MS Brain Health

OXFORD HEALTH POLICY FORUM

Brain health – time matters

Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and related conditions

2024 Report

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Foreword

Who among us can truly assert that we have no regrets? A son or daughter longs to ease the suffering of an ageing parent; a doctor desires the availability of better treatments, more time and adequate resources to improve the health of their patients, to alleviate pain and heartache. "If only …"

However, "if only" can become an impetus that shapes our goals and conjures a vision for change. Our hope is that this report will challenge each reader to see beyond "if only" and seize the opportunities that we have now.

In 2015, we had the privilege of developing the evidence-based policy report, *Brain health: time matters in multiple sclerosis*. Our vision was for the recommendations from that expert group to be shared widely to help to create a better future for people with multiple sclerosis (MS) and their families. Almost a decade later, we celebrate the dedication and hard work of the many authors, endorsers and supporters who responded to the calls to action.

The 'MS Brain Health' initiative has had a truly positive impact on the MS community. Building on the report's recommendations, a diverse group of MS experts identified the priority quality indicators that should define standards of MS care using a Delphi consensus process. Then followed the development of a globally applicable 'quality improvement tool', piloted in 17 MS centres, that enabled the participants to identify specific areas for local improvement. The concepts of self-management, early intervention and adopting a brain-healthy lifestyle have been welcomed by many advocacy groups and patient organizations, and are becoming increasingly accepted by people with MS. So, why are we still banging this drum?

An update of our original report is timely for many reasons. Importantly, this current report has been expanded beyond MS, to include other, related neuroimmune conditions: neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). These rare, disabling diseases have similar symptoms to MS, but different underlying drivers of the disease process. Anyone involved in clinical, societal or policy decisions concerning these conditions needs to understand the differences between them, to ensure that they are diagnosed and treated appropriately. Although there have been many advances in the field of MS, NMOSD and MOGAD need to be understood better and receive more support.

On the MS front, new knowledge about the processes that underlie disease progression is driving us to rethink previous assumptions about treatment. Ongoing research into the link between infection with the Epstein-Barr virus (EBV) and MS could lead to the possibility of preventing MS by vaccinating against EBV. Advances in the fields of diagnosis and monitoring also call for fresh approaches. In addition, the important work by groups such as MSBase and the European Register for Multiple Sclerosis in collecting standardized real-world data is helping to fill the gaps in our knowledge.

The group's recommendations echo many of the themes from our previous report, which can be applied broadly to neuroimmune diseases. If you can make a difference to someone with one of these rare disabling diseases, we trust our report will challenge and inspire you to act while you can.

Gavin Giovannoni and **Helmut Butzkueven**, co-Chairs 2024 report

A word on language

This report is aimed at a wide range of professional and geographically diverse audiences and has been written to be understood by all readers.

- Describing individuals
  - How best to refer to people with medical conditions is an emotive and sometimes controversial question. The word 'patient' is appropriate in a medical context, but may be too clinical for a person living in the community. Terms such as 'service user', 'client' and 'consumer' are used in some countries and settings, but they often do not translate well elsewhere.
  - In this report, the authors have chosen to use the word 'patient' when the setting is strictly clinical, but 'person with multiple sclerosis' (MS) (or neuromyelitis optica spectrum disorder [NMOSD]/myelin oligodendrocyte glycoprotein antibody-associated disease [MOGAD]) in other contexts.
  - It should also be noted that most work in this area focuses on the sex one is born with rather than gender.[1]
- Inclusion of additional conditions
  - In this report, compared with our original report,[2] the scope has been expanded to include other neuroimmune conditions and the focus is on updating the evidence base, as well as including information relevant to NMOSD and MOGAD. We believe that the recommendations will be more broadly translatable across neuroimmune diseases.
- Relapses
  - There is variation in the literature when referring to intense exacerbations or flare-ups of symptoms that are experienced by people with NMOSD and MOGAD, with the terms 'attacks' or 'relapses' both used.
  - In this report, we will use 'relapses' throughout because this is consistent with the terminology used in MS.
- Holistic management
  - In this report, holistic management refers to an approach to care that considers the whole person and acknowledges the interdependence between biological, social, psychological, emotional and spiritual aspects of well-being.
- Social drivers of health
  - In this report, the term 'brain health drivers' has been used in contexts in which 'social determinants' could be used. This is in recognition that no one is determined to have bad health outcomes, rather that there are recognized factors that can contribute to outcomes.

Executive summary

Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are related, lifelong diseases. There are no cures and, particularly when undiagnosed, misdiagnosed or not treated early and effectively, they can severely affect many aspects of people's lives.

This report builds on our 2015 policy report, *Brain health: time matters in multiple sclerosis*, to include advances made in our understanding of MS and encompass improvements in practice standards, policy developments and emerging science. As per the 2015 report, the authors recommend specific actions to achieve the best possible outcome for people living with these diseases and the overarching theme remains clear – to act early and take a person-centred approach to care, regardless of geographic or economic barriers.

Therapeutic strategies for each of the three diseases that offer the best chance of minimizing ongoing disease activity early in the disease course need to be widely and urgently adopted. When disease activity is not addressed early, increasing disability – such as difficulty walking and vision problems – risks imposing a heavy burden on people and their families. This leads to substantial economic losses for society, due to diminished tax revenue and increasing care costs that could have been avoided. It is bad health economics.

Timely diagnosis is therefore of critical importance, alongside early treatment initiation with effective therapies. People often face considerable delays in diagnosis and treatment initiation, and the non-specific nature of symptoms can contribute to misdiagnosis. Actions to avoid protracted diagnostic journeys such as the right to additional opinions, increased access to specialists and awareness among referring clinicians, and improved access to specialized diagnostic procedures are needed.

Despite outstanding progress in research and development into treatment and detection innovations, treatment access remains limited in many countries. Regulatory bodies, healthcare authorities, payers and budget holders can all help to improve early access to effective therapies that offer optimal treatment outcomes (also known as 'flipping the pyramid'). Relevant bodies need to consider the costs to all parties when conducting economic evaluations, and support research and development into novel therapeutic strategies.

Effective and regular monitoring of disease activity and the formal recording of this information forms a cornerstone of the treatment strategy recommended by the authors. Paying close attention to comorbidities (including depression), lifestyle factors and modifiable brain health drivers, and monitoring visible and hidden symptoms of disease worsening or progression, such as cognitive changes, are part of an optimal approach to care. The results of clinical examinations and brain scans will enable personalized treatment for every patient. Standardization of these outcomes can also generate long-term real-world evidence that can be used to evaluate therapeutic strategies, and should set the outcome targets to which relevant stakeholders should be held accountable.

But most critical is to involve people proactively in shared decision-making and empower them to manage their diagnosis through holistic care and to adopt a lifestyle that maximizes their brain health (e.g. not smoking, keeping as active as you can, improving sleep). The goals should be to provide a person-centred, integrated approach to care, not forgetting about the key role disease-specific peer support and community organizations can play, and to direct patients and their families to them as standard practice.

In this report, the author group presents a thorough set of recommendations and the rationale for them with the hope that strong political will and societal commitment will improve the outcomes for all people with MS, NMOSD and MOGAD. Enabling and promoting widespread adoption of these recommendations has the potential to maximize lifelong brain health. The key is to start somewhere; even small changes can make a difference to individuals, families, societies and economies.

My experience, my reality

The following stories are fictional accounts, based on known patient experiences with neuroimmune conditions. These scenarios may apply to a person living with MS, NMOSD, MOGAD or related conditions. We hope these provide some context about how these diseases intersect and relate to the needs covered in this report.

Pascale, a former musician living with NMOSD

"My journey began with a mild blur in my vision, which soon became a thick fog, together with flu-like symptoms. My vision deteriorated until I lost sight in one eye. Doctors were baffled.

In one terrifying episode I was hospitalized, experiencing paralysis from the chest down. This mostly improved, but I was never the same afterwards. After being sent home, I struggled to get a referral to neurology. After 9 months, I saw a neurologist who diagnosed me with MS and started me on treatment. A year later my symptoms worsened and I was rushed back to the hospital.

New tests revealed I had NMOSD, not MS. The correct diagnosis was a relief, but I was angry and afraid. A delayed diagnosis meant I didn't get the right treatment and so my NMOSD relapses weren't prevented. I lost much of my vision and can no longer walk unaided. I have to retrain to be able to work and for now I rely on my family. Despite having the right treatment now, the prospect of new relapses worries me.

My life and situation may have been different if I had an early diagnosis. Raising awareness about rare neuroimmune conditions and getting a timely diagnosis is crucial to prevent others from going through my experience."

Amelia, a company director living with MS

"Nine months ago, I received the life-altering diagnosis of MS. Initially, my health team was incredible; they diagnosed me swiftly and provided support. They recommended infusion therapy, known for its effectiveness in halting new lesions and relapses. I felt hopeful and fortunate. Yet, the path to treatment has been fraught with challenges. Despite the early diagnosis, I have been waiting to secure an infusion spot in the day unit to receive my first treatment. The healthcare system is overwhelmed, busy and underfunded, making it impossible for me to receive the timely care I desperately need. Policymakers need to take action and help to drive change. That is why I advocate to strengthen patients' rights and help to protect our dignity.

Recently, I noticed an unsettling sensation – my eye started to ache and my vision became blurry. For me, this is a new symptom of MS. Each day that passes without treatment intensifies my anxiety. I understand the progressive nature of MS and the importance of early intervention. The delay is threatening my future quality of life and independence."

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Samantha, a graphic designer living with NMOSD

"Living with NMOSD for the past 6 years has been a tumultuous journey. Initially, the tablets prescribed to me failed to prevent relapses, leaving me in a constant state of uncertainty and fear. However, following a transition to infusion therapy, I experienced a significant improvement in my condition. I live in Asia and the health system in my country doesn't cover the cost of infusion therapy. Despite having private insurance, it only covers about half of the treatment cost and I pay the rest.

Adding to the financial difficulties of treatment, NMOSD has severely affected my hands, making my usual work impossible. I've lost a lot of my income as a result. My family has been incredibly supportive, pooling their resources to help cover my treatment expenses, but our financial situation is becoming increasingly strained. The prospect of having to revert to tablet treatment is terrifying – I fear the relapses may return and worsen my health. Given our financial difficulties, I may have no choice soon.

My story highlights the need for accessible and affordable treatment options for people with neuroimmune conditions worldwide and the need for retraining schemes so we can continue to earn a living. I hope in the future people won't need to choose between their health and their finances."

John, an accountant living with MS

"At 36 years old, I've been living with MS for 12 years. When I was first diagnosed, I started on injectable therapy. Despite this, I was still having relapses. Eventually, my neurologist switched me to oral treatment. Since then, I haven't had any relapses, and my MRI scans have shown no new lesions. My neurologist assures me that my disability – measured by EDSS score – is stable at 3.0.

Two years ago, running and walking long distances was manageable, but now my body doesn't cooperate. I track my activity using my smartwatch and since then there's been a steady decline of over 30% in my activity levels. I've asked about switching to a more effective therapy, but because my MS is considered inactive, I don't qualify for higher-efficacy treatments. My neurologist mentioned that I might be experiencing early progression independent of relapse activity, or 'smouldering MS'.

Though outwardly I'm told my condition is stable, I feel the slow, insidious progression. It's affecting not only my hobbies, but it's now beginning to affect both my professional and personal life, changing my sense of identity. Every day is a challenge; I celebrate the small victories, adapt to my changing physical abilities and fight for better treatment."

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Section 1. An emerging spectrum of related diseases

Multiple sclerosis (MS) is a common, lifelong, disabling disease that is well known among healthcare professionals (HCPs); however, challenges during diagnosis and treatment still remain. Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are related diseases that are often mistaken for MS; these diseases also impair the lives of those affected by them, but have several important differences. These similarities and differences need to be understood so that each disease can be managed appropriately and the people with the diseases are supported to live their best possible lives.

MS: rethinking a disabling disease

MS is a disease caused by the immune system mistakenly attacking cells in the brain, optic nerves (nerves that connect the eyes to the brain) and spinal cord, collectively known as the central nervous system (CNS). Because the CNS links everything the body does, MS can cause many different symptoms and it affects many aspects of people's lives. These symptoms include problems with vision and balance, as well as changes in the way people think or feel. MS is a leading cause of non-traumatic neurological disability among young adults in many countries.[3] Its symptoms typically start between the ages of 20 years and 50 years[4] and cause long-term, irreversible, physical and mental disability over time.[5,6] The findings of an international MS charity, published in the Atlas of MS, estimated that 2.8 million people had MS in 2020, an increase of 30% since 2013.[7]

Damage to the CNS from MS results in the formation of lesions or plaques (areas of acute injury) that can be seen on brain scans such as magnetic resonance imaging (MRI), or more widespread damage that is more difficult to observe on scans.[5,8] The symptoms of MS are highly variable and depend on the location and extent of damage within the CNS; they commonly include fatigue, impaired vision, tingling sensations or numbness, muscle weakness or stiffness, and mobility problems.[3,6,9] During the early phase of MS, these symptoms may occur in isolation, in variable combinations or during relapses (that is, intense, short-lived exacerbations of symptoms) and may or may not cause ongoing impairment (**Figure 1**). MS is progressive and degenerative; consequently, over time, symptoms worsen in some people.[5,6]

Importantly, the brain has an inbuilt neurological reserve – a finite capacity to retain function by remodelling itself to compensate for damage.[10] Despite the presence of mechanisms in the CNS to repair nerve damage, this repair is often incomplete, some nerve cells are irreversibly destroyed and the brain and/or spinal cord begins to atrophy (decrease in volume).[11,12] This resultant increase in the rate of atrophy is higher in people with MS than in people who do not have MS.[2]

It has long been understood that MS disability progression can be caused by relapses. Relapses occur because of focal damage to the nervous system and can result in a temporary or permanent worsening of physical and/or cognitive abilities.[6]

However, a proportion of people with MS experience disease progression and worsening even while exhibiting no obvious 'focal' inflammatory activity (i.e. relapses or new lesions in a specific area that can be seen on MRI scans). This type of disease progression in MS

