Webcast Transcript
From the Frontlines: New Avenues In MS Research for 2013
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PANELISTS
Dr. Timothy Coetzee, Chief Research Officer of the National MS Society

Dr. Stephen Krieger, Neurologist, Corinne Goldsmith Dickinson Center for MS and Assistant Professor of Neurology at the Mount Sinai School of Medicine

Dr. Ellen Mowry, Assistant Professor of Neurology at Johns Hopkins University

Dr. James Salzer, Professor, Departments of Cell Biology and Neurology; Co-Director of the Center of Excellence for Multiple Sclerosis at NYU Langone Medical Center

PRESENTATION
Kate Milliken: Hello, and thank you for joining the National MS Society's Live Webcast. This is From the Frontlines: New Avenues In MS Research for 2013. I'm Kate Milliken, your moderator, and I've been living with MS since 2006.

As we begin 2013, there is much to look forward to. We are excited to have several emerging therapies that are advancing through the pipeline, as well as progress towards finding ways to restore function and improve quality of life.

The National MS Society is propelling research forward with a comprehensive strategy. This year, we dedicated almost $44 million to support over 350 new and ongoing projects, everything from discovery research to therapy development.
New projects the Society launched include the International Progressive MS Collaborative, which is the largest effort to date to speed research to stop progressive forms of MS; a clinical trial testing whether green tea extract can protect the nervous system from damage and new studies into the potential of adult stem cells and umbilical cord cells as a source of nervous system repair cells.

Today, we're here to address questions that we know matter to our viewers, such as what research progress was made during 2012? What is on the research horizon for 2013? What progress has been made to repair MS damage? And what is the microbiome, and what does it mean for MS?

To help us explore these issues, I am pleased to be joined by four panelists who recognize these important efforts and work tirelessly to advance research, knowledge and clinical care. Let me introduce them.

Dr. Stephen Krieger, Neurologist, Corinne Goldsmith Dickinson Center for MS and Assistant Professor of Neurology at the Mt. Sinai School of Medicine. Dr. Krieger is a clinician and educator, and takes part in a number of MS clinical trials.

Dr. Krieger: Thank you for having me.

Kate Milliken: Next, we have Dr. James Salzer. Dr. Salzer is Professor of Cell Biology and Neurology, and Co-Director of the Center of Excellence for MS New York University Langone Medical Center. He is currently investigating the signals required to drive new myelin sheath formation in MS, including the potential role of stem cells in the brain as strategies for myelin repair. Thank you.

Dr. Salzer: Hi, Kate. Pleased to be here.

Kate Milliken: Thank you. Great to have you here.

In addition, we have Dr. Ellen Mowry. Dr. Mowry is the Assistant Professor of Neurology at Johns Hopkins. In addition to other ongoing research, she leads a Society-funded clinical trial to see whether Vitamin D supplementation can reduce MS disease activity.
**Dr. Mowry:** Thanks for having me, Kate.

**Kate Milliken:** You're welcome. Finally, we have Dr. Tim Coetzee. Dr. Coetzee is the Chief Research Officer of the National MS Society. Dr. Coetzee leads the Society Global Investment in MS Research. He is responsible for a diverse portfolio of research initiatives and recently spearheaded an effort to establish a global collaboration focused on research in progressive MS.

**Dr. Coetzee:** Glad to be with you, Kate.

**Kate Milliken:** Thank you. It's great to have all of you guys. So, let's get this discussion started.

We have a number of questions that we've already received from viewers that we'll be answering. For those of you watching live, you can submit questions during the webcast and we'll try to get to as many as possible.

So, Dr. Krieger, let's begin with you. What would you say are some advances that have happened in 2012 that you think will positively affect people living with MS?

**Dr. Krieger:** Well, Kate, I think just as a testament to what we're doing in the field of MS, it's been a very exciting past couple of years and 2012 was no exception. A lot of things have happened in this past year.

A number of our medicines that are coming through clinical trials, finished those clinical trials in 2012, which is extremely exciting because this is the final stage of testing before a medication can become available. One finished its clinical trials and was approved by the FDA just this past fall, in October. It's a medicine called teriflunomide, which was approved for relapsing-remitting MS and relapsing forms of this disease.

In addition, when we use a medicine called natalizumab, we are trying to maximize the benefits of a medicine like this against some of the risks that go along with it.

So, one of the developments this past year, in 2012, was a blood test for something called the JC antibody. This allows us to figure out who's at risk for certain adverse events and who is at much less risk so we can pick the right...
medicine for the right person. It's sort of a paradigm we're trying to develop as we move forward in this disease.

**Kate Milliken:** Wow. More specific treatment.

**Dr. Krieger:** Absolutely.

**Kate Milliken:** Dr. Coetzee, from your perspective as a kind of overseer of this world, what did you see in 2012 as happening?

**Dr. Coetzee:** Well, you know by what Steve mentioned, having new treatments coming is an important step.

We have thousands of researchers working around the world and the way researchers get the word out is they publish papers. There were 4,000 papers published in 2012, which is a lot of important research.

You know, I think the other thing that I'd want to emphasize is that besides treatments that are therapies, we're also looking at things like rehabilitation, addressing cognition, addressing symptoms; really looking at the whole person.

I think that's the other aspect in 2012, we made some steps forward in applying new ways of addressing MS. Now, the conversation between the physician and the person who lives with MS isn't just about what therapy to take but what other strategies we can use to manage our disease.

**Kate Milliken:** Yes. A little bit more of a holistic approach.

**Dr. Coetzee:** Absolutely.

**Kate Milliken:** Dr. Mowry, in speaking of kind of the holistic look, one of the things that have come up is Vitamin D. It's something you've been largely involved with. So I'm curious in that realm -- Vitamin D -- what is some of the progress that's been made?

