



## **Webcast Transcript**

**What's new in MS research and treatment**

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## MODERATOR

**Dr. Patricia O'Looney**

*National MS Society - VP - Biomedical Research*

## PANELISTS

**Dr. Loren Rolak**

*University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic*

**Dr. Peter Calabresi**

*Johns Hopkins MS Center - Professor - Neurology, Director*

**Dr. Robert Fox**

*Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director*

## PRESENTATION

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Good afternoon. Thank you for joining the National Multiple Sclerosis Society's webcast on "What's new in MS research and treatment". I'm Dr. Patricia O'Looney, Vice President of Biomedical Research at the Society. This is an exciting time in MS research and treatment and we have gathered some of the leading MS experts today to share information on important progress that is leading us closer to a world free of MS.

Our first panelist is Dr. Loren Rolak, who is Professor of Clinical Neurology at the University of Wisconsin at Madison and also Director of the MS Center at the Marshfield Clinic in Marshfield, Wisconsin. Dr. Rolak will discuss oral and other new therapies. Also joining us is Dr. Peter Calabresi, who is Professor of Neurology and Director of the Johns Hopkins MS Center in Baltimore, Maryland. Dr. Calabresi will cover the latest news in nervous system repair and protection.

Our third panelist is Dr. Robert Fox, who is staff Neurologist and Medical Director at the Mellen Center for Multiple Sclerosis, as well as Associate Professor of Medicine at the Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio. Dr. Fox will provide us with an update on just some of the CCSVI research underway.

We will have a question-and-answer period following each of the presentations. Please feel free to submit your questions using the interactive feature at the bottom of your screen. Please focus on questions related to the topics discussed by each panelist. We will answer as many questions as we can.

We think you will find that the speaker presentations themselves will answer many of the pre-event questions we have received from our more than 1,900 registrants. If you have questions related to your personal medical condition, please contact your healthcare provider or the National MS Society's Information and Resource Center at the number shown on your screen, 1-800-344-4867.

I would like to begin our program now with a brief overview on multiple sclerosis. MS is a complex and widely variable disease. It is a chronic, often disabling disease that attacks the central nervous system. Symptoms may be mild, such as numbness, or severe, such as paralysis or loss of vision. The progress, severity and symptoms of MS are unpredictable and vary from one person to another.

We do not know the cause of MS and at present we have no cure. While there are seven FDA-approved disease modifying therapies that are at least partially effective against the disease, as most joining this webcast know, they are not effective for everyone, nor do we currently have any approved therapy for the primary progressive form of MS.

Right now, the most effective means of reducing disease activity and future deterioration in relapsing MS has been shown to be early and continued treatment with one of these disease modifying agents. Many people with MS find it hard to get on and stay on a therapy that typically



doesn't make them feel better now, but rather serves as an insurance policy against an unknown future. This difficulty is often compounded by the fact that the current therapies are injected or infused and are not without side effects or risk.

We are pleased that there are new oral and infrequent-dose therapies either already under consideration for use or in late-stage development. This will result in people having additional choices. With more effective and easier to take therapies, it would encourage more people with MS to seek treatment earlier in the course of this lifelong disease and to stay on treatment once it is begun.

More importantly, the availability of new therapies will provide long-awaited options for those people who do not respond to the current treatments or are unable to tolerate the side effects. I now would like to introduce to you Dr. Loren Rolak from the University of Wisconsin, who will talk to you about oral and other new therapies on the horizon. Dr. Rolak?

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Yes, thank you, Dr. O'Looney. It is so gratifying that MS research has provided us with therapies that block some MS attacks and reduce the activities of disease. Nevertheless, our current therapies are just not good enough. They are only partially effective, and so some relapses will still break through. They also have significant side effects for many patients.

Because they have to be given by injection or by intravenous treatment, they can also be painful and difficult, so some patients cannot tolerate them at all and therefore have to take their chances with no treatment.

Now is an exciting time in MS research because suddenly there's an explosion of new therapies. Many of these are pills that could easily be taken by virtually anyone with MS. Several seem to be even more effective than the therapies we have now. However, some of these therapies also have a high-risk profile and they will require thoughtful, well-informed treatment decisions. It's likely that these new therapies will completely alter the way MS is treated, however.

If we could have the next slide, please? It will show us the first drug I want to talk about, which is called Dalfampridine and goes by the brand name Ampyra. This unique medicine is different from all the others we will talk about because it was not developed to block relapses of MS or prevent progression of the disease. In fact, it has no effect on the MS cells. Instead, it was developed to treat just the symptoms caused by the underlying MS, specifically, it was developed to improve walking.

Now, the brain sends messages down to the legs to tell them to walk and in some MS patients those messages do not get through. The MS has damaged the myelin around the nerves and without the myelin the nerves could not transmit the brain's messages. What if the signal from the brain was so strong that it shot right on through the areas without myelin and kept going down to the legs so you could walk better? This is the idea behind Ampyra. It boosts up nerve transmission so powerfully that it doesn't matter if MS damages your myelin because the signal gets through anyway. You will then walk more normally.

The studies with this drug that led to approval by the FDA just a few months ago show that some people with MS will respond to the drug, whereas others will not. There seem to be responders who walk better when taking the drug, and nonresponders who do not benefit. There's no way to predict in advance, so doctors and patients will need to decide whether this is a medication they would like to try.

If we could have the next slide, please, we will talk about another new drug, the newest therapy designed to suppress MS itself and thus block future relapses, and this is fingolimod. By the way, if you think MS drugs have strange names, I think you're right. Even doctors have trouble with some of these tongue-twisters. But fingolimod is a drug that blocks the immune system that participates in MS attacks. It prevents them from getting into the brain or spine.

A recent study of more than a thousand patients from 22 countries treated for two years showed 55% fewer attacks compared to patients on a placebo who are not taking the drug. It seemed the disability was about 30% less over this time, and MRI scans also looked better in patients receiving the treatment. The drug is also a convenient one pill once a day.



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However, there is the potential for side effects to be considered, and we don't yet have long-term data. Some people had some mild slowing of their heart rate or a slight rise in blood pressure, but nothing very serious. Because the drug does change the immune system, there is a possibility of more infections and so this will have to be watched carefully if the drug becomes available.

Recently, just on June 10th, an advisory committee recommended by the FDA approved fingolimod for us to use, and we're hopeful it will become available perhaps as early as September or October. Meanwhile, trials are already underway to test its effects on primary progressive multiple sclerosis. For those patients whose MS is slowly progressive, without having actual relapses, we will be able to see if fingolimod will help them.

Could we have the next slide, please? This will show us about Cladribine. Cladribine is not really a new drug at all but, rather, it is available now but to treat some types of leukemia. Doctors realized that the way the drug changes the immune system to fight leukemia would probably also fight MS. A major research trial was therefore done over a thousand patients, 32 countries, treated for almost two years. This is also an oral drug with a series of pills you take every few weeks, and then that alters the immune system for up to a year into the future.