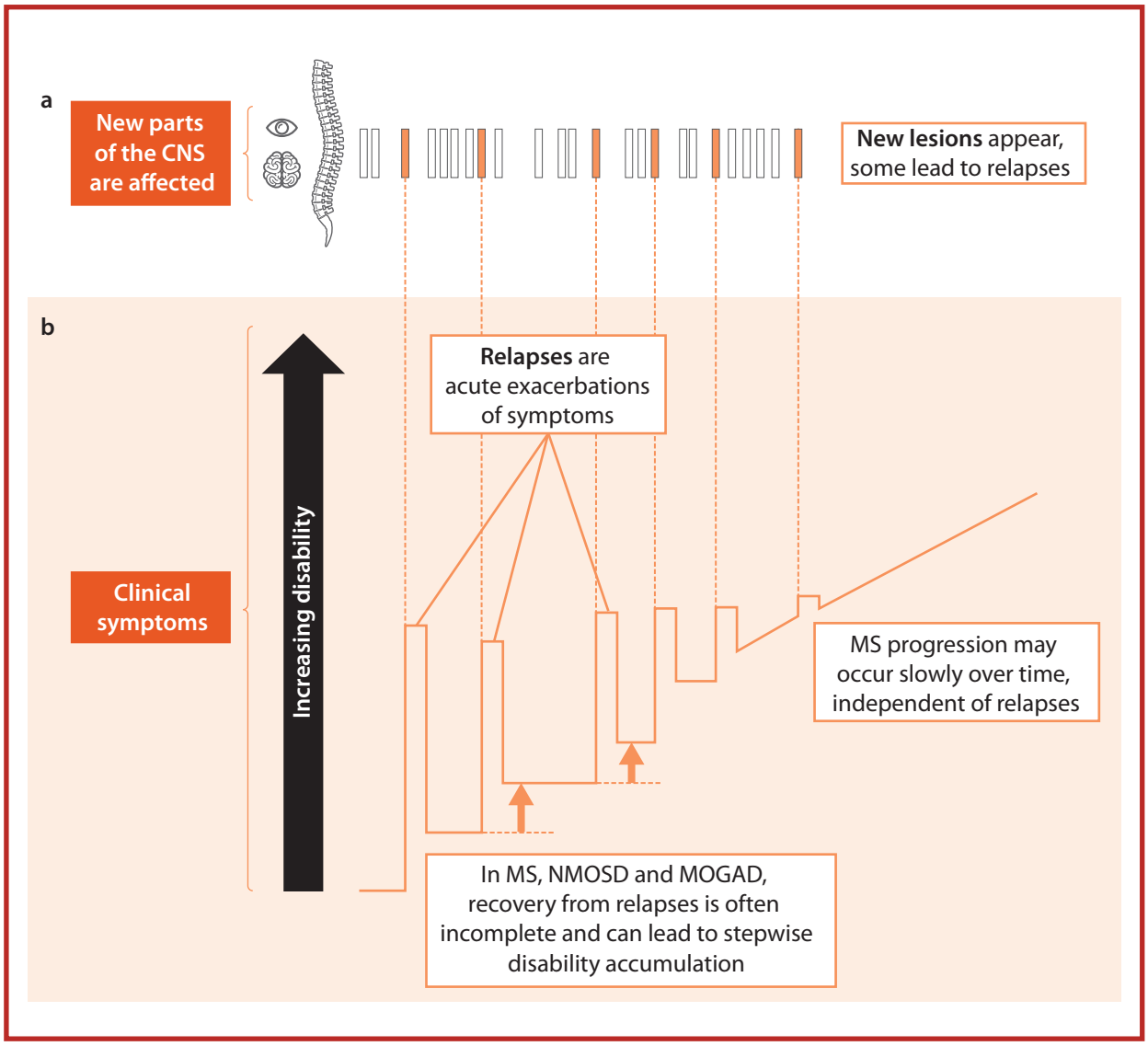

Figure 1. a. The brain, CNS or optic nerves may be progressively or suddenly damaged, leading to relapses with new or worsening symptoms for a period of time. b. The disease course and disability accumulation are often driven by relapses, from which there may be incomplete recovery. Image adapted from the original *Brain health: time matters in multiple sclerosis* report with the permission of Oxford PharmaGenesis, © 2015.[2]

CNS, central nervous system, MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

is called progression independent of relapse activity (PIRA), and is also referred to as smouldering MS.[13] The disease progression implies that MS is exacerbated by localized inflammatory activity in the CNS, not driven by it. Thus, spread out (diffuse) and chronic smouldering processes that affect the entire CNS play a causative role in MS (**Figure 2**). These processes include the following.[13-16]

- Peripheral infections and contributions from viruses.
- Lifestyle factors.
- Age-related damage to nerve cells.
- Neurodegeneration – the progressive deterioration of the structure and function of the nervous system, caused by the loss of neurons or their function in the CNS.
- 'Excitotoxicity' – the damage or death of nerves that can occur when there are excessively high levels of certain neurotransmitters (such as glutamate) and chemicals in the brain.
- Nerve cell damage in the CNS caused when the normal processes that protect the brain malfunction.

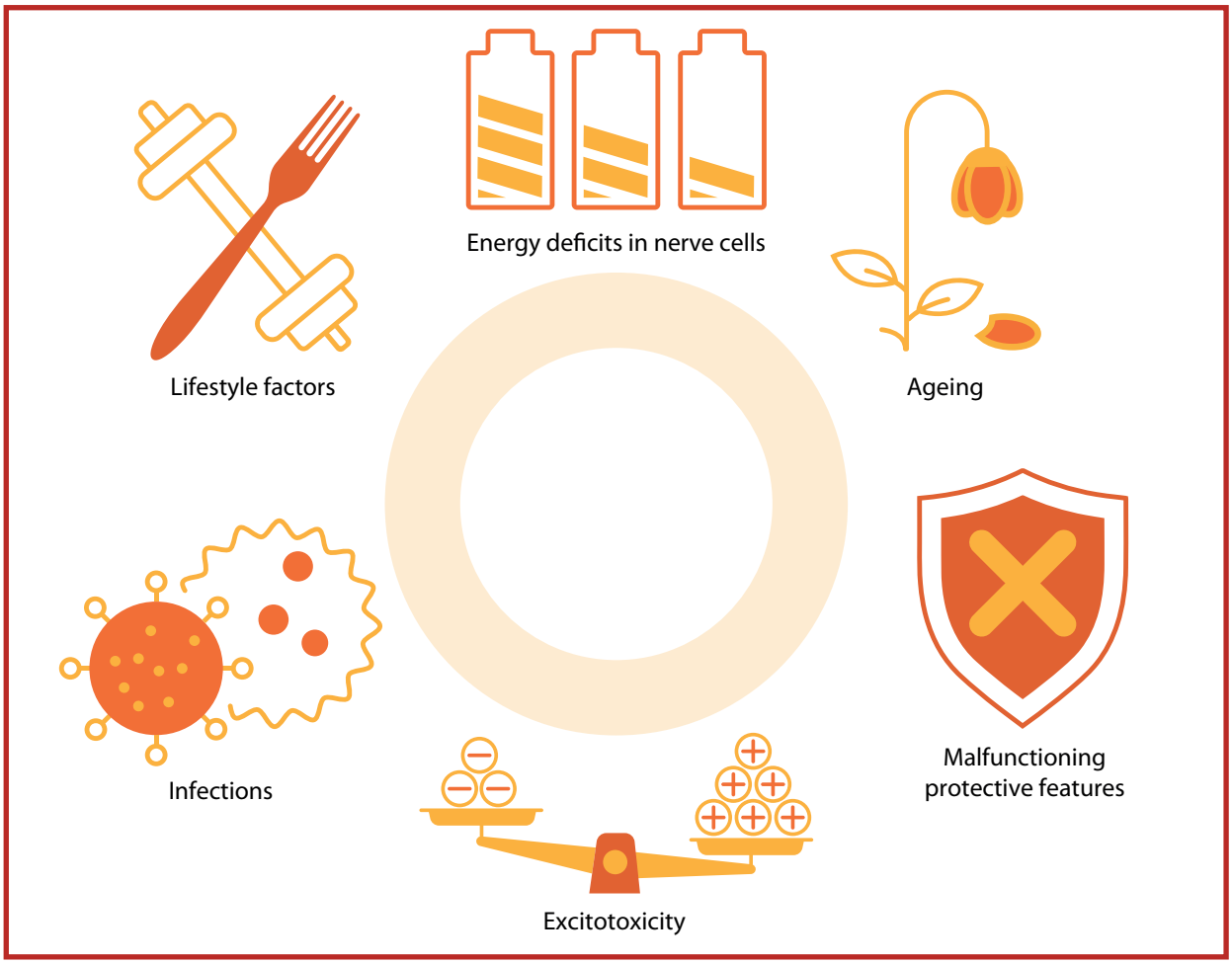

Figure 2. Several potential mechanisms can contribute to PIRA/smouldering MS (please see text for further details).

MS, multiple sclerosis; PIRA, progression independent of relapse activity.

NMOSD and MOGAD: rare, related diseases

NMOSD and MOGAD are rare, disabling diseases caused when the immune system mistakenly attacks cells in the CNS. They have symptoms that overlap with MS, but there are different underlying drivers of the disease process.[17,18] The non-specific nature of the symptoms can contribute to misdiagnosis, highlighting the need for access to specialists[19,20] and the option of additional opinions. A second opinion can be helpful to people who do not feel their concerns are being taken seriously.

NMOSD

NMOSD is primarily a disease of the spinal cord and optic nerves. The approximate age of onset is between 32 years and 45 years of age.[21]

Between 0.7 and 10 people in every 100 000 people have NMOSD and it occurs more commonly in Black (~10/100 000 people) and East Asian (~5/100 000 people) populations than in other Asian and White populations (Arab, Austronesian and South Asian and White, <1.5/100 000 people).[22-24] It is also 5–9 times more common in women than men.[25-27]

NMOSD can cause vision problems and/or weakness, numbness and/or paralysis, caused when the optic nerves and/or spinal cord become inflamed.[28] This often happens over hours to days in severe episodes. It is these relapses that predominantly drive disability worsening (**Figure 1**). Although periodic and uncontrolled relapses are common, approximately 20% of people do not experience repeated relapses.[29] More research is needed on

the disease progression that may happen independently of relapse activity; however, preliminary evidence suggests that it is rare.

MOGAD

MOGAD has an age of onset around 30 years old and it is rarer than NMOSD.[30] Globally, between 1.3/100 000 people and 2.5/100 000 people have MOGAD, with no obvious variation linked to sex, race or ethnicity.[30]

Symptoms of MOGAD can include paralysis, pain, visual impairment, fatigue, stiffness and spasticity.[19,31] Acute inflammation affecting the brain and spinal cord (disseminated encephalomyelitis), swelling in certain brain areas (cerebral cortical encephalitis) and changes in the area of the brain that controls coordination and balance (cerebellar presentations) are other symptoms.[20,32,33] Relapses are periodic and often unpredictable (**Figure 1**), although approximately 30–50% of people with MOGAD do not have repeated relapses.[29,32,34] Research from Germany also suggests that neurodegeneration may be slower in MOGAD than NMOSD, with slower disability development over time and lower accumulation of disability following relapses.[29] As with NMOSD, more research is needed to evaluate potential disease progression independent of relapses and what this means for long-term management.

Section 2. Impact on people and society

At diagnosis, MS, NMOSD and MOGAD can present with a wide range of symptoms depending on which parts of the CNS are affected.[35–38] The lifelong nature of these diseases means that, although not guaranteed, accumulating disability may occur even when the diseases are managed effectively. Over time, these effects can extend to multiple social and economic facets, presenting a substantial challenge to the person as well as society (**Figure 3**). A holistic approach in addressing these facets alongside optimization of treatment is therefore needed to ensure that patients can live their best lives.

Impact on the people living with these diagnoses

Even the early stages of MS can have a negative impact on day-to-day activities and lead to a reduced ability to work.[2,39,40] Cognitive impairment is frequently reported as an issue that people face[41] and a study from Norway reported persistent or sporadic fatigue in approximately 80% of people with MS.[42] Over time, accumulating and progressive disability (measured by increased Expanded Disability Status Scale [EDSS] scores; **Figure 4**)[43] can affect the person's mobility and overall quality of life.[44–47] Rates of employment also decline if disability increases, which can put financial strain on the person living with the disease and on society, due to loss of tax revenue.[48]

For people with NMOSD or MOGAD, each relapse has the potential to require hospitalization and can cause irreversible disability (only 1 in 5 people recover fully after a relapse).[49,50] Incomplete recovery following relapses can lead to cumulative neurodegeneration, progressive neurological disabilities, visual impairment, blindness, paralysis and early death.[18,51,52] The wide-ranging and heterogeneous symptoms also impact quality of life substantially. One of the major drivers of this impact for people with NMOSD is nerve pain.[53] People with MOGAD in Germany consistently reported that pain and depression have a significant impact on their quality of life.[54] Additional symptoms that impair quality of life include impaired mobility, effects on mood, bowel/bladder dysfunction, visual impairment, sexual dysfunction and inability to work.[50,55,56]

The burden associated with living with these diseases falls not only on the person but also on the people close to them. Research in the USA[57] showed that anxiety was common among people caring for a person with NMOSD, and a review of the available literature observed similar psychological consequences for those caring for people with MS.[58] Survey data from 131 caregivers for people with MS in Greece showed that high stress, poor mental health and poor physical health reduced their ability to care and negatively affected their own well-being.[59]

Despite the importance of considering the full spectrum of symptoms and how they change across the course of these diseases, collating data is challenging. Registries that track disease progression and also capture social service outcomes can help to demonstrate the wider burden that people and their caregivers may experience. Despite the potential benefits, survey insights from 35 European countries showed that fewer than half of them had a national MS registry,[60] and even fewer capture all facets of the disease.

