Smouldering-Associated Worsening in Multiple Sclerosis: An International Consensus Statement on Definition, Biology, Clinical Implications, and Future Directions

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Despite therapeutic suppression of relapses, multiple sclerosis (MS) patients often experience subtle deterioration, which extends beyond the definition of "progression independent of relapsing activity." We propose the concept of smouldering-associated-worsening (SAW), encompassing physical and cognitive symptoms, resulting from smouldering pathological processes, which remain unmet therapeutic targets. We provide a consensus-based framework of possible pathological substrates and manifestations of smouldering MS, and we discuss clinical, radiological, and serum/cerebrospinal fluid biomarkers for potentially monitoring SAW. Finally, we share considerations for optimizing disease surveillance and implications for clinical trials to promote the integration of smouldering MS into routine practice and future research efforts.

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Introduction

Multiple sclerosis (MS) is considered a disease predominantly driven by focal inflammation and demyelination of the central nervous system (CNS) mediated by the adaptive immune system. The current classification system is based on separate clinical stages, including relapsing–remitting (RR), secondary progressive (SP), and primary progressive (PP) courses[1] and places emphasis on the white matter (WM) focal inflammation, which represents the biological substrate for clinical relapses and new magnetic resonance imaging (MRI) lesions and has been the ubiquitous target of disease-modifying treatments (DMTs).

In a large proportion of people with MS (pwMS), we succeed at therapeutically inducing disease remission with no evidence of inflammatory disease activity (NEIDA). However, despite stable inflammatory parameters, pwMS often experience disability worsening, highlighting a dissociation between focal inflammatory mechanisms and those accounting for the accumulation of disability in a more indolent fashion, and arguing against the current phenotypic distinction of separate relapsing and progressive stages.

Recent studies demonstrated that, in addition to relapse-associated worsening (RAW), progression independent of relapse activity (PIRA) occurs from the early RR phase,[2,3] indicating that MS is underpinned by a biological continuum with different pathological mechanisms tightly intermingled since the earliest stages of the disease.[4] However, subtle accumulation of symptoms and signs is often not captured by the definition of PIRA, which is predominantly based on clinical scales of motor performance, but it is largely insensitive to worsening in other clinical domains.

Pathology, neuroimaging, and clinical insights support a paradigm shift in our understanding of the biological mechanisms within the CNS that contribute to MS worsening.[4,5] The gradual accumulation of physical and cognitive disability is driven by smouldering pathological processes via biological substrates, which are different from those of acute focal damage and remain an important unmet therapeutic target.[6]

To date, there is no uniform definition of smouldering disease in MS, nor of its clinical manifestations and pathological substrates. In this context, we previously reviewed the biological perspective of pathological drivers within the CNS responsible for smouldering disease in MS.[6] Here, we set out to define clinical and radiological manifestations of smouldering processes, its underlying biology and biomarkers. We provide consensus statements and recommendations to integrate the concept of smouldering disease in MS into clinical practice, to discuss its implications for clinical trial design and regulatory pathways, and to promote research activities to understand better its pathological mechanisms.

Methods

An international panel of 15 MS experts from 8 countries across Europe, the United States, and Canada convened in June 2021 to develop a consensus on smouldering disease in MS. This panel was selected based on clinical experience, scientific background and expertise, and geographical representation. The panel met several times to discuss various aspects of smouldering disease. First, it was debated and eventually agreed, which categories had to be addressed. This led to the identification of key domains in line with panelists' expertise, which were selected as subjects for subsequent debates and included: definitions, pathological drivers, the role of aging, clinical and paraclinical manifestations, implications for routine clinical practice, clinical trial design, and regulatory pathways. Second, for each category, a leading expert was selected to coordinate the effort of a subgroup of panelists responsible for developing statements related to their respective topic. Finally, the whole panel of experts debated and reached agreement on proposed statements covering each domain. The Delphi method was used to anonymously establish the level of agreement on the 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) for each statement, and a consensus was defined as ≥75% who strongly agree or agree to each statement. In addition, when voting, experts were given the opportunity to provide anonymous comments on how statements could be potentially modified and improved. The surveys were facilitated independently by a medical consultant using the Welphi online survey platform with 100% involvement of all 15 panelists at every stage of the review. Modifications to statements were made over a maximum of 3 rounds. A total of 41 statements were proposed, with 29 finally reaching consensus (≥75% of agreement), whereas 12 statements were discarded. Among the rejected statements, some did not reach the minimum required threshold of 75% level of agreement, whereas others because of partial overlapping wording were merged and then re-surveyed again to check the level of agreement among panelists. All experts agreed on the full contents of the final statements and recommendations.

Clinical Case

A 40-year-old woman with an 8-year history of relapsing–remitting MS (RRMS) was previously treated with different platform DMTs, but experienced clinical and radiological disease breakthrough and accumulated mild disability (Expanded Disability Status Scale [EDSS][7] score of 2). After being switched to high-efficacy treatment, over the last 4 years she has remained free of relapses and new

MRI activity (new/enlarging T2 lesions or gadolinium-enhancing lesions), with stable EDSS score. However, she has complained of "feeling worse," particularly over the last 18 months. Although her walking is not impaired, she has noticed reduced tolerance to exercise, for example, after running 2km, she would limp in her right leg (previously affected by a relapse with complete recovery). In addition, she was more easily fatigued and needed to stop walking after ~45 minutes. Overall, she felt cognitively slower and reported "brain fog," with difficulties performing complex tasks at work. However, the lack of radiological progression on yearly MRIs and the absence of new pathological signs on examination implied "stable" disease, and her neurologist reassured her that her therapy was working.

The clinical vignette highlights the limitations of the current phenotypic classification of MS.[1] Given her low level of disability, most physicians would consider such a person as being in the RR phase and her recent worsening would not fulfil clinical criteria for progressive disease.[1] Even the current definition of PIRA[8] may not capture her subtle worsening of symptoms and signs. Her gradual and slow decline, manifesting despite the successful therapeutic suppression of focal inflammatory activity and lack of quantifiable clinical changes using currently available metrics, indicates ongoing pathological processes in the CNS, which could be referred to as "smouldering-associated worsening" (SAW) (Table 1).

Clinical Manifestations of Smouldering Disease in MS

As illustrated in the clinical vignette, pwMS often experience more than we can currently assess with conventional clinical outcome measures, such as the EDSS[7] or the Multiple Sclerosis Functional Composite (MSFC).[9] Our current model of managing MS is anchored on crude estimates of physical disability (ambulation and pyramidal function) and is overly reliant on identifying relapses and new MRI lesions as the principal markers of disease activity. With longer disease duration and with older age, the frequency of relapses and ensuing RAW, decreases,[10] whereas the probability of experiencing progressive symptoms increases.[11] However, throughout the natural history of MS, and even in its earliest RR phase, acute attacks are accompanied by an underlying subtle progressive course, encompassing a wide range of physical and cognitive symptoms,[11] which can remain clinically undetected for years, cautioning against mistakenly interpreting the lack of acute focal inflammation as a marker of disease stability (Fig 1).

