BREAKTHROUGH MS
NEW RESEARCH
Fall 2021

National MS Society Commits Nearly $7 Million for Targeted Research Projects and Rescue Funds for those disrupted by COVID-19

The National MS Society recently began funding 13 new research projects focusing on detecting MS at its earliest stages, before obvious symptoms appear. The projects are a result of the Society's first Request for Applications that targets a critical gap in Pathways to MS Cures priorities of stopping MS, restoring lost functions, and ending the disease by preventing more cases. This targeted research initiative on early detection, released in collaboration with the MS Society of Canada, is key to being able to both stop the disease at its earliest stages, before it injures the nervous system, and to prevent its onset.

Among the new projects funded are ones by Harvard and University of British Columbia investigators who are using long-range health data to detect early, unrecognized warning signs of MS; researchers at Sweden's Karolinska Institute who are mapping out windows of exposure to explain how combinations of risk factors may lead to MS; and University of California, San Francisco researchers who are developing profiles of early exposures to infectious agents such as viruses to understand whether they play a role in triggering MS later.

A portion of the Society's new $7 million investment went toward research "rescue" supplements to 22 of its funded investigators to enable critical work that had been disrupted by COVID-19 to continue with additional time and funding.

NEW PROJECTS SUMMARIZED INSIDE:

Pathways to Cures:

National Multiple Sclerosis Society

Pathways to Cures: STOP/How do we stop disease activity and progression?

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. Two key objectives have been targeted for the next three years: to advance the STOP pathway: early detection before symptoms appear, and precision medicine for individualized treatment and lifestyle strategies to prevent further progression.

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Jeff Bulte, PhD
Johns Hopkins University
Baltimore, Maryland
Award: Request for Applications
Term: 10/1/2021-9/30/2023; **Funding:** $321,851
Paid by the Marilyn Hilton MS Research Fund

Title: MALDI identification of CEST MRI biomarkers that may precede and predict the onset of disease in Multiple sclerosis

Summary: Researchers at Johns Hopkins are using MRI to see if there are biochemical and other changes in the brain before MS symptoms start, to create an early detection tool for earlier treatment.

Background: Developing ways to detect MS before it begins its destructive course on the nervous system may offer opportunities to stop the disease in its path. Professor Bulte's team has seen hints on advanced MRI brain scans that there are early biochemical changes occuring before symptoms become apparent. Now they want to identify the origins of these signals to see if any of them can be developed as biomarkers for early detection of MS.

The Study: The team is using a new scanning technique, called matrix-assisted laser desorption ionization (MALDI) imaging, to investigate detailed information about brain cell products and molecules along the course of MS-like disease in rodents. They are examining MR images and tissue samples they have already obtained to codify early changes.

What is the potential impact for people with MS? Once the specific molecules have been well defined as potential biomarkers, detecting changes in their concentration before the onset of disease may offer unique opportunities for early intervention, and the development of new therapies to prevent damage.

Leigh Charvet, PhD
New York University Langone Medical Center
New York, New York
Award: Request for Applications
Term: 10/1/2021-9/30/2023;
Funding: $324,990 PENDING
Title: Intra-Individual Variability in Cognitive Performance as a Marker of Prodromal Disability in MS
Summary: Researchers at New York University are cataloging subtle variations in thinking speed to see if they can be an early predictor of future disability in MS and inform ways to stop progression.

Background: Cognitive impairment is a common and often disabling problem in MS. While we can detect cognitive problems once they reach the level of clincal impairment, there remains an urgent need for a way to identify those at risk for cognitive impairment before the onset of disability. Prof. Charvet's team is seeking to measure risk before disability occurs.

The Study: This team has developed a way to measure subtle inconsistencies in cognitive processes using simple computer-based reaction time tests. They are now testing this method in an existing cohort of people whose cognitive function had been tested for a previous study using standard clinical tests. They also are recruiting a sample of persons at risk for MS to study this method in before MS is apparent. They are testing whether results correlate with a new neuroimaging method measuring brain activity, indicating that this process might constitute an early biomarker for cognitive impairment.

