Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/battle-of-the-biomarkers-assessing-key-factors-in-prognosis-monitoring-therapeutic-decision-making-for-disease-worsening-in-multiple-sclerosis/14683/

Released: 03/21/2023
Valid until: 03/21/2024
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Battle of the Biomarkers: Assessing Key Factors in Prognosis, Monitoring, & Therapeutic Decision-Making for Disease Worsening in Multiple Sclerosis

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Battle of the Biomarkers: Assessing Key Factors in Prognosis, Monitoring, and Therapeutic Decision-Making for Disease Worsening in Multiple Sclerosis,” is jointly provided by Purdue University College of Pharmacy, Office of Continuing Education and Professional Development, Purdue and Efficient LLC, and is supported by an educational grant from Novartis Pharmaceuticals Corporation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Shin:
So welcome to the Battle of the Biomarkers. Thank you for spending your lunch with us. Alright, so this is an industry sponsors satellite symposium. So this disclosure is here that this has been provided by Purdue University and Efficient CME. So everything we're presenting here has been assessed to qualify for CME.

I'm Bob Shin, I'm happy to be here and introduce my faculty brief. I'm at Georgetown in Washington, DC. And next to me is Dr. Jiwon Oh, who's from University of Toronto in Canada, and all the way to my left Dr. Enrique Alvarez, who's at the University of Colorado in Aurora. So we're all clearly authorities on the subject. So without further ado, these are our disclosures.

So we already heard about how important it would be for you to answer as many questions as you can in advance because actually in a few moments, we want to see what people's opinions are on the subjects. At the end, there's going to be evaluations, which allow you to claim your CE credit. Alright.

So just in terms of an overview and really what we hope the purpose of this debate would be about would be just recognize, as you've been attending this meeting, you know that we're learning a lot more about multiple sclerosis and the way brain damage occurs early on. We also are blessed to have a number of treatment options, but I think we're still struggling to understand how to best utilize those options. And very excitingly, an increasing number of biomarkers have been proposed or are being worked on to help us do better in terms of again, answering these challenges in terms of treatments.

So I'm going to jump right in to our first module of three. And here, we're going to actually try to weigh the different prognostic biomarkers that we've been learning about in terms of which do we think is most valuable.

Alright so our first debate topic: which are the most meaningful and actionable biomarkers or clinical indicators at an initial assessment? So we have a newly diagnosed patient? What assessments or biomarkers would you feel are most useful at that initial assessment? Other than, if you will, traditional measures, which would be sort of, you know, clinical relapses, and conventional MRI? Alright, I'd already been haranguing you about answering these questions. So just going to move forward and take a look and see what kind of answers we've got. So you can see it is sort of all over the map. Here we see serum biomarkers are quite popular. And there's been a lot of interest in different ones such as serum neurofilament light chain, etcetera. But actually, we also have votes for things like brain volume, age, maybe more advanced MRI markers. We just had a presentation here on things like that, and even just going along with

age, things like how long have they had MS. Alright, so these are your responses. So this is the audience response. We'll see what we came up with. So I voted for brain volume at the time. And Dr. Oh, I think you're more of the serum biomarker. You're looking at it like you don't even recognize these. You've seen this is what you put down in cognition. Dr. Alvarez was focusing more on years of diagnosis. Actually for this session, actually, I think each of us is going to speak briefly. Later on, we'll probably hone it down to just one versus one. But for here, I think we're all going to talk a little bit. So I think, Enrique, you have the floor.

Dr. Alvarez:
Yeah. So it looks like I picked the losing side to begin with. So I guess I have the most ground to cover. So I picked age. I think just one of the maybe the parts of it is maybe practical prognostic factor thing. And I think it's because it's readily available, easy to get. I think it also is one of the things that we could still see and have good data for.

So this is some work that we did looking at patients treated, you'll see similar curves from natural history data, that as patients age, you'll get a decrease in the number of disease activity, whether you look at MRIs or relapses, very similar data. So these were patients that actually started therapy and were followed for 2 years. And just how much disease activity we had and looking at it by age. And one of the things that we ended up splitting it out by looking at orals versus infusible, so high-efficacy versus medium-efficacy type therapies. And what we noticed was that you do get to a point where the drugs are not very different from each other. So it looked like age was something that we could use as a marker for trying to kind of figure out, you know, helping us decide on therapies. Whereas you start to kind of look at older patients, there's less difference between these drugs. But as you look at younger patients, that we have an advantage of that. And the difference for us came out to be about 54.2. If you look at clinical trial data, very similar data from ___05:31, it was around 40 years of age. So we found that this was a helpful marker.

I think age also then tells us not just about efficacy for the drugs, but also tells us about the risk associated with the drug. So it's kind of something that is easy to

get, but also tells us a lot of different things. Here are two different studies, one was 1,000 patients between us and NYU at the top panel, looking at 1,000 patients on rituximab and serious infections associated with it. And what you can see is that there's definitely an effect of age. When you start to do multivariate models, including stepwise analysis with it, that age factor maybe disappears a little bit. And that has to do because of the other factor that we looked at, which was disability. And there was other things that went into this model. But if you look at the odds ratio, for example, for disability, it's 8.5-fold increased risk by a time that a patient becomes wheelchair bound. And that becomes an issue because patients accumulate disability with age, and so they're both tied into the same thing. If you look at them separately, you can see that he still has that effect.

The other factor that falls into it is from the COViMS dataset for COVID. And if you look at the right columns, where it looks concentrates on death, you can see this huge effect of death associated with age, also sex, with men having more of a higher risk of death. And then again, this ambulation factor. And what I point out is, again, these big odds ratios associated with that. But here, age is not just giving us a marker for efficacy of the drugs or how likely they are to have disease activity, but also for risk in these patients.