The continued work of groups like MSBase,[61] Big MS Data Alliance,[62] Patient Reported Outcomes for Multiple Sclerosis (PROMS Initiative)[63] and other projects following the European Register for Multiple Sclerosis (EUReMS) seek to collect standardized real-world data to assess

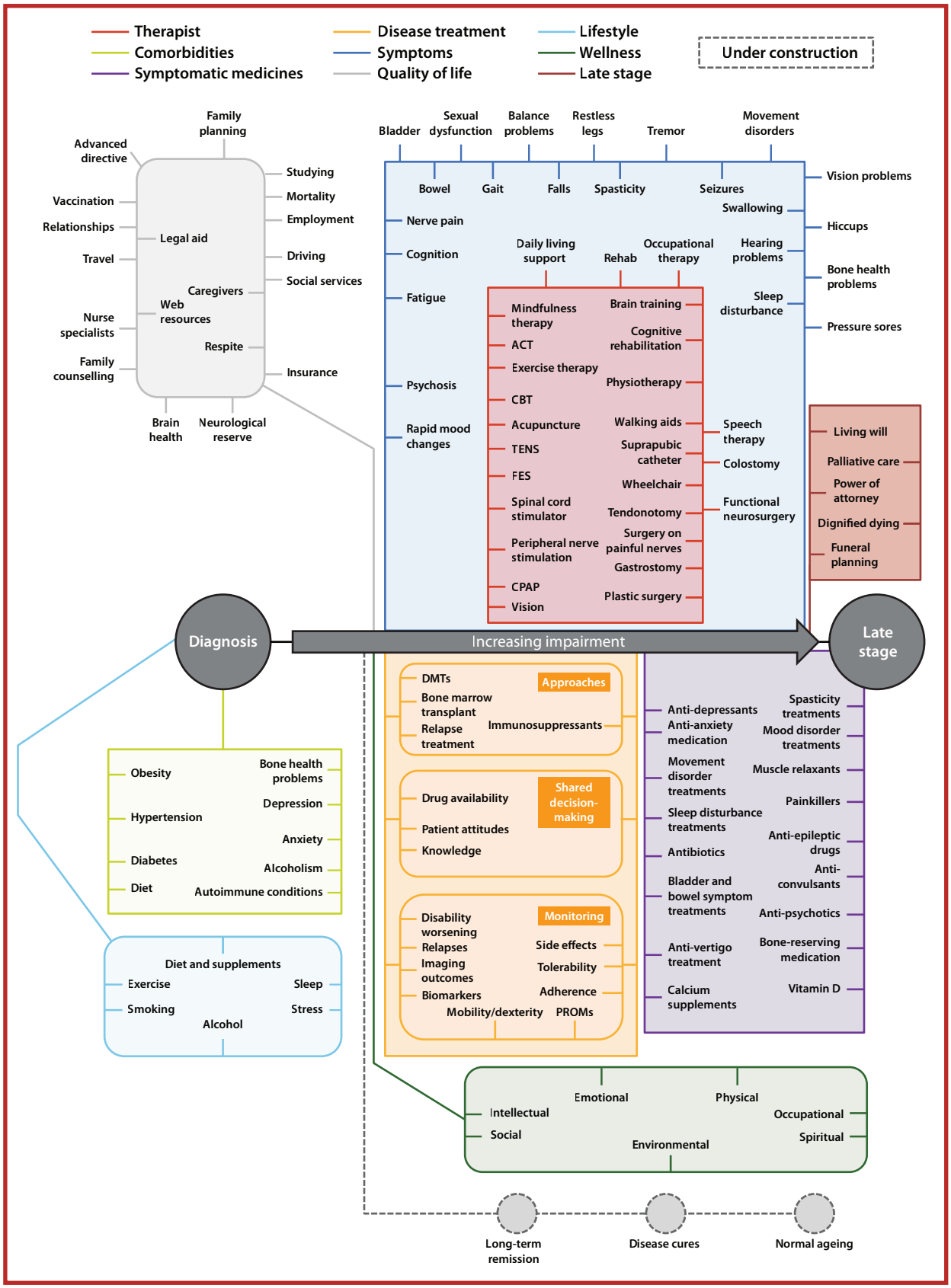

Figure 3. The burden associated with increasing disability in MS, NMOSD and MOGAD can affect many areas of life and require wide-ranging support. Image provided by Professor Gavin Giovannoni, © 2024.

ACT, acceptance and commitment therapy; CBT, cognitive behavioural therapy; CPAP, continuous positive airway pressure; DMT, disease-modifying therapy; FES, functional electrical stimulation; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PROM, patient-report outcome measure; TENS, transcutaneous electrical nerve stimulation.

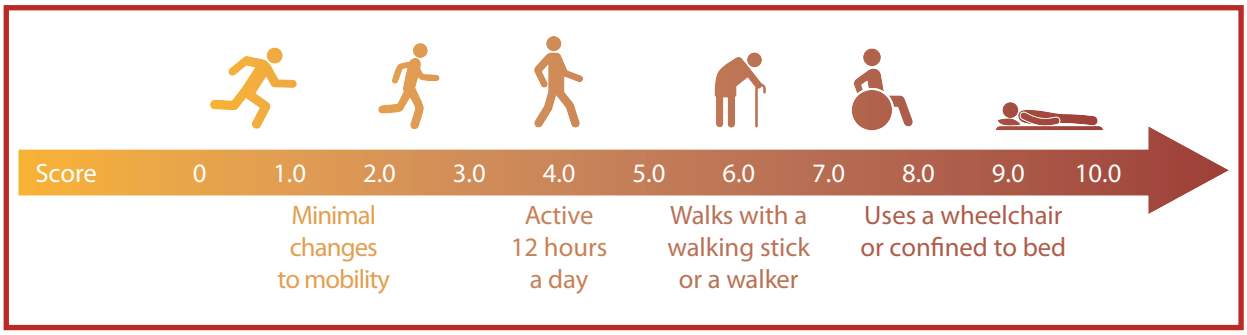

Figure 4. The Kurtzke Expanded Disability Status Scale allocates increasing numerical values to greater levels of physical disability (0, normal neurological functioning; 10.0, death).[43]

accumulation of burden. Projects such as the Impact of Multiple Sclerosis Symptoms (arranged by the European Multiple Sclerosis Platform [EMSP]) will help to assess how MS symptoms affect everyday life.[64] We recommend utilizing real-world data to allow for the assessment of long-term cost-effectiveness of disease-modifying therapies (DMTs) alongside ongoing societal burden. Collection of standardized data about the burden of NMOSD and MOGAD should also be prioritized because, in many instances, the full burden of rare conditions is hard to quantify.[65] Such data could then be used to ensure appropriate social support is provided to people and their caregivers.

Economic impact on people and society

It is important when discussing the value of treatments to recognize that the economic burden of these diseases includes a wide range of direct costs (e.g. medical appointments, hospitalizations, tests, formal care, medical devices and medicine) and indirect costs (e.g. various out-of-pocket expenses, informal care and income losses affecting people, their caregivers and the entire economy through lack of tax revenue).[66] For the purpose of this report, we summarize the economic impact in relation to people with these diseases, their caregivers and wider society, as well as health and care systems (**Figure 5**).

The lack of standardized approaches to methodology and cost category inclusion within economic analyses means that comparisons of absolute costs across countries are difficult.[67,68] However, some themes do emerge.

The need to minimize disease activity

There is a clear link between accumulating disability, relapses and increased costs, which speaks to the need to optimize care to reduce costs.

- Across 16 European countries of varying economic statuses, the mean annual cost per person with MS was estimated at €22 800 for those with an EDSS score of 0.0–3.0 (none to a moderate disability, but fully ambulatory), rising as disability increases to €37 100 for EDSS scores of 4.0–6.5 (increased ambulatory difficulties that require assistance, e.g. a crutch) and €57 500 for EDSS scores of 7.0–9.0 (substantial ambulatory difficulties or restricted to bed).[48]
  - Work by MS Australia also observed trends in total costs that were consistent with these European examples.[69]
- Evidence from a German registry showed that incremental changes in disability increase costs in patients with MS, with each 0.5-step increase in EDSS score adding a mean of €3643 to total costs; this increase is more pronounced at higher EDSS scores.[70]
- Reviews summarizing available evidence showed that costs for patients with moderate disability were 1.4–2.3 times higher than for patients with only mild disability, while

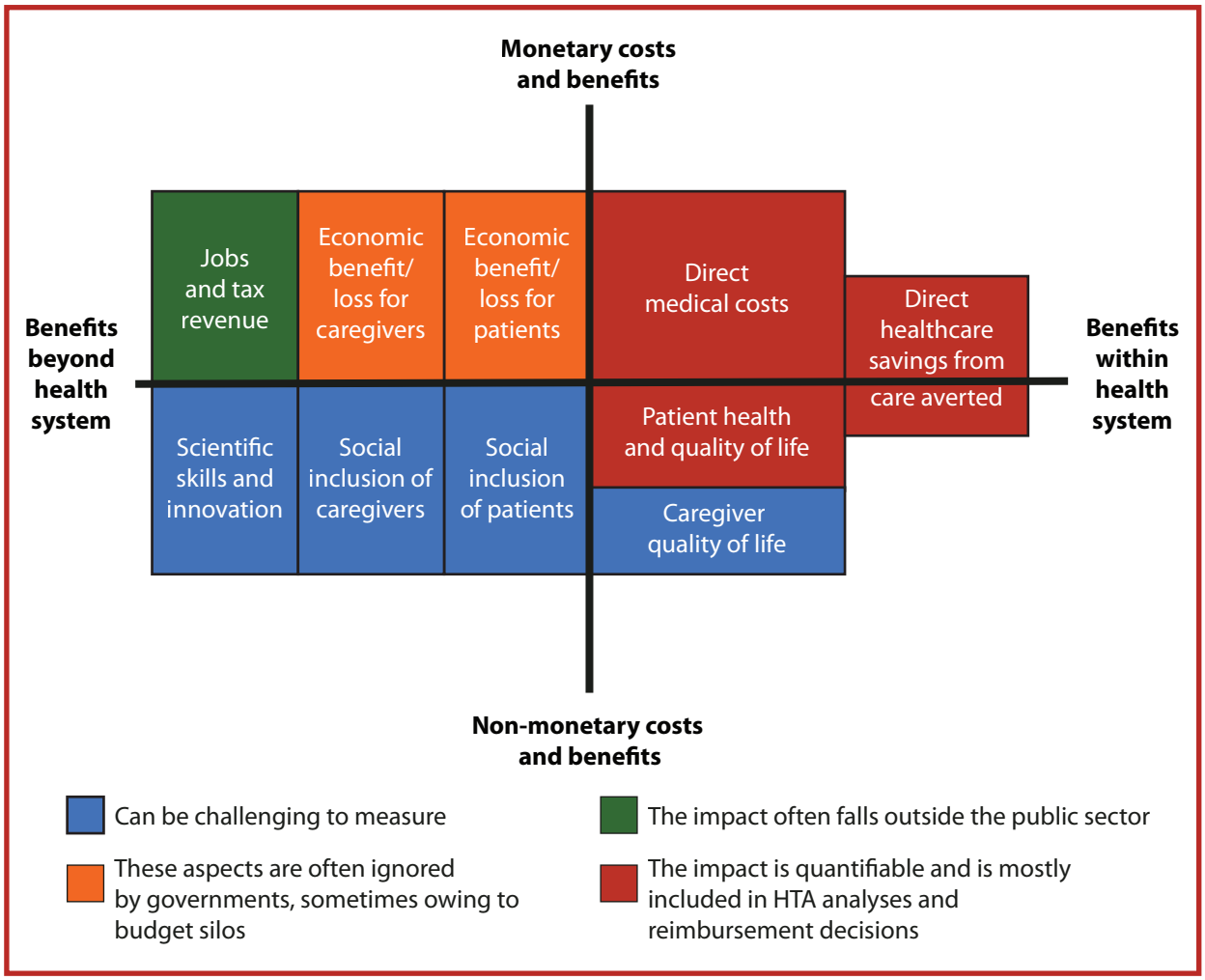

Figure 5. The value that effective treatment provides can be realized across several areas.

HTA, health technology assessment.

patients with severe disability have 1.8–2.9 times higher total costs than patients with a mild disability.[67,71,72]

- A German study estimated a mean annual cost of illness per person with NMOSD or MOGAD at €59 574, with annual costs ranging from €34 992 for EDSS scores of 0.0–3.0 (none to a moderate disability, but fully ambulatory) to €129 687 for EDSS scores of 6.5–8.5 (substantial ambulatory difficulties or restricted to bed for much of the day).[73]
- Data from a UK study conducted in 2022 estimated mean total healthcare costs over 3 months of £5623 per person with NMOSD (i.e. £22 492 per annum). Importantly, costs were substantially higher for patients with increased disability (£32 717 for patients with EDSS scores of 8.0–9.5 [patient who is bedbound for much of the day or permanently bedbound], compared with £562 for patients with EDSS scores of 0.0–4.0 [able to move around]).[74]

The very substantial costs due to relapses must also be considered. The mean cost associated with MS relapses during a 3-month reporting window across 16 European countries was estimated at €2188 in people with EDSS scores of 0.0–6.0 (i.e. a sample of people who required up to intermittent assistance to move from place to place),[48] and at US$9849 in members of a US patient support group for people with MS and a mean EDSS score of 4.1 (i.e. a sample of people who were, on average, fully able to move from place to place).[75] Data from 1363 people with NMOSD in the USA indicated a mean annual total cost of treating relapses of US$10 070 per person.[76] Treatment strategies

that aim to avoid relapses therefore have an obvious potential for long-term savings.

People with these diagnoses, their caregivers and wider society

As discussed above, these diseases all have the potential to not only drive a need for care but also affect people's ability to work. That in turn increases the risk of reduced tax revenues and increased need for disability support.[77] In 2015, a UK Multiple Sclerosis Society report found that 80% of people with MS gave up work within 15 years of diagnosis.[78] Data from Denmark and the UK show that the proportion of people with MS in receipt of social benefits is approximately a third higher than people who do not have MS.[79–81] Information on social security support is limited for people with NMOSD or MOGAD; however, barriers to their continued employment and advancement have been noted in research in the USA.[82]

A combined literature review and survey of people with MS in nine European countries (Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden and the UK) reported the potential benefits of timely treatment on employment income.[83] With timely treatment, the yearly gains in hours worked amounted to €3000 additional income per person and an estimated overall increase of €155.3 million in employment income across the nine countries.[83] Importantly, these values are likely to be an underestimate because they do not account for people who may have switched to lower-paid or part-time employment if they did not receive early and effective treatment. It also highlights the value of efforts to enable people to stay in the workforce through, for example, further education.

