Transforming Multiple Sclerosis Care Through Precision Medicine

Multiple sclerosis (MS) is a neurological condition where the immune system attacks the nerve fibers thereby affecting the functions of the brain and spinal cord. It affects about 2.8 million people worldwide and leads to symptoms that can vary from person to person depending on the amount of nerve damage. Predominantly affecting women, MS presents at a highly productive stage of life and may significantly impact affected individuals, their caregivers and families.

Research continues to change how MS is understood and treated and precision medicine has the promise of improving care for MS. Researchers at Penn have made significant strides in slowing disease progression and we are talking to Dr. Amit Bar-Or, director of the Penn MS program to learn about the advances made in diagnosis and treatment of MS and understand how precision medicine can improve quality of life for MS patients. Providing the patient perspective is Mellisa Cook, a long time MS survivor and husband-wife Dan and Jen Digmann who each have MS.

Full Transcript:

Shweta Mishra: Welcome to CureTalks everyone. Today, we are discussing the Role of Precision Medicine in Transforming Multiple Sclerosis Care. I am Shweta Mishra, and we have with us today Dr. Amit Bar-Or from the University of Pennsylvania. Dr. Bar-Or is Melissa and Paul Anderson President's distinguished Professor of Neurology, Chief of the Division of Multiple Sclerosis and Related Disorders and Founding Director of the center for Neuroinflammation and Neurotherapeutics at the University of Pennsylvania. Joining us on the panel are patient advocates and long-time Multiple Sclerosis survivors, Melissa Cook, and husband and wife, Dan and Jen Digmann. Welcome to CureTalks everyone. It's a pleasure to have you all here today.

Jen Digmann: Thank you for having us.

Dr. Amit Bar-Or: Thank you.

Shweta Mishra: Dr. Bar-Or before we delve into how Precision Medicine can help improve Multiple Sclerosis care. I think it's important to talk a bit about what are the causes of Multiple Sclerosis. So how far have we come in understanding what are the causes? Is it our genes, is it our environment, is the food that we eat, the sun that we get, or is it the infections that we deal with? Do we have some better understanding today as compared to a few years back?

Dr. Amit Bar-Or: So, we do have more understanding but there remain some questions to still answer, and MS can be thought of as a condition that like some other conditions where the immune system is attacking parts of the body, parts of self, these are referred to autoimmune conditions where there are multiple different genes that can confer risk. There are over 250 variants that have now been identified, each one is contributing with a very small amount of risk and not a single one of them is abnormal per say, these are normal variance. But if a person happens to have a certain concentration of them, that sets the stage for the genetic risk of MS. So, Ms is not a genetic condition, like some others where there's a 50/50 chance of having a condition, but there is a genetic contribution clearly. At the same time, the genes alone will not be sufficient, and we've heard a lot for instance, about EBV virus, as one of the potential environmental triggers of MS, which is pretty firmly implicated as a necessary, but insufficient risk factor. Most everyone with or

without MS will eventually have EBV. So, EBV is seemingly necessary, but not sufficient. And then there are other risk factors environmentally such as low Vitamin D levels, smoking, including second-hand smoking, overweight, and these play out over probably a window of risk in early life that then sets the stage for developing some dysregulation of a person's immune system that spills over into attacking self, in this case, the central nervous system.

Shweta Mishra: Thank you. Thank you for that information doctor and we do know that women are three times more likely to develop MS, compared to men. And when a condition affects women more than men, we tend to investigate the hormones, right? So, do we suspect the same here in MS and does that contribute to higher incidence in women? And if so, what are the differences in how MS presents in men versus women as a result of this?

