Understanding the Impact
of Disease Activity on Future Disability in Multiple Sclerosis
The therapeutic goal in multiple sclerosis (MS) is to control disease activity and delay irreversible disability.¹

MS is a chronic immune-mediated disorder of the central nervous system (CNS) characterized by inflammation, demyelination, and neurodegeneration that causes significant disability.¹

There are approximately 400,000 adults in the US who have been diagnosed with MS.² Two phenotypically distinct patterns of disease activity are seen from disease onset—relapsing forms of MS (RMS) and primary progressive MS (PPMS).¹

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### Relapsing Forms of MS¹

Acute relapses with full or partial recovery; stable in between. May transition to a progressive accumulation of disability with or without relapses (SPMS)³

**85%-90% of MS patients**

### Primary Progressive MS¹

Progressive accumulation of disability from onset, without relapses or periods of remission³

**10%-15% of MS patients**

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Abbreviation: SPMS, secondary progressive MS.
A comprehensive evaluation of MS includes 3 key measures of disease activity that may be predictive of future disability \(^4\)\(^-\)\(^11\).

Relapses, MRI lesion activity and rapid disability progression early in the disease course are 3 important factors which may predict advanced disability in the future.*

*As measured by Expanded Disability Status Scale (EDSS).
Relapses occurring early in the disease course may predict future disability⁷,⁸

More frequent relapses in the first 5 years of MS predicted a shorter time to advanced disability (EDSS 6.0 or walking with a cane)⁷

Retrospective review of 2477 patients with definite relapsing-onset MS for which 11,722 post-onset relapses were recorded over a mean follow-up of 20.6 years.

While annualized relapse rate (ARR) is a common clinical trial end point, it is only one of many predictors of future disability and does not reflect all disease activity.⁴

Abbreviation: EDSS, Expanded Disability Status Scale.
Looking beyond relapses for signs of disease activity

Other indicators of disease activity, including MRI lesion activity and rapid disability progression from onset of disease, may be predictive of future disability.

MRI lesion activity as a predictor

≥2 Gd-enhancing lesions

9× GREATER RISK OF SEVERE DISABILITY

≥1 new T2 lesion

15× GREATER RISK FOR DISABILITY PROGRESSION

• ≥2 Gd-enhancing lesions appearing in years 1 and/or 2 of DMT was associated with a 9-fold increase in the risk of severe long-term disability progression (defined as a median EDSS of 8 or a median 5-point change in EDSS from baseline)

Multicenter, observational, 15-year follow-up study of 136 RMS patients who completed ≥2 years in a pivotal trial of an interferon.

• One or more new T2 lesions on MRI increased the risk of disability progression (≥1-point increase in EDSS) greater than 15-fold, even in the absence of clinical relapses

Observational, open-label, prospective and post-marketing study of treatment-naive patients treated with an interferon-beta formulation for at least 1 year. Patients underwent at least 2 MRI scans at baseline and 1 year. Disability progression was defined as a ≥1-point increase in EDSS confirmed in 2 consecutive exams separated by at least 6 months.

Abbreviations: DMT, disease-modifying therapy; Gd, gadolinium; MRI, magnetic resonance imaging.
Looking beyond relapses for signs of disease activity (cont’d)

Rapid disability progression from onset as a predictor

A shorter time from disease onset to EDSS 4 was significantly associated with a shorter time to EDSS 6.

<table>
<thead>
<tr>
<th>Disability Progression Category</th>
<th>Median Time from MS Onset to EDSS 6 (years)</th>
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<tbody>
<tr>
<td><strong>Rapid</strong> (&lt;2 years from MS onset to EDSS 4)</td>
<td><strong>6.3</strong></td>
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<tr>
<td><strong>Moderate</strong> (2 to 5 years from MS onset to EDSS 4)</td>
<td><strong>8.1</strong>a</td>
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<tr>
<td><strong>Slow</strong> (&gt;5 years from MS onset to EDSS 4)</td>
<td><strong>20.7</strong>b</td>
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*a* P = 0.003 vs rapid progressors

*b* P < 0.001 vs rapid progressors

Cohort study of 1844 MS patients that evaluated clinical variables at disease onset and the predictive value of reaching disability milestones of EDSS 4, 6, and 7 using Kaplan-Meier survival analysis.
When evaluating the MS category and making population health decisions, consider all key measures of disease activity

The US National Multiple Sclerosis Society (NMSS) and Consortium of Multiple Sclerosis Centers (CMSC) suggest that MRI lesions, relapses, and disability progression are all measures that should be used to assess disease activity.6,12

“Because it is uncertain which outcome measures correlate best with future function, clinical trials that use a combination of outcome measures, including both clinical and confirmatory MRI measures, should be judged as stronger evidence than those that rely on only a single measure.”

—American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee

Figure adapted from Weiner HL. Ann Neurol. 2009;65(3):239-248.