MolDX: Predictive Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis CAC Meeting Transcript

Moderator Dr. Charnot:

We have just started the recording of this CAC meeting in compliance with CMS. For the record, prior to doing so, I announced that Palmetto GBA would make an audio recording of the CAC meeting and consented on behalf of Palmetto GBA.

Moderator Dr. Charnot:

Thank you for joining us this afternoon as we discuss predictive testing to guide targeted therapy selection in rheumatoid arthritis. We are joined today by, hopefully three, subject matter experts in this field. I will take the opportunity to introduce them now. We have Dr. Eugene Huffstutter, CAC representative for the Tennessee Rheumatology Society and Partner at Arthritis Associates in Hixson, Tennessee, Dr. Greg Niemer, CAC representative of the South Carolina Rheumatism Society, and a Partner of Low Country Rheumatology and Dr. Kerrin Burte, if you joined, President of Tristate Arthritis & Rheumatology. Dr. Burte, have you joined the call?

Dr. Kerrin Burte:

I am here. This is audio only, correct? No Zoom or visual?

Moderator Dr. Charnot:

That's correct. It's audio. Thank you for joining us today. Great. Let us begin. We are basically meeting to discuss the evidence available regarding predictive testing to guide targeted therapy selection in rheumatoid arthritis. We have provided our subject matter expert panelists with questions for discussion. Panelists, as you respond to each question, we ask that you first state your name so we know who is speaking, and also please rate the confidence in the evidence being utilized for each key question. We ask that you use a scale of one to five, one being low confidence and five being the highest confidence.

Moderator Dr. Charnot:

We will now begin our discussion. Each of our panelists will have the opportunity to respond to each question. So with that, I know you have all received the questions and have had an opportunity to review. So we'll start with the first question. Again, I just ask that you state your name before responding. The first question is please describe the level of certainty in the evidence supporting the selection of first-line and alternate medical therapies for rheumatoid arthritis as outlined in the American College of Rheumatology guidelines. Dr. Burte, would you like to go first?

Dr. Kerrin Burte:

Well, I'm sorry I don't have a... I got the list of references, but not a list of the questions. Could you please repeat the question? I don't see a list. I've got a lot of emails from you guys, but not a list of the questions. So I'll listen to them carefully and respond as we go.

Moderator Dr. Charnot:

We did send it. We'll send it again for you, certainly.

Dr. Kerrin Burte:

Please. I've got my email up right now.

Moderator Dr. Charnot:

I'll repeat the question and perhaps we can have Dr. Huffstutter go ahead as you're waiting to receive it in print. So the first question is please describe the level of certainty in the evidence supporting the selection of first-line and alternate medical therapies for rheumatoid arthritis as outlined in the American Colleges Rheumatology guidelines. Dr. Huffstutter, Would you like to go ahead?

Dr. Eugene Huffstutter:

Sure. The list of references that you've given is quite extensive and it's very difficult to sort through many of these. When we talk about rheumatoid arthritis patients, there are really different definitions. There are definitions that we use in studies where these people have just pure rheumatoid, that they may require them to be seropositive or CCP positive or both. Then I'm a clinical rheumatologist, so the majority of my time is seeing patients, and so many of my patients have comorbid conditions. I think that some of the trials listed did include patients like I see. For instance, they'll have a lot of comorbid conditions and whatnot and not just pure rheumatoid arthritis. Question, and eventually I'm going to get around to giving you a number, and I apologize for my verbose answer here, but when we're basing this, it's really complicated because the technology behind this testing is novel. It's something new for rheumatologists, and I think that trying to understand the technology that's involved is challenging. That being said, and trying to answer your question as succinctly as I can for the patients that I would see, I would give it a four.

Dr. Greg Niemer :

So this is-

Moderator Dr. Charnot:

If I could just-

Dr. Greg Niemer :

... This is Dr. Niemer-

Moderator Dr. Charnot:

... Add a clarifying. I'm sorry, go ahead, Dr. Niemer.

Dr. Greg Niemer :

No, go ahead. Go ahead. I'm sorry.