The other thing that we looked at was years since diagnosis. This became a little bit more complicated, kind of similar analysis, you can see on the right side, the earlier the patient is away from diagnosis, the separation between orals and infusibles. And when we start looking at adjusted models before and after 12 years since disease duration, after 12 years, we don't see a difference; under 12 years, we see a difference.

So again, I think these are factors that can help us for something that's really easy to kind of get.

Dr. Oh:
So I thank you, Dr. Alvarez, for highlighting why certain demographic factors may be of utility prognostically. I think he did show some good data showing the relevance of age. But I think the bottom line is it's pretty clear that from a clinical standpoint, we're actually not very good at prognosticating in general. And when I was asked this question, I did select a number of emerging measures that I think will be relevant. But I think what I'm trying to say is right now we don't have great ways to prognosticate. And we need better ways. And these are some emerging tools that I do you think in the very near future will be of relevance.

So in terms of a specific criteria, I always think it's good to look at a framework as to what makes a good prognostic biomarker. And I think this is a really kind of shortlist of what criteria need to be met for some sort of emerging measure to be useful in the clinic from a prognostic standpoint. So I think, first of all, there needs to be the demonstration that this measure, whatever it is, does have the ability to accurately prognosticate. And what we mean by that is with the lens of MS, we're referring to some sort of measure that you can measure towards the beginning of disease that, over time, has good correlations with clinical outcomes. In addition, this measure should have some sort of biological plausibility as to why we're measuring it and why it makes sense to measure this to accurately prognosticate. There should be very good clinical data, validating the utility of this measure, whatever it is. And then this seems like a

boring factor, but this is probably the most important factor related to why there are so many different measures used in research, but ultimately, they don't make it into clinical practice. And this is because of logistical issues related to availability, accessibility, time, money, all of these things, which factor into why many advanced measures ultimately don't make it into the clinic.

So for the measures that I'm going to talk about, I just want to look at it in the lens of all of this short checklist because it will give you an idea as to why I think that they're not used now, but in the very near future, they very well could be useful.

So there's many, many different advanced imaging measures, and Dr. Shin will be telling you about one of our oldest imaging measures, which is measuring brain volume. But amongst the various imaging measures, I do think that there's quite a bit of potential for something called paramagnetic rim lesions, or PRLs for short. You've probably heard quite a bit about this in recent years. But the reason why the imaging field is focusing so much on these PRLs is because when you use the appropriate iron-sensitive sequences, around some white matter lesions, you may be able to visualize a rim of hypointensity. And because the sequences that you use to detect PRLs are sensitive to iron content, this is thought to represent a rim of activated microglia. And the reason why we care so much about this is because these PRLs likely represent, at least for the most part, chronic active lesions, which we know is probably a major driver of central nervous system compartmentalized inflammation, which we think is a major driver of relapse independent progressive disease biology.

So we've never been able to measure these before. We know that MS is characterized by many white matter lesions that we see on MRI. In fact, this is one of the most useful paraclinical measures that we use, but a subset of these lesions, you know, are chronic active lesions, and we now have ways to measure this.

So the reason why we care so much about this is, theoretically, again, this is likely a major driver of progressive disease biology. And there have been a number of studies emerging, showing the clinical relevance of paramagnetic rim lesions, including studies that have looked at people with various subtypes of MS. And they've shown that having a certain threshold and above of paramagnetic rim lesions is strongly associated with worse motor and cognitive outcomes. Even in presymptomatic MS or radiologically isolated syndromes, PRLs have been shown to be relevant to developing MS over a number of years, which clearly demonstrates its prognostic potential even in the earliest stages of MS. And across the spectrum of MS, there have been associations, again, even in RIS with cognitive impairment.

So as you can see, when we go back to that checklist, this imaging measure does meet a lot of the factors that I talked about. The lingering issue, though, as with many advanced MRI measures is this logistical issue of access of optimally detecting these lesions. Access to the sequences that are required and the technical expertise. So it's not yet ready for primetime use. However, it's not that complicated of an advanced imaging technique. And there clearly are reasons why there is a prognostic potential for this imaging measure, which is why I think amongst the various imaging measures available, if we sort out some of these technical issues, it likely will be very useful in the clinic moving forward.

Other measures, you've probably heard a lot about different fluid biomarkers, including serum neurofilament and GFAP. There's biological plausibility as to why it may be useful to measure both of these proteins in the blood. Because both of these represent neuroaxonal destruction. There's very good evidence from clinical trials as well as in larger cohort studies demonstrating that the level of serum neurofilament, or GFAP, or a combination of them are relevant to clinical outcomes, both in the short and long run. There have been a number of studies showing that levels of serum neurofilament predict conversion of RIS or CIS to MS, as well as relationships with global disability over time. And again, it may not just be one of these fluid biomarkers, but a combination that is highly relevant to prognosis.

Again, based on that checklist, I was talking about lingering challenges include access and the funding to do this. And then things like setting appropriate thresholds for people of different ages with different comorbidities. But all of these things are being sorted out and I do believe again, of the emerging measures. These two may be useful in the near future for prognostication.

Finally, I'm looking at a clinical measure. Cognition seems to be quite valuable in terms of the ability to prognosticate. And this is because cognitive deficits have been described not just in the later stages of MS, but across the entire spectrum of MS, including radiologically isolated syndrome. And administering a very simple test that takes really just a few minutes, like the Symbol Digit Modality Test, which can be done on paper, or even using iPads, is an easy and quick way to screen for cognitive deficits in MS, which again, across the spectrum of MS has been associated with poor clinical outcomes. So because of this, this is not necessarily something that is routinely done in busy clinical centers where typically you don't have more than 30 minutes to see an MS patient in follow-up, and it's difficult to get through everything. However, it seems like this may be something very useful to incorporate a standard of care when you're thinking about trying to prognosticate in people with MS.

