Pathways to Cures for Multiple Sclerosis Research Roadmap

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Introduction

Multiple Sclerosis (MS) is a growing global health challenge affecting nearly 3 million people with significant public health and economic impacts[1]. While significant progress has been made in the development of effective disease-modifying treatments (DMT's) for relapsing forms of MS, we still lack a fundamental understanding of all the pathological processes that drive disease, we lack effective treatments for progressive forms of MS, and cures remain elusive. The National Multiple Sclerosis Society is focused on achieving breakthroughs to cures for MS. Progress towards this goal will be hastened by having a roadmap that describes the knowledge gaps, milestones and research priorities that will lead to cures for everyone living with MS.

In this report, we share the Society's Pathways to MS Cures Research Roadmap. The Roadmap was developed in consultation with numerous stakeholders including scientific experts, health care providers and people affected by MS. The Roadmap has also been reviewed and endorsed by many leading global MS patient and professional organizations (Table 1). We hope this report will inspire the alignment of global resources on the most pressing questions in MS research and accelerate scientific breakthroughs that lead to cures for everyone living with MS.

Development of the roadmap

The Roadmap was developed through engagement of the National MS Society's Scientific Advisory Committee, National Board of Directors, and the Pathways to MS Cures Task Force composed of key global scientific thought leaders and people affected by MS (*Supplemental Table 1*). In addition, the perspectives of over 300 people with MS were obtained and incorporated in the Roadmap through a survey conducted in collaboration with the Accelerated Cure Project for Multiple Sclerosis. This survey established that the definition of a cure was different depending on an individual's perspective, but the responses could be grouped into three main categories, (1) stopping the MS disease process, (2) restoring lost function by reversing damage and symptoms, and (3) ending MS through prevention.

The scientific foundations of the Pathways were developed and refined by the Task Force and Scientific Advisory committees as well as input and endorsements from leading global MS patient and professional organizations, research funders, and other stakeholders. We see these endorsements as a critical step that will help align resources on the most promising areas of research and accelerate progress towards scientific breakthroughs required to find cures for MS.

In the following paragraphs, we outline the key objectives, barriers, potential solutions, and recommendations for implementation of strategies to advance each of the pathways in the Roadmap.

The Stop Pathway

The Roadmap defines stopping MS as achieving a state of no new disease activity or CNS injury, no worsening of daily living or quality of life, and no change in disease manifestations. By stopping all forms of disease activity and tissue injury, we prevent the accumulation of disability and create a permissive environment for myelin and axonal repair and other pathways that promote restoration of function. The opportunities for stopping MS disease activity span from the sub-clinical to later stages of disease (Figure 1).

Current knowledge

Much has been learned about the role of the immune system in MS pathogenesis, aiding the development of numerous DMT's that target different cells and pathways. Most of these therapies directly modulate the adaptive immune system or impact immune cell trafficking. In addition, induction therapies have shown promise in clinical studies of aggressive forms of relapsing MS[2]. Having multiple treatment options with different mechanisms of action and efficacy, adverse event profiles, and routes of administration offer the opportunity to personalize treatment.

Despite successes in relapsing MS, there are far fewer therapeutic options for people living with progressive forms of MS. Several challenges exist for the development of DMT's for this form of disease. For example, it is unknown whether primary and secondary progressive MS have similar biological underpinnings. Animal models that more closely recapitulate the disease course and pathology of progressive MS are lacking.

There is a need for more sensitive and specific endpoints that would allow rapid proof of concept clinical trials. Attention is turning to innate immunity and central nervous system (CNS)-compartmentalized inflammation as promising areas of study. It is becoming clear that there are both protective and destructive interactions taking place between cells of the innate immune system and neurons and glia in the CNS. This knowledge is starting to reveal targets for possible pharmaceutical intervention.

