

Accelerated Cure Project for MS

October
2017



*Accelerating research towards a
cure for multiple sclerosis*

Dear Friends,

Clinical research is the study of health and illness in people. It is the way we learn to prevent, diagnose and treat illness. Clinical research helps translate basic research (done in labs) into new treatments and information that will benefit patients. The field of clinical research encompasses many types of trials, including clinical trials. Our first article takes a detailed look at clinical trials, including the terminology associated with them and the many ways they can be classified.

In the second article, Dr. Farren Briggs discusses recent research to identify biomarkers for MS.

This month's newsletter also features an article on the Multiple Sclerosis RNA test recently developed using samples from the ACP Repository by researchers at IQuity Specialty Diagnostics and Vanderbilt University.

Our partner spotlight this month is Smart Patients. Smart Patients is a unique online community that offers people affected by disease support and education about their illness.

We appreciate your interest in our newsletter and hope that you are enjoying the beautiful fall foliage.

The Accelerated Cure Project Team

Clinical Research – A Deeper Look

Clinical research is the study of health and illness in people. It is the way we learn to prevent, diagnose and treat illness. Clinical research helps translate basic research (done in labs) into new treatments and information that will benefit patients. A clinical trial is one type of clinical research study. Clinical trials are done to determine whether new drugs or treatments are safe and effective. Clinical trials can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses. Clinical trials can vary in size and cost, they can be done on an inpatient or outpatient basis, and they can involve a single site or multiple sites. Some clinical trials involve healthy subjects, and others pertain to patients with specific health conditions who are willing to try an experimental treatment.



The testing of medical treatments in clinical trials has two main goals. The first is to determine the treatment's "efficacy" or "effectiveness" (whether the treatment works well enough for its intended purpose). The second goal is to determine the treatment's "safety" (whether the treatment is safe enough). Neither efficacy nor safety is an absolute criterion. Both are evaluated relative to the treatment's intended use, what other treatments are available, and the severity of the disease or condition. In all cases, the benefits of the treatment must outweigh the risks.

The person that leads a clinical study is called a principal investigator (PI). People often confuse clinical research or clinical trials with medical care, especially when an individual's doctor is also the PI of their clinical trial. When a patient receives medical care, it is according to a doctor's plan of care developed specifically for each patient. If a patient participates in a clinical research study, the PI and the patient must follow a set plan called the "study protocol", which is designed by the study sponsor. The sponsor is the person or company that is responsible for the initiation, management and financing of the clinical study. The protocol ensures that all researchers perform the trial in the same way on similar subjects and that the collected data is comparable across all subjects. Protocols cannot be adjusted for individual patients, however protocols do include steps to follow if patients aren't doing well. It's important to understand that a clinical trial is an experiment, which means that the answer to the research question is unknown. Patients

may or may not benefit directly by participating in a clinical trial, which is why whether or not to participate in one is an important topic to discuss with your doctor.

If a clinical trial is “open label”, subjects and researchers are aware of the drug being given. In some clinical studies, participants may be assigned to receive a placebo (an inactive product that resembles the treatment being studied). Comparing a new treatment with a placebo can be the fastest and most reliable way to demonstrate the new treatment’s therapeutic effectiveness. Placebos are not used if a patient would be put at risk by not having effective therapy. Potential study participants are told if placebos will be used in the clinical trial before they enroll. A “randomized study” is one in which subjects are randomly assigned to separate groups to receive different treatments (neither the researchers or subjects can choose which group). At the time of the clinical trial it is not known which treatment is best. In some randomized studies subjects receive either the study treatment or a placebo. A “blinded study” is one in which the participants do not know which study treatment they receive. If the clinical trial is “double-blind”, the researchers also do not know which treatment participants receive. The double blind study method helps minimize the effects of any bias on the part of participants or researchers. If participants do not know which group they are in, their beliefs about the treatment are less likely to influence the outcome. If researchers do not know which group subjects are in, their feelings or biases will not influence how subjects may respond or how data is collected.



One way of classifying clinical trials is by the researcher’s role in the study. In an “observational study”, the investigators observe subjects and measure their outcomes. The participants in such trials do not receive any treatment but may be asked to provide information or blood samples. The ACP Repository and iConquerMS™ are examples of observational studies. In an “interventional study” (or clinical trial), the investigators give participants a particular medicine or other therapy to compare the treated subjects with those receiving no treatment, or the standard treatment. The researchers then measure how the participants’ health changes.



