

Charting a Global Research Strategy for Progressive MS – An International Progressive MS Alliance Proposal

Prof Alan J Thompson, MD,¹ Prof William Carroll, MD,² Prof Olga Ciccarelli, MD,¹ Prof Giancarlo Comi, MD,³ Prof. Anne Cross, MD,⁴ Alexis Donnelly, MS,⁵ Prof Anthony Feinstein, MD,⁶ Prof Robert J. Fox, MD,⁷ Anne Helme, PhD,⁸ Prof Reinhard Hohlfeld, MD,⁹ Robert Hyde, PhD,¹⁰ Pamela Kanellis, PhD,¹¹ Douglas Landsman, PhD¹² Prof Catherine Lubetzki, MD,¹³ Prof Ruth Ann Marrie, MD¹⁴ Julia Morahan, PhD¹⁵ Prof Xavier Montalban, MD¹⁶ Bruno Musch, MD,¹⁷ Sarah Rawlings, PhD¹⁸ Prof Marco Salvetti, MD^{19,20} Prof. Finn Sellebjerg, MD,²¹ Caroline Sincock, PhD²² Kathryn E Smith, MA,²³ Jon Strum, BA,²⁴ Paola Zarin, PhD,²⁵ Timothy Coetzee, PhD^{12*}

¹University College London, London, United Kingdom

²University of Western Australia, Australia

³Vita-Salute San Raffaele University, Milan, Italy

⁴Washington University St. Louis, St. Louis, United States

⁵International Progressive MS Alliance, Dublin, Ireland

⁶Sunnybrook Institute, Toronto, Canada

⁷Cleveland Clinic, Cleveland, United States

⁸MS International Federation, London, United Kingdom

⁹Ludwig Maximilians University of Munich and Munich Cluster of Systems Neurology, Munich, Germany

¹⁰Biogen, Cambridge, United States

¹¹MS Society of Canada, Toronto, Canada

¹²National Multiple Sclerosis Society, New York, United States

¹³Salpêtrière Hospital, Paris, France

¹⁴University of Manitoba, Winnipeg, Canada

¹⁵MS Research Australia, North Sydney Australia

¹⁶Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona Spain

¹⁷Genentech, San Francisco, United States

¹⁸MS Society, London, United Kingdom

¹⁹Centre for Experimental Neurological Therapies (CENTERS), Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University of Rome, 00189 Rome, Italy;

²⁰Istituto Neurologico Mediterraneo (INM) Neuromed, 86077 Pozzilli, Italy

²¹Copenhagen University Hospital - Rigshospitalet, Glostrup, Denmark

²²International Progressive MS Alliance, Glasgow, Scotland

²³International Progressive MS Alliance, Lyme, United States

²⁴International Progressive MS Alliance, Los Angeles, United States

²⁵Italian Multiple Sclerosis Foundation, Genoa, Italy

***Corresponding Author:**

Timothy Coetzee, PhD
National Multiple Sclerosis Society
733 Third Avenue
New York, NY 10017
USA

Email: timothy.coetzee@nmss.org
Tel: +1 518 334 3711

Abstract

Progressive forms of multiple sclerosis (MS) affect more than 1 million individuals globally. Recent approvals of ocrelizumab for primary progressive MS and siponimod for active secondary progressive MS have opened the therapeutic door, though results from early trials of neuroprotective agents have been mixed. The recent introduction of the term ‘active’ secondary progressive MS into the therapeutic lexicon has introduced potential confusion to disease description and thereby clinical management. Sustaining and accelerating progress will require greater understanding of underlying mechanisms, identification of potential therapeutic targets, biomarker discovery and validation, and conduct of clinical trials with improved trial design. Encouraging developments in symptomatic and rehabilitative interventions are starting to address ongoing challenges experienced by people with progressive MS. We need to manage these challenges and realise the opportunities in the context of a global research strategy, which will improve quality of life for people with progressive MS.

Introduction

Multiple Sclerosis (MS) is a growing global neurological challenge affecting 2.8 million individuals worldwide.¹ A large proportion of these individuals either live with a relapsing form (RMS) and/or a progressive form of MS - the latter either Primary Progressive MS (PPMS) which is progressive from the outset, or Secondary Progressive MS (SPMS). Arriving at a precise global estimate of the prevalence of progressive forms of MS remains difficult. Prior to the availability of disease-modifying treatments, natural history studies of MS estimated that 50% of individuals diagnosed with RMS would transition to SPMS within 10 years of initial diagnosis and 90% would transition to SPMS within 25 years of initial diagnosis.²⁻⁵ In addition, it is estimated that 15% of individuals are diagnosed with PPMS.⁶ Taken together it is reasonable to conclude that in excess of one million individuals globally currently live with one of the progressive forms of the disease.

Since publication of the International Progressive MS Alliance's initial scientific strategy statement in 2012, we have seen the achievement of a significant milestone - approval of the first MS treatments for progressive disease, ocrelizumab (for PPMS) and siponimod (for active SPMS).⁷⁻⁹ While these agents demonstrated modest efficacy with respect to confirmed time to disability progression, their addition to the clinician's toolbox nonetheless signals a hopeful start to a potential new therapeutic era - similar to that previously seen in relapsing MS. In addition, observational studies support the possibility that intervention with disease-modifying treatments can reduce the risk of transition from RMS to SPMS and improve disability outcomes in patients with active SPMS.^{10, 11} Together, these developments point to the prospect that therapeutic interventions can alter the natural history of the disease and improve outcomes for those individuals concerned about developing or living with SPMS.

Despite positive developments in the field, major gaps persist in both the treatment and management of progressive disease.¹² Over the past 5 years the emergence of global engagement and collaboration of many stakeholders to address these challenges has been a welcome development. In. Collective efforts by the International Progressive MS Alliance, national patient organizations, government, industry together with researchers and clinicians have drawn much needed attention to the challenges of progressive MS. Although this effort has catalyzed scientific progress, much work remains to address the remaining scientific gaps so that people with progressive MS can have access to a robust therapeutic toolbox of pharmacological and non-pharmacological interventions.^{13, 14} In this paper, we review recent progress, highlight continued knowledge and propose, on behalf of the International Progressive MS Alliance, a global research strategy for progressive MS.