Dr. Amit Bar-Or: Yeah. So, one of the things that helps us also implicate likely hormones, is that in fact we've been involved over many years with paediatric onset Multiple Sclerosis. It turns out that this happens, much less commonly, most of the MS presents in adulthood. But some people living with MS, realize in retrospect or come to attention in the Paediatric age group. And what's interesting there is that the sex ratio is one to one pre-puberty and then you see the female predilection. So that argues pretty strongly that it's something about puberty and likely hormonal changes associated with puberty that increase the background risk of someone developing Multiple Sclerosis. Historically, we've recognized that when a woman develops MS, she may tend to have a higher frequency of a MS but that overall, the disability that this person may experience over time may not accumulate quite as quickly compared to males where MS is less common, the frequency of relapses is somewhat less on average and yet they tend to progress or lose neurological function more quickly on average. And I emphasize on average, because this is really one of the hallmarks of Multiple Sclerosis, and I'm sure members of the panel here would agree, is that one person's experience with MS, male or female can be very, very different. Even MS that occasionally occurs in families may manifest very, very differently from one family member to another. So, these are average differences which get you thinking about what the reasons maybe but it's more complicated than merely saying MS is more severe in males for instance than females.

Shweta Mishra: Thank you and coming to Precision Medicine, so your cutting-edge research focuses on Precision Medicine to drive it towards achieving permanent remission for MS and stopping the progression of MS and preventing its onset. So, could you talk a bit about this initiative and share how you see Precision Medicine improving care for Multiple Sclerosis patients?

Dr. Amit Bar-Or: Yeah. So, I mean, the way that you set up the question, it sounds very ambitious. And in fact, those are our ultimate goals as a field, right? And we've been fortunate that over the years we've tried to and I think have had some success in pushing the envelope a little bit on this concept. And I'll sort of take a step back just by saying that we just mentioned how heterogenous or different MS or the experience of living with MS can be across individuals. And there are multiple reasons why that is the case they include social factors, vocational factors, etc, but also biological factors, which is sort of, one of the pieces that we've been missing in terms of better understanding the complexity of why MS differs across individuals including the natural history of what MS is like for an individual. And also, whether they will respond better or less well to a certain treatment in terms of both the benefit of the treatment but also the potential risks of the treatment. So, people are different. You will remember terminology of personalized medicine or individualized medicine over the years and the reason actually as a side note for moving towards Precision medicine, as opposed to those is because individualized, the personalized, really suggest that if you have 100 individuals with MS, there should be a hundred different approaches. And that's probably not exactly the case, in other words, we clearly need to do better than one size fits all. But it is more likely the case that if you look at 100 individuals with MS, there maybe five or six different types of subgroups that have practical implications in terms of treatment choices, what to start with, when to stop, what to switch to etc. Ultimately, our goal is to help individuals achieve durable remission of their MS without having to continue to be on treatment. That is, many I think would consider that to be a form of cure. Although, for those who already have problems with function, a cure means fixing things that are also broken and that's something that this particular platform is not directly geared towards doing. But one point, I will make early on is that while the

platform has mostly involved in the context of what can we measure in the periphery that may meaningfully capture relevant aspects of MS. That what we are also doing is we're pushing the envelope increasingly on trying to get a similar kind of approach for spinal fluid cells, that will inform us on what's happening within the central nervous system. And I think may be relevant, both for progressive MS and for repair for progressive MS. Again, with the principle of what can we measure that will allow us to better understand the individual's immune response or nervous system response profile that could then feed into clinical decision-making. And I would emphasize that we are in relatively early days and so that what I can describe in more detail the specific questions will capture where we are now, but the bigger picture vision is what exactly you are alluding to, which is something for the future.

Shweta Mishra: Thank you. That sounds very hopeful and promising doctor. So let me now invite the panel to join the discussion. First up, we have Melissa Cook, who is an author and blogger, and a long time Multiple Sclerosis survivor. Melissa, welcome again, and please take it away.