Moderator Dr. Charnot:

Thank you for providing the rating and understand that the rating is really related to evidence around the first-line versus alternate therapies and how you would choose to select one over another. If there's any additional comments you'd like to make, by all means, we want this to be a discussion. I wanted to just allow you to elaborate a little bit further if there's anything further you'd like to discuss before we move on to our other panelists.

Dr. Eugene Huffstutter:

I appreciate the opportunity to do that. I think I've been rather verbose in my first answer and I'm interested in what Greg and the other panelists have with their comments also.

Moderator Dr. Charnot:

Okay. Thank you. Thank you for that. Dr. Niemer, please.

Dr. Greg Niemer :

Yeah. My interpretation of the first question is just, evidence supporting selection of first-line and alternate medical therapies for rheumatoid, not related to a novel like PrismRA. This is just the evidence supporting how we make decisions in our treatment. Is that correct?

Moderator Dr. Charnot:

That's absolutely correct. And that's-

Dr. Greg Niemer :

... Okay.

Moderator Dr. Charnot:

... Currently with the current available evidence. And then if you wanted to add, in addition with evidence sort of provided by testing, as you mentioned by tests like the PrismRA, we'd be happy to hear a lot of that information.

Dr. Greg Niemer :

Okay. I mean, historically, and this is because we haven't really had any specific tests to help us to make our selection, it's all based upon data. When it comes to safety and efficacy of treating rheumatoid arthritis, we also rely heavily upon the ACR guideline. And I think that Dr. Singh's guidelines are referenced in all of the articles that y'all presented to us. The selection is a typically starting with a disease modifying drugs, such as methotrexate or Plaquenil, or there's a list of disease modifying drugs that have been around the longest, and we have the most data supporting them. And that's typically considered your first-line treatment, and then you move on to biologic treatments, If a patient has not responded well all to a disease modifying therapy, or maybe they can't tolerate a disease modifying therapy. And then your decision making, as far as which biologic to use, again, sometimes is predicated on how long the medications have been on the market, safety, and efficacy data associated with them.

Dr. Greg Niemer :

And then also just comfort levels of physician and prescribing the medications as far as significant head to head data between the biologics or being able to know with a specific patient which biologic you should start with. There's really not a lot of evidence supporting how you differentiate between biologic therapy. Sometimes you do in do it based upon safety. Say for instance, if a patient has a history of cardiovascular disease or I'm sorry, congestive heart failure, then you probably stay away from TNF blockers, so there's some things that may prevent you from wanting to use a certain type of biologic treatment, but otherwise, certainty in the evidence supporting the selection of first-line alternate medical therapies, I would say a three at best, because we're going based upon historical data and nothing more objective than that.

Moderator Dr. Charnot:

Thank you for that. And Dr. Burte, have you received the questions in print?

Dr. Kerrin Burte:

Yes. I would say four. Dr. Singh's guidelines, they're qualified some as high evidence, very good evidence, low evidence based on different factors. So most of the scenarios with the different types of rheumatoid arthritis patients are addressed in those criteria, people with mild rheumatoid arthritis, you might tend to start on Plaquenil Sulfasalazine, more severe methotrexate, and sometimes very quickly to methotrexate, onto a biologic as the other consultants are saying. There each scenario, is addressed as high confidence, medium confidence, low confidence based on the literature. So that when you're talking about the first-line therapy, a new rheumatoid arthritis patient, I'd say four rather the... My number would be four.

Moderator Dr. Charnot:

Thank you. So, to follow up on your response, it sounds like a lot of the evidence is really, or the practice is really centered around safety and efficacy profile, severity of symptoms and things like that. Would you say that there's a general approach to first-line? So if we forget the alternate medical therapies at this point, is there something else that we should know regarding how US clinicians would select a first-line therapy outside of the things that you've already discussed?

