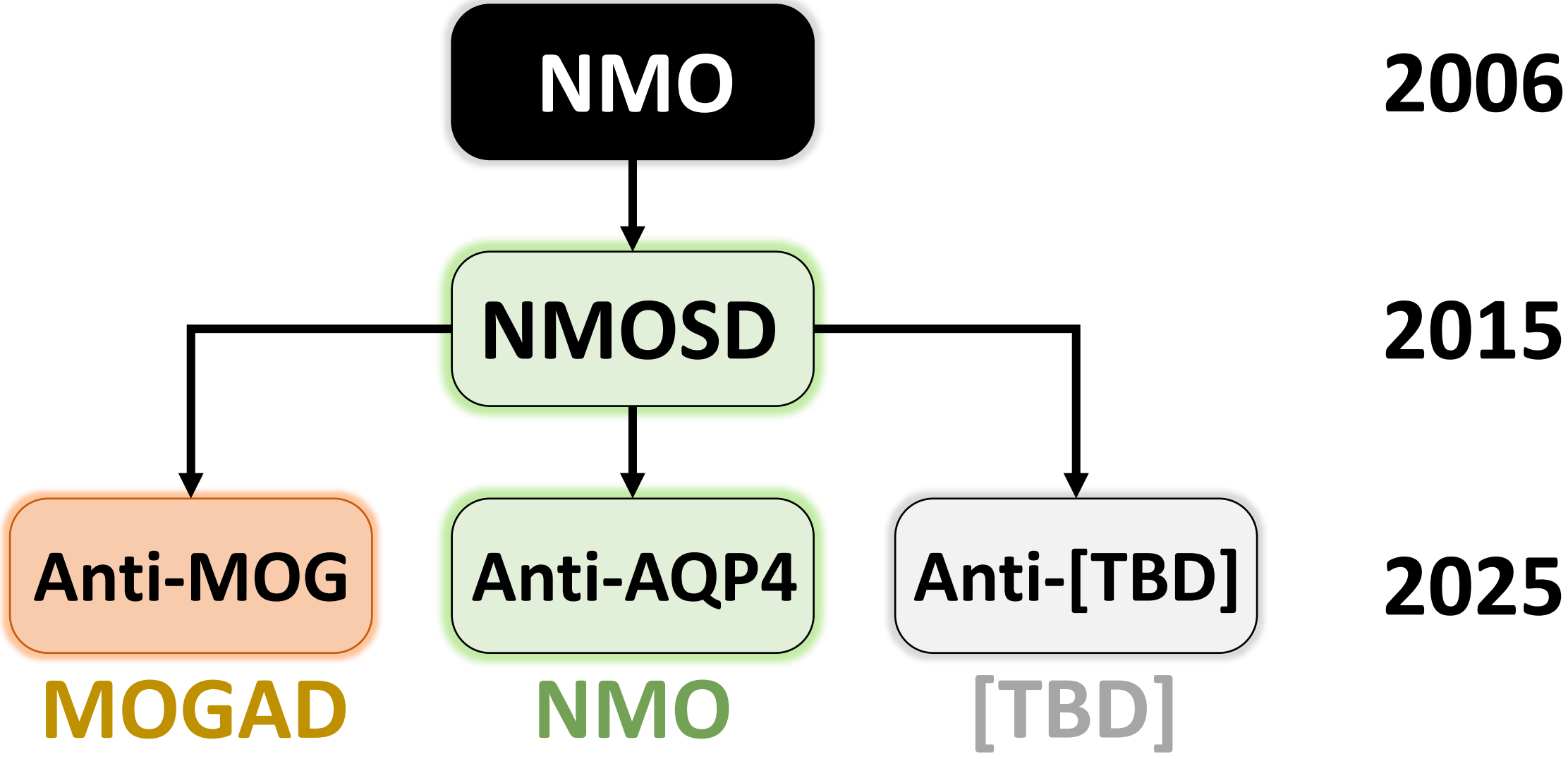
Source: Clarivate Analytics [2024] ***Web of Science*** (accessed 7-31-2024)

Progress in Diagnosis & Improved Clinical Care

Year	Mean Global Prevalence [A*]	Misdiagnosis Rate (e.g. MS) [B*]	Annual Relapse Rate [C*]	Active Clinical Trials [D]	FDA Approved Therapeutics [E]
2008	1/1M	75%	1.5	0	0
2015	1/100K	45%	0.5	4	0
2024	7/100K	15%	0.15	>35	4

[A-C] **Source**: Estimates from published articles (PubMed; Web of Science; accessed 7-31-2024)
[D] **Source**: NIH ClinicalTrials.gov (accessed 7-31-2024)
[E] **Source**: U.S. Food & Drug Administration (accessed 7-31-2024)

Evolving Clinical Paradigms to Help All Patients



Source: GJCF Symposium at ECTRIMS [2023] ***IPND–2025 International Consensus Group***

Example Recent Highlights in NMOSD Research

- Efficacy of certain approved therapies gets even better over time
- Crosswiring among IFNs and IL-17 in mediating NMO pathogenesis
- New assays to detect anti-AQP4, anti-MOG or other Ab in testing
- Importance of vaccination to prevent serious infection recognized
- New insights into genetic correlates of risks are being discovered
- Biomarkers to forecast relapses in time to mitigate are emerging
- Limitations of traditional disability testing are becoming clearer

Source: GJCF Symposium at ECTRIMS [2023]

Countless Efforts Toward a Single Goal: Cure

132 ICC Experts

35 Countries

15 Annual RT

15 Annual PD

600 Studies

221 NIH Grants

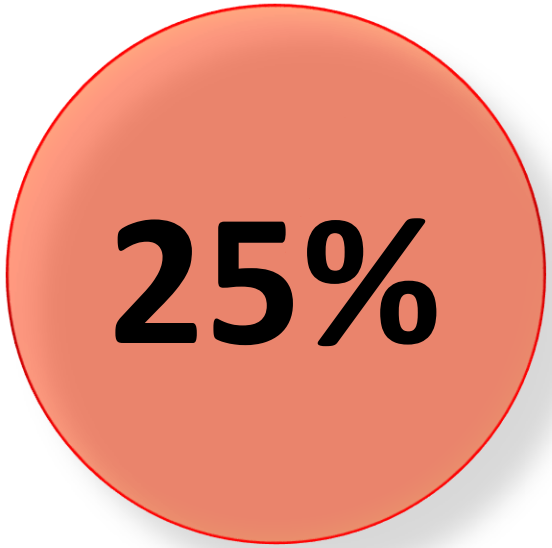
4 Congresses

1 Goal

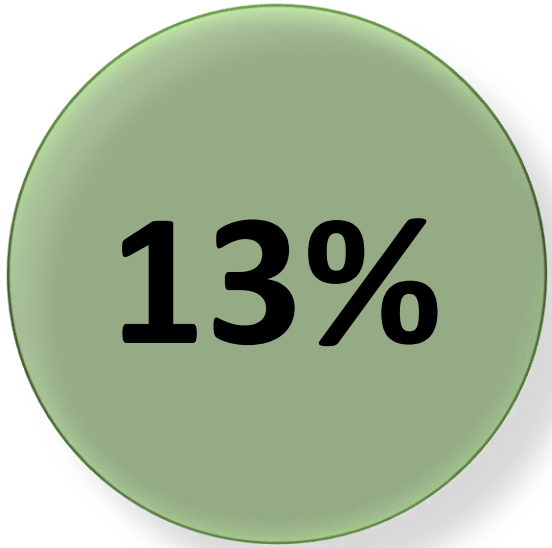
Source: Clarivate Analytics [2024] ***Web of Science;*** NIH RePorter [2024] (accessed 7-31-2024)

Unmet Needs

Relapses Can Occur Even on Best Therapeutics



Non-Approved Therapeutics



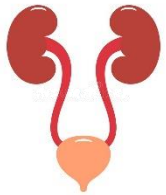
FDA-Approved Therapeutics



Therapeutics Collectively

Source: Guthy-Jackson Charitable Foundation Pre-Roundtable Survey / Estimates Accessed: 7-31-2024

Even Best Therapeutics Have Known Risks



Urinary tract infections due to MDR, XDR and enteroinvasive pathogens



Respiratory tract infections due to MDR, XDR and capsule (+) pathogens



CNS infections due to *Neisseria* sp., vaccine–evasive or latent pathogens



Infusion reactions that can range from mild to potentially life-threatening

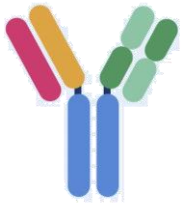


Uncertainty about long-term risks such as cancer or reproductive issues

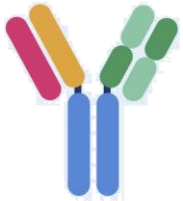
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Source: Quartuccio [2019] ***J Adv Res*** 15:87-93; Barreras [2022] ***Neurol*** 99:e2504

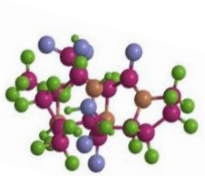
Next Wave Candidates Also Have Risks



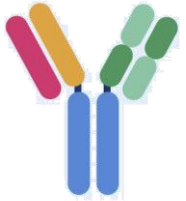
Complement Inhibitors



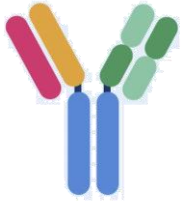
CD20 / CD19 Inhibitors



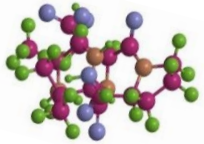
Novel BTKis



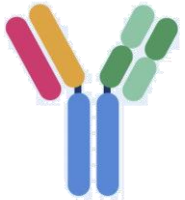
IL-17 / IL-23 Inhibitors



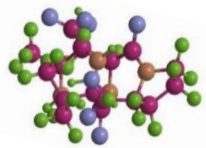
CD38 (NK) Inhibitors



Hi-Aff S1P Inhibitors



BAFF Inhibitors



JAK-STAT Inhibitors

Source: ClinicalTrials.gov [2024] Accessed 7-31-2024. ***Search term***: Neuromyelitis optica / NMOSD.

50+ Year Old Rescue Therapies Need Innovation



Cortico-Steroids



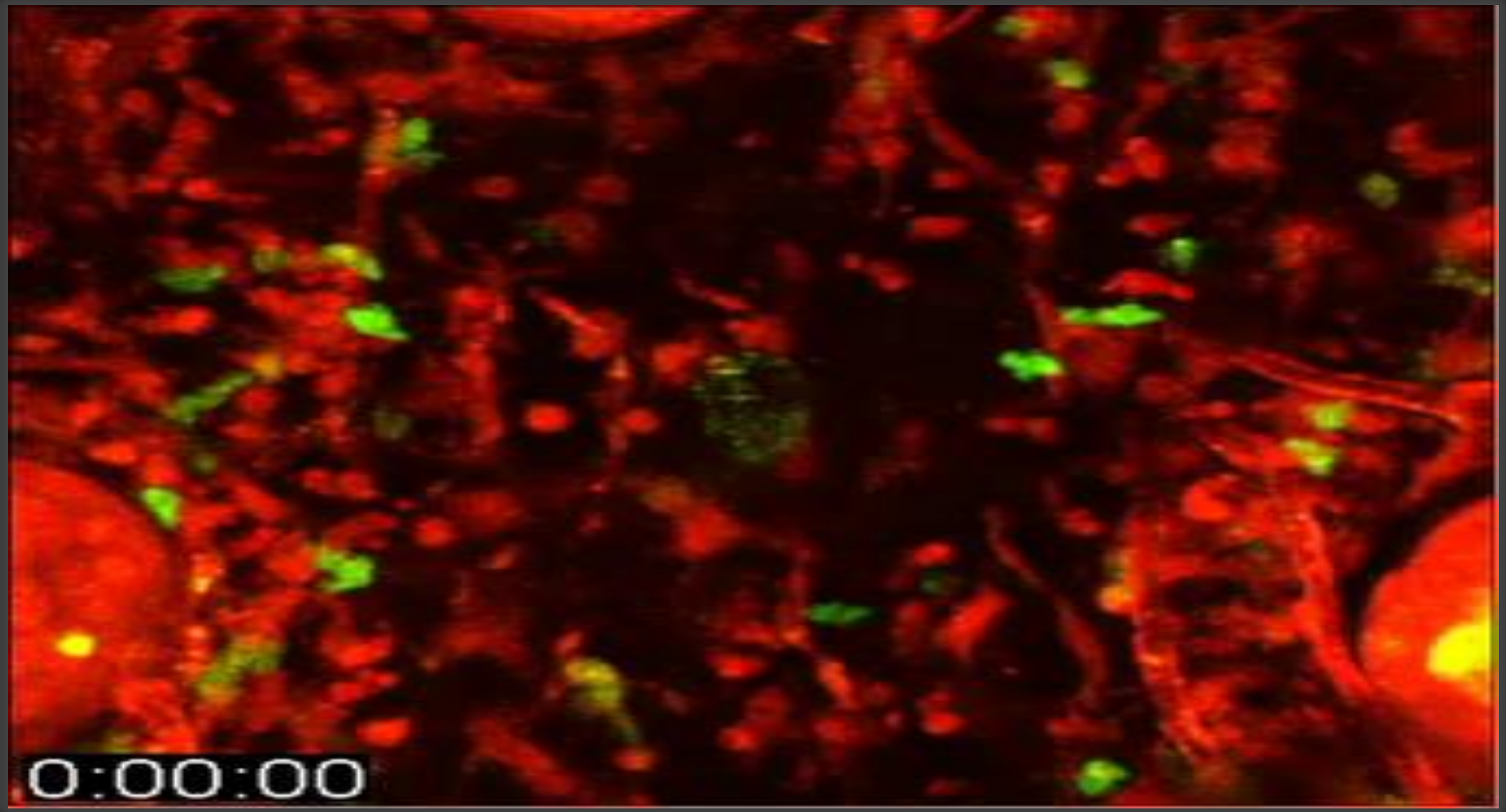
Plasma Exchange



IVIG Therapy

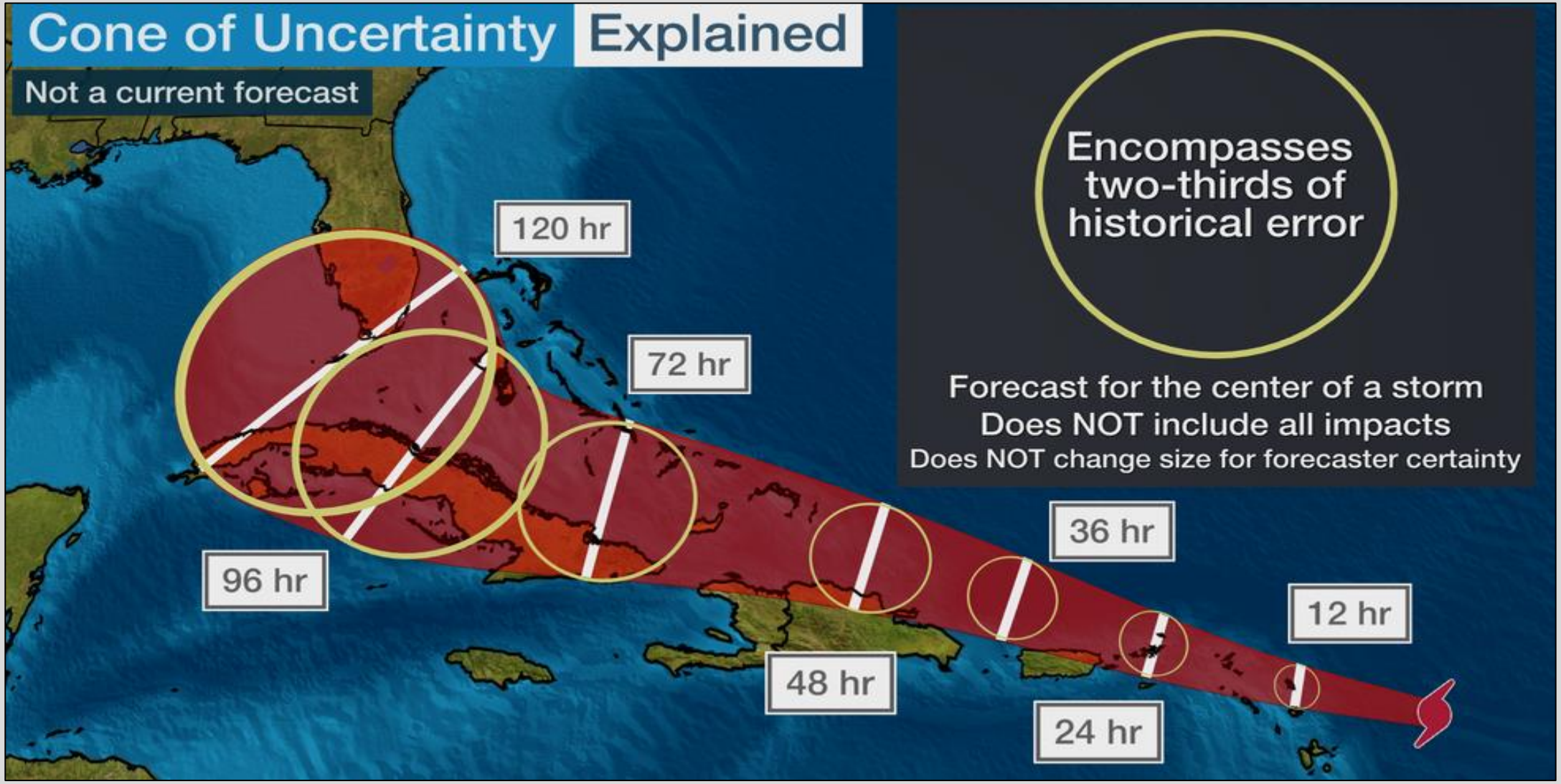
Source: Benedek [2011] ***Clin Exp Rheum*** 5(68):5-12

Syntax: Changing Context Over Time



Source: Lammermann T *et al.* [2013] ***Nature*** 498:371-375

NMOSD Relapses Have Been Hard to Predict



Source: Weather Channel [2024] / Accessed 7-31-2024: www.weather.com

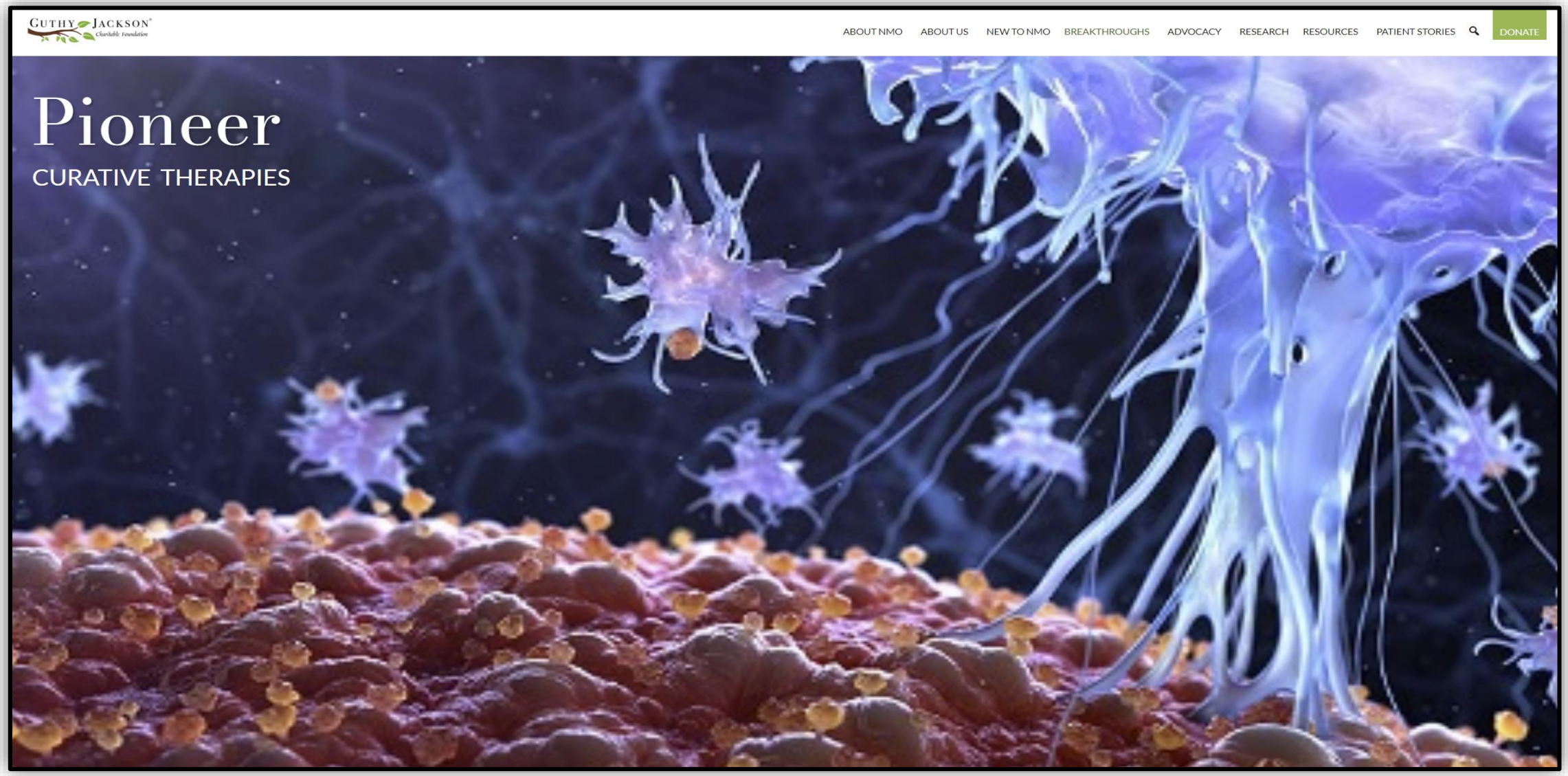
New Opportunities

Averting Risks & Improving Lives: New Era of NMO

- **Transition to therapeutics having clinical trial evidence of efficacy**
- **Personalize therapeutic regimens guided by precision biomarkers**
- **Mitigate risks of infection via full immunization regimen strategy**
- **Surveillance using prognostic biomarkers to forewarn of a relapse**
- **Intervene with novel rescue therapies to minimize relapse impact**
- **Accelerate toward curative therapies with Ag-specific tolerization**

Source: Guthy-Jackson Charitable Foundation [2024] / Access: www.guthyjacksonfoundation.org/pioneer

Innovating Curative Therapies for NMO & Beyond



Source: Guthy-Jackson Charitable Foundation [2024] / Access: www.guthyjacksonfoundation.org/pioneer



Rather tolerization asks an immune system to actively participate in a new process of peace.

Tolerization does not ask an immune system to cease its functions or wait on the sidelines…

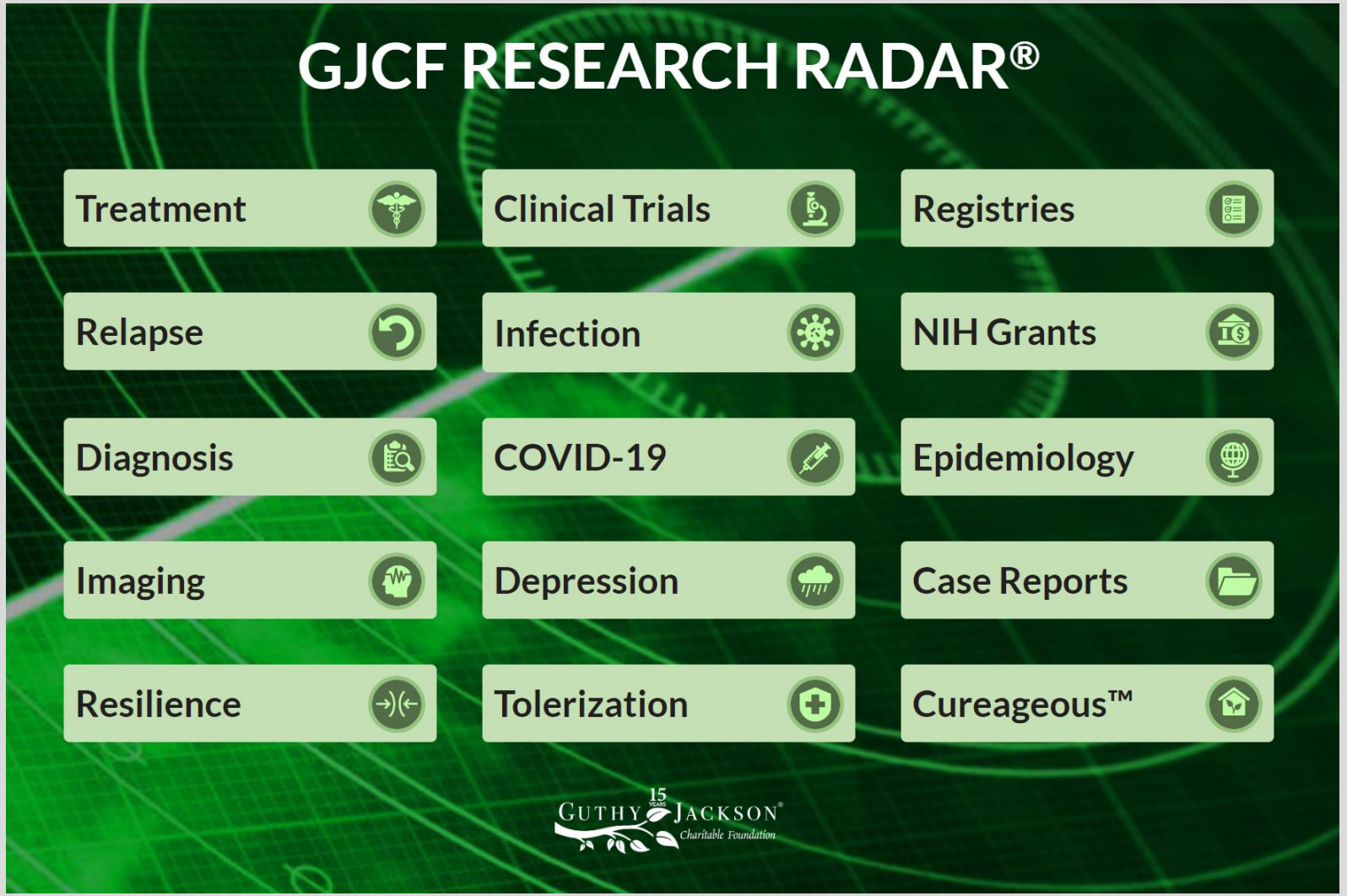
Banksy [2005] ***Rage, The Flower Thrower***

New GJCF Toolkit

GJCF *Research Radar*:™ Knowledge at Your Service

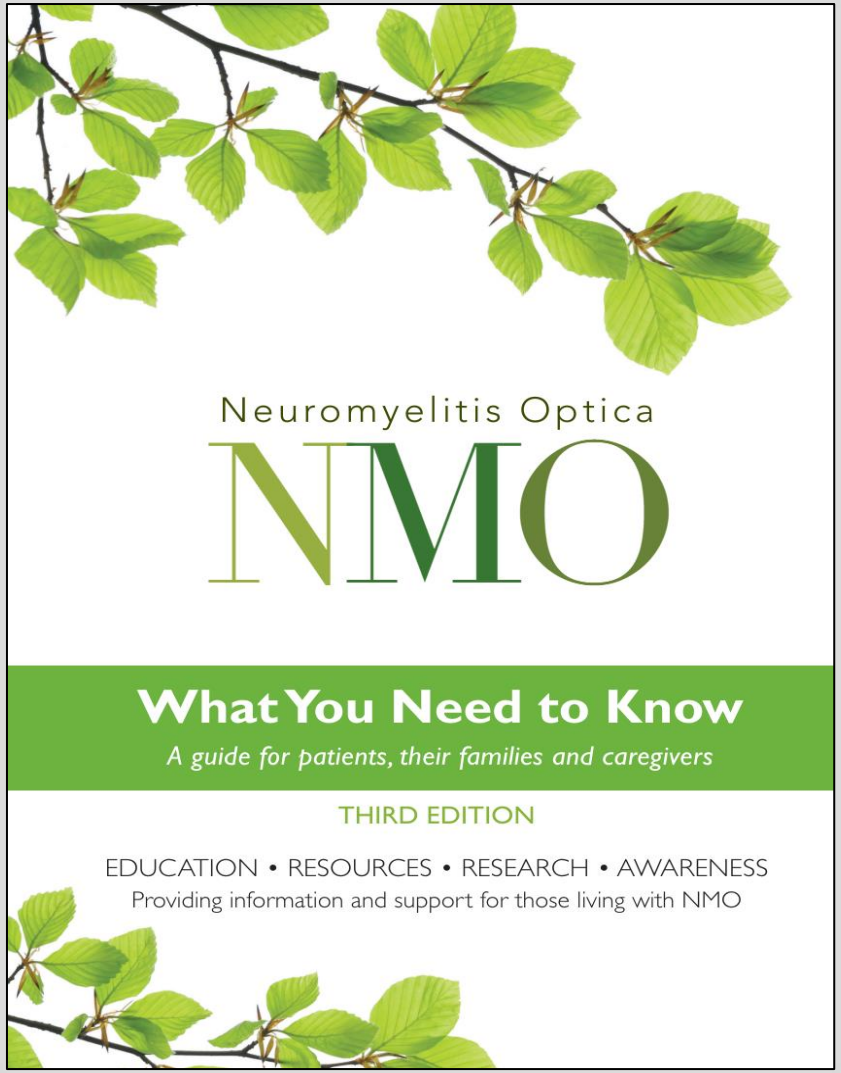
Ready When You Are:

LAUNCH DASHBOARD



Source: GJCF Website [2024] Access: www.guthyjacksonfoundation.org

Updated Reference Information at Your Fingertips





Guthy Jackson Charitable Foundation

Interactive Pocket Guide to NMOSD Therapeutics†

Healthcare Provider & Patient / Evolving Version 6.15.24 / © 2019-2024 Guthy-Jackson Charitable Foundation

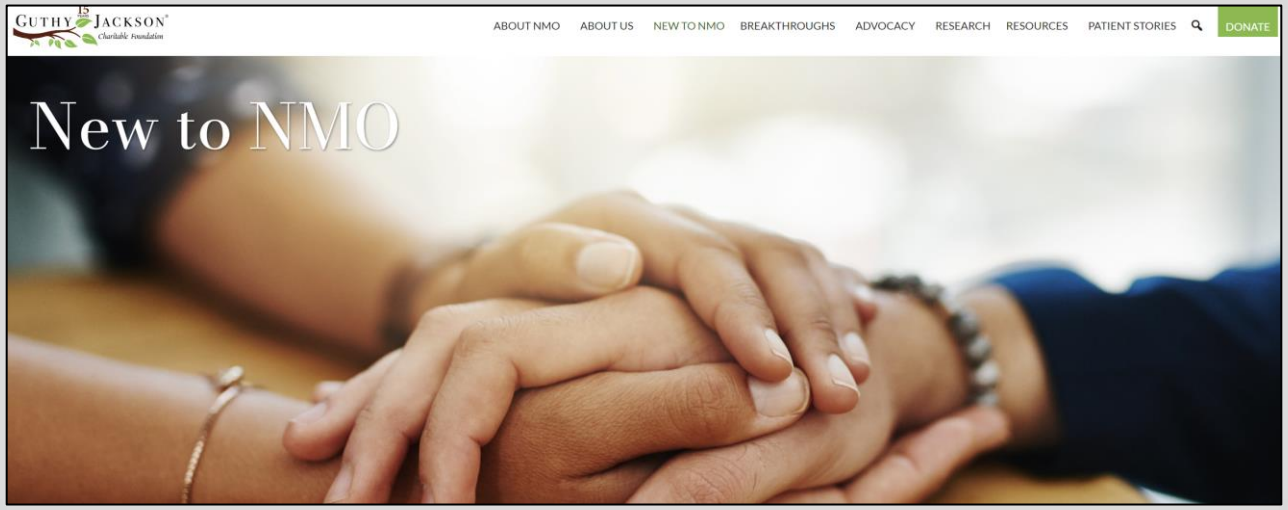
FDA–Approved Therapeutics | Non-Approved (Off-Label) Therapeutics

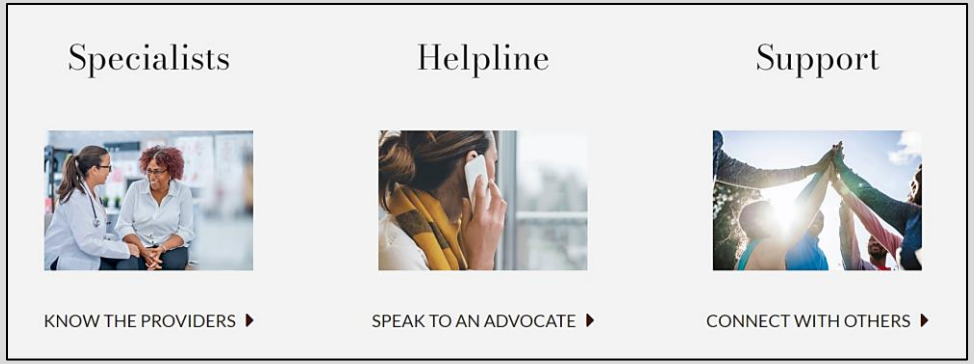
Feature	Soliris®	Uplizna®	Enspryng®	Ultomiris®	Rituxan®	Actemra®	CellCept®	Imuran®
Medical Name	Eculizumab (Alexion/AZ)	Inebilizumab (Amgen)	Satralizumab (Genentech)	Ravulizumab (Alexion/AZ)	Rituximab (Genentech)	Tocilizumab (Genentech)	Mycophenolate (Roche)	Azathioprine (Prometheus)
Disease Target	Complement Protein C5	CD19+ B Cells	IL-6 Receptor	Complement Protein C5	CD20+ B Cells	IL-6 Receptor	T and B Cell IMPDH Enzyme	DNA & RNA Synthesis
Clinical Trial Name	PREVENT	NMOmentum	SAkura Sky SAkura Star	CHAMPION	RIN-1	TANGO	MONICA	TANGO
Trial / Study Publication	NEJM 2019	Lancet 2019	NEJM 2019 Lancet 2020	Ann Neurol 2023	Clinical Study Lancet 2020	Clinical Study Lancet 2020	Clinical Study Front Imm 2018	Clinical Study Lancet 2020
Clinical Trial Efficacy †	Yes; See Data (Mono/Poly)	Yes; See Data (Mono Tx)	Yes; See Data (Mono/Poly)	Yes; See Data (Mono/Poly)	Non-Trial Data (Mono/Poly)	Non-Trial Data (Mono/Poly)	Non-Trial Data (+ Steroid)	Non-Trial Data (Mono/Poly)
U.S. FDA Status	Approved Jun 27, 2019	Approved Jun 11, 2020	Approved Aug 17, 2020	Approved Mar 25, 2024	Not Approved ♦	Not Approved	Not Approved	Not Approved
Package Insert	Soliris® FDA Label	Uplizna® FDA Label	Enspryng® FDA Label	Ultomiris® FDA Label	Rituxan® FDA Label	Actemra® FDA Label	CellCept® FDA Label	Imuran® FDA Label
Approved Indication	Anti-AQP4+ Age 18+ Yrs	Anti-AQP4+ Age 18+ Yrs	Anti-AQP4+ Age 18+ Yrs	Anti-AQP4+ Age 18+ Yrs	Not Approved	Not Approved	Not Approved	Not Approved
Medication Guide Summary	Soliris® Medication Guide	Uplizna® Medication Guide	Enspryng® Medication Guide	Ultomiris® Medication Guide	Rituxan® Medication Guide	Actemra® Medication Guide	CellCept® Medication Guide	Imuran® Medication Guide
Status in < 18 Yrs	Not Approved; Clinical Trial; Used in HUS	Not Approved; Consult Peds Neurologist	Not Approved; Outcomes in Adolescents	Not Approved; Approved for HUS and PNH	Approved for NHL, RA, GPA; MOGAD Data	Approved for SJIA and PJIA	> 3 months old; Consult Peds	Peds Data; Consult Peds
Status in Pregnancy	Data Available; Consult Neuro	Data Pending; Consult Neuro	Data Pending; Consult Neuro	Data Available; Consult Neuro	Data Available; Consult Neuro	Data Available; Consult Neuro	**Avoid Use** (Fetal Harm)	**Avoid Use** (Fetal Harm)
Status in Comorbidity	Consult Neurologist	Consult Neurologist	Consult Neurologist	Consult Neurologist	Consult Neurologist	Efficacy Intact [see TANGO]	Consult Neurologist	Consult Neurologist
Safety Warning*	**Box Warning:** Nm Infection	No Specific Warning	No Specific Warning	**Box Warning:** Nm Infection	**Box Warning:** IRxn;TLS;PML	**Box Warning:** TB & Opp Infxn	**Box Warning:** Preg; Infxn; CA	**Box Warning:** Cancer; Infxn
Safety Precaution*	IRx; Infection; Nm Infection	IRx; Infection Ab; PMN	Liver Function; Cho; WBC; PLT	IRx; Infection; Nm Infection	IRx; Infection Ab; PMN	Liver Function; Cho; WBC; PLT	Infection; Tox; Malignancy	Infection; Tox; Malignancy
U.S. FDA REMS	REMS Required	REMS Not Required	REMS Not Required	REMS Required	REMS Not Required	REMS Not Required	REMS Not Required	REMS Not Required
Pre-Use Screening	None Required	HBV; JCV; TB Serum IgG	HBV; TB; Liver Function	None Required	HBV; JCV; TB Serum IgG	HBV; TB; Liver Function	Liver Function; Blood Cell Cnt	TPMT Enzyme Level
Required* Vaccines Δ	FDA Required *see ACIP Δ	Standard *see ACIP	Standard *see ACIP	FDA Required *see ACIP Δ	Standard *see ACIP	Standard *see ACIP	Standard *see ACIP	Standard *see ACIP
Laboratory Monitoring	None Specifically Required	B Cell Count; Ig Levels; Neutrophils	Liver Function; Neutrophils; Lipid/LDL; PLT	PLT count; Liver / Kidney Function	Infection; B Cell Count; Total Ig; PMN	Liver Function; Chol & Lipids; WBC / PLT Cnt	Routinely Blood Cell Cnt; Bleeding Issues	Routinely WBC Count; Infxn; Cancer
Maintenance Dosing	Uniform Dose (1,2 g)	Uniform Dose (300 mg)	Uniform Dose (120 mg)	40/60/100 kg (2.4/2.7/3.0g)	Per Body m² (~375mg/m²)	Uniform Dose (8mg/kg; 4wk)	Uniform Dosing (up to 2 g/d)	Per Body Mass (2-3 mg/kg/d)
Mode of Dosing	Intravenous Infusion	Intravenous Infusion	Subcutaneous Injection	Intravenous Infusion	Intravenous Infusion	Intravenous Infusion	Oral Tablet	Oral Tablet
Mono or Poly Tx	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro	± Add On; Consult Neuro
Induction Regimen	Every Week First 4 Doses	Every 2 Weeks First 2 Doses	Every 2 Weeks First 3 Doses	Loading Dose for 2 Weeks	Every 2 Week Half-Doses	Every 2 Weeks First 3 Doses	Loading Dose; Consult Neuro	Loading Dose; Consult Neuro
Routine Regimen	Every 2 Wks Infusion	Every 24 Wks Infusion	Every 4 wks Injection	Every 8 Wks Infusion	Every 24 Wks Infusion	Every Wk Injection	Usually Daily if Oral	Usually Daily if Oral
PLEX or IVIG Re-Dosing	Re-Dose < 60 min Post-PLEX	Consult Neurologist	Consult Neurologist	Re-Dose < 4 hours Post-PE/IVIG	Consult Neurologist	Consult Neurologist	Consult Neurologist	Consult Neurologist
Company Website	Soliris® Website	Uplizna® Website	Enspryng® Website	Ultomiris® Website	Rituxan® Website	Actemra® Website	CellCept® Website	Imuran® Website
Patient Support	OneSource® Website	Horizon BYS® Website	Access Solutions® Website	OneSource® Website	No NMOSD Aid Program	No NMOSD Aid Program	No NMOSD Aid Program	No NMOSD Aid Program

† *Important*: content is reference information only; it neither expresses nor implies recommendations for therapy. Consult the FDA-approved label.
* Label Box Warnings & Precautions per the U.S. FDA [2024]; consult the specific package insert for each particular therapy approved for use in NMO.
Δ U.S. CDC Advisory Committee on Immunization in Persons with Altered Immune Competence (ACIP) [2021] Recommendations (www.cdc.gov/acip)
♦ Approved for NMO by the Japanese Ministry of Health (Japan) but not by the FDA (U.S.)
Key: Tx = therapy; IRx = infusion reaction; REMS = Risk Evaluation & Mitigation Strategy; PLT = platelet; Nm = serious *N. meningitidis* infection; TB = tuberculosis; HBV = hepatitis B virus

Source: GJCF Website [2024] Access: www.guthyjacksonfoundation.org

Credible Insights into Patient Real-World Experience



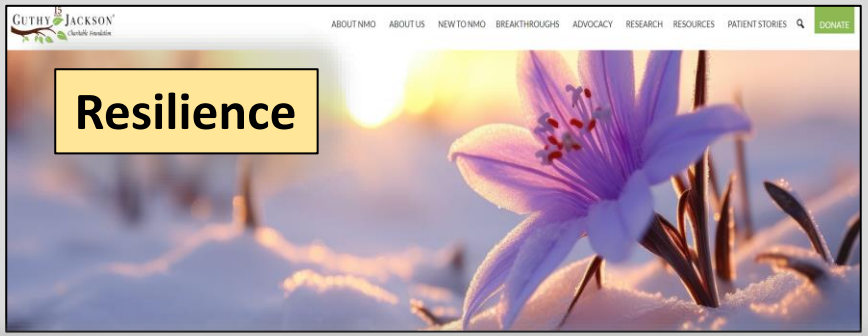






Source: GJCF Website [2024] Access: www.guthyjacksonfoundation.org

Life-Enhancing Tools for All NMOSD Stakeholders



Live life fully through the lens of resilience



Know about relapse & how to be prepared



Keep pace with the GJCF *Research Radar*™

Source: GJCF Website [2024] Access: www.guthyjacksonfoundation.org

NMO as a Key

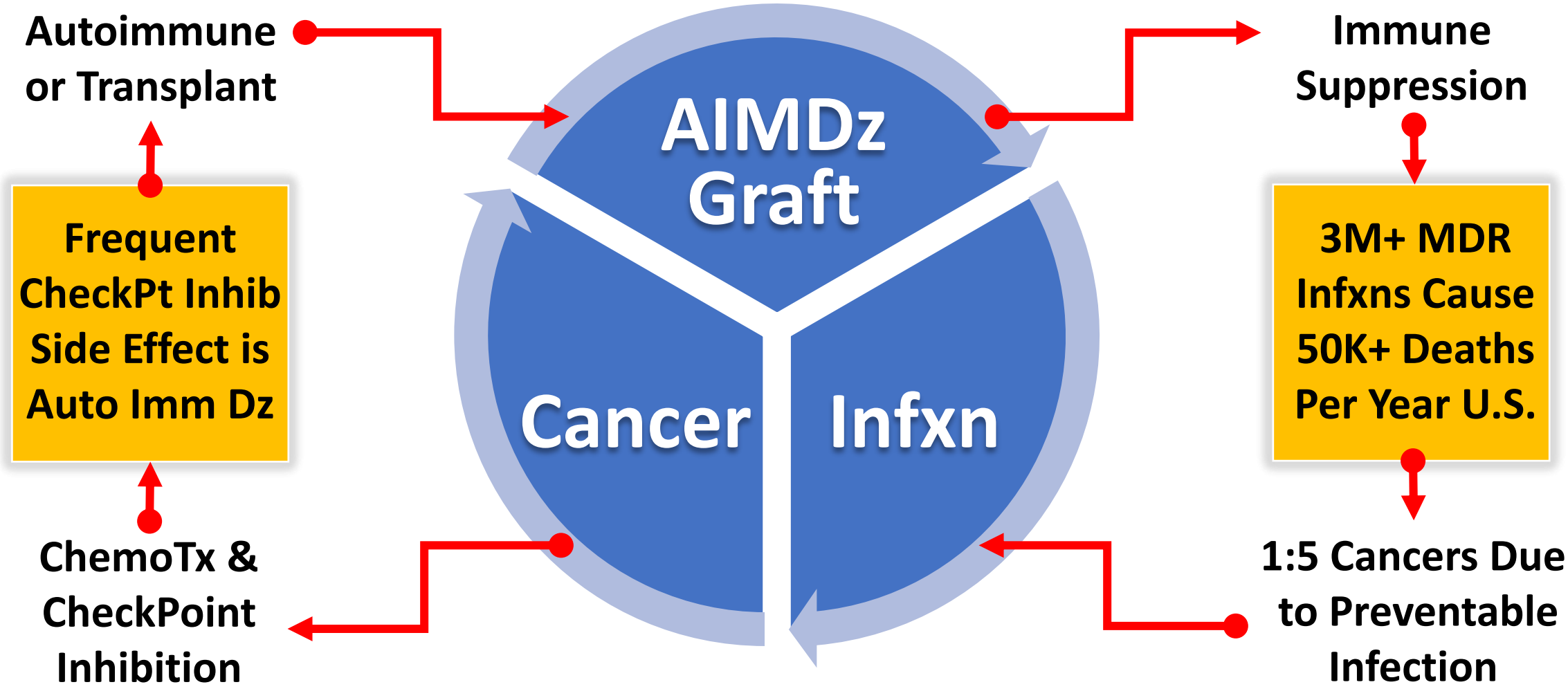


Rise of Autoimmune Disease

- 100+ Distinct Autoimmune Diseases Known
- 8%+ of Population (24M US; 640M Globally)
- Prevalence ~ Equal to Heart Dz; 2X > Cancer
- AutoIDz Tx → Cancer / Cancer Tx → AutoIDz
- Survival Propensity Suggests an ID Trade-Off
- Special Cases: Autoimmune Diseases of CNS
- NMO Represents the Model Target for Cure
- Unmet Need: Pioneer Curative Tolerization

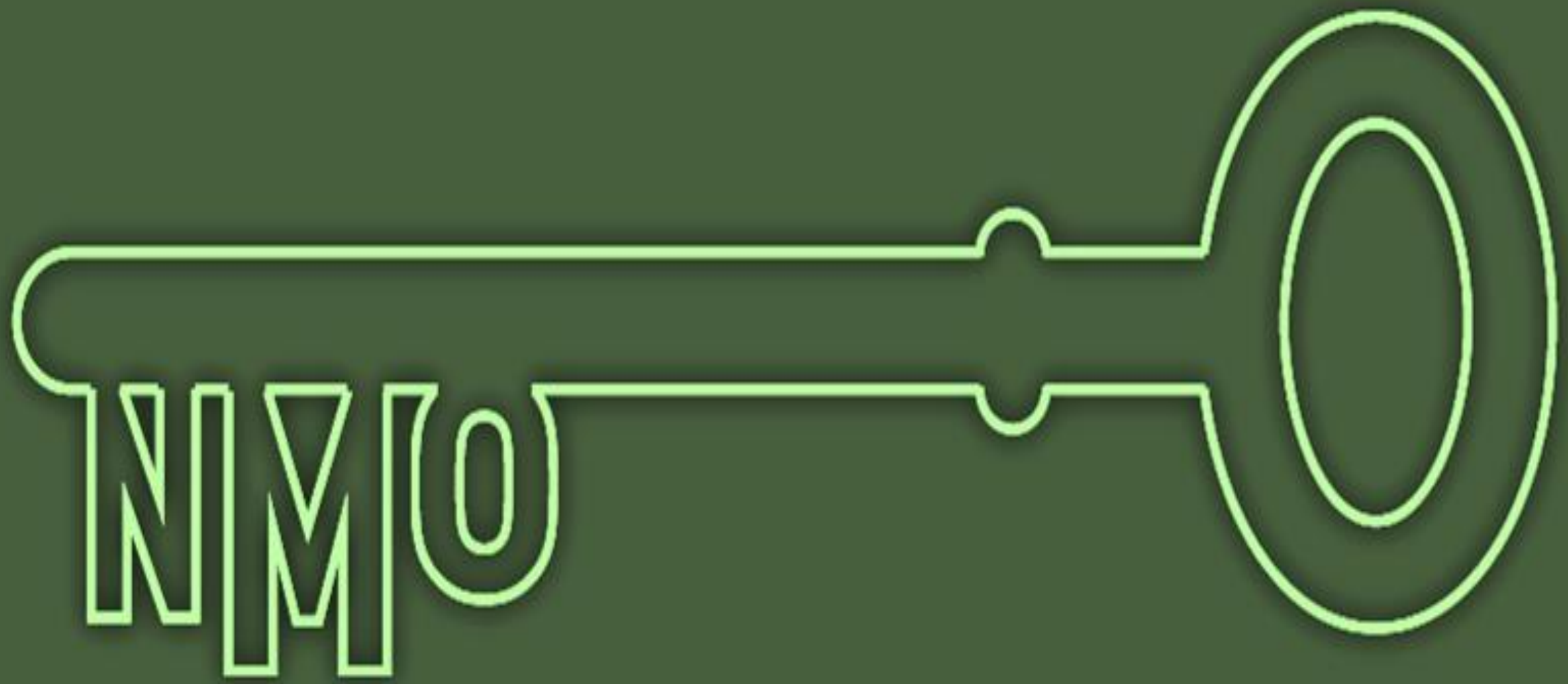
Source: ***Science*** [2023] 380:468–490

Vicious Cycle of Immunological Diseases



Source: ***Yeaman MR*** [2021] Vatican Council on Inflammatory Diseases. New York.

NMO: The Little Disease That Did



Source: Jackson & Yeaman [2017] ***The Power of Rare*** / Villabella Press / Simon & Schuster

GJCF Mission: Solve NMOSD Once & For All



Promote – *advocacy for all to enhance access & quality of life*



Predict – *relapses, risks, disease course & therapeutic benefits*



Protect – *against relapse harm, SAEs and permanent disability*



Pioneer – *curative therapies using tolerization & regeneration*

Source: Guthy-Jackson Charitable Foundation [2024] Website: ***Breakthroughs***

On the Opportunity for Bold New Solutions

“ If one looks into the future
and an idea today seems like science fiction –
it may be wrong…
but if it does not look like science fiction –
it will definitely be wrong… ”

Christine Peterson
NASA Space Strategist
Founder Foresight Institute

Source: Peterson C [2008] ***The Shape of Things to Come*** [lecture]

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Inebilizumab-cdon and NMOSD:
What's New in 2024

Kristina Patterson, MD, PhD
Senior Medical Director-Neuroimmunology
Amgen Medical Affairs

Guthy Jackson Charitable Foundation Symposium
August 2024

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Disclosures

- Kristina Patterson is an employee of Amgen and owns stock

FOUNDED
1980

GLOBAL HQ
Thousand Oaks, California, USA

EMPLOYEES
27,000+

 # OF PATIENTS REACHED
13 million
ANNUALLY

R&D INVESTMENT
$4.8 billion
IN 2023

DONATIONS
$2.5 billion*
Through
AMGEN SAFETY NET
FOUNDATION IN 2023

MARKETS
~100

TOTAL REVENUE
$28.2 billion
IN 2023

*Valued at wholesale acquisition cost.

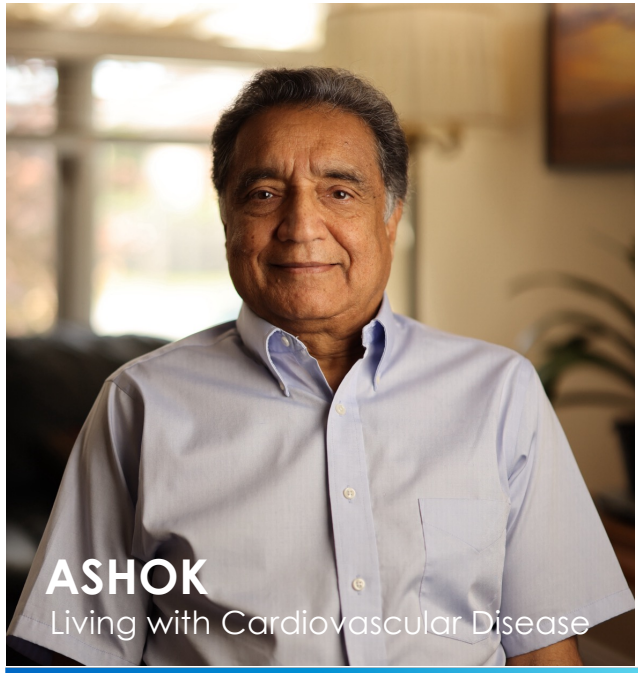
Our Therapeutic Areas Focus



ONCOLOGY



INFLAMMATION



GENERAL MEDICINE



RARE DISEASE

We serve millions of seriously ill patients living with cancer, cardiovascular disease, inflammatory diseases, rare diseases, and more.

We Serve Patients Suffering from Serious Illness



ESTHER, living with neuromyelitis optica spectrum disorder (NMOSD)

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Inebilizumab-cdon for the Treatment of Neuromyelitis Optica Spectrum Disorder (N-MOmentum)



Please see the Full Important Safety Information on slides 7-9 and visit UPLIZNAhcp.com for the **Full Prescribing Information**.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

UPLIZNA (inebilizumab-cdon) is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

IMPORTANT SAFETY INFORMATION

UPLIZNA is contraindicated in patients with:

- A history of life-threatening infusion reaction to UPLIZNA
- Active hepatitis B infection
- Active or untreated latent tuberculosis

WARNINGS AND PRECAUTIONS

Infusion Reactions: UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Administer pre-medication with a corticosteroid, an antihistamine, and an anti-pyretic.

Important Safety Information continues on slides 8-9.

INDICATION AND IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Infections: The most common infections reported by UPLIZNA-treated patients in the randomized and open-label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). Delay UPLIZNA administration in patients with an active infection until the infection is resolved.

Increased immunosuppressive effects are possible if combining UPLIZNA with another immunosuppressive therapy.

The risk of Hepatitis B Virus (HBV) reactivation has been observed with other B-cell-depleting antibodies. Perform HBV screening in all patients before initiation of treatment with UPLIZNA. Do not administer to patients with active hepatitis.

Although no confirmed cases of Progressive Multifocal Leukoencephalopathy (PML) were identified in UPLIZNA clinical trials, JC virus infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies and other therapies that affect immune competence. At the first sign or symptom suggestive of PML, withhold UPLIZNA and perform an appropriate diagnostic evaluation.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating UPLIZNA.

Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.

Important Safety Information continues on slide 9.

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INDICATION AND IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Reduction in Immunoglobulins: There may be a progressive and prolonged hypogammaglobulinemia or decline in the levels of total and individual immunoglobulins such as immunoglobulins G and M (IgG and IgM) with continued UPLIZNA treatment. Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion especially in patients with opportunistic or recurrent infections.

Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA.

Adverse Reactions: The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia.

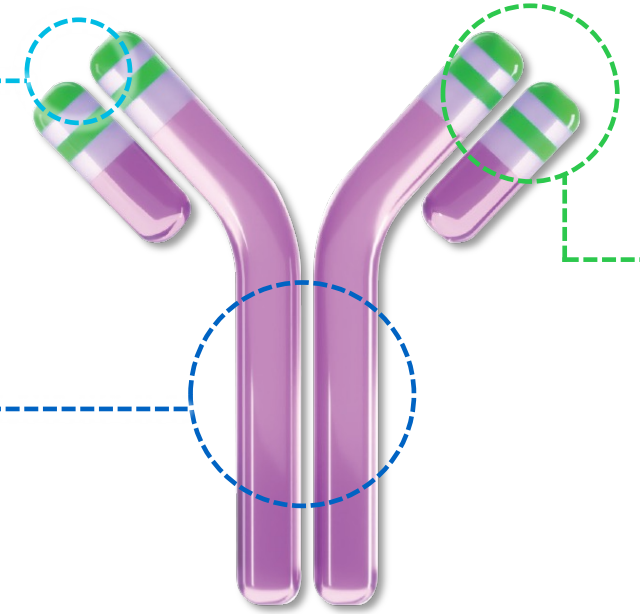
Please see the Full Prescribing Information at UPLIZNAhcp.com.

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Inebilizumab-cdon: Differentiated Mechanistic Profile

Optimized for human CD19 binding

Inebilizumab-cdon is a glycoengineered humanized IgG1κ anti-CD19 monoclonal antibody that targets* plasmablasts and plasma cells[1-4]



Humanized F(ab) portion

Compared to chimeric designs, humanized designs are associated with reduced immunogenicity, improved tolerability, and decreased potential for infusion related reactions[5,6]

Glycoengineered design

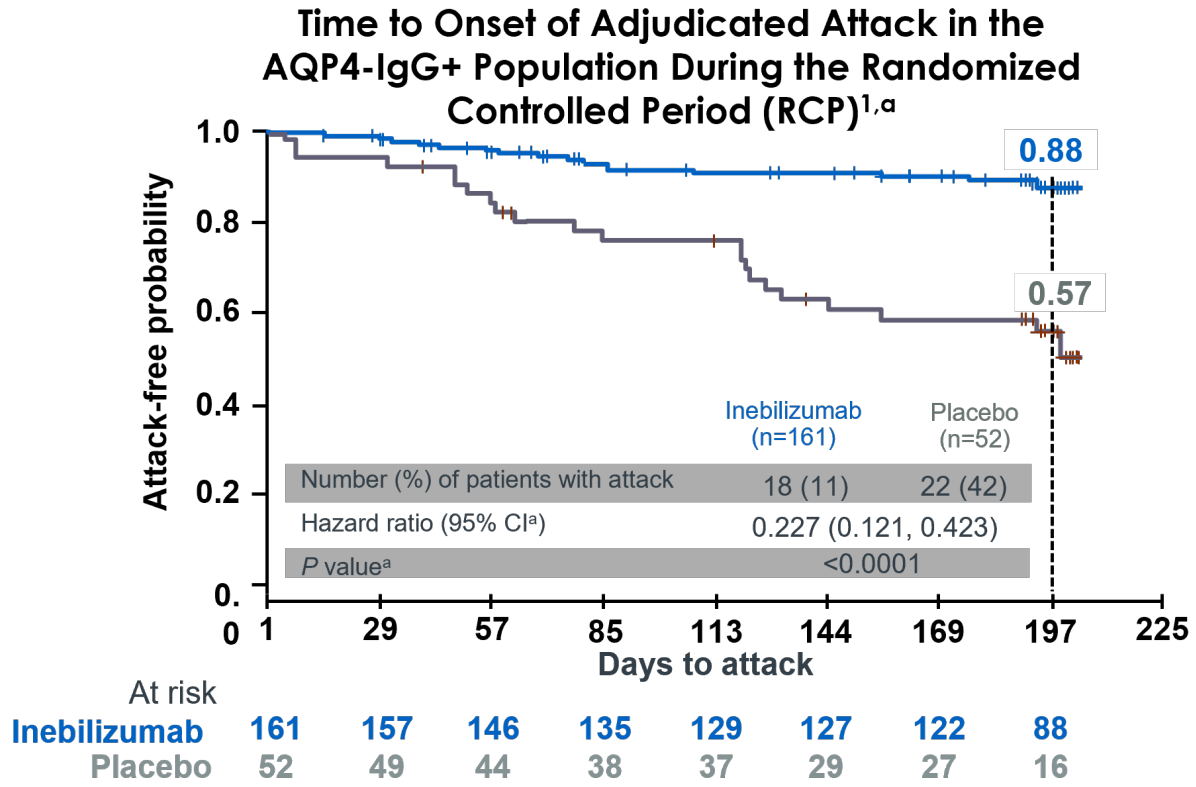
Specifically bioengineered to provide efficacy in those that may have a certain genetic polymorphism that can cause diminished responses to other monoclonal antibody therapies[7,8]

*The precise mechanism by which inebilizumab-cdon exerts its therapeutic effects in NMOSD is unknown.

CD, cluster of differentiation.

1. UPLIZNA (inebilizumab-cdon) [Prescribing Information] Horizon. 2. Chen D, et al. *J Clin Med*. 2016;5(12):107. 3. Forsthuber TG, et al. *Ther Adv Neurol Disord*. 2018;11:1-13. 4. Bennett JL, et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e104. 5. Hwang WYK, Foote J. *Methods*. 2005;36(1):3-10. 6. Harding FA, et al. *mAbs*. 2010;2(3):256-265. 7. Herbst R, et al. *J Pharmacol Exp Ther*. 2010;335(1):213-222. 8. Pereira NA, et al. *mAbs*. 2018;10(5):693-711.

Inebilizumab-cdon Monotherapy Significantly Reduced Risk of NMOSD Attacks



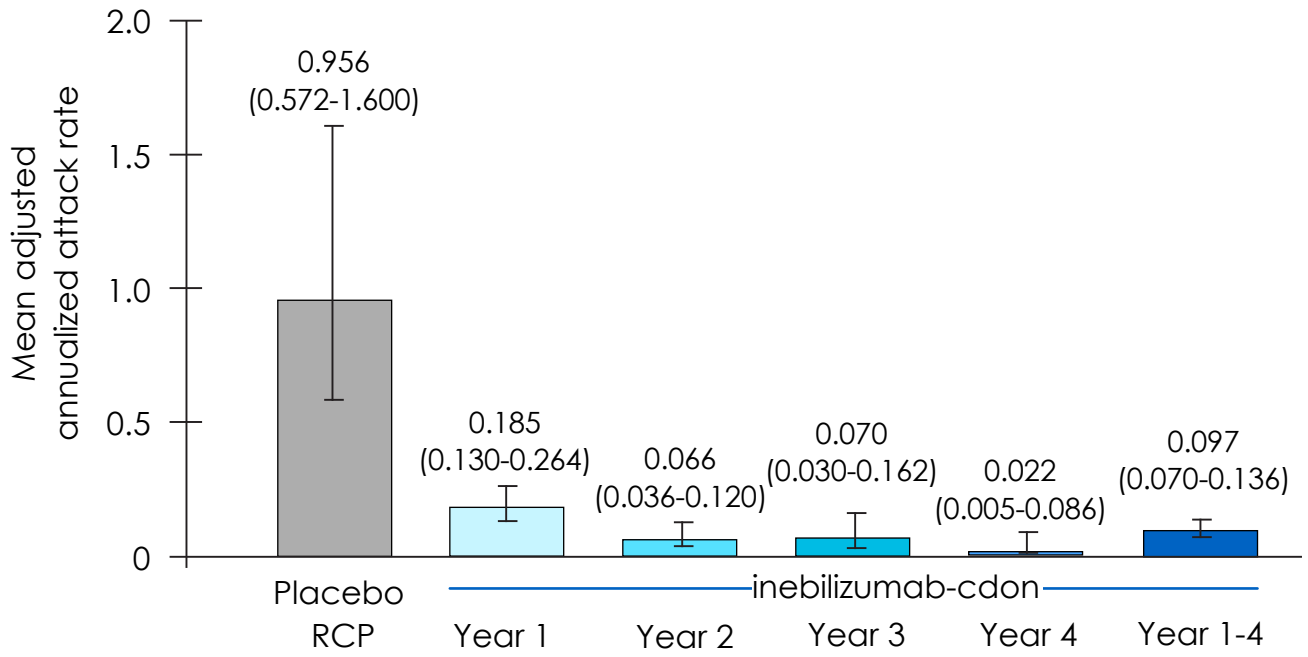
89% of patients on inebilizumab-cdon were **attack free** through 28 weeks, with a 77% reduction in attack risk compared with placebo[1,2]

[a]A Cox regression method, with placebo as the reference group. Data include AQP4-IgG–seropositive patients. Data points represent the latest risk percentage measurement before the specified time point. Error bars represent 95% CI estimated by negative binomial regression.
AQP4, aquaporin-4; CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder.
1. Cree BAC, et al. Lancet. 2019;394(10206):1352-1363. 2. UPLIZNA (inebilizumab-cdon) [Prescribing Information] Horizon.

Annualized Attack Rates With Long-Term Inebilizumab-cdon Treatment

- End-of-study adjusted annualized attack rates[a] were:
  - 0.092 (95% CI: 0.067-0.13) for the **any inebilizumab-cdon population**
  - 0.097 (95% CI: 0.070-0.14) for the **any inebilizumab-cdon AQP4-IgG+ subgroup**

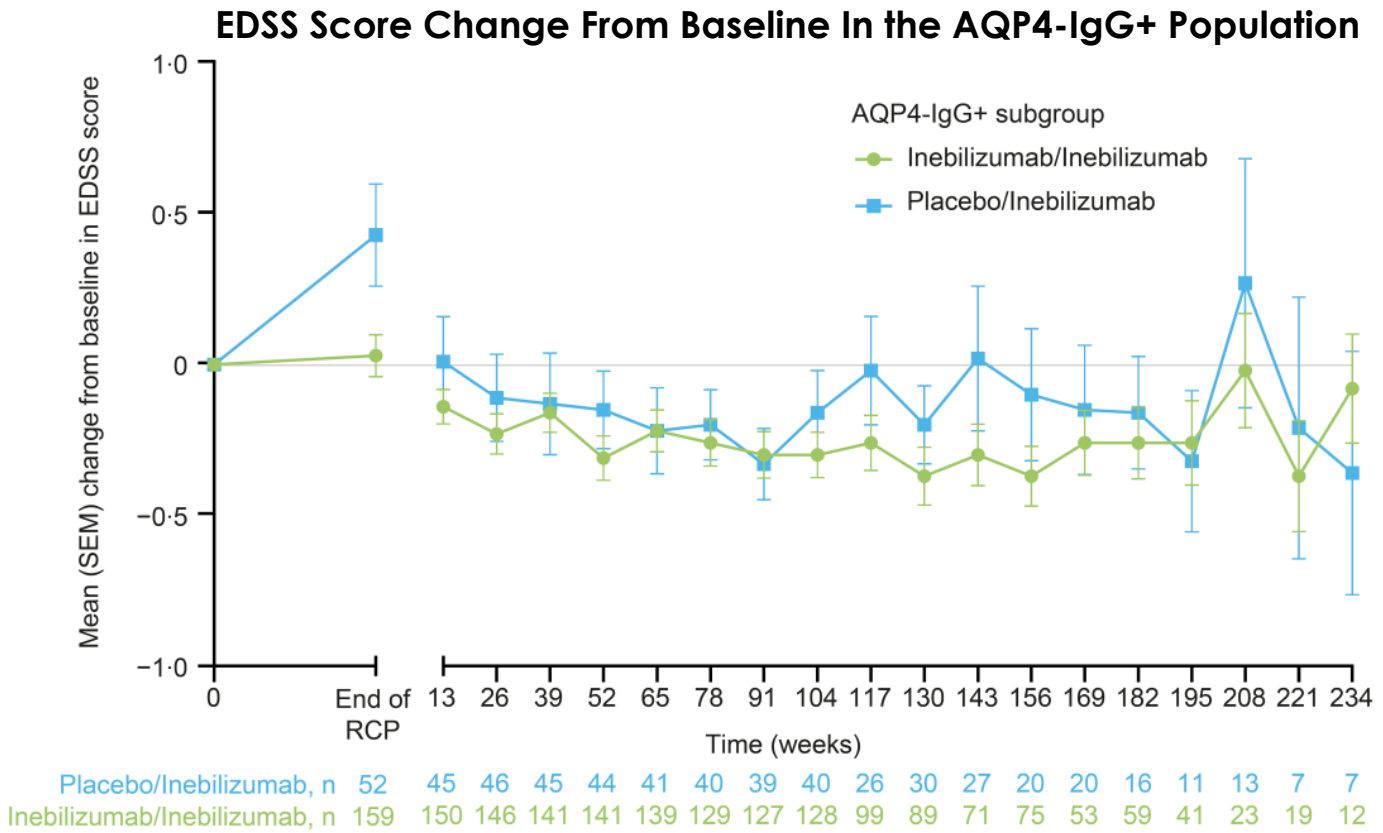
Time to first attack and annualized attack rates in any inebilizumab-cdon AQP4-IgG+ subgroup[b]



[a]Adjusted annualized attack rates were calculated using a negative binomial model based on the total number of adjudication committee—determined attacks normalized by the total person-years of exposure. [B]'Any inebilizumab-cdon' refers to all participants who received inebilizumab-cdon at any point during the RCP or during the OLP and incudes both AQP4-IgG+ and AQP4-IgG- participants.
Consider open-label treatment phase study limitations when interpreting results. The OLP was not blinded, not controlled, and included inherent self-selection bias for remaining in the trial. During the OLP, a total of 42 patients (19.4%) discontinued, of which 5 patients (2.3%) discontinued due to adverse events.

AQP4-IgG+, aquaporin-4 immunoglobulin G seropositive; OLP, open-label period; RCP, randomized-controlled period.
Cree BAC, et al. *Lancet Neurol*. 2024;6(23):588-602.

Disability Scores With Long Term Inebilizumab-cdon Therapy Compared to Placebo

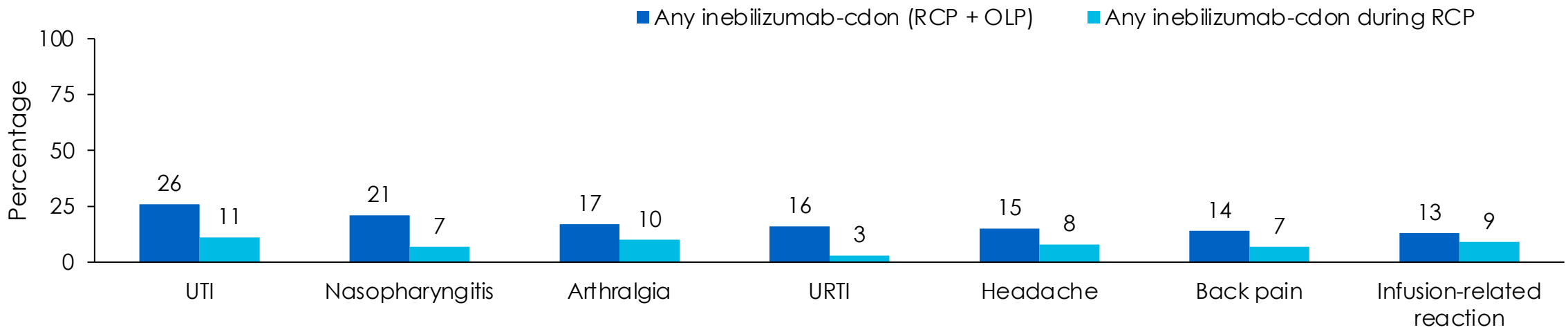


Participants completing the RCP could enroll in the OLP. Some participants did not join the OLP, which is reflected in the differences in participant numbers between 'End of RCP' and 'week 13'.
Consider open-label treatment phase study limitations when interpreting results. The OLP was not blinded, not controlled, and included inherent self-selection bias for remaining in the trial. During the OLP, a total of 42 patients (19.4%) discontinued, of which 5 patients (2.3%) discontinued due to adverse events.
The EDSS analysis included visits during an attack, with EDSS progression driven by the expected increase in EDSS at the time of attack. Therefore, these results should not be interpreted as impacting disability independent of attack reduction. Additionally, subjects were not followed up for the same amount of time, resulting in missing data which may have introduced biases into the analysis. Subjects with missing data are imputed as worsening.
AQP4-IgG+, aquaporin-4 immunoglobulin G seropositive; OLP, open-label period; RCP, randomized-controlled period; inebilizumab/inebilizumab, randomized to inebilizumab/inebilizumab in the OLP; Placebo/inebilizumab, randomized to placebo/inebilizumab in the OLP
Cree BAC, et al. *Lancet Neurol*. 2024;6(23):588-602.

Most Frequent Treatment-Emergent Adverse Events

- Across both study periods, 3% of the 225 participants permanently discontinued treatment owing to inebilizumab-cdon-related treatment-emergent adverse events (TEAEs)

Most frequent TEAE occurring in >10% of inebilizumab-cdon-treated participants



UTI Was the Most Common Treatment-Emergent Adverse Event

OLP, open-label period; RCP, randomized controlled period; TEAEs, Treatment-emergent adverse events; URTI, upper respiratory tract infection; UTI, urinary tract infection.
Cree BAC, et al. *Lancet Neurol*. 2024;6(23):588-602.

Thank you

Titles of Recently Presented Posters From EAN

- Improvements in Pain and Quality of Life After Inebilizumab in Attack-Free NMOSD Participants
- Safety of Inebilizumab in Participants Over 50 and 65 Years of Age With Neuromyelitis Optica Spectrum Disorder (NMOSD)

Recently Published Papers

- Cree BAC, et al. Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial. *Lancet Neurol*. 2024 Jun;23(6):588-602.
- Osborne B, et al. Case report: Transition from anti-CD20 therapy to inebilizumab for 14 cases of neuromyelitis optica spectrum disorder. *Front Neurol*. 2024 Apr 16;15:1352779.

In Press

- Bennett et al. B Cell And Aquaporin-4 Antibody Relationships With Neuromyelitis Optica Spectrum Disorder Activity. *ACTN*. 2024. [in press]

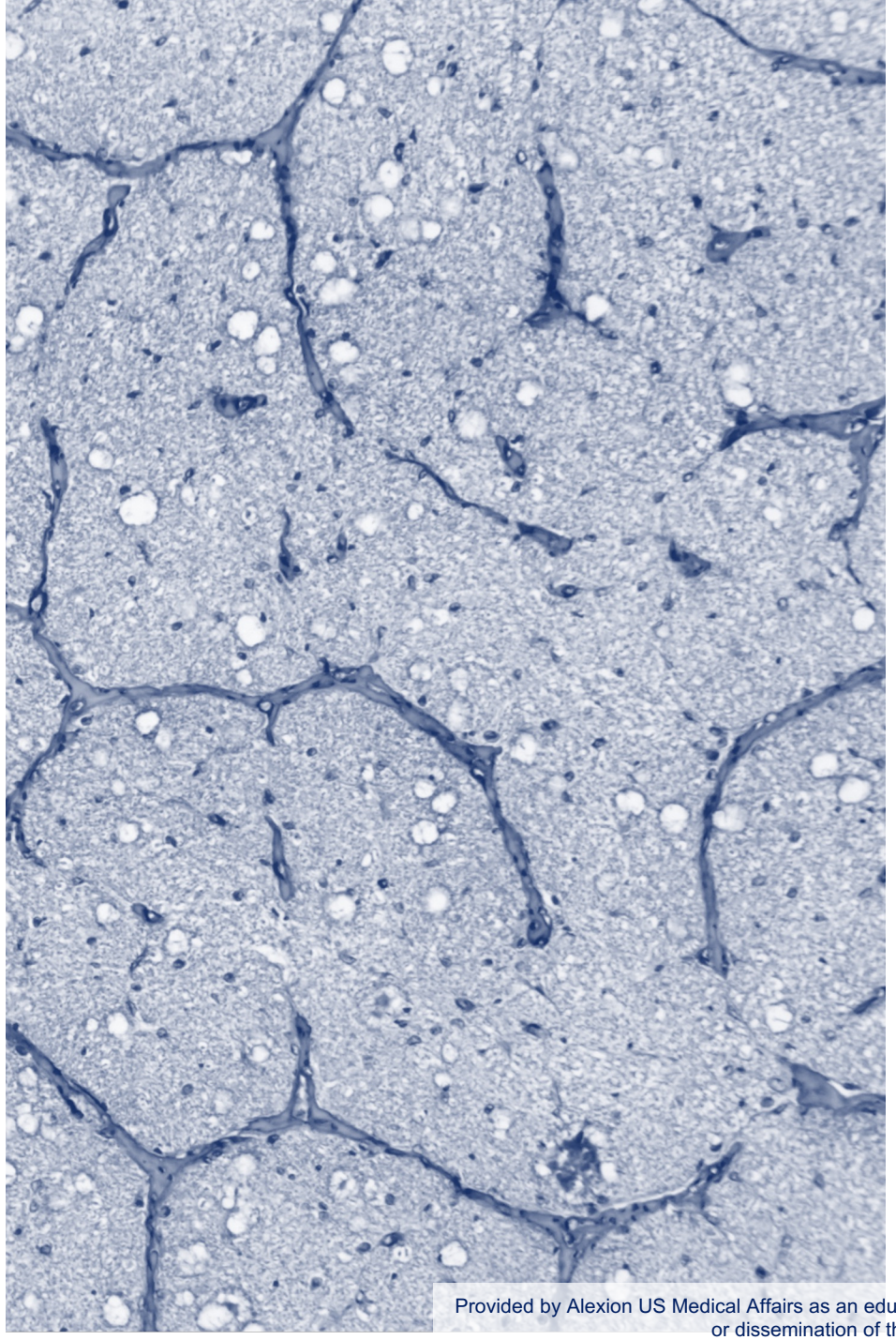
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Thank You



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The Guthy-Jackson Charitable Foundation: International NMO Roundtable Conference 2024



LOKESH JHA, MD
Executive Director

Therapeutic Area Head, Neurology
US Medical Affairs

ALEXION®
AstraZeneca Rare Disease

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SPEAKER DISCLOSURES

- Research Funding for CHAMPION-NMOSD and CHAMPION-NMOSD Long-term Extension and presented analyses was provided by Alexion, AstraZeneca Rare Disease

- Lokesh Jha is an employee and hold stocks of Alexion, AstraZeneca Rare Disease

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

PRESENTATION OBJECTIVES



Alexion's commitment to rare disease and neurology



Recent long-term efficacy and safety data of ravulizumab in NMOSD



Review meningococcal infection risk associated with eculizumab and ravulizumab

NMOSD, neuromyelitis optica spectrum disorder

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS® (ravulizumab-cwvz), and SOLIRIS® (eculizumab), both complement inhibitors, increase the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1*)]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS or SOLIRIS, unless the risks of delaying ULTOMIRIS or SOLIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS or SOLIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, ULTOMIRIS and SOLIRIS are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2*)].

SEE ADDITIONAL IMPORTANT SAFETY INFORMATION

ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA.
SOLIRIS® (eculizumab) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA.

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

Neuromyelitis Optica Spectrum Disorder (NMOSD)

ULTOMIRIS and SOLIRIS are indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive.

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

ALEXION BY THE NUMBERS

30 YEARS OF EXPERIENCE[1] in complement biology across **3** CORE THERAPEUTIC AREAS[1]

- NEUROLOGY
- HEMATOLOGY
- NEPHROLOGY

Select Therapeutic Approval History[2,3]

2007 — SOLIRIS® (eculizumab) approved for the treatment of patients with PNH

2011 — SOLIRIS approved for the treatment of patients with aHUS

2017 — SOLIRIS approved for the treatment of adult patients with anti-AChR antibody-positive gMG

2018 — ULTOMIRIS® (ravulizumab-cwvz) approved for the treatment of patients with PNH

2019 — SOLIRIS approved for the treatment of adult patients with AQP4-Ab+ NMOSD

ULTOMIRIS approved for the treatment of patients with aHUS

2022 — ULTOMIRIS approved for the treatment of adult patients with anti-AChR antibody-positive gMG

2024 — ULTOMIRIS approved for the treatment of adult patients with AQP4-Ab+ NMOSD

SOLIRIS® Data cutoff: October 1, 2022		ULTOMIRIS® Data cutoff: December 31, 2022
2,113 patients in **40** clinical trials	Estimated cumulative exposure in all completed and ongoing clinical studies[4]	1,637 patients in 24 clinical trials
78,416.3 PY in **36,991 patients**	Global + US cumulative exposure from postmarketing experience[4]	**12,957.2 PY**

Ab, antibody; **AChR,** acetylcholine receptor; **aHUS,** atypical hemolytic uremic syndrome; **AQP4,** aquaporin-4; **gMG,** generalized myasthenia gravis; **NMOSD,** neuromyelitis optica spectrum disorder; **PNH,** paroxysmal nocturnal hemoglobinuria; **PY,** patient-years; **US,** United States.

1. History. Alexion.com. Accessed June 14, 2024. https://alexion.com/our-company/history **2.** Soliris. Prescribing Information. Alexion Pharmaceuticals, Inc. **3.** Ultomiris. Prescribing Information. Alexion Pharmaceuticals, Inc. **4.** Data on file. Alexion Pharmaceuticals, Inc.

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion Medical Affairs for educational purposes only, not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

Preventing attacks should be the primary treatment goal in NMOSD[1]

Among patients with anti-AQP4-Ab+ NMOSD:



41%

go blind in at least one eye within 5 years after diagnosis[a,2]



34%

experience permanent motor disability within 6 years after diagnosis[b,3]



23%

need a wheelchair within 6 years after diagnosis[b,3]



9%

die after a median disease duration of 6 years[b,3]

Over 90% of patients with NMOSD experience attacks that may lead to cumulative, irreversible neurological disability[c,4,5]

[a]The study collected data from 140 patients who tested AQP4+ at the Mayo Clinic in the USA and were diagnosed with NMO
[b]The study described the clinical outcomes of 106 patients with AQP4+ NMOSD from the UK and Japan
[c]Based on a retrospective review of medical records of 187 patients with NMO/NMOSD undergoing evaluation during 5-year period
AQP4-Ab+, aquaporin-4 antibody-positive; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder

1. Wingerchuk D et al. Handb Clin Neurol 2014;122:581-99; 2. Jiao Y *et al. Neurology* 2013;81:1197–204; 3. Kitley J *et al. Brain* 2012;135:1834–49; 4. Jarius S *et al. J Neuroinflammation* 2012;9:14; 5. Mealy MA *et al. Arch Neurol* 2012;69:1176–80

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

ULTOMIRIS® (ravulizumab-cwvz) in anti-AQP4 antibody-positive NMOSD

RESULTS FROM THE CHAMPION-NMOSD LONG-TERM EXTENSION PERIOD

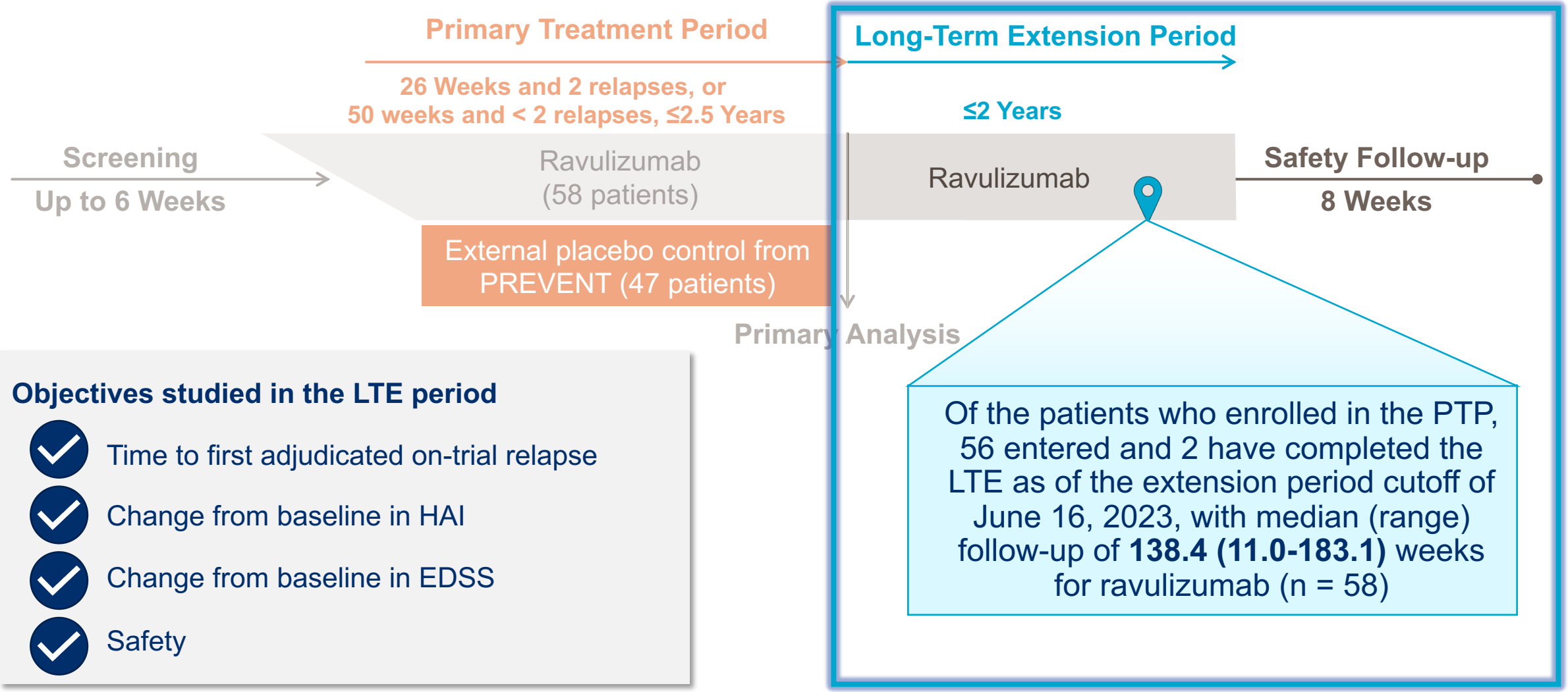
DATA PRESENTED AT AAN 2024

ALEXION AstraZeneca Rare Disease | US MEDICAL AFFAIRS NEUROLOGY

AQP4, anti-aquaporin 4, NMOSD, neuromyelitis optica spectrum disorder

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

CHAMPION-NMOSD INCLUDED A 2-YEAR, LONG-TERM EXTENSION PERIOD



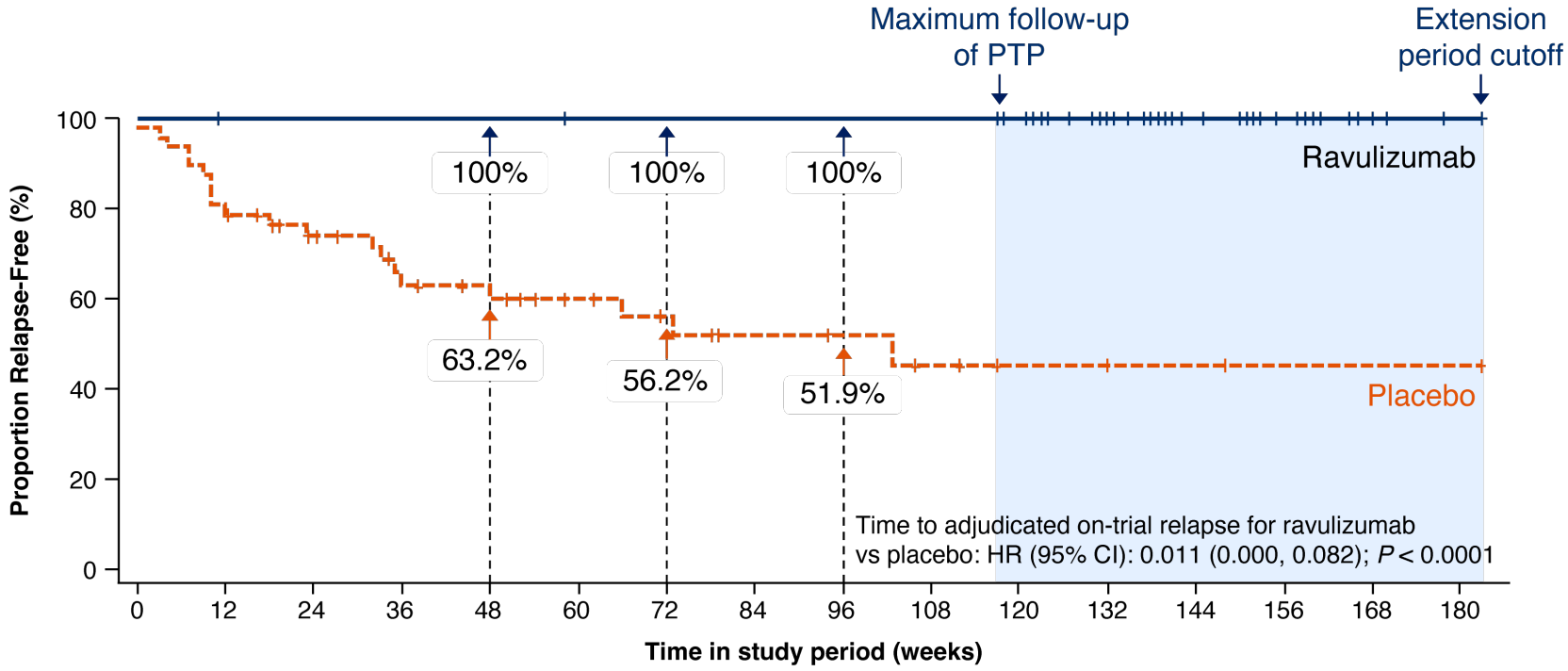
Objectives studied in the LTE period

- Time to first adjudicated on-trial relapse
- Change from baseline in HAI
- Change from baseline in EDSS
- Safety

EDSS, Expanded Disability Status Scale; **HAI,** Hauser Ambulation Index; **LTE,** long-term extension; **PTP,** primary treatment period.
Pittock SJ, et al. Poster presented at: the 9th Annual ACTRIMS Forum; February 29 – March 2, 2024; West Palm Beach, Florida.

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

PTP AND LTE: TIME TO FIRST ADJUDICATED ON-TRIAL RELAPSE AND ASSOCIATED RELAPSE RISK REDUCTION



Number at risk:

Ravulizumab	58	57	57	57	57	56	56	56	56	56	52	40	21	12	5	1
Placebo	47	38	30	24	21	16	13	10	9	6	5	5	4	3	3	3

- **No patients** had an **on-trial adjudicated relapse** in the ravulizumab group (153.9 PY of follow-up) during the PTP and LTE
- The HR of time to first adjudicated on-trial relapse for ravulizumab compared with placebo was 0.011 (95% CI, 0.000 to 0.082). This is an **RRR of 98.9%**

Tick marks indicate censoring of data.

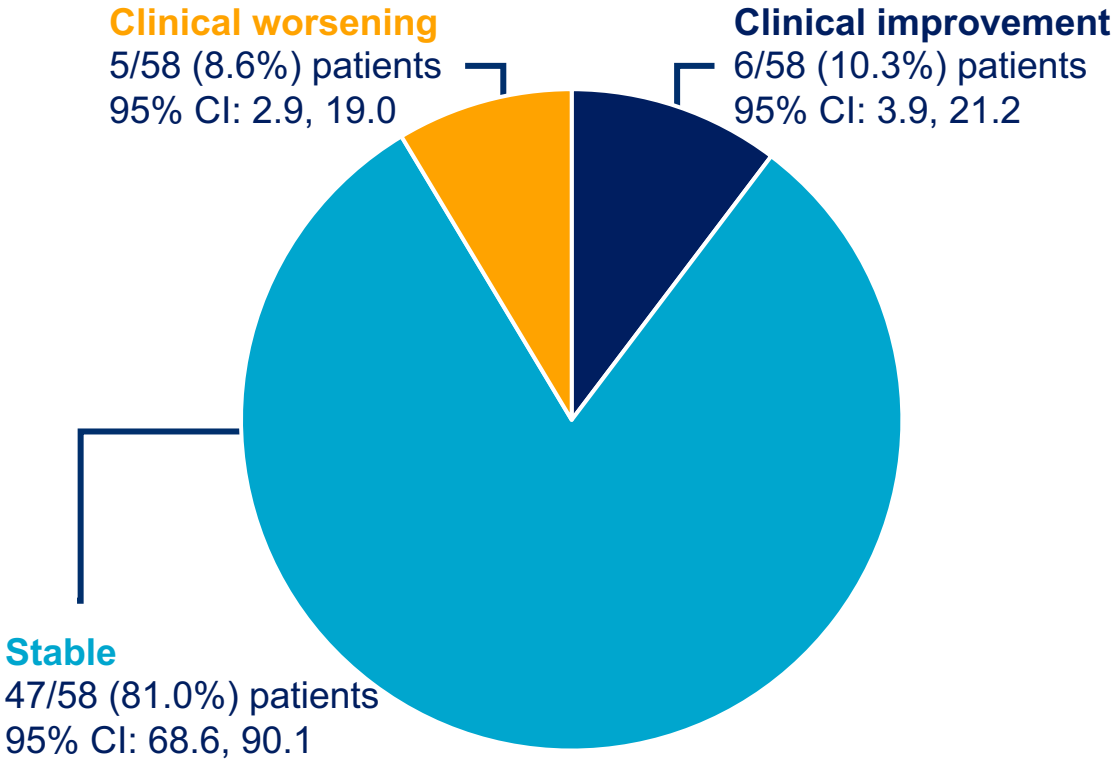
CI, confidence interval; **HR**, hazard ration; **LTE,** long-term extension; **PTP,** primary treatment period; **PY,** patient-years; **RRR,** relapse risk reduction.

Pittock SJ, et al. Poster presented at: the 9th Annual ACTRIMS Forum; February 29 – March 2, 2024; West Palm Beach, Florida.

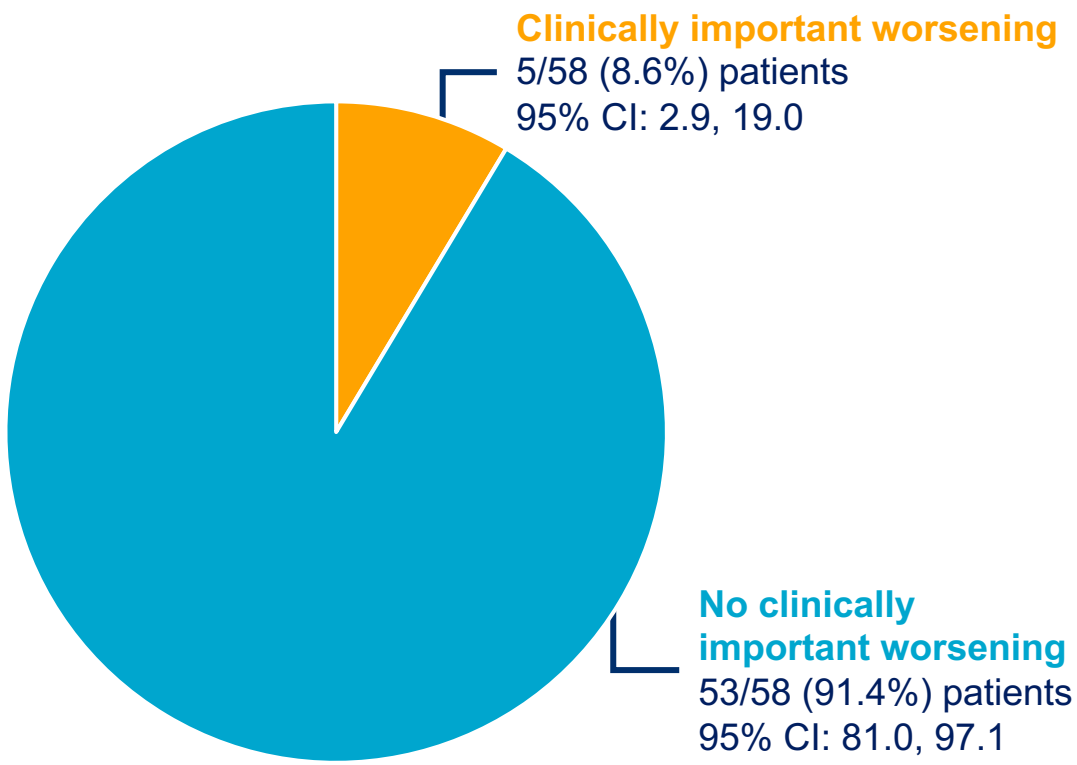
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PTP AND LTE: CHANGE FROM BASELINE IN HAI AND EDSS SCORES

Clinically important change from baseline in HAI score[a]



Clinically important change from baseline in EDSS score[b]



[a]Clinically important change in HAI score is conditional on the baseline value and was defined as worsening if baseline score was 0 and ≥ 2-point increase or if baseline score was > 0 and ≥ 1-point increase; as improvement if baseline score was ≥ 2 and ≥ 1-point decrease; and as stable if baseline score was 0 and ≤ 1-point increase, baseline score was 1 and ≤ 1-point decrease, or baseline score was ≥ 2 and did not change. Percentages may not add up to 100% due to rounding. [b]Clinically important worsening in EDSS score is conditional on the baseline value and was defined as ≥ 2.0-point increase from a baseline score of 0.0, ≥ 1.0-point increase from a baseline score of 1.0-5.0, or ≥ 0.5-point increase from a baseline score of > 5.0.

CI, confidence interval; **EDSS,** Expanded Disability Status Scale; **HAI,** Hauser Ambulation Index; **LTE,** long-term extension; **PTP,** primary trial period.

Pittock SJ, et al. Poster presented at: the 9th Annual ACTRIMS Forum; February 29 – March 2, 2024; West Palm Beach, Florida.

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PTP AND LTE: SUMMARY OF TEAES AND TESAES

AE category[a]	Ravulizumab (N = 58; 154.4 PY)[b]		
	Events, n	Rate per 100 PYs	Patients, n (%)
Any TEAE	522	338.1	55 (94.8)
Any TEAE related to trial agent, as determined by investigator	60	38.9	27 (46.6)
Any TEAE according to severity[c]			
Severe	20	13.0	13 (22.4)
Moderate	138	89.4	38 (65.5)
Mild	364	235.8	50 (86.2)
Any TESAE	18	11.7	15 (25.9)
Related to trial agent, as determined by investigator	4	2.6	4 (6.9)
Meningococcal infections	2	1.3	2 (3.4)
Death	1	NA	1 1(1.7)
TEAE leading to discontinuation of agent	3[d]	1.9	1 (1.7)

- There were no new cases of meningococcal infection in the LTE
- One patient died during the LTE period
  - The cause of death was attributed to hypertensive heart disease, unrelated to ravulizumab

[a]Excluding NMOSD relapses. [b]Data were collected in the ravulizumab-treated patients in the PTP and LTE to the data cutoff. [c]TEAEs reported as grade 1 were mapped to mild, grade 2 to moderate, and grades 3-5 to severe. [d]The 3 TEAEs that led to withdrawal from study drug occurred as part of the same clinical sequelae in a single patient.

AE, adverse event; **LTE,** long-term extension; **NA,** not applicable; **PTP,** primary trial period; **PY,** patient-years; **TEAE,** treatment-emergent adverse event; **TESAE,** treatment-emergent serious adverse event.

Pittock SJ, et al. Poster presented at: the 9th Annual ACTRIMS Forum; February 29 – March 2, 2024; West Palm Beach, Florida.

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PTP AND LTE: TEAES OCCURRING IN OVER 10% OF PATIENTS

AE category[a]	Ravulizumab (N = 58; 154.4 PY)[b]	
	Events, n	Patients, n (%)
Any TEAE	522	55 (94.8)
TEAE occurring in >10% of patients		
COVID-19	28	26 (44.8)
Headache	32	19 (32.8)
Urinary tract infection	14	9 (15.5)
Upper respiratory tract infection	15	8 (13.8)
Back pain	11	8 (13.8)
Arthralgia	7	7 (12.1)
Nasopharyngitis	9	6 (10.3)
Pyrexia	7	6 (10.3)
Diarrhea	6	6 (10.3)

[a]Excluding NMOSD relapses. [b]Data were collected in the ravulizumab-treated patients in the PTP and LTE to the data cutoff.

LTE, long-term extension; **NMOSD,** neuromyelitis optica spectrum disorder; **PTP,** primary trial period; **PY,** patient year; **TEAE,** treatment-emergent adverse event.

Pittock SJ, et al. Poster presented at: the 9th Annual ACTRIMS Forum; February 29 – March 2, 2024; West Palm Beach, Florida.

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Post-Marketing Incidence and Outcome of Meningococcal Infection In Patients Treated With Eculizumab or Ravulizumab

DATA PRESENTED AT AAN SUMMER 2024

ALEXION AstraZeneca Rare Disease | US MEDICAL AFFAIRS NEUROLOGY

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

Background

- The terminal complement inhibitors eculizumab and ravulizumab are effective treatments approved for AChR-Ab+ gMG, AQP4-Ab+ NMOSD, and other indications[1,2]
- Targeted inhibition of the terminal complement pathway increases patients' susceptibility to infection with some encapsulated bacteria, including *Neisseria meningitidis* (*Nm*), while preserving proximal complement and other arms of the immune system[3]
- Due to the increased *Nm* infection risk associated with complement inhibitors, patients should be vaccinated against *Nm* at least 2 weeks before initiating treatment[1,2]
- Other comprehensive risk mitigation measures implemented include antibiotic prophylaxis, REMS, patient counseling and education materials, as well as patient safety cards[4-6]
- Recent analyses reported cumulative exposure-adjusted global *Nm* infection and mortality rates in eculizumab- and ravulizumab-treated patients in the post-marketing setting[7]

Objective

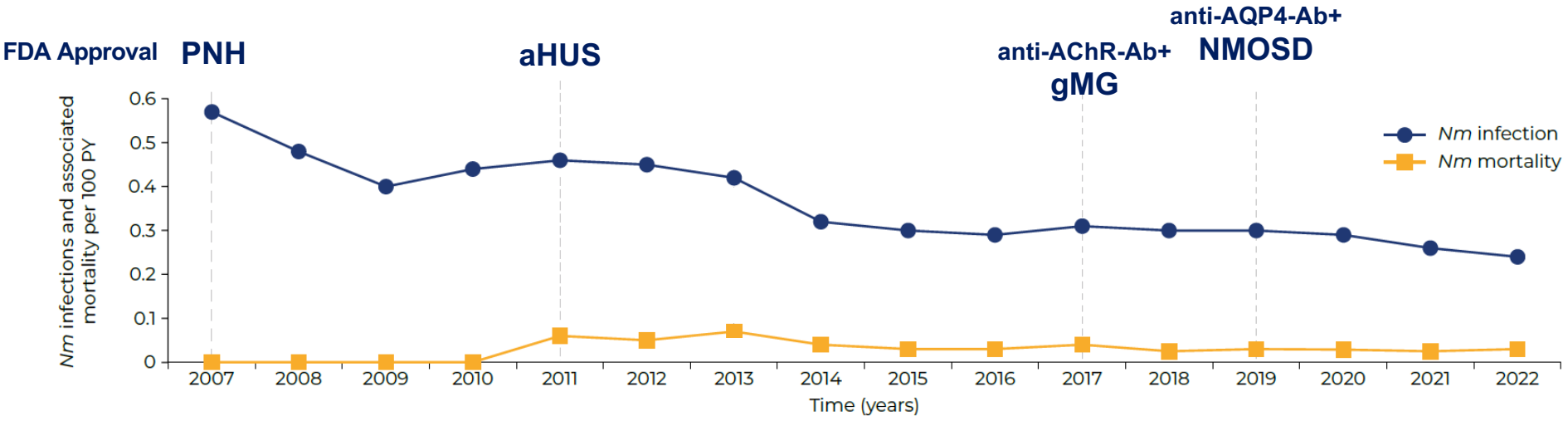
- To report the cumulative exposure-adjusted *Nm* infection and mortality rates in the US post-marketing setting for eculizumab- or ravulizumab-treated patients across approved indications (with specific focus on NMOSD and gMG)

AChR-Ab+ gMG, anti–acetylcholine receptor antibody–positive generalized myasthenia gravis; AQP4-Ab+ NMOSD, anti–aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder; *Nm*, *Neisseria meningitidis*; REMS, Risk Evaluation and Mitigation Strategies.

1. SOLIRIS® (eculizumab) injection, for intravenous use. Prescribing information. Alexion; 2024; 2. ULTOMIRIS® (ravulizumab-cwvz) injection, for intravenous use. Prescribing information. Alexion; 2024; 3. Skattum L, et al. *Mol Immunol*. 2011;48:1643-55; 4. SOLIRIS REMS (Risk Evaluation and Mitigation Strategy). 2020. Available from: https://solirisrems.com/ (Accessed 18 May 2024); 5. ULTOMIRIS REMS (Risk Evaluation and Mitigation Strategy). 2022. Available from: https://ultomirisrems.com/ (Accessed 18 May 2024); 6. Berry I, et al. *MMWR Morb Mortal Wkly Rep*. 2024;73(5):99–103; 7. Fam S, et al. *Mult Scler J*. 2023;29(3S):403–4.

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CUMULATIVE *Nm* INFECTION AND ASSOCIATED MORTALITY RATES AMONG ECULIZUMAB-TREATED PATIENTS IN REAL-WORLD CLINICAL PRACTICE (GLOBAL)



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
PY	75	560	1414	2581	4083	6544	10 046	14 789	20 798	28 108	36 447	44 542	53 798	62 341	70 679	78 416
Nm infections	0.57	0.48	0.40	0.44	0.46	0.45	0.42	0.32	0.30	0.29	0.31	0.30	0.30	0.29	0.26	0.24
Nm mortality	0.00	0.00	0.00	0.00	0.06	0.05	0.07	0.04	0.03	0.03	0.04	0.02	0.03	0.03	0.03	0.03

- Despite an increase in patient exposure due to eculizumab approval for gMG and NMOSD, the rates of *Nm* infection in eculizumab-treated patients have steadily decreased
- The cumulative rate of *Nm* associated mortality in eculizumab-treated patients has remained stable over time

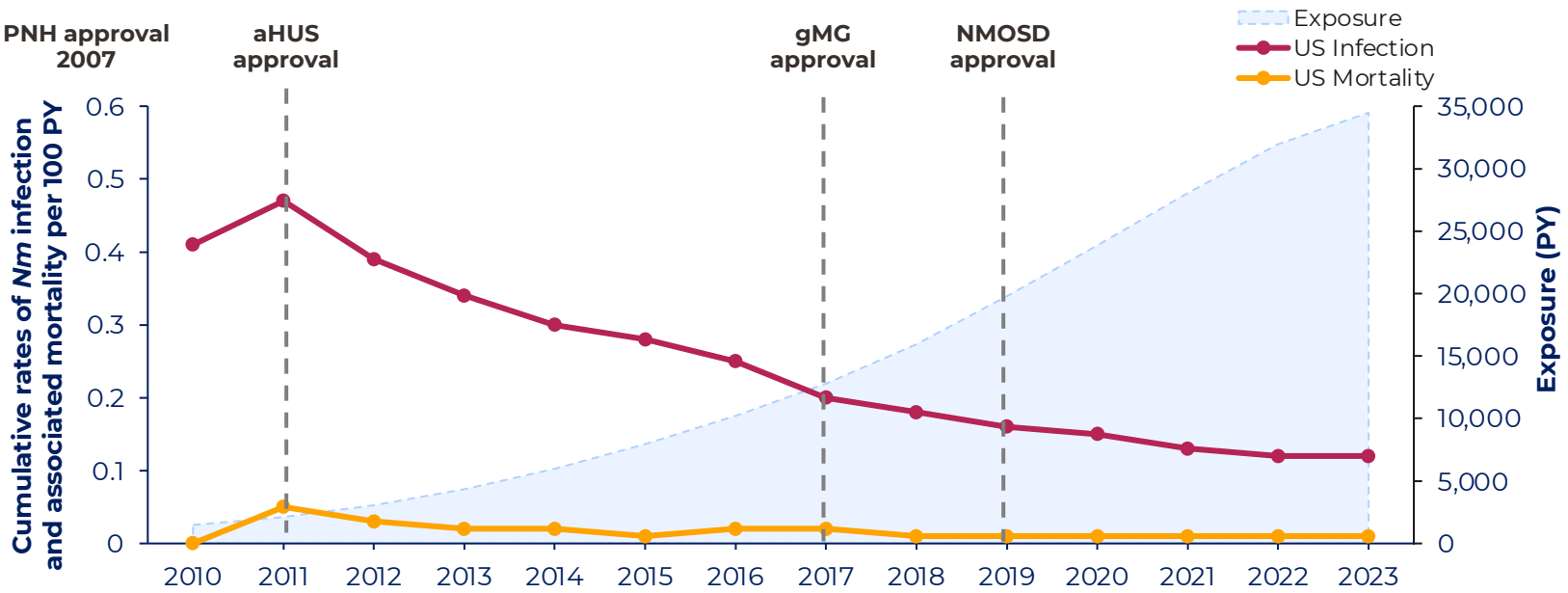
Data are expressed as cumulative rate per 100 PY and are inclusive of PNH, aHUS, gMG and NMOSD (indications approved in March 2007, September 2011, October 2017 and June 2019, respectively). The cut-off date for these data was October 2022. These data have not been updated since presentation at the European Academy of Neurology meeting 2022.

aHUS, atypical haemolytic uraemic syndrome; **Ab+**, antibody-positive; **AChR,** aceteylcholine receptor; **AQP4**, aquaporin-4; **FDA**, US Food and Drug Administration; **gMG**, generalized myasthenia gravis; **Nm**, Neisseria meningitidis; **NMOSD**, neuromyelitis optica spectrum disorder; **PNH**, paroxysmal nocturnal haemoglobinuria; **PY**, patient-years.

Fam S, et al. Poster #P410 presented at Poster presented at the 9th Joint ECTRIMS-ACTRIMS Meeting (MSMilan2023), 11–13 October 2023, Milan, Italy.

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CUMULATIVE REPORTED *Nm* INFECTION AND ASSOCIATED MORTALITY RATES WITH ECULIZUMAB IN THE US



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
***Nm* infection**	0.41	0.47	0.39	0.34	0.30	0.28	0.25	0.20	0.18	0.16	0.15	0.13	0.12	0.12
Mortality	0	0.05	0.03	0.02	0.02	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01
PY	1458	2122	3078	4356	5975	7945	10,237	12,811	15,975	19,790	23,857	28,029	31,941	34,484

To minimize Weber Effect, the graph starts in 2010 when there was at least 1000 PY of eculizumab exposure. Eculizumab data cutoff date: October 1, 2023. Total rates include all meningococcal cases, including those seen during off-label and unknown use. Exposure determined for approved eculizumab indications only.

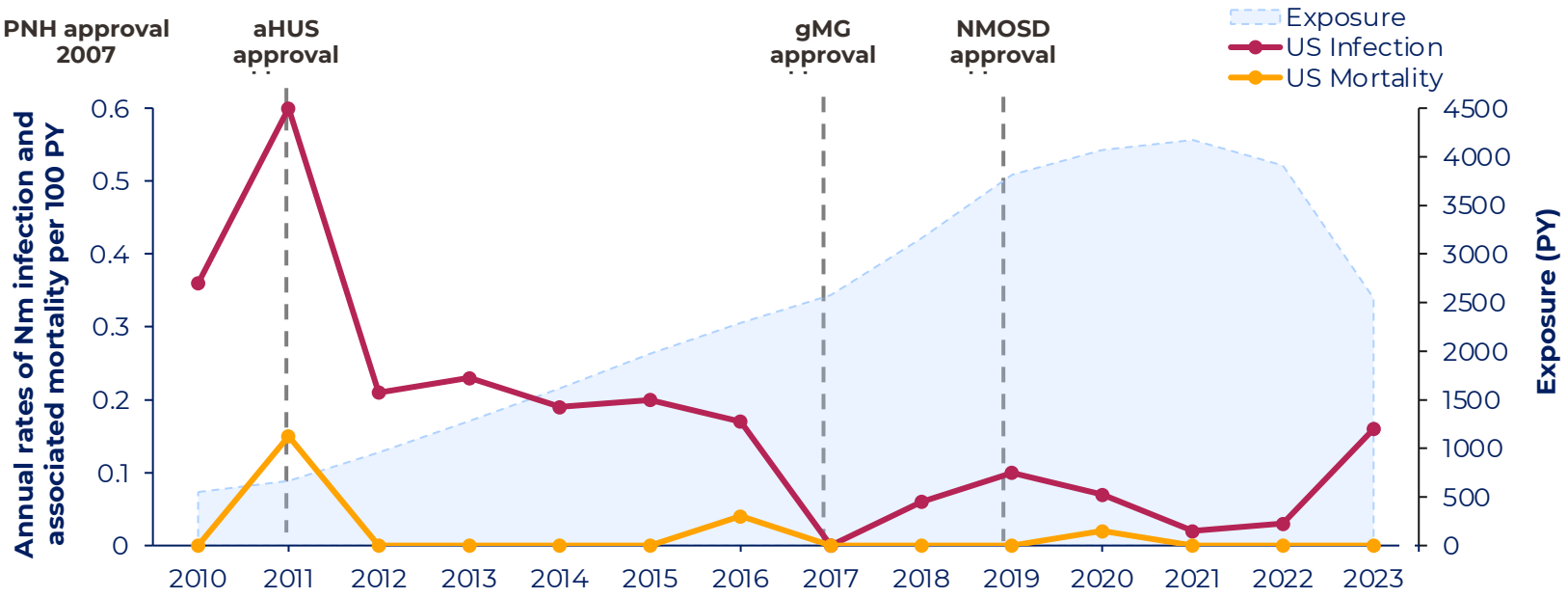
aHUS, atypical hemolytic uremic syndrome; gMG, generalized myasthenia gravis; *Nm*, *Neisseria meningitidis*; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years.

Pandya S, et al. Oral Poster #076 Presented at 2024 AAN Summer Conference on July 20th, 2024 in Atlanta, GA.

- Cumulative exposure: the total summed amount of patient exposure to eculizumab since its first approval in 2007
  - Infection and mortality rates are also cumulative and expressed per 100 patient-years
- There have been 34,484 patient-years of cumulative exposure to eculizumab in the US across all approved indications since 2007
- In 2023, cumulative US *Nm* infection rate in eculizumab-treated patients in the US was 0.12 per 100 patient-years across all approved indications
- There is more confidence in the cumulative rates with increasing exposure over time

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

ANNUAL REPORTED *Nm* INFECTION AND ASSOCIATED MORTALITY RATES FOR ECULIZUMAB IN THE US



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
***Nm* infection**	0.36	0.60	0.21	0.23	0.19	0.20	0.17	0	0.06	0.10	0.07	0.02	0.03	0.16
Mortality	0	0.15	0	0	0	0	0.04	0	0	0	0.02	0	0	0
PY	549	665	956	1278	1619	1970	2292	2575	3163	3815	4067	4172	3912	2543

- Annual exposure: the amount of patient exposure to eculizumab in any given year
  - Infection and mortality rates are also annual and expressed per 100 patient-years
- Annual rates of *Nm* infection in the US have been relatively stable over time among patients receiving eculizumab

Eculizumab data cutoff date: October 1, 2023. Total rates include all meningococcal cases, including those seen during off-label and unknown use. Exposure determined for approved eculizumab indications only.

aHUS, atypical hemolytic uremic syndrome; gMG, generalized myasthenia gravis; *Nm*, *Neisseria meningitidis*; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years.

Pandya S, et al. Oral Poster #076 Presented at 2024 AAN Summer Conference on July 20th, 2024 in Atlanta, GA.

Please see slides 4 and 22-27 for Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), including Boxed WARNING, regarding serious and life-threatening or fatal meningococcal infections for ULTOMIRIS and SOLIRIS. ULTOMIRIS® (ravulizumab-cwvz) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. SOLIRIS® (eculizumab) [Prescribing Information]. Alexion Pharmaceuticals, Inc., Boston, MA. Provided by Alexion U.S. Medical Affairs as an educational service. Not for promotion. Duplication, distribution, or dissemination of this document is prohibited. **ML-9903-US-1845 | July 2024**

CUMULATIVE *Nm* INFECTION AND ASSOCIATED MORTALITY RATES AMONG PATIENTS WITH NMOSD TREATED WITH ECULIZUMAB IN THE US

		Number of *Nm* infections	Number of *Nm* fatalities	PY estimated exposure	*Nm* infection rate (per 100 PY)	*Nm* mortality rate (per 100 PY)
Eculizumab	**NMOSD**	2	0	1988	0.10	0

- As of October 1, 2023, US post-marketing *Nm* infection rate in eculizumab-treated patients with NMOSD was 0.10 (exposure: 1988 patient-years)
- No *Nm* fatalities have been reported for eculizumab-treated patients with NMOSD in the US

Eculizumab data cutoff date: October 1, 2023. Ravulizumab was not approved for NMOSD in the US at data cutoff (approved March 2024).
Nm, *Neisseria meningitidis*; NMOSD, neuromyelitis optica spectrum disorder; PY, patient-years.

Pandya S, et al. Oral Poster #076 Presented at 2024 AAN Summer Conference on July 20th, 2024 in Atlanta, GA.

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Thank You!

Lokesh Jha MD

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Select Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab)

BEFORE STARTING TREATMENT WITH ULTOMIRIS OR SOLIRIS, ALL PATIENTS SHOULD RECEIVE:

- **A MEDICATION GUIDE**
- **ULTOMIRIS OR SOLIRIS PATIENT SAFETY INFORMATION CARD**

ALEXION® AstraZeneca Rare Disease | US MEDICAL AFFAIRS NEUROLOGY

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CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

- ULTOMIRIS® (ravulizumab-cwvz) and SOLIRIS® (eculizumab), both complement inhibitors, increase a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.
- Revaccinate patients in accordance with ACIP recommendations considering the duration of either ULTOMIRIS or SOLIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS or SOLIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including both ULTOMIRIS and SOLIRIS. The benefits and risks of treatment with either ULTOMIRIS or SOLIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis.*

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WARNINGS AND PRECAUTIONS (cont'd)

Serious Meningococcal Infections (cont'd)

- Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.
- Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS and SOLIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS® and SOLIRIS® (eculizumab) REMS

- Due to the risk of serious meningococcal infections, ULTOMIRIS and SOLIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.
- Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of either ULTOMIRIS or SOLIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of either ULTOMIRIS or SOLIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months or 3 months following either ULTOMIRIS or SOLIRIS treatment, respectively.
- Further information is available at www.UltSolREMS.com or 1-888-765-4747.

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WARNINGS AND PRECAUTIONS (cont'd)

Other Infections

- Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.
- ULTOMIRIS and SOLIRIS block terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae,* and to a lesser extent, *Neisseria gonorrhoeae.*
- **SOLIRIS ONLY***: Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients.*
- Patients receiving either ULTOMIRIS or SOLIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Thromboembolic Event Management

- The effect of withdrawal of anticoagulant therapy during treatment with either ULTOMIRIS or SOLIRIS has not been established. Treatment should not alter anticoagulant management.

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WARNINGS AND PRECAUTIONS (cont'd)

Infusion-Related Reactions

- Intravenous administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.
- Administration of SOLIRIS may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related reaction which required discontinuation of SOLIRIS. Interrupt SOLIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

- **ULTOMIRIS®** (ravulizumab-cwvz) **:** Most common adverse reactions in adult patients with NMOSD (incidence ≥10%) were COVID-19, headache, back pain, arthralgia, and urinary tract infection. Serious adverse reactions were reported in 8 (13.8%) patients with NMOSD receiving ULTOMIRIS
- **SOLIRIS®** (eculizumab)**:** The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion.

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

- Concomitant use of ULTOMIRIS or SOLIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS or SOLIRIS.

Neonatal Fc Receptor Blockers

- Concomitant use of ULTOMIRIS or SOLIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS or SOLIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS or SOLIRIS.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information for ULTOMIRIS and SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, provided at this presentation, also available on https://alexion.com/Documents/Ultomiris_USPI.pdf and https://alexion.com/Documents/Soliris_USPI.aspx.

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RETURN TO BOXED WARNING

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Satralizumab : Clinical Trials to Real-World Outcomes

Aug 3, 2024

Shervin Gholizadeh, PharmD, PhD
Principal Medical Science Director

The USPI can be found at the following link: https://www.gene.com/download/pdf/enspryng_prescribing.pdf

Satralizumab (ENSPRYNG) is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Satralizumab is currently not approved for the treatment of Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD) and Autoimmune Encephalitis (AIE).

M-US-00024692 v1.0 07/31/2024
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Shervin Gholizadeh is a Genentech employee.

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Prescribing information may vary depending on the applicable approval in the respective country. Therefore, before prescribing any product, always refer to applicable local materials such as USPI and/or the Summary of Product Characteristics (SmPC).