**Dr. Mowry:** That's great. So, we've known a lot about Vitamin D for some time. We've known for some time, for example, that MS is more common the farther away from the equator we are and that sunlight is also less common in that group of people. People have looked at Vitamin D since we know most of our Vitamin D does come from the sun.
One group in Harvard demonstrated that among members of the military, those with the highest levels of Vitamin D were actually protected from subsequently getting MS.

Studies that we've done more recently show that among people who already have the disease, lower levels of Vitamin D are associated with increased risk of attacks, the association was pretty strong actually.

So, in children, for example, higher Vitamin D level by 10 nanograms per milliliter -- which isn't very much -- was associated with about a one-third reduction in the risk of subsequent attacks. A similar strength of association was shown in adults between higher levels of Vitamin D and developing new MS spots on the MRI scan.

We have some recent data as well showing higher levels of Vitamin D may be associated with less damage to the nerves themselves, which is really important for people with all kinds of MS because we think it is that underlying nerve damage that might be what happens to cause progression of disease.

Kate Milliken: I happen to know from the National MS Society website that Vitamin D is one of the biggest hot topics that you want to know about it.

Dr. Salzer, obviously MS is largely kind of influenced by myelin. So, can you give kind of a brief explanation of what myelin is?

Dr. Salzer: Sure. So, myelin is an insulation that surrounds nerve fibers. It's made by a cell in the central nervous system, the brain and spinal cord, called the oligodendrocyte. MS is associated with loss of myelin.

So, what does myelin do? Myelin is important for speeding the trafficking of electrical impulses and information down a nerve. It's critical for its nerve conduction. It's critical for the survival of the axon, the nerve fiber. It provides nourishment and protects the nerve fiber.

When you have MS, in an acute attack one of the first things, the hallmarks, would be the loss of either the speed of conduction or blockade in impulse propagation. That would be associated with a neurologic deficit.
To come back to Ellen's point, in patients that have the disease for a long time one of the complications is frequently loss of the axons -- the damage to the axon. That's thought to be because they've lost their myelin and so they're more vulnerable. And that is certainly in secondary-progressive phase a major source of morbidity in the disease.

Kate Milliken: Where do you come in, in terms of your research, with stem cells and myelin?

Dr. Salzer: First of all, I would say stem cells are a general topic in the field of medicine. It is an explosive area and it's going on across all disciplines.

Our own research is, we do many things, but we have a project that we started with the support of the MS Society. Effectively, one of the questions, it turns out, there are stem cells that are resident within the adult brain. There are also many progenitor cells, so they are slightly different but they are both immature cells that can repair.

We looked specifically at the stem cells and found that, in a mouse model, they are recruited into the lesion site and do repair. Moreover, we found that we can root them in more effectively by targeting specific proteins. We may come back to that later.

Kate Milliken: Absolutely. Dr. Coetzee, what are some of the research priorities that the National MS Society has?

Dr. Coetzee: Sure. When we think about MS, obviously, our vision is a world where there's no MS. Our research priorities are really around stopping the disease, restoring what's been lost and ultimately ending the disease forever. Those are the three big buckets -- stop, restore and end.

When we think about our research priorities and you take those big three buckets and you drill down into them, we're looking in funding work in how do we stop progression and develop new therapies that can really address the progressive forms of the disease.

It's focusing on work like what Jim is talking about, restoring what's been lost, repairing myelin, rebuilding the brain, whether it's stem cells or some sort of natural rebuilding process that we can facilitate.
We also want to look at rehabilitative strategies, figuring out how to bring a holistic approach so that we can address both function as well as symptomatic treatments and really address those aspects of the disease.

Ultimately, I think what everybody wants to know is what are the risk factors and when are we going to solve this disease? How are we going to cure it? And to do that, you really need to pursue a lot of very interesting and important leads.

Covering all of that, the umbrella, is that we need a lot more researchers like Dr. Krieger, Dr. Salzer and Dr. Mowry. Our focus is to both address these critical research areas but also create bigger capacity in the world to solve this disease faster.

Kate Milliken: A lot of stuff you mentioned there, one thing for sure, even that I've heard from my perspective because I'm living with MS, is progressive MS. A lot of people with progressive MS are angry that they're not being treated or addressed or looked at.

I'm curious, Dr. Krieger, can you explain why so many therapies are on the market and none of them are working for progressive MS? Why is that?

Dr. Krieger: Well, I think it's a good question. Different forms of multiple sclerosis can be defined in different ways. We commonly talk about relapsing-remitting MS, which is the form that most MS takes, especially in its early years of relapses or attacks of neurological dysfunction followed by remissions.

When we talk about progressive MS, what we mean is that rather than being characterized by these relapses and remissions, the condition gradually worsens. Folks develop new symptoms incrementally and accumulate symptoms over time and can accumulate significant disability over time.

It is certainly frustrating for both people living with MS and, I think, for those of us who are taking care of them and trying to do the best for them.

Progressive MS has been a challenge for us because most of our medicines to date have worked on the immune system. They work to teach the immune system to leave the myelin alone, to leave the central nervous system alone. That's one of the ways our medicines stop relapses from happening, they stop lesions from forming, as Dr. Mowry was describing.
But in progressive MS, that is less the driving force. It doesn't seem to be as actively inflammatory of the form of the disease and so our anti-inflammatory medicines don't seem to stop it with as much potency.

I think there are a lot of things that we don't yet understand about progressive disease. The MS Society has worked diligently to try and tease out why this worsening occurs. Why do folks with progressive MS lose their axons, as Dr. Salzer was describing? Is it because they've lost their myelin and lack nourishment? Or is there something else going on -- a whole other process that we haven't yet fully understood?