In the pooled analysis of the OPERA trials, among people with RRMS early in the disease course (mean disease duration of 6 years), most of the disability accumulation occurred as a result of PIRA.[8] Similarly, in the Italian MS registry, from the second year of onset of the RR phase, PIRA events were more commonly reported than RAW.[12] In the Barcelona RRMS cohort, 66% of confirmed disability accumulation episodes were unrelated to relapses.[2] Furthermore, in a large cohort of people with RRMS from pooled randomized clinical trials, it was shown that up to 50% of events leading to disability accumulation were unrelated to overt relapses.[3]

The definition of PIRA relies on EDSS[7,8] or EDSS-Plus[13] increase and it is, therefore, mainly related to motor impairment. Moreover, SAW is a broader umbrella concept, which encompasses PIRA, but also includes a wide range of gradually worsening symptoms independent of relapses that remain undetectable on standard assessments especially in early disease stages, including subtle motor impairment, cognitive slowing, fatigue, neuropathic pain, bowel/bladder, and sexual dysfunction (Table 1 and Fig 2). Cognitive impairment can be observed during the prodrome of MS[14] and in a significant proportion of people with radiologically isolated syndrome (RIS),[15] or at the onset of the RR phase.[16] The relentless accumulation of fatigue,[17,18] bladder/bowel and sexual dysfunction,[19] and depression[20] throughout the evolution of MS can lead to functional worsening unrelated to clinical or subclinical relapses. In addition, early in the disease course, among subjects with no walking impairment, transient exercise-induced neurological deficit (eg, foot drop) or early fatigability are commonly reported.[21] Although this might initially be a reversible phenomenon, over time it can become more prominent and more easily triggered by exertion as a result of subtle progressive disease deterioration. Functional network compensation[22] may explain the difficulty of detecting early deterioration, which may become evident through neurological stress tests. Progressive symptoms might also emerge with challenging tasks, requiring the simultaneous activation of several networks.[23]

Pathological Drivers of Smouldering Disease in MS

The combination of widespread inflammatory and degenerative injury, including anterograde and retrograde axonal degeneration, coupled with the failure of compensatory mechanisms, such as remyelination and neural plasticity, is believed to result in SAW.[4] Although our understanding of smouldering disease in MS is still incomplete, mounting evidence supports a central role for CNS-intrinsic biological processes, even early in the course of MS, which are considered distinct from mechanisms underlying relapses and the occurrence of WM focal demyelination.[24–28] Recent genome-wide association studies shed light on the genetic

TABLE 1. Definition and Clinical Manifestations of Smouldering Disease in MS: Consensus Rates

Statement	5-point Likert scale of agreement percentages (%) from Delphi review				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Definition					
Smouldering disease in MS is an umbrella term characterizing chronic pathobiological processes occurring in the CNS, beyond acute inflammation, associated with neurodegeneration and may manifest clinically as physical worsening, functional deficits and cognitive decline	100	0	0	0	0
Clinical manifestations					
Clinical disease worsening may be associated with relapses (RAW) and/or associated with smouldering disease, which could be termed 'smouldering associated worsening' (SAW)	100	0	0	0	0
Smouldering disease in MS and SAW are not just associated with progressive onset MS or the later stages of relapse onset MS, but may be observed throughout the clinical course of MS and may even precede clinical diagnosis	100	0	0	0	0
PIRA, as measured by the EDSS and EDSS-Plus, is a clinical manifestation of SAW and should not be used interchangeably with smouldering disease in MS	87	13	0	0	0
SAW may be the result of prior or ongoing smouldering pathological mechanisms. It encompasses motor and non-motor manifestations, accumulating in an indolent fashion	93	7	0	0	0
SAW refers to a trajectory of worsening, often subtle, over time and requires regular monitoring	100	0	0	0	0

CNS = central nervous system; EDSS = Expanded Disability Status Scale; EDSS-Plus = EDSS, timed 25-foot walk test, on 9-hole peg test; MS = multiple sclerosis; PIRA = progression independent of relapse activity; RAW = relapse-associated worsening; SAW = smouldering associated worsening.

factors implicated in MS severity, suggesting that pathways related to neuronal and glial mechanisms play a potential role in determining the disease outcome.[29,30]

Although an association observed in vitro, in vivo, and ex vivo studies does not necessarily imply a mechanistic causal relationship, cautioning against drawing definitive conclusions, the pathological drivers of smouldering disease in MS potentially include several major categories, such as microglial activation around chronic active lesions (CALs) with B and T cell interaction,[31] B cell activation within the CNS linked to cortical demyelination,[28] astrocytic-driven chronic neuroinflammation,[32] and intrinsic deficits of neuronal metabolism and function[33–35] 35 (Table 2).

A network of various glial, immune, and neural cells is likely to contribute to the pathology underlying SAW. This is reflected by the cellular composition of CALs behind a relatively closed blood–brain barrier that contains activated microglia, astrocytes, oligodendrocytes, as well as lymphocytes.[24,36] In addition, diffuse microglial activation and signs of oxidative injury are abundant in normal-appearing white matter (NAWM) and are linked to axonal injury.[37] Overall, although they can have a homeostatic role in MS, microglia predominantly drive other disease-

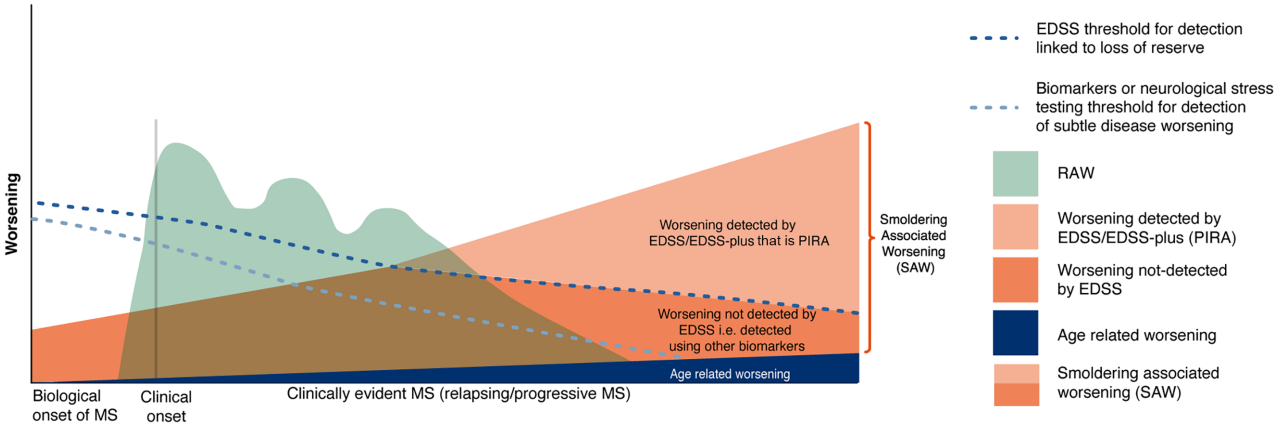

FIGURE 1: Multiple domains of disability accumulation in multiple sclerosis. Permanent loss of function can result from relapses (RAW) or from SAW. RAW events are more commonly observed in the early disease stage, but they then become more sporadic. Over the disease course SAW, encompassing a wide range of physical and cognitive symptoms, gradually accumulating in absence of relapses, clinically emerges and becomes more easily detectable. Within the umbrella of SAW, PIRA events are defined by changes on EDSS and EDSS-Plus, whereas other subtle symptoms can be detected by changes in stress tests and biomarkers levels, in combination with age driven biological changes, leading to exhaustion of compensatory mechanisms. 9HPT = 9 holes peg test; EDSS = Expanded Disability Status Scale; EDSS-Plus = worsening on EDSS; PIRA = progression independent of relapse activity; RAW = relapse associated worsening; SAW = smouldering associated worsening; T25FW = timed 25 feet walking tests.