Melissa Cook: Thank you. So, I found your information, very interesting because I meet a lot of the criteria that you listed for people with MS. As female, I was 15 when I was worked out for my first MS. At that time back in the 80s they didn't have these are the diagnostic ability to come up with a diagnosis for me at the time and was another 15 years almost before they were able to do that. I have low vitamin D, if I don't supplement, I grew up in significantly smoky home, second-hand smoke was a big deal for me, with pretty heavy smokers and a small home and I've had symptoms of Epstein-Barr in the past. So, I found that quite interesting, I took note for my blog. My first question for you is I'm on a treatment that has been highly effective for me for nine years, but I have a friend who tried the same medicine, only to have her MS spiral out of control, which then we go along with what you're saying different bearing. Is there data in Precision medicine that Alliance DNA to the best DMT or Disease Modifying Treatment for most patients today?

Dr. Amit Bar-Or: So the simple answer is not yet and I'll answer at two levels first, even before talking, about DNA specifically, is there anything today that we can measure that would clearly distinguish between the two of you and the answer is that where we are is that we think figured out what it is that we need to measure, and we now need to apply that measurement to people, like yourself, to people like your friend and then to many others to identify what the signature is that defines your immune response propensity, your MS versus someone else's MS. So, the advances that we've made in terms of the platform which really has been cobbled together over many, many years of work, not just by us, but many colleagues, nationally and internationally is to get to a point where we now believe there's good reason, I think to believe that we can measure things. And we have some proof of principle just to make sure that it's identified as something that actually has traction because we have been able to show already that certain individuals who respond better or worse to a given treatment have a very different biological profile that can predict that. So, we have made some headway, that's not quite the same as saying let's look at two different individuals and say what is best for them. It will come from added information. And when you asked specifically about DNA, the DNA makeup of a person is almost certainly relevant for this. What's really interesting to understand is that before DNA can actually have any impact on biology, the DNA has to be transcribed to RNA, that has to be translated to protein and each one of those steps and additional steps, introduces a whole bunch of variability. And the reason I mention that is because the very same DNA may end up producing factors that are very different even in identical twins, who share the DNA, which is why most identical twins. If there's one who has MS, still the great majority of the siblings with identical genes will not get MS. So, just to make the point that DNA is one piece of the puzzle, but it won't be the complete puzzle. And it's exactly as I think you're alluding to that DNA is one of the layers, but we want to be measuring the expression of the what we call RNA, which is the message that goes from DNA to the actual protein that is kind of the business end of the immune system and the nervous system, and the platform that we're discussing actually integrates those different layers. And that's one of the things that I think makes it more likely to end up having practical and important applications.

Melissa Cook: So, in the past, I have been very sick. I went out on permanent medical disability, 11 years ago. You would know it today as I started this medicine, nine years ago and my life has changed and I have multiple autoimmune diseases that this medicine is controlling, doesn't work for everybody. But it works for

me, and it controls all of the autoimmune. So, my question to you is how effective has Precision medical treatment been in controlling MS in research or may even have research on this yet?

Dr. Amit Bar-Or: Yeah, that's a great question. And in fact, one of the ways of thinking about, I'll mention in a few words, what Precision platform captures and that will help fully answer your question. Different groups over the years have focused on different elements of the immune system. Historically people said MS is a condition mediated by T cells of the immune system. And then we have therapies that Target B cells selectively and suddenly, MS is a B cell mediated condition. Well, in fact, it's neither that nor the other, it is a combination. It's about interactions between different types of cells. And each one of those cell types be it the T cells, or the B cells have subsets that are more, pro-inflammatory, and others that are anti-inflammatory and that is actually normal. We need to have something that will ignite a response when appropriate against a virus, but we also need something that regulates that response so that we focus on the virus and our pro-inflammatory response, doesn't spill over into self-injury. So normally there's constantly this balance that needs to be struck between effectors and regulators of T cells, of B cells, of myeloid cells and other cells of the immune system. And the idea is that something about the different combinations of these interactions is not quite right in individuals who have MS, or one or more autoimmune conditions. We now with the platform are measuring this and we increasingly realize that each of the conditions that you or others may have sometimes in combination, be it, let's say a mess or thyroiditis or inflammatory bowel disease, celiac disease, etc. Each of these conditions in their own silo have said, oh T cells are a problem or B cells are a problem, Myeloid cells are a problem and what our platform is beginning to enable us to do again early days, but I think very exciting is instead of thinking about silos of each disease, in which each of these cell types has been implicated thinking across what that means is that some people with MS, type 1 diabetes, IBD-Inflammatory Bowel Disease, may have a particular regulatory T-cell problem. For them the right treatment would be treatment X, other people with these conditions may have a different predominant problem for whom anti cd20 as a B-cell targeted therapy would be the right answer. And so, where we are, is we have hints that it is attractive I think conceptually, but we have more than just the concept. We have growing evidence that this paradigm makes sense, and we will eventually translate, and you might see one day, believe it or not, clinical trials of a new therapy that include people with different conditions with the same therapy which has been considered kind of blasphemous to date.