It's hard to develop the best medicines for something that we have an incomplete understanding of.

So, I think we are trying to learn more about progressive MS on one hand and on the other hand, we're trying to develop medicines that will address it. Those two things are happening together, they are happening in tandem.

I'm encouraged by the fact that in 2012 and in 2013, there are a number of clinical trials looking at medicines to try and stop progressive MS, both in what we call primary-progressive and secondary-progressive MS, as well as a whole host of investigations at the lab level to try and better understand those forms of the disease to slow them down and to restore function, as Dr. Coetzee said.

Kate Milliken: Dr. Salzer, I'd love to open that question to you, too. From your perspective, how are you dealing with progressive MS?

Dr. Salzer: So, I would distinguish, and I defer to Dr. Krieger, the primary and secondary distinction; I think our focus and the focus of people that are interested in restoring function - not to slight primary-progressive MS - but there's a general sense that that secondary progression reflects the fact that there's been a failure to repair and to re-myelinate. So, the axons are still there but they're vulnerable. The goal is to come up with strategies, stem cells or otherwise, to try and promote repair.

Then a second aspect of that, of course, is nerve protection. There's a period of vulnerability and if we can sustain the integrity of the axon, even when it's lacking a myelin sheath, then you eventually, even if remyelination is slow, there's the ability to remyelinate it.
Our work in our own lab is more on the myelination side but there is a lot of interest in many labs around the world in neuro-protection. I'll just stop there.

**Kate Milliken:** Great. So, we actually have a question from the web from Christen. I will start with you, Dr. Coetzee, but I think Dr. Mowry, you might have something to add to this, too. What do we know about the prevention of MS?

**Dr. Coetzee:** That's a good question. I think preventing MS is part of that "how do you end this disease forever." I think part of it is trying to figure out what makes a person, puts a person at risk for developing the disease. So is there some sort of genetic or environmental contribution? And what are those genetic and environmental factors that make a person more susceptible to the disease?

We funded, through a lot of international work by the Society and government funding, a large study that teased out what are some of the genetic basis for what contributes to MS. I think things like exposure to Vitamin D, exposure to potential viruses really can set a person up for the developing of the disease.

I think as we think about prevention, we need to tease those out before we can actually think, begin to sort of proactively look at preventing the onset of the disease.

But I will say, and I'd like if Ellen could comment on this, that Vitamin D is one of those areas where people say if we were to address the Vitamin D issue, could we prevent the onset of the disease and there's been some suggestion of that. I think that's an exciting possibility that we could think about. I'll let Dr. Mowry address that.

**Dr. Mowry:** Great. I try to think about MS as a perfect storm of genes and environment coming together. The combination of genes and environment is probably different in each person with MS. So, even if you have normal Vitamin D, you still could get MS.

We definitely need to understand better what these environmental factors are that underlie MS. Although we know a few of them -- low Vitamin D, probably infection with Epstein-Barr virus, and cigarette smoke exposure. My guess is that there are many more factors that remain to be uncovered. If we're
able to uncover those, we'll be better able to address things from a preventive standpoint.

What can we do with the information we have now? I certainly encourage my patients who have children to consider talking with their pediatricians about whether their children should be on Vitamin D.

We don't have a study yet that shows that taking Vitamin D will prevent the disease. Vitamin D isn't safe for everyone and so I don't recommend, just as a blanket statement, that people take it. But, certainly, I think it's something worth discussing.

Cigarette smoking is also a very easy, low-hanging fruit. If you're a smoker with MS, if you have children that are at risk for MS, abolishing smoking…

Kate Milliken: It's a proven correlation, right?

Dr. Mowry: Yes. That's right. Abolishing smoking in the household is one easy step that people can take to reduce their risk.

Kate Milliken: That's true. There was something you were going to add?

Dr. Krieger: I was just going to add that I think there was this old school idea that we would ultimately find the cause of MS. I think that as we've understood the biology better, and recognizing that MS is such a diverse condition, I don't think any two people have precisely the same experience with it. I think it's, in a sense, naïve to think that we're going to find one cause of something that is so diverse and affects people in so many different ways.

I think this idea of a perfect storm is right on. There's a lot of factors that are actually in play here. I think it deserves to be looked at from a lot of different avenues at once.

Kate Milliken: As somebody, again, living with MS, this perspective changing feels very hopeful because it's opening a spectrum. Right? That maybe there are other things that can move forward faster.

So, Dr. Mowry and Dr. Krieger, you both have received Sylvia Lawry Fellowships from the National MS Society. I'm curious how those have affected your research? Dr. Krieger, let me start with you.
Dr. Krieger: You know, I'm very grateful to the MS Society because they supported me when I was starting out in this field. I got into the field of MS, in part, because I was inspired by the stories of folks that I was involved in taking care and I wanted to be a part of that.

I was also inspired by the amount of work that was going on in the field now. I just felt that this was an incredibly hopeful time and something that I could really, hopefully, contribute a little bit to.

The Sylvia Lawry Fellowship that the MS Society supports, trains people to think about research in MS and how to conduct clinical trials and how to think critically about them. I think my role is, to some extent, is a researcher, obviously but I also think of myself as a clinician and an educator.

I think one of the ways that the Lawry Fellowship has helped me as a clinician and as an educator is to think really clearly about what it takes to prove that something is meaningful in MS. What it takes to prove that something works and how to separate, what I often tell my patients, how to separate myth from fact.

I think being able to do that requires being trained in understanding the science behind MS, and how studies are done and trials are performed to prove that something works.

