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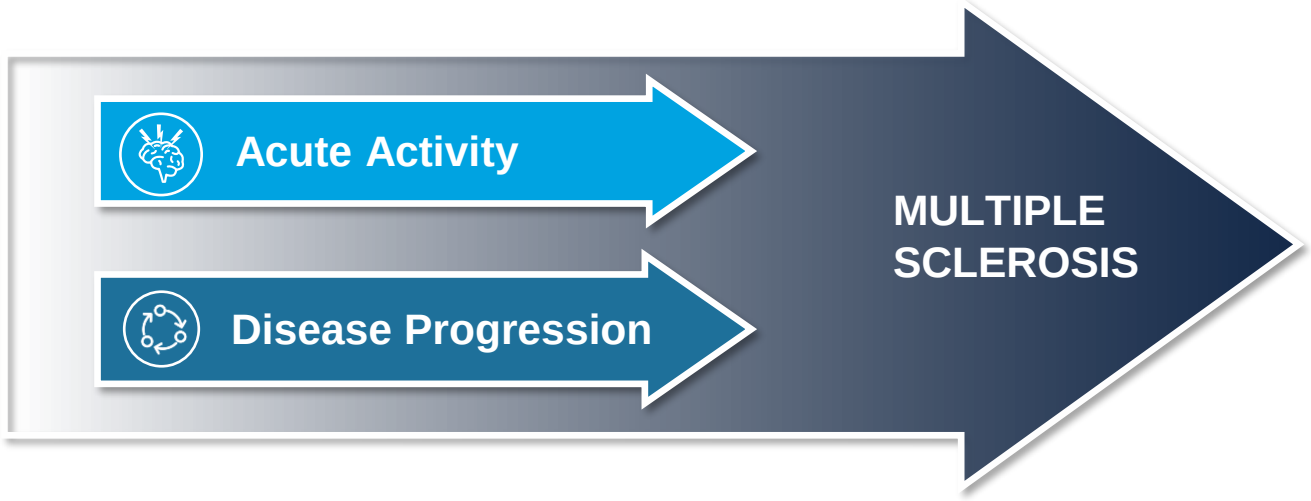
DISEASE PROGRESSION IN MULTIPLE SCLEROSIS

This is a medical resource for scientific information and is intended for healthcare providers practicing in the United States.
Current as of July 2024.

MS CLINICAL COURSE MAY BE BETTER CHARACTERIZED AS A CONTINUUM

MS may not consist of a 2-phase disease, but rather a layering of **activity and progression *across a continuum***.[1]



Important Implications[1,2]

Elucidating key mechanisms that underpin disease progression and identifying appropriate measures to quantify disease pathology has implications for:

Treatment targets

Regulatory decision-making

Clinical care
Earlier identification of disease progression

MS, multiple sclerosis.

1. Patel J, et al. Pract Neurol 2023; 2. Krieger SC, et al. Neurol Neuroimmunol Neuroinflamm 2016;3(5):e279; 3. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88.

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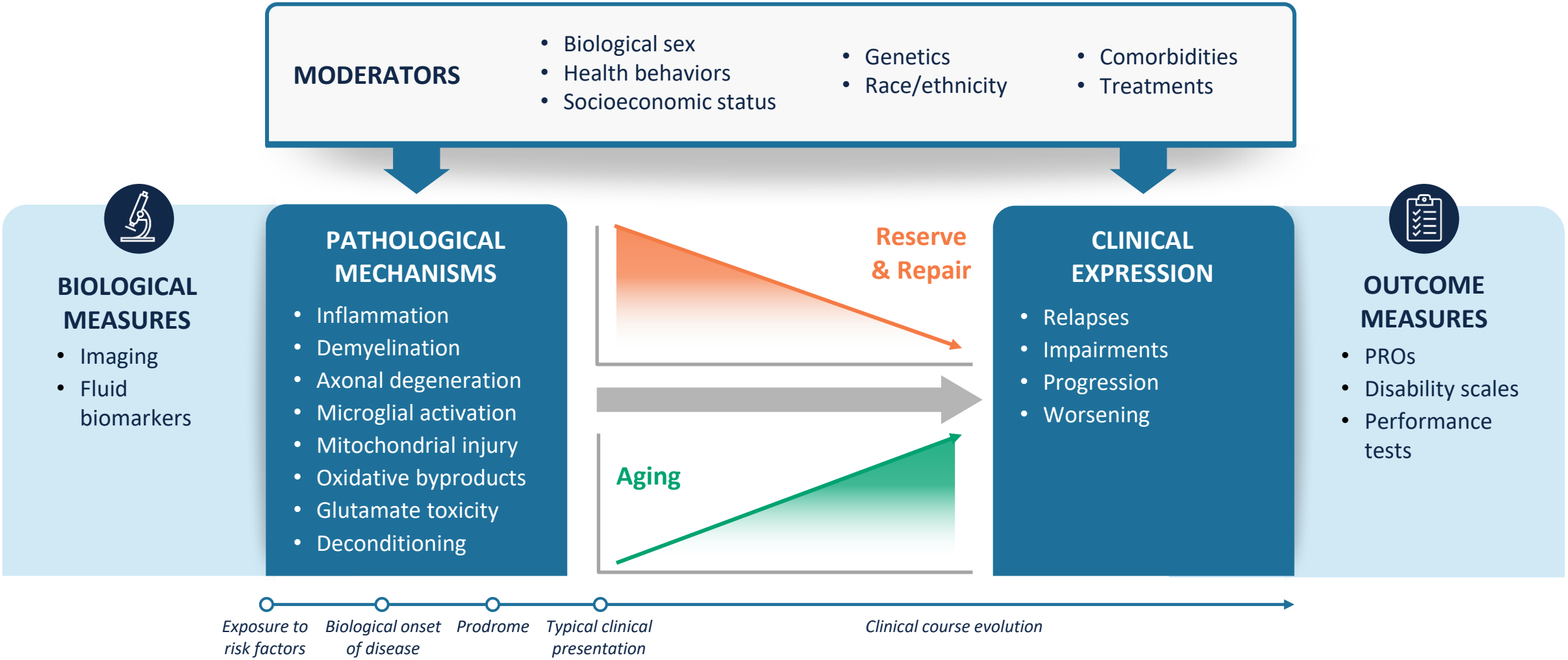
INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



MS, multiple sclerosis; PROs, patient-reported outcomes.

1. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88.

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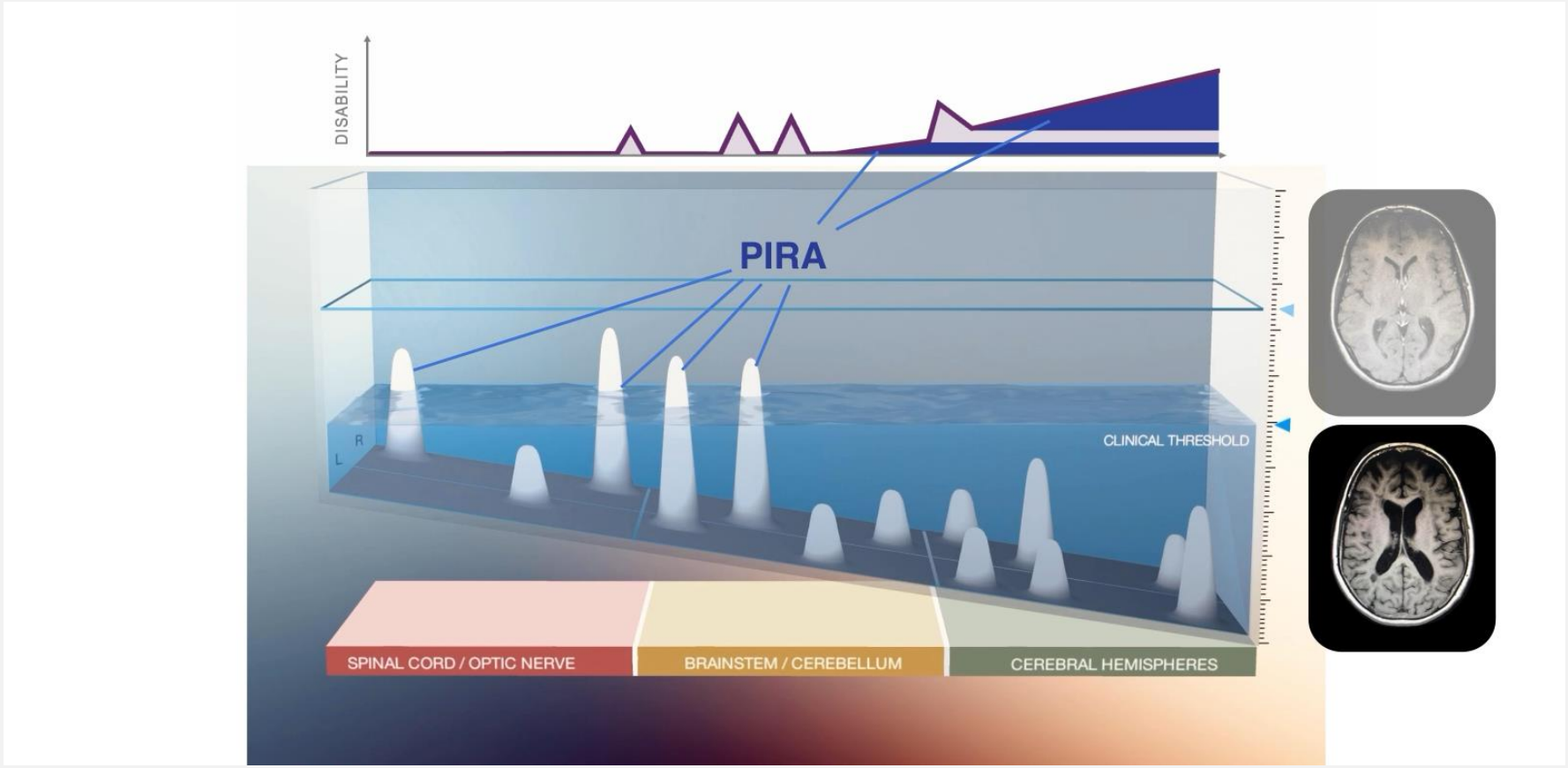
HOW CAN WE CONCEPTUALIZE THE EVOLUTION OF MS DISEASE?