Dr. Eugene Huffstutter:

From a practical standpoint, this is Dr. Huffstutter. A lot of this is dictated by insurance requirements and also local carrier determinations. You know we've helped develop those, and a lot of them are based on just what we're used to doing. For instance, I've been in practice for 37 years, and so, when I came into practice in 84, methotrexate was not actually FDA approved, even though we were using it. And it was based on... To me, and when you look back over time, the studies that were used, were very less robust than more current data that we have now for rheumatoid arthritis. So I think a lot of it just has to do with what we're used to doing and what we're comfortable doing. And if we're really analyze the data, I think that some of the newer agents even be more efficacious if we were to be able to use these agents earlier in disease.

Dr. Eugene Huffstutter:

However, practicality of that in terms of the expense of these medicines, kind of prohibits a lot of their early adopt. And if you can control patient's disease with less expensive medicine, then you certainly want to do that and want to be prudent in terms of the way you care for patients with not only caring for the joints, but also the financial resources of the patients and the system. I really think that when you look at the data that supports, for instance methotrexate, which is in the guidelines, there's not nearly as much evidence as there are for other agents. And some of the other agents that have been approved more recently actually have really robust data if they're used as first-line agents. So I think it's not as complicated simply just looking at the science.

Moderator Dr. Charnot:

Thank you. If anyone who's not speaking would please mute yourself because there is some level of background noise. Thank you. So it seems like there's also sort of a culture of a comfort level of doctors, as you said, and also a cost consideration regarding what doctors are willing to prescribe. Can you perhaps provide some insight in terms of the newer medications that you're referring to, where there

might be additional evidence? You mentioned methotrexate as being an older one without enough evidence, but what are some of the newer ones that you were referring to?

Dr. Eugene Huffstutter:

Well-

Moderator Dr. Charnot:

... Or at least the classes of, I mean, we don't have to call them out by name.

Dr. Bien-Wilner:

This is Dr. Bien-Wilner, can we focus on that question on the biologics?

Dr. Eugene Huffstutter:

And I think that's the big jump. I think that most rheumatologists will try to control patients with traditional DMARDs. And these are things like methotrexate, Leflunomide, Plaquenil, Sulfasalazine, and rarely these days azathioprine Imuran, because I think, if you fail two or at the most three disease modifying agents, they're going to move on to the class of biologics. And then when you look at rheumatoid arthritis in that class, there are five agents that are FDA approved, that block tumor necrosis factor to a certain extent. Then there's a T-cell agent, B-cell agent. There's the IL-6, there are two agents there. And then there's the new smaller molecules that I almost call them designer molecules because they don't occur in nature, they're specifically designed to block second signals. And those are the Janus kinase inhibitors of which there are three currently approved for use in the United States for rheumatoid arthritis.

Dr. Bien-Wilner:

Can I ask a follow up question? It's Dr. Ben Wilner again. This is really to all the experts on the panel. Are you aware of any evidentiary basis for selecting one biologic over another?

Dr. Greg Niemer :

And is this based upon... I think that has... This is Dr. Niemer. This has to be defined as to what you're basing that upon. Is it based on efficacy, is it based upon safety? Certainly there are certain situations I mentioned earlier, like with patients with congestive heart failure, that you'd want to avoid TNF blockers, patients that are at higher risk of infection or have a risk... Strong history of non-melanoma skin cancers, TNF blockers may not be the best option in those patients. The patient has a history of diverticulitis, then interleukin 6 blockers would want to be avoided. So there are certain situations more based upon potential adverse events where you'd want to avoid a certain class of biologic therapy.

Dr. Bien-Wilner:

So that's great. That's exactly the kind of, of information we're looking for from you guys. And I'll maybe follow that up with another question, when you're considering a biologic, so you've moved past your first-line therapy, is there a standard process that you would go through in consideration? Does every rheumatologist just have their own way of selecting what the appropriate biologic may be? I guess I'm saying, is there an established process, is there an established rubric? Is there any guideline and more specifically, is there any evidentiary basis for how you would select the most of appropriate biologic, those side effect profiles aside, which you've very nicely already clarified?