Efforts at biological phenotyping are promising avenues to understand both relapsing and progressive disease heterogeneity and identify new therapeutic targets, and recent single cell profiling studies have led to the discovery of multiple populations of microglial cells and astrocytes which may allow more precise intervention. A recent machine learning study using data derived from thousands of MRI scans obtained from well-controlled clinical trials and cohort studies have identified three MS phenotypic subtypes that are independent of the clinically defined forms[3]. The subtypes predict disability progression and may have value in predicting treatment responses. While much of the discussion above has focused on stopping MS with DMTs, certain comorbidities such as obesity and smoking clearly negatively impact disease progression[4]. Identifying approaches that promote lasting lifestyle changes and address comorbidities are also components of the Stop pathway. The Stop pathway includes two major objectives, (1) Early Detection and (2) Precision medicine.

Early Detection

There is growing consensus on the importance of early application of disease-modifying interventions to minimize CNS damage, potentially delay progression of MS, and maximize function[5]. This suggests that an

earlier MS diagnosis or the identification of individuals at high risk for a future diagnosis could benefit long-term outcomes. Individuals with clinically isolated syndrome (CIS) likely meet requirements for an early MS diagnosis, since as many as 85% of such individuals will proceed to clinically definite MS within 2 years[6]. Treatment with interferon beta-1b in subjects with CIS was shown to delay the conversion to clinically definite MS[6]. This study also found early treatment improved quality of life, cognition, and imaging outcomes.

There is emerging evidence that the MS disease process starts decades before it becomes clinically apparent and also includes a prodromal phase characterized by non-disease specific clinical symptoms[7]. Retrospective reviews of medical records and health utilization have uncovered evidence of increased healthcare usage five to ten years before a first clinically evident demyelinating event or MS diagnosis. The types of symptoms reported such as pain, anxiety, and others, do not provide the specificity needed for diagnosis, but may be reflections of an underlying early disease process. Recent studies also provide evidence for neurodegeneration occurring long before an MS diagnosis. Longitudinal sampling from a cohort of US military veterans revealed that elevated serum Neurofilament Light chain (NfL) levels preceded MS diagnosis by 6 years[8]. Some individuals without clinical signs of MS are found to have brain lesions suggestive of MS. These asymptomatic individuals with radiologically isolated syndrome (RIS), are also at an increased risk for an MS diagnosis[9]. More recently, an increased CSF NfL concentration in RIS has been identified as a risk factor for later transition to clinically definite MS[10]. Not everyone with RIS or CIS will go on to develop definite MS. The earliest phases of MS onset and development of biological markers, health data, and sociological features to help identify onset, define biology-based phenotypes, and improve the diagnostic process are needed. Identification of the prodromal period of MS necessitates a set of

diagnostic tools with defined thresholds. There is an opportunity to intervene during this pre-clinical phase of MS and delay, reduce or perhaps even stop the development of significant disability.

Precision Medicine

MS is a heterogeneous disease and each person with MS experiences the disease differently. Treatment choice is a personal decision balancing DMT risk and efficacy and may also be influenced by the policies of payers. Early treatment is desirable and has been shown to impact long-term disease trajectory[6]. Research is underway to determine whether an escalation or higher-efficacy first-line treatment approach offers better long-term outcomes. Analysis of active lesions over time and space suggests that different immune-effector mechanisms may predominate in individuals at different times[11].

Given that heterogeneity may also exist at the patient level, an evidence-driven approach that could prognosticate outcomes would help frame the full benefits and risks of any specific treatment and help guide the selection of an optimal therapy for a given MS patient at a given point in time. Learnings from other disease areas such as oncology, where precision medicine approaches have been incorporated as standard care, should be considered. MS clinicians already have experience utilizing precision medicine in clinical practice. The determination of JC virus (JCV) status prior to and during treatment with natalizumab is an example of precision medicine used to risk-stratify and monitor safety. In addition, MRI is commonly used to track brain lesion activity as part of ongoing disease management. Additional non-invasive biomarkers are needed that will allow the tracking of different aspects of disease activity.