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Satralizumab: A Quick Overview in NMOSD

Satralizumab: Proven Efficacy & Safety in Phase 3 Studies, Approved in 85 Countries with more than 4000 Patients Treated Worldwide[1]

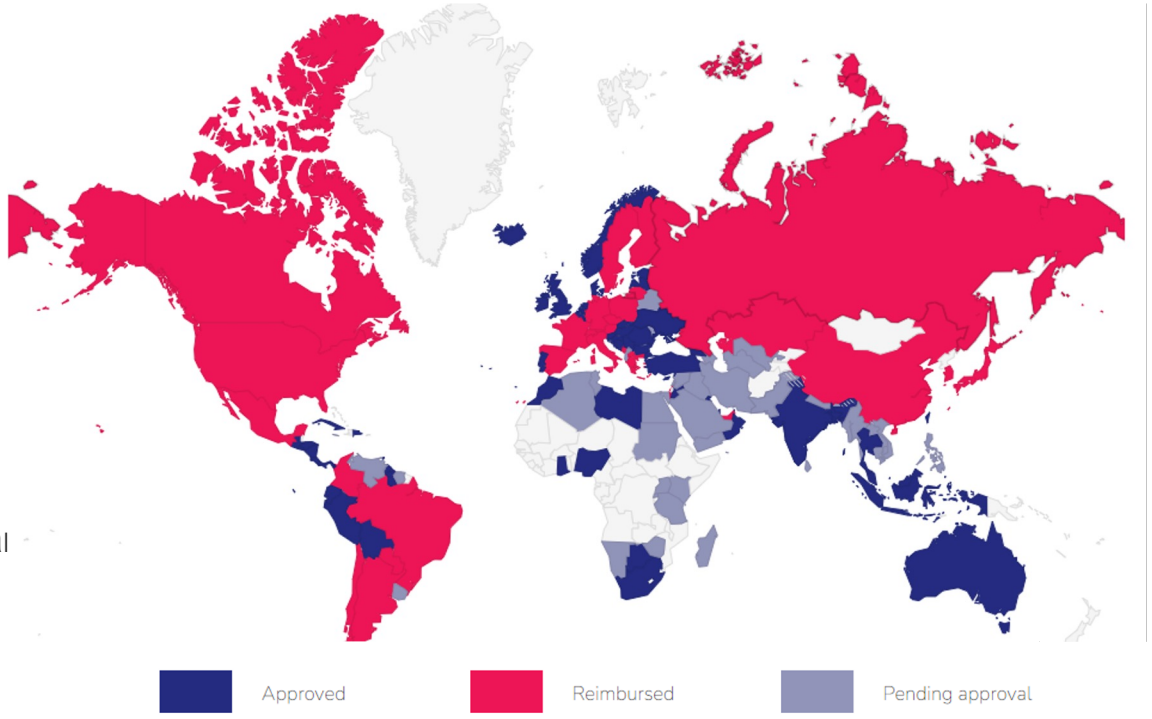
What we know from the SAkuraSky and SAkuraStar double-blind periods:

Satralizumab was approved for treatment of NMOSD in adult patients who are AQP4-antibody positive.

Satralizumab significantly reduced the risk of **protocol-defined relapse (PDR)** and **severe PDR** compared with placebo[2]

Satralizumab demonstrated a **favourable safety profile**

Satralizumab is approved in 91 countries, including the United States, Canada, Japan, South Korea and the European Union, a applications are under review in additional countries

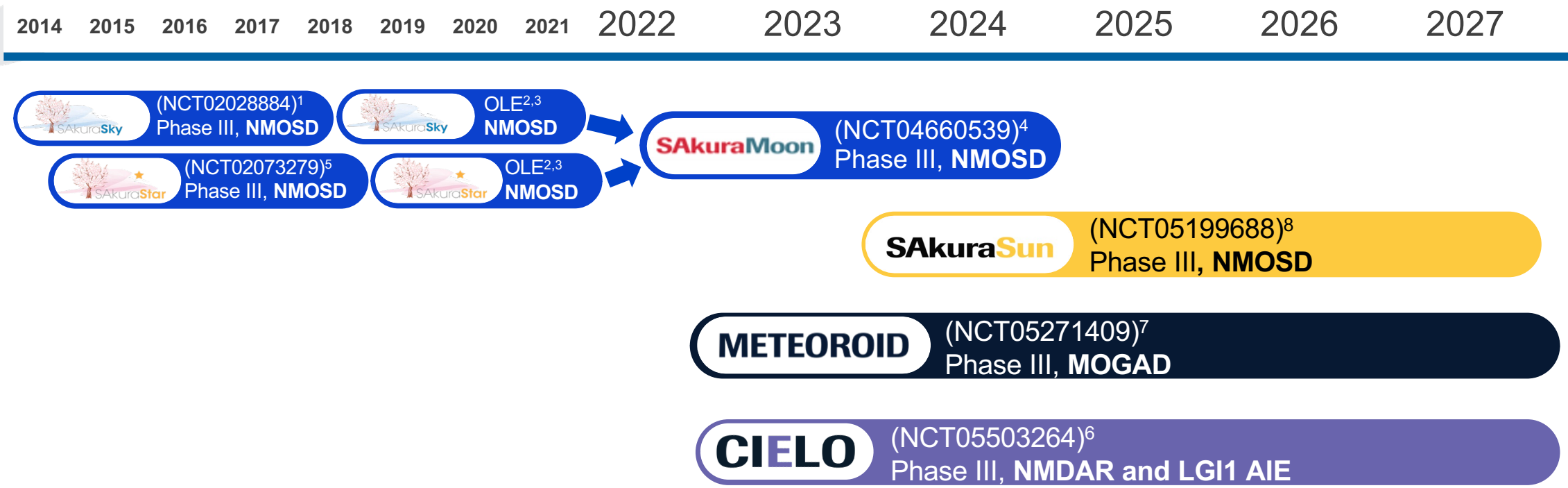


AQP4, anti-aquaporin-4; NMOSD, neuromyelitis optica spectrum disorder.

1. PBRER v7, 2024, 2. Kleiter, I., et al. *Neurology(R) Neuroimmunology & Neuroinflammation*, 2022, e200071.

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Satralizumab is being evaluated in several phase 3 studies across four autoimmune indications



AIE, autoimmune encephalitis; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension; TED, thyroid eye disease; NMDAR N-Methyl-D-Aspartate Receptor; LGI1, Leucine-Rich Glioma Inactivated 1

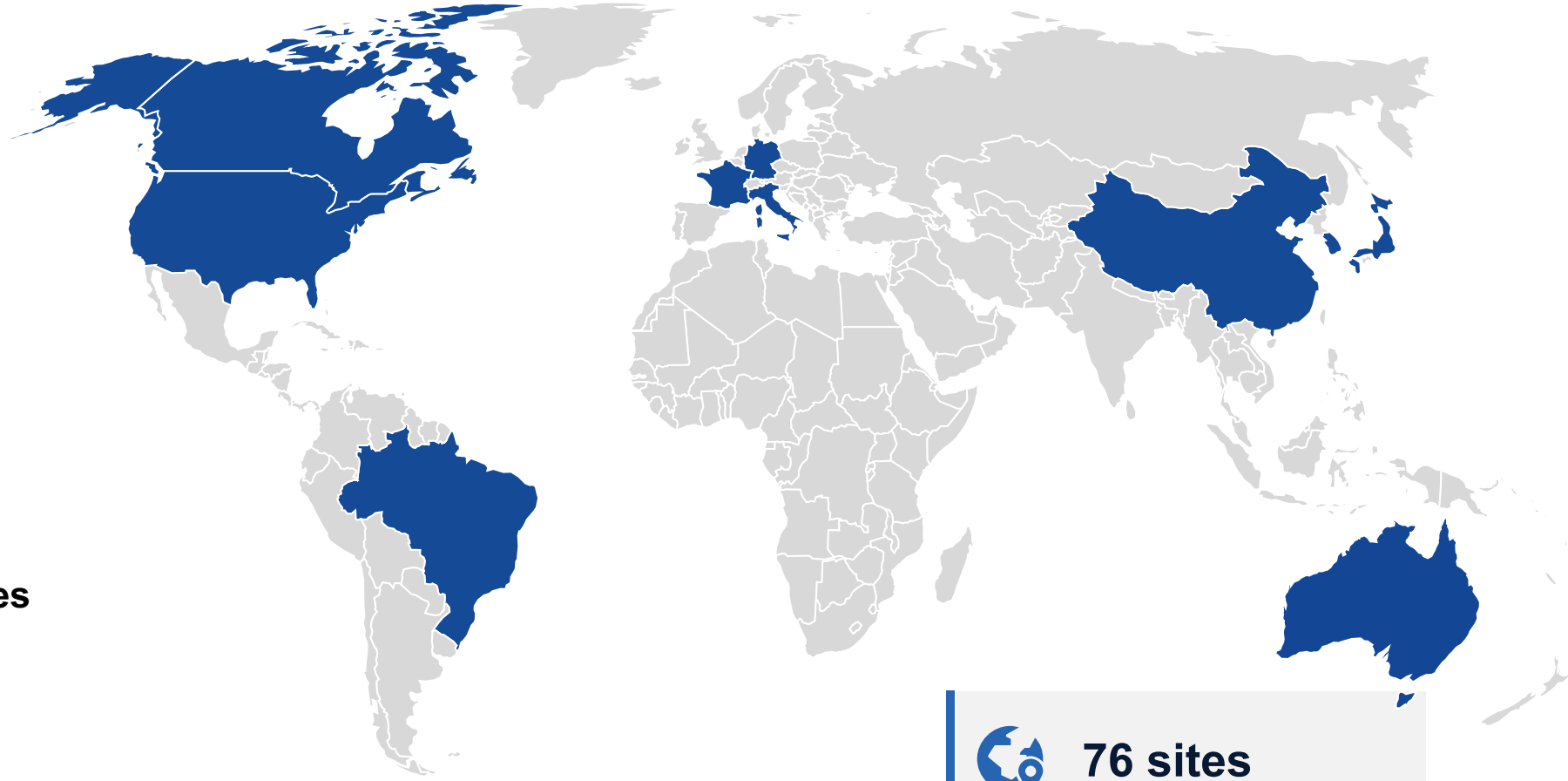
1. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 2. Kleiter I, et al. *Neurol Neuroimmunol Neuroinflamm* 2023;10:e200071. DOI:10.1212/NXI.0000000000200071; 3. Yamamura T, et al. *Mult Scler Relat Disord* 2022;66:104025; 4. ClinicalTrials.gov. SAkuraMoon. Available at: www.clinicaltrials.gov/ct2/show/NCT04660539. Accessed April 2024; 5. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412; 6. ClinicalTrials.gov. CIELO. Available at: https://clinicaltrials.gov/ct2/show/NCT05503264. Accessed April 2024; 7. ClinicalTrials.gov. METEOROID. Available at: https://clinicaltrials.gov/ct2/show/NCT05271409. Accessed April 2024; 8. ClinicalTrials.gov. SAkuraSun. Available at: www.clinicaltrials.gov/ct2/show/NCT05199688. Accessed April 2024; 9. ClinicalTrials.gov. SatraGO1. Available at:. https://clinicaltrials.gov/study/NCT05987423. Accessed April 2024; 10. ClinicalTrials.gov. SatraGO2. Available at: https://clinicaltrials.gov/study/NCT06106828. Accessed April 2024.

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METEOROID Country Participation

10 participating countries:

- Australia: 11 sites
- Brazil: 4 sites
- Canada: 4 sites
- France: 3 sites
- Germany: 7 sites
- Italy: 7 sites
- Israel: 1 site
- Japan: 14 sites
- Korea, Republic of: 3 sites
- USA: 22 sites



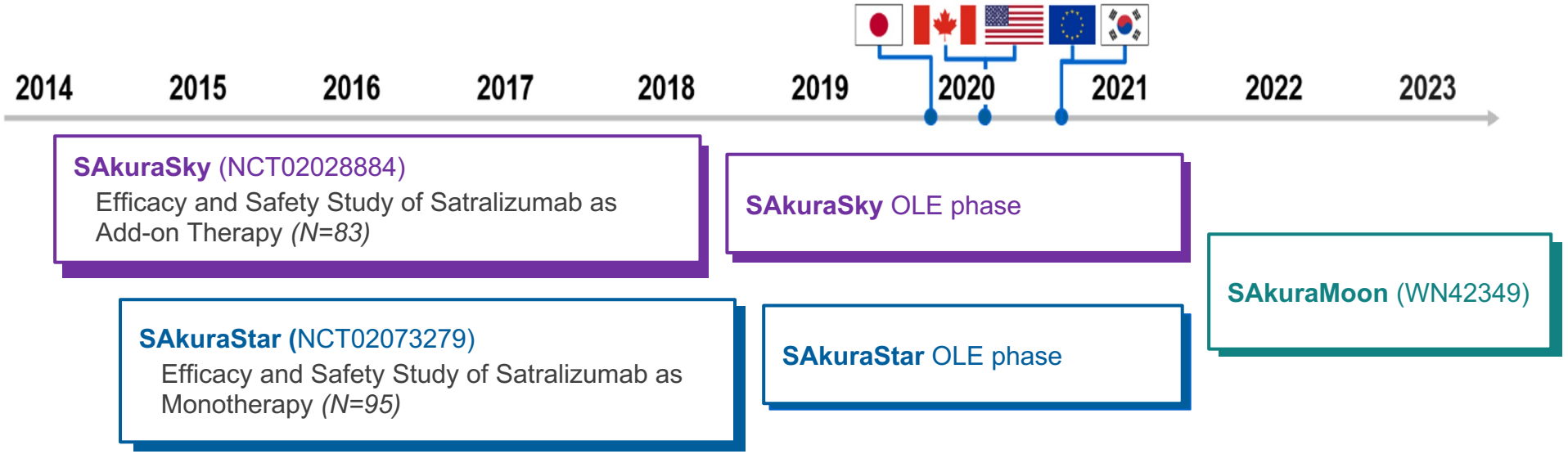
76 sites

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From Clinical Trials to Long-Term Analysis

NMOSD is a lifelong disease, a patient's maintenance therapy must remain effective, safe, and tolerable over time

With **up to 8.9 years of patient exposure** to satralizumab in the SAkuraSky and SAkuraStar studies, we have the opportunity to review long-term outcomes



NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension.
Palace J, et al. 76th Annual Meeting of the AAN 2024, Denver, CO, USA (Hybrid); April 13–18, 2024 Oral Presentation 002

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Bridging Clinical Data with Real-World Outcomes

Real-World Data: Complementing Clinical Trials for Satralizumab in NMOSD

- **Domains in Which Real-World Evidence Augments Clinical Trial Outcomes for NMOSD Therapeutics**
  - **Switch Patterns**:
    - Significant transitions from other DMTs to satralizumab
  - **Diversity in Data**:
    - Higher representation of African American and Hispanic patients
  - **Co-existing Autoimmune Conditions**:
    - Observed pattern: Notable presence of NMOSD patients with co-morbidities like Lupus, RA, and Sjögren's disease
    - Suggests potential consideration for broader MOA treatments in this subset. Further study needed

DMT: Disease Modifying Therapies, MOA: Mechanism of Action, RA: Rheumatoid Arthritis

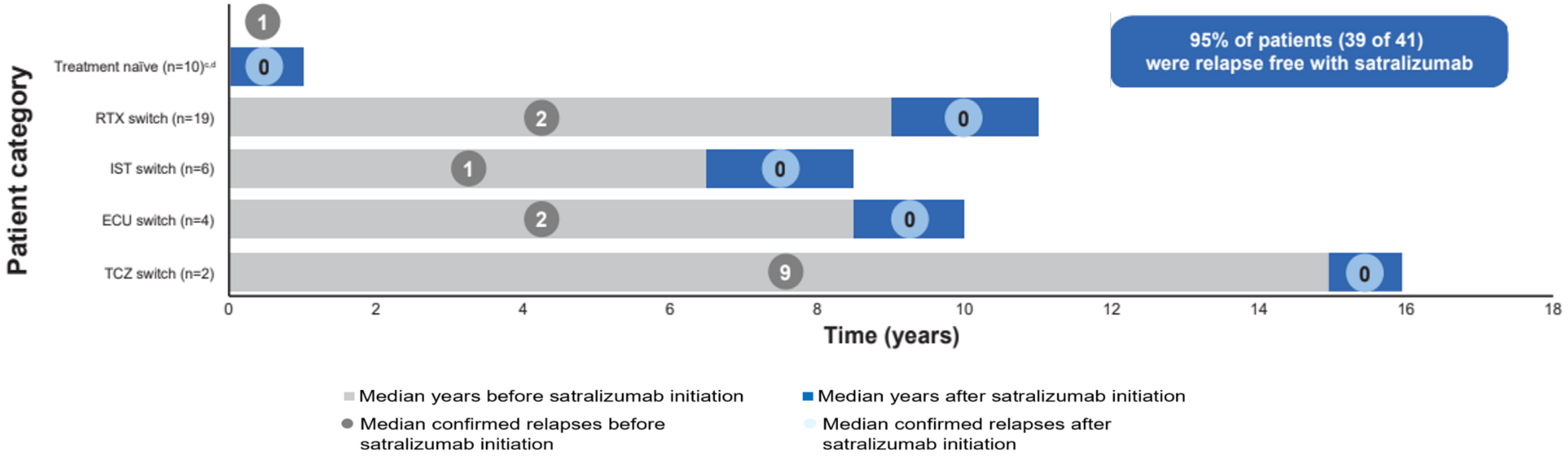
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Comparative Relapse History : Pre and Post Satralizumab Initiation[a]

Objective: To describe the experience with satralizumab in adults with AQP4-IgG+ NMOSD in clinical practice

Methods: Case information for adults with AQP4-IgG+ NMOSD who had received satralizumab for ≥6 months was obtained from US healthcare providers between April 2022 and August 2023

Median confirmed relapses[a] by patient category over time[b]

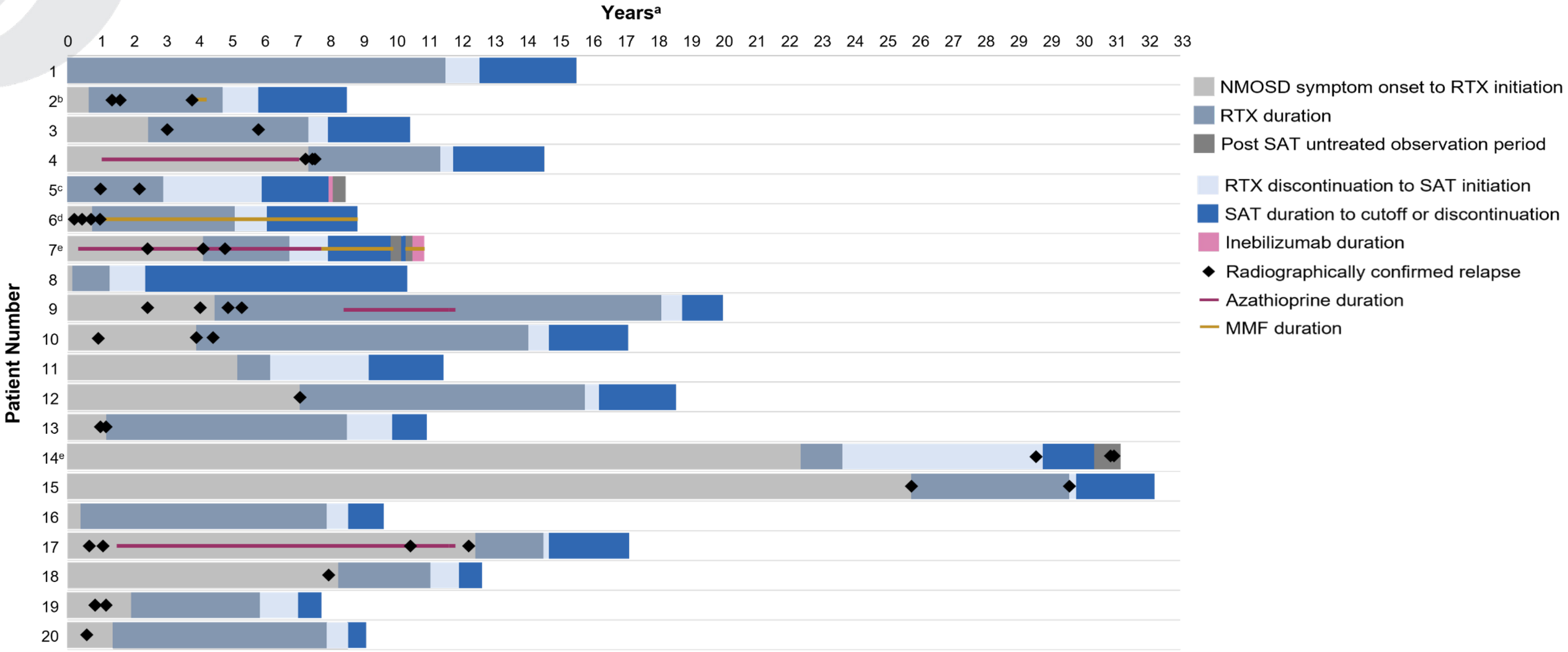


ECU, eculizumab; IST, immunosuppressants; TCZ, tocilizumab; RTX, rituximab.
[a]Only relapses after initial attack are shown in this figure. Min-max of median relapses as follows (before satralizumab; after satralizumab): treatment naïve, 0-2; 0-1; RTX switch, 0-5; 0; IST switch, 0-2; 0; ECU switch, 1-2; 0; TCZ switch, 5-13; 0. [b]As of August 2023, 2 patients have permanently discontinued satralizumab due to adverse events. [c]One patient presented with optic neuritis in 1997 but received no preventative treatment and was symptom free until February 2021. [d]For treatment naive patients, median years before satralizumab initiation was 0.

Aboud, et al. Poster P1036, presented at the 2023 Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 25–28, 2023; Milan, Italy

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Deep Dive: Patient Treatment Transitions from Rituximab

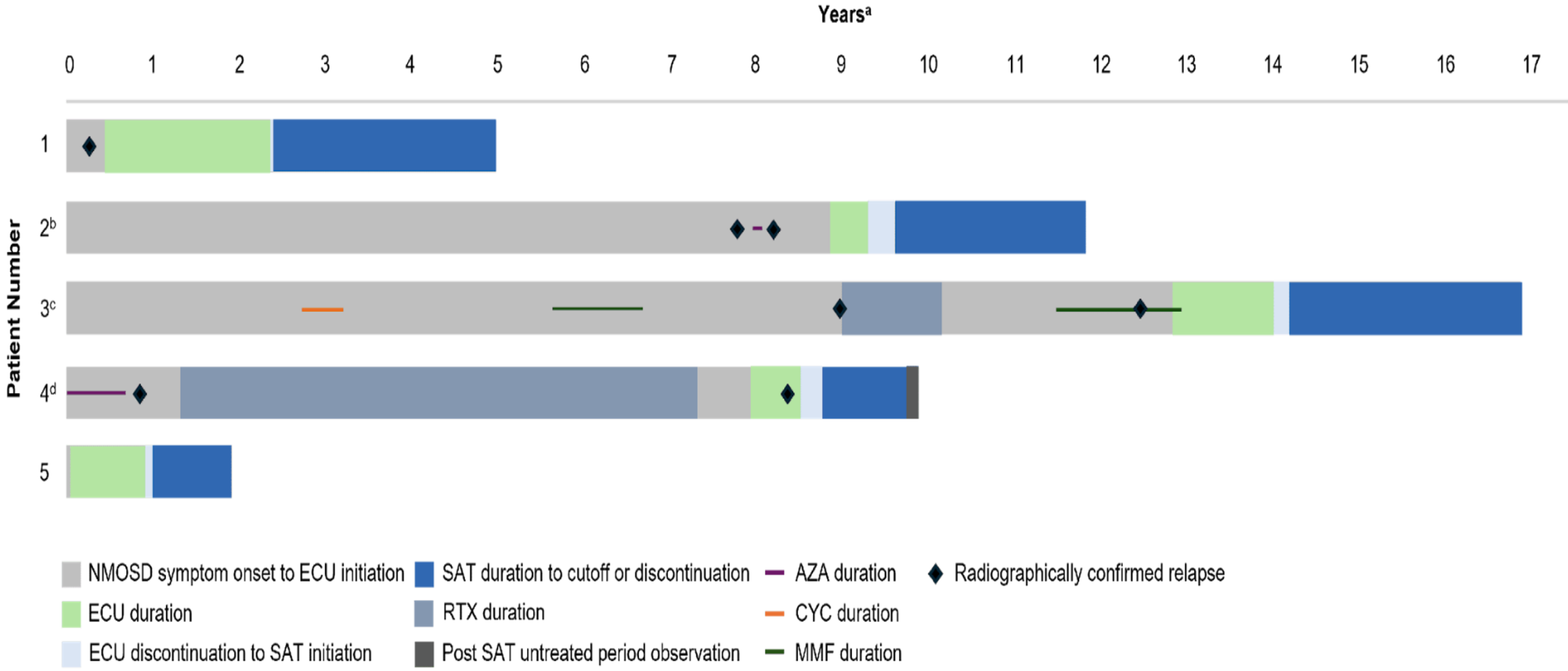


MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; RTX, rituximab; SAT, satralizumab.[a]Length of bar indicates time from symptom onset to data cutoff. [b]MMF prescribed briefly during fifth year; exact duration and months unknown. [c]Patient discontinued satralizumab due to loss of insurance; no preventative treatment as of data cutoff.[d]Patient experienced ≥4 radiographically confirmed relapses prior to receiving satralizumab. Dates unknown. [e]Patient discontinued satralizumab due to right-sided weakness (no objective documentation and not considered a relapse).

Data on file

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Deep Dive: Patient Treatment Transitions from Eculizumab



AZA, azathioprine; CYC, cyclophosphamide, ECU, eculizumab; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; RTX, rituximab; SAT, satralizumab.[a]Length of bar indicates time from symptom onset to data cutoff.[b]Patient received AZA for a brief period; exact duration and timing unknown.[c]Exact date of discontinuation of ECU unknown. Patient had 4 months of interrupted satralizumab treatment due to insurance issues; exact timing of interruption unknown.[d]Patient received AZA with long-term corticosteroid taper. Patient deceased; last dose of satralizumab 2 months before death. Data on file

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Safety data for satralizumab in NMOSD

- Overall, all patients maintained disease control with satralizumab, with few adverse events reported
  - One patient temporarily paused satralizumab for 1 dose due to transient neutropenia
  - One patient permanently discontinued satralizumab due to asymptomatic neutropenia
  - One patient permanently discontinued satralizumab due to right-sided weakness (no objective documentation and not considered a relapse)

	All patients N=41
Any adverse event, n (%)[a,b]	14 (34)
Adverse events	
Elevated liver function tests (ALT, AST)	2 (5)
Hyperlipidemia	5 (12)
Leukopenia	3 (7)
Neutropenia	3 (7)
Other[c]	7 (17)
Adverse events leaving to discontinuations, n (%)[d]	2 (5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NMOSD, neuromyelitis optica spectrum disorder.
[a]Adverse events thought to be related to satralizumab. [b]All AEs were reported to US Drug Safety as required. [c]Other includes nasal congestion and sore throat (n=1), contact dermatitis and postinflammatory hypopigmentation of the foot (n=1), right sided weakness (n=1), thrombocytopenia (n=2), lymphopenia (n=1), and transient abdominal bloating after injection (n=1). [d]One patient permanently discontinued satralizumab due to asymptomatic neutropenia (which transiently resolved after discontinuation of satralizumab but then recurred) and 1 patient permanently discontinued due to right-sided weakness (no objective documentation and not considered a relapse).

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Limitations and future directions

- The limitations of this presentation are those inherent to case reports, including the small number of patients, partially missing data and the retrospective design

- The duration of treatment with satralizumab was shorter than the duration of previous NMOSD treatment in all patients; thus, comparison of the number of relapses with each treatment should be evaluated with caution

- Despite these limitations, this case series provides valuable real-world data on patients with AQP4-IgG+ NMOSD who received satralizumab as the initial preventative treatment and after previous treatment with biologics, including long-term rituximab, and conventional ISTs

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Department of Neurology
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Therapeutic Transition: Rationale & Actuation

Jeffrey L. Bennett, MD, PhD

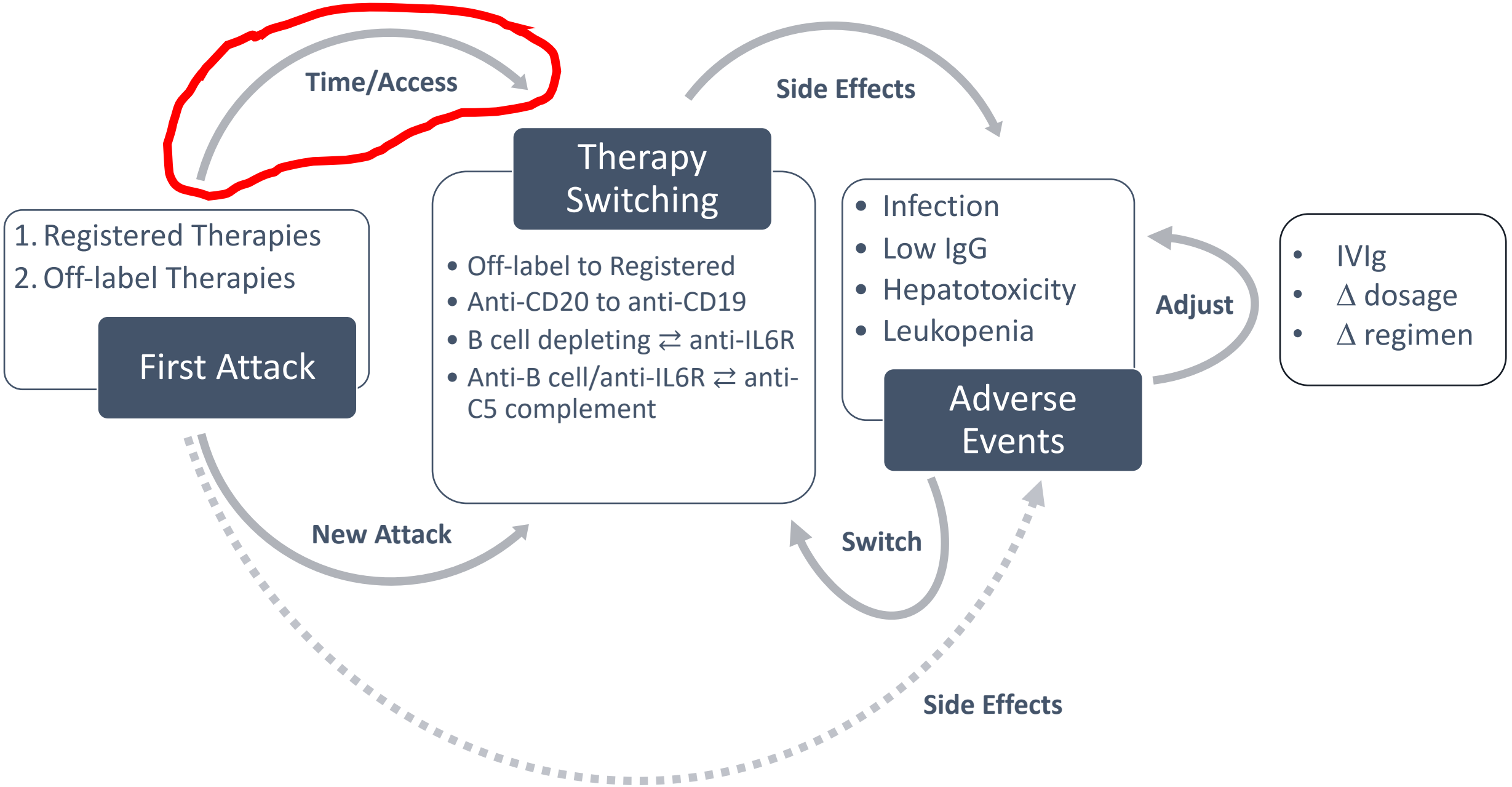
Gertrude Gilden Professor
Departments of Neurology and Ophthalmology
Programs in Neuroscience and Immunology
University of Colorado School of Medicine

2024 NMO Roundtable Conference: Beyond
August 3, 2024

Disclosures

- Dr. Bennett has received personal compensation for serving as a Consultant for Horizon Therapeutics, Genentech, TG Therapeutics, Reistone Bio, Roche, Antigenomycs, Chugai, Mitsubishi Tanabe, EMD Serono, Beigene, Novartis, and ImCyse.
- Dr. Bennett has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Clene Nanomedicine and Roche.
- Dr. Bennett has received personal compensation for serving on a Speakers Bureau for Alexion.
- Dr. Bennett has received personal compensation for serving as an Expert Witness for Podoll and Associates, Pavich Law, and Patterson and Associates.
- Dr. Bennett has received research support from Novartis and Alexion.
- Dr. Bennett has received intellectual property interests from a discovery or technology relating to health care.
- Dr. Bennett has received publishing royalties from a publication relating to health care.

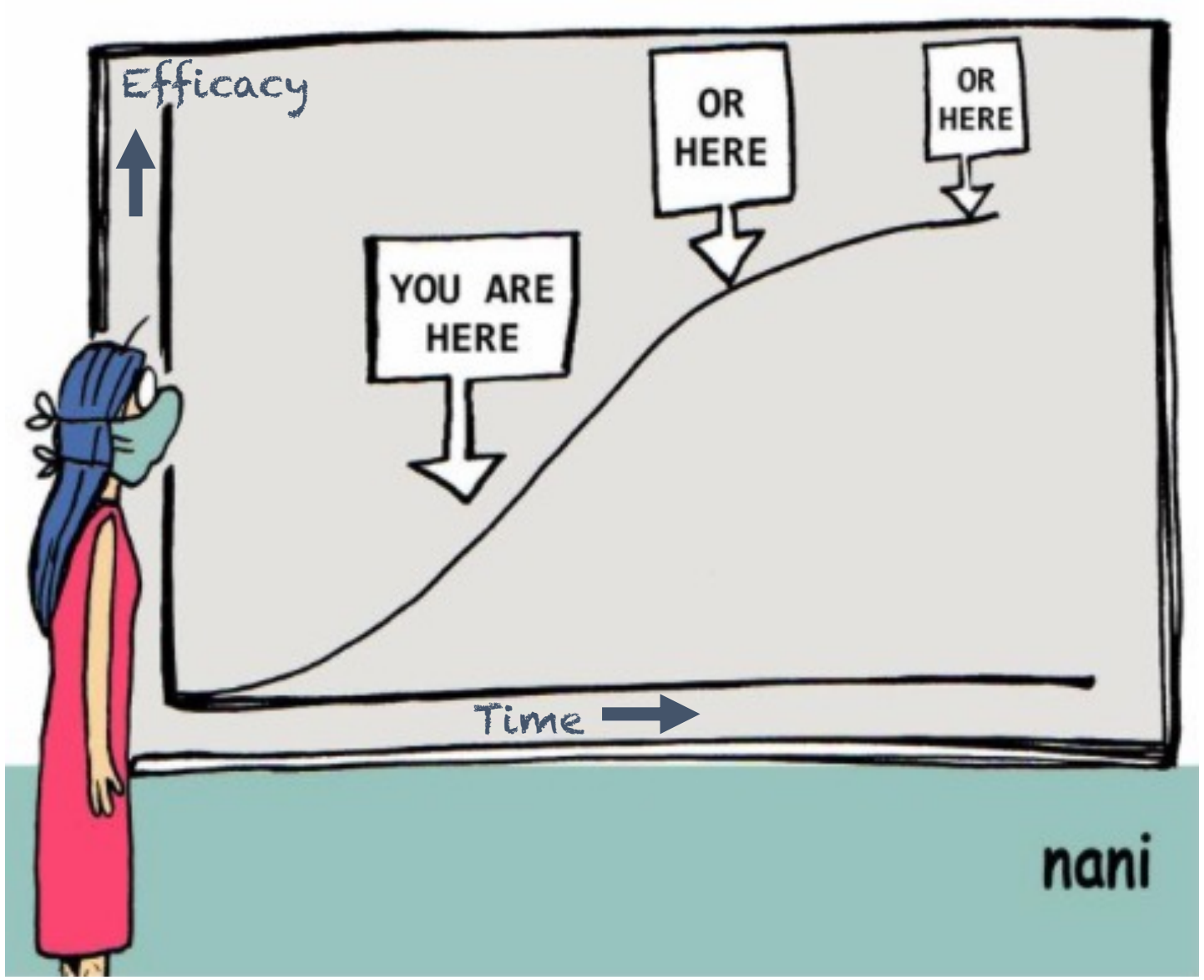
NMOSD Treatment Algorithm



Patient Initiated on Off-Label Therapy

30-year-old Afro-Caribbean woman with AQP4-IgG seropositive NMOSD.

- **Bilateral vision loss**
  - **20/150 R eye; 20/80 L eye**
- **Hepatitis B core antibody positive**
- **Stable on azathioprine – 1.5 years**



Annualized Attack Rate on Off-Label Therapies

Treatment	Dosage	Pre-Treatment Annualized Attack Rate	Post-Treatment Annualized Attack Rate
Azathioprine[1]	< 2 mg/kg/d	2.09	0.82
	≥ 2 mg/kg/d	2.20	0.52
	All	2.18	0.64
Mycophenolate[2]	2 g/d	1.06	0.39
Cyclophosphamide[2]	468-774 mg/m^2	1.30	0.92
Rituximab[2,7]	1-2 g q6 mo	1.17	0.25-0.33
PREVENT Placebo[3]	Baseline IS	2.07	0.35
SakuraStar Placebo[4]	Placebo	1.50	0.41
SakuraSky Placebo[5]	Baseline IS	1.40	0.32
RIN-1 Placebo[6]	Prednisone	0.70	0.32

1. Costanzi et al. (2011). Neurology, 77:659.
2. Torres et al. (2015) J Neurol Sci 351:31.
3. Pittock et al. (2019). NEJM 381:614
4. Traboulsee et al. (2020) Lancet Neurol 19:40
5. Yamamura et al. (2019) NEJM 381:2114
6. Tahara et al. (2020) Lancet Neurol 19:298
7. Barreras, Neurology Live (2022)

IS - immunosuppressant

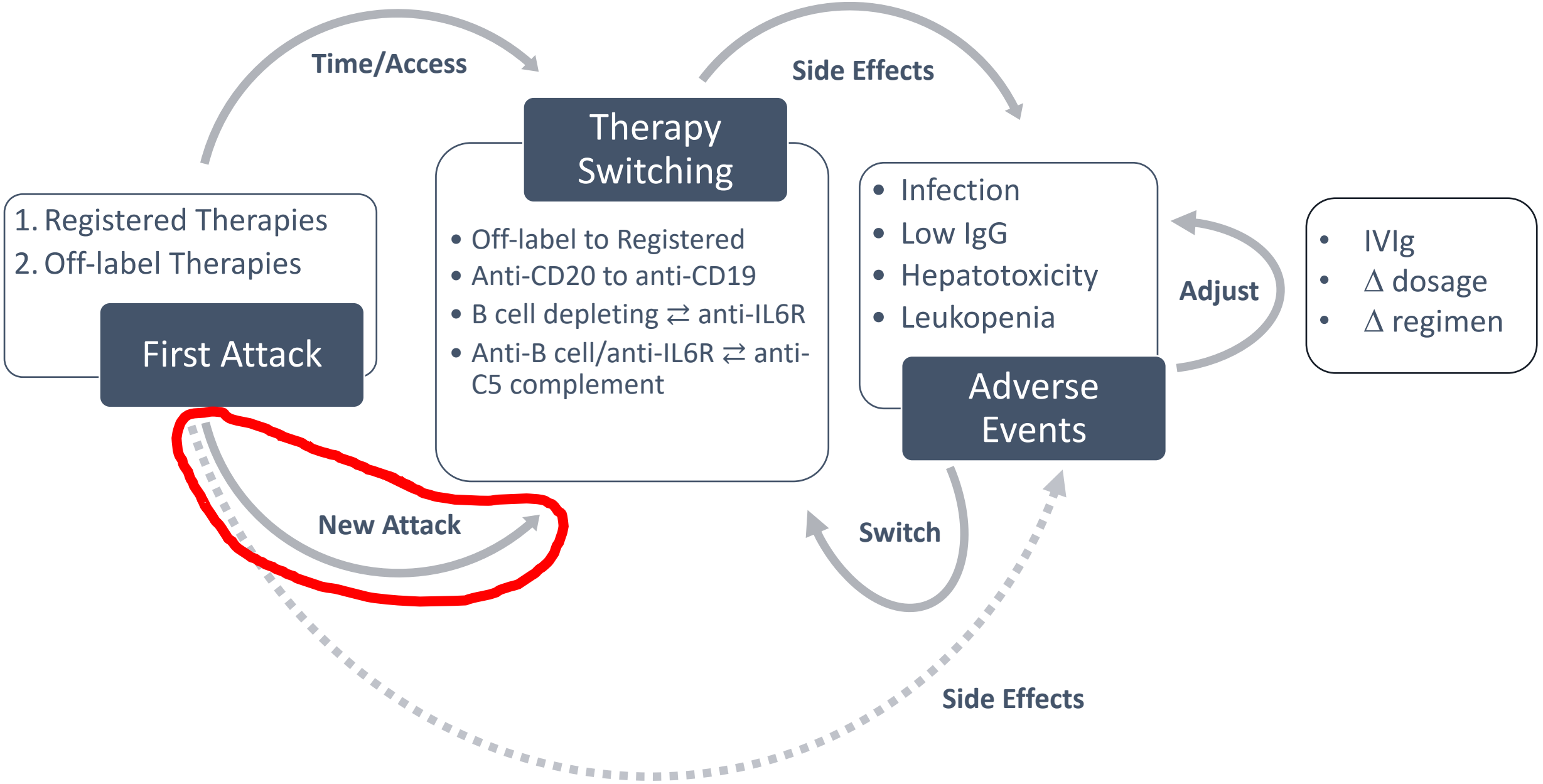
Approved NMOSD Therapeutics

Treatment	Relapse Risk Reduction, %	Hazard Ratio (95% CI)	P Value	OLE Annualized Attack Rate
Eculizumab*[1,2]	94	0.06 (0.02-0.20)	< .001	**0.025 (95% CI: 0.013-0.048)**
Inebilizumab[3,4]	77	0.227 (0.121-0.423)	< .0001	**0.097 (95% CI 0·070–0·14)**
Satralizumab[5-7]	78	0.21 (0.06-0.75)	.0143	**0.09 (95% CI: 0.06–0.12)**
	74	0.26 (0.11-0.63)	.0014	
Ravalizumab*[8]	98	0.014 (0.00-0.103)	.0001	**Not reported**
Rituximab[9,10]	NA	NA	NA	**0.03 – 0.08**

- **Eculizumab and Ravalizumab are only available through a Risk Evaluation and Mitigation Strategies (REMS) program.**
- **NA – not available due to small patient population**

1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614-25.
2. Wingerchuk et al., *Ann Neurol*. 2021;89:1088-1098
3. Cree BA, et al. *Lancet.* 2019;394(10206):1352-1363.
4. Cree BA, et al., *Lancet Neurol*. 2024.
5. Yamamura T, et al. *N Engl J Med*. 2019;381:2114-2124.
6. Traboulsee et al. *Lancet Neurol*. 2020;19(5):402-412.
7. Traboulsee T et al., *AAN Abstract*. 2023; S5-001.
8. Pittock SJ et al. Ann Neurol. 2023 Jun;93(6):1053-1068.
9. Tahara M et al., Mult Scler Relat Disord. 2022 doi: 10.1016/j.msard.2022.103730.
10. Bruschi et al., Neurol Ther. 2023; Aug;12(4):1375

NMOSD Treatment Algorithm



Attack on Therapy

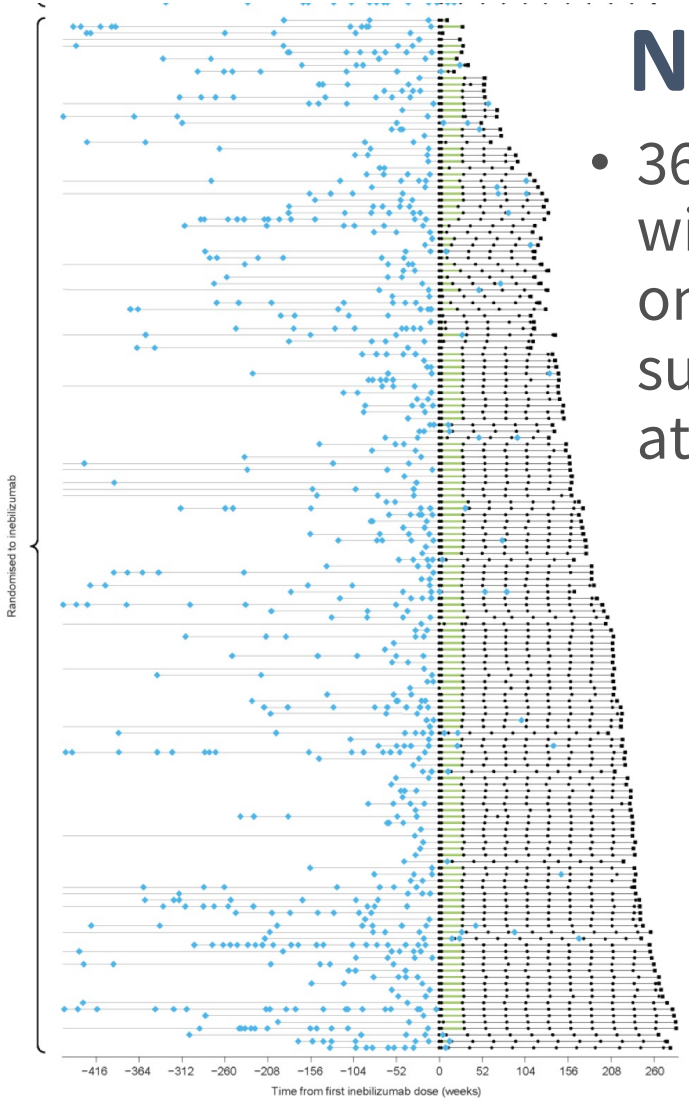


26-year-old African-American woman with AQP4-IgG seropositive NMOSD.

- **Left optic neuritis**
  - **20/15 R eye; 20/25 L eye**
- **Inebilizumab s/p loading dosage**
- **New right optic neuritis: 20/50**

No further attacks for 3 years

Most Patients on Approved Therapies Do Not Have Recurrent Attacks Despite Early Relapses



N-MOmentum

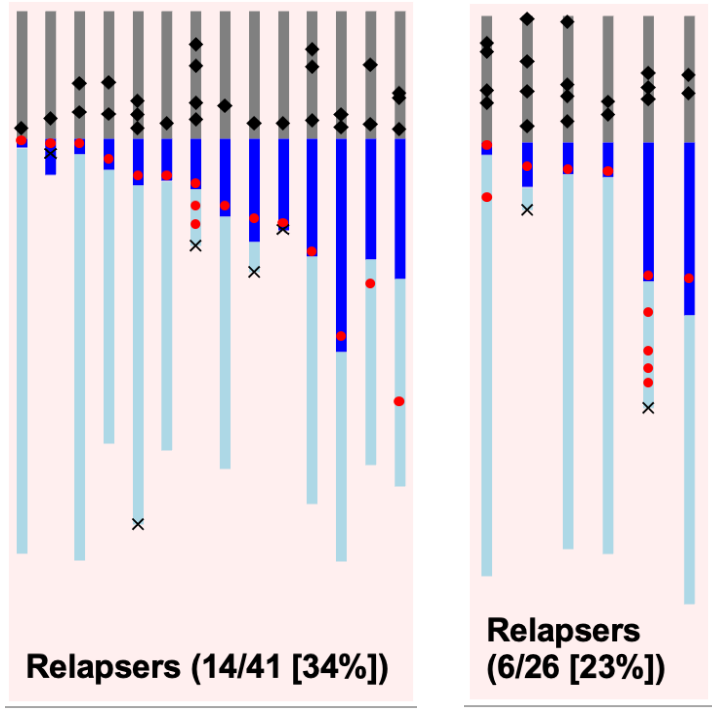
- 36 (77%) of 47 patients with adjudicated attacks on inebilizumab were subsequently attack-free at the end of 4 years.

Time Interval	HR
Overall	**0·146 (95% CI: 0·100, 0·213)**
0-6 months	0·201 (0·101, 0·401)
6-12 months	0·150 (0·045, 0·502)
12-18 months	0·093 (0·021, 0·416)
18-24 months	0·094 (0·008, 1·088)
24-30 months	0·074 (0·010, 0·528)
30-36 months	0·080 (0·007, 0·932)
36 months-end	0·065 (0·002, 1·751)

Cree BA, et al., *Lancet Neurol*. 2024.

Sakura Sky/Star

- 14 of 17 patients receiving satralizumab were subsequently attack free at the end of 4 years.



Bennett et al.,*ACTRIMS Forum 2023*, February 23–25, San Diego, California, USA

Attack on Therapy



28-year-old Caucasian woman with AQP4-IgG seropositive NMOSD.

- **Bilateral ON and TM attacks**
  - **Treated as MS for 13 years.**
- **Rituximab 1000 mg every 6 months**
  - **4 relapses over 4 years**
  - **CD19 count - 0**

Switch to inebilizumab

No further attacks for 4 years

What to switch to?

1. Registered Therapies
2. Off-label Therapies

First Attack

New Attack

Therapy Switching

- Off-label to Registered
- Anti-CD20 to anti-CD19
- B cell depleting ⇄ anti-IL6R
- Anti-B cell/anti-IL6R ⇄ anti-C5 complement



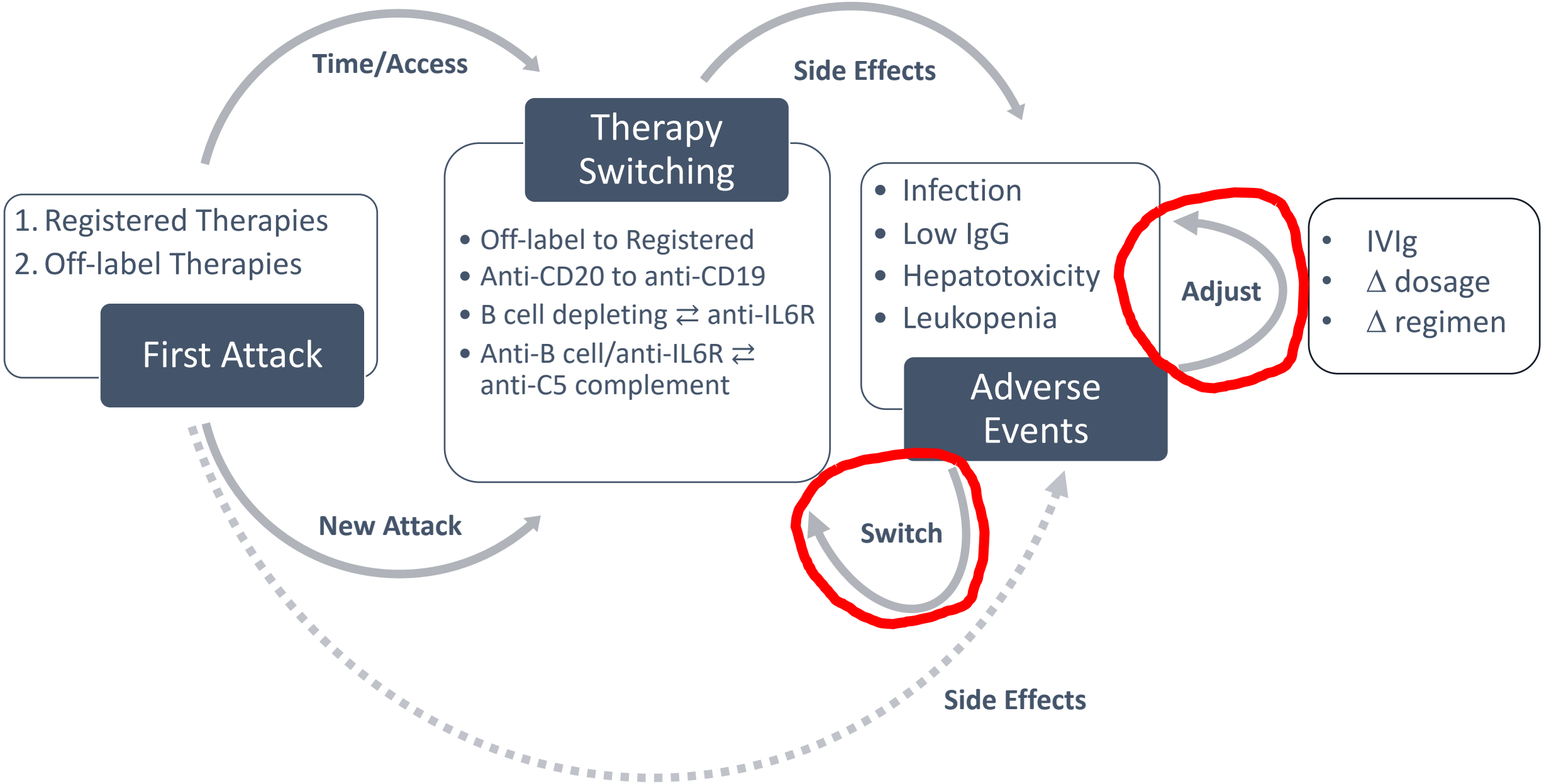
Case-by-Case Basis

- Prior Treatments
- Comorbidities
- Access

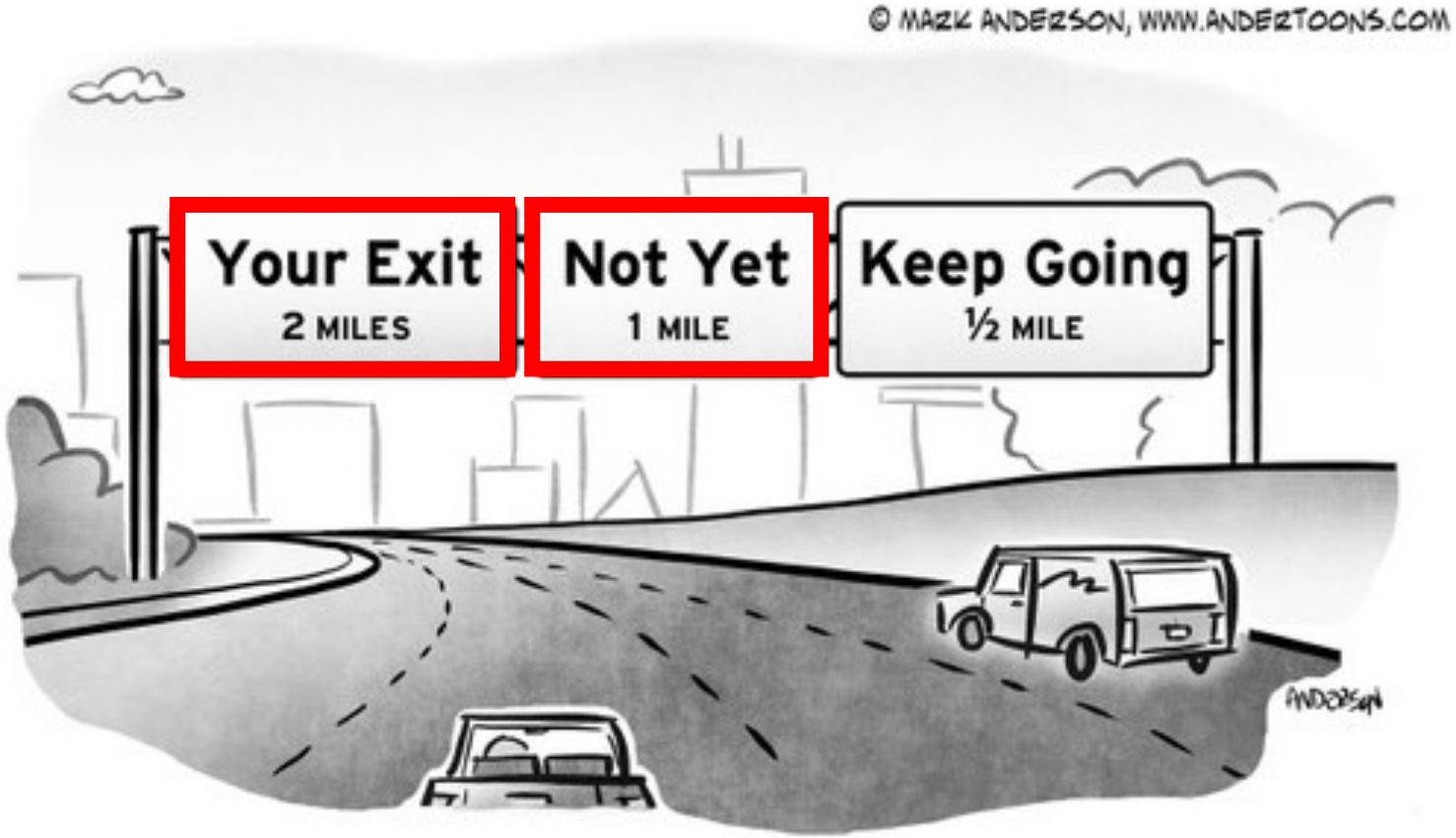
Switching Therapy for NMO Disease Activity

- Overlap Therapy
  - Rituximab → Inebilizumab
  - Inebilizumab/Rituximab/Satralizumab → C5-IT
  - Rituximab/Inebilizumab/C5-IT → Satralizumab
  - Satralizumab/C5-IT → Inebilizumab
- Bridging
  - Prednisone Taper

NMOSD Treatment Algorithm



Side Effects on Therapy



61-year-old Caucasian woman with AQP4-IgG seropositive NMOSD.

- Cervical Myelopathy/Tonic spasms
  - RX: inebilizumab, carbamazepine, sulfamethoxazole-trimethoprim
- 1 mo. – Leukopenia (WBC -1.3)
  - Carbamazepine ➜Lacosamide
  - D/C antibiotics

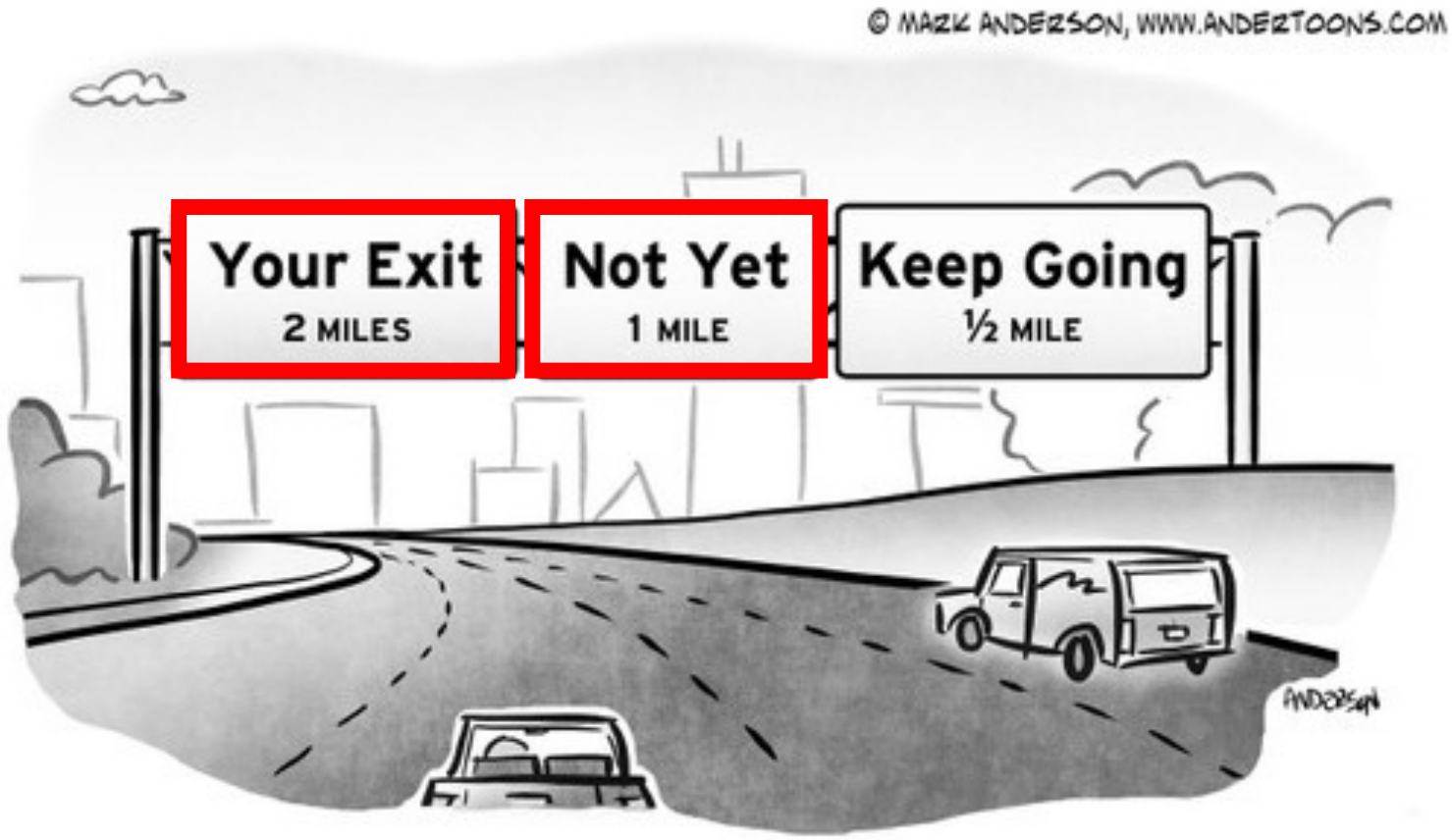
12 months later on inebilizumab

- IgG 1,701 ➜ 604 ➜ 241
- IVIg
  - Pyelonephritis

Switch to eculizumab

No further attacks for 4 years

Side Effects on Therapy



55-year-old Caucasian woman with AQP4-IgG seropositive NMOSD.

- Right ON – NLP vision
  - RX: Rituximab
- Infusion reactions
  - Myalgias - days
  - Migraines

Oral prednisone (3 days pre- to 7-days post)

- Brief success → requires longer post-Rx
- Satralizumab
  - Worsening migraines

Switch to inebilizumab

No infusion reactions or migraines for 2 years

Switching Therapy for Side Effects/Tolerance

- Minimize Overlap
  - Rituximab → Inebilizumab
    - Next scheduled infusion
  - Rituximab/Inebilizumab → C5-IT
    - Dosing 2 weeks prior to scheduled infusion
  - Rituximab/Inebilizumab → Satralizumab
    - 1 month prior to scheduled infusion
  - Satralizumab/C5-IT → Inebilizumab
    - Overlap with last infusion/injection

Therapeutic Transition: The Art and Science of NMOSD

- Current Therapy
  - Oral immunosuppressant
  - Biosimilar
  - Approved Therapy
- Treatment response
  - Relapse free?
  - Duration of treatment?
- Adverse Events
  - Treatment related?
  - Administration related?
- Physical/Social/Financial Circumstances



Minimizing NMOSD Therapy-Associated AEs & SAEs

Hesham Abboud, MD, PhD

Director of Neuroimmunology, Associate Professor of Neurology

Case Western Reserve University School of Medicine

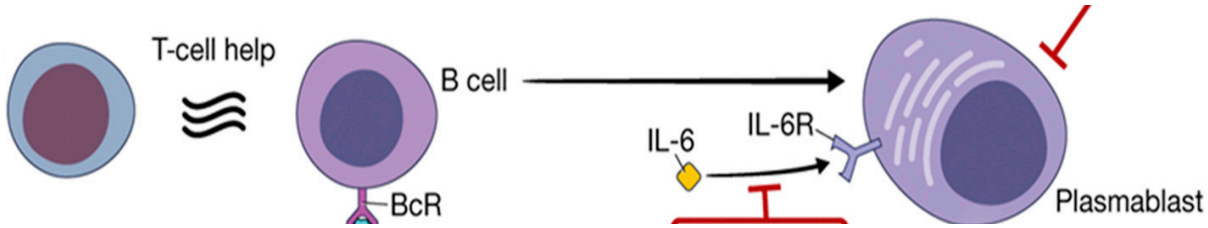
University Hospitals Cleveland Medical Center

Disclosures

- Consultant and/or speaker for Biogen, BMS, Genentech, Alexion, Horizon/Amgen.
- Grant or Research Support (paid to institution): Novartis, Sanofi, BMS, Genentech, UCB, COREVITA/GJF.
- Royalties: UpToDate

Pathogenesis of NMOSD: therapeutic implications

Blood



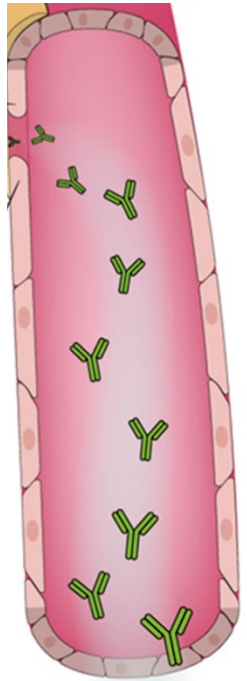
Non-selective immunosuppression:
MMF
AZA
Steroids

Selective B-cell depletion (anti-CD20): rituximab

IL-6 inhibition:
Satralizumab
Tocilizumab

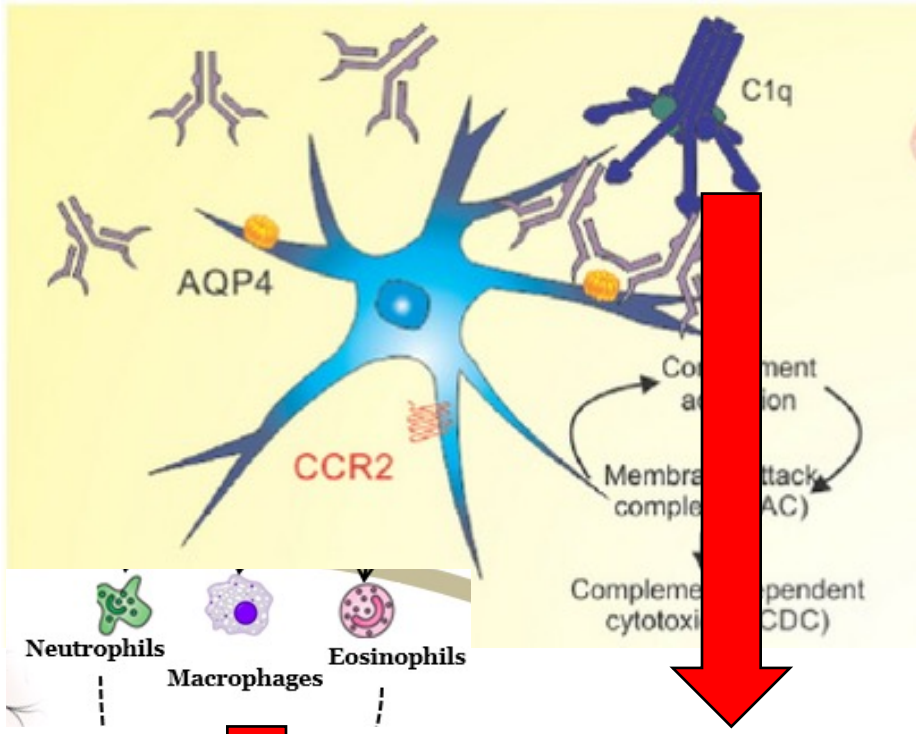
Selective B-cell and plasmablast depletion (anti-CD19):
Inebilizumab

BBB



Plasma exchange (PLEX)

CNS



Steroids

Complement inhibition:
Eculizumab
Ravulizumab

Adverse events associated with NMOSD therapies

AE category	Adverse events	Serious adverse events
Infections	URTIs, UTIs, SSTIs, CNSIs	PNA, pyelonephritis, sepsis, meningococcal disease; OIs
Blood cells and related lab abnormalities	Mild/asymptomatic: leukopenia, lymphopenia, neutropenia, low IgG	Severe/symptomatic leukopenia, lymphopenia, neutropenia, low IgG
Infusion/injection reactions	Itching, erythema, nausea, dizziness, palpitations	Severe hives, SOB, anaphylaxis
Liver injury	Asymptomatic elevation in liver enzymes; triglyceridemia	Liver injury
Fetal risk	Lack of data, laboratory abnormalities, impact vaccine response	Teratogenicity, infection, impact vaccine safety
Paradoxical/autoimmune effects	Mild/skin reactions	Treatment-related relapses, rebound disease, iatrogenic demyelination, psoriasis, IBD

Composite Infection Risks in NMOSD

- Increased infection risk in NMOSD is multifactorial:
  1. Immobility increases the risk of skin and lung infections.
  2. Bladder dysfunction increases the risk of urinary and genital infections.
  3. NMOSD medications increase the risk of common and serious infections.
  4. Some NMOSD medications decrease the effectiveness of vaccines.
  5. Steroid therapy, PLEX, and frequent hospitalization increase the risk of infection further.

Minimizing infection risk

General measures:

















Minimizing infection risk

Special mitigation strategies for NMOSD patients:



Well fitted wheelchairs



Avoid pressure ulcers



Intermittent catheterization



Change foley

Leveraging Protective Immunization

- **Immunization Required for Some NMOSD Therapeutics**
  1. Eculizumab – full vaccination regimen vs. meningococcal disease
  2. Ravulizumab – full vaccination regimen vs. meningococcal disease
  3. Vaccination against *H. influenzae*, *St. pneumoniae, B. pertussis* and other infections also recommended when using C5 inhibition
  4. Appropriate immunization portfolio also recommended in NMOSD biologic therapeutic regimens targeting CD19, IL-6R and CD20
  5. Consider halo immunity for patients at high risk of serious infections

- **Attenuating Minimal Risks of Vaccine-Induced Relapses**
  1. Overall risks of vaccine-induced relapse are statistically minimal
  2. Pre-vaccine oral steroid + antihistamine may further reduce risk
  3. Provider and patient education of vaccine benefits is critical

Minimizing infection risk

Special mitigation strategies for NMOSD patients:



Avoid overcrowded poorly ventilated gatherings



Avoid unnecessary ER visits



Avoid unnecessary steroids



Special vaccines for immunocompromised: pneumovax, meningitis, shingles, COVID19 boosters

Minimizing infection risk

- Role of the treating physician:
- Screening for dormant infections before starting treatment: Hepatitis, TB.
- Ensuring immunity against certain viruses: VZV, COVID19.
- Complete recommended vaccines prior to starting treatment.
- Ensure intake of seasonal and booster non-live vaccines while on treatment.
- Avoiding live-vaccines while on treatment.
- Selection of long-term treatment.
- Monitoring immune cell counts and IgG levels when indicated.
- Advise medical teams in case of active infection.
- Symptomatic treatment of bladder dysfunction, spasticity, etc.
- Avoid unnecessary hospital admissions and steroid therapies.

Inebilizumab

- Anti-CD19 humanized monoclonal antibody: depletes B-cells and some plasmablasts and plasma cells.
- Overall rates of infections, laboratory abnormalities, and infusion reactions were relatively low during the NMOMENTUM clinical trial and open label extension.
- Rates of adverse events with inebilizumab seem lower than other B cell depleting therapies but experience is limited, and overall rates of infection are greater than untreated individuals.

Mitigation of inbelizumab risks

Adverse events	Mitigation strategies
Hypogammaglobulinemia (13%)	- Screen baseline and periodic IgG levels while on treatment. - Avoid in those with baseline low IgG - Consider IVIG replacement in patients with low IgG and recurrent infections. - Consider switching to other therapies.
Neutropenia (12%) / absolute lymphopenia (5%)	- Screen baseline and periodic cell counts. - Avoid in those with baseline low counts. - Consider switching to other therapies if severe or symptomatic.
Recurrent or serious infections including hep B and complicated COVID19 (3%)	- Screen hepatitis panel, TB, VZV IgG, SARSCOV2 IgG, JCV IgG before treatment. - Hepatology consult and treatment of dormant hepatitis B before starting treatment – or avoid all together. ID consult for latent TB. - Monitor JCV IgG positive patients for PML signs and obtain brain MRI when suspicious. - Encourage standard vaccination and administer VZV and COVID19 vaccines before treatment. Consider HBV vaccine for high risk patients . - Recommend seasonal non-live vaccines while on treatment, check serology after. - Avoid live vaccines while on treatment - Avoid in patients unvaccinated against COVID19. - Delay treatment in actively infected patient. - Consider switching to other therapies..

Mitigation of inebilizumab risks

Adverse events	Mitigation strategies
Infusion reactions (9%)	- Pretreat with IVMP, acetaminophen, anti-histamines. - Hold or slow infusion rate for mild reactions, stop for severe.
Treatment-related relapses (frequency unknown but most relapses occur early after treatment initiation)*	- Overlap with oral steroids at the beginning of treatment
Fetal risk	- Delay dose in pregnant females. - Discuss implications on infant B cells and vaccine administration in case of exposure during pregnancy.

** Cree BAC, Kim HJ, Weinshenker BG, et al. Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial. Lancet Neurol. 2024 Jun;23(6):588-602.*

Satralizumab

- IL-6 receptor blocker
- Subcutaneous self injection at home.
- Does not deplete immune cells.
- Less impact on vaccine response compared to B cell therapies.
- Overall favorable safety profile from clinical trials and open label extensions.

Mitigation of satralizumab risks

Adverse events	Mitigation strategies
Leukopenia (14%), Neutropenia (10%) (lymphopenia and low IgG reported with tocilizumab)	- Screen cell counts at baseline, 4-8 weeks after initiation, and periodically after that. - Avoid in those with baseline low counts. - Consider switching to other therapies if severe or symptomatic.
Recurrent or serious infections (3%)	- Screen for hepatitis panel, TB, VZV IgG, SARSCOV2 IgG, JCV IgG before treatment. - Hepatology consult and treatment of dormant hepatitis B before starting treatment – or avoid all together. ID consult for latent TB. - Encourage standard vaccination including HBV and administer VZV vaccines before treatment in non-immunized patients. - Recommend seasonal non-live vaccines while on treatment. - Avoid live vaccines while on treatment - Delay treatment in actively infected patient. - Infection can happen without fever.
Liver injury (elevation of liver enzymes > 3 times normal in 3%)	- Screen liver enzymes at baseline, monthly after treatment for three months, every three months for the first year, and periodically after that. - Interrupt treatment if liver enzymes > 5 times normal level. Stop treatment if concomitant bilirubin elevation. - Avoid in hepatic patients.

Mitigation of satralizumab risks

Adverse events	Mitigation strategies
Increased cholesterol (13%) and TGs (20%)	- Check baseline lipid profile and compare to levels after treatment - Healthy diet, exercise, statins, niacin
Increase in body weight (30%)	- Monitor - Healthy diet, exercise,
Thrombocytopenia (26%, typically asymptomatic)	- Check baseline platelet count and periodically after treatment.
Injection reactions (9% mostly mild and local)	- Local measures - Stop treatment in case of severe reaction.
Fetal risk (unknown)	- Avoid in pregnant females

Eculizumab and Ravulizumab

- Complement inhibitors, act on the final step of the inflammatory reaction.
- No significant immunosuppression except for increased risk of meningitis and other encapsulated bacteria. Risk of common infections also slightly increased.
- Eculizumab maintenance dose: intravenous infusion every two weeks.
- Ravulizumab maintenance dose: intravenous infusion every eight weeks.
- No impact on vaccine response.

Mitigation of eculizumab and ravulizumab risks

Adverse events	Mitigation strategies
Meningitis (Neisseria meningitides): 3.5% = >10,000 fold increased risk compared to the general population	- Full vaccination regimen required against *Neisseria meningitis* ACWY (quadrivalent) and B (monovalent) variants 2 weeks before treatment initiation. Vaccination recommended against *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Bordetella pertussis* - If starting treatment on urgent basis. Vaccinate as soon as possible and initiate meningitis prophylaxis (cipro, rifampin, ceftriaxone, or azithromycin) - Avoid in those with high risk for meningitis. - Vaccination reduces but does not eliminate risk: monitor closely for signs of meningitis and initiate workup and treatment on suspicion. - REMS program
Other infections with encapsulated bacteria (*N. gonorrheae, St. pneumoniae, H. influenzae)*	- Consider vaccination. - Avoid in high risk patients. - Monitor for signs of infection and initiate treatment on suspicion. - Aspergillosis a potential risk.
Leukopenia (5%), lymphopenia (5%)	- Check baseline and periodic cell counts.
Infusion reactions (very rare and typically mild)	- Interrupt treatment and administer appropriate supportive measures.

Recommended meningococcal vaccination schedule for patients on complement inhibitors

TABLE 4. Recommended vaccination schedule and intervals for persons with persistent complement deficiencies* (including patients using a complement inhibitor)† — Advisory Committee on Immunization Practices, United States, 2020

Age group	Serogroups A, C, W, and Y meningococcal conjugate vaccines MenACWY-D (Menactra, Sanofi Pasteur)§ *or* MenACWY-CRM (Menveo, GlaxoSmithKline)¶ *or* MenACWY-TT (MenQuadfi, Sanofi Pasteur)**	Serogroup B meningococcal vaccines MenB-FHbp (Trumenba, Pfizer) *or* MenB-4C (Bexsero, GlaxoSmithKline)
2–23 mos	**Primary vaccination:** MenACWY-D (aged ≥9 mos): 2 doses ≥12 wks apart *or* MenACWY-CRM if first dose at age • 2 mos: 4 doses at 2, 4, 6, and 12 mos • 3–6 mos: See catch-up schedule§§ • 7–23 mos: 2 doses (second dose ≥12 wks after the first dose and after the 1st birthday)	No recommendations for use of MenB vaccines in this population††
2–9 yrs	**Primary vaccination¶¶:** MenACWY-D*** *or* MenACWY-CRM *or* MenACWY-TT: 2 doses ≥8 wks apart **Boosters (if person remains at increased risk)†††:** • Aged <7 yrs: Single dose at 3 yrs after primary vaccination and every 5 yrs thereafter • Aged ≥7 yrs: Single dose at 5 yrs after primary vaccination and every 5 yrs thereafter	No recommendations for use of MenB vaccines in this population††
≥10 yrs	**Primary vaccination††:** MenACWY-D *or* MenACWY-CRM *or* MenACWY-TT: 2 doses ≥8 wks apart **Boosters (if person remains at increased risk)†††:** Single dose at 5 yrs after primary vaccination and every 5 yrs thereafter	**Primary vaccination††:** MenB-FHbp: 3 doses at 0, 1–2, and 6 mos *or* MenB-4C: 2 doses ≥1 mo apart **Boosters (if person remains at increased risk)§§§:** Single dose at 1 yr after completion of primary vaccination and every 2–3 yrs thereafter **Note:** MenB-FHbp and MenB-4C are not interchangeable

Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep 2020;69(No. RR-9):1–41

Rituximab

- Anti-CD20: depletes B cells. Main DMT for seronegative NMOSD and still used in many AQP4-IgG positive patients.
- Chimeric: higher rates of infusion reactions compared to inebilizumab.
- Higher rates of low IgG compared to ocrelizumab. Risk increase with dose and duration of treatment.*
- Risk of serious infection increased in MS/NMOSD patients with low IgG, low ALC, and prolonged use.*

Mears V, et al., J Neuroimmunol. 2023, Kim SH et al., N2 2022, Langer-Gould A, et al., N2 2024,

Mitigation of rituximab risks

Adverse events	Mitigation strategies
Hypogammaglobulinemia (10-40%)	- Check baseline and periodic IgG levels while on treatment. - Avoid in those with baseline low IgG - Consider IVIG replacement in patients with low IgG and recurrent infections. - Consider switching to non depleting agents in seropositive patients.
Neutropenia (6%) / absolute lymphopenia (53%)	- Check baseline and periodic cell counts. - Avoid in those with baseline low counts - Consider switching to non depleting agents in seropositive patients.
Recurrent or serious infections including hep B and complicated COVID19 (15%)	- Check hepatitis panel, TB, VZV IgG, SARSCOV2 IgG, JCV IgG before treatment. - Hepatology consult and treatment of dormant hepatitis B before starting treatment – or avoid all together. ID consult for latent TB. - Monitor JCV IgG positive patients for PML signs and obtain brain MRI when suspicious. - Encourage standard vaccination and administer VZV and COVID19 vaccines before treatment. Consider HBV vaccine for high risk patients . - Recommend seasonal non-live vaccines while on treatment, check serology after. - Avoid live vaccines while on treatment - Avoid in patients unvaccinated against COVID19. - Delay treatment in actively infected patient. - Consider switching to FDA-approved therapies in seropositive patients.

Mitigation of rituximab risks

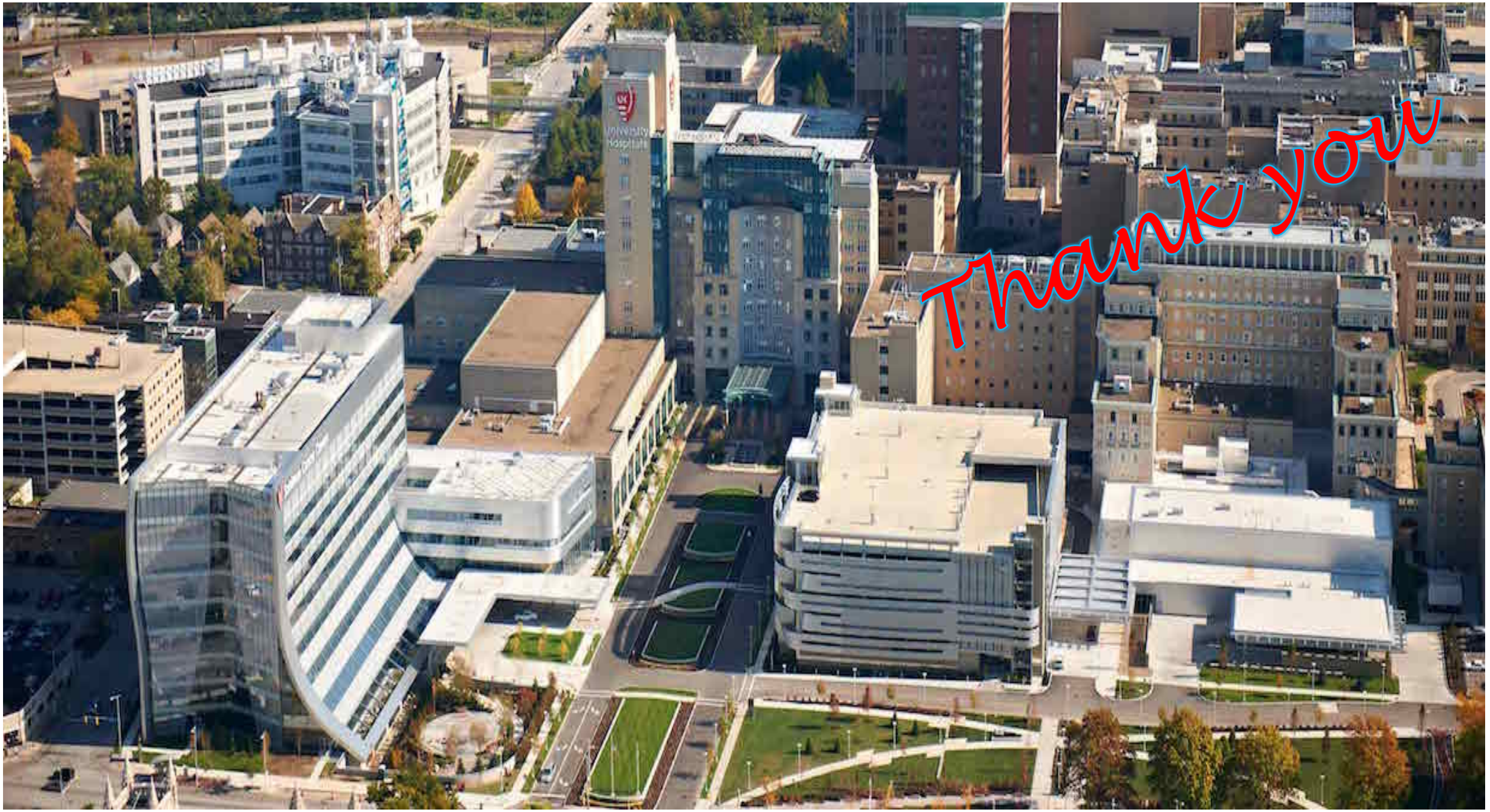
Adverse events	Mitigation strategies
Infusion reactions (30%)	- Avoid in patients with multiple allergies and history of drug intolerance. - Pretreat with IVMP, acetaminophen, anti-histamines. - Administer in facility equipped with supportive measures (O2, epinephrine, etc.) - Cardiac monitoring during infusion. - Hold or slow infusion rate for mild reactions, stop for severe.
Treatment-related relapses (up to 43% in 1 report)	- Overlap with oral steroids at the beginning of treatment
Iatrogenic autoimmunity (very rare)	- Avoid in patients with coexisting IBD or psoriasis.
Fetal risk	- Delay dose in pregnant females. - Discuss implications on infant B cells and vaccine administration in case of exposure during pregnancy.

Summary

- Immunotherapies for NMOSD are highly effective but have several side effects and potential risks.
- An increase in common and serious infections is seen with all therapies. NMOSD patients are at increased infection risk even without treatment.
- Specific risks are associated with specific treatments:

- Hepatitis B, complicated COVID19 and UTI: B cell depleting therapies.
- Meningitis and other encapsulated bacteria: complement inhibitors.
- Liver injury: IL6 receptor antagonists.
- Infusion reactions: possible in any biologic therapy; greater if non-fully humanized

- Several mitigation strategies can minimize the risks associated with NMOSD therapies including laboratory monitoring before and during treatment, screening for dormant infections, vaccination prior or during treatment, monitoring for and timely treatment of infections, proper case selection for each DMT, among others.
- Collection of real-life data is very important for a better understanding of the full safety profile of the new approved therapies.


Thank you

Therapeutic Issues in Autoimmune Comorbidities

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Institutes of Regional Health Research
& Molecular Medicine
University of Southern Denmark

2024 GJCF NMO Roundtable, Los Angeles 2 – 4. August, 2024

No disclosures



Agenda

- Background:
  - NMOSD, MOGAD, S/DS-NMOSD and autoimmunity
  - Putative mechanisms of occurrence of autoimmune comorbidity (AC)
- Characterization of the pattern of AC
  - The prevalence of AC
  - AC and clinical outcome
- AC: a therapeutic challenge

Four criteria for an autoimmune disease

1. The disease should be associated with humoral or cell mediated autoimmunity √
2. The autoantigen should be identified √
3. The disease should be transferred by pathogenic antibodies or T-cells √
4. The disease should be experimentally induced by presentation of an autoantigen from the target organ √

AQP4-IgG+NMOSD MOGAD

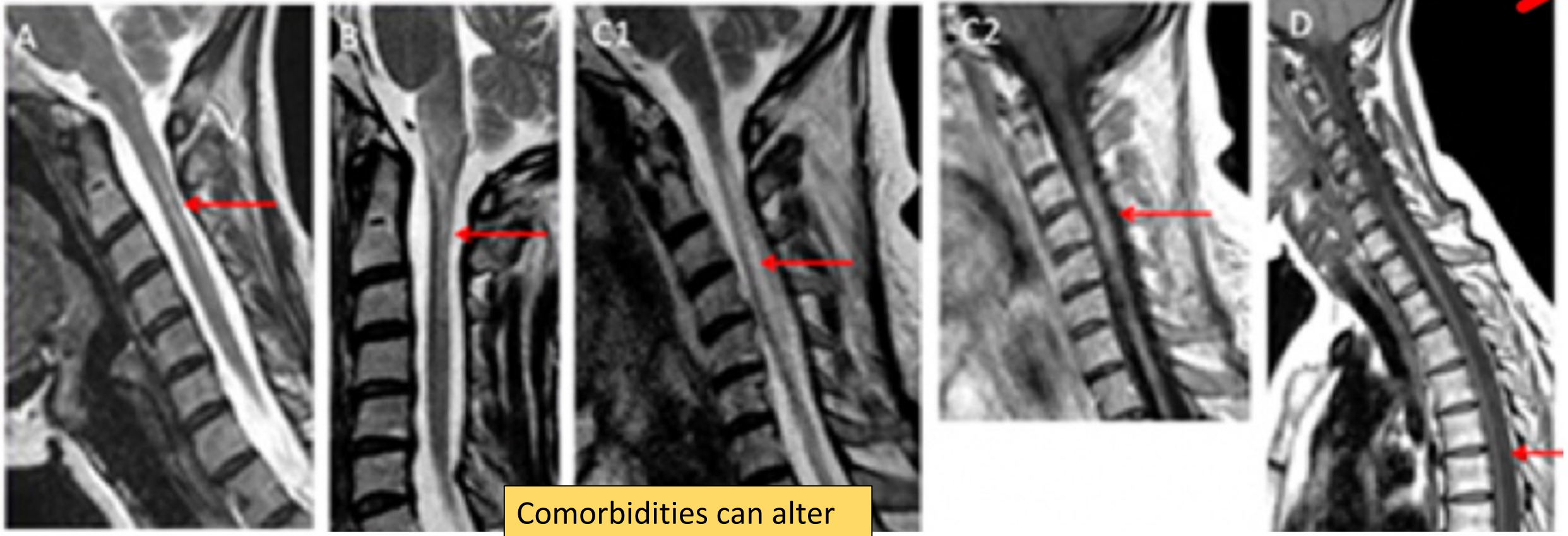
Indirect evidence for autoimmunity:

1) Clinical coexistence with other autoimmune diseases

2) The disease course should be prevented or improved by immunosuppressive therapy

Rose and Bona Immunol Today 1993

Does comorbidity contribute to neuro-axonal injury?



Antiphospholipid syndrome
Rheumatoid arthritis
Coeliac disease

Comorbidities can alter clinical presentation; need to be considered when making treatment decisions

- Motor and sensory deficits ranging from paresthesia to paresis
- Bladder, bowel and/or erectile dysfunction
- Neuropathic pain

Asgari et al. Neurology 2011; MSJ, 2012; Shahmohammadi et al. MSRD 2019; Barzegar et al. MSRD 2021; Exuzides et al. Neurol Sci. 2021; Gholizadeh et al. J. Neurol. 2023
Fig. adapted from Jarius et al Nature 2020;

Autoimmune diseases share extensive comorbidity

- Autoimmune diseases affect approximately one in ten individuals
- 25% of patients with autoimmune disease develop AC
- Poly-autoimmunity: Coexistence of 2 autoimmune diseases
- Multiple autoimmune syndrome (MAS): co-occurrence of ≥ 3 autoimmune diseases
- MAS may delay the diagnosis

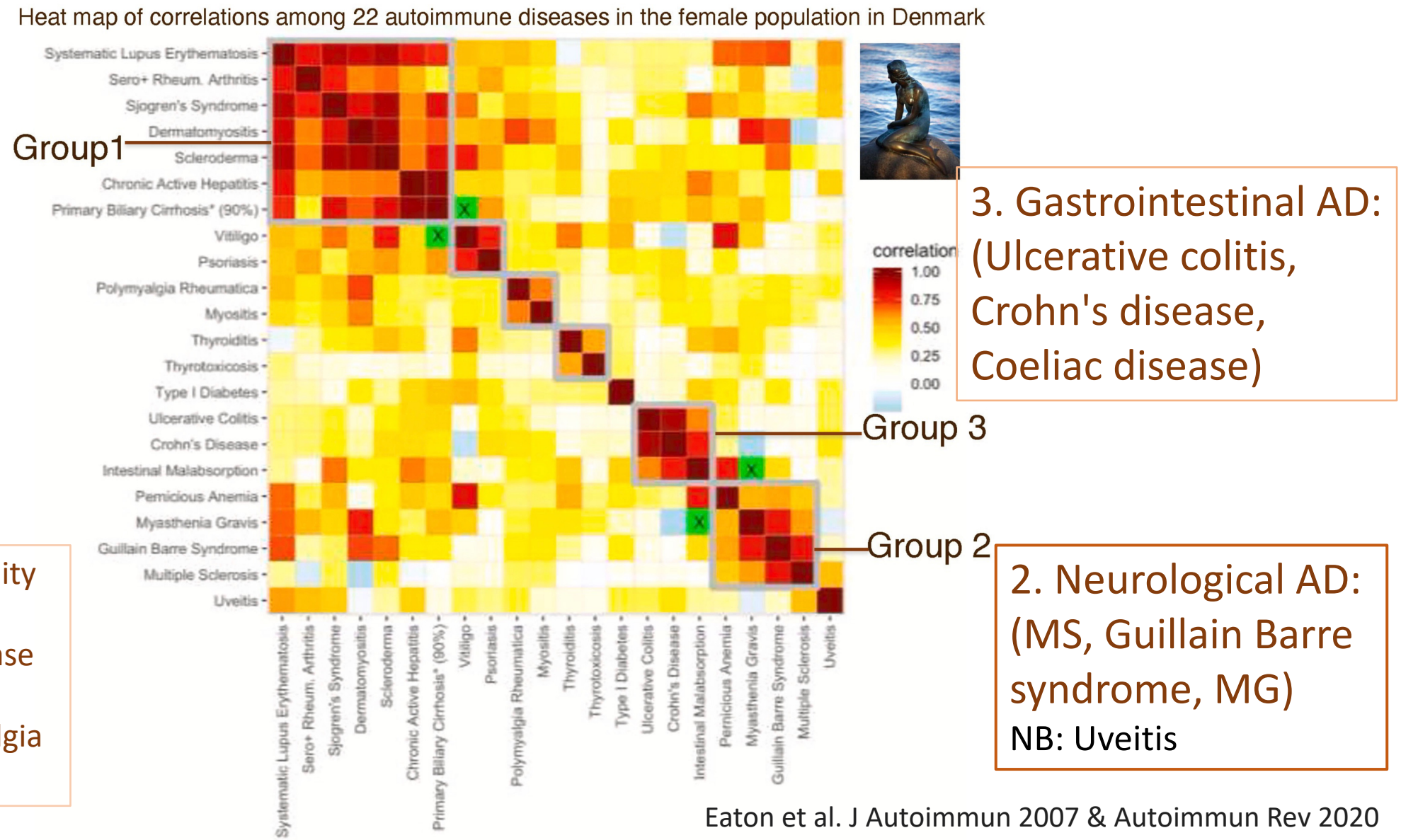
  - Can we characterize the pattern of clustering of AC?
  - What is the time span from symptom onset of NMOSD or MOGAD and AC?
  - Can AC affect the treatment strategy?

Conrad et al. Lancet 2023

Specific autoimmune diseases cluster together

A visual characterization of the pattern of autoimmune comorbidity

1. Lupus family: (SLE, RA, Dermatomyositis, SS, Scleroderma)
NB: Chronic active hepatitis and Primary biliary cirrhosis (anti-nuclear antibodies)



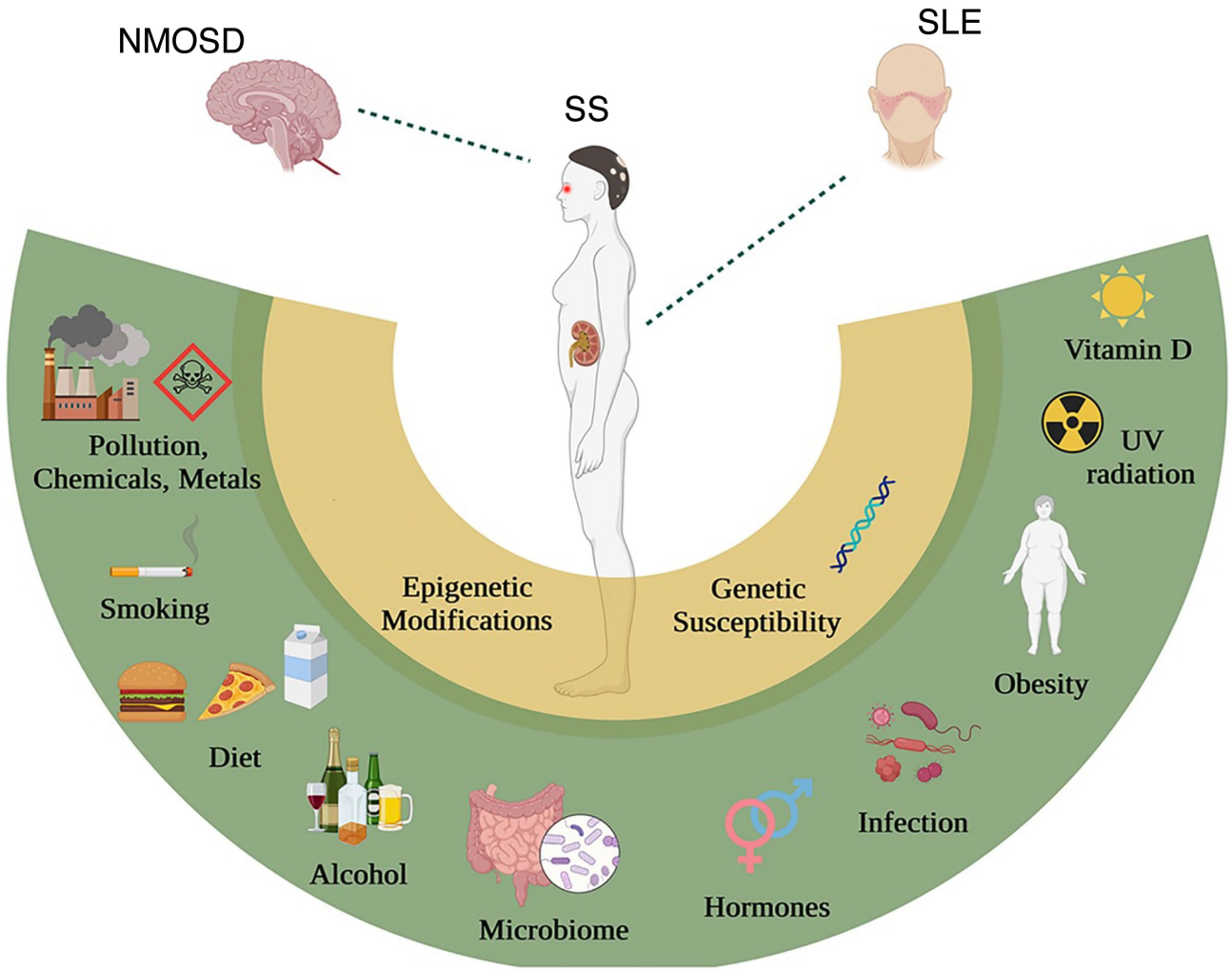
3. Gastrointestinal AD: (Ulcerative colitis, Crohn's disease, Coeliac disease)

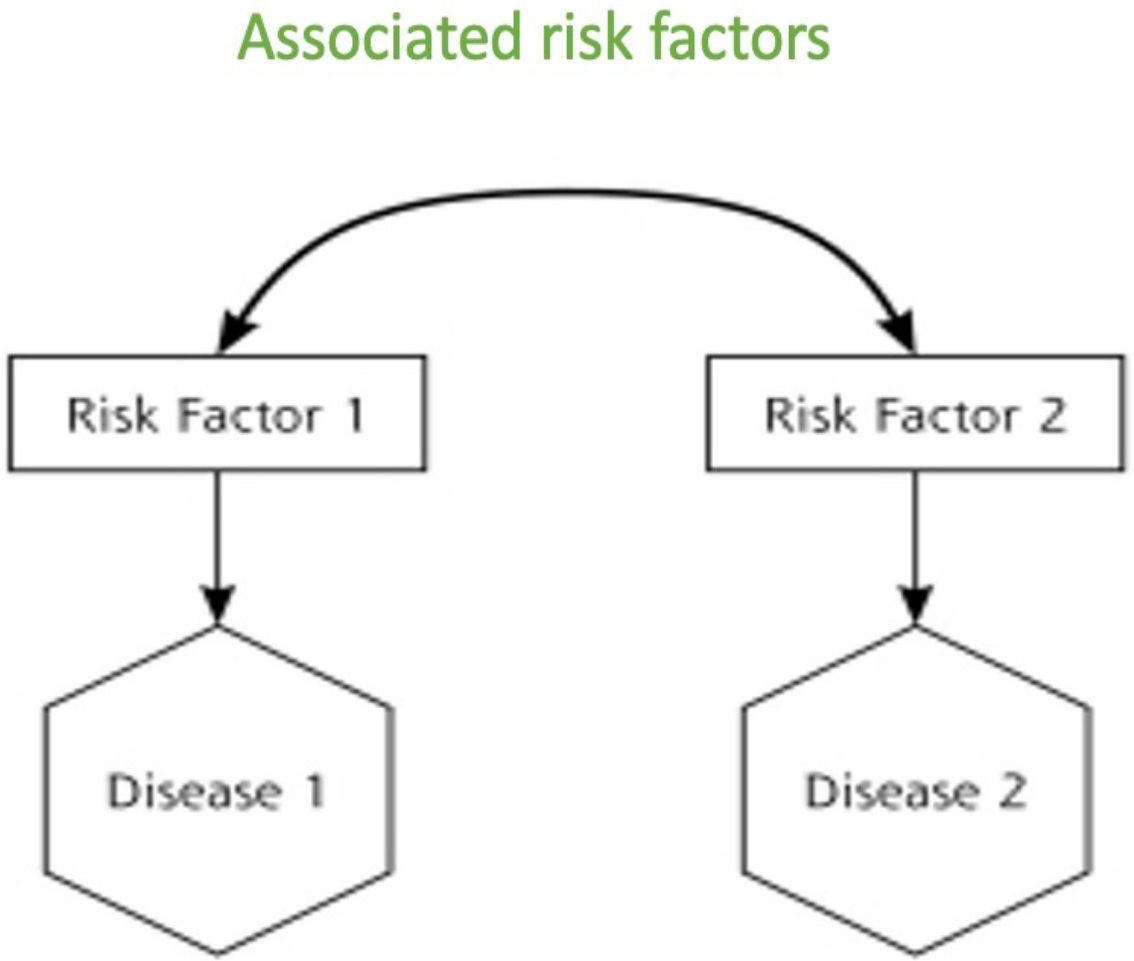
In addition, high comorbidity were observed between: Autoimmune thyroid disease /type 1 Diabetes, Vitiligo/Psoriasis, Polymyalgia Rheumatica/Myositis

2. Neurological AD: (MS, Guillain Barre syndrome, MG)
NB: Uveitis

Eaton et al. J Autoimmun 2007 & Autoimmun Rev 2020

Causes of Autoimmune Comorbidities





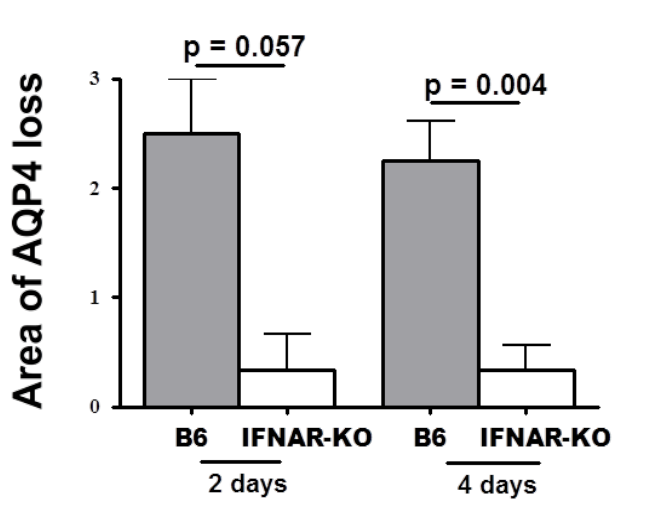
Shared genetic risk associations across ten Pediatric-age-of-onset autoimmune diseases. Meta-analysis

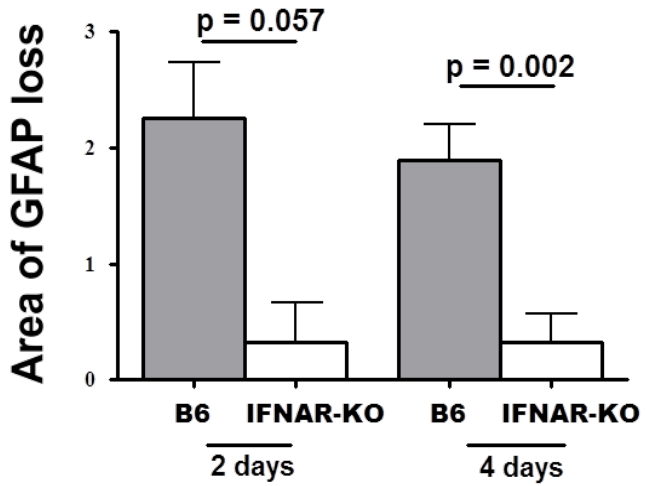
- A case-control study including more than 6,035 cases and 10,718 population-based controls.
- Genome-wide association (GWAS)
- 19 of the identified gene sites were shared by at least three autoimmune diseases
- Involvement of signaling pathways of TH1, TH2 and TH17 cells, JAK-STAT, and interferon in multiple autoimmune diseases.
- In another study: MHC class I-related biological processes and the interferon-gamma-mediated signaling pathway have been suggested to be involved in the pathogenesis of NMOSD coexisting with autoimmune thyroid disease, SLE, and SS.

Li et al Nat Med 2015; Wang et al. Front Immunol. 2022

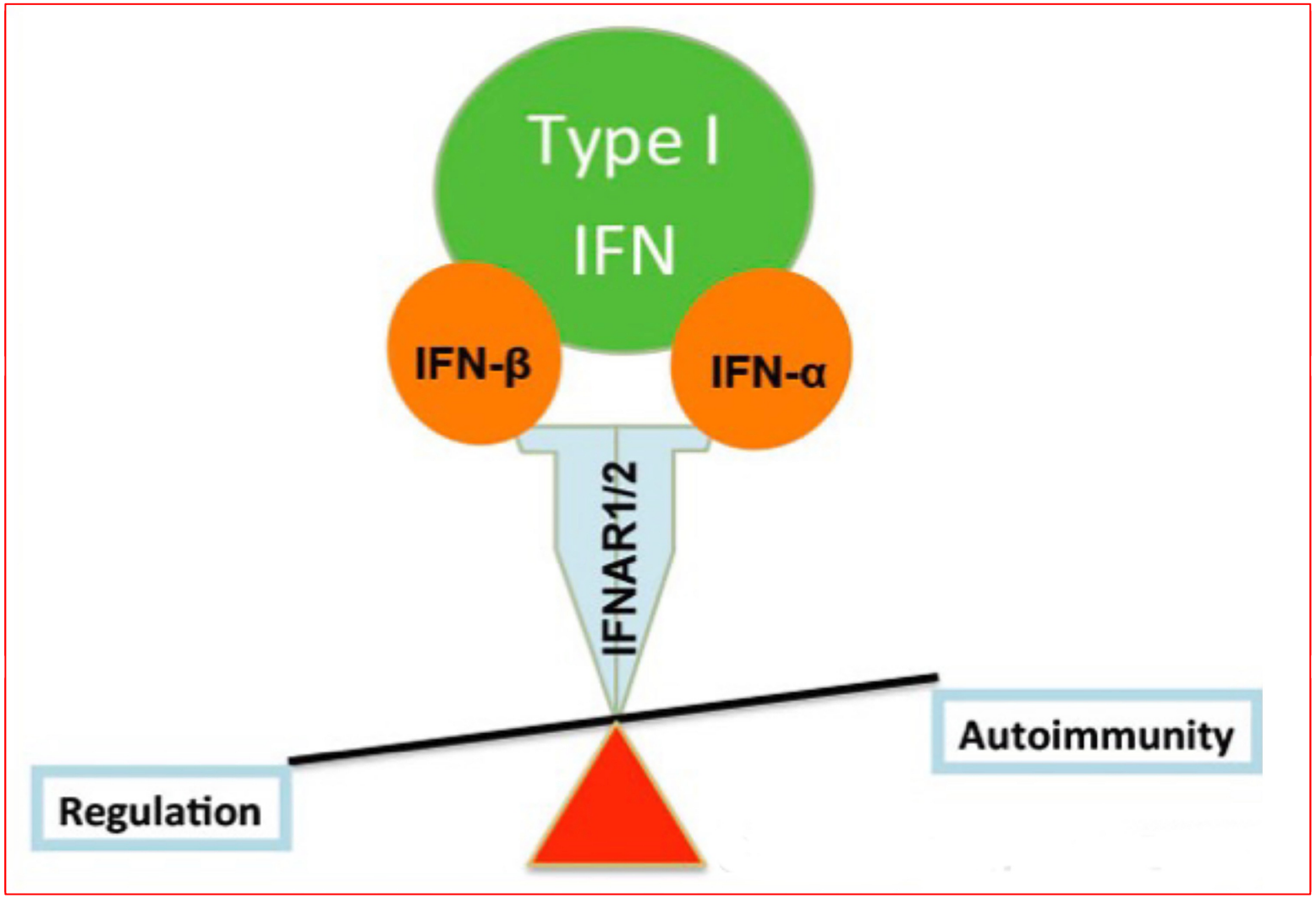
Genetic autoimmune dependency of NMOSD

Type I interferon signaling



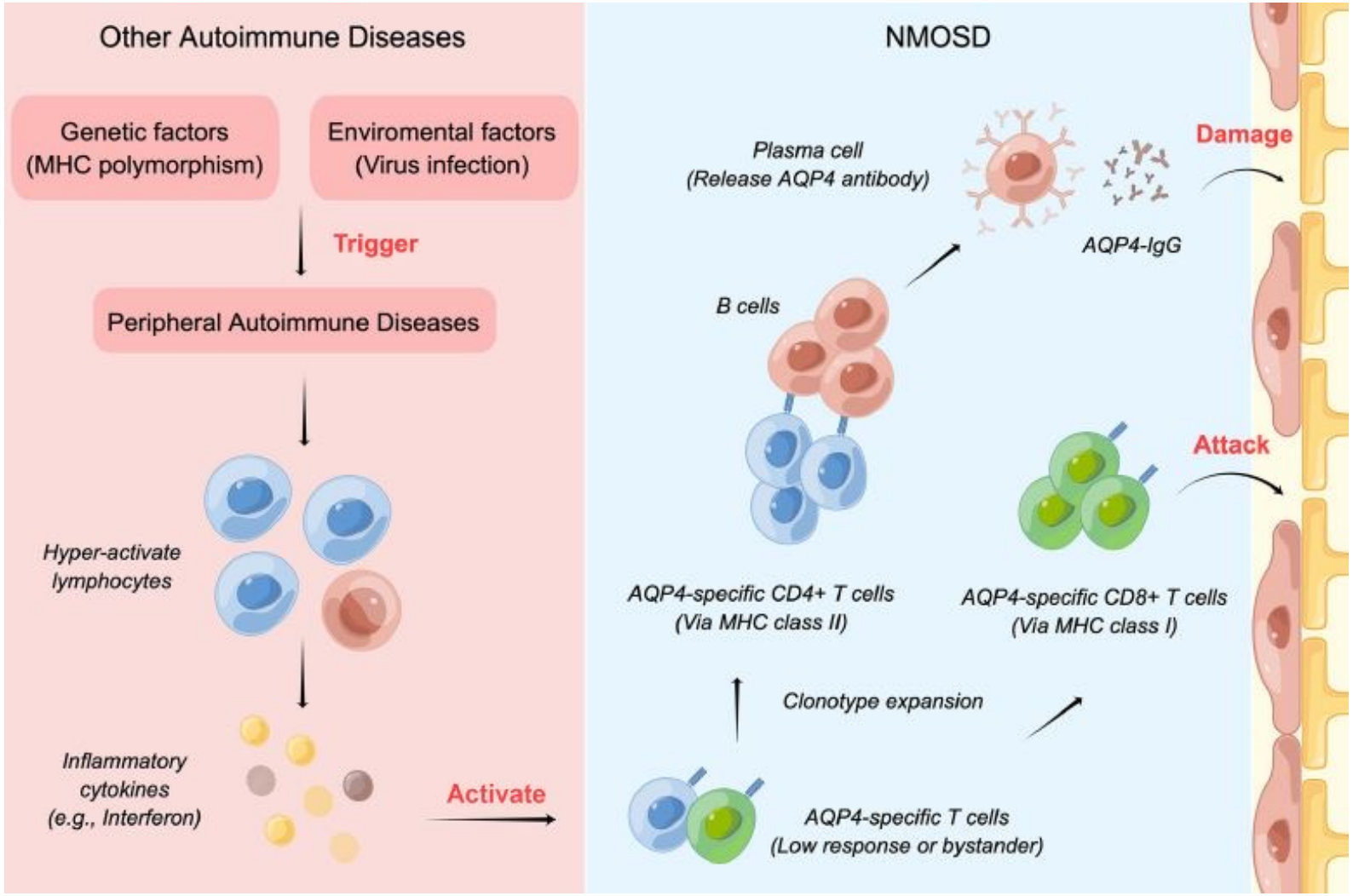






Asgari et al. Neurology 2011; MSJ, 2012; JNI 2013; Clin. Develop. Immun. 2013; JNS 2014; Khorooshi, et al. 2013, Exp. Neurology; Soerensen et al. Front Neurol. 2021; Wlodarczyk et al. Glia. 2021

The mechanism of NMOSD coexisting with other autoimmune diseases



Wang et al. Front Immunol. 2022

Autoimmune diseases associated with NMOSD: A literature review

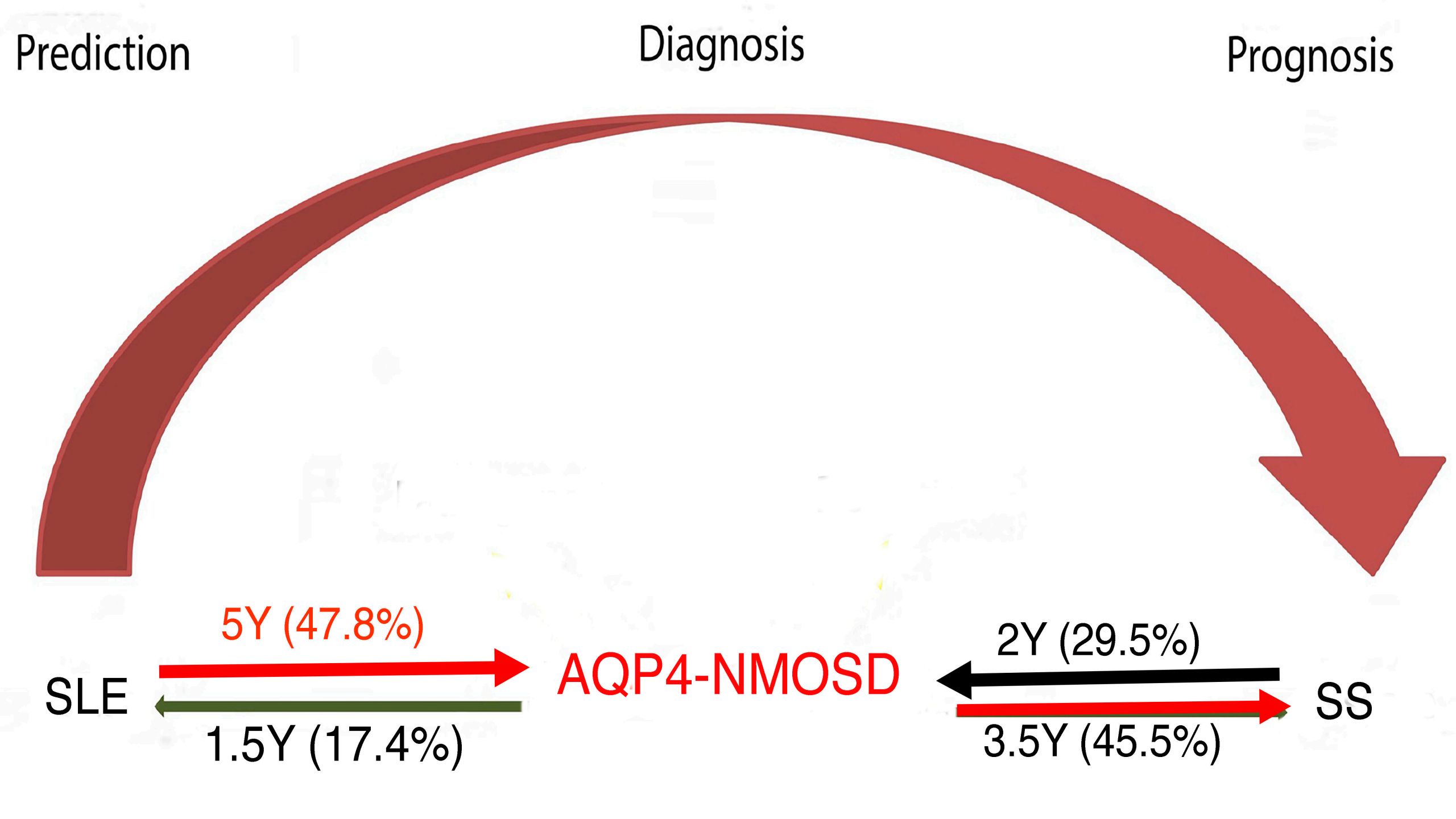
Characteristics	SS and NMOSD	SLE and NMOSD	MG and NMOSD
Female (%)	87.9%	94.7%	93.75%
AQP4-IgG+	83.7%	81.8%	81.3%
After NMOSD diagnosis (%)	57.4%	26%	18.8%
LETM, TM ON	50% 30.6	42.1% 21.1%	39.58% 54.17%

Shahmohammadi et al. MSRD 2019

AQP4-IgG and MOG-IgG autoimmunity in a population-based cohort of patients with SLE

Patient characteristics	NPSLE, *n* = 45	ANA, *n* (%)	dsDNA, *n* (%)	Anti-Ro, *n* (%)	Anti-rib., *n* (%)	Anti-La, *n* (%)	APA, *n* (%)	ACA, *n* (%)	b-2GA, *n* (%)	AQP4-IgG, *n* (%)	MOG-IgG, *n* (%)
CNS											
Cerebrovascular disease	16	7 (44%)	6 (38%)	0 (0%)	1 (6%)	5 (31%)	10 (63%)	7 (44%)	9 (56%)	0 (0%)	0 (0%)
Demyelinating syndrome	2	1 (50%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Migraine	3	1 (25%)	0 (0%)	0 (0%)	1 (25%)	1 (25%)	1 (25%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)
Myelopathy	2	1 (50%)	1 (50%)	1(50%)	0 (0%)	1 (50%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)
Seizure disorders	6	3 (50%)	3 (50%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)	2 (33%)	2 (33%)	0 (0%)	0 (0%)
Cognitive dysfunction	5	2 (40%)	2 (40%)	1 (20%)	1 (25%)	3 (60%) 3 (60%)	3 (60%)	3 (60%)	0 (0%)	0 (0%)	
Mood disorder	4	1 (25%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)
Psychosis	2	1 (50%)	2 (100%)	0 (0%)	1 (25%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
PNS											
Mononeuropathy	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Myasthenia gravis	2	2 (100%)	1(50%)	1(50%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	1(50%)	0 (0%)
Cranial neuropathy	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)
Polyneuropathy	8	4 (50%)	3 (38%)	3 (38%)	1 (13%)	3 (38%)	4 (50%)	3 (38%)	3 (38%)	0 (0%)	0 (0%)
Small fiber neuropathy	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (25%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)
Plexopathy	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)

Asgari et al. Neurology 2014 & Mult Scler. 2018

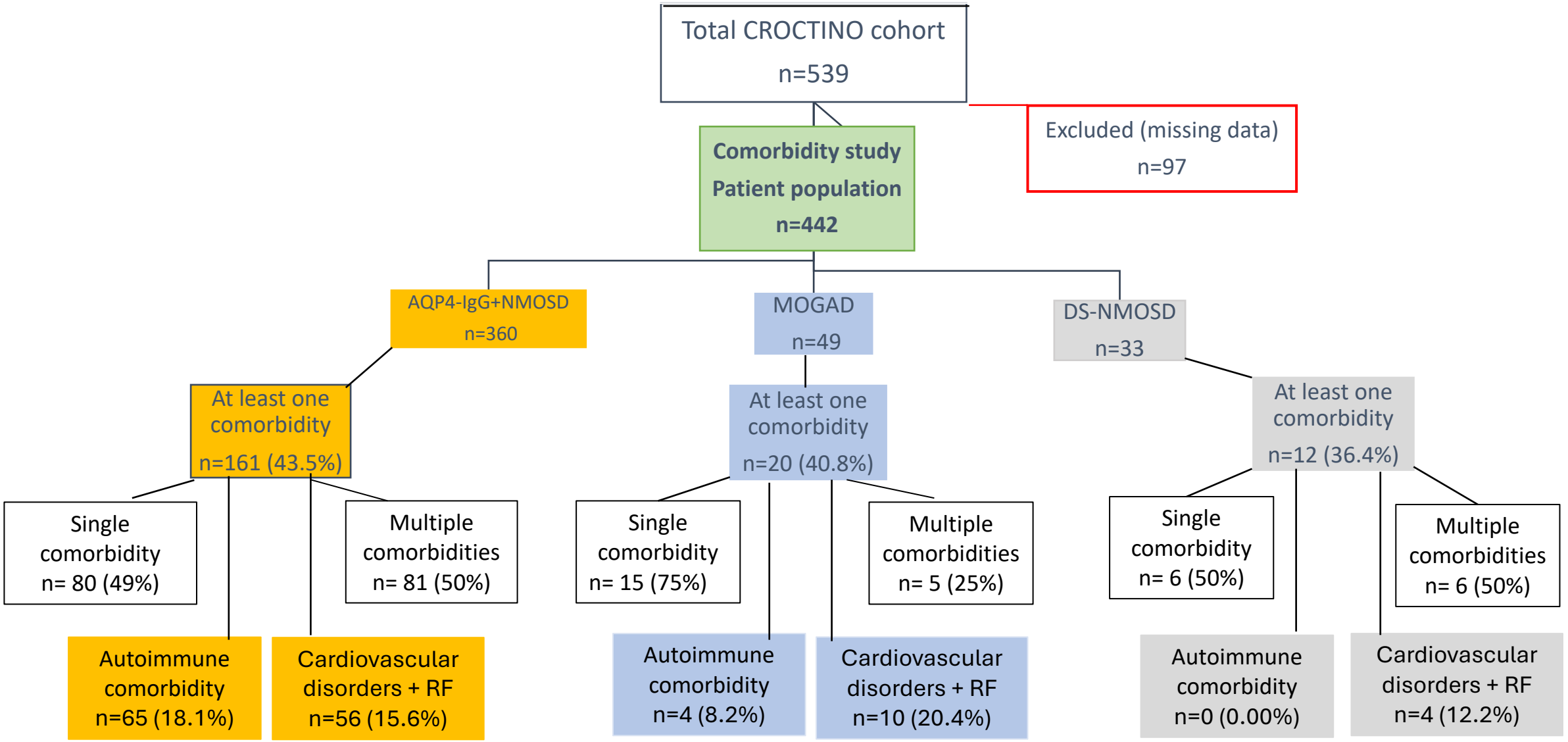

Prediction
Diagnosis
Prognosis
5Y (47.8%)
SLE
1.5Y (17.4%)
AQP4-NMOSD
2Y (29.5%)
3.5Y (45.5%)
SS

MOGAD and autoimmune comorbidity

- In a large cohort of MOGAD and AQP4-IgG + NMOSD concomitant autoimmunity was less common in MOGAD compared to AQP4-IgG + NMOSD
- ANA was positive in 43% of AQP4- IgG+ NMOSD but only 7% of MOGAD patients
- Concomitant autoimmune disorders were observed in 45% of AQP4-IgG + NMOSD, and 11% of MOGAD patients
- In a systematic review: The most common autoimmune disease with MOGAD was anti-NMDAR-EN, followed by autoimmune thyroid disorders, and the most common autoantibody was ANA, followed by AQP4-IgG (double-positive MOG-IgG and AQP4-IgG (70 cases).