What is the potential impact for people with MS? This work will advance us towards a clinical screening tool that can be used easily and even remotely to detect people most at risk for cognitive impairment in MS. Ultimately, this marker may help to develop interventions that prevent disability progression.

Ruth Dobson, MBBS, PhD
Queen Mary University of London
London, United Kingdom
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $293,324 PENDING
Paid by the Marilyn Hilton MS Research Fund

Title: Window of opportunity: examining modifiable risk factors and prodromes of Multiple Sclerosis in UK primary care datasets

Summary: Queen Mary University London researchers are using medical records from people of different backgrounds to identify symptoms occurring before an MS diagnosis, and potentially developing tools for identifying those at the highest risk of MS.

Background: Do medical records hold the key to early detection of MS? Previous research suggests that people with MS tend to use health services and fill more perscriptions in the five years before they are diagnosed with MS. Dr. Dobson's team is trying to see whether they can use medical records to detect early MS, especially in people of different genders, ethnicities, and backgrounds.

The Study: The team will use healthcare data from millions of people to identify specific groups of symptoms that occur prior to MS onset, and examine whether these groups of symptoms vary between people of different genders, ethnicities, or other backgrounds. They will see whether these groups of symptoms can predict who will have evidence of MS on MRI scans of people without known MS, and whether adding someone's genetic information helps to predict who will have evidence of MS on MRI scans. Finally, they will investigate whether any signals may be suitable to target for treatment to reduce the risk of developing definite MS.

What is the potential impact for people with MS? Ultimately, this study will inform clinical trials focusing on preventing MS in people at the highest risk of developing definite MS.

Daniel Hawiger, MD, PhD
Saint Louis University
St. Louis, Missouri
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $298,545
Paid by the Marilyn Hilton MS Research Fund

Title: Detecting autoimmune potential of CD4+ T cells in the early MS disease process

Summary: Saint Louis University investigators are search for novel immune cell fingerprints that would indicate pre-symptom MS to speed diagnosis earlier in the disease.

Background: Immune cells called T cells have been implicated in the immune attacks that damage the brain and spinal cord in MS. Current MS therapies can dampen immune activity, but these therapies are introduced only after MS becomes apparent, when the disease has already begun to cause tissue damage. This damage might be minimized if MS could be treated earlier.

The Study: Dr. Hawiger's team believes that the culprit T cells acquire unique molecular characteristics before they fully commit to becoming aggressors. They are using advanced techniques to identify characteristic molecules in relevant T cells from people with MS early in the disease course. Their earlier work identified specific patterns of gene activity within T cells that helps to identify cells that commit early to becoming aggressors. Building on this work, the team will search for a signal or biomarker that detects this early MS disease process and which could be used in earlier diagnosis.

What is the potential impact for people with MS? A successful outcome of this project would fill a major gap related to an early diagnosis of MS. In addition, the results may lead to the identification of molecules involved in MS onset, providing new targets for improved therapies.

Marwa Kaisey, MD
Cedars-Sinai Medical Center
Los Angeles, California
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $322,819

Title: Detecting Multiple Sclerosis Before the Onset of Neurological Deficits

Summary: Cedars-Sinai researchers are searching for a marker in the blood that could help diagnose MS earlier, which may enable better treatment outcomes.

Background: MS diagnosis can be difficult, and no one test can determine whether someone has MS. Diagnosis requires careful evaluation of symptoms, neurologic exam, magnetic resonance imaging (MRI), and sometimes spinal fluid to determine if the person fits the detailed diagnostic criteria. Even with the proper time and testing, diagnostic mistakes occur. Diagnosis can be delayed, and a person's MS untreated for months or even years.This team aims to evaluate new blood tests for MS diagnosis using samples collected from a study that is testing an MRI marker of MS, called the central vein sign (CVS).