The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) classify clinical trials according to their purpose. “Prevention trials” look for better ways to prevent disease. These trials may include medicines, vitamins, vaccines, or lifestyle

changes. “Diagnostic trials” are conducted to evaluate the presence or absence of disease as a basis for treatment decisions in symptomatic individuals. “Screening trials” look for the best way to detect early disease or risk factors for disease in large numbers of apparently healthy individuals. “Treatment trials” test new treatments, or medical devices. “Quality of life trials” explore ways to improve the comfort and quality of life for individuals with chronic illness. “Epidemiological studies” look to identify the patterns and causes of diseases in groups of people. Finally, “genetic studies” aim to better understand how a person’s genes and illnesses may be related. For example, genetic research may explore ways in which a person’s DNA makes him or her more or less likely to develop a disease. This may lead to development of tailor-made treatments based on a person’s genome.

A third classification of clinical trials is whether the trial design allows changes based on data collected during the trial. “Adaptive trials” allow modifications to the trial and/or the statistical procedures of the trial, and then use interim results to modify the trial as it proceeds. In this way, drugs that have a therapeutic effect and patient populations for whom the drug is appropriate can be more quickly identified. “Fixed trials” are not modified once initiated and results are not assessed until study completion.

Clinical trials can also be classified according to whether or not they are considered beneficial. A “therapeutic trial” is one in which the treatment being studied is likely to benefit participants in some way (for example, a clinical trial for a new MS drug). A “non-therapeutic trial”, on the other hand, is one that is unlikely to produce any direct benefit to the participants involved (for example, tracking the long term health effects of chemotherapy). Non-therapeutic studies often lead to therapeutic ones.

Therapeutic clinical trials are classified by phase. Each phase relates to how close the drug is to being both approved for use by regulatory authorities, and proven clinically safe and effective for its stated purpose. Each phase has a different purpose and helps researchers answer a different question. Phase 1 trials are often the first trials for the treatment under study done in humans (with prior testing being done in lab animals). Testing in phase 1 trials is done in a small group of people (20 to 80) to determine safe dose ranges, and begin to identify side effects. Phase 2 trials involve a larger group of participants (100 to 300) to determine the treatment’s effectiveness and to further evaluate its safety. Phase 3 trials test with large groups of people (1,000 to 3,000) to confirm the treatment’s effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that

will allow the treatment to be used safely. Phase 4 trials are post-marketing studies that identify more information about the long-term effects of new drugs and treatments. Phase 4 studies involve patients that have been taking the new drug for a considerable period of time and can continue throughout a drug's lifetime of active medical use.

People participate in clinical trials for a variety of reasons. Many, with and without disease, participate to help others and to contribute to moving science forward. Individuals with an illness may also participate to receive the newest treatment. Clinical trial participants often see clinical trial staff more frequently for study visits than they would normally see their physician for standard care. Some see this additional care and attention as a benefit. Participation in clinical trials is key as they offer hope for many people and an opportunity to help researchers find better treatments in the future.

The Continued Pursuit of Biomarkers in MS *By Farren Briggs PhD, ScM*

Over the last several decades researchers have greatly increased their efforts to identify biomarkers for multiple sclerosis (MS). Unfortunately, only a few of these studies have been successfully translated into clinical tools – but with the rapid acceleration of new methods to detect proteins, gene transcripts, and other molecules, it is likely there will be great advances soon. In general, a biomarker must have a few key traits: it must **1)** be reliably measurable, **2)** be able to detect those with the trait of interest (must be sensitive), and **3)** not falsely determine those without the trait of interest as having it (must be specific; therefore low false positives).

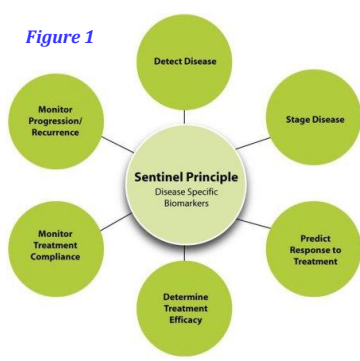
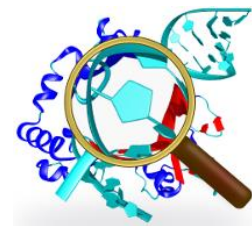


Figure 1

Biomarkers can play a critical role in several aspects of clinical research and hopefully, in clinical care (Figure 1). Of particular relevance to MS would be the ability to detect the disease (improving diagnosis), determining stage of disease (disease transition), predicting response to disease modifying therapies, and overall enhanced individual and group risk assessments. This month there were several studies reporting on research of biomarkers for various aspects of MS, but I will focus on only one study, which presented impressive findings.