The most advanced fluid biomarker in development is NfL. Neurofilament light is a neuronal structural protein released through any cause of neuroaxonal injury and can be monitored with a blood test. Numerous retrospective studies[12,13] and prospective analyses of phase 3 trials in relapsing MS[14] suggest that the concentration of NfL in serum, plasma, and CSF is a useful predictor of disease worsening at the population level. Correlations have been observed for acute disease activity and prediction of subsequent MRI lesion activity, brain volume loss, relapse rate, and worsening of disability. Recent studies on age and sex effects in normal adults show increased and more variable sNfL in subjects over 60 years of age[14]. Understanding normative characteristics for sNfL is essential to enable clinical utility. Other proteins such as glial fibrillary acidic protein (GFAP), released by astrocytes, are being investigated as potential biomarkers.

Additional imaging and fluid biomarker approaches are needed that will further inform and possibly predict disease course and will allow tracking of neuroinflammation, myelination status, cortical lesions and the distinct pathologies of relapsing remitting and secondary progressive MS. An improved understanding of genetic and environmental factors that influence disease course is also highly desirable. Data driven algorithms combining clinical data and known genetic and environmental risk factors, with biological and imaging biomarker data, may present a pathway to optimized monitoring and treatment to Stop MS.

Recommendations

The relationship between acute inflammation, compartmentalized inflammation, and neurodegeneration needs to be better understood to allow more precise intervention and the development of new therapeutic approaches (Table 2). Health data and sociological features may help

identify earlier onset and defining phenotypes biologically may further improve the diagnostic process to allow earlier, personalized interventions. Better biological markers and tools, including improved predictive models, will lead to a better understanding of the biology and heterogeneity of MS. Biomarkers informed by research into disease mechanisms, powered by carefully monitored cohorts with high quality longitudinal samples and curated data, may enable an understanding of the prodromal phase. Finally, better coordination of properly collected longitudinal cohorts may capture diversity and answer key epidemiological questions.

The Restore pathway

The Roadmap defines the Restore pathway as reversing symptoms and recovering function to enable full participation in society. While DMT's can limit the occurrence of relapses and in some cases delay disease progression, they have limited capacity to enhance or restore function in later stages of disease. This pathway explores the opportunity to enhance regeneration and remyelination, as well as focus on strategies to reverse symptoms and improve quality of life through improved cognition, strength, endurance, and decreased burden from symptoms.

One focus is on integrating the study of pathophysiological mechanisms and their association with functional capacity, as well as rigorously evaluating the potential that restoration of function might, in turn, enhance neuroplasticity and remyelination. An integrated approach is needed that enhances remyelination, neural regeneration, and neuroplasticity, while optimizing the extent to which wellness behaviors, rehabilitation, self-care, and exercise promote reversal or diminution of symptoms. The development and

improvement of outcomes, as well as the advancement of clinical intervention trials that measure neural recovery and its impact on a person's life after diagnosis and across MS types is critical to enable full participation in society. Opportunities for advancing the restore pathway span from the subclinical through later stages of disease, although it is likely that earlier interventions will be more successful (Figure 1). The Restore Pathway includes two main objectives, (1) Regeneration and (2) Restoration of Activity.

Current Knowledge

Regeneration

Remyelination requires myelin producing oligodendrocytes that produce new myelin sheaths in the CNS. The brain generates oligodendrocytes from oligodendrocyte precursor cells (OPCs) throughout life, but the efficiency of natural remyelination declines with age. There is evidence that remyelination can be enhanced with a youthful milieu, and that endogenous cells can be targeted through remyelination-enhancing therapies[15]. Mechanisms that underlie remyelination failure in MS are not fully understood and are thought to occur through a combination of inhibitory factors, including some derived from the immune system, where recent evidence suggests certain oligodendroglia may negatively impact remyelination[16] and where inhibition from secreted factors released by both infiltrating immune cells (cytokines) and resident glia (proteoglycans) also play a role. Even though aging is generally thought to negatively impact remyelination, recent studies suggest that mature oligodendrocytes can participate in remyelination[17].