Melissa Cook: Would we go along with my telling my friends who have rheumatoid arthritis you need to try my MS medicine because I was out of control with rheumatoid arthritis?

Dr. Amit Bar-Or: That's an interesting comment because it may be absolutely true for the medicine that you're on for some people, but not all people. And we, in fact, one thing we already know you may know about the anti-TNF therapies, which are very good for rheumatoid arthritis for many patients, but they actually make MS worse, right? So, not every treatment that works for one autoimmune condition works for another. It may even make it worse and then we started with not all people, even with the same condition ought to be on the identical treatment.

Melissa Cook: That might explain why my rheumatoid arthritis was out of control when I was on a different medicine.

Dr. Amit Bar-Or: That's exactly right.

Melissa Cook: My next question is, if you have a crystal ball right in front of you and you can look at it and tell us, when do you think we will have access to Precision medicine in MS? What would you say?

Dr. Amit Bar-Or: The crystal ball question, right? So, I think that we are inching our way and we are getting more and more measurements that provide small titbits of important, but still limited insights. So, you've heard of Neurofilament light chain- NF-L probably that's something that we relatively recently, when I say relatively recently, I mean the last few years have identified as a measurement that we now can measure easily and reliably and simply attainable samples. So those are they sound like boring details but in fact for something to be useful those are elements that make a biological measurement practical versus entirely

impractical, right? And so, you need to think, always as what may be translated in a practical way and then, of course, what is the biology that it's capturing? So, NFL is really interesting in that can capture changes in MS activity and predict worse MS activity, which is already useful for us to incorporate and we're beginning to figure out how to do that in practice as one aspect of precision medicine, some people have a bigger abnormality, some people have a lesser abnormality, but NFL is a product of injury to the nerve and its axon. So that's something that's already happened, and we want to have Precision medicine, that predicts something before it happens, right? So yes, if someone has bad MS, they're likely to have bad MS. Although of course there's variability. So, if you find someone who has high NFL, treat them with something more highly effective to try to limit their NFL. But ideally you would measure something even before that and be able to guide treatment. So, we are inching our way and our platform, which has been recognized relatively recently as at least people think of it, as an important advance, is one that combines multiple different measurements so that hopefully, we can at the same time, get a broader more integrated view of multiple different aspects that contribute. And by doing so, I think we have the chance for the same platform to get useful information for more people for whom the platform is applied. But to your very practical question of can you go out tomorrow and use this type of platform. The answer is still no, I hope with crystal ball question that within three to four years, we will actually be able to use it meaningfully in a more broad kind of application.

Melissa Cook: Thank you. So, where can we keep track of the current research and the current body of knowledge as it stands, so as it progresses, we can keep checking in and find out where you're at.