The Study: Dr. Kaisey and colleagues are collecting blood samples from the 400 subjects in the CVS study. They are testing levels of three blood markers to see whether these tests done at the beginning of the study can identify people who have a true diagnosis of MS at the end of the study. They are also interested in whether the tests can identify MS in people with unusual symptoms that do not meet MS criteria (for example, vague neurologic symptoms or an abnormal MRI without MS symptoms). They also are testing a set of markers that are involved in blood vessel damage, which may serve as a diagnostic test for MS.

What is the potential impact for people with MS? If successful, this team may identify new blood biomarkers of MS, possibly leading to a blood test for MS that would revolutionize the MS diagnostic process.

Darin Okuda, MD
The University of Texas Southwestern Medical Center
Dallas, Texas
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $299,814 PENDING

Title: Improved risk stratification in radiologically isolated syndrome (RIS) through identified serum and CSF biomarkers

Summary: Researchers at UT Southwestern and collaborators are searching for a marker in the blood or spinal fluid that will help predict whether a person with incidental MRI brain lesions will go on to develop MS.

Background: In some people, areas of tissue damage (lesions) are oberved on brain MRIs that have the typical appearance and location of MS lesions, yet these individuals have no history of neurological symptoms. This group is known as having radiologically isolated syndrome (RIS). Some of them go on to develop MS, and some do not. Key markers within the blood and spinal fluid from people with RIS may help to predict which people with RIS will go on to develop MS.

The Study: Dr. Okuda's team is studying four of the largest cohorts of people with RIS. Blood and spinal fluid from 327 subjects with RIS will be explored. A variety of analytical methods, including artificial intelligence, will be used to examine the relationship between the most promising biomarkers and emerging clinical symptoms. This project focuses on known markers of injury to nerves and supporting cells, and will be tracking changes in markers over 96 weeks.

What is the potential impact for people with MS? Being able to determine levels of risk for developing MS in individuals with RIS is essential not only for reducing psychological stress, but in recognizing those who would benefit from rigorous monitoring or treatment.

Teri Schreiner, MD, MPH
University of Colorado Denver
Denver, Colorado
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $329,995
Title: Detection and Risk in Earliest MS
Paid by the Marilyn Hilton MS Research Fund

Summary: University of Colorado researchers are examining close family members of people with MS in search of early evidence and risk factors that could be combined to predict the future onset of MS.

Background: The risk of developing MS in the general population is relatively low, but it is about 5 times higher for first-degree relatives – siblings, parents, and children of those with MS. During the period before obvious MS symptoms appear, some people may show not only brain MRI changes, but also indicators in blood (so-called biomarkers), and other changes in physical, cognitive, and emotional function. Dr. Schreiner's team is seeking such signs that can be used together to define a "risk score" for developing MS.

The Study: Dr. Schreiner and colleagues are leveraging their ongoing studies of first-degree relatives of people with MS that collect detailed information on nerve and immune blood markers, genetics, demographics, and cognitive testing. They are re-examining 125 people in these studies two years after their intitial study visit. They are separating people into groups who go on to develop MS, those who develop some signs of MS, and those whose scans remain normal, and are looking at all the known and potential markers of MS risk in each group.

What is the potential impact for people with MS? People with MS often worry about whether their children or siblings will develop MS also. This team hopes to be able to counsel people with MS and their family members about the future risk of developing MS among relatives.

Helen Tremlett, PhD
University of British Columbia
Vancouver, Canada
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $144,500 Plus co-funding from the MS Society of Canada

Title: Heterogeneity in the MS prodrome and impact on disease progression (PrOMS-HD)

Summary: University of British Columbia researchers, along with collaborators across Canada and Sweden, are searching medical records for early, unrecognized warning signs of MS to enable pre-emptive treatment.

Background: MS can be hard to recognize because early symptoms can be vague or non-specific. Studies by this team have shown that healthcare use is higher than expected years before the person realizes that they have MS. But it is not clear if men and women, or people of different ages and backgrounds are affected differently at the earliest stages of MS.