The MS Topographical Model



MS, multiple sclerosis.

Krieger SC, et al. Neurol Neuroimmunol Neuroinflamm 2016;3(5):e279.

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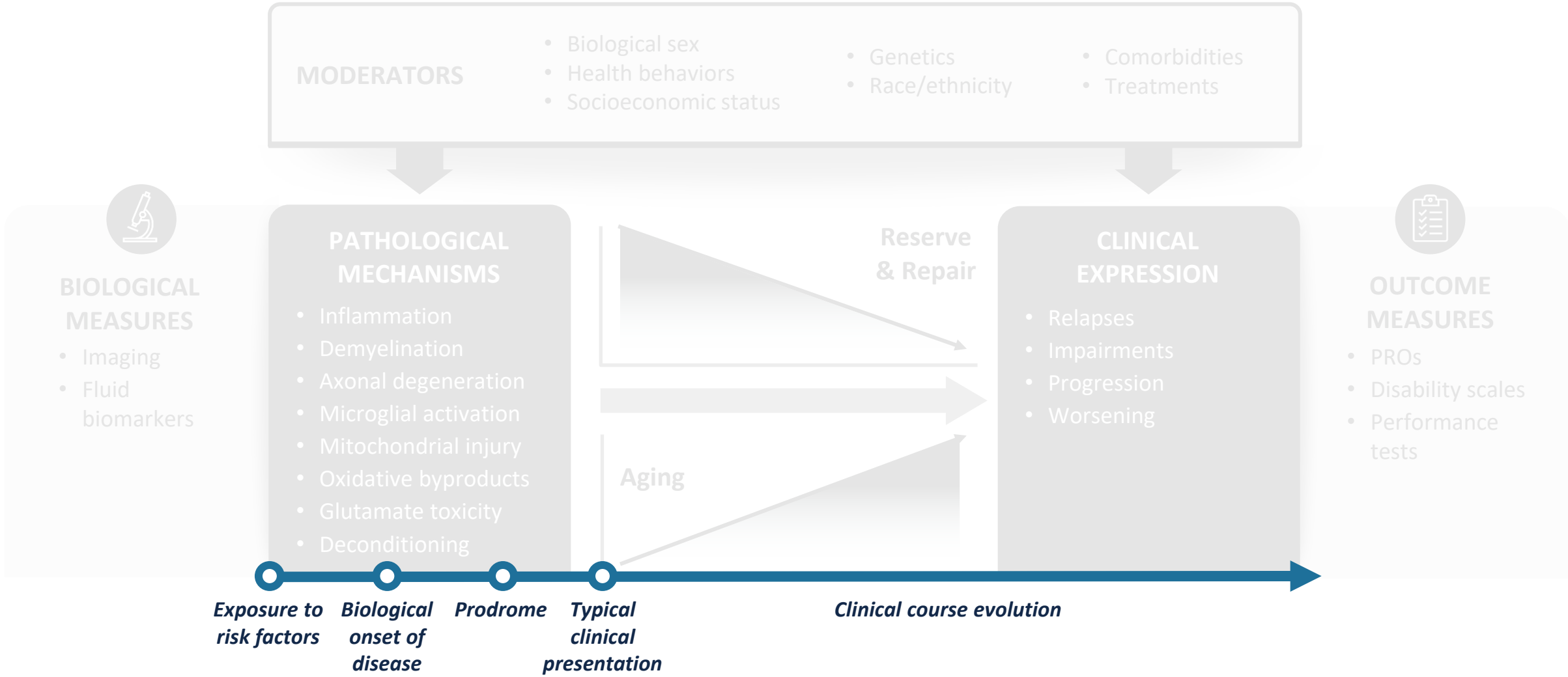
WHEN DOES DISABILITY PROGRESSION START?

INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



MS, multiple sclerosis; PROs, patient-reported outcomes.

1. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88.

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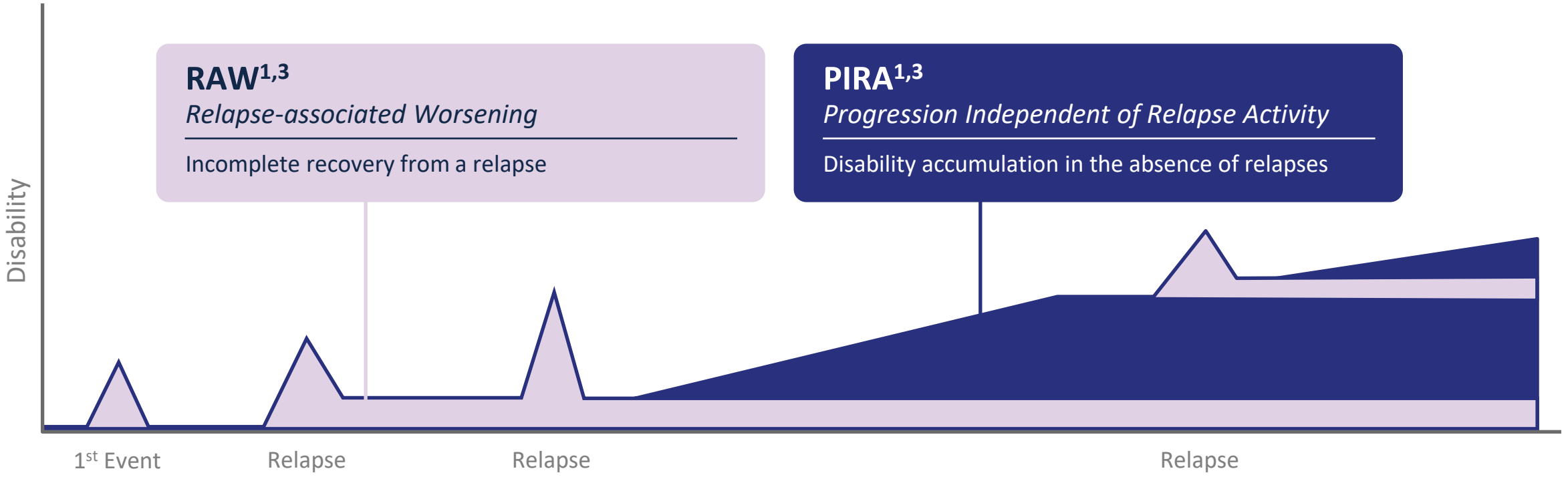
DISABILITY PROGRESSION CAN OCCUR EARLY, AND MAY ACCUMULATE IN TWO DISTINCT WAYS[1,2]



Although there is growing evidence that PIRA is a significant contributor to disability accumulation in MS, there is currently no harmonized definition of PIRA.[4]

MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening.

1. Cree BAC, et al. Ann Neurol 2019;85(5):653-666; 2. Tur C, et al. JAMA Neurol 2023;80(2):151–160; 3.Portaccio E, et al. Brain 2022;145(8):2796-2805; 4. Müller J, et al. JAMA Neurol 2023;80(11):1232-1245.