Progressive MS – A Persistent Clinical Challenge

Identifying the onset of progressive MS in the individual patient remains a clinical challenge. Currently, this determination is made retrospectively using a combination of assessments by a skilled clinician.^{15, 16} Currently, we lack effective tools to prospectively assess if and when an individual transitions from relapsing to progressive MS but there are emerging efforts to leverage large patient databases to develop algorithmic tools to aid clinicians.^{17, 18} Moreover, advances in our understanding of the pathophysiological mechanisms of the disease suggest that multiple pathogenic mechanisms are present in an individual patient at any given time and that these mechanisms are expressed clinically with some variability. Thus, in an individual patient, the onset of progressive MS most likely begins close to a confluence of two major factors: (1) the accumulation of CNS damage, due to inflammatory disease mechanisms, combined with (2) an accumulation of neuroaxonal damage that overwhelms extant CNS compensatory mechanisms (Figure 1). The precise point at which an

individual patient enters clinically apparent progressive disease and the rate of progression will vary, depending on a number of moderating factors. These include biological sex, gender, race, comorbidities, possibly genetic factors, and utilization of disease modifying treatments (DMTs) along with the aging process.^{19,20} There is also some evidence that the onset of progression does not take place at the same time in different central nervous system pathways and areas, nor do we fully appreciate how sustained immunotherapy influences this process.^{10,21,22}

Recent Progress

Pathophysiological Mechanisms

A better understanding of the mechanisms underpinning or moderating progression is fundamental to expanding the therapeutic repertoire. Recent efforts have revealed important new insights in aspects of immune-mediated inflammation and neurodegeneration. It is thought that in MS there are two types of inflammation.²³ One is characterised by acute focal invasion of immune cells giving rise to active demyelinated plaques in the white matter, the other by slow formation of immune cell aggregates in connective tissues spaces such as the meninges and perivascular spaces. The latter type of inflammation gradually increases with disease duration and patient age. It is associated with subpial demyelinated lesions in the cortex, slowly expanding lesions in the white matter, and diffuse neurodegeneration in the white and grey matter²³⁻²⁶

The role of the innate immune system is of interest with a particular focus on the control of pathological astrocytes by microglia.²⁷⁻³³ Recently NOD-leucine rich repeat and pyrin containing protein 3 (NLRP3) inflammasome has been shown to be overactive in monocytes in PPMS, and canonical NLRP3 inflammasome activation with a combination of ATP plus lipopolysaccharide was associated with increased IL1-Beta production.^{32,34} The mechanisms underpinning progression,

however, go far beyond inflammation and likely involve failure of normal maintenance and repair mechanisms, including remyelination. Mechanisms driving neurodegeneration include axonal loss and involve the interrelationship between demyelination, astrocyte pathology mitochondrial dysfunction and neuronal vulnerability.^{31, 35, 36} Other factors such as the role of complement genes, biological aging as reflected in telomere shortening and microstructural changes in the spinal cord are also being considered.^{19, 37, 38} Grey matter damage has also been implicated to the onset of the progressive phase and the development of disability.^{22, 39-42}

Tools – Biomarkers, imaging modalities, functional measures

Another challenge is the absence of biomarkers signaling progression, that are scientifically sensitive and specific enough to justify their use in phase II and phase III clinical trials. A major difficulty is disentangling how much of a change of a given biomarker is due to neurodegenerative mechanisms underlying progression or to acute inflammation driven by peripheral immune mechanisms. Several imaging markers have been explored to good effect in the Phase II trial of ibudilast, which evaluated grey matter atrophy and whole brain atrophy, along with advanced MRI measures including magnetization transfer imaging and diffusion tensor imaging.^{43, 44} Recent studies have identified some potential biomarkers of progression: imaging biomarkers include slowly expanding lesions on brain MRI (which could be a correlate of smoldering demyelination and axonal loss in chronic active lesions) and changes in N-acetyl aspartate concentration, which indicates neuroaxonal integrity and mitochondrial function.^{40, 45} Other approaches, including OCT and a revisiting of visual evoked potentials, are also being explored.^{46, 47}

The measurement of serum neurofilament light (NfL) has been assessed in a number of recent studies looking at both acute and chronic changes in MS.⁴⁸⁻⁵¹ An association with the development

of disability has been described. The growing body of evidence associated with NfL has also stimulated global efforts to determine its utility as a tool for drug discovery and clinical management of the disease.^{52,53} A critical aspect of this work is the need for longitudinal examination of patient cohorts to examine the utility of NfL in measuring progression independent of relapse activity. Recent work in natalizumab-treated patients illustrates this complexity and the need for careful consideration of NfL as a tool in clinical management of progressive MS.⁵⁴

Clinical Trials of Investigational Drugs

Recent Phase III trials in progressive MS demonstrated that ocrelizumab in PPMS and siponimod in SPMS modestly reduced the risk of confirmed disability progression, while trials of the water soluble B vitamin; biotin, in PPMS and SPMS, and natalizumab in SPMS and fingolimod in PPMS were unequivocally negative.⁵⁵⁻⁵⁹ However, if we are to have a major impact on progression we need to develop agents that provide neuroprotection and/or encourage repair, and here the picture is less clear. There have been a number of phase II trials of putative neuroprotective agents. The innovative multi-arm MS-SMART trial evaluated three agents, amiloride, fluoxetine and riluzole, but showed no benefit of any of the therapies. An earlier study of fluoxetine was also negative.^{60,61} However, a recent study of ibudilast showed positive results on several imaging outcomes (see earlier section).^{43,44} Very recently, masitinib, an oral tyrosine kinase inhibitor that selectively targets mast cell activity and microglia activity, was reported to significantly reduce the risk of disability progression in a double-blind placebo controlled phase III study.⁶² In addition to these advances, a review of ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (as of April 2021) found a number of ongoing clinical trials (Phase 0/I to Phase III) of agents and interventions in progressive MS. Given the considerable attrition associated with drug

development, more trials would be desirable, but, nonetheless, this augurs well for the future (Figure 2).

Rehabilitation and Symptom Management

Evaluating interventions in the fields of symptomatic management and rehabilitation in progressive MS remains a major challenge - as noted recently in a call for action by a work group convened by the International Progressive MS Alliance.⁶³ People with progressive MS are looking for rapidly translatable approaches that treat their disease now, while the longer term disease-modifying treatments are developed. Fortunately, there have been well constructed studies demonstrating for example the benefits to motor function from a very practical standing frame programme; along with careful studies examining the benefits of exercise on fatigue as well as cognition⁶⁴⁻⁶⁷ The last of these areas is currently being evaluated in an innovative multi-center international clinical trial.⁶⁸

Three Areas Requiring Renewed Focus and Effort

Understand Progression

A fundamental challenge in progressive MS is the continued poor understanding of the mechanisms initiating and perpetuating disease progression. This limitation hampers efforts to identify biologically plausible treatment targets, that are essential for efficient drug discovery. Continued exploration of the fundamental mechanisms of disease, using both computational systems, animal models and human studies, will be required. This work would be stimulated by the establishment of robust data sharing platforms that leverage machine learning and related artificial intelligence tools to develop new insights into biological pathways contributing to progressive disease. Drug discovery networks – whether existing or new efforts – can build on these insights to identify new or

repurposed agents with potential to treat progressive MS. Furthermore, the pipeline of new therapeutic agents may be expanded by careful, innovative design of short, efficient exploratory human clinical trials to provide insights into disease progression. They may also serve as an initial proving ground for agents suitable for later stage clinical trial strategies which can further expand the pipeline of agents to be tested in larger clinical trials.⁶⁹ An additional consideration would be the development of more biologically-based descriptors of the clinical course of the disease. Efforts in this area are under way under the auspices of the International Advisory Committee on Clinical Trials in MS.¹⁶

Accelerate Clinical Trials

Study design is a critical consideration for accelerating clinical trials of progressive MS treatments. The current two-arm clinical trial paradigm – while largely reasonable for relapsing MS agents – poses significant challenges for progressive MS trials, given the large numbers of patients that must be enrolled and the long duration required to ascertain a clinical effect, using conventional clinical outcome measures (e.g. Expanded Disability Status Scale).⁷⁰ One solution may be the use of adaptive, multi-arm and multi-stage trial designs to evaluate multiple agents simultaneously and in a potentially more cost effective manner.⁶⁹ Encouraging examples of this are the MS-SMART trial of three agents in progressive MS and the recently launched OCTOPUS trial.^{60, 71, 72} A very recent innovation is the use of Simon (2 stage) trial designs to screen compounds for non-futility.^{73, 74} This approach, while far from a definitive demonstration of effect, can act as an efficient screen to identify promising therapeutic candidates relatively quickly. Such efforts are welcome, perhaps even overdue, and should inspire similar efforts globally.