In addition to economic loss incurred through impact on employment, we also need to consider that care costs increase dramatically with increasing disease burden.[48] These costs typically fall outside of the healthcare systems and instead are paid by social care budgets and/or by people with these diseases and their families. Nearly a third of people with MS need care, which can take many forms, and about 80% of which is provided 'informally' by unpaid caregivers such as relatives.[84] In the UK, a Multiple Sclerosis Society report in 2019 found that 6 in 10 people with MS paid additional costs to meet their social care needs, with 4 in 10 people relying on some degree of unpaid care from family and friends.[85] Furthermore, a 2019 study by the think tank RAND found that, globally, almost half of people with MS received informal care at a mean of 30 hours per week.[86] People in Europe with severe MS (EDSS scores of 7.0–9.0; i.e. a patient who uses a wheelchair or is restricted to a bed) also required approximately 200 hours of informal care each month.[48] A previous systematic review of informal care costs in MS showed that worsening disability increased costs by up to 10 times.[87]

Work by the neuromyelitis optica study group (NEMOS) in Germany showed that indirect costs contribute the largest proportion to overall economic burden associated with MOGAD.[73] Global data suggest that at-home care is required by 70% of people with NMOSD or MOGAD.[88] Data from Germany estimated a working time reduction of 4.4 hours per week per person caring for someone with severe NMOSD or MOGAD.[73] The mean costs of informal care for people with NMOSD provided by friends or family over a 3-month period ranged from £13 150 to £24 560 in a UK 2022 survey.[74] Informal care costs in Germany also rose substantially with increasing disability for people with NMOSD or MOGAD (mean annual cost, €16 460; ranging from €5210 for mild disability [EDSS scores of 0.0–3.0] to €40 477 for severe disability [EDSS scores of 6.5–8.5]).[73]

Health and care system

It is important to consider direct costs in the context of the value that treatments can provide and the potential that they have to help to avoid disability accumulation. As with other complex lifelong diseases, the cost to the healthcare system is substantial. A systematic review of USA cost analyses showed that MS is associated

with increased medication use and inpatient, outpatient and emergency department visits, as well as increased duration of hospital stay.[89] A previous systematic review showed that the annual direct costs of MS in the USA ranged from US$16 614 (2006) to US$72 744 (2017).[89] An analysis by MS Australia compared costs (reported in 2021 AUD) in Australia with those in 15 European countries of varied economic statuses and showed that the mean annual direct costs were AUD39 964 (ranging from AUD10 525 in the Czech Republic to AUD65 072 in Sweden).[69]

For people with NMOSD, data from Germany showed that annual direct medical costs incurred were approximately three times higher than for people who did not have NMOSD (€12 913 per person vs €4667 per person, respectively).[90] In the UK, increased costs related to NMOSD were driven by more frequent hospital admissions (and longer length of stay), higher numbers of outpatient appointments and increased pharmacy prescription costs compared with people who did not have NMOSD.[76] In Colombia, the direct cost of treating NMOSD was driven by the costs associated with treating relapses.[91]

Although the direct costs of MOGAD have not been studied extensively, data from 212 people with NMOSD or MOGAD in Germany observed that the annual direct costs included factors such as medication (€9786 per patient [38% of direct costs]), inpatient hospital care (€5199 per patient [20% of direct costs]) and costs for formal care (€3674 per patient [14% of direct costs]).[73]

Given these costs, it is critical to recognize the value of optimizing treatment, and findings from the international MSBase and Swedish registries[92] and a registry in Italy,[93] as well as systematic review findings,[94] have shown the potential value of early effective treatment of MS with DMTs. However, restrictions on treatment access can result from drugs not being reimbursed and/or available in certain healthcare systems.

Unequal access to the full spectrum of MS DMTs is hence also a critical issue. In 57% of countries, patients need to cover some or all of the cost of their MS DMTs via their own finances,[95] which can have a major influence on treatment choice but also indicates how important these treatments are to people.[96] In countries with no universal healthcare systems, lower socioeconomic status was also associated with reduced access to highly effective MS DMTs.[97] However, in the UK (which has a universal national health service), prescribing patterns of DMT class did not correlate with socioeconomic status,[98] suggesting that inequity patterns probably differ among countries.

Internationally, physician surveys have revealed availability, let alone affordability, of some newer MS DMTs to be limited in Latin America and, particularly, South-East Asia.[99,100] Furthermore, the affordability of one of the earliest established DMTs across 40 countries was shown to be stretched in many of them.[101] Affordability was weakest in Morocco, Jordan, Peru, Brazil and Argentina, where people would have to pay more than an equivalent of 20 days wages for a month's dose.[101]

For NMOSD, a global study across 52 responding countries found a mean cost for a typical person's treatment to be US$3819 annually in 2018.[102] This study found that while treatment costs were covered partially or wholly by public insurance in all 15 high-income countries surveyed, 92% of 12 low-income countries reported that patients' costs were not covered by public insurance at all.[102] Indeed, less than 10% of the population in low-income countries could afford 1 year of treatment without incurring catastrophic health expenditure (over 40% of household disposable income).[102] Being unable to pay for treatment and medical care, which is known to then in turn escalate the personal as well as financial burden, was also a

problem (minor or major) for 65% of people with NMOSD in the USA.[50]

More can be done to support people with NMOSD or MOGAD to ensure access to effective early treatment.[103] The challenges experienced are consistent with those in other rare and/or orphan diseases, with data collection from small patient populations a notable challenge to expanding treatment access.[65] Another consideration that countries will need to make is how to adjust pricing and/or affordability criteria to new treatments that are being approved for use in people with these diseases because they are likely to be considerably more expensive than older treatments or off-label therapies used to date.[73,104]

It is important to note that these sources were published before the impact of the inclusion of some DMTs for MS on the World Health Organization (WHO) Model List of Essential Medicines.[103] It will be important to monitor how this inclusion impacts access for people with these diseases.

Shifting perspectives within economic evaluations

The information outlined in this section shows the importance of considering all benefits and costs. Most countries evaluate treatments for inclusion in health benefits packages; however, the costs to wider society, such as social services, informal care and productivity losses faced by people with these diseases and their caregivers, are considered only in a secondary analysis – or not at all.[105–107] Many countries focus their evaluations of the effect of new treatments on health benefits for patients themselves, and often only on extended life expectancy (e.g. not accounting for impact on productivity, or the health and productivity of their caregivers) and the changes in direct healthcare costs (rather than costs incurred by social services and/or people for their wider care and their potential employment losses).

Whether these broader benefits are considered or not can result in considerable variation in health technology assessment agency assessments of the value of new treatments.[108,109] It also needs to be recognized that societal costs across countries can differ because of contextual factors, including healthcare system organization and financing, and the availability and use of healthcare services and social service systems that govern sickness, disability and retirement.[110]

An economic evaluation examining any potential intervention should quantify all relevant costs and benefits pertinent to a decision to adopt the treatment.[111] Given that meaningful health improvement can mitigate the substantial indirect costs associated with these diseases, economic evaluations should take a societal perspective to ensure that potential benefits to people and their caregivers are considered in any analysis.[110,112] Indeed, taking a societal perspective within economic evaluations changed the recommendations or conclusions in 10 out of 15 studies assessed in a systematic review of previous economic evaluations in MS.[106] Most health decision-makers only accept a health sector perspective and this situation could be improved with a more holistic approach that takes into account health sector, social sector and wider societal perspectives and novel value elements.[113–115]

Section 3. Importance of timely diagnosis, early treatment and effective regular monitoring

In the absence of cures for MS, NMOSD and MOGAD, timely diagnosis enables access to care that can prevent future relapses, reduce disease activity and slow disease progression.[20,28,116,117]

Globally, common barriers to early diagnosis of these diseases include: awareness of early clinical symptoms among patients and HCPs; access to the neurological medical specialists who would typically make the diagnosis; social barriers; and access to appropriate diagnostic tools (**Figure 6**).[19,20,118] Diagnosis of these diseases is often complicated by overlapping clinical presentations with other diseases and their heterogeneous disease courses.[19,20,119]

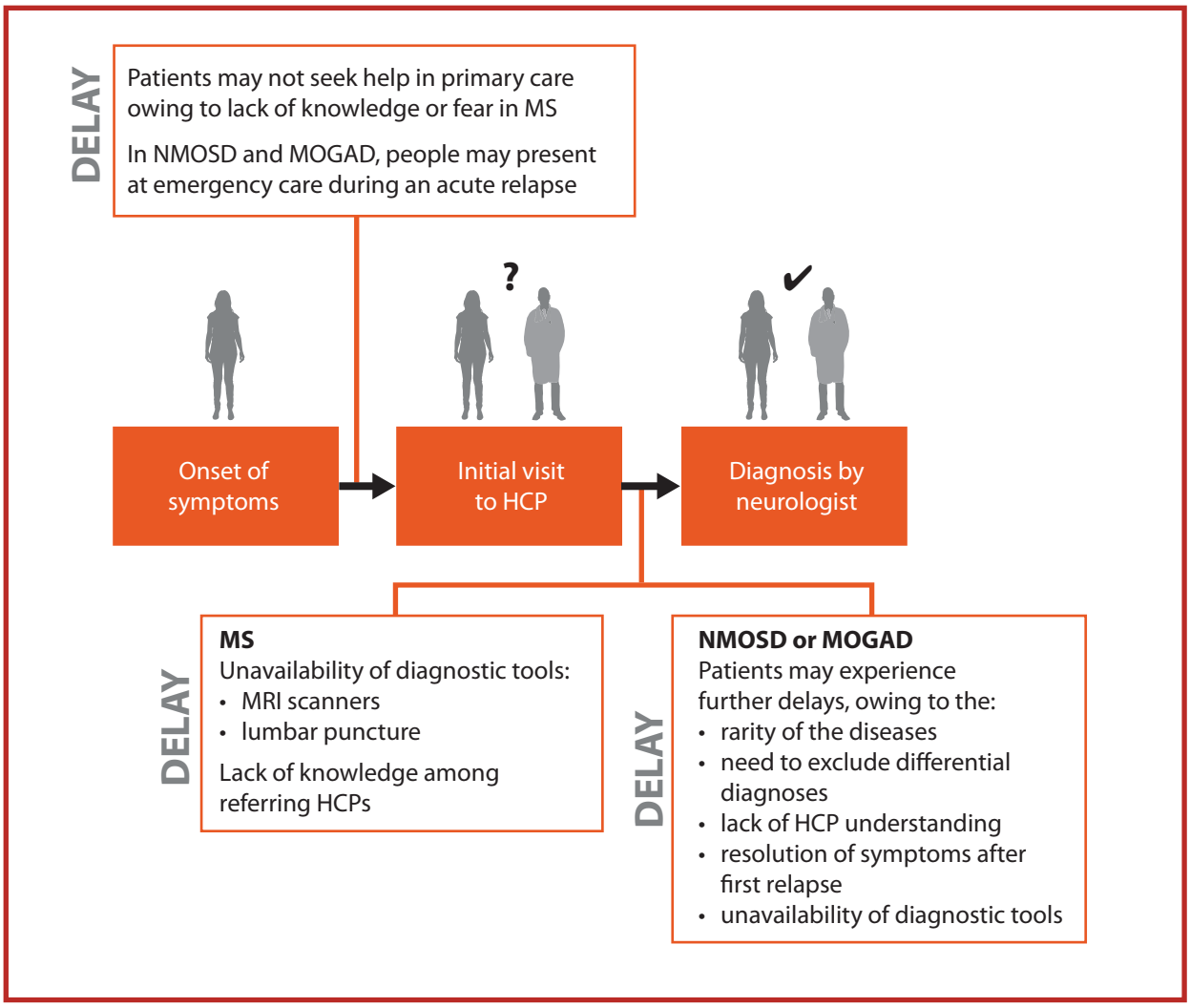

Figure 6. Delays between initial onset of symptoms and diagnosis are common. Image adapted from the original *Brain health: time matters in multiple sclerosis* report with the permission of Oxford PharmaGenesis, © 2015.[2]

HCP, healthcare professional; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Data from the USA showed that only 11% of people (16 of 144) had NMOSD initially diagnosed following their first contact with the healthcare system.[19] Furthermore, based on international survey responses, MS was given as the first diagnosis for approximately 30% of people with MOGAD who received an alternative diagnosis before MOGAD was diagnosed.[20] These events delay the initiation of effective treatments and put patients at risk of experiencing additional relapses.[19,20,120,121]

Timely diagnosis

Disease awareness

A person first experiencing symptoms consistent with MS, NMOSD or MOGAD is likely to visit a general practitioner, or, if they experience more severe unforeseen medical problems, seek emergency care. Vision problems may also occur early in the course of these diseases and so people may initially visit an optician and/or ophthalmologist.[19,20] Often, these professionals have limited experience of these diseases.[19,20,119]

Improving general awareness of early symptoms of these diseases among HCPs who are likely to encounter undiagnosed patients would facilitate appropriate onward referral to an appropriately trained specialist, and thus aid timely diagnosis.[19,20,119] Therefore, it is key that further education about the importance of referral to specialist care is included in the curricula for medical and nursing students and also in ongoing professional development pathways after qualification. The latter should go beyond being part of mandatory education, and further education could be achieved through webinars,[122] online courses[123] and peer-to-peer educational programmes between specialist neurologists and other professions.[124]

Access to specialist neurologists and nurses

Ease of access to neurologists varies according to a range of factors, including regional or national health protocols, and it is especially difficult when healthcare resources are limited.[118,125] Access to MS HCPs, specialist teams and diagnostic facilities varies widely around the globe. Statistics from the MS International Federation showed that, globally, there are 0.3 MS specialist neurologists per 100 000 people.[126] In high-income and upper-middle-income countries, this figure is 0.4 per 100 000 people,[126] with a substantial disparity when compared with lower-middle-income countries and low-income countries, with 0.01 and 0.02 MS specialist neurologists per 100 000 people, respectively.[126] This situation is likely to be even worse in diseases such as NMOSD and MOGAD, which are rarer and more prone to misdiagnosis.[19,20] It should also be noted that specialist nurses play an essential role in care, providing education, counselling and assistance navigating complex health systems, and supporting lifestyle changes.[127] However, in high-income countries, there are 0.4 MS specialist nurses per 100 000 people, falling to 0.1 per 100 000 people in upper-middle-income countries, and with none recorded in lower-middle-income and low-income countries.[128] These data highlight important areas in which recruitment and training are needed.

There have been projections that even in countries that currently have an adequate supply of neurologists for managing MS, there may be shortages in the coming years,[129] highlighting the need for novel approaches. Creation of rapid access models (e.g. Fast Neuro in the USA), which speed up referrals to outpatient neurology services, have shown benefits in decreasing waiting times and reducing emergency department patient volume for patients presenting with symptoms consistent with possible NMOSD or MOGAD.[130] Resources, including the WHO intersectoral global action plan for epilepsy and other neurological disorders, may also help to guide effective care pathways.[131] In the case of rare disorders such as NMOSD and MOGAD, cross-border approaches serve as another model for how outcomes may be improved: for example,

European Reference Network sites in France and Germany aim to collaborate and share knowledge, reducing the need for patients to travel to receive expert care.