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UCSF EPIC COHORT STUDY: RELAPSE ACTIVITY WAS NOT THE MAIN DRIVER OF LONG-TERM DISABILITY[1]

PATIENT POPULATION

- **(n=480)**
- **UCSF MS-EPIC Dataset**
- Patients with **CIS or RRMS**
- Followed for up to 10 years

STUDY DESIGN

- Prospective, longitudinal, observational cohort

RESULTS

RELAPSES WERE NOT ASSOCIATED WITH:

- **Long-term disability worsening* (p=0.736)**
- **Confirmed disability worsening* (p=0.551)**

EVIDENCE IN CONTEXT

Data were consistent with 2 simultaneous processes[1,2]:

Focal demyelinating lesions visible on brain and spinal cord MRI that correlate with relapses

A more diffuse process that contributes to brain and spinal cord atrophy

- This is largely independent of relapses or focal lesion formation
- May be the most important contributor to long-term MS disability

*__Confirmed disability worsening__: worsening maintained for 2 consecutive annual visits; __Long term disability worsening__: increase in disability between baseline and the midpoint of the study, with confirmation of worsening 5 years thereafter. Disability was measured by EDSS, T25FW, 9HPT, and SDMT.

CIS, clinically isolated syndrome; EPIC, expression/genomics, proteomics, imaging, and clinical; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting MS; UCSF, University of California, San Francisco.

1. Cree BAC, et al. Ann Neurol 2019;85(5):653-666. 2. Bischof A, Papinutto N, Keshavan A, et al. Annals of Neurology. 2022;91(2):268-281.

PIRA WAS SEEN EARLY IN THE MS DISEASE COURSE IN A COHORT STUDY[1]

PATIENT POPULATION

- **(n=1128)**
- **MS Center of Catalonia**
- Patients with a **first demyelinating event**
- Followed for a median of 10.5 years

METHODS

- Retrospective analysis

RESULTS

*DISABILITY & PIRA**

37% (n=419) had **at least 1 confirmed disability accumulation (CDA)†**

66% — **277 of 419 had at least 1 PIRA event**
86 patients (31%) developed PIRA within the first 5 years of the disease.

34% — **142 of 419 had all their CDA episodes qualify for RAW**

26x greater risk of developing severe disability (EDSS 6)

In patients with PIRA within the first 5 years of MS compared with patients whose first PIRA appeared later in the disease. (HR, 26.21; 95% CI, 2.26–303.95; P=0.009)

*PIRA: experiencing CDA in the EDSS scale at 6 months during a period free of relapses. A period free of relapses was the time between 2 consecutive relapses, starting 3 months after a relapse (or 6 months after the first dymyelinating event).
†CDA: increase in the EDSS scores of 1.5, 1.0, or 0.5 if the baseline/rebaseline EDSS score was, respectively, 0, 1.0 to 5.0, or greater than 5.0.
CDA, confirmed disability accumulation; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening.

1. Tur C, et al. JAMA Neurol 2023;80(2):151–160.

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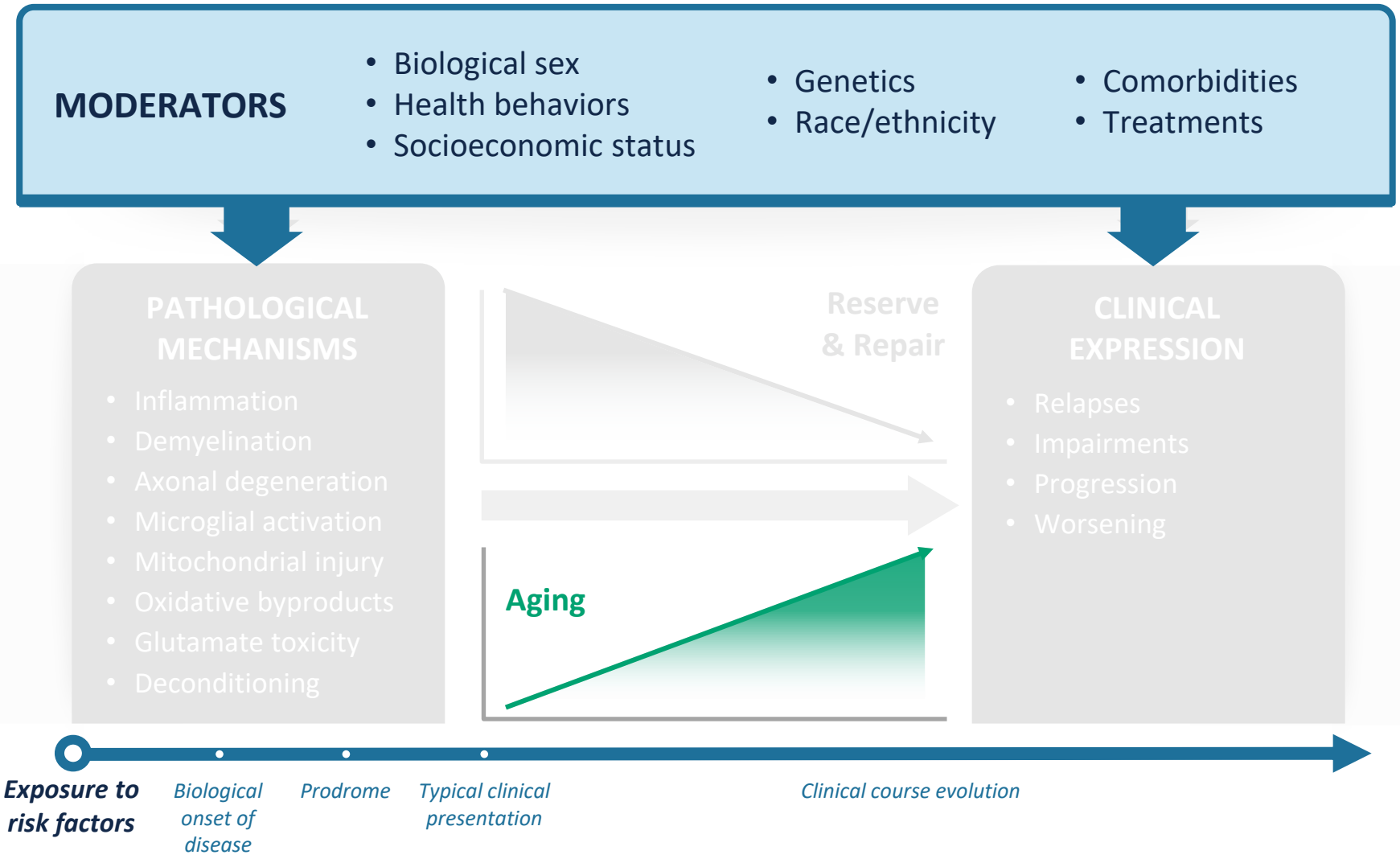
WHAT FACTORS CAN CONTRIBUTE TO DISEASE PROGRESSION?

INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



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1. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88.

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SOME FACTORS THAT MAY CONTRIBUTE TO MS DISEASE COURSE INCLUDE:

Age[1]

- Older age at diagnosis
- Older chronological age
- Age-associated decrease in reserve and repair capacity
- Immune senescence

Sex[1]

- Males may have more severe disease progression at younger ages
- However, many women catch up post-menopause

Race/Ethnicity[2-5]

- Black patients may exhibit greater pathological/MRI biomarkers of progression and disease activity

Social Determinants of Health[6]

- Ethnic/racial disparities and inequities
- Socioeconomic status
- Healthcare access
- Health literacy

Genetic Factors[7,8]

- HLA-associated genetic variants increase risk for developing MS
- Certain gene alleles (rs10191329, rs149097173) may contribute to disease severity

Environmental Factors[9,10]

- Low vitamin D levels
- Low sun exposure
- Epstein Barr virus infection
- Smoking

Duration of Disease[11]

- Longer duration of disease

Comorbidities[12,13]

- Comorbidities, such as vascular disease (e.g., cardiovascular disease, hypertension, diabetes) may contribute to disability progression in MS

HLA, human leukocyte antigen; MS, multiple sclerosis; MRI, magnetic resonance imaging.

1. Graves JS, et al. Lancet Neurol 2023;22(1):66-77; 2. da Gama PD, et al. Biomed Res Int 2015;2015:217961; 3. Xue H, et al. Mult Scler Relat Disord 2023 Nov;79:105047; 4. Howard J, et al. PLoS One 2012;7(8):e43061; Erratum in: PLoS One 2013;8(6); 5. Gray-Roncal K, et al. Neurology 2021;97(9):e881-e889; 6. Okai AF, et al. Neurology 2022;98(24):1015-1020; 7. Isobe N, et al. JAMA Neurol 2016;73(7):795-802; 8. International Multiple Sclerosis Genetics Consortium & MultipleMS Consortium. Nature 2023;619(7969):323-331; 9. Pitt D, et al. Neurol Neuroimmunol Neuroinflamm 2022;9(6):e200025; 10. Wu J, et al. Eur J Neurol. 2024; 31:e16269; 11. Stanikić M, et al. Mult Scler Relat Disord 2022;67:104084; 12. Marrie RA, et al. Neurology 2010;74(13):1041-7; 13. Nociti V, et al. J Pers Med 2023;13(11):1524.