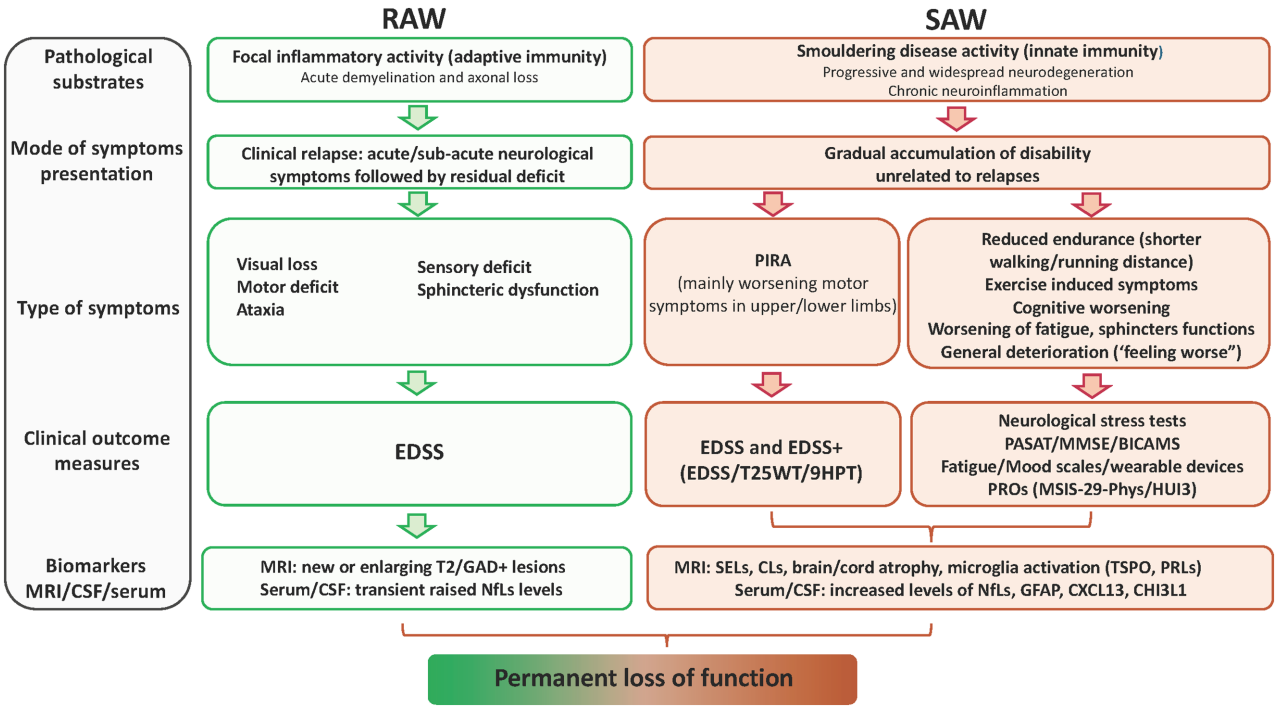

FIGURE 2: RAW and SAW are the 2 clinical phenomena leading to permanent loss of function. RAW and SAW are underpinned by different pathological substrates and present with different clinical manifestations. RAW can be detected with conventional clinical and imaging monitoring tools (EDSS and MRI measures of focal inflammatory activity). SAW encompass PIRA, but also other subtle cognitive and physical symptoms unrelated to relapses and accumulating in an indolent fashion, which can be unraveled by implementing more comprehensive monitoring with clinical, imaging, and serum/CSF outcome measures not routinely used in clinical practice. 9HPT = 9 holes peg tests; BICAMS = brief international cognitive assessment for MS; CHI3L1= chitinase-3-like protein; CLs = cortical lesions; CSF = cerebrospinal fluid; 1CXCL13 = chemokine ligand 13; EDSS = Expanded Disability Status Scale; GFAP = glial fibrillary acidic protein; HUI3 = health utility index; MMSE = mini mental state examination; MRI = magnetic resonance imaging; MSIS-29-Phys = MS impact scale; NfLs = neurofilaments; PASAT = paced auditory serial addition test; PIRA = progression independent of relapse activity; PRLs = paramagnetic rim lesions; PRO = patient reported outcome; RAW = relapse associated worsening; SAW = smouldering associated worsening; SELs = slowly expanding lesions; T25WT = timed 25-foot walk test.

TABLE 2. Pathological Drivers and Aging Related to Smouldering Disease in MS: Consensus Rates

Statement	5-point Likert scale of agreement percentages (%) from Delphi review				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Pathological drivers					
Smouldering disease may include various pathologic processes including chronic neuroinflammatory and degenerative biological mechanisms affecting white matter, cortex, spinal cord and deep gray matter structures	93	7	0	0	0
Pathological, experimental, and genetic evidence support a central role of biological processes within the central nervous system tissue for smouldering disease in MS, which occur early and progress throughout the course of the disease	93	7	0	0	0
The biological substrates for acute focal inflammatory activity appear to be different to the diffuse, smouldering inflammatory processes occurring in the CNS	93	0	7	0	0
There is a complex interplay between glial (eg, microglia) and other immune cells (incl. astrocytes, B- and T-cells) as orchestrators of compartmentalized immune responses in chronic CNS inflammation	100	0	0	0	0
Reactive microglia, astrocytes and tissue-resident adaptive immune cells serve as immunological drivers of diffuse smouldering inflammation within the CNS	100	0	0	0	0
Aging					
MS, like other chronic neurological disorders, is associated with accelerated aging	80	13	0	0	7
Aging reduces central nervous system reserve or resilience, which may precipitate SAW becoming clinically apparent earlier and has an impact on smouldering-related measures and biomarkers, which may require adjustment for age	93	0	0	0	7

CNS = central nervous system; MS = multiple sclerosis; SAW = smouldering associated worsening.

promoting processes, including increased phagocytosis, demyelination, and aberrant synaptic pruning.[38]

The presence of B and T cells within the chronically inflamed CNS and the inflammation of leptomeninges are also of interest to smouldering disease in MS. Within CALs[24,36] and as CNS-localized, B cells have been shown to induce tertiary lymphoid tissue formation within the brain meninges where inflammatory aggregates, sometimes resembling ectopic lymphatic follicles, accumulate and associate with adjacent subpial cortical demyelination.[27,39]

In addition, a recent study suggests Th17 pathway involvement in acute demyelinating lesions formation,[40] indicating its potential pathological relevance in smouldering disease activity. However, in a previous phase 2 trial the anti-interleukin 17 (anti-IL 17) antibody failed to meet the primary endpoint[41] leaving the question open on whether therapeutically targeting IL-17 related pathways can impact positively on the disease course. Th17 cells are outnumbered by CD8+ T cells with a tissue-resident phenotype,[42] which cannot be targeted by currently available therapies.