The Study: With collaborators from across Canada and Sweden, Professor Tremlett will seek clues to health care use in multiple large health-related databases in Sweden and two Canadian provinces. The databases track visits to the hospital, doctor, and medications used. In Sweden they also contain information on sick leave from work. The team will use advanced statistical methods to look for patterns in people with MS even before they are diagnosed. By comparing these patterns to people without MS, they can identify early warning symptoms of MS. They will also look at whether these patterns differ for people of different ages, sex, and backgrounds, and whether the number or type of symptoms are related to future MS disability.

What is the potential impact for people with MS? This study has the potential to raise awareness of the early features of MS and promote timelier recognition, diagnosis and management of MS. It will also help determine whether some people with certain early signs are at greatest risk for severe disease, offering an opportunity for early preemptive treatment.

Pathways to Cures: END/How do we prevent MS?

Ending MS is defined as no new cases of MS. Two key objectives have been targeted for the next three years to advance the END pathway: primary prevention and secondary prevention. Primary prevention involves limiting exposures to 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 preclinical/clinical stages of disease to reduce or eliminate the risk for developing MS.

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Lisa Ann Gerdes, MD
University Hospital LMU Munich Germany
Munich, Germany
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $297,000
Paid by the Marilyn Hilton MS Research Fund

Title: Disease-triggering potential of microbiota in prodromal MS

Summary: Researchers in Munich are studying gut bacteria in twins with and without MS to identify possible risk factors that trigger MS.

Background: Recently the bacteria of the gut, called microbiota, have received great attention as a new potential risk factor of MS. Numerous studies have started to explore the role of the microbiota in MS but as yet, no consistent picture has emerged. Dr. Gerdes and colleagues are taking a new approach to explore the idea that the disease process of MS is initiated in the gut by a distinct set of bacteria. The composition of the gut microbiota varies from person to person. Typically, the human "microbiome" in the gut of a given person contains billions of bacteria. Searching for MS-triggering bacteria is like searching for a needle in a haystack.

The Study: Dr. Gerdes's team is leveraging the MS Twin Study to attack this problem. In this unique cohort of 88 twin pairs, one twin has MS whereas the other is healthy. Because each twin pair has identical genes, there is no "genetic noise" when their microbiomes are compared. By analyzing and comparing the microbiome of these twins, the researchers hope to gain access to the earliest stage of the disease process. They also are using a mouse model that develops MS-like disease when exposed to bacteria from humans' small intestines.

What is the potential impact for people with MS? Once disease-inducing bacteria are known it should be possible to screen for people who are at high risk for developing MS, and facilitate initiation of early or even preventive treatment.

Kassandra L. Munger, ScD
Harvard School of Public Health
Boston, Massachusetts
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $282,092
Paid by the Marilyn Hilton MS Research Fund

Title: Expanding our understanding of the MS prodrome phenotype—a prospective study in two large cohorts of women

Summary: Harvard researchers are using long-range health data to detect early signs of MS up to 15 years before symptoms appear.

Background: There is growing consensus that MS starts well before symptoms appear, and that catching it earlier would improve treatment outcomes. Figuring out how to identify people who may have MS is a challenge in the absence of typical symptoms.

The Study: Dr. Kassandra L. Munger and team are testing the possibility, in two long-term groups of women tracked in the Nurses Health studies, that there may be signals of early manifestations of MS well before it is diagnosed. They are comparing women who eventually developed MS with those who did not, looking at treatment for depression or anxiety, lower physical activity, and higher incidence of neurological conditions, pain, tiredness, and bladder complaints. They are using advanced computing methods to identify medical conditions and lifestyle habits that alone or in combination may be novel features of the MS pre-diagnosed phase.

What is the potential impact for people with MS? This study has the potential to "reset" the date of MS onset to an earlier time, which may enable earlier diagnosis and treatment, and enable deeper research into what causes MS.

Jorge Oksenberg, PhD
University of California, San Francisco
San Francisco, California
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $309,679

Title: Integration of polygenic risk scores with non-genetic risk factors to improve risk prediction in MS

Summary: UCSF scientists are combining genetic profiles with demographic and environmental variables to identify people with elevated risk for developing MS.