In this study, which was just recently completed and submitted to the FDA, treated patients had 57% fewer relapses and disability was slowed by about 33%. The drug is well-tolerated but there were side effects in some people including, again, the chance for infections or serious change to the immune system. Again, this will need to be watched carefully.

Could we have the next slide, please? Yet another exciting treatment to prevent future relapses is Alemtuzimab. This therapy is given in the vein for several consecutive days and then it does not have to be given again for an entire year. During that year, relapses of MS are considerably reduced.

In a recent large trial, patients were given either shots of interferon or a course of intravenous Alemtuzimab, and over the next two years the group receiving Alemtuzimab had 70% fewer relapses. In some, their level of disability also improved.

Now, any drug strong enough to alter the course of MS is also strong enough to cause side effects, and some patients treated with Alemtuzimab have had problems, problems with thyroid gland or problems with blood clotting. A large-scale trial is now underway to try to capitalize on the drug's benefits while minimizing the complications. On June 15th, the FDA announced that when this is completed it will fast-track the drug by analyzing the results much more quickly than usual. The next slide, please?

There are some other oral treatments, again, pills, that are being developed as therapy for MS. Teriflunomide is chemically related to a drug that is now used to treat rheumatoid arthritis which, like MS, seems to be an autoimmune disease. Research trials thus far with MS patients have shown that when it is taken as a pill, either alone or added on to interferon injections, it may suppress MS relapses and improve MRI changes.

The first full-scale study is expected to finish up just this fall, and there are other ongoing trials which should be finished in time for submission to the FDA by 2012. Another oral therapy is Dimethyl fumarate, or BG00012. Unlike so many MS treatments that alter the immune system, this drug has little or no immune effect. Instead, it's different. It strongly reduces inflammation and it strengthens the healing and protective cells and protein.

Studies using special MRI techniques have shown that when taken as a pill, one pill three times a day, the drug has significant beneficial effects, and two major studies are now well underway to meet the FDA requirements for approval.

Laquinimod is another once-a-day oral drug which not only alters the immune system and protects myelin from attack, but it may also increase levels of some of the protective proteins and therefore provide even more benefits for MS. It has already been fast-tracked by the FDA and there are two major trials now that will be concluding soon. May we have the next slide, please.

So we can talk about Progressive MS. Because not all patients with MS experience relapses of their symptoms, some have a more progressive course where problems appear slowly and steadily and there's a gradual worsening, often without any remission or any improvement. These kind of progressive symptoms are much harder to treat than relapses.



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As I noted earlier, there is a large-scale trial of oral fingolimod in people with primary progressive MS. Also, there's a study of an oral medication called Idebenone which has begun at the National Institutes of Health to see if this can stop progressive symptoms. Now, this drug blocks some of the processes that take place in the body to break down and destroy cells. Therefore, a drug like this might be able to protect the nervous system from deteriorating and therefore prevent any further progression.

Another innovative approach to Progressive MS is a trial in England testing the ability of a derivative of marijuana called cannabis which they make into a pill form to see if this will protect the nervous system from harm. This is a large trial involving almost 500 people with Progressive MS and it's now underway. Please remember that if you want more information on any of the therapies we're discussing, it is available at the National MS Society website, [www.nationalMSSociety.org](http://www.nationalMSSociety.org).

So, in conclusion, very soon we expect to have completely new and different approaches to treating MS including some oral drugs that should be more easy, more convenient, and powerful. Each approach will have a different risk versus benefit and you'll need to consider that, but all will have to meet the rigorous safety requirements for FDA approval.

This good news also means that choosing the right treatment plan for any one specific MS patient now is probably going to involve more decisions and in a way may even be more difficult. As these therapies become more widely used, their true benefits and their true risks may become more, clear, and so treatment approaches may gradually shift over time. For patients already responding to their current MS treatments, there may be no need at all to add or switch to any new drug. So all of these are decisions you will need to discuss with your own healthcare professional.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Well, thank you, Dr. Rolak. This is truly exciting. I know you can only in the time limit touch upon a few of the many drugs that are in the pipeline, but this is truly exciting.

### QUESTION AND ANSWER

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Before we move to our next speaker, I would like to ask you some questions now that we have received from our participants.

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Oh, great.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

And we welcome all our participants across the world. So the first question is actually coming from Michael in the UK, the United Kingdom. And it pretty much follows up what you were just talking about in terms of treatment options. Michael asks how a possible new oral agent like fingolimod could fit into one's therapy. So I don't know if you can comment, Dr. Rolak, as a clinical neurologist how - what are some of the decision options that you and your patients will talk about?

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Sure. Wow, from the UK. Thank you for logging in, Michael. This is an excellent question and, in fact, I think it is the most important question to ask. What will these new strong oral therapies mean for you personally, for any given patient? But I'm afraid I'm going to have to give an incomplete answer because with these drugs treatment really will be very individual.



I will be thinking about, as a neurologist seeing MS patients, questions like how old is this person with MS and therefore maybe how long are we going to have to continue treatment. How active is the MS? How many attacks has he or she had, how mild is their disability, are they planning a pregnancy? Frankly, do you want to be the first person on your block to take the new drug or do you want to wait awhile? There are a lot of decisions to sit down and talk about with your healthcare provider. So this really is going to be – I'm not trying to be evasive; it really is going to be a very individual thing. Good luck with that, Michael.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

And I guess, you know, sometimes these things are the good things to do is to have more options and more decisions. Perhaps it's always best in people with MS.

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Absolutely.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

And we kind of have two similar questions from Claudia and Barbara and we didn't require people to say where they were calling from or submitting their questions, so it's just Claudia and Barbara out there.

And they ask about Ampyra and you touched upon that a little bit, Dr. Rolak, about Ampyra being more of a symptomatic treatment, but do you know yet or does anyone really know yet about whether or not Ampyra can be used at the same time a one of these other possibly oral disease modifying therapies?

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Well, it's true that Ampyra is brand new and these new drugs, oral drugs we're talking about are just emerging, and so we haven't really had a chance to very scientifically compare people who are taking both at the same time.

From what we know about the drugs, it seems they should be safe and I would expect there's no reason why a person on Ampyra to help with the walking, for example, could not be taking one of these oral medications at the same time. I think that's something we doctors are going to start doing, and then see if it's safe or not. I suspect it will be.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

And if I may, maybe I should ask my own question, Dr. Rolak, because I know so many of our participants out there are interested in progressive, primary progressive. You talked about fingolimod, but I'm sure they're probably interested. Are there any other therapies, and why haven't we had any therapies for primary progressive? So I don't know if you can answer that question in a brief period of time.

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

It's a very good question, and I think I've been very pleased that not only the National MS Society but also other organizations, like the federal government, have begun to shift a lot of research emphasis on the progressive form. There are a lot of reasons that it's harder to study. One is that, as you mentioned, we don't really know the cause of MS and it's much less clear what the immune system is doing in Progressive MS compared to relapsing MS. And so we've not been able to find a good target to treat for the progressive forms of MS.