Closely associated with overlying meningeal inflammation, focal gray matter (GM) damage follows a surface-in gradient with increased neuronal loss and microglial activation in the most external cortical layers,[28] determining extensive demyelination and atrophy, which become prominent in the late stage of MS.[37] Results from post-mortem tissue studies show more than 50% of lesions with mixed active features, further emphasizing the role of pathological hallmarks of smouldering inflammation, which are remarkably pronounced even at the time of death.[43] Further evidence for a pathophysiological role of CNS-compartmentalized B cells was provided by transcriptomic analysis of clonally expanded B cells in the cerebrospinal fluid (CSF)[44] and by the increase of B cell-supporting follicular Th cells.[45] In addition, astrocytes recruited by infiltrating immune cells and microglia can shift into a disease-promoting state that perpetuates chronic inflammatory processes,[46] directly impairing neuronal metabolic support.[47] Mitochondrial and metabolic dysfunction is believed to be a key pathway for neurodegeneration in MS.[33]

Within the immune microenvironment, as multiple different cellular players act synergistically in specific CNS compartments (such as CALs or cortical GM) contributing to neuronal dysfunction and neuronal loss, it might be necessary to develop therapeutic strategies targeting multiple pathways simultaneously.[5]

The Role of Aging

As pwMS become older, with the gradual shift of the clinical phenotype from relapsing to progressive disease,[48] the clinical manifestations of SAW emerge and become more detectable. The interconnection between smouldering pathological processes and aging is complex and may be bidirectional. Smouldering disease in MS may promote premature biological aging of the CNS, whereas age-driven biological changes may also enhance the effect of smouldering mechanisms, eventually resulting in accelerated aging of the brain.[49,50]

The exhaustion of compensatory mechanisms[51] and the age-related decrease in CNS remyelination efficiency[52] can explain to some extent the gradual occurrence of symptoms related to smouldering disease with older age (Table 2). Furthermore, the presence of shortened telomeres, as a result of aging, correlates with greater disability,[53] and accelerated biological aging in MS can lead to epigenetic changes and cellular senescence, contributing to disease progression.[54] In MS brains, glial cells have been shown to age significantly faster than controls.[55] In addition, although this has not been demonstrated in MS as yet, astrocytes with aging are known to switch to a proinflammatory phenotype,[56] which might contribute to the loss of neurons and oligodendrocytes,[32] whereas age-related myelin fragmentation can induce microglial senescence and dysfunction,[57] potentially impairing the clearance of myelin debris, leading to decreased remyelination.[58] Finally, with growing older, the increased occurrence of vascular comorbidities[59] can negatively impact on brain reserve,[51] further enhancing smouldering pathological processes.

Because the brain ages faster in MS, brain-predicted age difference could be a potential imaging surrogate marker of brain health to monitor smouldering disease in MS.[50] Although it may not always be possible to disentangle clinical changes related to smouldering disease from what it is expected to be related to physiological aging and comorbidity, future efforts should be focused on the implementation of outcome measures that take into account age-related decline in neurological functioning to refine the assessment of clinically relevant disease worsening.[60]

CSF/Serological Biomarkers of Smouldering Disease in MS

Several CSF and blood biomarkers have been proposed potentially to reflect the pathophysiology of smouldering disease in MS, which may be clinically useful for identifying and monitoring SAW (Table 3). Peak levels of neurofilament light (NfL) concentrations in CSF and blood are observed during the occurrence of relapses and of new MRI contrast-enhancing lesions, but it might also correlate with the extent and rate of neuro-axonal loss,[61] because it has been shown to have prognostic value for long-term disability accumulation,[62] to reflect treatment response[63] and to predict the risk of experiencing PIRA.[64] In addition, higher concentrations of serum NfL were found among individuals with more paramagnetic rim lesions (PRLs) on MRI,[65] which are a negative prognostic indicator.[66]

Glial fibrillary acidic protein (GFAP) levels are considered a promising biomarker for monitoring SAW. GFAP concentrations reflect astrocyte and microglial activation,[67] predict GM volume loss,[68] and appear to be unrelated to the occurrence of clinical relapses.[68] Some studies also suggested its predictive role for future disability worsening of MS,[69] although this was not confirmed in a recent analysis of a large cohort of secondary progressive MS (SPMS) cases.[70] Interestingly, the combination of elevated z-scores of serum NfL and GFAP was found to be associated with a significantly increased risk of disability worsening and PIRA.[68]

The CSF concentration of chitinase 3-like 1 (CHI3L1, also known as YKL40) is a marker of

TABLE 3. CSF/Serological Biomarkers, Imaging Biomarkers and Clinical Markers Related to Smouldering Disease in MS: Consensus Rates

Statement	5-point Likert scale of agreement percentages (%) from Delphi review				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
CSF/serological biomarkers					
Biomarkers reflecting activation of microglia and astrocytes within the CNS such as GFAP, CHI3L1, and CXCL13 are potential markers for smouldering MS	100	0	0	0	0
Future research should explore potential CSF and blood biomarkers that are associated with clinical features and/or imaging findings characteristic for smouldering disease in MS. It is most likely that combinations of biomarkers may reflect pathological processes in smouldering MS	93	7	0	0	0
Imaging biomarkers					
Smouldering disease activity imaging biomarkers include global and regional brain and spinal cord atrophy, progressive changes in normal appearing gray and white matter. Focal CALs (SELs, PRLs, TSPO-PET, cortical lesions) are more specific to SAW while advanced MRI techniques (MTI, MWI, DTI, MRS, TSPO-PET) may also reflect RAW.	87	13	0	0	0
SELs may capture CALs, are more common than PRLs, and only partially overlap with PRLs. Ongoing research of SELs is evaluating its detection, feasibility, predictability, and specificity in both clinical practice and clinical trial settings	93	7	0	0	0
PRLs may be promising biomarkers of chronic active lesions in white matter and efforts are ongoing to further investigate and validate its feasibility in clinical practice	87	7	7	0	0
TSPO-PET imaging may be a promising biomarker of microglial and astrocyte activation in smouldering disease in MS. Availability, high cost, radiation exposure to patients and complex analysis limit its use in routine clinical care and clinical trials	93	0	7	0	0
Cortical lesions are relevant to clinical disease worsening associated with smouldering neuroinflammation. New MRI sequences are able to detect cortical pathology and may be a promising tool for future use in clinical practice and clinical trials	100	0	0	0	0
Clinical markers					
SAW may not be detected solely on routinely used clinical outcome scales such as EDSS/EDSS-Plus, which may be insensitive to subtle symptoms and/or signs, requiring additional monitoring and vigilance of all clinical domains	100	0	0	0	0
Routine clinical monitoring needs to go beyond conventionally used measures (eg, EDSS/EDSS-Plus), and will need to include PROs, digital biomarkers, cognitive, and other neurological stress tests to detect SAW	100	0	0	0	0

CALs =chronic active lesions; CHI3L1 = chitinase 3-like 1; CNS = central nervous system; CSF = cerebrospinal fluid; CXCL13 = chemokine ligand 13; EDSS = Expanded Disability Status Scale; GFAP = glial fibrillary acidic protein; MRI = magnetic resonance imaging; MS = multiple sclerosis; PET = positron emission tomography; PRLs = paramagnetic rim lesions; PROs = patient reported outcomes; RAW = relapse-associated worsening; SAW = smouldering associated worsening; SELs = slowly expanding lesions; TSPO = 18-kDa translocator protein.

astrocyte damage or activation, and to some extent, of macrophage and microglial activation.[71] Therefore, it is plausible that CHI3L1 levels might reflect chronic inflammation involved in smouldering disease in MS. CHI3L1 is not only expressed in the rim of CALs and by astrocytes in close proximity to activated microglia,[72] but its CSF concentration also correlates with the number of PRLs among pwMS with a first demyelinating event.[73] Overall, higher CSF CHI3L1 concentrations have been associated with increased risk of disability worsening and of experiencing progressive disease phenotype.[71]

Chemokine (C–X–C motif) ligand 13 (CXCL13) is a chemokine that is increased in CSF during disease activity in MS. Together with its receptor CXCR5, CXCL13 controls the organization of B-cells in lymphoid follicles and might, therefore, be of interest as a biomarker of meningeal inflammation and of the formation of ectopic lymphoid follicles in the brain.[39] Specific CSF profiles at diagnosis, with high levels of CXCL13, distinguish pwMS at higher risk of disease activity and of developing more severe cortical damage.[74] Moreover, high levels of CXCL13 were found to correlate with microglial activation.[75]

Intrathecal immunoglobulin production at MS diagnosis appears to predict disease progression. In particular, high levels of CSF IgM were found to be associated with worse prognosis[76] especially when they are accompanied by high CSF NfL levels.[77]

Although a correlation with the biology underlying SAW has not been demonstrated yet, the most promising biomarkers for smouldering disease in MS appear to be GFAP, CXCL13, and CHI3L1 (Table 3). In addition, intrathecal immunoglobulin production and several chemokines have the potential to reflect other smouldering pathological processes. The measurement of these biomarkers is not currently implemented in routine clinical practice, warranting further studies to establish their potential role as markers of smouldering activity.

