Webcast Transcript
From the Frontlines: What’s New in MS Research for 2012
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MODERATOR
Dr. Timothy Coetzee - National Multiple Sclerosis Society - Chief Research Officer

PANELISTS
Dr. Amit Bar-Or – Dr. Amit Bar-Or is Associate Professor of Neurology and Associate in Microbiology and Immunology at McGill University, and a practicing neuroimmunologist at the Montreal Neurological Institute. He established and directs the Experimental Therapeutics Program and serves as Scientific Director of the Clinical Research Unit. He leads a research team studying basic principles of immune regulation, immune-neural interactions and stem cell biology, and how these relate to physiologic processes, injury and repair in the human central nervous system.

Dr. Robert Fox - is Staff Neurologist and Medical Director at the Mellen Center for Multiple Sclerosis which is a part of the Cleveland Clinic Foundation. He is also an Associate Professor at the Cleveland Clinic Lerner School of Medicine. Dr. Fox’s current research interests focus on clinical trials in MS, innovative MRI techniques to evaluate tissue recovery after injury and the effects of MS treatments, as well as MS patient decision-making and tolerance to risk. In addition, he is directing studies evaluating chronic cerebrospinal venous insufficiency, commonly known as CCSVI, in MS. He is a team leader for many clinical trials, including being the global coordinating principal investigator for a Phase III clinical trial of BG-12, one of the new oral therapies that is in testing for relapsing-remitting MS. He also serves as the Managing Director of NARCOMS, which is the North American Research Committee on MS Patient Registry. This currently follows over 15,000 MS patients through semi-annual surveys.
**Dr. Colleen Hayes** - is Professor of Biochemistry at the University of Wisconsin-Madison. Dr. Hayes and her collaborators were the first to propose that vitamin D obtained from sunlight exposure of the skin might be a natural inhibitor of MS due to the ability of the vitamin D hormone to selectively eliminate autoimmune T cells. With support from the National MS Society and others, her team has been studying the influence of vitamin D in mice with MS-like disease. Dr. Hayes was the co-chair of the Vitamin D summit and has been spearheading the idea of an MS prevention trial.

**Dr. Robert Miller** - who is Vice President for Research and Technology Management, the Director of the Center for Translational Neuroscience, the Allen C. Holmes Professor of Neurological Diseases, and a Professor of Neurosciences at Case Western Reserve University in Cleveland, Ohio. Dr. Miller has a primary interest in Central Nervous System neural development and nervous system repair. In addition to leading a large research team, Dr. Miller is collaborating with the Society’s subsidiary Fast Forward to study the use of stem cells as possible MS treatment. He is also a principal investigator with the Myelin Repair Foundation.

**PRESENTATION**

**Dr. Coetzee:** Hello, and thank you for joining the National Multiple Sclerosis Society's live webcast; *From the Front Lines, What's New in MS Research for 2012.*

I'm Dr. Timothy Coetzee, Chief Research Officer of the National MS Society and the moderator of today's webcast. We're here in Chicago, where we've just finished an exciting summit asking the question, can we prevent MS with Vitamin D?

We have two of the participants here this evening to share some of the exciting outcomes from the summit with you. This summit caps off a year of exciting progress in MS research. I'll be discussing some of this progress with our cutting-edge investigators.

As we move into 2012, we look forward to several emerging therapies which continue to advance through the pipeline, as well as progress towards the crucial goals of finding ways to restore function and improve quality of life.
The National MS Society continues to propel research forward with a comprehensive research strategy. This year, we provided nearly $40 million to support over 325 new and ongoing projects, including everything from discovery research to the society's commercial therapy development efforts through Fast Forward. New projects we launched included clinical trials testing new ways to protect the nervous system from being damaged in MS, studies of adult stem cells and natural molecules that may stimulate repair in the nervous system, and studies on viruses and bacteria that may be involved in triggering immune attacks in people with MS.

We've also been collaborating to create a global consortium focused on research and progressive MS. There is power in numbers, and the more inclusive we are the easier it will be to tackle progressive MS.

Each of our panelists this evening understands the power of collaboration. They lead and are members of wide spread research networks that can speed crucial research on many questions in MS. Let me introduce them so that we can dive right into the exciting developments we expect in 2012.

Dr. Amit Bar-Or is Associate Professor of Neurology at McGill University. He is a practicing Neuro-immunologist at the Montreal Neurological Institute, where he also established and directs the Experimental Therapeutics Program. Dr. Bar-Or was a leading participant in this week's vitamin D summit.

Welcome, Amit.

Dr. Amit Bar-Or: Thanks, Tim.

Dr. Timothy Coetzee: Next we have Dr. Robert Fox. Dr. Fox is Staff Neurologist and Medical Director at the Mellen Center for Multiple Sclerosis, which is part of the Cleveland Clinic Foundation. He is also an Associate Professor at the Cleveland Clinic Learner School of Medicine.

In addition, he is directing studies evaluating chronic cerebral spinal venous insufficiency commonly known as CCSVI in MS. He also serves as the Managing Director of NARCOMS, which is the North American Research Committee on MS Patient Registry. This registry follows over 15,000 MS patients through semi-annual surveys.

Thanks for being here, Bob.
Dr. Robert Fox: It's a pleasure.

Dr. Timothy Coetzee: We also have Dr. Colleen Hayes. Dr. Hayes is Professor of Biochemistry at the University of Wisconsin, Madison. Dr. Hayes and her collaborators were the first to propose that vitamin D obtained from sunlight exposure of the skin might be a natural inhibitor for MS.

With the support of the National MS Society and others, her team has been studying the influence of vitamin D in mice with MS-like disease. Dr. Hayes was the Co-Chair of the Vitamin D Summit.

Welcome, Colleen.

Dr. Colleen Hayes: Thank you, Tim.

Dr. Timothy Coetzee: Finally, we are also joined by Dr. Robert Miller who is Vice President for Research and Technology Management at Case Western Reserve University in Cleveland, Ohio.

