Research Priorities: Pathways to Multiple Sclerosis Cures

The National MS Society is focused on achieving breakthroughs to cures for multiple sclerosis. Our progress will be hastened with a roadmap that describes the knowledge gaps, milestones and research priorities that will lead to cures for everyone living with MS. The roadmap was developed in consultation with scientific experts, health care providers and people affected by MS. We believe the Pathways to Cures Roadmap 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.

The Roadmap includes three Pathways: STOPPING MS disease activity, RESTORING function by reversing damage and symptoms, and ENDING MS by preventing new cases.

NOTE: If you would like advice about whether and how your research may fit with these priorities, please reach out to a research staff person.

Goal 1: STOP pathway -- No more disease activity

Stopping MS is defined as achieving a state of no new disease activity, no worsening of daily living or quality of life, and no change in disease manifestations or clinical activity in people living with either relapsing or progressive forms of MS. Understanding disease heterogeneity across diverse populations of people with all forms of MS over time is important to stopping disease activity and protecting the central nervous system from further assault, and to create a permissive environment for myelin repair and other restoration efforts. Achieving a better understanding of the mechanism of progression as MS evolves over time will inform future therapeutic strategies. People with MS will play an active role in the pathway. As digital tools and technologies advance, data may be used to improve detection of changes in disease course, to monitor and measure neuroprotective processes, and to advance toward precision medicine tailored to individuals. Similarly, these tools might aid in supporting lifestyle modifications to benefit wellness.
**STOP**

**Goal: No More Disease Activity**

**Target #1**

**EARLY DETECTION**

Reduce or eliminate the impact of MS before neurological deficits accumulate in an individual with MS

**WHAT WE KNOW**
- Early intervention leads to improved outcomes
- Disease activity exists in asymptomatic individuals
- Neurodegeneration can occur early in the disease and is often masked by CNS plasticity and reserve

**WHAT WE DON’T KNOW**
- Exactly which biomarkers (fluid/imaging/digital/genetic) identify an individual likely to develop MS prior to expression of overt clinical manifestations required to confirm diagnosis
- A full understanding of the early pathological events that lead to the initiation of MS
- Whether interventions targeted at the very earliest stages of MS will stop disability progression

**WHAT WE NEED**
- Multi-modal biomarker algorithms that identify MS at the earliest point in time
- An understanding of the biological processes driving early MS compared to later stage disease
- A better understanding of the heterogeneity of preclinical phases of MS in diverse populations
- Interventions that target the earliest disease-causing pathways and the ability to determine if a person with MS is likely to respond
- To know how environmental and epigenetic factors impact early disease

**WHAT WE WILL DO**
- Advance research on early detection of MS before the onset of neurological deficits
- Enhance the impact of existing registries, data and biospecimen repositories
- Advocate and inform the MS research community on best practices in biomarker development
- Convene meeting to augment our current understanding of preclinical MS

**Target #2**

**PRECISION MEDICINE**

Achieve no worsening of daily living or quality of life, and no change in disease manifestations, for each individual with MS

**WHAT WE KNOW**
- MS is heterogeneous (pathologically and clinically)
- Biomarkers are being validated as predictors of subclinical activity and correlates of disease progression
- Lifestyle influences disease progression

**WHAT WE DON’T KNOW**
- Factors that determine the heterogeneity of MS pathology
- Precisely which biomarkers identify who will respond to a particular therapy and when a therapy is no longer effective
- Which therapies pose an increased risk to an individual
- The relationship between inflammation and neurodegeneration
- How to measure the transition to secondary progressive MS

**WHAT WE NEED**
- Multi-modal biomarker algorithms to determine MS prognosis
- New molecular targets to mediate neuroprotection
- Improved utilization of resources (genetic database, cohorts) to enable improved therapeutic efficacy in all forms of MS and diverse populations

**WHAT WE WILL DO**
- Promote research to provide clinical validation of well-established biomarkers as predictors of response to therapy
- Encourage continued development of therapeutic strategies for progressive forms of MS
- Foster collaboration to facilitate advances in precision medicine.
- Advocate for MS-relevant biomarker qualification by external agencies, industry, and foundations
Goal 2: RESTORE Pathway -- reverse symptoms, and recover function to enable full participation in society

MS can result in many different symptoms, including vision loss, pain, fatigue, sensory loss, impaired coordination, mobility, and cognitive and mood changes. Symptom severity and duration varies from person to person. Historically, rehabilitation aims to improve symptoms, with medical management of the disease kept separate. There is data supporting the idea that restoration of function, not only symptom management, is possible in MS.