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Because it's also slower, in other words, relapses happen quickly, and the progressive form is more slow, it simply takes longer to study so a trial underway to see if the drugs works for progressive MS can end up being a very long trial. So that kind of inhibits the research a little bit. Luckily, really, the emphasis is shifting more onto that and so I'm real pleased about that.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Oh, that's wonderful. And one final question from Shannon in Idaho. You touched upon this also, Dr. Rolak, about side effects, but maybe if we just focus on fingolimod because that's coming along most recently in the pipeline and was recommended. Could you talk a little bit more about the potential side effects of the oral medications? I think you touched upon lung function and things like this.

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**Dr. Loren Rolak - University of Wisconsin - Professor - Clinical Neurology, Director - MS Center at The Marshfield Clinic**

Sure. I think the oral medications will certainly be easier to tolerate and have few side effects in at least one way, that way being they're not an injection or they're not an IV, and so for some people who have trouble with injections and needles, obviously, that's one effect or side effect they don't have to worry about. But like any drugs, these oral medications can have other sorts of side effects.

Because they all affect the immune system, we have two concerns. The immune system protects us, that's what it does, protects our bodies. It protects us from two things. It protects us from cancer and it protects us from infections. So what we're looking for in these oral drugs is to see over time whether there will be any increased risk of things like cancer or any increased risk of things like infections.

In the studies that have been done using the current doses over one or two years, they seem quite safe. But we'll want to see over time and with larger numbers of people what the side effects are. The individual drugs are going to have their individual side effects and each person might respond to them differently. But the issues of suppressing the immune system and watching for either cancer or infections are going to be the overriding issue, I think, for all of the drugs in general.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Well, thank you, Dr. Rolak, just for your terrific guidance here and for your helpful presentation. So thank you.

## PRESENTATION

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Let's now move to our next panelist, Dr. Peter Calabresi from Johns Hopkins, and the topic of repair and protection of the central nervous system. As many of you may know, the Society has three research goals: To stop MS in its track, restore lost function, and to end MS forever – to stop MS in its tracks and to reverse the damage and restore function is where nervous system repair and protection come in. We need to stop the immune system from attacking the brain and spinal cord, and in particular, we need to stop damage to myelin and the underlying nerve fibers.

Myelin is like the insulation surrounding electrical wires, and as Dr. Calabresi will describe shortly, myelin wraps around the nerve fibers, which is also called the axons. It protects the axon and speeds nerve conduction. The axons carry nerve signals, and when they are damaged it leads to dysfunction and long-term disability. Nervous system repair and protection are crucial if we're going to stop MS progression and restore function.

We are so excited by the progress that's being made in these areas around the world, and I'm so pleased that we have a leader in the field with us today. I'd like now to introduce to you Dr. Peter Calabresi. He will talk about the encouraging work underway in nervous system repair and protection.

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**Dr. Peter Calabresi - Johns Hopkins MS Center - Professor - Neurology, Director**



## What's new in MS research and treatment



Thank you, Patricia, and hello, everyone on the call. It's really my pleasure to be on this call, and in the next few minutes I hope to just convey some of my real enthusiasm about what's happening in the field of MS, in large part thanks to the MS Society for funding just an incredible amount of research.

As you've already heard from Dr. Rolak, we're really making great progress with oral therapies and new therapies that will likely have great impact in the early stages of MS, but the clear unmet need is for progressive disease and the later stages of disease in the hope that we can actually prevent people from worsening in that stage, or even repair function.

So while I won't have time to take you through the really hundreds of different strategies that people are taking on to try to study this, I'm going to try to convey to you the overall picture of what's happening, what areas that we're studying, and then provide a few examples, specific examples, of how some of these research strategies are actually being translated into clinical trials for people with MS. Next slide, please?

So in the slide that's coming up now you can see a graphic that explains the different stages of how we think MS happens. In a very general sense, we believe that immune cells, T-cells, although probably other cells as well, become activated in the peripheral blood and then cross the blood-brain barrier and go into the brain and spinal cord, where they launch an attack on the myelin, the coating around the nerves, and the nerve fibers themselves, which are depicted at the bottom of the graphic as green cylinders.

That nerve unit with the myelin wrapping around it is what transmits information from the brain down to the arms and legs and sensory information from the arms and legs back up to the brain and for visual pathways, as well. And so this unit is very important. It is the whole focus of understanding tissue protection and repair. But as Dr. Rolak pointed out, it's very important to realize that we can actually protect the nervous system early on in the disease by impacting on the immune cells, the T-cells, and so we can actually protect at various different stages the immune cell trafficking process.

Then we're working on strategies to protect on the other side of the blood-brain barrier where the immune cells then go on to cause damage. And, finally, there will be strategies to try to repair myelin or perhaps make the nerves and cells more resistant to damage or even someday regenerate those nerves.

On the next slide, which I think has already come up, is a little graphic just telling you a little bit about what myelin does. And we've known for years that myelin's important for efficient conduction of nerve impulses, but increasingly we recognize that it's very important for protecting the nerves.

So I like to make analogies, and if you think about myelin sort of wrapping around the nerves and providing a protective coating to them, it may be that that's one of its very important functions, much like a tree without its bark becomes more susceptible to the elements, that nerves need to have myelin. We know that nerves, once they become unmyelinated, are unhappy and eventually will undergo a slower, progressive degenerative process. So understanding how we can remyelinate is an important strategy for protecting the underlying nerves. Next slide, please?

So here, you see a graphic of these myelinated nerves with the sausage-like myelin wrapping around the inner fiber that we call the axon that transmits the information, and just showing you that the process probably happens slowly so that there are little bits and pieces of myelin that get chewed up and destroyed. And as I'll speak to later, we're understanding that early in these processes that Mother Nature has developed mechanisms to naturally repair some of that myelin, so people can have attacks and then recover from it.

We're working on ways to try to, obviously, enhance that recovery or tap into that natural mechanism to see if that might be one sort of obvious strategy for repairing. Of course, if that ultimately breaks down, then we're looking at more artificial means of transplanting cells in to repair the myelin or protect the axon. Next slide. So here you can see a somewhat more complicated schematic of the various different areas that people are doing research.

I might mention at this point that we are really privileged at Johns Hopkins to be one of the four tissue repair teams around the world that are taking this project on globally. There are hundreds and hundreds of very smart researchers around the world working on MS, and the MS Society is supporting collaborative projects with some distinct features of each of the teams and some overlapping features.

Some of the teams are working specifically on stem cells. Others are working on understanding myelination and remyelination. Some are working on protecting the nerve wires, the axons, and we get together and compare notes and discuss different strategies. This has actually led to



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new areas of research within our institution and a very nice cross-talk and cross-fertilization of information. I'll show you some examples of some of the progress that's coming from there.

But you can see in the lower right-hand or lower left-hand corner the primary goal in early MS is to block the immune cells from attacking the myelin and nerves. I'll point out that with some of the successful therapies that we have now, we think people are accruing significantly less disability because of the success of these therapies and that in some cases, if we have people who have an attack and we totally stop the inflammation, people seem to have much better recoveries. So this is encouraging.