Another critical barrier is the lack of a validated biomarker or outcome measure to enable shorter phase 2 clinical trials. The development of treatments for relapsing forms of MS was revolutionized by the adoption of reduction in gadolinium enhancing lesions as a proof-of-concept measure in Phase 2 trials. A similarly powerful tool(s) is needed in progressive MS. Volumetric imaging measures such as whole brain atrophy or volumetric MRI percentage brain volume change are being used in clinical trials but these require long studies, typically 96 weeks, to detect measurable changes. Such lengthy timelines when compared to the shorter intervals required in relapsing trials (typically 24 weeks for a trial measuring reduction in gadolinium enhancing lesions) pose a significant challenge for investigators and companies seeking to move agents into Phase 3 trials in progressive MS.^{44, 60, 75}

The development and validation of fluid biomarkers such as NFL as well as other imaging modalities should lead to shorter studies which accelerate and enable progress.^{50, 53, 76, 77} Moreover, efforts such as the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC), the global Patient Reported Outcomes Initiative for MS (PROMS) and the proposed EDSS plus will contribute to development of new or modified outcome measures, but additional efforts are needed.⁷⁸⁻⁸² An intriguing possibility is the use of smartphone sensor-based digital outcome assessments. While still in the early stages, recent work demonstrated that an app-based tool – Floodlight PoC – along with a smartwatch accurately captured reliable and clinically relevant measures of functional impairment in MS, in this area points to a future where ubiquitous digital tools could be leveraged to enhance research and clinical care.^{83, 84}

Finally, the ongoing challenge of phenotypic classification of the disease continues to impact clinical trials of progressive MS agents. This challenge introduced a measure of confusion due to the

differing applications of the 2013 clinical course descriptors used in the review and approval of ocrelizumab and siponimod by both the US Food and Drug Administration (FDA) and the European Medicines Agency and compounded by the FDA's retroactively expanding approval of agents for RMS to include active SPMS.^{9, 16, 85} Coordination among regulatory authorities and the MS patient and clinician community, in relation to disease phenotypes, is essential if we are to avoid undue complexity and confusion in patient recruitment, trial design, and subsequent treatment approvals.

Improving Wellbeing

The final area for global prioritization is improving the wellbeing of persons with progressive MS. Unfortunately, this area remains poorly addressed with considerable gaps in the development of novel rehabilitative and symptomatic interventions that can meaningfully enhance quality of life for persons with progressive MS. There are, nevertheless, an abundance of potential interventional targets in the domains of physical and cognitive health, emotional wellbeing, social support and comorbidities (Figure 3). A welcome development is the recently launched CogEx clinical trial – the first multi-country, multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise.⁶⁸ Continued progress in these areas will require development of a coordinated global rehabilitation and symptom management research strategy with targeted initiatives in areas that have appropriate scientific readiness. Foundational efforts will also be needed to address areas requiring further development (e.g. methodological or workforce gaps).⁶³

Critical steps going forward

The research and clinical progress, together with the raised profile of progressive MS, over the last five years is a cause for hope. Clinical trials of approved treatments for progressive MS as well as

those with negative outcomes are providing valuable insights and experience for the design and conduct of future trials. Moreover, there is growing appreciation of the importance of quality-of-life interventions in enabling patients with progressive MS to participate fully in society leading full and productive lives. While significant challenges remain, there are opportunities for impact provided the community prioritizes efforts to understand progression, accelerate clinical trials, and to enhance well-being of those with progressive MS (Table 1).

All parties – people affected by progressive MS, patient groups, funders, academia, industry, regulatory authorities – have a role to play and ideally should be engaged, coordinated and encouraged to work together (Figure 4).⁸⁶ Perspectives of people affected by Progressive MS must be incorporated across the research continuum to ensure proper focus on what matters to them. Engaging people with Progressive MS, as a key stakeholder, in research and measuring impact on outcome that matter most to them, will give research the direction to make all the relevant stakeholders co-accountable for social and wellbeing needs related to progressive MS.⁸⁰ This involvement can take many forms, such as inclusion of people with MS in establishing research agendas, contributing to design of clinical trials, planning for and communicating research results, informing funding decisions and/or other parts of the research continuum. A recent example of such inclusion is the EU-funded MULTI-ACT initiative that has developed a framework to incorporate the perspectives of people with brain diseases in setting research agendas and in evaluating research impact.⁸⁷ These endeavors and others point to a future where patients contribute distinctively and meaningfully to the development transformational treatments.

Funders will need to sustain investments in ongoing programmes and consider new ways of catalyzing progress. The impact of these investments will be further enhanced by meaningful

coordination of research agendas at the national and international levels. Global multi-disciplinary and multi-stakeholder collaborative efforts like the International Progressive MS Alliance and a number of related strategic alliances (e.g. International Advisory Committee on Clinical Trials in MS, imaging networks in Europe and North America -, MAGNIMS and NAIMS respectively – and the UK MS Society multi-arm clinical trial platform - OCTOPUS – among others) will be critically important in directing efforts to refine our descriptions of progressive MS, accelerating drug discovery, and ensuring efficient conduct of clinical trials. Finally, robust efforts must be undertaken to ensure knowledge translation and implementation of interventions by health systems and clinicians. Fortunately, the field of implementation science points the way to success in such endeavors.⁸⁸ The well-established Quality Enhancement Research Initiative (QUERI) led by the United States Veterans Administration is one pertinent illustration of how quality of care can be improved with a sustained focus on measuring the health, economic and cultural impacts of scientific investments.^{89,90} Without similar efforts, we risk advancing knowledge without concomitant benefits being realized by people with progressive MS.

Conclusions

Addressing the needs of people with progressive MS remains a central challenge for the MS community. While there has been considerable progress in understanding the pathophysiological mechanisms of progressive MS, much remains to be understood. Moreover, the emergence of modestly effective treatments for progressive forms of the disease - while a source of hope - , are just a beginning. Continued and coordinated efforts by the global scientific, clinical and patient advocacy community will be critical to ensure sustained progress towards a future where fewer individuals are affected by progressive MS and where those with progressive MS have access to a suite of comprehensive and effective treatments. The International Progressive MS Alliance and its

member organizations and many supporters affirm their commitment to invest in the proposed research strategy and call on the global research community to join in these collective efforts to find solutions and deliver hope to those affected by progressive MS.

Funding Sources

This work was supported by the International Progressive MS Alliance. The funder provided financial support for convening activities of the authors to inform development of research strategies discussed in this paper.