Preserving and repairing myelin is likely to be one of the best ways we can prevent neurodegeneration. Exploring additional ways to slow down or stop neurodegeneration should reveal strategies that mitigate progressive forms of MS. In addition, the integration of repair and maintenance of repaired tissue with rehabilitation efforts is critical.

Translation of knowledge from basic mechanisms to functional impact is needed to optimize treatment, manage symptoms, and ultimately restore function for people living with both relapsing and progressive forms of MS. For this to occur, translational research using animal models of MS focused on understanding pathophysiological mechanisms as well as the study of human behavior and symptomatic therapies will be needed.
### Target #1

**REMYELINATION**

**WHAT WE KNOW**
- Myelin repair occurs early, but eventually fails
- Some of the cells/factors/pathways that promote/inhibit myelin repair
- The key pathways/targets needed to overcome repair failure
- How neuron-glial and glial-glial interactions impact repair
- How oligodendroglia may act as antigen presenting cells and contribute to axonal pathology
- How to limit damage, induce full repair and maintain myelin stability
- To what degree regional differences in CNS impact repair
- How age, sex, ethnicity, race, and genetics impact repair

**WHAT WE DON’T KNOW**
- To stop neurodegeneration and demyelination
- To clarify the functional heterogeneity of cells involved in repair
- A better understanding of the role for aging, sex, ethnicity, race, and genetics
- New targets for therapeutics that promote repair
- Accurate measurement of myelin and nerve fiber breakdown
- Better imaging/ fluid biomarkers for earlier readouts of remyelination and reversal of tissue damage
- Better animal models for repair

**WHAT WE NEED**
- Better outcome measures, quantitative and qualitative
- Sensitive, valid, and clinically meaningful measures of disability
- New clinical rehabilitation trials that are sufficiently powered
- Expanded access to rehabilitation therapies for all – via the use of technology and policy
- Better imaging/ fluid biomarkers for earlier readouts of remyelination and reversal of tissue damage
- Better animal models for repair

**WHAT WE WILL DO**
- Encourage further study of the physiological mechanisms involved in remyelination and neural repair
- Develop outcome measures and biomarkers to detect successful regeneration and functional recovery
- Foster imaging community and speed development of MS specific imaging methods and tools that relate to remyelination and function

### Target #2

**RESTORE ACTIVITY**

**WHAT WE KNOW**
- People with MS have a variety of symptoms that decrease their quality of life
- Disease modifying therapies don’t improve symptoms
- Rehabilitation interventions can improve symptoms (e.g., cognition, motor, psychosocial)
- Comorbidities affect symptoms, wellness behaviors, and potentially progression
- Loss of ability impacts capacity to care for oneself and stay employed
- Technology can be used to enhance physical activity

**WHAT WE DON’T KNOW**
- Mechanisms underlying the effects of rehabilitation on the central nervous system
- How to enhance neuroprotection and tissue regeneration with rehabilitation
- Proper dosing of intervention to facilitate optimal change in individuals
- Best outcomes to track symptoms, monitor progression, or tailor interventions
- Mechanisms to improve fatigue, pain, mood, cognition, bowel, and bladder function
- The extent that exercise can facilitate remyelination processes

**WHAT WE NEED**
- Better outcome measures, quantitative and qualitative
- Sensitive, valid, and clinically meaningful measures of disability
- Large clinical rehabilitation trials that are sufficiently powered
- Expanded access to rehabilitation therapies for all – via the use of technology and policy
- Outcomes that can be used to individually tailor interventions