He is also the Allen C. Holmes Professor of Neurological Diseases and a Professor of Neurosciences at Case Western Reserve. Dr. Miller's research is focused on the development of the central nervous system as well as nervous system repair in MS. He is also a principle investigator with the Myelin Repair Foundation.

Thank you for being here, Bob.

Dr. Robert Miller: My pleasure.

Dr. Timothy Coetzee: Well, let's get started right now, but first, I'd like to also invite our audience members to type their questions into the text box at the bottom right of the screen, then click on the submit button, and we'll be sure get your question answered.

Amit, let's begin with you. What would you say are some of the most exciting advances that have been made, over say the last 18 months which may have had a positive impact on the lives of people who live with MS?

Dr. Amit Bar-Or: Well, there have been several, Tim. I think I'll mention three. The first is that not long ago, the first oral therapy for multiple sclerosis has been approved and there are several additional ones that are likely to get approved in the
next year, year and a half, or so. That, of course, is going to be a very major impact on patients.

The second is that there is a new generation of therapies that seem to be targeting new aspects of MS including ones that do get into the central nervous system. So, here, we hope we will be affecting not just the immunology of MS, but the neurobiology of MS.

And the third is that there have been some important strides, although still a ways to go, in understanding the biology that underlies progressive MS and this is, of course, one of the most important puzzles for us to solve.

Dr. Timothy Coetzee: Certainly. So, Bob, same question for you. What would you say are the most exciting advances in the last 18 months that can have a real positive impact?

Dr. Robert Fox: I'll add three more to Amit's three. One is that we developed our first therapies specific for progressive MS patient, and that's a pill to help with walking problems that progressive MS patient have.

Secondly, we've learned a lot about risk stratification or understanding which patients are at risk for different complications from therapies. This has helped us tailor which therapies we recommend to which patients.

Thirdly, we've learned a lot about MRI and how to use MRI to monitor response to therapy. Now we've been able to shorten the amount of time it takes to understand whether a patient is responding to their MS therapy, and we shortened it from a couple of years down to as short as six months.

Dr. Timothy Coetzee: That's some great progress. Colleen, you've been interested in vitamin D for many years, can you tell us briefly what we know about vitamin D and its connection with MS?

Dr. Colleen Hayes: Yes, very briefly, we know that there is a strong association between low vitamin D levels and a high risk of MS, and conversely a strong association between high levels of vitamin D and a low risk of MS.

We also know that in people who already have a diagnosis of MS those with the highest levels of vitamin D have the lowest risk of relapse, and conversely those with the lowest levels of vitamin D have the highest risk of relapse.
So this association has been documented all over the world and it is so strong and so consistent and so universally observed that many scientists now believe this association must be telling us about a cause and effect relationship, and if that's the case, we may be able to actually use this information to reduce MS risk possibly even reduce MS relapses.

**Dr. Timothy Coetzee:** So another reason for me to take my vitamins. Bob, you are an expert in myelin. Can you remind our audience what myelin is and what role plays in MS?

**Dr. Robert Miller:** Myelin is the fatty insulation that surrounds the neuronal processes in the brain and spinal cord and out to the limbs. It does several things. It insulates individual axons so that they don't cross over and get their wires crossed. It also facilitates and accelerates the conduction of information along those axons. It's a little bit like the wires in your electrical circuits.

If the installation is lost then the wires will cross, and you will not get a good conduction. What happens in MS is that the myelin breaks down and axons fail to conduct so the brain can't tell the limbs what to do, and you end up with a functional deficit.

**Dr. Timothy Coetzee:** I see. So, let's just also talk a little bit about neuroscience and brain research in stem cell research. It's an exciting area. What are some of the advances that have been made in brain research and stem cell research?

**Dr. Robert Miller:** I think stem cell research is one of the most exciting areas at the moment in neurobiology. There are two things that really moved forward over the last two or three years. One of them is that we have now come to understand that the adult brain has neural stem cells that can be activated to promote repair in injury if we could only control those cells.

The second advance I think that's really useful is that we now know that other cells apart from neural stem cells can actually promote functional recovery in animal models of multiple sclerosis.

So we think that they can both promote neural cell proliferation and generation as well as regulate the immune response. Perhaps they are multi-pronged, and can be used as a multi-pronged approach to treat the disease.
**Dr. Timothy Coetzee:** That's very exciting. Amit, let's talk a little bit about the immune system involvement in MS. There have been some recent advances looking not just at the classic immune T cells in MS, but a lot of attention is being paid to B cells in MS, and what the promises for their -- what are the implications for studying B cells in MS?

**Dr. Amit Bar-Or:** You're right, Tim. People used to think of MS as a condition that is mediated by T cells of the immune system and lo and behold recent studies have shown that by removing only B-cells of the immune system from the circulation of people who have MS there's a very substantial decrease in new clinical relapses.

So it is no longer a question of whether B cells are involved, but how and they seem to be doing so by interacting with the T cells and contributing to new MS activity.

**Dr. Timothy Coetzee:** So it's like there are multiple types of cells and targeting some can really have a beneficial effect in MS, targeting B cells can really change MS?

**Dr. Amit Bar-Or:** Exactly, and these treatments, if approved, will turn out to be administered at much lesser frequency than the current treatments, and if the safety profile is also reinforced, these could be an interesting option for many people with MS.

**Dr. Timothy Coetzee:** Wow, that's exciting. And we just touched on this, so what you're saying is that there are subsets of cells than and that there are some T cells and B cells that are involved in the attacks, and really touching on specific ones could allow a person to only touch on the MS and not other aspects of the immune system?

**Dr. Amit Bar-Or:** We've certainly learned that amongst both the B cells and the T cell populations there or what we might consider in the context of MS to be good guys versus bad guys. We need to get better at only targeting the bad guys and perhaps even promoting the good guys to acquiesce as much as we can of the inflammation that hurts people with MS.

**Dr. Timothy Coetzee:** Very exciting. So, Bob Fox, you're one of the investigators who are part of the team funded by the National MS Society and the MS Society of Canada to investigate the CCSVI or chronic cerebral spinal venous insufficiency in MS, can you give us an update and your take on the debate?