So the bottom line is, all of the markers that I talked about do seem to fulfill many of these checklist requirements. The advanced

imaging measure PRLs, as well as

fluid biomarkers do not yet have wide availability or accessibility. And so this is why we need to sort through some of these logistical challenges before they become available, but cognition, specifically SDMT, may be very useful in this regard, because it does seem to meet all of these factors required for some sort of measure to be useful for prognostication.

Dr. Shin:
Alright. So for my part of this debate, I've actually chosen brain volume as a marker. And I would say, really everything that's been mentioned, these are actually all valuable markers. But if we had to pick one, I was going to aim for this.

And my line of thinking is everything actually Jiwon just said is totally true. You know, these markers increasingly are being recognized as able to correlate with or predict disability accumulation over time.

My argument, though, would be because those markers reflect something. They reflect, as you said, loss of brain tissue. And I would argue that well, we could also just directly look at how much brain tissue there is. So that's why I'd focus in on something like brain volume. And as you said, we've been doing this all along in our career, we look at people's MRIs. To Enrique's point, although age, exactly as you said, is going to be correlated with those factors, I also feel like for a given 50-year-old that there might be differences among them.

So I actually chose to show three MRIs of patients all born in 1972. Okay, see, three of my patients, they all have the exact same age. So this is the first patient where if I'm just looking to the left at this flare. You know, I can see a periventricular white matter lesion. But overall, I would say looks okay. This is a different patient, exact same age, a little bit more in the way of white matter disease. But the third patient in particular, to me, is alarming, you know. When I look at these ventricle size, I'm like that doesn't look normal for a 50-year-old. Right? So this is sort of subjective, but I might use my eyeballs. And if I had to predict who is going to have a harder time, who is at greater risk of disability, it's this third patient compared to let's say, maybe the first two.

I would also argue, however, that just eyeballing it might not really be enough because I don't know that I can tell the difference between this patient and this patient just on by my eyeball. So there are other tools. Obviously in clinical trials, we might have options that maybe you and I don't have access to as an individual practitioner, but already here today, not a biomarker, I have to hope in the future you can get a software package that can give you quantitative. This just happens to be isometrics. That wasn't one of my disclosures. I'm not really being contracted by these people actually, get free advertising. But I like obtaining these numbers if I can.

So this the first patient, by this analysis, has whole brain and gray matter volumes greater than 50th percentile. So I'm like, I kind of find that a little bit

reassuring. Now this patient where I could debate, you know, do those ventricles look large? Is this a large part of why I can just look at the numbers, and the whole brain and gray matter volume, actually, she's kind of borderline, you can see falling into about the 10th percentile; 90% of people in her age group actually probably have more brain volume. But it's this patient who falls off the curve. If I met her at diagnosis, and she is below the 1st percentile in brain volume and gray matter volume, 99.9% of people who are age have more brain volume, for me, this might alter my decision-making. So that's really my argument here, is that all of the biomarkers we're talking about ultimately reflect brain loss. And we don't like that.

And this is a tool that's here now that I think we can incorporate into clinical practice. Debatable, but maybe something we can use for prognostication. So this group matter is really the whole reason we even ask these questions. I'm going to turn it over to you should answer this. Basically, what matters in terms of choosing that initial therapy, again, for a newly diagnosed patient? What do you guys think?

Dr. Alvarez:
I think I agree with Jiwon in the sense of like, we don't have great prognostic factors. We have things that that you can look at. And I think that that's why we need new ones. But we pick wrong a lot of times. I think there's just big bell-shaped curves. And so trying to kind of refine these is going to be very important for us.

Dr. Shin:
Any other thoughts?

Dr. Oh:
You know, just I think when there is no magic prognostic measure, I think we need to use everything that we have. And also, don't underestimate the power of clinical judgment, because this is the art and science of medicine. And, you know, like people can have a long list of different negative or positive prognostic factors. But in the end, I think experienced neurologists often have a feeling of somebody that they're more worried about than others.

Dr. Shin:
Alright. Alright. Thank you very much. Alright.

So for our next module, we're going to shift focus a little bit, not talk about the markers in abstract, but really talk about monitoring, really, how do we distinguish between these concepts, which again, at this meeting, we're going to be talking a lot about. So relapse-associated worsening versus progression independent of relapse activity. In other words, important concepts, but can we even tell them apart?

So the first question here was really, are they even distinct entities? Can they be distinguished? Can relapsing versus progressive disease states be separated? And the second part of the question is, if so, you know, how should we evaluate them? Alright, and so we were asked these questions. The audience, wow, split, like right down the middle in terms of this, in terms of are they separate entities? Split. Alright. And should it be evaluated differently? It depends, is the majority opinion here?

Alright, well, when we were answering these questions, I kind of felt that yes, actually, they are separate entities and I did think it would affect management. However, my colleagues, I think I've lost audio here. Here we go. My colleagues had a different opinion. So actually, Dr. Oh, interesting, does not think that they're actually separate entities, but does think it should influence evaluation. And Dr Alvarez, the opposite way, that they are separate, but it shouldn't really affect our evaluation. And so I'm going to let you to duke it out. And I think Dr. Oh has the floor first.

Dr. Oh:
Okay. So I think anytime you describe a complex disease like MS, as clinicians and scientists, we want to establish some sort of framework that helps us to make sense of the disease entity. I think because of our need to categorize and kind of make sense of a nebulous disease, MS has traditionally been classified into relapsing and progressive MS subtypes.

