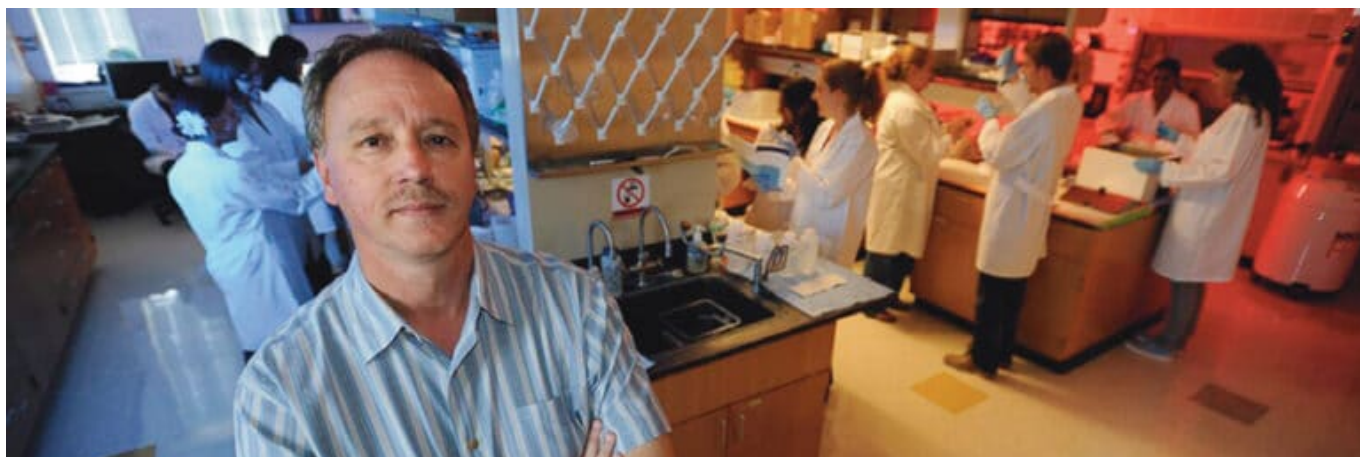


Predicting MS progression



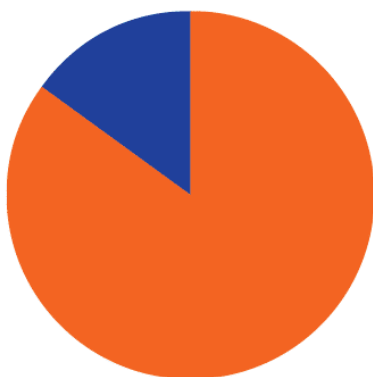
Using sophisticated new technology, researchers aim to understand why some people’s MS progresses more quickly than others’.

by Susan Worley

Most individuals with multiple sclerosis are well aware that the disease can be highly variable and unpredictable. Despite many recent advances, such as more sophisticated MRI scans, predicting a person’s disease progression, or prognosis, remains a significant challenge for neurologists—and a significant source of distress for people living with the disease. Even the ability to determine, at diagnosis, an individual’s specific type of MS (such as relapsing or progressive) remains limited and often requires repeated testing and examination over time.

Researchers are working to understand whose MS will progress, when and how rapidly.

- Approximately **85 percent** of people with MS are initially diagnosed with relapsing-remitting MS (RRMS).
- Approximately **15 percent** of people with MS are diagnosed with primary progressive MS (PPMS).



“After following a patient for a few years, a clinician’s ability to gauge the patient’s disease and predict progression may improve to some degree,” says Dr. Thomas Forsthuber, a researcher and professor of biotechnology at the University of Texas in San Antonio (UTSA). “However, we are still in need of a scientific method for predicting the clinical course of MS,

which would not only improve treatment selection but perhaps even help to prevent or reverse progression of the disease.”

The ultimate goal, says Dr. Forsthuber, would be the development of a simple, noninvasive test whose results would reliably forecast an individual’s risk for progression. Ideally, such a test would involve a simple blood test, or analysis of urine, stool or even saliva.

The first step on the road to developing such a test is the identification of fluid **biomarkers**—bodily substances that can be reliably measured and strongly associated with disease activity, in much the same way that blood sugar can be used to provide information about diabetes. Harnessing the power of complex, novel technology that can isolate, tag, quantify and compare such substances, researchers are closing in on biomarkers that may offer valuable information about disease progression.

A search for proteins

One promising field of biomarker research is that of **proteomics**—or the large-scale study of protein molecules, including their structure, function and changes in number over time. At UTSA, Dr. Forsthuber is the lead investigator of a proteomics study that began with an examination of proteins in the brains of mice. Using mice that have an animal version of MS, known as experimental autoimmune encephalomyelitis (EAE), and a novel application of technology designed to tag protein molecules, he and his colleagues are closely tracking changes in proteins that occur during various stages of the MS-like disease.

Dr. Forsthuber and his colleagues already have identified some proteins that undergo changes during exacerbations of EAE in mice. Once they have narrowed down the most compelling of these, they will begin to search for these molecules in the blood of the mice to find out which of these can predict disease progression. Because the proteins they are examining have human equivalents, it should be possible, eventually, to compare meaningful patterns of proteins in mice with patterns found in the blood of people with MS. The results of the study should not only provide insight into the causes of MS progression, but also may help to reveal silent activity (unseen on MRI) that takes place between relapses, known as subclinical progression.