This biomarker study, by Barbour *et al*, and published in the *Annals of Neurology*¹, had 3 research questions: **Q1)** Can we differentiate MS from non-MS? **Q2)** Can we differentiate relapsing remitting from secondary progressive MS? And **Q3)** Can we differentiate primary progressive from secondary progressive MS? The researchers sought to tackle these questions using measures on 1,128 proteins detectable in cerebrospinal fluid (CSF) from 310 individuals, who were split into a discovery and replication group. Using a suite of statistical tools, the researchers were able to near perfectly classify MS from non-MS samples using measures for 22 proteins, with an accuracy of **98%**! The non-MS samples came from healthy individuals, individuals with non-inflammatory neurological disorders, and individuals with other inflammatory neurological disorders. The 22 signals were predominantly immune-cell specific biomarkers – which is not surprising, but the specific combinations highlight new immune system relationships that are truly intriguing. Also important to note is that the biomarker set not only distinguished MS from healthy donors, but also from other neurological disorders.

The researchers were also able to do a very good job distinguishing relapsing remitting from secondary progressive MS (accuracy of **88%**). The proteins that most distinguished these stages of MS were markers predominantly released by cells in the central nervous system, especially neurons and oligodendrocytes. This reinforces the notion of the contribution of repair mechanisms and neurodegeneration (versus inflammation alone) in contributing to the change in disease course.



And last but definitely not least, primary progressive and secondary progressive MS were indistinguishable – the proteins did no better at classifying individuals in these groups than flipping a coin would have. These results are so fascinating. This, to me at least, suggests the underlying biological processes contributing to both stages of MS are not that different!

Overall, this project has highlighted multiple biological processes contributing to **both** MS onset and MS progression – and that CSF, though not easily accessible, holds great promise for MS biomarker development. What would be interesting is to see if others can now develop an equivalent biomarker panel for blood (which is easily accessible) using this knowledge.

1. <https://www.ncbi.nlm.nih.gov/pubmed/29059494>

New technology for MS diagnostics

[IQuity](#) is a start-up company, and ACP Repository partner, that is developing diagnostic methods for several diseases, including autoimmune disease. They recently launched a novel, blood-based diagnostic test for multiple sclerosis (MS), which could have a significant impact on the efficiency of diagnosis of the disease, allowing patients to be diagnosed and treated before significant tissue damage occurs. The Accelerated Cure Project's Repository samples have played an important role in the development of this technology, which can reduce the time for diagnosis to 7 days, a significant improvement over current diagnostic methods. Existing diagnostic methods consist of evaluation of clinical symptoms, analysis of cerebrospinal fluid and magnetic resonance imaging of the brain and spinal cord.

This new diagnostic test is based on a novel technology that allows the analysis of the activity of a patient's genes in a single drop of blood and gives a 90 percent accuracy rate in identifying disease. This "gene activity signal" can identify the presence or absence of disease at the cellular level. The technology was initially discovered and developed at Vanderbilt University by Dr. Tom Aune and his research team. IQuity, based in Nashville, Tennessee, has licensed the Vanderbilt technology and developed it further resulting in a tractable blood test called IsolateMS™. This work has been funded by \$2 million in seed money from the National Institutes of Health.

IQuity's new diagnostic test detects levels of specific molecules, called ribonucleic acids (RNA), in human cells. Proteins form the "building blocks" for human tissues and also regulate cell and tissue function in health and disease. Proteins are encoded by our genes. When individual genes are "read", the DNA code is transcribed ("expressed") into RNA. Some of these RNAs, called messenger RNAs (mRNAs), are "translated" into proteins including structural, enzyme and regulatory proteins. Other RNAs (regulatory RNAs) function as molecules that control the expression of genes. Both classes of RNA have been shown to exhibit distinct variations in expression that are characteristic of health and disease. MS has its own unique expression pattern that correlates with disease stage.