References

1. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS third edition. *Mult Scler* 2020; 26: 1816-1821.
2. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain* 2010; 133: 1914-1929. 2010/06/09. DOI: 10.1093/brain/awq118.
3. Confavreux C, Vukusic S, Moreau T, et al. Relapses and progression of disability in multiple sclerosis. *The New England journal of medicine* 2000; 343: 1430-1438. DOI: 10.1056/nejm200011163432001.
4. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989; 112 (Pt 1): 133-146. DOI: 10.1093/brain/112.1.133.
5. Ontaneda D, Thompson AJ, Fox RJ, et al. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. *Lancet* 2017; 389: 1357-1366. 2016/11/24. DOI: 10.1016/s0140-6736(16)31320-4.
6. McGinley MP, Goldschmidt CH and Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA* 2021; 325: 765-779. DOI: 10.1001/jama.2020.26858.
7. Fox RJ, Thompson A, Baker D, et al. Setting a research agenda for progressive multiple sclerosis: the International Collaborative on Progressive MS. *Mult Scler* 2012; 18: 1534-1540. 2012/08/25. DOI: 10.1177/1352458512458169.
8. US Food and Drug Administration. FDA approves new drug to treat multiple sclerosis, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm549325.htm> (2017 accessed August 11, 2017 2017).
9. Novartis. Novartis receives FDA approval for Mayzent® (siponimod), the first oral drug to treat secondary progressive MS with active disease, <https://www.prnewswire.com/news-releases/novartis-receives-fda-approval-for-mayzent-siponimod-the-first-oral-drug-to-treat-secondary-progressive-ms-with-active-disease-300819243.html> (2019, accessed April 16 2021).
10. Brown JW, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA* 2019; 321: 175-187. 2019/01/16. DOI: 10.1001/jama.2018.20588.
11. Lizak N, Malpas CB, Sharmin S, et al. Association of Sustained Immunotherapy With Disability Outcomes in Patients With Active Secondary Progressive Multiple Sclerosis. *JAMA Neurology* 2020; 77: 1-11. 2020/07/28. DOI: 10.1001/jamaneurol.2020.2453.
12. Thompson A and Ciccarelli O. Towards treating progressive multiple sclerosis. *Nature Rev Neurol* 2020; 16: 589-590. DOI: 10.1038/s41582-020-00421-4.
13. Fox RJ, Thompson A, Baker D, et al. Setting a research agenda for progressive multiple sclerosis: the International Collaborative on Progressive MS. *Mult Scler* 2012; 18: 1534-1540. 2012/08/25. DOI: 10.1177/1352458512458169.

14. Zaratin P, Comi G, Coetzee T, et al. Progressive MS Alliance Industry Forum: Maximizing Collective Impact To Enable Drug Development. *Trends Pharmacol Sci* 2016; 37: 808-810. 2016/08/20. DOI: 10.1016/j.tips.2016.07.005.
15. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278-286. 2014/05/30. DOI: 10.1212/wnl.0000000000000560.
16. Lublin FD, Coetzee T, Cohen JA, et al. The 2013 clinical course descriptors for multiple sclerosis: A clarification. *Neurology* 2020; 94: 1088-1092. 2020/05/29. DOI: 10.1212/WNL.00000000000009636.
17. Ramanujam R, Zhu F, Fink K, et al. Accurate classification of secondary progression in multiple sclerosis using a decision tree. *Mult Scler* 2020; 26: 1352458520975323. 2020/12/02. DOI: 10.1177/1352458520975323.
18. Lorscheider J, Buzzard K, Jokubaitis V, et al. Defining secondary progressive multiple sclerosis. *Brain* 2016; 139: 2395-2405. 2016/07/07. DOI: 10.1093/brain/aww173.
19. Krysko KM, Henry RG, Cree BAC, et al. Telomere length is associated with disability progression in multiple sclerosis. *Ann Neurol* 2019; 25: 2559-2569. 2019/09/04. DOI: 10.1002/ana.25592.
20. Tur C, Ramagopalan S, Altmann DR, et al. HLA-DRB1*15 influences the development of brain tissue damage in early PPMS. *Neurology* 2014; 83: 1712-1718. 2014/10/08. DOI: 10.1212/wnl.0000000000000959.
21. Giovannoni G, Tomic D, Bright JR, et al. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler* 2017; 23: 1179-1187. 2017/04/06. DOI: 10.1177/1352458517703193.
22. Eshaghi A, Marinescu RV, Young AL, et al. Progression of regional grey matter atrophy in multiple sclerosis. *Brain* 2018; 141: 1665-1677. DOI: 10.1093/brain/awy088.
23. Lassmann H. Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. *Front Immunol* 2018; 9: 3116. 2019/01/10. DOI: 10.3389/fimmu.2018.03116.
24. Magliozzi R, Howell OW, Nicholas R, et al. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. *Ann Neurol* 2018; 83: 739-755. DOI: 10.1002/ana.25197.
25. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology* 2015; 85: 18-28. 2015/04/17. DOI: 10.1212/wnl.0000000000001587.
26. Rodríguez-Lorenzo S, Konings J, van der Pol S, et al. Inflammation of the choroid plexus in progressive multiple sclerosis: accumulation of granulocytes and T cells. *Acta Neuropathol Commun* 2020; 8: 9. 2020/02/06. DOI: 10.1186/s40478-020-0885-1.
27. Absinta M, Lassmann H and Trapp BD. Mechanisms underlying progression in multiple sclerosis. *Curr Opin Neurol* 2020; 33: 277-285. DOI: 10.1097/wco.0000000000000818.
28. Rothhammer V, Kenison JE, Tjon E, et al. Sphingosine 1-phosphate receptor modulation suppresses pathogenic astrocyte activation and chronic progressive CNS inflammation. *Proc Natl Acad Sci U S A* 2017; 114: 2012-2017. 2017/02/06. DOI: 10.1073/pnas.1615413114.
29. Rothhammer V, Borucki DM, Tjon EC, et al. Microglial control of astrocytes in response to microbial metabolites. *Nature* 2018; 557: 724-728. 2018/05/16. DOI: 10.1038/s41586-018-0119-x.
30. Wheeler MA, Jaronen M, Covacu R, et al. Environmental Control of Astrocyte Pathogenic Activities in CNS Inflammation. *Cell* 2019; 176: 581-596.e518. 2019/01/17. DOI: 10.1016/j.cell.2018.12.012.
31. Liddel SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 2017; 541: 481-487. 2017/01/18. DOI: 10.1038/nature21029.