However, and we have all of these nice diagrams in our textbooks showing what relapsing MS looks like, what progressive MS looks like, but any clinician in the room knows that real life is never as nice and neat and categorized as textbooks. And we all know that in people with relapsing MS, we tend to see progression that is independent of relapses. And then we all know that sometimes you do categorize someone as progressive MS; yet, there are relapses that can be superimposed. And so I think this is just kind of an anecdotal illustration of the fact that our classification, while it's useful for many different things, is problematic because it doesn't necessarily reflect what we see in real life.

And I think one of the recent studies that really has driven this point home is a study that looked at the phase 3 ocrelizumab clinical trials, and this was led by Ludwig Kappos and colleagues. And I think this was a really interesting analysis because this was the relapsing MS clinical trials looking at people on ocrelizumab, as well as interferon beta-1a. And as we know, in these large phase 3 relapsing MS clinical trials, based on the inclusion and exclusion criteria, it's always a very early cohort of relapsing active patients that are recruited. So in this cohort, traditionally we would think that in early relapsing MS, the bulk of the progression events that are seen are supposed to be driven by relapses. And we think that this slow, smoldering progression is not something that we would typically see in early relapsing MS.

However, surprisingly, when this group looked at the OPERA I and II clinical trials and looked at what the proportion of people who progressed that were independent

of relapses were, and what the proportion of progression events that were related to relapses based on what we traditionally think we would expect that most of the progression events were likely related to relapses. But on the contrary, as you can see from these diagrams here, the vast majority of progression events in this early cohort of relapsing MS patients was related to PIRA, or progression independent of relapse activity. And this is technically what we use to classify people with progressive MS.

So based on this, I think it's very clear that our neat categorization does not really apply. And we all know this because we see this in clinic all the time. And this is why I believe that relapsing and progressive MS are not separate entities.

This is a diagram that was modified from a review article that was published way back in 2008. And, you know you're getting old, by the way, when 2008 seems like it was pretty recent, but that was actually 15 years ago. Anyway, as you can see, this was a review article authored by Amit Bar-Or, and even back in 2008 this diagram illustrates the fact that these peripheral relapse disease biologies and the CNS compartmentalized disease biology, which we think is responsible for progression in MS, really overlap across the entire spectrum of MS. And yes, there are different proportions of these disease biologies that you can see; however, it's very clear that there's a ton of overlap. And again, we see this in clinic all the time.

So it's really clear that the current categorization that we have where we very clearly dichotomize MS into relapsing or progressive MS. It's not really true. Just because again, as you can see, I think the diagram illustrates very well that these disease biologies are there all

the time from the very beginning across the entire spectrum of MS.

So I think I've pretty convincingly illustrated to you why I think relapsing and progressive MS are not separate disease entities. I think this has huge implications for clinical practice because all evaluation and monitoring should include assessments of both relapsing and disease biologies regardless of what subtype we have classified the patient as. And should it influence decision-making? Absolutely. And ultimately, when we do have therapies that hopefully are able to target that central compartmentalized inflammation, treatment selection should entirely be based on this assessment and the recognition that relapsing and progressive MS disease biologies exist across the entire spectrum, regardless of the categorization that we've given patients.

Dr. Alvarez:
Perfect. That was awesome. I think we're going to use the same words to argue the opposite sides of the same thing. So some apologies for that maybe.

So putting in pictures, what Jiwon just basically said that our words fail us, I think, when we're trying to kind of characterize these diseases, right?

These are two patients that by all ways to look at the disease are primary progressive patients, the arrows representing just MRI activity. And we can see that the rates of progression are very different, but that they're progressing nonetheless, and maybe how much or how much can we separate these relapses? It's hard to separate relapses if you can't really remit. And so the patient that's on the left as you're looking up, would be that patient that, you know, is that 20-year-old with so much inflammatory disease activity, that they really just are stacking their relapses. And it's hard to separate out.

And I still remember because we're old, you know, the days where these patients would not even get treated. And we would say they're primary progressive, we don't have any treatments approved for primary progressive disease, and they were not treated. And I think that, you know, the more classical sense of maybe a primary progressive patient, and also there. So even though we're using the same words, are they really the same thing, I think makes it tough.

To kind of drive that point a little bit is the dissociation in this video, of looking at relapse and progression. So as you'll see, spots, lesions, scars come, land, and go. The disability is indicated in blue, and you can see that as we start getting to this point that the amount of relapses kind of goes down, brain atrophy increases go down, but the disability increases. So it's a little bit of driving the same concept with the graphs just in a single patient, that Jiwon said, that there's a dissociation between these two processes.

Just to show a little bit of what happens in treated world. And so this is looking at NIDA data from ublituximab trials on top over the entire 2 years of the trial and the bottom over just the last year, so re-baselining, so actually, the last 18 months of that trial. And what you can see is if you look at the columns of T2 lesions versus CDP, the progression, as you can see, that there's a lot more lesions compared to CDP that we would see, for example, in the boxes for ublituximab in green, very similar ratios, as you might see in teriflunomide, over the entire trial. And then when you flip it over to the re-baselined data, we can see that the number of lesions really decreases versus the CDP is still there. So kind of a dissociation.

So suggesting that the pathology is different between relapses and progression. And so that's the argument for saying that they're different entities. And so I think we ended up basically saying the same thing in a different way, and maybe ended up at the same conclusion through different pathways a little bit. That might be the same disease, but different pathophysiology is within the same disease.

Dr. Shin:
All right, well, you know, frankly, I'm disappointed that you two had to agree. But sounds like you're saying two different components, but they coexist. And that's really what it comes down to, in terms of our thinking about MS. So this audience is looking for blood, though. So very disappointed.