**WHAT WE WILL DO**
- Promote the use of standard outcomes with emerging technologies such as wearables and smartphones
- Advance guidance in trial design for clinical rehabilitation trials
- Support the research and development of interventions that target functional recovery, including rehabilitation, lifestyle/wellness strategies, and symptom management in MS
- Promote expanded access to rehabilitation therapies via technology (telehealth) and policy
Goal 3: END Pathway -- No new cases of MS (prevention)
Ending MS is defined as no new cases of MS. Preventing new cases of MS will require population-based public health initiatives and individual-based interventions. Primary prevention involves identifying causal risk factors and limiting exposures to those MS risk factors in the general population. Secondary prevention focuses on individuals at high risk for MS and developing and deploying interventions in the period prior to clinical stages of disease to reduce or eliminate the risk for developing MS. While efforts will be made to advance both objectives, a focus on Secondary Prevention could potentially lead to the development of approaches with benefits for people living with MS in the near term.
END

Goal: No New Cases of MS

Target #1
PRIMARY PREVENTION
To prevent MS before it occurs by limiting exposure to MS risk factors in the general population

WHAT WE KNOW
• Some of the environmental risk factors for MS
• Some of the genetic/epigenetic risk factors for MS
• Incidence of MS in some regions of the world

WHAT WE DON’T KNOW
• Whether any risk factors are necessary and sufficient to cause MS
• The critical time frame for exposure to an MS risk factor
• The complete genetic/epigenetic contribution to MS etiology and how genes interact with environmental risk factors to cause MS in different populations
• Which public health interventions will reduce the risk for MS

WHAT WE NEED
• A better knowledge of all relevant risk factors for MS and whether any risk factor is necessary and sufficient to cause disease
• A full understanding of the genetic contribution to MS risk and how these factors interact with the environment
• Implementation of population-based interventions that reduce MS risk
• Interventions that prevent the onset of MS in the at-risk population

WHAT WE WILL DO
• Promote a better understanding of the genetic and environmental risk factors for MS in all populations
• Support the research and development of interventions that target MS prevention in the general population
• Advance research of behavioral changes that reduce the risk for MS and promote policies that support implementation of these behaviors

Target #2
SECONDARY PREVENTION
To reduce or eliminate the impact of MS before onset of signs/symptoms by identifying pre-clinical MS in the high-risk population

WHAT WE KNOW
• Emerging knowledge of imaging/fluid biomarkers that identify pre-clinical MS
• Early evidence that detailed medical history and neurological testing can contribute to identifying individuals at high risk for MS
• Ongoing trials of interventions in radiologically isolated syndrome with the potential to slow or even prevent MS
• Some of the biological pathways involved in the initiation of MS

WHAT WE DON’T KNOW
• Precisely which biomarkers identify risk for developing MS, when they become detectable, and what thresholds identify an individual as being at risk
• Which interventions are going to delay or stop the further development of MS in an individual
• What aspects of a medical history and/or neurological test will contribute significantly to identifying people at high risk for MS
• A full understanding of the early pathological pathways/events that lead to the initiation of MS
• Whether interventions targeted at the very earliest stages of MS will slow down or stop disability progression

WHAT WE NEED
• Screening tools that identify MS in its earliest stages with enough confidence to trigger initiation of disease modifying interventions
• Discovery of biomarkers that detect pre-clinical MS
• A better understanding of the critical biological pathways driving the earliest stages of disease
• Interventions that target the earliest disease-causing pathways and the ability to determine which treatment will work for which person
• A better understanding of the pathways driving non-lesional pathology/neurodegeneration that leads to the progressive stage of disease

WHAT WE WILL DO
• Promote the development of biomarkers and screening tools that identify people at high risk for MS and subsequent implementation into clinical practice
• Accelerate discoveries that increase our knowledge of the biological underpinnings of both lesional and non-lesional MS pathology
• Support the development of therapeutic approaches that target the early pathological events in MS