Removing impediments to natural myelin repair, stimulating endogenous OPCs, and transplanting cells with the potential to promote repair[18] provide opportunities for immune modulation, neuroprotection, or repair

in people with MS. Further studies are needed to focus on the cell biology of remyelination and evaluate emerging molecular pathways.

The use of demyelinating animal models such as cuprizone and lysolecithin have strengths as well as limitations, and they need to be better optimized, or new tools need to be developed, to better represent MS. Most DMT's for MS target the inflammatory autoimmune process, yet we know there is an urgent need for therapies that provide neuroprotection, axonal growth and/or remyelination in the setting of an inflammatory or non-inflammatory immune system. Clarifying the functional heterogeneity of OPCs, the role of aging, and the roles of other neural cells in repair offer promising opportunities to expose additional new targets for regeneration.

Promoting neuroprotection, synaptic plasticity, and strategies to inhibit neurodegeneration are also promising approaches for reducing disability and restoring function in MS. Studies of neuroprotection and synaptic plasticity have primarily involved rodent models and show considerable involvement of neural networks of the hippocampus, basal ganglia, and cerebellum[19]. Pathology studies in MS show significant declines in the number of synapses in the hippocampus, as well as receptors and molecules involved in synaptic plasticity and glutamate neurotransmission[20]. Recent work shows that CNS inflammation affects synaptic transmission and that immune-mediated alterations to synaptic plasticity may be a contributing factor to the pathogenesis of MS-related cognitive impairment and reversing any of these areas could offer functional benefits. Targeting SARM1 inhibitors to block pathological axon degeneration and associated functional decline is an example of new strategies that should be tried in MS[21,22]. Understanding how to

protect neurons and why some clusters of neurons are more resilient than others provide new opportunities for therapeutic approaches.

Restoration of Activity

Accurately evaluating disease progression and disability is important for understanding the biology of regeneration, testing therapeutic approaches, guiding treatment, and informing personalized care. Imaging measures have expanded substantially and have proved to offer a quantitative and objective way to evaluate MS disease progression but have limited ability to track myelin changes over time in the brain or spinal cord[23]. Brain imaging methods such as magnetization transfer imaging and diffusion transfer imaging offer opportunities to evaluate the evolution of acute white matter lesions, whereas other methods such as myelin water imaging, susceptibility weighted imaging and PET allow for the evaluation of chronic white matter lesions[24]. Collaborative studies are needed to target remyelination more precisely and develop better imaging tools that specifically measure changes in myelination.

To different extents, imaging measures have been shown to relate broadly to disability[25]; however, these studies have almost entirely focused on the Expanded Disability Status Scale (EDSS) as the measure of disability. The EDSS is a rating scale that assesses overall disability, placing a greater emphasis on walking function over other symptoms such as spasticity, fatigue, cognitive dysfunction or hand dysfunction[26]. Impairment based outcome measures that detect disability progression and provide specific information about the impairment can be used to tailor treatment interventions for each person based on the specific symptom or based on patient reported feedback, as in the Fatigue Severity Scale. While these clinical outcome measures can describe and, in some cases, predict disability, they are not sensitive enough to

detect either early disease progression or the results of regeneration. Emerging technologies using remote monitoring wearable devices may offer insights into early detection and disease progression. Biomarkers that relate to the disease process or symptoms could also be important tools for managing MS. Development of appropriate outcome measures that singularly or in combination quantify neural regeneration and are associated with specific measures of impairment would improve clinical decision making and expedite the study of clinical interventions.