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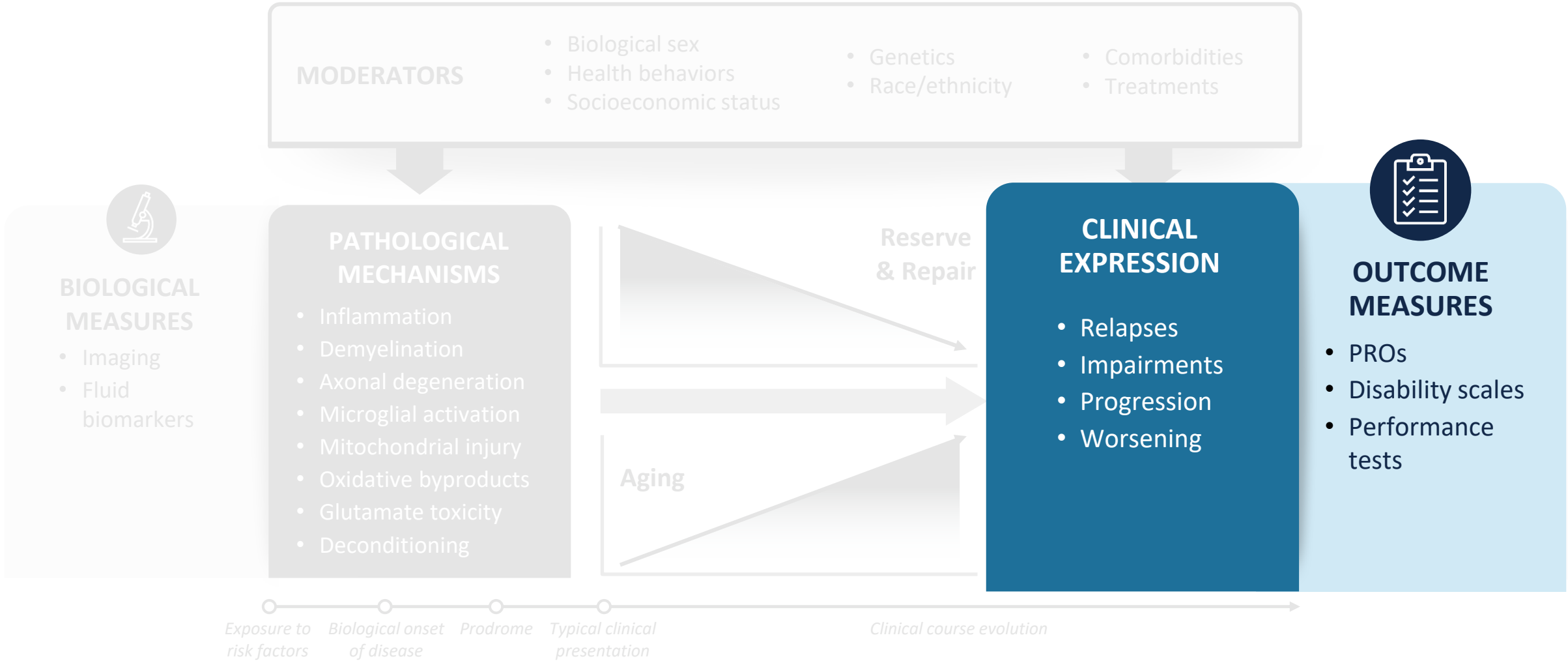
HOW DO YOU MONITOR DISABILITY PROGRESSION CLINICALLY?

INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



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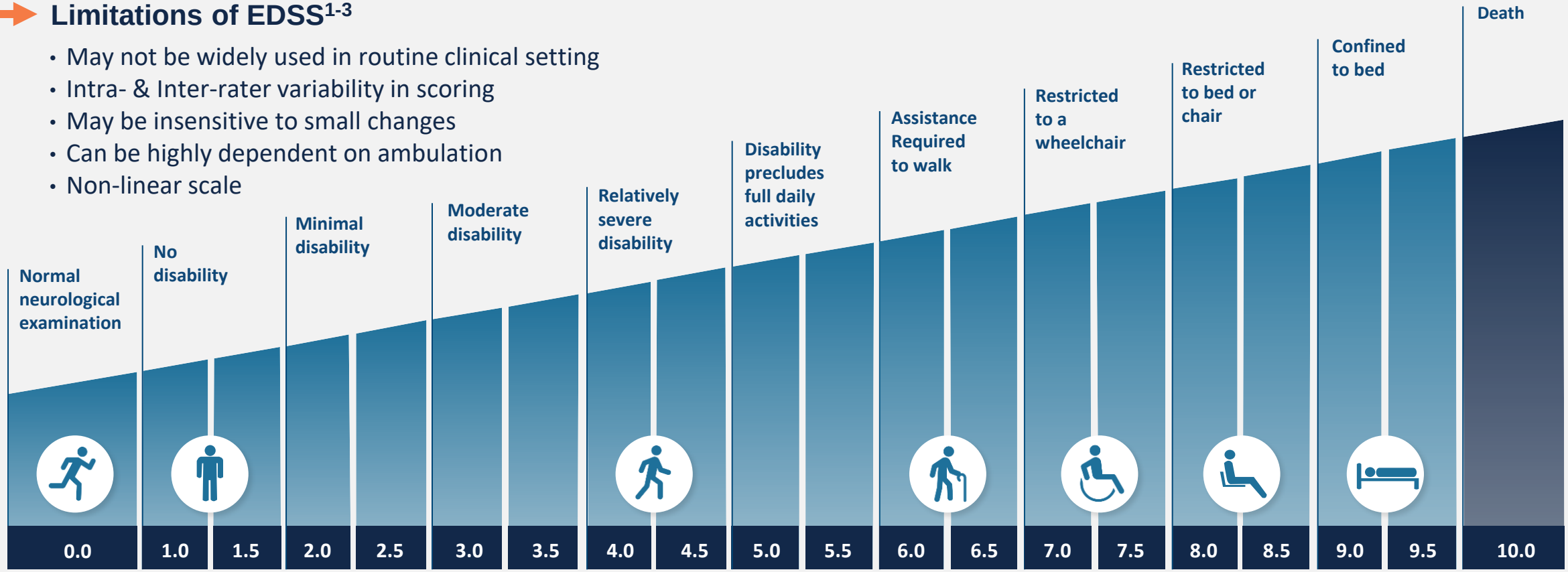
LIMITATIONS OF THE EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS is a Standard Disability Measure Used in Clinical Trials

Limitations of EDSS[1-3]

- May not be widely used in routine clinical setting
- Intra- & Inter-rater variability in scoring
- May be insensitive to small changes
- Can be highly dependent on ambulation
- Non-linear scale



Adapted from: Buzzard KA, et al. *Int J Mol Sci*. 2012;13:12665-12709.
EDSS, Expanded Disability Status Scale.
1. Krieger SC, et al. Mult Scler. 2022;28(14):2299-2303; 2. Kosa P, et al. Ann Clin Transl Neurol 2018;5(10):1241-1249; 3. Meyer-Moock S. BMC Neurology 2014, 14:58

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DIGGING DEEPER: EARLY AND REGULAR ASSESSMENT OF COGNITION AND FATIGUE MAY UNCOVER SUBTLE SIGNS OF PROGRESSION[1-3]

Progression may not be readily apparent from one clinic visit to another.[1]

For example, cognitive decline occurs over periods of 10–20 years and might not be as easily captured over a shorter period of time.

COGNITIVE IMPAIRMENTS[5,6]

43-70%

of people with MS have reported cognitive impairment

AAN Quality Measures Working Group:

- Clinical interview and standard neurological examination is **not sufficiently sensitive** to detect cognitive impairment in MS
- There is a need for **regular, brief, and accurate cognitive screening**

FATIGUE[5,7]

80%

of patients with MS experience fatigue with reduced physical activity level of daily functioning.

AAN Quality Measures Working Group:

- **Addressing fatigue will improve quality of life** as individuals are anticipated to have decreased fatigue and increased ability to function at work and home

AAN, American Academy of Neurology; MS, multiple sclerosis.