Although not addressing all issues relating to the low density of services, digital solutions such as telemedicine may help to spread specialist knowledge across geographical locations or provide access for people in remote or rural locations.[2,129] Learnings from the COVID-19 pandemic may also drive an increased uptake of such approaches, as was the case in South America.[132] These potential benefits should also be balanced against potential access challenges relating to socioeconomic status and disease-related impairments based on data from North America.[133]

Clinical test availability

To diagnose these diseases correctly, a series of steps need to be undertaken: reviewing clinical symptoms and relapses; taking images of the brain, spinal cord and/or eye; and laboratory tests looking for proteins in the blood and/or spinal fluid.[28,32,134] For NMOSD and MOGAD, this process also includes antibody tests to identify the key disease-contributing molecules, for which the timing in relation to relapses is important, and the sensitivity of the tests is improving continuously.[28,32] Increased sensitivity, specificity and accuracy of antibody tests for NMOSD or MOGAD should improve the diagnosis time and journey for people with these diseases.

However, overall challenges to accessing diagnostic tests exist. A global study using data from the MS Atlas observed that people suspected of having MS did not complete recommended testing because of the cost of tests and/or feasibility of travel that was required.[118] Access to the correct testing modalities and clear guidelines about which tests should be ordered represent continued challenges in this area.

Diagnostic criteria

The established diagnostic criteria for MS are not always used consistently in clinical practice.[135] In one global study using data from the MS Atlas, 66% of respondents reported at least one barrier to the adoption of the most used diagnostic criteria,[118] which were the McDonald criteria from 2017.[134] Lack of awareness and training for neurologists were highlighted as the most common barriers to use of the diagnostic criteria in low-income countries.[95]

The diagnostic criteria for NMOSD[28] and proposed criteria for MOGAD[32] will need to be clearly defined and continuously refined in line with improvements in our understanding and availability of diagnostic tests.

Because the evidence base that underpins diagnostic criteria continues to evolve, we discuss the upcoming consensus papers in the Future perspectives section.

Early treatment

Ensuring access to the full range of approved treatment options available for these diseases and agreeing on these via shared and informed decision-making between patients and their managing clinician (who may not be a specialist), are critical to ensuring that patients receive the best possible care. When combined with effective monitoring, treatment failure can be acted upon quickly and treatment approaches can be changed when disease activity has not been minimized in response to treatment (**Figure 7**).

Access to disease-modifying treatments

Currently, more than 20 MS DMTs have been approved and these differ in the ways that they work and how they are administered.[136,137] Across major drug approval agencies in the USA, Europe and Japan, only four therapies are approved for long-term management of

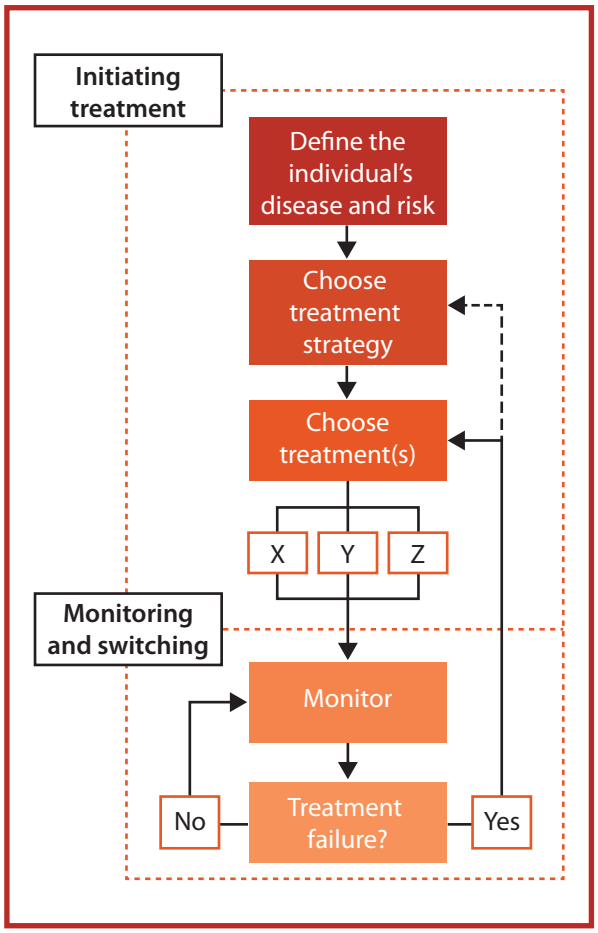

Figure 7. Early treatment initiation for MS, NMOSD and MOGAD should be combined with effective monitoring to allow for timely switching in the event of treatment failure. Image adapted from the original *Brain health: time matters in multiple sclerosis* report with the permission of Professor Gavin Giovannoni, © 2014.[2]

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

NMOSD.[138] Furthermore, there are no approved therapies that are specific for the long-term management of MOGAD, but clinical trials are currently ongoing and sometimes drugs that suppress the immune system are used off-label.[17,29]

The DMTs available for the treatment of people with MS include those that were approved in the 1990s for relapsing forms of MS (referred to as 'established DMTs' in this report) as well as those approved after the year 2000 that have different mechanisms of action from established DMTs (referred to as 'newer' DMTs in this report).

Some of these newer DMTs have an evidence base supporting efficacy superior to that of an established DMT, which may include head-to-head clinical trials or real-world evidence.[2,109] However, in 2022, 14% of countries worldwide had no regulator-approved DMTs, rising to 60% in African countries and 70% among low-income countries.[95] Analyses also observed a mean lag of 2.6 years from market authorization until new therapies are included in updated clinical guidelines.[139]

Bibliometric analysis revealed that MS research and therapy development are still predominantly conducted in Western high-income settings, with authors from the USA publishing 12 770 research papers cited 610 334 times, Italy publishing 4310 papers cited 128 079 times and the UK publishing 3503 papers cited 184 932 times (between 1945 and 2021).[140] Although the number of published research articles has increased by 79.3% over the past 20 years, research conducted by and for authors in low-income or middle-income countries and the Global South remains a comparatively small part of the overall research landscape,[140] with patients in these countries also less able to access newer treatments.[99,100]

Patterns of research and development in MS also reflect the unequal availability of global research funding. An analysis of non-profit and government grants allocated between 2021 and 2023 found that 2088 of 2346 identified research projects (89%) were conducted in either North America or Europe.[141] Despite increased focus on widening and deepening the MS research environment since an analysis of the MS research landscape in 2001,[142] with MS patient organizations joining together to coordinate and publish a global research strategy in 2022,[143] relatively few funding sources are available to MS researchers in low-income or middle-income countries (e.g. the MS International Federation McDonald and Du Pre grants).[144] It is therefore important to widen the global MS research landscape in future years to improve research and

development progress, as well as evaluation and access to new DMTs for people with MS across the globe, not only in high-income geographies.

Some DMTs for MS are now included on the WHO Model List of Essential Medicines.[103] This was based on evidence for their potential benefits and harms, their value for money, their impact on outcomes that matter to patients and the ease with which they could be adopted globally.[125] It is hoped that this will enable greater equity in access to treatment globally. It is also true that equality in access to treatments varies by MS disease stage. There are a broad range of DMTs available for people with MS that display active inflammatory disease, defined by clinical or imaging features, enabling patient and HCP choice.[122,123] Once a transition to non-relapsing/non-active disease has been decided, there are no DMT options available to date. Nonetheless, some compassionate off-label uses of therapies may be granted.[145] Treatment options are also limited for people who initially present with progressive MS, with one DMT available.[146] Achieving equitable access to MS DMTs therefore remains a global challenge.[2]

Achieving the best outcomes

Once the decision to initiate treatment has been made, treatment choices can be influenced by several factors including disease course, personal attitudes, values, goals, age, knowledge and preferences.[147,148] This is why shared decision-making is essential. Treatment sequence restrictions, such as only allowing people with MS access to some DMTs after they have first experienced treatment 'failure' with an established DMT, may also apply.

In MS, it has previously been practice to initiate treatment using established DMTs and then only change to newer DMTs at a later time if required in the context of disease progression. However, the consensus is now that high-efficacy DMTs should be used early in treatment (**Figure 8**). Patients who initiate early treatment with newer, higher-efficacy DMTs (also known as 'flipping the pyramid') have improved health outcomes, with significantly lower rates of relapses and disability progression in the 10–15 years following treatment initiation, compared with people who started treatment with established lower-efficacy DMTs.[136] These findings are supported by additional registry studies[92,93] and systematic literature review findings.[94] Worldwide, 25% of countries do not use newer DMTs, increasing to 50% in lower-middle-income countries, with no access in low-income countries.[95] Country and regional prescribing guidelines governing DMT initiation need to evolve in parallel with diagnostic criteria to prevent unnecessary loss of neurological reserve, loss of brain tissue, deterioration in brain health and disability progression.[2]

In NMOSD and MOGAD, early diagnosis, prompt treatment of acute relapses[17,18,149,150] and seeking to prevent future relapses as soon as a definite diagnosis is established are key to avoiding cumulative neurological damage caused by recurrent relapses (**Figure 9**).[19,27,29,138,149] A misdiagnosis of MS can also potentially multiply risk for the person because some treatments for MS have been reported to trigger severe relapses in NMOSD.[138] This highlights the critical importance of early and accurate diagnosis for people with these diseases.

Long-term management of NMOSD and MOGAD focuses on preventing future relapses.[138,150] Advice in clinical guidelines about ordering of therapies and approaches to help people with NMOSD who do not test positive for specific antibodies (aquaporin-4 antibodies) are ongoing needs.[138] As research into NMOSD and MOGAD continues, it is hoped that access to long-term treatment options can be expanded globally.

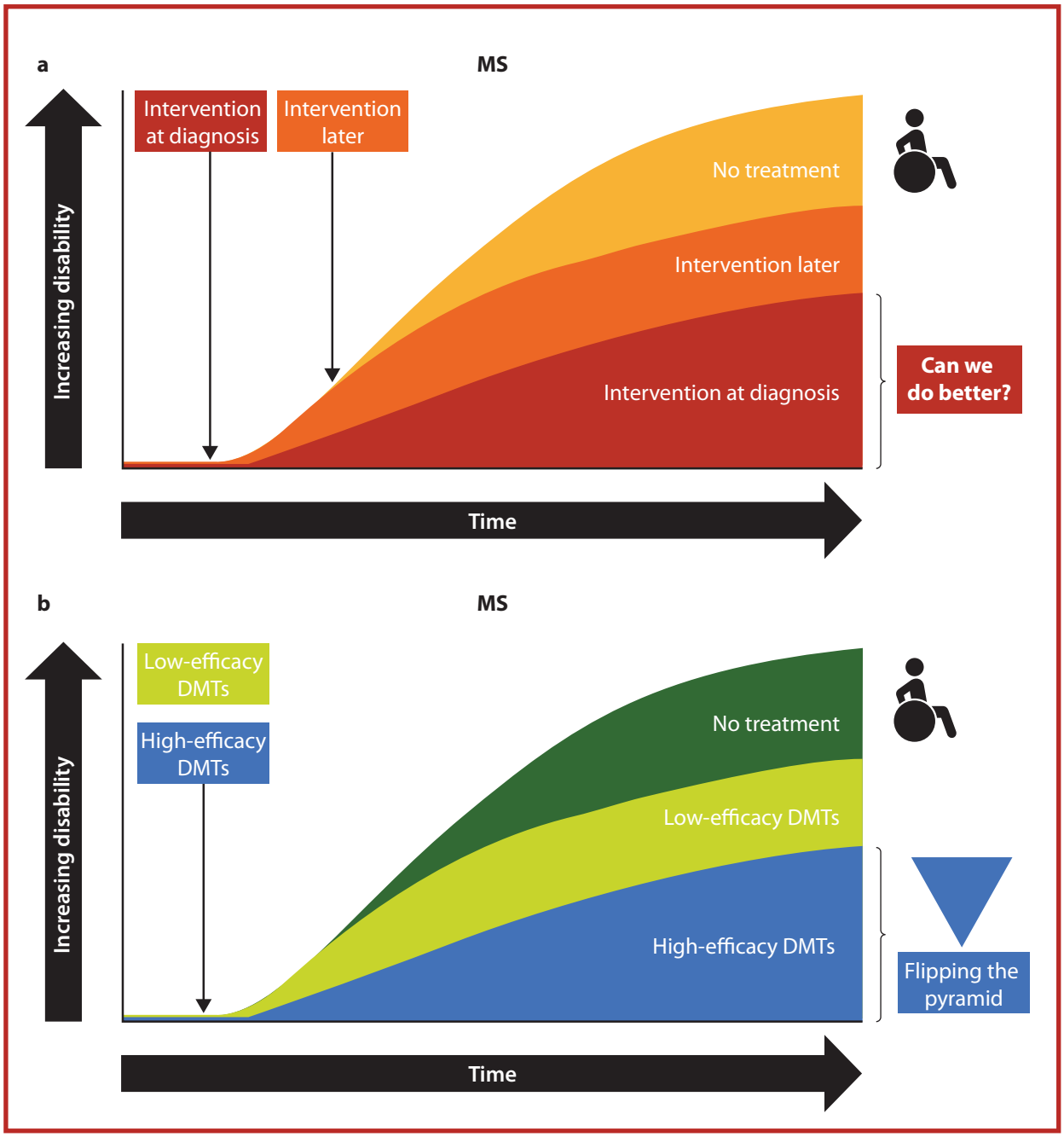

Figure 8. In addition to the benefits of early treatment with a DMT for people with MS (a), the consensus now is that high-efficacy DMTs should be used early (b). Image adapted from the original *Brain health: time matters in multiple sclerosis* report with the permission of Oxford PharmaGenesis, © 2015.[2]

DMT, disease-modifying treatment; MS, multiple sclerosis.