Clinical trials are already underway exploring pharmaceutical approaches and cell-based therapies to facilitate remyelination and neural repair. This process has proven to be difficult, highlighting deficits in both measurement tools and validated targets. A phase 2b, multi-arm trial of three neuroprotective drugs[27] failed to provide evidence for neuroprotection in patients with secondary progressive MS (SPMS), and that followed mixed results from two highly anticipated clinical trials interrogating the remyelinating effects of anti-LINGO antibodies in optic neuritis and relapsing-remitting MS (RRMS)[28]. Topline data from a recent open-label phase 2 clinical trial evaluating the safety and efficacy of autologous mesenchymal stem cells delivered intrathecally reported improvement in physical abilities, vision, and cognition along with a decrease in inflammatory biomarkers.[29] Data is needed from larger studies to provide additional evidence.

Tools to screen compounds that promote remyelination[30] also provide promise for identifying new therapies. High-throughput screening resulted in the first randomized clinical trial to show evidence of remyelination in MS using clemastine fumarate[31]. Other high-throughput screening approaches have identified molecules that enhance the formation of oligodendrocytes and ultimately remyelination[32]. Ongoing clinical trials of bruton kinase inhibitors[33], and early phase trials of new drugs exploring novel

pathways that block neurite growth inhibition[34] provide promising avenues for enhancing repair of the CNS. Clinical trials using biologic outcomes sensitive to regeneration and behavioral markers sensitive to functional recovery are critical components for optimizing recovery and guiding clinical care.

Studies have proved that, in MS, exercise is safe, can improve strength, cardiorespiratory fitness, walking, symptomatic fatigue, cognition, and overall is an effective symptomatic treatment in MS[35]. Clinical trials have begun to evaluate combining exercise with other symptomatic treatments such as cognitive rehabilitation, and/or medications, with positive results[35]. The effects of exercise in modifying the disease or even reducing the risk of MS is also being evaluated[36]. Exercise studies provide preliminary evidence of the potential impact of exercise on neuroprotection and regeneration in animal models and humans[36,37]. Studies of cardiac rehabilitation provide a powerful example of how rehabilitation can improve quality of life and drive recovery. This building evidence highlights the perspective that long-term and large-scale human studies in MS can be tailored to assess and measure the neuroregenerative and neuroprotective benefits of exercise and other rehabilitation interventions.

There are a variety of rehabilitation strategies to support preventative, restorative, compensatory and maintenance strategies to address symptoms of MS. Dysfunctions in balance and gait are a leading concern for people with MS, with increasingly pronounced impairments in persons with progressive MS[38]. The evidence supporting rehabilitative strategies is growing but varies in methodological quality and is largely confined to small cohorts with mixed phenotypes of MS included, making translation difficult[39]. Wearable technology has emerged as a useful tool to collect long term data assessing function in the real-world setting[40]. Further research is needed to develop effective rehabilitation approaches incorporating

appropriate study design and outcome measurement and evaluating type and intensity of interventions. Integrating mechanistic studies and rehabilitation approaches through novel collaborations can inform and expand our understanding of regeneration and rehabilitation and their impact on each other.

Recommendations

The course of MS is heterogenous and results in a variety of symptoms affecting a person's quality of life. There are data supporting the idea that neuro-regeneration and restoration of function are possible in MS. Mechanisms underlying the eventual failure of repair are not fully understood in MS, thus limiting generalizability and application to clinical trials (Table 3). Preserving and repairing myelin is likely to be one of the best ways to prevent neurodegeneration. Translation of knowledge from basic mechanisms to functional impact is needed to optimize treatment, manage symptoms, and ultimately restore function for people with MS. In sum, it is important to build the knowledge base integrating mechanisms with rehabilitation so that they inform one another and drive breakthroughs for restoring function.