The next step would be, number two, to prevent the myelin-forming cells from dying. So there appear at the tissue level to be different kinds of MS, some where the myelin-forming cells that we call oligodendrocytes survive and can remyelinate, and then in other types perhaps these will be patients with progressive disease from onset, those cells don't seem to survive. So a goal, there, would be to try to get new myelin-forming cells to come from deep parts of the brain through natural repair mechanisms – or, if that doesn't work, to transplant them with stem cells from an outside source.

The third major area of therapy for MS repair would be to boost new myelin formation, again by activating dormant myelin-forming cells in the brain or transplanting cells. And then, finally, the fourth area would be to supply protective growth factors to keep nerves alive or to promote health of these tissues. Increasingly, we're understanding that there are a variety of different nerve growth factors that can be used to promote nerve health and even regeneration.

Some of this information is coming from people who study spinal cord injury and nerve regeneration in that context. So it's important that we continue to collaborate and discuss with our colleagues who think about different disease processes because there are many examples in medicine of important lessons being learned. Again, this is one of the great things about the tissue repair collaborative teams is the cross-talk with other institutions around the world.

So if we could go to the next slide. Here are some more concrete examples of progress that has happened, again much thanks of the MS Society's support. Natalizumab is the therapy that's now on the market. People know it as Tysabri that's being given to close to 70,000 people with MS.

And if you look at the clinical trial Phase III data, it was 92% effective in blocking the new gadolinium enhancing lesions that we see on MRI. As a result of this, it reduces what we call tissue destructive lesions or what are sometimes called T1 black holes. So that's really fantastic news and again evidence that if you stop the attack early on, you can prevent the brain from undergoing damage and atrophy that will lead to more permanent disability.

Of course, there is a concern for side effects, and there have been ongoing cases of PML (progressive multifocal leukoencephalopathy). Fortunately, at this point, it seems that those cases are plateauing at around 1 in 1,000 – but we'll have to see what the long-term consequences of the treatment are. But, in general, I would say that it's a major success story for early MS.

Oral therapies, as you heard, are poised to gain FDA approval. One point I wanted to mention about FTY-720, or fingolimod, is that in addition to reducing the inflammation and the active lesions, it's unique in that it's one of the only drugs that we have that seems to get into the brain. It's very lipophilic, which means it likes fatty substances like myelin. In fact, if you label fingolimod with a tracer and look where it goes, it goes right to the white matter tracks where the myelin is.

That is encouraging, because it may have secondary beneficial effects inside the brain independent of the anti-inflammatory effects in blocking cells from coming into the brain. In fact, some excellent researchers in Montreal and other places have shown some direct effect on the myelin-forming cells, perhaps encouraging them to repair and remyelinate more efficiently. So those secondary benefits of the drug will continue to be studied and this is one of the hopes as to why it might be effective in primary progressive MS and that trial has already begun.

In addition, some other drugs that were initially thought to be anti-inflammatory and were tested early on in MS have serendipitously been found to actually not have anti-inflammatory effects but have beneficial effects on the MRI that suggest that they may be tissue-protective. So a drug called ibudelast was studied in Europe and, fortunately, an MRI colleague [Dr. Fred Barkoff] was looking at the T1 black holes in these patients and found that there were fewer destructive lesions even though there was no change in the number of inflammatory enhancing lesions. And that's a very unique property which is not one that we typically see.



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Typically, we see drugs of anti-inflammatory, some slightly beneficial effect on the T1 black holes. But in this case there was no effect on the inflammation and a significant effect on the T1 black holes, which has raised the idea that this drug may have a primary beneficial effect in protecting tissue from being destroyed. Based on that, there is significant interest in moving forward with tissue protection trials of this drug.

Next slide. So now moving on to remyelination. It actually was described many years ago that there could be partial remyelination in the brain and spinal cord, but like many things, this was somewhat overlooked and has now sparked new interest in the capacity to have natural repair.

So how does this process happen? Normally, we know that the peripheral nerves can remyelinate extremely well. So after a disease like Guillain-Barre, patients will, if they survive the acute attack, fully recover – but in MS the attacks increasingly become more and more severe. But perhaps we could tap into this natural mechanism and enhance this remyelination.

So on the next slide, one can see the different strategies that we're thinking about taking. One could perhaps use stem cells and the two types of stem cells that are there are the endogenous stem cells, which live within our body, or the kind that would be transplanted from another human source, or exogenous stem cells.

The endogenous ones, as I mentioned, go by a variety of different names. There are neuro stem cells. There are stem cells that only can function to become either new astrocytes or new oligodendrocytes. The myelin-forming cells, and those are the ones that are of particular interest, and it turns out that many of these sort of lay in a dormant state in our brain because when there's no trouble, there's no need for these stem cells to be working and they have natural brakes, if you will, that keep them in that dormant state.

By understanding how these cells get turned on and off, researchers have been able to develop strategies to turn these cells on and get them to turn into new myelin-forming cells. So I will explain in a couple of minutes how this is being translated into a therapy.

But on the other side, the long-term hope would be that perhaps even exogenous stem cells could be transplanted into patients and turn into myelin-forming cells and repair the myelin, or maybe even some day turn into new nerve cells that could grow back on wires that would reconnect parts that had been more permanently damaged.

Of course, there's been much talk about embryonic stem cells, and in addition to the political obstacles, which are somewhat being relieved, there continue to remain biological obstacles about how to get those cells to do what we want them to do and to behave themselves. Because of their incredible capacity to turn into any cell, we also want to make sure that they don't become a rogue tumor cell. So quite a bit of research remains to be done to figure out how to most effectively use those cells.

Another interesting kind of stem cell is called the IPS, or inducible pluripotent stem cell. One of the exciting features of this cell is that perhaps any cell in the body could be reprogrammed to do something different from what it became.

So, for example, some researchers have suggested that skin cells or fat cells could then be reprogrammed to become a myelin-forming cell or a different type of cell in the body. The major advantage of this would be that perhaps someday we could take cells from the same person, reprogram them, and put them back in the person, which would avoid the issue that one gets from transplanting cells from another donor of tissue rejection.

And the final kind of exogenous stem cell that's in clinical trials in other parts of the world and close to clinical trials in the US, is the Mesenchymal stem cell, and this is most commonly obtained from bone marrow, although there are other Mesenchymal sources around the body from which these can be obtained.

The research to date suggests that they may have the capacity to do many things. A predominant effect is one of actually suppressing some of the inflammation, both in the periphery and perhaps in the brain, and the hope would be that they might actually enhance the environment of the brain to be more conducive to repair or even facilitate repair. But the exact details through which these Mesenchymal stem cells work has not quite yet been sorted out. Next slide.

So, again, here are some real-life examples. One company has developed a system of blocking the brakes or releasing the brakes on these oligodendrocyte or myelin-forming cell precursors in the brain. It's called anti-LINGO, and by delivering a monoclonal antibody that blocks this surface receptor, they have been able to show that we can wake up these dormant cells and get them to turn into myelin-forming cells, both in a



## What's new in MS research and treatment



tissue culture dish – that was in 2005. And then in laboratory animals with an MS-like disease in 2007 – and this is now in Phase I first in human clinical trials for safety and toxicity. So it's very exciting that we're actually remyelinating drugs and actually going into people at this time.