**Dr. Robert Fox:** Sure. First just to make sure everyone knows about CCSVI, this is a hypothesis about what causes MS and that it is caused by a blockage of veins
[draining] the brain and spinal cord; a little bit different from the immune hypothesis, and obviously having different implications regarding treatment.

There are seven research grants that were awarded by the US and Canadian MS Societies and we are a recipient of one of them fortunately back in Cleveland. One of the things that we've learned and in comparing our experience with the other centers is that the ultrasound assessment, which is what has been described as the assessment for CCSVI, is a lot trickier than we had originally thought.

This is an area of the body that has not been well-studied in the past. The arteries are studied quite well for things like stroke and heart disease, but the veins -- the draining veins, there's not as much known about them, and so recognizing what is pathologic or disease and what is just normal variation is not quite clear and how to use the ultrasound tool to evaluate that is still being worked out.

**Dr. Timothy Coetzee:** It's a lot of work to do. There's also, in some of your research I understand you've been looking at some of the autopsy materials and are looking inside people's veins in autopsy material, what have you learned there and what have you learned in comparing that to people who don't have MS?

**Dr. Robert Fox:** We have a tissue donation program at the Cleveland Clinic where MS patients can donate their tissues to our research program after death. And we have modified the consent form for that program to allow patients to donate their veins -- their neck veins and spinal cord veins, for us to further evaluate the CCSVI hypothesis.

The idea is that if this is truly related to MS then we should be able to see something at autopsy. We have preliminary data that we presented this past fall on seven MS patients and six non-MS controls. And what we found is that there was no difference between the MS patients and the non-MS patients in the stenosis or the narrowing of the veins in the neck and drain in the spine.

But what we did see at what seemed to be a higher frequency in MS patients were abnormalities within the veins. These were membranes and various things that we're still learning about and still studying that are contained within the veins and could well impact the flow of blood in patients that have these.

I'll quickly add that just the presence of these abnormalities does not necessarily prove the CCSVI hypothesis. And certainly, a lot more work needs to be done to understand if this truly is a real observation and whether it's related to the disease and
whether intervention would then improve the disease. So, we're still a long way off in terms of that.

**Dr. Timothy Coetzee:** We'll look forward to seeing more progress on that later next year. Colleen, I understand that immune cells are built to receive communications from vitamin D or, in other words, they have receptor sites for vitamin D. Can you tell us what that means in terms that people -- the average person on the street could understand?

**Dr. Colleen Hayes:** You know, that was the original question that led me to be interested in this field. Why does a lymphocyte need a vitamin D receptor? Because we've known for a very long time that vitamin D is necessary for strong bones and teeth, but no one realized that it's also acting in white blood cells.

It's actually needed by those white blood cells to control their functions. They do have the receptor for vitamin D hormone, and in those white blood cells it seems to be controlling not just their functions but how long they live.

So when there isn't enough vitamin D and they are not receiving that communication and that instruction it appears that they make some mistakes. And they can mistakenly target tissues of a person's own body, and when that happens we call that autoimmune disease.

So, this is very exciting because it gives us an entire new look inside the white blood cell and how it may be receiving information that originally comes from the sunlight.

**Dr. Timothy Coetzee:** So actually, this ties into my next question for you, Colleen. As I mentioned earlier you were the co-chair of the summit looking at whether or not we know enough today about trying to prevent MS using vitamin D supplements. What are some of the highlights of the meeting that people living with MS would find interesting?

**Dr. Colleen Hayes:** Well, I think I would list three. The first highlight for me is that we had scientific experts come from all over the world to discuss this question; do we know enough to prevent this disease, and how will we test that idea?

We had investigators meet us from Canada. We had others from Canada -- the United Kingdom. We had Finland represented, Australia, Argentina, and New Zealand. It was a very international group -- a very exciting intense discussion. So, that was the first highlight for me.
The second highlight would have to be a genetic finding that came from the UK and was just announced last week and was presented for the first time at this meeting. And that genetic work implicated the vitamin D pathway in MS, and gave us greater certainty that this is indeed a pathway that is connected to MS.

I think the third highlight for me is that we have a plan. At the end of our intense two days of work, we came up with a plan that we think will test this hypothesis -- can we prevent MS with a vitamin D supplement? And we'll be going forward to refine that plan, and I hope, launch it soon.

Dr. Timothy Coetzee: Terrific. And it was a great two days -- really inspiring. Well, Bob, I know earlier you talked about stimulating myelin. Researchers talk about two different ways of stimulating myelin repair in people with MS.

One is to rev up stem cells that are already in the brain getting them to do a better job of repairing the nervous system. The other idea is actually bringing in new players with replacement T cells with the kind of cell therapy. What kind of progress are we seeing on these two fronts?

Dr. Robert Miller: Well, Tim, it's important to remember that it's only in the last few years that we really realize that the brain -- the adult brain, has stem cells that are capable of being activated to promote repair.

I think there are two areas where we're beginning to look at being able to rev up those cells -- why don't they repair normally, and can we make them repair better? So pharmaceutical treatments, drug treatments that are beginning to be targeted in that area. And also stem cell treatments that are targeted at the brain's own stem cells. So, these are revving up the potential for recovery within the patient's own brain.

But the idea that you can do a transplant of cells that will then augment or help the repair process has been around for a long time. I think that people have now been able to generate oligodendrocyte precursors. These are the precursor cells to the myelinating oligodendrocytes in the brain and spinal cord.

And we can, in some models, transplant those directly into the brain and spinal cord where there are injuries. The problem with multiple sclerosis is that there are multiple areas. And this makes it very difficult to think of doing a direct transplantation of oligodendrocyte precursors; even the patient's own oligodendrocyte precursors into the brain and spinal cord.
It's become clear over the last year or so that actually you target cells into areas of damage in the brain and spinal cord through the bloodstream. If you put cells into the veins of animals they will hone on or target areas of damage. Perhaps we can direct our oligodendrocyte precursors or our reparative cells to areas of damage.