1. Kalb R, et al. Mult Scler. 2018 Nov;24(13):1665-1680; 2. Ayache SS, et al. Neurophysiol Clin 2017;47(2):139-171 ; 3. Brandstadter R, et al. Mult Scler 2020;26(13):1752-1764; 4. Rae-Grant A, et al. Neurology 2015;85(21):1904-8; Erratum in: Neurology 2016;86(15):1465; 5. American Academy of Neurology. Multiple Sclerosis Quality Measurement Set 2020 Update. Available at https://www.aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/multiple-sclerosis/2020-ms-quality-measurement-set.pdf. Accessed May 14, 2024. 6. DeLuca GC, Yates RL, Beale H, Morrow SA. Brain Pathol. 2015;25(1):79-98. 7. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/ms-symptoms/fatigue. Access date: July 2, 2024

RADIEMS COHORT STUDY: MS PATIENTS EARLY IN DISEASE COURSE DEMONSTRATE COGNITIVE CHALLENGES COMPARED TO HEALTHY CONTROLS [1]

PATIENT POPULATION

- **RADIEMS Cohort**
- **Patients with CIS or early RRMS (n=185)**
- **Healthy controls (n=50)**

METHODS

- Patients were compared to matched healthy controls using a comprehensive neuropsychological battery of tasks assessing:
  - **Cognitive efficiency**
  - **Memory**
  - **Rapid word generation**
  - **Rapid automatized naming (RAN)**

RESULTS

WORD-FINDING DIFFICULTY WAS COMMON

The only cognitive complaint reported more by patients than healthy controls ($p<0.001$)

IMPACT OF WORD-FINDING DEFICITS ON PATIENTS

Patients with self-reported word-finding deficits performed more slowly on only the RAN performance tasks, ***but not other*** cognitive domains or tasks

BRAIN IMAGING FINDINGS

Thinner left parietal cortical gray matter (driven primarily by the left precuneus) predicted impaired RAN performance

CIS, clinically isolated syndrome; MS, multiple sclerosis; RRMS, relapsing-remitting MS; RAN, rapid automatized naming; RADIEMS, Reserve Against Disability in Early MS.

1. Brandstadter R, et al. Mult Scler 2020;26(13):1752-1764.

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RADIEMS COHORT STUDY: EARLY MS PATIENTS WITH A NORMAL EDSS DISPLAY NEUROLOGIC DEFICITS COMPARED TO HEALTHY CONTROLS, [1,2]

PATIENT POPULATION

- **RADIEMS Cohort**
- **Patients with CIS or early RRMS (n=63 with EDSS 0)**
- **Healthy controls (n=50)**

METHODS

- Patients were compared with healthy controls, using high-challenge composite measures of:
  - **Upper extremity coordination** (Nine-Hole Peg Test [9HPT], Grooved Pegboard)
  - **Balance** (NIH Toolbox Balance, Balance Boards)

RESULTS

STANDARD CLINICAL TESTS: DID NOT REVEAL DIFFERENCES

Traditional clinical measures (EDSS, T25FW, and 9HPT) did not reveal differences between patients and healthy controls.

HIGH CHALLENGE TESTS: PATIENTS WITH EDSS 0 PERFORMED WORSE

Patients with EDSS 0 performed worse than healthy controls on:

- **Coordination** (p=0.039)
- **Balance** (p=0.008)
- **Composite (all 4 tasks)** (p=0.006)

IMAGING

In the full EDSS 0 cohort, poorer composite function was associated with:

- **Higher T2 lesion volume**
- **Lower normalized thalamic volume**

CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; 9HPT, Nine-Hole Peg Test; NIH, National Institutes of Health; T25FW, Timed 25-Foot Walk; RADIEMS, Reserve Against Disability in Early MS.

1. Krieger SC, et al. Mult Scler. 2022;28(14):2299-2303; 2. Brandstadter R, et al. Neurology 2020;94(13):e1395-e1406.

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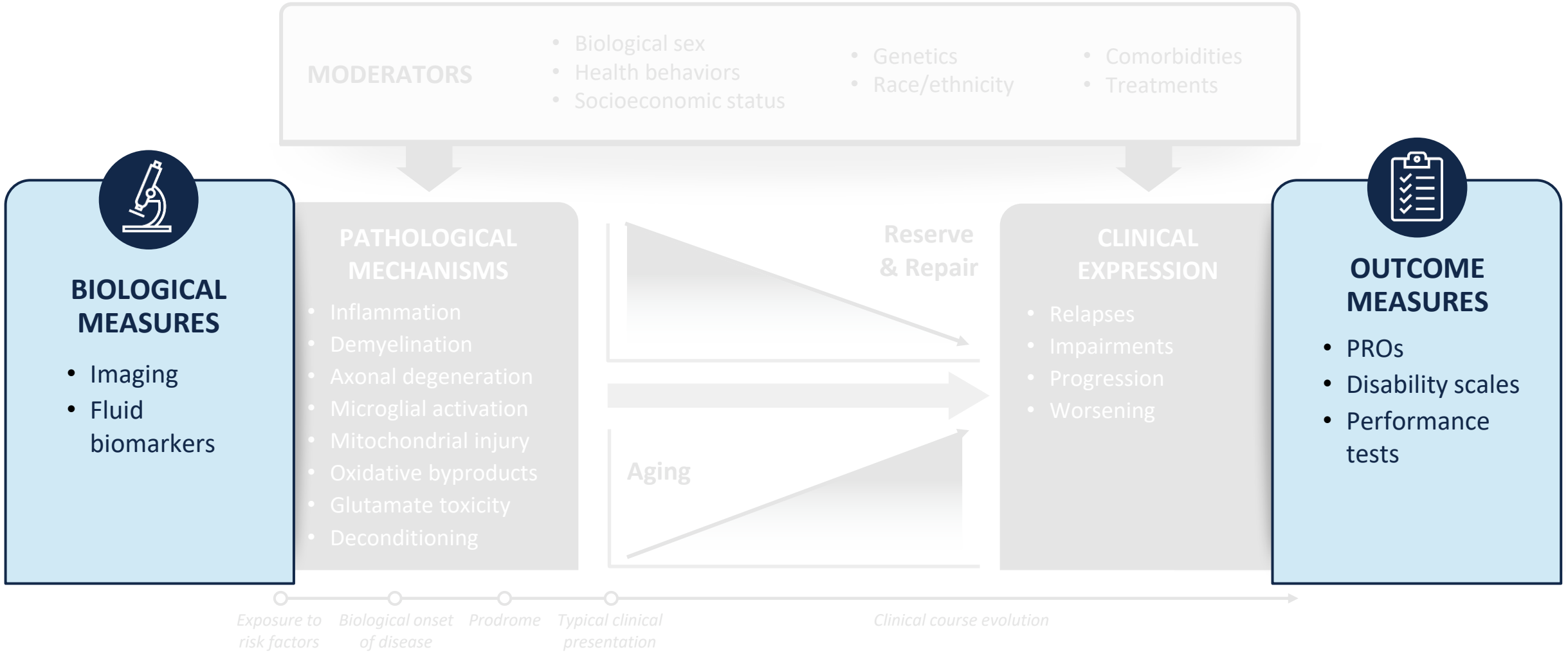
WHAT OTHER WAYS ARE THERE TO MONITOR DISEASE PROGRESSION?

INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



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DIGGING DEEPER: EMERGING IMAGING TECHNIQUES

Areas of Active Research in Imaging: CNS Atrophy and Chronic Inflammatory Activity[1]

Chronic Active Lesions (CALs)[2]

- Presence of activated microglia and/or macrophages at their edges
- Indicative of chronic inflammatory activity

Paramagnetic/Iron Rim Lesions (PRLs)[1,3,4]

- *Associated with disability and disease progression*
- Form when activated microglia and macrophages respond to myelin and oligodendrocyte injury
- Characteristic dark rim due to iron uptake

Slowly Expanding Lesions (SELs)[1,2]

- *Associated with disability and disease progression*
- Can be used to detect chronic lesion activity
- Identified through longitudinal series analysis of acquired T1w and T2w MRIs

Rapid, Noninvasive Imaging of Optic Neuritis: Optical Coherence Tomography (OCT)[5]

Residuals of Optic Neuritis (Optic Nerve Inflammation)[5]

- OCT measurements associated with *MS disability (EDSS changes) and MRI indicators (eg, brain atrophy, lesion load)*

CALs, chronic active lesions; CNS,central nervous system; EDSS, Expanded Disability Status Scale; MRI,magnetic resonance imaging; MS, multiple sclerosis; OCT, optical coherence tomography; PRLs, paramagnetic rim lesions; SELs, slowly expanding lesions.