The End Pathway

The Roadmap defines the End Pathway as no new cases of disease. There is a growing appreciation that, along with a number of other autoimmune and neurological conditions, MS may be a preventable disease. One of the objectives of the End pathway is to prevent MS in the general population, commonly referred to as primary prevention. Primary prevention of MS will require population-based public health initiatives that reduce or eliminate exposure to putative risk factors and perhaps could also involve more targeted

measures among individuals considered to be at high risk for developing MS. The second objective of the End pathway focuses on identifying MS in its earliest (prodromal) stages to delay or prevent onset of classical clinical manifestations, defined as secondary prevention. Some of the approaches for achieving secondary prevention overlap with the early detection approaches described in the Stop pathway. Opportunities for preventing MS precede exposures to environmental risk factors and extend through the subclinical stages of disease (Figure 1).

Current Knowledge

Primary prevention

The goal of primary prevention is to prevent MS in the general population before it occurs by limiting exposure to modifiable MS risk factors. The cause of MS is not yet known, but progress has been made in identifying contributing factors and biological pathways that increase the risk of developing MS. Environmental risk factors such as low serum levels of vitamin D,[41] adolescent obesity,[42] tobacco smoking,[43] infection with EBV and in particular, symptomatic primary EBV infection[44,45], while not yet proven to be causal, have been consistently linked with an increase in MS risk.

In addition, a family history of MS is among the strongest risk factors, and more than 230 common gene variants have been identified that contribute to MS risk, with the strongest being multiple risk alleles in the major histocompatibility complex[46,47]. The genetics and environmental exposures driving MS risk have

mostly been studied in Caucasian populations. There is a strong need to determine whether these same factors are driving the risk for MS in other racial and ethnic groups.

Even in the absence of full knowledge of the cause of MS, strategies for preventing MS may be achievable in the next few years. Compelling evidence currently exists to support preventative, near-term, public health approaches such as vitamin D supplementation,[45] childhood obesity prevention[48], and EBV vaccination[49,50]. A better understanding of all factors and their interactions that can trigger MS, as well as cooperation and buy-in by public health agencies and policy makers to the concept of MS as a preventable disease are needed to prevent MS. However, public health initiatives such as these are likely to also help prevent other disorders and could more effectively be advanced by collaboration and coordination with other disease specific advocacy organizations. It is also worth considering whether higher risk primary prevention strategies could be deployed for those with a greater risk for developing MS.

Secondary prevention

The goal of secondary prevention is to identify individuals in whom the biologic processes driving the disease have begun, but in whom classical clinical manifestations have yet to manifest. With this knowledge one could intervene during the prodromal stage of MS, including asymptomatic people with radiological findings highly suggestive of MS. Because secondary prevention interventions are likely to have greater risks and side effects, it would be ideal to identify individuals at highest risk for early intervention.

Prodromal periods are recognized in other autoimmune and neurodegenerative conditions like type-1 diabetes, rheumatoid arthritis, Alzheimer's and Parkinson's disease, and trials testing interventions designed to delay or perhaps prevent the onset of clinical disease in some of these conditions are underway[51]. Evidence supporting an MS prodrome is emerging. For example, up to half of neurologically asymptomatic individuals with MRI lesions discovered incidentally have been shown to develop MS within 10 years[9]. In addition, cognitive changes in the years preceding diagnosis of MS have recently been reported[52] in addition to other non-specific clinical symptoms[53]. Biomarkers like serum NfL are also emerging as possible contributors that could help identify individuals in the prodromal stage of MS[8]. It is likely that a Bayesian approach to estimating risk for developing MS that incorporates clinical, radiological and laboratory data could be developed and deployed that would establish the MS prodromal period with enough confidence that a low-to moderate risk disease modifying approach could be used to treat MS in the very earliest stages with significantly improved outcomes.

Recommendations

Accelerating research that leads to a better understanding of all the factors that play a role in the risk for MS in all different populations, such as environmental exposures, the microbiome, social determinants of health, and genetics/epigenetics, as well as the interactions among them that may increase risk will help get us closer to realizing primary prevention (Table 4). The cost-effectiveness of some public health initiatives for preventing MS may need to be proven to convince policy makers of their value.