Another fascinating strategy that we've taken some interest in is the idea that it has been known for years that thyroid hormones are important for developmental myelination. It was not fully appreciated that these might actually have beneficial effects in adult situations, but a researcher in France has been able to show that adult myelin-forming cells can be triggered by types of thyroid hormones – and perhaps these could be delivered in a way so as not to cause people to become hyperthyroid but to actually enhance myelination.

And then in terms of progress with stem cells – the first kind that will be tried in the United States are the human Mesenchymal stem cells, and this is actually going into clinical trials based out of the Cleveland Clinic. Next slide.

So in conclusion, really, I think we're going to be looking at combinations of therapies where we try to protect the upstream attack on the nervous system through more efficient and safe anti-inflammatories and looking at trying to target some of the downstream mechanisms of degeneration and then, ultimately, promoting remyelination and repair. There are just many, many different strategies which I can't talk about today that are happening and showing a lot of promise. So if we move on to the next slide.

I'd like to conclude by saying that all of these mechanisms by which the degeneration and the damages are happening are starting to become unraveled, and this will lead to a whole new array of therapeutic strategies and targets that will set the groundwork for future therapies. It's important for people to realize that all the research that went into the development of the anti-inflammatories that we have now for MS, started in 1993.

And for the last two decades really much of that research had to be done in the 1970s and 1980s. So I think we've really set the groundwork for protection and repair, and the truths will hopefully start to be formed very soon for getting into these new types of therapies. As you can see, the first remyelination drug is in human trials, and Mesenchymal stem cells are going into human trials in this country very, very soon.

So if we could just go to the last slide, my take-home message here is that we are definitely making progress. It's obviously not fast enough. I, unfortunately, see people every day who have progressive MS who are suffering from the disease.

But I remain very optimistic. For me, this has been one of the most exciting times in MS research. It's extremely hopeful and optimistic about what the future has to hold for us. I'll stop there. So thank you. I think we may have time for a few questions.

### QUESTION AND ANSWER

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

So you can imagine there are many questions on this. But we do have just a few minutes. Our first question is from Heidi in Texas. And Christiana in California had a similar question. This is about the stem cell clinics that are outside the United States, offshore clinics as they're sometimes referred to, in Central and/or South America. So could you comment, Dr. Calabresi, on these clinics and the results that we often hear from them?

**Dr. Peter Calabresi - Johns Hopkins MS Center - Professor - Neurology, Director**

Sure. So it's a little frustrating, as we don't really get complete information about what exactly they're doing in some of these clinics. The research is not done in nearly as rigorous fashion as it's done typically in the United States and in Europe.

So we're left with not really being able to fully interpret the results of some of the experiments. So, for example, the researchers aren't always forthcoming or provide detailed information about the kinds of stem cells that they're. Then the trials are typically not done in a controlled fashion.



We know from many, many years of MS research that there is a huge potential for placebo effect. So whenever you tell someone that you have an exciting new therapy that you think is going to make them better – this has a very powerful effect on the mind.

We all become hopeful. The doctors become hopeful. The patients become hopeful. In clinical trials where there have been placebo arms. We know placebo patients just get better for that reason. So one has to be very careful about making sure that the results are truly related to whatever is being done – that the patients in most of the stem cell work to date has been very exploratory, mostly looking at the safety.

There's not clear, definitive evidence that the stem cells are actually repairing tissues. It's possible, as I mentioned, that they may be having some anti-inflammatory effects, which would be good, but it's a different mechanism of action.

As I mentioned, the Mesenchymal stem cells are going to be in clinical trials in the United States. Dr. Jeff Cohen, I think, is the PI (principal investigator) of the Cleveland Clinic for this study. That's very exciting because I think that we'll have much cleaner and more rigorous information about how effective that approach is.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Terrific. It's important to emphasize to our audience that those Mesenchymal stem cells are actually from the patients themselves. Is that right? They're adult stem cells.

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**Dr. Peter Calabresi - Johns Hopkins MS Center - Professor - Neurology, Director**

That's correct. Those are the ones from the bone marrow that captures those cells and cultures them for a period of time to clean them up and get them into a state where they may be – and are better able to repair the tissues and put them back into the patients. So there's no concern about rejection from a foreign donor there, and there's no ethical concerns about embryonic stem cells.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

We have a question from Deborah in Florida. She asked the question, why does it seem like some nerves are more susceptible to damage than others in people with MS – especially with the nerves that control walking or vision?

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**Dr. Peter Calabresi - Johns Hopkins MS Center - Professor - Neurology, Director**

Well, I think the answer to that is that there are some nerves that we just notice more – so the nerve that brings the information from the back of the eye to the brain, the optic nerve, is a very tiny, small nerve. So all it takes is a bit of microscopic inflammation.

One notices immediately that there's impairment in vision, the same with anything that goes through the spinal cord. One quickly notices an area of blockage there so that one leg is dragging or becomes numb. That becomes very evident.

Some of the nerve pathways in the brain are not as obvious to us when they become dysfunctional, either because there are many redundant pathways or they carry functions that we don't utilize on a minute-to-minute basis – but they rely on for higher executive cognitive functioning. So unless we're using that part of our brain, we may not be aware of it.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

I think we have time for one more question before we move to our last panelist. This comes from Deb in North Carolina. I think we often hear this question – it's about cord blood. My sister just had a baby and banked her cord blood hoping that at some point it might be helpful to me (Deb) and others with MS. So Deb's asking, what is your outlook in terms of potential treatments for MS in the use of cord blood?



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**Dr. Peter Calabresi - Johns Hopkins MS Center - Professor - Neurology, Director**

Well, it's a tough question, because at this time (for the stem cells we could get out of cord blood) we don't know for sure how useful they will be and whether they will be any more useful than other sources of stem cells. So, certainly, if it's your sister there may be less of an issue in terms of rejection, but it's not a perfect match. So we don't even know for sure whether they would take.

The hope is that with these inducible pluripotent stem cells, that maybe we can derive from the patient's own body without having to go through all these complicated procedures, and expensive procedures, of saving cord blood. Someone told me that it's \$500 a year to bank in a freezer. We may end up ten years from now having a different technology where we can mix stem cells from fat cells or skin cells.

So I understand the desire to want to do this, and perhaps it will be beneficial. But perhaps we'll have other strategies that are a little bit easier to use. Right now, we just don't know yet. But the whole stem cell business is in very early stages, and there have been very few clinical trials as of yet.

### PRESENTATION

**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Well, thank you, Dr. Calabresi, for your encouraging presentation. It's now time to move to our third panelist, Dr. Robert Fox, from the Cleveland Clinic, who will provide an overview and update on chronic cerebral spinal venous insufficiency, or CCSVI.

I'm sure many of our participants have become familiar with CCSVI over these past several months. In the society's efforts to stop MS, restore function and end MS forever, we are committed to pursuing all promising leads wherever we find them. We are currently funding 375 research projects around the world.