1.Chertcoff A, et al. Neurol Clin 2024;42(1):15-38; 2. Calvi A, et al. Mult Scler 2023;29(3):352-362; 3. Hofmann A, et al. Acta Neuropathol 2023;146(5):707-724; 4. Reeves JA, et al. Mult Scler 2024;30(4-5):535-545; 5. Mirmosayyeb O, et al. J Neurol Sci 2023 Nov 15;454:120847.

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DIGGING DEEPER: FLUID BIOMARKERS

Select fluid biomarker candidates in MS: in Serum and CSF (unless otherwise specified)[1,2]

Immunomodulation and Inflammation

- CSF immunoglobulins (OCBs, kappa/lambda free light chains)
- Immune mediators and cytokines* *(CXCL13, CXCL12, sTACI, BCMA, CCL19, CCL21, sCD27, immune cell subset markers CD3, CD4, CD19, CD27)*

Astroglial Dysfunction

- glial fibrillary acidic protein (GFAP)
- sTREM2
- YKL-40

Neuroaxonal Damage

- Neurofilament light (NfL)
- Neurofilament heavy chain (NfH)

Myelin Biology/ Demyelination

- Myelin basic protein (MBP)
- Myelin oligodendrocyte glycoprotein (MOG)

CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MS, multiple sclerosis; NfH, neurofilament heavy chain; NfL, neurofilament light chain.

1. Yang J, et al. Int J Mol Sci 2022;23(11):5877; 2. Arneth B, et al. Clin Biochem 2022;99:1-8.

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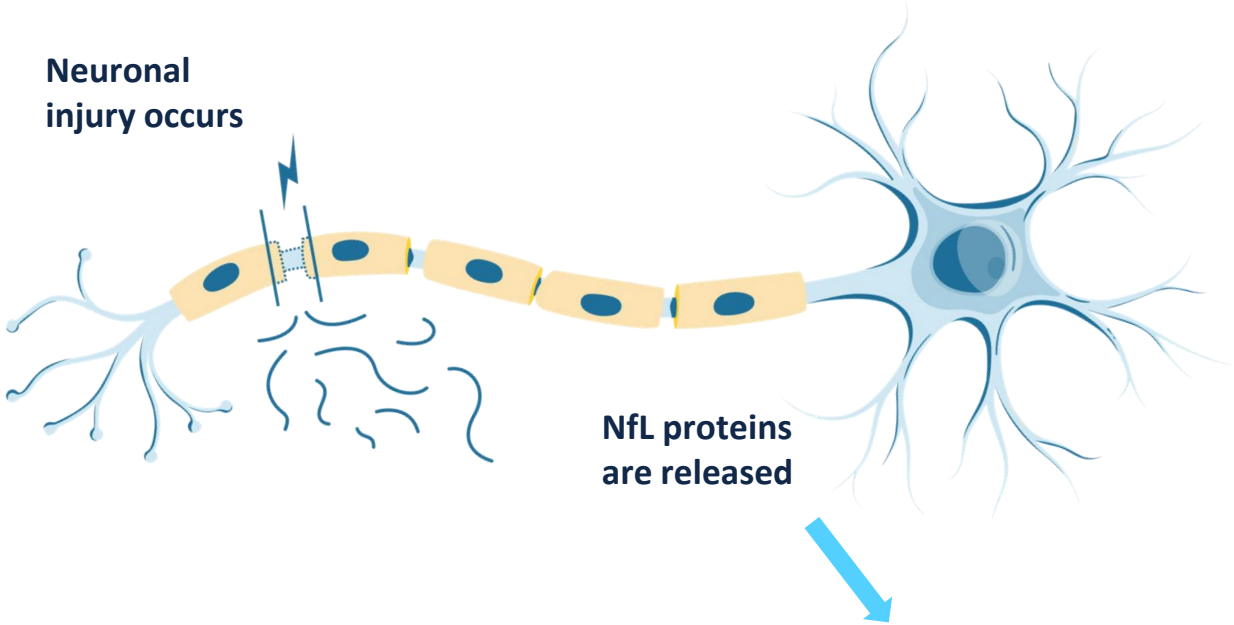
NEUROFILAMENT LIGHT (NfL) IS A BIOMARKER ASSOCIATED WITH DISEASE PROGRESSION

What is NfL?



Neurofilaments: structural cytoskeleton components of axons, exclusively expressed in neuronal tissue → **NfL is found in the extracellular space, CSF, and blood**

CSF, cerebrospinal fluid; Gd, gadolinium-enhanced; NfL, neurofilament light chain; MS, multiple sclerosis.

1. Giovannoni G. Brain 2018;141(8):2235-2237; 2. Bar-Or A, et al. Neurol Ther 2023;12(1):303-317; 3. Williams T, et al. J Neurol 2021;268(9):3212-3222; 4. Yuan A, et al. Cold Spring Harb Perspect Biol 2017;9(4):a018309; 5. Chertcoff A, et al. Neurol Clin 2024;42(1):15-38; 6. Barizzone N, et al. J Pers Med;12, 1430; 7. Benkert P, et al. Lancet Neurol 2022;21:246-57; 8. Sen M, et al. J Neurol 2023;270:1908-1930; 9. Ferreira-Atuesta C, et al. Front Neurosci. 2021;15:642384; 10. Abdelhak A, et al. JAMA Neurol. 2023;80(12):1317.

Why is NfL Important?

Increased NfL levels predict:

- **Degree of Axonal Damage:** NfL blood levels increase proportionally with the degree of axonal damage[1]
- **Inflammation & Neurodegeneration**: Elevated levels likely indicate both[2]

Correlates to Disease Activity and Progression[2,10]

- NfL in both CSF and serum correlate with disease activity (eg, Gd T1 lesions) and disease progression in patients with MS

NfL Can Be Applied to Large Cohorts[3-5]

- NfL quantification can be applied to large cohorts and clinical trials
- Development of sensitive assays enables detection in CSF and blood

Limitations of NfL

- NfL levels are also increased in other neurodegenerative diseases, increases with age, and decreases with BMI[6,7]
- Lack of standardized normal cutoff values that address confounding variables[7-9]

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DIGGING DEEPER: DIGITAL BIOMARKERS

Digital Biomarkers

- Objective, quantifiable physiological, and and behavioral data that are measured and collected by digital devices[1]

Digital biomarkers are increasingly available and enable[2]:

- Active & Passive Monitoring
- Ability to Measure Patient-Reported Outcomes
- Sensitive Tracking of Day-to-Day Changes in Function & Symptoms Between Clinic Visits

1. Dillenseger A, et al. Brain Sci 2021;11(11):15192; 2. De Angelis M, et al. J Clin Med 2021;10(11):2328.

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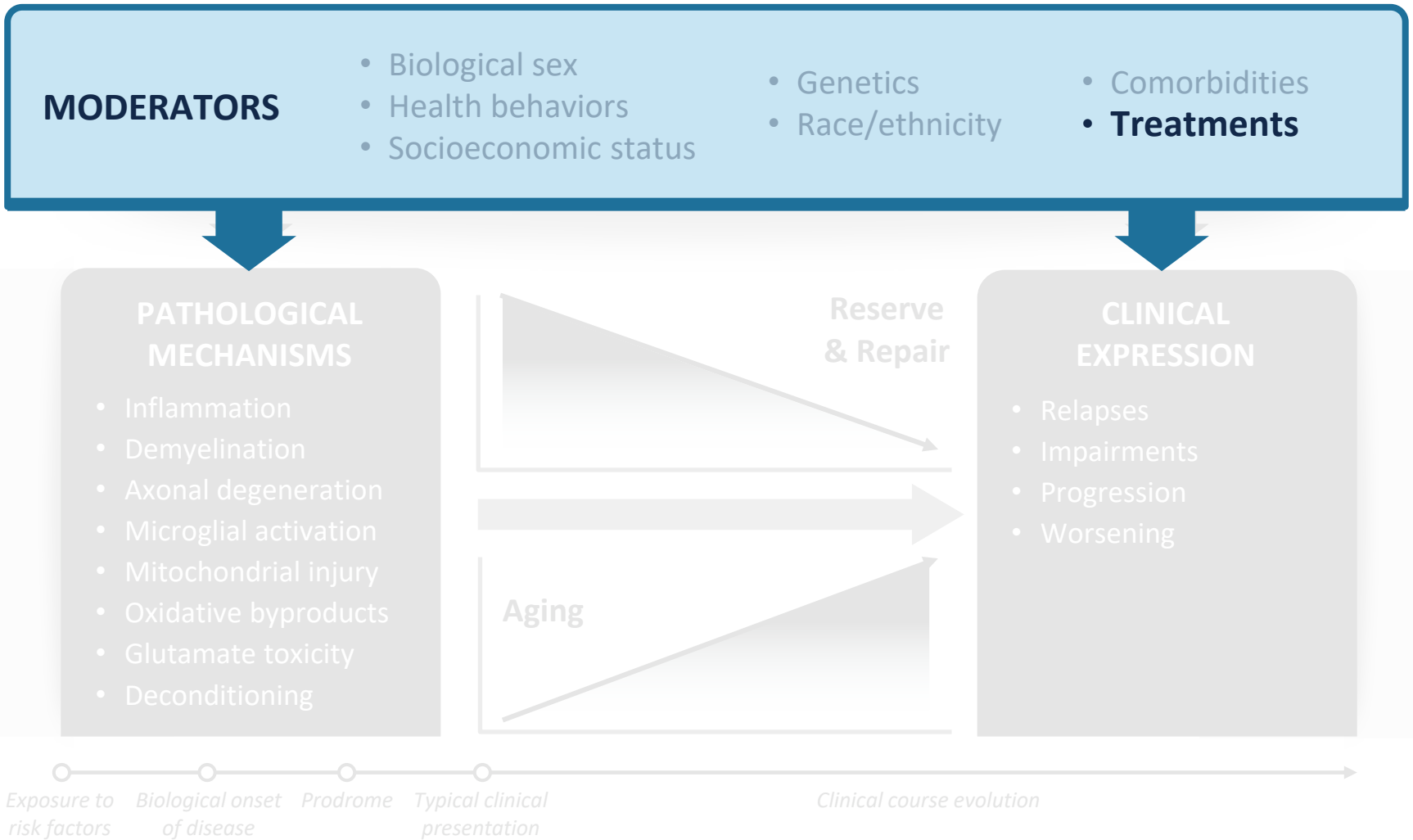
HOW DOES DETECTION OF DISEASE PROGRESSION INFORM MS TREATMENT?