Background: MS likely starts well before it causes symptoms, so by the time someone is diagnosed, the disease has already advanced and caused nervous system damage. Being able to identify people with a high risk of developing MS may enable early monitoring and intervention. Gene-environment interactions are important to understand because they offer insights into the biology of MS susceptibility, and enable screening to identify those at risk.

The Study: Professor Oksenberg is leading a team focusing on how a person's genes combine with lifestyle factors, demographics, and environmental exposures to increase MS risk. They are working to quantify these factors to develop "risk scores" to pinpoint individuals who are at high risk for MS. They are leveraging existing genetic and non-genetic databases and tissue banks and statistical tools to explore how multiple factors interact, with the help of well-studied people with MS from different backgrounds. They will also explore the biological mechanisms behind MS risk to develop a way to provide accurate, individualized information for people before they have been diagnosed.

What is the potential impact for people with MS? Having a tool that can predict whether a person is likely to develop MS could facilitate early diagnosis as well as the development and implementation of preventive interventions.

Tomas Olsson, MD, PhD
Karolinska Institutet
Stockholm, Sweden
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $298,040 PENDING
Paid by the Marilyn Hilton MS Research Fund

Title: Early detection of multiple sclerosis: a life-course epidemiological and biomarker approach

Summary: Researchers at Sweden's Karolinska Institute are taking advantage of a depth of national medical and other data to detect MS risk factors and windows of exposure to explain how combinations of factors lead to MS.

Background: The cause of MS is not known, but it seems to involve a combination of risk factors that increase the likelihood that an individual will develop the disease. These factors may be at play at birth and throughout childhood, adolescence, and adulthood. So far, most risk factor studies have focused on linking specific exposures to specific outcomes, and yet an individual's risk of MS is likely the result of complex mechanisms combining genetics, lifestyle and the social environment acting from birth or even across generations.

The Study: Professor Olsson and collaborators will integrate a wealth of MS gene studies, long-term health studies, and medical records, and information on lifestyle, sociodemographic factors to investigate the critical windows of exposures that may predict higher risk. They will also develop and test a predictive composite risk "score," and determine whether there are biomarkers or signs that can identify those at highest risk for MS before it develops.

What is the potential impact for people with MS? This work will bring insight into why some persons have higher risk for MS, while others remain at low risk. High-risk individuals may benefit from interventions that might prevent MS from developing.

Michael Wilson, MD
University of California, San Francisco
San Francisco, California
Award: Request for Applications
Term: 10/1/2021-9/30/2023
Funding: $310,313 PENDING

Title: Risk Factors for Preclinical MS: The ENGEMS Cohort (Environmental and Genetic Risks for MS)

Summary: UCSF researchers are developing profiles of early exposures to infectious agents such as viruses to understand whether they play a role in triggering MS later.

Background: There is evidence that viruses may play a role in the development of MS in people whose genes put them at risk. Antibodies are proteins that our immune system makes to target foreign agents like viruses, but they can also sometimes inappropriately attack our own body's self proteins. Dr. Wilson and colleagues are seeking to identify antibodies that can predict whether someone is likely to develop MS years before the disease causes obvious symptoms. They have access to blood samples from the Department of Defense through study collaborator Dr. Mitchell Wallin, taken from hundreds of soldiers years before a portion of them developed MS, and have new tools for probing these samples for specific antibodies.

The Study: Dr. Wilson's team is using novel techniques to assess for the presence of antibodies in a small volume of blood that may target the whole range of infectious viruses and also the whole range of human proteins. They are generating these "antibody profiles" for hundreds of people with MS before symptoms began and comparing them to hundreds of similar people (based on age, sex, race, geography, etc) without MS.

What is the potential impact for people with MS? Identifying blood-based biomarkers such as antibodies that can pinpoint people at high risk for developing MS can alter the landscape for diagnostics in MS, making sure that people at high risk for MS can get timely access to preemptive therapies.