It's allowed me to teach my patients about that. It's allowed me to teach the residents and other folks that are studying neurology that I work with to think critically and to be sort of very skeptical, but in the best possible way to really understand how we have used data to tell patients what they ought to do to make themselves better, to protect themselves against the disease. I think the Lawry Fellowship sort of set up my trajectory in that way, and I'm grateful for that.

Kate Milliken: Dr. Mowry?

Dr. Mowry: I echo most of Dr. Krieger's statements. I think, as clinicians, we spend a lot of our time training in how to work with patients. Certainly, that's the most important part of our jobs and the part that most of us cherish as first and foremost a priority.
The Fellowship itself, though, allows us to cut out some time from that training to really learn critically about how to do research well. I think when we're trying to do research to delve into some of these more complicated stories about risk of a disease and how to impact a disease in the long term in terms of prognosis, you have to have a good understanding of how to do research well.

The Sylvia Lawry Fellowship definitely gave me that time as well as the training to do that. In fact, one of the courses I took as part of the Fellowship, was a clinical trials course. That's actually when I designed the Vitamin D trial that I'm now conducting with the help of the National MS Society. It's been wonderful.

**Kate Milliken:** It's funny to not be in your world and hear about research. In some ways, I think people know that research is where it's at and it's making progress but on the other hand, it's a very frustrating thing not to understand. Like, for example, you are doing this amazing Vitamin D trial, you are still enrolling patients and you think, "God, what's taking so long? Why isn't this easier." So, how would each one of you respond very briefly to the devil advocate's side of your research if you want to look at it in kind of a negative way?

**Dr. Krieger:** Why does it take so long? Why is it hard?

**Kate Milliken:** Why does it take so long?

**Dr. Krieger:** Well, I guess I think we can all probably say something about that. I think one factor is that, you know, we don't completely understand MS yet. We're working on designing treatments for something that we have an incomplete understanding of. We're trying to build a foundation and the house at the same time, in a sense.

Another thing is that many of our treatments are preventative medicines. They are here to keep people well for the long term. And when I talk about taking care of somebody with MS, I talk to them about what their life is going to be like in five years, and in 10 years, and in 20 years and longer.

The clinical trials that we do take a couple of years just to try and show that we're really making a difference. So if it takes a few years to do each clinical trial, the sum total of that is it takes an awfully long time to prove that
something works, prove that it's safe and get it approved so that we can actually use it. I think it does take too long. But it's a huge amount of responsibility to develop things that are going to be safe for people for the long term. So, I think that's part of it.

Kate Milliken: Dr. Salzer?

Dr. Salzer: I'd echo a lot of what Stephen just said. Obviously, I'm more on the discovery side of the equation. Things that, in the world of animal models that look very promising, don't always translate. Then there's also the issue of, for example, taking stem cells, which it seems like a very attractive strategy and there are initial efforts to go forward with that. You have to worry about off-target or other effects that are real concerns, including, for example, the possibility that you get over-proliferation and maybe even a tumor if you're injecting cells.

So, while I think it's very promising, you have to balance the promise against the potential of what damage it might cause and of course, unexpected difficulties for the patient.

Kate Milliken: Anything on that?

Dr. Mowry: I could add that starting up a clinical trial is a little bit like planning a wedding. It seems like it should be pretty straightforward because you know it needs to happen. But in reality there's a lot of work that has to go into it before you can actually even begin.

So, there's a safety board at any institution that's performing a study that needs to read carefully through the protocol that you're proposing to make sure that they don't see any major red flags that will make it dangerous to enroll people. There is a lot of setup the same way that you need to order your cake and do the tastings. There's just a lot of work that goes into the starting up the trial.

It can take many months or even a year or more to start a trial. Then it takes a long time to recruit people into the study. Most studies have a restricted set of criteria for people who can join the study. So it's not like I can go to my entire population of people with MS and say, "Please, will you join my study?" I have to wait for the right people to come. Then they have to be willing and able to join the study, too. It does take some time to recruit.
Then once the study is even done, you have to get all the data together, have a statistician come help analyze the data.

So, in order to make it the safest possible process, I think, for the patients involved and to make sure that you do the best job and really get all the results down pat before you present your findings to the public, it does take some time.

**Kate Milliken:** Speaking of trials, we have a question from the internet from Barry. And this is for Dr. Krieger. I have progressive MS. Are there any clinical trials I can participate in?

**Dr. Krieger:** That's a good question. So, much like Dr. Mowry was saying that trials are sort of their own world. They have certain characteristics that they look for to try and get the right people into a particular trial to get the answers that they're looking for.

There are definitely clinical trials that are going on right now for medicines for progressive forms of MS. It doesn't mean that everybody would qualify or would fit in for every trial but they're definitely out there. As Dr. Coetzee said, the Society is supporting a lot of them and is involved in sort of coordinating and disseminating a lot of information about these trials.

I think you can find information about clinical trials for progressive MS, number one, on the web at www.clinicaltrials.gov. If you search clinicaltrials.gov for the key words, like progressive multiple sclerosis, it'll provide a list of what sort of studies are ongoing, which ones are recruiting people and where the sites are that they're looking for.

**Kate Milliken:** Clinicaltrials.gov.

**Dr. Coetzee:** Kate, I think that one of the things I'd add is certainly virtually every drug that's been approved for MS, as Steve alluded to, has been tested in progressive MS and didn't work for a lot of different reasons. In part, because of what we don't know about progressive MS.

I think the good news is that the research community, there isn't a meeting that I don't go to that people are talking about how do I tackle progressive MS. How do we move into this area because we've seen what we've been able to accomplish in treating relapsing-remitting MS. So, really, we've taken that
experience, which took a few years to develop, and we're really saying we know how long it took to develop something for relapsing-remitting MS. Now, how do we do this for progressive MS but faster?