And I think that emergence of our understanding of how that's targeted is going to be very exciting in the future.

**Dr. Timothy Coetzee:** So, could you imagine a future where a person goes into their doctor's office and they get an infusion of some stems cells in their doctor's office to repair their brain? Is that what you are saying, Bob?

**Dr. Robert Miller:** I think that the doctor's office is --

**Dr. Timothy Coetzee:** -- the future.

**Dr. Robert Miller:** I think in the future we already are seeing some clinical trials that are beginning to go on across the globe, where actually patients are receiving stem cells through their veins that are targeted towards trying to repair damage in the central nervous system. So, yes, it's not impossible.

**Dr. Timothy Coetzee:** That's exciting future. We're going to take some questions from our audience now, and these have come in over the web. Amit, I'm going to direct this question to you. It comes from Florence in Wisconsin who asks, how close are we being able to access these stem cell therapies that we were just talking about?

**Dr. Amit Bar-Or:** Bob had mentioned a couple of important points about the recent developments -- a lot being learned. There are different types of stem cells, and that's important because the different types of stem cells are in different phases of research and development.

While there are none that are currently approved, formally for use in the multiple sclerosis, as Bob had mentioned, there are several in clinical trials, Phase 1 and Phase 2 clinical trials.

If those turn out to show positive results in terms of both the efficacy and safety, one would hope to see the definitive Phase 3 studies evolve over the next few years, and then perhaps we'll get to a point where these become an actual part of the therapeutic armamentarium.
Dr. Timothy Coetzee: That's interesting. So another question comes from Valerie from Virginia who wants to know, what's new in research for those who have progressive MS.

Bob Fox, I'm going to ask you to take on that question.

Dr. Robert Fox: Sure. I think, over the last five to 10 years an important observation about progressive MS is that it's not relapsing MS. We've known that clinically, but we've had many clinical trials that have tried the therapies that work in relapsing MS and applied them to progressive MS, and they've been generally disappointing.

What we have done now is sort of gone back to the basics, and rethought through where we were not thinking as clearly as perhaps the could. One of the outcomes is a new collaboration, a consortium, that is being built now between different MS societies here in the US, in Canada and Europe as well, to try to join together into a think tank to put our forces together to better understand this, and it's divided into three areas.

One is in the animal model in basic science; to try to really get around what animal models do we have, what basic science models to we have, or do we need to develop to study this better?

Then, secondly, Phase 2 trials. Phase 2 trials are the proof of concept. It's sort of a testing trial to see does this drug look like it may have benefit. And we have a great marker for that in relapsing MS and that's new MRI lesions. And that's been a very effective marker for Phase 2 trial in relapsing MS. We don't have the equivalent in progressive MS, and we need to develop that.

And the third area is in clinical outcomes. What are the clinical measures that we use to measure the benefit or the potential benefit of a therapy in progressive MS? And so, by focusing on those three different areas, I think there is great hope for progress in the next few years.

Dr. Timothy Coetzee: Great. Colleen, I'm going to ask you a question. Angela is asking whether or not vitamin D can prevent MS in children of parents, uncles, cousins with MS.

Dr. Colleen Hayes: Well, Angela, I am glad you asked that question because that is exactly the question that was on our minds for the past two days of the vitamin D
summit. And, in fact, the experiment that we think might be the best one to go forward will actually involve that exact question.

We will be counting on all of the MS patients who are members of the societies around the world to help us ask that question. And I hope that, in the not-too-distant future, I will be able to say we know the answer and it was a good one.

**Dr. Timothy Coetzee:** Okay, great. Terrific. I do want to come back to Bob Fox and ask you -- Josephine in Ireland is asking about emerging therapies. So, we talked a bit about this consortium. How will the emerging therapies fit into that -- into the work of that group? Or, even are there any therapies now that are being tested on progressive MS?

**Dr. Robert Fox:** There are some therapies. Certainly, the stem cell therapies that we heard Bob Miller and Amit refer to, I think they hold great potential for therapies in progressive MS.

There's also some other areas of mitochondrial function. So, mitochondria is the energy machine of the cells. And we are coming to learn that that fails in progressive MS, and there may be some therapies that target protecting and strengthening the mitochondria.

There are other mechanisms, as Bob Miller was referring to, of neurobiology that we may be able to target into and to try to identify what therapies may be -- what mechanisms we should target therapies to find a drug that works.

**Dr. Timothy Coetzee:** Thank you. Bob Miller - two Bobs. This is fun. So, Bob William is asking, are there any clinical trials going on today for the new myelin repair therapies?

**Dr. Robert Miller:** It's important to remember that the notion of being able to repair myelin in the adult brain is very new. It takes time from the discovery of that to actually coming up with therapeutics, coming up with clinical trials.

As Bob Fox alluded to one possibility is that the stem cell trials that are beginning to take off now may have a real effect in being able to promote myelin repair. There is a clinical trial that has just gone through a Phase 1 trial from Biogen Idec where they have a drug, a molecule that is targeted toward trying to rebuild the myelin in MS patients.
But we are just at the beginning of this. I think if you ask me that question in three to five years’ time, there will be potentially many trials of many potential therapeutics targeted at the repair of myelin.

**Dr. Robert Fox:** Tim, let me just add one additional facet with progressive MS, and that is there is growing focus on the symptoms side of progressive MS. Yes, we do want to stop the underlying disease, but there is a myriad of symptoms that are part of our MS patients. And the development of the walking pill, as it's called, last year, I think, heralded a new phase of us doing trials.

Now there are trials and neuropathic pain, or the pain that seen in MS patients, and bladder problems and stiffness, and many others symptom areas of progressive MS that I think hold great potential for the next few years.

**Dr. Robert Fox:** Great. I'm so glad you brought that up because there is so much more to the dimensions of MS. Thank you, Bob.

I do want to ask Colleen a question from Ellen who wants to know how much time a person with MS should stay in the sunlight in order to make enough vitamin D.

**Dr. Colleen Hayes:** That's a question that's a little bit hard to answer. So let me give you an answer that is a serviceable answer for the general population. Most of us can spend 20 or 30 minutes in the sunlight in the summer and obtain enough sunlight to meet our bodies' needs.