INTERPLAY OF FACTORS CONTRIBUTING TO MS DISEASE



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DETECTION OF SUBTLE CLINICAL AND RADIOLOGICAL SIGNS, ALONG WITH EMERGING BIOMARKERS CAN AID IN TIMELY DISEASE MANAGEMENT

The goal of therapy is to target the underlying disease pathology early to prevent irreversible damage[1]

- Significant heterogeneity in disease presentation and progression exists among patients with MS[2,3]
- Poor prognostic factors and high disease activity increases risk of progression[3,4]

Consensus guidelines recommend early initiation of a DMT, however, a standardized treatment strategy has not yet been established[1,5]

An **"escalation approach"** starts with a lower- or moderate-efficacy DMT and escalates to a higher-efficacy DMT upon breakthrough disease activity.[5,6]

This approach aims to balance the potentially greater benefits and risks of high-efficacy DMTs[5]

Early initiation of a high-efficacy DMT aims to minimize the accumulation of neurological damage that occurs in the early stages of the disease.[5]

This approach strives to reduce long-term disability progression[5]

Clinicians should consider the balance between treatment goals, the safety profile of DMTs, and patient preferences when choosing a treatment strategy for the management of MS[5]

DMT, disease-modifying therapy.

1. Filippi M, et al. J Neurol 2022;269(10):5382-5394; 2. Arroyo Pereiro P, et al. J Neurol 2024;271(4):1599-1609; 3. Pitt D, et al. Neurol Neuroimmunol Neuroinflamm 2022;9(6):e200025; 4. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88; 5.Ontaneda D, et al. Lancet Neurol 2019;18(10):973-980. 6. Bou Rjeily N, Mowry EM, Ontaneda D, Carlson AK. *Neurologic Clinics*. 2024;42(1):185-201.

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ONGOING NATIONAL PUBLIC HEALTH RESEARCH AIMS TO INFORM MS TREATMENT PHILOSOPHY

	TREAT-MS: TRaditional versus Early Aggressive Therapy for Multiple Sclerosis	DELIVER-MS: Determining the Effectiveness of Early Intensive Versus Escalation Approaches for the Treatment of Relapsing-Remitting Multiple Sclerosis
Objective	**To Evaluate:** 1) Among patients at higher vs. lower risk for disability progression, whether a high-efficacy DMT early vs. starting with a traditional, first-line therapy, influences the intermediate-term risk of disability 2) Disability risk between individuals who switch from a traditional first-line medication to a high-efficacy DMT vs. those who switch to another traditional first-line therapy	**To Evaluate:** 1) Whether high efficacy DMT approach as initial therapy, is more effective than an escalation treatment approach in slowing brain volume 2) Which approach is more effective at improving patient reported outcomes (PRO) and clinical measures, and the safety and tolerability of each approach
Study Design	• Pragmatic, randomized clinical trial in the US • 900 participants with RRMS • Estimated completion 2025	• International, pragmatic, open-label, randomized clinical trial • 400 participants with RRMS (with an additional 400 in a parallel observational cohort) • Estimated completion 2030
Primary Outcome	Time to 6-month sustained disability progression (composite endpoint that includes EDSS change or 20% worsening on either of 2 components of the MSFC, T25FWT and 9HPT)	Annualized percentage brain volume loss from baseline to Month 36

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; 9HPT, Nine-Hole Peg Test; MS, multiple sclerosis; MSFC, MS Functional Composite; PRO, patient reported outcome; RRMS, relapsing-remitting MS; T25FW, Timed 25-Foot Walk.

1. Ontaneda D, et al. Contemp Clin Trials. 2020 Aug:95:106009; 2. Ontaneda D, et al. Lancet Neurol. 2019;18(10):973-980; 3. NIH. Available at: https://clinicaltrials.gov/study/NCT03535298. Accessed Feb 29, 2024; 4. NIH. Available at: https://clinicaltrials.gov/study/NCT03500328. Accessed Feb 29, 2024.

KEY TAKEAWAYS

EVOLVING VIEW OF MS

- A more contemporary view of MS appreciates that the clinical course of MS does not consist of a 2-phase disease, but rather represents the layering of both acute activity and progression across a disease continuum
- Disability progression can occur early, and may accumulate in **two distinct ways:**

Relapse-associated Worsening (RAW)

+

Progression Independent of Relapse Activity (PIRA)

CONTRIBUTING FACTORS

- Emerging evidence shows how a variety of factors may contribute to MS disease course (e.g., genetics, race/ethnicity, sex, age)

UNDERSTANDING PROGRESSION

- In the MS topographical model, both disease activity (lesions) and loss of functional reserve contribute to the manifestation of disability progression
- Progression of disease may go undetected by clinicians because current clinical measures may lack sufficient sensitivity to reliably detect disease progression.
- A variety of approaches are being evaluated to help facilitate monitoring of MS disease progression (e.g., clinical, imaging, fluid biomarkers, digital biomarkers)
- Ongoing research aims to inform MS treatment paradigms

MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening.

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APPENDIX

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WHAT FACTORS CAN CONTRIBUTE TO DISEASE PROGRESSION?

SOME FACTORS THAT MAY CONTRIBUTE TO MS DISEASE COURSE INCLUDE:

Age[1]

- Older age at diagnosis
- Older chronological age
- Age-associated decrease in reserve and repair capacity
- Immune senescence

Sex[1]

- Males may have more severe disease progression at younger ages
- However, many women catch up post-menopause

Race/Ethnicity[2-5]

- Black patients may exhibit greater pathological/MRI biomarkers of progression and disease activity

Social Determinants of Health[6]

- Ethnic/racial disparities and inequities
- Socioeconomic status
- Healthcare access
- Health literacy

Genetic Factors[7,8]

- HLA-associated genetic variants increase risk for developing MS
- Certain gene alleles (rs10191329, rs149097173) may contribute to disease severity

Environmental Factors[9,10]

- Low vitamin D levels
- Low sun exposure
- Epstein Barr virus infection
- Smoking

Duration of Disease[11]

- Longer duration of disease

Comorbidities[12,13]

- Comorbidities, such as vascular disease (e.g., cardiovascular disease, hypertension, diabetes) may contribute to disability progression in MS

HLA, human leukocyte antigen; MS, multiple sclerosis; MRI, magnetic resonance imaging.

1. Graves JS, et al. Lancet Neurol 2023;22(1):66-77; 2. da Gama PD, et al. Biomed Res Int 2015;2015:217961; 3. Xue H, et al. Mult Scler Relat Disord 2023 Nov;79:105047; 4. Howard J, et al. PLoS One 2012;7(8):e43061; Erratum in: PLoS One 2013;8(6); 5. Gray-Roncal K, et al. Neurology 2021;97(9):e881-e889; 6. Okai AF, et al. Neurology 2022;98(24):1015-1020; 7. Isobe N, et al. JAMA Neurol 2016;73(7):795-802; 8. International Multiple Sclerosis Genetics Consortium & MultipleMS Consortium. Nature 2023;619(7969):323-331; 9. Pitt D, et al. Neurol Neuroimmunol Neuroinflamm 2022;9(6):e200025; 10. Wu J, et al. Eur J Neurol. 2024; 31:e16269; 11. Stanikić M, et al. Mult Scler Relat Disord 2022;67:104084; 12. Marrie RA, et al. Neurology 2010;74(13):1041-7; 13. Nociti V, et al. J Pers Med 2023;13(11):1524.