How do we think about clinical trials that can tell us something about what's happening in the disease because it's not just us, researchers aren't the ones that start talking amongst ourselves that are going to determine what's effective. It's going to be in organizations like the FDA and they have pretty strict rules about what would be beneficial for a patient.

In order to get that approval, you have to show that it actually has a benefit and that's one of the questions that we have to solve is how do we demonstrate that something is actually having an impact on a person's disease? That's a high bar but what excites me is that all the researchers are talking to each other about this. People aren't working in isolation. I think we're going to actually be faster.

Kate Milliken: That's a change.

Dr. Coetzee: A total change. The community is actively engaged saying how do we solve this problem, recognizing that it's not an easy problem to solve. But they're very focused and that's what excites me about what we're able to do in the progressive field.

Kate Milliken: Dr. Salzer, I'd love to ask you just a little bit more about your research. So, you're working with stimulating myelin either in the brain or doing it outside of the brain, cell therapy. So, I'm curious about this.

Dr. Salzer: I'll just say I'm the tip of an iceberg of a much larger and incredibly talented worldwide community that is actively engaged.

There are two general strategies one could consider and I think there's been exciting progress in both of these. One is there are cells in the brain that are capable of repair, we've talked about those and they are stem cell progenitors. One of the challenges is understanding why they can't, they don't repair because we know, surprisingly, maybe 5% of the cells in your brain are these progenitor cells. They probably have other functions but they're frequently stalled and there's been a lot of progress in understanding what are some of the brakes.
If you take the metaphor of a car that's parked, you have to both release the parking brake and step on the gas pedal. There's progress both on the gas pedal side and in relieving the brake side from many labs. So far, looking promising in mice and, obviously, there's a lot of plans to move this into people.

Then on the replacement side, which is not what we do, but there has been amazing progress, I think; one of the exciting things we've talked about some of the great advances in the last year. One of the really exciting things to me is that people have been able to take these progenitor cells, embryonic progenitor cells, put them into a mouse that's completely deficient in myelin and effectively humanize that nervous system and repair the mouse's nervous system. Those mice now, instead of dying, they look completely normal.

It's sort of a proof of principle and there's now the first reports of trying to take that kind of approach to the pediatric patient population in a similar inherited disorder. I think we're at the very beginning stages of what I expect to be a really exciting period in MS research of taking things into the reparative phase.

Kate Milliken: Actually, literally repairing the nervous system.

Dr. Salzer: Literally. Yes.

Kate Milliken: Wow. Anything else anyone wants to add to that?

Dr. Coetzee: I would say what is amazing to me is that in probably less than five years we've gone from having what was a theoretical discussion about repairing the nervous system to now, actual clinical trials of drugs that could potentially repair the nervous system in the human beings; these kinds of proof of principles studies.

The important thing is to be able to have tools like MRI and other types of imaging to actually be able to look inside the nervous system of the individual to see are we having a benefit.

Just a few years ago we didn't have those tools. So I think that you're seeing the confluence of lots of different research. I think that's where you're getting collaboration between clinical scientists and the laboratory researchers that is
really powerful and I think exciting, and going to shorten the development timelines. I think that's a lot that we can be excited about.

**Dr. Salzer:** If I could just make one comment about the collaborative aspect. I give the MS Society a lot of credit for using funding to establish collaborative centers, not only overseas but within the US; it's really catalyzed interactions between researchers. I would say in our own program, the stem cell program that I've alluded to, that was part of a collaborative center award, it allowed us to take a flier and it brought together people with varying expertise. So, I want to give the MS Society a lot of credit for having that kind of vision and bringing collaborative science together.

**Dr. Coetzee:** Thank you.

**Kate Milliken:** You've seen a huge difference in how much progress is made.

**Dr. Salzer:** I think it's exactly what science should be doing. You want to lower the barriers and bring not only scientists from different disciplines together but also clinicians and scientists.

**Kate Milliken:** That's great, okay. We have a question. This is actually Jamie who is asking all of you guys, what does the future look like in regards to research on the genetic link between a parent with MS and their possibility of passing it on to their children? Dr. Mowry, I'll start with you.

**Dr. Mowry:** Well, I think a lot is known already about MS genetics. We know that there's a substantial contribution from genes in terms of MS risk but that isn't the whole picture. For example, if I had MS and I had an identical twin, her risk of getting MS would be, at most, about 30%. A person’s risk of getting MS if he or she has a parent with MS is much lower still.

So, I think what we're starting to realize is, although genetics is certainly very important, there is a lot of contribution of environment and other factors as well. I think the studies are trying to focus on what is that combination of factors rather than looking at either genes or environment in isolation.

**Kate Milliken:** Dr. Krieger, you want to add to that?

**Dr. Krieger:** I would just say that there's a very important step forward in terms of our understanding of genetics that came out a little more than a year
ago now, that's still quite recent, that involved over 9,000 patients in over 200 centers across the world to try and figure this out and identified a large number of potential or true genetic contributions to the risk of MS.

But, even still taken altogether, it only predicts a small amount of risk, which I think goes right back to what Dr. Mowry was saying. Even two people that are genetically identical, identical twins, have very different amounts of risk for the disease.

I think we've got a ways to go. But this is a good example, again, of the idea of multi-center collaborative work to try and find things that affect a huge population of people.

Kate Milliken: Sure.