But the problem comes when you live in a northern climate like Wisconsin, and from the fall through the spring the sunlight isn't strong enough to form vitamin D in your skin. And during that time you have to use a supplement.

Now, for MS patients, it can be a little tricky because they often have a sensitivity to heat, which means they don't need to be in hot summer sun. But I've learned that you can make vitamin D from the sun light you get in the shade. And you can also use a vitamin D supplements if you can't tolerate is being in the sun.

We need to help them understand that you can separate the light and heat in 20 minutes or 30 minutes. Now if you're a person with darker skin, you need a longer time.

**Dr. Timothy Coetzee:** Thank you. On that note, Amit, Janet is wondering if there is a specific daily dosage of vitamin D that is recommended for people with MS.
Dr. Amit Bar-Or: That's a great question, Janet, and it was also one of the top questions that this international group that Colleen had done such a wonderful job pulling together debated over the last two days.

So, while there are no formal guidelines at the moment, the sense is that about 4000 International Units per day is probably a dose that is going to be effective in terms of the changes we hope will turn out to impact MS activity, and also be eminently safe in large populations.

Dr. Timothy Coetzee: So, about 4000 units per day. That sounds like a good number. Bob Fox, you've also been asking people with MS how they weigh possible risks and benefits with potential therapies, what are some of the findings from your research that will help doctors and their patients make good treatment choices?

Dr. Robert Fox: Yes, through a grant from the National MS Society, we invited patients in the NARCOMS MS patient registry; this is a voluntary registry of MS patients who volunteer taking questionnaires and surveys twice a year. We invited them to take an additional survey on how they choose their MS therapies and what risks they tolerate with their MS therapies.

What we found is a very broad range of risk tolerance to MS therapies, from really not tolerating any risk at all, to tolerating a tremendous amount of risk. When we looked a little bit deeper in this data set we found that men tolerated risk a little bit more than women.

So, they tolerated more risk for the same benefit of an MS therapy than women. And patients with more progressive disability tolerated more risk than patients with less progressive disability.

This data and additional that we collected I think will help guide clinicians regarding what risk tolerance, or what risk patients may be willing to tolerate in their therapies. I would also add that this study was only possible due to the volunteer efforts of patients in NARCOMS. And if there are MS patients out there listening now who are not part of NARCOMS, I would invite them to take part.

They can register simply on the NARCOMS website, which is www.narcoms.org. And we welcome MS patients to come join us.

Dr. Timothy Coetzee: Thank you for your good work. Colleen, the National MS Society has just launched a clinical trial to look at the question of whether or not
vitamin D supplements can reduce the disease activity in people who already have MS. But now -- during the conference, you've discussed the idea of setting up a clinical trial to prevent MS in people who don't even have the disease yet.

What are some of the challenges of doing a prevention trial?

**Dr. Colleen Hayes:** Well, first, I'm very glad that the Society is funding those studies, so that we will get an answer to the question of whether vitamin D can benefit those people who have the diagnosis of MS.

What's very difficult about a prevention study is that this is a complex disease and we don't have any good way of predict who's going to get MS. It's also fairly rare. So, we are going to need to study a large number of people.

The other complicating factor is that we don't have any way to predict at what point the disease will strike. We're going to have to follow those people for a number of years in order to get an answer to this question.

**Dr. Timothy Coetzee:** So it will take a lot of partnership with people with families and working with you to do that.

**Dr. Colleen Hayes:** It will. We need those families to partner with us, and we need them all over the world to partner with us. So, we're looking forward to that. We have a good plan. I might just add that every hour another person is diagnosed with MS in the United States. In a year, we spend close to $30 billion caring for people who have MS.

So we think it's time to envision this study, can we actually stop this disease in some proportion of people. So, we are ready to go.

**Dr. Timothy Coetzee:** Well, let me ask the clinician. Amit, your thoughts on a large-scale prevention and some of the points that Colleen made.

**Dr. Amit Bar-Or:** I think the challenges are not trivial, but what one stands to gain by doing this is tremendous. If vitamin D indeed turns out to be able to prevent MS, this would be a terrifically simple, cost-effective, safe way in doing so, and Colleen had already alluded to the major, major impact that MS has on the lives of people in society.
The best way to do this, perhaps the only way to do this, is to mobilize the troops exactly as Colleen had said on an international level, and to really lobby vis-a-vis governments and societies to try to figure out how to team up. Because this type of prevention study will require very large numbers of individuals and very careful monitoring of very dedicated individuals with MS over time.

**Dr. Timothy Coetzee:** Bob, any thoughts on that?

**Dr. Robert Fox:** Well, I think one thing that's very attractive is that this is a simple and inexpensive therapy, which is an ideal therapy to target in a very large number of people to try to prevent MS.

As was already said, it's a rare disease, and so preventing a rare disease in large were people. But in terms of a safe and affordable therapy, it's hard to beat vitamin D.

**Dr. Timothy Coetzee:** Thank you. Let's talk to Bob Miller now about Fast Forward and the partnership that Fast Forward, the National MS Society's drug development subsidiary, is doing.

We recently invested in a company called Athersys that's testing the possible benefits of an adult stem cell therapy in mouse models of MS. Bob is one of the investigators for that effort. Can you tell us a bit about these cells, and what is it you're trying to do?

**Dr. Robert Miller:** If you think about stem cell therapies for a minute, one of the big questions is, is one stem cell the same as another stem cell? Are all stem cells grown under the same conditions? Does it make a difference?

If somebody's growing stem cells under one condition they're very effective, somebody's growing the same cells or different cells under a different condition, and they're less effective, how are we really going to understand how to manipulate and utilize those cells most effectively?

So what Athersys has done is that they have licensed a cell called a MAPC. This is a multi-potent. That means it can give rise to lots of different cells. Adult -- it comes from the adult -- actually adult bone marrow. P stands for precursor. It divides a lot. And, C is cell. So, it is an adult-derived proliferative stem cell.