In order to pursue new and unanticipated leads in MS, the National MS Society established the Rapid Response Fund. An example of this fund in action is the global outreach – an expedited review process that led to more than \$2.4 million we are devoting to the funding of our seven initial CCSVI grants in collaboration with the MS Society of Canada.

CCSVI is a phenomenon reported by Dr. Zamboni, who observed blockage and narrowing of the veins that drain the blood from the brain and spinal cord. The preliminary results of research conducted by Dr. Zamboni and others have been published in respected peer review journals. The Society shares in the public urgency to advance the understanding of CCSVI as quickly as possible.

There have been, however, conflicting results in the current reported studies. The seven new grants were chosen by an international panel of experts for having the greatest potential to quickly and comprehensively determine the significance of CCSVI in the MS disease process.

Adding clarity to the relationship between CCSVI and MS is essential in assisting people with MS to secure any treatment that they may consider. Medical institutions and healthcare providers require research data confirming the validity, necessity and safety of any procedure they provide. In their view, that data are not yet available as it relates to a relationship between CCSVI and MS.

The two-year grants will launch July 1, 2010. As work on the grants proceeds, researchers will be able to provide six-month updates on their progress. The seven projects include an integration of experts drawn from all key relevant disciplines, which will be discussed momentarily. Bringing together experts across these areas will help to facilitate understanding of CCSVI and MS as quickly as possible.

The United States and Canadian MS societies are also in discussion with the Multiple Sclerosis International Federation, which is based in London, to establish an international CCSVI research coordinating committee to consider and share CCSVI research data and information from ongoing work that is underway around the world. This will further speed the process.

For instance, it has been reported to us that Dr. Zamboni is in the process of devolving a randomized clinical trial comparing disease modifying therapy within and without the balloon venoplasty with sponsorship from the Italian government. Also, researchers at the University of Buffalo



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are undertaking a placebo-controlled trial involving 30 people with relapse-remitting MS. I'd now like to introduce you to one of the Society's new CCSVI grantees, Dr. Robert Fox, who is leading the Cleveland Clinic team.

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### **Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

Thank you very much, Dr. O'Looney. It's an honor to be a part of this program today and to share the excitement that is building about CCSVI, this new theory, new hypothesis, that we are evaluating in MS.

I'm going to divide my comments into three different sections; first, an overview of CCSVI, including the original reports by Dr. Zamboni; then, review some subsequent studies which have found some somewhat different results from the original ones; and then finally turn to a review of the seven projects that were recently funded by the US and Canadian MS societies.

So first, what is the background about this? Well, MS has long been considered primarily an immune disorder where the immune system is confused and inappropriately attacks the brain, the spinal cord and the optic nerve. For many years, that's what researchers have been evaluating in terms of understanding MS and developing theories for MS.

Then, there's been a new theory of MS pathogenesis, or the cause of MS. That is a venous outflow blockage from the brain and the spinal cord where the veins are obstructed and the backflow of blood causes injury and inflammation to the brain and the spinal cord.

Now, this new theory is actually somewhat of an old theory, having first been reported early in the 1900s. Here's a reference to a paper from 1935 describing a venular obstruction, or a vein obstruction, causing sclerotic plaques and multiple sclerosis. Next slide.

This theory was then brought back into view by Dr. Zamboni and his colleagues over the last few years. Dr. Zamboni is a vascular surgeon, so he has a lot of expertise in understanding the arteries and the veins, and he evaluated how they may be connected with multiple sclerosis.

So in his studies, he used ultrasound to look at the draining veins in the neck and in the brain and developed a five-point ultrasound criteria looking at both reflux – or backward flow of blood into the brain and the spinal cord – as well as stenoses, or blockages of veins in the neck and in the brain.

Of those five criteria, if a person met two or more of the five criteria, that was considered meeting the diagnostic criteria for CCSVI, or chronic cerebral spinal venous insufficiency. In his studies using CCSVI criteria, he evaluated 109 MS patients. All 109 met that criteria for CCSVI, meaning they met two or more of the five criteria. He and his colleagues also looked at 177 non-MS patients as a comparison group, or control group, and found that none of those patients, or 0%, met criteria for CCSVI. Next slide.

He and his colleagues then went on. Next slide, please. He and his colleagues then went on to do arteriograms, or actually venograms, using a catheter much like a heart angiogram – but this time into the veins – and using dye, evaluated the jugular veins as well as the azygos veins. The azygos vein is the vein that drains blood from the spinal cord.

What he found in many patients was this blockage. Now, that's shown here (on slide). The top row of pictures shows the venogram of the internal jugular vein before and after venoplasty. The black arrow in Panel A shows where there's a stenosis, or a narrowing. Panel B shows where a balloon was put across that narrowing and then blown up. Then, Panel C shows the result of the improved blood flow, or the decreased stenosis, that followed venoplasty.

The second row of pictures shows a venogram of the azygos vein, the vein that drains the spinal cord. In Panel A, one can see the stenosis, or the narrowing of the azygos vein. Then, Panel B shows after the balloon was passed across it and blown up – showing a decrease in the stenosis in that area. Next slide.

Dr. Zamboni then went on to report an open-label trial of balloon venoplasty. What he found was a resolution of all of the stenoses that he found following venoplasty. In terms of what happened to the MS patients in terms of their MS, the relapse rate was reported not to have changed over 18 months, but the proportion of patients that were free of relapses increased from 27% to 50%.



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The proportion with gadolinium-enhancing lesions, those are the lesions showing active inflammation, decreased from 50% to only 12%. Furthermore, he looked at a disability scale, the MSFC, or multiple sclerosis functional composite, as well as quality of life measures and found that these improved in patients after venoplasty compared to before venoplasty.

One other observation that he and his colleagues made was a re-stenosis of the jugular veins. That occurred in about half of patients by around 18 months after the original venoplasty. So about half of patients had a re-stenosis, or re-blockage, of their veins. This re-blockage was also then associated with relapses after the venoplasty. In the patients who had relapses, they were more likely to have a re-blockage of their veins. Next slide.

So why not embrace this hypothesis and recommend this procedure for all MS patients, because certainly this is a very exciting observation. It's a totally game-changing theory, changing this from an immune problem to primarily a blood flow problem.

Well, there are a couple reasons that raise some caution before we jump into this and embrace it fully. That is, that subsequent studies made some somewhat different observations. There are two I'd like to touch on here.

The first was done by Dr. Zivadinov and his colleagues at the University of Buffalo where they evaluated 500 people, including MS patients and healthy subjects and patients with other neurologic conditions. They found that in the MS patients, 56% of them had met criteria for CCSVI, so quite a bit lower than the 100% of the original Zamboni report.

Also, 22% of the healthy subjects met criteria for CCSVI, which obviously is much higher than what was seen with Zamboni reports. Also, and perhaps just as importantly, 43%, so pretty close to the proportion of MS patients, 43% of patients with other neurologic conditions, not MS, but other neurologic conditions – they also met criteria for CCSVI. So this raised the question of maybe the venous findings are not directly related to MS, but are related to some injury of the brain, perhaps a downstream or maybe an upstream effect of injury to the brain.