The IQuity diagnostic test is designed to provide a profile of RNA expression in MS which as Chase Spurlock, IQuity's CEO, has described, "...paints a molecular portrait of what's going on in an individual's cells at a given point in time, which can provide a picture of the presence of a disease." Dr. Spurlock explained further, "For diseases like multiple sclerosis, RNA signatures are detectable at the earliest stages of the disease



before extensive tissue damage is observed using more traditional diagnostic methods. Through machine learning, we were able to create computer algorithms that are capable of analyzing the RNA markers in a patient's blood sample, enabling providers to more accurately and quickly determine whether a patient does or does not have the disease." To learn more about iQuity's unique diagnostic tool for providers in the autoimmune field, visit <https://www.news-medical.net/news/20170320/Linking-RNA-to-autoimmune-diseases.aspx>

It is interesting to consider what role these diagnostic RNAs might play in the MS disease process. As mentioned earlier, many of the RNAs identified through Dr. Aune's work are messenger RNAs, which encode regulatory and other proteins that are known to perform specific functions in the inflammatory cascade and the immune response. A publication from this work showed that the RNA profiles were "highly dynamic as a subject progresses from *clinically isolated syndrome, through clinically definite MS to MS disease of some duration."¹

More recent work from the Vanderbilt group, using additional ACP Repository samples, has identified regulatory RNA disease markers that are now being phased into IQuity's diagnostic tests. These molecules control the expression of genes, and show distinct and consistent changes in MS disease².

These regulatory RNAs are particularly interesting when considered in the context of what are called "MS susceptibility loci." These are variant sites within the human genome that have been previously identified in a specific type of genetic study called genome wide association (GWAS). Over 200 genetic markers have been identified in DNA samples isolated from over 47,000 patients (including ACP's Repository donors) that are "associated" with disease. Some of these GWAS-identified loci encode proteins that are involved in the immune and

inflammatory responses. Interestingly, the majority of these loci do not fall within protein coding genes. One possible explanation for this is that these non-coding MS variant loci may encode RNAs that regulate, directly or indirectly, the expression of genes that encode the protein molecules that constitute the immune and inflammatory responses.

Consistent with the ACP policy of requiring that data be returned, some of the Vanderbilt data has been received by us, with more to come. This returned data is available on an “open source” basis to all investigators and has already been provided to several scientists who are performing further analyses on the data. These data are also being used by investigators to “dig deeper” into the patient samples that were used by Dr. Aune and his team. This additional research will provide an even greater understanding of patient gene activity during the MS disease process.

Every year 15,000 new MS and 45,000 clinically isolated syndrome diagnoses occur in the U.S. The ACP team is proud to have played a part in the groundbreaking discoveries of Dr. Aune and his team at Vanderbilt that enabled the launch of an exciting, new MS diagnostic blood test.

*Clinically isolated syndrome (CIS). A first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and/or demyelination.

1. Tossberg et al. Journal of Clinical Informatics 2013, 3:18
2. Aune et al. Journal of Autoimmunity 2017, 81:99

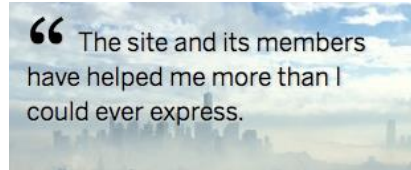
Partner Spotlight - Smart Patients

Smart Patients is a unique online community where members and their families dealing with a variety of illnesses can learn from each other about treatments and challenges by sharing questions and concerns. While providing members a safe environment to interact, this connected network also helps the healthcare system learn from all participants in order to serve them better. They do this by providing clinical providers



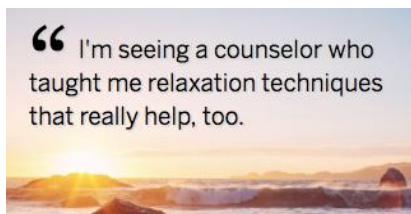
and researchers with an opportunity to ask the Smart Patients community important questions and receive their feedback.

The founders of Smart Patients, Gilles Frydman and Roni Zeiger, believe that tapping into the knowledge created by networks of engaged people can significantly improve healthcare. They recognize the wisdom gained by individuals as they live with their disease as a great resource and created a high quality forum for members to share their expertise with one another. This same forum also serves as a connection with the scientific community so that researchers have access to patient patterns and insights in order to determine the causes and improve treatment of diseases. The original focus of Smart Patients was in oncology but they have since expanded to working with people affected by many different diseases. Patients, family members, friends, patient advocates, and survivors are all part of the Smart Patients community. Members learn from conversations and can help each other on a wide variety of topics, including treatments and side effects, where to find help, how to cope with disease, end of life, research and clinical trials.