Regular monitoring

Regular monitoring of outcome measures is important for evaluating treatment effectiveness and safety, and may also be beneficial in monitoring disease progression. It should also include baseline tests prior to treatment initiation.[151] Current parameters that can be monitored may be measured clinically (e.g. disability progression and relapses), radiologically (using MRI) or in a laboratory (e.g. from a blood sample). They may also be reported by the person with MS or their caregiver (via patient-reported outcome measures [PROMs]; e.g. activity limitations, cognitive status or level of fatigue) or be assessed by an investigator (e.g. cognitive

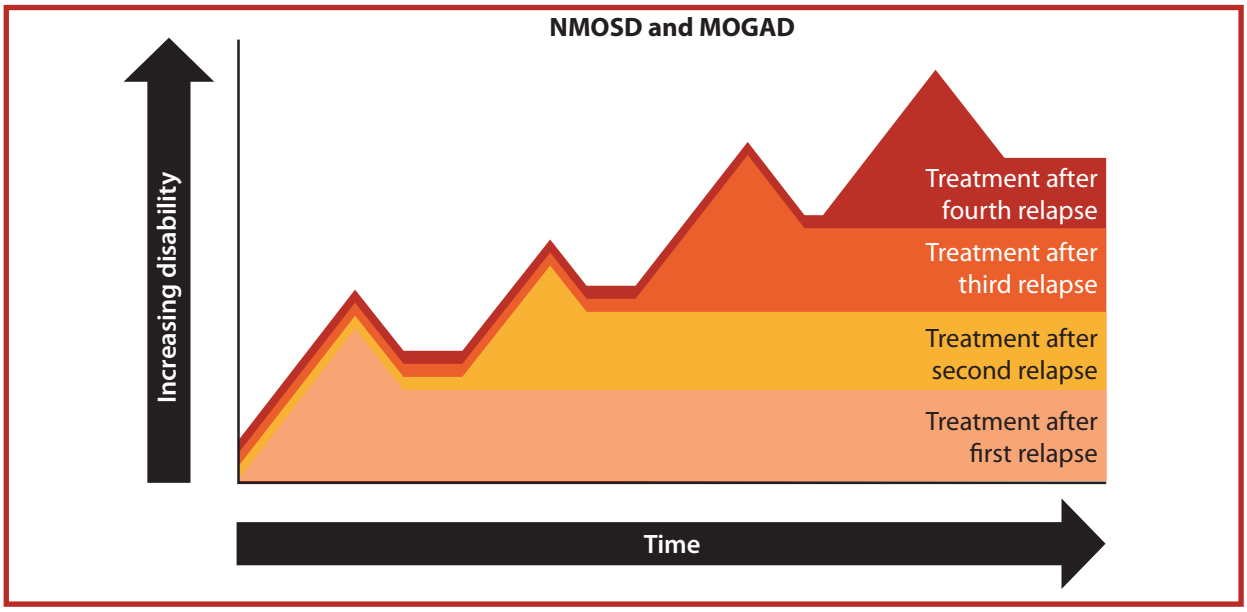

Figure 9. Avoiding relapses ensures better long-term outcomes for people with NMOSD and MOGAD.

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder.

assessments). In future, this may expand to digital monitoring.

Identification and validation of appropriate outcome measures is an important part of successful monitoring. Key outcome measures have been validated for MS and continue to evolve; these outcome measures are used in monitoring people with NMOSD, but there is a need for validation.[50,152] In MOGAD, there is a need to ascertain those who are at increased risk of relapsing disease and/or developing irreversible disability, and agreement is needed on which outcome measures will achieve this.[153]

Overall, a proactive approach to monitoring, with a clear treatment target, should be adopted as a core principle of clinical management. Accessible information for patients about the signs and symptoms that could indicate disease activity could also enable improved self-monitoring and sharing of information during consultations. Using effective clinician- and patient-driven outcomes monitoring would enable swift, shared decision-making in the case of treatment failure – that is, when disease activity has not been minimized in response to treatment.[2] Therefore, it makes sense to consider all indicators of disease activity, not just the clinical symptoms at the 'tip of the iceberg' (**Figure 10**).[2,13]

A growing data-sharing network across countries seeks to aid MS research and inform clinical practice, including regulations around monitoring.[154] Through international collaboration, a greater understanding of monitoring, treatment effects and disease predictions can be developed. Such activities can allow real-world data to be scaled up to co-create innovative approaches to timely care.[155]

Monitoring and responding to relapse activity

Studies consistently show a correlation between relapses in the first few years of MS and later levels of disability.[2] In NMOSD and MOGAD, relapses drive disability accumulation.[28] As such, people with these conditions should be monitored effectively to ensure that their treatment is sufficiently preventing or reducing the risk of a relapse happening.

However, relapses are not the only factor implicated in future disability progression, and

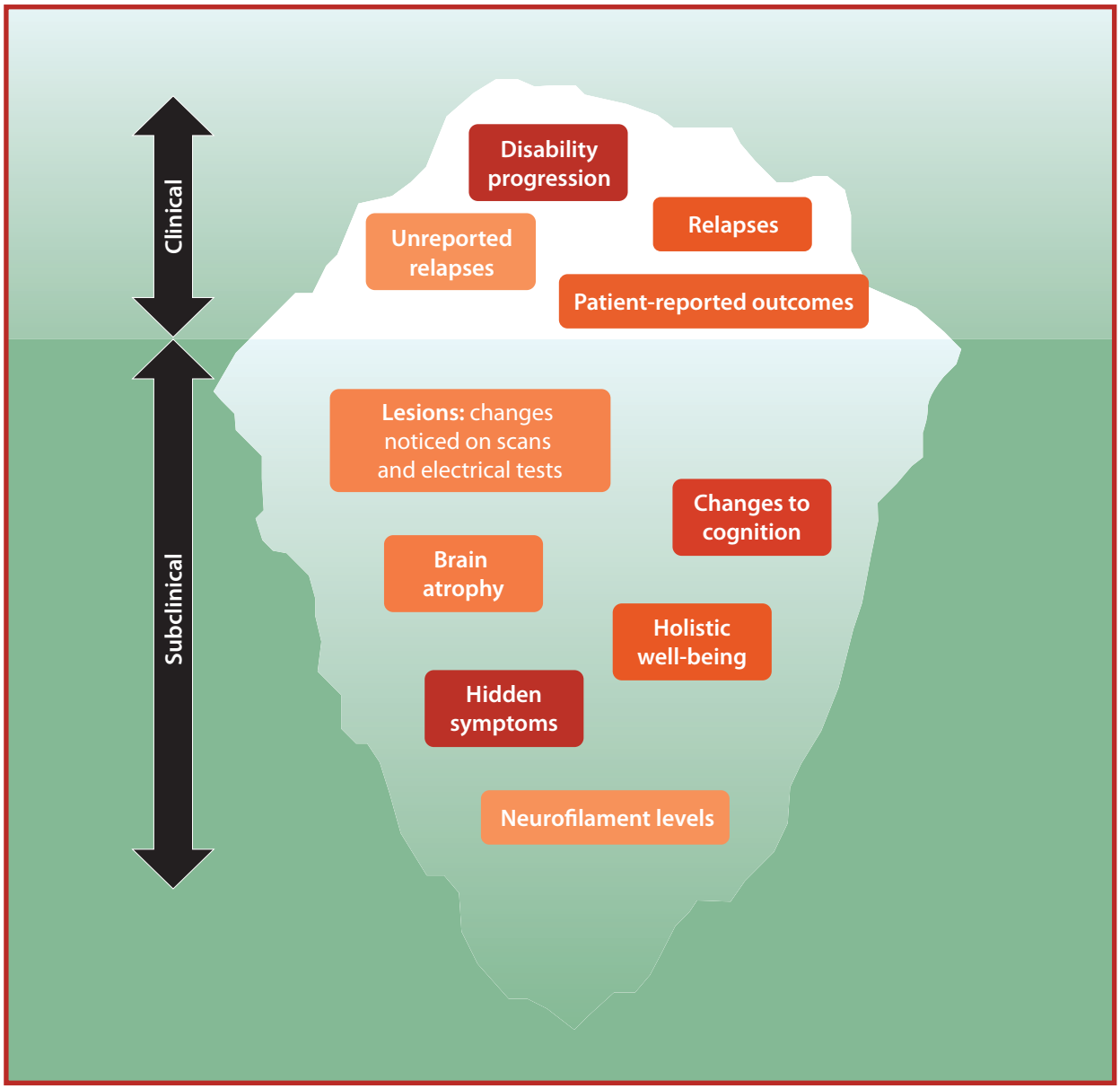

Figure 10. Monitoring clinical symptoms of MS, NMOSD and MOGAD should be supported by other measures of disease activity. Image adapted from the original *Brain health: time matters in multiple sclerosis* report with the permission of Professor Gavin Giovannoni, © 2014.[2]

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

there are drawbacks with simply using the recorded 'relapse rate'. Many relapses go unreported – nearly half of people with MS who responded to a recent UK survey indicated that they had failed to report a relapse to an HCP, and over one-quarter said that they had not reported their most recent relapse.[2] Whether or not a relapse is reported can depend on how frequently a person with MS sees a neurologist.[2,156] Remaining major challenges in NMOSD and MOGAD are a lack of universally accepted criteria for defining treatment failure or the need for a treatment switch, and a lack of outcomes that provide early identification of people in need of treatment modification.[50]

Use of medical imaging

Evidence gained from imaging scans of the brain, spinal cord and eye provide vital information needed during diagnosis, when making treatment decisions and as part of ongoing monitoring of these diseases.[2,157,158] However, in the Atlas of MS, 27% of countries globally lacked equipment or tests to monitor

treatment, which was a major barrier to people receiving DMTs.[95] This figure rises to approximately 60% of low-middle-income and low-income countries.[95]

With the increasing availability of MRI scanners,[2] including the development of portable scanners, the prospect of use in routine monitoring has become viable in an increased number of countries.[159] We continue to support expanding access to MRI scanners so that they can assist in treatment decisions.[160] Artificial intelligence (AI) models based on MRI and clinical features may also aid in distinguishing between NMOSD and other differential diagnoses, which could address a major challenge and speed up diagnosis and support monitoring.[161] However, MRI and other imaging approaches, such as optical coherence tomography, should not be used in isolation, with a full clinical picture being important.

Measurement of cognitive impairment

Since our previous publication,[2] there is increased evidence that monitoring cognition may help to track responses to therapy and identify early signs of disability progression.[162] Cognitive changes can occur in these diseases and are under-recognized residual symptoms for many people, which can affect emotional and psychological well-being. Changes to cognition can affect a person's social relationships with family, friends, caregivers and colleagues, and their daily activities.

The availability of validated measures of cognition in MS that are internationally accepted and translated should aid implementation.[163,164] Despite people with NMOSD or MOGAD reporting cognitive impairment as one of their key concerns, studies into the potential links in these populations are scarce.[165–167] Digital tests such as Brief International Cognitive Assessment for MS (BICAMS)[163] and the MSReactor measure visual attention and working memory, and they may become useful in the future.[162]

Monitoring cognitive changes may also give a more rounded view of a person's care and support needs while highlighting the value of approaches such as cognitive rehabilitation.[168] Cognitive rehabilitation may include behaviour modification techniques and other non-pharmacological interventions, which can significantly improve a patient's quality of life and independence.[168]

Benefits of self-monitoring and advanced technologies

Additional data provided by patients are emerging as critical factors that could play an important role in disease monitoring. These could include digital self-assessments, the use of health apps (in which patients need to manually input data) and passive monitoring (in which data could be collected via wearables or activity tracking apps on a phone). Information would be captured by the patient on a regular basis, increasing the consistency with which measurements are made, and digital health has the potential to capture small changes over time. Detailed health information and descriptions of daily experiences can be provided via technologies such as smartphone apps and activity trackers.[169] Adapting digital self-monitoring to individual situations, guidance on collecting the data and integration of self-monitoring into their treatment plans were aspects that people with MS said would support their use of self monitoring.[169] However, people may need support to use these technologies and to engage with them on a regular basis to collect effective monitoring data.

The lack of clinical tests to measure the full spectrum of symptoms experienced by people with these diseases means that assessment also can rely on self-reporting via PROMs. The advantages of data collected via strategically selected PROMs are increasingly appreciated by patients, clinicians, regulators and healthcare policymakers.[170,171] PROMs from clinical trial data are now included in many clinical approval processes for treatment, thus thorough

understanding of the available measures and careful utilization are important. One example of a relevant symptom that can be assessed using PROMs is fatigue; effective monitoring of fatigue could be of value because it affects many people with these diseases and drives reductions in quality of life and increased economic burden.[172–174]

Bringing patient insights into these measures could further enhance their validity. Groups such as the PROMS Initiative have conducted global surveys of people with MS to inform and fill in gaps in current PROMs using lived experiences.[63,175] Monitoring scales such as 'monitoring my multiple sclerosis' have been co-developed, encompassing broad and holistic parameters (e.g. physical health, relationships, energy and cognitive/mental health); upon testing, this measure was shown to have high reliability and validity, and was beneficial to people with MS and their healthcare teams.[176]

Compared with MS, there is only one PROM established for NMOSD, which is under further development and consideration, and there are no specific PROMs available for MOGAD.[177] There are, however, PROMs available for common symptoms experienced across these diseases, such as optic neuritis.[178]

Section 4. Optimal management and person-centred care

Since the publication of our previous report,[2] considerable research has shown the importance of taking a person-centred approach to care to ensure optimal outcomes for people with MS, NMOSD and MOGAD. This can be achieved via a holistic approach to care, which considers all the domains of a person's well-being as well as social, societal and community factors that affect quality of care, and can help each patient to live their best possible life. Person-centred care requires collaboration between the patient's family and healthcare team, as well as disease-specific peer support and community organizations, to provide an effective, tailored approach for each person.[19,20,179]

Empowerment to support decision-making

Shared decision-making can improve patient well-being, quality of life and treatment satisfaction. However, a 2024 survey in Europe and the USA concluded that about two-thirds of clinicians do not involve people with MS in their treatment decisions.[180] A personalized approach to treatment should also consider a patient's age, perceptions, ethnic background, and any co-existing psychological or physical conditions. The access to information from a clinician can help patients to ask questions and participate in decision-making.[181] The provision of accessible and evidence-based information and access to peer support empowers people to make informed choices about their care, to be forearmed for the potential challenges of stigma, prejudice and discrimination, and to optimize their quality of life. Although patient information about MS is widely available, many people with NMOSD or MOGAD do not receive such support, according to a US-based report[19] and a global patient survey.[20]

A 'brain-healthy' lifestyle

To maximize long-term brain health, a holistic and comprehensive management approach can complement early treatment (discussed in Section 3). Adopting a lifestyle that is good for brain health involves adopting recognized health behaviours such as maintaining good physical health, and improving social connections (which helps to engage specific areas of the brain).[179]

Optimizing physical health to support treatment outcomes

Optimizing physical health includes managing alcohol consumption, smoking cessation, engaging in regular physical exercise, maintaining a healthy weight, getting adequate sleep, and managing co-existing medical conditions such as high blood pressure, depression and other mental health disorders.[2]

Excessive alcohol consumption (currently or in the past) shortens survival in people with MS and should be managed.[182] Ongoing research has demonstrated a clear association between tobacco smoking and MS disease worsening;[183–185] therefore, people with MS should avoid smoking and exposure to cigarette smoke to maintain their brain health and benefit from symptom improvements.[186,187]

The benefits of physical activity and exercise are the most prominent brain health recommendations for people with MS[187] and should be widely promoted for effective management of the disease.[188] Cardiovascular and metabolic fitness correlates with

maintenance of brain volume and neurological reserve in MS.[189] Such approaches also support the management of comorbidities that affect cardiovascular and metabolic health, such as obesity, hypertension, hypercholesterolaemia, dyslipidaemia, diabetes mellitus and hypothyroidism.[179] Facilitated training sessions for people with reduced physical mobility[188] and exercise training for those with severe mobility disability[190] are examples of approaches that can be tailored as required.