Kunchok et al. *Mult Scler* 2021; Sato et al. *Neurology* 2014; Kitley et al. *JAMA Neurol* 2014; Molazadeh N et al. Mult Scler J Exp Transl Clin.. 2022

CROCTINO dataset



Samadzadeh et al. et al. 2024 in preparation

Influence of autoimmune comorbidity on outcomes

- Delay between onset of disease and diagnosis, e.g. spine MRI findings may be similar in both NMOSD and SLE
- Higher disease activity incl. increased no. of relapses in patients with AC, e.g. highly active NMOSD patients were 5 times more likely to have autoimmune thyroid disease than controls
- Multifocal CNS lesions as initial symptom was more common in the comorbidity group than in the non-comorbidity group
- Therapeutic challenge, e.g. less responsiveness to treatment
- Increased disability
- Mortality

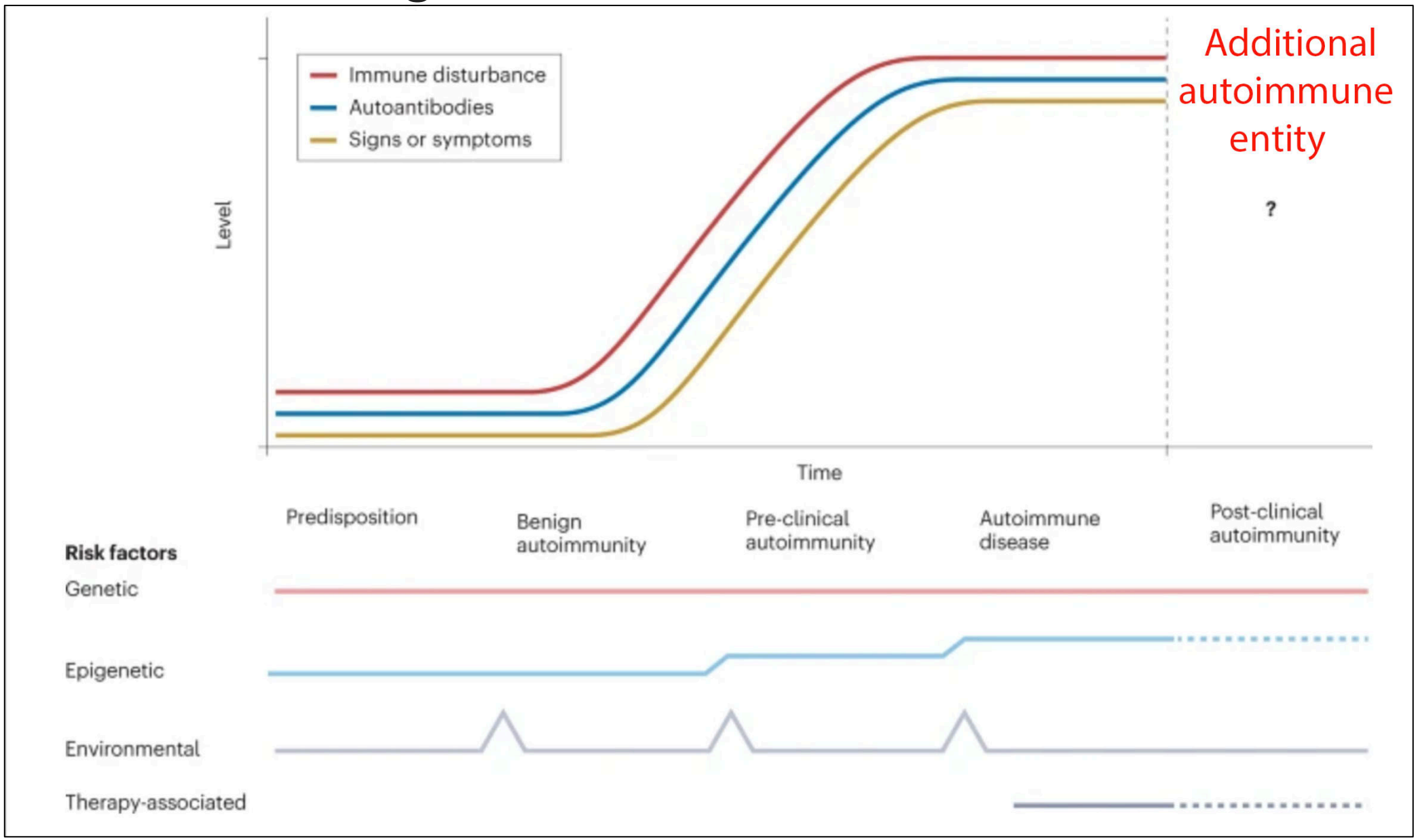
Cai L et al. J Clin Neurosci. 2023; Beekman et al. Neurol Neuroimmunol Neuroinflamm 2019; Barzegar et al.MSRD 2018; Ajmera et al. J Neurol Sci 2017

Index disease may result from treatment

- A female patient was diagnosed with NMOSD at the age of 16 years
- 6 years after the onset of NMOSD, following meningococcal vaccination, the immunosuppressive treatment was switched to monotherapy with iv infusions of eculizumab
- Eculizumab stabilized the NMOSD disease.
- She developed Type B insulin resistance (TBIR) 8 months after initiation of therapy
- TBIR is a rare autoimmune condition often associated with SLE.
- Recently, increased insulin resistance (IR) in patients with NMOSD has been suggested

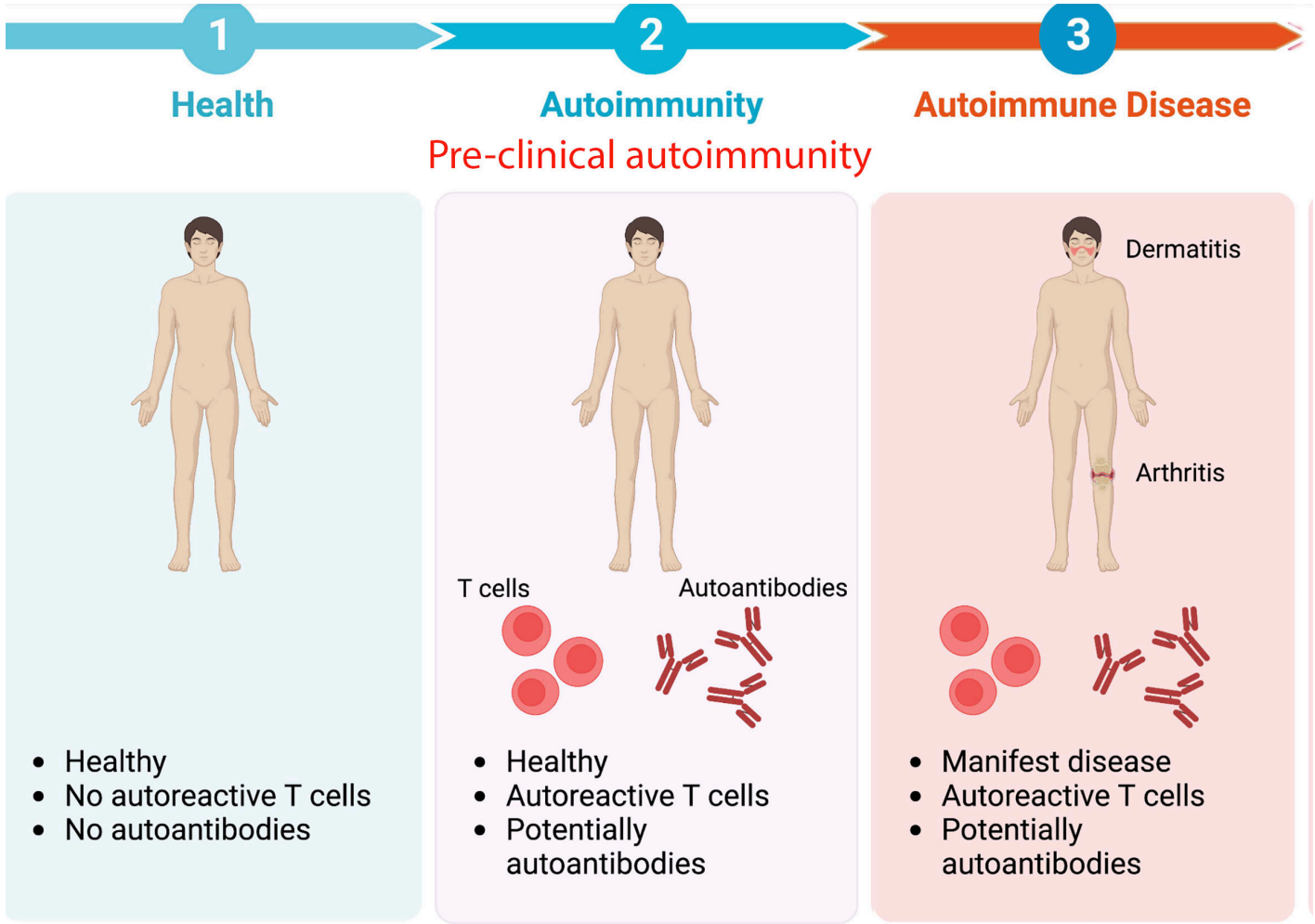
Doubrovinskaja et al. J Neurol. 2024

Pathogenesis of autoimmune disease



Pisetsky Nature 2023

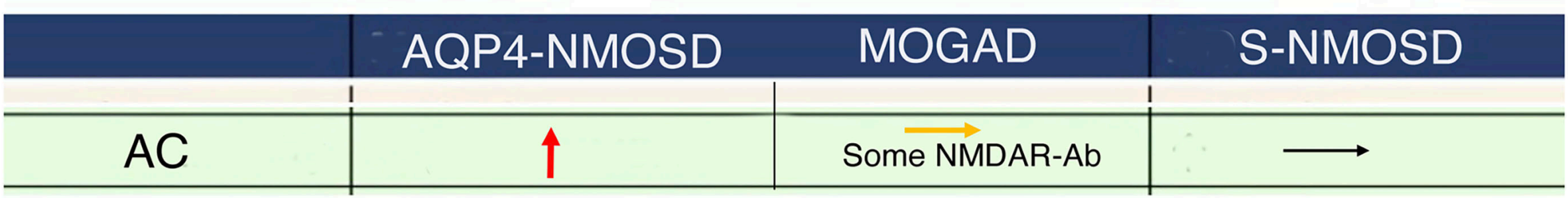
Transitional stages in the pathogenesis of autoimmune diseases



Hundt et al. Front Immunol. 2023

- General susceptibility to antibody-mediated autoimmune disease in AQP4-IgG+NMOSD, perhaps as a result of genetic abnormalities that regulate B cells
- Antibodies are valuable markers for diagnosis, classification and disease activity: ANA, anti-SSA, anti-SSB, AChR, TPO, TG2-IgA, insulin-Ab.

Unlike AQP4-IgG+NMOSD, S/DS-NMOSD lacks clustering of autoimmune diseases
Also, autoimmune diseases are less common in MOGAD



Conclusions



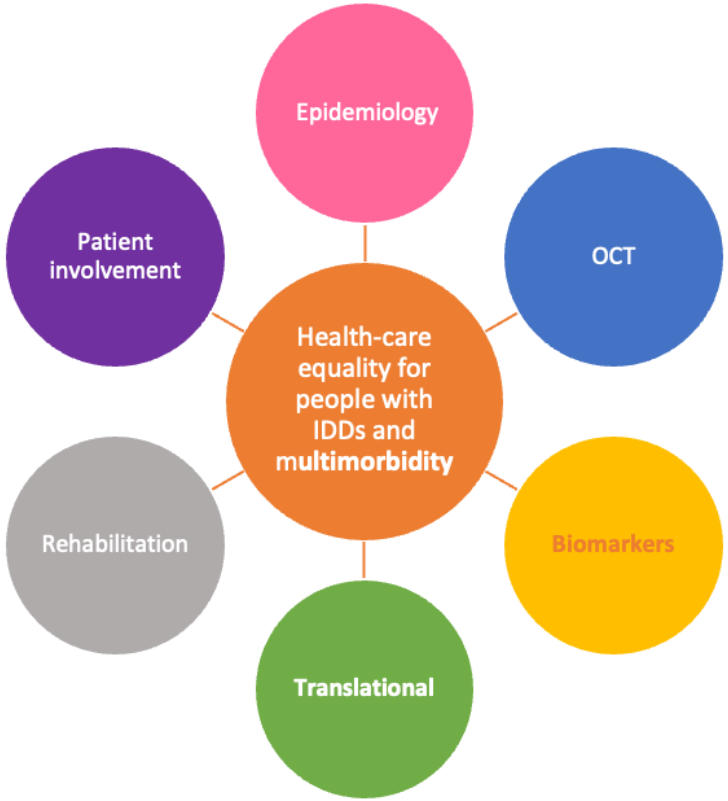
- High occurrence of autoimmune comorbidity indicate screening as routine part of AQP4-IgG+NMOSD care
- Monitoring autoantibody levels in at-risk populations enable early detection and the initiation of therapy to prevent tissue damage
- To simplify treatment and avoid disease exacerbation, knowledge of the beneficial and adverse effects of treatments in other autoimmune disorders is critical.
- An understanding of how autoimmune comorbidities interact with the diagnosis, treatment and clinical outcome needs further exploration

IMAGINE

Impact of Comorbidity on IDDs: Mechanisms and Therapeutic options (IMAGINE)

Collaboration

Relevance



Innovative Research

Synergy

SDU



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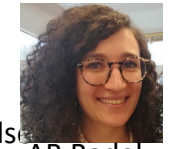

A Voss


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R.


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MW Niels


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K. Soelberg


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MN. Olesen

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Thank you for your attention



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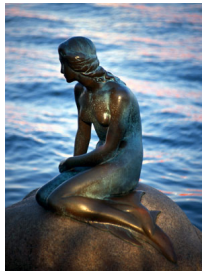

Epidemiological, clinical and immunological aspects of NMOSD and MOGAD



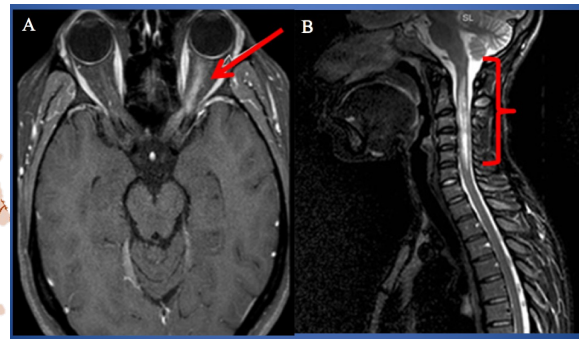


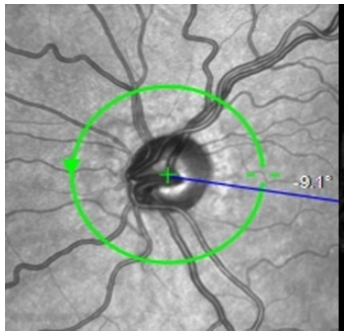




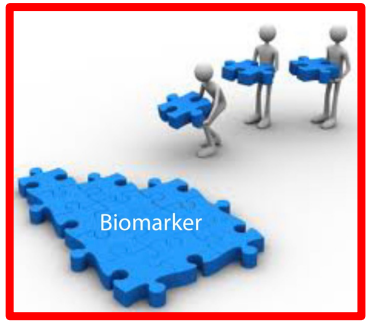



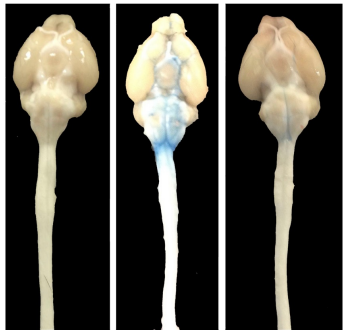












Pearls in Pathogenesis: NMO, MOGAD & SND



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Larsen-Chugg Distinguished Chair in Neurology,
Co-Director, Brigham Multiple Sclerosis Center, Brigham and Women's Hospital
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Director, Mass General Brigham Pediatric MS Center, Massachusetts General Hospital



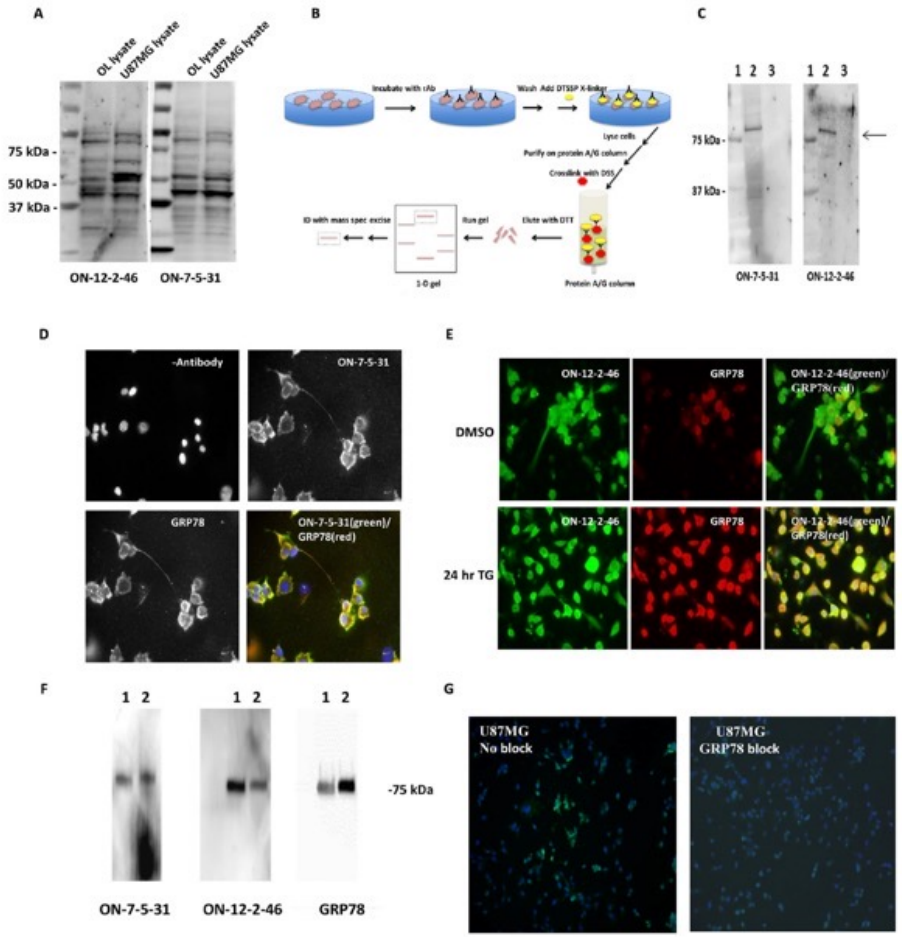
NMO, MOGAD, Seronegative NMO (SND)

- Pathology
- Target tissue/antigen
- Immunology
- Biomarkers
- Therapeutic targets
- Tolerance

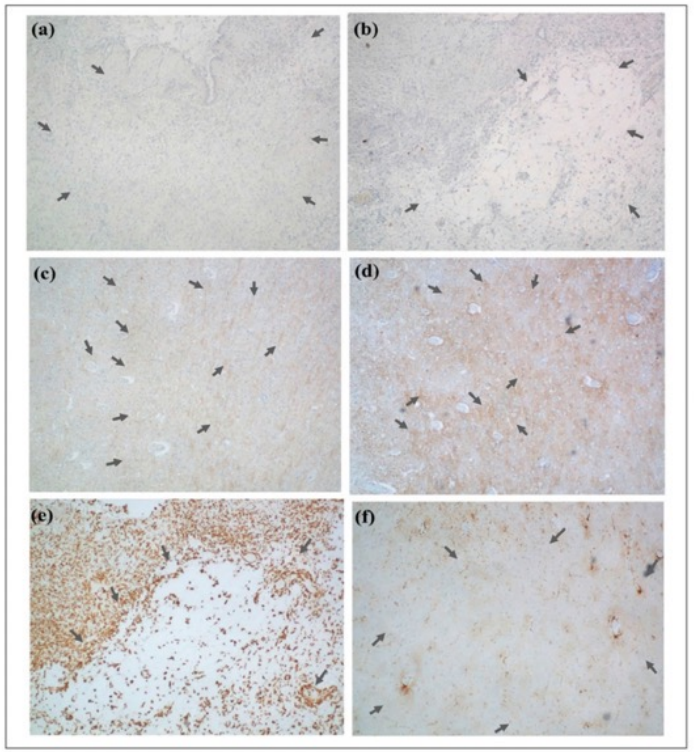
NMO
(AQP4+ NMO)

NMO – Pathology

Endothelial cell cell dysfunction – allow BBB breakdown?



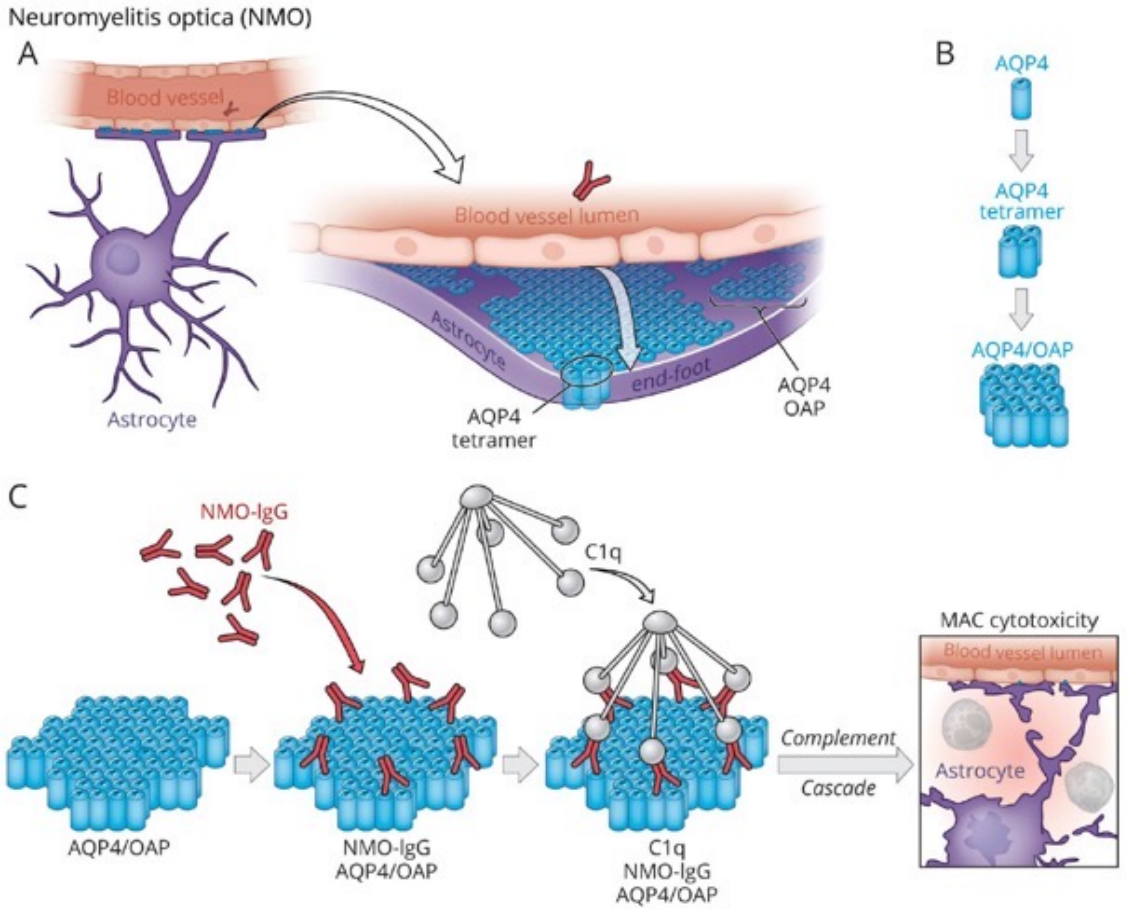
GRP78 Ab - Shimizu, Sci Translational Medicine, 2017



Microfibril associated protein 4 (MFAP) 4 co-localizes with AQP4 loss
Samadzadeh, MSJ 2023

NMO – Immunology

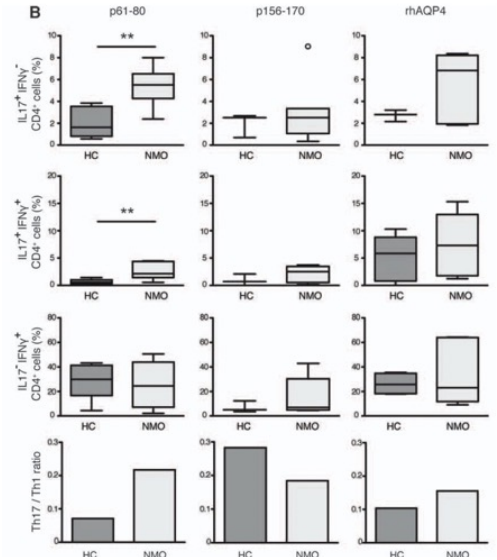
Antibodies target AQP4 OAP with C' activation

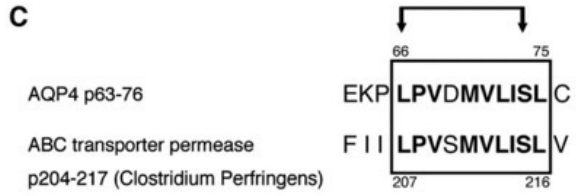


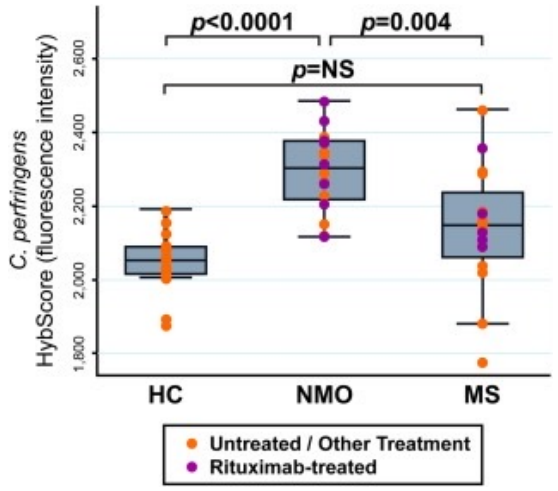
Moseley et al, N2, 2024

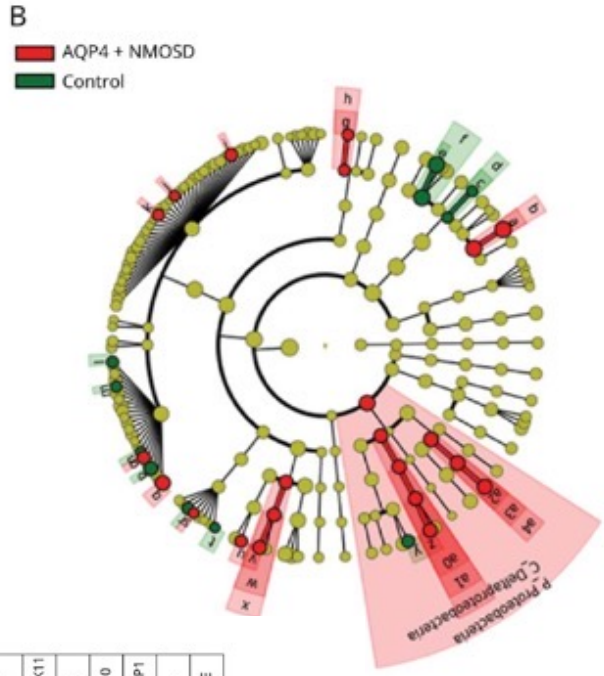
NMO – Immunology

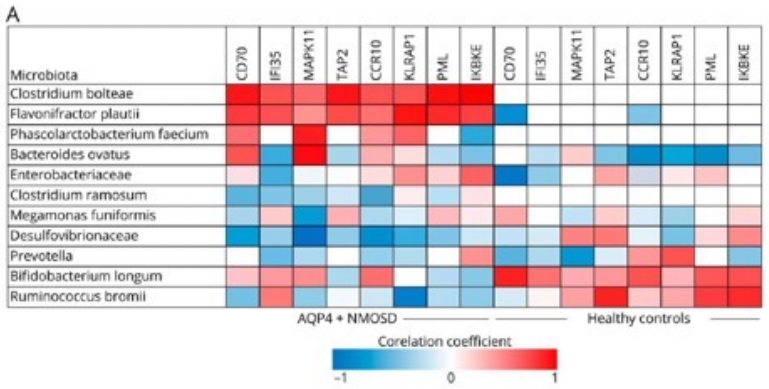
Th17 cells target AQP4 peptides with Clostridia molecular mimicry which is increased in the gut microbiome in NMO











Varrin-Doyer, Annals of Neurology, 2012

Cree, Annals of Neurology 2016

Pandit et al, N2, 2021

NMO - Biomarkers

Rodin and Chitnis, Frontiers in Neurology, 2024

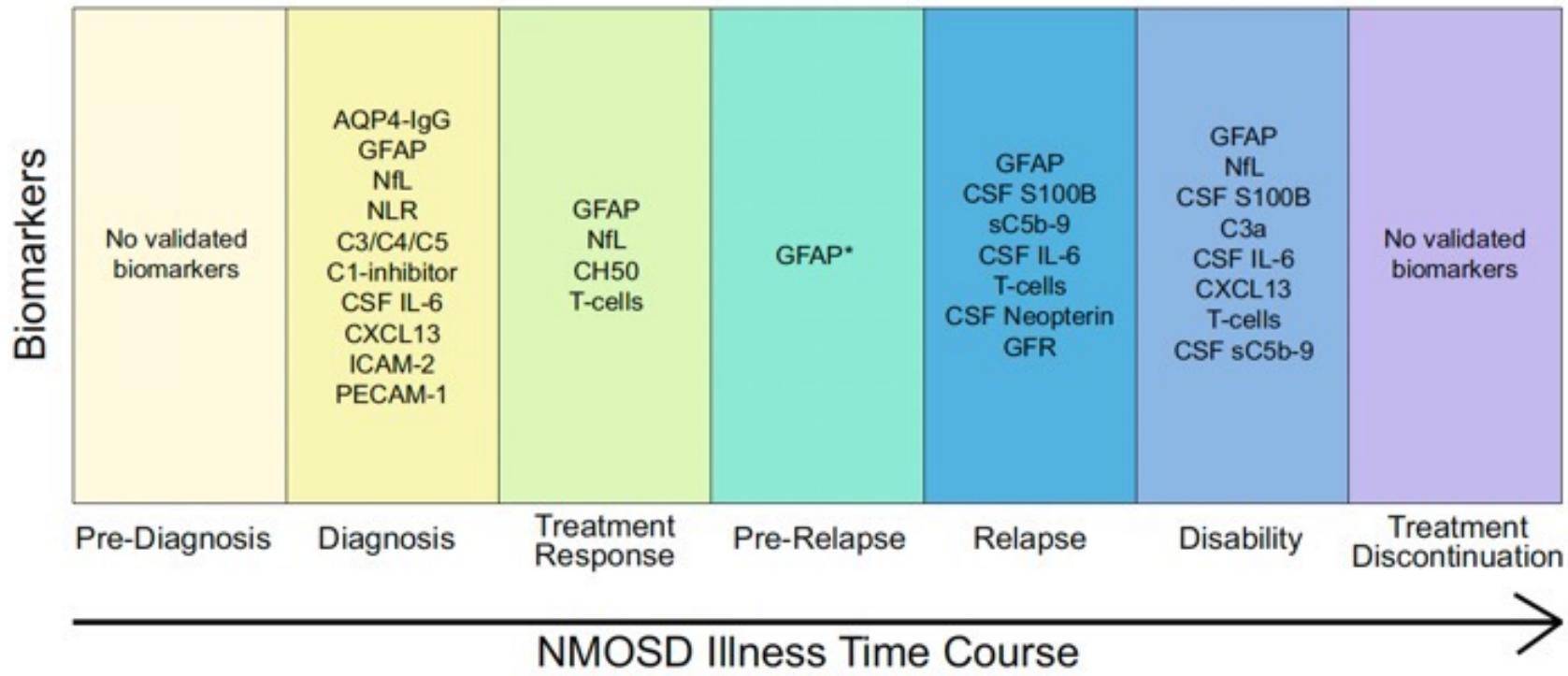
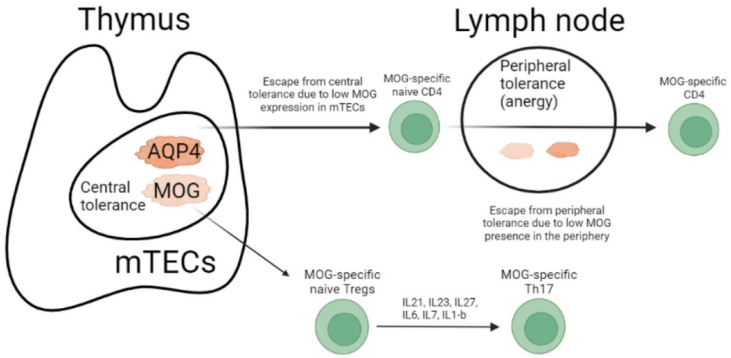
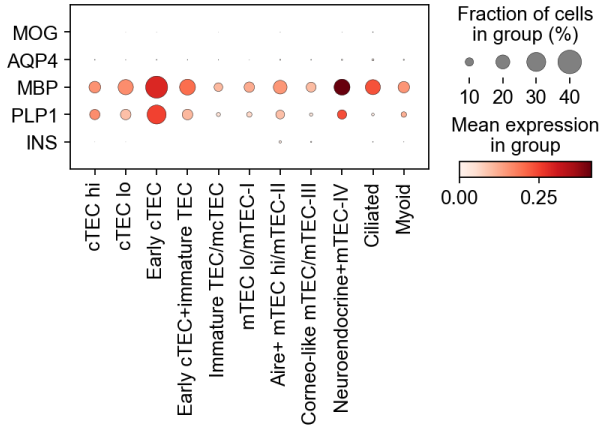


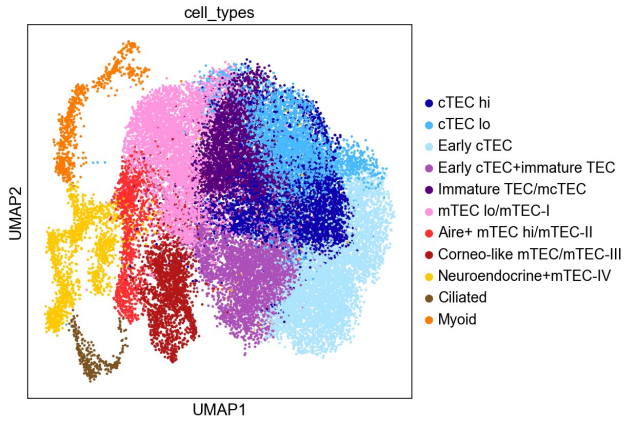
FIGURE 1
Summary of key NMOSD biomarkers and their clinical utility during various stages of disease. Except where indicated, all referenced biomarkers are from serum. *Relapse prediction for serum GFAP has only been shown within <1 week preceding relapse.

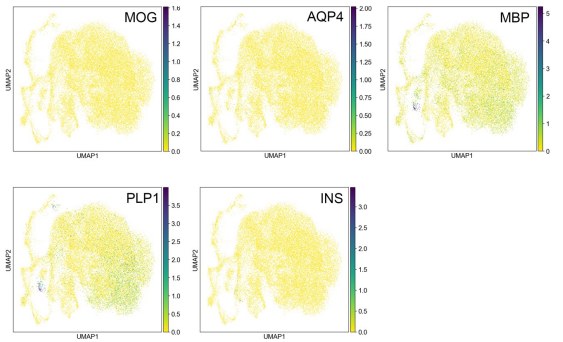
NMO – Tolerance

Reduced expression of MOG and AQP4 in the thymus may result in loss of central tolerance









Corbali, Parent, Chitnis, AAN 2024

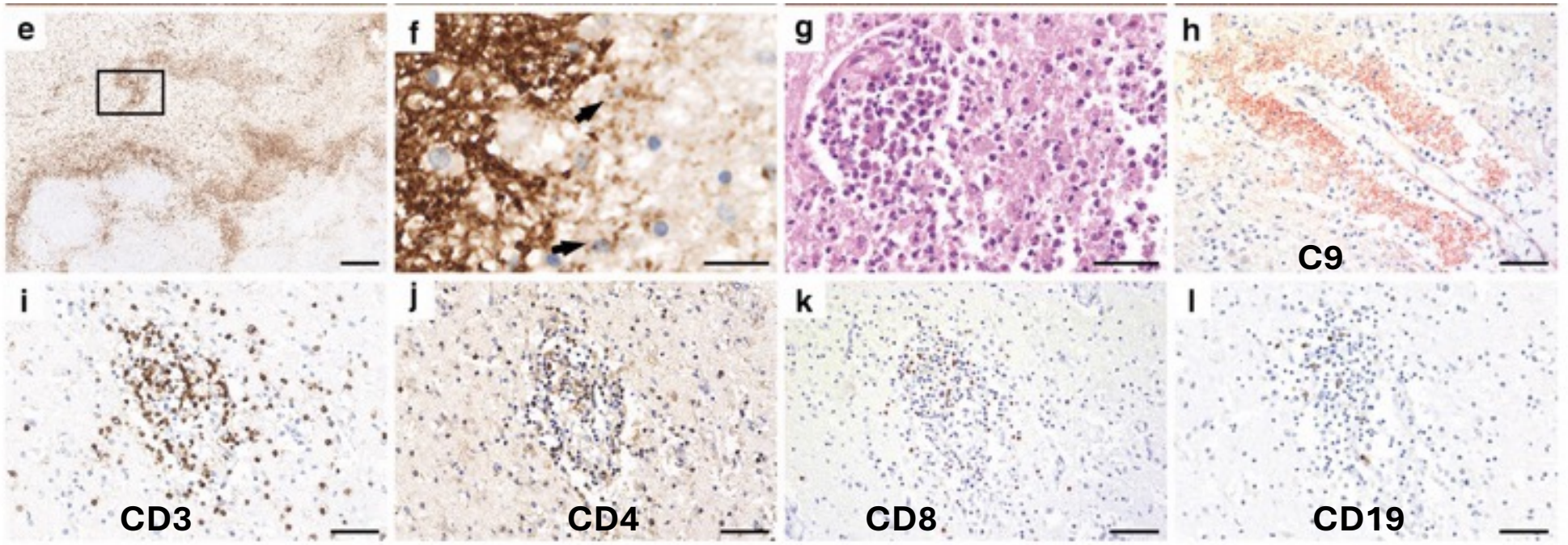
NMO - Advances and opportunities

- Complement – end organ
- B cells: CD19, CD20, CD27
- IL-6R inhibition
- Target antigen-specific T and B cells – TCR/BCR?
- Prevent molecular mimicry?
- Boost peripheral tolerance/regulation?

MOGAD

MOGAD – Pathology

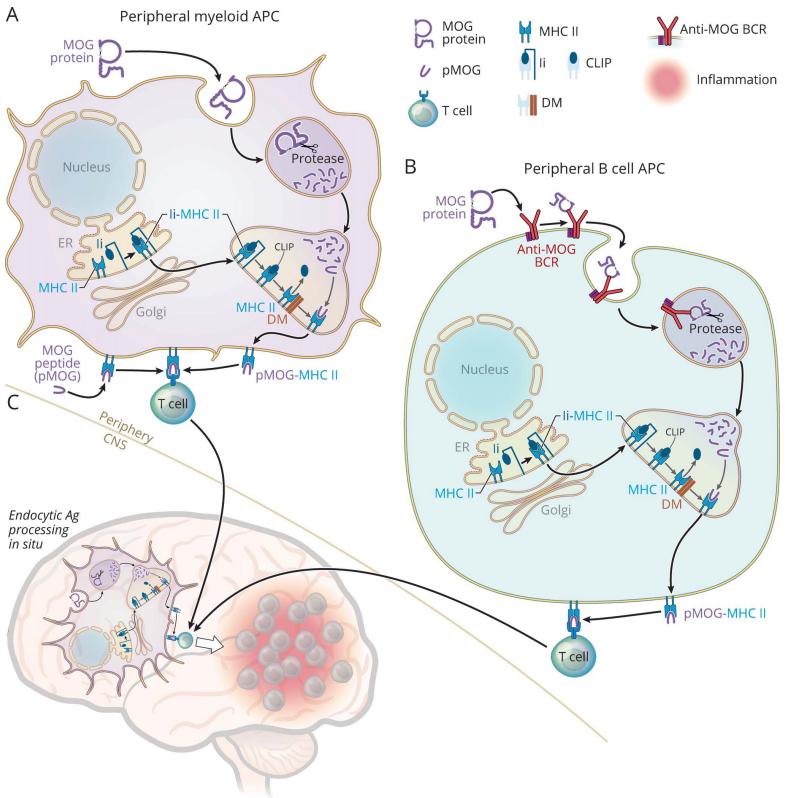
Predominance of CD4 T cells; limited complement activation



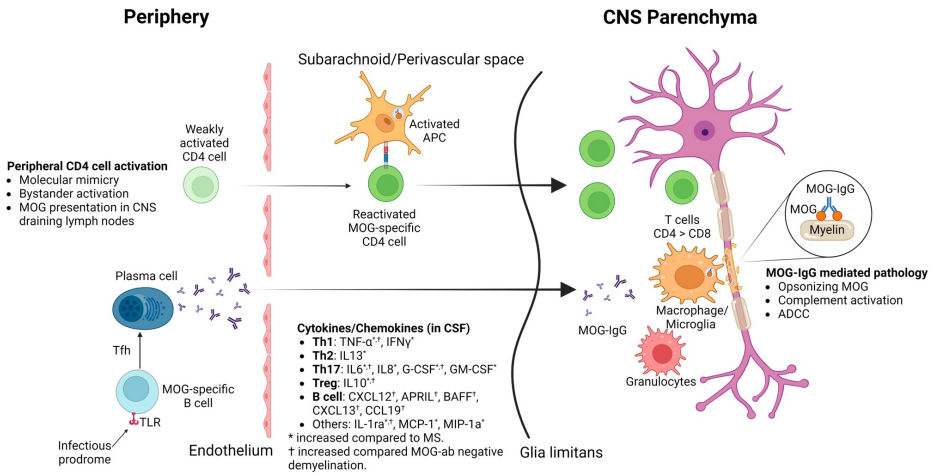
Hoftberger, Acta Neuropathologica, 2020

MOGAD – Immunology

Role of B cells, antibody and APC presentation of processed MOG to T cells



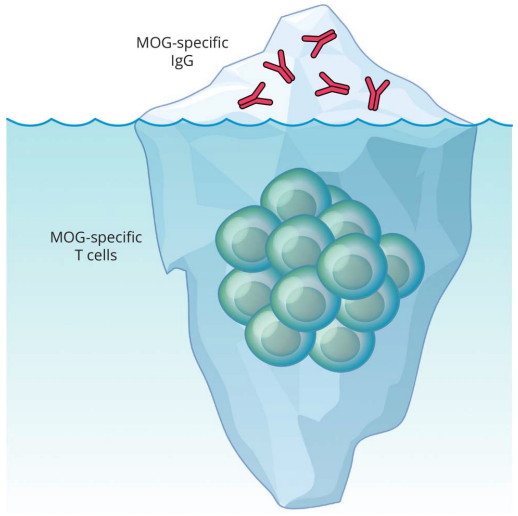
Moseley et al, N2, 2024



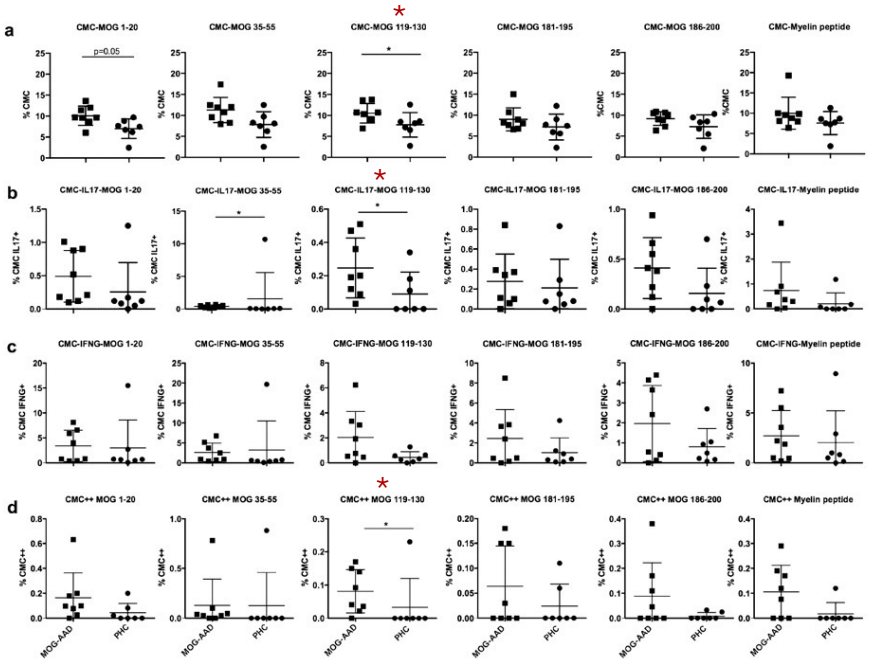
Corbali and Chitnis, Frontiers of Neurology, 2023

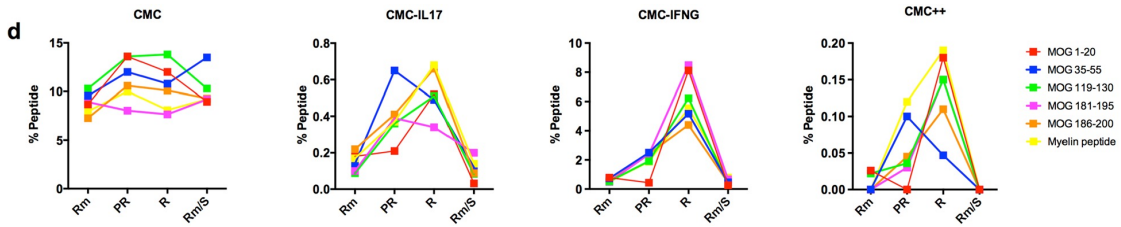
MOGAD Immunology

Increased MOG peptide-reactive central memory Th17 cells at relapse and vs. controls



Moseley et al, N2, 2024

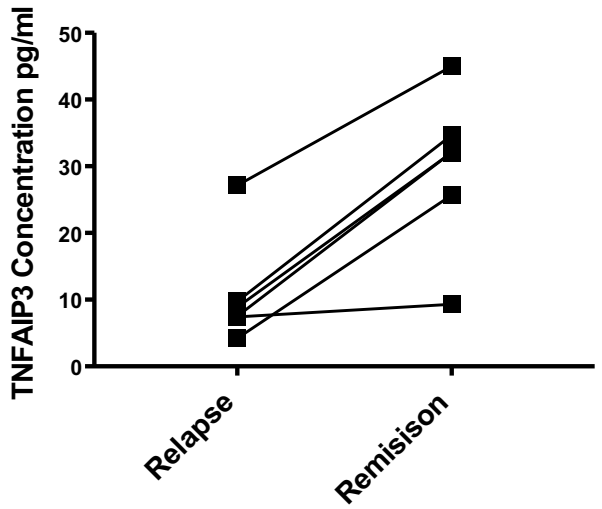




Saxena et al, Scientific Reports, 2020

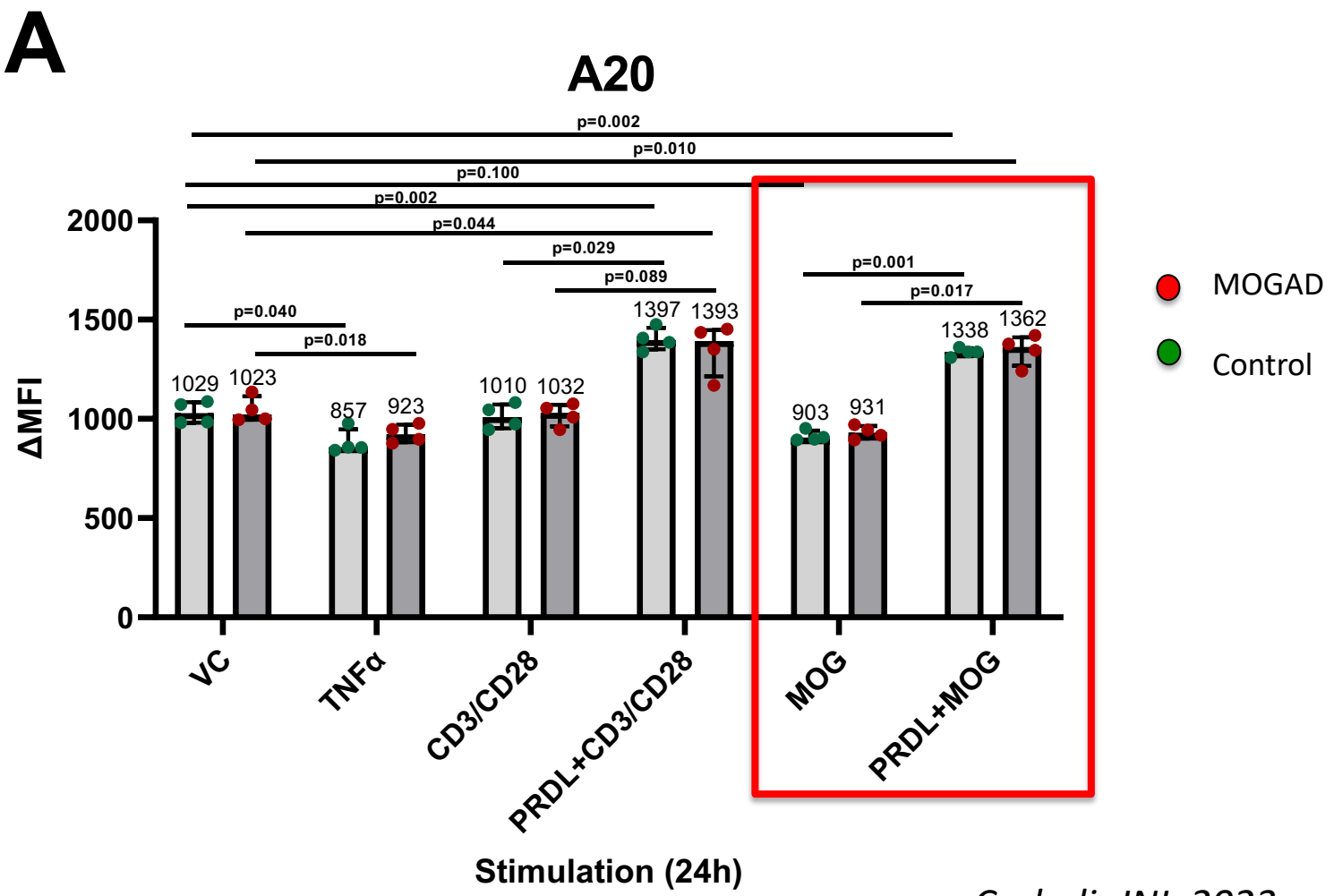
MOGAD Immunology

A20 (TNFAIP3) is decreased at relapse and increases in T cells with prednisolone treatment in vitro



(*P*=0.006)

Saxena, Scientific Reports, 2020



Corbali, JNI, 2023

MOGAD - Biomarkers

Corbali and Chitnis, Frontiers of Neurology, 2023

Potential biomarkers		MOGAD disease activity	Significance/implications	Therapeutic mechanism
MOG-IgG titer (9, 98, 139)	Serum	High titers required for diagnosis	Seronegative conversion indicates decreased relapse risk	FcRn blockers, IVIG, Plasmapheresis
NfL (140, 141)	Serum	Increased mostly in the first attack, then stay stable throughout the course	Significant axonal damage happens mostly in the first attack	
MBP (60)	CSF	Increased	Marker of demyelination	
GFAP (60, 141)	Serum	Stay stable during relapses	Spared astrocytes	
Tau (141)	Serum	Increased during relapses	Synthesized in axons and oligodendrocytes	
IL6 (72, 73, 113, 142)	CSF, serum	Increased in the CSF during relapses	Increased STAT3 activation could cause increased Th17	IL6 receptor blockers
			Impair BBB	
TNFα (42, 43, 143)	CSF	Increased in the CSF during relapses	May affect BBB through increased cell adhesion molecule expression (such as ICAM-1 and VCAM-1)	
A20/TNFAIP3 (123)	Serum	Decreased in the serum during relapses (individual level)	Increased NFKB activation	Steroids (increase)
	Intracellular		Steroid increase A20 expression in T cells	
N/L ratio blood (128)	Blood	Increased ratio during relapses	Could help differentiating relapse from pseudo-relapse	

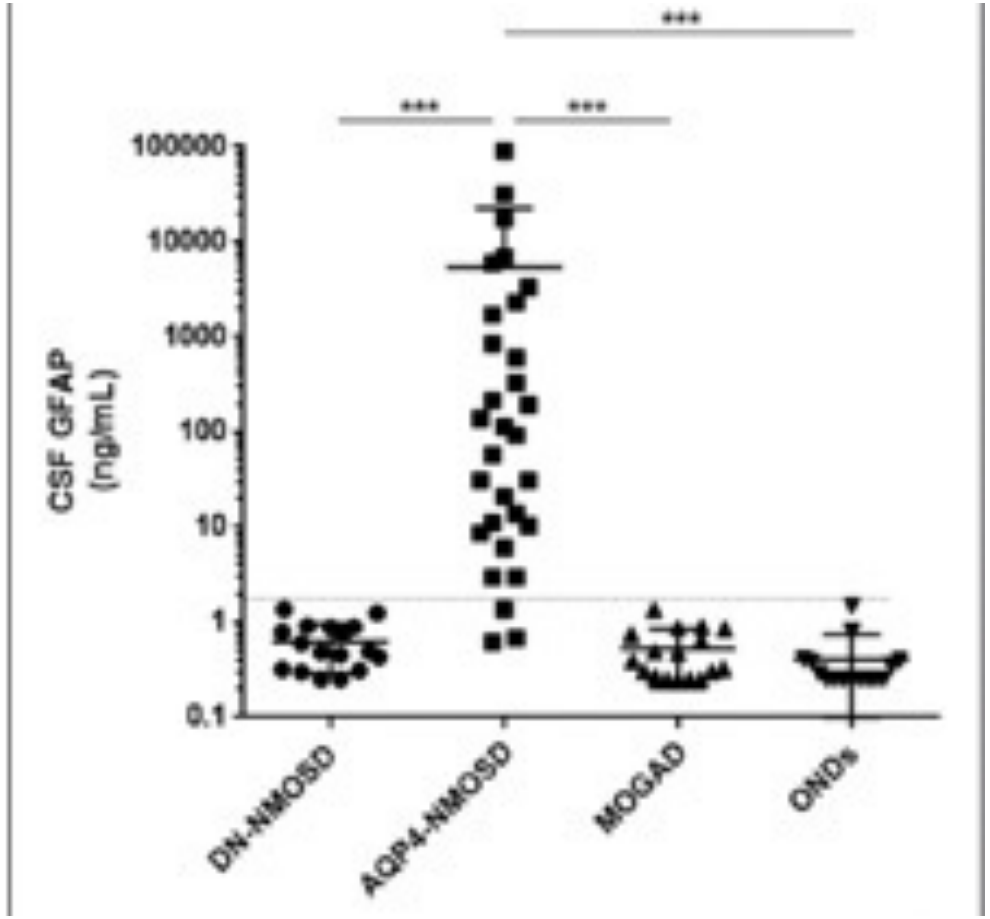
MOGAD – Advances and opportunities

- FcRN
- IL-6R inhibition
- Specific targeting of TCR/BCR?
- Antigen-specific tolerance?
- Deletion, regulation of autoreactive T cells?
- Biomarkers of relapse?

Seronegative NMOSD

Seronegative NMOSD – Biomarkers

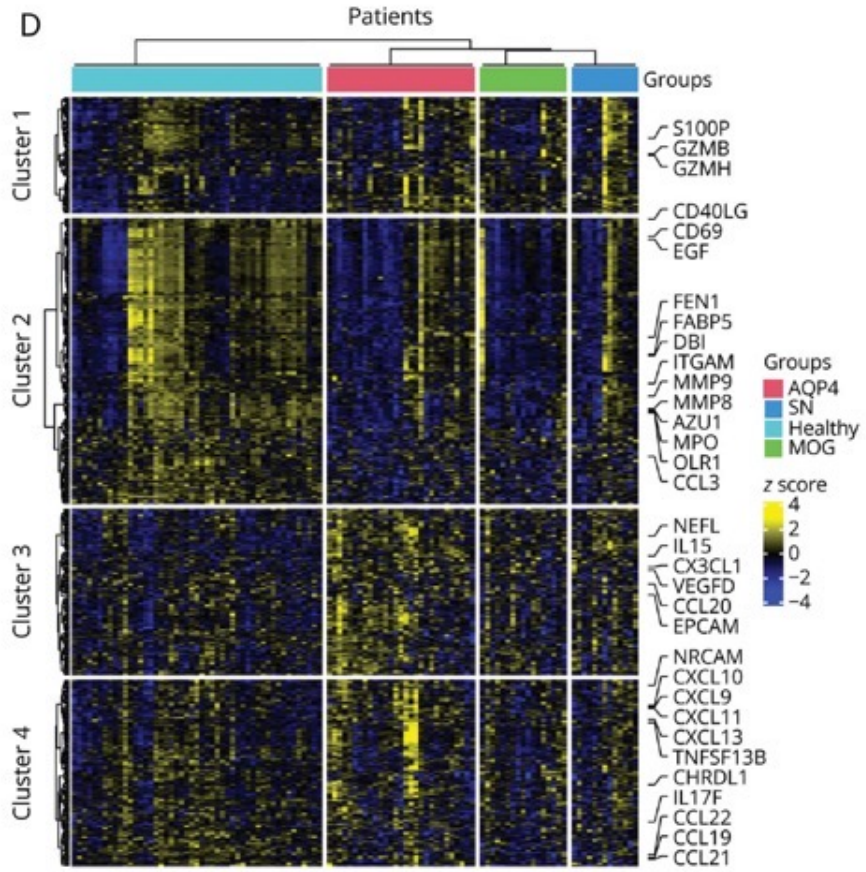
CSF GFAP levels are low in double seronegative NMOSD



Hyun, J. Neuroinflamm, 2022

Seronegative NMOSD - Biomarkers

WIF1 and DCTN6 are increased in serum of double seronegative NMOSD



- Wnt inhibitory factor 1 (WIF1) levels were significantly increased in SN-NMOSD compared with AQP4-NMOSD and MOGAD patients
- Dynactin-6 (DCTN6) levels were increased in SN-NMOSD compared with AQP4-NMOSD only

Gawde, N2, 2024

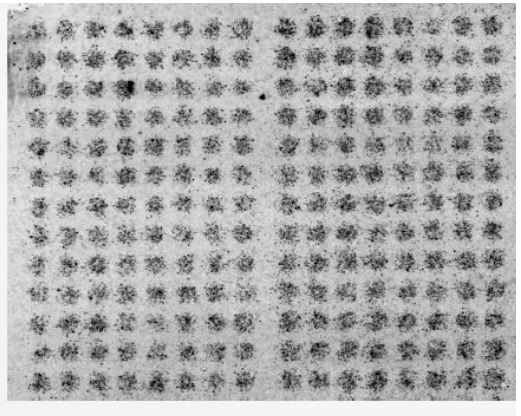
Seronegative NMOSD – advances and opportunities

- Improved definition of SND
- Biomarker studies informing pathogenesis – diagnosis by elimination?
- Definitive biomarkers?
- ->Exploration of pathogenesis and potential therapeutic targets

THANK YOU

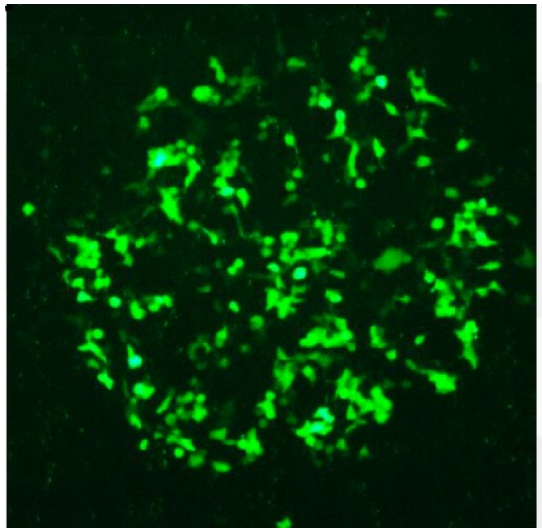
GUTHY JACKSON®
Chartitible Foundation

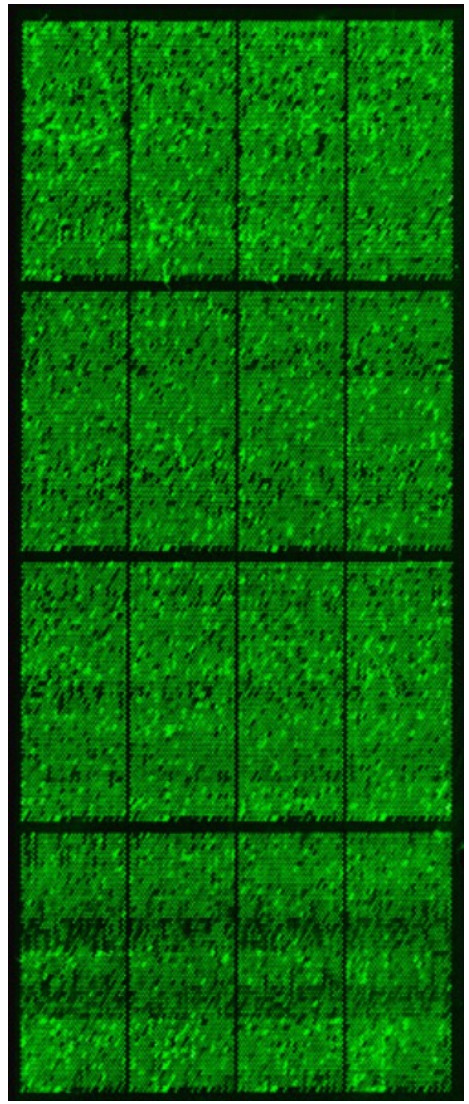
Updates on Assay Platforms for Serodiagnosis in NMOSD: Current Needs

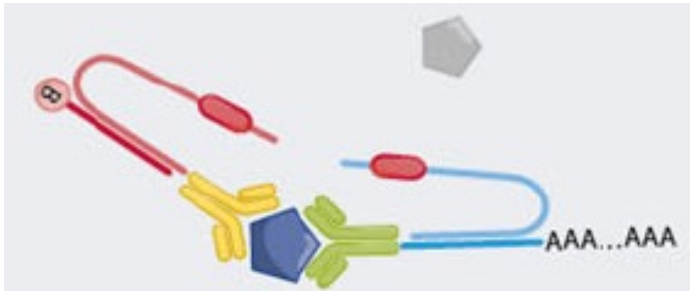


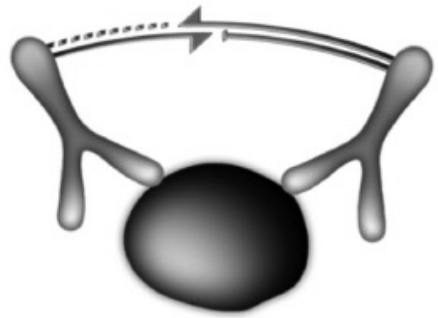
3rd August 2024







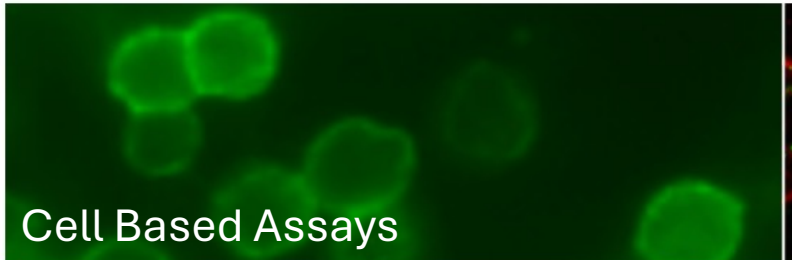


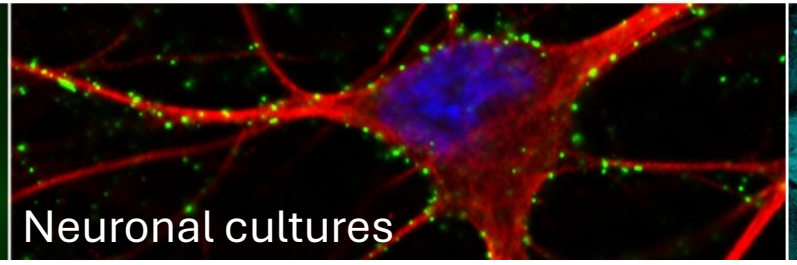


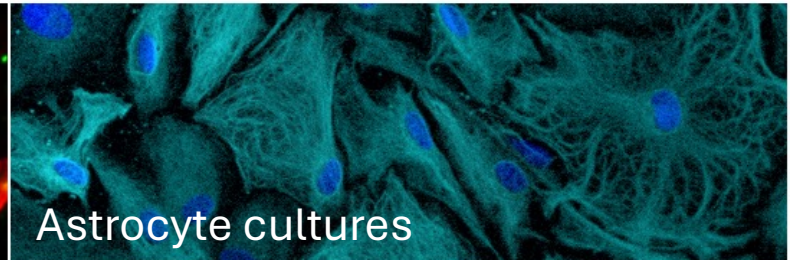
Patrick Waters PhD FIBMS FRCPath
Associate Professor, Co-Director Oxford Autoimmune Neurology Diagnostic Laboratory
University of Oxford

Disclosures

Patrick Waters is a named inventor on patents for antibody assays and has received royalties. He has received honoraria from Biogen Idec, Mereo Biopharma, Retrogenix, University of British Colombia, Euroimmun AG, UCB and Alexion; travel grants from the Guthy-Jackson Charitable Foundation; and research funding from Euroimmun AG. Oxford Autoimmune Neurology Diagnostic Laboratories performs live cell-based antibody assays.

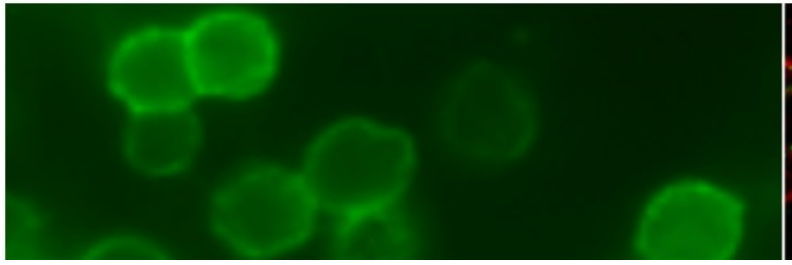
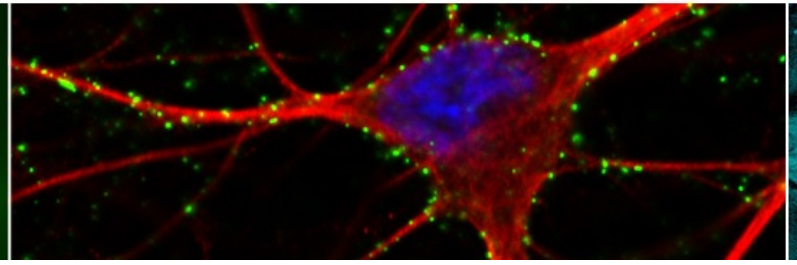
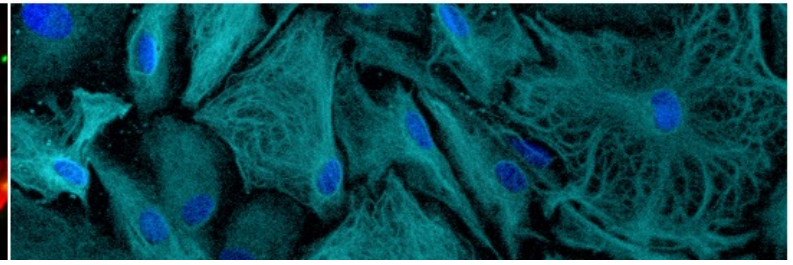






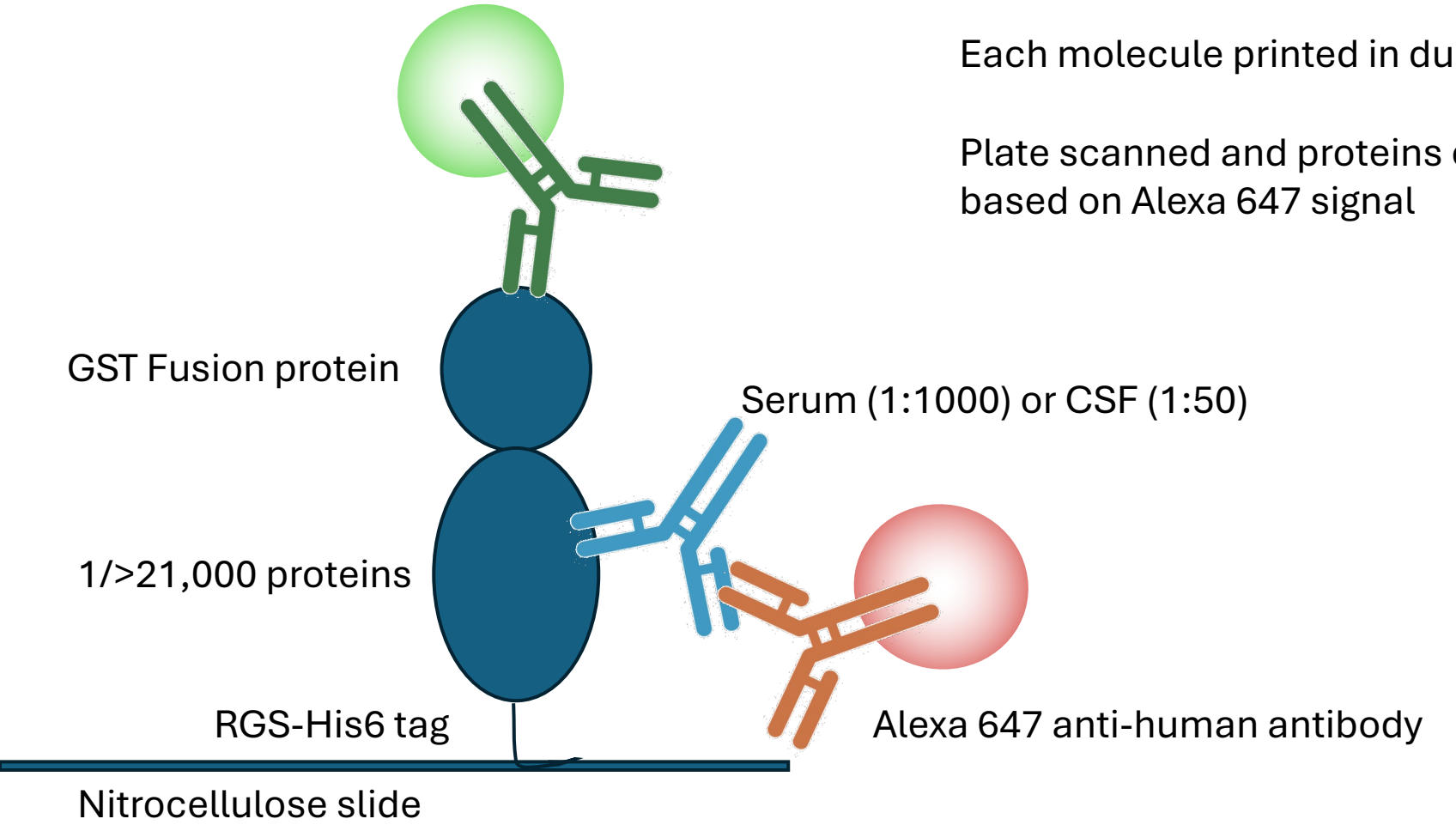
Current needs

1. Identify new targets in people with seronegative disease
2. Global access to affordable diagnostics for known targets
3. Rapid ‘bedside’ diagnostics
4. Confirmation of a relapse or disease activity in people with an established diagnosis

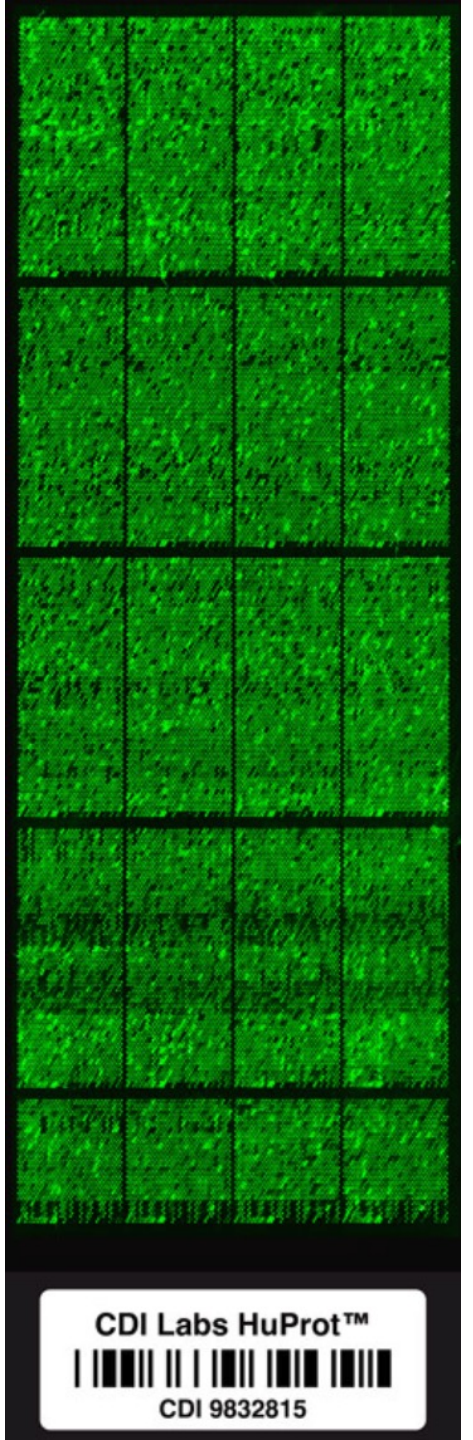
3D Structure is important for detection of pathogenic antibodies

HuProt v4.0 (CDI Laboratories, Puerto Rico – yeast expressed purified protein array)



Each molecule printed in duplicate

Plate scanned and proteins ordered based on Alexa 647 signal



McKeon... Mills N2 2023

3D Structure is important for detection of pathogenic antibodies

Sub-membrane targets

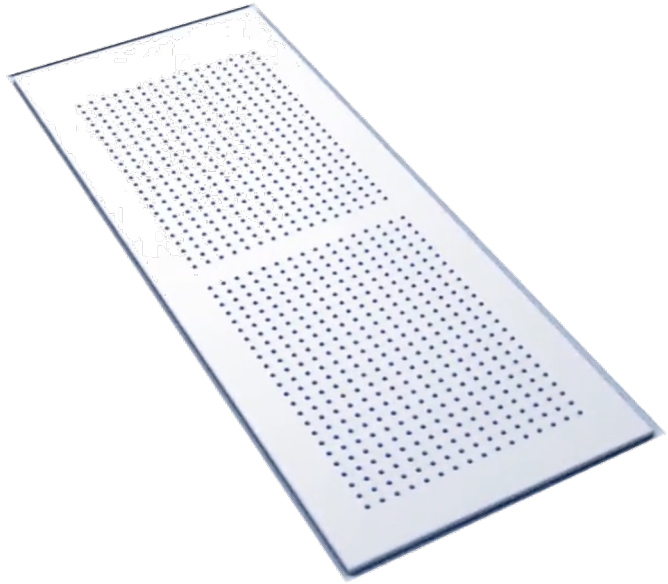
	Specimen tested	Overall protein rank
Known neural IgG		
AK5	Serum	2
AK5	CSF	26
Amphiphysin	Serum	1
ANNA-1	Serum	39
ANNA-1	CSF	2
ANNA-2	Serum	1
ANNA-3	Serum	2
CRMP5	Serum	3
CRMP5	CSF	3
GAD65	Serum	1
GAD65	CSF	1
GFAP	CSF	24
GRAF	CSF	10
KLHL11	Serum	362
KLHL11	CSF	305
Ma2	Serum	1
NCDN	Serum	1

Membrane targets

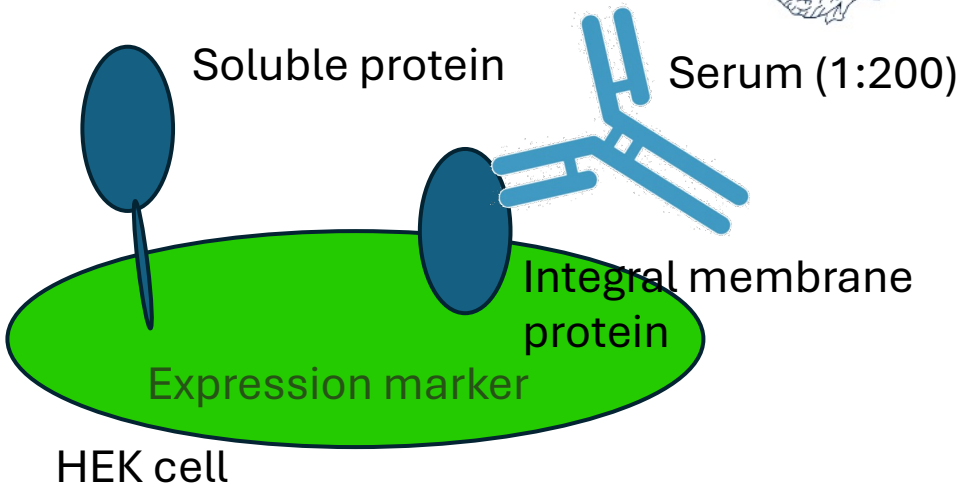
	Specimen tested	Overall protein rank
Known neural IgG		
AQP4	Serum	12,055
AQP4	CSF	18,010
$GABA_BR$ (Pt 1)	CSF	4896[b]
$GABA_BR$ (Pt 2)	CSF	Not detected[b]
GRAF	Serum	2324
IgLON5	Serum	17,010
IgLON5	CSF	20,899
LGI1	Serum	12,130
LGI1	CSF	21,661
MOG	Serum	878
NMDA-R	CSF	16,818
Patient IgG		
Neurexin3α (patient 1)	Serum	660

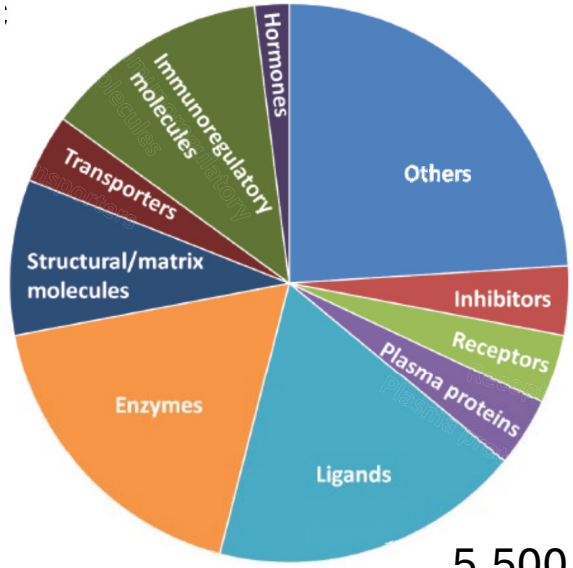
McKeon... Mills N2 2023

Retrogenix® Cell Microarray Technology (Charles River Laboratories)

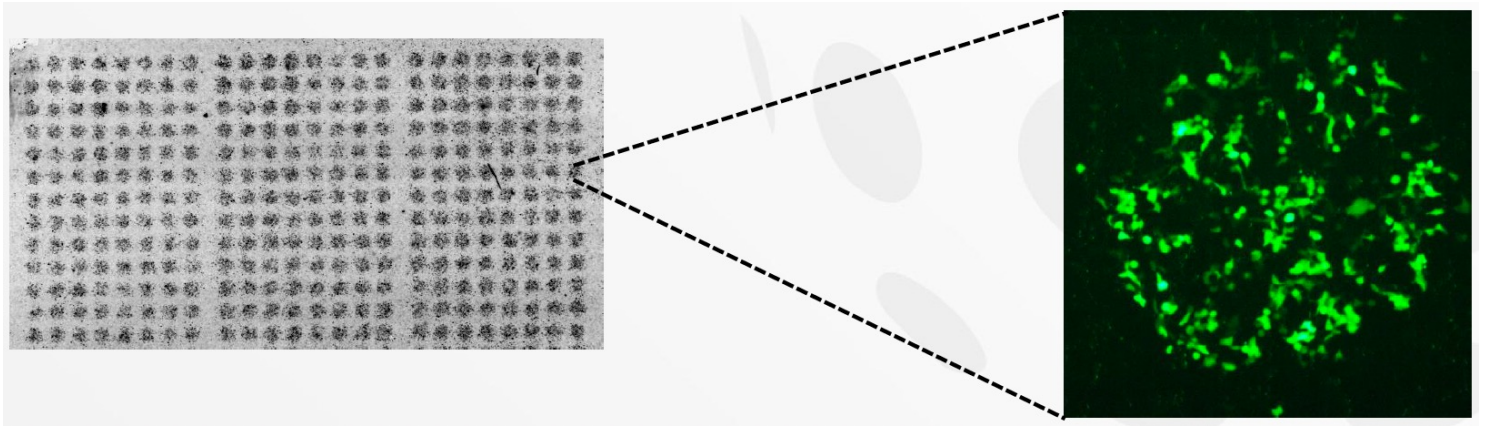








5,500 cDNA in 2020
>6,500 on CR website

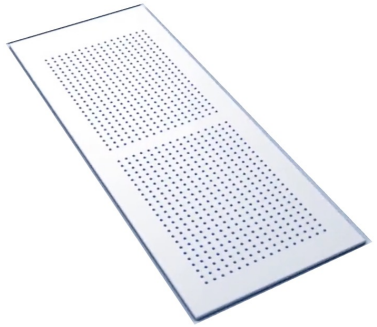


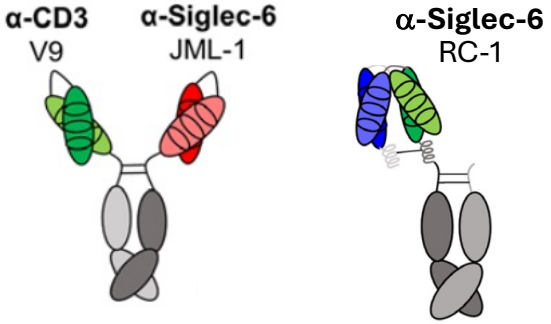
Freeth et al SLAS 2020
https://www.criver.com/products-services/discovery-services/screening-and-profiling-assays/retrogenix-cell-microarray-technology?region=3696

Retrogenix® Cell Microarray Technology (Charles River Laboratories)

Cancer Target[1-4]

Antibodies produced post alloHSCT a patient with CLL with a good response bound siglec-6

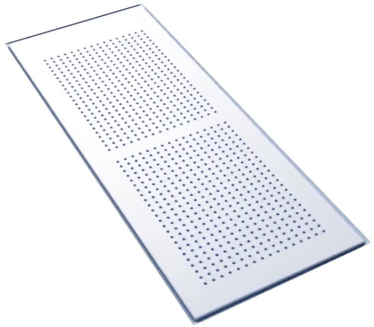




Off-Target effects of mAb[5]

Camrelizumab an anti-PD1 mAb - >80% treated patients developed capillary hemangioma

Camrelizumab also bound and stimulated VEGF2 Receptor which leads to capillary blood vessel proliferation



1. Chang et al. Cancer Immunology Research 2018
2. Cyr et al. J. Immunother Cancer 2022
3. Kovalovsky D et al Leukemia 2021
4. Jetani et al Blood 2021
5. Finlay et al mAbs 2018

Global access to affordable diagnostics against known targets
Rapid diagnostics

Diagnostic Fellowships

THE Sumaira FOUNDATION
ILLUMINATING THE DARKNESS OF NMOSD AND MOGAD

Africa Oxford Initiative

Sri Lanka

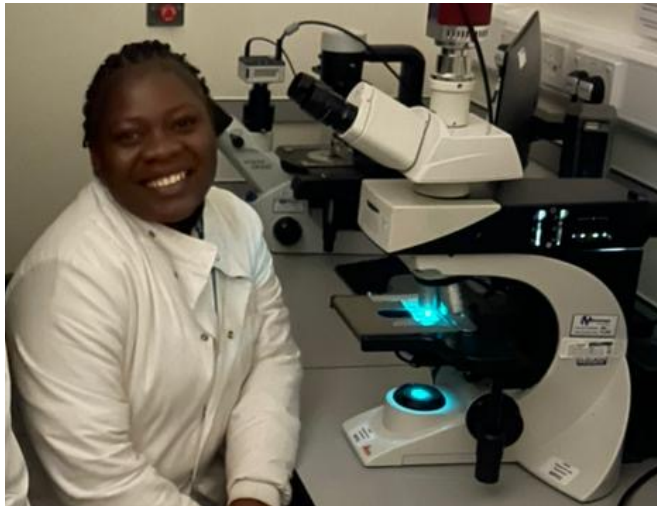




Mr. Wasantha Pushpakumara

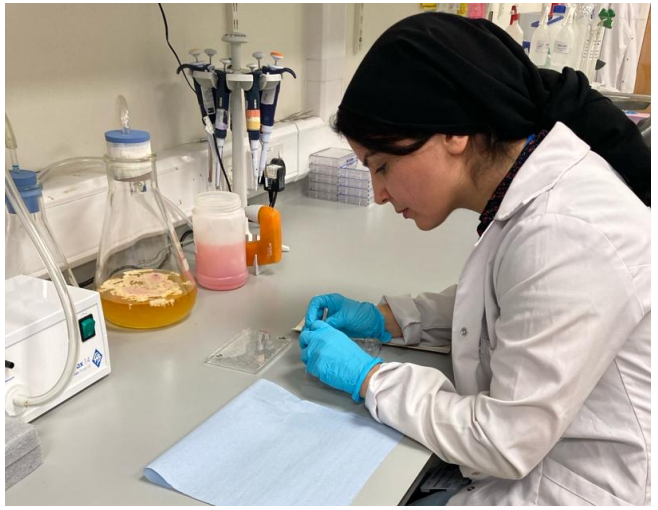
Dr. Danushka Dasanayake

Zambia



Ms. Caroline Kabwe

Iran



Dr. Zhila Maghbooli

Rapid idot

1. M23-AQP4 transduced HEK cell extracted arrays (differential centrifugation and native HPLC)
2. Control HEK cell extract
3. 25 ul serum diluted 1:10 with PBS
4. Sheep anti-human IgG – AP (alkaline phosphatase)
5. Substrate: BCIP/NBT

1.
2.



Yu et al JAMA Neurol 2023

Rapid idot method – Block is key to success

1. M23-AQP4 transduced HEK cells extract
2. Control HEK cell extract

Preconditioning of serum	**AQP4-IgG Negative**
None	
Liver powder pre-absorption	
1%BSA pre-absorption	
Blocking solution pre-absorption	

Yu et al JAMA Neurol 2023

Rapid idot method – Block is key to success

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Yu et al JAMA Neurol 2023

Rapid idot method – Block is key to success

1. M23-AQP4 transduced HEK cells extract
2. Control HEK cell extract

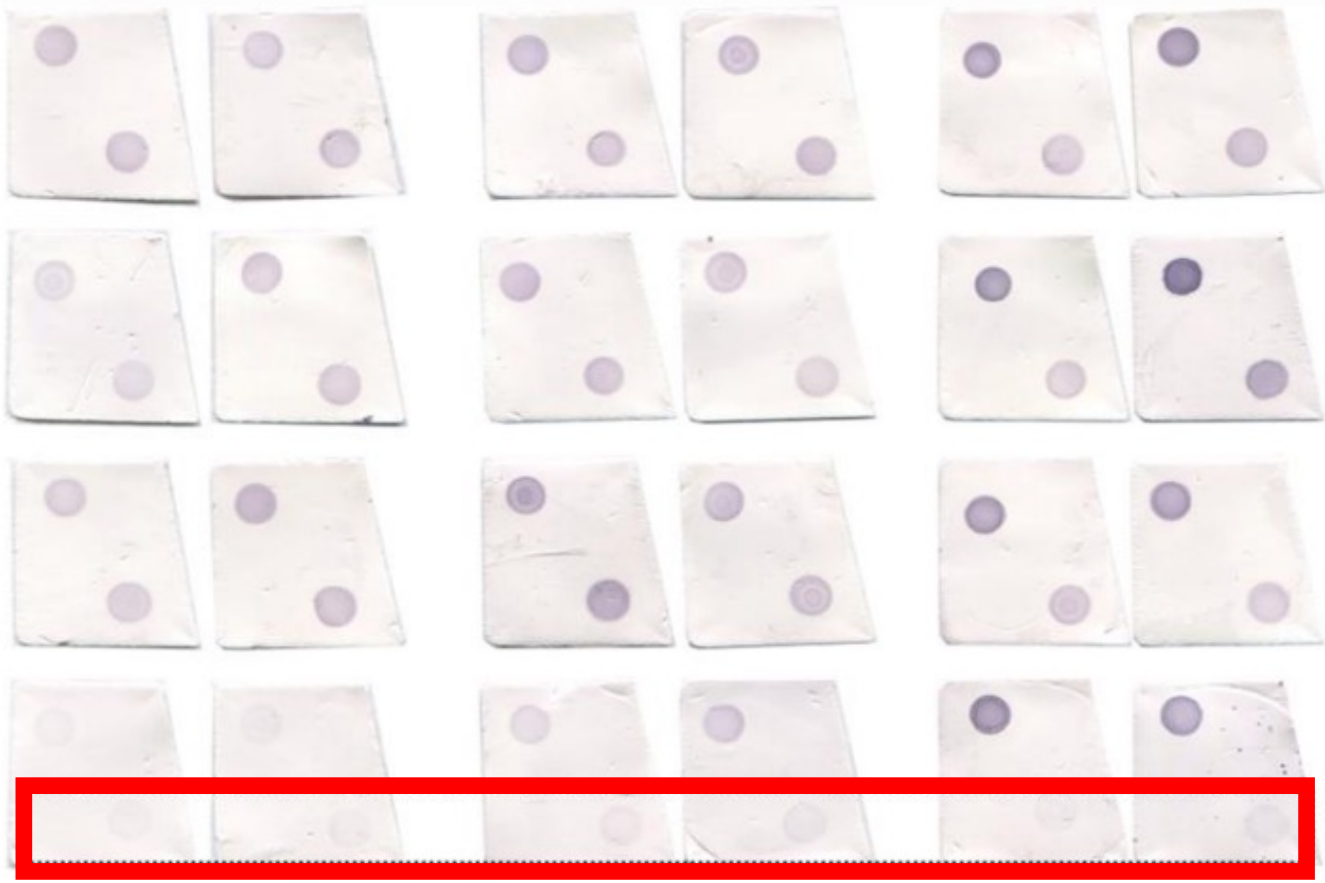
Preconditioning of serum	**AQP4-IgG Negative**
None	
Liver powder pre-absorption	
1%BSA pre-absorption	
Blocking solution pre-absorption	

Yu et al JAMA Neurol 2023

Rapid idot method – Block is key to success

1. M23-AQP4 transduced HEK cells extract
2. Control HEK cell extract

Preconditioning of serum	**AQP4-IgG Negative**	**Low titer**	**High titer**	**Nonspecific binding**
None				**High**
Liver powder pre-absorption				**High**
1%BSA pre-absorption				**High**
Blocking solution pre-absorption				**Low**



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Rapid idot method – Substrate is stable over 1 year

eTable 1. Stability evaluation of IDoT assay			
	Conditions	**n**	**Percent agreement**
Within-lot			**100**
	1 month	40	
	2 months	40	
	3 months	40	
	12 months	40	

Yu et al JAMA Neurol 2023

Rapid idot method – Data

Prospective multicentre study

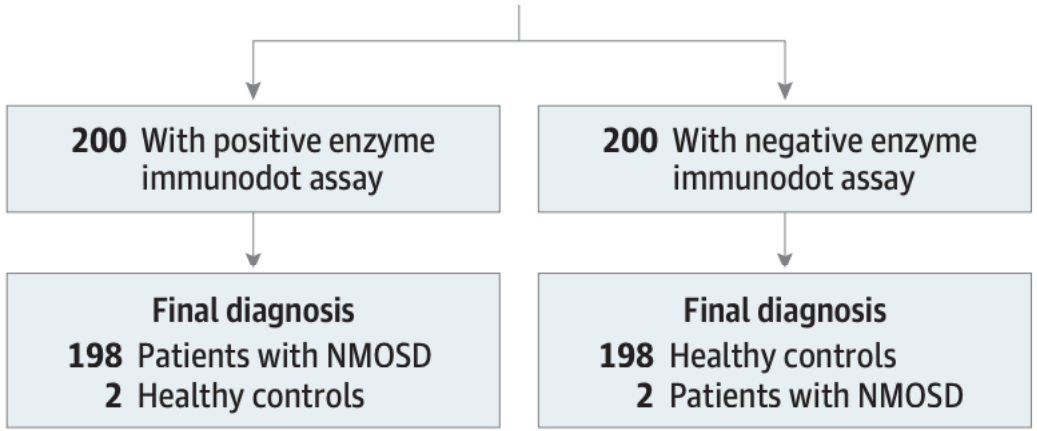
Patients The Third Affiliated Hospital of Sun yat-sen University, Guangzhou (China)

Patients First Affiliated Hospital of Fujian Medical University, Fuzhou (China)

Live M23 CBA Shaanxi Normal University (China)

200 CBA AQP4-IgG Live CBA Positive NMOSD

200 Healthy Controls



99% identity

99% identity

Other diseases

0/116 MS

0/50 SLE

0/34 SS

0/49 MG

1/22 HAM

0/4 Others

1/275 Total

Immunodot assay results	International cross-validation in Korea	
	Positive	Negative
Positive	47	1
Negative	0	25
Total	47	26

Prof. Ho Jin Kim

Yu et al JAMA Neurol 2023

Rapid idot method – Multicentre study

Coordinating centres
Matteo Gastaldi (Italy) Paddy Waters (Oxford)

Looking for £20K funding support for this project

Idot team (China)
Ying Fu, Ke Li
Wei Qiu, Xiaobo Sun
Yaping Yan, Rui Li, Jin Bi

Other Participating centres
Ho Jin Kim (South Korea)
Markus Reindl (Austria)
Romain Marignier (France)
Sean Pittock (USA)
Thashi Chang/Neelika Gathsaurie (Sri Lanka)
Zhila Maghbooli (Iran)
Lekha Pandit (India)
Sara Mariotto (Italy)



Samples from 7 centres
Rapid idot run at 9 centres
Live CBA – 5/6 centres
Fixed CBA – 1 centre

Test groups

1. AQP4-IgG positive. 2. MOG-IgG clear positive. 3. MS - Clinically definite. 4 Any difficult samples for any platform

Confirmation of a relapse or

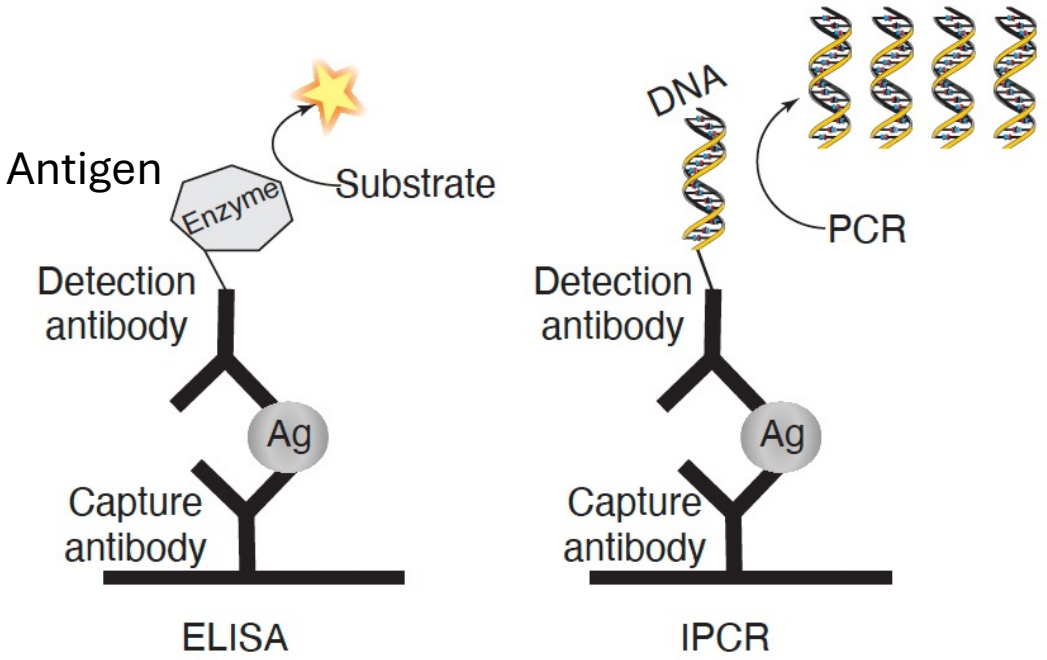
Evidence of disease activity in people with an established diagnosis

iPCR

molecules of antigen needed for detection

ELISA: 58,000,000 (5.8×10^6)

iPCR: 580 (5.8×10^2)

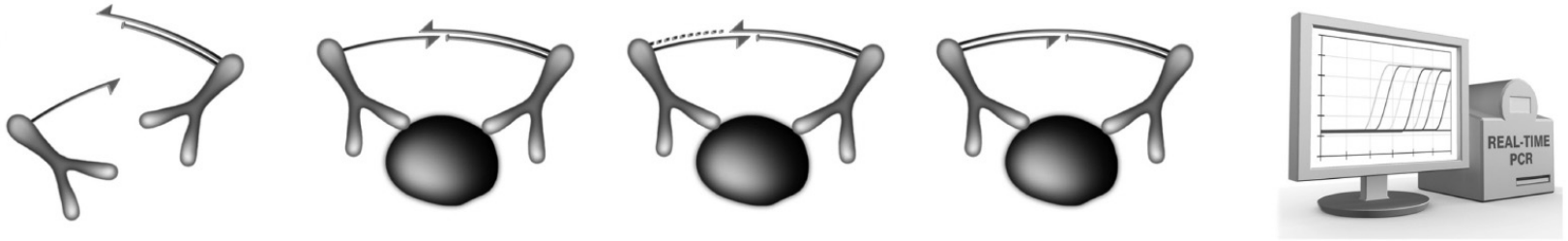


iPCR (depending on the molecule) is 5x to 1,000,000,000x more sensitive than ELISA in published head-to-head comparisons.

Sano et al Science 1992

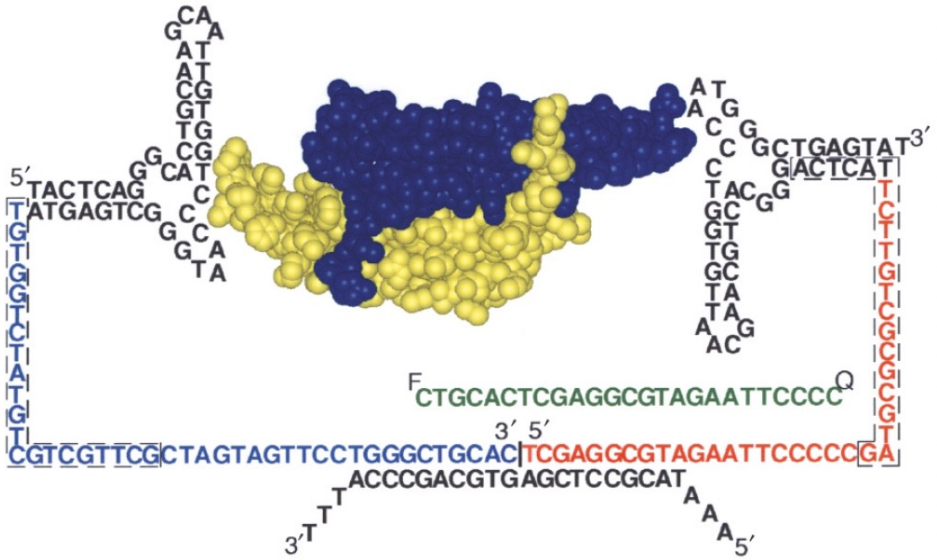
Sano et al Biotechnology 1991

Proximity extension assays



Antibody based

Proximity dependent DNA-ligation assays

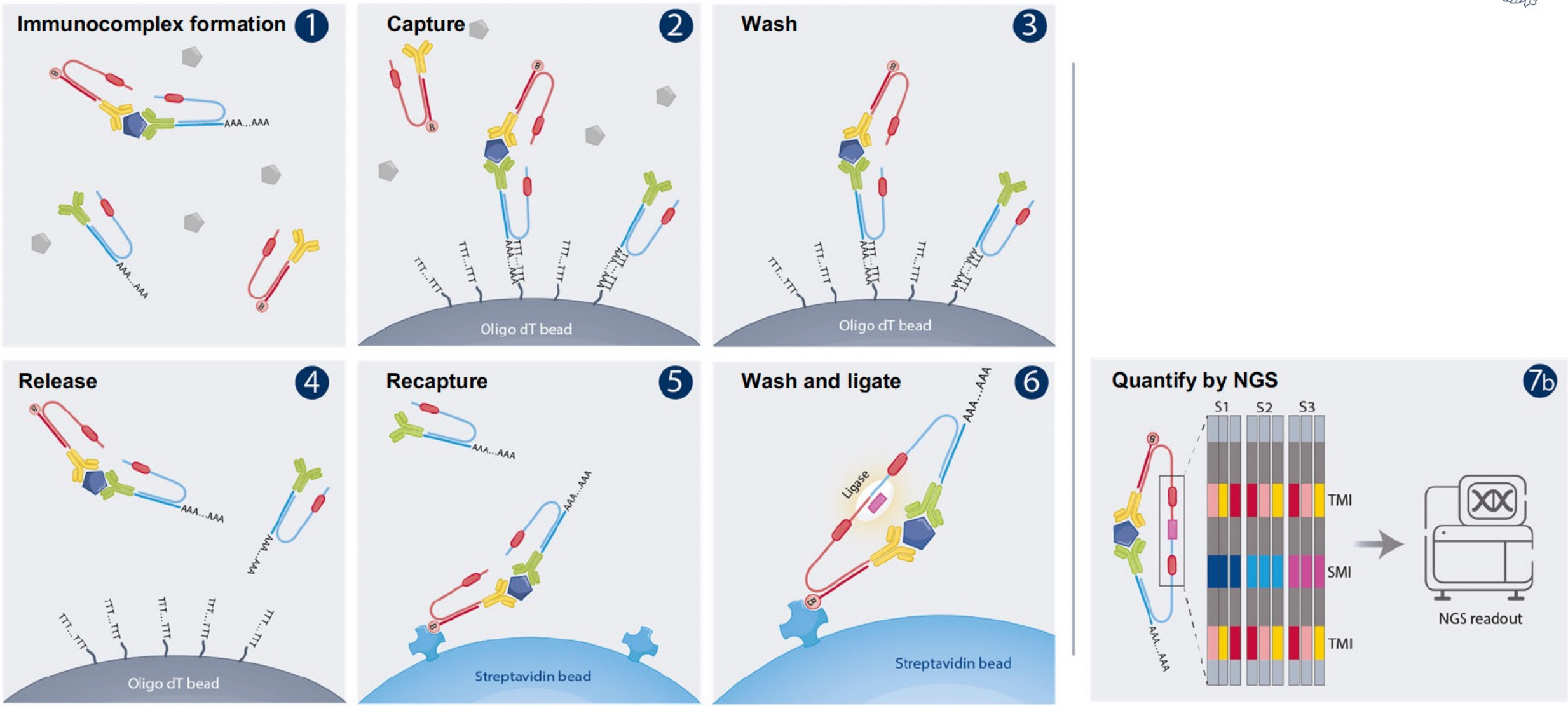


Aptamer based

Fredriksson et al Nat Biotech 2002
Lundberg et al Nucleic acids research 2011

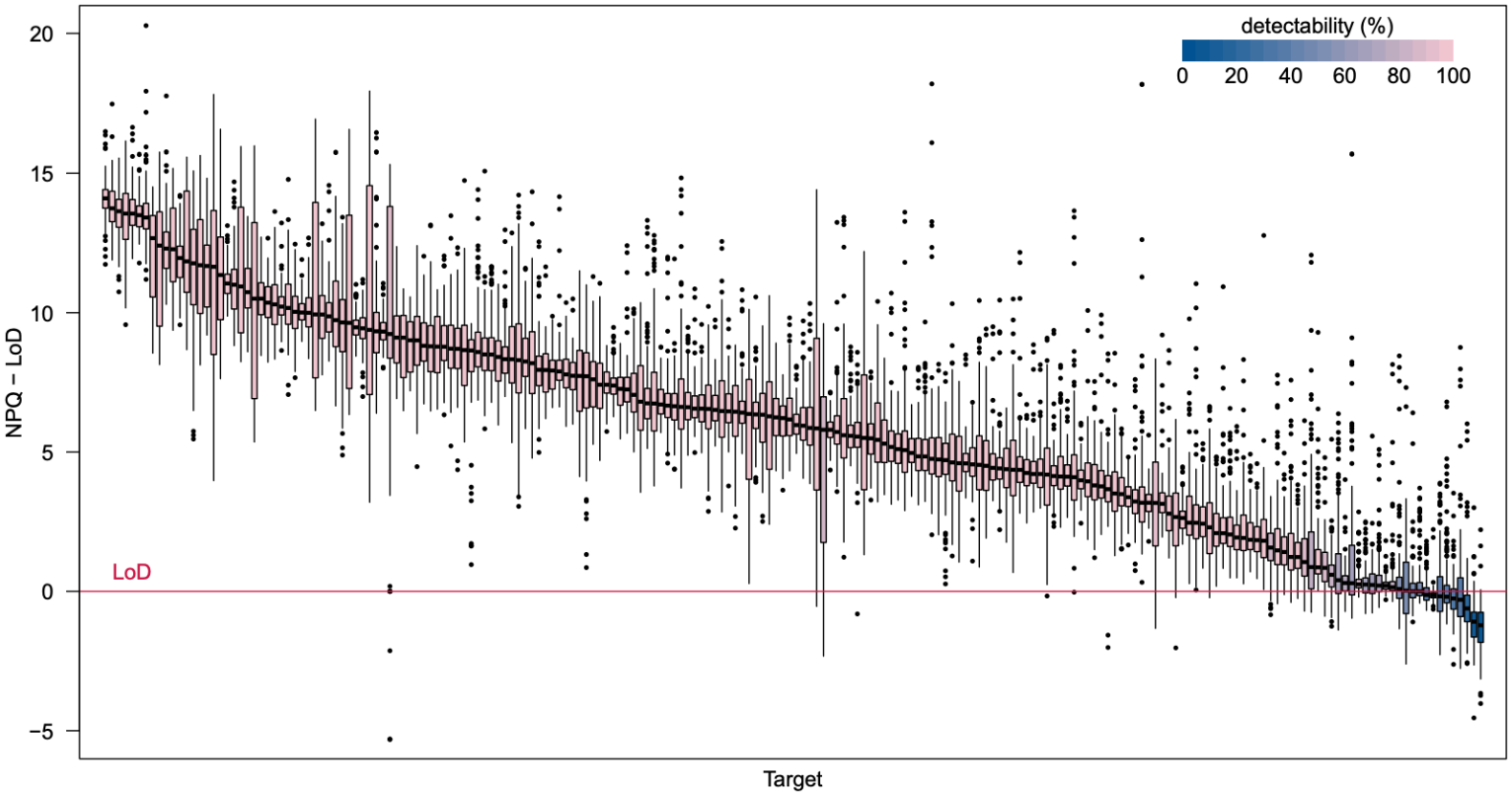
NULISA – Nucleic acid Linked Immuno-Sandwich Assay

All good for soluble molecules or with domains that are not affected by extraction from their native environment

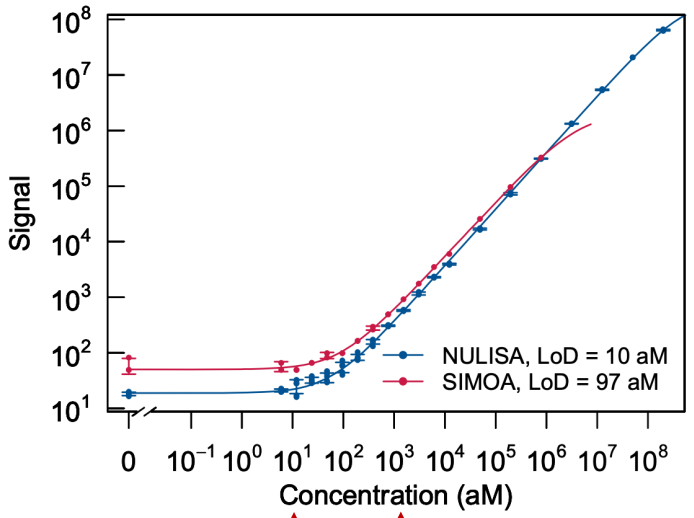


Feng et al Nat Comm 2023 – Alamar Biosciences

NULISA

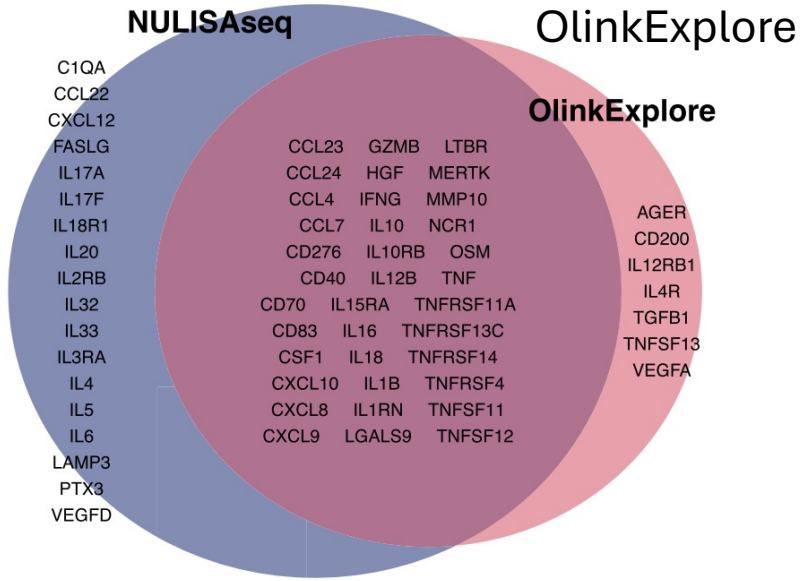


p24



10 1000
molecules

NULISAseq



151 samples, 204 targets

Summary

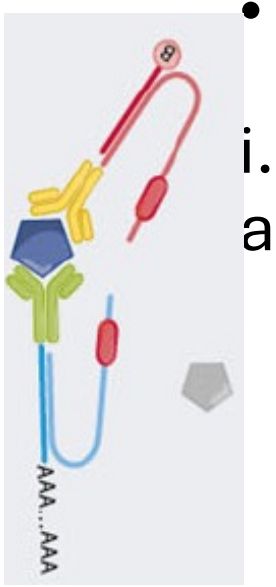


- Global access to affordable antibody testing is needed
- Rapid idot or alternative point of care testing may be possible



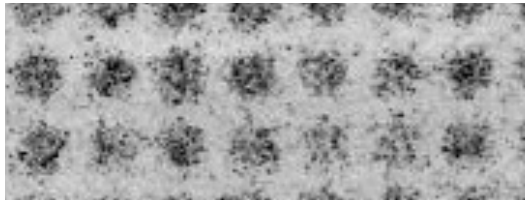


- Retrogenix cell microarray looks useful, if multisubunit channels are added to their repertoire it may be even more useful
- iPCR based techniques are at the Attomolar detection level



i.e. 10-1000 molecules. Only limitation now is pairs of high affinity antibodies or aptamers.

AQP4 specific mAb 50,000,000,000 (50 Billion ~12 ng)
to 600,000,000 (600 million ~150 pg)



IPND 2025 Diagnostic Criteria: Goals and Progress

Dean M. Wingerchuk, MD, MSc, FRCP(C)

Professor and Chair, Department of Neurology

Mayo Clinic, Phoenix/Scottsdale, Arizona

VIEWS & REVIEWS

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

OPEN

Dean M. Wingerchuk, MD, FRCP(C)
Brenda Banwell, MD, FRCP(C)
Jeffrey L. Bennett, MD, PhD
Philippe Cabre, MD
William Carroll, MD
Tanuja Chitnis, MD
Jérôme de Seze, MD
Kazuo Fujihara, MD
Benjamin Greenberg, MD
Anu Jacob, MD
Sven Jarius, MD

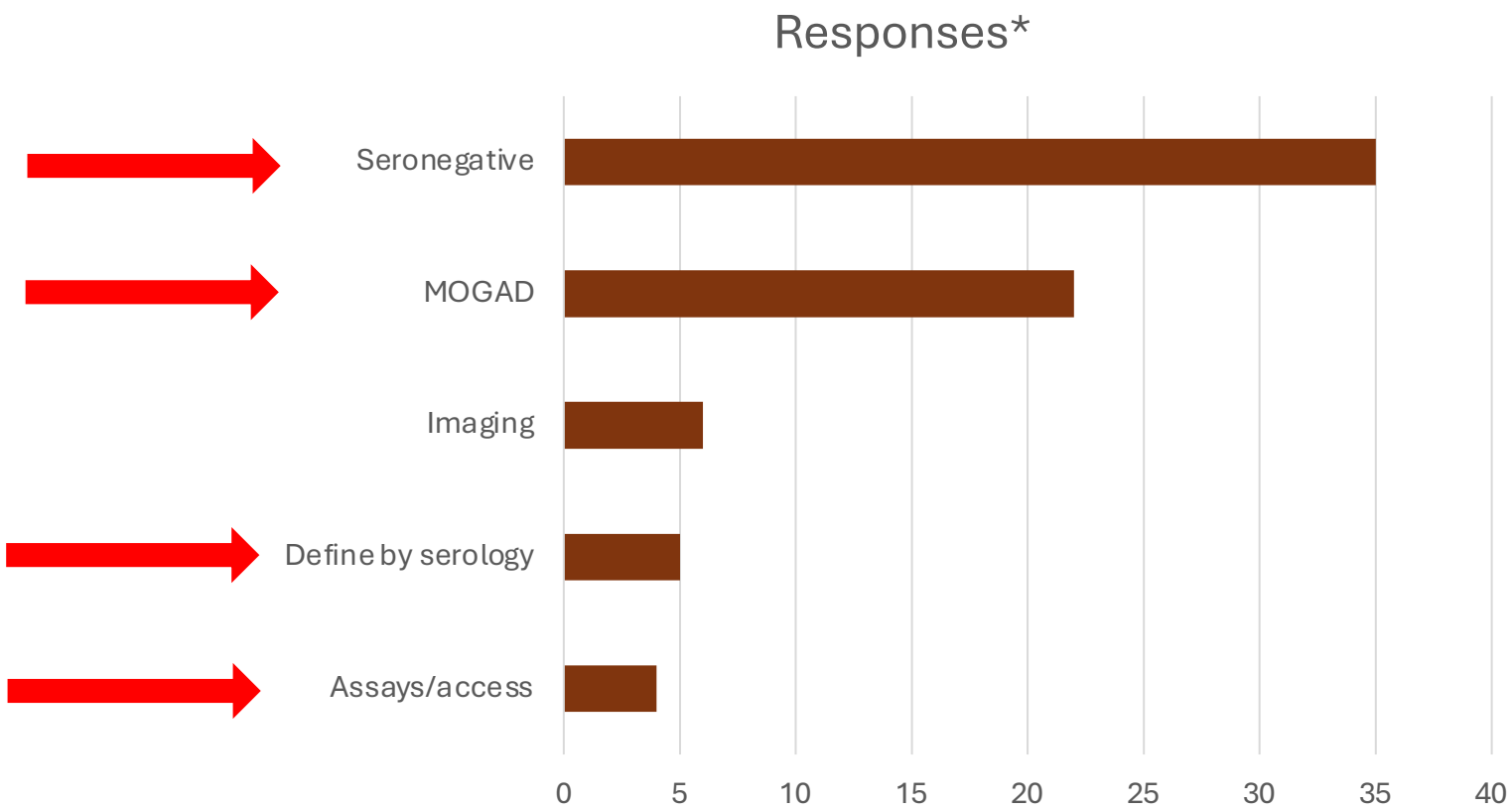
ABSTRACT

Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. The International Panel for NMO Diagnosis (IPND) was convened to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus. The new nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. The IPND also proposed validation strategies and achieved consensus on pediatric NMOSD diagnosis and the concepts of monophasic NMOSD and opticospinal MS. *Neurology*® 2015;85:177–189

- *The International Panel for NMO Diagnosis (IPND) was convened and charged with revising NMO diagnostic criteria for clinical decision-making…*

IPND 2025 Survey

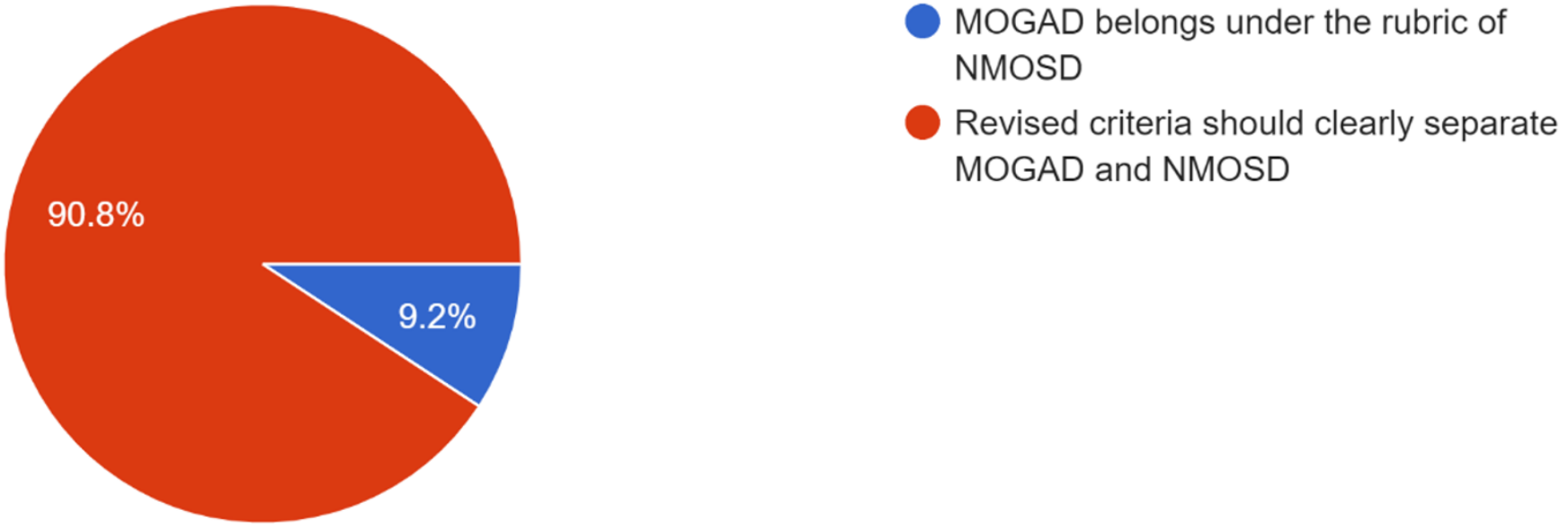
What is the most important issue you would like to see updated in revised IPND criteria?