A different angle

With funding from the International Progressive MS Alliance, Charlotte Teunissen, PhD, of the VU University Medical Center (VUMC) in Amsterdam, is also conducting a proteomics study, but taking a somewhat reverse approach. Using a powerful protein biomarker discovery tool called the SOMAscan®, she is identifying patterns of proteins in the blood of people with MS, which may help to predict progression by reflecting disease activity in the brain at different stages of the disease.



Charlotte Teunissen,
PhD. Photo courtesy of Dr.
Teunissen

“With only a few drops of blood from an individual, we can simultaneously analyze over a thousand different proteins,” says Dr. Teunissen. “We are using this information to establish molecular signatures—that is, unique patterns of proteins that indicate, for example, which protein molecules are elevated and which are reduced for each patient at various stages of disease.”

All of the people in Dr. Teunissen’s study provided blood samples at regular intervals over a period of four years, as did healthy controls (individuals without MS). Currently, the molecular signatures of people who experienced steep progression are being compared with those of individuals who experienced little or no progression after the blood donation. Already, Dr. Teunissen has identified inflammatory protein molecules that appear to be strongly associated with disease progression. Her hope is that further analysis will reveal not only clues to MS progression, but one or more relevant disease mechanisms that could become targets for medication development.

Mining the microbiome

Another promising avenue of MS biomarker research involves investigation of the bacteria that live in the human gut (the small and large intestines); these bacteria are collectively referred to as the gut microbiome. Because MS involves attacks of the immune system on the brain and spinal cord, it makes sense to search for clues to progression in the gut, the largest immune organ in humans.



Sergio E. Baranzini, PhD.

Photo courtesy of Dr.
Baranzini

“The microbiome is an important source of information about the body,” says Sergio E. Baranzini, PhD, professor of neurology at the University of California, San Francisco (UCSF). “In the intestines, extremely large numbers of bacteria come in close contact with cells that are part of the immune system, and can influence immune functioning. This is also where the immune system learns about what is happening outside of the body, because diet and environmental exposure affect the different bacteria that pass through the intestines and come in contact with immune cells.”

As lead investigator of the National MS Society-supported MS Microbiome Consortium and a principal investigator of the International MS Microbiome Study, Dr. Baranzini is working with colleagues to determine whether microbiome differences in people with MS can affect immune functioning in a way that is strongly linked with disease activity. Thanks to new technology that enables quick and relatively inexpensive DNA sequencing, says Dr. Baranzini, he and his colleagues have been able to examine the composition of bacterial communities in individuals with MS during different stages of disease, and compare their findings with data from healthy controls. To zero in on changes that are specific to MS, information obtained from each individual with MS must be compared with that of a healthy control from the same household (i.e., someone exposed to similar diet and environment).

Intriguing initial findings suggest that the microbiome may eventually help explain some causes of progression in MS. Ultimately, the team aims to determine whether probiotic strategies can interrupt the disease course. Dr. Baranzini and his colleagues also hope to learn whether the microbiome clearly plays a role in triggering MS. If they are able to establish such a role, transferring healthy bacteria to individuals who have MS may be key to preventing progression of the disease.

Detecting clues in data

Yet another powerful tool that may help solve the mystery of progression is **informatics**, which refers to a wide range of systems that store, process, manage and communicate information. In scientific fields, informatics can be used to discover patterns and reveal hidden truths in very large quantities of data.



Dr. Howard Weiner. Photo courtesy of Dr. Weiner

The SUMMIT consortium is an ambitious new project being funded by the Society, in which world-renowned MS centers will use such tools to unravel why and how MS progresses, with the goal of predicting and preventing progression. This five-year study brings together two MS Centers of Excellence: Harvard's Brigham and Women's Hospital and UCSF. Each institution has been carefully following groups of people with MS for nearly 10 years in studies known as CLIMB and EPIC, respectively. Using an array of advanced laboratory tests and imaging techniques, researchers have been collecting data from detailed molecular, cellular and genetic analyses, and compiling these into a single standardized set of data. Using technology capable of sifting through an enormous amount of information, these investigators are beginning to identify factors that may influence disease progression, in addition to known risk factors of smoking, sun exposure, gender and hormones. SUMMIT will extend and leverage these deep collections of information, clinical data, MRI images, questionnaires and biological specimens involving more than 1,000 people with MS.

"The integration of data from these two studies is providing us with a unique opportunity to examine the course of MS in a wide range of people, while analyzing a large number of variables, in an effort to determine why some patients progress more quickly than others," says Dr. Howard Weiner, professor of neurology at Harvard Medical School, and one of the lead investigators of the SUMMIT study.

"The SUMMIT data ultimately will be made available to other research groups around the world," Dr. Weiner adds, "and should serve as a foundation from which new projects, such as

efforts to develop new biomarkers, can be launched. We also expect to expand our study and add new research centers outside of the U.S. as the study continues.”

Susan Worley is a freelance medical writer in Bryn Mawr, Pennsylvania.

Learn more about the [International MS Microbiome Study](#).

To learn more about the studies used in the SUMMIT collaboration, visit [Partners Multiple Sclerosis Center](#) and the [UCSF Multiple Sclerosis Center](#).