The second study was just published online a couple weeks ago by [Dr. Doepp] and colleagues from a combined group out of Germany and the United Kingdom. They evaluated CCSVI in both MS patients and non-MS control groups. They found that none of the MS patients met criteria for CCSVI, and none of the non-MS controls met criteria for CCSVI. So clearly very different observations than what was originally reported by Dr. Zamboni and colleagues.

Another important point to make is that Dr. Zamboni's venoplasty study was unblinded and also had no control group. So there is a natural regression in MS disease activity that one can see in studies. Given the variable nature of MS, it's somewhat difficult to know whether the disease would have eased up without intervention or if it was related to the intervention.

In addition, sometimes in treatment one's hopes can influence the outcome. This is the so-called expectancy effect, or expectation effect. This effect has long been recognized, for over a century, in medicine and can have a very significant impact on the outcome of treatments – an impact both on patients as well as the clinicians who are providing the treatments.

For example, a recent phase III trial in multiple sclerosis found that the rate of relapses decreased by 45% during the trial compared to before the trial. Over half of the patients were free of relapses, and about 20% of patients reported an increase in their quality of life. But these patients were all part of the placebo arm of that trial. They were not on an active treatment but were on the same treatment during the trial as they were before the trial.

So this improvement was likely a combination – in that trial, anyway – a combination of the variable nature of MS and the expectancy effect. But whatever the explanation, it does emphasize the importance of control trials in understanding the true impact of any therapy in medicine, and this includes CCSVI.

Another important note is that the rate of complications from the venoplasty procedure is not really yet known. The Zamboni reports did not include the description of the complications of venoplasty. Subsequent to those reports, some serious adverse complications have been reported from other centers, including the death of a patient and another patient who required open heart surgery after the procedure.



## What's new in MS research and treatment



So clearly there are many unknowns that are related to CCSVI, particularly the conflicting reports of the prevalence of CCSVI and MS, some reporting 100% of MS patients, others in 0% of MS patients, and still others somewhere in between. So clearly, more studies are needed. Next slide.

So that leads into the CCSVI research program that has been initiated and funded by the US and Canadian MS societies. As alluded to at the beginning by Dr. O'Looney, this was a large grant competition where the grant applicants were reviewed by an external and international panel of experts in both MS and vascular disease who evaluated the strongest projects.

There were seven projects that were funded at eight sites, and they are shown here on the map: three US sites, including Madison, Wisconsin and Houston, Texas as well as our site at the Cleveland Clinic; in Canada, the sites included in Calgary, Ottawa, Saskatoon, Toronto and Vancouver. Next slide. So what are these projects going to do? Well, I'm not going to go through each project individually, but rather refer to what they will find as a group.

Over the next two years, these investigators will study over 500 MS patients, including pediatric MS. They will repeat the CCSVI assessments using ultrasound, following the same criteria that were originally developed by Dr. Zamboni and his colleagues.

They will also apply MR venography – this is using the MRI to visualize the veins – and will also use catheter-based venography to understand how the ultrasound findings correlate with what is seen on MRI and with the catheter-based venography.

They will compare the venous findings to over 600 non-MS controls. This will include healthy subjects, non-MS patients with neuro-inflammatory disorders; non-MS patients with atrophy, to evaluate whether it's just brain atrophy that leads to some of these venous changes; patients with other systemic autoimmune disorders that don't affect the brain; as well as the siblings of MS patients who don't have MS, to find out if this perhaps runs in the family but may not be related to MS.

The investigators will evaluate the relationship between CCSVI and the disease characteristics of MS. This will include the disease subtypes, relapse-remitting, secondary progressive, primary progressive and others; the disease duration, how long patients have had MS compared to what's found in the venous systems; MRI measures of injury, including the key to a lesion load and brain atrophy; also clinical disability and how the disease has evolved over time, with the theory that if this is related to MS that the more severe CCSVI findings would relate to more aggressive disease over time.

Next slide. In addition, these investigators will assess the reproducibility of CCSVI measurements. If this is going to be a useful tool, we need to understand if this is a reliable measure. So patients will be evaluated once and then brought back a week later and evaluated again to see are the findings consistent over time.

There will also be an evaluation of the correlation between ultrasound and MRV, or the MRI measures of the veins, as well as the catheter-based venography techniques. That is with the idea of what is the best imaging modality to assess CCSVI.

There will also be an evaluation of the venous tissues pathologically at autopsy. These are patients who are enrolled in a brain donation program. After they've died, they've agreed to donate their brain and spinal cord for MS research. In addition, the veins will be looked at to understand pathologically what is present to correlate with ultrasound findings in patients when they're alive.

Also, advanced MRI techniques will be used to investigate the association between CCSVI and MS pathology. So as I mentioned before, looking at brain atrophy – but also there are ways to look at iron deposition. Some theories have been raised about how CCSVI may cause increased iron deposition, leading to MS injury. So that will be looked at using some advanced MRI methods.

Also, all these studies will be performed blinded to the clinical status and the disease designation. So all of the investigators, the ultrasound technicians, the physicians who will be reading the ultrasounds and the MRVs, they will all be blinded as to what is the status of the individuals they are studying – whether an MS or a healthy control group – and the disease duration and so forth – so that the potential bias that can sometimes be present in open studies can be minimized as best as possible.



## What's new in MS research and treatment



Now because of the risk of intervention, which I had referred to earlier, and the current uncertainty of the CCSVI hypothesis, at this point, no intervention will be performed through these seven studies – although we had just heard from Dr. O'Looney about some intervention studies that are starting in other places. Next slide.

So it's fine to do these projects, but if you don't have personnel trained in what they're doing, the data that's derived from (the projects) is not necessarily very useful. It's perhaps no surprise to most of the listeners that MS neurologists don't know a whole lot about the venous system in the neck and draining the spinal cord.

So these studies involve professionals, or cert professionals, far beyond just the MS specialist, the MS neurologists. Nonetheless, MS neurologists are involved in each of these centers, including pediatric MS neurologists at some of the centers.

Other research professionals will include cerebrovascular neurologists; neuroradiologists; neurovascular imaging specialists; interventional radiologists, the ones that actually do the venography; vascular surgeons; cardiologists, because they have a tremendous amount of experience in performing ultrasound of both the veins and the arteries; vascular pathologists; neruopathologists: and anatomists to assist with the pathologic evaluation of the vein tissues that are obtained at autopsy; as well as biomedical engineers and biostatisticians.

Each research program will be carried out as well with oversight by the local ethics review board to ensure that these studies are performed appropriately. Next slide. So what's going to come out of all of this? Well, at the completion of these studies, we'll have several (learnings). One is we'll have independent evaluations of the CCSVI theory. So we will have a number of centers that will independently ask the questions about CCSVI and its connection with MS. We'll have a very good sense from this group of investigators and others around the world who are also looking at this, how to connect this to MS.

We will also have a clear understanding of the relevance of CCSVI to MS and will understand the reliability of the assessments, the ultrasound and the MRV assessments of CCSVI. We'll have a correlation of the non-evasive evaluations with the invasive venous measures. We'll also understand the pathologic correlates of venous insufficiency.