32. Fransen NL, Hsiao CC, van der Poel M, et al. Tissue-resident memory T cells invade the brain parenchyma in multiple sclerosis white matter lesions. *Brain* 2020; 143: 1714-1730. DOI: 10.1093/brain/awaa117.
33. Dal-Bianco A, Grabner G, Kronnerwetter C, et al. Long-term evolution of multiple sclerosis iron rim lesions in 7 T MRI. *Brain* 2021; 144: 833-847. DOI: 10.1093/brain/awaa436.
34. Malhotra S, Costa C, Eixarch H, et al. NLRP3 inflammasome as prognostic factor and therapeutic target in primary progressive multiple sclerosis patients. *Brain* 2020; 143: 1414-1430. 2020/04/14. DOI: 10.1093/brain/awaa084.
35. You Y, Joseph C, Wang C, et al. Demyelination precedes axonal loss in the transneuronal spread of human neurodegenerative disease. *Brain* 2019; 142: 426-442. DOI: 10.1093/brain/awy338.
36. Schirmer L, Velmeshev D, Holmqvist S, et al. Neuronal vulnerability and multilineage diversity in multiple sclerosis. *Nature* 2019; 573: 75-82. 2019/07/17. DOI: 10.1038/s41586-019-1404-z.
37. Fitzgerald KC, Kim K, Smith MD, et al. Early complement genes are associated with visual system degeneration in multiple sclerosis. *Brain* 2019 2019/07/09. DOI: 10.1093/brain/awz188.
38. Cortese R, Tur C, Prados F, et al. Ongoing microstructural changes in the cervical cord underpin disability progression in early primary progressive multiple sclerosis. *Mult Scler* 2021; 27: 28-38. 2020/01/22. DOI: 10.1177/1352458519900971.
39. Scalfari A, Romualdi C, Nicholas RS, et al. The cortical damage, early relapses, and onset of the progressive phase in multiple sclerosis. *Neurology* 2018; 90: e2107-e2118. 2018/05/16. DOI: 10.1212/wnl.0000000000005685.
40. Elliott C, Belachew S, Wolinsky JS, et al. Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. *Brain* 2019; 142: 2787-2799. DOI: 10.1093/brain/awz212.
41. Eshaghi A, Prados F, Brownlee WJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Ann Neurol* 2018; 83: 210-222. 2018/02/06. DOI: 10.1002/ana.25145.
42. Eijlers AJC, Dekker I, Steenwijk MD, et al. Cortical atrophy accelerates as cognitive decline worsens in multiple sclerosis. *Neurology* 2019 2019/09/04. DOI: 10.1212/wnl.0000000000008198.
43. Naismith RT, Bermel RA, Coffey CS, et al. Effects of ibudilast on MRI measures in the phase 2 SPRINT-MS study. *Neurology* 2020 2020/12/04. DOI: 10.1212/wnl.0000000000011314.
44. Fox RJ, Coffey CS, Conwit R, et al. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. *N Engl J Med* 2018; 379: 846-855. DOI: 10.1056/NEJMoa1803583.
45. Solanky BS, John NA, DeAngelis F, et al. NAA is a Marker of Disability in Secondary-Progressive MS: A Proton MR Spectroscopic Imaging Study. *AJNR Am J Neuroradiol* 2020; 41: 2209-2218. 2020/11/07. DOI: 10.3174/ajnr.A6809.
46. Hardmeier M, Leocani L and Fuhr P. A new role for evoked potentials in MS? Repurposing evoked potentials as biomarkers for clinical trials in MS. *Mult Scler* 2017; 23: 1309-1319. 2017/05/08. DOI: 10.1177/1352458517707265.
47. Sotirchos ES, Gonzalez Caldito N, Filippatou A, et al. Progressive Multiple Sclerosis Is Associated with Faster and Specific Retinal Layer Atrophy. *Ann Neurol* 2020; 87: 885-896. 2020/04/15. DOI: 10.1002/ana.25738.
48. Fox RJ, Raska P, Barro C, et al. Neurofilament light chain in a phase 2 clinical trial of ibudilast in progressive multiple sclerosis. *Mult Scler* 2021: 1352458520986956. 2021/02/26. DOI: 10.1177/1352458520986956.
49. Sormani MP, Haering DA, Kropshofer H, et al. Blood neurofilament light as a potential endpoint in Phase 2 studies in MS. *Ann Clin Transl Neurol* 2019; 6: 1081-1089. 2019/05/28. DOI: 10.1002/acn3.795.

50. Kuhle J, Kropshofer H, Haering DA, et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. *Neurology* 2019; 92: e1007-e1015. 2019/02/08. DOI: 10.1212/wnl.00000000000007032.
51. Siller N, Kuhle J, Muthuraman M, et al. Serum neurofilament light chain is a biomarker of acute and chronic neuronal damage in early multiple sclerosis. *Mult Scler* 2019; 25: 678-686. 2018/03/15. DOI: 10.1177/1352458518765666.
52. Manouchehrinia A, Stridh P, Khademi M, et al. Plasma neurofilament light levels are associated with risk of disability in multiple sclerosis. *Neurology* 2020; 94: e2457-e2467. 2020/05/22. DOI: 10.1212/wnl.00000000000009571.
53. Kapoor R, Smith KE, Allegretta M, et al. Serum neurofilament light as a biomarker in progressive multiple sclerosis. *Neurology* 2020; 95: 436-444. 2020/07/18. DOI: 10.1212/wnl.0000000000010346.
54. Bridel C, Leurs CE, van Lierop ZY, et al. Serum Neurofilament Light Association With Progression in Natalizumab-Treated Patients With Relapsing-Remitting Multiple Sclerosis. *Neurology* 2021 2021/09/11. DOI: 10.1212/WNL.0000000000012752.
55. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med* 2017; 376: 209-220. 2016/12/21. DOI: 10.1056/NEJMoa1606468.
56. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018; 391: 1263-1273. 2018/03/23. DOI: 10.1016/S0140-6736(18)30475-6.
57. Cree BAC, Cutter G, Wolinsky JS, et al. Safety and efficacy of MD1003 (high-dose biotin) in patients with progressive multiple sclerosis (SPI2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2020; 19: 988-997. 2020/11/24. DOI: 10.1016/s1474-4422(20)30347-1.
58. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2018; 17: 405-415. 2018/03/12. DOI: 10.1016/S1474-4422(18)30069-3.
59. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; 387: 1075-1084. 2016/02/02. DOI: 10.1016/s0140-6736(15)01314-8.
60. Chataway J, De Angelis F, Connick P, et al. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. *Lancet Neurol* 2020; 19: 214-225. 2020/01/26. DOI: 10.1016/s1474-4422(19)30485-5.
61. Cambron M, Mostert J, D'Hooghe M, et al. Fluoxetine in progressive multiple sclerosis: The FLUOX-PMS trial. *Mult Scler* 2019; 25: 1352458519843051. 2019/06/20. DOI: 10.1177/1352458519843051.
62. Vermersch P and Hermine O. MSVirtual 2020 – Platform Presentations FC04.01. *Mult Scler* 2020; 26: 1-42. DOI: 10.1177/1352458520974936.
63. Zackowski KM, Freeman J, Bricchetto G, et al. Prioritizing progressive MS rehabilitation research: A call from the International Progressive MS Alliance. *Mult Scler* 2021; 27: 1352458521999970. 2021/03/15. DOI: 10.1177/1352458521999970.
64. Freeman J, Hendrie W, Jarrett L, et al. Assessment of a home-based standing frame programme in people with progressive multiple sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis. *Lancet Neurol* 2019; 18: 736-747. DOI: 10.1016/s1474-4422(19)30190-5.