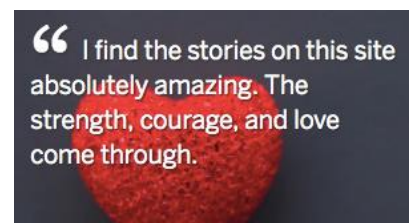


Smart Patients differs from other social communities in a number of ways. With Smart Patients there is no marketing or advertising, and members need not worry about [social listening](#) or [web scraping](#). Protecting the privacy of participants is paramount as described in their [Privacy Policy](#). Smart Patients asks for explicit permission from members before sharing any information that identifies individuals with partners such as medical centers or pharmaceutical companies. [HIPAA guidelines](#) are used to remove identifiable information (for example, names, locations, or email addresses) before it is shared. The Smart Patient privacy policy describes how anonymous information may be gathered and used.

Smart Patients [communities](#) are identified by disease or condition. New members are invited to join a community where they will receive help and advice from other patients and caregivers who have experience with their condition. After joining a community, participants can see conversations started by other members of their community and join in any that interest them.

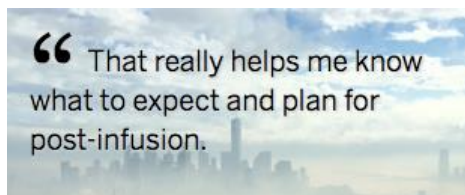


Conversations on topics that span disease



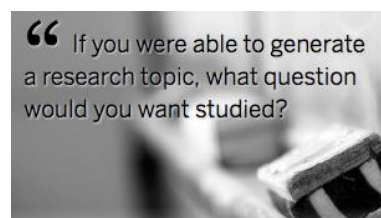
boundaries, such as fatigue and caregiver stress, can be viewed by members of many disease communities so that patients can also learn from people with other diseases about these common topics.

Sometimes members of Smart Patient communities need help with difficult or misunderstood topics during their conversations. In order to facilitate these interactions, Smart Patients offers “Ask the Expert” sessions in which experts in the topic of interest are invited into a community to answer questions. These sessions can complement what patients learn from their health care team and help them prepare questions for their next appointment.

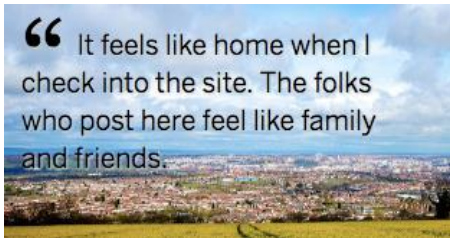


Clinical trials are a way for researchers to test promising new drugs and treatments, and gather information about their safety, effectiveness, dosage, and side effects. Many treatment options, especially for cancer and multiple sclerosis, are available only through clinical trials. Smart Patients believes that clinical trials should be incorporated into care options where appropriate, not just a last resort. They try to make it easier for participants to learn more about trials by having conversations about them. The Smart Patients website includes a [clinical trial search engine](#) that makes it easy for members to find trials, track clinical trials that are of interest, and discuss them with the community.

The Accelerated Cure Project is collaborating with Smart Patients by connecting the [iConquerMS™](#) portal with the [Smart Patients MS community](#). Through iConquerMS, researchers can connect with people with MS and also receive data collected via the iConquerMS portal in order to gain a better understanding of the patterns of multiple sclerosis and gain insight into its disease process. iConquer MS also offers its members the opportunity to provide input on future areas of research. The Smart Patients MS community connects people with MS with each other to share, interact, and learn from each other in a safe, supportive environment. This powerful collaboration not only addresses the needs of people with MS, but also extends the ability of iConquerMS to connect researchers with patterns and insights to figure out the causes of MS, determine who will respond best to various treatments, and find new and improved treatments for the disease.



The potential benefits of people sharing information with each other are profound. Smart Patients' mission is based on the belief that individuals become experts in their conditions and this knowledge can be an important resource to improve healthcare. They provide a



supportive, safe environment for participants to interact and learn from each other. This interaction offers members reassurance that they are not alone. Smart Patients also helps the healthcare system learn from patients by connecting patients and caregivers.

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