Alright. The next topic we're going to cover in this session kind of goes along with this, which is really how might we distinguish between relapse associated worsening and progression independent of relapse? Like, how could we tell if we thought that this was an important concept? And again, we were asked, and we all had slightly different answers. I went with digital tools, which you know, just want it to be sexy, I guess, or something. But Jiwon again, goes with her combination approach focusing in on her clinical acumen and the nihilist. Enrique is like, yeah, there's no great way to really tell these apart, maybe MRI is the best. So we're going to cut Enrique out of the conversation, deter nihilism. And we're going to focus on either digital tools versus maybe more traditional measures. So Dr. Oh.

Dr. Oh:
So I only have one slide to illustrate my argument. And I think I've said this already. But we talked about different ways to prognosticate earlier, but when it comes to monitoring disease, we're also really not great at that in MS clinical practice. And this is because,

regardless of whether you're trying to detect a relapse, or whether you're trying to detect whether an individual patient in front of you with MS has progressed, a large part of this is dependent on the patient's subjective reporting of the symptoms.

So let's just first focus on relapses just because you would think that this is something that's very easy to detect, that it's either there or it's not. You know, how could you ignore a relapse? But it turns out, because we typically see people with MS once every 6 to 12 months. You're often completely reliant on a patient reporting symptoms that are suggestive of a relapse. And we have again, in textbooks specific criteria that we're looking for, including, you know, characteristic symptoms of a demyelinating relapse, whether it's visual symptoms related to optic neuritis, or partial myelitis, or infratentorial symptoms, and the symptoms have to last for more than 24 hours.

But as you can imagine, there are very different thresholds that individual patients have to report symptoms. We all know that we have patients in our practice that literally will never show up to clinic unless they are not able to, say, ambulate or completely blind in one eye. And on the other hand, we have other patients that will show up with a laundry list of very brief symptoms that they've had, and they're worried about relapses. So, you know, based on people's thresholds of reporting, this is really what we rely on to detect clinical relapses. And so, as you can imagine, it's far from perfect.

In addition, when we think about monitoring progression, this is actually where it's really challenging in clinical practice. As you well know, MS is a disease that lasts for decades. And so, progression is not something that happens very quickly in most people. We do rely heavily on, again, a patient's subjective reporting of symptoms. They may tell you that, for instance, they were they used to be able to walk for 10 kilometers without resting, but now they can only walk for 7 kilometers without resting. But again, as you can see, these are all things that are dependent on a patient reporting them to you.

We do rely heavily on the neurological exam, which is really the basis of the Expanded Disability Status Scale score, or the EDSS. But we all know that there are huge limitations with the neurological exam. I always say this, it's good for localization and diagnosis, but when it comes to monitoring for slow progression that happens with a chronic neurological disease, it's far from perfect. And we know that there are issues with inter and intra-rater reliability with the neurological exam. The EDSS has ceiling and floor effects, is heavily weighted towards ambulation. You know, the list goes on. And these are the tools that we use to detect progression in clinical practice.

So knowing all of these limitations, again, and knowing that nothing is perfect, we don't have a magic imaging measure. And we don't have a magic fluid biomarker. And we don't have a magic clinical tool that will help us detect relapses verse and progression. I think it makes sense in an imperfect setting to use all of the tools that we have, including the patient's clinical history, the neurological exam, potentially imaging measures, advanced imaging measures, fluid biomarkers, if they're available, to be able to detect these clinical measures that are of relevance for people with MS in clinical practice.

Dr. Shin:
Alright. Well, I do also, in some sense, agree with what you're saying. These are important metrics, and this is what we have. But I think the flaw in really our practice is that we don't essentially continuously evaluate our patients.

So my argument would be this, you know, if I have two time points, and I have, you know, at the first time point patient was in such and such a state, and the next evaluation, the patient is worse. Okay. That's all the information I have. They were like this, when I assessed them at timepoint A, and they're worse at timepoint B. I don't know if this is the situation, that they're worse because they've had a relapse, and so they've now accumulated some disability due to that relapse, and hence have a new baseline. Or if that change was gradual, that they're worse now, because they have accumulated gradually, progressive disability. Alright. And so my argument is, that's really the piece that's missing, the clinical tools, examination skills, maybe even MRI, maybe biomarkers, yes, can tell us that the patient is worse now than they were before. But if I don't have information in between those assessment points, I can't really tell the difference between stepwise relapse-associated worsening and gradual progression independent of relapse activity.

So my argument is, we need to do something a little bit different than our traditional measures. And maybe, maybe digital tools offers us this. And again, missed opportunity for sponsorship, because this is just one possible digital tool. And you know, we could have a debate about what's the best. Should it be some sort of wearable? Should it be, you know, something on our phones? Should it be Elon Musk would like implant stuff into our skulls or something.

I'm using this as an example of some data from an app called Floodlight. It's a free download. It allows patients to do assessments on their phone at intervals, typically, let's say once a week, for example, they can do an assessment of cognition, some coordination tasks, put the phone in your pocket, go for a brisk walk and assess ambulation.

So this is just an example of one of my patients who's been doing this, this gentleman actually really likes doing it, his phone alerts him once a week, and he does a couple little things. And over time, we've accumulated this information. I just selected, in this case, cognition. It's a test similar to Single-Digit Modality Testing in a way. And my reading of this, I don't know if I could say this has been

validated in some way, but you know, over time, his scores seem reasonably, if not slightly improving with familiarity with the task.

The second line is different. This is one of the ambulation tasks. And I learned a lesson here because he was coming to my clinic and telling me, 'You know, I feel like my legs are getting weaker.' And I, you know, 'How are you doing?' Like, he's an avid golfer, 'you're playing 18?' 'Yeah, I can still play 18 holes of golf, and you know, but I just feel like my legs are not doing as well.' And I examined him, maybe I'm not, I don't have your skills. But I couldn't find any obvious increased weakness in that limb. But when we reviewed his data, we're you know, we just call it up and, you know, out of the app, it looked to me like there was a change that corroborated what he was saying; that his performance on this walking paths was gradually change - had changed over time in a gradual way. And we could have a debate about what we could do about this, if we're seeing this, but I'll be honest, this did lead to a conversation which in turn led to a change in therapy. I thought maybe I haven't really achieved my goal of shutting down your disease process.