Perhaps most importantly, we'll define an optimal target outcome for future trials if the clinical trials are indicated, which is the best outcome for us to measure if we are to intervene with CCSVI. So I think data from these studies will provide a comprehensive foundation upon which to develop the next steps regarding CCSVI and MS.

To summarize, CCSVI is an exciting, intriguing hypothesis of MS pathogenesis. It's really turning the MS field upside down and asking a completely novel question. For that, it's truly, truly exciting. Nonetheless, like with any new findings, the results really need to be replicated with additional rigorous studies to ensure the validity of what has been found and to give some clarity as to why other studies have not quite found what the original studies (of Dr. Zamboni) found.

Finally, given the risks of intervention and the possible need for repeat procedures, additional studies of CCSVI are needed now and are indeed getting underway. So with that, I will stop and take some questions.

### QUESTION AND ANSWER

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Thank you Dr. Fox. I would like to just tell you what wonderful and exciting studies these are going on. We look forward to the results. As you can imagine, we have many questions from our participants. We have a few minutes to ask you a few. Many of the questions that came in were related to whether or not one should be tested.

I know you can't give individual medical recommendations, but we have one question from Anne in Massachusetts who asks: Who should get tested for CCSVI? Should the person with relapsing-remitting MS? She would like to, obviously, avail herself of anything that may help alleviate symptoms or may have some improvements. So can you make a comment there, Dr. Fox?

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**



Sure, I'm just going to speak from my opinion. That is, at this point I'm not recommending my patients get tested for CCSVI. That's for a few reasons. First, the ultrasound testing is not yet established enough that general ultrasound technicians can perform it properly. This is a brand new (testing) that the ultrasonographers are being asked to do. For that, one needs to have specific training in order to do it properly.

Second, even if CCSVI is found by an appropriately trained technician, we don't know what to do about it. We really don't know if a venography and venoplasty will be effective. As we saw in the report from Dr. Zivadinov from Buffalo, almost a quarter of healthy individuals meet criteria for CCSVI but don't have MS and probably don't have any indication for any intervention.

As with any therapy, it comes down to the cost-benefit ratio. What are the risks of treatment and what are the benefits? Without a controlled trial and further studies, I think we really don't know the answer to either part of the tradeoff.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

A similar question comes from Lance. He talks about the improvements that we're seeing reported. You touched upon it a bit in your presentation – should people be travelling overseas? I guess it relates to with how you just answered the first question. But people are confused, I think, because they are hearing about positive reports for people travelling overseas. There's just a quandary of what to do.

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

Well, I think it goes back to without a controlled trial, we really can't tell. We know that patient expectations do have a strong influence on outcomes, including MS symptoms. So at this point, I'm not recommending patients go overseas to get this procedure, because I think we just don't know what the benefits might be and we don't know the complication risks.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

And a question from Melody in Ontario, Canada: What difference does it make if CCSVI and MS are related? If we have blocked veins, why shouldn't we treat them anyway?

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

Well, the venous system has tremendous redundancy and variability. When one vein is blocked, other veins can easily drain that tissue. Perhaps as an example, head and neck surgeons routinely remove the jugular vein in patients with a neck tumor. I don't know of any case where the removal of the jugular vein has led to the development of MS.

So just because a vein is blocked and doesn't have flow, it doesn't mean it should necessarily be opened. Or to put it another way, just because a vein doesn't have blood flow, it doesn't mean opening it will be of any benefit to the patient.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Related to that comes a question from Thierry in Quebec. We hear so many times about iron levels – her question is, if veins are blocked, aren't there increasing iron levels in the brain?

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

I think it's a bit premature to connect blockage of veins to iron, and it's also premature to connect iron with MS. That hypothesis has been put forward. But I think we don't really know enough about the connection between blocked veins and iron, and iron with MS. It's certainly not been shown that iron causes MS.



There are many disorders where when the brain is injured, iron deposition is left behind in the footprint of that injury. So whether iron is directly involved in the injury, or is just a following side effect of the injury, is unclear. I think those are important questions that we just don't have answers to yet.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

One final question is from Vicky in Ohio. She (asks), and I think you touched upon this too Dr. Fox: How do I get on recruitment lists for the future clinical trials when they become available?

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

Well, I'm going to turn that back to you and say I understand that the MS Society will be posting on their Internet site when the various locations will be enrolling CCSVI patients into their studies. Is that correct?

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

That is correct. Thank you, Dr. Fox. I was going to add that to (your answer), as well as in terms of if anyone is interested in future activities, please do visit ([nationalMSSociety.org](http://nationalMSSociety.org)). I do have one more question for you, Dr. Fox. This comes from Pam in Washington State. She was wondering if you could clarify about the ultrasounds used. We often hear about the Transcranial Doppler ultrasound. How will the technicians be trained? Could you talk about what the actual procedure involved – what would the patient actually experience?

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**Dr. Robert Fox - Mellen Center for Multiple Sclerosis - Staff Neurologist, Medical Director**

So the ultrasound is much like the ultrasound that patients get for their carotid artery. So if a patient is suspect or having found to have a stroke, an ultrasound of the carotid artery is often ordered. Instead of looking at the carotid artery, the jugular vein is evaluated.

However, it's a little tricky to evaluate the jugular vein in that it is a low pressure, very compressible structure. So if one pushes too hard on the vein, one can easily occlude it and create what appears to be a stenosis, but is just brought on by the transducer or the probe that's on the neck. So the technician needs to be trained on how to do that.

Also, what Dr. Zamboni had described in the criteria, which is the reflux and the degree of reflux that has to be done in a very precise way and requires training. One of the five criteria also involves looking through the bones of the brain into the veins in the brain. The veins in the brain are not something that the ultrasonographers routinely look at. But with some training, they can get oriented in terms of how to look at them and how to find them.

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**Dr. Patricia O'Looney - National MS Society - VP - Biomedical Research**

Well, thank you, Dr. Fox, for helping to bring so much clarity to the work under way in pursuing the CCSVI lead as it relates to MS disease process. Unfortunately, that is all the time we have for questions today. I would like to thank our three speakers, Dr. Rolak, Dr. Calabresi and Dr. Fox. I also would like to thank all of you for participating and submitting your questions. We hope that you found this session informative and timely.

Today's webcast and slides will be archived and available for viewing on the National MS Society's website at [nationalMSSociety.org](http://nationalMSSociety.org). If your question was not covered today, or if you have additional questions about MS and the topics addressed by our speakers, please visit the ([nationalMSSociety.org](http://nationalMSSociety.org)) or contact one of our MS Navigators in our information research center for help at 1-800-344-4867.



For additional details on emerging therapies and nervous system repair and protection, watch the Society's MS Learn Online programs located in our multimedia library also on our website ([www.nationalMSSociety.org/MSlearnonline](http://www.nationalMSSociety.org/MSlearnonline)). Thank you all again for joining us today, and please enjoy the rest of your day. Thank you.

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### Operator

This concludes today's conference call. You may now disconnect.

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