Athersys has developed a protocol -- the way to grow large numbers of these cells all of which are exactly the same. So that now you can take almost an off-the-shelf cell
therapy and ask it, do the same cells work in different conditions, do the cells work for more chronic -- in more chronic models of MS that might have some of the characteristics of progressive MS, and can you use those cells in multiple different people with similar outcomes?

So this is actually, I think, an exciting way forward. At the moment, we're at this stage of testing these cells to see whether they behave like other stem cells in our animal models of MS.

**Dr. Timothy Coetzee:** So really, you're trying to validate whether or not they can work, and if possible -- could you imagine that if it's successful there that the next stage is clinical trials looking at whether or not these cells work in people who have MS?

**Dr. Robert Miller:** One of the really exciting things is that Athersys already has FDA approval to use these cells in a variety of other clinical conditions including stroke, which is a neurological condition.

So, I can imagine that if our preclinical studies move and we have some Fast Forward investment because we had some preliminary data that looks very encouraging. I think if those move forward, we could move to a clinical trial quite rapidly.

**Dr. Timothy Coetzee:** That's very exciting. Amit, I know you're involved in the Canadian Pediatric Demyelinating Disease Network. I'm going to ask you a question that I get quite a few times myself.

Considering that so few kids have MS, why all this interest in pediatric MS? Can studying all of these kids help us understand adult MS?

**Dr. Amit Bar-Or:** It's a fair question. MS in children is certainly much less common than MS in adults, although we know that about one in 20 adults with MS will have had an initial episode in the childhood or pediatric age group, about 5%.

The importance of studying MS in children is twofold. One from a standpoint of the clinical need you can imagine how difficult it is for a child, the family, to be faced with such a diagnosis at such an age.

But then the question is, can MS in children teach us something very important about MS in adults? And the reason that we were very interested in this scientifically is that when someone has the first presentation clinically of MS in adulthood, we believe that
for the most part, their MS biologically almost certainly started years prior. And some very interesting studies in populations have suggested that the window of risk of acquiring MS is probably in early childhood, maybe even earlier.

So by definition, studying multiple sclerosis in children might give us a window that is much closer to the initiating mechanisms or what actually triggers MS in individuals, and then we might be able to capture those initial early mechanisms and impact them.

And I should make the point that this would be based on the assumption that MS in children is the same condition as MS in adults, and we actually have generated over the last few years from data to support that idea.

We look for the same risk factors that have been implicated as risk factors in adults on the genetic and environmental side, and indeed when looking at children who developed MS compared to the proper controls, whether you look at the genetics or at Epstein-Barr virus exposure or low levels of vitamin D, all of those behave exactly the same way as risk factors in the early-onset as the adult onset.

So, we're very excited about this window of opportunity to capture the very early initiating mechanisms of multiple sclerosis.

**Dr. Timothy Coetzee:** So, do you think it's possible that studying kids could actually give us the root cause of MS?

**Dr. Amit Bar-Or:** Well, it's certainly closest to when that happens. And the problem with studying it in adults is, again, that we are so far removed. You think neurologically, if you have a dis-regulation that contributes to the initiation of MS, there can be what we call epiphenomena or other things happening, and when we may discover abnormalities that just reflect the consequence as opposed to a cause.

The other thing that's very important to keep in mind is we should not assume that the mechanisms that initiate a condition are necessarily the same ones that propagate it. And, if we really want to prevent and stop MS from happening in the first place it's those initiating mechanisms that we need to understand.

**Dr. Timothy Coetzee:** So, how many kids are in your network in Canada?

**Dr. Amit Bar-Or:** At the moment, this is a study that involves 23 sites coast-to-coast in Canada, and there are over 320 children currently recruited and a total of 400 will be followed over a period of five years and hopefully more.
Dr. Timothy Coetzee: And I understand this is also an international collaborative effort; that there are groups in Canada, the US and really around the world studying the problems of pediatrics MS.

Dr. Amit Bar-Or: There are additional initiatives including national US-based centers that are dealing now very importantly with pediatric onset MS and, as you point out, international collaboration. So, this is certainly picking up.

Dr. Timothy Coetzee: There's a lot of collaboration around the world. Well, let's go back to our audience now. Jill in Ohio is wondering why most research and information focuses on relapsing, or remitting MS?

Bob Fox, I'm wondering if you want to comment on that.

Dr. Robert Fox: Sure. I think we have studied both. The reason there is more on relapsing MS is we've been more successful at relapsing MS. We have developed treatments in relapsing MS much more effectively than progressive MS. And, our MRI measures are more sensitive to the disease activity in relapsing MS and the response to treatment in relapsing MS.

And then going even further back, our animal models -- our original animal models looking at brain inflammation in mice and in rats, really focused around a relapsing model more than a progressive model.

So, it's really been because we've been successful and have developed effective therapies, and that's fed one into the other of there being more research on relapsing MS. But clearly, progressive MS is the big target now that we're shifting to, not that we're ignoring relapsing MS, but we have good mechanisms to study that. And we are now turning our focus to progressive MS.

Dr. Timothy Coetzee: Amit, or, Bob, or Colleen, do you want to add any more thoughts that? Bob?

Dr. Robert Miller: I think the mechanisms are different. So, it's been much easier for clinical organizations, for pharmaceutical companies to target the immune response that is driving the relapsing remitting MS.
Once you get to the chronic MS then since we don't really know how to treat it and we didn't really know we could treat within the central nervous system, I think that's why you're seeing this.

**Dr. Amit Bar-Or:** Well, I was just going to add to that that I think we had traditionally considered MS to be a condition of the central nervous system. Our treatments that are actually effective in relapsing remitting MS, we believe for the most part work in the periphery.

And the community is now appreciating more and more that MS is a condition where there are different compartments involved in different ways throughout the MS experience. So, the relapsing remitting aspect of MS is almost certainly triggered by waves of immune cells that are activated in the periphery and managed to access the central nervous system, and cause those focal lesions that Bob had mentioned are seen readily on MRI.

