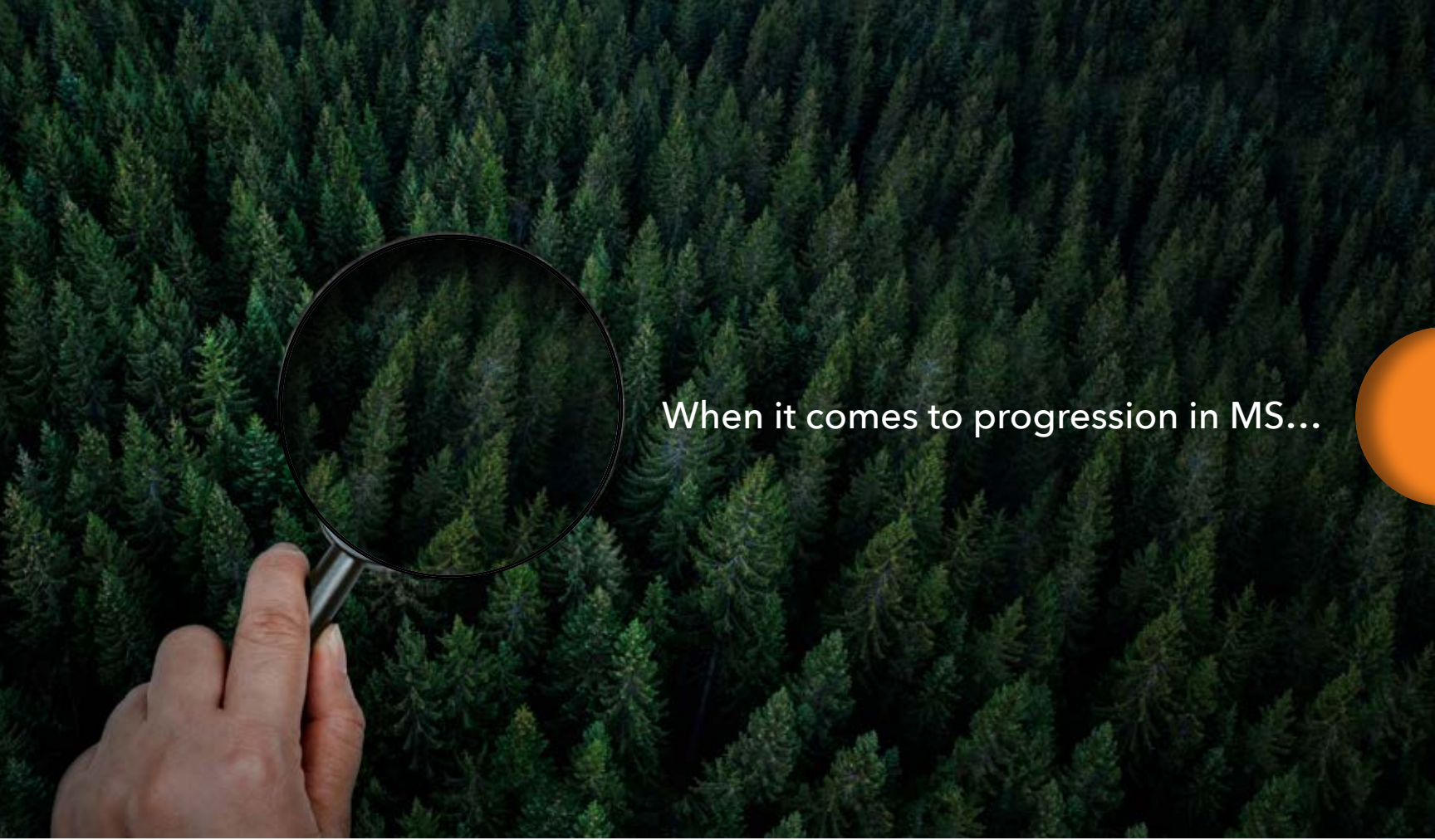

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Is there more
than **you** can see?

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Despite conventional treatment, disease progression remains the most significant unmet need in MS.

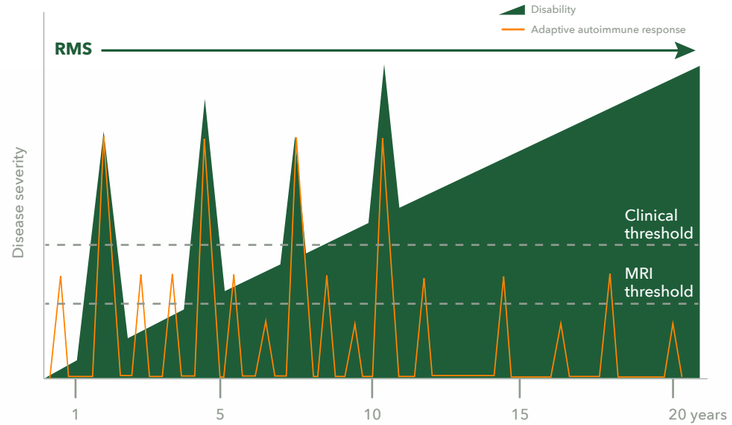
FPO

Progression is a combination of numerous pathological processes, blurring the lines between the clinical manifestations typically associated with RMS and PPMS.

In fact, patients with RMS often have accumulation of disability occurring independently of relapses. But this is often overlooked, making the detection of progression difficult because the brain is able to compensate for the progression that occurs in early stages of the disease.

By recognizing the gradual progressive change and pathological processes that occur from the start of MS, we can get ahead of progression.