So I just want to put this out there that the challenge, in my opinion, of relapse-associated worsening versus PIRA, is getting a sense of what's happening in this timeframe. We can rely on the history, but that's subject to recall bias and time proximity. And so maybe in the future, we're going to learn how to use digital tools to help us monitor better over time.

Okay. So we do have another topic and, you know, the time is going really fast. I think we're down to like 15 minutes or so. But this question was asked: Do any of our current MS disease-modifying therapies, literally dozens, at this point, help patients with inactive disease progression? This was our question. And we'll see what you guys thought. Now, be honest, the hilarious thing, because we all came up with the same answer, was maybe like a little bit. And

I'm not sure but I was tasked with maybe covering in your arguments, you guys are going to need to weigh in. So just in the interest of time, I just picked one example of a recent clinical trial. I think really all of the clinical trials tell us the same thing.

This was a trial, as you know, that we tried to focus specifically on secondary progressive MS. And this would be siponimod. And you can see that it hit its primary endpoint of reducing accumulation of disability over time. The challenge though, the good or bad thing, is this compound also suppresses relapses is greater than 50% reduction in relapses compared to placebo. So what's difficult is to disentangle the benefit in the reduction disability with the benefit in preventing the patient from having MS attacks. Alright. And this has been really just our challenge in the field. Actually, Enrique, I think you already showed some data that touched on this a little bit. But there have been other attempts to analyze it.

This is from Bruce paper, recognizing the challenge, tried to be creative in terms of using different models and statistical analyses. How do we tease out an effect of our MS disease-modifying therapies on disability progression separate from our medications, benefits in suppressing relapse, I'm not going to go into the entire paper, which I'm not sure I totally understood, if I'm really honest with you, it's a tough paper. But using different analyses, you can try to take out the effect. For instance, let's look at patients who actually did not have clinical relapses, and then see if there was a change in terms of their accumulation of disability. And that could go either way, they might have been responding to the therapy, or they might not have been very active. All I'm going to say in summary, what the data looks like is kind of everything that we just said, is that there may be a shift in favor of a treatment effect that our MS disease-modifying therapies may reduce disability accumulation, even separate from their effect on relapses. But to be honest, with our current treatments, that effect does appear to be fairly modest, obviously giving us a challenge in terms of the next generation options, which it would be awesome if they were - had demonstrated better efficacy in that realm.

So before actually, we go to this wrap, I don't know if you guys want to maybe help me do a better job. Any other comments on that concept of why did you say that you think maybe it helps a little bit? I'm not even going to let you look at this question. I'm going to just go back to this question. What do you guys think? Why did you guys say maybe a little?

Dr. Oh:
I think, you know, just similar to you, Bob, based on clinical trial data, I think it's important that we now have therapies for the first time that have been approved for use and progressive subtypes of MS, despite the fact that we talked about the categorization, you know, needs improvement. But those therapies are modestly beneficial at best. And so I think that was the maybe a little.

Dr. Alvarez:
I think it's a spaghetti plot a little bit, right? There's some people that seem to get a little bit more benefit than others and things like that. So for some people, maybe a little bit more, for some people a bit less. And I think that that's where, on average, it comes out to be a little bit.

Dr. Shin:
A little bit. Alright. So another group question, we can answer this maybe briefly: Do you think that this transition from these terms that, we're now using relapsing MS versus active SPMS, is this something that's clinically important?

Dr. Oh:
So I think it's very difficult to mark the transition between relapsing MS to active SPMS for all the reasons that I described earlier. It is only clinically important to me though because it determines what sort of access a specific patient has to different medications. So I think in the U.S., fortunately, it sounds like the FDA has taken this approach in recent years where MS therapies are approved across the spectrum of MS. This is unfortunately not yet the case in Canada. And so once I label somebody as having active SPMS versus relapsing MS, the types of therapies that are available to that individual dramatically differ. So as you can imagine, I'm very hesitant to label someone as having active SPMS just because none of the relapsing MS treatments will then be available for that patient.

So scientifically, I do not think this is important, and I think the transition is really difficult to actually mark. However, from a practical clinical standpoint, weight becomes of paramount importance.

Dr. Alvarez:
Ditto. To me, active means relapses and from a progression we showed, you know, Jiwon showed really nicely how progression starts very early. So it's potato-potato.

Dr. Shin:
So we have our last one, and we've got like lightning round at this point, I think we're at 15 minutes. Ready, set, go. Alright. So how about assessing our treatment - we have these options. We've made our decisions, how can we how do we assess whether we're achieving our goals? Whether the medications are working or not? When should we make therapeutic changes? So again, tying into biomarkers, what indicators or biomarkers would be most valuable for evaluating our treatment effect? And here, Enrique went with MRI activity. It's like the inverse of what we did earlier. I went with serum neurofilament light chain. And Jiwon was doing both. And since you obviously agree with both of us in one way or another, it looks like it's just going to come down to the two of us here. And so Enrique, go ahead.

Dr. Alvarez:
Perfect lightning round. So just to kind of talk about NIDA again, and kind of the breakdown of different effects. So I think the nice thing about it is, when you look at ofatumumab versus teriflunomide, in this case, and kind of re-baselining, the nice thing is when you look at the overall study - when the panel with a free of gadolinium-enhancing lesions, that you can see a really nice clear effect early, and then the re-baselining, that T2 then kind of catches up. But so I think MRI gives you sort of a grade evaluation early with contrast-enhancing lesions and later on with T2 lesions if you do re-baseline. And so I think it just provides a really sensitive measure to kind of see how the treatment effects go.