Biomarkers that indicate risk should be identified and made widely available. Although more biomarkers increase the accuracy of risk detection, this must be balanced with the difficulty in detecting them all in one person. A better understanding of the age at which risk factors act and when prevention interventions should begin will facilitate intervention. More information is needed about how to identify high-risk individuals, stratify risk, and select interventions that are tiered according to the strength of risk. Interventions should balance risk/benefit and be stratified according to the degree of an individual's risk, ranging from low-risk, long-term strategies such as vitamin D supplementation, dietary approaches, and vaccination against EBV, to higher-risk strategies such as immune-modulatory therapy. More evidence is needed for the causative role of known risk factors. Most of what is known about MS risk factors has been derived from largely white populations, leaving a gap in understanding how risk factors may differ across other racial or ethnic groups.

Better understanding of the critical biological pathways driving the earliest stages of disease is needed. Precisely which biomarkers and assessments identify risk for developing MS, when they change, and what thresholds identify an individual who is at increased risk are unknown. Which interventions will delay or stop further development of MS in an individual are currently unknown. Interrogation of comprehensive electronic health records and development of a statistical model of risk may be useful for identification of prodromal cases and prevention of development of definite MS. When MS actually begins is still not clear. Screening tools and biomarkers that identify MS in its pre-clinical stage with enough confidence to trigger initiation of DMTs are needed. A better understanding of processes that drive progression is needed.

Conclusion

Tremendous progress has been made in understanding of the pathogenesis and treatment of MS since the publication of a strategic review of MS research by the Institute of Medicine in 2000[54]. This progress has led to the development of numerous disease-modifying therapies and improved quality of life for many people with MS. Furthermore, it has led to optimism that we are close to breakthroughs that will lead to cures for MS. The Pathways to Cures Roadmap includes carefully considered recommendations of a large group of leaders in MS research and clinical care, as well as people affected by MS. We hope this report will inspire a heightened sense of urgency among research funders and better coordination of global research efforts focused on answering the key questions that will lead to cures for MS.

Implementation of the Roadmap will require strategic investments in the research priorities, avoiding silos and unhealthy competition, and encouraging multidisciplinary collaboration on an international scale. The endorsement of the Roadmap by many MS stakeholders is a strong starting point for better coordination and optimization of the global MS research and development investment. We encourage funders to consider both targeted investments in high priority research areas, and because it is not always possible to predict where the next breakthrough will come from, provide funding for high risk/high reward research that is more exploratory in nature.

It will also be important to update the Roadmap on a regular basis to reflect advances in our understanding of the Pathways and to account for the development of new technologies. We propose to convene a

biennial international meeting of global MS stakeholders to review progress on the Pathways to Cures milestones and to update the Roadmap to reflect contemporary knowledge of MS.

Finding cures for MS has taken much longer than anticipated when the National MS Society was founded seventy-five years ago, and although there remain significant obstacles, we have: (1) a passionate and committed global research community ready to execute the Roadmap, (2) a growing spirit of international collaboration and coordination of resources focused on research advancing the cure pathways, (3) a highly motivated and talented research workforce, and (4) a dedicated and well organized network of activists advocating for increased investments and coordination of MS research that inspires optimism that cures for MS are on the horizon.