*some respondents endorsed >1 issue

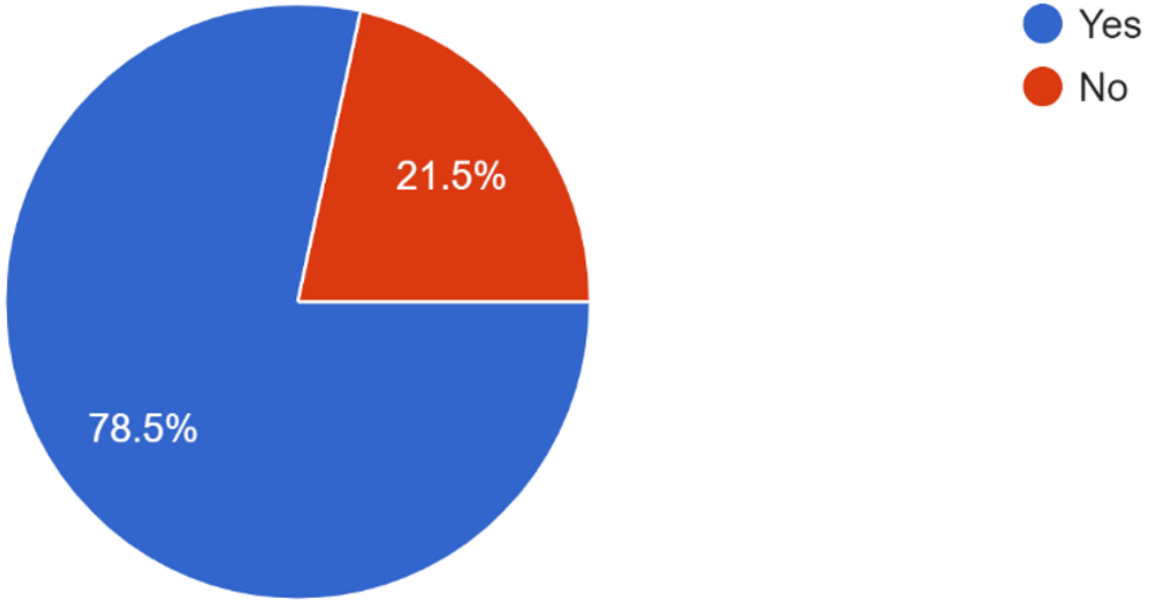
IPND 2025

Do you believe that MOGAD belongs under the rubric of NMOSD (e.g., that MOGAD is a subset or specific type of NMOSD) or do you favor the concept that MOGAD and NMOSD are distinct diseases and that revised criteria should clearly separate them?



IPND 2025

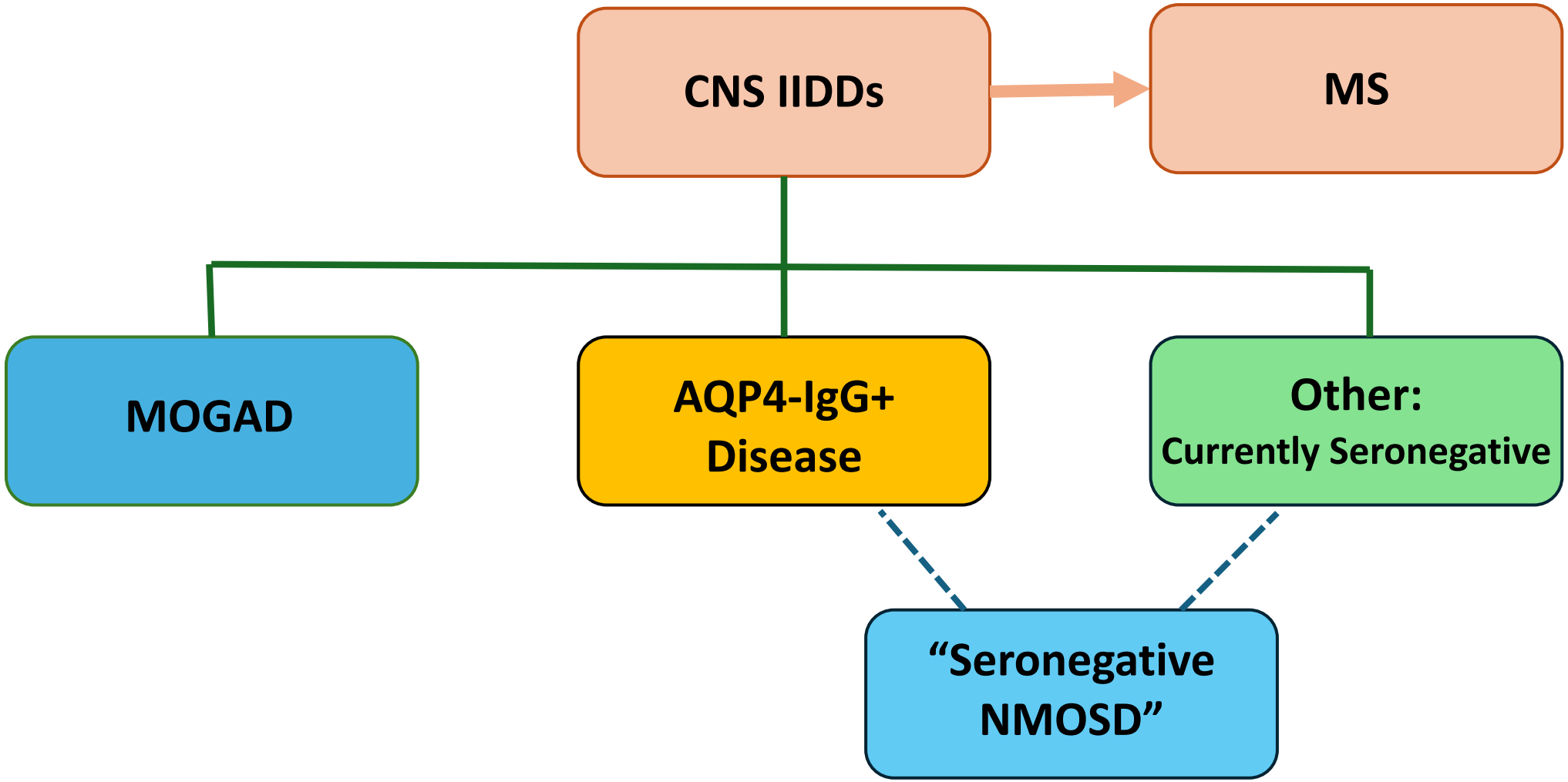
Should “NMOSD without AQP4-IgG” (the current IPND definition term) or so-called “double-seronegative NMO/NMOSD” be included in new diagnostic criteria?



IPND Objectives

- Develop contemporary definition, nosology, and nomenclature of NMOSD
- Distinguish NMOSD from MOGAD
- “Refresh” definition of NMOSD with AQP4-IgG
- Define ”seronegative” phenotype and associated features
- Prospectus

General Nosology



IPND 2025 Steering Committee

EXECUTIVE BRANCH:

- Brenda BANWELL
- Kazuo FUJIHARA
- Romain MARIGNIER
- Jackie PALACE
- Friedemann PAUL
- Brian WEINSHENKER
- Dean WINGERCHUK
- Michael YEAMAN

COORDINATING BRANCH:

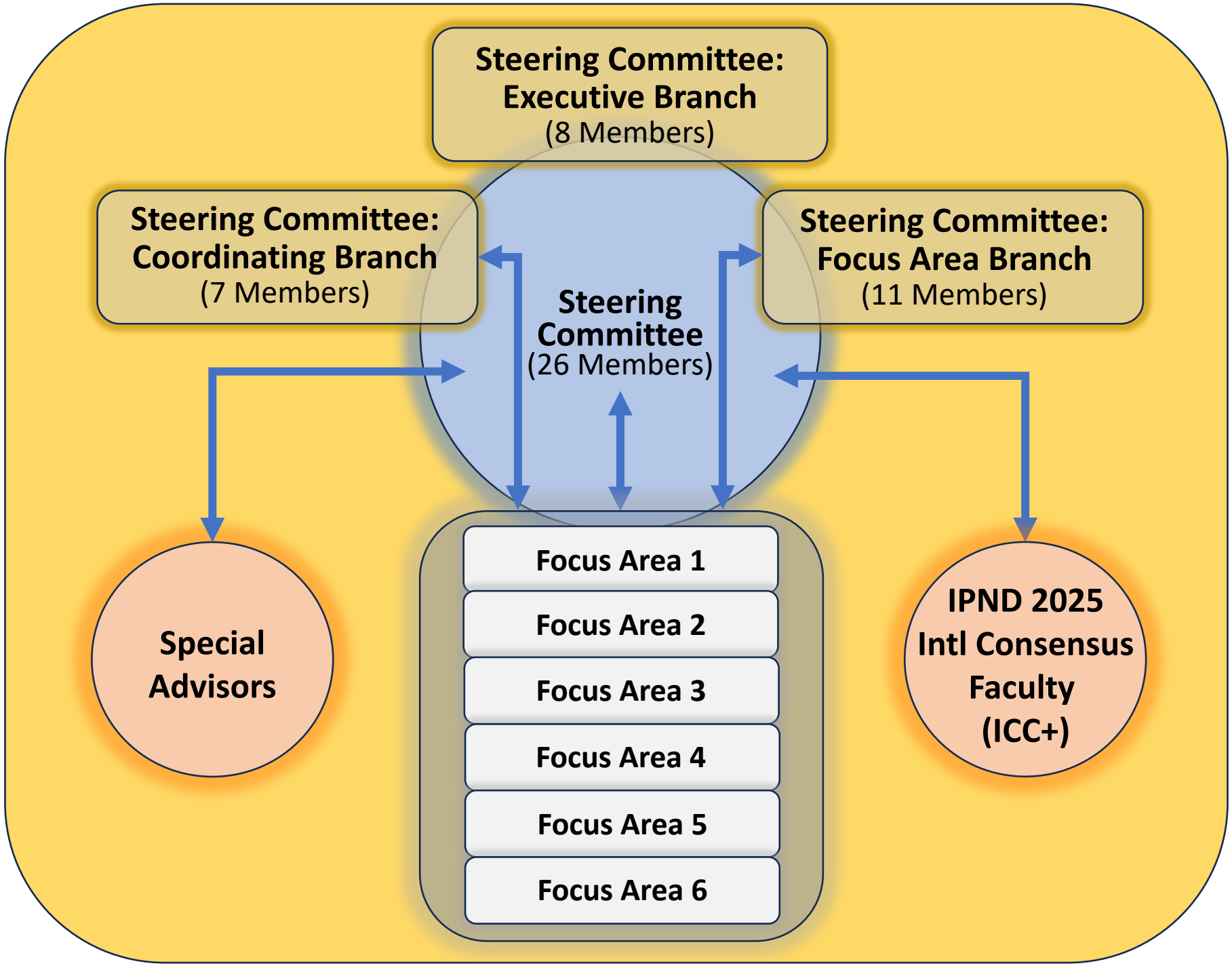
- Jeff BENNETT
- Najib KISSANI
- Ben GREENBERG
- Lekha PANDIT
- May HAN
- Darshi RAMANATHAN
- Silvia TENEMBAUM

FOCUS AREA BRANCH:

- Jorge CORREALE
- Maria Isabel LEITE
- Fabienne BRILOT
- Sean PITTOCK
- Eoin FLANAGAN
- Frederike OERTEL
- Orhan AKTAS
- Sara MARIOTTO
- Ho Jin KIM
- Maciej JURYNCZYK
- Ann-Katrin PRÖBSTEL

IPND 2025: Structure and Governance

- **Consensus-based process**
  - Balance practicality with inclusiveness
- **Steering committee**
  - Define scope, lead process
- **Advisory/Working Groups**
  - Representation
    - diversity, areas of expertise (clinical/MRI/serology/peds/etc)
    - equity & inclusivity (demography; international; career stage)
- **Contributors**
  - Derived from ICC
  - Additional feedback/expertise on select topics
- **Support**
  - Guthy Jackson Charitable Foundation



Focus Areas:

1. Clinical
2. Serology
3. Imaging
4. Biomarkers
5. Nosology
6. Seronegative

Focus Areas

- **”Refresh” – Focus on AQP4+ Disease**
  - 1 – Clinical Phenotype
  - 2 - Serology
  - 3 - Imaging
  - 4 - Biomarkers
- **Contemporary issues**
  - 5 - Nosology and Nomenclature
  - 6 - Seronegative

FA1: Clinical Phenotype

- Clinical features of AQP4+ disease
  - Reappraise clinical definitions
- Attack/Relapse – temporal characteristics
- Site-specific
- Adult vs Pediatric
- Red flags
- Prospectus

Surname	First Name	Region	Nation
CORREALE	Jorge	S. America	Argentina
LEITE	Maria Isabel	Europe	UK
JACOB	Anu	Asia	UAE
KIM	Su-Hyun	Asia Pacific	S. Korea
QUAN	Chao	Asia Pacific	China
HACOHEN	Yael	Europe	UK
ABBOUD	Hesham	N. America	USA
ROTSTEIN	Dalia	N. America	Canada

FA2: Serology

- AQP4-IgG assay methods
  - Reference standard method
  - Other and emerging assays (e.g. immunodot)
- Diagnostic accuracy
  - Reference standard (CBA) vs commonly available assays
- Seroconversion / Seroreversion rates
- Recommendations for clinicians
  - Test interpretation
  - Retesting, etc.

Surname	First Name	Region	Nation
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GASTALDI	Matteo	Europe	Italy
IORIO	Raffaele	Europe	Italy
REINDL	Markus	Europe	Austria
WATERS	Paddy	Europe	UK
KUNCHOK	Amy	N. America	USA
SATO	Douglas	S. America	Brazil

FA3: Imaging

- Update imaging features of NMOSD with AQP4-IgG
- Standard MRI sequences
- Use of MRI for disease monitoring
- Nonconventional MRI
- OCT

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SALAMA	Sara	Africa	Egypt
LIU	Yaou	Asia Pacific	China
NAKASHIMA	Ichiro	Asia Pacific	Japan
FINKE	Carsten	Europe	Germany
MARGONI	Monica	Europe	Italy
MESSINA	Silvia	Europe	UK
CHEN	John	N. America	USA
FADDA	Giulia	N. America	Canada
CARNERO CONTENTTI	Edgar (Junior)	S. America	Argentina

FA4: Biomarkers

- Evaluate molecular and cellular biomarkers
- Conceptual use of biomarkers: AQP4+ disease vs seronegative
  - Initial focus on GFAP, NfL, IL-6, complement, routine CSF tests
- Potential near-term use in diagnosis
- Standardization

Surname	First Name	Region	Nation
AKTAS	Orhan	Europe	Germany
MARIOTTO	Sara	Europe	Italy
VAKNIN-DEMBINSKY	Adi	Asia	Israel
MISU	Tatsuro	Asia Pacific	Japan
ARRAMBIDE	Georgina	Europe	Spain
COBO-CALVO	Alvaro	Europe	Spain
CHITNIS	Tanuja	N. America	USA
MELAMED	Esther	N. America	USA
MAO-DRAAYER	Yang	N. America	USA
SOTO DE CASTILLO	Ibis	S. America	Venezuela

FA6: Seronegative

- Evaluate performance/validity of 2015 criteria for AQP4-IgG negative/not available
- Determine if there are idiopathic non-MS/ AQP-/MOG- cohorts with AQP4+ biology (identical disease)
- Define seronegative NMO/SD clinical syndromes for practice and research
- Diagnostic guidance (testing/differential)
- Prospectus

Surname	First Name	Region	Nation
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PRÖEBSTEL	Ann-Katrin	Europe	Switzerland
APIWATTANAKUL	Mehta	Asia Pacific	Thailand
BROADLEY	Simon	Asia Pacific	Australia
SIRITHRO	Sasitom	Asia Pacific	Thailand
ALTINTAS	Ayse	Europe	Turkey
ASGARI	Nasrin	Europe	Denmark
DEIVA	Kumaran	Europe	France
HUDA	Saif	Europe	UK
KLEITER	Ingo	Europe	Germany
SECHI	Elia	Europe	Italy
RUPRECHT	Klemens	Europe	Germany
SEPULVEDA	Maria	Europe	Spain
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YEH	Ann	N. America	Canada
LANA-PEIXOTO	Marco	S. America	Brazil

FA5: Nosology and Nomenclature

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COORDINATING BRANCH:

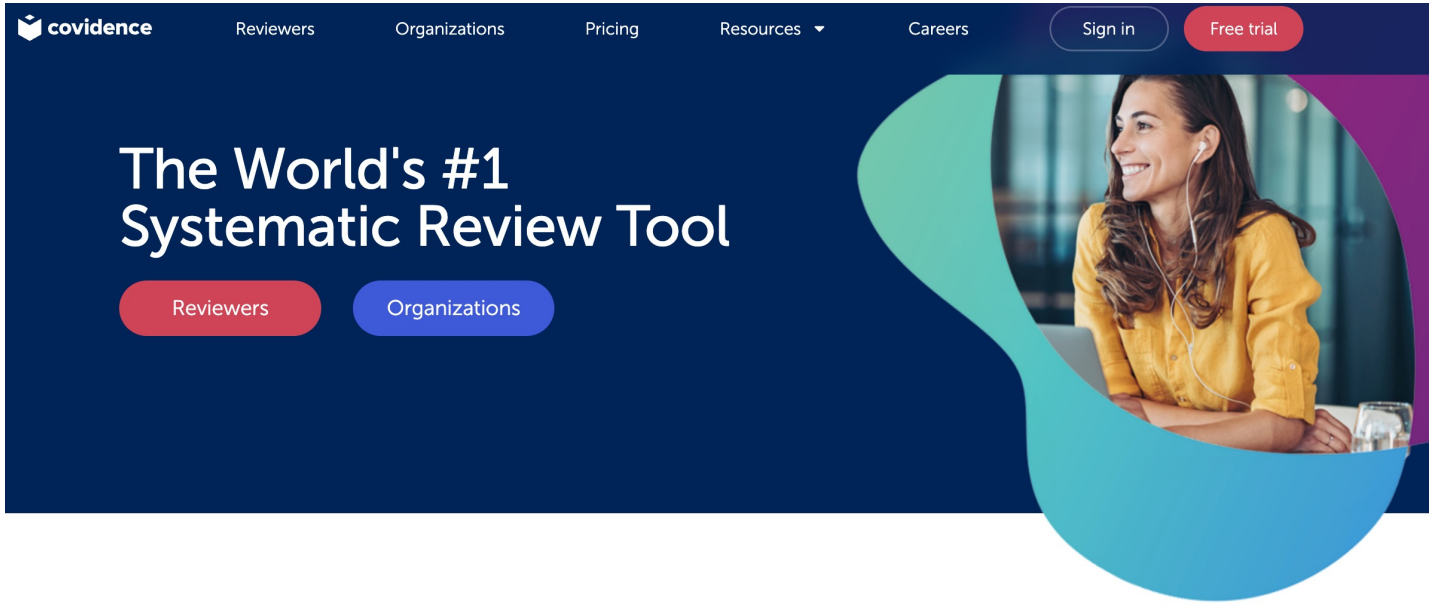
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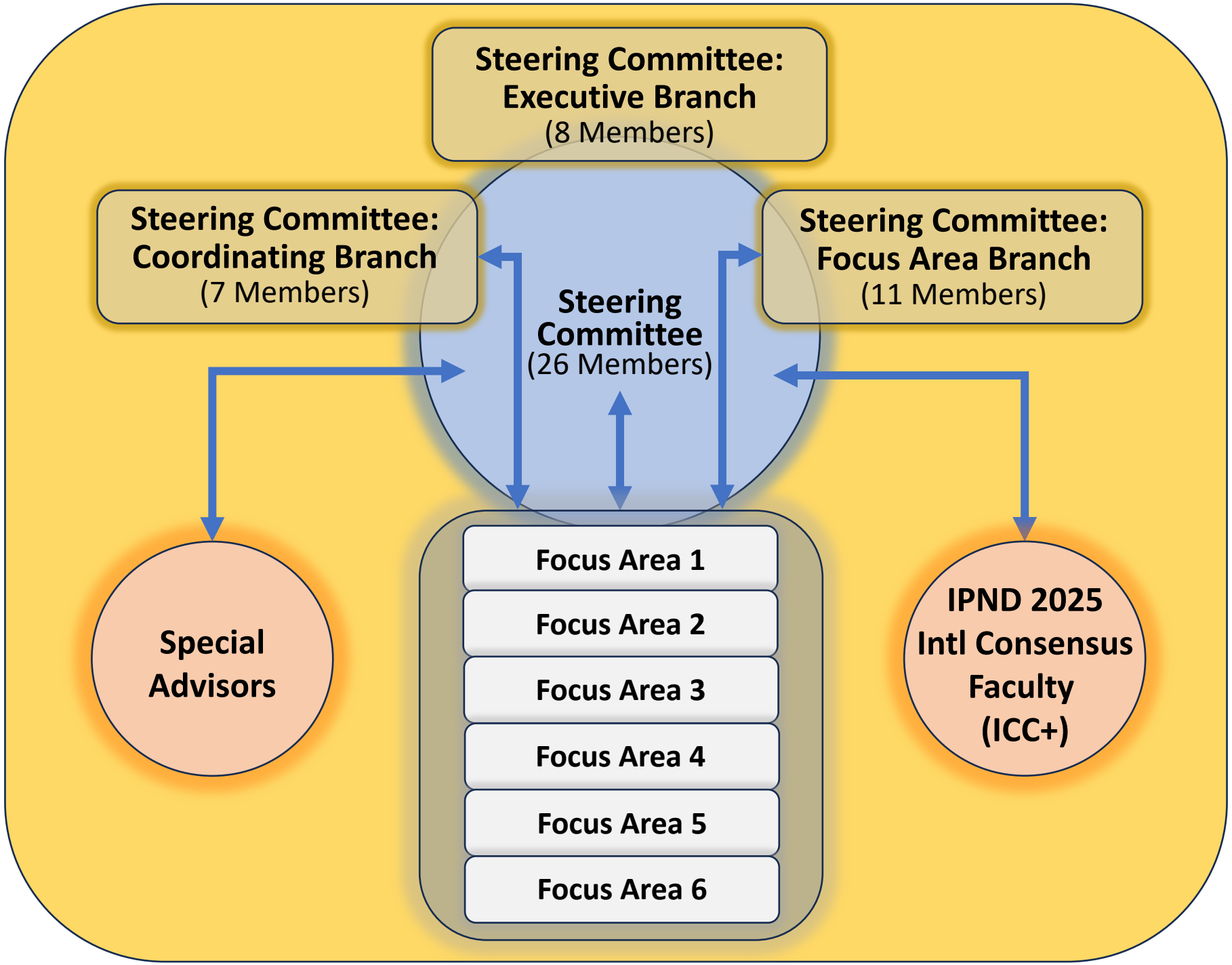
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- Frederike OERTEL
- Orhan AKTAS
- Sara MARIOTTO
- Ho Jin KIM
- Maciej JURYNCZYK
- Ann-Katrin PRÖBSTEL

IPND 2025: Methods

- Focused systematic literature search and reviews
- Assembly of evidence
  - Full-text paper reviews
  - Coordination between Focus Areas
- Consensus development



Literature search support: Lisa Marks, MLS, AHIP



Focus Areas:

1. Clinical
2. Serology
3. Imaging
4. Biomarkers
5. Nosology
6. Seronegative

IPND 2025: Special Advisors

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DE SEZE	Jerome	Europe	France
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IPND 2025: International Consensus Faculty

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AVASARALA	Jay	N. America	USA
BALABANOV	Roumen	N. America	USA
BICHUETTI	Denis	S. America	Brazil
BOYKO	Alexey	Europe	Russia
CARRUTHERS	Robert	N. America	Canada
DELGADO-GARCIA	Guillermo	N. America	Canada
DUJMOVIC BASUROSKI	Irena	N. America	USA
FLORES-RIVERA	Jose	N. America	Mexico
GALLEGUILLOS	Lorna	S. America	Chile
GERALDES	Ruth	Europe	UK
GOODMAN	Andrew	N. America	USA
HAVLA	Joachim	Europe	Germany
HELLWIG	Kerstin	Europe	Germany
HOR	Jyh Yung	Asia	Malaysia
JIMENEZ	Jorge	S. America	Colombia
KATZ SAND	Ilana	N. America	USA
KIM	Sung Min	Asia	S. Korea
KIMBROUGH	Dorlan	N. America	USA

Surname	First Name	Region	Nation
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KUMPFEL	Tania	Europe	Germany
LUBLIN	Fred	N. America	USA
MAIGA	Youssoufa	Africa	Mali
MATIELLO	Marcelo	N. America	USA
MOMTAZEE	Callene	N. America	USA
NEALON	Nancy	N. America	USA
O'CONNOR	Kevin	N. America	USA
PAOLILO	Renate	S. America	Brazil
PLANCHON POPE	Sarah	N. America	USA
QIAN	Peiqing	N. America	USA
REPOVIC	Pavle	N. America	USA
RILEY	Claire	N. America	USA
RINGELSTEIN	Marius	Europe	Germany
RIVERA	Victor	N. America	USA
ROJAS	Juan	S. America	Argentina
SA	Maria	Europe	Portugal
SAIZ	Albert	Europe	Spain
SERGUERA	Che	Europe	France
SHOSHA	Eslam	N. America	Canada
SIVA	Aksel	Europe	Turkey
STUVE	Olaf	N. America	USA
VILLOSLADA	Pablo	Europe	Spain
WILLEKENS	Barbara	Europe	Belgium
YAMOUT	Bassem	Asia	Lebanon

IPND 2025 Timeline

- 2021 — Discussions and formation of interest group
- 2022 — Survey of GJCF ICC – ECTRIMS (Amsterdam)
- 2023 Q1-2 — Organize Executive Committee, initiate project July 2023
- 2023 Q3 — Solicit nominations/areas of interest
- 2023 Q4 — Update at ECTRIMS (Milan) and develop project org structure
  Develop process for committee leadership and membership
  Draft IPND objectives
- 2024 Q1 — Invite, appoint, and orient leaders and members
  Finalize project objectives and timeline

IPND 2025 Timeline

- 2024 Q2 — Endorse final project objectives and timeline
  Complete literature search strategies
  Abstract reviews / Full-text availability and review
- 2024 Q3 — Assemble data summaries and consensus recommendations
- 2024 Q4 — Establish FA conclusions / IPND consensus
- 2025 Q1 — Primary manuscript submission

IPND 2025: Manuscripts

- **Primary manuscript**
  - Target: Lancet Neurology
  - Authorship
- **Spin-off manuscripts**
  - Facilitated by systematic literature reviews

Thank You! Onwards!

- **All 130 IPND contributors**
  - 26 Steering Committee
  - 43 Focus Area Members
  - 12 Special Advisors
  - 48 International Consensus Faculty
  - 1 Library Science Specialist (Lisa Marks, Mayo Clinic)

- **Guthy Jackson Charitable Foundation**
  - Jacinta Behne
  - Megan Behne
  - Terry Smith



15th GJCF NMO Roundtable Conference

(UCLA Luskin Conference Center, August 2~4, 2024)

Global Epidemiology of NMOSD, MOGAD & Seronegative Disease (SND)

Kazuo Fujihara[1,2] & Jyh Yung Hor[3]

1. Fukushima Medical University
2. Southern TOHOKU Research Institute for Neuroscience
3. Penang General Hospital

Disclosure (Kazuo Fujihara, M.D.)

Travel support:

Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, Asahi Kasei Medical, Daiichi Sankyo, Nihon, Teijin, VielaBio

Speaker honoraria:

Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, Asahi Kasei Medical, Daiichi Sankyo, Nihon, Teijin. Roche, Chugai, Alexion

Advisory Board:

Biogen, Mitsubishi Tanabe, Novartis, Chugai, Alexion, VielaBio

Grant for Research:

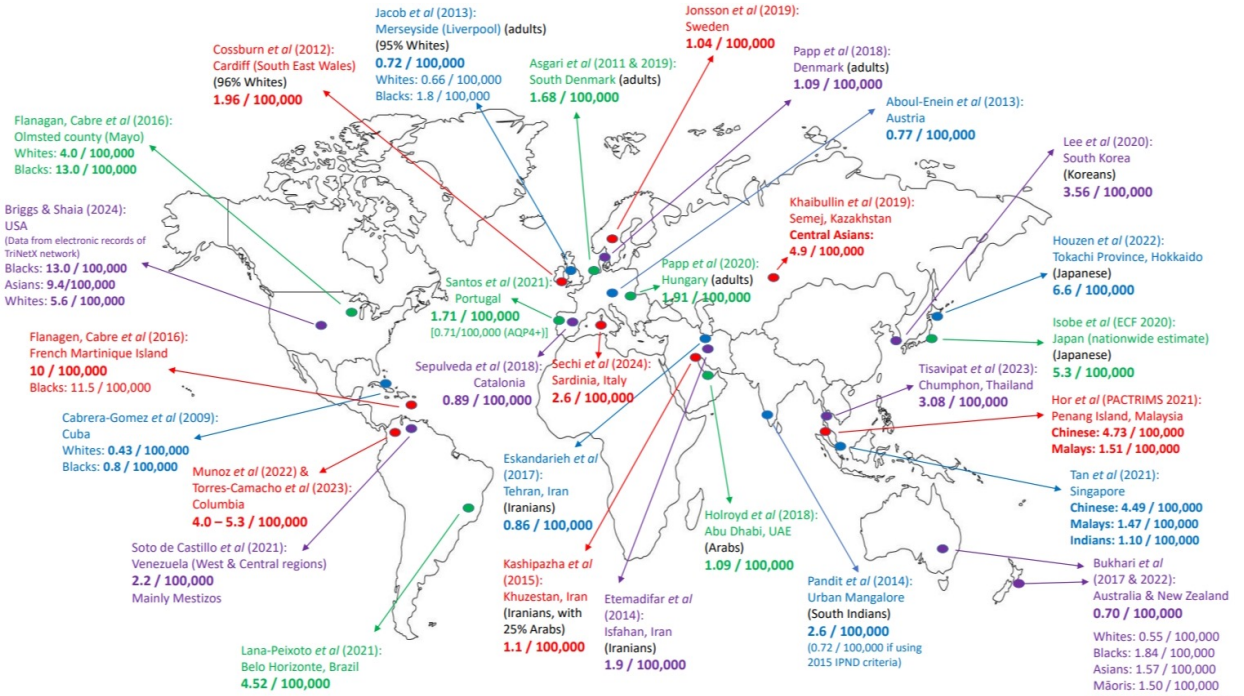
none

Key clinical & MRI features of MOGAD, AQP4-IgG NMOSD, SND and MS

	MOGAD	AQP4+NMOSD	SND	MS
Pediatric onset	Frequent	Extremely rare		infrequent
Sex distribution	F=M	F>M		F>M (after puberty
Disease course	Monophasic/relapsing	Most often relapsing		Relapsing/progressiv
Optic nerve	Severe, good recovery Bil, anterior, longitudinally extensive, ON sheath, ON head edema	Severe, poor recovery, Bil/Unil, posterior, longitudinally extensive, chiasmal		Mild~moderate, favorable recovery, Unil, anterior, short
Spinal cord	Severe, excellent recovery, LETM, H sign, conus lesion	Severe, poor recovery, LETM Bright spotty lesion		Mild~moderate, often good recovery, Multiple focal cord lesions;
Brain	Encephalopathy (eg, ADEM), seizures and cerebral cortical encephalitis WM, deep GM, middle cerebellar peduncle, large BS, and confluent cortical	APS, hypersomnolence Peri-IIIrd and -IVth ventricle, callosal splenium, internal capsule, and WM		Focal/polyfocal neurological deficits common, Multifocal, ovoid T2-WM lesions, Dawson's fingers, U-fibre lesions; **CVS**, **SEL**

(Modified from Banwell *et al*. Lancet Neurol 2023)

Population-based prevalence studies of NMOSD in the World



NO LATITUDE GRADIENT

Prevalence (per 100,000):

Whites: 1 - 2
Blacks: ~10
East Asians: ~5
Austronesians: ~2
South Indians: ~1
Central Asians: ~5
LATAM: 2.2 - 5
Africa (estimates):
0.004 (Ethiopia) ~ 0.14 (Morocco)

(Modified from Hor *et al*. Front Neurol 2020, Papp *et al*. Neurology 2021, Musubire et al. N2 2021, Kissani *et al*. OALIB J, Bukhari *et al*. JNNP 2017, Miyamoto *et al*. JNNP 2018)

F:M ratio: 8.89 : 1 (higher when AQP4+ case proportion is higher)

Mean onset age: 41.7 years (increases with population life expectancy) (Arnett *et al*. J Neurol 2024)

Increasing prevalence (total n of Pts) over time in some studies

	Prevalence of NMOSD per 100,000 population		
	2007	2016	
Martinique Island (Black population)	4.2	11.5	
	2011	2016	2021
Hokkaido, Japan	0.9	4.1	6.1
	2017	2020	2023
Penang Island, Malaysia (Chinese)	3.3	4.7	6.9
	2013	2022	
Sardinia	1.1	2.6	

In early years, likely due to increased detection & changing definition (NMO -> NMOSD)
But more recently, likely due to improved survival

Relatively stable annual incidence (new cases/year) over the years

A systematic review (Papp *et al*. Neurology 2021) :
French West Indies (1992-2007)
British Columbia (1986-2010)
Netherlands (6 years)
Abu Dhabi (7 years),
Denmark (7 years)
Catalonia (10 years)
Hungary (10 years)

Annual incidence

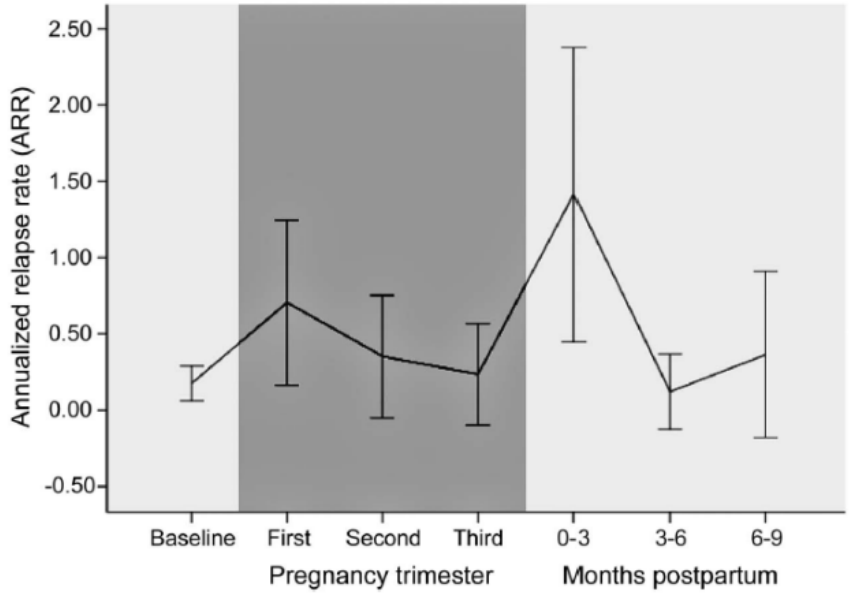
among:

Whites: 0.37 – 1.32 / million
African-Caribbean: up to 7 / million
East Asians: ~ 3 – 4 / million

Pregnancy

- High risk of relapse in early post-partum period
- Risk of relapse during pregnancy is not low

(Kim *et al*. 2012, Nour *et al*. 2016, Shimizu *et al*. 2016, Klawiter *et al*. 2017, Collongues *et al*. 2021)



Vitamin D:

- Inconclusive
- Some studies reported impact on disease activity and disability, but others reported negative associations

(Min *et al*. 2014, Shan *et al*. 2016, Jitprapaikulsan *et al*. 2016, Kusumadewi *et al*. 2018, Gao *et al*. 2019)

Smoking:

- Does not increase relapse rate, but may cause worse disability due to poor relapse recovery

(Messina *et al*. 2021)

Rheumatic and autoimmune diseases in NMOSD

1. **Systemic**
   Sjogren, SLE, RA, Anti-PL-Ab
2. **Organ-specific**
   2.1. **Neurological organ-specific**
   MG, AE, Neuropathies (AIDP, CIDP), etc
   2.2. **Non-neurological organ-specific**
   Thyroid (Hashimoto, Graves')
   GI and liver (AH, UC, etc)
   Skin (Raynaud, DM, Psoriasis, etc)
   Blood (AHA, etc)

(Shahmohammadi S, *et al*. MSARD 2019)

SLE was significantly associated with AQP4-IG+NMOSD but not with MOGAD (P<0.037) (Kunchok *et al*. MSJ 2021)

A link of AQP4-IgG+ with SLE but not with MS

Type I IFN signature (Feng X, *et al*. J Neurol Sci 2011),
A whole-genome sequence (Estrada K, *et al*. Nat Commun 2018)

Neoplastic diseases in NMOSD

BRIEF COMMUNICATION

Paraneoplastic neuromyelitis optica spectrum disorders: a case series

Eleonora Virgilio[1] · Domizia Vecchio[1,2] · Marco Vercellino[3] · Paola Naldi[1] · Fabiana Tesser[4] · Roberto Cantello[1] · Paola Cavalla[3] · Cristoforo Comi[2,4]

(Neurol Sci 2021)

3~25% of NMOSD cases – paraneoplastic?
cancer (breast, lung, uterine, etc), carcinoid, B cell lymphoma, monoclonal gammopathy, etc

(Pittock, Lennon. Arch Neurol 2008)

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Double-negative neuromyelitis optica spectrum disorder

Yan Wu, Ruth Geraldes, Maciej Juryńczyk and Jacqueline Palace

- **A rare entity**
- **A syndrome rather than a single disease**

  monophasic illness ~ chronic syndrome (AQP4+like/other mimics, eg. MS)

(Wu et al. Mult Scler 2023)

Three cohort studies of Double-seronegative NMOSD defined by the 2015 Criteria

1) Catalonia Population-based Study

	AQP4+ NMOSD (n=54)	MOG+ NMOSD (n=9)	Double seronegative NMOSD (n=11)
Prevalence	~0.64 / 100,000	~0.12 / 100,000	~0.13 / 100,000
Female	44 (82%)	5 (56%)	7 (64%)
<u>Ethnicity:</u> White Hispanic Black Asian Arab	 42 (78%) 6 (11%) 2 (4%) 2 (4%) 2 (4%)	 9 (100%) 0 0 0 0	 9 (82%) 2 (18%) 0 0 0
Age of onset	43y (10-76)	43y (18-63)	35y (13-60)
<u>Onset attacks:</u> Optic neuritis Myelitis ON + myelitis Area postrema syndrome Brainstem syndrome	 22 (41%) 25 (46%) 3 (6%) 2 (4%) 2 (4%)	 3 (33%) 2 (22%) 3 (33%) 1 (11%) 0	 3 (27%) 3 (27%) 4 (36%) 0 1 (9%)
Relapsing forms	51 (94%)	7 (77%)	5 (55%)

(Sepulveda *et al*., MSJ 2018)

2) Portuguese Nationwide Study

		Prevalence
AQP4 ab+ NMOSD	n=77	0.71 / 10^5
MOG ab+ NMOSD	n=67	0.65 / 10^5
Seronegative NMOSD	n=36	0.35 / 10^5

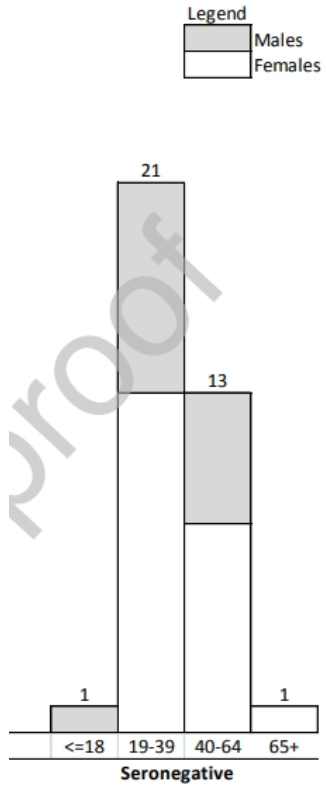
Female: 61%
Mean age of onset: 38 yrs

<u>Onset attack:</u>

Myelitis:	n=21 (58%)
ON:	n=9 (25%)
Myelitis & ON:	n=1 (3%)
Brainstem syndrome:	n=1
Supratentorial:	n=1
Myelitis & brainstem:	n=2
Myelitis & supratentorial:	n=1

Relapse : 100%

CSF OCB positivity:	n=5 (17%)



Age of onset

(Santos *et al.*, MSARD 2021)

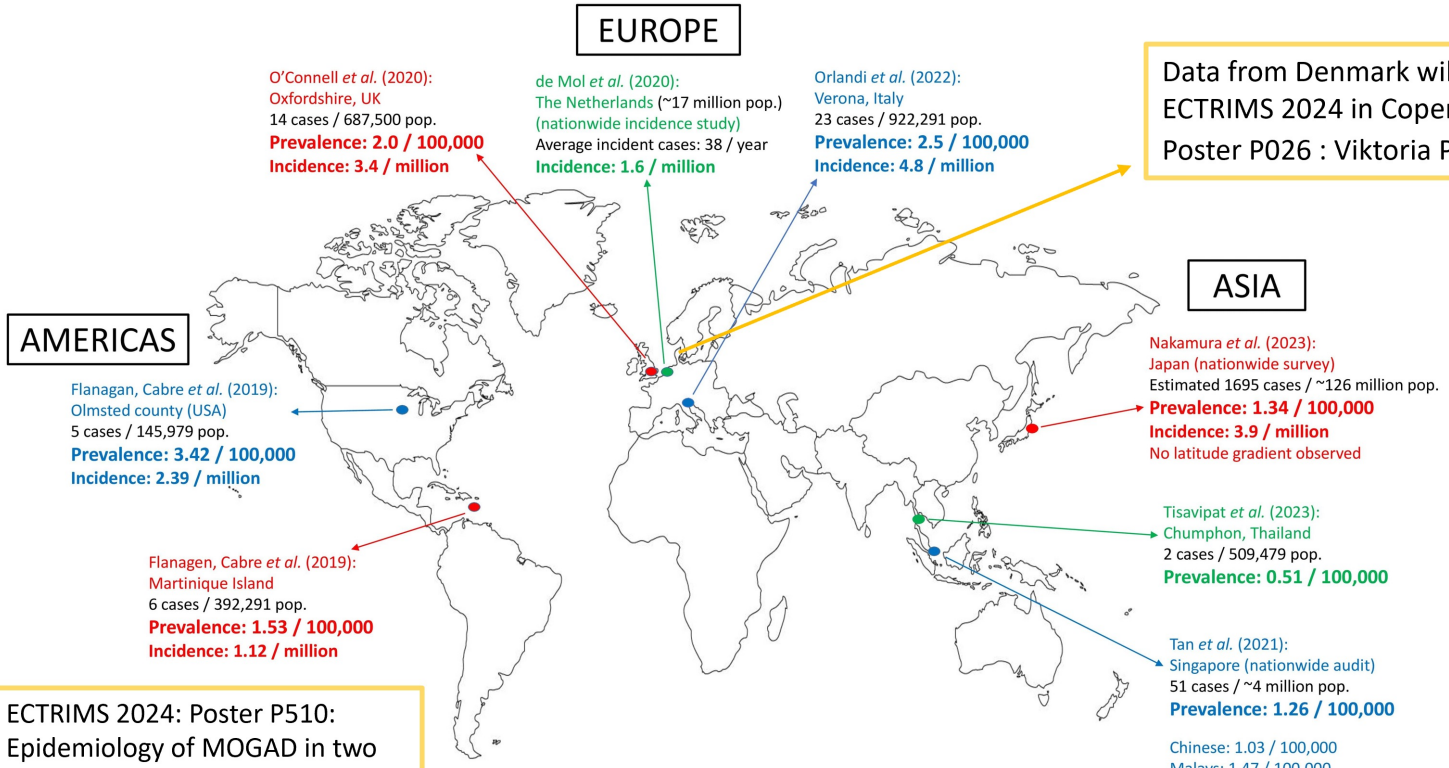
3) Population-based study in Chumphon Province, Thailand

AQP4+ NMOSD:	n=12
MOGA:	n=2
Seronegative NMOSD:	n=1

(Tisavipat *et al.*, MSARD 2023)

Proof

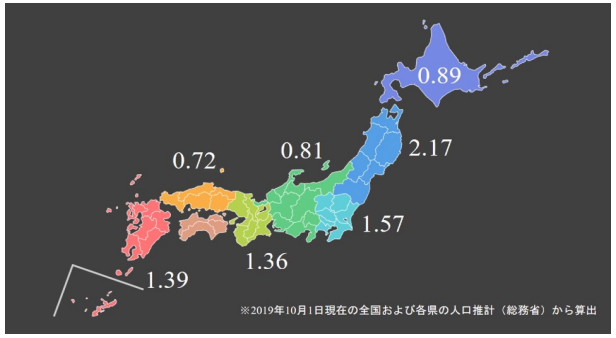
World Map Showing Population-Based Prevalence / Incidence Studies of MOGAD



(Hor *et al*. Front Neurol 2023)

Prevalence:
~1 – 2.5 / 100,000

Annual incidence:
~3 – 4.8 / million



No latitude gradient between northern and southern Japan

(Nakamura *et al*. MSJ 2023)

Prevalence & Incidence of MOGAD

	Prevalence (per 100,000)	Incidence (per million)	Compare with prevalence (per 100,000) of AQP4+ NMOSD
Europe:			
• Oxfordshire, UK	1.9	3.4	1.0
• Verona, Italy	2.2	4.8	
Asia:			
• Japan	1.34	3.9	5.3
• Singapore			
– Chinese	1.03		
– Malays	1.47		
– Indians	2.48		

(O'Connell *et al*. JNNP 2020; Orlandi *et al*. 2022; Nakamura *et al*. MSJ 2023; Tan *et al*. Neurol Clin Neurosci 2021)

Genetic / HLA Associations in MOGAD:

Dutch & UK studies: No strong HLA association

(Bruijstens *et al*. Neurol N2 2020; Grant-Peters *at al*. Ann Clin Transl Neurol 2021)

Guangzhou (China):

(1) DQB1*05:02-DRB1*16:02 haplotype in pediatric-onset MOGAD,

but no HLA association in adult-onset MOGAD (Sun *et al*. JNNP 2020)

(2) Non-HLA susceptibility loci: *BANK1*, *RNASET2*, *TNIP1* polymorphisms (Shu *et al*. J Neuroimmunol 2022)

Precedent Infection

~ 20 – 40% of MOGAD cases had infectious prodrome or precedent infection. (Hor *et al*. Front Neurol 2023)

In Japan nationwide MOGAD survey, precedent infection was more common in pediatric-onset group (39% in aged < 10 yrs) than in adult-onset group (13.5%).

(Nakamura *et al*. MSJ 2023)

common cold
pharyngolaryngitis
bronchitis
pneumonia
gastroenteritis
infections related to
- **influenza**
- **mycoplasma**
- **streptococcus**
- **chlamydia**

Post-vaccination

A small number of MOGAD cases had onset post-vaccination

Reported vaccines include:

Influenza	Japanese encephalitis
Measles / rubella	Diphtheria / tetanus / pertussis
COVID-19	

Post-COVID19 vaccination:

UK study:

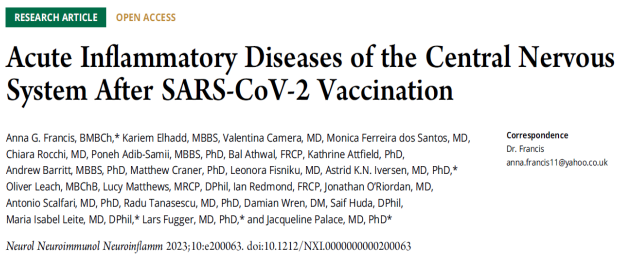
25 patients developed

acute CNS inflammatory disease:

12 : MOG-IgG+

2 : AQP4-IgG+

11 : seronegative



RESEARCH ARTICLE OPEN ACCESS

Acute Inflammatory Diseases of the Central Nervous System After SARS-CoV-2 Vaccination

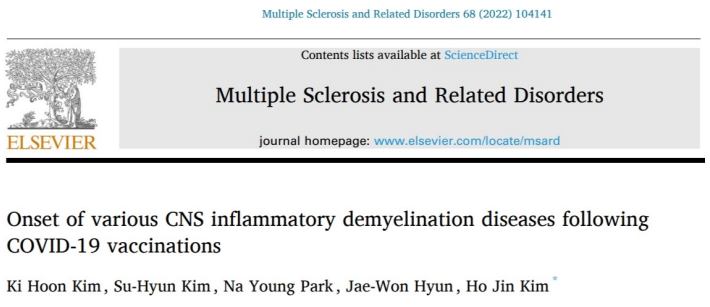
Anna G. Francis, BMBCh,* Kariem Elhadd, MBBS, Valentina Camera, MD, Monica Ferreira dos Santos, MD, Chiara Rocchi, MD, Poneh Adib-Samii, MBBS, PhD, Bal Athwal, FRCP, Kathrine Attfield, PhD, Andrew Barritt, MBBS, PhD, Matthew Craner, PhD, Leonora Fisniku, MD, Astrid K.N. Iversen, MD, PhD,* Oliver Leach, MBChB, Lucy Matthews, MRCP, DPhil, Ian Redmond, FRCP, Jonathan O'Riordan, MD, Antonio Scalfari, MD, PhD, Radu Tanasescu, MD, PhD, Damian Wren, DM, Saif Huda, DPhil, Maria Isabel Leite, MD, DPhil,* Lars Fugger, MD, PhD,* and Jacqueline Palace, MD, PhD*

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200063. doi:10.1212/NXI.0000000000200063

Korean study:

10 patients



Multiple Sclerosis and Related Disorders 68 (2022) 104141

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ELSEVIER

Onset of various CNS inflammatory demyelination diseases following COVID-19 vaccinations

Ki Hoon Kim, Su-Hyun Kim, Na Young Park, Jae-Won Hyun, Ho Jin Kim *

2 : Multiple sclerosis

2 : NMOSD

3 : MOGAD

3 : unclassified CNS-IDD

MOGAD and pregnancy

ARR decreased from 0.67 (95% CI: 0.40–1.10) during the pre-pregnancy period to 0 (0–0.21) during pregnancy and to 0.22 (0.09–0.53) during the first year post-partum.

(Carra-Dalliere et al. MSJ 2022)

MOGAD and neoplasm

MOG-antibody is a low-risk antibody for paraneoplastic neurological syndrome.

In an Italian cohort, only 2 (1.3%) of 150 MOGAD patients had tumor association – (1) 59y.o. male – non-Hodgkin lymphoma; (2) 64y.o. male – melanoma

In a literature review – 17 cases were identified – commonest association: teratoma (4 cases)

(Trentinaglia *et al*. Front Neurol 2023)

MOGAD and co-existing antibodies

NMDAR-ab is the commonest co-existing neuronal surface antibodies.

In a lab study, 14 of 376 (3.7%) samples (serum or CSF) positive for MOG ab also positive for NMDAR ab.

>200 cases were reported in the literature of dual positivity of MOG ab and NMDAR ab.

(Kunchok *et al*. MSJ 2021; Molazadeh *et al*. MSJ-ETC 2022)

Some issues of MOG-IgG detection in the diagnosis of MOGAD

1) CSF-restricted MOG-IgG positivity

MOG-IgG	Seropositive, CSF-negative	Seropositive, CSF-positive	Seronegative, CSF-positive
Italy (n=16), Mariotto, Neurology 2019	31%	50%	19%
UK (n=118), Pace, JNNP 2021	56%	41%	3%
Korea (n=40), Kwon, N2 2023	30%	47%	23%
Japan (n=133), Matsumoto, Brain 2023	13%	71%	17%
Multicentor (n= 255), Carta, Neurology 2023	31%	57%	12%
Italy (n=55), Greco, JNNP 2024	58%	35%	7%
Canada (n=28), Burton, J Neurol 2024	82%	18%	0%
US (n=83), Redenbaugh, Neurology 2024.	10%	79%	11%
Australia (n=114), Reynolds, Ann Clin Transl Neurol 2024	45%	52%	3%

(prepared by Dr. Yuki Matsumoto)

2) Isolated MOG-IgA positivity

In DN for AQP4-IgG andMOG-IgG(1126/1339;84%),
isolated MOG-IgA was identified 6% (3/50) of NMOSD, 2% (5/228) of other CNS demyel dis, and 1% (10/848)) of MS
but in none of HC (0/110).

(Gomes *et al*. JAMA Neurol 2023)

3) Exclusive or predominant MOG-IgG3 serpositivity

(Jarius *et al*. J Neurol 2024)

Comparison of AQP4+NMOSD, MOGAD & SND

	MOGAD	AQP4+NMOSD	SND
Pediatric onset	Frequent	Extremely rare	Infrequent (Onset 32~43y)
Sex distribution	F=M	F>M	F=or>M
Disease course	Monophasic/relapsing	Most often relapsing	Monophasic/relapsing (24~100%)
Optic nerve	Severe, good recovery Bil, anterior, longi ext, ON sheath, ON head edema	Severe, poor recovery, Bil/Unil, posterior, longi ext, chiasmal	Moderate~severe, relatively poor recovery, Unil in many, Rare chiasmal involvement
Spinal cord	Severe, excellent recovery, LETM, H sign, conus lesion	Severe, poor recovery, LETM Bright spotty lesion	Moderate~severe, relatively poor recovery, LETM
Brain	Encephalopathy (eg, ADEM), cerebral cortical encephalitis	APS, hypersomnolence	Lesions in some, rare/no APS
Prevalence	Relatively constant	Higher in Blacks, East Asians and Native Americans Probably increasing (stable incid)	Lower than MOGAD/AQP4+
N-S gradient	no	no	?
ARR in postpartum	Not increased	Higher	?
Post-infection/vaccine	20~40%/in some	Relatively rare	?
Coexisting AI/neoplasm	Uncommon (except NMDAR-ab)	Not uncommon	AI 12.9%

Emerging Molecular and Cellular Biomarkers in NMOSD

Yang Mao-Draayer, MD, PhD

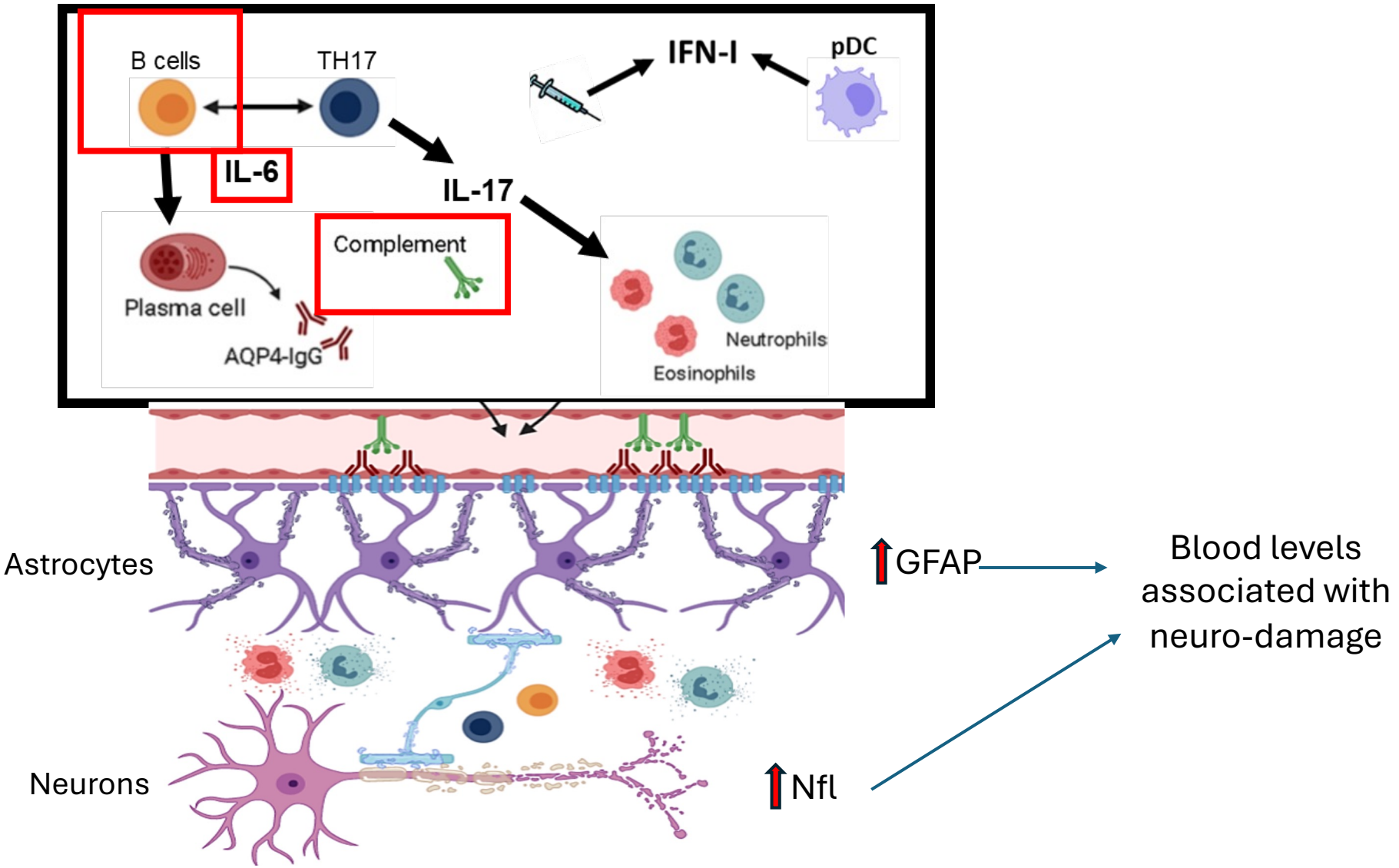
Professor and Director of Clinical and Experimental Therapeutics

Multiple Sclerosis Center of Excellence
Autoimmunity Center of Excellence
Arthritis and Clinical Immunology Research Program
Oklahoma Medical Research Foundation

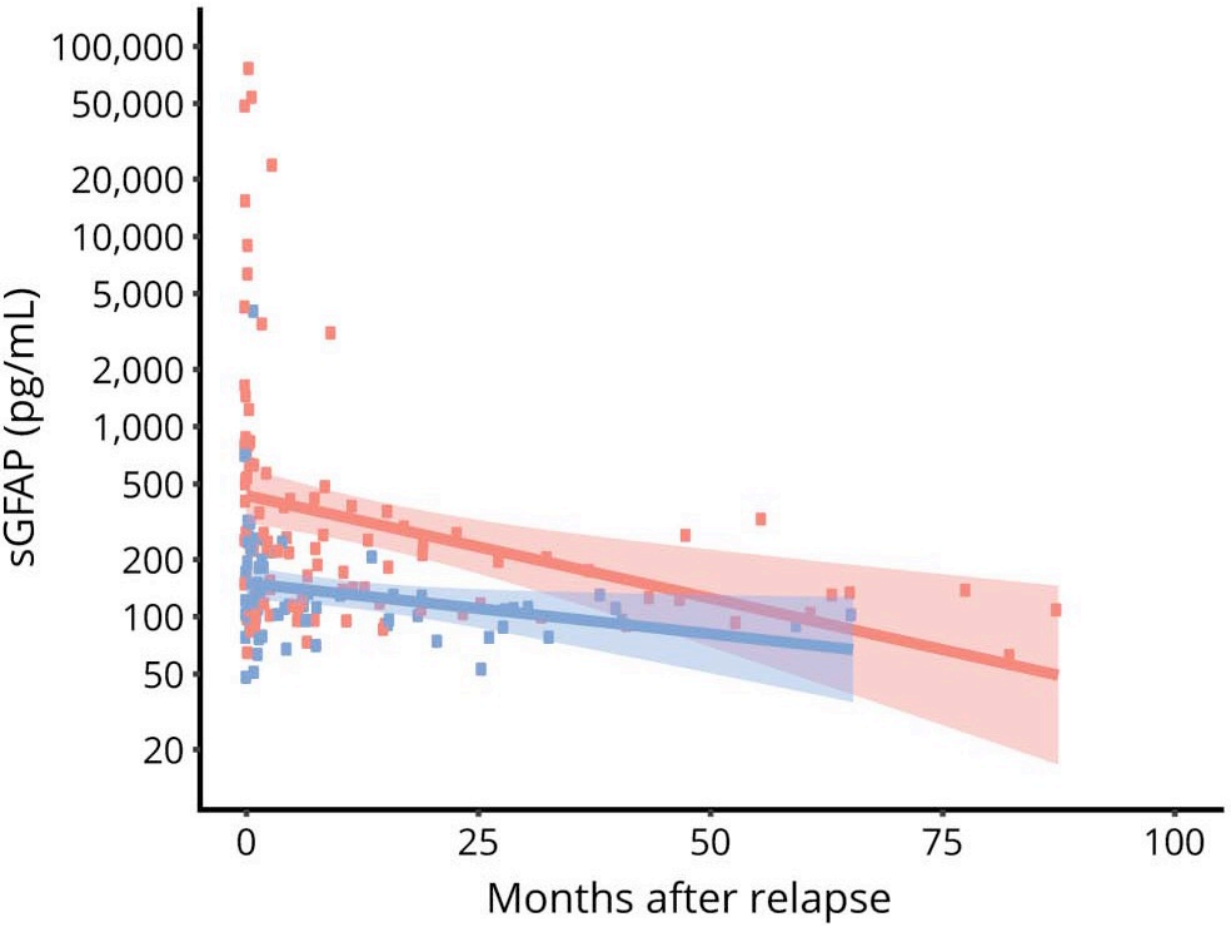


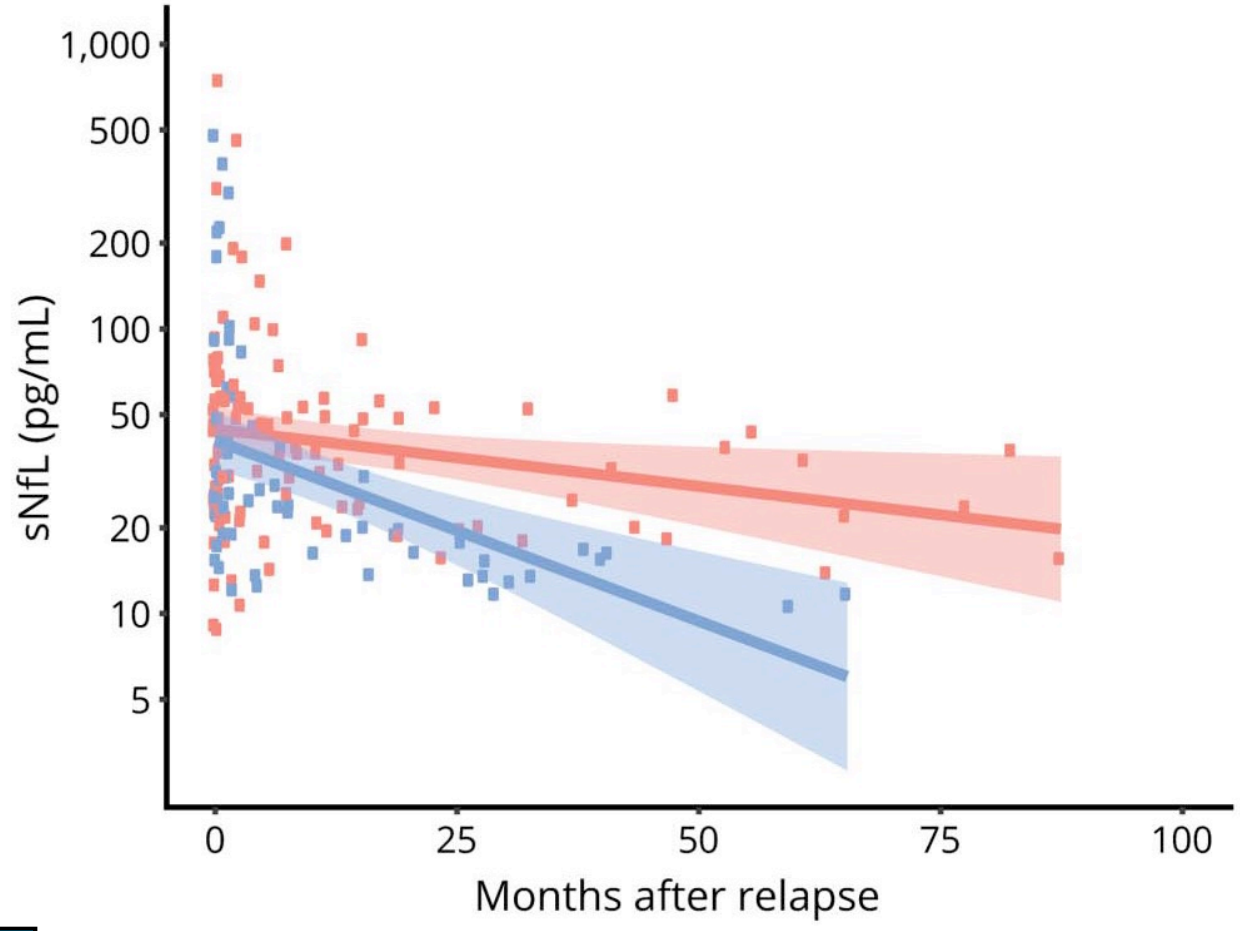
DISCOVERIES THAT MAKE A DIFFERENCE

Immune pathogenesis of NMO



Longitudinal Changes in GFAP and NFL after relapse

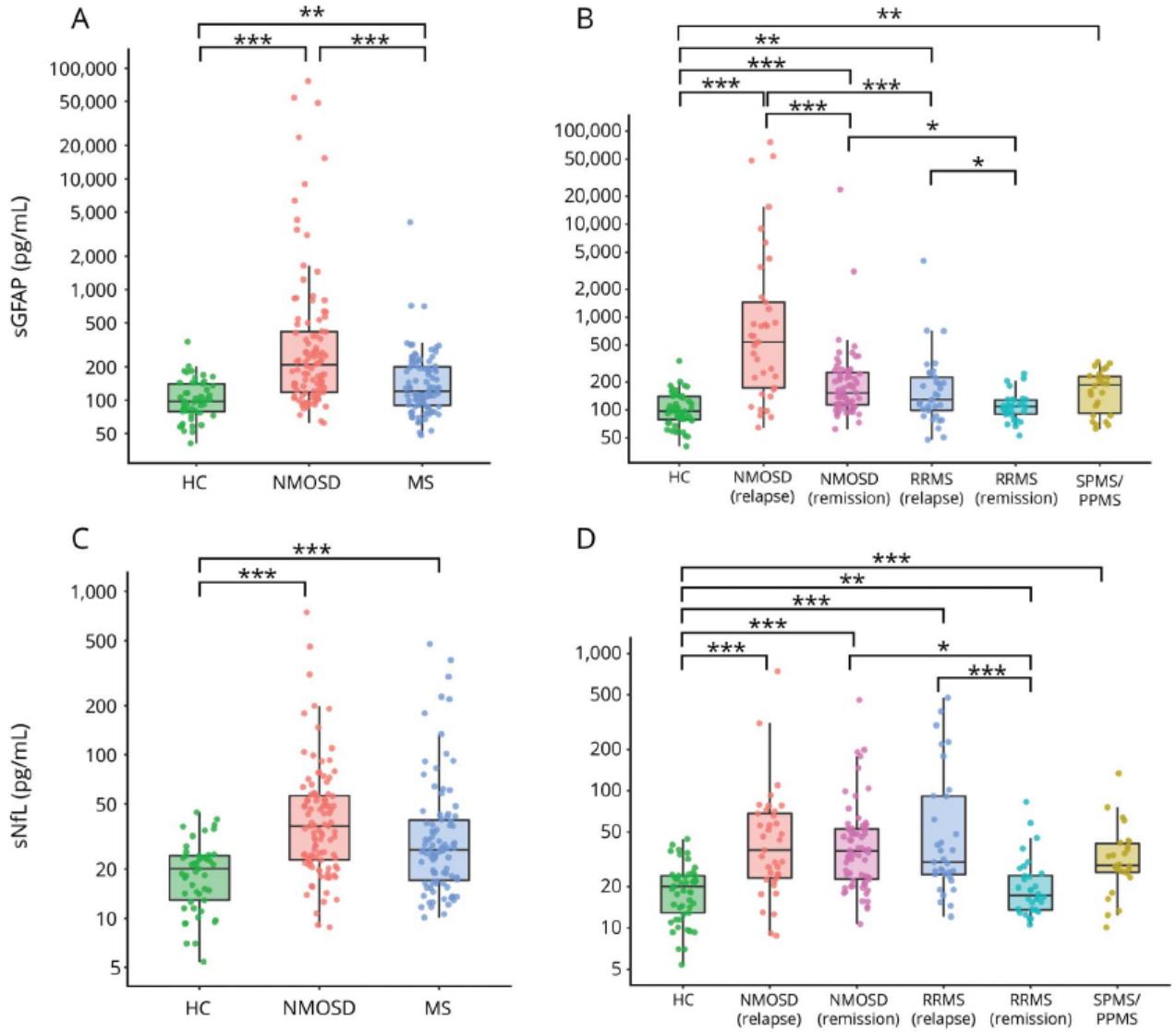




MS
NMO

Watanabe et al. Neurology 2019

GFAP levels are reduced during remission in NMO

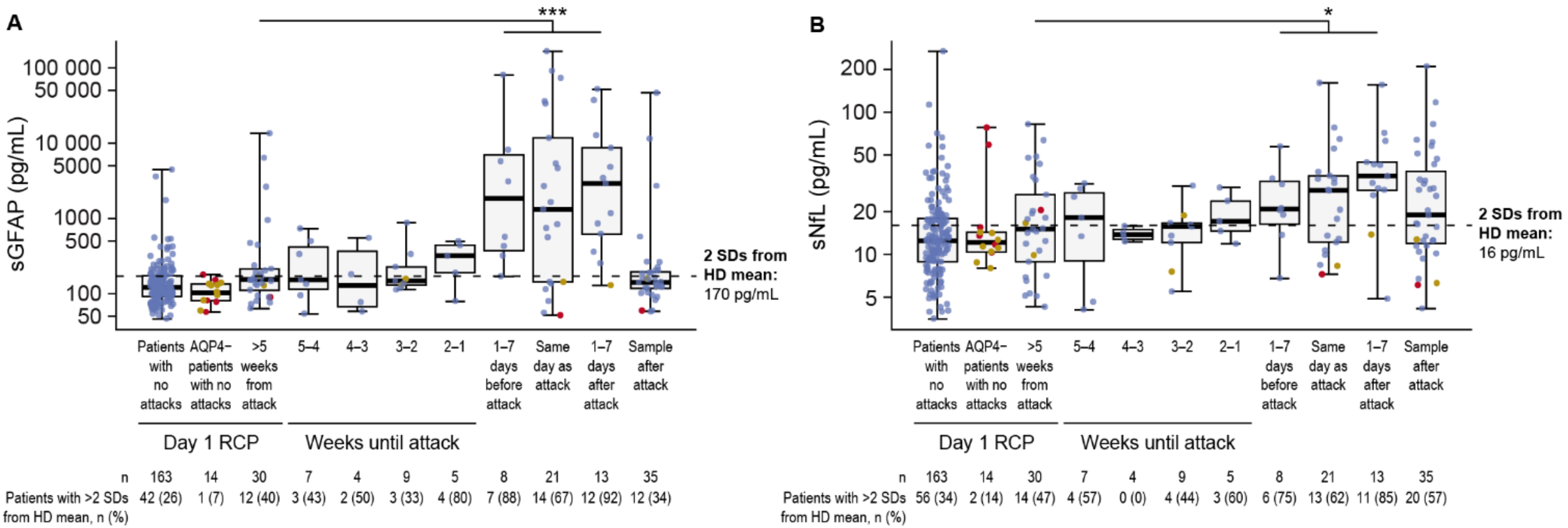


GFAP levels are associated with EDSS and relapse

NFL levels are associated with EDSS not relapse

Watanabe et al, Neurology 2019

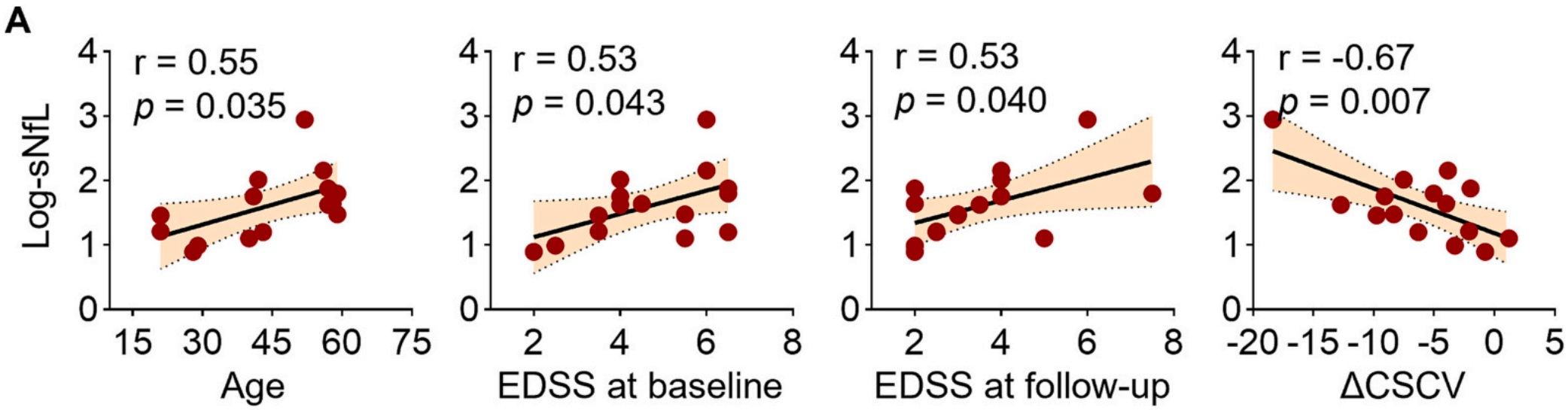
GFAP (not NFL) tracks with relapse



Aktas O et al. N-Momentum study, JNNP 2023

Nfl associated with EDSS and spinal cord atrophy during remission

Relapse at Baseline



Treatments : rituximab, tocilizumab

Follow up is 1 year.

Li Yl, et al. JNI 2023

Are there molecular and cellular signatures in NMO patients?

Collaborators

Dr. Friedemann Paul, *Charité Universitätsmedizin, Berlin*

Dr. Robert Axtell, *OMRF*

- **Proteomics:** Serum protein profiling of patients
- **Transcriptomics:** Whole blood RNA profiling

Study design for NMOSD biomarkers



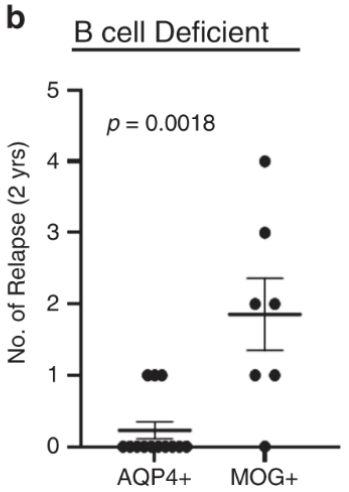
96 NMOSD patients
- 53 AQP4+
- 25 MOG+
- 18 DN

49 Healthy Controls



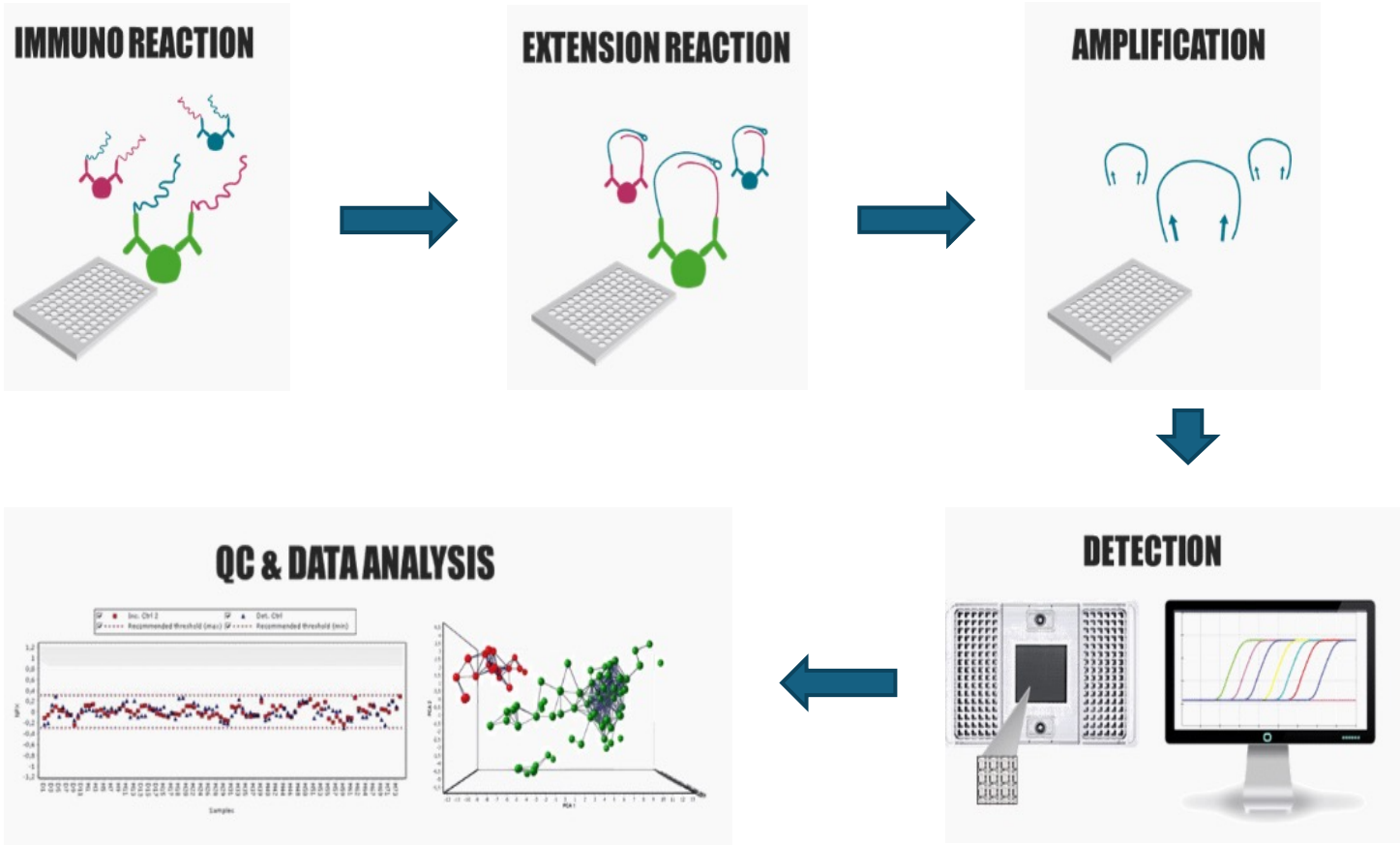
Serum proteomics

Distinguish between AQP4+, MOG+ and DN-NMOSD patients



Differences in effect of BCD in AQP4+, MOG+ and DN-NMOSD patients

Proximity Extension Assay (PEA) - Olink Proteomics

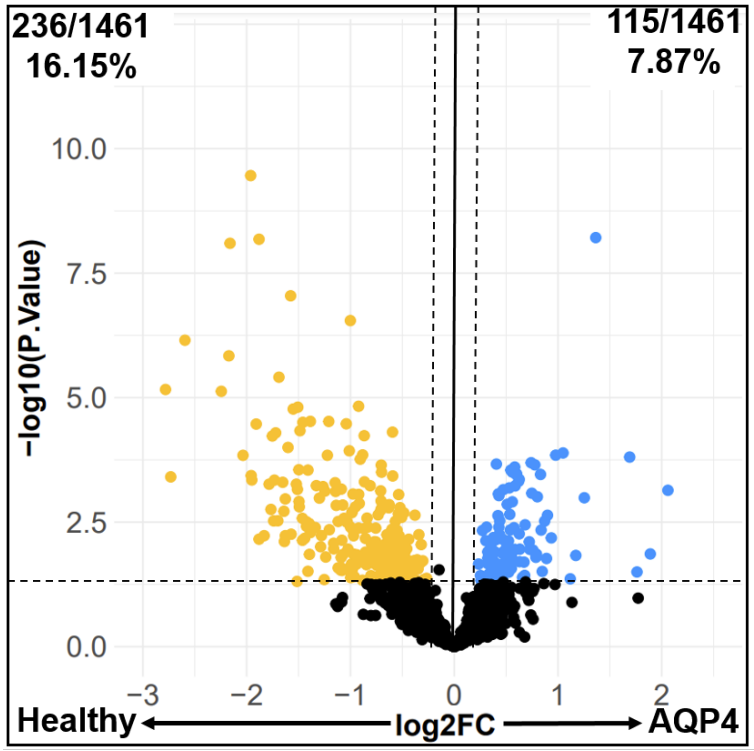


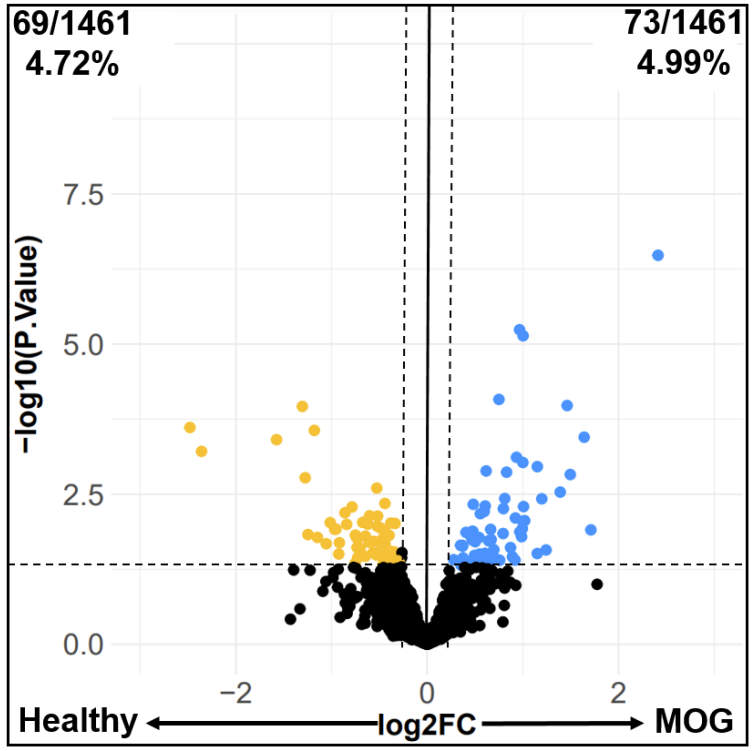
Why use PEA?

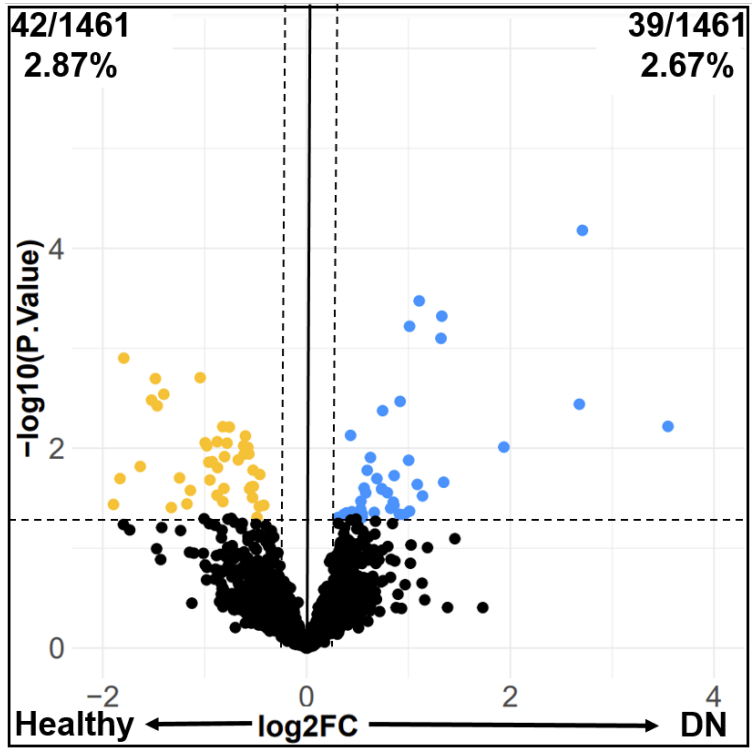
1. Highly sensitive compared to standard ELISAs
2. Low chance of antibody cross-reactivity compared to other multiplexing assays
3. Requires very little sample volume

4. **Measures over 1500 serum proteins in one aliquot of sample**

Serum protein profiles distinguish NMOSD subgroups from healthy controls

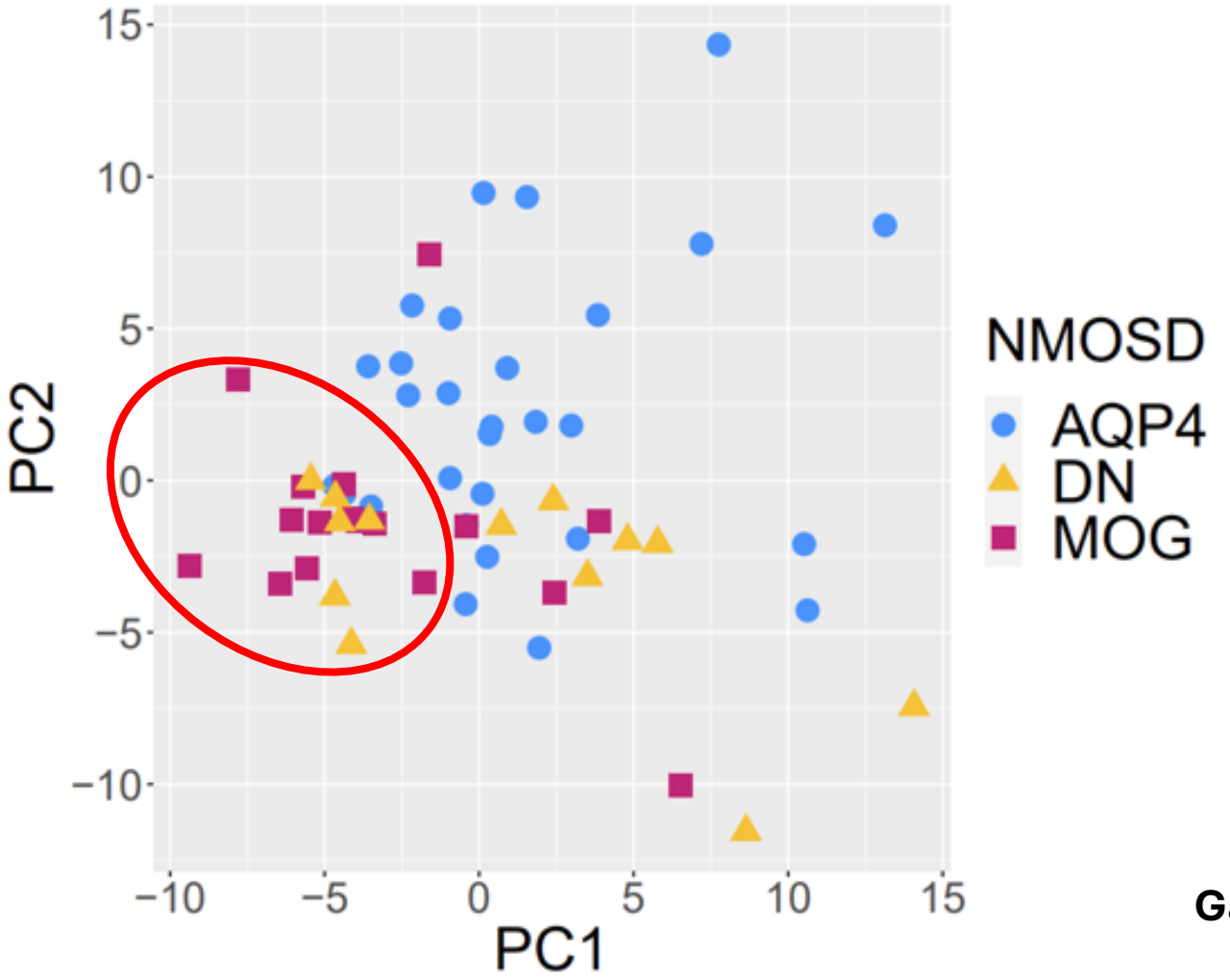






Gawde S et al. Neurol Neuroimmunol Neuroinflamm 2024

Serum protein profiles distinguish between NMOSD subgroups



- Overall serum protein profiles can distinguish NMOSD subgroups.
- Overlap between serum protein profiles of MOG-NMOSD and DN-NMOSD patients

Gawde S et al. Neurol Neuroimmunol Neuroinflamm 2024

Serum protein profiles distinguish NMOSD subgroups from healthy controls

AQP4-NMOSD

MOG-NMOSD

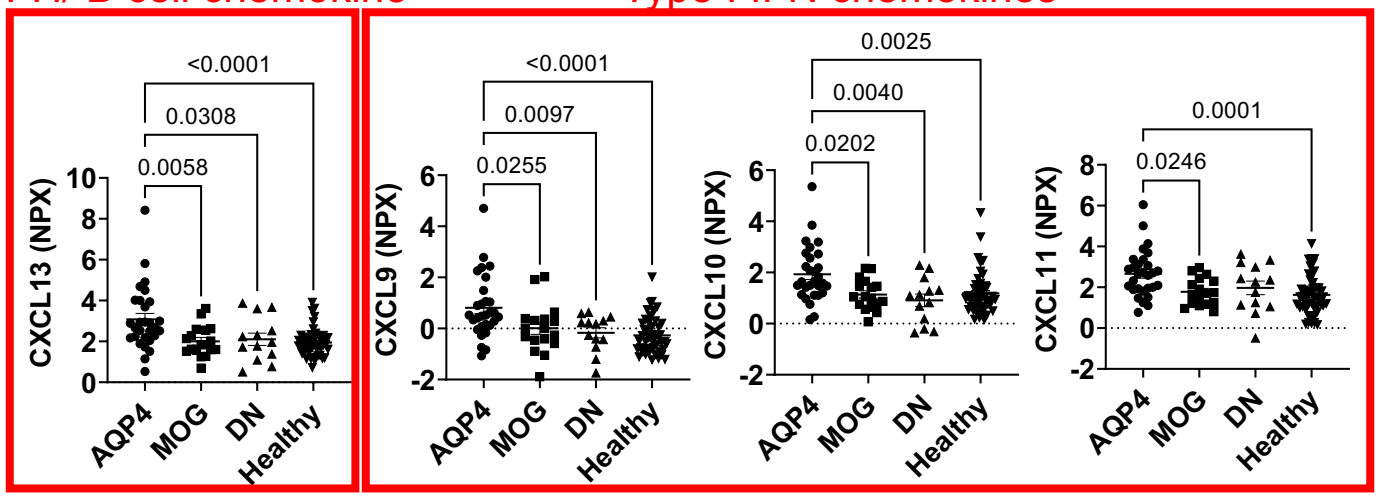
DN-NMOSD

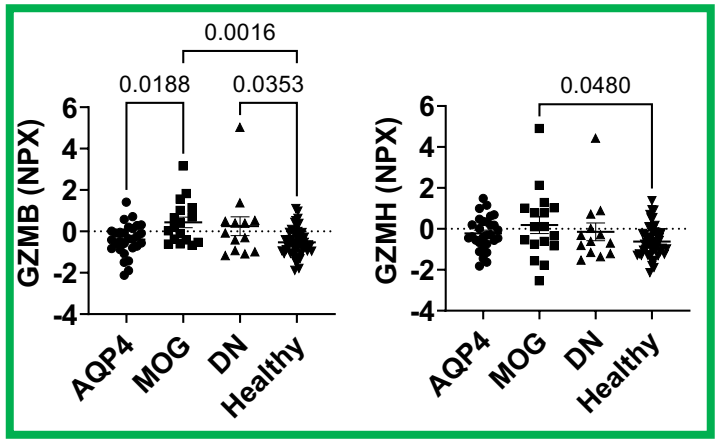
TFH/ B cell chemokine

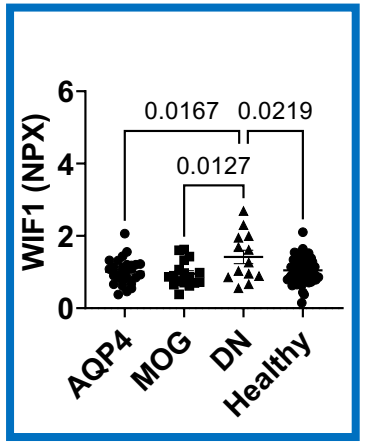
Type I IFN chemokines

Granzymes

Wnt inhibitory factor 1







Gawde et al. N2 2024

Short Summary

- Type I IFN-induced chemokines CXCL9, CXCL10 and CXCL11 are elevated in AQP4-NMOSD.
  - Indicate that pathogenic processes in AQP4-NMOSD are driven by type I IFN

- CXCL13, which is a T follicular helper (TfH)/ B cell chemokine, is elevated in AQP4-NMOSD.
  - Indicate that these cells are involved in pathogenesis of AQP4-NMOSD

- Granzyme B and H levels are increased in MOGAD.
  - MOG-reactive CD8+ T cells could be involved in MOGAD pathogenesis

- Serum protein profiles of DN-NMOSD are more similar to MOGAD than AQP4-NMOSD



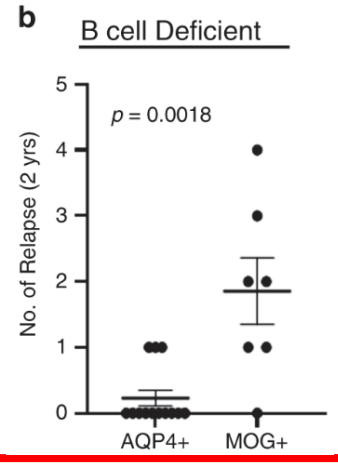
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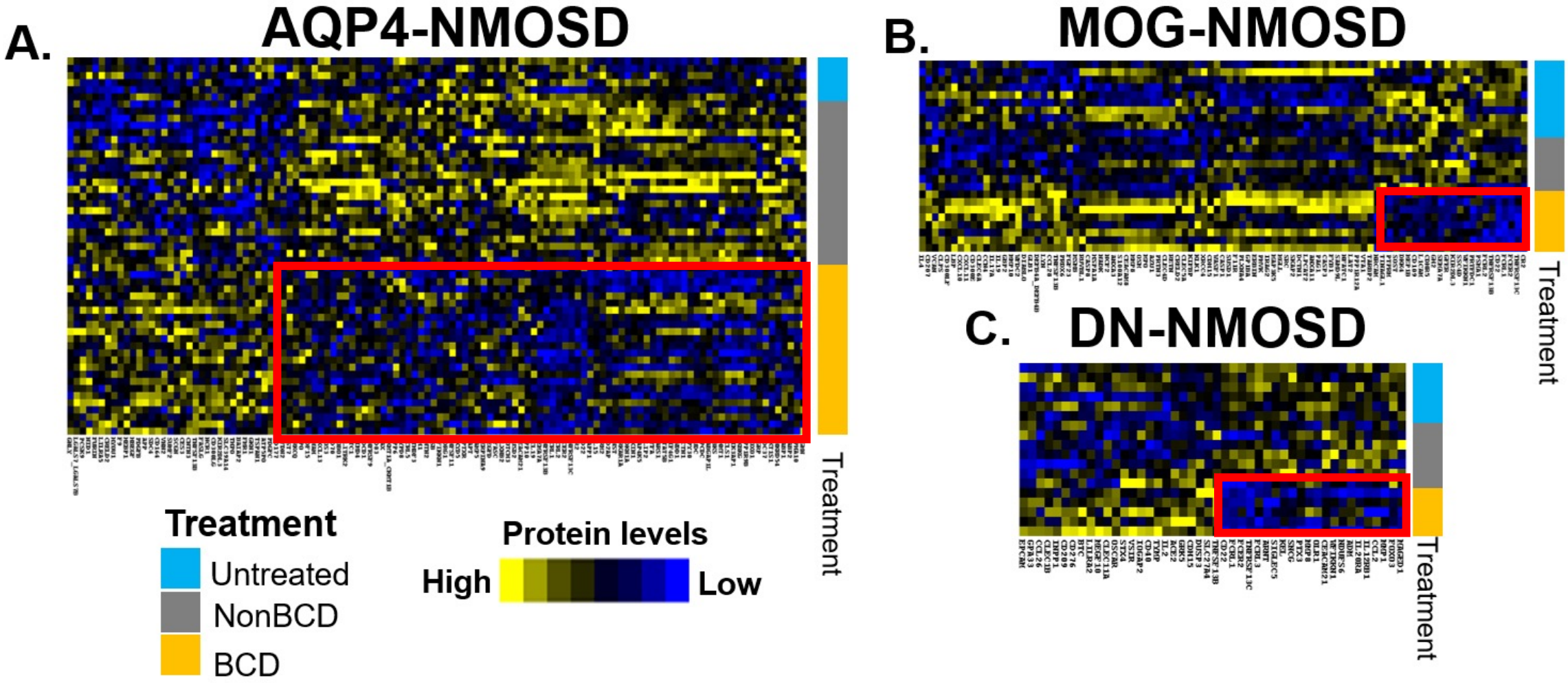
Serum proteomics

Distinguish between AQP4+, MOG+ and DN-NMOSD patients



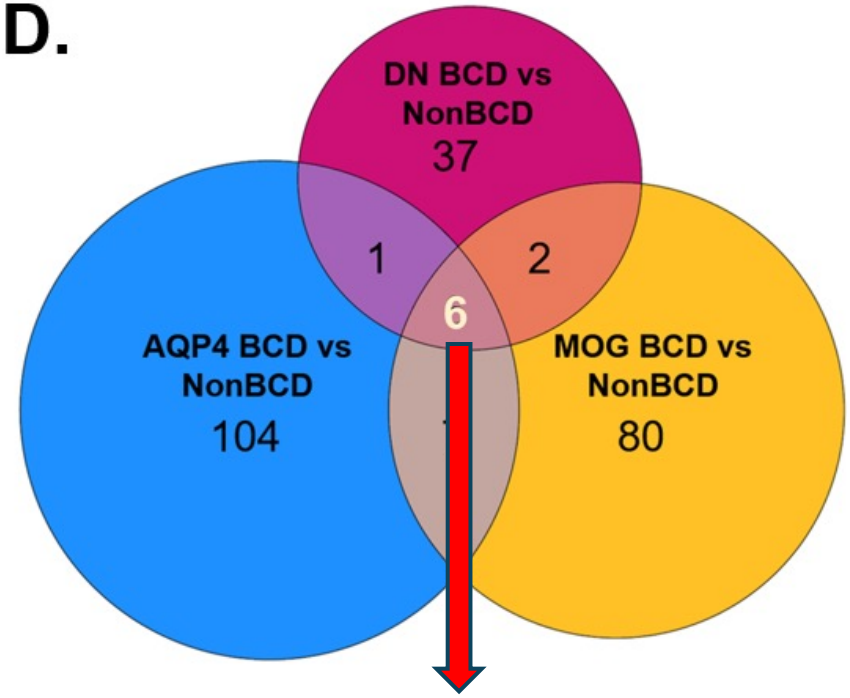
Differences in effect of BCD in AQP4+, MOG+ and DN-NMOSD patients

BCD alters serum protein profiles of NMOSD subgroups



Serum proteins indicate B cell depletion in NMOSD subgroups

D.



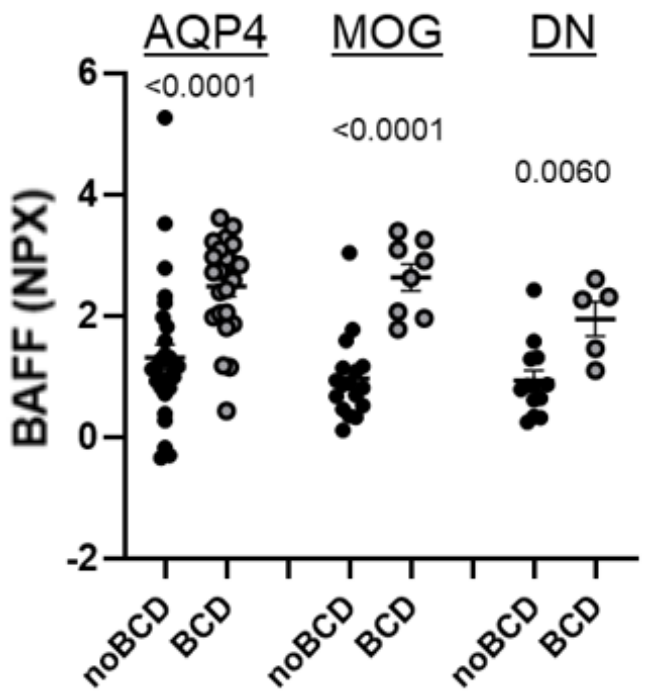
Common proteins

BAFF → ↑ with BCD

B cell associated proteins

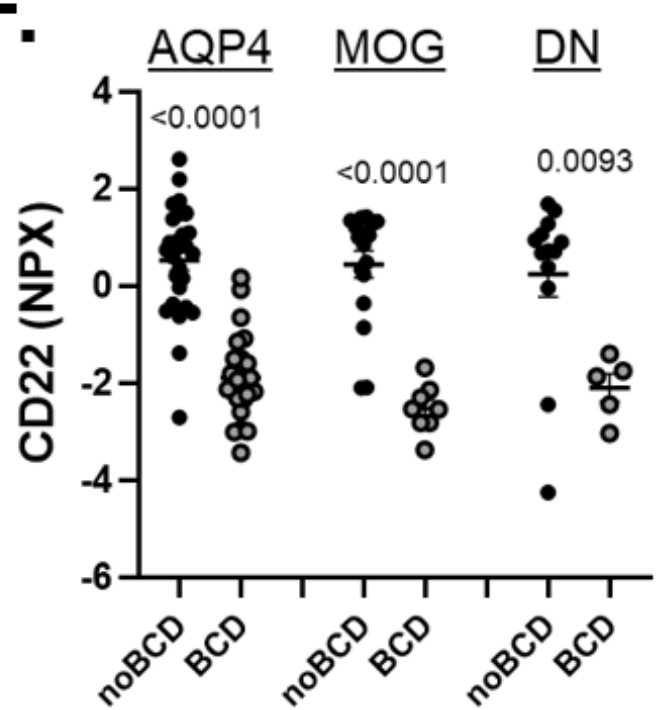
FCER2
TNFRSF13C
WFIKKN1
FCRL1
CD22
↓ with BCD

G.



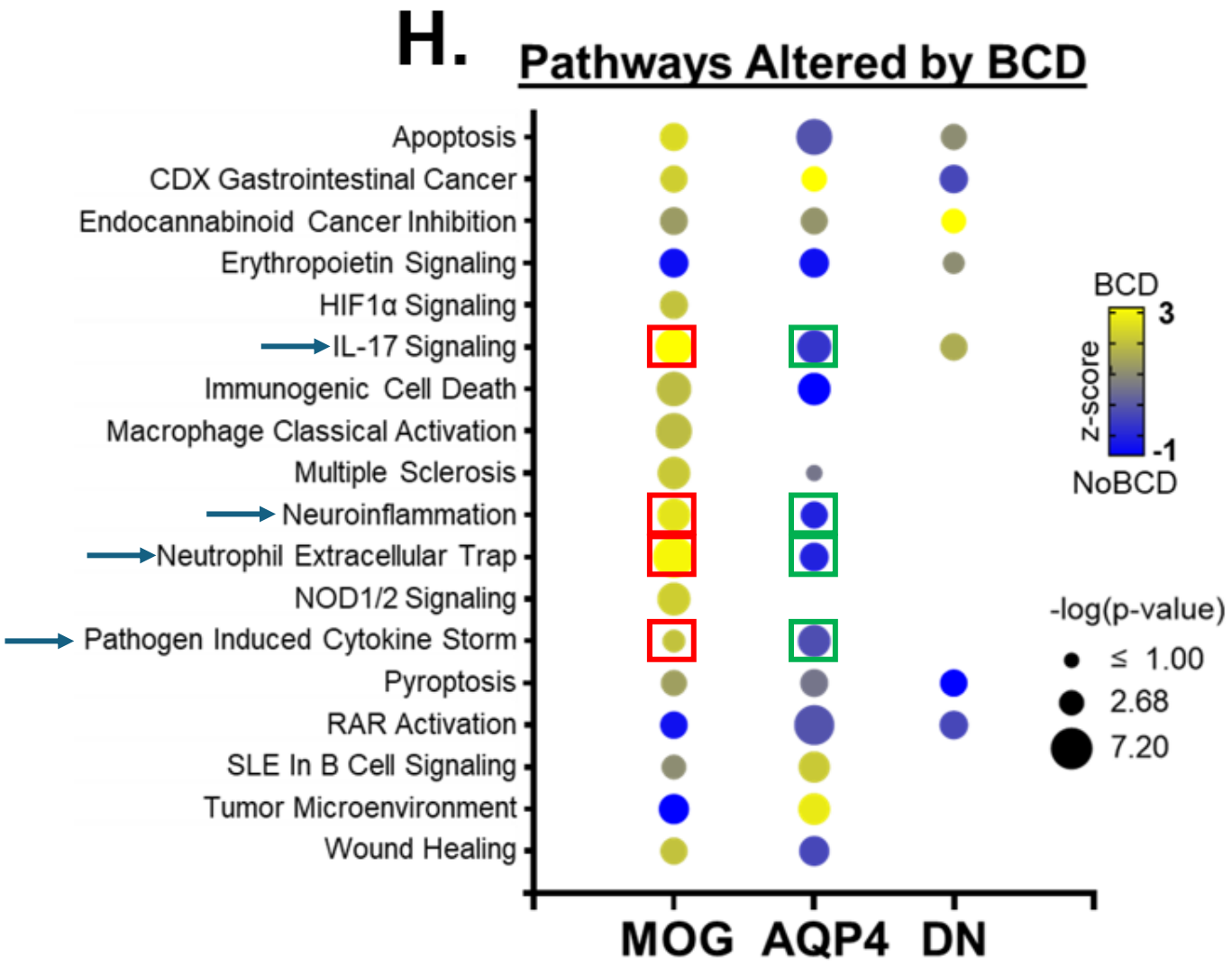
B cell survival factor (BAFF)

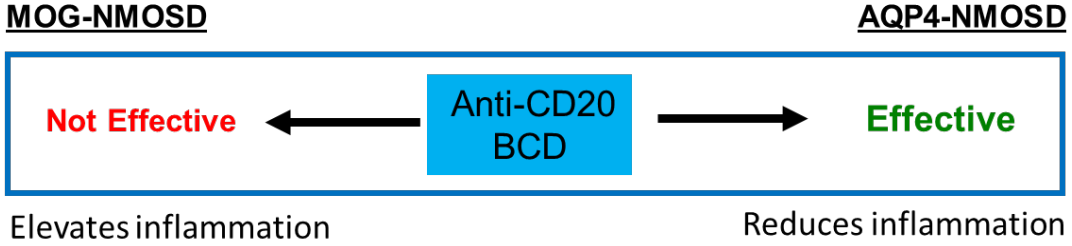
F.

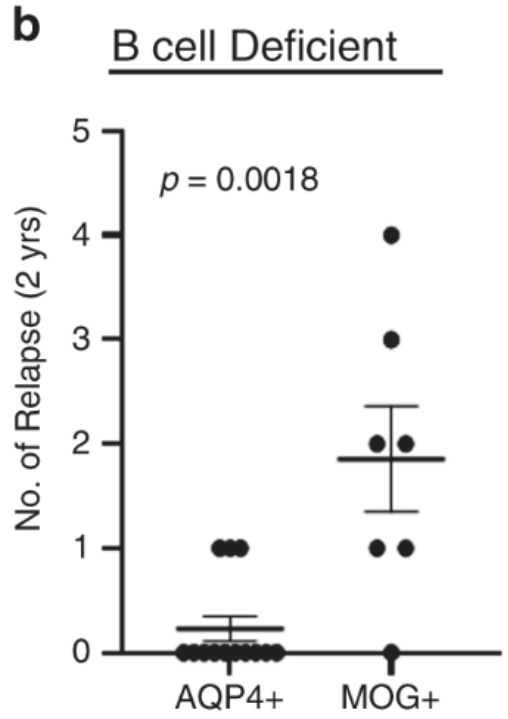


Expressed on B cells

BCD differentially modulates inflammatory pathways in AQP4 and MOG-NMOSD patients





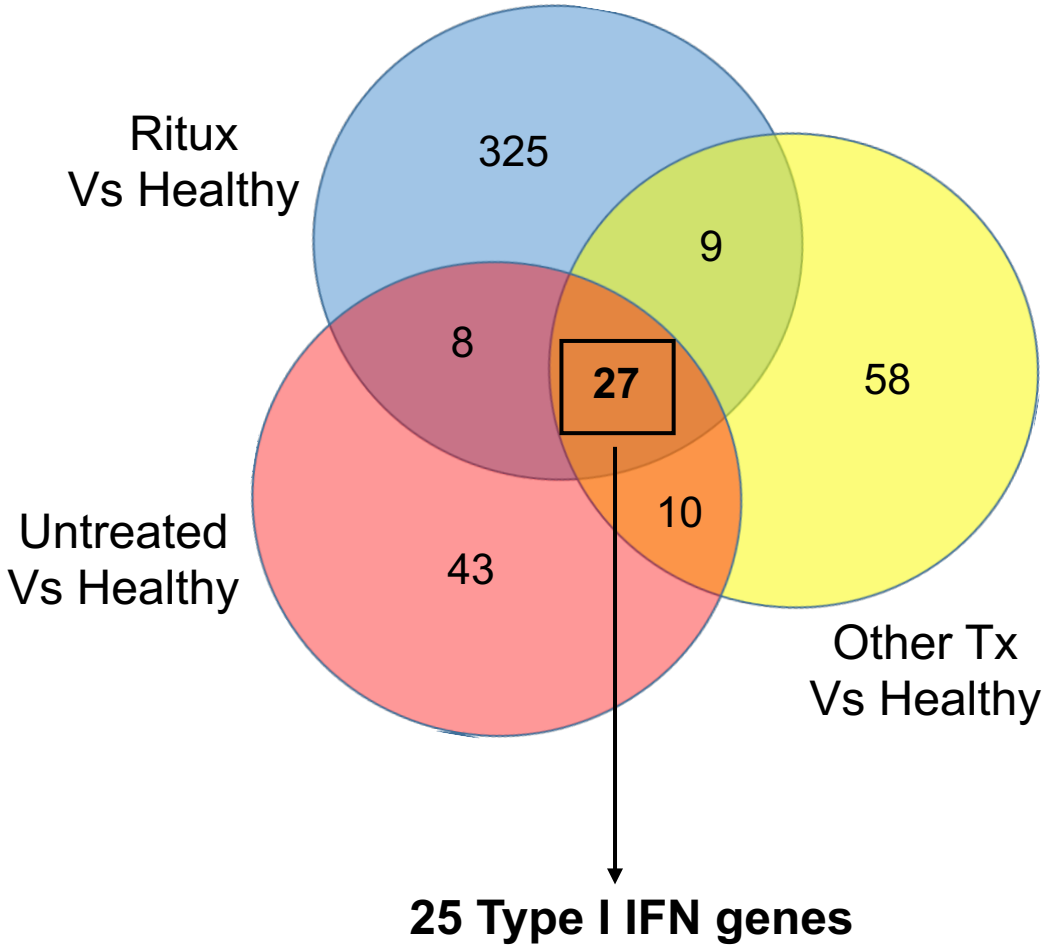


Gawde S et al. Neurol Neuroimmunol Neuroinflamm 2024

Short Summary

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- Granzyme B and H levels are increased in MOGAD.
- Serum protein profiles of DN-NMOSD are more similar to MOGAD than AQP4-NMOSD
- Anti-CD20 BCD differentially modulates inflammatory signaling pathways in AQP4-NMOSD and MOGAD.

RNA profiles of NMO patients

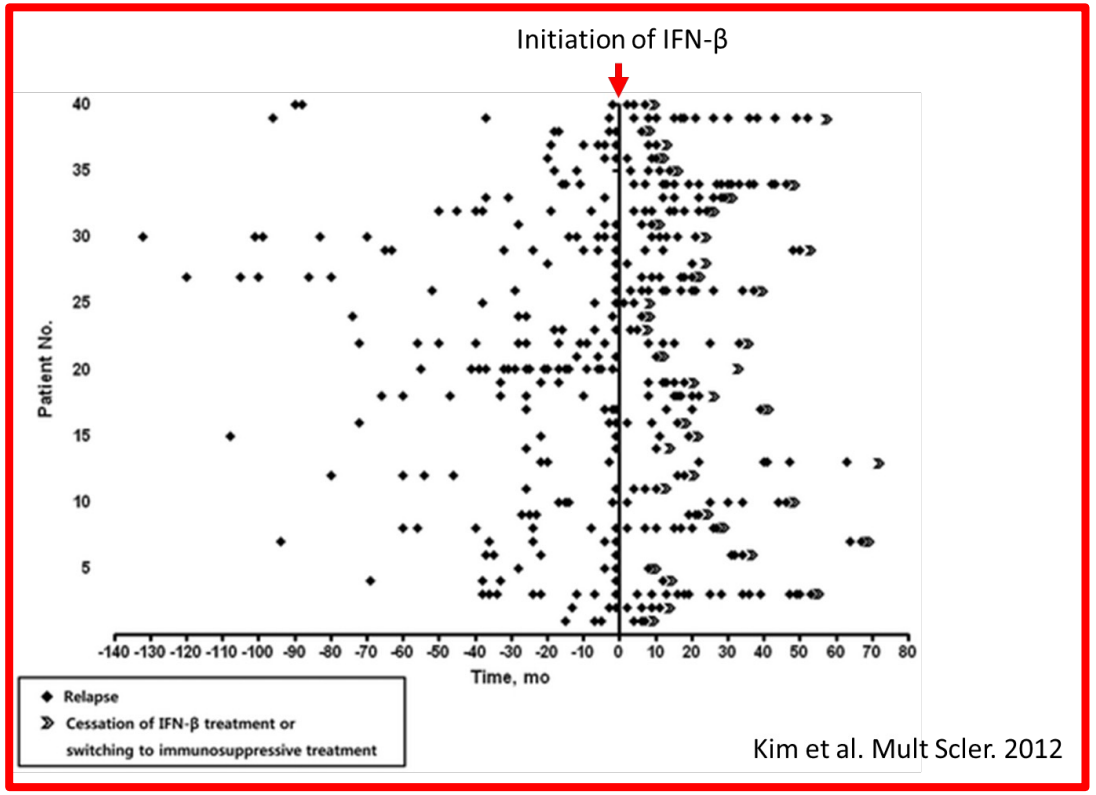


Agasing et al. Mao-Draayer...Axtell. *Nature Communications* 2020

Transcriptomics

Recombinant Type I IFN treatment induces NMO relapses

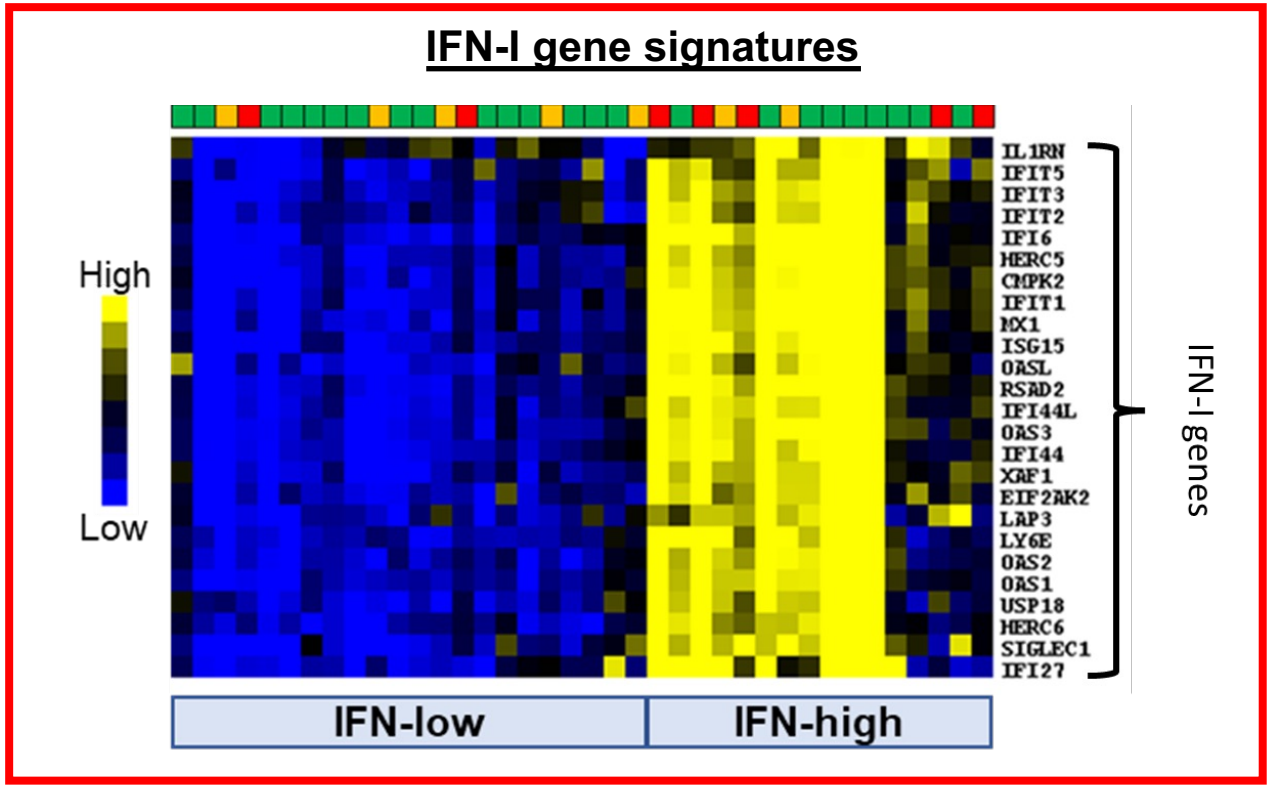
- **Interferon Beta (Type I IFN)** (FDA approved for Multiple sclerosis) **worsens NMOSD**



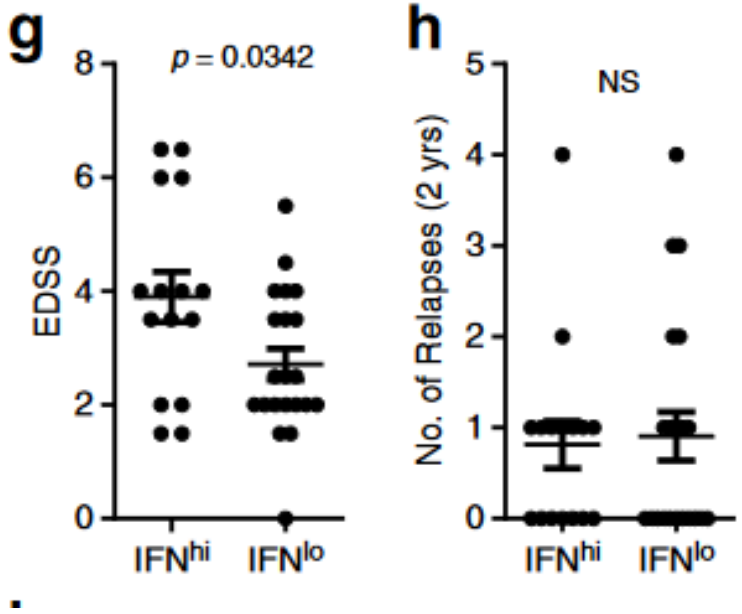
Kim et al. Mult Scler. 2012

Endogenous Type I IFN is associated with severe persistent disability in NMO

Transcriptomics (IFN-signatures)



Clinical Outcomes



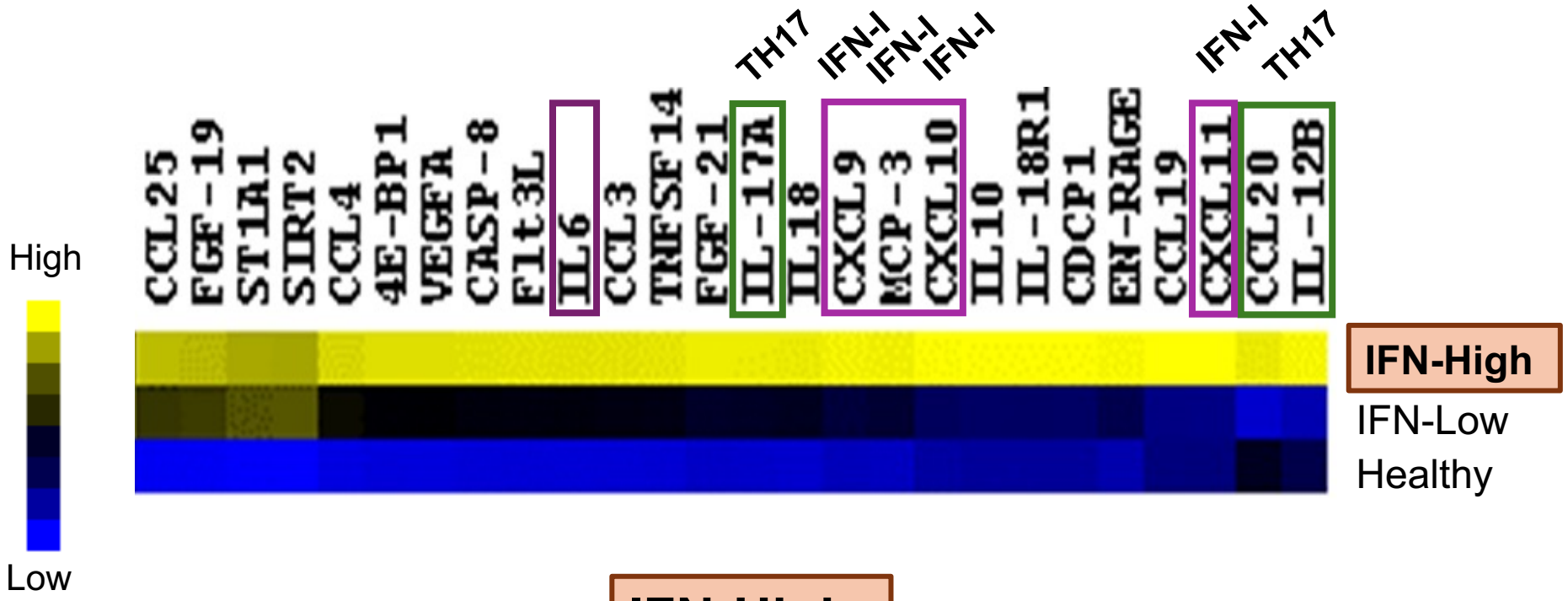
Findings

- Interferon signatures are elevated in NMOSD.
- IFN signatures can stratify NMOSD: IFN-high and IFN-low
- IFN-high patients had ↑ serum IL-17 cytokines and IL-6.
- IFN-high patients had severe disability (but not relapses)

nature COMMUNICATIONS

Agasing et al. Mao-Draayer...Axtell *Nature Communications* 2020.