Dr. Amit Bar-Or: Absolutely. So, I mean, the traditional ways, of course, is to follow the science advancements, put out as sort of part of the literature. The literature is not often particularly friendly for people who don't necessarily have a scientific background. So, one of the things that we've focused on over the years, is the catchphrase is knowledge translation. And actually frankly this discussion that we're having now is a good example of how we try to share information about things that may not as readily be accessible. I think the MS Society, of course, is a source of information that is not designed to sell anything, it's designed to try to give people access to relatively recent information with some translation in there. I would encourage you not to be shy, reach out to me directly if you want updates of any type. But one of the things that we do, of course, is we disseminate information in the meetings, the meetings include sessions that have people living with MS who come in and we've had, I think a lot of very important discussions about this and one particular example, is we're about to launch a study along the lines of trying to find a way to establish durable remission meaning your MS is halted without having to be on an ongoing treatment. We are about to launch a study that is supported by the NIH- The National Institute Institutes of Health is part of our Autoimmunity Center of Excellence, that will randomize people to discontinue a treatment and see how people do because we believe that we can establish and learn about durable remission. And this initiative, I'm giving is an example would involve the patient advocacy group and will involve an opportunity for very proactive exchanges of information, so that we understand better the priorities as seen from the perspective of yours and others living with MS and can feedback information. And if you're interested or you know of someone who may be interested in being part of that, please reach out to me directly and we'll make sure that you're involved.

Melissa Cook: Thank you for your answers. And yes, I'm interested. I spoke to my urologist just yesterday and it's only been nine years since my last new symptom and I'm a candidate to come off medicine in the next year. So, he said in our next appointment will probably try to take me off medication.

Dr. Amit Bar-Or: That's where we're exactly hoping to go with the field. And we right now will be partly guessing right but will be guessing with some insight and I hope we can do better than that in the near future.

Shweta Mishra: Of course, thank you, Melissa. Great to hear that. Next up I would like to invite Dan and Jen Digmann, a Michigan couple empowering people with MS through their nationally recognized blog and podcast. Dan and Jen, the floor is yours. Please go ahead.

Jen Digmann: Thank you Dr. Bar-Or. I was wondering personally very selfish Dan and I have both been

living with the disease for more than two decades. How do you say Precision medicine, benefiting people like us or people in our community that have been living with the disease for a while?

Dr. Amit Bar-Or: It's a great question. So, one has to do with how long the people keep on a treatment. And is there a point at which the treatment is no longer necessary or may no longer be helpful, but they still be exposing people to risk and that relates to what Melissa was referring to before. But it's something that our community is, actually formally studying, there are several different studies, as you may know, like the DISCOMS – discontinue MS clinical trial. And what we are planning to do is to be able to apply the platform in the context of studies like that so that we can formally evaluate whether particular measurements will identify those individuals in whom stopping a treatment may be the right thing to do or perhaps the wrong thing to do or should there be a switch. So that's one perspective. The other, which I alluded to before is, as I'm sure you know over the years and partly, it's got to do with the pattern of MS and what contributes to injury in MS and partly it's got to do with being less young, right? This concept of aging of the immune system or immune senescence, where many immune responses with normal aging are somewhat diminished. And that's why people who are particularly elderly are more susceptible to infection, or have lesser vaccine responses, more risk of cancer. But to a lesser degree, those changes can also be relevant to the observation that relapsing MS activity tends to be more frequent early on and less and less and less and in many people diminishes entirely, even if you look under the surface with MRI as we should be looking because a lot of it is subclinical. Well the point being that the utility of medicines that target that aspect of the immune response may be diminishing over time and we won't know unless we measure it. So, that's another perspective. And the other, of course, is that while at the moment, our tools for precision immunology, are largely being applied peripheral samples, like blood samples that are most relevant to the biology of relapses because the relapse biology, we think of, as immune cells, that get inappropriately activated in peripheral immune compartments and then traffic through the blood where we can sample and capture them on their way to the central nervous system. So that is relevant and useful already and will be increasingly so for relapses but very important question for people who no longer have relapses and may have different degrees of progression is how can we apply and develop Precision neuroimmunology to the neurobiology or the inflammation that is within the central nervous system and I was alluding to that with what we and others have been doing at the level of sampling spinal fluid with new approaches to measure, not just the fluid compartment, which you're familiar with we often do as part of early MS diagnostics, but also to look at the cellular profiles, which are beginning to teach us much more about progressive MS and how people differ. So, that heterogeneity that may guide different treatment choices. So, that's a bit of a mouthful about the different perspectives on the periphery and the central nervous system and measurements, that may be increasingly relevant to people like you who have been living with MS for decades.