65. Manjaly ZM, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019; 90: 642-651. 2019/01/25. DOI: 10.1136/jnnp-2018-320050.
66. Langeskov-Christensen M, Grøndahl Hvid L, Nygaard MKE, et al. Efficacy of High-Intensity Aerobic Exercise on Brain MRI Measures in Multiple Sclerosis. *Neurology* 2021; 96: e203-e213. 2020/12/03. DOI: 10.1212/wnl.0000000000011241.
67. Langeskov-Christensen M, Hvid LG, Jensen HB, et al. Efficacy of high-intensity aerobic exercise on cognitive performance in people with multiple sclerosis: A randomized controlled trial. *Mult Scler* 2020: 1352458520973619. 2020/11/25. DOI: 10.1177/1352458520973619.
68. Feinstein A, Amato MP, Bricchetto G, et al. Study protocol: improving cognition in people with progressive multiple sclerosis: a multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise (COGEx). *BMC Neurol* 2020; 20: 204. 2020/05/22. DOI: 10.1186/s12883-020-01772-7.
69. Dangond F, Donnelly A, Hohlfeld R, et al. Facing the urgency of therapies for progressive MS - a Progressive MS Alliance proposal. *Nature Rev Neurol* 2021 2021/01/22. DOI: 10.1038/s41582-020-00446-9.
70. Tur C, Moccia M, Barkhof F, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. *Nature Rev Neurol* 2018; 14: 75-93. 2018/01/12. DOI: 10.1038/nrneurol.2017.171.
71. Connick P, De Angelis F, Parker RA, et al. Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART): a multiarm phase IIb randomised, double-blind, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis. *BMJ Open* 2018; 8: e021944. 2018/08/30. DOI: 10.1136/bmjopen-2018-021944.
72. Society UM. Full steam ahead with our ‘mega-trial’ for progressive MS, <https://www.mssociety.org.uk/research/latest-research/research-blog/full-steam-ahead-our-mega-trial-progressive-ms> (2021, accessed April 16 2021).
73. Koch MW, Sage K, Kaur S, et al. Repurposing Domperidone in Secondary Progressive Multiple Sclerosis. *A Simon 2-Stage Phase 2 Futility Trial Neurology* 2021; 96: e2313-e2322. DOI: 10.1212/wnl.0000000000011863.
74. Fox RJ and Kryscio RJ. A New Way to Identify Promising Therapies for Progressive Multiple Sclerosis. *Neurology* 2021; 96: 833-834. DOI: 10.1212/wnl.0000000000011862.
75. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet* 2014; 383: 2213-2221. 2014/03/19. DOI: 10.1016/s0140-6736(13)62242-4.
76. Kuhle J, Nourbakhsh B, Grant D, et al. Serum neurofilament is associated with progression of brain atrophy and disability in early MS. *Neurology* 2017; 88: 826-831. 2017/02/01. DOI: 10.1212/wnl.0000000000003653.
77. Gasperini C, Prosperini L, Tintoré M, et al. Unraveling treatment response in multiple sclerosis: A clinical and MRI challenge. *Neurology* 2019; 92: 180-192. 2018/12/26. DOI: 10.1212/WNL.0000000000006810.
78. LaRocca NG, Hudson LD, Rudick R, et al. The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability. *Mult Scler* 2018; 24: 1469-1484. 2017/08/11. DOI: 10.1177/1352458517723718.
79. Patient Reported Outcomes for MS (PROMS) Consortium. European Charcot Foundation.

80. Bricchetto G and Zaratin P. Measuring outcomes that matter most to people with multiple sclerosis: the role of patient-reported outcomes. *Curr Opin Neurol* 2020; 33: 295-299. DOI: 10.1097/wco.0000000000000821.
81. Cadavid D, Cohen JA, Freedman MS, et al. The EDSS-Plus, an improved endpoint for disability progression in secondary progressive multiple sclerosis. *M Mult Scler* 2017; 23: 94-105. 2016/07/11. DOI: 10.1177/1352458516638941.
82. Patient-reported outcomes in the spotlight. *Lancet Neurol* 2019; 18: 981. DOI: [https://doi.org/10.1016/S1474-4422\(19\)30357-6](https://doi.org/10.1016/S1474-4422(19)30357-6).
83. Montalban X, Graves J, Midaglia L, et al. A smartphone sensor-based digital outcome assessment of multiple sclerosis. *Mult Scler* 2021: 13524585211028561. 2021/07/15. DOI: 10.1177/13524585211028561.
84. Graves JS and Montalban X. Biosensors to monitor MS activity. *Mult Scler* 2020; 26: 605-608. 2020/01/23. DOI: 10.1177/1352458519888178.
85. Coetzee T and Thompson AJ. Unified understanding of MS course is required for drug development. *Nature Rev Neurol* 2018; 14: 191-192. 2018/01/12. DOI: 10.1038/nrneurol.2017.184.
86. Salvetti M, Lubetzki C, Kapoor R, et al. Steps towards Collective Sustainability in Biomedical Research. *Trends Mol Med* 2018; 24: 429-432. 2018/03/24. DOI: 10.1016/j.molmed.2018.03.001.
87. Multi-ACT - A Collective Research Impact Framework, <http://multiact.eu> (accessed March 20, 2021).
88. Bauer MS, Damschroder L, Hagedorn H, et al. An introduction to implementation science for the non-specialist. *BMC Psychol* 2015; 3: 32. 2015/09/18. DOI: 10.1186/s40359-015-0089-9.
89. US Department of Veterans Affairs. QUERI – Quality Enhancement Research Initiative, https://www.queri.research.va.gov/tools/impact_framework.cfm (accessed September 27 2021).
90. Kilbourne AM, Elwy AR, Sales AE, et al. Accelerating Research Impact in a Learning Health Care System: VA's Quality Enhancement Research Initiative in the Choice Act Era. *Med Care* 2017; 55 Suppl 7 Suppl 1: S4-S12. 2016/12/21. DOI: 10.1097/MLR.0000000000000683.

Table 1 – Recommendations for areas of global research focus

Priority Area	Potential Strategies
Understand progression	<p>Data sharing to facilitate identification of pathophysiological mechanisms and potential new targets</p> <p>Drug discovery networks</p> <p>Exploratory clinical studies of new agents targeting new biologic pathways</p>
Accelerate clinical trials	<p>Innovation in clinical trial design</p> <p>Clinical trial data sharing to facilitate trial design, validation of outcome measures, and discovery and validation of imaging and functional biomarkers</p> <p>Development of imaging and functional biomarkers for use in clinical trials and clinical care</p> <p>Development of fluid biomarkers for use in clinical trials and clinical care</p>
Improve well-being	<p>Development of a global targeted rehabilitation and symptom management research strategy</p> <p>Global coordination of rehabilitation research</p> <p>Development of a robust pipeline of rehabilitation researchers and programs</p>