Dr. Kerrin Burte:

I mean the best, the best answer I think, or the best guideline we have is the ACR guideline, which it doesn't necessarily specify one specific type of biologic that you would start first. There are several options. That would fall under I guess the first-line treatment with biologics before you move on to a second-line because of the nuances with potential safety issues. And that's the reason why the ACR guidelines are written as they are so that the rheumatologist has the Liberty to choose between several different options.

Dr. Bien-Wilner:

So if I can just sort of follow that up with a statement and I just want to know if you would say that statement is correct or incorrect based on your understanding, the other-

Unknown Attendee:

... I'm sorry. I don't Understand who's speaking right now or who just-

Dr. Bien-Wilner:

... Dr. Bien-Wilner.

Moderator Dr. Charnot:

... I'm sorry.

Dr. Bien-Wilner:

Dr. Bien-Wilner.

Moderator Dr. Charnot:

Okay. Thank you.

Dr. Bien-Wilner:

You derailed my train of thought. Let me take to step back and say it again or consider again. The statement I want to make, and I want to get the panel's feedback on, is to date, to your understanding, there is not any evidentiary basis for why you would choose one biologic over another.

Dr. Eugene Huffstutter:

I think this is Dr. Huffstutter, and I think Greg has mentioned some specific cases about safety. There are also some other evidence for particular patient that you'd want to use a particular product. For instance, one of the TNFs is a PEGylated product that doesn't cross the placenta and is has data for women who want to get pregnant or breastfeed so that if you've got someone in that category, then you'd want to use that as your first biologic agent. There's also some evidence with one of the... With the T-cell drug that's approved for rheumatoid arthritis, that if they are dual positive for rheumatoid factor and CCP positive, they may have better efficacy than other agents, although that was a retrospective analysis and wasn't prospective in looking at it. But I think there are nuances that each of us, as clinicians will look at for individual patients.

Dr. Eugene Huffstutter:

For instance, I've got patients that are given a self-injection that when I look at what they get from the pharmacy, or obviously not compliant with their medicine, so that if I were left to my own devices and could choose what I wanted, I would have that patient either come to the office for administration of drug, either injection or infusion, because they're obviously not compliant. And if you're not compliant, you're not going to get as good a result. So I think I understand your question. You're trying to figure out as a director, you're trying to look and you've got this group of rheumatoid, how does a clinician decide what's the right drug for the right patient? And a lot of this is really nuance in terms of knowing that particular patient and those particular patient characteristics, as opposed to a large trial where you've randomized people head to head, and you're trying to figure out what's the best drug

Dr. Bien-Wilner:

Answer to my question. And I guess if I could summarize, and again, let me know if I'm not summarizing accurately, but that for each individual patient, there's a great number of considerations that are made in selecting the appropriate drug. And that may include specifics around that patient's condition and as well as side effect profiles.

Dr. Eugene Huffstutter:

Dr. Huffstutter again, I would agree with that statement.

Dr. Kerrin Burte:

This is Dr. Burte, I'd agree also. There's some newer information that at one of the Jack inhibitors, Rinvoq was a little bit superior at six months to another medication, TNF inhibitor Humira, as far as head to head studies, I'm now aware of a whole lot more that help us decide which one to start first, besides the considerations, the nuanced considerations of the patients and their other medical conditions that we have to keep in mind.

Moderator Dr. Charnot:

Thank you.

Dr. Kerrin Burte:

And that as well

Moderator Dr. Charnot:

Thank you all. This is Dr. Charnot-Katsikas. I just want to add a clarifying statement to that summary. So I wanted to ask a follow up question then regarding efficacy. I know you mentioned that in one particular, as well as our questioning medical directors. So regarding safety, we understand that you're making a lot of decisions because of safety, profile, and tolerability, well as some other considerations, cost, compliance method of delivery, those types of issues, but in terms of efficacy alone, if we take that piece and separate it from everything else, can you sort of address the... If there's anything further to address regarding efficacy in terms of these biologics and how you know, what evidence exists around them? You've mentioned one retrospective analysis, but if there's more to say about this, please do that to clarify. So we can understand if there's any differences in your opinion, on that front as well.