Imaging Biomarkers of Smouldering Disease in MS

Clinicians rely primarily on the radiological detection of new focal inflammatory lesions as a marker of therapeutic response. However, it is not uncommon to see individuals who continue to worsen in the absence of new focal lesions, indicating a disconnection between clinical disease severity and radiological inflammatory lesions load,[78] which warrants the identification of alternative markers that more comprehensively capture SAW. Slowly expanding lesions (SELs), PRLs, positron emission tomography (PET) using radioligands specific for microglia, and imaging measures of cortical damage have demonstrated clinical relevance for pathological substrates underpinning smouldering disease in MS (Table 3).

Slowly Expanding Lesions

MRI defined SELs show continuous concentric expansion over time[79,80] and may be a biomarker of CALs, one of the potential pathological substrates of SAW. SELs can be detected with conventional MRI sequences. By using MRI measures sensitive to myelin content and microstructural tissue integrity (magnetization-transfer imaging, myelin water imaging, diffusion tensor imaging, and quantitative T1 signal change), it has been demonstrated that MRI defined SELs are distinguished by greater tissue destruction compared to non-SEL T2 lesions.[81] The reported occurrence of SELs varies substantially across studies, but a high proportion (60–90%) of pwMS has at least 1 SEL, and a variable proportion (up to 46%) of all T2 lesions can be identified as MRI defined SELs.[82–84] The variability observed among studies may be attributed to different populations and methods used to identify the slow expansion of lesions. A larger number and/or a higher proportion of T2-lesions that are MRI defined SELs distinguish patients exhibiting a progressive course, compared to patients experiencing relapsing disease.[82] In addition, the presence of MRI defined SELs has been associated with a higher risk of disability progression.[82,85] Overall, much remains to be clarified about SELs, including optimal detection methodology, the time frame in which they should be measured, and how best to use and interpret their presence and change in clinical trials and clinical settings. Above all, the pathological processes underlying MRI defined SELs remains to be fully established. An important caveat is that MRI defined SELs do not necessarily correspond to pathologically defined SELs, which may explain the substantial lack of overlap between SELs and PRLs. Therefore, MRI defined SELs can be sensitive to CALs, but not specific, which represents a limitation that must be acknowledged during their evaluation.

PRLs

PRLs, also referred to as iron rim lesions (IRLs), are detectable on susceptibility-based MRI and have been validated pathologically as CALs with iron-laden macrophages and microglia activation.[66,86–88] Several acquisition and post-processing methods have been used to detect PRLs, including single-echo and multi-echo gradient images from which susceptibility weighted imaging, phase, T2*/R2* and quantitative susceptibility mapping can be derived. Each method offers advantages, but also has potential limitations, and it remains to be established, which technique performs better.[80]

Compared to rimless T2-lesions, PRLs are larger, expand over time,[66,88] and are distinguished by a higher degree of tissue injury in the core[66,89] Recent studies show varying levels of overlap between SELs and PRLs, with 7 to 17% of SELs corresponding to PRLs in 1 study[81] in contrast to ~50% in another.[84] The minimal overlap between PRLs and MRI defined SELs is likely to be multifactorial. First, it is plausible that some CALs may not be visible as PRLs because of a relatively small amount of iron not meeting the threshold for MRI visibility,[90] although such lesions still slowly enlarge making them identifiable as MRI defined SELs. Second, several pathobiological processes, including demyelination and chronic inflammation, are likely to account for the slow expansion over time, making MRI defined SELs sensitive, but not specific to CALs.

PRLs have been shown to occur from the earliest stages of MS[91] to be associated with worse clinical and radiological outcomes[66] and to be related to the occurrence of cognitive impairment even among subjects with RIS.[15] In addition, when detected in juxtacortical regions, PRLs were found to correlate with the severity of cortical demyelination.[92] Over the course of the disease, PRLs tend to naturally appear and disappear as the microglia accumulate and subsequently lose iron, becoming quiescent.[88] The longevity and natural disappearance of PRLs may be a challenge in clinical trials, although changes in their microstructural properties can be seen within 2 years.[66] Ultra-high field MRI, such as 7 Tesla (7T) is considered the gold standard for the detection of PRLs, although they can also be visualized at 1.5T and 3T too.[80] There are numerous susceptibility-based acquisition and post-processing techniques currently being used to visualize PRLs, and it is currently unclear, which technique is best at detecting and characterizing PRLs.[93] Large, multicenter studies comparing acquisition and post-processing techniques to detect PRLs will be required to answer this question.[80] Overall, PRLs are an appealing candidate for monitoring SAW in clinical trials and in clinical practice in the future, with further evaluation and validation ongoing.[80]

PET Imaging

Radioligands binding to the 18-kDa translocator protein (TSPO) and PET can be used to evaluate chronic inflammation in MS brain tissue.[94] On activated innate immune cells and on a subset of astrocytes, which have increased density in specific brain regions, the TSPO molecule is upregulated, translating into increased TSPO ligand binding.[94] Using TSPO-PET, widespread smouldering inflammation can be quantified in vivo both in the NAWM and in the GM of MS brains, as well as at the edge of a proportion of CALs, which corresponds to microglial activation, as shown by pathological studies.[94]

TSPO-binding was found to predict the conversion of clinically isolated syndrome (CIS) to RRMS,[95] to be increased in the brains of SPMS cases, compared to RRMS and healthy controls, and to be associated with the rate of brain atrophy and disability accumulation,[96] as well as with serum NfL concentrations.[97] In addition, the degree of TSPO-binding in the thalamus, in the NAWM, and at the edge and core of CALs was shown to predict the occurrence of clinical worsening independent of relapses,[98,99] further highlighting its potential role as a biomarker for SAW. However, TSPO-PET is currently not widely accessible in clinical practice because of its challenging technology and limited availability, high cost, limitations related to patients' radiation exposure and to complexities in image analysis and modelling. Ongoing work for standardizing TSPO-PET analysis pipelines and for developing novel ligands able to more specifically differentiate activated microglia with different functional properties[100] may facilitate the use of PET imaging in the future as an outcome measure in clinical trial assessing treatments targeting smouldering MS pathology.