Dr. Coetzee: And I'd say one of the things about the genetics piece is that, what Steve and Ellen have alluded to is it's not the whole story. One of the other pieces that we're learning about when we talk about the environment, it's not just exposure to viruses and the like. What we're learning is that the environment can also impact on how the genetics of your nervous system works. There are these environmental interactions and some of the work that we're funding is actually looking at how does the environment affect the genetic makeup. How does it adjust it in ways that we don't fully appreciate. Again, …

Kate Milliken: But which in some way makes it not genetic.

Dr. Coetzee: It's not genetic. We call it epigenetic. It influences it. But, you know, the idea is that there are other factors in the environment that we don't fully understand even how they talk to the genes that each of us has.

I think it makes the story a bit more complex but when we do these large scale genetic studies, what it says is, "OK. What are the genes we're supposed to be looking for?" Then are there other things that we now need to figure out that are talking. It's a complex web, actually.

Dr. Salzer: But just to follow up on that point, when you talk about identical twins being genetically identical in the age of epigenetics, they may not actually be completely identical and that's a new avenue to explore obviously.
Kate Milliken: That's unbelievable.

Dr. Krieger: Exactly.

Kate Milliken: Are there any certainties in science?

Dr. Coetzee: Well, there is one certainty, I would say, what is so great about this conversation is that this kind of work -- what we call epigenetics -- of the environmental impact on the nervous system comes out of really what we call very basic research. Stuff that's not even in MS but the government funds it for our advocacy efforts at NIH. There are a lot of researchers around the world who have contributed to that and now their research is being applied in people.

I think that just emphasizes why we have to continue to invest in some of that really kind of basic discovery stuff. We never know where it's going to apply in a human setting. I think that's one of the things I take away from that discussion as well.

Kate Milliken: And what all of you masochists think is really exciting, that's even more confusing. *(Laughter)*

Dr. Mowry, you are starting enrolling patients in your Vitamin D trial and I know it's a process but I'm curious, when do you think people who really want to know about Vitamin D will have some sort of answer of amounts and efficacy?

Dr. Mowry: So, the trial is expected to run for two years. Once we've completed enrolling, about two years after that we should have an answer. We're hoping to do that enrollment within, say, the next 6 to 9 months, so not too long. It seems like a long time, but we're working fast and furious.

We'll have some information about dose but we are only comparing one high dose to a second dose, the recommended daily dose. I think there'll be future studies, depending on the result of our work to determine if that's right where we want to be or should we be a little higher or lower. I think this is a really important first step in determining yes or no, is Vitamin D helpful for folks with MS.
Kate Milliken: Great. Question from the web. This is actually for Dr. Mowry. Theresa wants to know if it's wise to obtain a specific Vitamin D level?

Dr. Mowry: That's a great question. From an MS perspective, again, we're not 100% sure that supplementation is helpful for MS. So, with that caveat, we are starting to check levels in our patients and provide supplementation, knowing that we might be doing the wrong thing, maybe Vitamin D isn't helpful.

What levels do I aim for? I usually aim for levels above 40 nanograms per milliliter. That was the cutoff above which people were protected from getting MS in that large Department of Defense study I talked about earlier.

Then I usually top off that range around 60 nanograms per milliliter because in our studies of children and adults we saw that levels up to that level protected people from new attacks and new spots showing up on the MRI. Could levels higher than 60 be helpful? They might be, but we're not sure. So, we're sort of aiming for that 40 to 60 range right now.

Kate Milliken: Can you translate that -- and you may not be comfortable answering this question in terms of how much somebody should take in terms of international units.

Dr. Mowry: Right. Each person is different so I usually recommend that people talk with their doctor, get a blood level check first and then I usually aim for between 2,000 to 4,000, depending on where a person starts off with.

Again, it's really variable per person so the best thing is to talk to with your doctor and get a level checked. Make sure it's safe for you to take Vitamin D because some people probably shouldn't take too much. Then start taking the dose your doctor recommends and have a level rechecked a few months later.

Kate Milliken: Great. Dr. Coetzee, you are working with progressive MS. It's now the focus of the international progressive MS collaboration. Tell us about that.

Dr. Coetzee: Sure. This is, again, an exciting initiative that came out from really a realization that people are telling us that we need to address progressive MS and the research community says how do we work together.
We and our partners at the Canadian MS Society, at the U.K. MS Society, the Italian MS Society, the Dutch MS Society and the MS International Federation, which is an umbrella group that covers all of the MS Societies around the world, came together really with a very simple mission to say how do we work together to pool our resources, to pool our brain power to really address areas of progressive MS.

We've been working together over the last year and a half to figure out how do we do this. We all fund research in different ways. So, what research are we funding that touches on progressive MS.

Then to identify what are the gaps that we aren't currently funding or that the research community says needs to be addressed. Then the next phase is how do we begin to tackle those in a really intentional and fast manner because, really, we want to drive ourselves towards action.

One of our big steps is next week we're bringing together close to 200 of the leaders in the world in MS, coming together to talk about this and to really share information and really hit key issues. Like we still don't quite know how to study progressive MS in the laboratory, we don't have good models for that. We still don't have a lot of good strategies for doing clinical trails to discover a new drug or test it in the important Phase III clinical trials.

Then we hear frequently from people who live with progressive MS, "While you're discovering those new drugs, how do I live with the disease? How do I address the symptoms? Are there rehabilitative strategies, so that while we're discovering these new treatments, I can have an improved quality of life."

Rather than try and do all those others in isolation from each other, we're bringing all the people together to say how do we tackle these simultaneously. It's a tall order. I think what excites me is that, first of all, you have five MS Societies, other partners coming to the table. This is not a "Let's study this for five years and then come up with a plan." There's a plan and a strategy to say we're going to start funding research, we're going to do it now and we're going to share it.