MS is an inflammatory disease that is progressive from the start[1]



DETECTING PROGRESSION IN MS IS DIFFICULT SINCE THE BRAIN CAN COMPENSATE EARLY IN THE DISEASE[2]

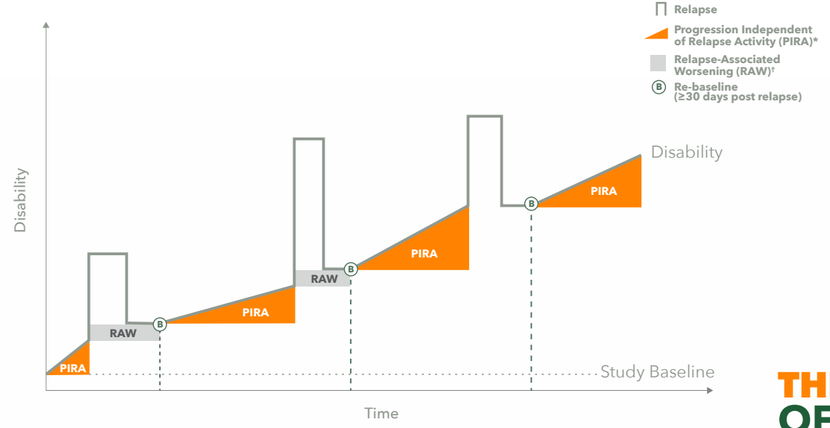
MS may be seen as a disease continuum in which the extent of RAW and PIRA varies.

FPO

Relapse-associated worsening (RAW) is the disability accumulation that occurs as a result of a relapse and prevents patients from fully recovering. Unlike RAW, progression independent of relapse activity (PIRA) often goes unrecognized, since it is a gradual and underlying progressive course that is only evident over longer periods of time.

For better clarity in characterization of confirmed change, Lublin et al. suggested reserving the term progression for only when disability accumulation occurs independent of relapse activity.

Disability accumulates in two ways: relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA)[3]



*Composite PIRA disability is assessed using a re-baselining approach to ascertain event independence of relapse activity. The baseline reference assessment (EDSS/T25FW/9HPT) was re-baselined at each relapse and thereafter defined as the first available assessment ≥30 days after each onset of relapse.

†Composite RAW events were defined as a disability increase from fixed study baseline occurring ≤90 days after the onset of a protocol-defined relapse.

THE MAJORITY OF DISABILITY WORSENING IS INDEPENDENT OF RELAPSE

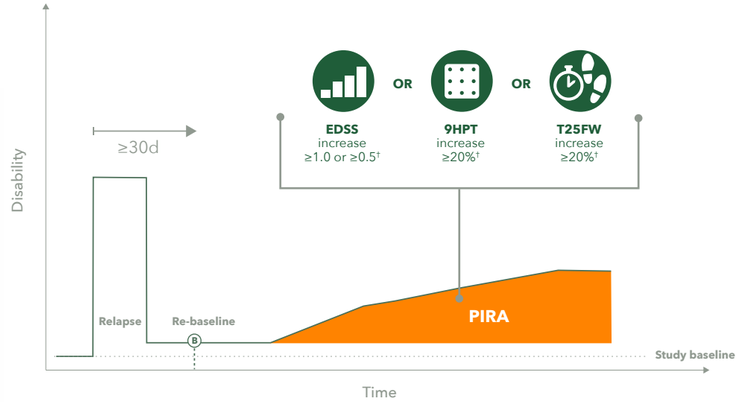
Expanding the assessment of PIRA to a composite of three main endpoints (EDSS or T25FW or 9HPT)

FPO

PIRA may represent a more appropriate outcome to detect and measure progression in relapsing forms of MS; as such, a multi-component measure of disability captures aspects of disease progression potentially missed with EDSS alone.

In order to ensure that this gradual worsening is independent of relapse, it is important to "re-baseline" approximately 30 days after each defined relapse has occurred. At subsequent timepoints, it is determined whether or not the patient has had a significant change in disability, compared to the re-baselined level.

How can PIRA be detected?*[3,4]



*Composite PIRA was assessed using a re-baselining approach to ascertain event independent of relapse activity; the baseline reference assessment (EDSS/T25FW/9HPT) was re-baselined at each relapse and thereafter defined as the first available assessment ≥30 days after each onset of relapse; the re-baselined disability assessment could not be inferior to the original study baseline value; no protocol-defined relapse should occur between baseline reference assessment and initial disability accumulation (IDA), as well as within 30 days after IDA and 30 days prior to and after IDA confirmation.

†PIRA was defined as a disability increase measured by EDSS (increase of ≥1.0 if baseline EDSS ≤5.5, or ≥0.5 if baseline EDSS >5.5) or ≥20% increase in the T25FW or ≥20% increase in the 9HPT confirmed after ≥12 or ≥24 weeks.

PIRA IS A COMPOSITE MEASURE OF UNDERLYING PROGRESSION INDEPENDENT OF RELAPSES

References: 1. Kotelnikova E, Kiani NA, Abad E, Martinez-Lapiscina EH. Dynamics and heterogeneity of brain damage in multiple sclerosis. *PLoS Comput Biol*. 2017;13(10):e1005757. doi:10.1371/journal.pcbi.1005757. **2.** Fox RJ, Cohen JA. Multiple sclerosis: the importance of early recognition and treatment. *Cleve Clin J Med*. 2001;68:157-171. **3.** Kappos L, Butzkueven H, Wiendl H, et al, on behalf of the Tysabri® Observational Program (TOP) Investigators. Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. *Mult Scler J*. 2018;24(7):963-973. **4.** Cree BAC, Hollenbach JA, Bove R, et al. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol*. 2019;85(5):653-666.

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