Cortical Pathology Measures

The extent of focal demyelination within both the cortical and deep grey matter (GM) strongly correlates with the rate of disease progression and its underlying mechanisms are believed to be unrelated to WM demyelination.[28,37,101] Cortical lesions (CLs) can be detected from the early phases of MS,[102] and its progressive accumulation over time is associated with a higher risk of converting to SPMS[101,103] and of accumulating severe disability in the long term.[104] Moreover, long-term data suggest that CLs may be one of the neuropathological substrates of cognitive impairment.[105]

With the use of neurite orientation dispersion and density imaging (NODDI), among others, it has been demonstrated that, beyond focal injury, there are diffuse microstructural abnormalities in the normal-appearing cortical and deep GM, including cortical neurite loss, simplification of cortical dendritic arborizations and cytoarchitectural complexity, suggestive of neurodegeneration.[106] Significantly more pronounced neurite loss was found in the GM of individuals with progressive disease, compared to RR groups,[107] and in the WM and spinal cord of pwMS, compared to healthy controls,[108] highlighting the potential role of NODDI for monitoring pathological processes accounting for disability accumulation independent of focal inflammatory activity.

In addition, diffuse GM atrophy, including measures of cortical atrophy, has been shown to occur from the

early stages of the disease and to correlate with long-term disability accumulation.[103,109] Given its relationship with disability progression and PIRA,[110] several clinical trials have started including global and regional brain atrophy as an imaging biomarker for monitoring tissue damage.[111] Novel therapies targeting mechanisms believed to contribute to SAW may also slow GM atrophy. Although atrophy measures mirror the end result of various pathobiological processes resulting in tissue destruction and, therefore, are not specific to only smouldering disease processes, they can certainly be useful markers of pathological damage related to SAW. However, important technical limitations persist for the assessment of GM pathology radiological markers (CL and atrophy). Most CLs remain undetected by 1.5/3.0T MRI,[112] whereas 7T MRI can visualize only 52% more CLs than the best-performing 3T MRIs.[113] Imaging protocols, including non-conventional sequences, such as 3 dimensional (3D) -DIR, 3D-phase-sensitive inversion-recovery, magnetization prepared rapid gradient echo (MPRAGE), and MP2RAGE have substantially improved the assessment of CLs in vivo even in a 3T MRI scanner,[114–116] and therefore, could be used in future clinical trials. Further efforts will have to focus on additional imaging measures, as outlined above, that are more specifically correlated to biological mechanisms underlying SAW, and together with atrophy measures can shed more light on the extent of microstructural tissue damage driving smouldering disease in MS.

Clinical Markers of Smouldering Disease in MS

Routinely used clinical and paraclinical tools are not adequately sensitive to unmask relapse-free clinical worsening, especially early in the disease course, and the lack of surrogate markers or universally accepted definition for continuous disability worsening makes this challenging to monitor even by the most experienced physicians. The EDSS score is widely used as an outcome measure of neurological impairment and disability in MS,[7] but its changes are not sufficiently dynamic to reflect SAW, and its use is limited by floor and ceiling effects, and by both intra- and inter-rater variability.[6]

The implementation of composite clinical outcome measures, such as the MSFC[9] and the EDSS-Plus (also termed Overall Disability Response Score [ODRS])[13] represents an attempt to overcome these limitations, because they allow more comprehensive and earlier characterization of disease worsening, enhancing our ability to pinpoint relatively subtle changes in disability. By combining the EDSS with the timed 25-foot walk (T25W) and 9-hole peg test (9HPT), the EDSS-Plus can capture wider aspects of disability worsening.[13] Among SPMS cases from the placebo arm of the IMPACT study, 59.5% experienced disability progression as measured by the EDSS-Plus, whereas only 24.7% met the conventional definition of disability accumulation using the standard EDSS definition.[13] In line with these observations, in the combined post hoc analyses of the ocrelizumab OPERA trials, with the implementation of the EDSS-Plus it has been demonstrated that the presence of PIRA occurs in a large proportion of RRMS with stable inflammatory parameters.[8] In addition, the ODRS was found to be a sensitive and enhanced tool for detecting progressive deterioration among pwMS with RRMS and SPMS from the AFFIRMS and ASCEND trials,[117] further demonstrating the value of composite outcome measures for unmasking elements of disease progression (independent of relapses) especially in the early stages.

However, subtle accumulation of symptoms and signs often does not even fulfil the yet unvalidated definition of PIRA.[118] This is predominantly based on clinical scales mainly capturing changes in motor performance, but to a large extent insensitive to worsening in other clinical domains, such as cognitive performance, which is an important aspect of smouldering disease in MS. Attempts have been made to integrate the EDSS with the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and with orientation tests (such as Mini Mental State Examination [MMSE]), which unmasked cognitive impairment otherwise undetected with standard clinical assessments.[119]

Overall, composite outcome measures cannot be easily incorporated in routine practice, and a major challenge will be validating alternative measures that need to be multidimensional to provide a deeper insight into clinically meaningful changes characterizing smouldering disease in MS. Similar to cardiac stress tests, which are an integral part of an interventional cardiologist's work-up, neurological stress tests should be used to assess neurological reserve by objectively measuring walking and/or running distances and times, cognitive reaction times, gait and balance analyses, and visual tests (Table 3). Three-dimensional gait analysis has been implemented to capture exercise-induced walking deterioration, which can be highlighted among individuals with moderate neurological disability (EDSS <3.5).[120] An accurate assessment of fatigue, bladder/bowel symptoms, and sexual function can also help to uncover clinical evidence of SAW. Wearables and sensor-based monitors provide a unique opportunity to monitor individuals in a day-to-day setting.[121] Using engineered gloves, hands, and fingers fine motor performance can be accurately monitored, unmasking subtle worsening impairment, even among subjects with RIS.[122]

Beyond traditional monitoring by healthcare professionals (HCPs), self-monitoring tools and patient-related outcome measures (PROs) should be routinely used to estimate the impact of smouldering disease on daily functioning.[123] Several studies highlight the potential value of PROs in monitoring subtle disease worsening, although evidence supporting its correlation with pathological processes underlying smouldering disease in MS are still lacking and more robust data are required to better understand how such tools can serve as markers of SAW. The United Kingdom MS registry is based on data collection from pwMS periodically filling out online questionnaires covering many aspects of the impact of MS on daily life. The physical MS impact scale (MSIS-29-Phys) was used to assess the impact of fatigue[124] and smoking[125] on walking ability, highlighting its potential as an outcome measure for SAW. In addition, recent analyses of the ORATORIO trial provided further evidence in support of the MSIS-29-Phys and Fatigue Score Motor and Cognition questionnaires as useful tools for predicting disability progression.[126] However, fatigue trajectories can remain relatively stable over long time, implying that fatigue scales might have limited utility as dynamic measures. In this context, the combined use of PROs scales and wearable devices[121] might hold greater potential for monitoring subtle clinical deterioration resulting from SAW.

The Health Utilities Index 3 (HUI3) represents another potentially useful PRO measure with strong psychometric properties, which was found to be more efficient in detecting change in disability than other measures.[127] Bayas and colleagues[128] demonstrated that an online survey is considered an appropriate tool to gain valuable insights into the pwMS's perceived disease course. Continuous worsening of symptoms independent of relapses in the previous 12 months was reported by the vast majority (88.9%) of RRMS cases with marked-to-severe disability and over half of cases with no or mild-to-moderate disability.[128]

With this array of clinical markers to detect subtle changes or worsening, there arises a compelling argument for the seamless integration of these tools into routine clinical practice, and for supporting a paradigmatic shift in routine MS management.

Integration into Clinical Practice

Evidence of smouldering pathology and progression across the spectrum of MS, even in the earliest stages, warrants a revision of the disease clinical phenotypes descriptors.[4,6,11] Among pwMS, we suggest using relapsing or progressive disease courses only as supplemental non-diagnostic descriptors to inform disease management. In addition, HCPs should acknowledge that "clinically stable" individuals may still worsen in several physical and cognitive domains, feeling ignored and frustrated because of their unrecognized clinical deterioration. As an expert panel, we have set out several examples of probing questions that can help to uncover SAW in routine clinical practice (Table S1).