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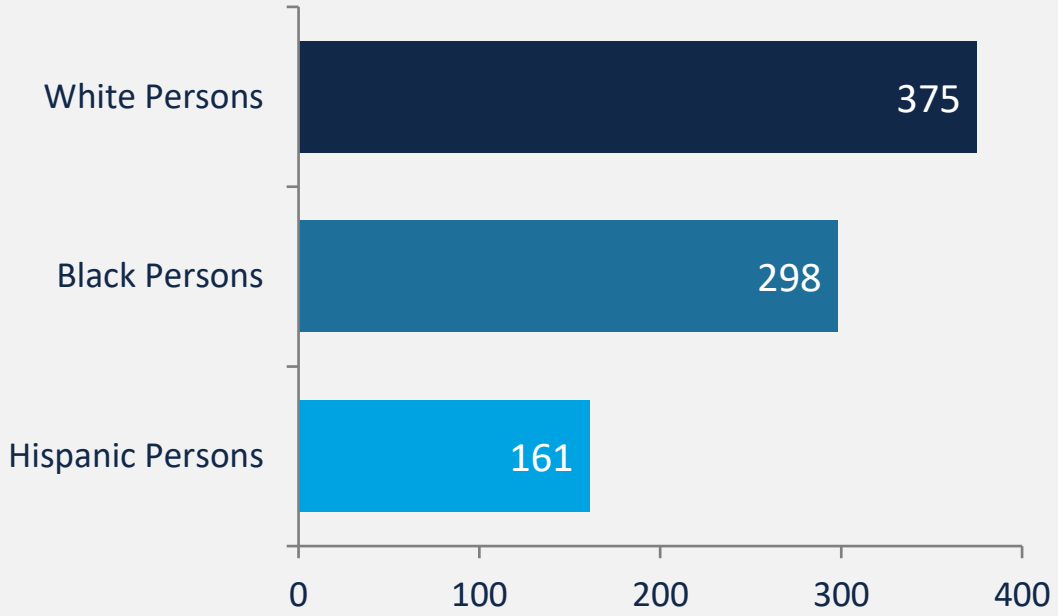
THE PREVALENCE OF MS IN BLACK AND HISPANIC PERSONS IS GREATER THAN PREVIOUSLY RECOGNIZED

Historically, MS was thought to primarily affect **White persons of Northern European ancestry**[1]

Recent studies have shown that in the United States (US), **the prevalence of MS in Black and Hispanic persons is greater than previously recognized**[2]

2010 cumulative prevalence of MS per 100,000 US adults[3,a]



Retrospective cohort analysis of administrative health claims data including 744,781 adult MS cases (2008-2010)

[a]95% CIs were 374 to 376 for White, 296 to 301 for Black, and 160 to 163 for Hispanic persons.
CI, confidence interval; MS, multiple sclerosis.
1. Khan O, et al. *Neurol Clin Pract*. 2015;5(2):132-142. 2. Amezcua L, McCauley JL. *Mult Scler*. 2020;26(5):561-567. 3. Hittle M, et al. *JAMA Neurol*. 2023;80(7):693-701.

BLACK PATIENTS WITH MS MAY SUFFER FROM GREATER DISEASE BURDEN

Black patients reported **greater symptom severity on**

all 12

SymptoMScreen domains compared to White patients[1,a]

Black patients had

2.6x

higher prevalence of rapidly progressing MS compared to White patients[2,b]

Compared to White patients with MS, **Black patients** showed[3]:

- **Faster progression of mobility impairment**
- **Wheelchair dependence 8 years earlier**
- **Cane use 6 years earlier**

The identification of patients who may have greater risk of progression because of factors that may influence disease course may be helpful to clinical practice.

[a]Domains of the SymptoMScreen include mobility, dexterity, vision, fatigue, cognition, bladder function, sensory function, spasticity, pain, dizziness, depression, and anxiety. [b]Based on MSSS scores ≥9.6 (7.3% vs 2.9% in Black and White patients, respectively; p<0.001)
MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Scale.

1. Kister I, et al. Neurol Clin Pract 2021;11(4):335-341; 2. Kister I, et al. Neurology 2010;75(3):217-23; 3. Cree BAC, et al. Neurology 2004;63(11):2039-45.

GENETIC FACTORS ASSOCIATED WITH DISEASE PROGRESSION

Genetic variants associated with the risk of developing MS have been identified and now there is evidence for genetic drivers of MS severity[1]

A GWAS of the age-related MS severity score performed in 12,584 people with MS, and replicated in 9,805 further cases, investigated genetic factors determining progression[1]

3.7 YEAR SHORTER

median time to require a walking aid in homozygous carriers of rs10191329 in the *DYSF-ZNF638* locus

3.3 YEAR SHORTER

median time to require a walking aid in carriers of rs149097173 in the *DNM3-PIGC* locus

28% **of brain atrophy** was associated with the minor allele rs10191329*A, in another study[2]

GWAS=genome-wide association study.

1. International Multiple Sclerosis Genetics Consortium & MultipleMS Consortium. Nature. 2023;619(7969):323-331. doi:10.1038/s41586-023-06250-x. 2. Gasperi C, Wiltgen T, McGinnis J, et al. Ann Neurol. 2023;94(6):1080-1085. doi:10.1002/ana.26807

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CONTRIBUTIONS OF AGING TO PROGRESSION

Older age at disease onset has been associated with poorer prognosis, including reaching ambulatory disability milestones earlier and a higher likelihood of progressive features[1,2]

Increased chronological age is associated with non–relapse-related progression[3]

Age-related pathophysiological processes:[1-4]

- **The rate of remyelination decreases** through adult life[1]
- The **aging immune system** is characterized by chronic low-grade systemic inflammation which negatively impacts repair pathways and exacerbates microglial activation[1]
- Chronic neuroinflammation in MS increases **oxidative stress**[1]
- **Telomere shortening** associated with aging is accelerated by oxidative stress and DNA damage, and is associated with higher disability accumulation[5]
- **Reproductive aging** and decreased sex steroid hormone production can impact inflammation and neurodegeneration[1,6]

DNA, deoxyribonucleic acid; MS, multiple sclerosis.

1.Graves JS, et al. Lancet Neurol 2023;22(1):66-77; 2.Confavreux C, Brain 2006;129(Pt 3):595-605; 3. Kuhlmann T, et al. Lancet Neurol 2023;22:78–88; 4. Graves J. Presented at CMSC; Aurora, CO, USA; May 31–June 3, 2023. Oral presentation; 5.Krysko KM, et al. Ann Neurol 2019;86(5):671-682; 6.Graves JS, et al. Neurology 2018;90(3):e254-e260.

CONTRIBUTIONS OF MENOPAUSE AND OVARIAN AGING TO PROGRESSION

While men typically experience more severe disease progression at younger ages, women catch up post-menopause[1]

Estrogen may have protective effects and reduced levels of estrogen may contribute to disease progression[2]

- Concentrations of anti-Mullerian hormone (AMH), a biomarker of perimenopause, decline over the course of a woman's lifespan and are a surrogate marker for **ovarian aging** in women[1,3]
  - In a study of women with MS (n=412) and healthy controls (n=180), lower **AMH concentrations were strongly associated with disability and gray matter loss independent of chronological age and disease duration[3]**
    - Multivariable analysis **at baseline demonstrated that 10-fold lower AMH level was associated with:**
      - ▲ **0.43-higher EDSS score** (95% CI 0.15–0.70, p=0.003)
      - ▼ **0.25-unit lower (worse) MS Functional Composite z score** (95% CI −0.40 to −0.10, p=0.0015)
      - ▼ **7.44mm³ lower cortical gray matter volume** (95% CI −14.6 to −0.30; p=0.041)

These findings suggest that reproductive aging contributes to disease progression in women with MS, and that the **perimenopause stage might be a risk factor for conversion to progressive disease**

AMH, anti-Mullerian hormone, CI, confidence interval; EDSS, Expanded Disability Status Scale, MS, multiple sclerosis,

1. Graves JS, et al. Lancet Neurol 2023;22(1):66-77; 2. Bove R, et al. Front Neurol 2021;12:554375; 3. Graves JS, et al. Neurology 2018;90(3):e254-e260.

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