And then maybe my argument against NFL is probably a little bit more kind of to talk about this. So I think I have a few problems with NFL. One is in the example, for example, this is from siponimod in secondary progressive patients. When you look at the patients without contrast-enhancing lesions, you see flatlines in both of the treatment arms, so really no effects. So as a treatment response, we don't see any. And then with contrast-enhancing lesions, what happens a little bit as you see this initial spike, so it's a very delayed measure of what's happening in these patients. And then you can see that it takes up to 2 years to really see a nadir of that NFL. So it's not a very responsive, it's a very slow delay. This isn't just specifically to siponimod, we see it with ocrelizumab, flatlines for PPMS patients on ocrelizumab. And when you look at the effects on contrast-enhancing lesion in patients who have contrast-enhancing lesions, a very slow decline that takes up to 2 years to kind of see that decline. So it's just not a very sensitive measure that happens to that.

And if we look at individuals, it gets even more complicated. You just need to look at it very often. You see that top patient, if you don't happen to catch that peak, you miss it. It doesn't have a memory like T2 lesions do so you'll skip it and forget it. And then if you look at the middle panel, for example, you'll see a patient that doesn't spike until the next time, when that patient has a relapse. Or it's like the follow-up, it takes four weeks for the levels to bump up after the patient initially had a relapse. And so, I think it's just not a very sensitive delayed issue.

Dr. Shin:
Alright. Well, I do have to admit, I mean, I think your objectives are valid. And in this case, I think using essentially a serum biomarker, my argument would really be more about the promise of it in terms of the concept. And actually Jiwon already mentioned how much work there would have to be done in order to really use this.

But to me, the concept in my mind, is what we'd really like to be able to do is not recognize when an attack or relapse has occurred, but maybe predict when that's going to occur, and that it might occur. And I think that was kind of the promise, perhaps, is that maybe we could find a biomarker that would allow us to detect, for instance, let's say we're not achieving our goals in terms of preventing neuronal loss, as you said, maybe this right now isn't the most sensitive marker. That would

be great if, hypothetically speaking, I could identify a patient who had progression independent of relapse activity, smoldering disease, did not have much change on MRI, but I could somehow detect that in the serum. You know, we may not be there yet.

And then again, secondly, the idea of would there be a potential marker that could identify a patient who is going to have a clinical relapse and take action? So I don't think I'm going to win this part of the debate. But that was really my slide.

Alright. A second part the question in our lightning round, should radiologic activity and a clinical relapse be approached differently when they occur together than if they occur separate? In other words, if a patient a clinic relapse and enhancing lesion on MRI, okay, is that different from a patient who has a new lesion on MRI or enhancing lesion on MRI and no clinical symptoms? Or patient who has an attack, but we can't detect a lesion on MRI? And so there was a difference here. I'm sure that would be approached differently, but in this case, we're going to see what Jiwon and Enrique have to say because they came down on different sides of this topic.

Dr. Oh:
So I think this diagram illustrates it all. And actually, I was told by a mentor many years ago that any neurological disease talk always has to have an obligatory iceberg slide. So this is the obligatory iceberg slide. But for MS, this really, really is applicable because, as we know, what we monitor clinically, are relapses. And we talked about the difficulties with monitoring relapses. And we monitor for disability progression, but we know that there is so much more happening beneath the surface when you're thinking about the totality of MS disease activity.

Studies have shown that MRI disease activity occurs 10 to 20 times more frequently than clinical relapse activity. So it's very clear that monitoring for clinical relapses alone is not sufficient. And then we know that the development of new MRI lesions is completely relevant to relapses. And I think the study that best illustrates this was a study done by Maria P.S. Romani a number of years ago, where she collected data from over 20 phase 3 MS clinical trials of relapsing MS and found that a treatments' effect on new T2 lesions strongly correlates with an R squared value of 0.71 with the treatments' effect on relapses. So there's many, many different studies that have shown this. But I think this is really the definitive study that has shown the relevance of monitoring not just for relapses, but new MRI lesions, because this really is the imaging correlate of a relapse. It's clear that the MS community has embraced this. Any treatment guideline that you look at, regardless of whether it's the modified RIO criteria, or the Canadian treatment optimization recommendations, put a lot of value into even clinically silent, new MRI disease activity.

So it's very clear, at least in my mind, that regardless of whether it's a relapse, or the MRI version of a relapse, it's clear that we need to take both of these into account when thinking about treatment decisions.

Dr. Alvarez:
So I totally agree with that argument. I think the approach to it, to me, is a little bit different because there's relapses and then there's relapses. And I think one of the problems that we have, again as definitional, in the sense that a lot of our relapses tend to probably, my suspicion is be pseudo relapses, especially with high-efficacy therapies when we look at this.

So I'm going to skip this one just at a time and concentrate on this one.

You've seen these similar graphs. If we look at ublituximab bars, actually the top bars in general, and you look at the ratios between lesions to relapses, as we saw, it's a nice consistent number, it's a 3 to 1 lesions to every relapse that we see. In this case, it was probably closer to 20 to 1 when we look at most of the natural history studies and things like this. When we look at the re-baseline data, and especially in the ublituximab arm, what we noticed is that now there's basically almost 3 relapses for every MRI lesion. So what happened? I don't think all the new lesions happened to be in the spinal cord, that maybe were missed on the MRI, the lesions became so small that we can't pick them up on MRI. I think the problem that we're facing is that we're getting a lot of patients who are coming in with, 'I think I have a relapse,' and what they're probably having is a pseudo relapse. And so that's why I treat them a little bit differently because I want to see an MRI lesion. I'm like, that's inflammatory disease activity, I'm going to go for it. When I see a relapse, I take a little bit of an extra step and I get concerned, maybe I need to treat a UTI or I need to treat something else with it.