Naturally, HCPs are uncomfortable identifying and discussing smouldering disease in MS, because there are no licensed treatments for preventing SAW yet. However, openly discussing smouldering disease with pwMS should facilitate managing their expectations about current MS treatment targets. Although DMTs impact positively on the natural course of the disease,[129] the therapeutic suppression of focal inflammatory activity might have a limited effect on the pathological substrate of smouldering disease.[6] Despite NEIDA, SAW may still occur, albeit at a lower rate than when pwMS are on treatment.[8] Overall, it remains unclear whether SAW occurs in all pwMS, as a minority experience more favorable outcomes with a disease course that remains relatively stable over the years.[130] This is more likely to occur when aggressive therapeutic management with high-efficacy DMTs is implemented early in the disease.[131]

The impact of smouldering disease in MS can also be potentially minimized by implementing a holistic management approach. This implies not only addressing MS-specific processes, but also preventing and/or treating comorbidities, which are known to be associated with poor MS outcome.[59] In addition, several potentially modifiable factors play important roles in determining the disease severity. Poorer health behaviors, such as smoking,[132] lack of regular physical exercise, and unhealthy dietary habits have been shown to correlate with lower quality of life,[133] and social isolation, loneliness, unemployment, and low social capital were found to predict poorer prognosis.[134] Overall, efforts should focus on promoting brain health[135] by optimizing lifestyle factors, including regular exercise,[136] stopping smoking,[125] maintaining a healthy diet[137] and good sleep patterns. Because physical activity plays an important role in general wellbeing, over recent years, yoga has gained increasing interest as an intervention that can potentially improve symptoms and quality of life among pwMS.[138] This can be an attractive option to empower pwMS and encourage their active involvement in disease management. Finally, individuals with SAW may be eligible for clinical trials or be enrolled in non-drug interventions such as lifestyle, wellness, social, and cognitive rehabilitation programs to optimize brain health,[139] which may positively impact some of the mechanisms driving their disease worsening (Table 4).

TABLE 4. Integration into Clinical Practice and Implications for Clinical Trial Design and Regulations: Consensus Rates

	5-point Likert scale of agreement percentages (%) from Delphi review				
Statement	**Strongly agree**	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**
Integration into clinical practice					
People with MS must be aware of smouldering disease to manage expectations of what current DMTs can realistically achieve	93	0	0	7	0
People with MS reporting worsening function, not detectable in routine practice, should be acknowledged as having possible SAW and should be offered more detailed testing. SAW should be proactively sought out, investigated, and each domain (overt or subtle) of worsening symptoms and/or signs should be managed appropriately	93	7	0	0	0
Identifying SAW may allow people with MS to benefit from non-drug interventions (eg, cognitive rehabilitation) and potentially be eligible for clinical trials targeting smouldering pathology	93	7	0	0	0
Optimized management of MS should include a holistic approach beyond focusing on MS-specific processes, to include preventing and/or treating comorbidities known to accelerate smouldering disease in MS	100	0	0	0	0
Implications for clinical trial design and regulations					
Regulators need to acknowledge the multifaceted nature of MS beyond RAW, in particular SAW, and should progress past sole reliance on EDSS and EDSS-Plus when assessing the effectiveness of DMTs targeting smouldering disease in MS	93	0	0	7	0
Clinical trials targeting smouldering disease in MS will need to include multi-domain outcome measures. These include neurological stress-tests, age-adjusted outcomes and surrogate markers, reflecting the impact of MS on different domains that are not captured by conventional outcome measures	100	0	0	0	0
New trial methodologies, including combination therapies and adaptive designs, will need to be developed to investigate smouldering disease in MS	100	0	0	0	0

DMTs = disease-modifying treatments; EDSS = Expanded Disability Status Scale; EDSS-Plus = EDSS, timed 25-foot walk test, on 9-hole peg test; MS = multiple sclerosis; RAW = relapse-associated worsening; SAW = smouldering associated worsening.

Implications for Clinical Trials and Regulations

Historically, clinical trials in MS have focused on endpoints that have allowed the development and approval of therapies primarily modulating relapses. To be clinically meaningful, outcomes should have "face validity" or be strongly linked to quality-of-life measures (EMA Guideline EMA/CHMP/771815/2011, Rev. 2). Although

relapses, EDSS, and MRI measures provide important information, they offer, at best, a limited view of the underlying smouldering biology of MS and arguably underrepresent true clinical disease activity, particularly from a patient perspective.

We advocate for regulators to incorporate the concept of smouldering disease into clinical trials to target SAW, which can include other endpoints, reflecting disease deterioration independent of new focal inflammatory activity. Multimodal sets of validated radiological, clinical, body fluid biomarkers, and PROs should be implemented to measure and monitor SAW using composite outcomes (Table 4). This will help capture meaningful clinical changes and relate to clinical stages to be useful in clinical trials.[140]

Although the EDSS-Plus potentially provides a more sensitive measure of physical disability accumulation, it does not place emphasis on cognitive impairment and does not provide information on longitudinal changes in disability.[117] Surprisingly, only a small proportion of phase III clinical trials include cognitive evaluations in their analyses.[141] The integration of the EDSS with the BICAMS and with MMSE can help to assess cerebral functional system scores more accurately.

Fatigue also has a major impact on pwMS, yet its assessment as an outcome is underrepresented in trials of DMTs,[142] highlighting an important unmet therapeutic need.

With respect to imaging, over the last 2 decades, several clinical trials have incorporated imaging biomarkers of global and regional brain atrophy to monitor treatment effect on CNS tissue loss.[143] High efficacy DMTs have been shown to significantly slow brain volume loss.[144,145] MRI and PET biomarkers of microglia activation and CALs have certainly opened the avenue to new studies assessing the potential effect of therapies on pathological pathways driven by the innate immune system.[94] MRI-defined SELs and PRLs are additional biomarkers of radiological disease progression in the absence of measurable acute inflammation.[66,81,86,88] Dynamically combining SELs, PRLs, and CALs detected by microglia-specific PET ligands may offer a promising outlook for the multifaceted progression of MS. Finally, efforts should be made to standardize the use of quantitative structural and functional MRI techniques for the detection and measurement of biological mechanisms harboring normal-appearing WM and GM of both the brain and spinal cord in the setting of clinical trials. Overall, there is an urgent need for synergistic work between the scientific community, industry, stakeholders, and regulatory agencies to accelerate the validation and implementation of these biomarkers and of composite measures (including multimodal assessments measures). Assessing sample size and appropriate study design will need to immediately follow these efforts.

Discussion

By using the Delphi method, our international panel of experts aimed to provide clinicians and scientists with consensus statements covering several aspects of smouldering disease in MS. The selection of panelists was based on clinical experience, scientific background and expertise, and geographical representation. This ensured expert and unbiased views on a wide range of key scientific areas. However, we acknowledge that an independent panel of pwMS, would have provided additional useful perspectives and insights about several aspects of smouldering MS. Our conclusions were built on emerging clinical, radiological, and pathological evidence supporting a paradigm shift in our understanding of the mechanisms contributing to disease worsening. Our ultimate goal was to unify the diverse and disparate views on smouldering MS. It is now generally accepted that PIRA is a key determinant of MS worsening from the earliest disease phase, but its quantification is based on EDSS/EDSS-Plus, which can capture only to some extent clinically meaningful deterioration. Although PIRA is likely to be accepted by regulators as an outcome measure in clinical trials, several shortcomings prevent its implementation in routine clinical practice, because its definition requires a re-baseline and 3- to 6-monthly assessments to confirm worsening, it does not incorporate biomarkers, it is not underpinned from a biological perspective, and it does not acknowledge the effects of aging. We recognize PIRA as one of the components of smouldering disease in MS, but in view of its limitations, it should be reserved for EDSS-based metrics. Here, we challenge the dogmatic view of MS by proposing the concept of SAW, encompassing PIRA, but also a wide range of physical and cognitive symptoms gradually worsening in absence of relapses, which cannot be quantified by EDSS/EDSS-Plus (Fig 2). SAW reconciles smouldering pathobiological processes affecting the CNS with worsening disability in multiple domains and addresses many of the shortcomings of PIRA.