But what happens is that, in addition to that biology, there's a biology that evolves and develops within the central nervous system itself. We think of it as compartmentalized within the central nervous system. And, it's that biology that has been largely inaccessible to most of our treatments that are applied and work in the periphery.

But the new generation of treatments includes the ones that do get from the periphery into the central nervous system, where they will have the opportunity to target inflammation and the neurobiology of MS, hopefully both at the level of protection and ultimately repair.

**Dr. Timothy Coetzee:** So, it sounds like really we need to start thinking holistically about how we stop some of that inflammation, restore some of that function, and really take a comprehensive approach to MS. Thank you.

Drew from Washington says that he wants to understand -- he understands that there is more than one risk factor for MS such as viruses and genes. So, how does all of this fit together with vitamin D?

Colleen, I think that's a question for you.

**Dr. Colleen Hayes:** Amit explained that we know of environmental factors that seem to be associated with MS risk, and we know about genetic factors that are associated. And within this environmental component, he mentioned Epstein-Barr virus and vitamin D.
I think of it as a triangle, with the genes here, vitamin D here, Epstein-Barr virus here. And what we are trying to understand scientifically is how the sides of the triangle interact. So we have learned in the past year or two about multiple interactions between the genes and vitamin D. There is a mutual regulation. Vitamin D is controlling some genes, and some of those genes are controlling vitamin D.

The missing piece of the puzzle is where this Epstein-Barr virus fits into the equation. We don't know about the relationship between vitamin D and Epstein-Barr virus, and similarly, we don't know about the relationship of the virus to the genes.

Somehow -- I've heard people term this a perfect storm. There's a perfect storm of having multiple risk factors accumulating and the disease developing, and that's what we're trying to understand; the timeline and the interactions.

**Dr. Timothy Coetzee:** Thank you. Diane sends this question as well. Should people with MS have their vitamin D levels checked on a regular basis?

**Dr. Amit Bar-Or:** Colleen may wish to add to this, but it's probably a good idea for everybody, including people with MS to have their vitamin D levels checked at least initially, and then for people with MS to have that level checked and work with their physician to figure out what type of vitamin D supplementation might bring them up into a level that is desirable.

We should keep in mind that the great majority of people, not just individuals with MS, but in this part of the world, are actually deficient in their vitamin D levels.

**Dr. Timothy Coetzee:** Wow.

**Dr. Colleen Hayes:** I would add that the estimates for fair-skinned people is more than half of us are vitamin D deficient, and for darker-skinned people, that number is up to 70%, 75%. So, it really is a massive health problem. And I think Amit has exactly the right approach. We need to get a baseline to work from, and then work with a physician to bring it up.

**Dr. Timothy Coetzee:** Right. So, one more question, and then we're going to go to the live questions. Another question for Amit from Bill wants to know if there are predictors as to what the course of MS will look like an individual. Can we know when a person is newly diagnosed with MS what the course of the disease is going to look like for them?
**Dr. Amit Bar-Or:** The reality is that we're still not terrific at this type of what we call prognostication at the level of an individual. We have data that's been collected in very good studies over a long period of time that give us a sense of averages.

So, on the average, if an individual starts with a progressive course of MS, if they are males as opposed to females, if they have problems early on that involve what we call the motor system, meeting mobility issues, those are all considered to be predictors of not doing as well down the road. But, again, one needs to keep in mind this is a game of averages, people can be very different.

What's probably the best predictor is, as Bob had mentioned a couple of times, are the newer insights into the imaging. And, using brain MRI in particular to understand early on either at the very first scan or the difference between the first and subsequent scan is beginning to give us additional tools to predict what might happen down the road.

**Dr. Robert Fox:** Tim, I would add that what's perhaps more important than thinking about what is my likelihood of progressing versus not is, am I on an effective therapy? And that's probably a much more important question, particularly in the relapsing phase of the disease. Is my therapy controlling the disease?

And that is the bigger question rather than oh, I'm a male and so I'm not going to do as well. You can't change that anyway, but you can change what therapy you're on and how you're responding to that.

**Dr. Timothy Coetzee:** Absolutely. Great. So, this is great. We've got a lot of questions in coming from the web. So, I want to -- we want to take a look at some of those.

Bob Miller, for you, Norm from Wisconsin is asking, what does the future look like for remyelination therapies? What will we see... the question is? Is it a stem cell, a drug? What do you see?

**Dr. Robert Miller:** I see a combination. I think that to promote myelin repair to drive functional recovery in the central nervous system, you're also going to have to regulate the immune response.

So I think some stem cells, the mesenchymal stem cells and perhaps even neural stem cells are able to act as immunosuppressants and to stimulate repair. But, I think, the
future for recovery within the central nervous system is going to be therapies that are directly targeted the axon, the neuronal component, and the oligodendrocyte.

Remember that it's not just myelin that's lost. It's myelin that is lost, and then the axons are damaged. We need to repair the axons to maintain the axons, and then to repair the myelin. And, I think, that's where people are really beginning to focus their attention.

**Dr. Timothy Coetzee:** Great, thank you. Bob Fox, for you, Marianne would like to know how far is the CCSVI from being an actual therapy for people with MS?

**Dr. Robert Fox:** Well, I think were still a little ways away from CCSVI. I still think it's a hypothesis about MS and not a treatment. We need to do a couple things.

First, we need to really understand how to evaluate it using the ultrasound tool, which is the main assessment tool for CCSVI. We then need to understand if what we find is truly related to the disease, or is it just associated and not really part of a causal link of the disease.

And then, we need to have treatment -- if those turn out to be positive than treatment trials need to evaluate whether intervention has a benefit for patients or not. So, there are a large number of steps that need to be done.

There is, in the planning stages, a safety trial that's in the planning stages in Canada. That will provide us some additional data as well. I think we're still a fair bit away.

**Dr. Timothy Coetzee:** Amit, a question from Judith in Oregon. This is regarding an oral medication. She writes, now that some oral medications have been out and approved for a while, are they proving to be as effective as some of the injection therapies people are on?

