# 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.

2/24/21

## 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 symptoms appear *in an individual with MS*

**WHAT WE KNOW**
- Early intervention leads to improved outcomes
- Disease activity exists in individuals without symptoms
- Nerve degeneration can occur early in the disease and often goes undetected because of natural repair processes and reserve

**WHAT WE DON'T KNOW**
- Exactly which biomarkers (fluid/imaging/digital/genetic) identify an individual likely to develop MS prior to signs and symptoms 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**
- Algorithms to analyze multiple biomarkers 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 variability of pre-symptom 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 external and inborn risk 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 banks
- Advocate and inform the MS research community on best practices in biomarker development
- Convene meeting to augment our current understanding of early MS

## Target #2

### PRECISION MEDICINE

Achieve individualized treatment and lifestyle strategies to prevent further progression, *for each person living with MS*

**WHAT WE KNOW**
- MS is a variable disease
- Biomarkers, like blood tests and imaging, are on their way to being proven to predict early signs of disease and provide value in monitoring disease progression
- Lifestyle factors like diet, exercise and other medical conditions influence disease progression

**WHAT WE DON'T KNOW**
- Factors that determine the variability of onset and course
- 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 nerve degeneration
- How to measure the transition to secondary progressive MS

**WHAT WE NEED**
- Algorithms to analyze multiple biomarkers and determine MS prognosis
- New molecular targets to promote nerve protection
- Better use of date resources (genetic databases, patient cohorts) to inform therapy selection in all forms of MS and in diverse populations

**WHAT WE WILL DO**
- Promote research to validate 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.

# RESTORE

## Goal: Reverse symptoms and recover function to enable full participation in society

## Target #1

### REGENERATION

Improve or enhance tissue repair/ regeneration to reverse or slow MS progression and improve symptoms

**WHAT WE KNOW**
- Myelin repair occurs early, but eventually fails
- Some of the cells /factors/pathways that promote/inhibit myelin repair

**WHAT WE DON'T KNOW**
- The key pathways/targets needed to overcome repair failure
- How specific cell interactions impact repair
- How myelin-making cells may contribute to immune activity that damages axons
- How to limit damage, induce full repair and maintain myelin stability
- To what degree regional differences in the brain and spinal cord impact repair
- How age, sex, ethnicity, race, and genetics impact repair and brain rewiring

**WHAT WE NEED**
- To stop nerve degeneration and myelin damage
- To clarify the full variation of cells involved in repair
- To better understand the role for aging, sex, ethnicity, race, genetics, and other factors
- New targets for therapeutics that promote myelin and nerve repair
- Accurate measurement of myelin and nerve fiber breakdown
- Better imaging/fluid biomarkers for earlier readouts of myelin repair and reversal of tissue damage
- Better animal models for repair

**WHAT WE WILL DO**
- Encourage further study of the physiological mechanisms involved in myelin 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 myelin repair and function

## Target #2

### RESTORE ACTIVITY

Advance implementation of rehabilitation, wellness, lifestyle, and symptom management strategies to recover function and enhance quality of life

**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 and physical activity interventions can improve symptoms (e.g., cognition, motor, psychosocial)
- Other medical conditions (comorbidities) affect symptoms, wellness behaviors, and 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**
- Exactly how rehabilitation and exercise impact the central nervous system
- How to enhance neuroprotection and tissue regeneration with rehabilitation
- Proper dosing of intervention to facilitate optimal change in individuals
- Best ways 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 myelin repair processes

**WHAT WE NEED**
- Better outcome measures, quantitative and qualitative
- Sensitive, valid, and clinically meaningful measures of disability
- Large rehabilitation clinical trials that are sufficiently designed to prove effectiveness
- 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

**BROAD 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 onset 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

**AT-RISK PREVENTION**

To reduce or eliminate the impact of MS by providing specific guidance to *high-risk populations*

**WHAT WE KNOW**
- Emerging knowledge of imaging/fluid biomarkers that identify early signs of MS before symptoms occur
- 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 early MS before symptoms appear
- 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 nerve degeneration that leads to progressive stages of MS

**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 nerve degeneration
- Support the development of therapeutic approaches that target the earliest pathological events in MS