Overall, RAW and SAW are the disease's 2 main clinical phenomena, which are underpinned by different pathology, both leading to permanent loss of function. In our current disease management model, residual deficit from relapses can be detected with conventional clinical and radiological tools, whereas more comprehensive assessments with clinical, imaging, and serum/CSF outcome measures, which are yet not routinely implemented, are required to unravel manifestations related to SAW (Fig 2). We acknowledge the lack of a uniform definition of smouldering MS, and we have developed a consensus-driven new lexicon (Table S2) to explain smouldering pathology and SAW to facilitate communications among patients, HCPs, and other stakeholders and to promote its integration in clinical practice. We highlight the

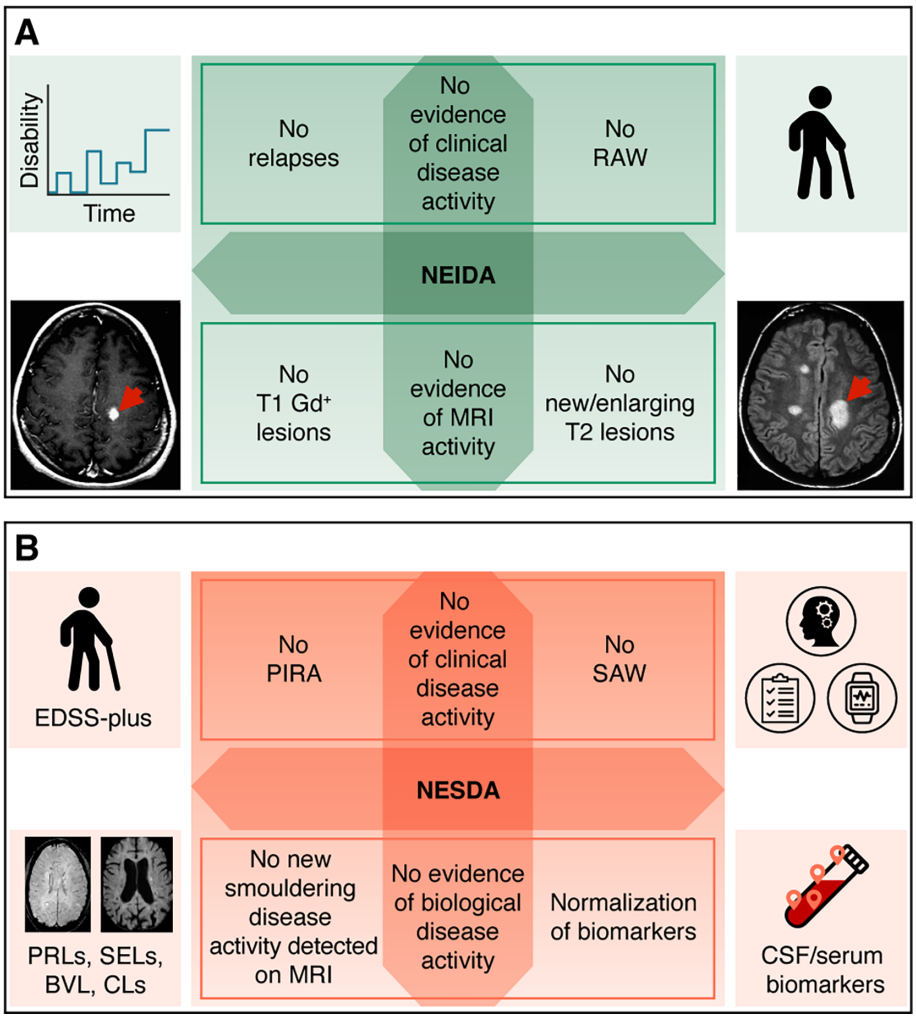

FIGURE 3: Therapeutic control of disease activity parameters in multiple sclerosis. In addition to preventing mechanisms underlying RAW, preventing smouldering pathological processes underlying SAW will become the dominant goal of future therapeutic strategies. (A) NEIDA is defined by the lack of new relapses (RAW) and of new magnetic resonance imaging (MRI) activity; (B) no evidence of smouldering disease activity (NESDA) is the defined by lack of clinical evidence of SAW, including PIRA. Changes related to SAW can be measured with cognitive tests (SDMT), PROs, stress tests, fatigue scales, wearable devices (digital markers), imaging biomarkers (SELs, PRLs, CLs, and brain atrophy), CSF/serum biomarkers (NfL, GFAP, CHI3L, and CXCL13 levels). NEIDA, absence of clinical (relapses) and MRI (newT2/GAD+ lesions) focal inflammatory activity. 9HPT = 9 holes pegs test; CHI3L1 = chitinase 3-like 1; CLs = cortical lesions; CXCL13 = chemokine ligand 13; EDSS = Expanded Disability Status Scale; GFAP = glial fibrillary acidic protein; NEIDA = no evidence of inflammatory disease activity; NESDA = no evidence of smouldering disease activity; NfL = neurofilaments light; PIRA = progression independent of relapse activity sustained progression measured by EDSS and EDSS-Plus (worsening on EDSS, T25FW or 9HPT); PROs = patient-reported outcomes; PRLs = paramagnetic rim lesions; RAW = relapse associated worsening; SAW = smouldering associated worsening; SDMT = single digit modality test; SELs = slowly expanding lesions; T25FW = timed 25 feet walking tests.**

importance of addressing the pathogenesis and treatment of MS beyond acute focal inflammatory activity (relapses and focal MRI lesions), and beyond the target of NEIDA (Fig 3). In addition to current treatments addressing mechanisms underlying RAW, preventing smouldering pathological processes and SAW will become the dominant goal of future therapeutic strategies, aiming at inducing MS remission with no evidence of smouldering disease activity (NESDA) (Fig 3).

In parallel, we urge the MS community to routinely incorporate imaging and fluid biomarkers, neurological stress tests, and PROs to detect SAW and to monitor various aspects of disease worsening more comprehensively. Blood NfL levels, whole brain, cortical and regional atrophy measurements, and quantification of PRLs are most likely to be standardized in the near term, and therefore, adopted by the wider MS community. Future efforts should be focused on developing improved and sensitive metrics for quantifying and documenting SAW in clinical practice, and in both phase 2 proof of concept and phase 3 registration trials.

Furthermore, we emphasize the need to revise the current disease classification system, clinical trial designs,

and trial endpoints to incorporate these insights and to promote a dialogue with regulators and health authorities on the limitations of current management. Finally, our consensus advocates for research into addressing pathobiological processes underpinning smouldering disease in MS, which can become targets of future treatments.

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Author Contributions

All authors were involved in conception and design of the study, reviewing literature and selecting data to be presented, and drafting and revising the manuscript and figures for content.

Potential Conflicts of Interest

Nothing to report.

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