Dan Digmann: Thank you, then moving forward, how accessible will the Precision medicines be for the MS Community like, for people like us that don't live close to your facility or even close to an MS specialist. How accessible will that be when it's available?

Dr. Amit Bar-Or: That's a great question. And I think that what's going to happen at least in the first few years is that the platforms are going to be available at a small number of sites that can establish that framework. Of course, as soon as you think that you can measure something meaningful, there's a lot of interest in the community to try to develop that including through intellectual property and companies and start-ups etc. I already alluded to some of the very real kind of boring but critical details of being able to take something from a sophisticated academic lab, where you have people who can do all sorts of magical things to something that is really practical, where a sample can be sent and shipped across states to a lab that can still reliably measure this information. So, I anticipate that realistically this is going to take, I mentioned to Melissa, 3-4 years to be in a position where measurements can be identified as meaningful. And then several additional years to be able to make it more readily available. My experience historically growing up in a place that had relatively limited resources. See, my father is a clinician scientist managing in the face of limited resources, was how do you turn something from, first doesn't need to be fancy to start with maybe not, but if it does need to be fancy, to start with, how can we quickly make it simpler and less expensive and more accessible. So that is a very important mantra that we live, we hope to be able to live by. We certainly

are thinking of it.

Dan Digmann: Thanks.

Jen Digmann: Okay. And I am always fishing this probably difficult question. But how do you see Precision medicine moving us closer to a cure for Multiple Sclerosis, or do you see that happening?

Dr. Amit Bar-Or: Yeah, I do. And I think we already have some ideas, the one I sort of was referring to in the context of this discontinuation trial, a cure almost certainly means something different to different people, right? And so, if you think of someone who has relatively early MS, and whenever I'm in a conversation with someone where MS is being considered as a new diagnosis, I make the point of saying that we think of your MS as part of the new MS. And what I mean by that is people diagnosed today with MS have a very very different prospect over the next decades then people were diagnosed 10 20, 30 years ago. That's an important message to hear, the other is that while the decision about which treatment to start is an important one, it is not necessarily the biggest decision you will ever make in your life. It is one that is not a marriage. It's the right decision now, because that's what makes sense now, and we continue to monitor and we can change and where precision neuroimmunology will come in, is being able to make better decisions earlier on that will keep individual people's MS in check. And some people will say, if I find a medicine and will never get worse, that's a cure, that's a form of a cure. Others will say for me to consider the cure, I want to no longer be on a medicine that I need to be on all the time, and I think that that is going to not be one size fits all but where the precision neuroimmunology measurement can come in is to identify this 20% of the population starting this treatment can start it early and stop after two years and not need anything else, but the other 80% need something else or different. So, we will with this precision medicine approach gradually be able to identify additional subgroups of individuals living with MS to help make the best decision with them for them.

Jen Digmann: Thank you, that was such a good answer. Thank you. That's good.

Dan Digmann: And with that, I guess the news release about the research said the goal is one-size-fits-all approach to clinical trials and treatment to developing more personalized treatment plans that work best for each person with MS. And this all sounds really promising but then the question is how quickly do you foresee these personalized plans being developed in terms of like living with MS, it's always like get on a treatment as soon as you can was like is what kind of delay is there from when you say, okay, I'm going to do this to figure out what treatment is? I mean, how quickly will that happen?