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Table 1. Organizations endorsing the Roadmap (TBD)

Table 2. Stop pathway recommendations and research priorities

Gap	Action	Outcome
An understanding of mechanisms driving the MS prodrome	Fund research into early detection of MS before accumulation of neurological deficit	Processes contributing to MS risk are clearly defined; therapeutic interventions are implemented at the earliest point in time, leading to improved clinical responses
Longitudinal biomarker studies	• Enhance the impact of cohorts, registries, and repositories • Facilitate access and utilization by MS research community • Promote best practices in biomarker development and evaluation	Existing and new biomarkers enable early detection of disease activity
Research based framework to select the best therapy for individual patients (e.g., precision medicine)	• Promote research to provide clinical validation of multi-modal biomarker approaches to predict response to therapy. • Foster collaboration between diverse biomarker fields	Robust multi-modal biomarkers are fully integrated into clinical practice guidelines to support clinical decisions Partnerships are expanded to develop and implement better tools for precision medicine
Therapies for progressive forms of MS	Promote investment in clinical testing of therapeutics that modulate pathways in progressive MS	Putting a STOP to both relapsing and progressive injury mechanisms in each individual patient

Table 3. Restore pathway recommendations and research priorities

Gap	Action	Outcome
Physiologic mechanisms involved in regeneration and repair	Design and conduct studies to understand the role of aging, sex, genetics and other factors associated with regeneration	Identification of new targets for promoting myelin repair
MS specific outcome measures (biologic, imaging and clinical) that are sensitive to regeneration and/or functional recovery	• Develop consensus around the identification of outcome measures • Design and conduct research to identify outcomes that: - Can detect and measure myelin regeneration - Can detect meaningful recovery of function - Are associated with both regeneration and meaningful recovery of function	Identification of outcomes that can be used in clinical trials to test pharmacologic and rehabilitation interventions, and once approved can be used to guide use of therapies in clinical practice
Trial design, that fosters the development of rehabilitation and wellness interventions	• Advance guidance of clinical trial design • Facilitate and fund clinical intervention trials that target functional recovery, symptom management, rehabilitation or wellness strategies	Clinical intervention trials are implemented and evidence from those trials are used for the development of clinical guidelines
Standard outcomes across clinical trials	• Promote the use of standardized of outcomes across rehabilitation and wellness clinical trials • Develop consensus around standard outcomes to remotely measure and monitor functional recovery	Existing and new outcomes measures are identified and used for clinical trials

Table 4. End pathway recommendations and research priorities

Gaps	Actions	Outcomes
Full knowledge of MS risk factors that are necessary and sufficient to cause MS and the time frame for exposure	• Convene experts to develop a blueprint for accelerating research of risk factors • Promote knowledge generation of MS risk factors by research funders	Development of approaches to reduce the risk of MS are developed and validated
Availability of public health interventions that reduce or eliminate exposures to MS risk factors	• Partner with other advocacy groups to advocate for testing of interventions that prevent disease similar to MS • Test interventions with the strongest potential to reduce or eliminate the risk for MS (e.g., EBV vaccine)	Identification and deployment of public health strategies that reduce the risk for MS in the general population
A complete understanding of the genetic and epigenetic contributions to MS risk and etiology	• Build on the progress made by the International MS Genetics Consortium and others to identify the complete genetic/epigenetic risk for MS • Focus on understanding the genetic basis of disease heterogeneity • Develop a better understanding of gene environment interactions	New approaches for prevention and treatment of MS that reduce the burden of disease
A full understanding of the early pathological pathways that lead to initiation of MS	• Coordinate global resources to accelerate progress on elucidating the pathways contributing to the initiation of MS • Emphasize studies of pediatric onset MS	New approaches for prevention and treatment of MS that reduce the burden of disease
Fluid/imaging/clinical indicators that identify people at high risk for developing MS	• Promote research of biomarkers and clinical indicators of MS risk • Integrate fluid, imaging, clinical data into a risk staging algorithm	Development of tools for MS risk staging
Identification/implementation of interventions that prevent onset of MS in the high-risk population	• Accelerate research of interventions that could prevent the onset of MS • Support the clinical development of interventions that could delay or prevent onset of MS	Develop and deploy strategies that reduce or eliminate the risk for MS in the high-risk population

Supplemental Table 1: Coinvestigators (Advisors)

Name	Location	Role	Contribution
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Figure 1. The evolution of MS and opportunities for cures.