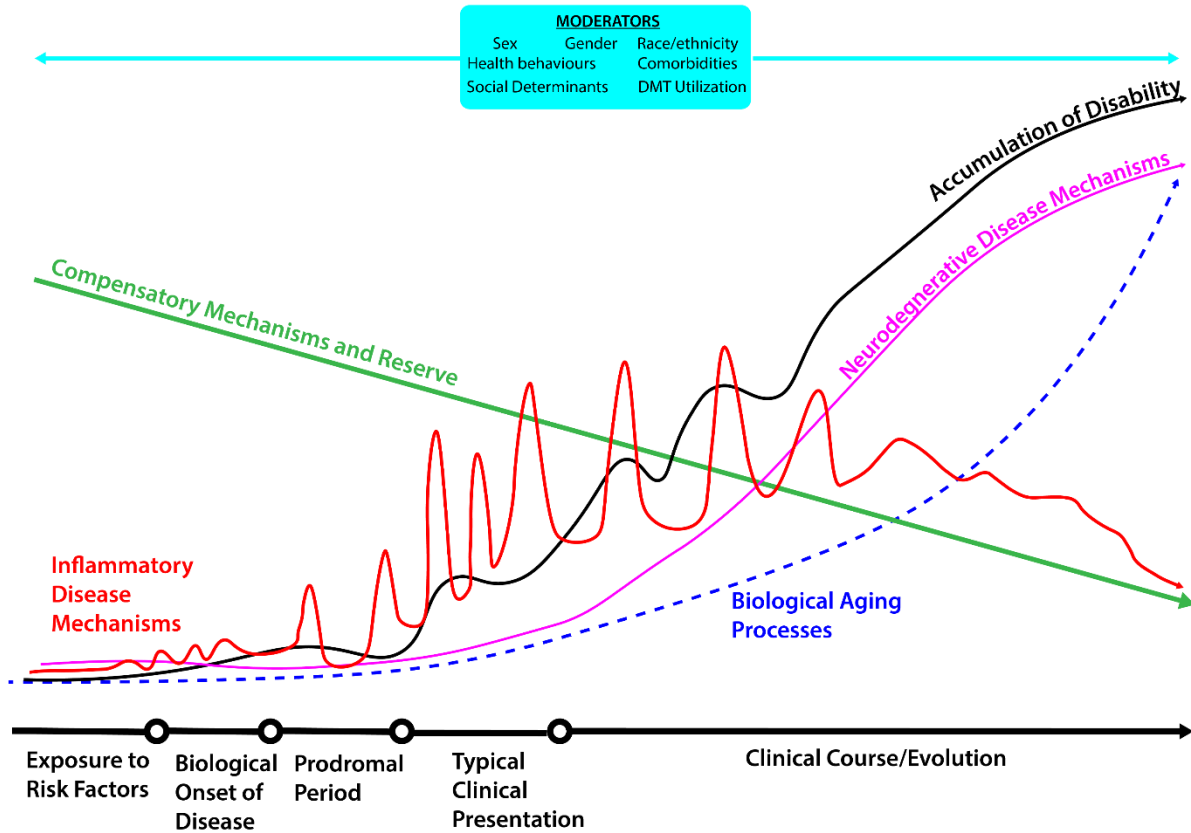


Figure 1 – Pathways Influencing Development of Progressive MS: The accumulation of disability and development of progressive MS likely reflects a combination of factors including damage arising from inflammatory disease mechanisms, neurodegenerative mechanisms, and biological aging. These processes are likely attenuated by compensatory mechanisms and reserve during the early- to mid-stages of the disease, but over time these compensatory processes are depleted. Moderators such as sex, gender, socioeconomic status, DMT utilization likely exert positive and negative influences on progression and the development of progressive MS.

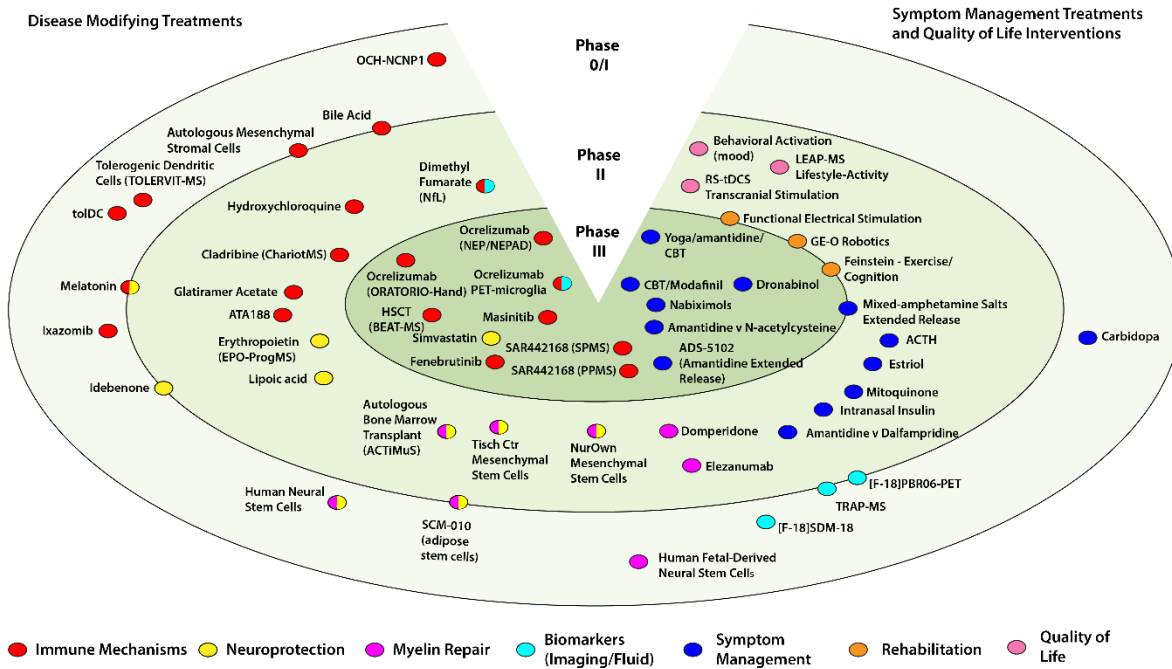


Figure 2 – Progressive MS Treatments in Clinical Development. Active clinical trials evaluating agents in progressive MS and registered with ClinicalTrials.gov or World Health Organization International Clinical Trials Registry Platform as of April 2021 are illustrated. Trials are positioned based on their stage of development and agent or intervention profile (disease modification or symptom management/quality of life). Phase 0/I studies are in the outermost ring, with Phase II and III studies reflected in the inner rings. Phase I/II and II/III studies are placed on the borders of the respective rings.