Patient advocacy organizations, disease-specific peer support and community organizations can also help, with resources such as *Can Do Multiple Sclerosis*.[191,192]

Evidence relating to the benefits of approaches that seek to improve diet and gut health vary greatly, but a common theme is the value of maintaining a healthy body weight.[2,187]

Sleep disturbances are common among people with MS,[193] and poor sleep has a long-term, negative impact on the disease.[179] Decreased sleep quality also contributes to the disease burden associated with NMOSD,[194] and is a significant contributor to fatigue in people with MOGAD.[172] Improving sleep patterns in these populations is a growing area of interest.

Management of comorbidities

The need to address comorbidities to improve health outcomes and quality of life is consistent in these diseases. Studies in MS have demonstrated a clear link between worse outcomes and poorly controlled comorbidities.[195] It is also a growing challenge in the management of NMOSD. Up to 30% of people with NMOSD have at least one additional autoimmune disease (most commonly systemic lupus erythematosus, Sjögren's syndrome or autoimmune hypothyroidism), and high rates of non-autoimmune diseases such as cardiovascular disease and diabetes have been reported.[196] A previous systematic review of the available literature also showed that depression, anxiety and sleep disturbance are experienced by a high proportion of people with NMOSD.[197]

Importantly, all of these factors that influence brain health do not exist in isolation and are likely to have additive, or even multiplicative, effects.[1]

Integrated care approaches

Specialist care and management are best delivered by an integrated care model, which includes medical, nursing and allied health teams across primary and social care.[3] Often, it is not possible for general practitioners, primary care physicians or general neurologists to have a thorough understanding of these diseases, nor do they have the resources available to them to support the often-complex needs of people with these diseases and their families; this supports the need for the establishment of an integrated care team.[2,179,198] These teams can be comprised of specialist neurologists and nurses, alongside neuropsychologists, clinical psychologists, physiotherapists and occupational therapists, with access to a broad range of specialists such as continence specialists, dieticians, community health workers or other relevant allied health professionals. Essential to an integrated care team is the delivery of person-centred care, which ensures that the team works together to develop holistic management plans that meet the goals and needs of each patient, and that they develop an approach to monitoring health and the effectiveness of treatment that is achievable and acceptable to the patient.[199,200] An example of the sorts of services that may be required to manage changes in physical functioning is provided in **Figure 11**.

One potential approach to delivering this care would be through the development of MS or Neuroimmunology Care Units (may also be known as centres of excellence or comprehensive care centres).[199] The main objective of specialist care units is to provide

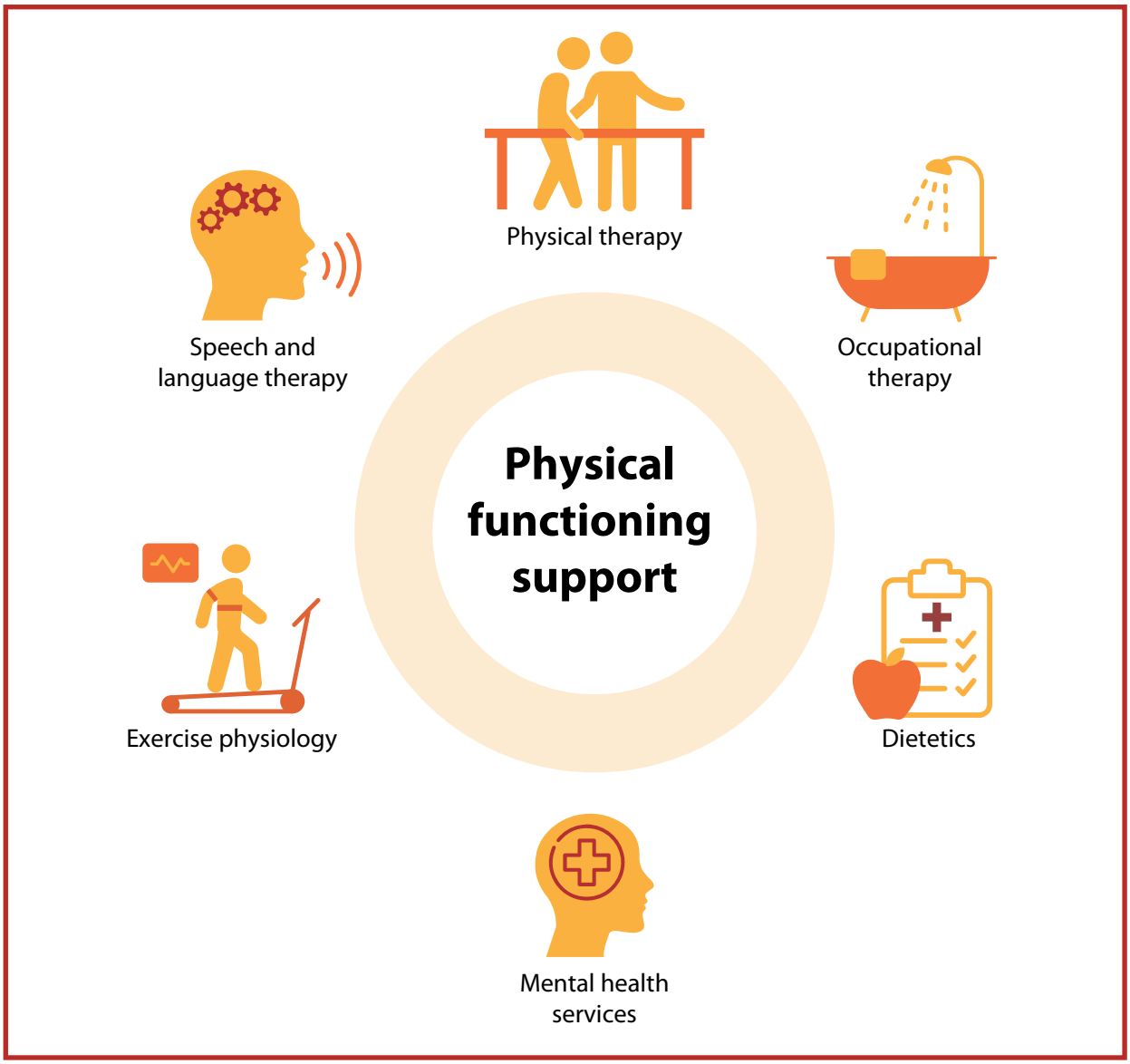

Figure 11. Multiple specialties can be required to co-operate while helping to support physical functioning in people with MS, NMOSD and MOGAD; these may include the examples shown, among others.

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

patients, their families and caregivers with access to specialist expertise and a comprehensive, holistic approach to their care management, increasing the likelihood of patient and caregiver satisfaction. The value of these approaches is likely to extend to overall societal costs because they can help people to continue working and reduce the costs of subsequent care.[125,126] Irrespective of the service name, integrated care is important in providing optimal management, together with integrated community services.

A fundamental aspect of integrated care is the recognition of the impact of brain health drivers on health outcomes and the need to identify those most at risk (and therefore in need of different/personalized and comprehensive support) so that effective interventions can be provided.[198,201] To support the development of these plans, researchers have developed screening tools, which could help by assessing the relationships between brain health drivers (e.g. unhealthy lifestyle, social isolation, lack of informal support and financial instability) and identify those who are most at risk.[1,179,202]

Rehabilitation is another important consideration in integrated care. However, lack of reimbursement means that people cannot access many of these therapy services. In 84% of countries surveyed in the Atlas of MS, rehabilitation services were not available, were too expensive (therefore rationed) or access was too slow.[95]

Mental health support for patients and caregivers

Living with a long-term debilitating disease has the potential to erode many aspects of the lives of patients and their caregivers, including mental health. Evidence from Sweden also showed that people with MS and depression were at a higher risk of disability progression than those without depression, highlighting the need for early recognition and treatment of mental health conditions in people with MS.[203] Cognitive behavioural therapy, adaptive coping techniques and music therapy, whether in isolation or in combination with physical training, can be beneficial.[179,187]

Challenges of age-related symptoms

Comorbidities play an increasing role in treatment as people age. Given the complexity of age-related changes, it can be challenging to determine whether health changes are due to disease progression, ageing or a comorbidity.[204] The presence of two or more long-term health conditions also means that polypharmacy (the need to take multiple medicines) is common in people with MS, which can influence treatment choices.[205] It is also important to note that treatments for MS symptoms (including those to treat spasticity, bladder problems and pain) can impact brain health.[205] Despite these situations posing challenges to clinicians and people with MS, there is a lack of data to guide clinical management.[206]

Understanding the effectiveness in older populations of DMTs for MS remains an area in need of research, in part due to the restricted age range of people who participate in clinical trials.[204] Most people with MS have the disease diagnosed between the ages of 20 years and 50 years, and 60% of them will experience disease progression before they are 75 years old;[207] therefore, more evidence is needed to determine the interplay between diseases and ageing.[204,208]

The effectiveness of MS treatment in older populations is becoming better understood as people who started receiving established DMTs (developed in the 1990s) or newer DMTs (developed after the year 2000) at diagnosis approach older age.[204] Research so far suggests the immune system begins to slow with age, shifting the mechanisms of MS damage from inflammatory to neurodegenerative[207] and posing different challenges in treatment. Older patients may tolerate treatment less well than younger patients and experience more side effects.[207] Therefore, holistic approaches are very relevant to this age group, particularly in patients with comorbidities receiving polypharmacy.

Women's changing health needs

MS and NMOSD are more common in women than in men.[25–27,209] Women with these diseases will need special consideration through key stages and changes of life – puberty, family planning, pregnancy, breastfeeding, infertility treatment and menopause[179,209] – so it is imperative that they receive equity of care, care that recognizes specific needs and support with any unique socioeconomic effects through each of these transitions.[210]

Previous studies have shown that changes in female hormones over time are associated with changes in the course of MS.[209] Useful MS guidelines are now available to support family planning, including treatment of infertility, and pregnancy,[211] and updated recommendations provide guidance for conceiving while receiving treatment and when to stop treatment before stopping contraception.[212–215] MS may become more active in the postpartum period than during pregnancy and should be carefully monitored.[216] More recently, understanding has

improved about which MS DMTs are compatible with breastfeeding, enabling more choice for women who wish to breastfeed their babies.[217] Conversations between women and their healthcare team before, during and after pregnancy should consider their condition, their preferences, treatment and possible effects on pregnancy, birth and breastfeeding.

A growing number of small studies have indicated that pregnancy symptoms may also worsen NMOSD disease activity.[218] Indeed, increased preparation and monitoring have been recommended for women with NMOSD who are considering pregnancy,[219] to take into account treatment changes and the timing and frequency of dosing.[219]

Women with MS will likely be living with the disease through the menopause and may have worsening MS symptoms before, during and afterwards.[220,221] MS symptom worsening may also be linked to overall age-related changes, but changes in hormone levels at this time are more likely to play a key role.[221] Healthcare teams should consider all stages of the menopause and address all potential symptoms, as well as natural MS disease development, when tailoring treatment plans,[222,223] particularly challenges relating to sleep quality, mood and vasomotor symptoms (e.g. hot flushes).[179,224]

Critical social factors that enhance life

Non-medical drivers, including societal and structural factors, can influence population health outcomes and should be factored into holistic approaches to care.[225] Many factors, such as cognitive impairment, fatigue, mood changes and reduced mobility, may result in a loss of social connectedness, which can worsen emotional well-being and reduce quality of life.[1,2,165] Approaches such as peer support, community organization support, social prescribing and lifestyle medicine are various ways that can connect people to activities and services in their area. These services support their practical, emotional and social needs, can help to reduce feelings of loneliness and isolation, and should be tailored to individual circumstances.[1,226,227]

Social participation

Reduced social participation is a major challenge posed by the symptoms of these diseases, increasing disability and financial constraints.[1] Individual factors such as visual impairment are an additional challenge that lead to diminished participation in social activities, as reported in a study of people with NMOSD in China.[228] The work of patient organizations, disease-specific peer support and community organizations can provide solutions to help in this area.[229–232] Another key aspect of maintaining social participation is supporting people to remain in work.

Continued employment

The age of onset of all these diseases means that they affect people who have the potential for many decades of employment.[2] These people face the possibility of losing their jobs or having to reduce their working hours and deal with lost income during their early careers, according to European,[48] US[82,233] and global reports.[88] Minimizing the risk of physical disability and cognitive impairment through effective disease treatment[2] are fundamental ways to help people to remain in employment.[1,234] We also cannot underestimate the positive impact of work on well-being and physical and mental health, and as an effective form of socialization.

Adapting workplaces or amending job roles can also help people to remain in employment.[2,235] Occupational therapists and clinicians have a key role in providing training to employers to support workers with MS and disabilities effectively, as shown by a study in Italy.[236] Practical steps may include offering flexible working and promoting a healthy work–life balance. Other interventions range from legal obligations to financial reward or recognition

schemes, as suggested by insights from Europe.[83] Legal protections against dismissal from employment due to a health condition should also be among basic legislative standards. Online peer support and training for people with MS aiming to remain in work are in early development via the MS WorkSmart initiative.[237] This is an interactive platform for people with MS in Australia to connect with each other and learn about workplace advocacy, disability accommodations, self-care techniques and managing the impact of MS on their career.