IFN-High NMO is characterized by elevated IL-6 and TH17 responses



IFN-High

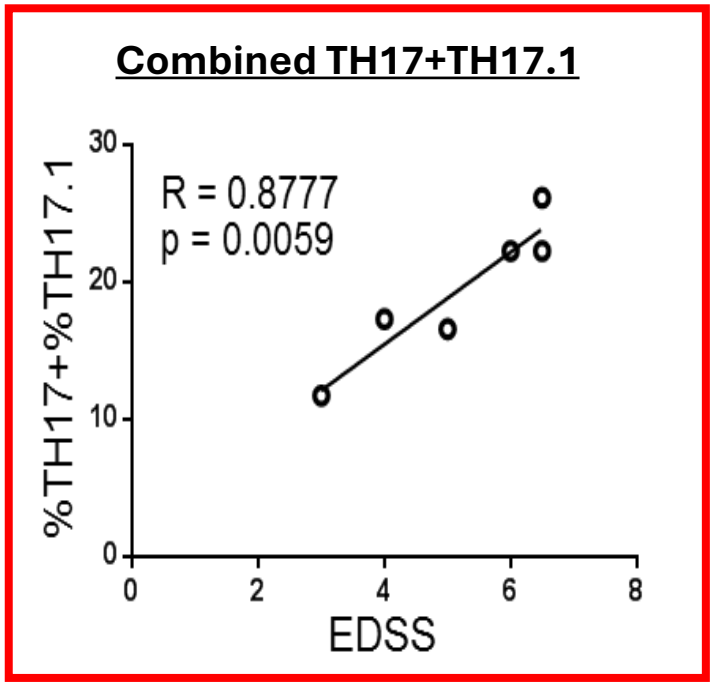
TH17 responses – ↑IL-17A, ↑IL-12p40, ↑CCL20
IFN-I signatures – ↑MCP-3, CXCL9, CXCL10, CXCL11
IFN-I/TH17 signatures – ↑IL-6

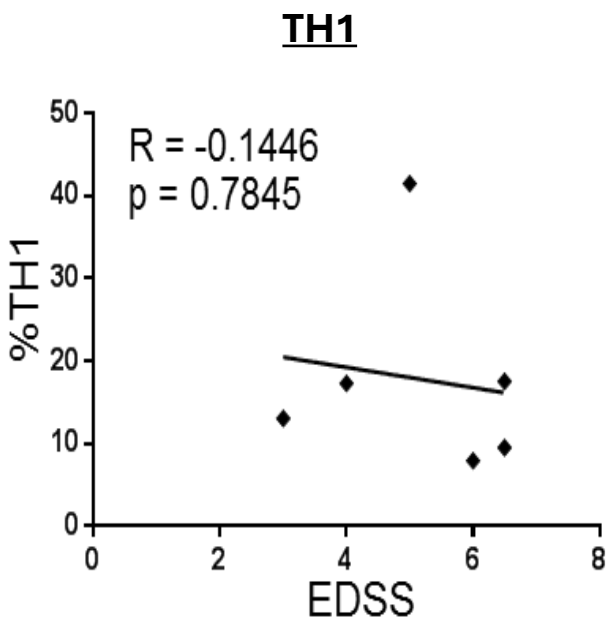
Agasing et al. Mao-Draayer...Axtell. *Nature Communications* 2020

Proteomics

TH17 cells in PBMCs are correlated with EDSS

Variables	NMOSD
Total no.	6
Age, year, mean (SD)	45.6 (17.3)
Sex F/M (%F)	4/2 (67.7)
Serological status, N (%)	
AQP4-Ig+	6 (100)
MOG-Ig+	0 (0)
Treatment, N (%)	
None	6 (100)
EDSS, mean (range)	5.2 (3 - 6.5)

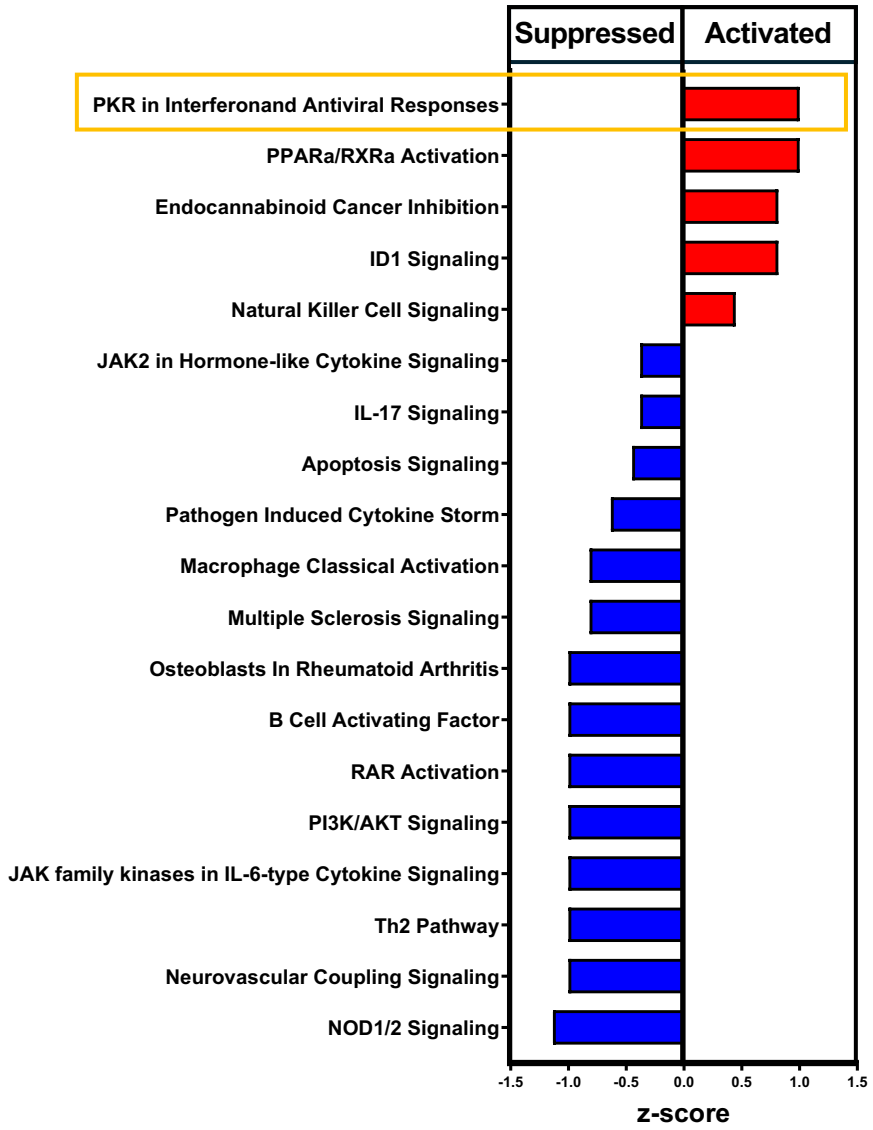




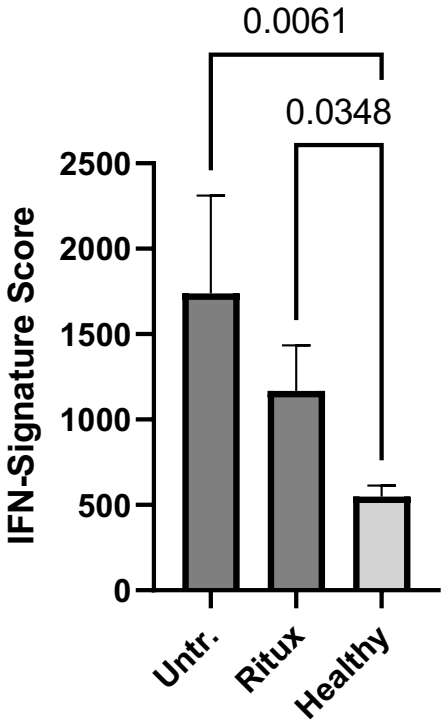
Agasing et al. Mao-Draayer...Axtell *Nature Communications* 2020

B cell depletion does not reduce IFN-signatures in NMO

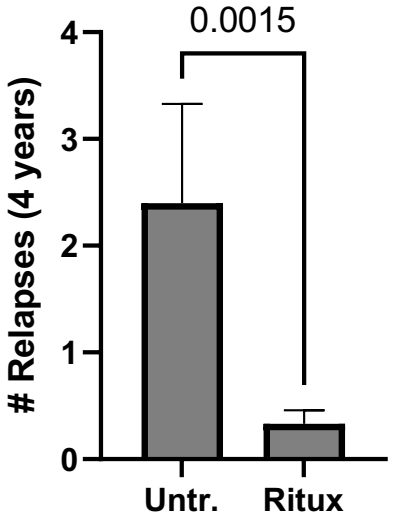
Serum Proteomics signatures affected by BCD



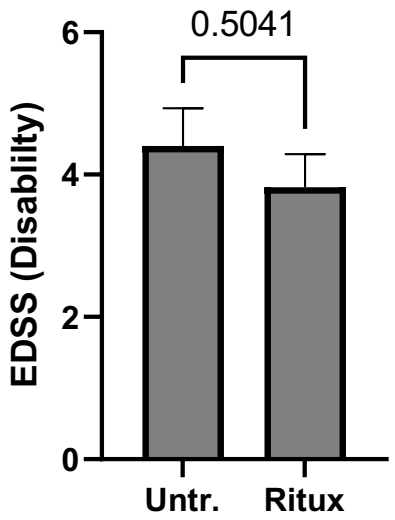
Transcriptomics



Little effect on IFN-Sig.



Reduce Relapses



Little effect on EDSS

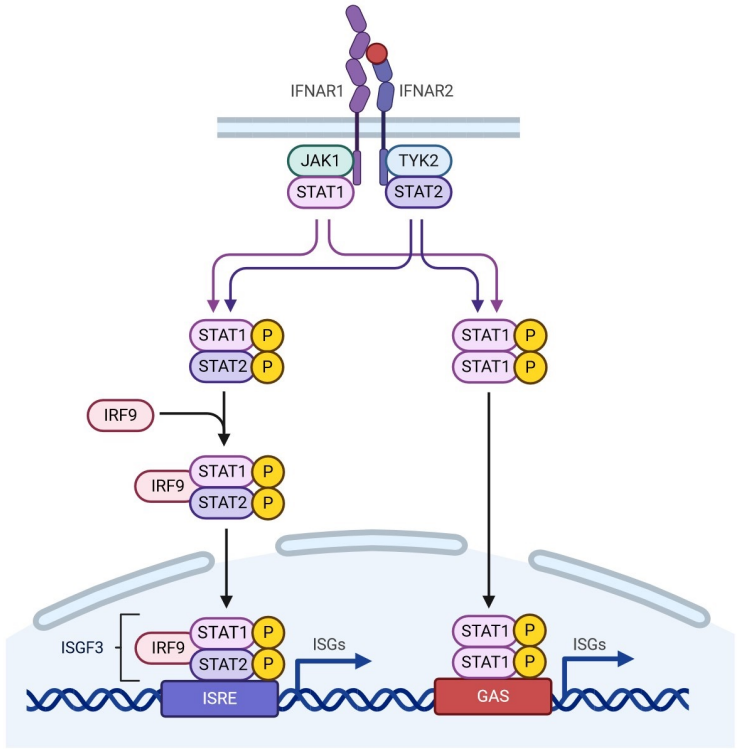
Gawde et al. N2 2024

Blockade of Type I IFN in NMO

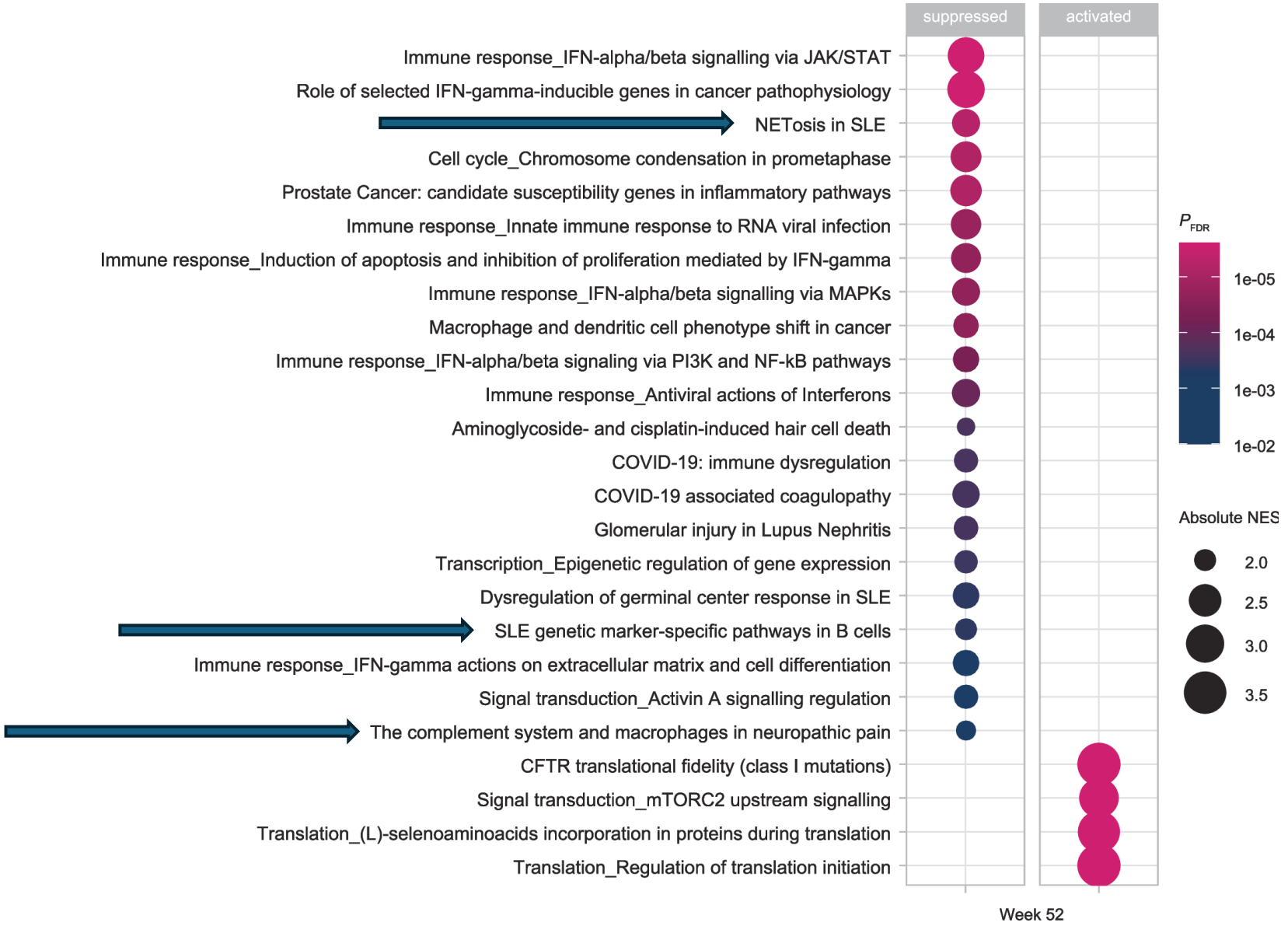
- Type I IFN is elevated in NMO and is associated with worse disability and neuro-damage.
- Current DMTs continue to have worsening symptoms/disability.
- Current DMTs (anti-CD20) do not reduce IFN-gene signatures.
- **Could the addition of anifrolumab to standard of care benefit patients?**

Anifrolumab-IFN receptor blocker

- Anifrolumab is an antibody that binds and blocks the type I IFN receptor.
- It is approved for treating systemic lupus erythematosus (SLE)
- Proteomic studies of SLE trials (TULIP1 and TULIP2) show anifrolumab reduces several biological pathways implicated in NMO pathology.

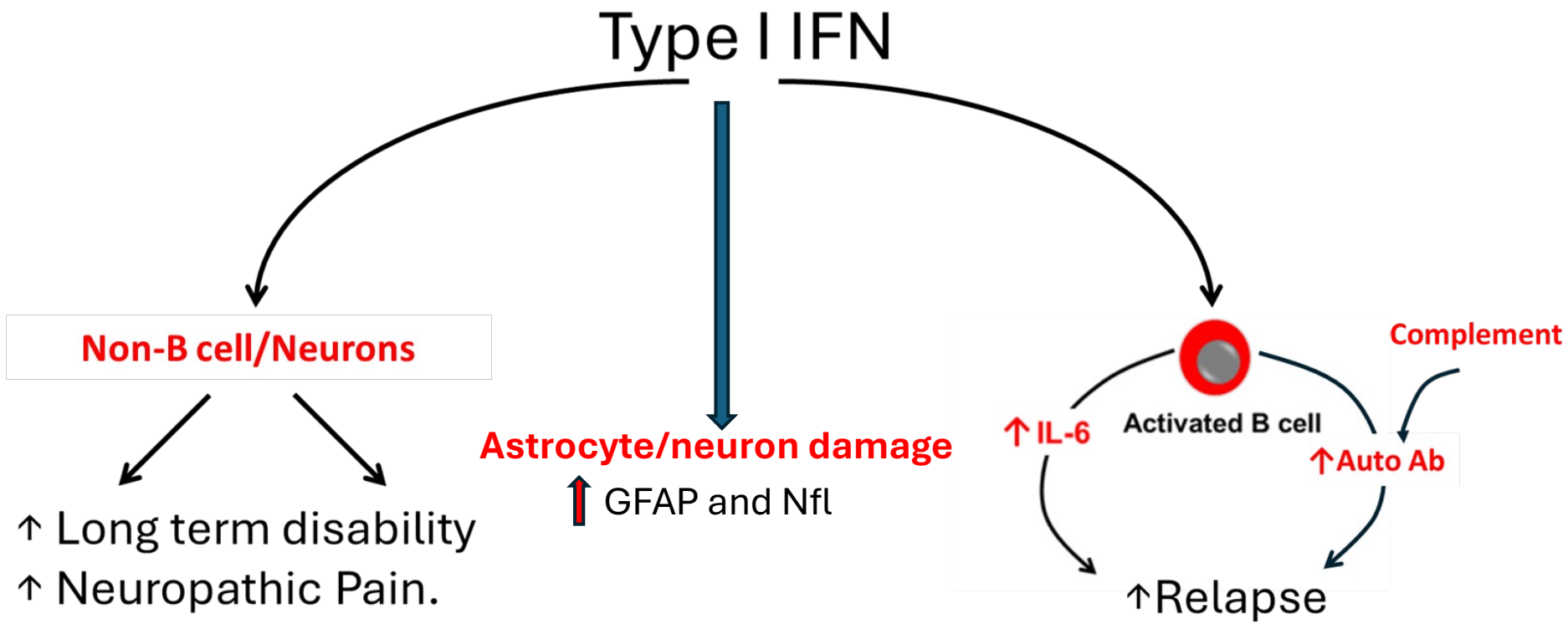


Anifrolumab Downregulates the Complement System, Neutrophil Activity, B cell activity in SLE



Baker T et al. SLE, 2024

Hypothesis: anifrolumab will reduce severity of relapses AND may attenuate long-term disability in NMO



Current approved NMOSD therapies target B cell/antibody functions.
Type IFN modulates B cell activity/function and drive neuronal hypersensitivity (pain).
IFN blockade could offer multimodal therapy benefits for NMOSD.

OMRF NIAID ACE Project 2024-2029: NASCAR Clinical Trial for NMO

Double-Blind, Placebo Controlled Trial in **N**euromyelitis Optica of **Anifrolumab** to **S**tandard of **C**are for **A**cute **R**elapses and Worsening Symptoms

- OMRF—central site
  - Chair: Yang Mao-Draayer, MD, PhD, Professor and Director of Clinical and Experimental Therapeutics
  - Mechanistic Chair: Robert Axtell, PhD, Associate Professor
- Other potential trial sites: Washington U., UAB, NYU, U Chicago, Cleveland Clinic, University hospital Cleveland, Henry Ford, U Wisconsin, U Mass, Swedish, Hackensack Meridian Health, Mount Sinai, USC, Cornell, U Rochester
- AstraZeneca
- Rho and NIH/NIAID

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Thank you note

- Our patients and family members…

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Imaging Biomarkers of Disease Status & Relapse

Frederike Cosima Oertel, MD/PhD
Experimental & Clinical Research Center (ECRC)
MDC Berlin and Charité-Universitätsmedizin Berlin

CHARITÉ - UNIVERSITÄTSMEDIZIN BERLIN | Gliedkörperschaft der Freien Universität Berlin und Humboldt-Universität zu Berlin

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Imaging biomarkers of disease status & relapse

Spinal cord involvement

Optic nerve involvement

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Spinal cord involvement – acquisition protocol

Sagittal and axial T2-weighted MRI
& Post-contrast T1-weighted images
with complete visualization of the spinal cord

Single/multiple intramedullary T2-hyperintensities
Involving grey and/or white matter
Acutely with contrast enhancement

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Spinal cord involvement – acute phase sagittal MRI



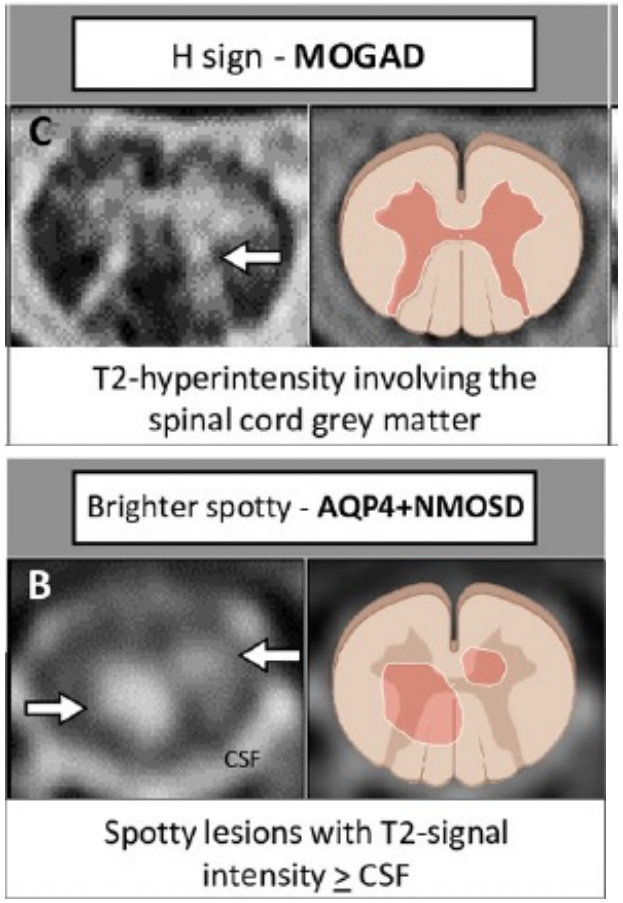
Lesion location:
Cervical or thoracic, not useful for differential diagnosis
(but conus involvement should trigger testing for MOG-ab)

Lesion length (cut-off 3 segments):
Short T2-hyperintense lesions often centrally located & together with T1 hypointensity in 14-15% of AQP4+NMOSD. BUT 92% of NMOSD with short lesions will subsequently have longitudinally-extensive lesions
Longitudinally extensive T2-hyperintense lesions are most common in NMOSD (up to 90% of recurrent cases) and include focal cord swelling, concomitant T1-hypointensity (70%)

Cacciaguerra et al. Frontiers 2022

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Spinal cord involvement – acute phase axial MRI



Lesion location:

Central pure gray matter involvement or mixed gray-white matter involvement, usually affecting > 50% of the cross-sectional area

Key findings:

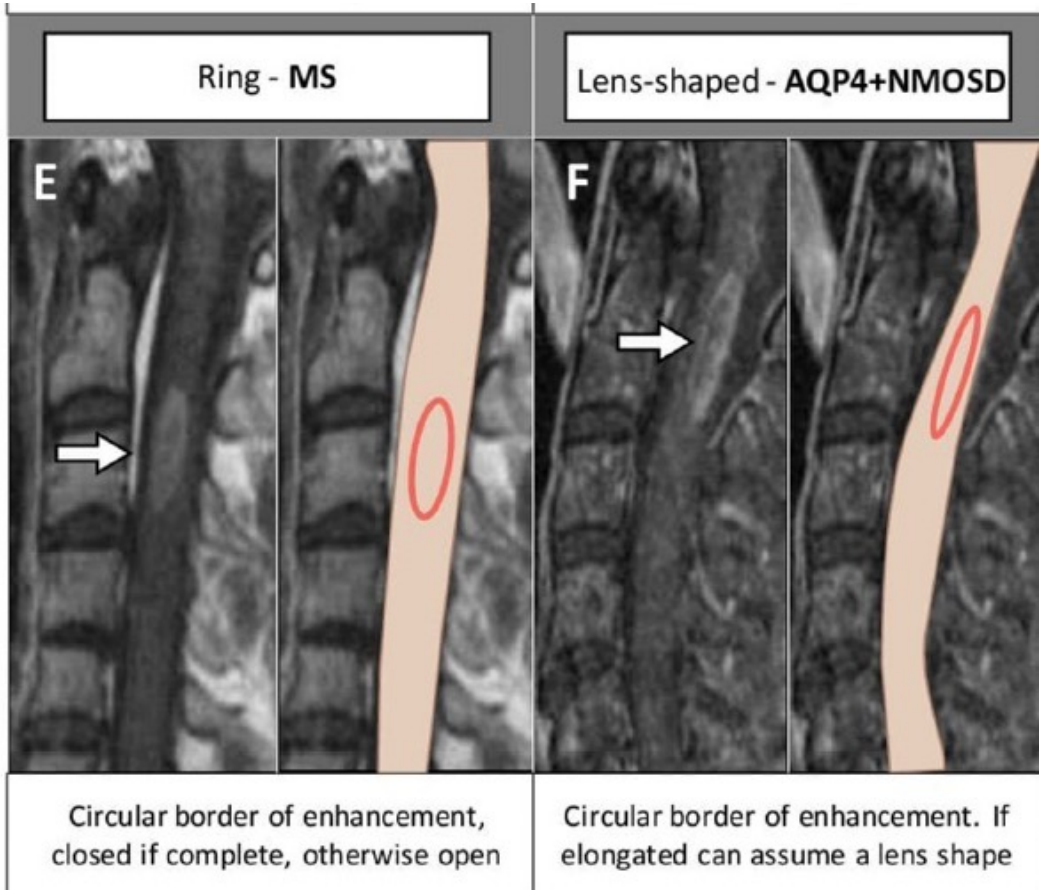
H-shape common in MOGAD (30%) but also seen in AQP4+NMOSD (10%)

Brighter spotty lesions (30-50%) in AQP4+ NMOSD

Cacciaguerra et al. Frontiers 2022

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Spinal cord – acute phase MRI enhancement



Enhancement:

Lesion enhancement common: often longitudinally extensive, patchy or ring-like (up to 30%), rarely persists >3 months

Ring enhancement can be lens- or ellipsoid shaped (vs. ring in MS)

Longitudinally extensive leptomeningeal enhancement possible but less common

Cacciaguerra et al. Frontiers 2022

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Spinal cord involvement – chronic phase

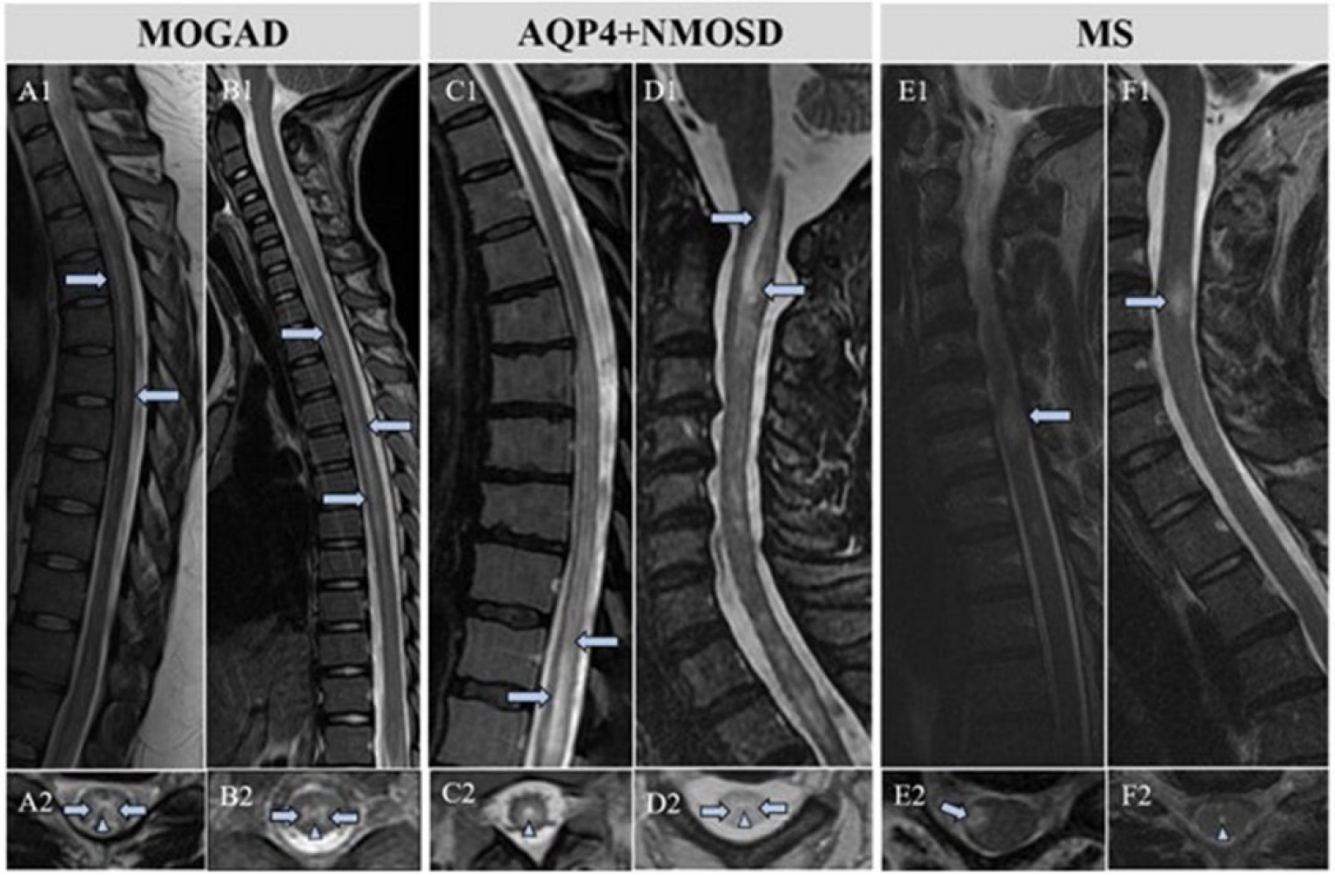
Follow-up MRI with same sequences ~ 3 months after baseline with complete visualization of the spinal cord

Fragmentation: into shorter lesions within 3 months or resolution (~5%, CAVE MOGAD)
Persistent enhancement for >2 months only in 12% of AQP4+NMOSD
Focal atrophy in AQP4+NMOSD and MS

Cacciaguerra et al. Frontiers 2022

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Spinal cord involvement – what's new?



Central canal T2-hyperintensity:
Pseudo-dilatation of ependymal canal (local edema) causing brighter T2-signal

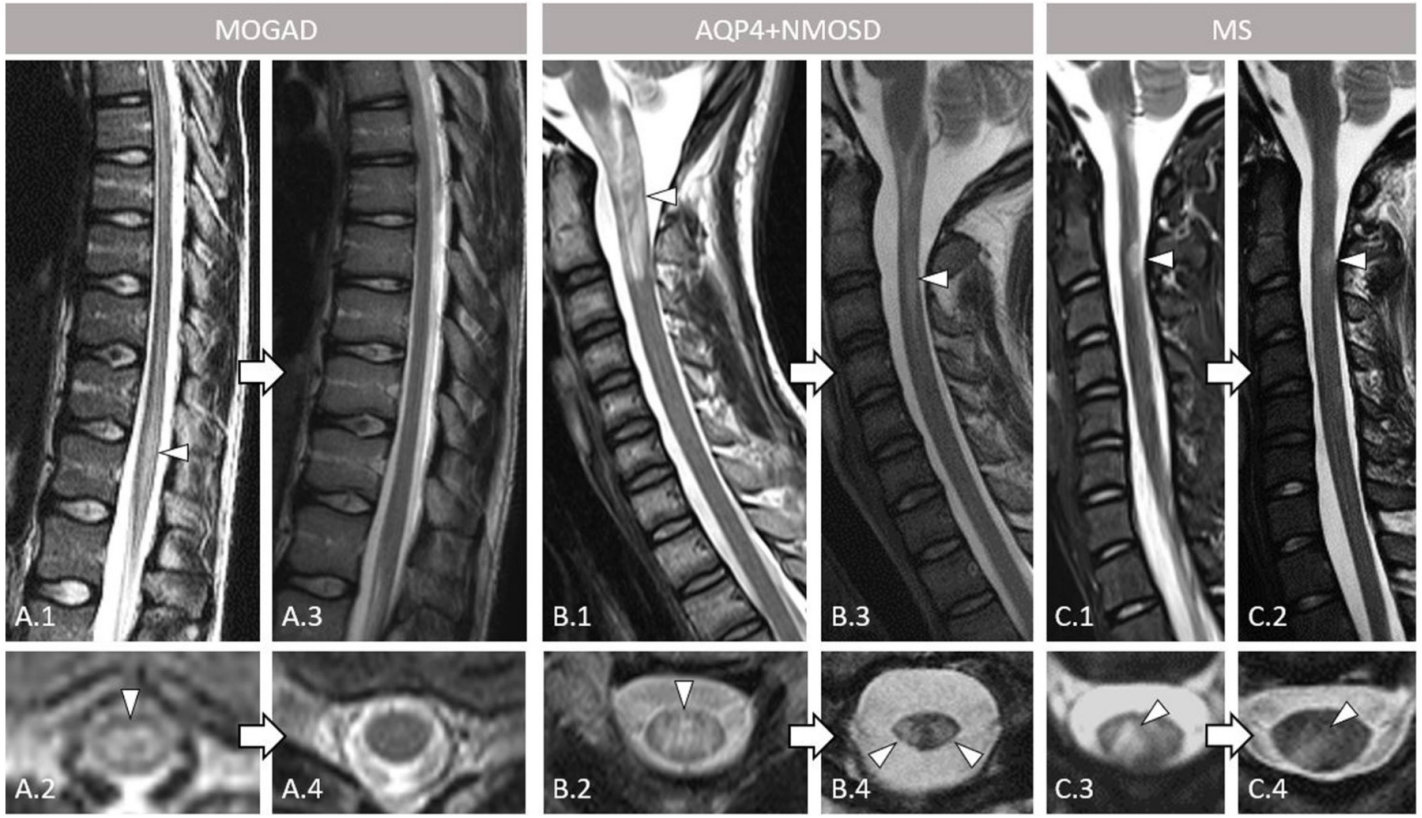
Frequent in MOGAD (29%) and AQP4+NMOSD (35%), but not MS
T1-hypointensity more common in AQP4+NMOSD (46%) vs. MOGAD (11%)

37 AQP4-IgG+ NMOSD **63 MOGAD** **26 MS**

Webb et al J Neurol Sci 2023

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Spinal cord involvement – what's new?



Lesion resolution in pediatric disease:
Follow-up MRI ~1.5-2 years after acute MRI

Resolution of index T2-lesion: 0% in AQP4+NMOSD vs. 67% in MOGAD vs. 8% in MS

Resolution of all T2-lesions: 0% in AQP4+NMOSD vs. 58% in MOGAD vs. 8% in MS

Persistent enhancement: 29% in AQP4+NMOSD vs. 0% in MOGAD vs. 0% in MS

8 AQP4-IgG+ NMOSD	**21 MOGAD**	**27 MS**
14 (4-16) years	7 (2-17 years)	15 (3-17 years)

Redenbaugh et al Mult Scler 2023

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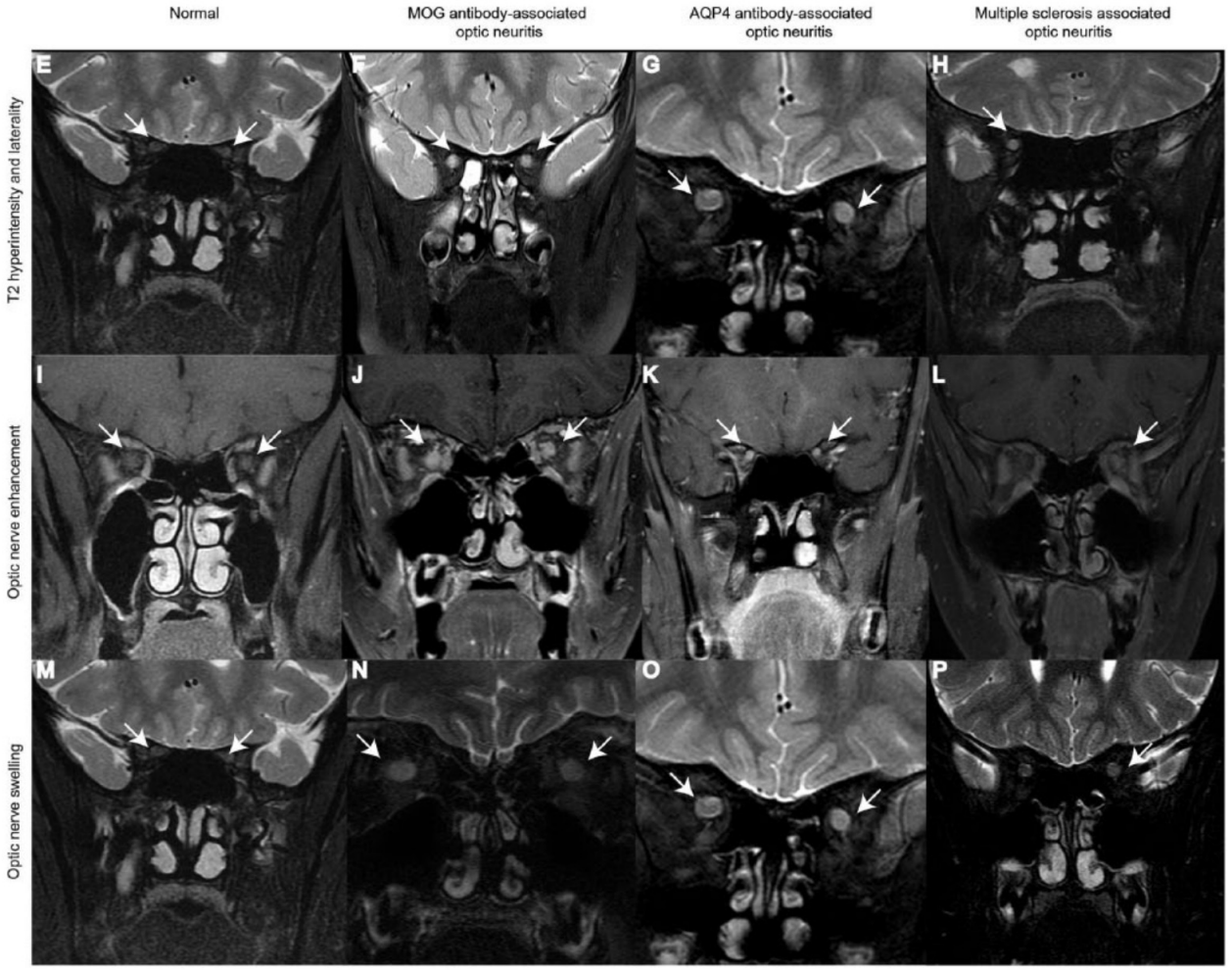
Optic nerve involvement – acquisition protocol

T2-weighted orbital MRI with orbital fat saturation
& Post-contrast T1-weighted images
OCT ring scan (RNFL) and macular scan (GCIPL) of both eyes

Ramanathan et al. MSJ 2015

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Optic nerve involvement – acute phase orbital MRI



Laterality:
Bilateral (82% AQP4+NMOSD, 84% MOGAD) > unilateral (MS)

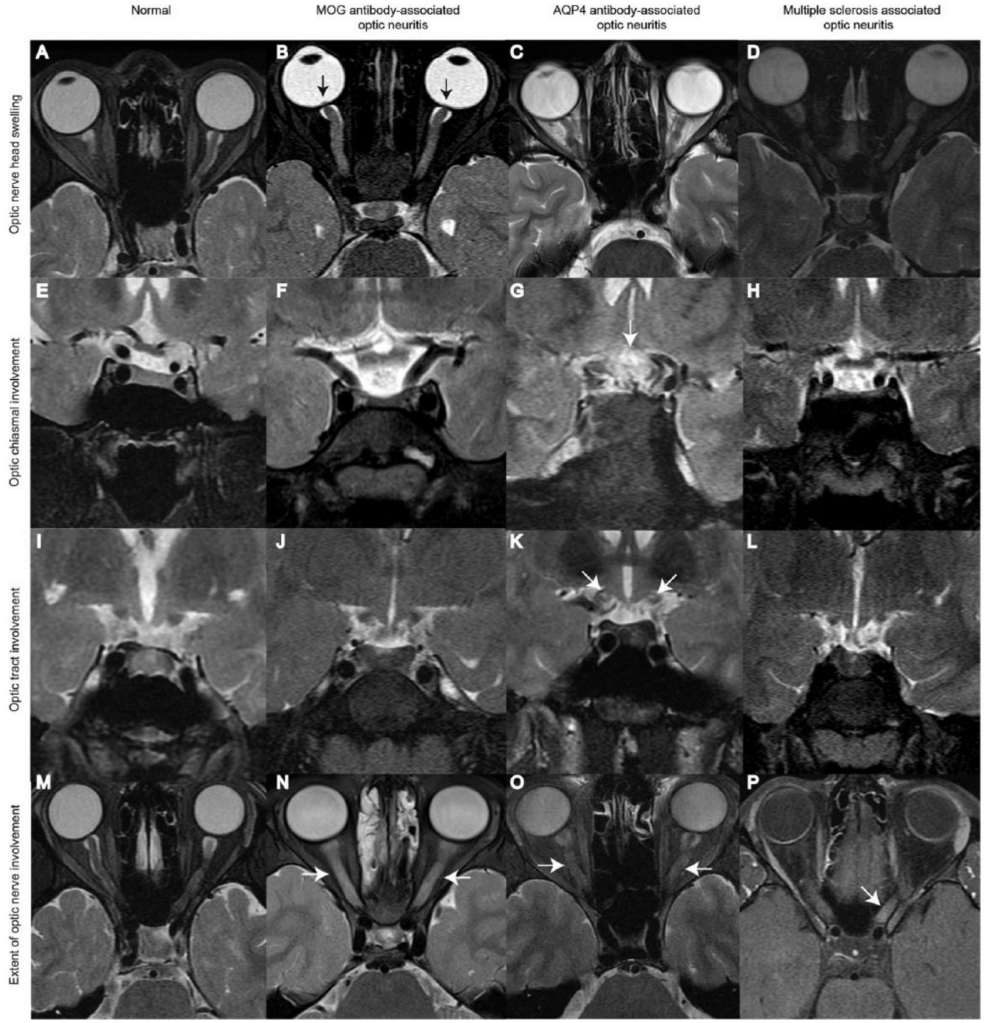
Enhancement (100%):
Bilateral intracanalicular optic nerve enhancement in AQP4+NMOSD vs. retrobulbar (MOGAD & MS)

Optic nerve swelling:
Bilateral (AQP4+NMOSD, MOGAD) > unilateral (MS)
Can be absent in AQP4+NMOSD

Ramanathan et al. MSJ 2015

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Optic nerve involvement – acute phase orbital MRI



Location:

ONH (9%): bilateral (MOGAD) vs. absent (AQP4+NMOSD, MS)

Chiasm (64%): involved in AQP4+NMOSD, but not MS & MOGAD

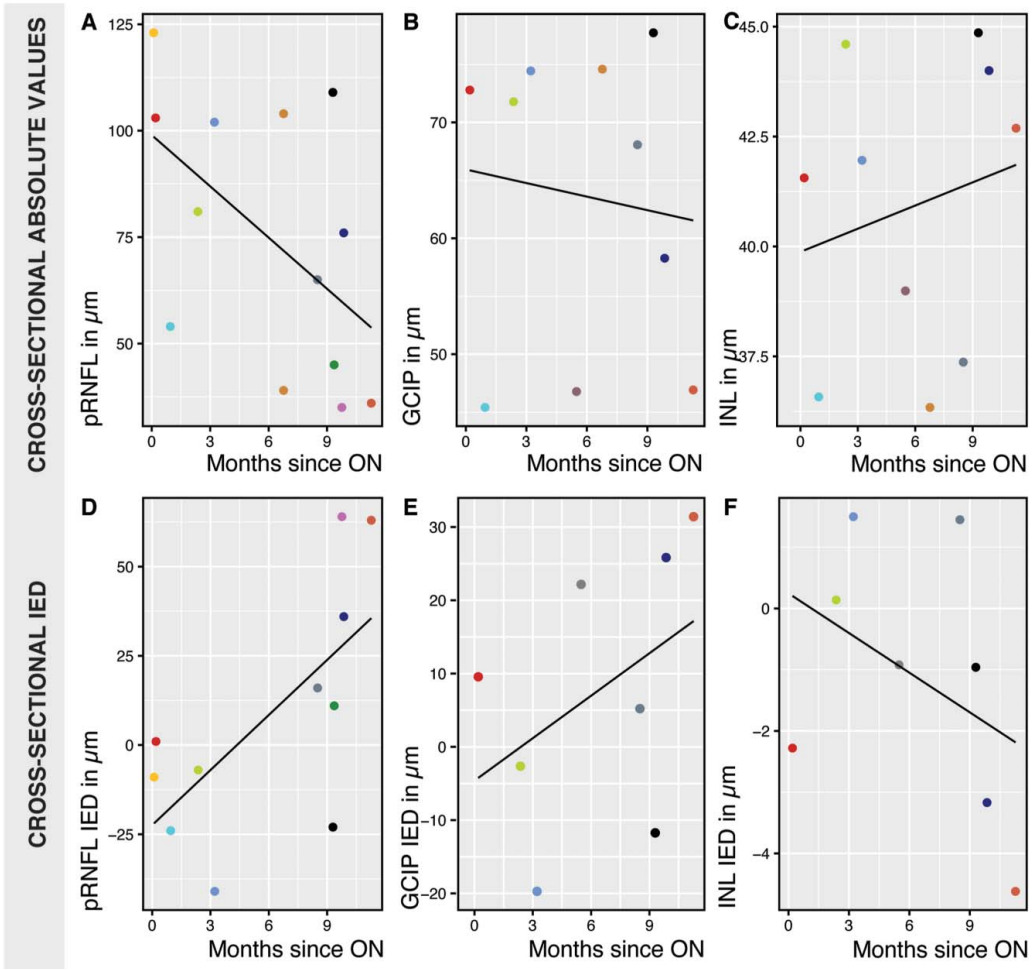
Optic tract (bilateral 45%): involved in AQP4+NMOSD, but not MS & MOGAD

Longitudinally extensive in AQP4+NMOSD (100%) & MOGAD (95%) [median 23mm] but mostly focal in MS [median 10mm]

Ramanathan et al. MSJ 2015

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Optic nerve involvement – acute phase OCT



Acute OCT findings

No severe disc edema (consider MOG-ab testing)

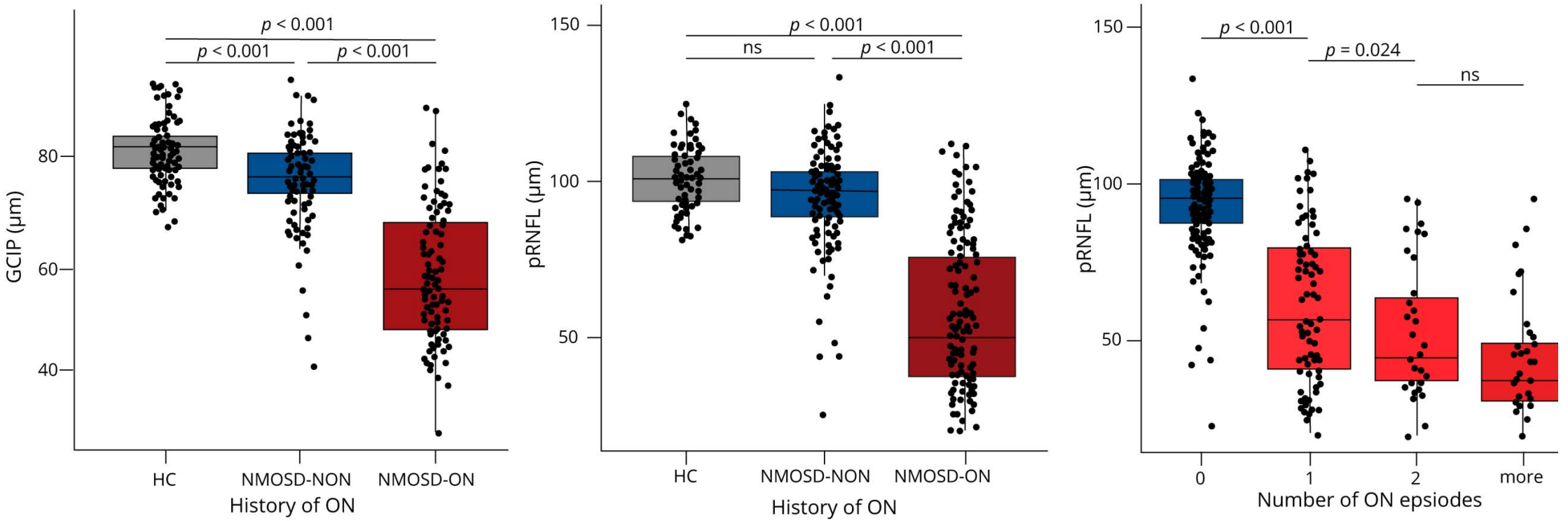
Post-acute OCT findings

Fast thinning of GCIPL (and subsequent RNFL)

Oertel et al. J Neuroophth 2023

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Optic nerve involvement – chronic phase OCT

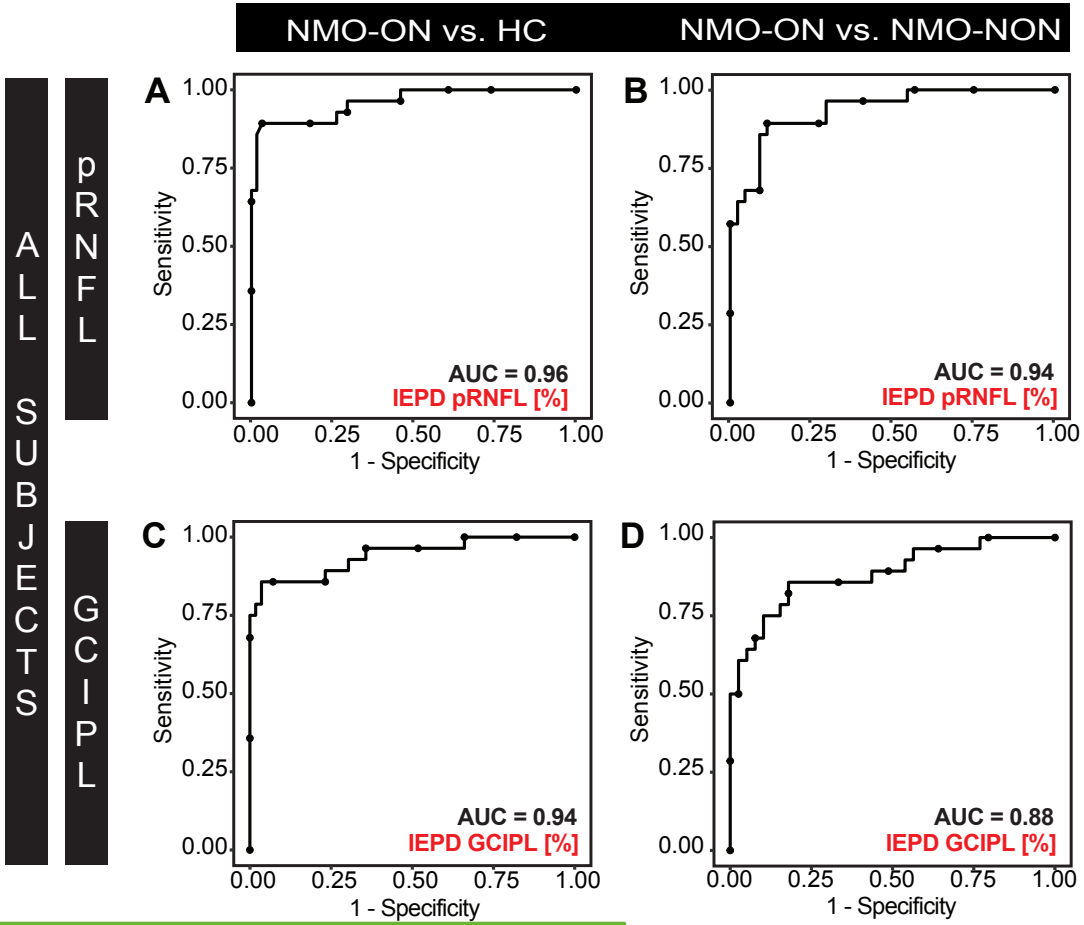


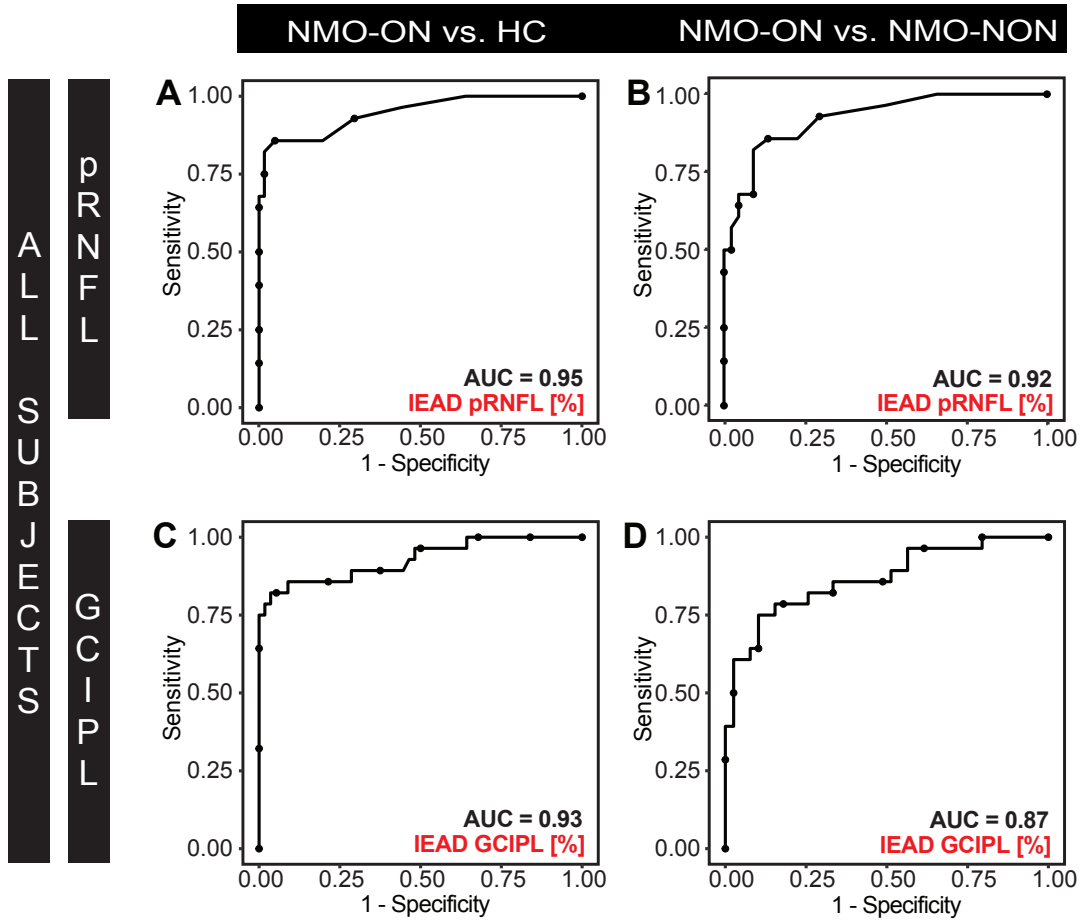
283 AQP4-IgG+ NMOSD **72 HC**

Oertel et al. Neurology – Neuroimm & Neuroinflamm 2021

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Optic nerve involvement – chronic phase OCT



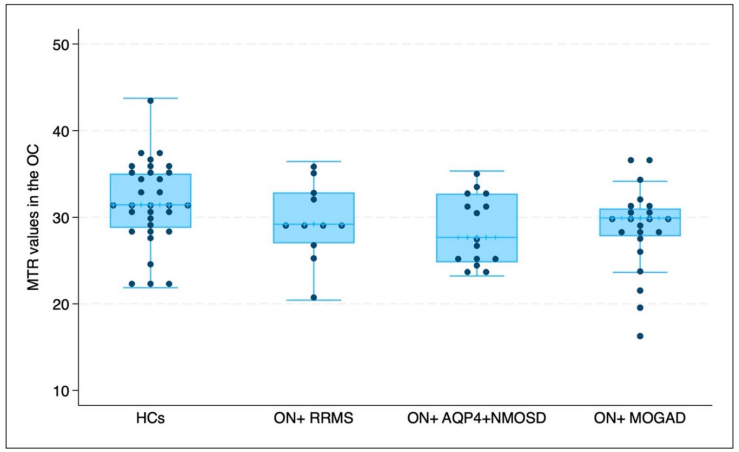


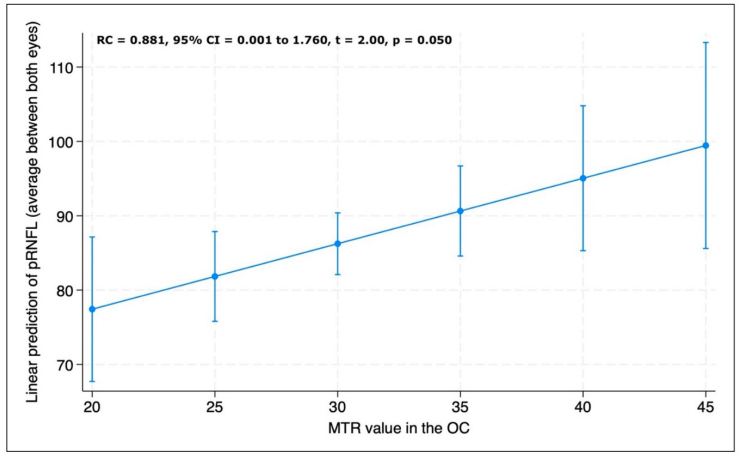
73 AQP4-IgG+ NMOSD **62 HC**

Oertel et al. Journal Neurol Neurosurg Psych 2023

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Optic nerve involvement – what's new?





Magnetisation transfer ratio (MTR) as a promising MRI technique to quantify chiasmal involvement

Measurement of the exchange of proton magnetization between tissue macromolecules and mobile water molecules

Associated with myelin content, early demyelination & axonal loss

ON+ optic chiasmal MTR lower in AQP4+NMOSD (p=0.02) & MOGAD (p=0.01) vs. HC, but not RRMS

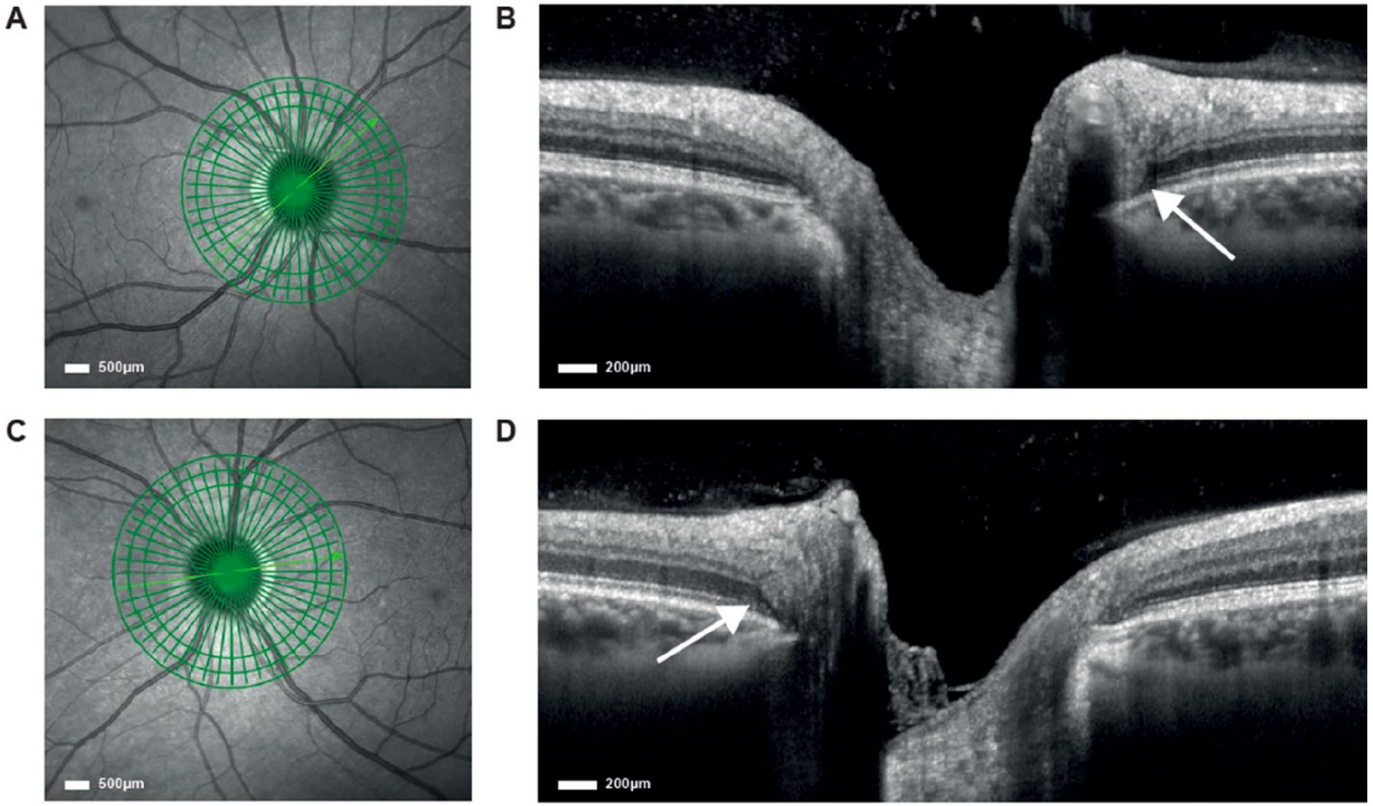
ON- optic chiasmal MTR lower in AQP4+NMOSD vs. HC (p=0.04), but not RRMS or MOGAD

24 AQP4-IgG+ NMOSD **28 MOGAD** **28 MS** **32 HC**

Bianchi et al. MSJ 2024

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Optic nerve involvement – what's new?



Peripapillary hyperreflective ovoid mass-like structures (PHOMS)

17% AQP4+NMOSD vs. 14% MOGAD vs. 4% HC

No association with neuroaxonal damage

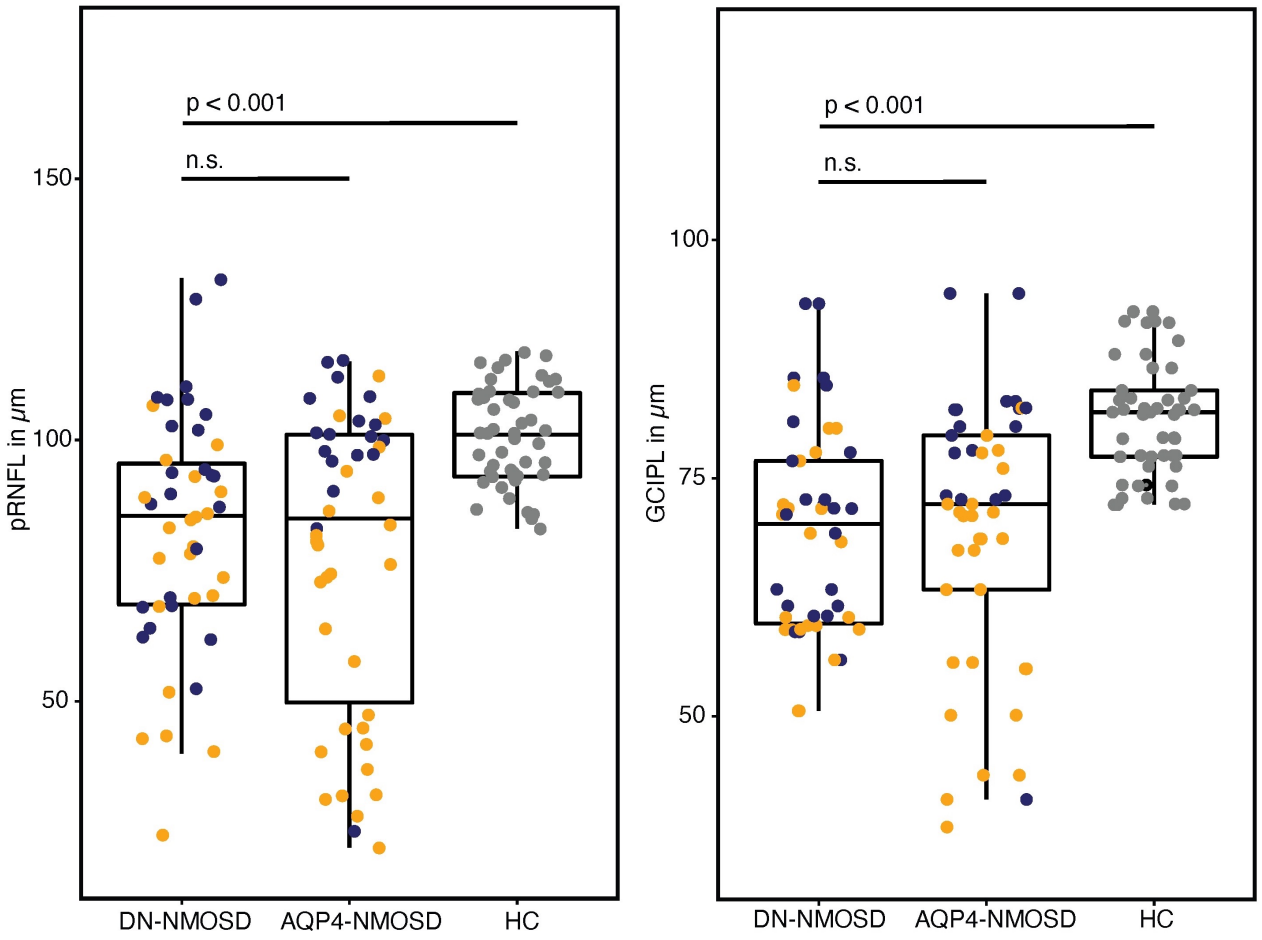
Pathophysiological significance unclear

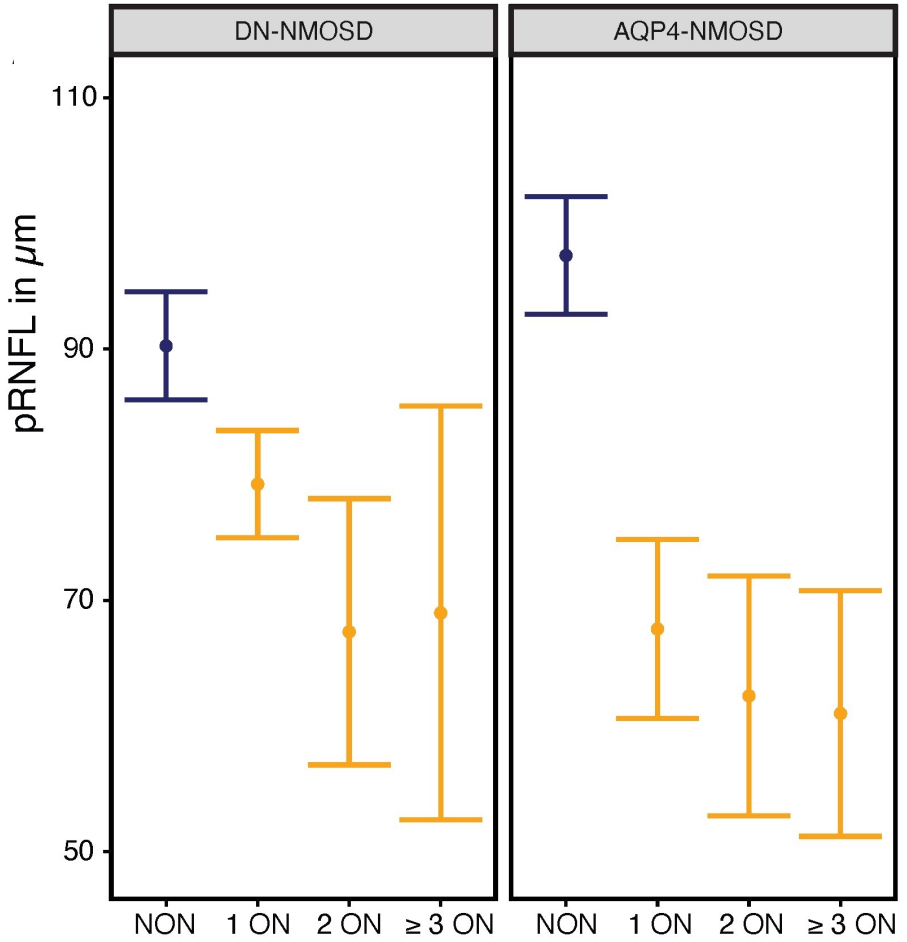
47 AQP4-IgG+ NMOSD **44 MOGAD** **47 HC**

Gernert et al. Neurology – J of Neurology 2023

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Optic nerve involvement – what's new?





25 AQP4-IgG+ NMOSD **25 DN-NMOSD** **33 HC**

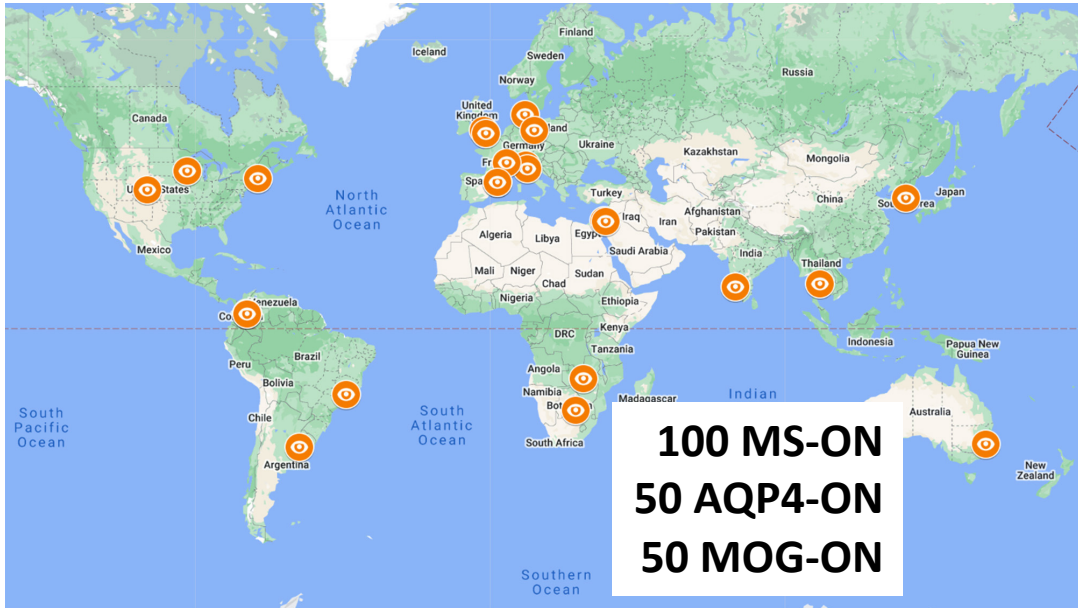
Oertel et al. Neurology – Neuroimm & Neuroinflamm 2024

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Acute Optic Neuritis Network (ACON)

Verifying functional benefits of early corticosteroids in optic neuritis employing a global, multi-racial prospective study including people with MS-ON, AQP4-IgG+ ON, and MOG-IgG+ ON.

Primary outcome	**High-contrast visual acuity** at 6 mo. (stratified by diagnosis and days since onset)
Secondary outcomes	**Low-contrast visual acuity**
	pRNFL, GCIPL (OCT)
	Brain lesion number/volume, ON characterization score (MRI)
	QoL and PROM (including NEI-VFQ)



Asseyer et al. Frontiers 2023

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Thank you.

Translational Neuroimmunology Lab

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Prognostic Biomarker Signatures of Relapse in NMOSD

Alessandra Breschi



Executive Summary

Longitudinal serum samples from 126 CIRCLES patients diagnosed with NMO were analyzed through mass spectrometry to identify circulating proteins associated with NMO relapse events.

This presentation summarizes the methods and results from the analysis of the proteomic data acquired from these samples.

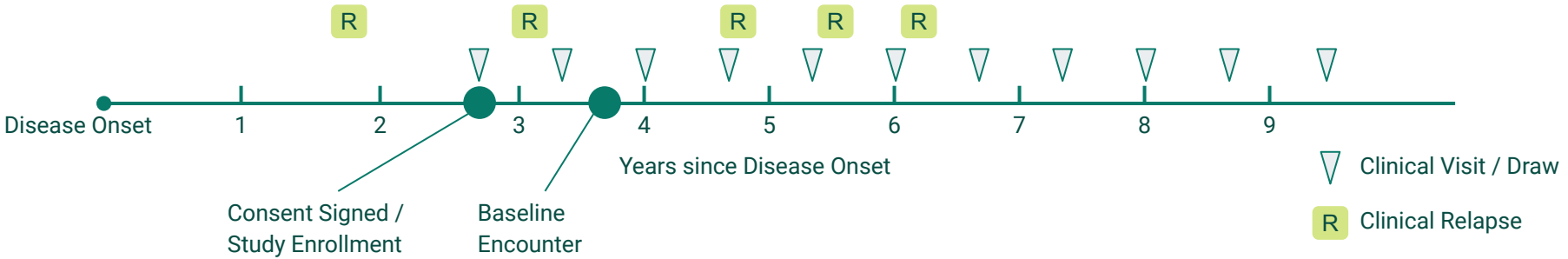


Agenda

- Experimental Design
- Cohort Characterization
- Modeling Techniques
- Results
- Conclusions

Longitudinal Samples Selected from CIRCLES Study

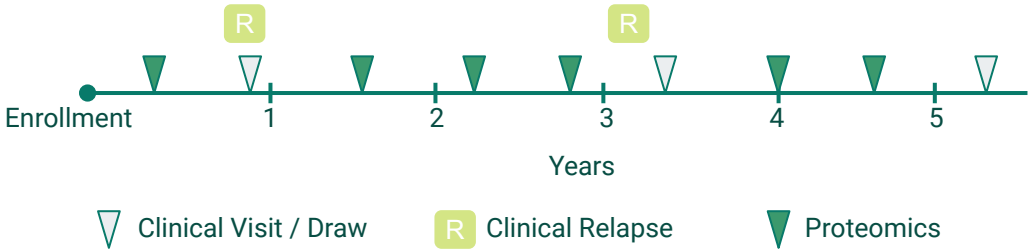
- Samples for this study were a subset of samples collected from NMO patients enrolled in the CIRCLES study. Selected NMO patients were diagnosed 2-10 years before joining CIRCLES.
- After consenting to enroll in the study (enrollment date), patients undergo a baseline encounter, after which they are officially part of the study.
- For each patient, biospecimens were collected at 6-month intervals.
- Relapses were evaluated regardless of these intervals and validated by neurologists.



Samples Were Excluded Based on Proximity to Relapse

Exclusion criteria:

- Samples collected at the time of relapse.
- Samples collected within 180 days of previous relapse.
- Last samples collected without a subsequent relapse.
- Samples without treatment information.

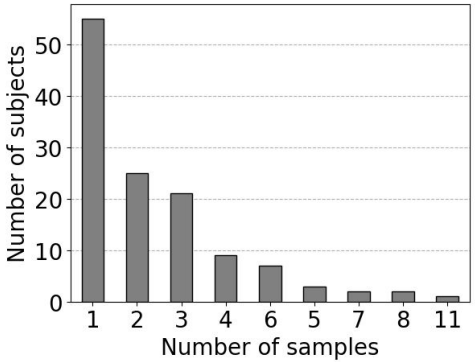


Samples Were Processed in 4 Experimental Batches

- In total, **305 samples** were processed through the proteomic pipeline in 4 experimental batches:
    - A uniform distribution of demographics and time-to-relapse events across batches was ensured to mitigate batch effects.

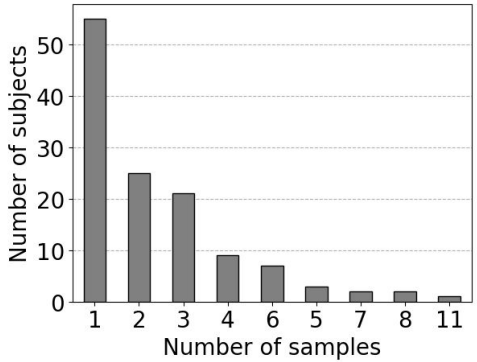
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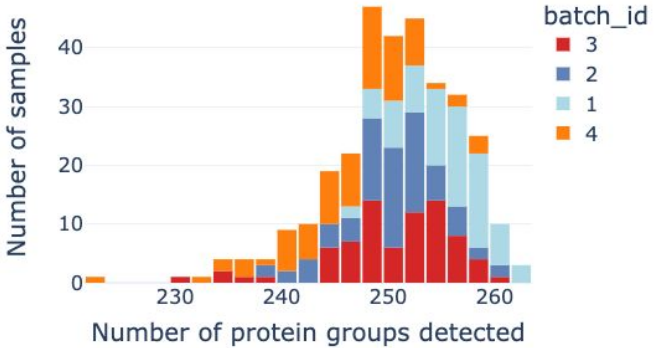
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- In total, **305 samples** were processed through the proteomic pipeline in 4 experimental batches:
  - A uniform distribution of demographics and time-to-relapse events across batches was ensured to mitigate batch effects.
- For half the patients only one sample was available for proteomics.
- 1 sample excluded due to quality issues.
- 265 proteins detected across all samples.



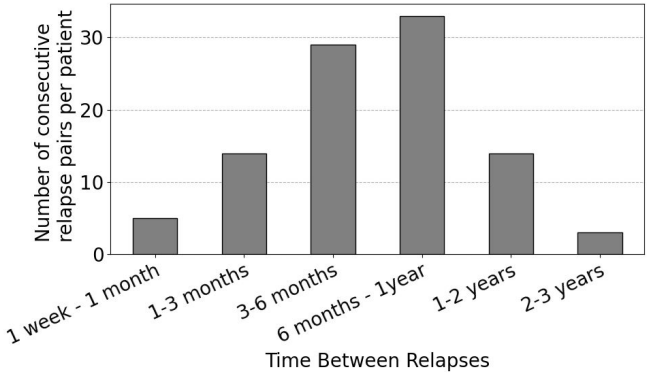


Study Demographics Aligned with NMO Demographics

- Majority of the patients are females (86%); Average age at onset was 35 years; 64% anti-AQP4+, 8% anti-MOG+.
- Race breakdown:
  - White (52%), Black or African American (25%), Hispanic or Latino (14%), Asian (7%).

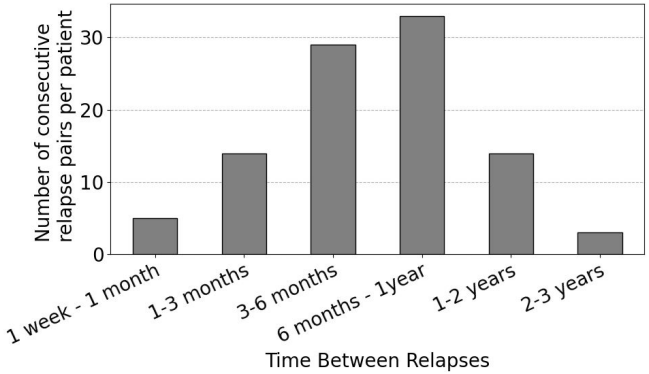
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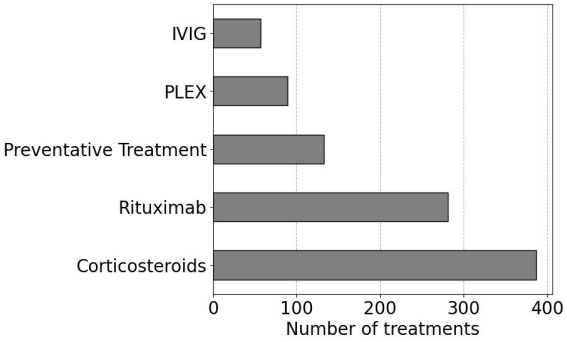
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- Since enrollment we observed 225 relapse events across all patients (avg 1.8 per patient).
- Relapses were usually re-occurring between 3 months and a year.



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- Since enrollment we observed 225 relapse events across all patients (avg 1.8 per patient).
- Relapses were usually re-occurring between 3 months and a year.
- Patients received acute and long-term treatments, which were divided in 5 groups for analysis.





Multiple Models to Identify Consistent Biomarkers

Patient timelines contain multiple types of information to include in computational models.

Data available for each patient:

- **Events**:
  - Relapses
  - Sample collection, ie proteomics & blood contamination indices
  - Treatments (start and end dates)

Time-varying

- **Covariates**:
  - Sex
  - Race
  - Antibody status (APQ4 & MOG)
  - Proteomics batch

Patient level constants

Modeling techniques with increasing levels of complexity:

1. Binary classification
2. Survival Analysis with Naive Cox Models
3. Time-Varying (time-dependent) Survival Analysis

Modeling 1: Logistic Regression

Assign a label to each sample: *will the patient experience a relapse in the next ... days after sample collection?* and fit a logistic regression model.

Threshold = 120 days (~4 months) → This yields ~20% of positive labels.

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Pros

- Easy interpretation of the model.
- Easy access to a probability of relapse.
- Simple dataset - one row per sample.

Cons

- Does not take into account treatment information.
- Relies on selection of threshold.
- With the current threshold, unbalanced classes.

Modeling 2: Survival Analysis with Naive Cox Models

The Cox model can be seen as an extension of traditional regression models that take into account censoring, ie the patient did not experience the event before the end of the study.

Each sample is **independently** assigned to its next relapse or censoring event. We fit a simple Cox Model Proportional Hazards model to this survival data.

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Pros

- Easy interpretation of the model.
- Takes into account censoring events.
- Simple dataset - one row per sample.

Cons

- Does not take into account treatment information.
- Each interval is considered independently even if they belong to the same patient timeline.

Modeling 3: Time-Varying Survival Analysis

Similar to the Naive Cox Model analysis, but **models the entire patient timeline**:

- The timeline is divided into non-overlapping intervals to fit a time Time-Dependent Cox model.
- **Treatments** are included in interval design.

Modeling 3: Time-Varying Survival Analysis

Similar to the Naive Cox Model analysis, but models the entire patient timeline:

- The timeline is divided into non-overlapping intervals to fit a time Time-Dependent Cox model.
- Treatments are included in interval design.

Pros

- Takes into account treatment data.
- Takes into account precise interval durations and censoring events.
- Takes into account full patient timeline.
- Does not consider samples independently.

Cons

- Prediction in a time-varying setting is not trivial.
- Complex dataset and intensive pre-processing.

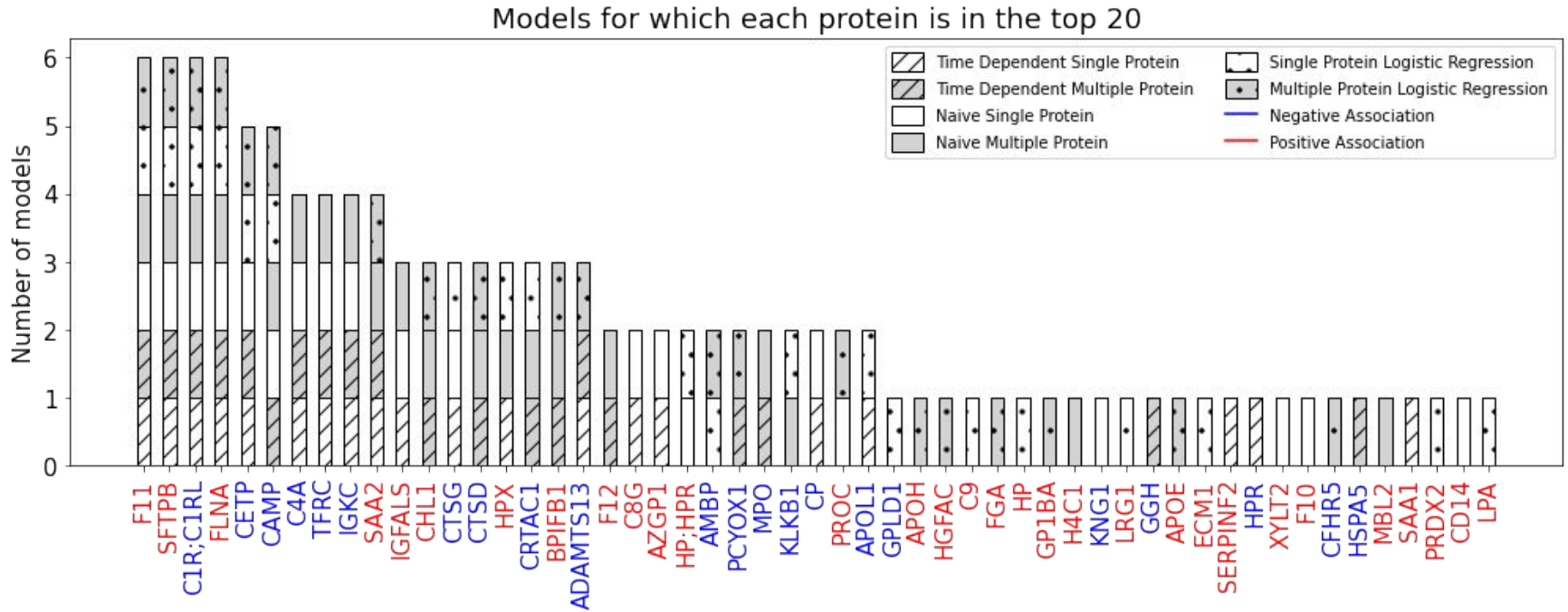
Additional Modeling Considerations

- Both multiple and single protein modeling were used:
  - **Multiple Protein**: Fit one model on the full data with all the proteins. In this case L1 regularization was used to help with feature selection and dimensionality reduction.
  - **Single Protein**: Fit 265 independent models, taking into account only the expression from one given protein at a time.
  - Previously defined covariates, such as demographics information, were included in both models.

Additional Modeling Considerations

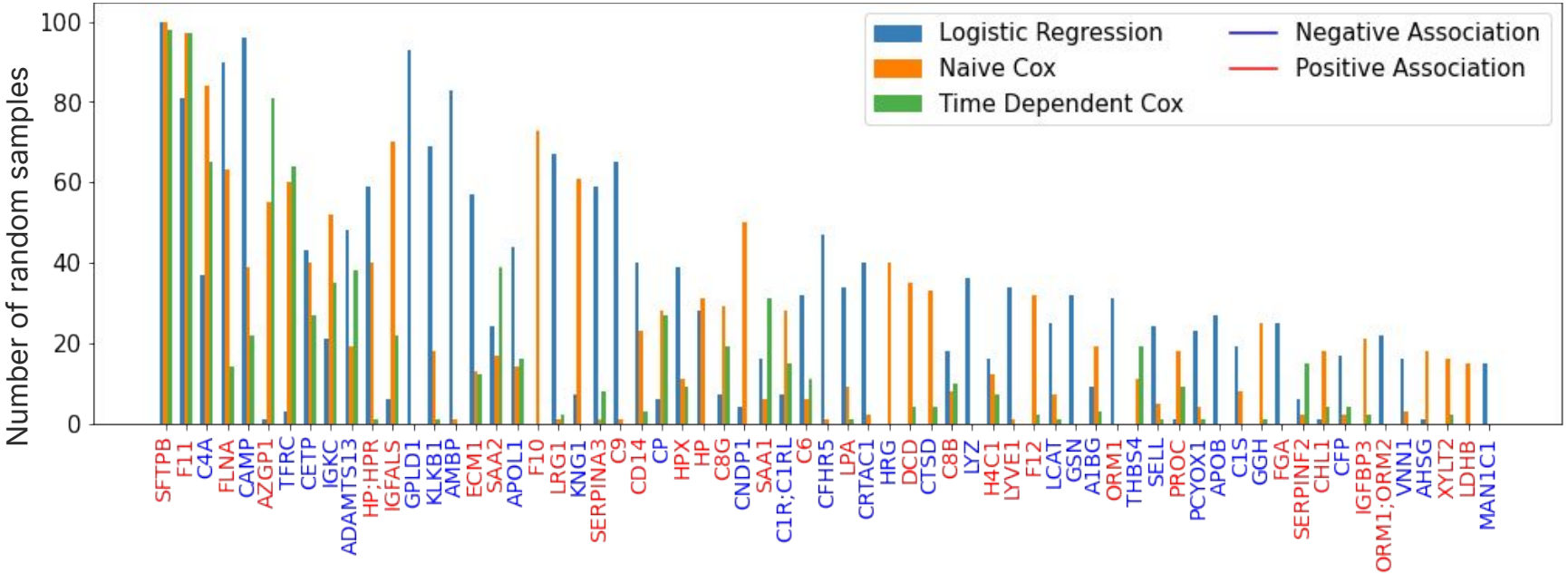
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  - **Single Protein**: Fit 265 independent models, taking into account only the expression from one given protein at a time.
  - Previously defined covariates, such as demographics information, were included in both models.
- **Random sampling** with replacement: we randomly sampled **80% of the subjects** and ranked the genes based on a given random subset for all models. We repeated this 100 times.
  - Ranking techniques: Genes were ranked by absolute average coefficient across repetitions for each model.

Proteins with Strongest Association with Relapse Are Consistent Across Modeling Strategies



Single-Protein Models Yields Consistent Biomarkers

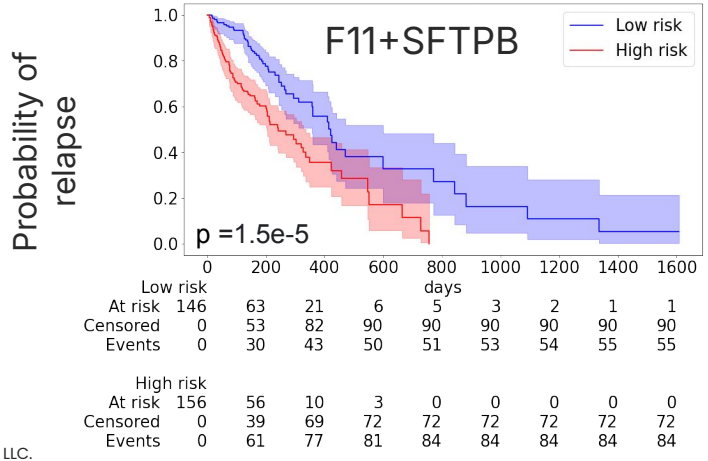
Proteins are ranked by the number of random samples where they had non-adjusted p-value below 0.05 (not possible with L1-regularized multiple-protein models).



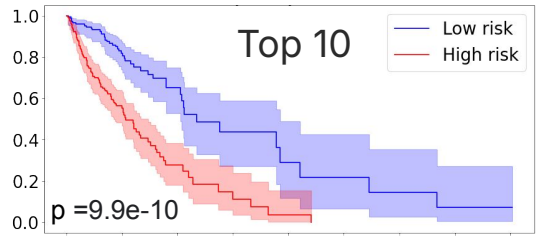
Proof-of-Concept Risk Score Based on Top Proteins

Proteins with the strongest association with relapse might be used to build a relapse risk score. The median predicted survival time from this cohort can be used as a cutoff for stratifying patients into high and low risk groups.

This **will require additional validation** experiments to quantify selected biomarkers in a low throughput quantitative setting, further analysis to optimize the protein signature and an external validation cohort to test the predictive power of such a risk score.



Low risk									
At risk	146	63	21	6	5	3	2	1	1
Censored	0	53	82	90	90	90	90	90	90
Events	0	30	43	50	51	53	54	55	55
High risk									
At risk	156	56	10	3	0	0	0	0	0
Censored	0	39	69	72	72	72	72	72	72
Events	0	61	77	81	84	84	84	84	84



Low risk									
At risk	145	69	21	6	4	3	2	1	1
Censored	0	52	90	99	99	99	99	99	99
Events	0	24	34	40	42	43	44	45	45
High risk									
At risk	157	50	10	3	1	0	0	0	0
Censored	0	40	61	63	63	63	63	63	63
Events	0	67	86	91	93	94	94	94	94

Many Candidate Proteins Were Reported in Previous NMO Studies

- **Coagulation and complement pathways**: The interplay between coagulation and complement pathways is an emerging line of research [1]:
  - Factors XI (**F11**), X (**F10**) XII (**F12**) and filamin A (**FLNA**) are involved in coagulation and have been shown to be differentially expressed in multiple sclerosis and NMO patients ([2], [3], [4]). They are positively associated with NMO relapses in our analysis
  - Complement 1 (**C1R**) and complement 4 (**C4A**) are complement proteins that have already been identified as biomarkers of interest in NMO [5]. They are negatively associated with relapses in our analysis

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- **Cerebrospinal fluid (CSF) and nervous system damage**: These markers might pass the blood brain barrier which is more permeable in NMO patients [6]:
  - Surfactant protein B (**SFTPB**) is predominantly produced in the lungs, but has also been detected in the central nervous system and CSF [7].
  - Serum amyloid A (**SAA1/SAA2**) is increased in response to neuroinflammation [8] and has been reported in relationship to NMO and multiple sclerosis in other studies [9].

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More literature search and experiments are needed to substantiate a biological explanation for the association of the top candidate proteins and NMO relapse.

Conclusions

- Thanks to this collaboration, we generated the largest collection of proteomics data from serum samples of NMO patients: ~300 samples from 100+ patients.
- Multiple modeling techniques and sampling were used to obtain a more robust set of potential biomarkers.
- Two proteins, F11 and SFTPB, emerged at top candidate biomarkers associated with NMO relapse.
- Several top candidate proteins are involved in coagulation pathways and neural damage response.
- **Further experiments and analysis** will be needed to confirm the top candidates as biomarkers of NMO relapse.

Acknowledgements





Michael R. Yeaman

Terry J. Smith

CIRCLES Study Group

The Patients

Elea Bach

Yuliang Wang

Megan Carroll

Charles C. Kim

References

References

1. Coagulation and complement: Key innate defense participants in a seamless web
2. Thrombin generation and activity in multiple sclerosis
3. Identification of Novel Serum Proteins Associated with Myelination and Cholesterol Transport in Neuromyelitis Optica Spectrum Disorders by Mass Spectrometry
4. Quantitative proteomic analyses of CD4 + and CD8 + T cells reveal differentially expressed proteins in multiple sclerosis patients and healthy controls
5. Plasma Complement 3 and Complement 4 Are Promising Biomarkers for Distinguishing NMOSD From MOGAD and Are Associated With the Blood-Brain-Barrier Disruption in NMOSD
6. Blood-brain barrier resealing in neuromyelitis optica occurs independently of astrocyte regeneration - PMC
7. The Detection of Surfactant Proteins A, B, C and D in the Human Brain and Their Regulation in Cerebral Infarction, Autoimmune Conditions and Infections of the CNS | PLOS ONE
8. Serum Amyloid A Protein as a Potential Biomarker for Severity and Acute Outcome in Traumatic Brain Injury - PMC
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Appendix

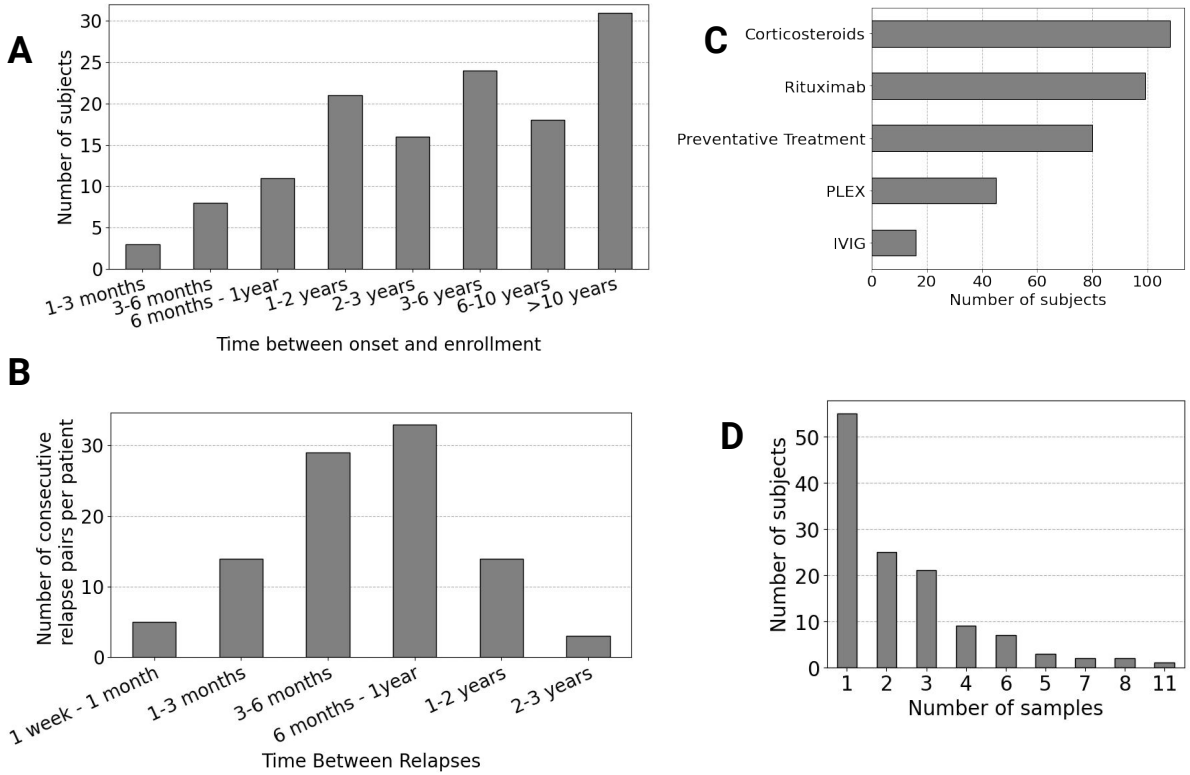


Figure 1. Longitudinal cohort characteristics. A) Distribution of times between onset and enrollment, computed on the full cohort. **B)** Distribution of the time between relapses, computed on the subset of the cohort who has more than one relapse. **C)** Number of patients who have received each treatment. **D)** Distribution of the number of samples per subject, computed on the full cohort.

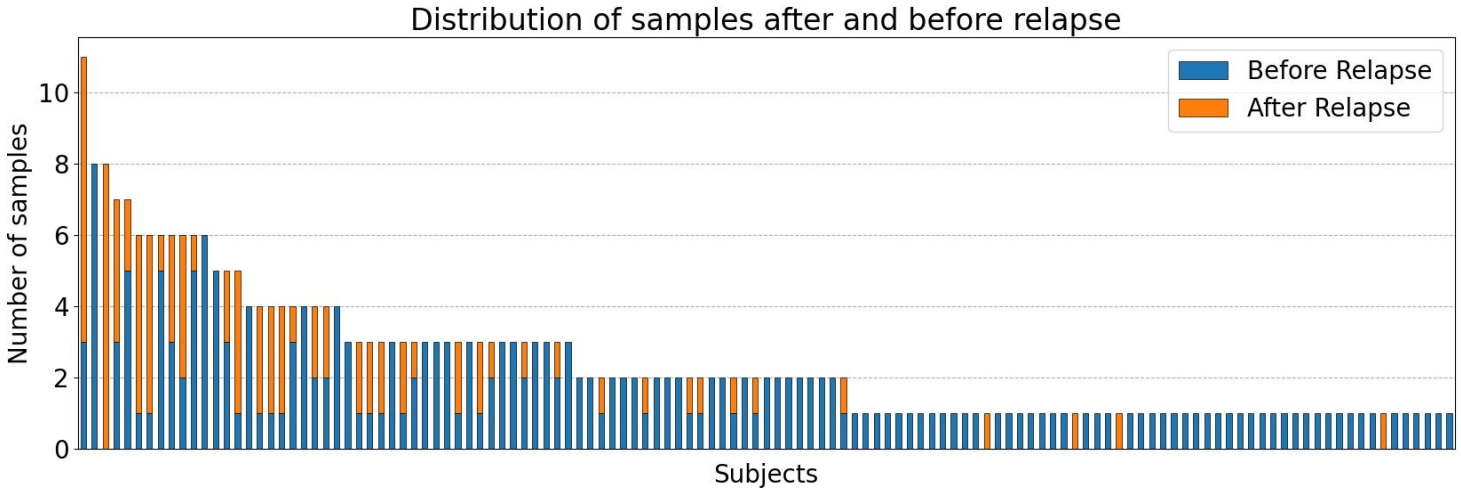
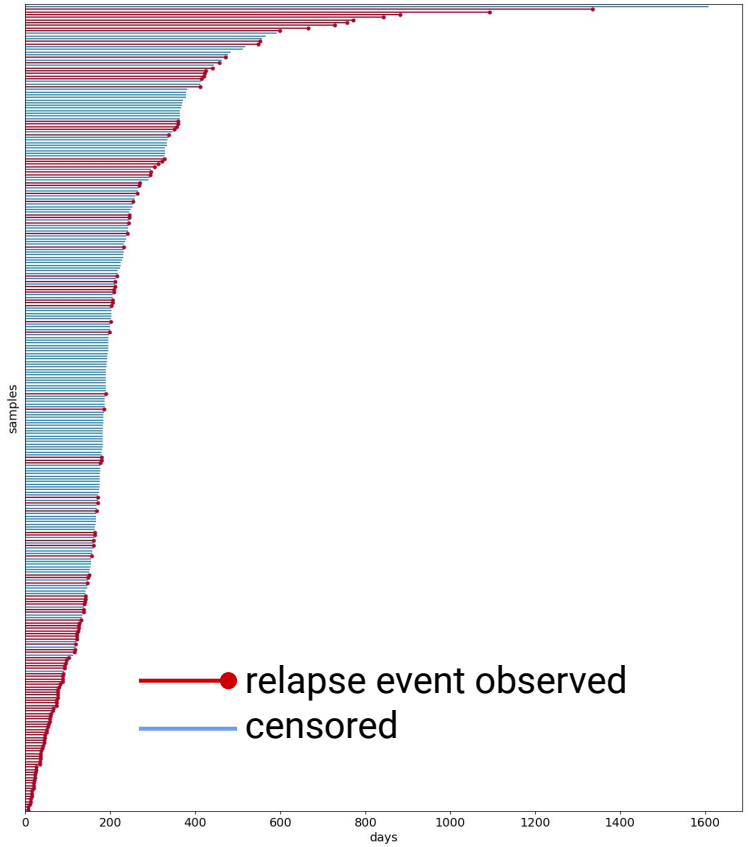


Figure S3. Temporal relationship between sample collection and relapses. Distribution of the number of samples collected after or before a relapse for all subject, computed on the full cohort. A sample collected between two relapses is classified as before a relapse in this case.

Naive Intervals

- Most intervals built with method are shorter than 1 year.
- Each interval starts when a sample is collected.
- An interval can be right-censored if the patient is lost for follow-up or if another sample was collected.
- Each sample is treated independently, even if they are derived from the same patient.



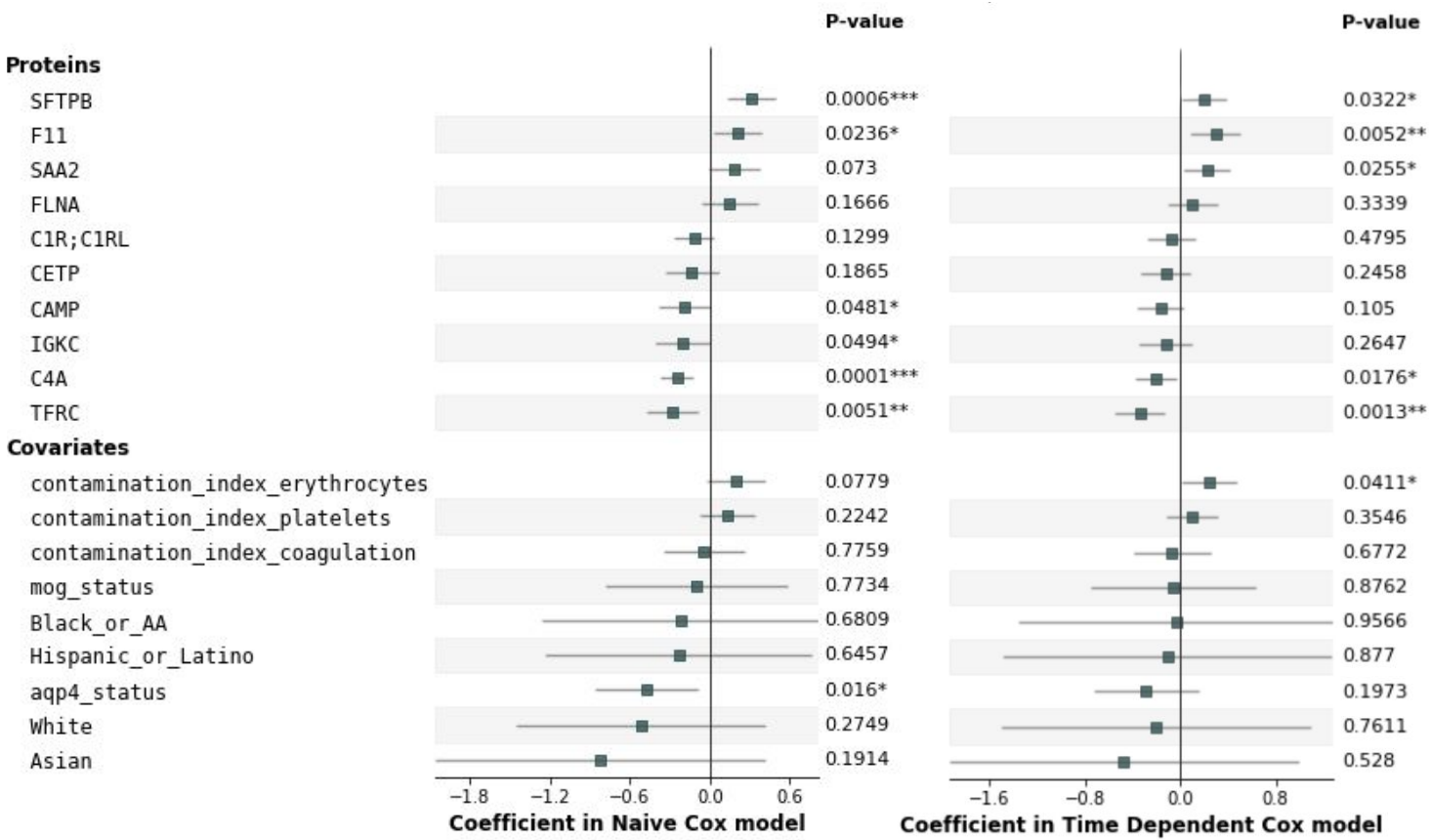


Figure S7. Summary forest plot of Naive Cox and Time Dependent Cox models fit on decaprotein signature and clinical covariates. The exponential of the coefficient for protein X can be interpreted as the hazard ratio for protein X. This measures how the risk of relapse changes for a one unit increase in the expression of protein X.

Proteomics Data Normalization

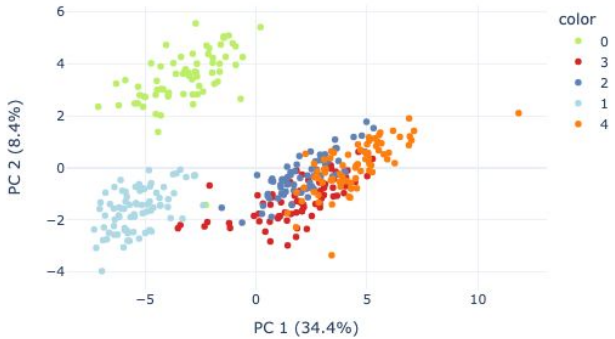
Proteomics data processed using the Compbio proteomics pipeline based on Dia-NN, **265** detected proteins.

We perform **sample level** and **protein level** normalization :

- Sample-wise standard scaling, mean and std computed ignoring the non detected values
- Clipping values with Z-scores with absolute values above 2.5
- Setting values of non detected proteins to -2.5.
- Column-wise standard scaling

Sample level

Protein level



PCA of gene expression values, grouped by batch*

*batch 0 is the batch from phase 1 of the collaboration

Modeling 2 & 3: Survival Analysis

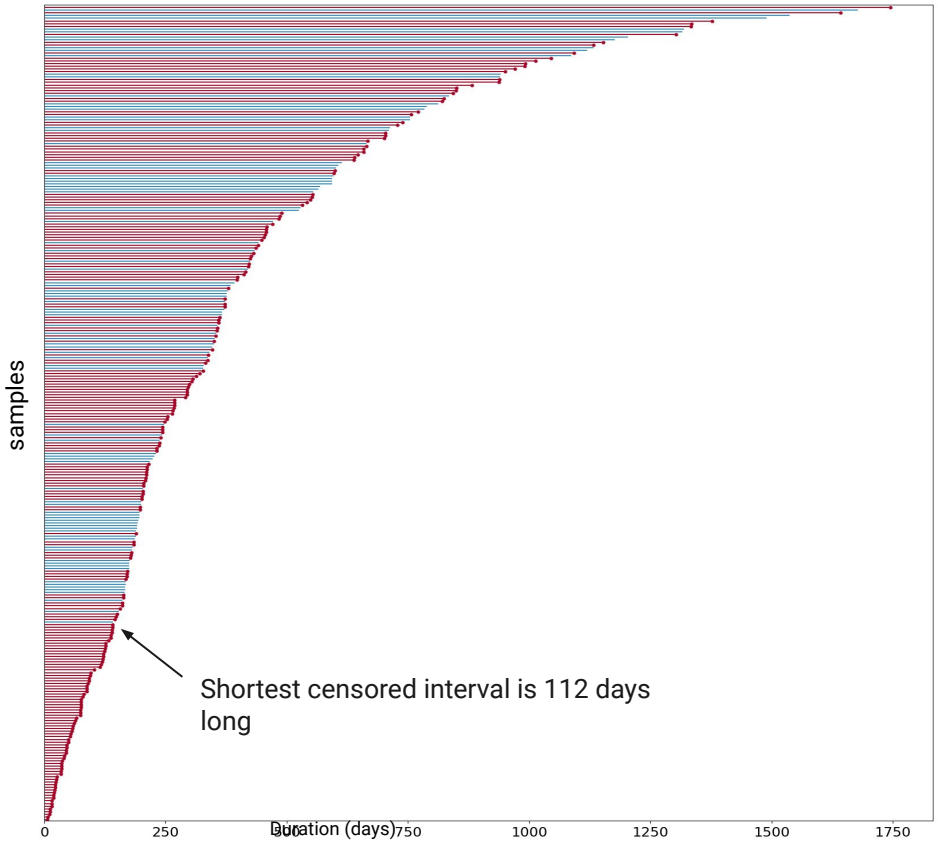
- It's the branch of statistics that deals with the analysis of time-to-event data (in our case the event of interest is a relapse)
- It deals with the issue of **censoring**: it is possible that not all the events have occurred during the observation period or that some subjects have been lost to follow up before experiencing the event (right censoring)
- The **Cox model** can be seen as an extension of traditional regression models that take into account censoring
- It can be evaluated using the **Concordance Index**
- Data for traditional survival analysis are in the form :

subject	duration	event
1	10	1
2	3	0
3	2	1
4	25	0

The subject had the event at time 10

The subject was censored at time 3 and the event was not observed

Distribution of Naive Interval Duration Censoring only by Relapse

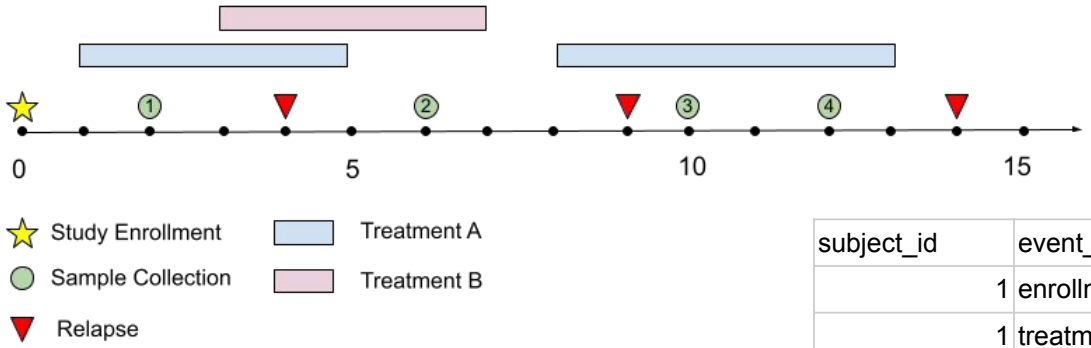


Plot of timelines for all 305 samples

: relapse event observed

: censored

Example timeline



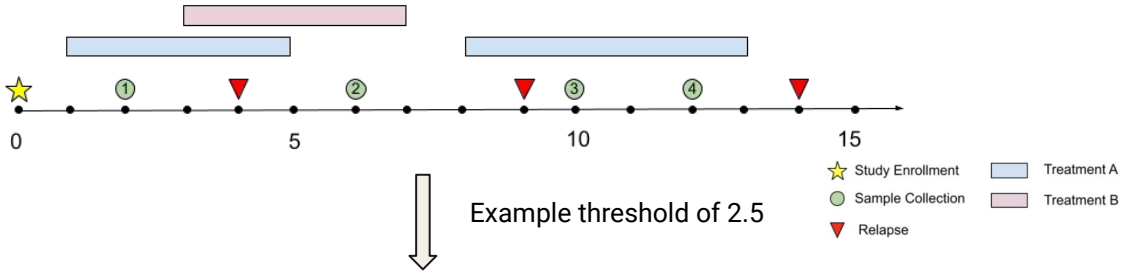
Original Data

subject_id	event_type	start_date	end_date	event_id
1	enrollment	0	0	
1	treatment A	1	5	
1	sample collection	2	2	1
1	treatment B	3	7	
1	relapse	4	4	
1	relapse	4	4	
1	sample collection	6	6	2
1	treatment A	8	13	
1	relapse	9	9	
1	sample collection	10	10	3
1	sample collection	12	12	4
1	relapse	14	14	

Modeling 1: Classification

Assign a label to each sample : *will the patient experience a relapse in the next ... days after sample collection ?* and fit a logistic regression model.