As I said, it's a tall order, we've got a lot of things to do. I'm excited because we have been able to make so much progress in other aspects of MS that we've learned a lot over there and we intend to apply it to progressive MS.
Kate Milliken: Great. We have another web question for all of you. A lot of viewers are looking for an update on BG-12. What can you tell us? Dr. Krieger, let me start with you.

Dr. Krieger: Sure. So, I have said that we have had a number of successful Phase III trials in 2012. A couple of those trials were for this medicine, which its research name was BG-12. It's also known as dimethyl fumerate, which is its structural name. Now it's even got a brand name but we won't get into that.

The drug succeeded in two Phase III clinical trials. This is for relapsing forms of MS. These were two large trials done internationally, a combined total of around 1,600 patients. BG-12 prevented relapses very successfully. It prevented new spots and lesions on the MRI successfully.

It's a twice-a-day pill. Actually, it started as twice-a-day and three times a day, so, we'll see but the twice-a-day form seemed to have worked. It has a decent safety profile and we think a good tolerability and side effect profile.

It has been submitted to the FDA in the United States. The FDA is set to make a decision on this by the end of March. All signs point to its likely approval in the first half of this year, which will give us another oral medicine, another pill, with good efficacy to use for relapsing-remitting MS.

Kate Milliken: Great. Anyone else want to add something? That was pretty good.

Dr. Coetzee: That was good. I think one of the things I would add also, BG-12 is coming towards approval faster than many other therapies. There was a lot of experience using it in another form -- not for MS but for another disease.

I think what's an exciting aspect of this is that yes, it still took two trials at two years apiece. But they were able to really move through to getting it through Phase III much quicker. All that knowledge we've gained about how to do clinical trials really helped us do it much better and faster. Having things like MRI has really changed how we do clinical trials and I think that's a really important piece of the progress we're making as well.
**Kate Milliken:** Dr. Mowry, let's go back to you. Talking about new things to study in the microbiome. Tell us about this.

**Dr. Mowry:** Sure. This is actually a really fascinating area of MS research. I think we're going to hear a lot more about this in the coming years.

When we talk about the microbiome, what that really refers to is the collection of bacteria and viruses and other organisms that normally live on our bodies and within our bodies. So, these can be on the skin, in our nose, but largely the things we're talking about, most people are talking about right now, are bacteria that are in the gut.

There are trillions of bacteria in our guts at all times. These bacteria do a lot of important work for us. Some of the things that they do include helping us absorb nutrients from food. Well, the gut is also a place where the immune system is talking to the environment and it's thought that these bacteria might be teachers of the immune system.

The bacteria come into us early in life when we're infants. They might actually be instructing immune cells about what is part of our bodies, that shouldn't be attacked, and what is not part of our bodies and should be attacked.

We know that in autoimmune diseases like MS, the immune system is actually off. It thinks that part of our brain, the myelin, doesn't belong and attacks it. So there's a hypothesis that perhaps there's some mis-education or misdirection of the immune system and that part of this might occur in the gut.

Perhaps there are alterations in the number of bacteria or in the types of bacteria that are in the gut that are causing that misfiring of the immune system.

So, that's already been studied in several other autoimmune diseases. For example, inflammatory bowel diseases like Crohn's and ulcerative colitis. In fact, there have been some alterations in gut bacteria.

There are some studies in the animal model of MS suggesting that you can change some of those bacteria and increase the risk of the animal model of the disease or increase the severity of it.
So, I think this is a really exciting area of research where we could learn some very important information that might be a great example of where the environment and genetics and the immune system come together. Also, where we could make a difference through dietary or other modifications of those gut bacteria.

**Kate Milliken:** Dr. Salzer, just because we're nearing the end, I do want to know in terms of the myelin research that you're working on, when is that all going to trials?

**Dr. Salzer:** Let me say there are trials that are ready, I alluded to this before, there's an inhibitor that was identified and studied at Biogen and they've actually done, they've started a clinical trial on this. It's an inhibitor repair, presumably of the normal stem cells.

In terms of taking an approach of some of the new signals that were found to ameliorate or improve myelination in mouse models, I think -- this gets to the question you asked before about why does it take so long.

So, I think there are a number of candidates that are looking promising in mouse models. I think we've got to expand that up. Then the question of how you make that jump from a mouse to a person is a challenge. When do you have enough information to be able to go there.

So, I'm not giving you an answer because I really don't know. I would expect it's going to happen over the next, probably, if these results hold up, over the next three or four years. I would imagine there would be ongoing trials that are Phase I trials in people but that's a guess. Tim, do you want to --

**Dr. Coetzee:** I think Jim's right. I'll give you an answer. I think the good news about this is I think the jump is going to, we are going to be able to make it faster because the technology is just different from when we started working in the field a few years ago.

I think that being able to look and see where myelin is, at this meeting that we'll be at, that I referenced, next week, where we'll be talking about if you're going to do a remyelinating strategy in a person, what would you look for? What would be the outcome for the person getting better? Those are questions we don't have the answer to.
I think just a few years ago, the clinicians would say, "Let's not even bother with that conversation." So, I think actually we're in a much better place and I think it's a reason to be excited.

**Kate Milliken:** Well, I feel even in this whole conversation, to me, again, the layperson and the least intelligent person at this table dealing with science, that there has been a little bit of a shift of mindset. I always like to think, having been diagnosed, that I do like to say that it's a good time to get MS because there is a lot going on. I feel like there's just been a bigger, you know, whether it's scientists collaborating, whether or not it's looking at a holistic approach, there's something that's changing that is really encouraging.

Dr. Krieger, in 2013, what are some areas you think we'll be able to see some really significant results?