Dr. Amit Bar-Or: Yeah. So, all of us already use certain aspects of an individual's experience with MS to try to discuss with them, what makes sense as at least the most sensible treatment to start with. The precision neuroimmunology platform that we're talking about here wants to add an important biological layer of what can we measure biologically to complement the considerations. And I anticipate that within a couple of years we will be able to do that, not to everybody out there but at least do it in a way that will help some people have more informed discussion about the best decisions for them. And as we iteratively learn how to make that measurement more accessible to be able to have that be used by many many others. The comment about personalized and each individual again, that is a little bit frankly of marketing language, okay? But it is not inappropriate to indicate that it is really meant for each person, but again, it's not necessarily 100 people, 100 different approaches. It's each person which for you is the best of let's say five or six approaches. That's still individualizing for you, but not necessarily. It's different for every one of the people out there. And the question about individualization or at least this precision approach again, is applicable to understanding what the start, when to stop, what the switch to. And as the next data sets come in and one of the best ways of getting information, that helps us improve how we apply this is by measuring these things in more and more people in an organized way to be able to relate the biological measurement to how people do and learn from that, how to improve the way we applied, for the next group of people. So, I mentioned that because the correct term is iterative, right? We're constantly trying, this isn't a done deal. This is now somewhere farther ahead than it has ever been. But it is far from a done deal and as we continue to learn with people's help, I think we can get better and better and more and more broad in the application.

Dan Digmann: Thank you, that's just so encouraging to hear all that. Thank you so much.

Shweta Mishra: Thank you Dan and Jen. Thank you, Dr. Bar-Or. Before we wrap up Dr. Bar-Or, what would your message or advice be to someone who was newly diagnosed with Multiple Sclerosis?

Dr. Amit Bar-Or: Well, I think the word that you just heard – hope is a very good one and I tend to avoid promising things that I can't keep, and I think that no one chooses to have Multiple Sclerosis. But again, the new MS is very, very different from the old MS. And I think that's a very important, appropriate and reassuring statement for people to hear, especially as they're grappling with a new diagnosis and what does it mean and what does it mean in terms of family and family building invocation etc. I think undoubtedly issues and challenges that you all have been facing in a very real way over the years. And that's true for everybody who's facing a new diagnosis of MS. So, I think that doesn't make it easy but hopefully easier in terms of the initial impact of a new diagnosis. And similarly, that our treatments now are very different than what we had before we used to have to consider a trade off between something that was more effective against my MS but was riskier. And now we have treatments that are very effective at least for certain aspects of the MS and at the same time really well tolerated and quite safe at least for a while. So that's different and that is something that we can again I think indicate early on and the other is that whatever you choose to do today to try to limit injury from MS is not going to be the last thing and it's not a marriage for life and that we are and this is where the hope comes in going to be able to do better and better and move closer and closer to keeping every person's MS in check ultimately without ongoing treatment. But even if it is with ongoing treatment, as long as that treatment is sufficiently safe and well, tolerated that too many people will be considered to be as close to a cure as practically they might seek. I must say that we still have a lot of people living with MS, who may be are viewing themselves, not quite as having the new MS because they've been living with it for a while, and we clearly need to push the envelope on understanding how to fix things that are injured, not just prevent new injury and that has to do with repair, regeneration. We think that limiting further injury is key to enabling repair including intrinsic or endogenous repair by the person's own nervous system. And also means that we have a more permissive environment for repair, that may be facilitated with new generations of treatment so there are multiple new treatments in the pipeline that are particularly looking at repair and regeneration which in my mind represents an important unmet need.

Shweta Mishra: Thank you, thank you for that, message of hope Dr. Bar-Or. With that I think it's time to wrap up today's show. And thank you for a great and informative session, Doctor. Melissa and Dan and Jen, thank you for joining and guiding the panel. We also thank the University of Pennsylvania. This talk will be made available on CureTalks.com. So, until next time we meet thank you everyone, have a great day.

Thank you.