Threshold = 120 days (~4 months) → This yields ~**20%** of positive labels.



subject_id	start_date	end_date	duration	sample_id	label
1	2	4	2	1	1
1	6	9	3	2	0
1	10	14	4	3	0
1	12	14	2	4	1

Pros

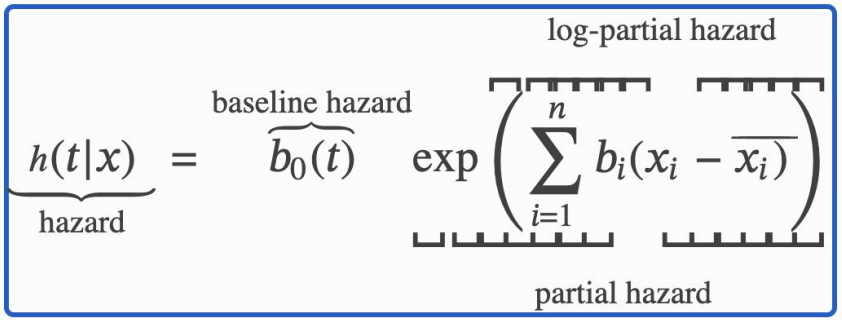
- Easy interpretation of the model
- Easy access to a probability of relapse
- Simple dataset - one row per sample
- Can be evaluated with classification metrics

Cons

- Does not take into account treatment information
- If we increase threshold to define labels, we lose some data
- With the current threshold, unbalanced classes

Cox Model

- Can be seen as an extension of traditional regression models that take into account censoring
- The log-hazard of an individual is a linear function of their covariates *and* a population-level baseline hazard that changes over time : [1]



- Proportional Hazards Assumption : the hazard ratio is constant, the effects of the covariates do not change over time
- We can add **L1 or L2 regularization terms**

1. Survival regression — lifelines 0.27.7 documentation

Concordance Index

- Metric used to evaluate survival models, can be seen as a generalization of the AUC
- Represents a model's ability to correctly provide a reliable ranking of survival times based on individual risk scores.

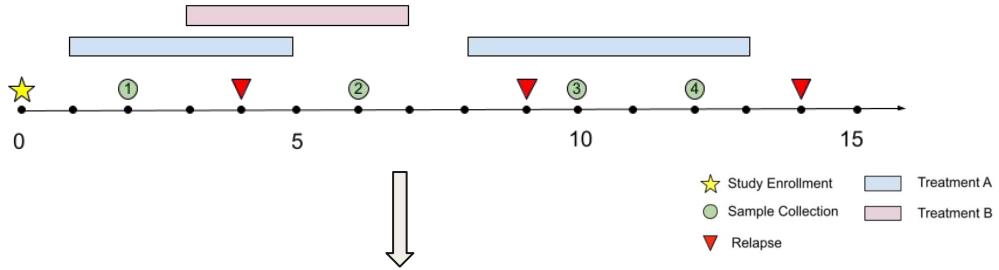
We loop over all possible pairs of subjects, for each subject i and j, we look at their risk scores r_i and r_j and their time to event T_i and T_j.

- If both i and j are not censored, then i and j are **concordant** if $r_i < r_j$ and $T_i > T_j$ (the subject with the highest risk of the event indeed experiences the event first), they are **discordant** otherwise.
- If both i and j are censored, we disregard the pair as there is no way to know who had the event first
- If j is censored and i is not:
  - If $T_i > T_j$ there is no way to know who had the event first, we disregard the pair
  - If $T_i < T_j$, we know that i had the event first, then the pair is **concordant** if $r_i > r_j$ and discordant otherwise.

$$\text{C index} = \frac{\#(\text{concordant pairs})}{\#(\text{concordant pairs}) + \#(\text{discordant pairs})}$$

Modeling 2: Naive Survival Analysis intervals

Assigns each sample to its next relapse/censoring event if censored. Fit a Cox Model PH to this survival data.



subject_id	start_date	end_date	duration	event	sample_id
1	2	4	2	1	1
1	6	9	3	1	2
1	10	14	4	1	3
1	12	14	2	1	4

Pros

- Easy interpretation of the model
- Takes into account precise interval durations
- Takes into account censoring events
- Simple dataset - one row per sample
- Can be evaluated with the C-index

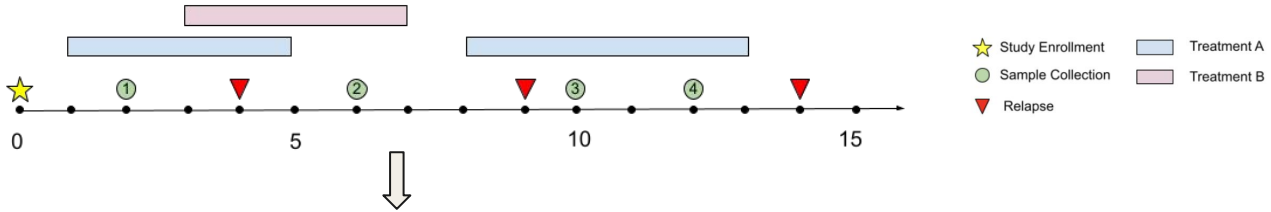
Cons

- Does not take into account treatment information
- Bias can be introduced by the fact that some time-points are counted ‘twice’ (ex : time interval from 12 to timepoint 14)
- We consider each interval independently

Modeling 3: Time Dependent Intervals splitting rules

- We break the timeline into **non-overlapping intervals**.
- Each time-varying covariate change and relapse triggers the start of a new interval and the end of the previous one.
    - For the time varying covariates that did not trigger the split, previous value carried forward.
    - The covariate(s) that triggered the split will have their value change to the new value
    - If a relapse event triggered the split, the event field of the previous interval will be set to 1 and a new interval is started with all other previous values of the covariates.

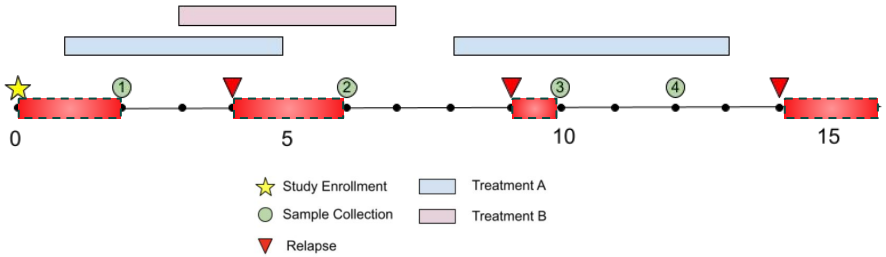
Time Dependent Intervals



subject_id	start (enrollment = 0)	stop (last known date = 15)	split_type	event	sample	treatment A	treatment B
1	0	1	treatment A : start	0		0	0
1	1	2	sample collection	0		1	0
1	2	3	treat B : start	0	1	1	0
1	3	4	relapse	1	1	1	1
1	4	5	treatment A : end	0	1	1	1
1	5	6	sample collection	0	1	0	1
1	6	7	treatment B : end	0	2	0	1
1	7	8	treatment A : start	0	2	0	0
1	8	9	relapse	1	2	1	0
1	9	10	sample collection	0	2	1	0
1	10	12	sample collection	0	3	1	0
1	12	13	treatment A : end	0	4	1	0
1	13	14	relapse	1	4	0	0
1	14	15		0	4	0	0

Time Dependent Intervals Exclusion Criteria

- We exclude intervals that do not have proteomics data associated with them, i.e. the intervals that are before the first proteomics data collection.
- We exclude intervals after a relapse and before the next sample collection → previous proteomics data collected before a relapse will likely not be representative of the protein expression state right after the relapse



subject_id	start (enrollment = 0)	stop (last known date = 15)	split_type	event	sample	treatment A	treatment B
			treatment A :				
1	0	1	start	0		0	0
1	1	2	sample collection	0		1	0
1	2	3	treat B : start	0	1	1	1
1	3	4	relapse	1	1	1	1
1	4	5	treatment A : end	0	1	1	1
1	5	6	sample collection	0	1	0	1
1	6	7	treatment B : end	0	2	0	1
1	7	8	treatment A : start	0	2	0	0
1	8	9	relapse	1	2	1	0
1	9	10	sample collection	0	2	1	0
1	10	12	sample collection	0	3	1	0
1	12	13	treatment A : end	0	4	1	0
1	13	14	relapse	1	4	0	0
1	14	15		0	4	0	0

Burdens of Disease: Disparities in Acute Healthcare

Guthy-Jackson Charitable Foundation, International NMOSD Roundtable Conference, August 2, 2024

Annette Langer-Gould, MD PhD

Regional Lead, Translational Neuroscience

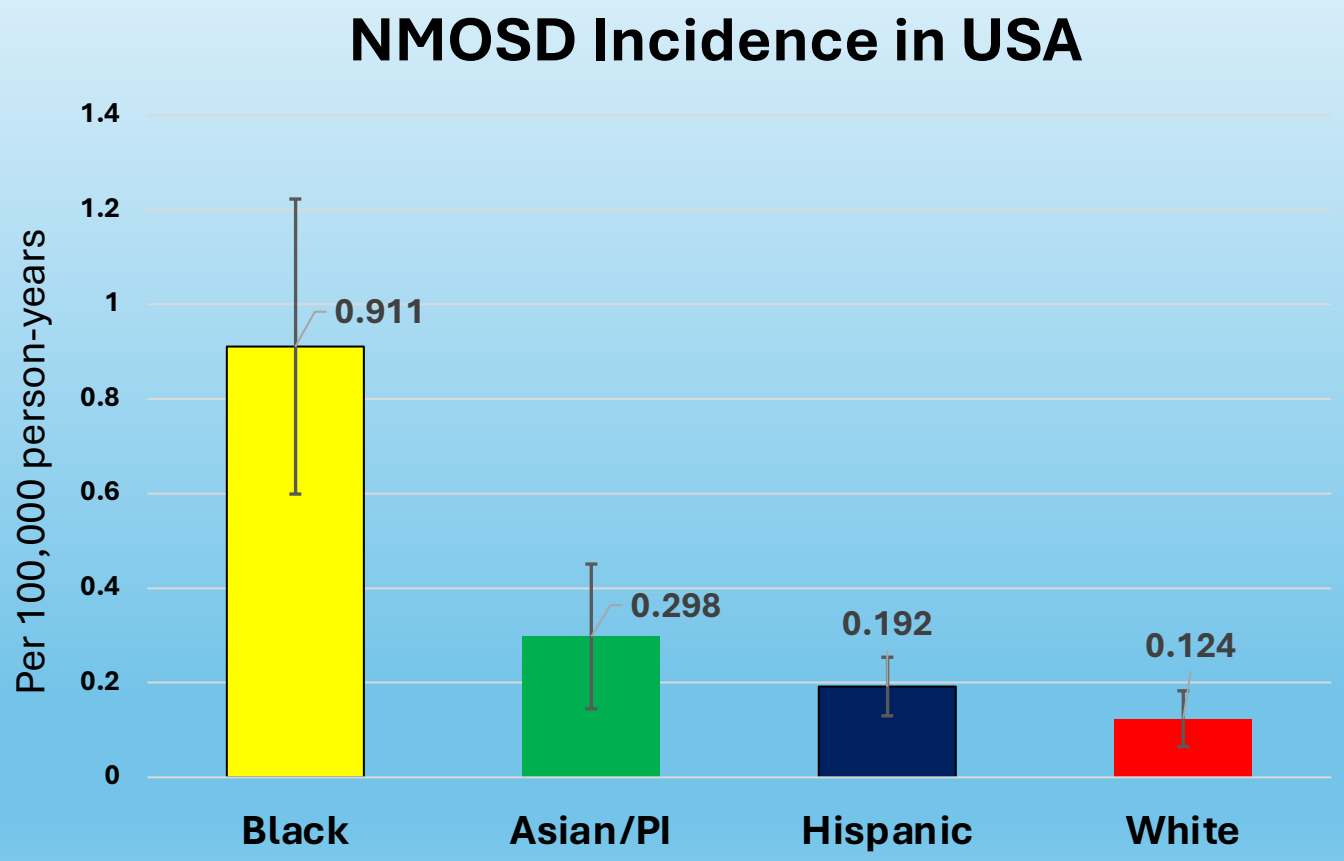
Southern California Permanente Medical Group/Kaiser Permanente

Bernard J Tyson Kaiser Permanente School of Medicine

Overview

- Review definitions
- Drivers of Disparities and Inequities in Acute Healthcare
- Barriers to Timely & Accurate NMOSD diagnosis
- Global inequities in NMOSD treatments
- Patient example
- Suggestions for improving equity in acute NMOSD care

Definitions: Acute Healthcare, Disparities



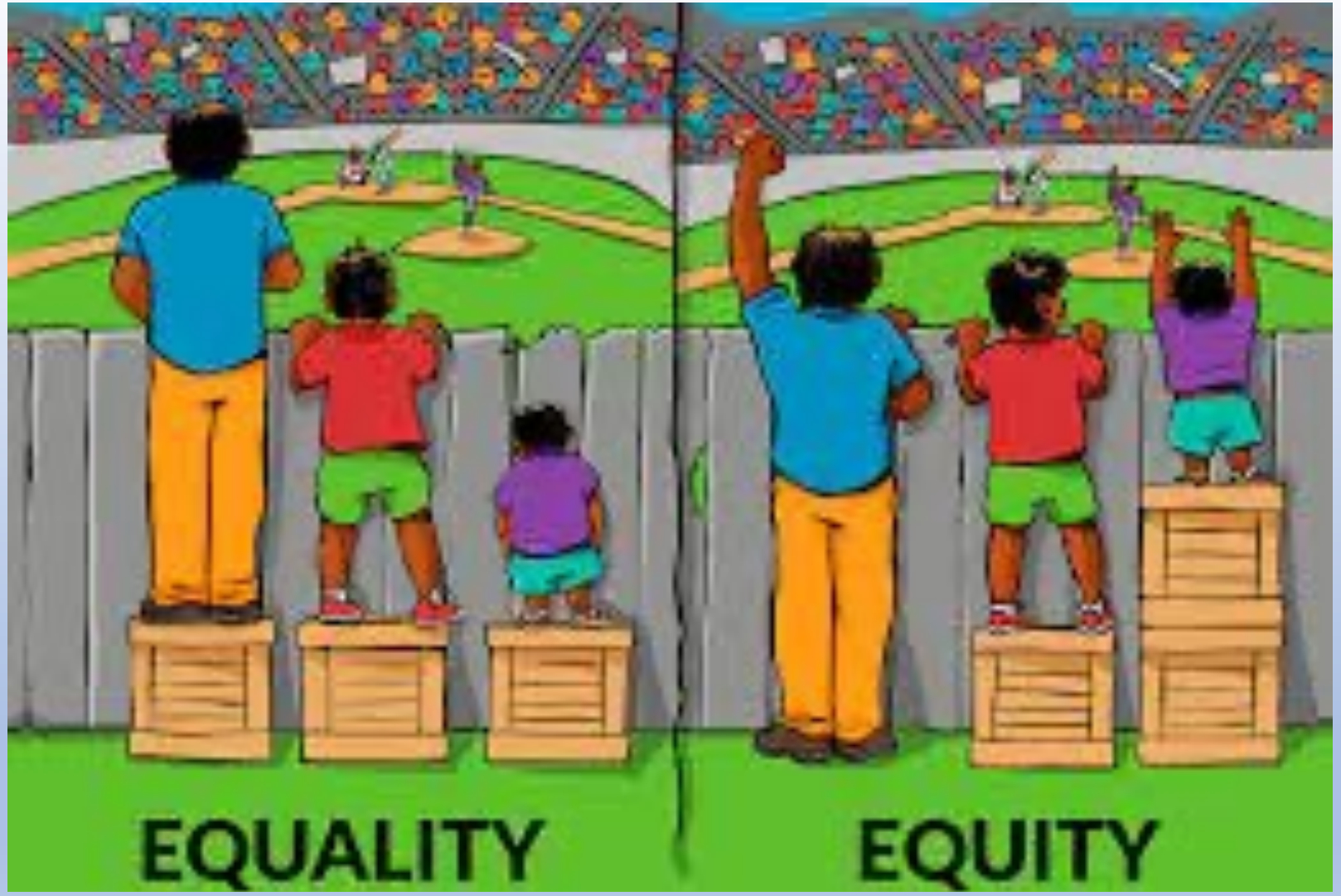
KP Southern California 2013-2022 age- and sex-standardized to the 2020 USA census, n=103

Treatment of relapses

Disparity=difference in a characteristic [NMOSD incidence by a characteristic [race and ethnicity]

Group assignment can be race or ethnicity, age, gender, etc.

This pattern in NMOSD incidence is consistent with global studies



Wanting everyone to have the same good health outcomes = Health Equity

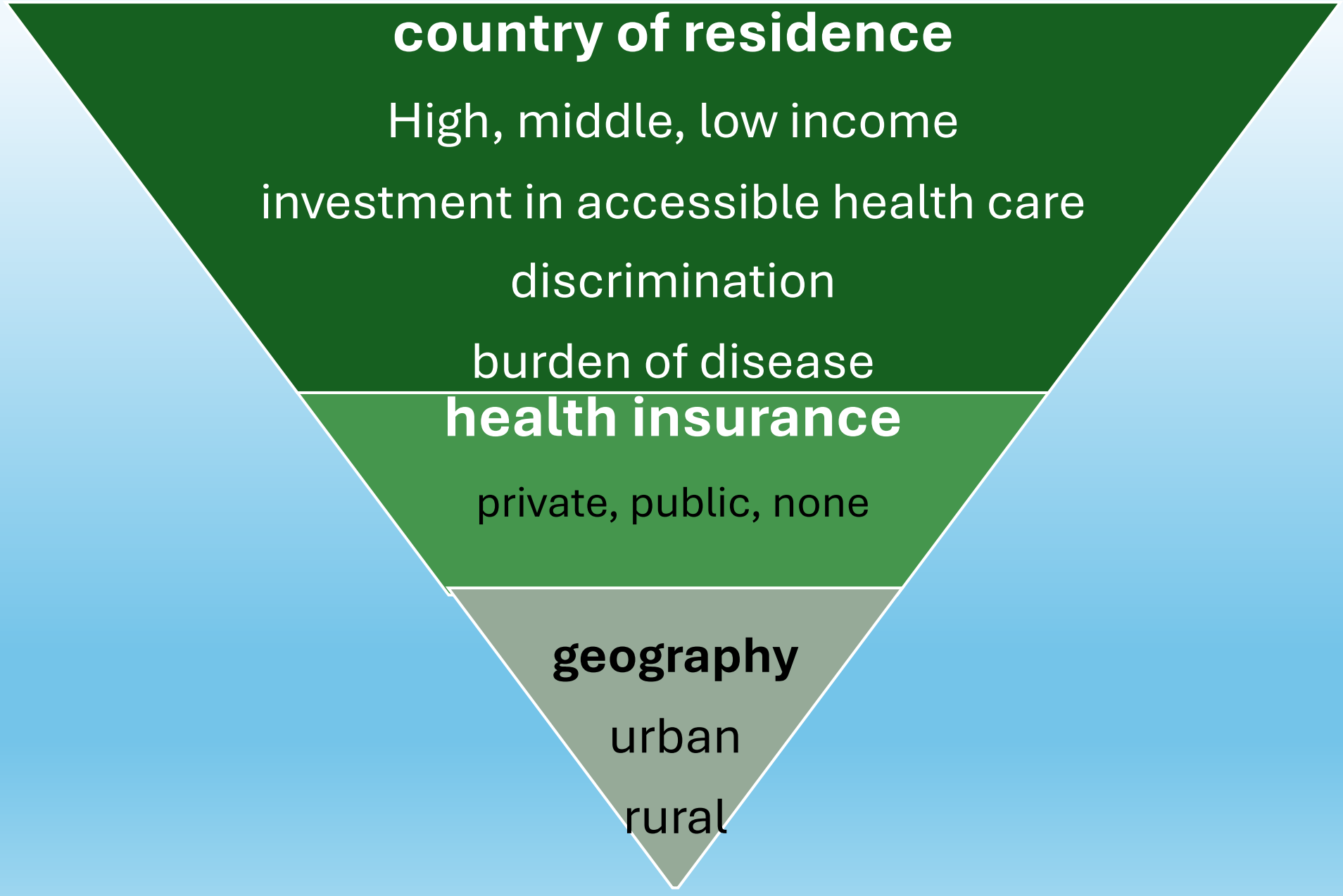
Why does equity in acute NMOSD care matter?

Disparities in NMOSD outcomes driven by

1. Misdiagnosis/diagnostic delays due to healthcare access and quality
2. Severity Relapse and access to acute treatments (e.g. plasma exchange/PLEX), especially in untreated patients (e.g. onset relapse)
3. Initiation of appropriately effective NMOSD treatments
4. Age, comorbidity burden
5. Clinical presentation other than optic neuritis or transverse myelitis contribute to diagnostic delays (e.g, area postrema syndrome, hypothalamic syndromes)

The magnitude of these contributors to outcomes is not well understood and worthy of further investigations

Drivers of Disparities in Acute Healthcare

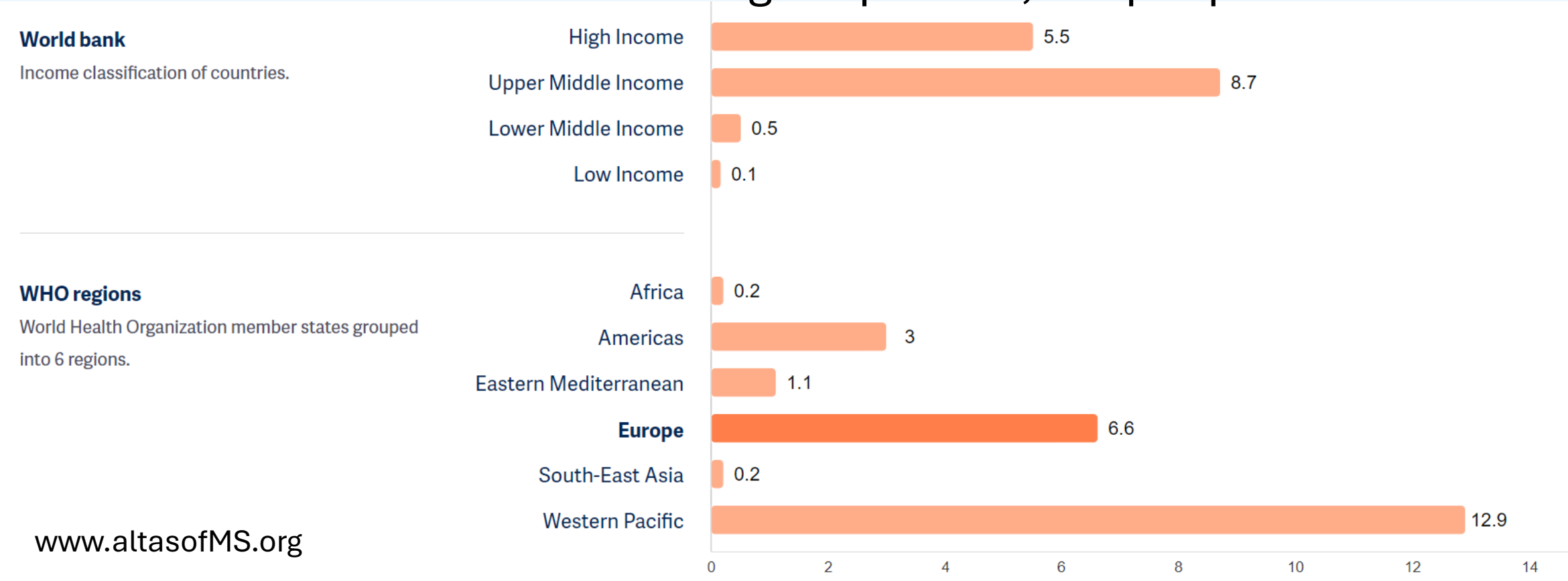


Timely & Accurate Diagnosis

Facilitated by neurologists, MRIs, AQP4 Ab testing

Global Inequity in Access to Neurologists:

Number of Neurologists per 100,000 people



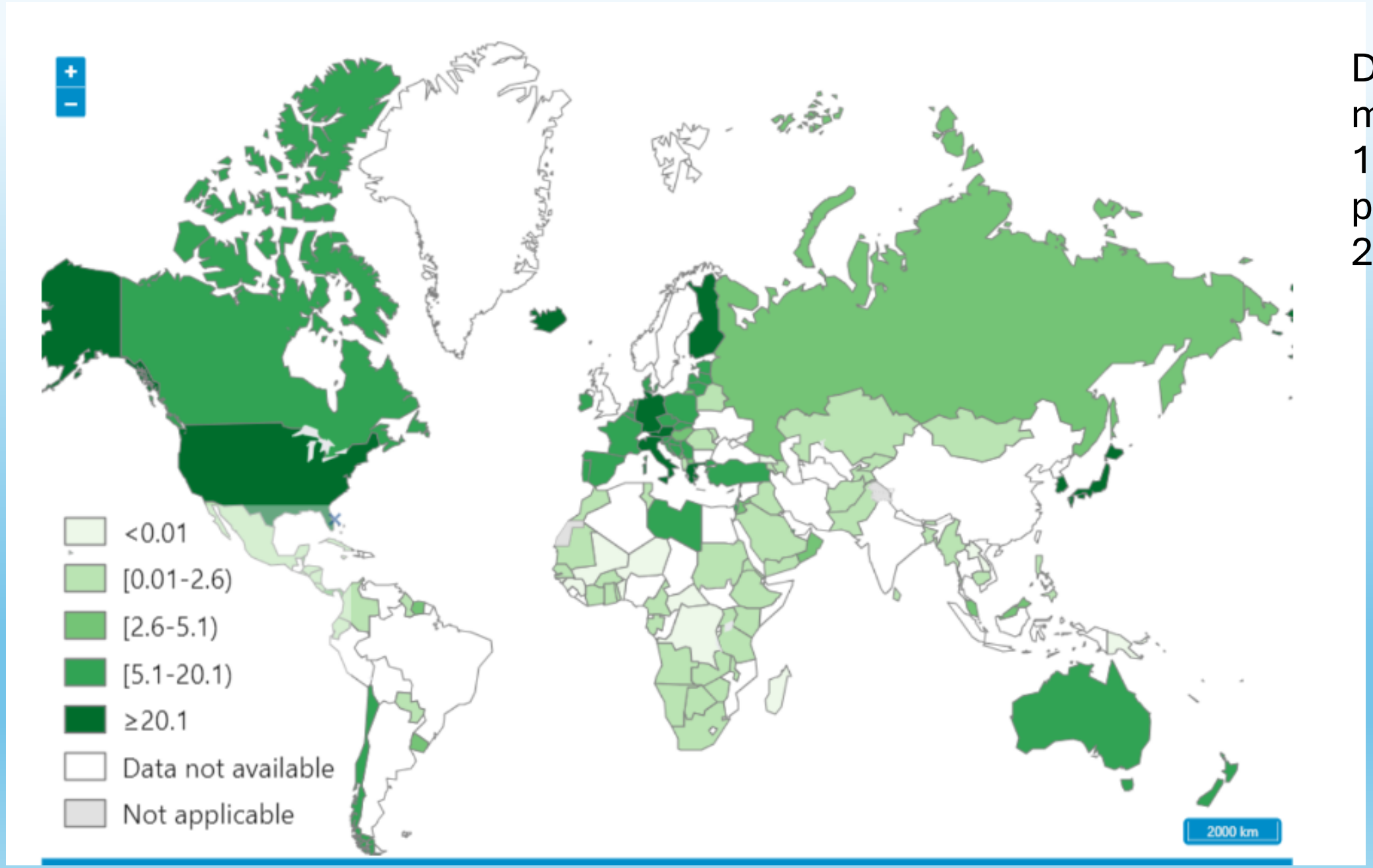
www.altasofMS.org

Varies widely within groups:

High Income: Germany 10, Japan 7.1 USA 5, Canada 2.8

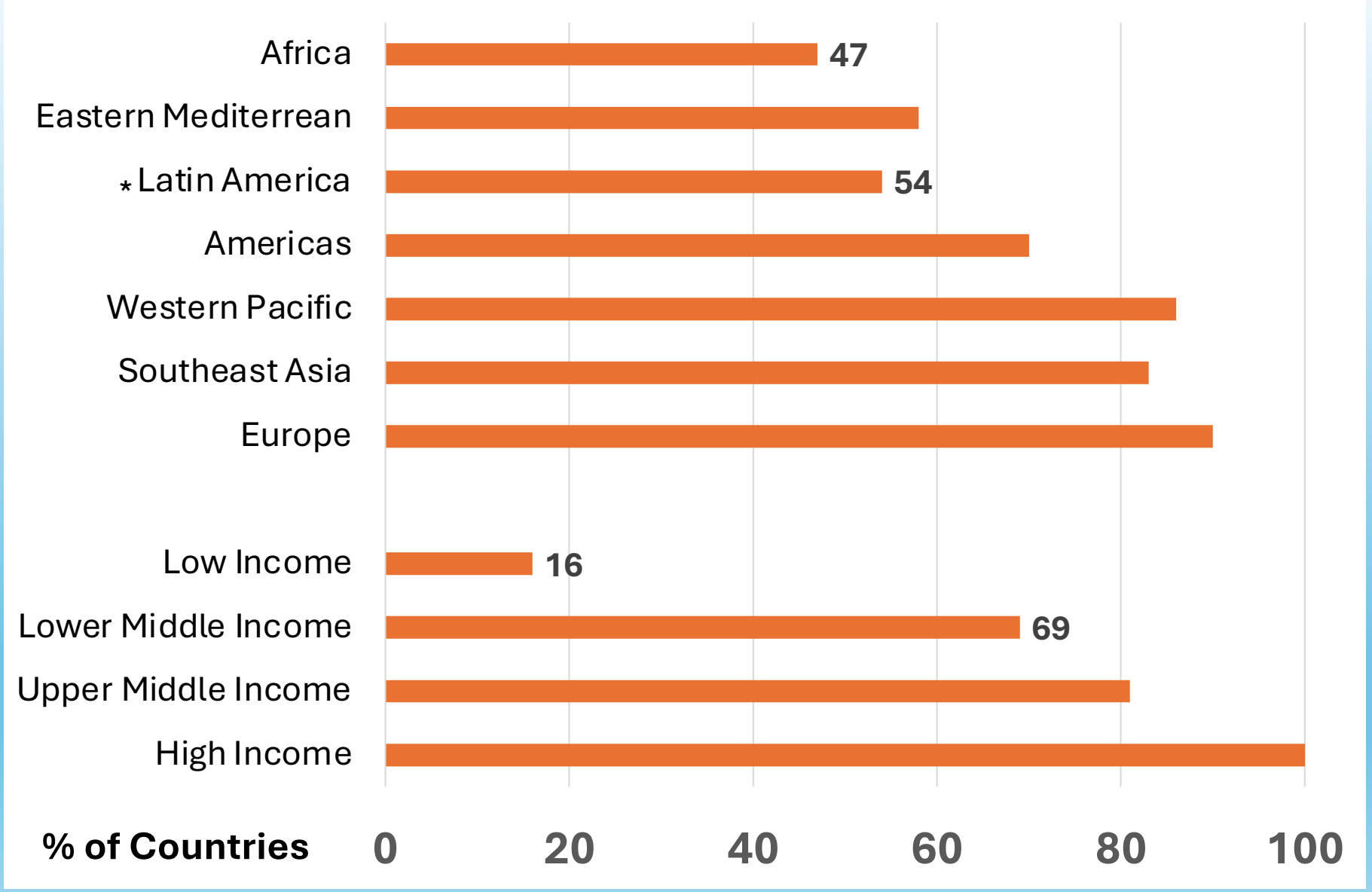
Upper Middle Income: Argentina 2.7, Brazil 2.5, Mexico 0.8; Armenia 10.1, China 14

Western-Pacific: China 14, Japan 7.1, Australia 2.1, New Zealand 1 (South Korea not reported)



Density of MRI machines per 1 million people: WHO 2024

Global Inequities in Availability of AQP4-Ab testing



Survey study by K. Holroyd et al, MSARD, 2019

*Latin America survey study by Rojas JI et. Al, Jrnl Neurol Research, 2021

Inequities in Access to NMOSD Treatments

Reduce the need for acute care by reducing the frequency and severity of NMOSD relapses

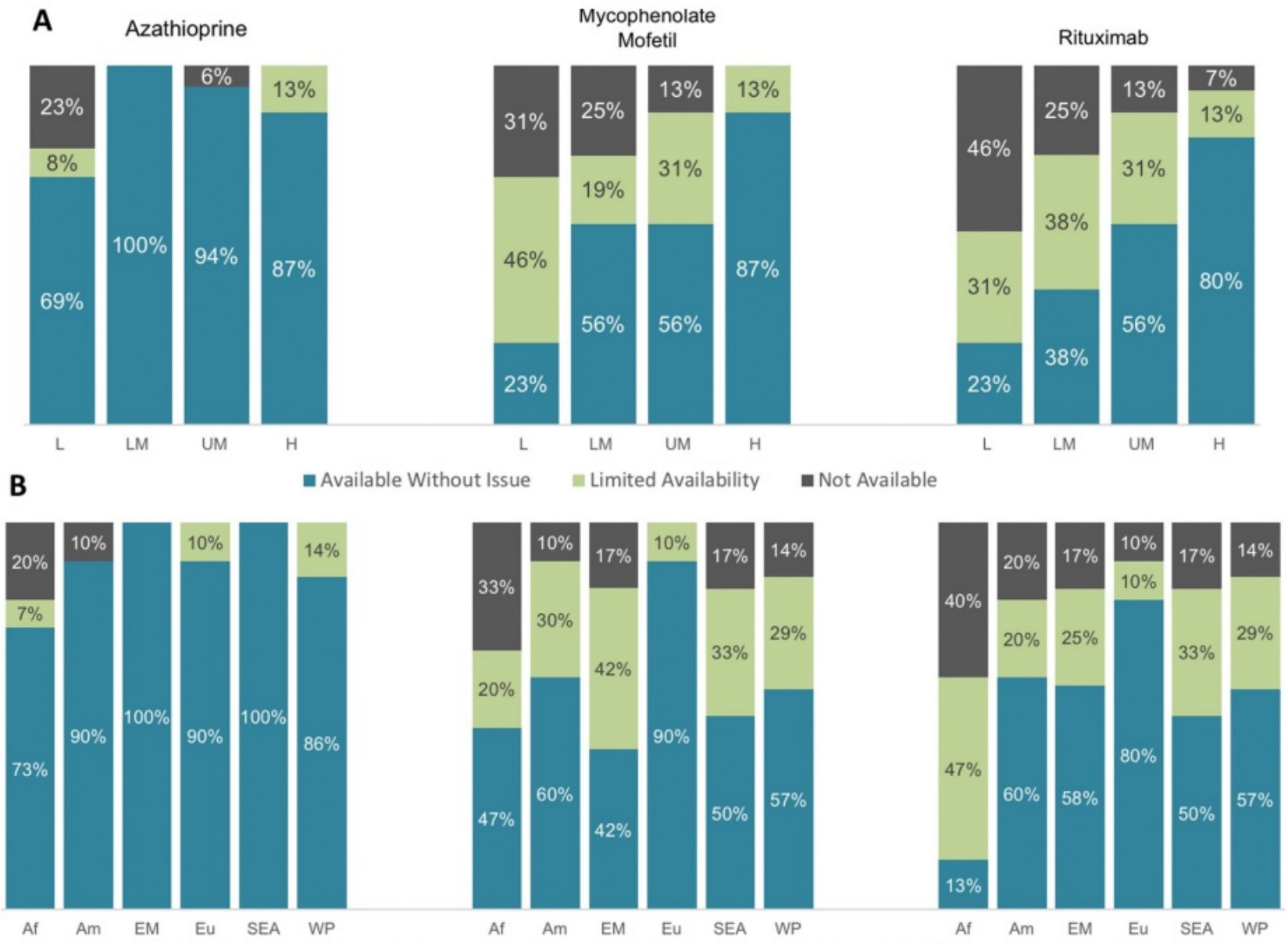


Fig. 3. Availability and accessibility of long-term NMO treatments by A) World Bank income status and B) WHO World Region of responding countries.

LIMITED AVAILABILITY OF LOW COST NMOSD TREATMENTS GLOBALLY

Survey data from 2018

Advocacy needed, worth repeating this study

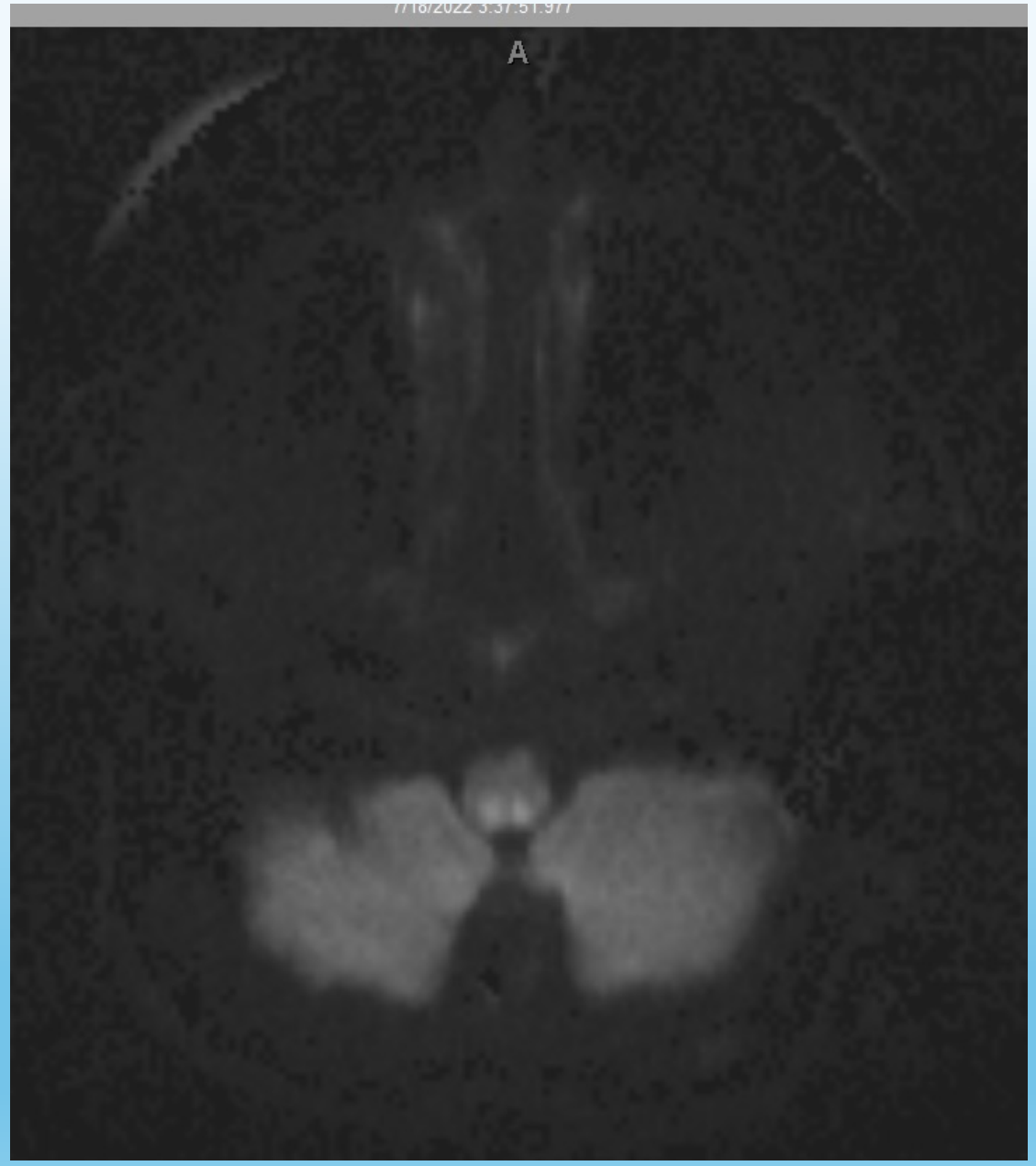
Patient example:

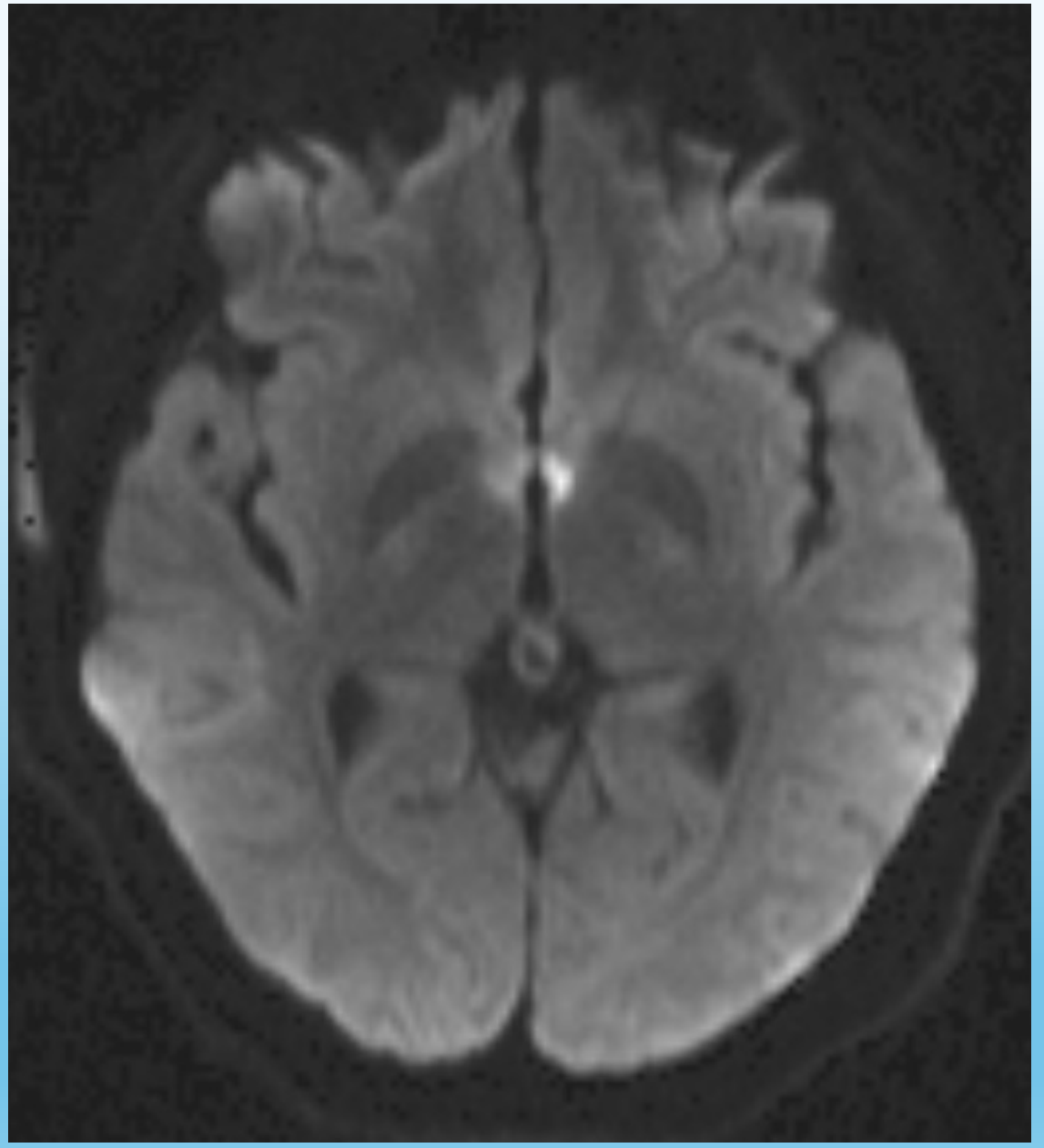
- 19 y/o female of Asian descent no significant PMH, lives in rural California, seen in urgent care for intermittent nausea and vomiting in late June after eating fast food with friends.
- Progressed to intractable N/V and hiccups
- 7/8 admitted to local hospital for GI work-up. Hyponatremic and briefly hypokalemic.
- During admission became increasingly lethargic and started hallucinating with dysphagia, difficulty handling secretions, NG tube placed and CSF was obtained.
- Revealed marked lymphocytic pleocytosis (580 wbc) and elevated protein. Started on antiviral, anti-fungals and antibiotics. EEG was normal. GI work-up negative. ANA 1:80 positive.
- Dx with acute encephalitis. Parents told prognosis very poor
- 7/11 brain MRI (~2 weeks after symptom onset and 2 days after acute decompensation) normal (not leptomeningeal enhancement) but sequences were limited

Patient example continued:

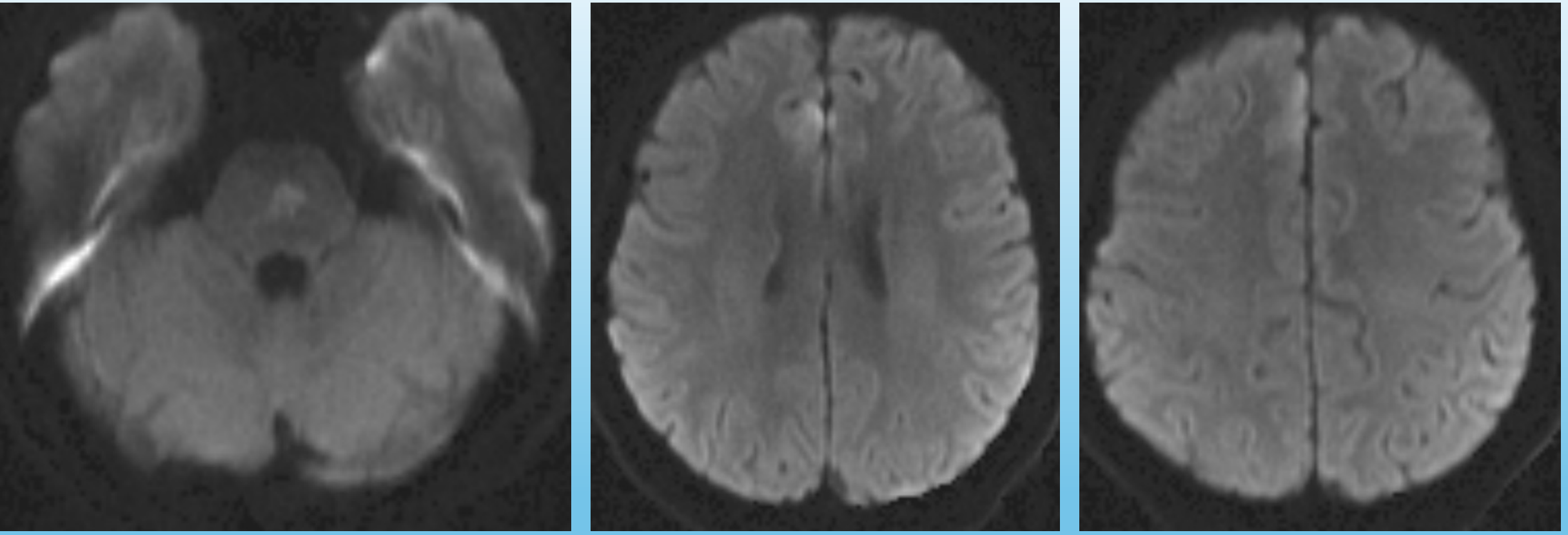
The NEXT DAY

- 7/12 developed weakness in hands and arms, iv solumedrol
- 7/14 transferred to Los Angeles Medical Center for higher level of care, profoundly lethargic, dysarthric, tetraparetic 5- to 4+ left arm, 4 both legs except 1 left dorsi- and plantar flexion. Seen by an MS specialist.
- 7/15 Foley placed, repeat CSF 92 WBC, 92% lymphocytes, protein wnl (43)
- 7/18 repeat brain MRI "*pt with no pmhx presented with altered mental status and b/l arm and leg weakness after possible viral infections, suspicious for autoimmune encephalitis*."



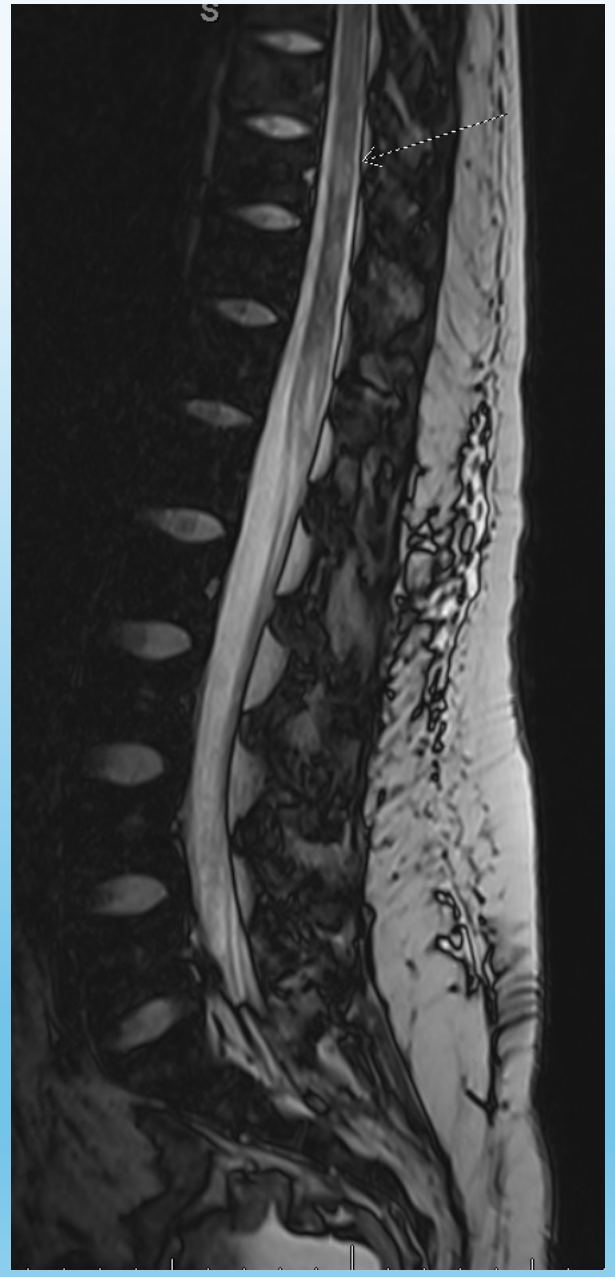


NMOSD not mentioned in differential diagnosis by radiologist

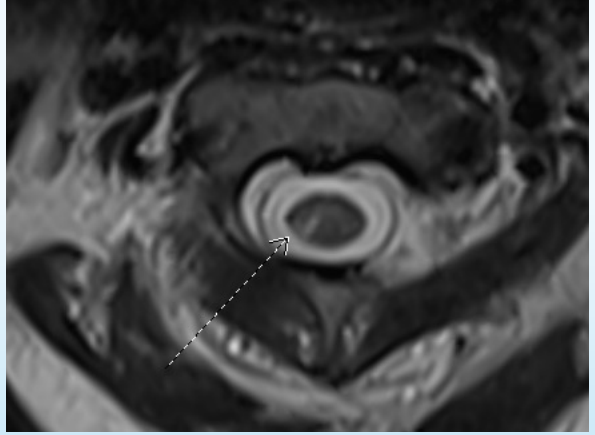


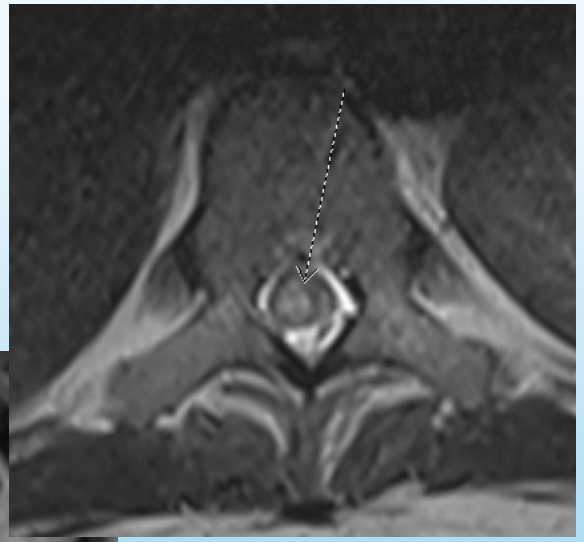
Patient example continued:

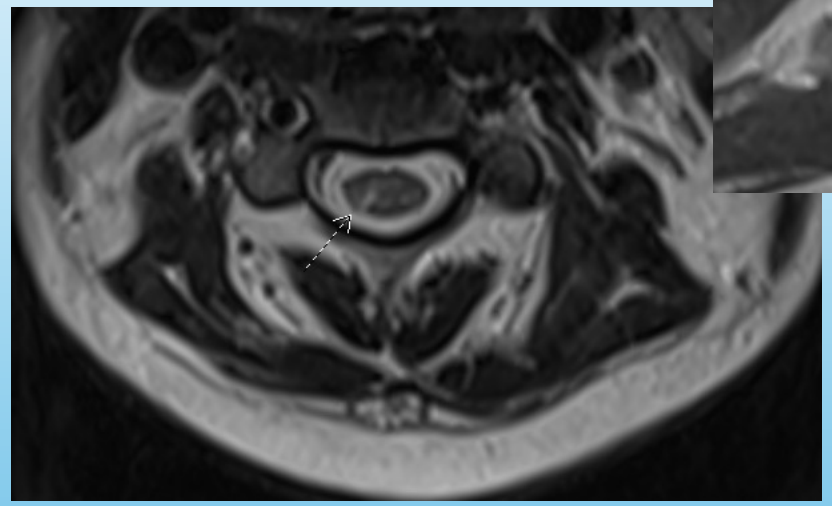
- PLEX started from presumptive diagnosis of autoimmune encephalitis
- ~1 month after symptom onset, s/p 10 days iv solumedrol and 5 rounds of PLEX, level of alertness has improved (intermittently briefly awake) but
- Paraparesis markedly worse, asymmetric left leg weaker (1) than right (2), areflexic in legs.
- urinary retention unable to sense need to urinate or defecate
- Spinal cord imaging obtained and AQP4 Ab returned positive CBA, confirmation testing sent to Mayo, titer 1:1000 (even after PLEX)
- Treated with RTX and Cytoxan (2 doses), maintained on RTX 1g q6mo
- 2 years later excellent recovery

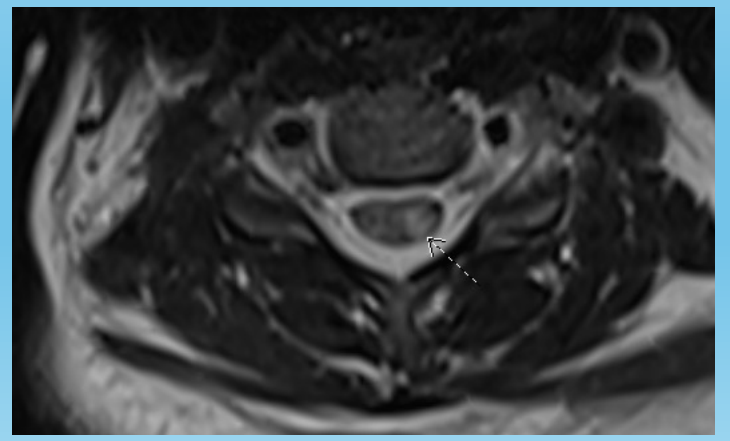

S

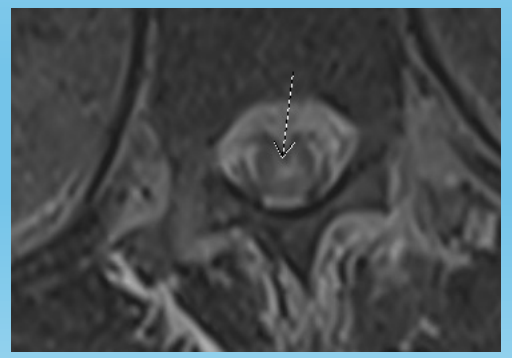

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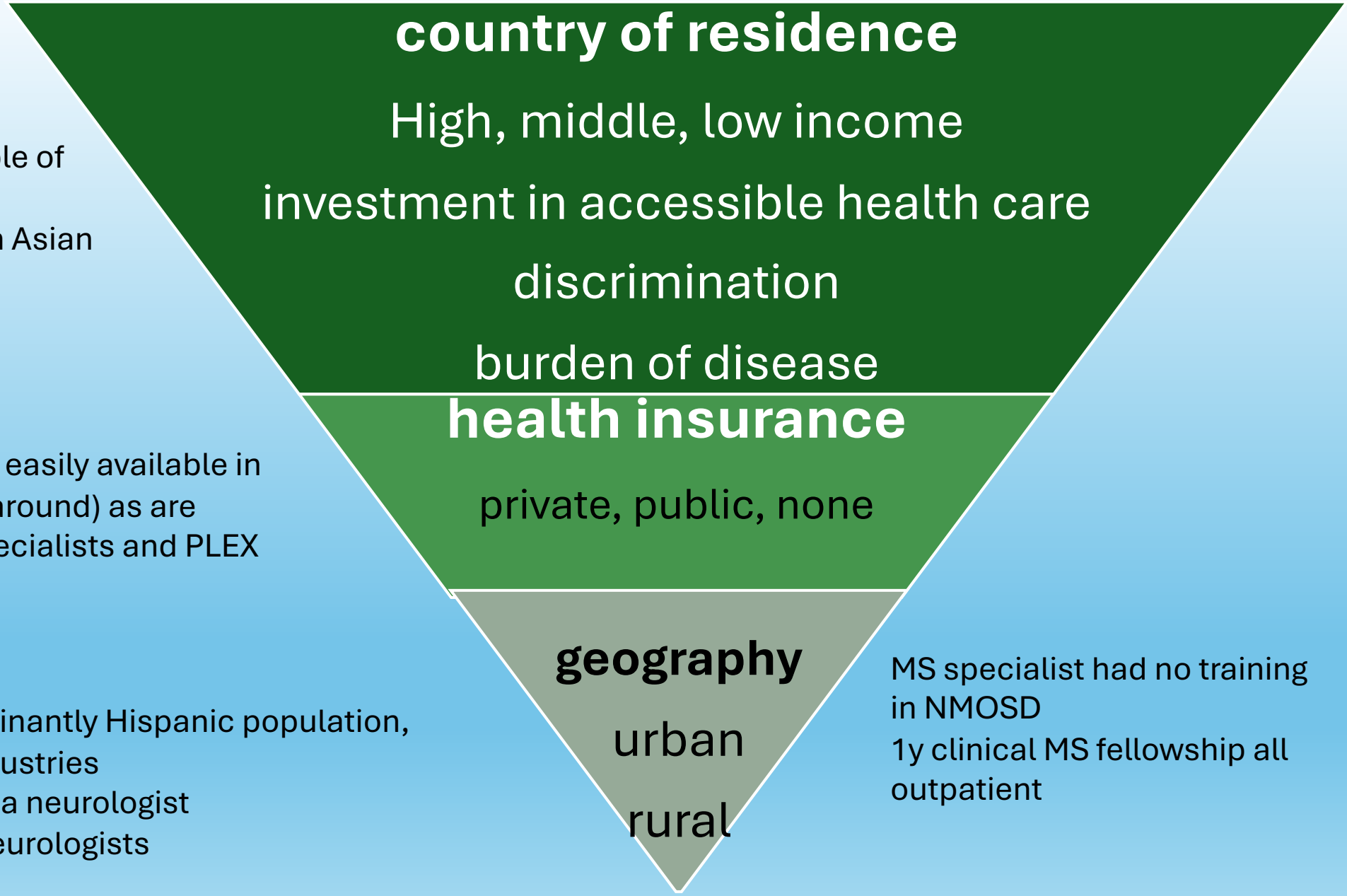








Patient Example: Improving Equity



High income country
Discriminates against people of color
Higher burden of NMOSD in Asian Americans

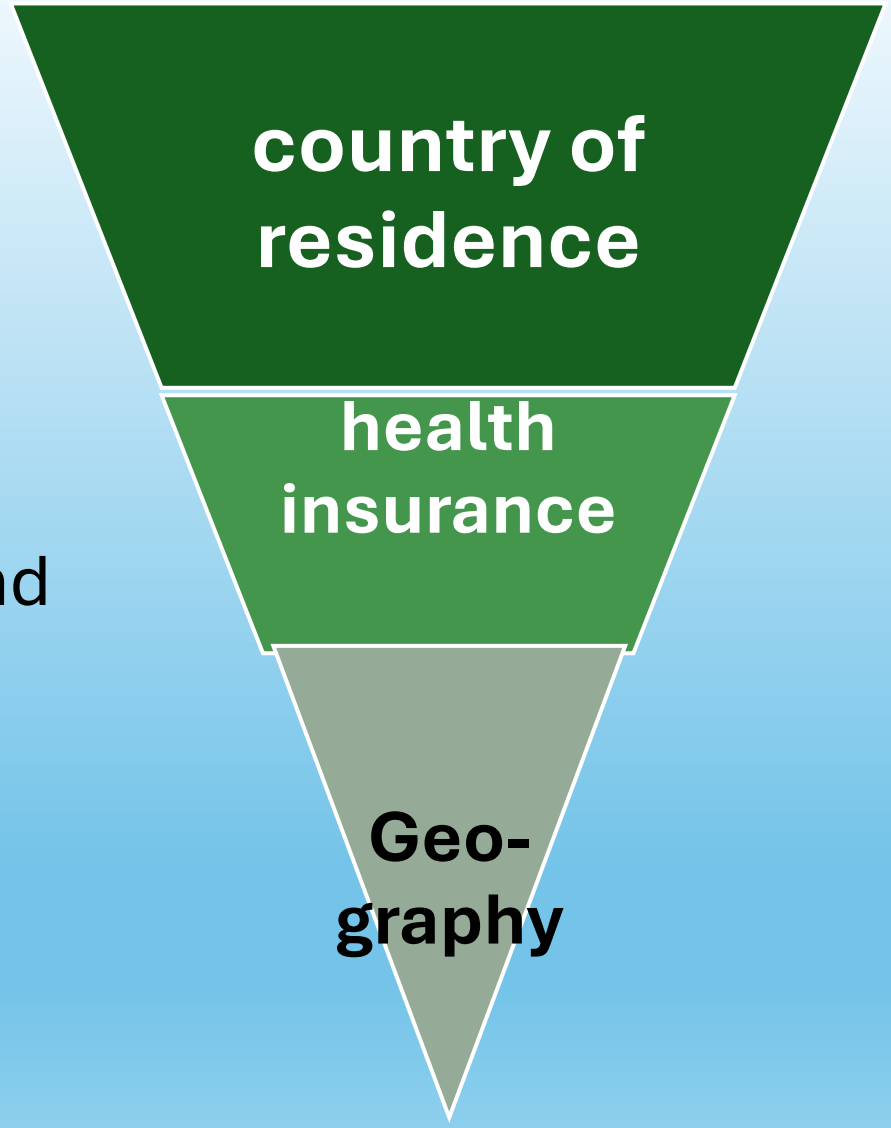
Private health insurance
Cell-based AQP4 IgG testing easily available in main hospitals (~2 day turn around) as are neuroimmunologists, MS specialists and PLEX machines

<u>Residential segregation</u>:
Lives in Rural Area, predominantly Hispanic population, agriculture and oil main industries
Local hospital did not have a neurologist
Community often has no neurologists

MS specialist had no training in NMOSD
1y clinical MS fellowship all outpatient

Improving Equity in Acute Care

- Training neuroimmunologists
  - Collaborating with NMSS, include inpatient experience
  - Board certification
- Raising awareness
  - Educating colleagues ICU, GI, Radiology
- Improving access to neuroimmunologists and neuroradiologists
  - Tele-health
- Access to acute care (PLEX, rituximab)
- Training patients in self-advocacy (in case of future relapses)



Thank you!

- Guthy-Jackson Charitable Foundation
- Kaiser Permanente Southern California MS and Related-Disorders research team
  - Jessica B Smith, MPH
  - Bonnie H Li, MS
  - Neurology Residents: Angus Lee, DO and Ina Iordanova, DO
  - Kaiser Permanente Medical Students:
    - Sakar Budhathoki, Kathyrn Schwartzmann, Sam Alsalek, Viridiana Herndandez-Lopez

PLEX & IVIG in Acute Relapse Settings

No treatments have been licensed for acute treatment in NMOSD nor MOGAD

Jacqueline Palace

Disclosures: Jacqueline Palace has received support for scientific meetings and honorariums for advisory work From Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Amgen, Vitaccess, UCB, Mitsubishi, Amplo, Janssen. Grants from Alexion, Argenx, Clene, Roche, Medimmune, Amplo biotechnology. Patent ref P37347WO and licence agreement Numares multimarker MS diagnostics Shares in AstraZenica. Her group has been awarded an ECTRIMS fellowship and a Sumaira Foundation grant to start later this year. A Charcot fellow worked in Oxford 2019-2021. She acknowledges partial funding to the trust by Highly specialised services NHS England. She is on the medical advisory boards of the Sumaira Foundation and MOG project charities, Is a member of the Guthy Jackon Foundation Charity and is on the Board of the European Charcot Foundation and a member of MAGNIMS and the UK NHSE IVIG Committee and chairman of the NHSE neuroimmunology patient pathway and ECTRIMS Council member on the educational committee since June 2023. Currently on the ABN advisory groups for MS and neuroinflammation and recently on neuromuscuscular diseases advisory group.

NMOSD PLEX

NMOSD PLEX

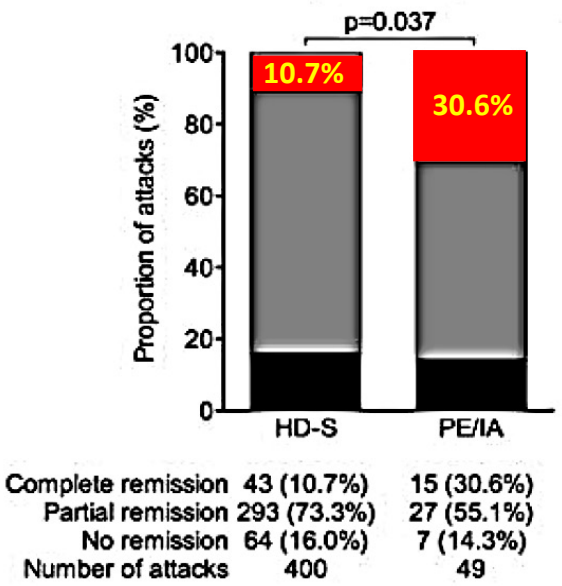
Kleiter et al, Ann Neurol 2016;79:2016

871 attacks in 185 patients
84% AQP4-Ab +ve
analysed: all, TM, ON, ON+TM attacks,

No difference in high dose MPred vs PLEX/IA 1st line except

TM: ↑ complete remission w PLEX/IA

TM



CR complete remission
PR partial remission
NR no recovery

TABLE 3. Factors Associated with Complete Remission from NMO Attacks

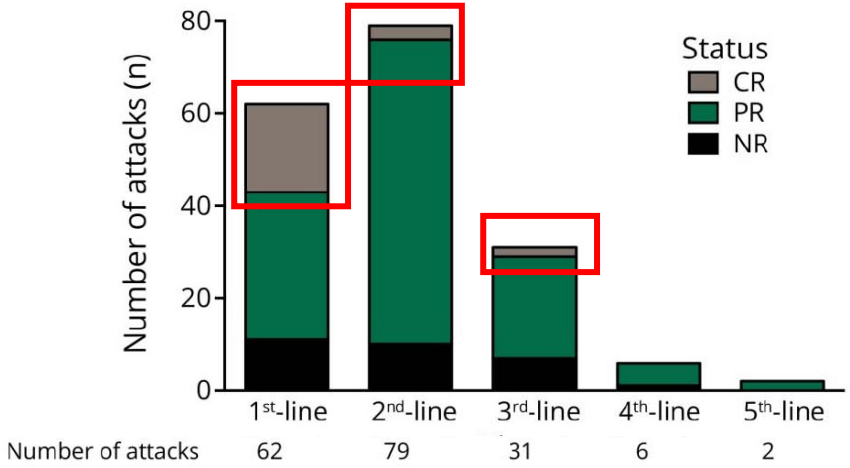
Factor	Multivariate Analysis	
	p	Odds Ratio (95% CI)
Female gender vs male	0.125	0.509 (0.21–1.21)
Age at attack per 1 year	0.011	0.973 (0.95–0.99)
Time from onset of disease to attack per 1 year	0.796	0.993 (0.94–1.05)
AQP4 positive vs negative	0.536	1.417 (0.47–4.27)
NMO vs NMOSD	0.756	1.148 (0.48–2.74)
MY present vs absent	0.002	0.382 (0.21–0.70)
MY+ON present vs absent	0.633	1.315 (0.43–4.06)
Time since previous attack per 1 month	0.289	1.008 (0.99–1.02)
CR of previous attack vs NR+PR	<0.001	6.847 (3.65–12.84)
Time from onset of attack to start of therapy per 1 day	0.083	0.952 (0.90–1.01)
PE/IA as 1st course vs HD-S	0.006	4.383 (1.54–12.50)
Other therapy as 1st course vs HD-S	0.205	3.176 (0.53–18.99)
Center number	0.396	0.983 (0.94–1.02)

NMOSD aphoresis

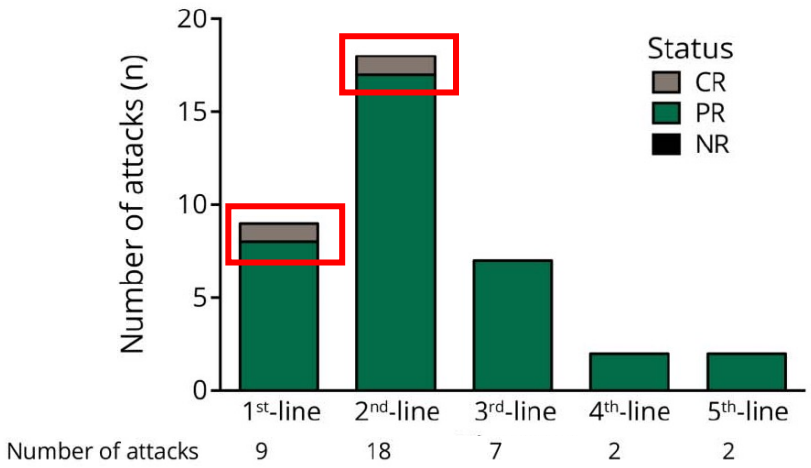
Kleiter et al, *Neurol Neuroimmunol Neuroinflamm* 2018;5:e504.

230 attacks in 105 patients, w descriptive data 192 PLEX, 38 IA
Analysis 139 attacks in 79 patients
87% AQP4-Ab +ve

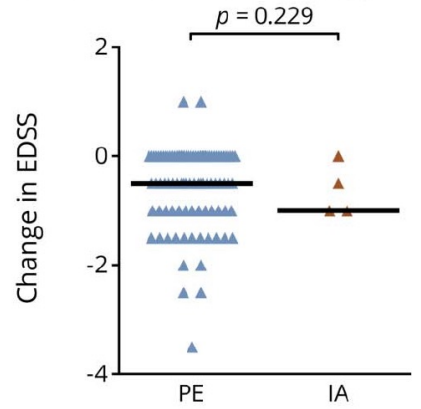
A. Remission status PE



B. Remission status IA

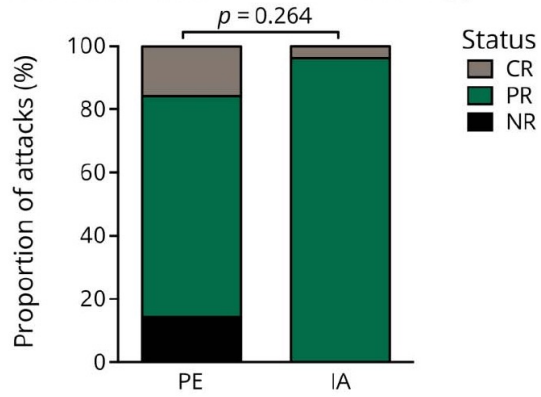


D. EDSS after 1st- or 2nd-line therapy



	PE	IA
Median	-0.5	-1.0
Mean	-0.526	-1.700
SD	0.730	2.439
Number of attacks	97	5

Remission status after 1st- or 2nd-line therapy



	PE	IA
Complete remission	22 (15.8%)	1 (3.8%)
Partial remission	97 (69.8%)	25 (96.2%)
No remission	20 (14.4%)	0
Number of attacks	139	26

NMOSD aphoresis

Kleiter et al, *Neurol Neuroimmunol Neuroinflamm* 2018;5:e504.

230 attacks in 105 patients, w descriptive data 192 PLEX, 38 IA
Analysis 139 attacks in 79 patients
87% AQP4-Ab +ve

E. Remission status according to delay of PE or IA

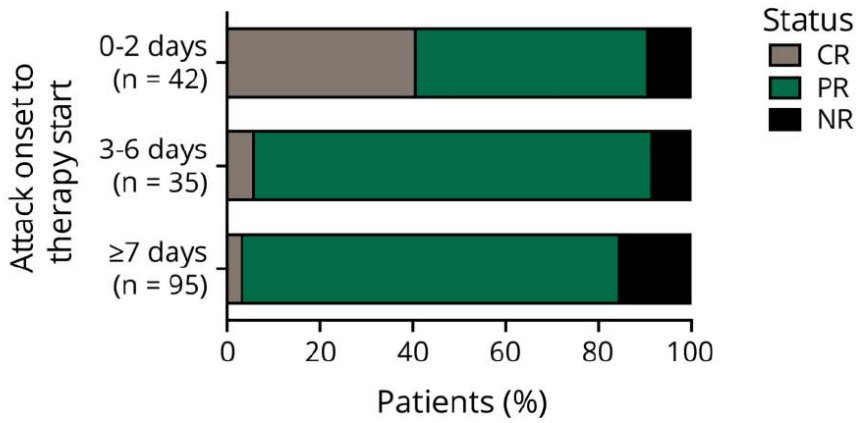


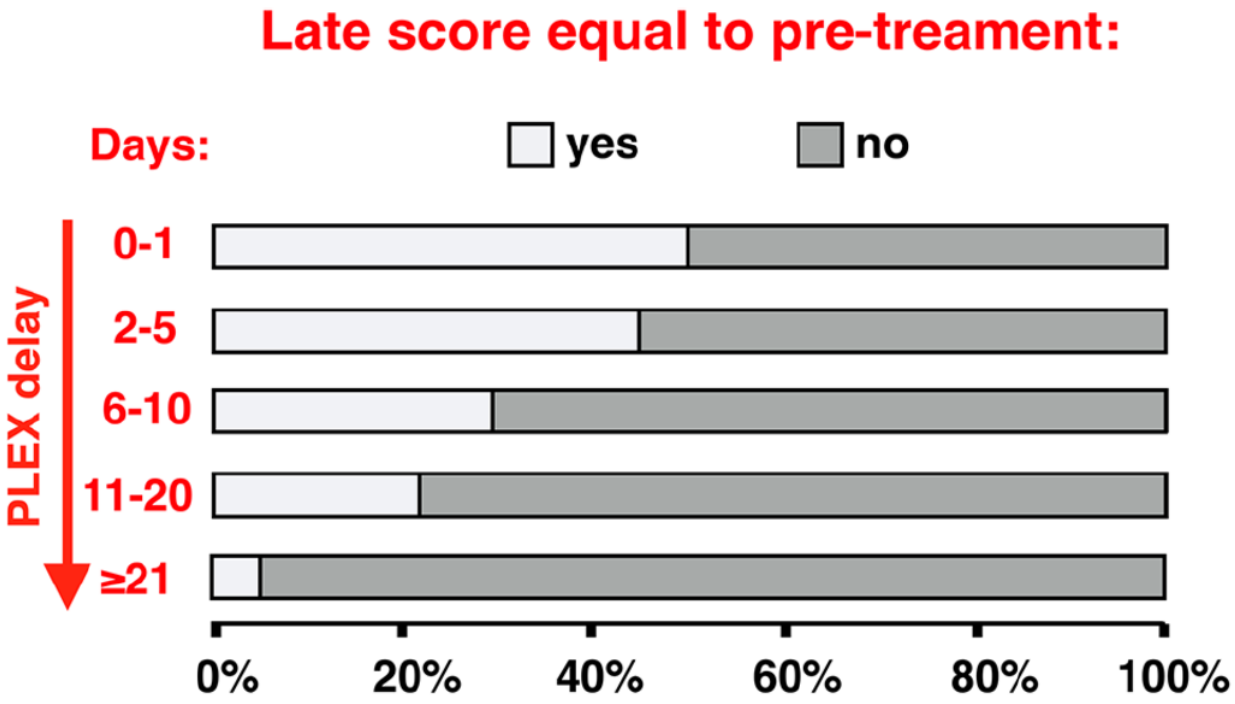
Table 3 Factors associated with complete remission from NMOSD attacks after apheresis therapy

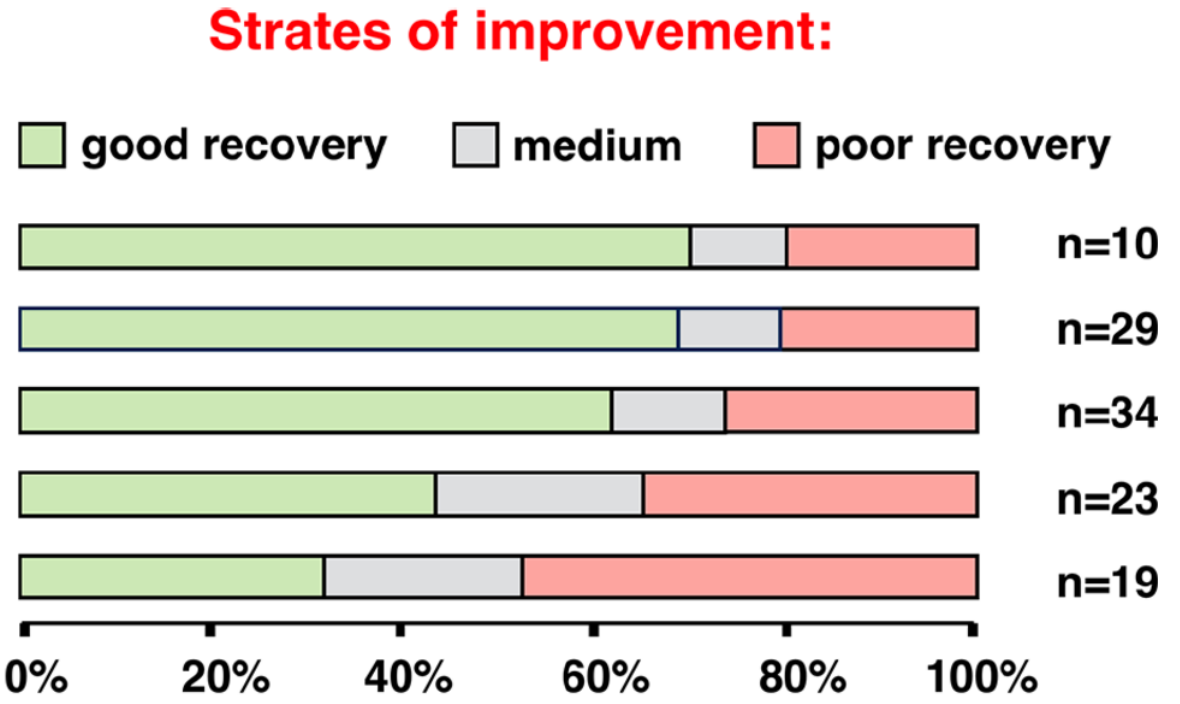
	Multivariate analysis	
	***p* Value**	**OR (95% CI)**
Female sex (vs. male)	0.456	3.447 (0.13–89.40)
Age at attack (per 1 y)	0.081	0.925 (0.85–1.01)
Time from onset of disease to attack (per 1 y)	0.247	0.926 (0.81–1.06)
AQP4-ab positive (vs negative)	**0.019**	**33.338 (1.76–631.17)**
NMO (vs NMOSD)	0.316	2.951 (0.36–24.41)
MY present (vs absent)	0.726	1.350 (0.25–7.2)
Isolated ON or MY (vs simultaneous ON + MY)	**0.046**	**4.709 (1.03–21.62)**
Prophylactic immunotherapy present (vs absent)	0.532	1.683 (0.33–8.63)
Time from onset of attack to start of therapy (per 1 d)	**0.014**	**0.937 (0.89–0.99)**
First-line apheresis therapy (vs second-line)	**0.047**	**12.271 (1.04–144.91)**
PE (vs IA)	0.107	4.946 (0.71–34.59)

0.63 7 days
0.16 30 days

NMOSD time to PLEX

N=60 treated with PLEX,
66% AQP4+ve,



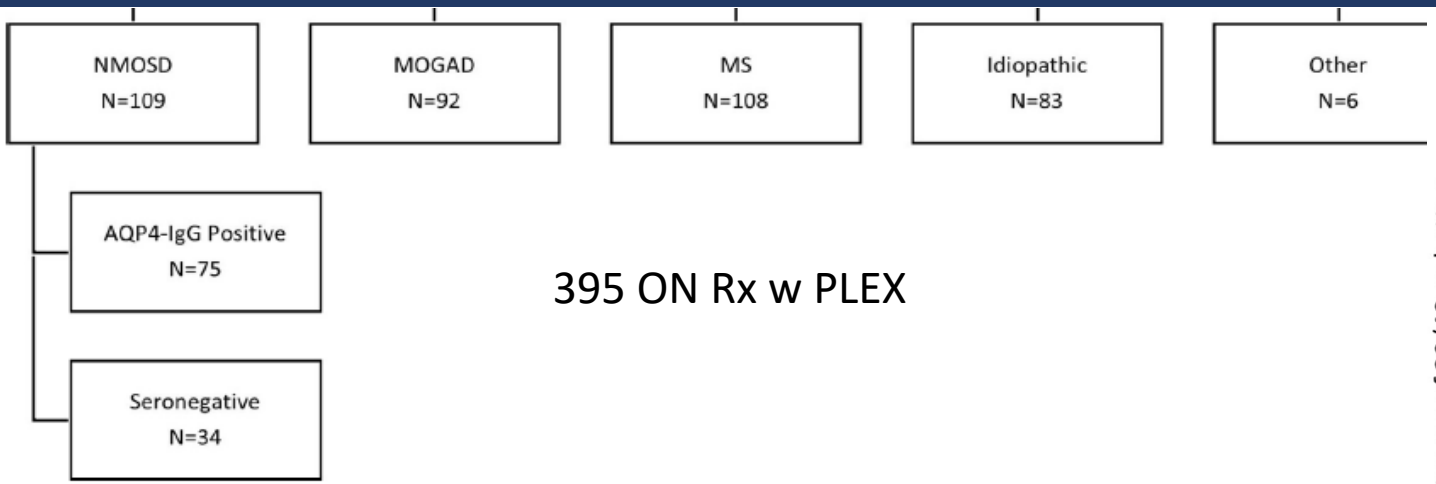


OR 5.3 CI given within 5 days vs ≥ 11 days

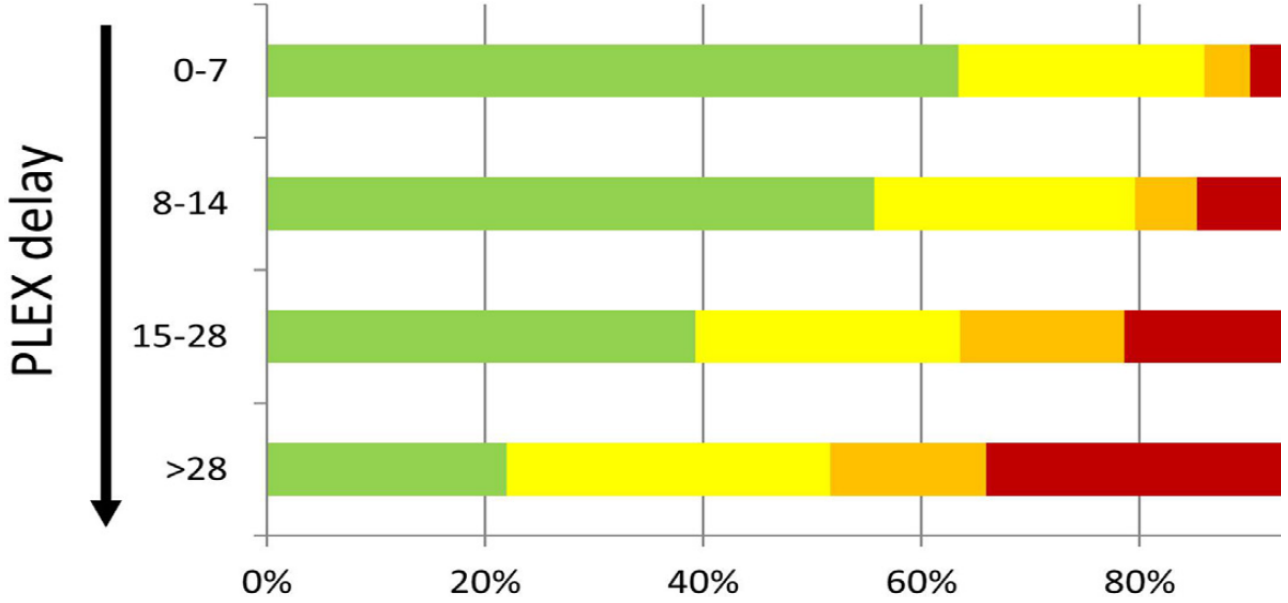
Bonnan M, *et al*. *J Neurol Neurosurg Psychiatry* 2018;**89**:346–351. doi:10.1136/jnnp-2017-316286

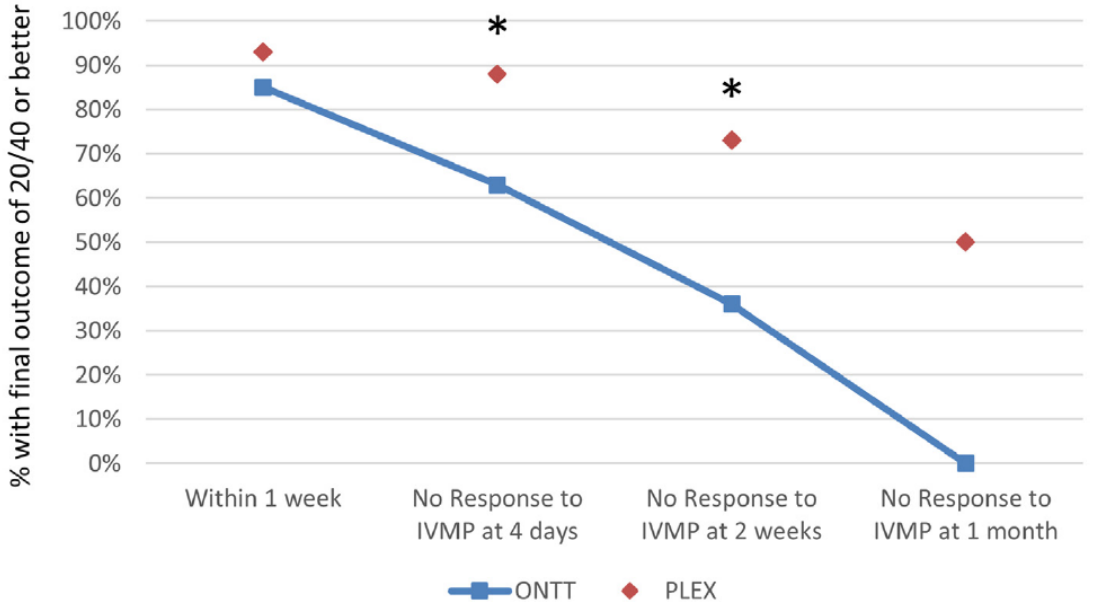
All PLEX

ON and PLEX



395 ON Rx w PLEX





Vision 20/200 or worse

There is currently no treatment approved for the management of MOGAD.

AQP4, aquaporin-4; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; ONTT, optic neuritis treatment trial; PLEX, plasma exchange; Rx, medical prescription.

Chen JJ, et al. *Am J Ophthalmol*. 2023;252:213-224.

NMOSD IVIG

NMOSD: IVMP vs IVMP then IVIG

	IVMT + IVIG		IVMT	
Patients, No.	20		39	
Events, No.	31		72	
AQP4-ab serostatus	per event			
Positive	27	90% (27/20)	41	95% (41/43)
Negative	3		2	
Unknown	1		29	

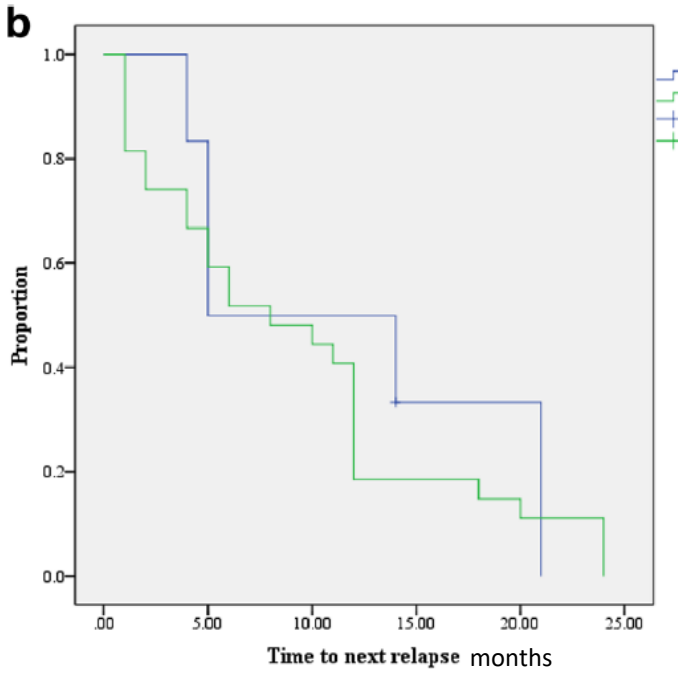
	IVMT + IVIG	IVMT	*p* value
EDSS			
Acute attack	6.24±1.64	3.97±1.26	<0.001
Discharged	4.55±1.63	2.95±1.29	<0.001
ΔEDSS	1.63±0.77	0.94±0.65	<0.001
Onset attack	2.33±1.17 (*n*=6)	1.37±1.10 (*n*=27)	>0.05
Relapsed	1.54±0.75 (*n*=25)	0.81±0.39 (*n*=45)	<0.001
AQP4-Ab seropositive	1.70±0.91 (*n*=27)	1.02±0.81 (*n*=41)	0.003

Lin *et al* Neurological Sciences (2021) 42:3857–3863

NMOSD: IVMP vs IVMP then IVIG

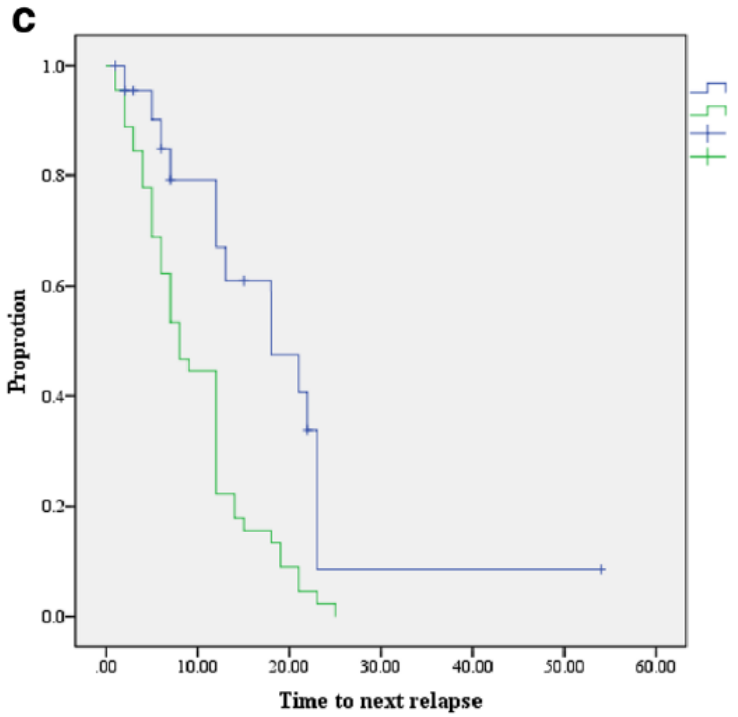
Time to relapse

Onset attack



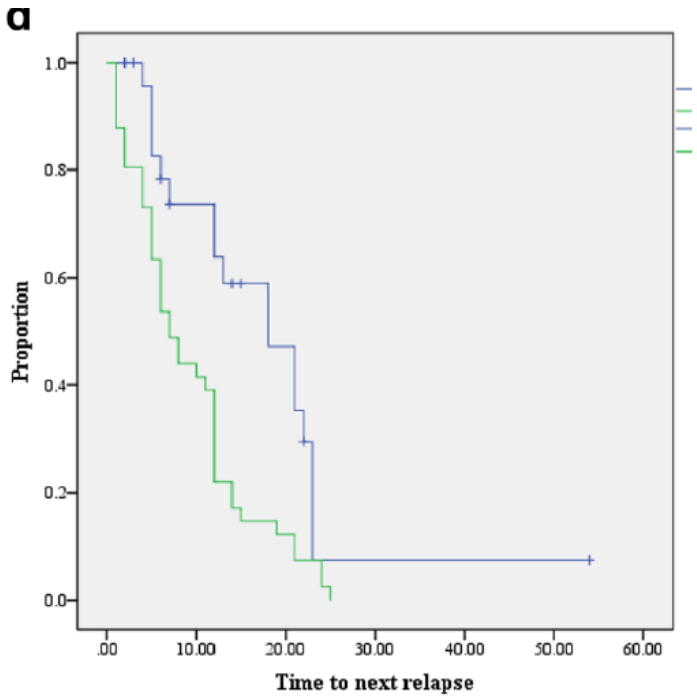
ns

relapse



p=0.001

AQP4



p=0.003

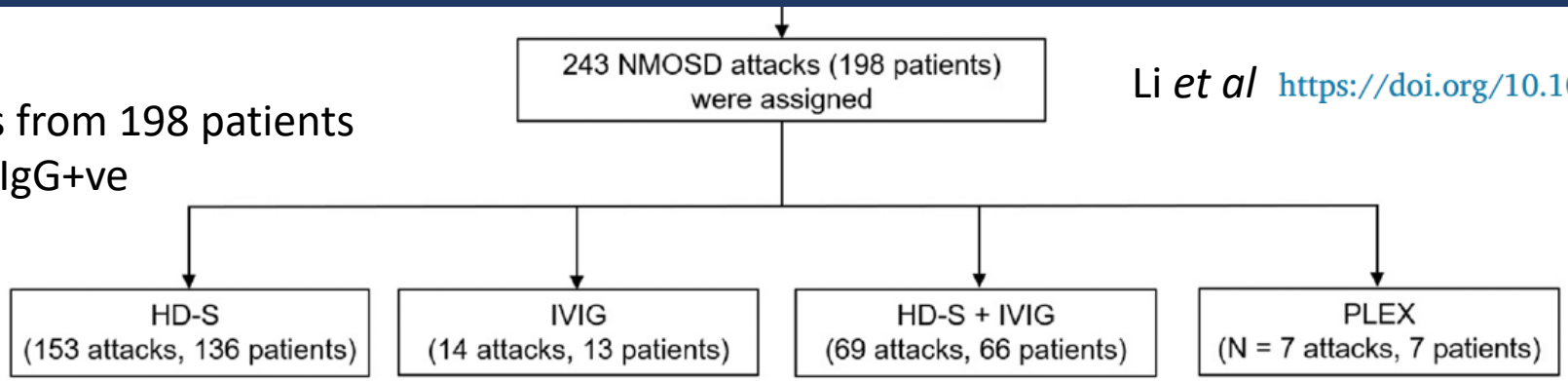
IVMP + IVIG

IVMP

Lin *et al* Neurological Sciences (2021) 42:3857–3863

NMOSD: IVMP vs IVIGH

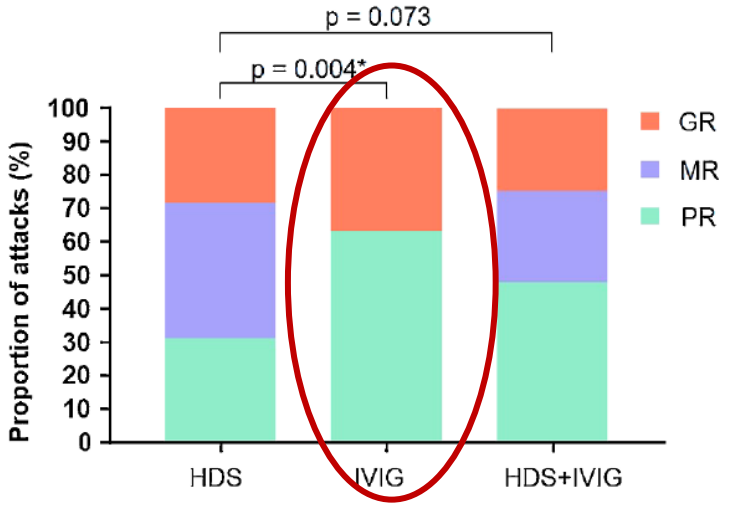
243 attacks from 198 patients
70% AQP4 IgG+ve



more myelitis

Li *et al* https://doi.org/10.1016/j.msard.2020.102325

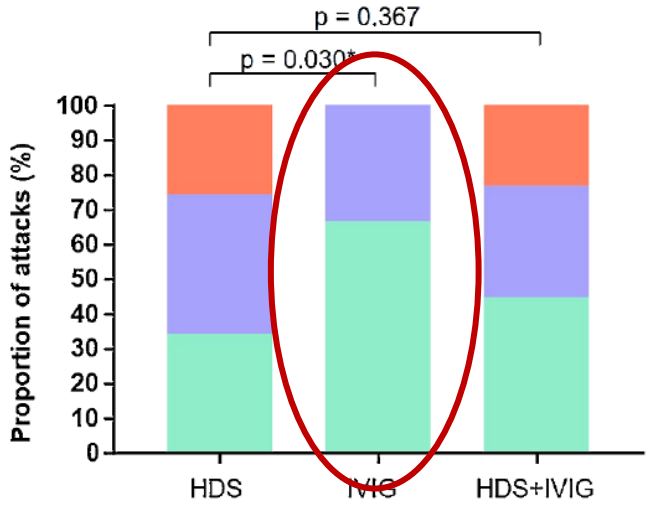
B



	HDS	IVIG	HDS+IVIG
Good remission	44 (28.7%)	0 (0.0%)	17 (24.6%)
Moderate remission	62 (40.5%)	5 (36.7%)	19 (27.5%)
Poor remission	47 (30.8%)	9 (63.3%)	33 (47.8%)
Number of attacks	153	14	69

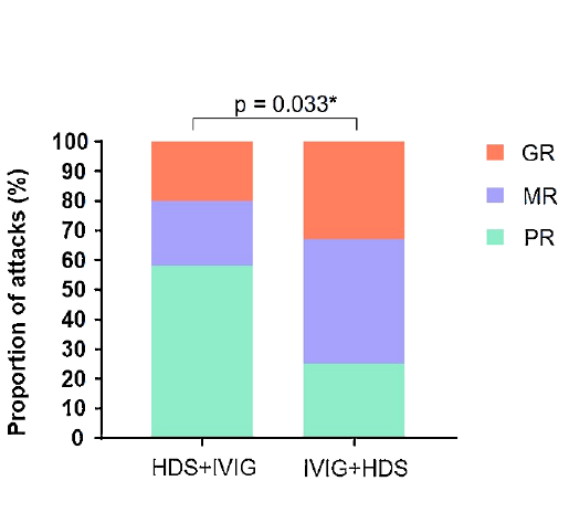
C

AQP4+ve



	HDS	IVIG	HDS+IVIG
Good remission	26 (25.5%)	0 (0.0%)	11 (23.4%)
Moderate remission	41 (40.2%)	3 (33.3%)	15 (31.9%)
Poor remission	35 (34.3%)	6 (66.7%)	21 (44.7%)
Number of attacks	102	9	47

D



	HDS+IVIG	IVIG+HDS
Good remission	9 (25.0%)	8 (33.0%)
Moderate remission	10 (22.0%)	10 (42.0%)
Poor remission	26 (58.0%)	6 (25.0%)
Number of attacks	45	24

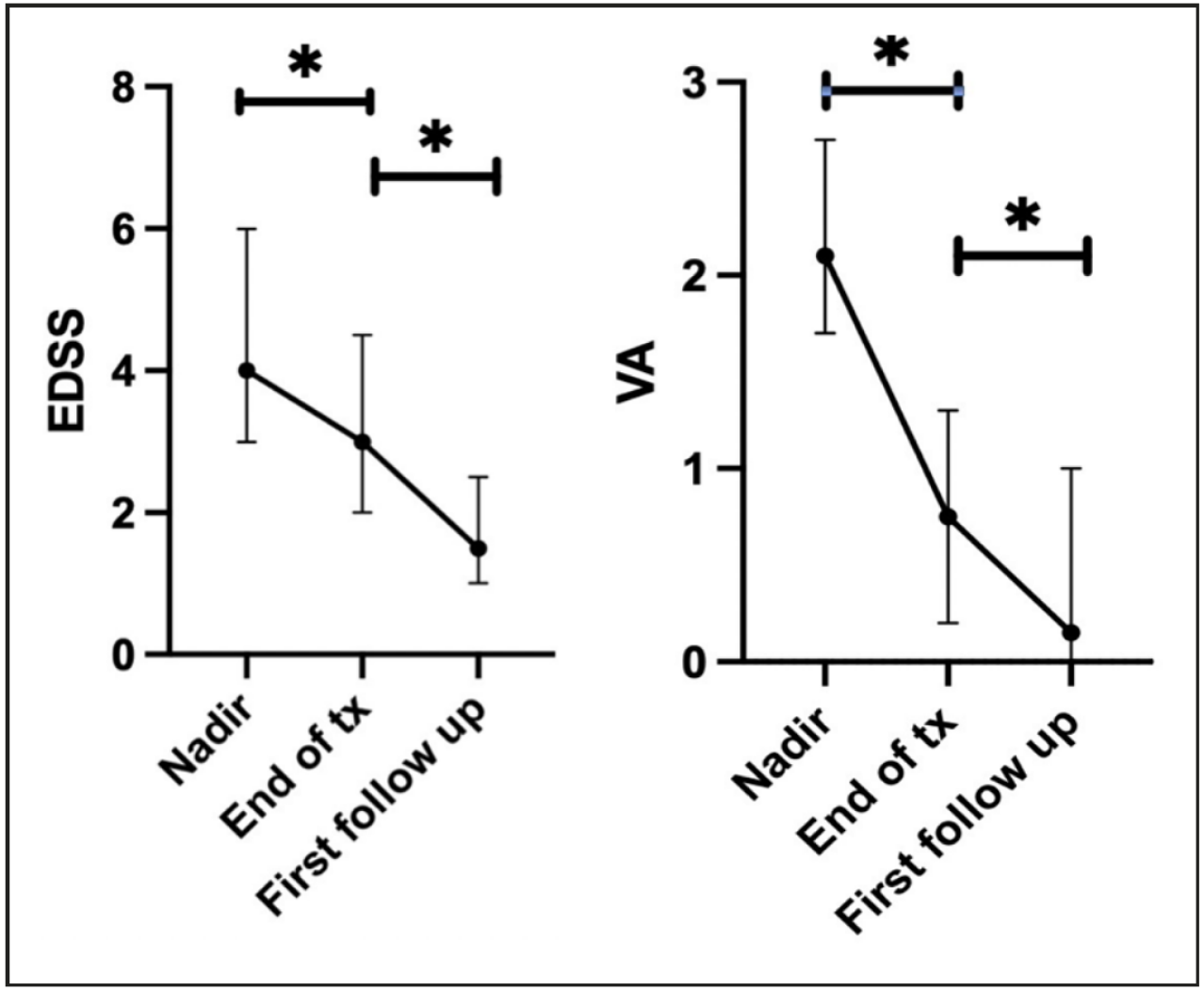
severe attacks HDS+ IVIG better than HDS

MOGAD IVIG

MOGAD: IVIG

39 attacks in 39 patients

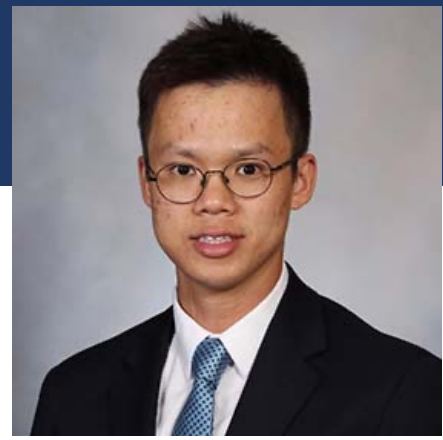
5 countries
Follow up ≥3 months
high dose (≥2g/kg) vs low dose no real diff



Lotan *et al* *Multiple Sclerosis Journal*
2023, Vol. 29(9) 1080–1089

MOGAD PLEX

MOGAD: PLEX

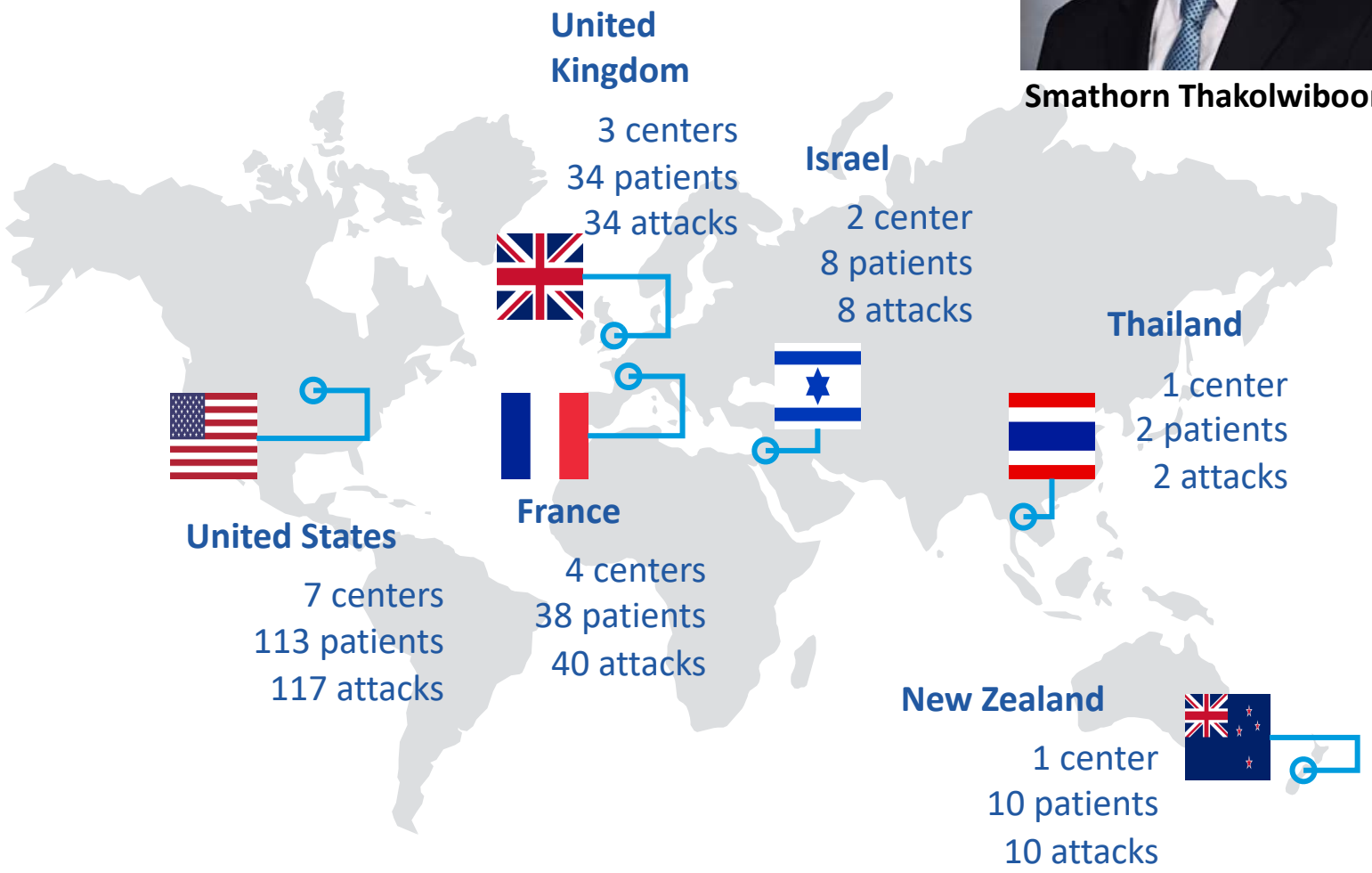


Smathorn Thakolwiboon

Method

Study design

- International multicenter
- Retrospective cohort
  - 18 centers
  - 205 patients
  - 211 attacks
- Outcome evaluation at least 3 months after PLEX



Method

Outcomes



Early relapse (30d post attack, <3/12 after PLEX)



Complete recovery



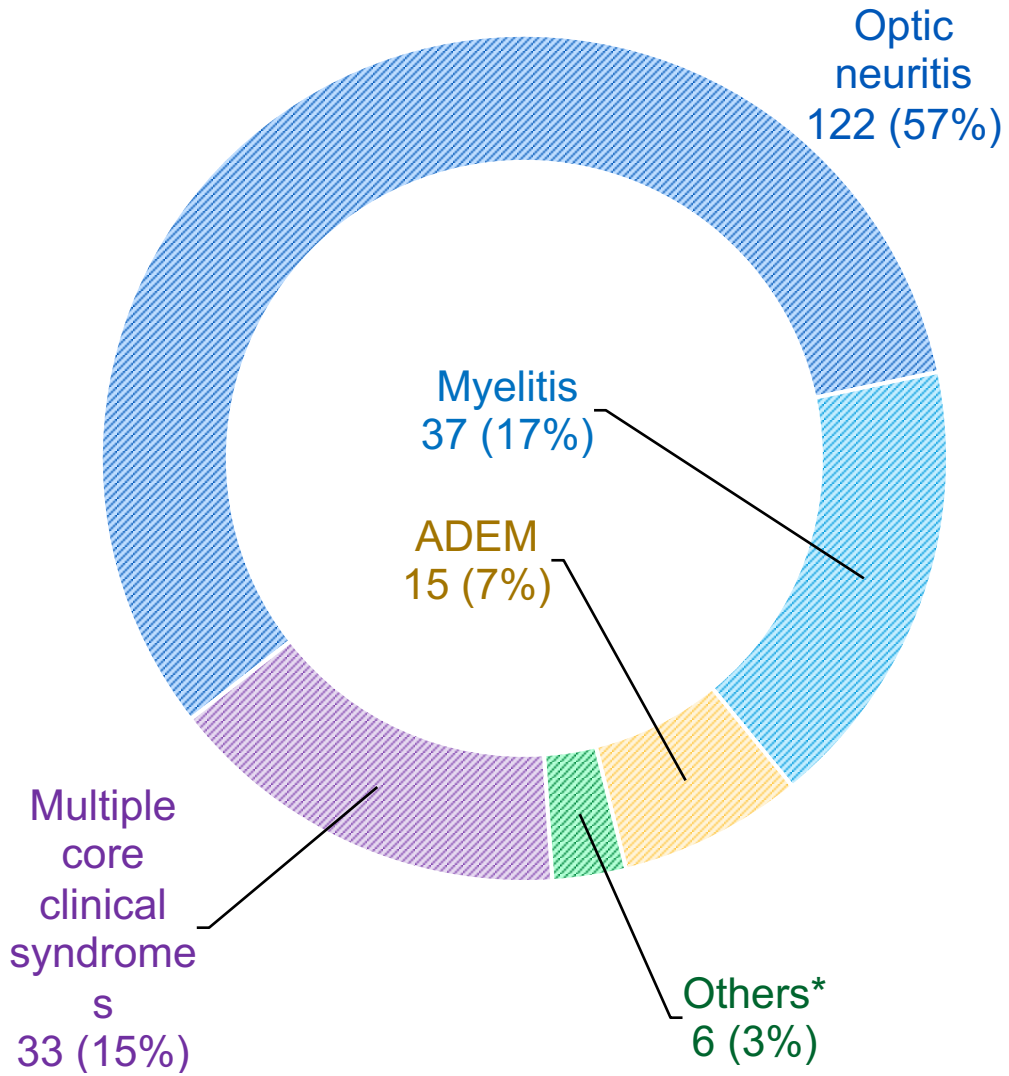
Clinically significant improvement

≥1.0 if EDSS ≤5.0, ≥0.5 if EDSS >5.0 or VA 3 lines better

Results

205 patients, 146 1st attacks,19% <18yrs

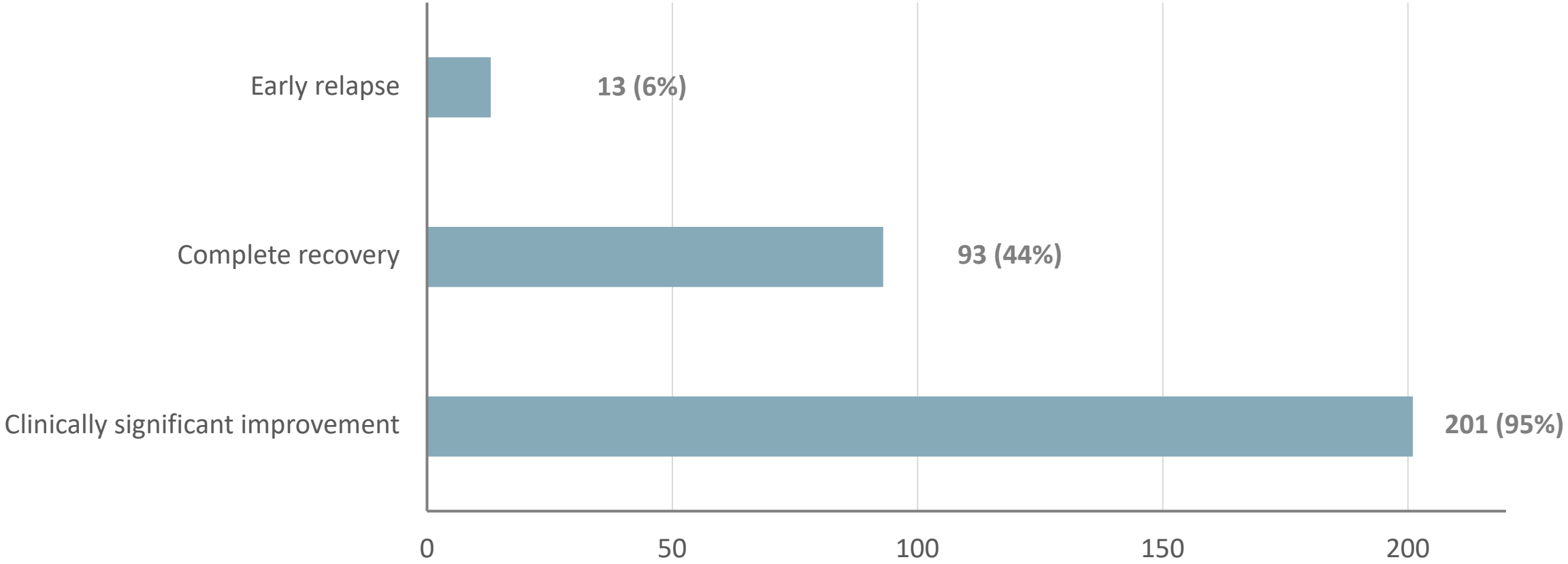
- PLEX as the first line therapy 33 (16%)
- Additional acute therapy
  - High-dose steroid 209 (99%)
  - IVIG 25 (12%)

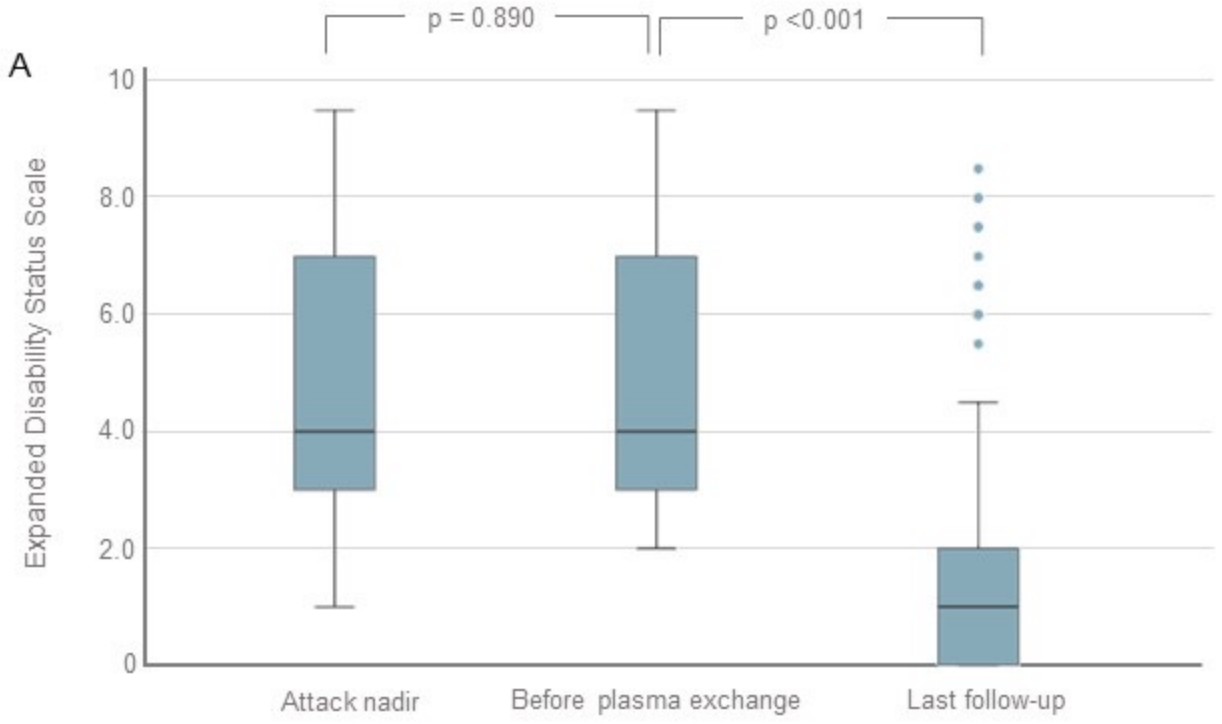


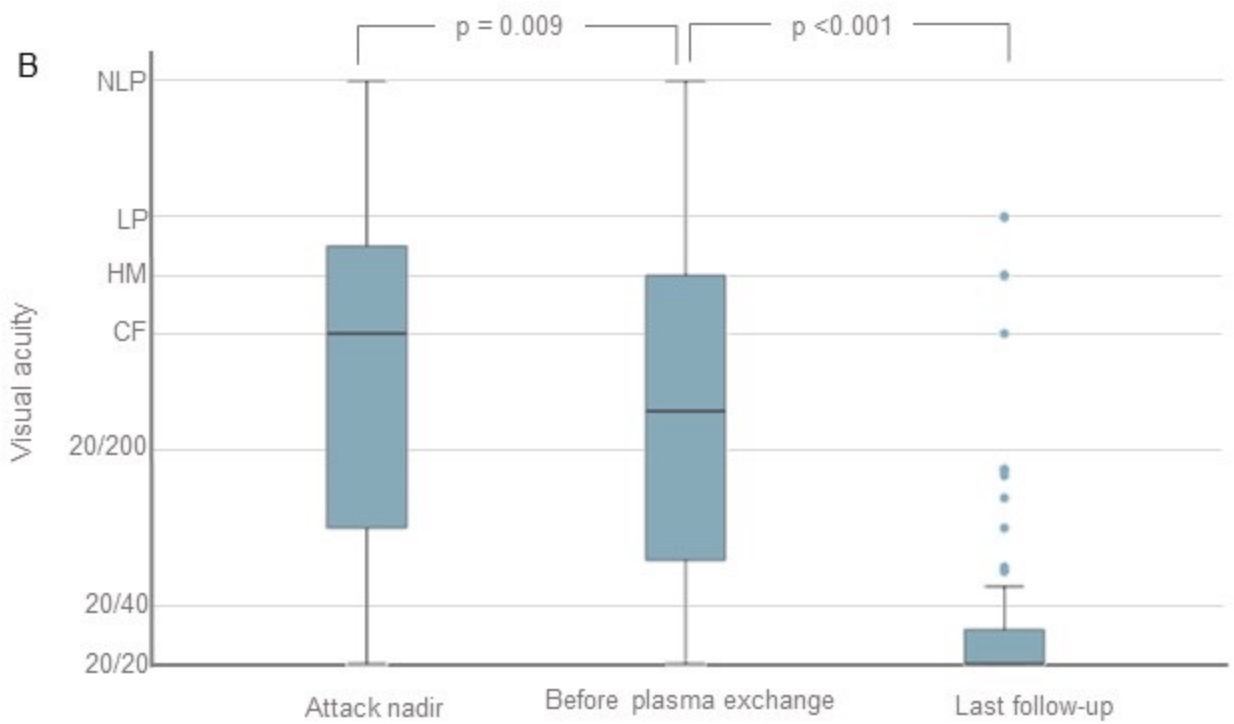
* Cerebral polyfocal deficit 1, brainstem or cerebellar deficit 1, and cerebral-cortical encephalitis 1

Result

Treatment outcomes




A
p = 0.890
p <0.001
Expanded Disability Status Scale
10
8.0
6.0
4.0
2.0
0
Attack nadir
Before plasma exchange
Last follow-up


B
p = 0.009
p <0.001
Visual acuity
NLP
LP
HM
CF
20/200
20/40
20/20
Attack nadir
Before plasma exchange
Last follow-up

New data

Results

Outcome predictors

Early relapse

- Logistic regression did not identify any outcome predictor for early relapse

Complete recovery

First attack	**0.33 (0.14-0.78)**
EDSS at nadir	**0.71 (0.57-0.88)**
Time to PLEX	**0.98 (0.96-0.99)**

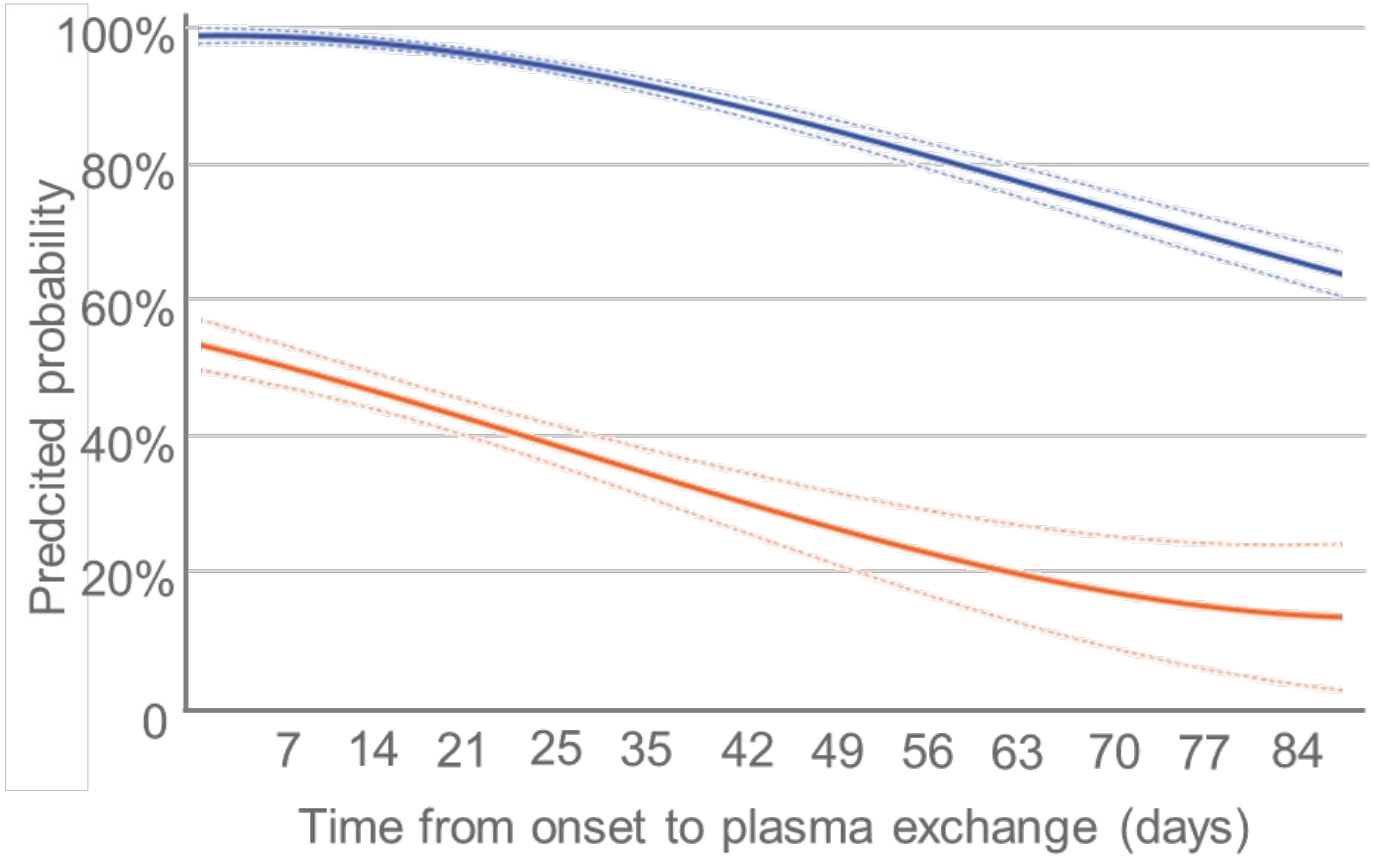
Clinically significant improvement

	OR (95%CI)
EDSS at nadir	0.93 (0.71-1.24)
Time to PLEX	**0.92 (0.87-0.97)**

Results

Effect of timing of PLEX

New data



Clinically significant improvement

Complete recovery

Discussion

PLEX in MOGAD

- Delayed plasma exchange decreases the likelihood of recovery
- Similar to prior studies of PLEX in NMOSD[1,2]
- Early MOG IgG washout potentially reduce damage resulting from complement activation and antibody-dependent cellular toxicity

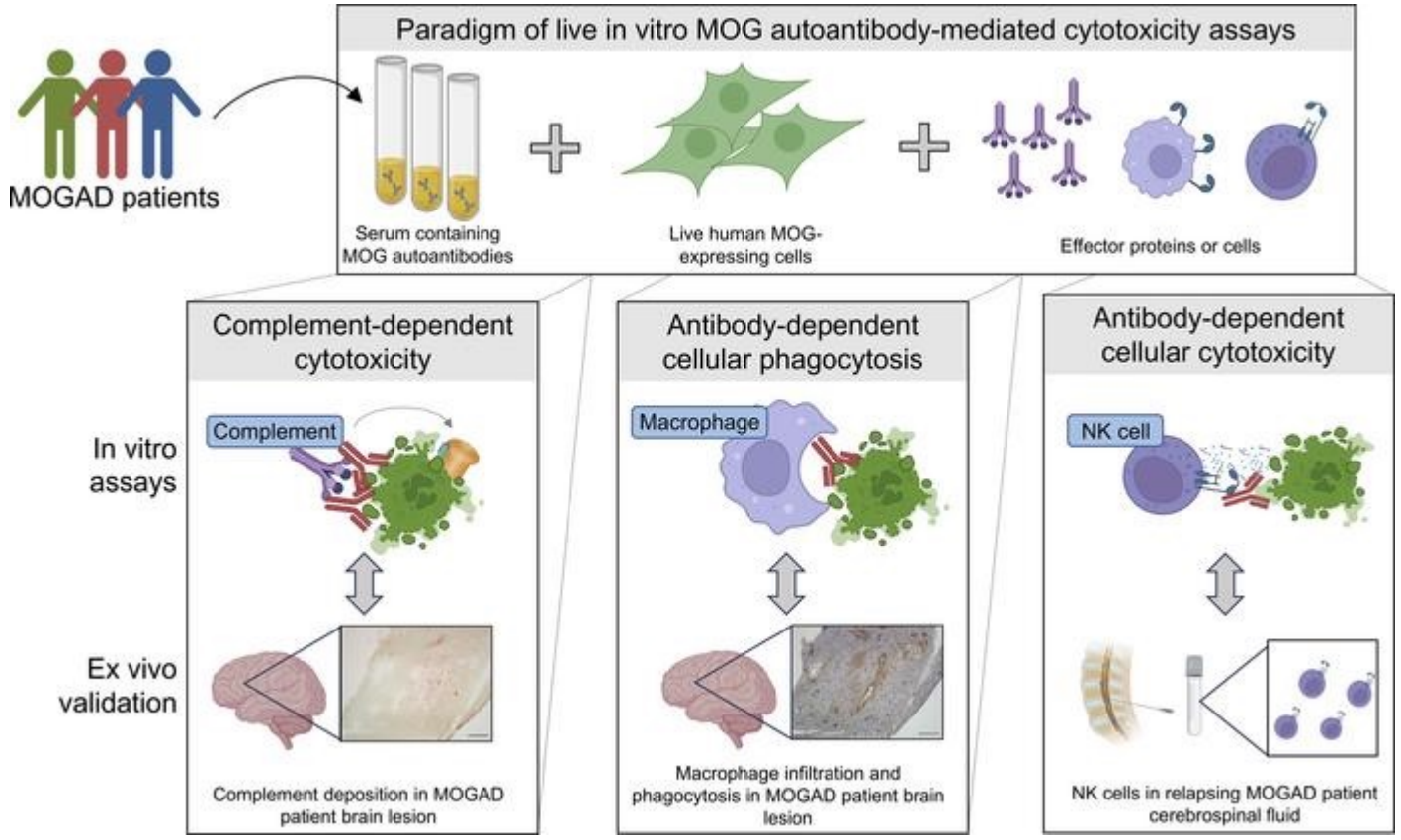


Figure from Yandamuri SS, et al. *JCI Insight* 2023;8(11):e165373

[1] Kleiter I, et al. *Neurol Neuroimmunol Neuroinflamm* 2018;26(5):e504

[2] Bonan M, et al. *J Neurol Neurosurg Psychiatry* 2018;89(4):346-351

Conclusions

- Convincing data that PLEX works in AQP4-NMOSD and MOGAD and earlier the better
- Practical issues to giving to all patients first line, and very early (late still worthwhile)

  vs selecting those less likely to do well (AQP4: older, TM, prev poor recovery,

  MOGAD: 1st attack, severe nadir)

- IVIG data less clear, ? Less effective than MP in NMOSD

  studies limited and numbers low
- Add on better outcomes in NMOSD, ? Order important

- AQP4 neg NMOSD (not DSN-NMOSD) may respond differently:

  1 PLEX study AQP4 pos better response than neg (large ↑ OR CR)

  1 IVIG study AQP4 pos vs all worse outcome (↓ % CR)

  maybe just chance observations, or MOGAD within the group

MASSACHUSETTS GENERAL HOSPITAL
NEUROLOGY

HARVARD MEDICAL SCHOOL

Novel Rescue Strategies for Relapse

Michael Levy, MD, PhD

Associate Professor

Research Director, Division of Neuroimmunology & Neuroinfectious Disease

Acute vs. Preventive



Acute

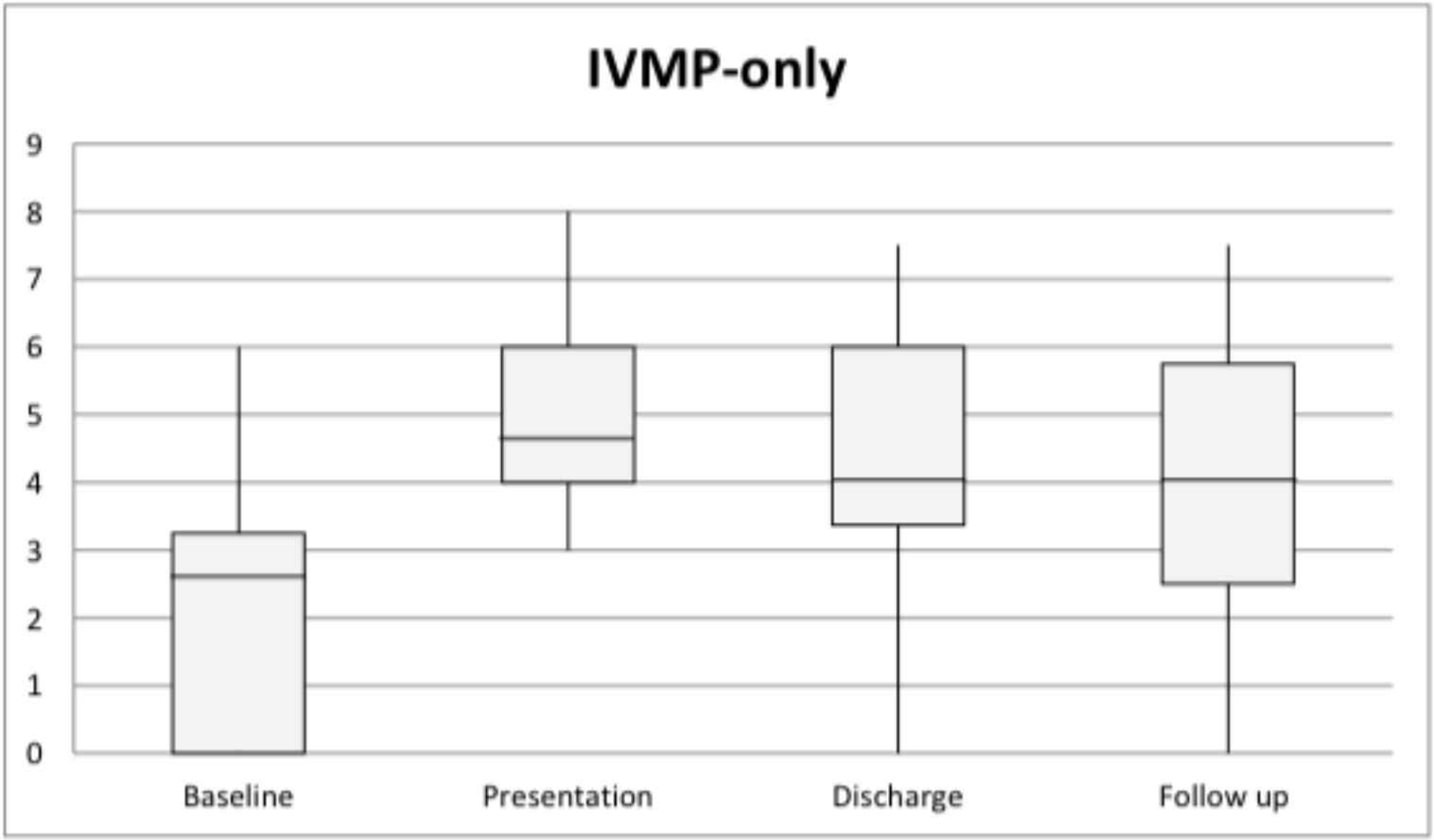


Preventive

Acute: Standard of Care

- Methylprednisolone IV 1000 mg daily x5 days
- In parallel: PLEX 1-1.5 volumes x5 cycles

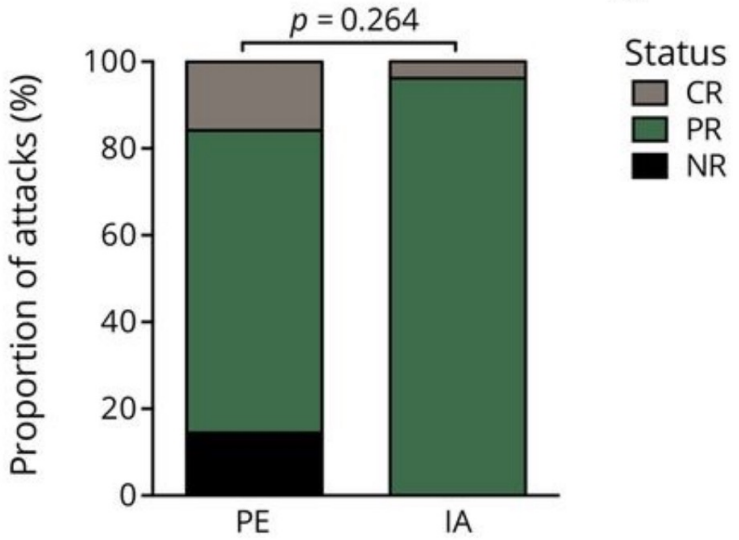
Steroids Only for Acute NMO



Abboud H. *Multiple Sclerosis Journal*. Mult Scler. 2015 Apr 28.