**Dr. Krieger:** Sure. I think this is a nice conversation because we get to talk about what's at the beginning stages and what's at the science level, and then what's sort of about to come to fruition.

I'll take that latter part and say that in 2013 we already talked about the next likely oral medicine to be approved for MS, which is BG-12 sitting with the FDA right now. I expect that that will be another disease-modifying therapy for MS that will become available for people this year.

A second medicine that has already come through Phase I, Phase II, and Phase III trials, and they're done and they were successful is an infusion medicine, which is called alemtuzumab. We also make the names as long and complicated …

Kate Milliken: I was going to say, do you practice those in the mirror?

**Dr. Krieger:** I do, you have to. Alemtuzumab is a medicine that's very different than a lot of other things that we've used for people with MS before because it's given by infusion for just a few days in a row, then not again a year later.

Unlike all of our other medicines which are given daily, or several times a week, or once a week, et cetera, this is a medicine given just a few days in a row and then not again for another year; then a few days in a row and not again for a year or maybe for many years. We always talk about MS as being a
marathon, not a sprint. This is the medicine that sort of takes that to heart, in
a sense, and works for the long term.

This alemtuzumab is not a simple medicine. It certainly has a set of side
effects and concerns with it that we're going to have to think about very
carefully. But I am hopeful that that will come to light in 2013. It has already
finished its trials, so that's two likely medicines for 2013. I'll turn it over to my
colleagues.

Kate Milliken: Great. Dr. Salzer, from your perspective?

Dr. Salzer: The question reminds me, if I can paraphrase Yogi Berra,
predictions are really difficult, especially about the future.

I think one area in the glial stem cell universe that I'm sure is going to be
coming out in the next year or so is that we are now, and this is, again, the
community of stem cell biologists have learned how to reprogram even a skin
cell to effectively make them a stem cell. They're called induced pluripotent
stem cells.

This was only discovered five or six years ago and won a Nobel Prize last year.
Effectively, you can take someone's skin cell, reprogram it and then root it to
any kind of cell you want. I know it sounds like science fiction, but it's actually
now happening. There's a lot of effort across many fields because this then
avoids the problems of embryonic cells and hetero cells from someone else,
they're your own cells.

In the myelin community, there's a lot of interest in trying to take such cells
and turn them into these progenitor cells. Those are essentially cells that are
already on first base. They're not in the batter's box, but they're already on
first base. They've already started the process of turning to myelinating
oligodendrocytes.

So, I'm trying to be confident that we're going to be hearing those kinds of
stories coming up this next year.

Kate Milliken: Okay. Dr. Mowry?

Dr. Mowry: Well, I think in terms of the larger studies that Dr. Krieger was
talking about, we've seen some recent data suggesting that new formulations or
new ways of dosing some of these older medications, the injectable medicines, might be quite effective for MS, so, pegylated interferon, and, hopefully, that will go up to the FDA. Using glatiramer less frequently might also go up to the FDA.

I think that the riluzole study, which is sponsored by the National MS Society, should have results this year. This was actually a study looking at what other medication already in use for Lou Gehrig's disease, or ALS, prevents some of the underlying nerve damage that we know happens in MS. That's using as an outcome some of these advanced MRI measures. So, that's going to be very exciting.

Finally, I think there's been a sort of a rebirth of studies looking at medications to help symptoms that are ongoing, things like spasticity, or bladder problems or pain. More studies, I would say, recently than I have seen in the past several years. So that'll be really nice as well to have some new things to try to help people with symptoms that are already occurring.

Dr. Coetzee: So, I don't have --

Kate Milliken: You can be the overview guy.

Dr. Coetzee: I'll be the overview guy. Great. Obviously, all the stuff that my colleagues said is going to be important for 2013. Other things I think about how we take on issues like how does nutrition affect MS. What are the variables there and how do we understand the importance of diet and things like exercise and other lifestyle related pieces that can really touch on the whole person as we think about MS that way.

We're starting to hear about other factors such as how does obesity potentially impact a person's course of the disease; these other factors that can contribute. I think all of that are things that I think we're going to be, maybe not have all the answers in 2013, but certainly launching.

The other thing I do from an overview is I look at the talent that's coming into the field. We have some great talents here and as I look at the programs and the people that we interact with, I mean, there's so many more young scientists looking at MS saying how can I solve that problem? How can I get involved in this?
I think we have some challenges getting more doctors. We need more MS specialists like the ones at this table. I think I'm really hopeful about the future because people are seeing MS as a disease in which they can really have an impact. That's, I think what we'll see more of in 2013.

**Kate Milliken:** There's been as much of an impact in this condition than in any other neurological disease. I think that says a lot.

**Dr. Coetzee:** Absolutely. I mean, when you think about it, in 1992 there weren't any treatments and no disease-modifying treatments, in 2013, we could potentially have 10 or 11. That's unparalleled in any other neurological disease. What that says to me is we've made great progress in relapsing-remitting MS. It also says to me we have got to do something about progressive MS. We just cannot simply let that stand.

**Kate Milliken:** So, you three MS specialists don't even think about stop working.

I want to thank our panelists, Dr. Stephen Krieger, Dr. James Salzer, Dr. Ellen Mowry, and Dr. Tim Coetzee for being here today and sharing their expertise with us.

I also want to thank you, our viewers, for joining us today. If your question wasn't answered, please speak directly to your healthcare provider or visit the society website at nationalmssociety.org. You can also contact the Society's Information Resource Center and speak with one of our MS Navigators at 1-800-344-4867.

Please note that today's webcast will be archived and available for viewing at nationalmssociety.org. Thank you all and goodbye from New York.