Quality of Life Intervention Targets

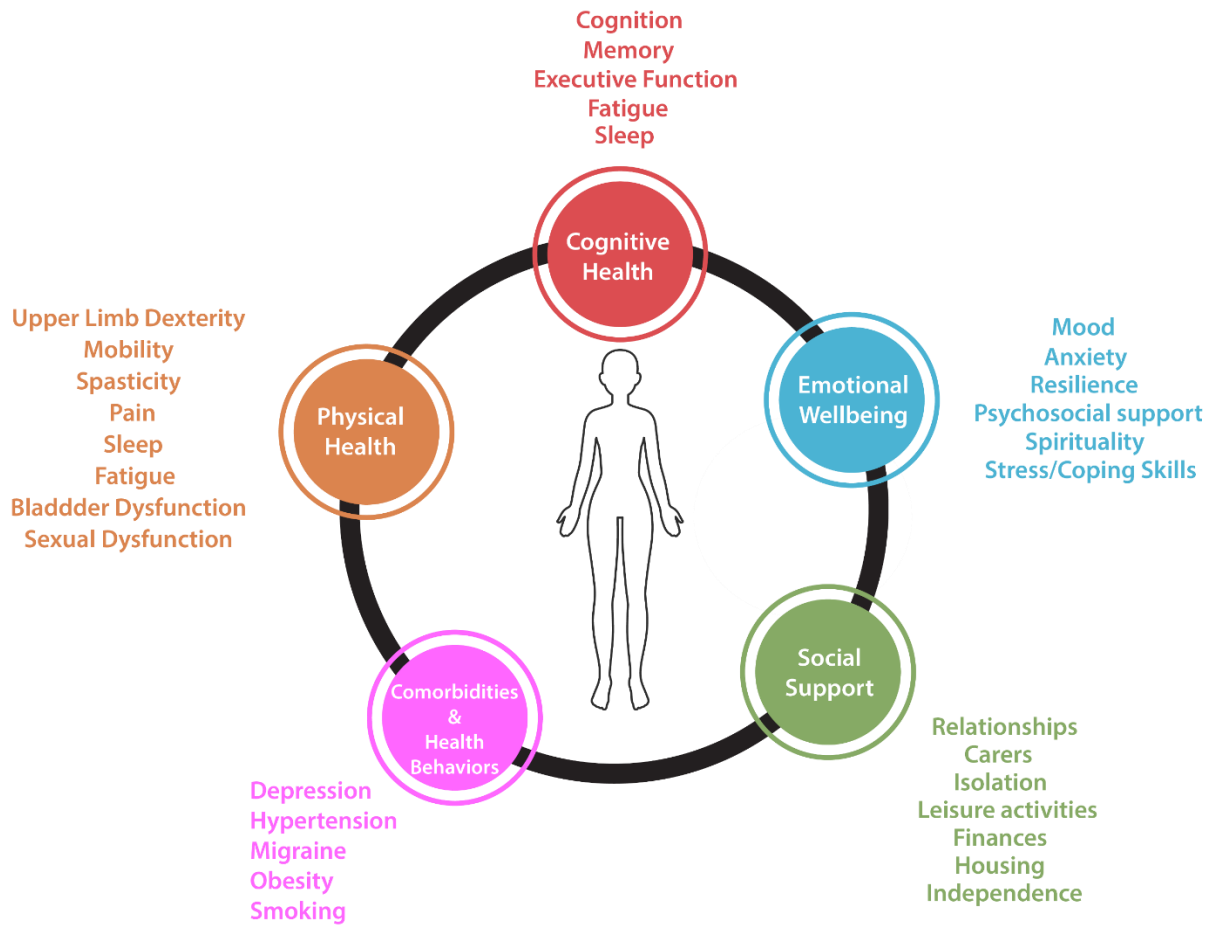


Figure 3 – Quality of Life Intervention Targets. Potential targets for quality-of-life interventions in progressive MS span several inter-related domains. While some are directly associated with disease mechanisms (e.g. cognition, pain) others are associated with other disease indications (e.g. hypertension) or social support mechanisms (e.g. care providers, housing) that affect quality of life.

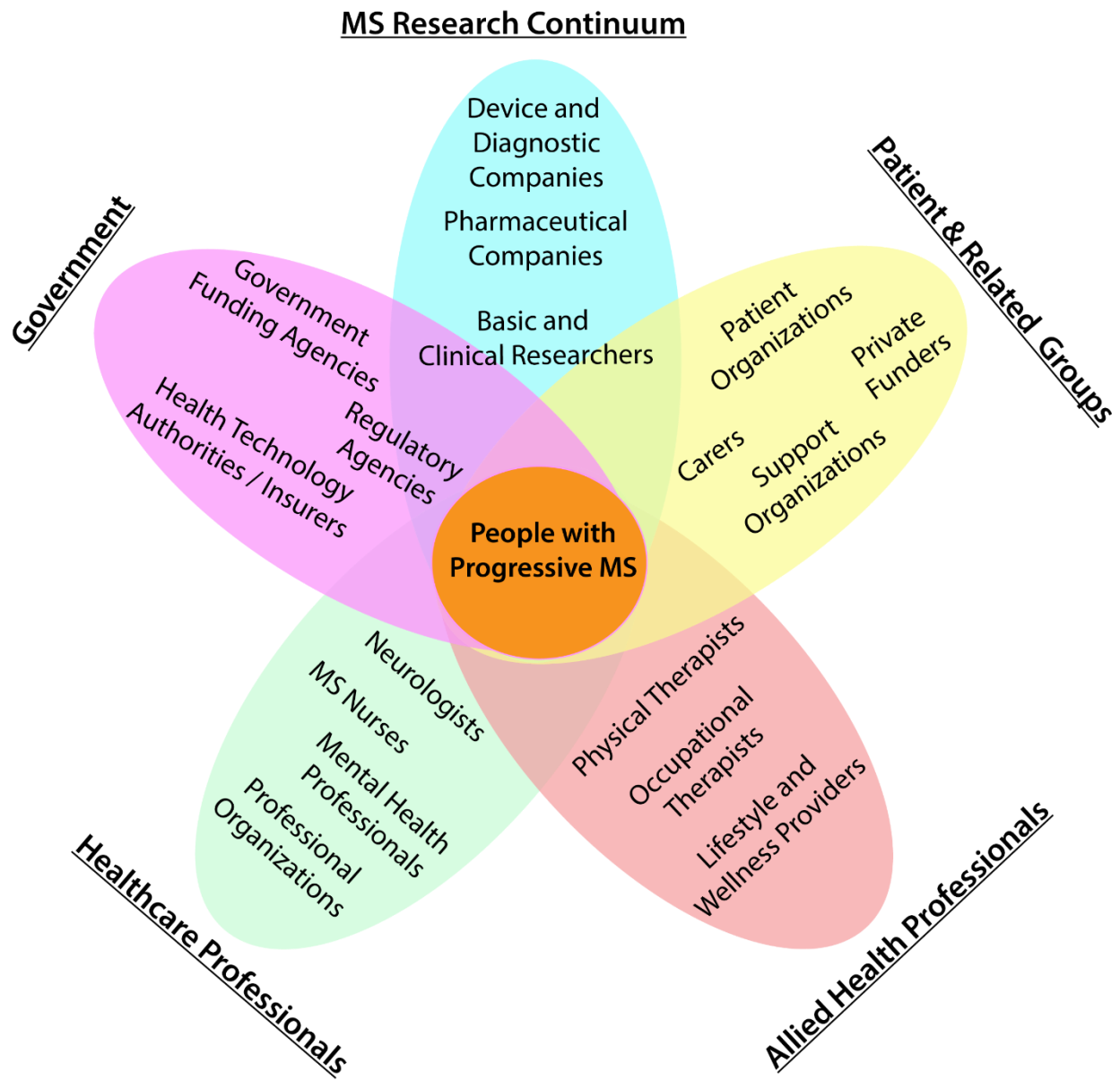


Figure 4 – Stakeholders in the Progressive MS agenda. Addressing the challenges of MS is a multi-stakeholder effort spanning patient organizations, clinical professionals, government, and industry.