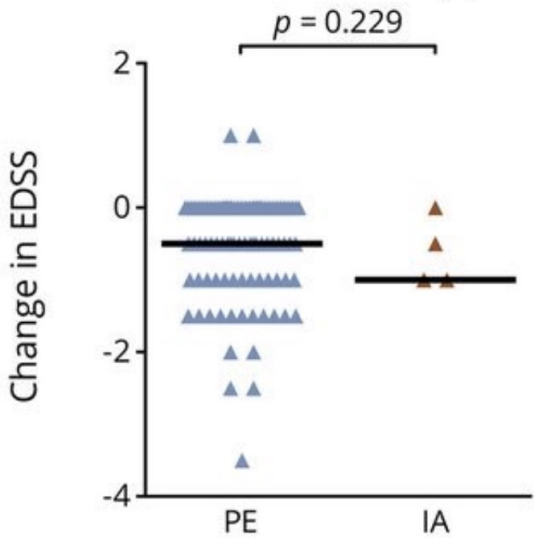
Therapeutic Plasma Exchange

C. Remission status after 1st- or 2nd-line therapy



	PE	IA
Complete remission	22 (15.8%)	1 (3.8%)
Partial remission	97 (69.8%)	25 (96.2%)
No remission	20 (14.4%)	0
Number of attacks	139	26

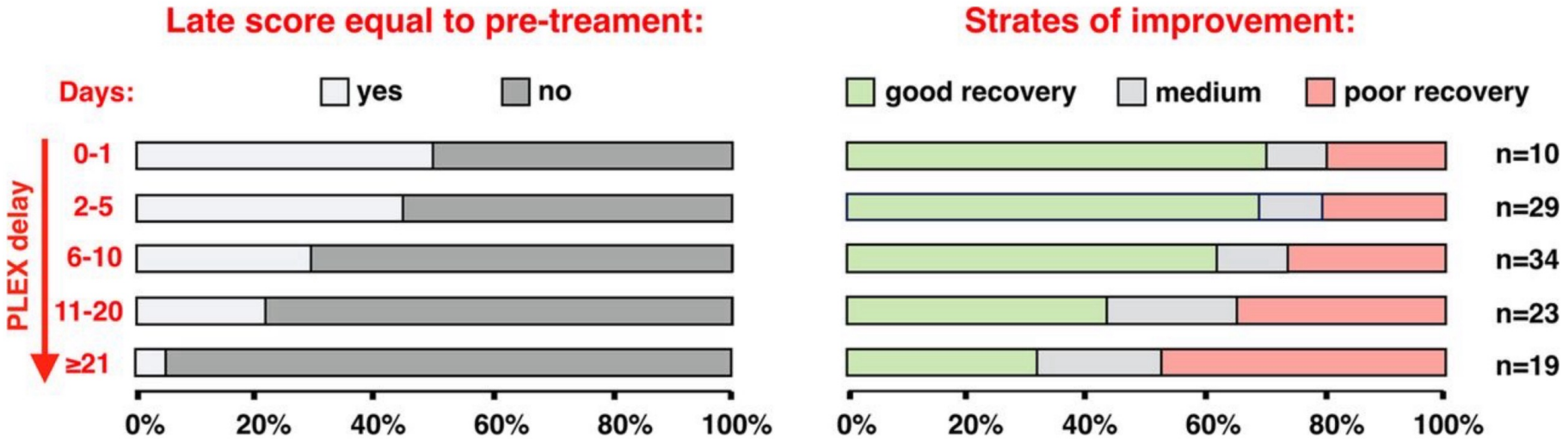
D. EDSS after 1st- or 2nd-line therapy



	PE	IA
Median	-0.5	-1.0
Mean	-0.526	-1.700
SD	0.730	2.439
Number of attacks	97	5

Kleiter I, Gahlen A, Borisow N, *et al.* Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm 2018; 5:e504.

Time to Exchange



Bonnan M, Valentino R, Debeugny S, *et al.* Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. J Neurol Neurosurg Psychiatry 2018; 89:346–351.

Beyond Steroids + PLEX

Case Series/Studies

- C1 esterase inhibitor
- Avastin (bevacizumab)
- Acute B cell depletion (ublituximab)
- IVIG
- Batoclimab (FcRN)

Experimental

- Sivelestat
- Alpha-1 antitrypsin

Case Reports

- Eculizumab

“Kitchen Sink”

- Combination therapy

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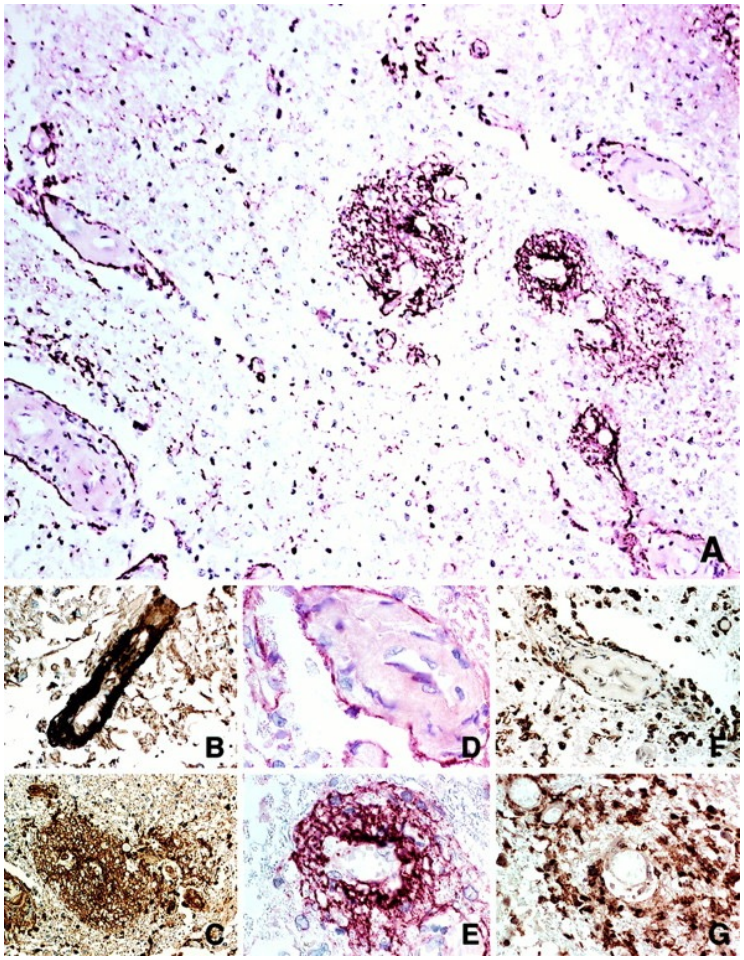
Case Reports

- Eculizumab

“Kitchen Sink”

- Combination therapy

C1-esterase inhibitor (Cinryze)



Lucchinetti CF. *Brain*. 2002 Jul;125(Pt 7):1450-61.

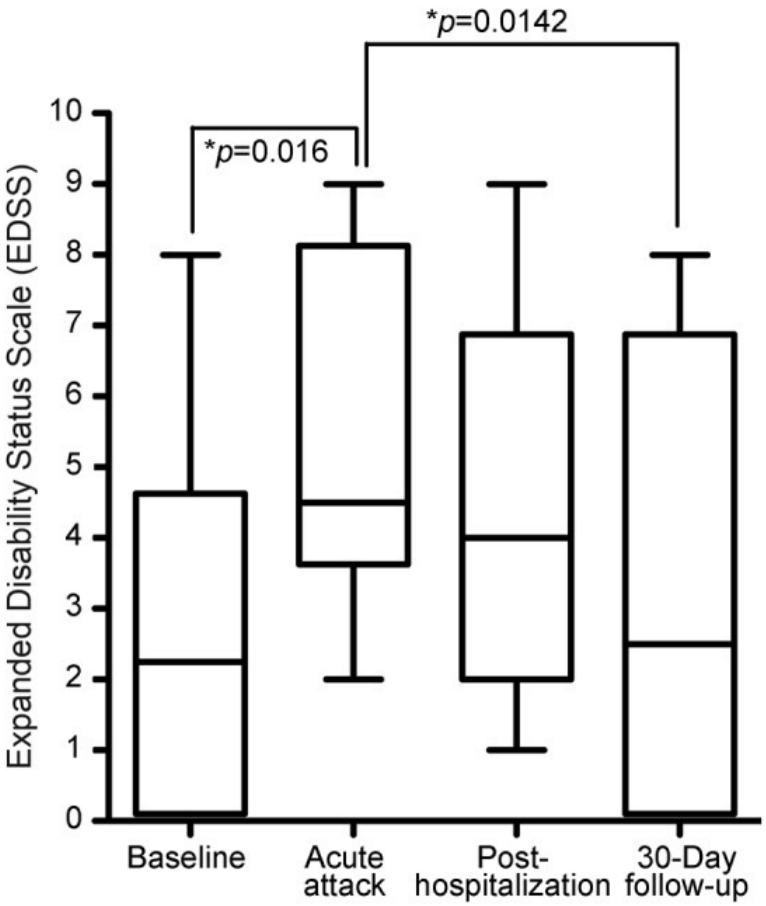
Cinryze Trial for Acute NMO



- 10 • Patients screened for eligibity
- 10 • Patients enrolled
- 10 • Patients received intervention (C1-esterase inhibitor)
- 10 • Patients who completed the study

Levy M. *Neurol Neuroimmunol Neuroinflamm*. 2014 Apr 24;1(1):e5.

Cinryze Trial for Acute NMO



Levy M. *Neurol Neuroimmunol Neuroinflamm*. 2014 Apr 24;1(1):e5.

Blocking VEGF: Bevacizumab

VEGF increases blood brain barrier permeability.
Blocking VEGF decreases blood brain barrier permeability.

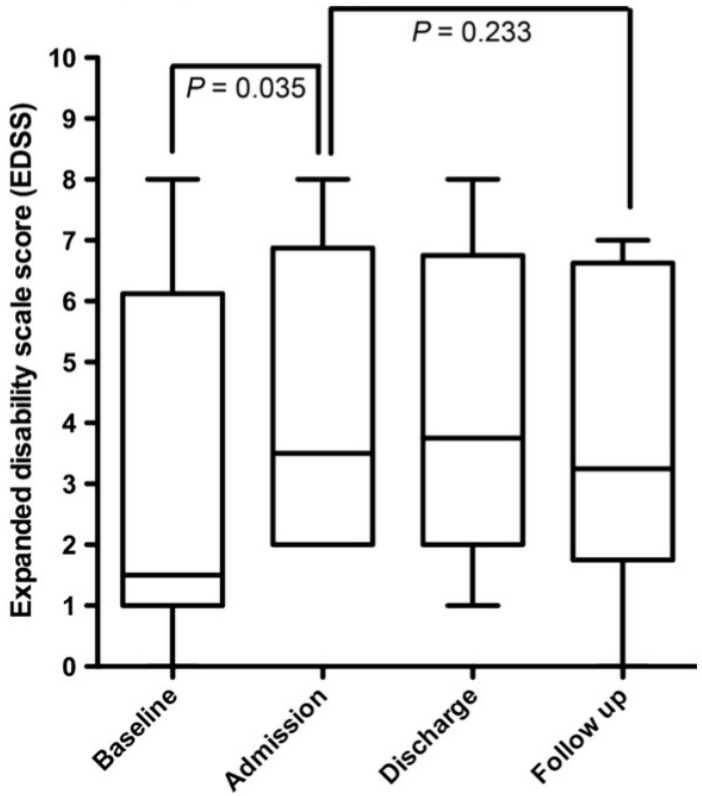


10	• Patients screened for eligibility
10	• Patients enrolled
10	• Patients received intervention (bevacizumab)
10	• Patients completed study @ 90 days

Mealy M. *Clin Exp Neuroimmun*. 2015 Jul 28.

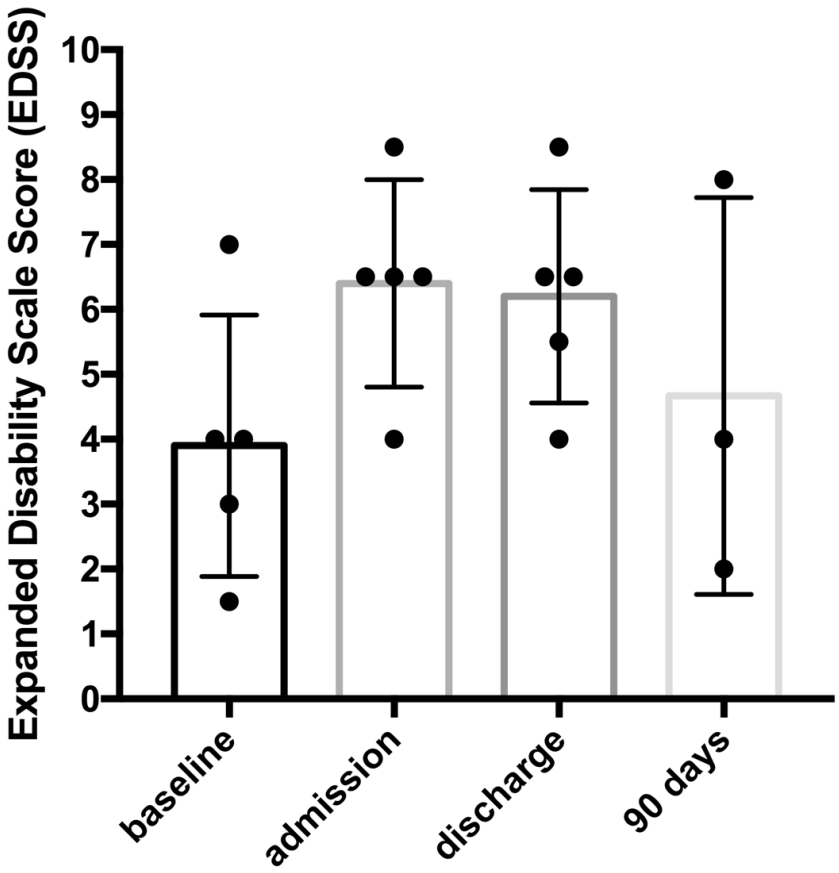
Blocking VEGF: Bevacizumab

VEGF increases blood brain barrier permeability.
Blocking VEGF decreases blood brain barrier permeability.



Mealy M. *Clin Exp Neuroimmun*. 2015 Jul 28.

Acute Trial #3: Ublituximab



Mealy M. *Medicine (Baltimore).* 2019 Jun; 98(25): e15944.

IVIG (vs. PLEX)

Comparison of efficacy of plasma exchange versus intravenous immunoglobulin as an add-on therapy in acute attacks of neuromyelitis optica spectrum disorder

Garima Siwach[1] | Rekha Hans[1] | Aastha Takkar[2] | Chirag Kamal Ahuja[3] | Divjot Singh Lamba[1] | Vivek Lal[2] | Ratti Ram Sharma[1]

[1]Department of Transfusion Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[2]Department of Neurology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[3]Department of Radiodiagnosis and Imaging, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

TABLE 2 Expanded disability status scale (EDSS) score at different time points in two groups.

EDSS score at different time points	Group 1 ($n = 29$) Median (IQR)	Group 2 ($n = 14$) Median (IQR)	p-value Group 1 versus Group 2
Baseline	7.5 (5.5)	7.25 (5.5)	0.83
Day 10	7.0 (5)	6.5 (5.5)	0.79
3 months	6 (4)	6.0 (5)	0.85
Delta change in median score from baseline to 3 months	−1.5	−1.25	0.39
p-value*	0.00	0.00	–

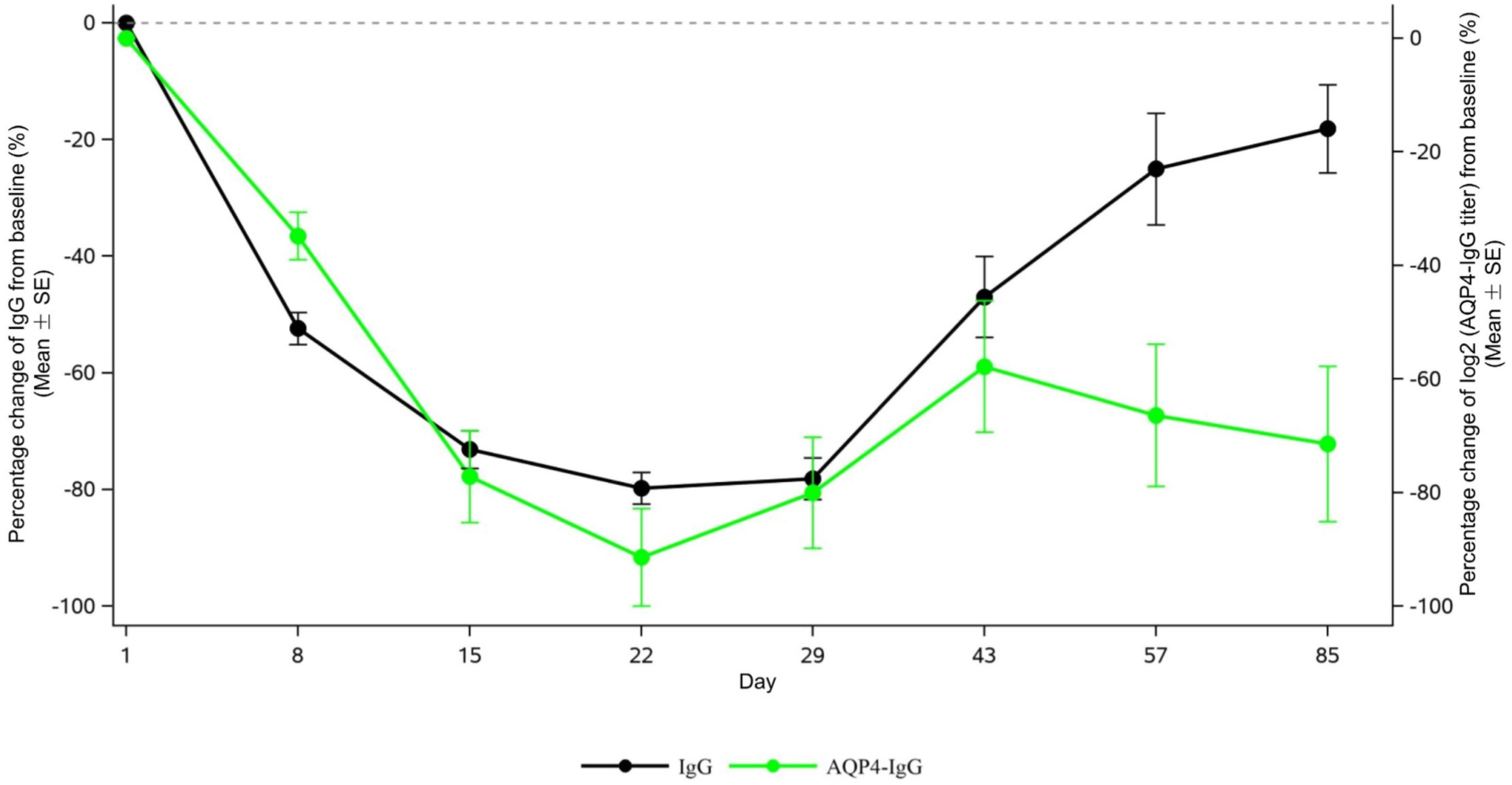
*Overall difference in score at different time points within the groups.

FcRN: Batoclimab

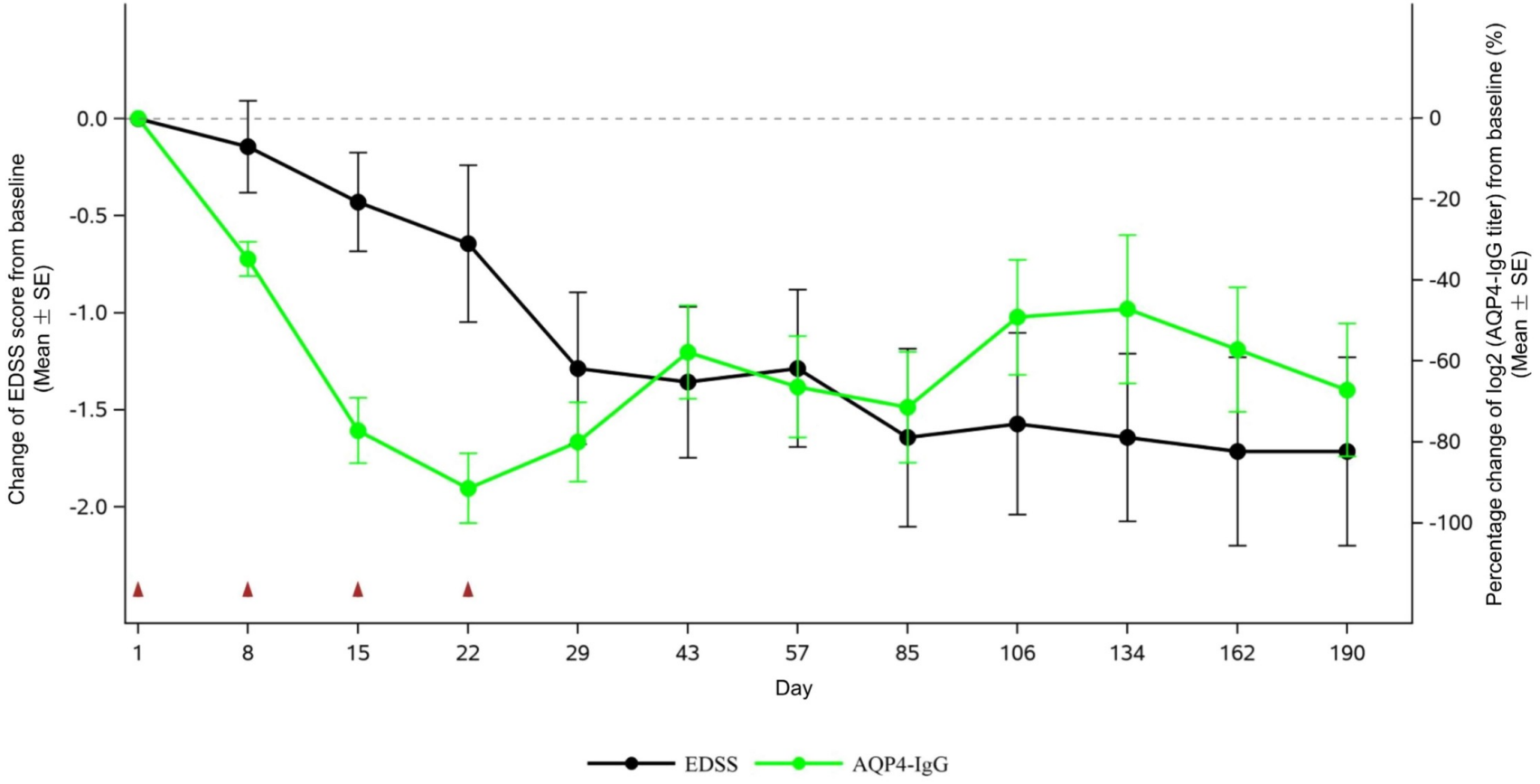
Batoclimab as an add-on therapy in neuromyelitis optica spectrum disorder patients with acute attacks

Yuge Wang[1] | Xiaonan Zhong[1] | Honghao Wang[2] | Yu Peng[2] | Fudong Shi[3] | Dongmei Jia[3] | Huan Yang[4] | Qiuming Zeng[4] | Chao Quan[5] | Jingzi ZhangBao[5] | Michael Lee[6] | Jun Qi[6] | Xiaoxiang Chen[6] | Wei Qiu[1] | Batoclimab NMOSD Study Group

FcRN: Batoclimab



FcRN: Batoclimab



Beyond Steroids + PLEX

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“Kitchen Sink”

- Combination therapy

Sivelestat

Mult Scler. Author manuscript; available in PMC 2012 Apr 5.
Published in final edited form as:
Mult Scler. 2012 Apr; 18(4): 398–408.
Published online 2012 Feb 16. doi: 10.1177/1352458512440060

PMCID: PMC3319834
NIHMSID: NIHMS362184
PMID: 22343184

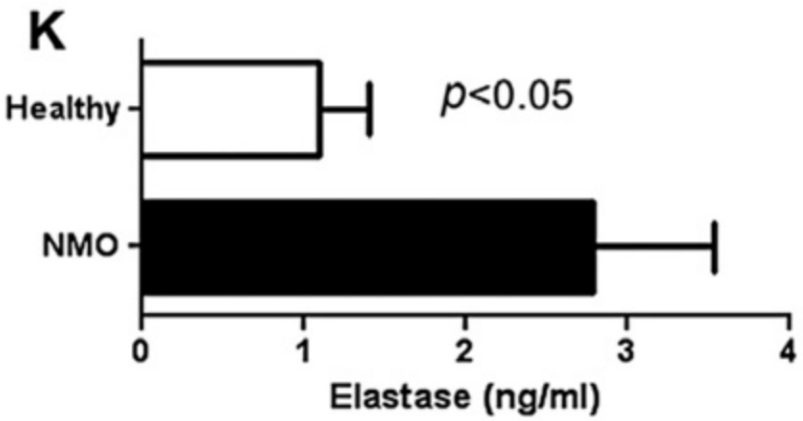
Protective effect of an elastase inhibitor in a neuromyelitis optica-like disease driven by a peptide of myelin oligodendroglial glycoprotein

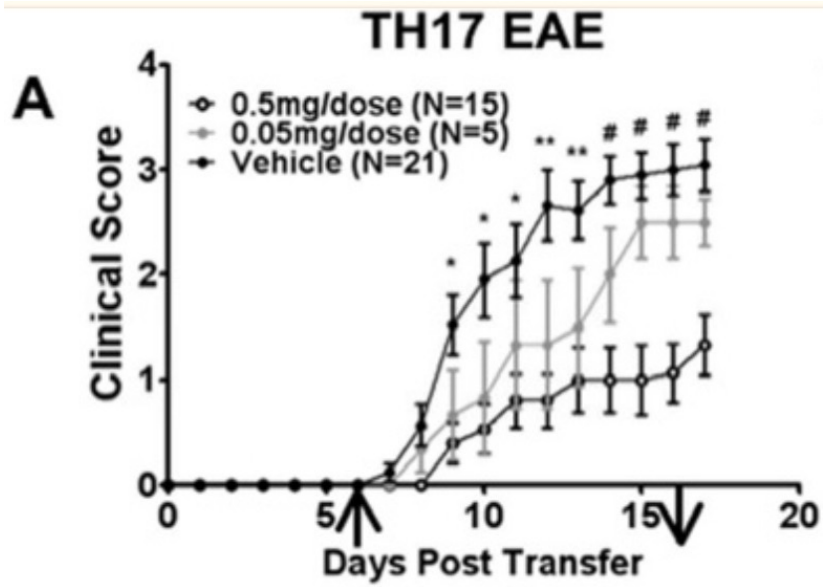
Katja Herges,[1] Brigit A de Jong,[2] Ilan Kolkowitz,[1] Caitlin Dunn,[1] Gil Mandelbaum,[1] Rose M Ko,[3] Alexander Maini,[1] May H Han,[1] Joep Killestein,[4] Chris Polman,[4] Alexandra L Goodyear,[1] Jeffrey Dunn,[1] Lawrence Steinman,[1] and Robert C Axtell[1]

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[1]Department of Neurology and Neurological Sciences, Stanford University, USA.
[2]Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.
[3]Department of Medicine, Division of Blood and Marrow Transplantation, Stanford University School of Medicine, USA.
[4]Department of Neurology, VU Medical Center, Amsterdam, The Netherlands.
Corresponding author(s): Robert C Axtell/Lawrence Steinman, Beckman Center B002, Department of Neurology, Stanford University, Stanford, California, 94305, USA. axterobe@stanford.edu or steinman@stanford.edu

Sivelestat


K
Healthy
NMO
p<0.05
0
1
2
3
4
Elastase (ng/ml)


TH17 EAE
A
0.5mg/dose (N=15)
0.05mg/dose (N=5)
Vehicle (N=21)
Clinical Score
0
1
2
3
4
0
5
10
15
20
Days Post Transfer

Beyond Steroids + PLEX

Case Series/Studies

- C1 esterase inhibitor
- Avastin (bevacizumab)
- Acute B cell depletion (ublituximab)
- IVIG
- Batoclimab (FcRN)

Experimental

- Sivelestat
- Alpha-1 antitrypsin

Case Reports

- Eculizumab

“Kitchen Sink”

- Combination therapy

Beyond Steroids + PLEX

Case Series/Studies

- C1 esterase inhibitor
- Avastin (bevacizumab)
- Acute B cell depletion (ublituximab)
- IVIG
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Experimental

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Case Reports

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Case report: Eculizumab

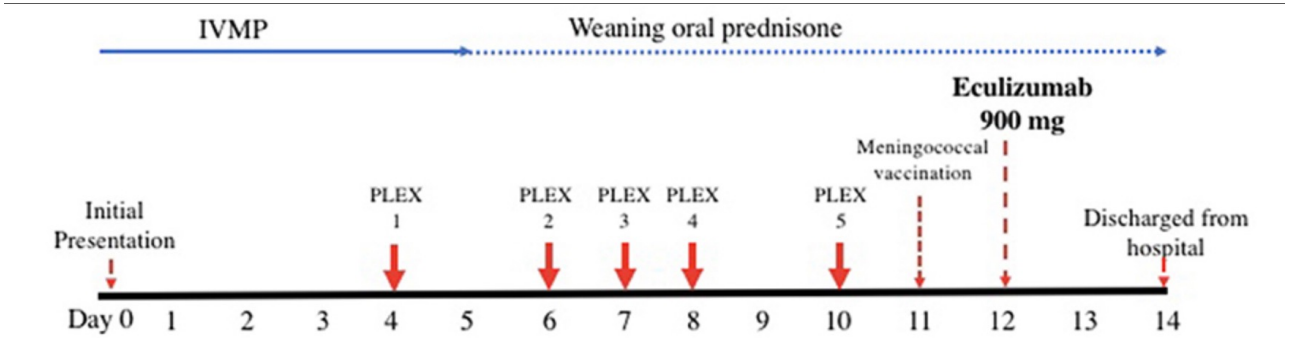
Eculizumab for acute relapse of neuromyelitis optica spectrum disorder: Case report

Sophie Chatterton[1] John Douglas Edward Parratt[1,2] Karl Ng[1,2*]

[1] Department of Neurology, Royal North Shore Hospital, Sydney, NSW, Australia
[2] School of Medicine, University of Sydney, Sydney, NSW, Australia

Case report: Eculizumab





Case report: Eculizumab



The patient's visual acuity promptly improved to counting fingers with her left eye 2 days after eculizumab commencement and she was able to be discharged home after her first infusion, 2 weeks following her initial presentation. At follow-up 2 and 5 months later, she remained on maintenance eculizumab without complications and there was evidence of ongoing improvement in her left eye visual acuity but still significant loss of central vision. Given the chronicity of her right eye visual impairment, no improvement was expected or found.

Collaboration: Eculizumab cases

Do you have cases of acute NMO relapses treated with eculizumab?

Send me a text!

410-979-8297

Beyond Steroids + PLEX

Case Series/Studies

- C1 esterase inhibitor
- Avastin (bevacizumab)
- Acute B cell depletion (ublituximab)
- IVIG
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Experimental

- Sivelestat
- Alpha-1 antitrypsin

Case Reports

- Eculizumab

"Kitchen Sink"

- Combination therapy

Combination Therapy





GUTHY JACKSON Charitable Foundation

Emerging Technologies For Immune Tolerization

Michael Yeaman, PhD, MSc

Distinguished Professor of Medicine
Chief, Division of Molecular Medicine
Director, Institute for Infection & Immunity
Vice Chair, Department of Medicine
UCLA School of Medicine & Harbor-UCLA MC

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15th NMO International Roundtable Conference
Los Angeles / August 2, 2024

Disclosures

- **Founder**: NovaDigm Therapeutics, Inc. (vaccines)
  Tegos Therapeutics, LLC (anti-infectives)
  ImmunoTx, LLC (immunotherapeutics)
  Metacin, Inc. (music neuroscience)

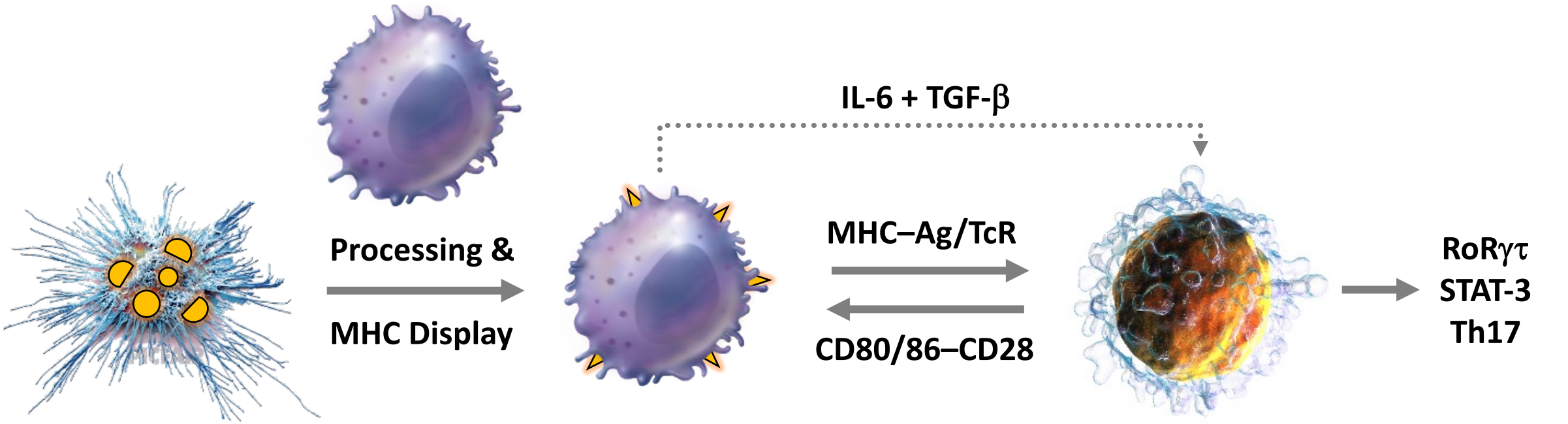
- **Grants**:

NIH U19 AI-172713	NIH R01 AI-139244
NIH U01 AI-124319	NIH COVID-19 SPARTA
NIH R01 AI-309241	DoD CDMRP JW-190421
NIH R01 AI-310380	DoD CDMRP JW-160125

- **Advisor**: Advisor, Guthy-Jackson Charitable Foundation
  AstraZeneca; Genentech–Roche; Amgen
  Vatican Council; US NIH; US DoD; XPrize

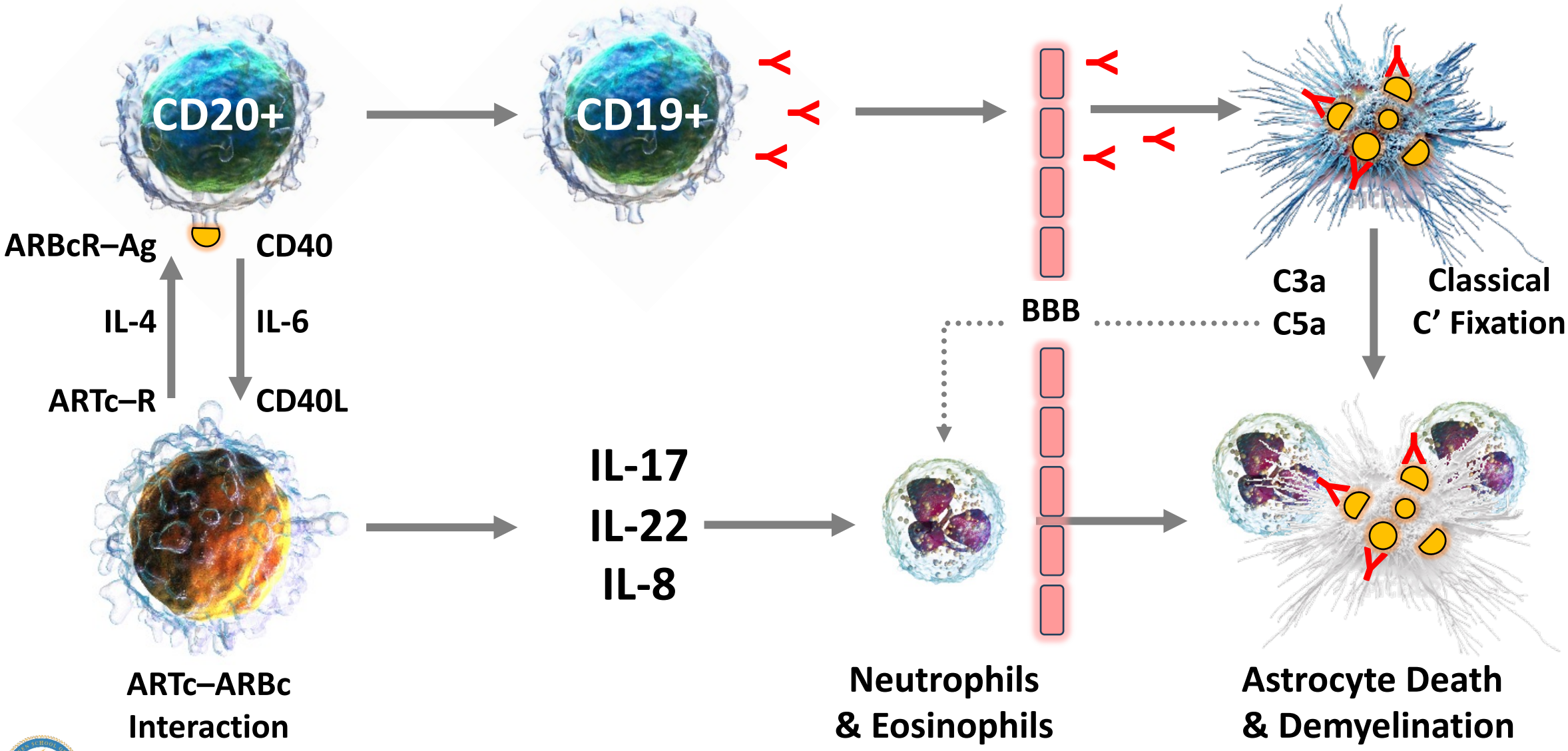
Pathogenesis

Current Understanding: Pathophysiology in NMO



Source: Steinman L *et al.* [2016] ***Neurology / N2*** 3:e276; Bar-Or L *et al.* [2016] ***Neurology / N2*** 3:e277
Nishiyama S *et al.* [2024] ***Sci Rep*** 14(1):3146

Current Understanding: Pathophysiology in NMO



Source: Wingerchuk D & Lucchinetti CF [2022] ***NEJM*** 387(7):631-639

Immune Tolerance

What is Immune Tolerance ?

Immune tolerance is how your immune system protects you against internal or external threats such as cancer or infection, ***without harming*** any healthy molecules, cells or tissues that make up the body.

Put another way, immune tolerance is the ***system of checks & balances*** that prevents the immune system from targeting healthy cells and tissues.

Immune System Discerns Self vs. Non-Self

Guthy Jackson Charitable Foundation

Healthy Molecules
Healthy Cells
Healthy Tissues
Wound Healing
Normal Growth



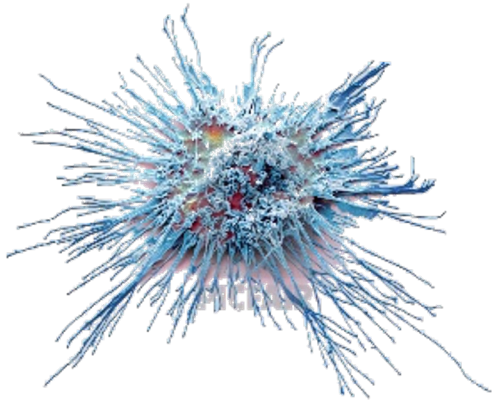
Immune System



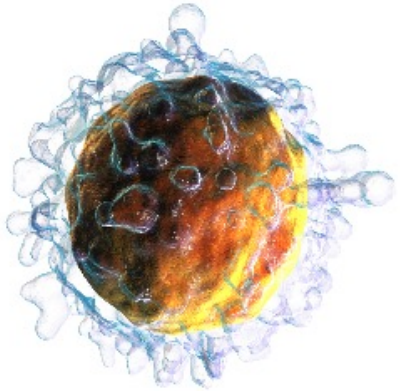
Pathogenic Microbes
Pre-Cancerous Cells
Cancers or Tumors
Poor Wound Healing
Abnormal Growth

Which Cells are Key to Tolerization ?

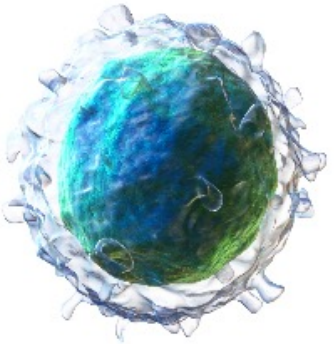
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Antigen Presenting Cells

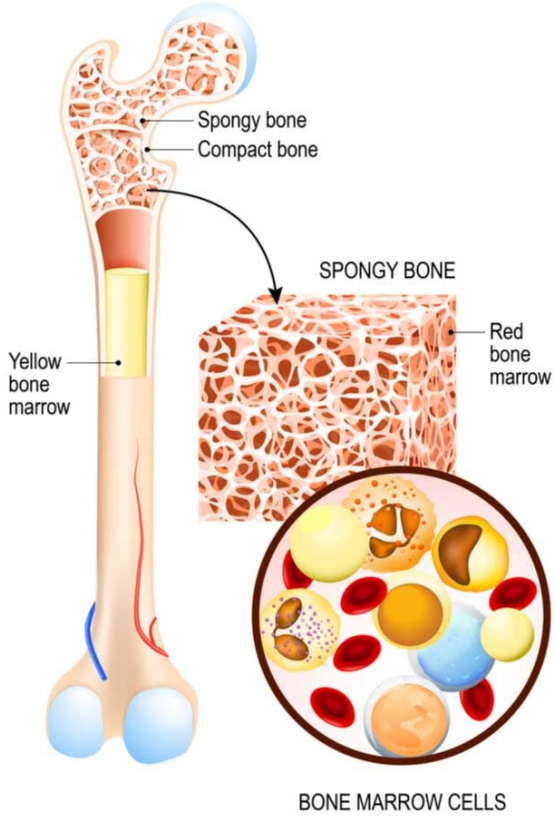


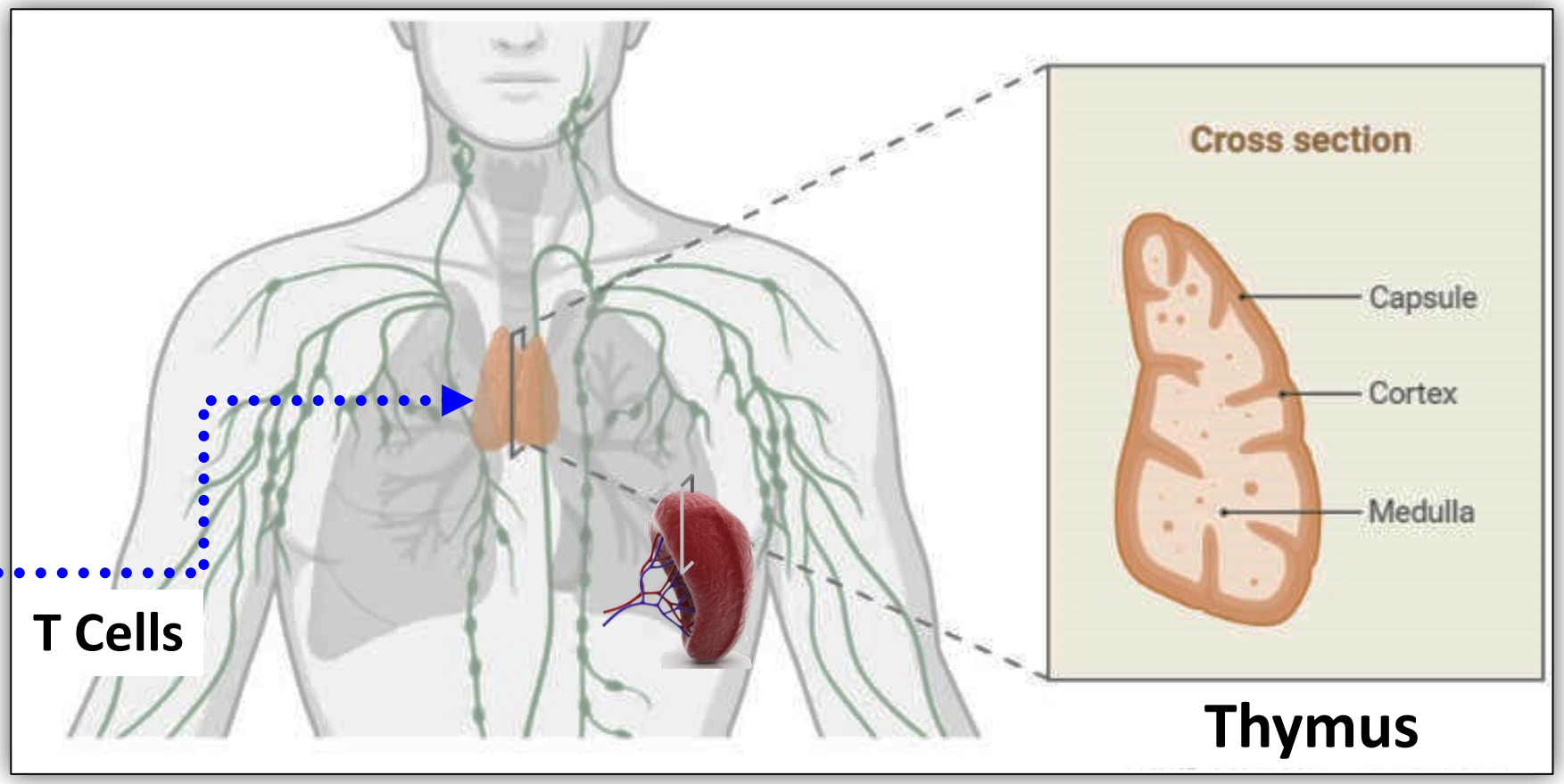
T Cells (T Lymphocytes)



B Cells (B Lymphocytes)

The Thymus: T Cell University

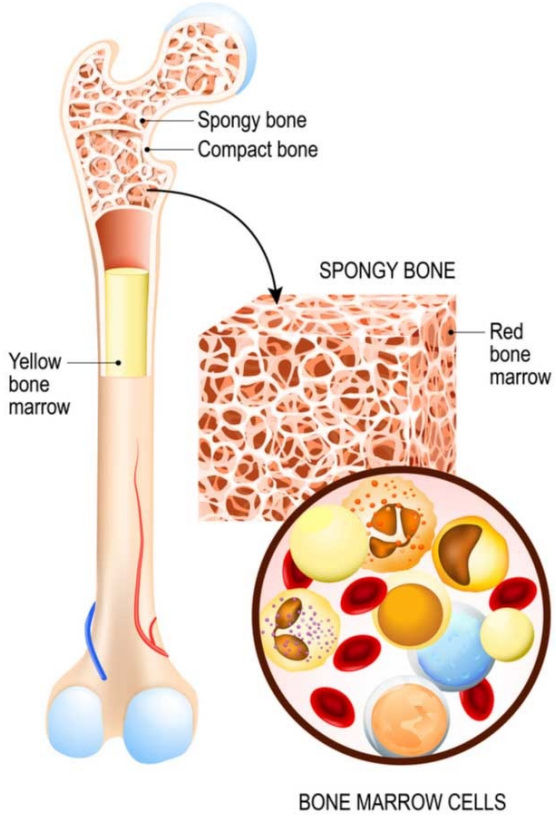


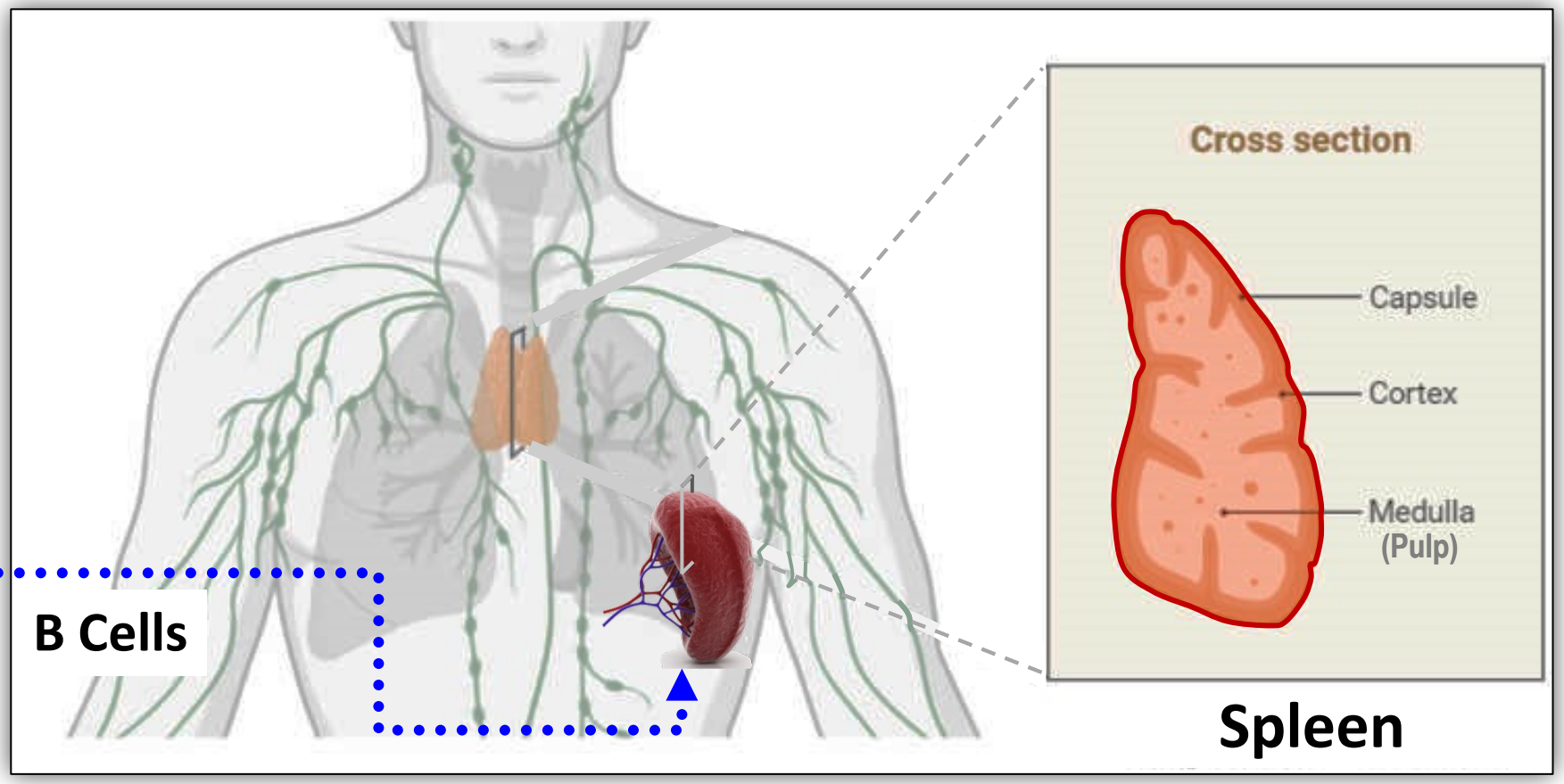


T cells
B cells
White Blood Cells
Red Blood Cells

T cells made in the bone marrow move to the thymus to be tested three ways

The Spleen: B Cell University





T cells

B cells

White Blood Cells

Red Blood Cells

B cells made in the bone marrow move to the spleen to be tested three ways

T Cells & B Cells Must Pass Three Exams:

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1. **Can they recognize the antigen-presenting cell ?**

   Yes → **No → Removal [-]**

2. **Can they do the molecular handshake with APC ?**

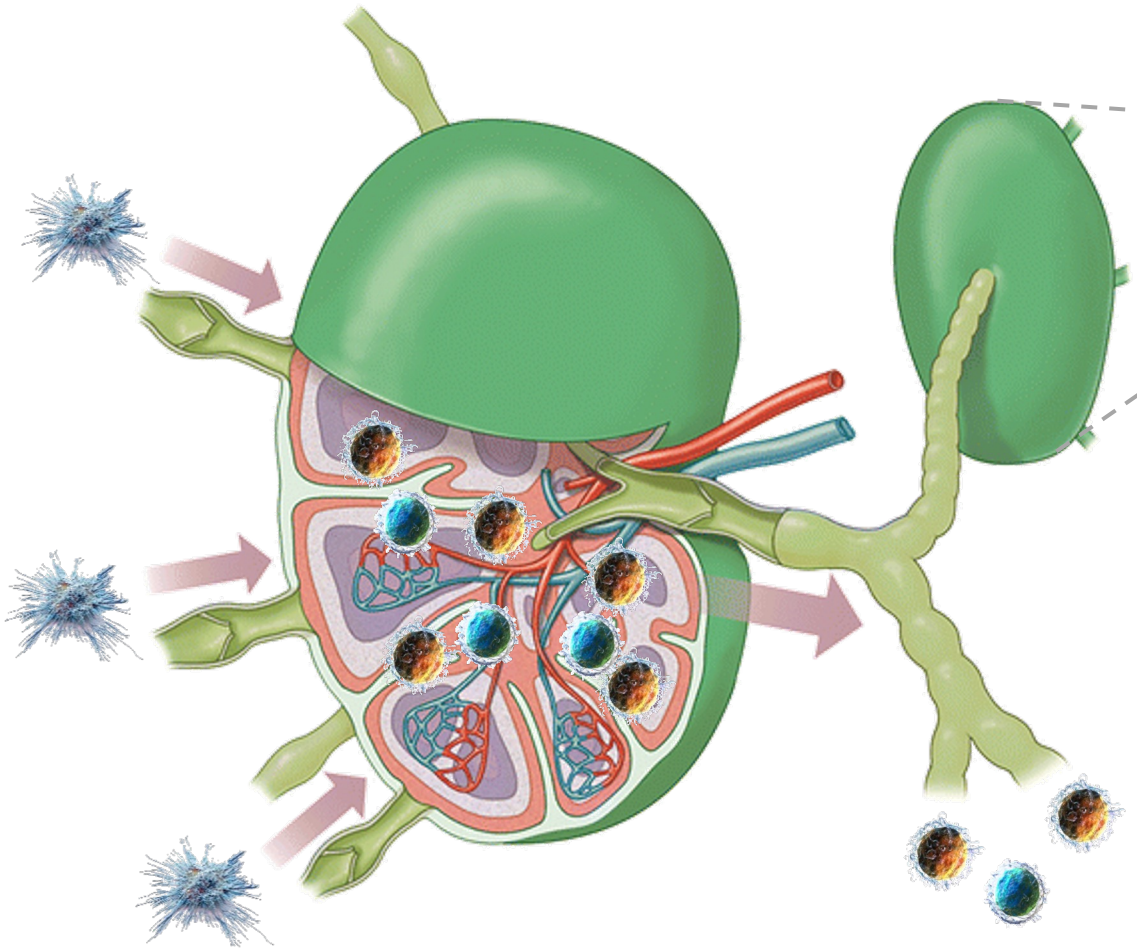
   Yes → [+] **No → Removal**

3. **Can they distinguish between self vs. non–self ?**

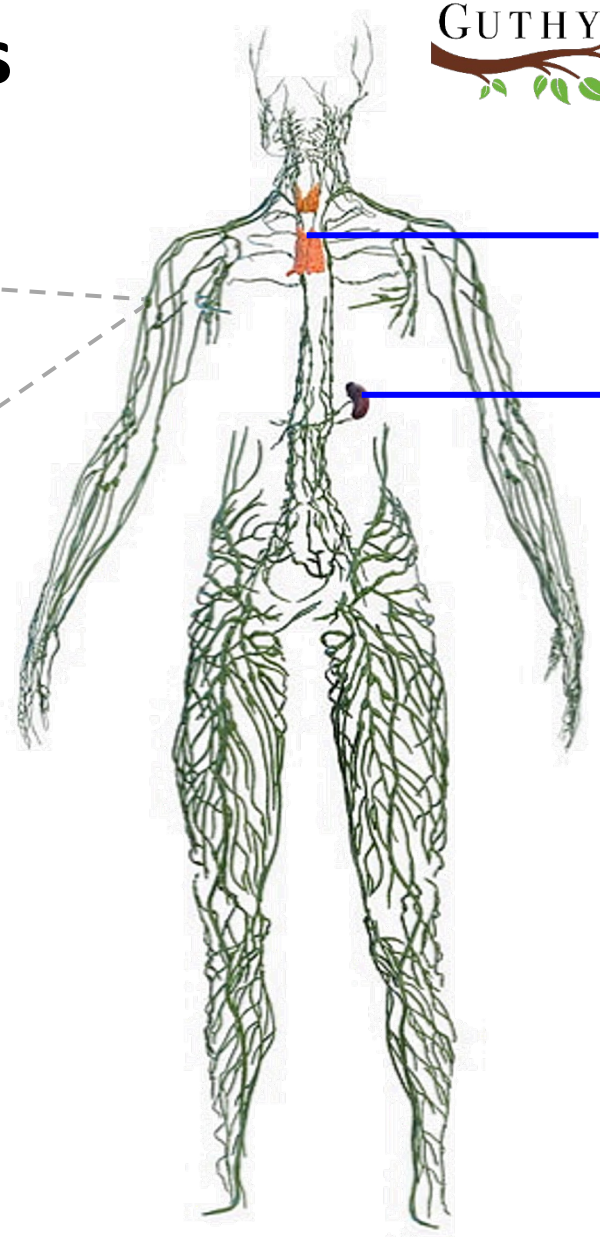
   Yes → **No → Removal [-]**

Only 1% of T and B cells Successfully Pass All Three Exams

Graduate T & B Cells Move to Lymphatics

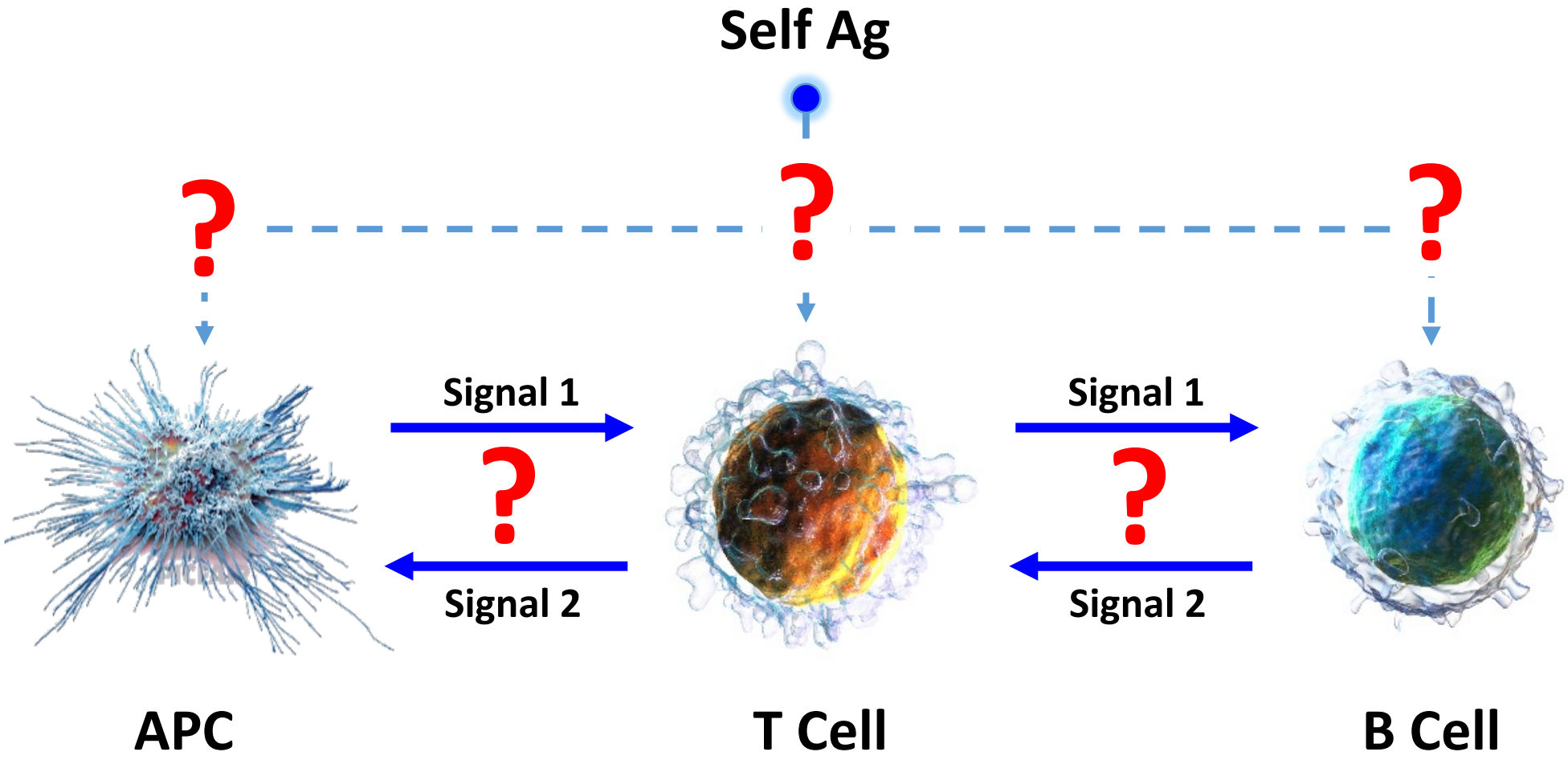


Lymph Node



How is
Immune Tolerance Lost ?

Loss of Immune Tolerance: Mistaken Identity



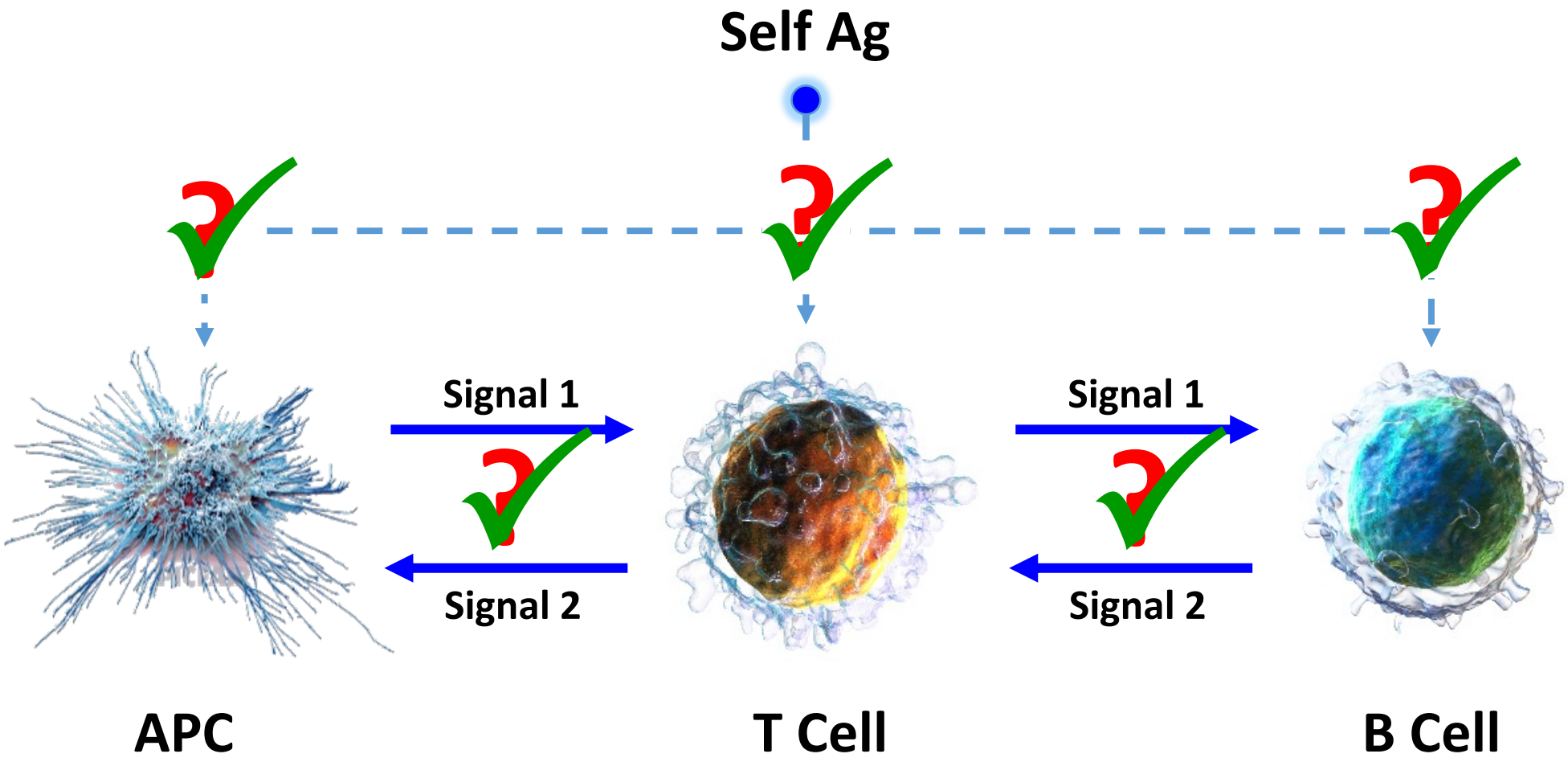
What Causes Loss of Immune Tolerance ?

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 Abnormal Place or Structure of Self-Ag	DNA / RNA
 Dysfunctional Antigen Presenting Genes	MHC System
 Dysfunctional T or B Cell Receptor Genes	RAG System
 Infectious Disease, Neoplasia or Cancer	Ag Mimicry
 Pregnancy or Allograft Transplantation	HLA System

How Can Immune Tolerance be Restored ?

Restoring Immune Tolerance



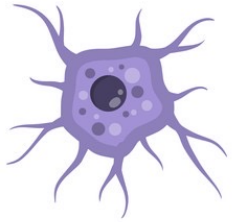
How Immune Tolerance be Restored ?

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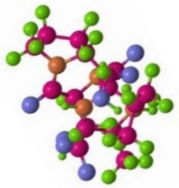
	Correct Gene Mutations or Dysfunction	DNA Editing
	Correct Production or Protein Structure	RNA / Folding
	Reprioritize APC, T cell, B cell Response	Deviation
	Delete Auto-Reactive APCs, T or B cells	Censoring
	Re-Educate APCs, T cells and/or B cells	Re-Program

Technologies

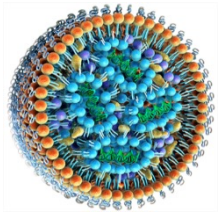
Emerging Technologies Focus on NMO Tolerization



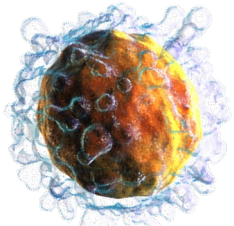
Dendritic Cell Vaccines



Engineered Epitopes



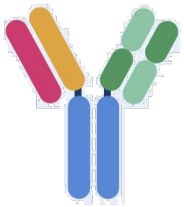
Tolerizing NPs



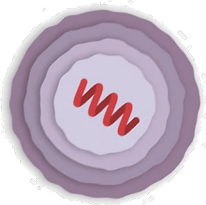
CA/ART Therapy



Ag-Specific CP Inhibition



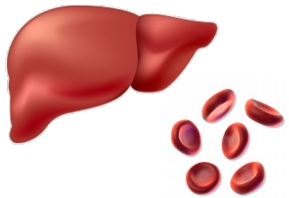
HLA–G Tolerance



Inverse Vaccines



Marrow Rebooting



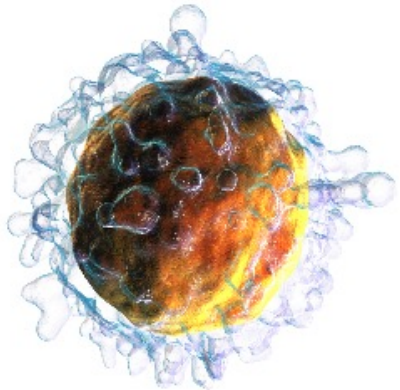
Endogenous Tolerance



Programmed Cell Death

Source: Guthy-Jackson Charitable Foundation [2024] / Access: www.guthyjacksonfoundation.org/pioneer

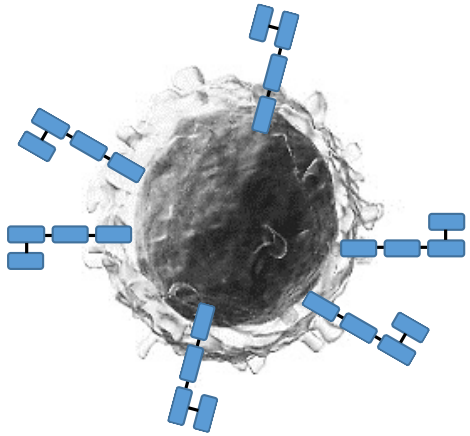
Example: CAR-T or CAAR-T Cell Therapy



Healthy T Cell (from Patient)

CA/AR

Modify in Lab



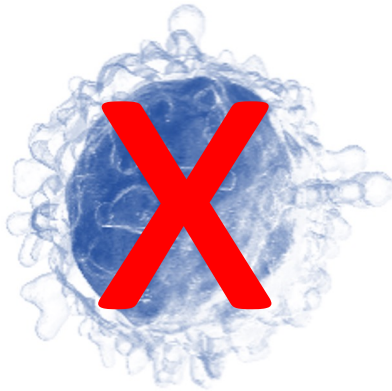
CAR-T or CAAR-T Cell (Return to Patient)

Delete

Delete



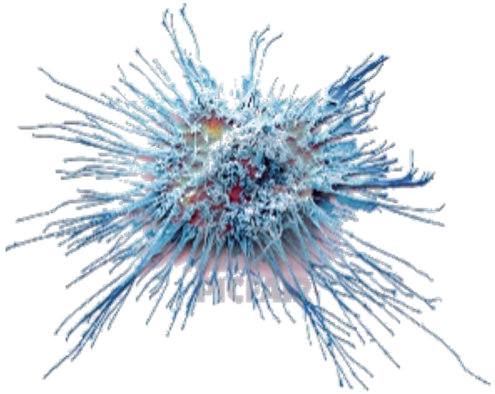
Autoreactive T Cell (in Patient)



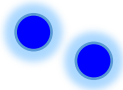
Autoreactive B Cell (in Patient)

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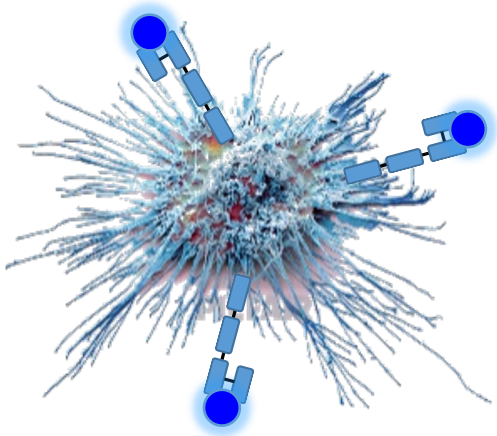
Example: Dendritic Cell / APC Vaccines



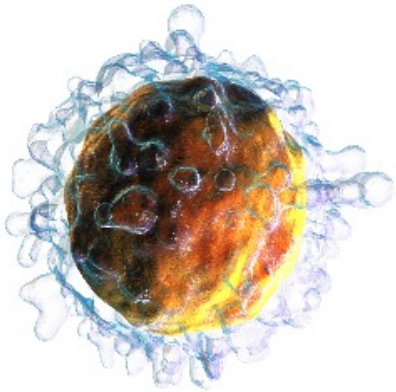
Dendritic Cell
(from Patient)



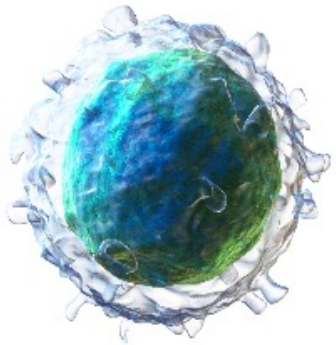
Conditioning



Tolerizing DC
(Return to Patient)



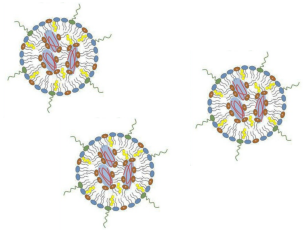
Tolerize T Cell
(in Patient)



Tolerize B Cell
(in Patient)

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Charitable Foundation

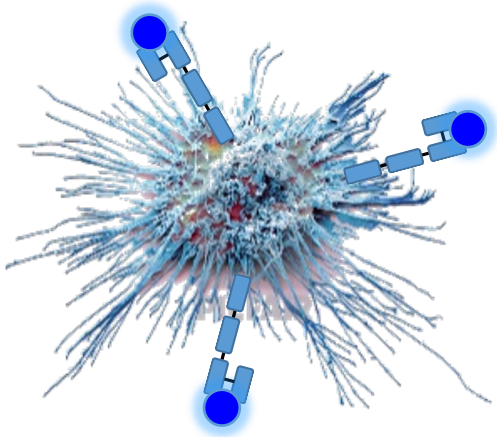
Example: Inverse RNA or DNA Vaccines



Inverse Vaccine (into Patient)

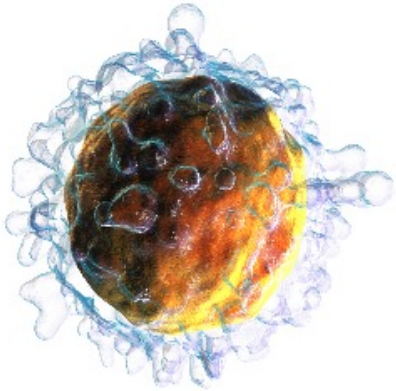
Auto-Ag Encoding Nucleic Acid

Tolerizing DNA or $\Delta\Psi$ mRNA in NP



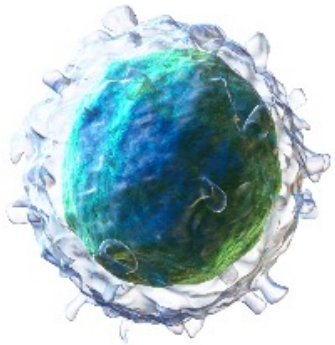
Tolerizing DC (in Patient)

No 2nd Signal



Tolerize T Cell (in Patient)

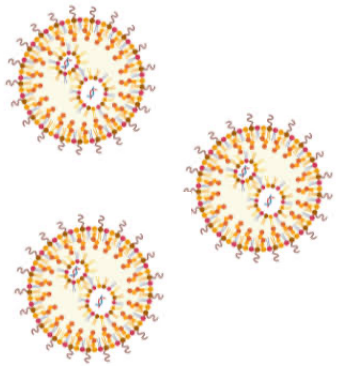
No 2nd Signal



Tolerize B Cell (in Patient)

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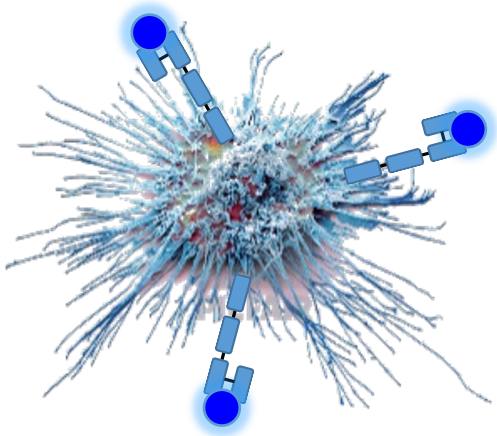
Example: Tolerigenic Nanoparticles



Tolerigenic Nanoparticle (into Patient)

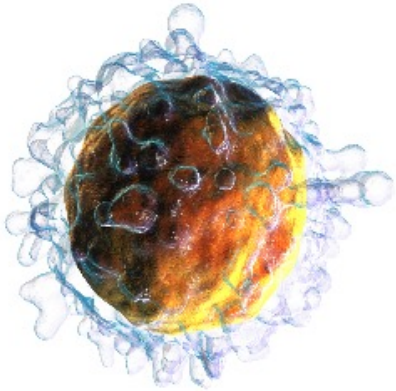
Autoantigen or Peptide

Tolerizing NP Formulation



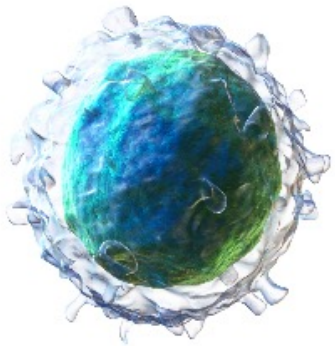
Tolerizing DC (in Patient)

No 2nd Signal



Tolerize T Cell (in Patient)

No 2nd Signal



Tolerize B Cell (in Patient)

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Is Tolerization a Treatment or Cure ?



TREATMENT

Therapy that induces temporary immune tolerance to an auto-antigen
Occasional re-dosing may be needed; no need for immune suppression



CURE

Therapy that induces permanent immune tolerance to an auto-antigen
Re-dosing would be unnecessary; no need for immune suppression

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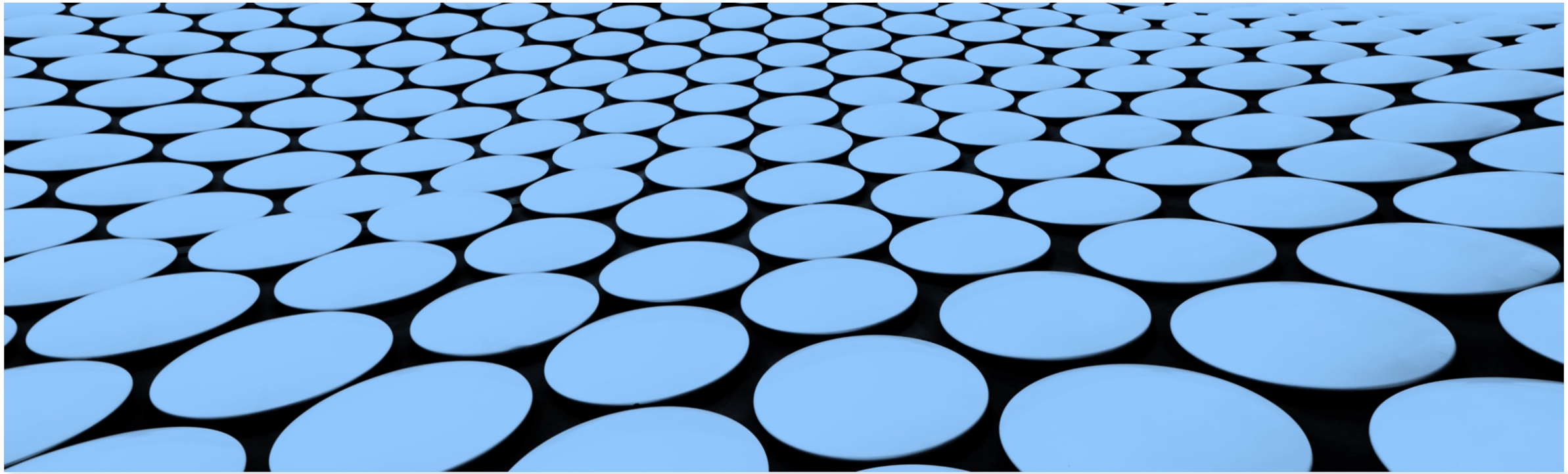
We are Cureageous.™

www.GuthyJacksonFoundation.org

CLINICAL TRIAL ECOSYSTEM FOR IMMUNE TOLERIZATION

BRIAN WEINSHENKER MD,

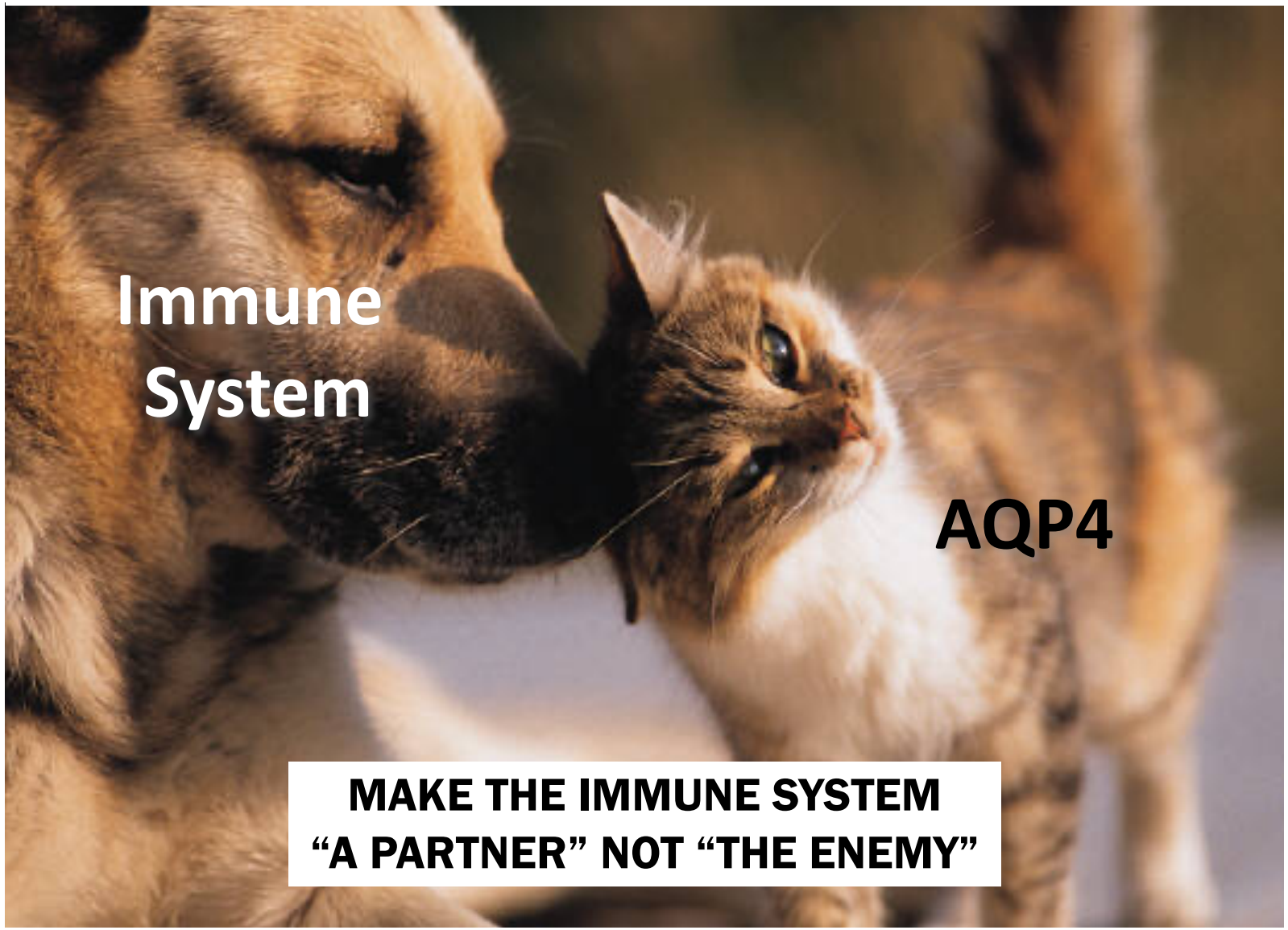
UNIVERSITY OF VIRGINIA



Ultimate Goal: Curative Therapy

ULTIMATELY A CURATIVE STRATEGY WILL REQUIRE DURABLE OR PERMANENT INTERFERENCE WITH MECHANISMS THAT LEAD TO AUTOREACTIVE ANTIGEN PRESENTATION AND PROPAGATION OF IMMUNE MISRECOGNITION TO HUMAN PROTEINS SUCH AS AQP4, MOG OR OTHER DISEASE-SPECIFIC AUTOANTIGEN

Basic Premise of Immune Tolerization



Ideal Features of Tolerizing Therapies:

- More Specific
  - Antigen-targeted
  - Critical immune effectors
- Boosts Tolerance
  - Enhances regulation
  - Central or peripheral
- Long-Term Efficacy
  - Extended dosing intervals
  - Potential permanent cure
- Improved Safety
  - Less immunosuppressive
  - Spares host defenses
- Better Tolerability
  - Fewer off-target effects
  - Autologous / Inert

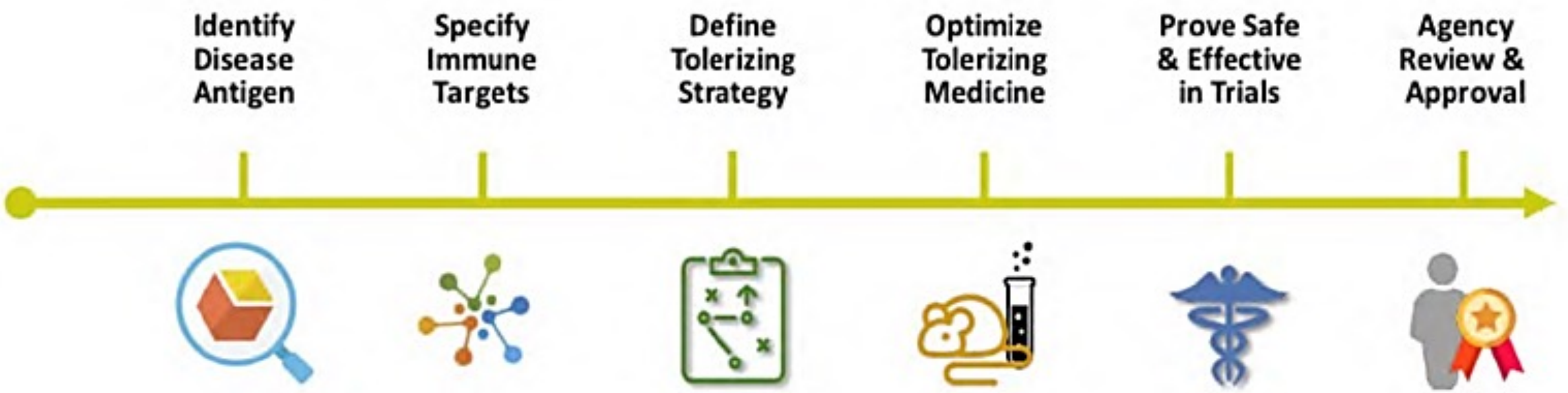
Source: *3rd GJCF Summit for Immune Tolerization* [2023] Access: *www.guthyjacksonfoundation.org*

NMO: Ideal Model for Immune Tolerization

- ☑ **Auto-Ag AQP4 & critical epitope targets are known**
- ☑ **Pathogenic mechanisms and pathways established**
- ☑ **Specific clinical phenotypes & relapse adjudication**
- ☑ **Robust & increasing prevalence in US & worldwide**
- ☑ **Orphan disease status and fast-track opportunities**
- ☑ **4 approved drugs: relapses occur; key AEs & costs**
- ☑ **GJCF assets: CIRCLES, genotypes, patient synergies**

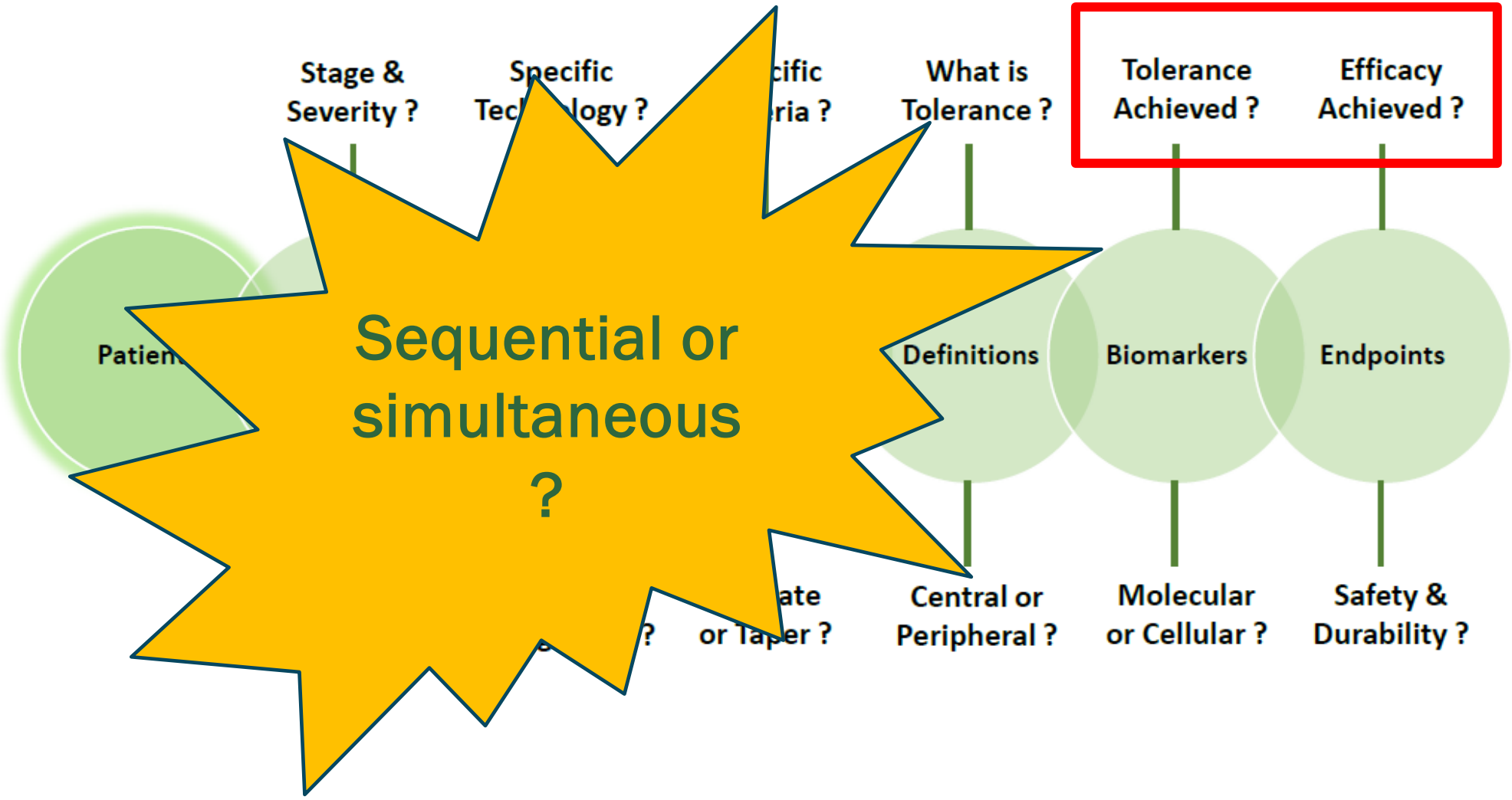
Source: ***3rd GJCF Summit for Immune Tolerization*** [2023] Access: ***www.guthyjacksonfoundation.org***

Roadmap to Immune Tolerization Cures



Source: GJCF-ITN-NIH Tolerization Summit [2016] Access: ***www.guthyjacksonfoundation.org***
Modified from ***Immune Tolerance Network*** [2022] Access: ***www.immunetolerance.org***

Key Concepts in Tolerization Trial Design



Source: ***3rd GJCF Summit for Immune Tolerization*** [2023] Access: ***www.guthyjacksonfoundation.org***

Potential Investigative Strategy

INVESTIGATIVE STRATEGIES



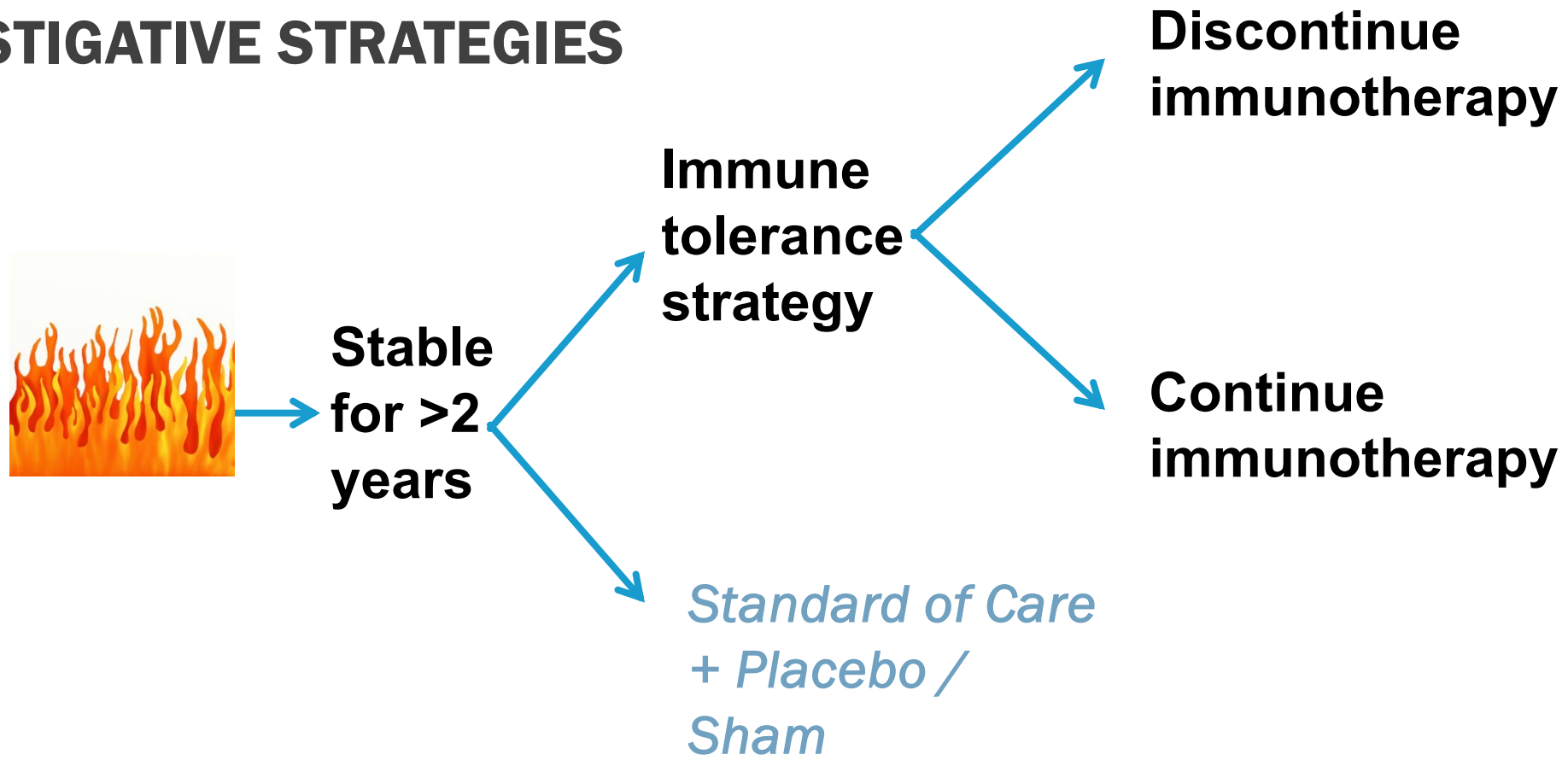
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Not feasible

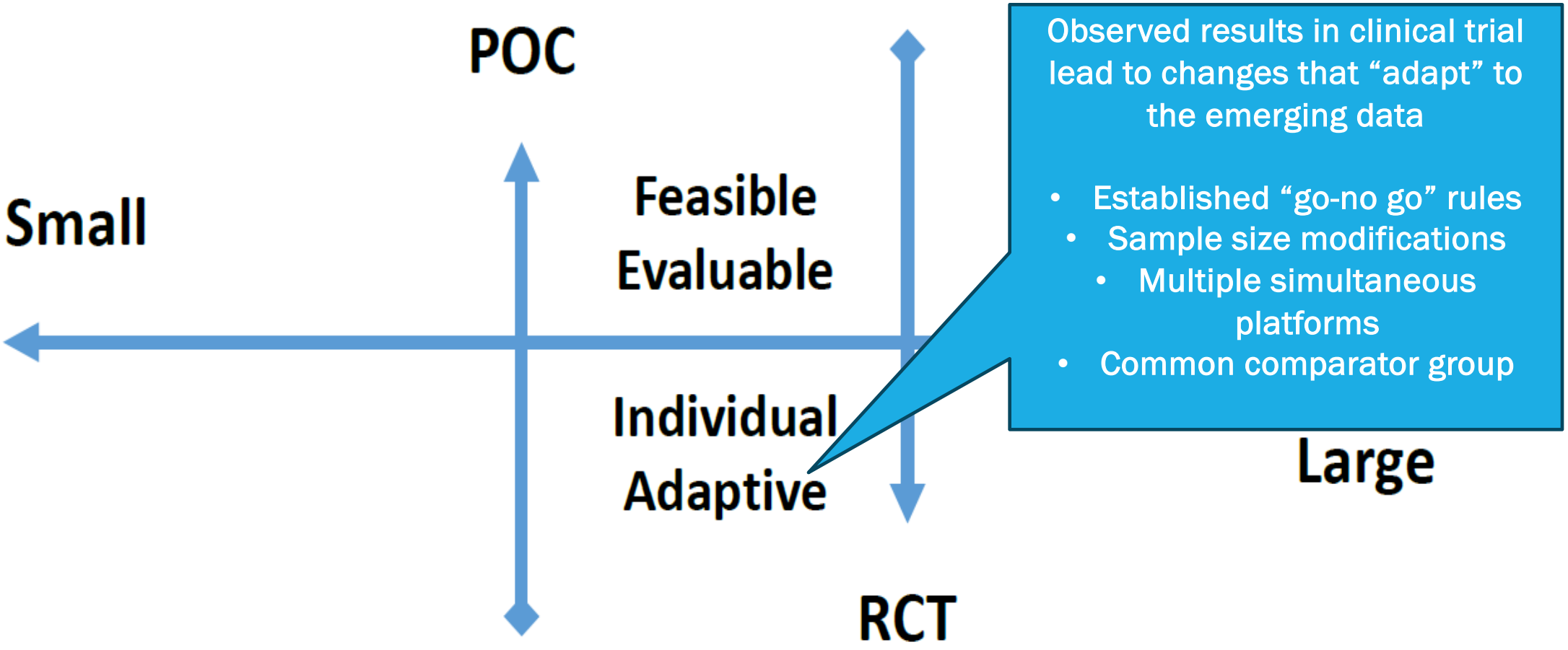
Source: *3rd GJCF Summit for Immune Tolerization* [2023] Access: *www.guthyjacksonfoundation.org*

Potential Investigative Strategy



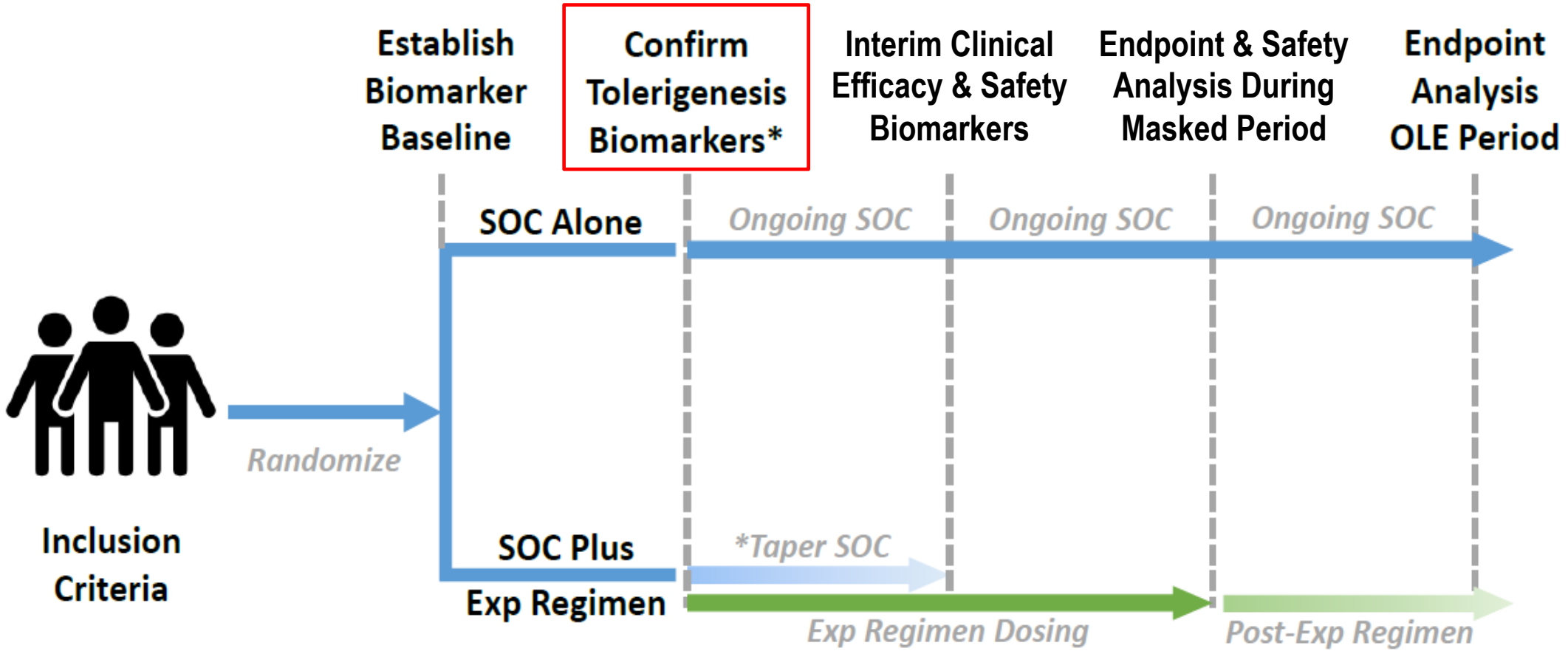
Source: *3rd GJCF Summit for Immune Tolerization* [2023] Access: *www.guthyjacksonfoundation.org*

Tolerization Clinical Trial Options



Source: ***3rd GJCF Summit for Immune Tolerization*** [2023] Access: ***www.guthyjacksonfoundation.org***

Clinical Trial Consensus Working Model



SOC = Standard of Care

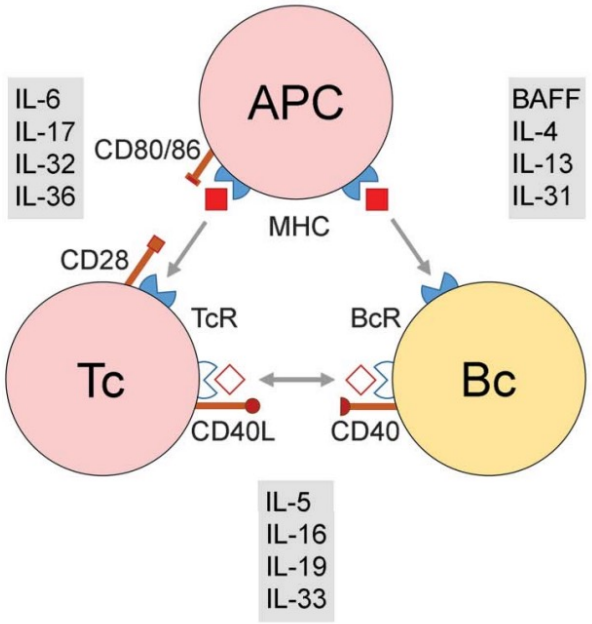
OLE = Open Label Extension

Source: ***3rd GJCF Summit for Immune Tolerization*** [2023] Access: ***www.guthyjacksonfoundation.org***