**Dr. Amit Bar-Or:** There are different types of oral therapies. Bob had mentioned one that is a symptomatic treatment, the walking pill as you had mentioned. There is one treatment that's been approved, Gilenya, for relapsing remitting MS. And that, in fact, was studied in one of the large phase clinical trials head-to-head with one of the injectable therapies and was clearly better than the injectable at treating relapses.

All medications that are in late phase clinical trials at the moment are also looking quite good relative to the expected from the injections.
**Dr. Timothy Coetzee:** Okay. Colleen, for you, a question from Vicki. Can you take too much vitamin D?

**Dr. Colleen Hayes:** It's very difficult to take too much vitamin D. There are some rare cases in the literature where a mistake was made, for instance, in fortifying milk or in formulating a tablet and too much vitamin D by a massive amount was added. But, no, under normal circumstances, you can't.

Your body, of course in the sun, has mechanisms to limit the amount of vitamin D you make, so that will be limited. And then, what we're suggesting the in the way of supplements is safe by a large margin. So, I wouldn't have that concern. My concern would be having too little.

**Dr. Timothy Coetzee:** Okay, great. So, Bob Miller, for you question from Sasha. She is interested in having a sense for where do the United States stand in terms of the other countries in stem cell therapy?

**Dr. Robert Fox:** I think the stem cell therapy in multiple sclerosis has actually been a really good example of collaboration worldwide. There are strong centers in Italy. There are strong centers in the United Kingdom. There are strong centers emerging in Germany. And, in the United States we have some strong centers too.

Our focus is been largely on adult stem cell therapies, that's patient derived stem cell therapies rather than other populations, but I think that we are all at the same level of understanding.

**Dr. Timothy Coetzee:** That's great. So, I think, it really is a changed landscape. Before we wrap up, I'd like to ask each of you what we can be looking for from research in 2012.

Amit, can you name one or two areas where you think there are going to be significant progress in 2012 that will help people with MS?

**Dr. Amit Bar-Or:** Well, I'd say on two fronts I think that there hopefully will be some of the newly approved therapies that are going to have an even bigger bang for the buck in terms of the impact on eliminating new relapses.

And then, the research that has been very intensive in the areas of understanding some of the underpinnings of the progressive biology that we've discussed, hopefully
will be moving forward to generate more and more molecules that will start getting into the clinical trials.

There already are far more clinical trials looking at progressive MS than previously. And while this will still take some years to emerge with effective therapies, this is where of course the greatest unmet need lies.

**Dr. Timothy Coetzee:** Okay, great. Thank you. Bob, what can we look forward to being excited in 2012?

**Dr. Robert Fox:** Well, I left my crystal ball in Cleveland, so it's a little hard to be certain, but I do think by the end of 2012 or early 2013, we will have one or two new oral therapies for relapsing MS out in general clinical use. It's hard to really know how they will go through the various approval processes, but I'm optimistic that we will have additional treatment options for patients.

I think we will have more clinical trials for progressive MS available. And that brings up that patients who are out there looking to get involved in research there's a lot of different research that they can get involved in. Some may be interested in clinical trials, but there are many other biomarkers and imaging and registries for them to get involved in to be a part of us moving this forward.

And, finally, I think by the end of 2012, we should have many of our questions answered regarding the CCSVI hypothesis; probably not all of them, but at least moving forward in getting a few more of those questions answered.

**Dr. Timothy Coetzee:** Lots of progress. Colleen, I know you're passionate as well about vitamin D in a lot of areas. Can you make a prediction about progress in 2012?

**Dr. Colleen Hayes:** Well, it's difficult to make a prediction, but let me tell you what I'm hopeful about. I know that you will hear more from the vitamin D summit task force. You're going to hear some detailed plans. We're going to put them together, and we're going to make them public, and we hope we'll get started soon.

The other thing that I look forward to either late in 2012 or maybe the year beyond is the beginning of the results coming from the trials that the Society has funded to help us answer the question whether vitamin D is going to benefit people who have MS. And I'm going to take a bet that the answer is going to be yes, it will. That's what the pilot data shows, so that's my prediction.
Dr. Timothy Coetzee: I'm excited. Bob Miller, your predictions for 2012 and neuroscience and how brain research is going to help people with MS.

Dr. Robert Miller: I think there are two areas that I would focus on. One is, we talked a lot about stem cell therapies. We've shown, I think, that stem cells are actually quite effective treatments. What we don't understand is how they work.

So, I think, that in 2012 you're going to see a discovery of how the stem cells are actually working. That's going to allow us to select, or even direct, new stem cells which are much more effective.

The other area that we haven't really touched on and, I think, is going to be incredibly important is to be able to take patients' cells, that is skin cells, and dedifferentiate them into what are called induced pluripotent stem cells, IPS cells, which we can then drive to turn into any cell type that we want, including oligodendrocytes.

And we can begin to interrogate whether it's the T cells, whether it's the oligodendrocytes, whether it's the B cells, or whether it's the other cells in the body that are actually defective or that are being manipulated by the environment. And I think that the notion of being able to make patient-derived stem cells turn into different cell populations is very exciting for the next year.

Dr. Timothy Coetzee: Exciting future ahead. Well, that's all the time we have for questions today. You've shared some really exciting progress. I think our audience will agree that there's a lot going on around the world to stop MS in its tracks, restore function, and end the disease forever.

I am so impressed by the dedicated researchers like our panelists and the work they and their colleagues are doing to improve the lives of people with MS. I'd like to thank our panelists for your time this evening and for the important work that you do.

I'd also like to thank all of you for participating and submitting your questions. We hope that you found the program informative and timely. Today's webcast will be archived and will be available for viewing at the National MS Society's website nationalmssociety.org.

If your question wasn't covered today, or if you have additional questions about MS and the topics addressed by our speakers, please visit the National MS Society's website, nationalmssociety.org, or contact one of our MS navigators in our Information Resource Center for help at 1-800-344-4867.
For additional webcasts that you can view on demand, please visit webcasts in the MS Society's multi-media library at nationalmssociety.org. Thank you, and good-night.