Personal safety

People with MS are at a higher risk of domestic or caregiver abuse than the general population;[1] therefore, safety concerns are paramount.[238] In particular, women with MS may be at increased risk of physical intimate partner abuse and verbal abuse. Women with MS in the USA with greater neurological disability were more likely to experience verbal abuse than those with lower levels of disability.[239] A study from Norway suggested sexual abuse is more widespread in women with MS than in women without MS.[240]

MS clinicians and wider healthcare teams can play an important role in detecting abuse. For example, a database of 830 patient appointments at one academic MS centre in the USA showed no reports of abuse or neglect.[239] Conversely, a survey at the same organization showed that 38% of people with MS had experienced abuse, 15% of them within the past 12 months.[239] This discrepancy shows that training for HCPs (particularly clinicians), alongside guidelines and policies for managing such difficulties, are needs in this area.[238] Furthermore, improved communication is required among HCPs across disciplines (e.g. psychiatry, primary and emergency care, sexual health, obstetrics or social care) to detect potential indicators of abuse in patients who they interact with.[241]

Equitable access: about more than money

Demographic differences and how they shape access to healthcare are important considerations in addressing disparities.[1]

Lower socioeconomic status is associated with a reduced level of quality of care and reduced access to treatment and specialist care in many countries, which can affect outcomes.[1,198] A systematic review of 57 studies relating to primary-care and MS-specialist visits found that low socioeconomic status was a barrier to accessing specialist physician visits, despite it being associated with an increased need to access primary care physician appointments.[242] Data from the European Social Survey encompassing 21 countries showed that people with high socioeconomic status were more likely to access healthcare specialists than people with low socioeconomic status.[243] These observations are important, given the vital role that specialist care plays in treating people with these diseases.

In many countries, it has been found that underrepresented groups often experience challenges in accessing the healthcare system.[3] The mistrust towards the healthcare system, which has been shown to affect health outcomes and treatment adherence, needs to be addressed by many countries.[57,244] For example, in the USA, retrospective studies highlighted that African American and Hispanic American people with MS have worse symptoms and self-reported health than White people.[245] Interviews with African American women living with MS in the USA reported that they often experience delays in diagnosis, which they report as partly owing to: clinicians' and their own perceptions that MS is most common in White people; social barriers in seeking medical support; and challenges navigating the healthcare system.[246] Recruitment to clinical studies also needs to reflect the racial/genetic prevalence of these diseases so that the factors relevant to treatment can be better assessed.[1]

Health literacy

The WHO defines health literacy as the ability of people to gain access to, understand and use information in ways that promote and maintain good health for themselves, their families and communities.[247] A previous systematic review of the available literature indicated that sufficient health literacy can lead to improvements in the physical and mental health of people with MS.[248] It can also improve their self-care and medication adherence, leading to improved health outcomes and reduced healthcare utilization.[248,249] Health literacy can also be a factor in a person's ability to navigate an often complex healthcare system, in obtaining a diagnosis and during ongoing treatment and care. Patients should be actively involved in care decisions because this has been shown to improve adherence and result in better health outcomes.[248]

The need for equitable healthcare access could also be addressed through education of HCPs and targeted engagement with underserved communities.[229–232] One such best practice example of an awareness campaign is the VISIBL-MS awareness campaign in the USA; this is a multilingual tool in English and Spanish, educating people about the early symptoms of MS and who is at highest risk.[250]

With the development of healthcare-specific large and small language models using AI, opportunities exist to further improve public symptom awareness. However, for diversity, equity and inclusion, it is important to expand regular healthcare outreach practices beyond usual networks, to reach particularly vulnerable groups. Learnings from Europe linked to the COVID-19 pandemic showed that community and charity group engagement helps people to navigate healthcare systems.[251]

Support for caregivers

As previously discussed, the responsibility of caring for people with NMOSD has a substantial impact, with one in five loved ones of people with NMOSD in the USA reporting depressive symptoms,[252] and caregivers in the UK reporting the need to change their roles inside and outside the home.[253] A combined literature review and analysis covering nine countries in Europe concluded that providing support for caregivers through dedicated training, counselling, psychological and financial assistance should align with the European Care Strategy for caregivers and care receivers.[83] Support for caregivers therefore presents an essential element to optimizing care management.

Future perspectives

In the preceding sections, we highlighted the key advances that have been made since the publication of our original 2015 report, *Brain health: time matters in multiple sclerosis*. We have also gone beyond MS and looked at how similar proactive and holistic approaches to care can help people with NMOSD or MOGAD. We recognize that progress will continue, and there are important areas in which developments will occur in the coming years.

A key factor will be the expanding role of AI and technology in addressing access and care challenges.

Disease understanding

As our understanding of what causes these diseases improves, new approaches to prevention and care may become available. The past decade has seen a wealth of new research into the causal link between infection with the Epstein-Barr virus (EBV) and MS because of the effects EBV has on the CNS, the immune system and nerve cells.[254] It is now widely agreed that EBV exposure is required for a person to develop MS, but it is insufficient on its own to trigger it; instead, it appears that a variety of factors adding up to a 'perfect storm' are required to initiate MS disease onset.[254] However, because EBV infection appears to be necessary for MS development, future clinical guidelines around the prophylaxis, management and treatment of MS may consider vaccination against EBV or attenuation of the mechanisms by which EBV participates in MS pathogenesis.[254–256] Continued research is needed to see if similar mechanisms, in terms of previous viral/bacterial infection, may play a role in the development of NMOSD or MOGAD.

Disease classification

As described in Section 3, diagnostic criteria play a fundamental role in ensuring accurate diagnosis. Further understanding of how these diseases initially present may also mean that diagnosis can be made earlier than is currently the case. It is also anticipated that over the coming year, revised diagnostic criteria will become available for MS and NMOSD. It will be important to see how these updates affect disease classification and subsequent prescribing practices. Workshop meetings arranged by the European Committee for Treatment and Research in Multiple Sclerosis will also lead to the publication of consensus guidelines covering topics including treatment guidelines and differential diagnosis across different populations. Raising awareness of consensus guidance and stratifying recommendations to ensure that they are relevant to different populations will be key to making sure that their findings are adopted.

The future of treatment

Throughout this report, we have described that the presentation and development of these diseases result in wide-ranging symptoms that are different for every person. It may therefore be the case that future treatment involves combination or dual-therapy approaches. Preliminary studies in MS suggest that there may be benefits to such regimens, but large studies are needed to confirm that the benefits would extend across all patients. More research is required to see if similar approaches may be beneficial for NMOSD and MOGAD alongside expanding access to current therapies. It will also be important to monitor how access to treatment is affected by inclusion of therapies in the WHO Model List of Essential Medicines.

Prospective monitoring parameters

Monitoring may be most effective when it takes a holistic view of the person affected, combining their medical signs with experiences that they report and changes in non-visible symptoms. There is growing interest in a range of biomarkers that can help to complement these approaches.[257,258] The key information needed to demonstrate the value of biomarkers is whether they assess an outcome that is relevant to people, to prove how accurately they measure the outcome and whether they can be adopted in clinical practice to support decision-making.

Biomarkers

A biomarker is something measurable in the body that indicates the presence or progression of a disease or condition. It could be a molecule, gene, protein or cell that can be detected through various tests, such as blood work or imaging. Biomarkers are used to diagnose diseases and monitor treatment effectiveness. Recent studies indicate that several proteins are uniquely present in the cerebrospinal fluid (CSF) of people with MS and have the potential to serve as biomarkers.[259] For NMOSD or MOGAD, promising candidate biomarkers include antibody titres, cytokine profiles, complement factors and markers of astroglial damage.[50,260]

Neurofilament light chains (NfL) are the protein 'scaffolding' of nerve fibres and are released into the CSF and then blood when damage occurs. NfL levels could be a useful measurement of MS disease activity and have also been trialled to inform treatment strategies.[261,262] Over several years, reduced levels of NfL correlate with reduced rates of disability progression.[259] However, NfL levels may not correlate well enough in all people with MS to be a predictive biomarker of progression. They mostly rise with acute inflammatory damage and are not considered to be a marker for PIRA/smouldering MS. NfL has also been noted as a potential marker of disability following relapses in people with NMOSD.[260] However, before NfL can be fully utilized as a biomarker, it will be important to establish standardized normal cut-off values (e.g. adjusting for age and sex), and define optimal sampling frequency and thresholds for longitudinal measurements.[261] If these aspects can be addressed, NfL levels have the potential for adoption as an indicator of subclinical disease activity that is accessible even in countries where there are few MRI scanners.

As our knowledge of candidate biomarkers improves, we may further understand their relevance in diagnosis, ongoing monitoring and treatment adjustment.[50,258] Inclusion of biomarkers within standard monitoring programmes is expected to help to predict future outcomes.

AI

Finally, a word on AI. As we move toward identifying the right outcomes for different groups of people, AI-based solutions may support the capture and interpretation of complex data.[263] Early studies have suggested that AI analysis can detect differences in cognitive test results between people with MS and people without MS.[264] Applying AI technology to the analysis and use of health data – particularly when it has been patient-generated or patient-reported – has the potential to enable the holistic approach needed to improve prognosis, prevent and treat progression and improve lives. However, AI technology will only successfully make it into the clinic if it is fully acceptable to people.[265] People with these diseases would need to be involved in future applications for this to address the usefulness of certain sets of data, support concerns about privacy and data security, and understand their needs.

Recommendations

Not every nation, community and institution will achieve all recommendations. The key is to start somewhere; even small changes can make a difference to individuals, families, societies and economies.

Minimize delays in the diagnosis of MS, NMOSD and MOGAD and in the time to treatment initiation

Education

- Ensure that education of HCPs and further/specialist education of family and primary care physicians, emergency staff and opticians include knowledge of all potential symptoms and the importance of prompt referral to specialist neurology services.
- Ensure that the curriculum for HCPs relating to MS knowledge includes the risk of misdiagnosing MS in people who have NMOSD, MOGAD or a related disorder.
- Ensure HCP education helps HCPs to ask their patients the right questions, especially about hidden symptoms, to ensure the best possible two-way dialogue and shared decision-making.

Specialist services

- Improve access to general and specialist neurology care. In parallel, invest in community-based services.
- When possible, promote the delivery of integrated care via Neuroimmunology Care Units or other kinds of specialized care centres, centres of excellence or comprehensive care centres.
- Improve the availability of diagnostic tools such as MRI scanners and internationally standardized protocols to expedite the diagnostic process.
- Strive to increase the number of doctors, nurses and other HCPs who specialize in the management of MS, NMOSD and MOGAD.
- Leverage digitalization and AI to ensure remote access to specialist knowledge and care.

Treatment principles

- Ensure national guidelines align with international guidelines for diagnostic criteria and treatment management targets, including early treatment and early access to more efficacious treatments.

Advocacy and information

- Support local, national and regional patient advocacy groups.

See every patient as a person and ensure an optimal approach to care

Holistic and shared care

- Enable an integrated care approach.
- Ensure a person-centred approach is reflected in public health policy, guidelines, budgets and other political texts that provide political accountability.
- Ensure the right to and practical availability of specialist care and additional opinions.
- Mandate a shared decision-making process.
- Ensure the reliable presence of necessary interventions and make the full range of DMTs available to people, regardless of their treatment history and diagnosis.
- Mandate the inclusion of lifestyle prescriptions, which HCPs need to support people to live a brain-healthy lifestyle.
- Ensure that HCPs and, when appropriate, patients are resourced to monitor disease activity in people with MS, NMOSD or MOGAD, taking advantage of AI and other innovative technology approaches when possible.
- Ensure that patients and, if appropriate, caregivers are educated about visible and hidden symptoms of disease worsening or progression following diagnosis.
- Ensure equity of rights and opportunities, including personal safety protection, social care, disability and employment rights regardless of sex, gender, race, ethnicity, age, level of disability or socioeconomic status.

Data collection and monitoring

- Agree and implement standardized data collection techniques, protocols and data sets (nationally and internationally) to track clinical and subclinical events in routine practice.
- Allow for the consistent availability of treatment for as long as it provides benefit. In the case of a suboptimal response, HCPs and patients can make a prompt decision about whether to switch therapy in a shared decision-making process.
- Promote cross-border collaboration on research.

Consult the most robust evidence base possible and generate further evidence to make good decisions about therapeutic and management strategies and access to care for people with MS, NMOSD and MOGAD

Value to society

- Ensure affordable treatments: people with life-changing diseases should be able to access crucial interventions without financial hardship.
- Improve access to vocational rehabilitation and/or supported employment, assisted living and disability benefits.
- Include a societal perspective encompassing the full scope of patient and caregiver burden in all economic evaluations of healthcare interventions.
- Encourage resource investment into approaches that reduce the long-term costs of managing and living with MS, NMOSD and MOGAD.
- Support public registries that capture care and social services data, allowing all stakeholders transparent access to relevant findings from real-world data.

Self-monitoring and self-management

- Support patient engagement and self-management through information, PROMs and patient-reported experience measures.
- Establish harmonized approaches, such as a registry for secondary uses of patient data.

AI, artificial intelligence; DMT, disease-modifying therapy; HCP, healthcare professional; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PROM, patient-reported outcome measure.

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Abbreviations

ACT	Acceptance and commitment therapy
AI	Artificial intelligence
BICAMS	Brief International Cognitive Assessment for MS
CBT	Cognitive behavioural therapy
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
DMT	Disease-modifying therapy
EBV	Epstein-Barr virus
EDSS	Extended Disability Status Scale
EMSP	European Multiple Sclerosis Platform
EUReMS	European Register for Multiple Sclerosis
FES	Functional electrical stimulation
HCP	Healthcare professional
HTA	Health technology assessment
MOGAD	Myelin oligodendrocyte glycoprotein antibody-associated disease
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NEMOS	Neuromyelitis optica study group
NfL	Neurofilament light chains
NMOSD	Neuromyelitis optica spectrum disorder
PIRA	Progression independent of relapse activity
PROM	Patient-report outcome measure
PROMS Initiative	Patient Reported Outcomes for Multiple Sclerosis Initiative
TENS	Transcutaneous electrical nerve stimulation
WHO	World Health Organization

Currencies

AUD	Australian dollars
£	pound sterling
€	euros
US$	US dollars

OXFORD HEALTH POLICY FORUM

Brain health – time matters

2024 Report

MS Brain Health