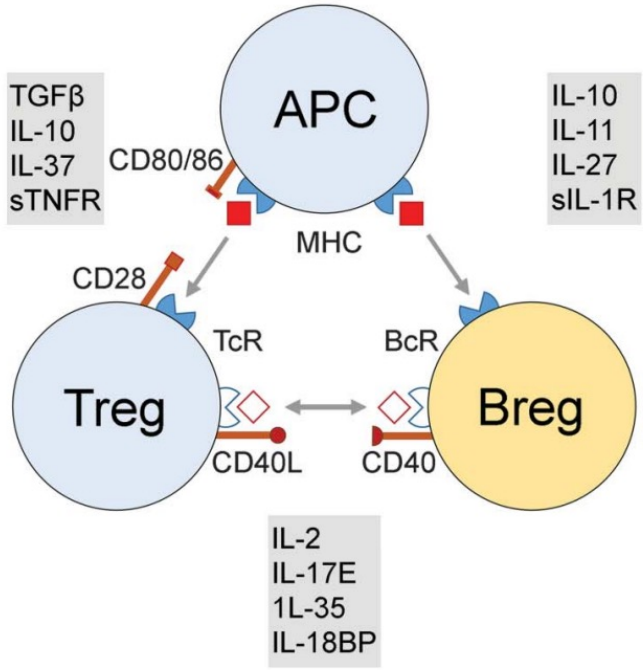
Biomarkers of Immune Tolerization

- Antigen reactivity
- B cell activation
  - AQP4-IgG/MOG-IgG titers
  - Class switching in cervical lymph nodes
- Cell subsets
  - T vs B cell
  - Effector vs suppressor
- Autoreactive cells
- Cytokine signatures:
  - IFN alpha
  - Th2/Th1
    - Confounding by cytokine release (e.g. CAR-T therapy)

Autoreactive



Tolerigenic



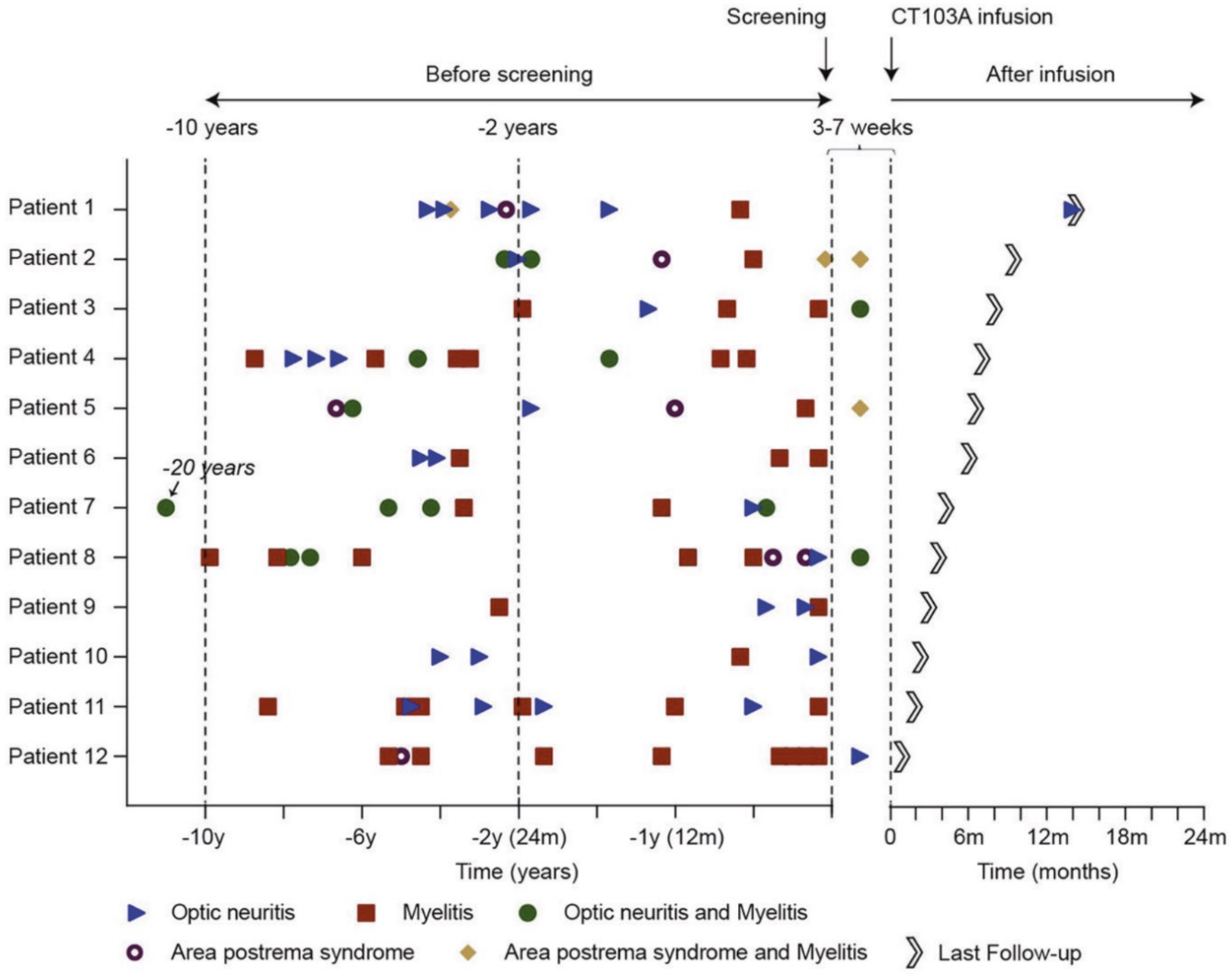
Source: Steinman *et al.* [2016] ***Neurology / N2*** 3(5)e:276

Equecabtagene Autoleucel in AQP4-IgG+ NMO

- **BCMA aka TNFRSF17 aka BAFF Ligand**
- **fhCT103A Autologous Anti-BMCA CAR-T**
- **12 Patients – Median Age 49.5; 83% F**
- **History: ARR ≥ 2 and Tx-Refractory Dz**
- **All Patients Experienced Grade 3 AEs**
- **Pan-Cytopenia and/or CRS; No ICANS**
- **UTI, CMV Common ID Issues; No PML**
- **No Patient Needed Tocilizumab (CRS)**

RESULTS

- **No Relapse in 11/12 Pts Up to 14 Mo**
- **Anti-AQP4+ Titer: 1:1400 down to 1:5**
- **Median EDSS: Pre = 7.0 vs. Post = 4.5**
- **IASO Biotherapeutics files BLA (China)**

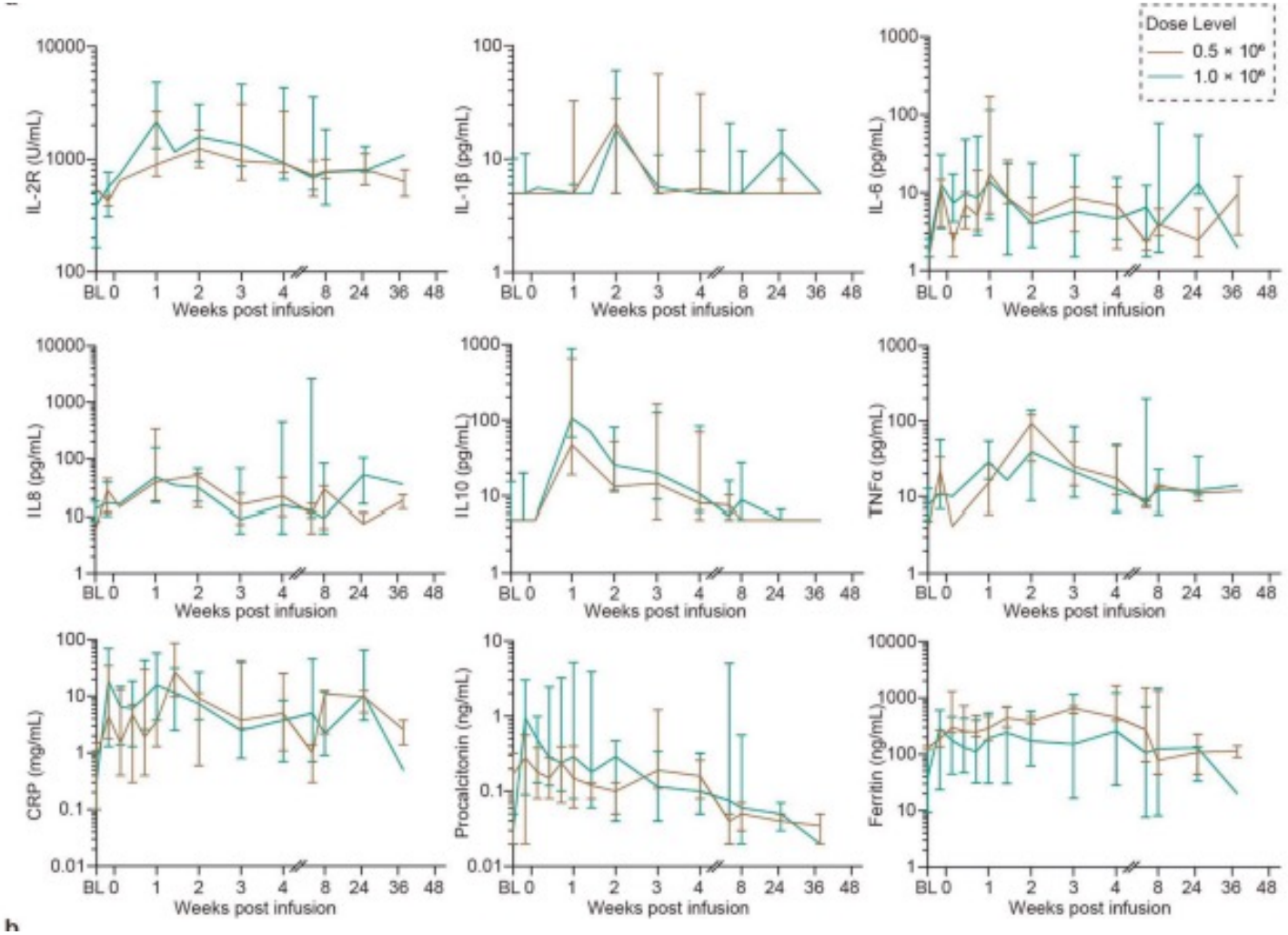


Source: Qin *et al.* [2023] ***Nature / Sig Trans Targ Ther*** 8:5

Equecabtagene Autoleucel in AQP4-IgG+ NMO

BIOMARKERS

- Antigen reactivity
- B cell activation
  - AQP4-IgG/MOG-IgG titers
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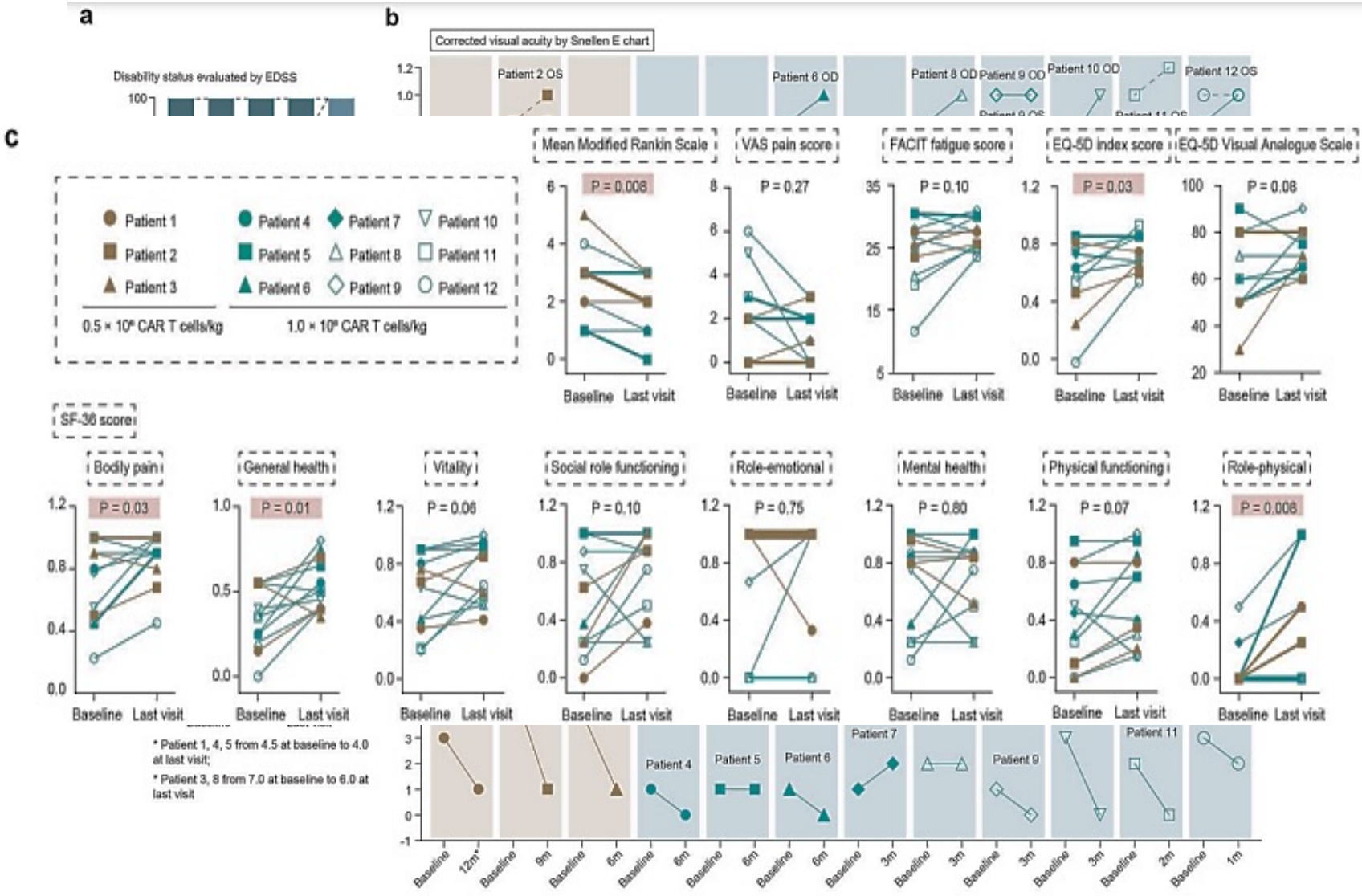


Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory…
Qin et al.
Signal Transduction and Targeted Therapy (2023)8:5
https://doi.org/10.1038/s41392-022-01278-3

(continued)

CLINICAL EFFICACY

- Relapses
- MRI activity
- GFAP and markers of cellular injury
- Disability
- Fatigue
- Pain



Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory…
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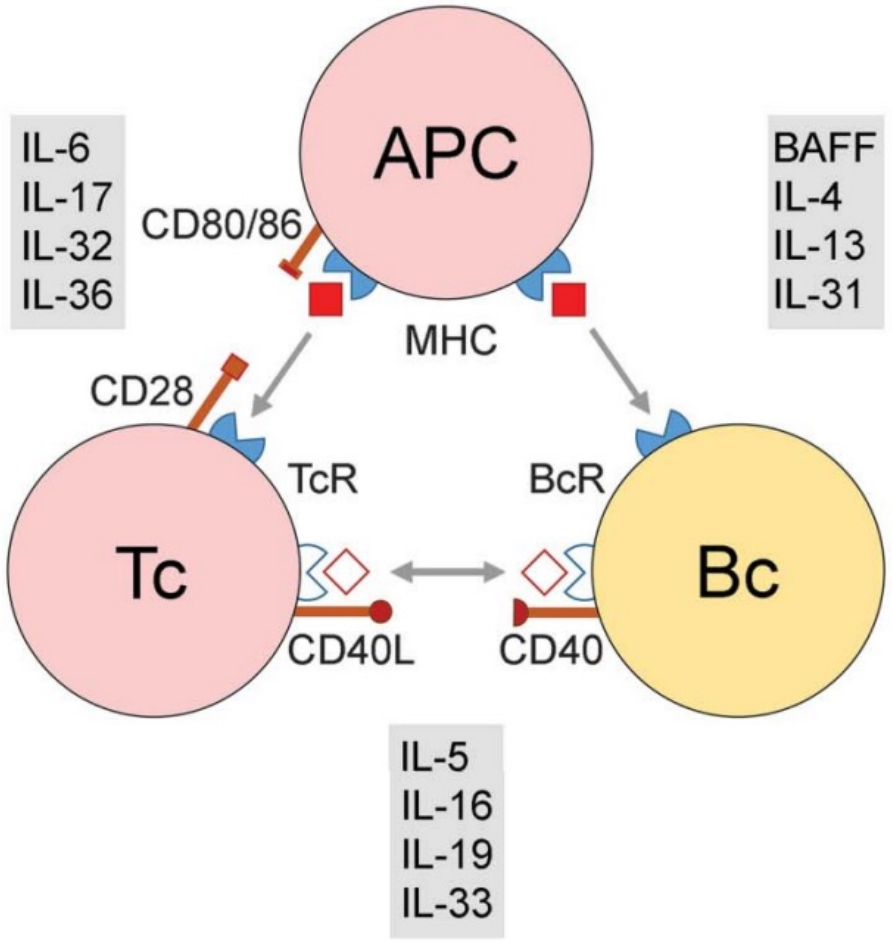
Summary & Prospectus

Key Trial Design Questions & Challenges

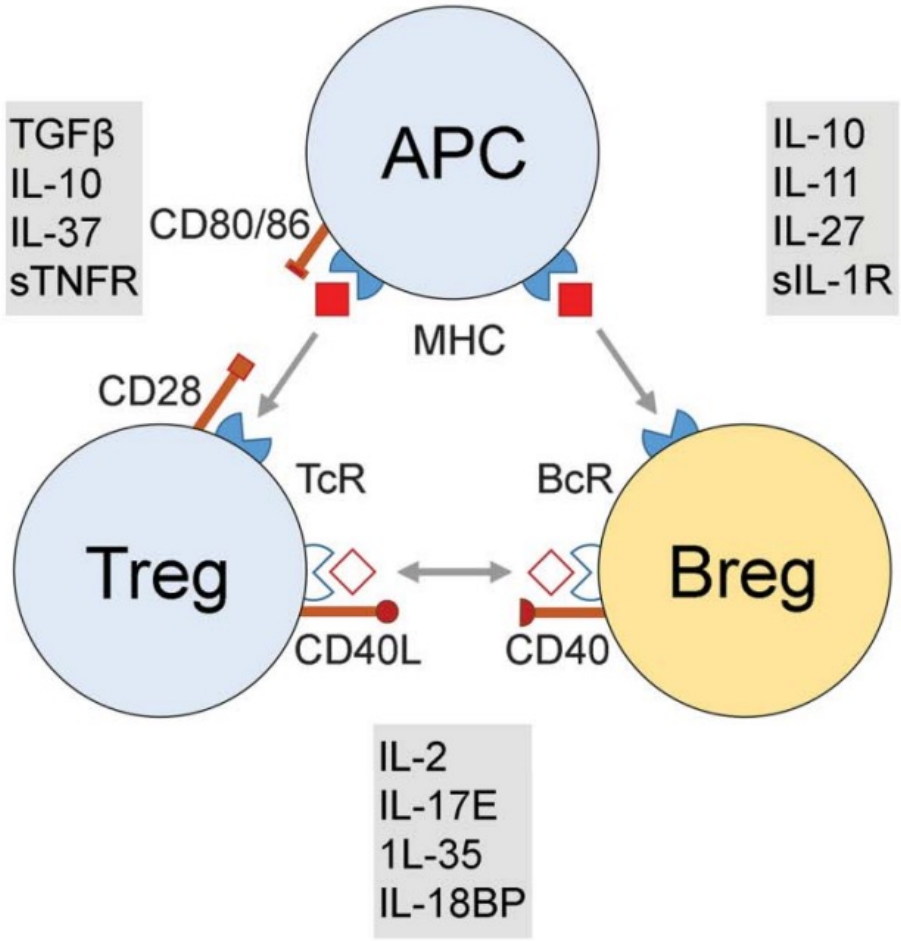
- Which patients: *Stable or Failing Treatment* ?
- Disease stage: *Early Onset or Later in Course* ?
- Technology platforms: *Priorities & Comparators* ?
- Tolerigenesis biomarkers: *Known or Needed* ?
- Safety signals: *Relapse and Key Adverse Events* ?
- Efficacy signals: *Remission & Reduced Disability* ?
- Treatment history: *Current and Past Heterogeneity ?*
- Concomitant therapy: *Reduced informativeness; mitigate risks ?*
- Comparator group: *Modified Placebo Control (SoC) ?*
- Endpoints: *Credible Non-relapse Metrics of Efficacy ?*
- Trial network: *Multi-Platform and Adaptive Designs ?*
- Durable efficacy: *Boosting vs. Permanently Curative ?*

Biomarkers of Immune Tolerization

Autoreactive



Tolerigenic

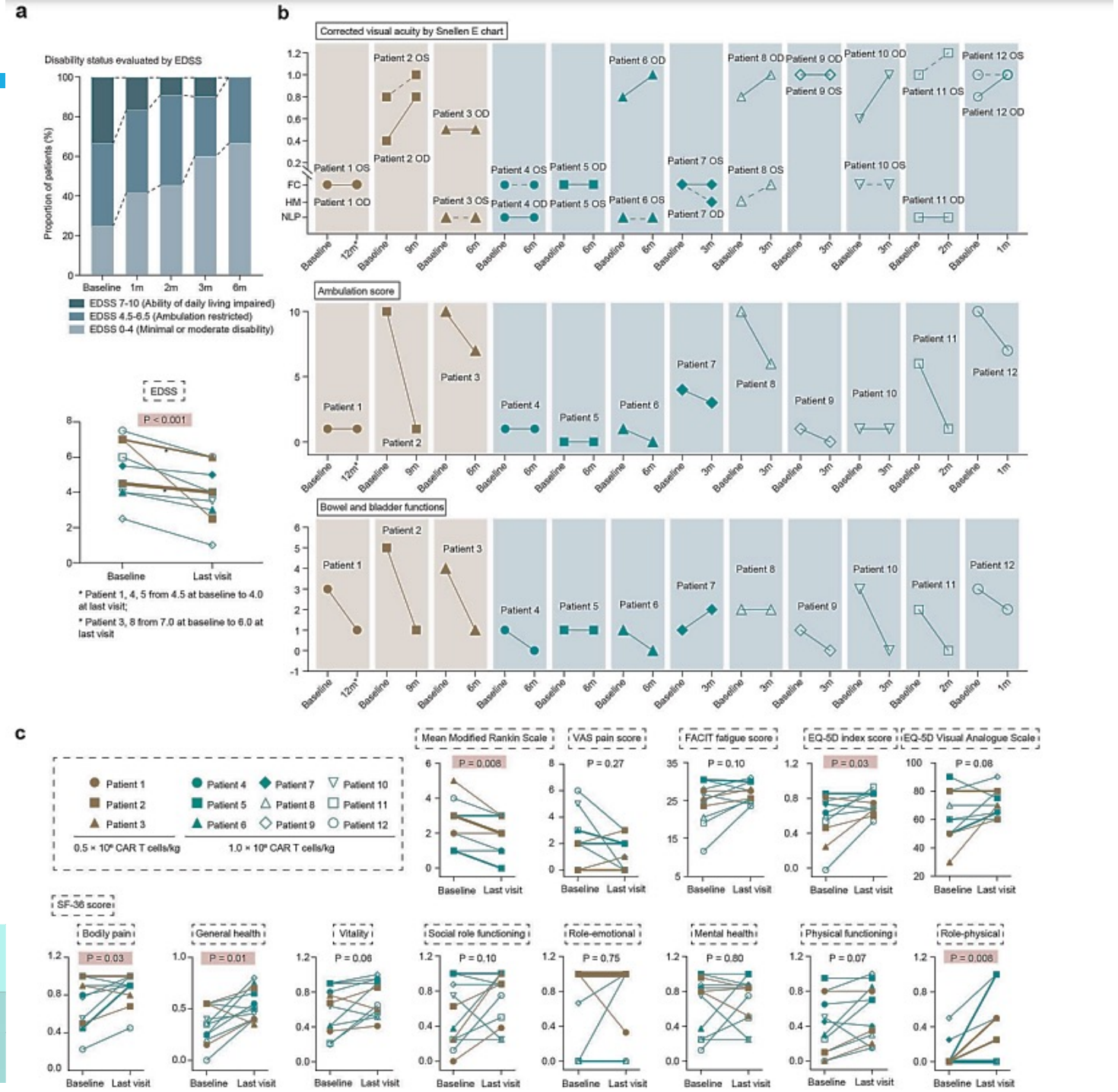


Source: Steinman *et al.* [2016] ***Neurology / N2*** 3(5)e:276

(continued)

CLINICAL EFFICACY

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Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory…
Qin et al.
Signal Transduction and Targeted Therapy (2023)8:5
https://doi.org/10.1038/s41392-022-01278-3

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Charitable Foundation

"It was an honor for me to participate in the 15th NMO Roundtable and I learned a lot from the presentations and discussions. I cannot thank you enough for your organizing such a wonderful event again."

-Kazuo Fujihara, MD
Tohoku University



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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

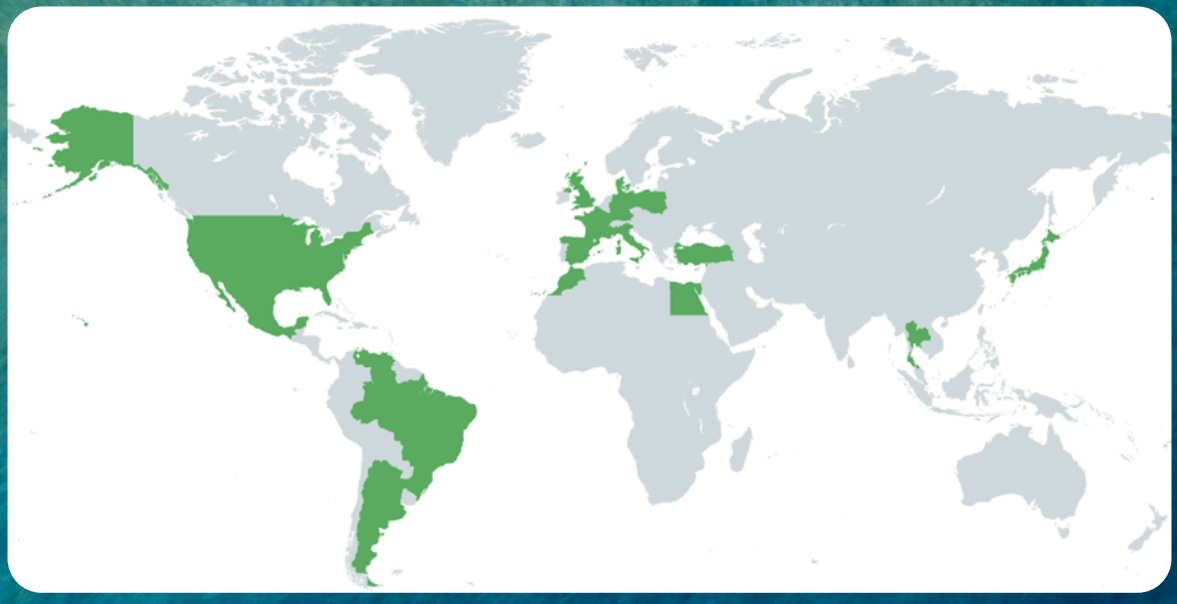
Survey Respondent Stats

SURVEY RESPONDENTS: GJCF ICC MEMBERS

COUNTRIES REPRESENTED: 17 COUNTRIES

AVERAGE YEARS IN PRACTICE: 20 YEARS

AVERAGE COHORT SIZE: 117 PATIENTS

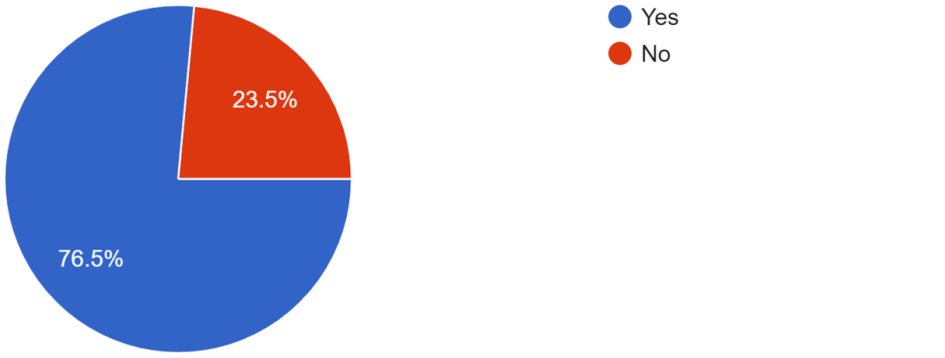


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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

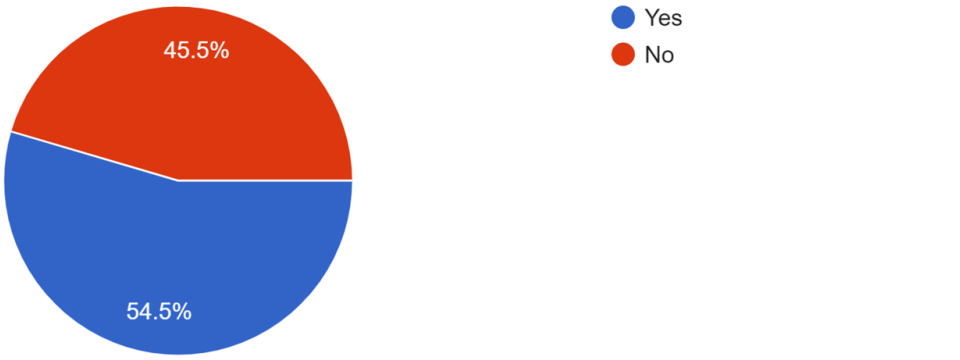
Optimizing the Impact of Highly Effective Therapies

Do you have access to prescribing approved therapies in your practice?



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Do you prescribe an approved therapy for patients at first onset of disease?



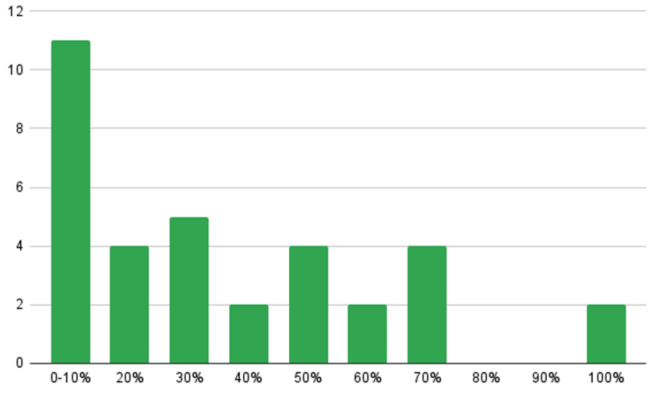
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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

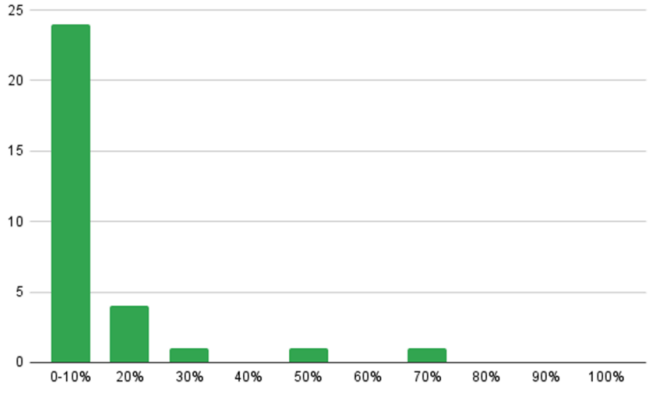
Optimizing the Impact of Highly Effective Therapies

What percentage of your patients are receiving approved therapies for NMO?



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What percentage of your NMO patients on approved therapy have relapsed in the last year?



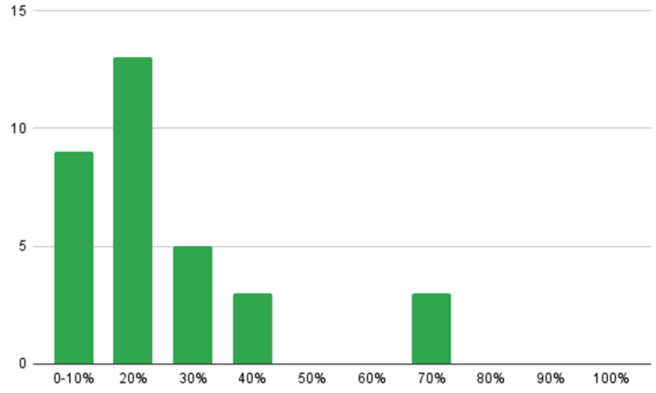
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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

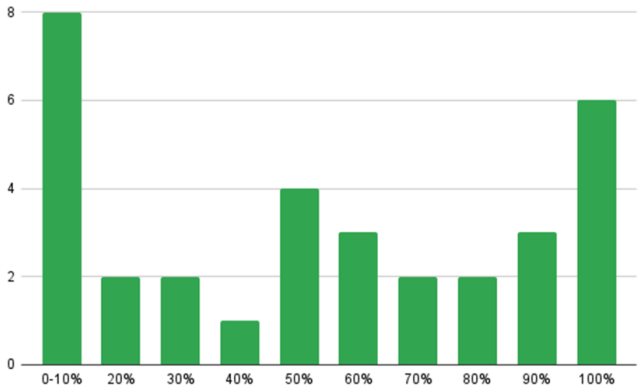
Optimizing the Impact of Highly Effective Therapies

What percentage of your NMO patients **not on approved therapy** have relapsed in the last year?



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What percentage of your MOGAD or SN-NMOSD patients are receiving off-label therapies approved for NMO?

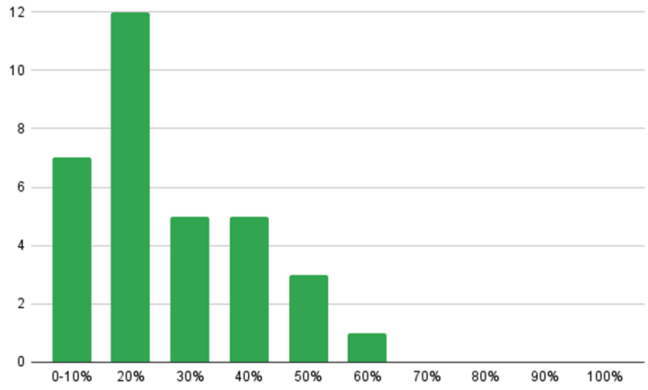


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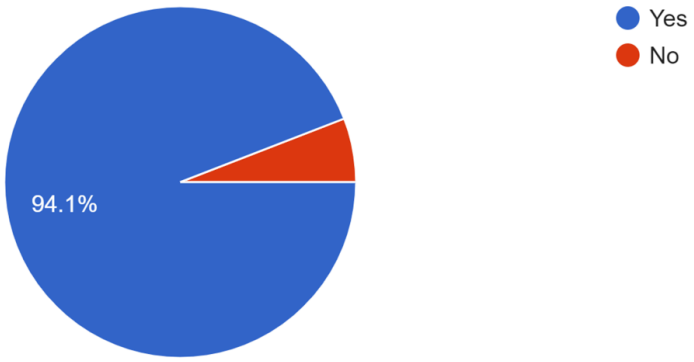
PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Optimizing the Impact of Highly Effective Therapies

What percentage of your MOGAD or SN-NMOSD patients have relapsed in the last year?



Do you recommend changing to an approved therapy at time of relapse?

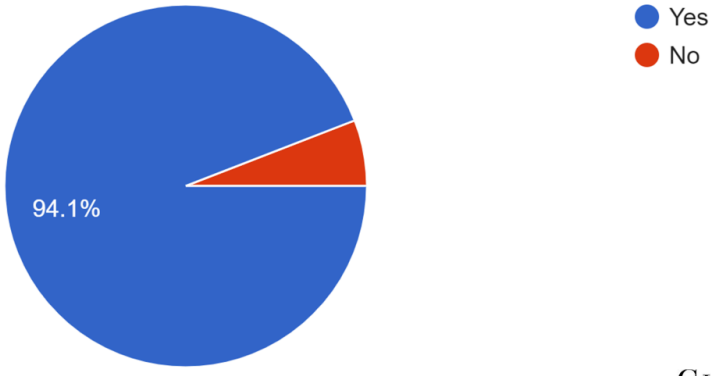


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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

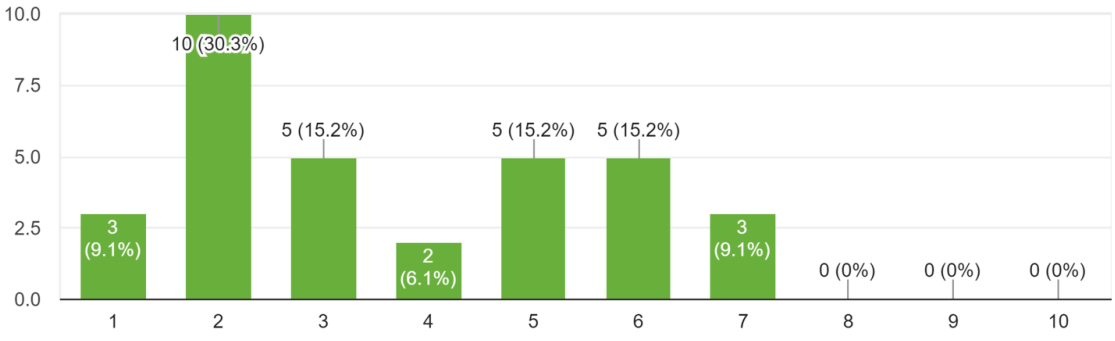
Optimizing the Impact of Highly Effective Therapies

Do you consider changing to approved therapy if significant AEs/SAEs but no relapses?



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What degree of impact do infusion or infection AEs & SAEs have on your patients?



1= Mild
10 = Severe

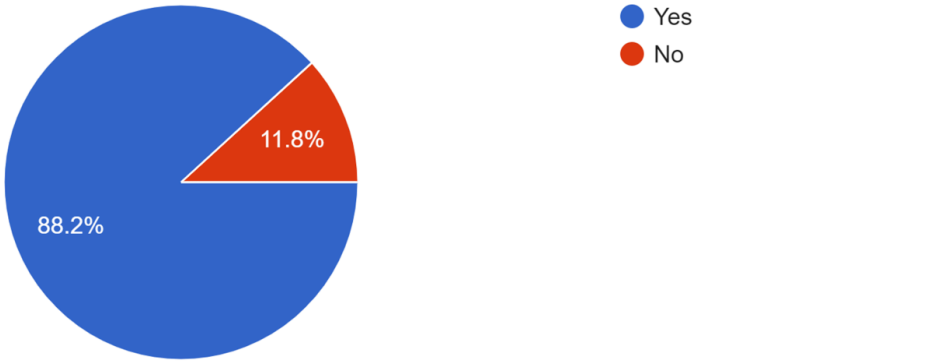
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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Optimizing the Impact of Highly Effective Therapies

Do you modify therapeutic regimens in patients with autoimmune comorbidities?



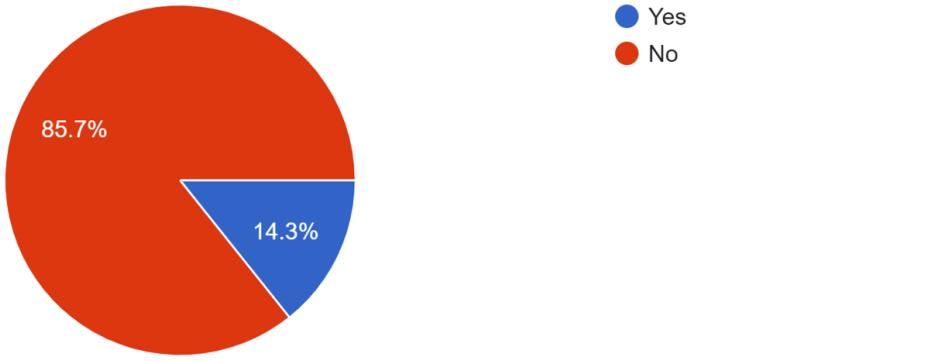
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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Pathogenesis, Serology, Diagnosis & Epidemiology

AQP4+ NMO, MOG+ MOGAD & Seronegative NMOSD have common immunologic origins?



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The greatest immunologic difference among NMO, MOGAD & SN-NMOSD is:

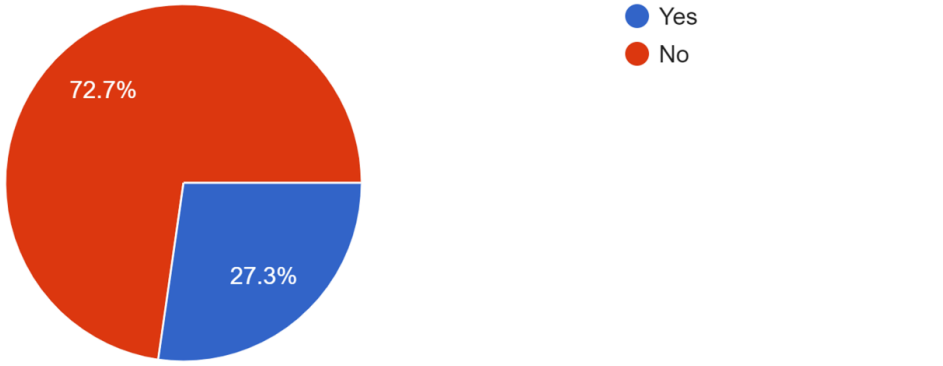


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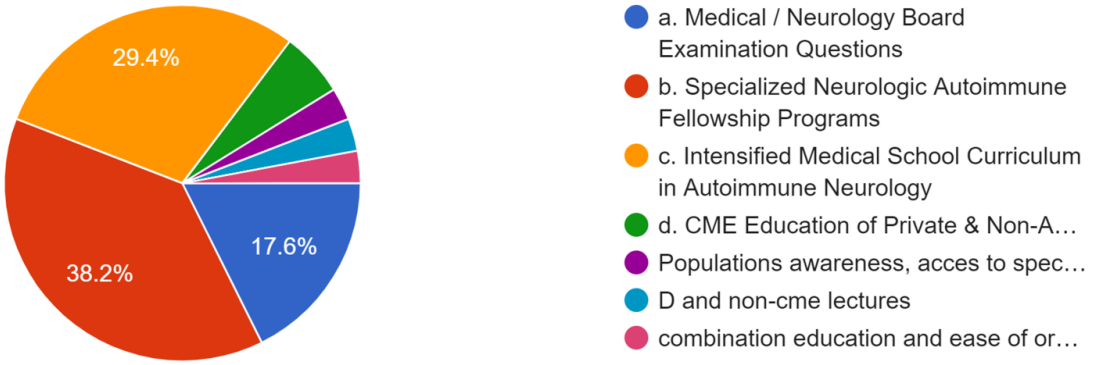
PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Pathogenesis, Serology, Diagnosis & Epidemiology

The Immunodot serological assay platform will replace cell-based assays in diagnosis?



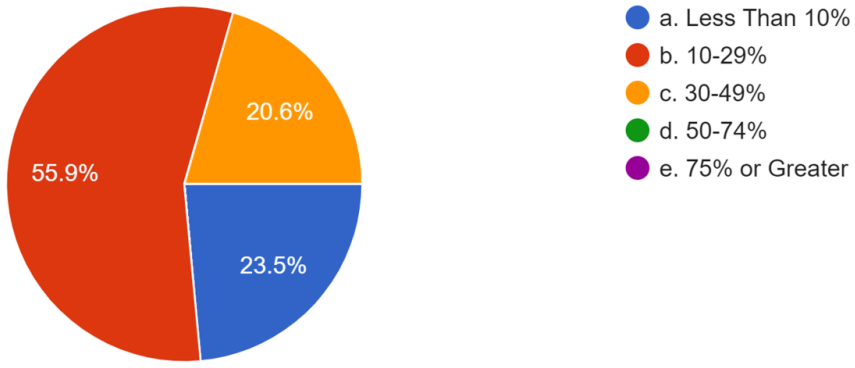
Improved diagnostic awareness & accuracy will be achieved primarily through which action:



PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Pathogenesis, Serology, Diagnosis & Epidemiology

What percentage of patients are currently misdiagnosed with MS or like diseases globally?

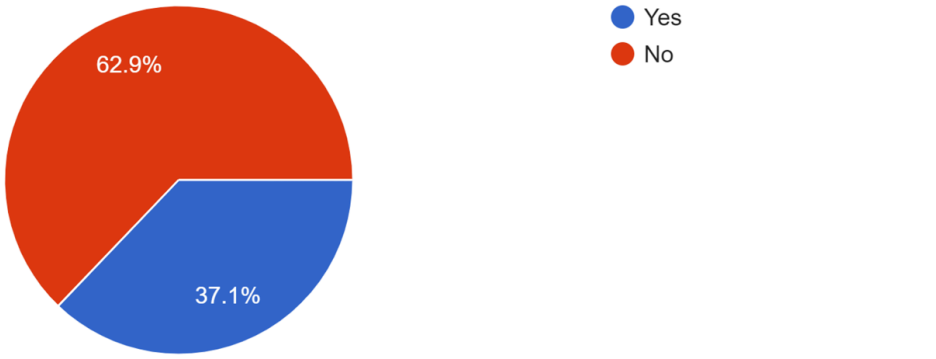


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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

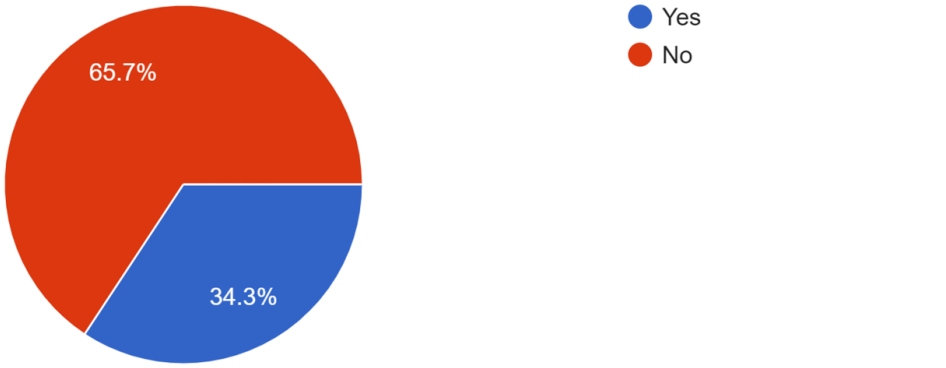
Emerging Molecular, Cellular & Imaging Biomarkers

NMO, MOGAD & SN-NMOSD have common molecular biomarkers of disease activity status?



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NMO, MOGAD & SN-NMOSD have common cellular biomarkers of disease activity status?

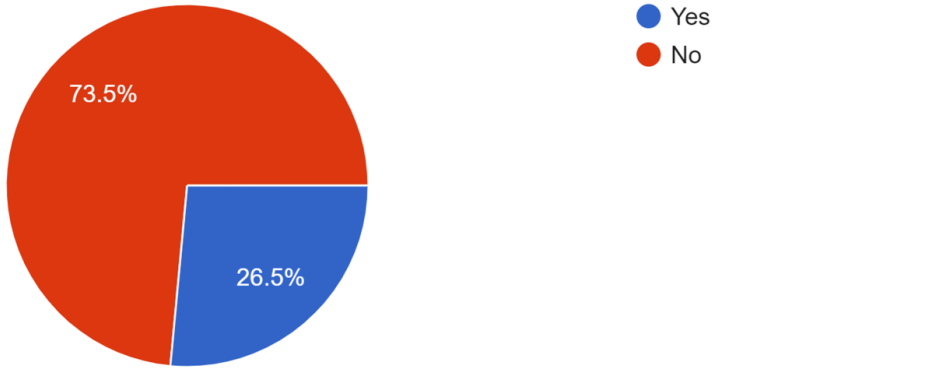


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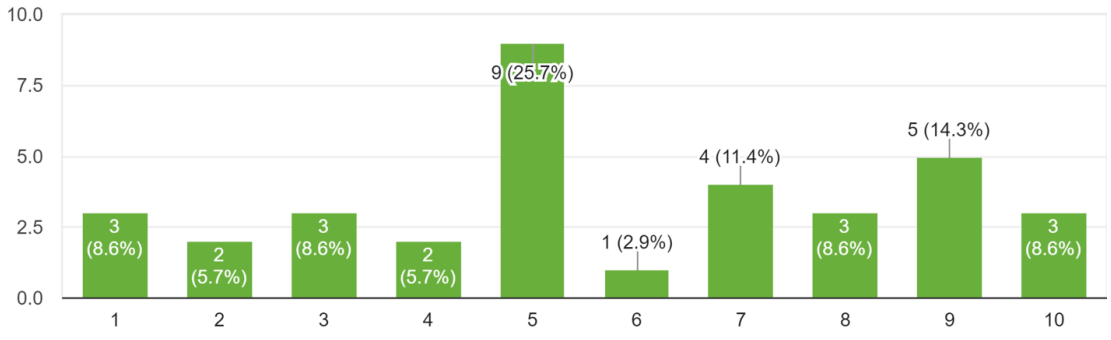
PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Emerging Molecular, Cellular & Imaging Biomarkers

Imaging biomarkers correlating with disease prognosis exist but require AI for detection?



How likely are you to customize therapeutic choice or dosing based on biomarker data?



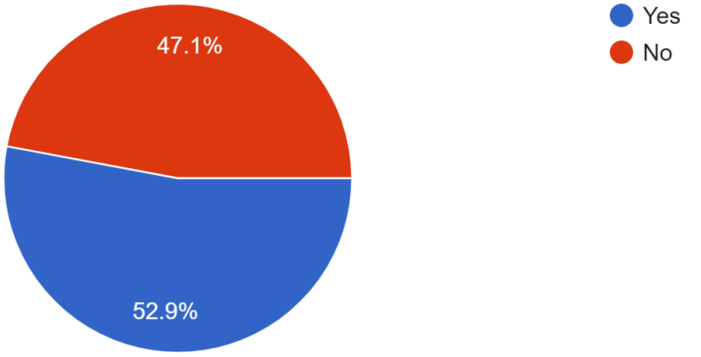
1= Unlikely
10 = Definitely

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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

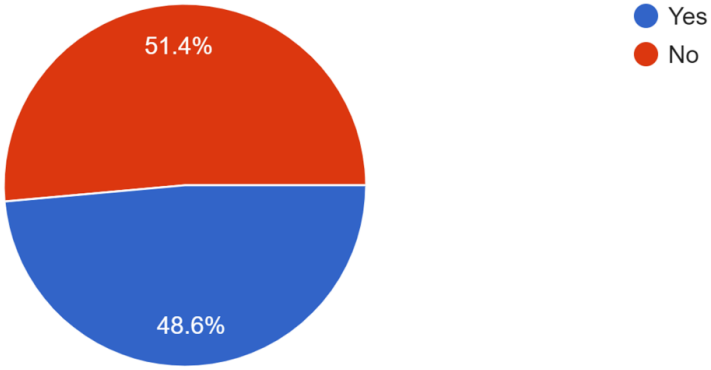
Emerging Molecular, Cellular & Imaging Biomarkers

A serum biomarker signature that predicts relapse >30 days in advance is a realistic goal?



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A biomarker that enables accurate risk of disease onset will emerge in the next decade?

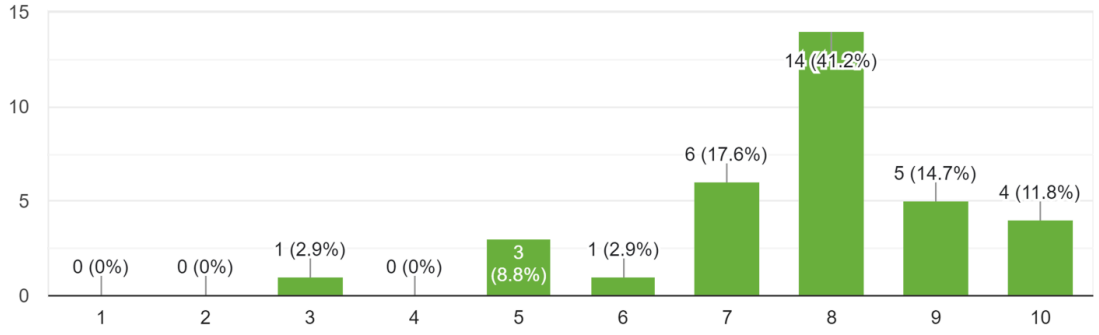


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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

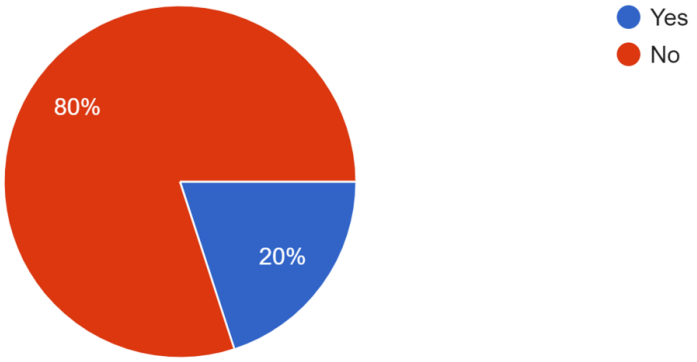
Improving Rescue Interventions for Acute Relapse

Describe your degree of standardization in adjudicating NMOSD relapses vs. pseudorelapses.



1= Highly Variable
10 = Highly Consistent

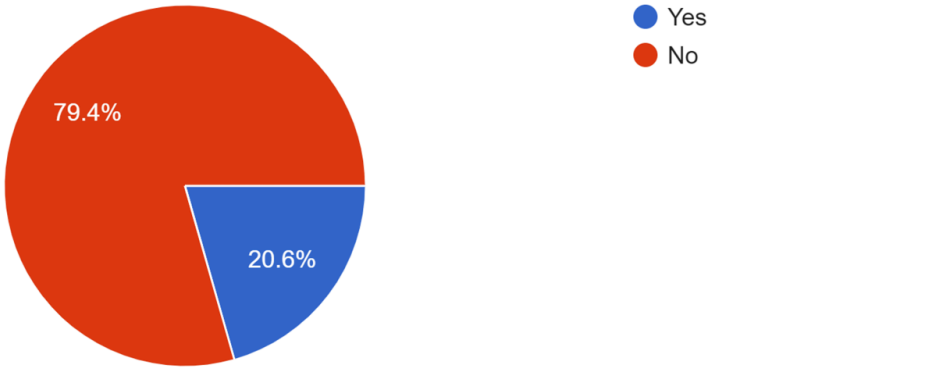
Relapse is the only significant health threat to patients experiencing NMO, MOGAD or SN-NMOSD?



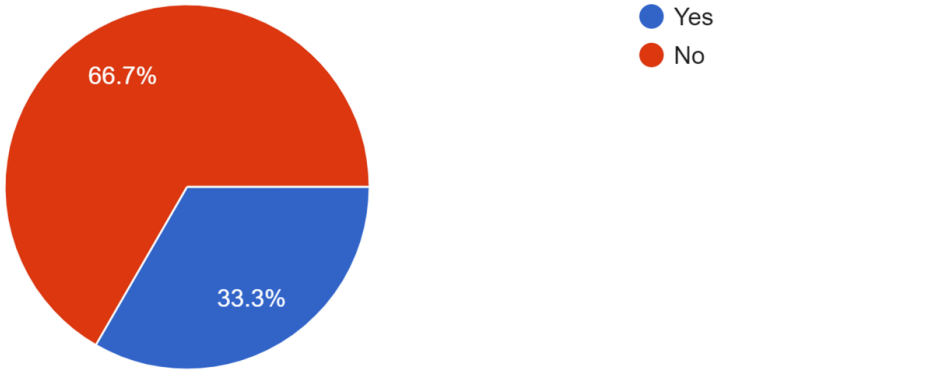
PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Improving Rescue Interventions for Acute Relapse

Existing regimens for treating acute relapse are sufficient to prevent relapse-imposed disability?



PLEX or Plasma Exchange do not create the need for redosing monoclonal antibody therapeutics?

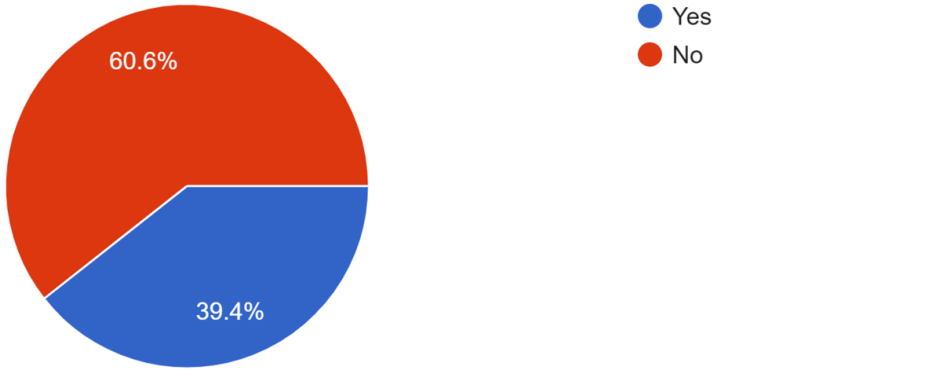


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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

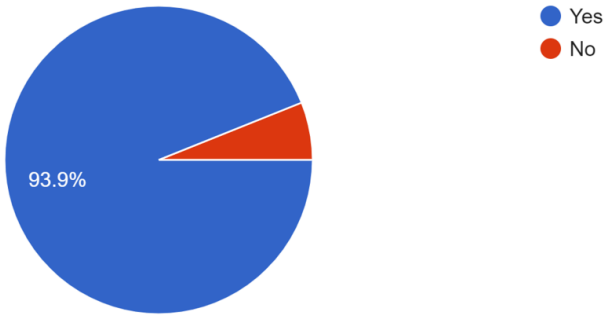
Improving Rescue Interventions for Acute Relapse

IVIG does not create the need for redosing monoclonal antibody therapeutics?



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Existing approved therapies may be repurposed for use in acute relapse mitigation?



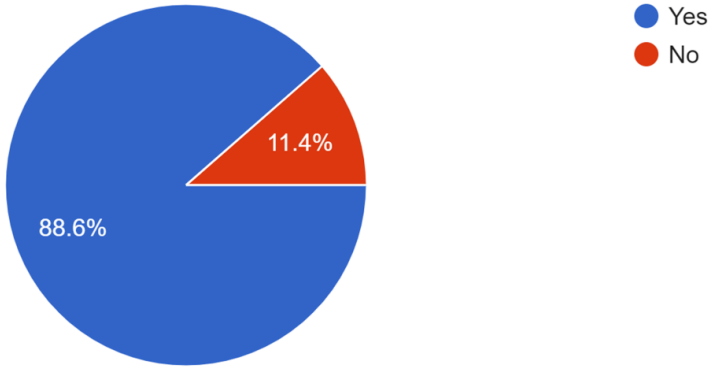
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PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Improving Rescue Interventions for Acute Relapse

Novel strategies and therapeutics are needed to address unmet needs in acute relapse?

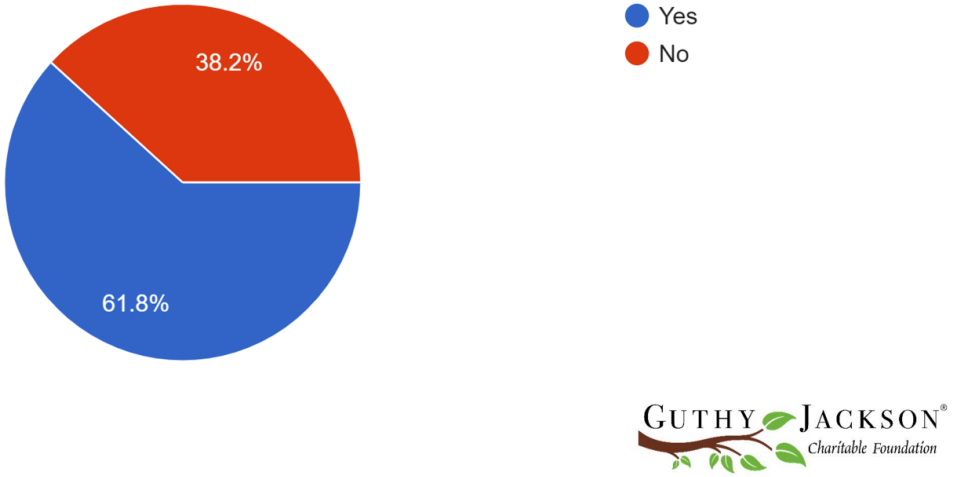


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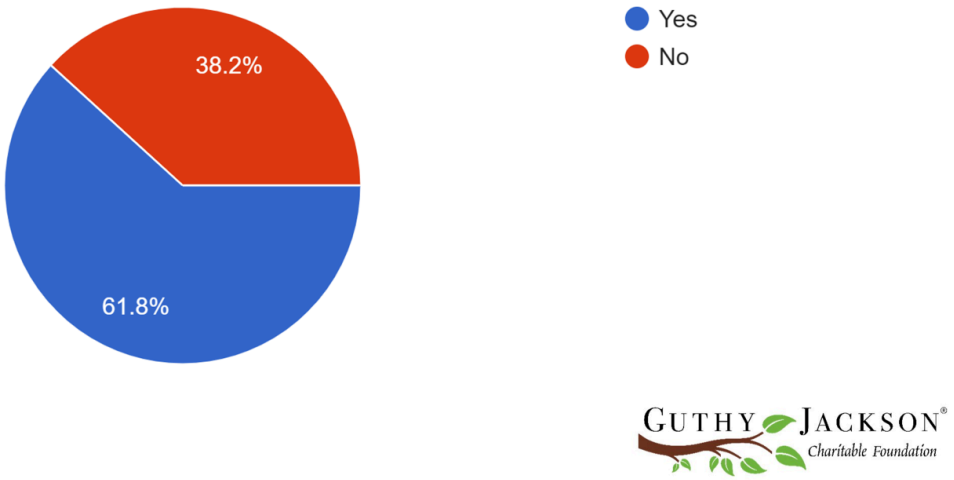
PRE-ROUNDTABLE CONFERENCE SURVEY RESULTS

Accelerating Toward Curative Therapies

Antigen-specific tolerization will be regulatory-approved for NMO or MOGAD by 2030?



Antigen-specific tolerization will be regulatory-approved for NMO or MOGAD by 2030?



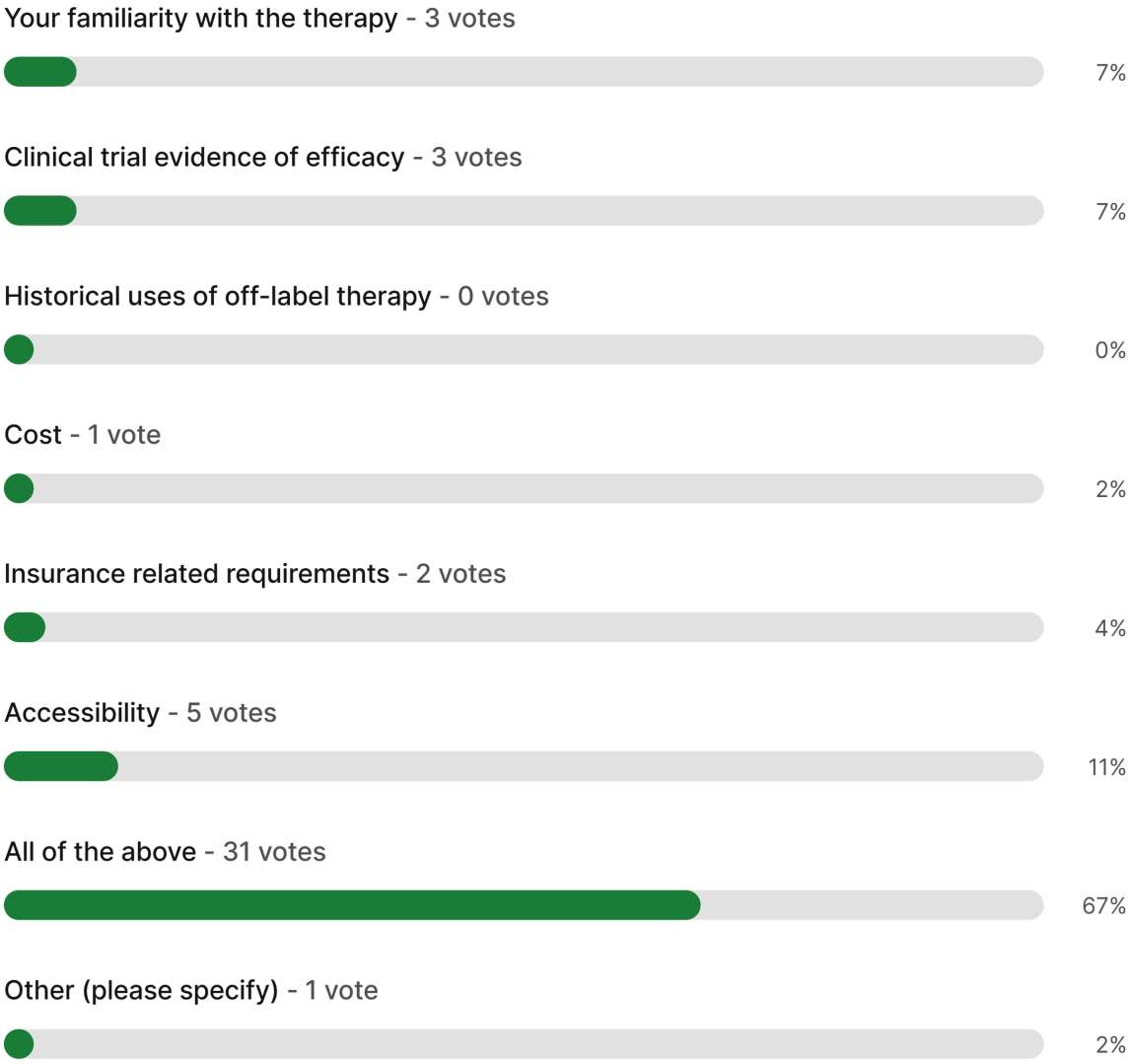
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session I: Optimizing Impact of Highly Effective Therapies

What factors influence your choice of therapy at disease onset?

Multiple Choice Poll | 46 votes | 46 participants



slido

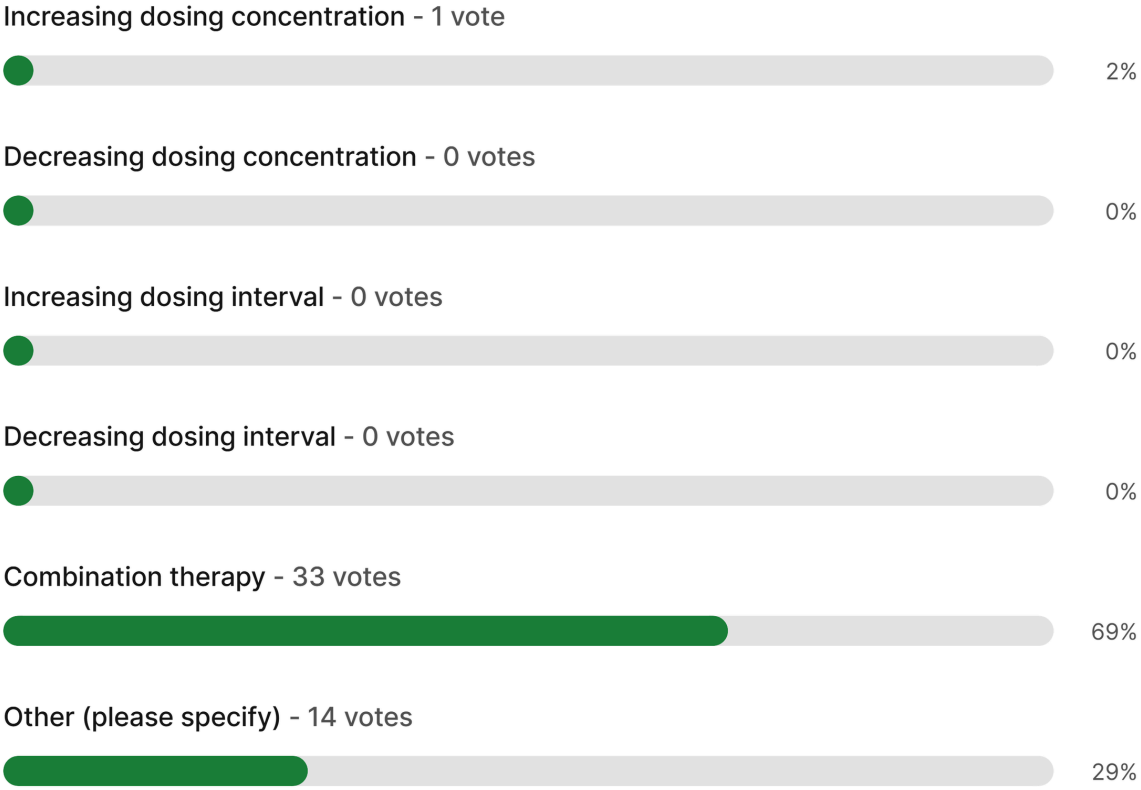
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session I: Optimizing Impact of Highly Effective Therapies

How do you modify your therapeutic regimens in patients with autoimmune comorbidities?

Multiple Choice Poll · 48 votes · 48 participants

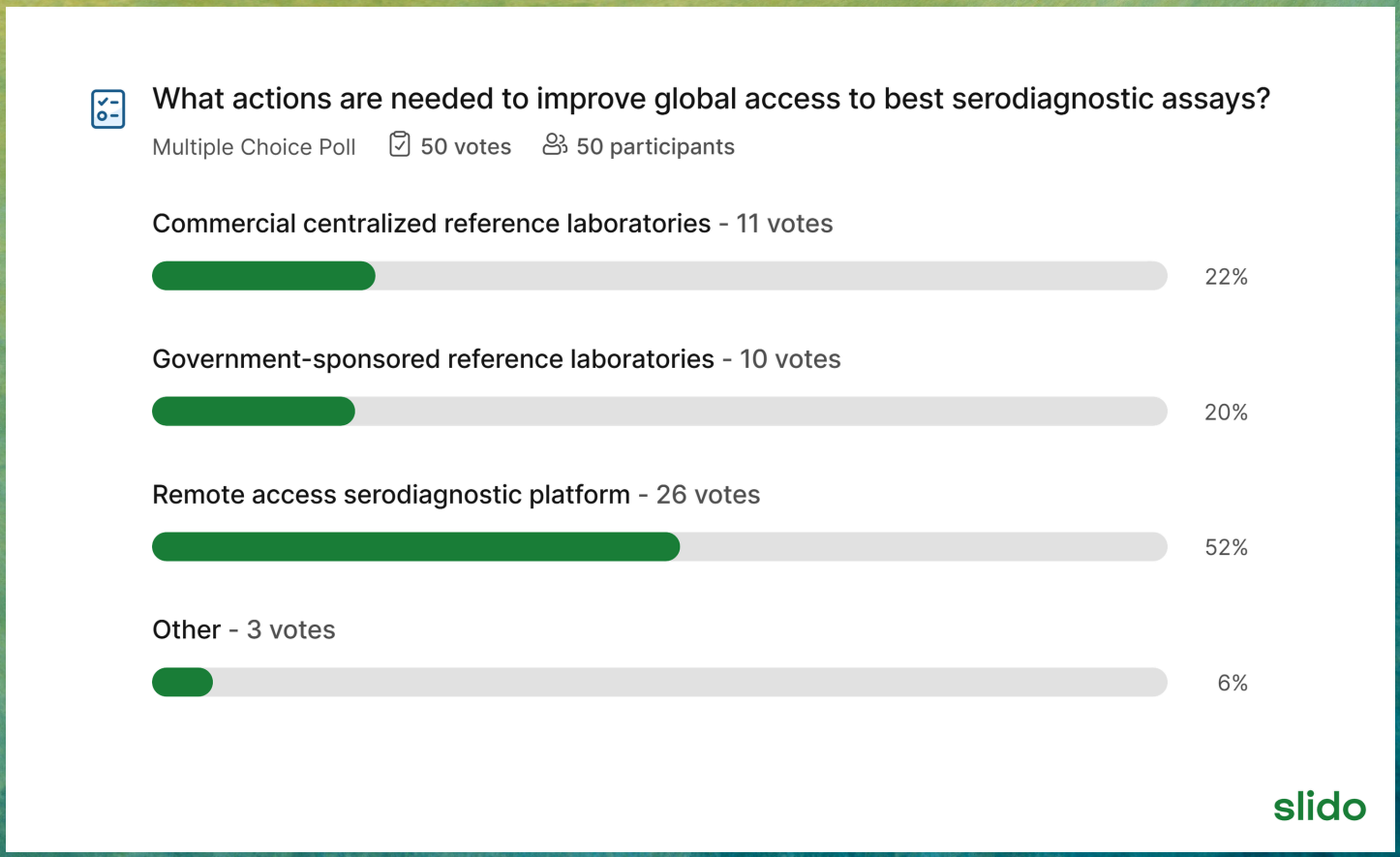


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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session II: Latest Insights into NMOSD Laboratory & Clinical Sciences



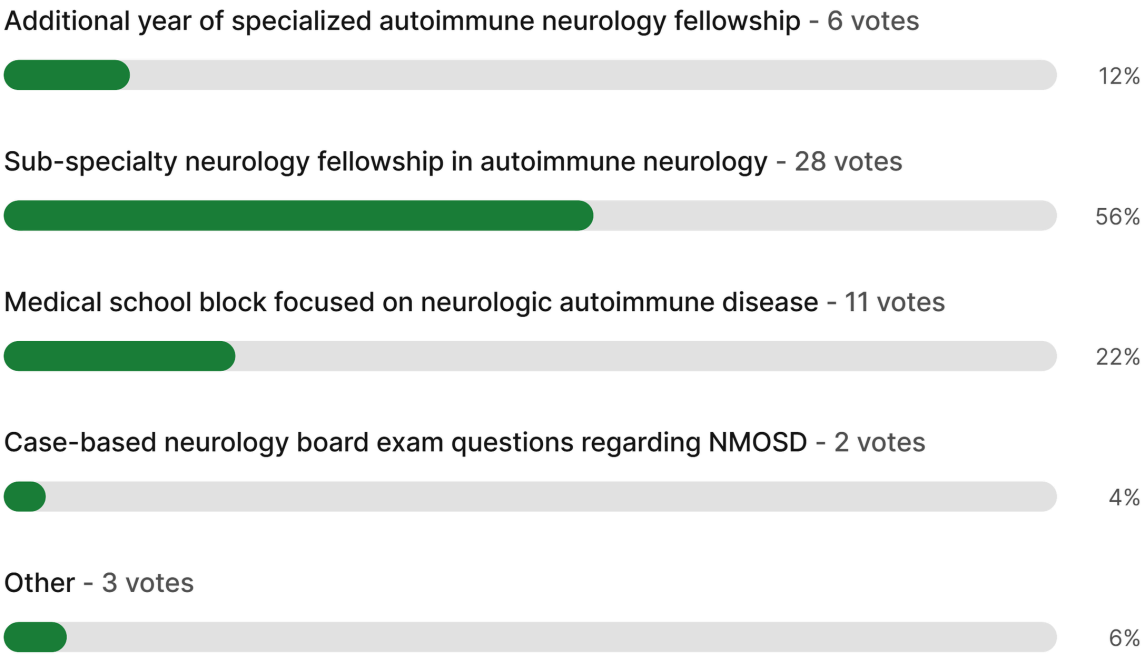
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session II: Latest Insights into NMOSD Laboratory & Clinical Sciences

What actions are best to improve trainee diagnostic accuracy in NMOSD?

Multiple Choice Poll | 50 votes | 50 participants



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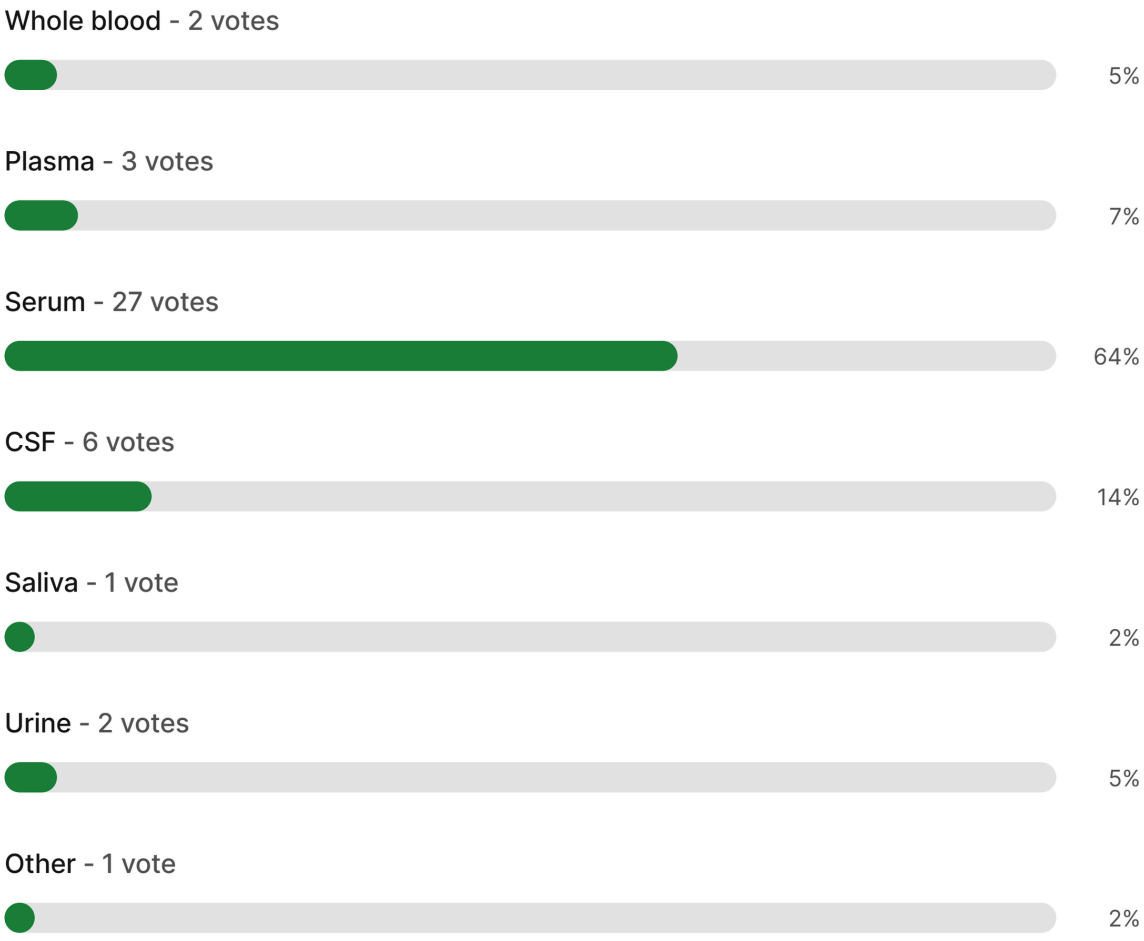
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session III: Emerging Molecular, Cellular & Imaging Biomarkers

The best biological sample for biomarker detection in NMOSD is:

Multiple Choice Poll | 42 votes | 42 participants



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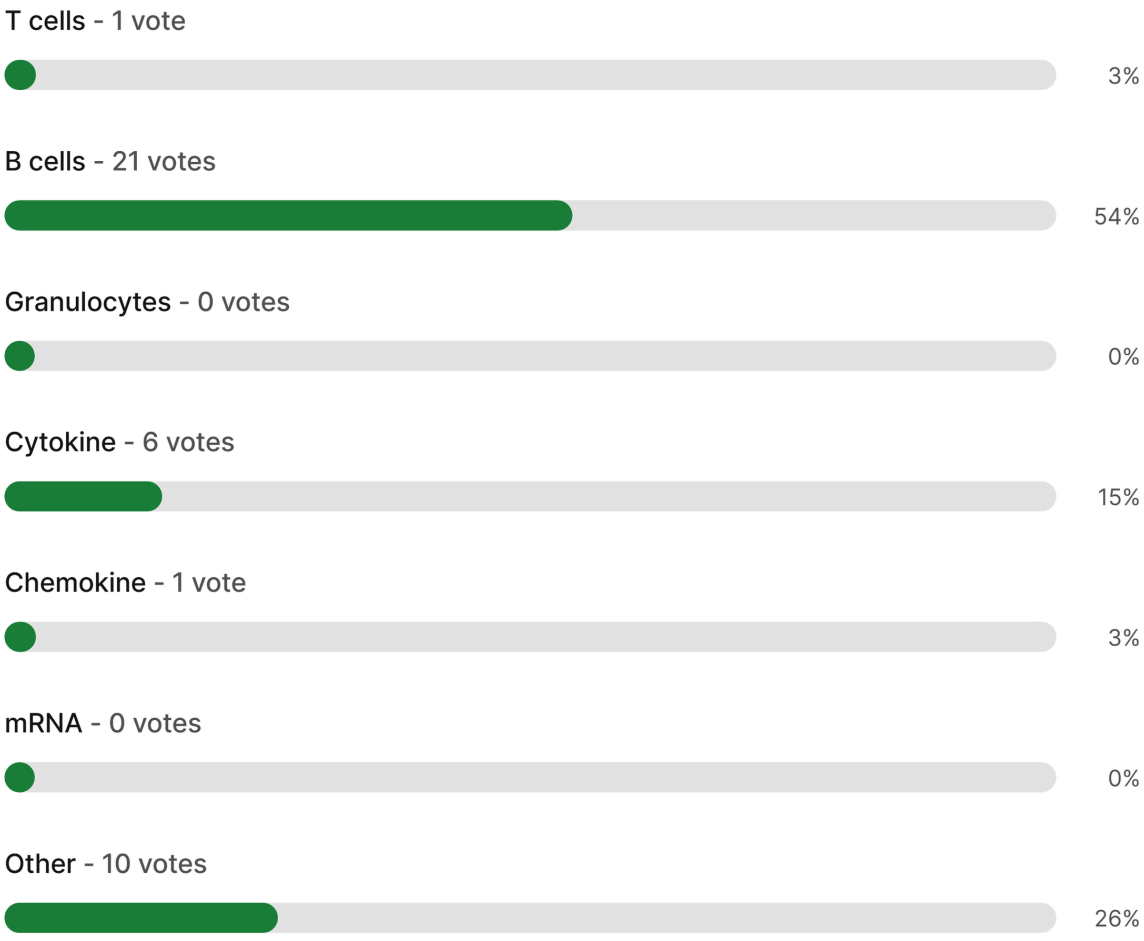
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session III: Emerging Molecular, Cellular & Imaging Biomarkers

The best immunological sample for biomarker detection in NMOSD is:

Multiple Choice Poll | 39 votes | 39 participants

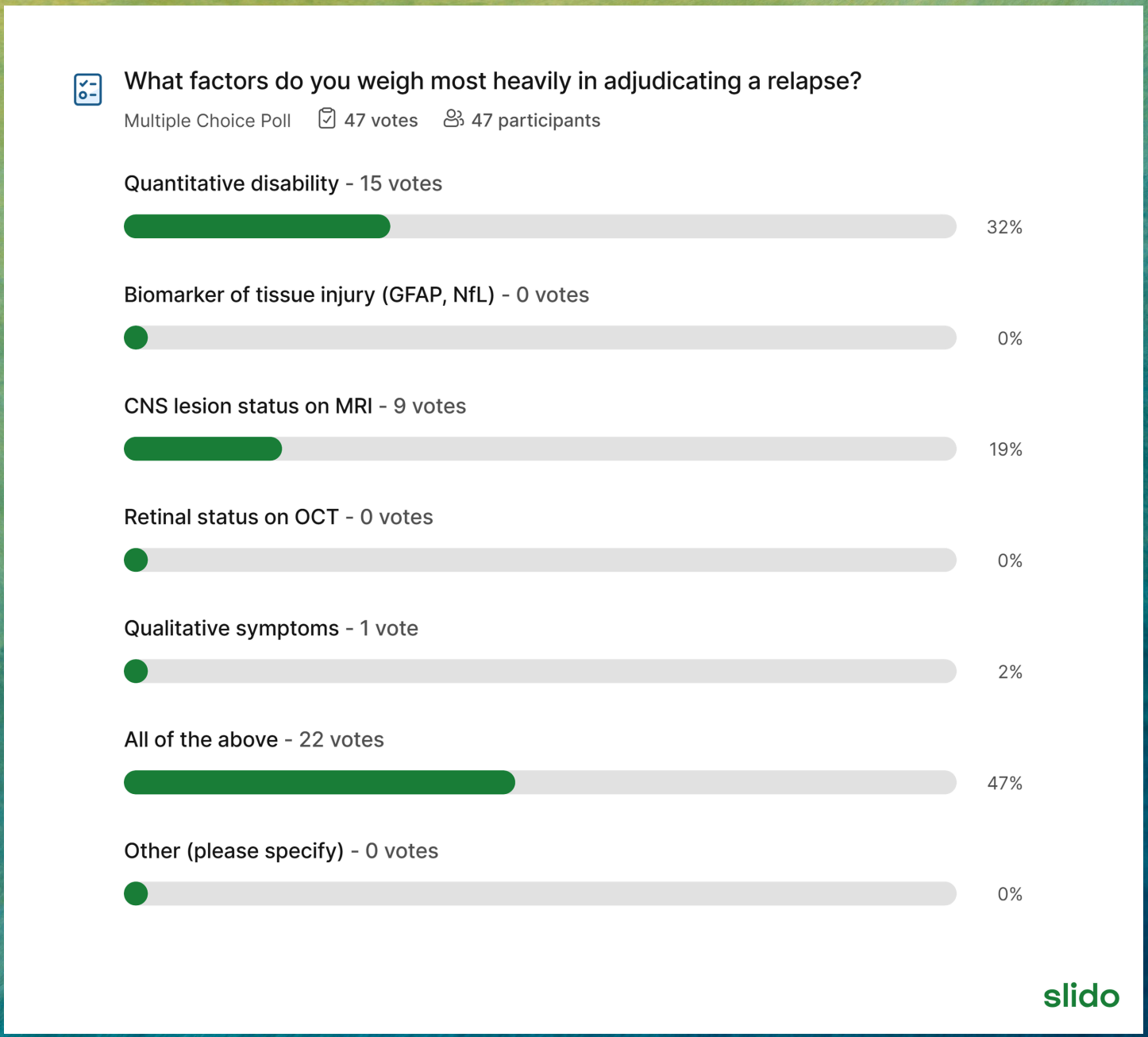


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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

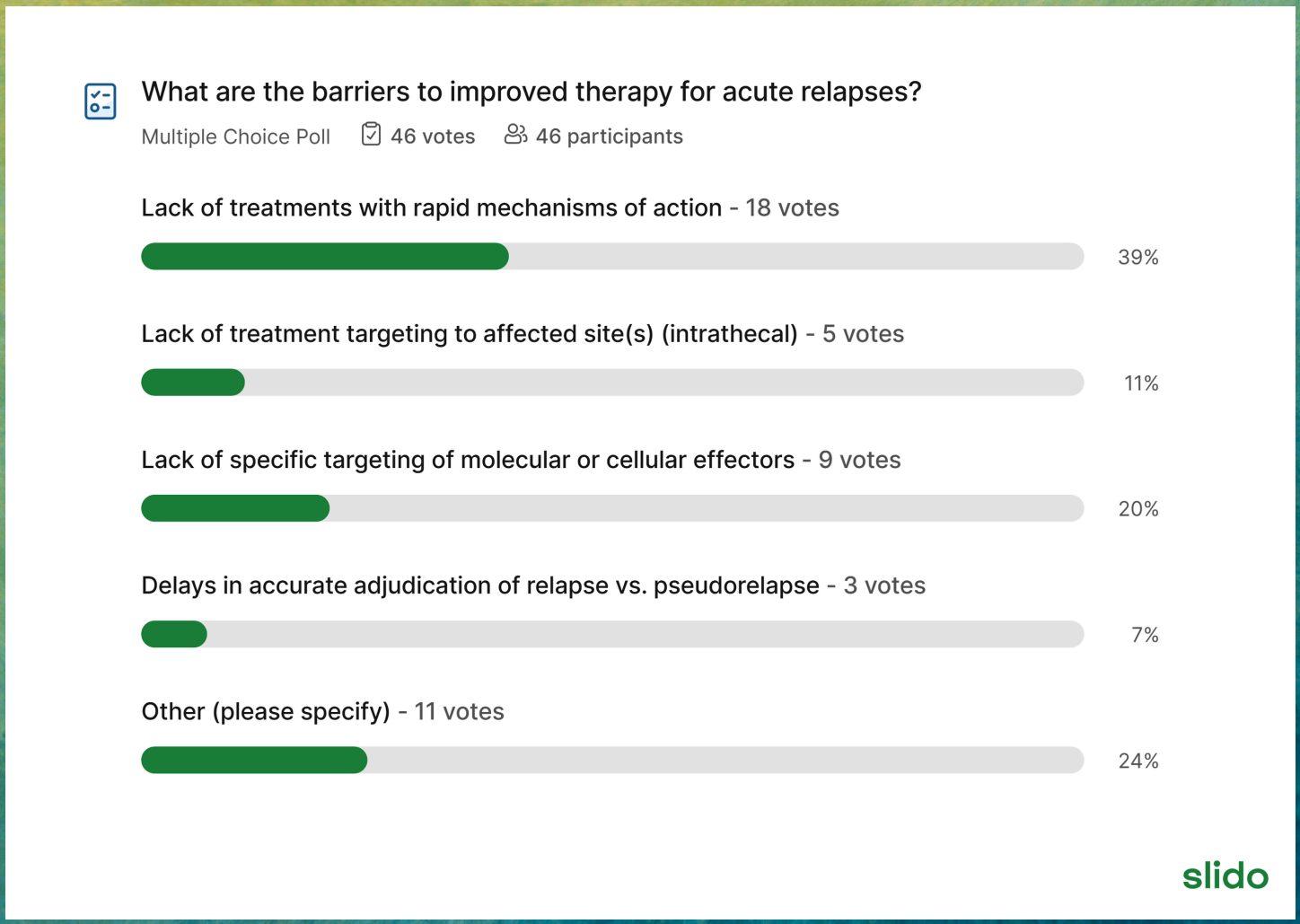
Session IV: Improving Rescue Interventions for Acute Relapse



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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session IV: Improving Rescue Interventions for Acute Relapse



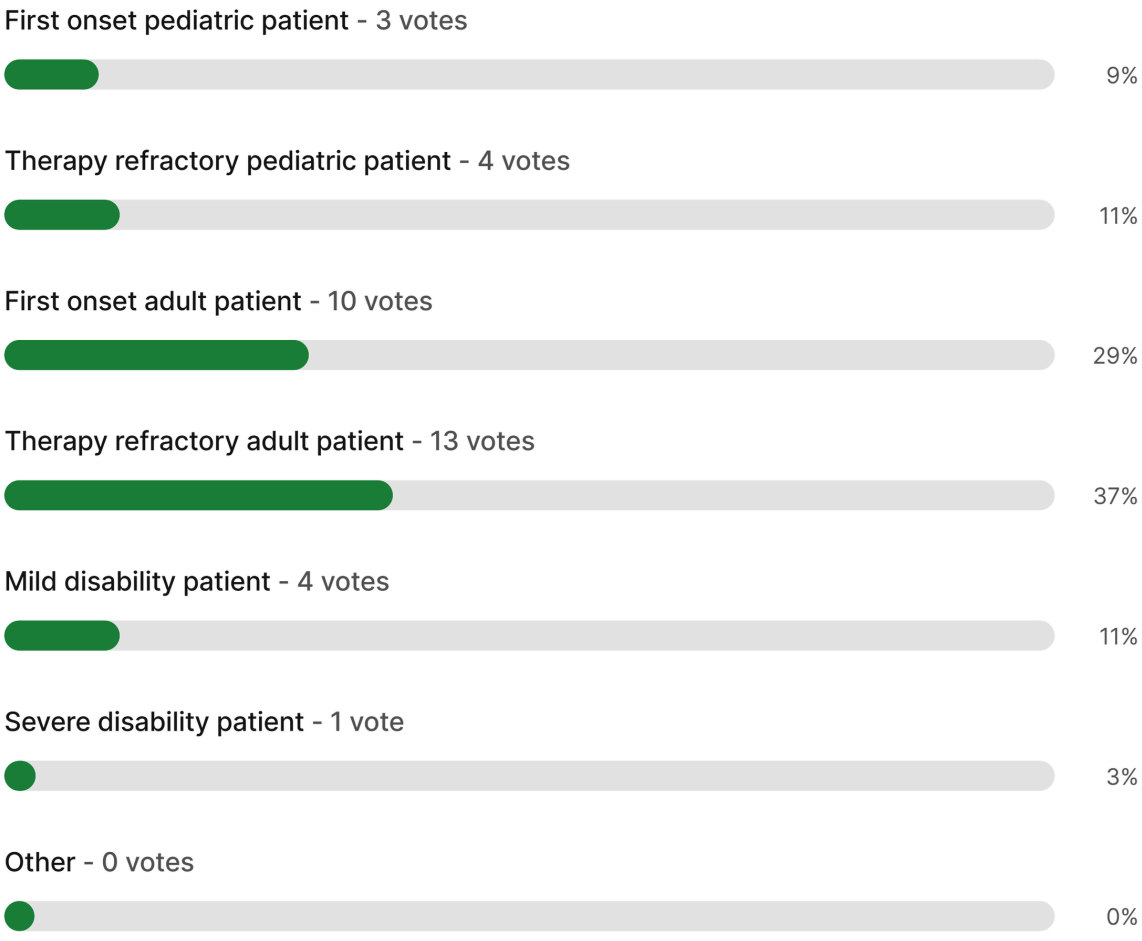
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session V: Accelerating Toward Curative Therapeutics

Which of your patients would be best suited to consider tolerization therapy?

Multiple Choice Poll | 35 votes | 35 participants



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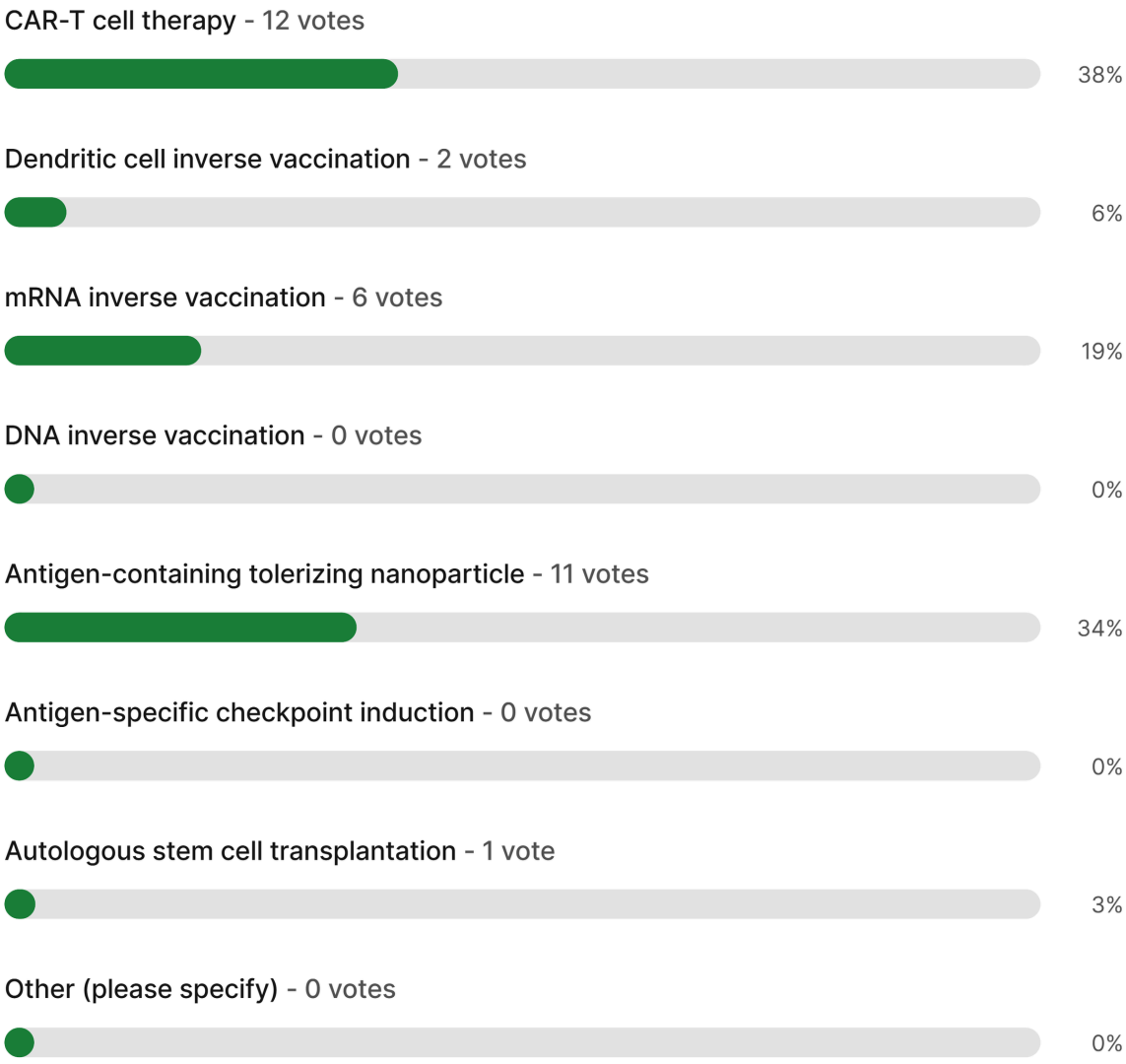
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LIVE ROUNDTABLE CONFERENCE SURVEY RESULTS

Session V: Accelerating Toward Curative Therapeutics

Which tolerization technology do you feel is most promising to succeed?

Multiple Choice Poll | 32 votes | 32 participants

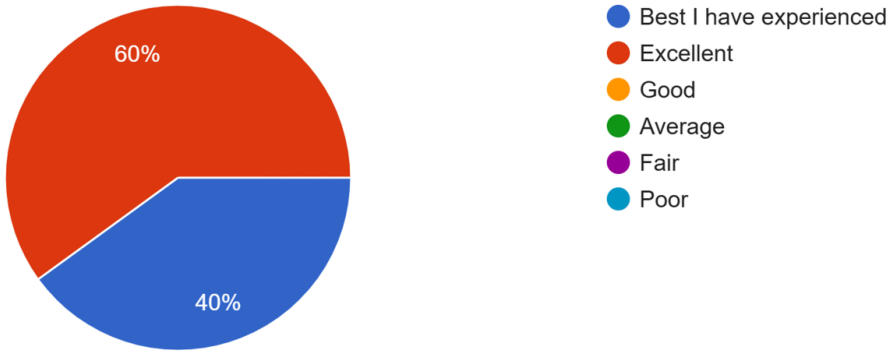


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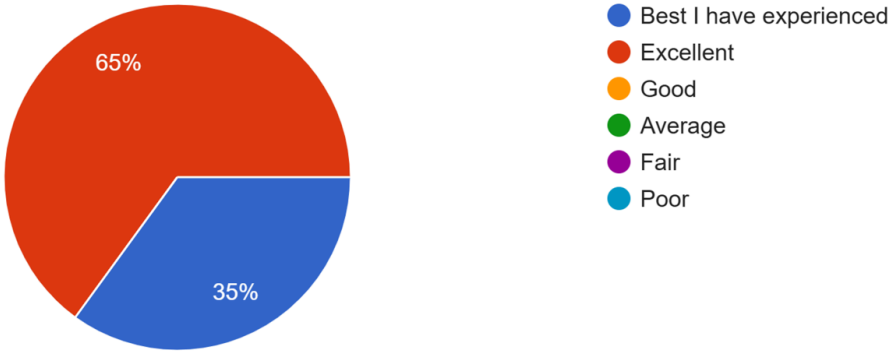
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

Overall, the logistics for this conference were:



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Overall, the collaborative spirit for this conference was:

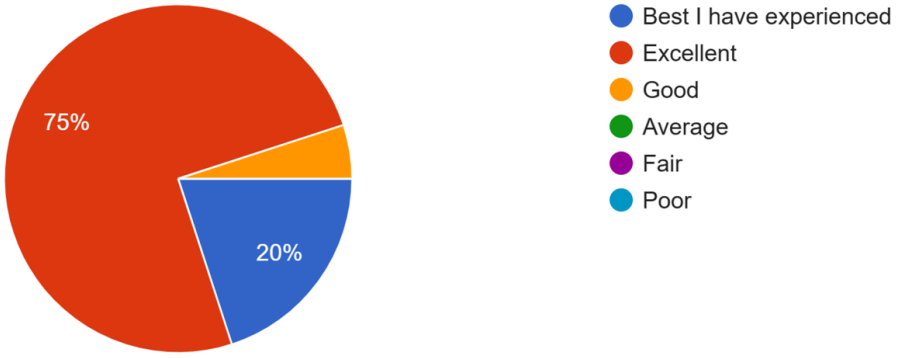


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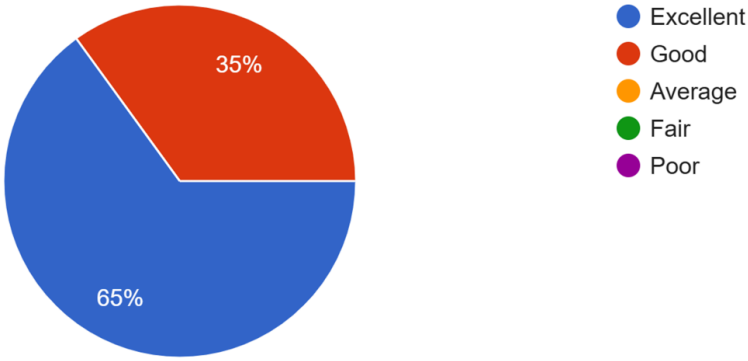
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

Overall, the presentation content and discussion was:



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During this conference, my opportunities for participation and input were:

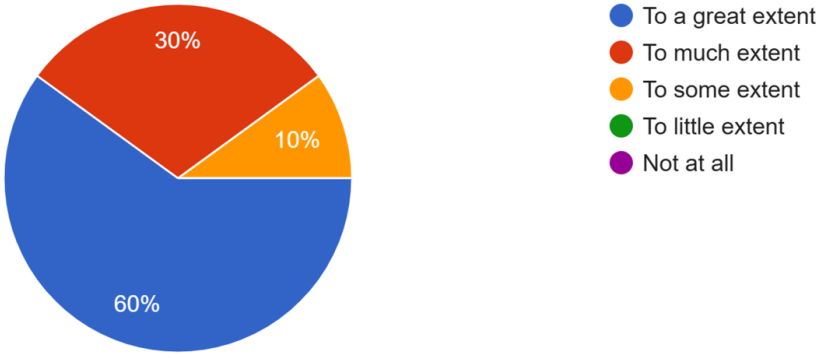


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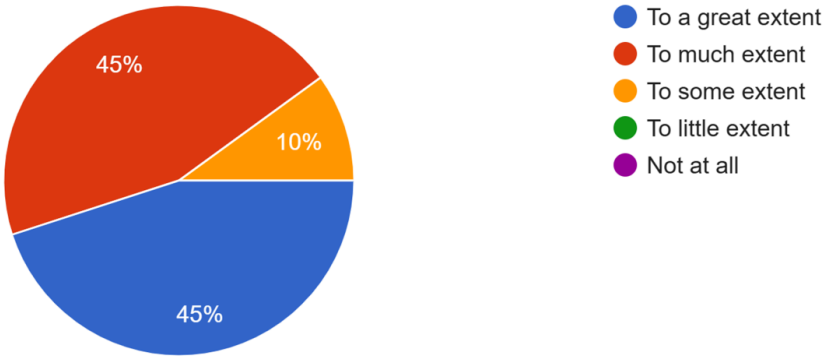
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

The conference increased my awareness of current scientific research in NMOSD:



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The conference increased my awareness of current clinical practice in NMOSD:

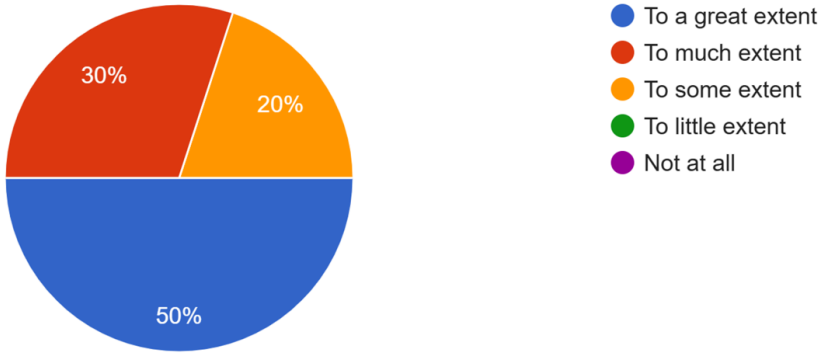


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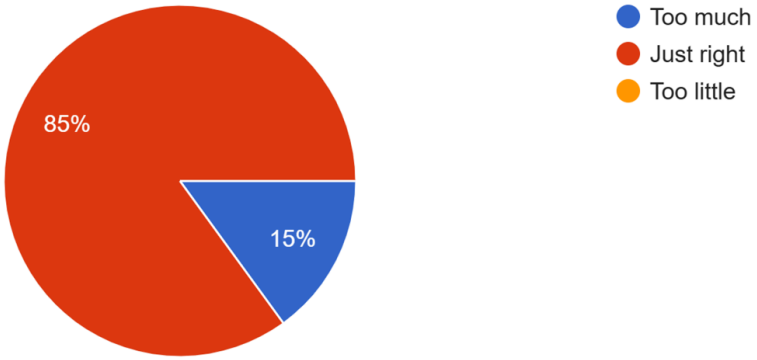
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

I plan to apply presentation content in my professional role(s):



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The amount of information presented and discussed was:



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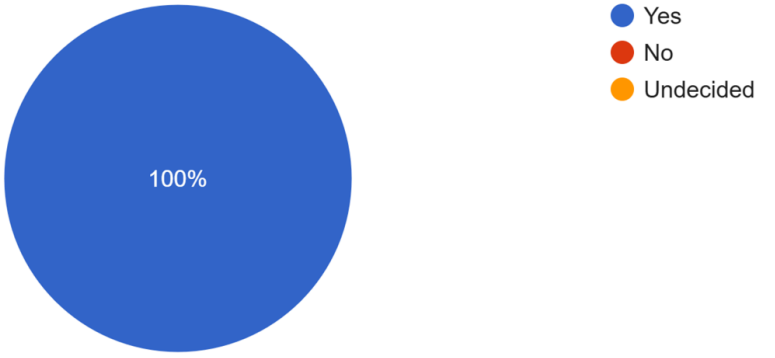
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

Would you prioritize attending this conference annually?



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Would you recommend attendance of this conference to a colleague?

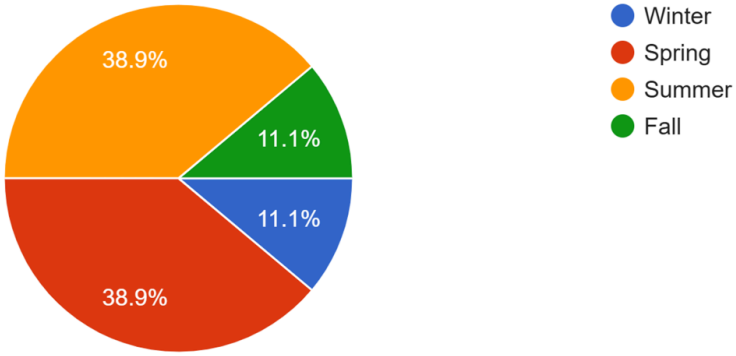


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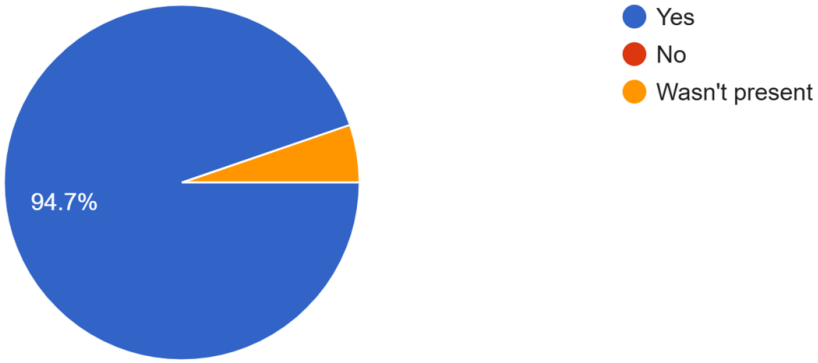
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

What time of year is most feasible for you to attend?



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Did you find the Opening Session informative?

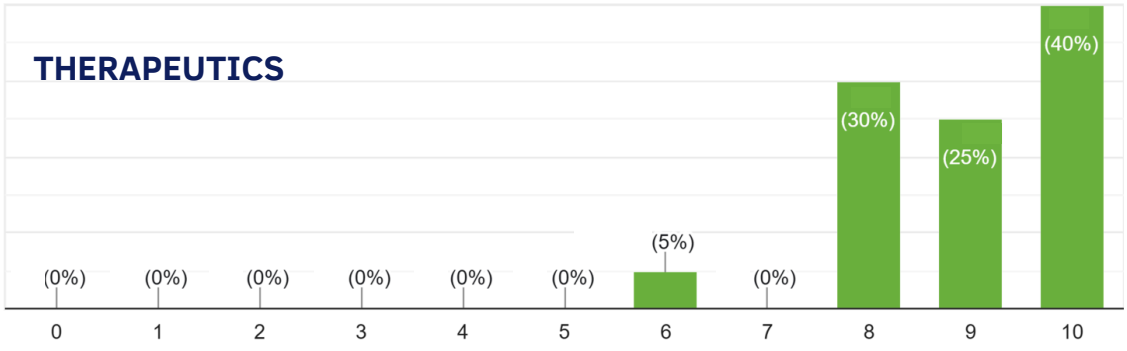


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POST ROUNDTABLE CONFERENCE SURVEY RESULTS

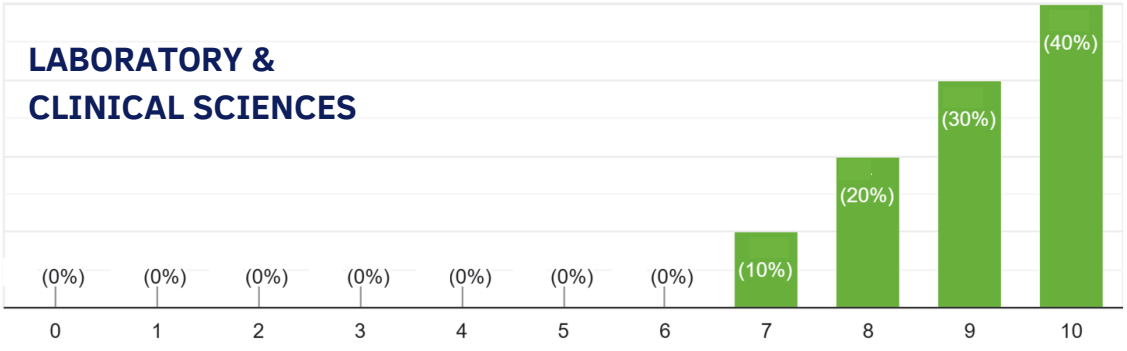
Please rate the content of Session I for its up-to-date information:



0=Poor
10=Outstanding

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Please rate the content of Session II for its up-to-date information:

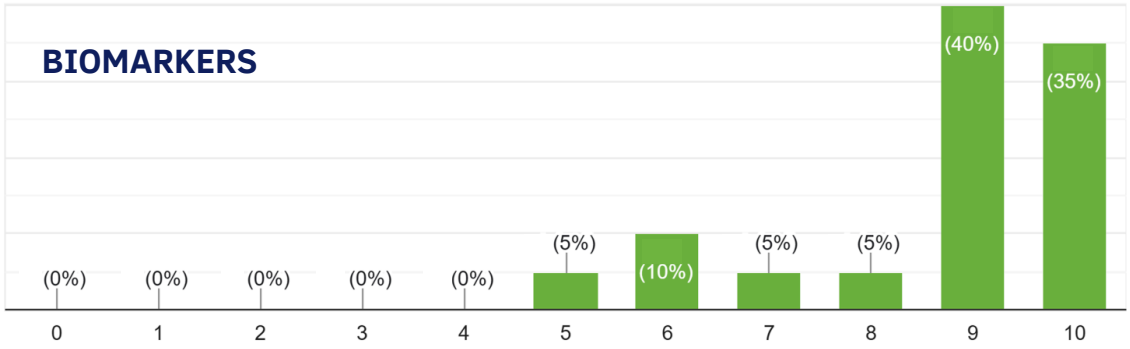


0=Poor
10=Outstanding

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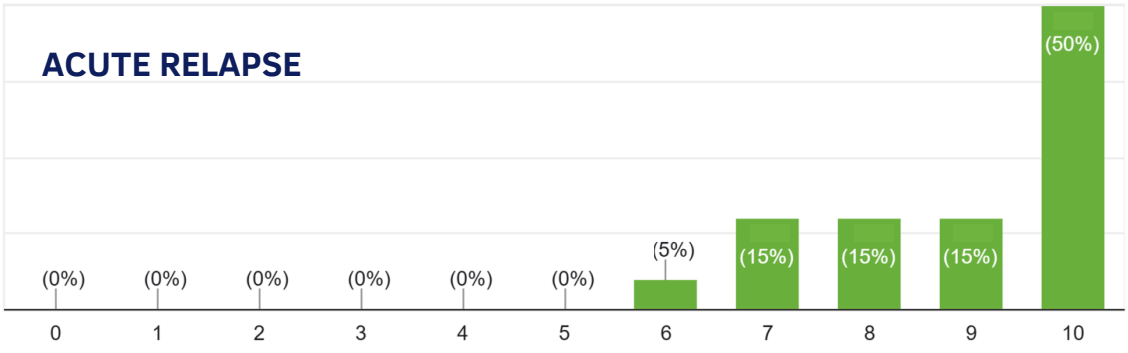
POST ROUNDTABLE CONFERENCE SURVEY RESULTS

Please rate the content of Session III for its up-to-date information:



0=Poor
10=Outstanding

Please rate the content of Session IV for its up-to-date information:

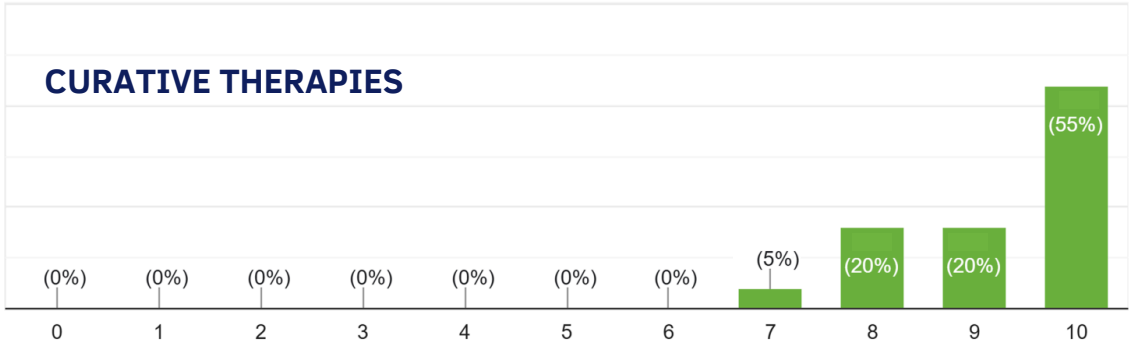


0=Poor
10=Outstanding

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POST ROUNDTABLE CONFERENCE SURVEY RESULTS

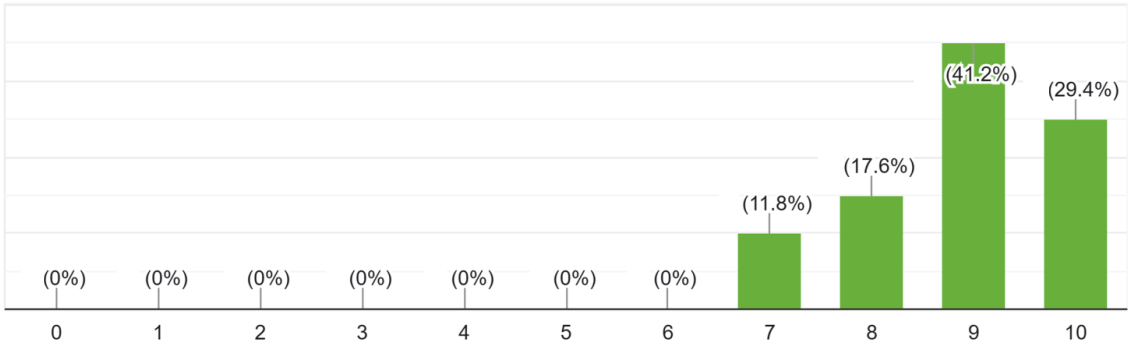
Please rate the content of Session V for its up-to-date information:



0=Poor
10=Outstanding

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Please rate the content of the Consilience & Next Steps Session for its up-to-date information:



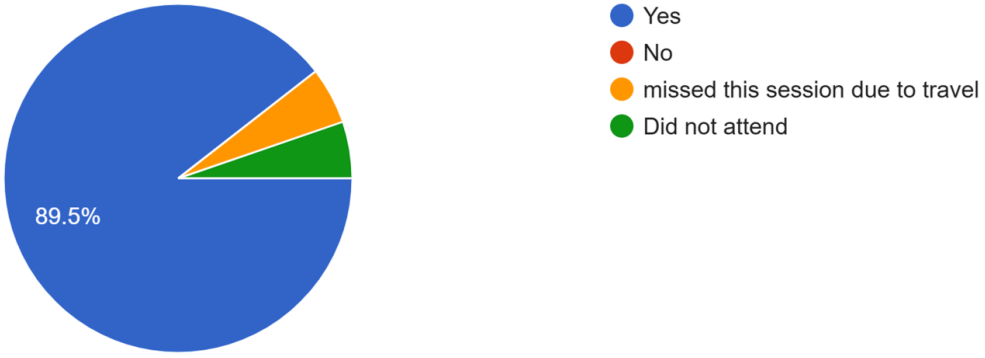
0=Poor
10=Outstanding

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POST ROUNDTABLE CONFERENCE SURVEY RESULTS

Did you find the Consensus Session informative?



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"It was a very successful event, and I know all my NMO colleagues enjoyed the opportunity to be together and catch up on what's going on in NMO and with each other."

-Brian Weinshenker, MD
University of Virginia



2024 GJCF NMO Roundtable Conference



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2024 GJCF NMO Roundtable Conference
Los Angeles / August 2-4, 2024

Selected GJCF Website Links:

Homepage:	https://guthyjacksonfoundation.org/
2024 Roundtable:	https://guthyjacksonfoundation.org/events/2024-international-nmo-roundtable-conference/
Research Radar:	https://guthyjacksonfoundation.org/research/
Breakthroughs:	https://guthyjacksonfoundation.org/priorities/
Tolerization:	https://guthyjacksonfoundation.org/priorities/pioneer/
GJCF NMO App:	https://guthyjacksonfoundation.org/nmoresources/
Newly Diagnosed:	https://guthyjacksonfoundation.org/newly-diagnosed/
10 Steps Forward:	https://guthyjacksonfoundation.org/10-steps-forward/
Patient Guide:	https://guthyjacksonfoundation.org/tools-for-download/
Advocacy:	https://guthyjacksonfoundation.org/priorities/promote/
Hear My Voice:	https://nmostories.org/
Tx Pocket Guide:	https://guthyjacksonfoundation.org/therapeutics/

Selected GJCF Video Links:

The NMO Story:	https://guthyjacksonfoundation.org/videos/the-nmo-story/
Power of Rare:	https://guthyjacksonfoundation.org/videos/the-power-of-rare/
Behind the Mystery:	https://guthyjacksonfoundation.org/videos/neuromyelitis-optica-behind-the-mystery-of-nmo-preview/
NMO Tolerization:	https://guthyjacksonfoundation.org/videos/nmo-tolerization/
Pioneering a New Scientific Research Model	https://guthyjacksonfoundation.org/videos/scientific-research-model/

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