Dr. Shin:
All right. So we are really down to the wire. And then in order to be able to answer even a couple of questions, Enrique, you and I are going to have to do like 30 second answers. Alright. In general, should we discontinue therapy and an older patient with stable disease? It depends. Alright. So Enrique, you and I sort of disagreed on this. So 30 seconds, should you discontinue and why?

Dr. Alvarez:
So a couple of case examples of patients that walk routinely into the clinic. I think in the past, when we were dealing with interferons, these patients would just simply not come into the clinic anymore, stop their therapy, and be gone because they hated the therapies. It's gotten a little bit harder now that patients tolerate our therapies a lot better. And I think because of risks and other things like this, it is something that we need to think about and discuss with patients. It is tricky. It's a hard discussion to have. It might need to be broken

down and discussed over several visits. I think there's a lot of kind of the benefit-risk discussion that kind of comes into it. We need to talk about age, years of stability, disability level. These are data that I showed kind of previously, with the number of attacks coming down with age, but as risk going up as disability level accumulates. Maybe you want to consider de-escalation before stopping just as a consideration step. And then just to kind of introduce the DISCO study, where if we look at relapses, we didn't really see a difference between people who stayed and those that stop. Now there's certain criteria, right? The patients needed to be over 55, they needed to be stable for at least 5 years. The one patient that did relapse, so we can see on the bottom was a 55-year-old; actually so the one patient that relapsed that had an MRI and disease activity was a 55-year-old. So maybe we need to look at 60-year-olds. Or try to figure out better who to consider this in. But I think that it's something that we need to think about with patients just because of the risks associated with the treatments.

Dr. Shin:
Alright. Well, my argument is really anecdotal. This is a patient, you know as you said, they walk into a clinic every day, she's 72 years old, she had been on a disease-modifying therapy for many years, had not had relapse in over a decade, couldn't even remember her last relapse, maybe some mild right leg weakness stable for years and had MS. But she had seen someone and been evaluated and his recommendation, 'Well, given how well you're doing at this age, I don't think it even really makes sense for you to continue therapy.' So she did discontinue. Unfortunately, she's an avid pianist, and actually she came to my clinic because she had begun to have trouble with her left hand, she was starting to have trouble. And when we imaged her, she had had actually a new lesion, a new cervical cord lesion had developed after she had stopped. So she was not happy. And this kind of looks a little like you.

But you know, the truth is we're not sure and most patients are in fact going to be stable. But as you said, it's really going to come down –

Dr. Alvarez:
If we could pick those few, that would be awesome, yes.

Dr. Shin:
Alright. So I think we're going to try to squeeze in a couple of questions in the literal minutes that we have left. So I'm really going to select here for the questions that you've asked. Somebody asks about this: What about the good old passage of time to distinguish RAW from PIRA? What do you guys think about just waiting I guess to see how they do? Relapse-associated worsening versus PIRA?

Dr. Oh:
I mean, that ultimately, the good old passage of time is what will allow us to determine this. But you know, much like in the stroke world, we're now moving into an era of MS treatment, where we talk about time as brain and spinal cord. So can we afford to allow for the passage of time to know whether we're looking at RAW and PIRA? And I would say that's risky.

Dr. Shin:
Alright.

Dr. Alvarez:
If the patient is stable, the patient's stable, oops, now they're in a wheelchair. Yeah, and what happened to stability?

Dr. Shin:
Right, right. That's the challenge, right is waiting until they show us is kind of late. If we could figure it out early would be great. One more question, if we can squeeze it in. Somebody asked from the beginning of our debate: If our current prognostic indicators are not enough to make clinical decisions, how do we even choose initial therapy? Should everyone get high efficacy therapy in the beginning? Yes! You go. Yes. Yeah, easier. Just forget that debate. Just put them all on high efficacy therapy.

Dr. Alvarez:
Because you don't have to think about it. Right? No, I think the nice thing about high-efficacy therapies eliminates all the prognostic factors, right? When you look at a lot of these prognostic factors, the patients with high NFL versus low NFL end up doing about the same, people with a lot of disease activity versus no disease activity looked the same. If you look at drugs that are kind of low-medium efficacy, the prognostication becomes very important, because that's where you see the separation. But I think with high-efficacy therapy, we demonstrated we can't prognosticate well, and we can kind of ameliorate that a little bit by choosing the right drugs.

Dr. Shin:
Right. Jiwon, any last words? Close us out.

Dr. Oh:
So I don't think everyone should go on high-efficacy therapy. I think we have a lot of room for improvement for prognosis. But like I said

earlier, and I feel like a broken record, when there is no magic bullet, you use everything that you have, and you use clinical judgment. And so, I think that based on what we know, we use what we know when you make treatment decisions based on the imperfect combinations of prognostic factors that we have.

Dr. Alvarez:
Sounds like we have our next –

Dr. Shin:
Our next debate right, next - Okay. Alright.

Look, I want to thank you guys for attending. I think we're pretty much right on time. So I want to thank my colleagues, Dr. Oh and Dr. Alvarez, for a stimulating debate. Thank you.

Announcer:
You've been listening to CME on ReachMD. This activity is jointly provided by Purdue University College of Pharmacy, Office of Continuing Education and Professional Development, Purdue and Efficient LLC, and is supported by an educational grant from Novartis Pharmaceuticals Corporation. To receive your free CME credit or to download this activity, go to reachmd.com/CME. Thank you for listening.