Dr. Greg Niemer :

So this is Dr. Niemer. Oh, I'm sorry.

Dr. Kerrin Burte:

No. Go ahead, Greg. Go for it.

Dr. Greg Niemer :

I was going to say, there is not, in my personal opinion based upon looking at the data, there's no definitive head to head studies that would say that you start with one biologic versus another. And this kind of gets to the crux of this talk is that, you have some patients that are probably more TNF driven, as far as the main cytokine that's driving their inflammatory process. You have others that may be more B-cell driven. And that's kind of the challenge that we have as rheumatologists and physicians, is trying to find which class best controls that person's disease, because what we call rheumatoid arthritis is... It's not like everyone's inflammatory process is exactly the same. Each patient is a little different as far as what's driving their disease.

Dr. Greg Niemer :

That's why it's good to have different options, but that's what makes it challenging as far as which direction we go initially, because when I'm seeing a patient, I know they have active rheumatoid arthritis. There's nothing that tells me that they're going to respond to a TNF blocker better than they would respond to a B-cell... Some medication that specific for B-cells or Jack inhibitor or an IL-6 blocker. So that's the challenge.

Moderator Dr. Charnot:

Thank you. And that's a good segue into our next question as well. So, we're asking, how robust is the evidence supporting TNF inhibitors as first-line therapy? But then the subsequent question to that is, what is the rationale for the practice given that only about a third of patients will adequately respond to this class of treatment?

Dr. Eugene Huffstutter:

Yeah, I was perplexed. This is Dr. Huffstutter- by that, because how are you judging adequate response? Are you wanting complete remission or low disease activity? Because the best predictor of being able to achieve remission or low disease activity, is disease device. And it's not really not therapy. If you can catch these people early and treat them aggressively, you're much more likely to get them into remission. And I always explain it to my patients is, when you have an inflammatory disease like rheumatoid arthritis, it's like your house is on fire. And if you can put that fire out, when it's on a stove and a kitchen fire, and put a little lead on the grease fire and smother it, you're happier with the result until you wait until the house is engulfed in flames. And the fire department comes and chops up the house and sprays a lot of water and you can look at this same analogy in your rheumatoid.

PART 1 OF 4 ENDS [00:23:04]

Dr. Eugene Huffstutter:

Out of water. And you can look at this same analogy in your rheumatoid patients where you've got a problem with their immune system causing inflammation that's destroying joints and other organs. And you've got to be aggressive with that early to control that, or you're going to get, to me, a poor result because the inflammatory system kind of feeds on itself and can really get these patients, their disease activity grows exponentially, or can in certain individuals. So that, I was wondering how you wanted to define adequacy of treatment with this.

Moderator Dr. Charnot:

Well, thank you for that question. And perhaps we should jump to question four, because that's a question we wanted to ask you as clinical experts in the field. Because we understand that there's, how should we be defining clinical response in rheumatoid arthritis? And is there a variability in the definition used by practicing rheumatologists or in the literature or in the practice guideline? like the ACR20 versus the ACR50. So perhaps we should address that in tandem as we think about this question, because that's exactly something we wanted to ask you all as experts to help us with.

Dr. Eugene Huffstutter:

So before I completely monopolize this call, I'll make one comment and then I'll let my other distinguished colleagues speak because they've got a lot more to say than I do. But you mentioned the ACR20 and 50 and that's to me an artificial thing that was devised to basically get drugs on the market, because you wanted to show a percent improvement. So for the medical directors that are not rheumatologists, what that refers to is a 20% improvement in swollen and tender joint count. Plus a 20% improvement in three of five other things having to do with a health assessment questionnaire, which is a series of questions that assess functionality of a patient, visual analog scales for pain, for global disease activity and then physician global activity of how they view this. So you could have someone who's really, really sick and get a 50% improvement and still have a lot of swollen and tender joints.

Dr. Eugene Huffstutter:

So it's a measure of improvement, not really of disease activity, which is where you look at other measures like clinical CDIs, SDIs, DAS scores. I know that that Greg has the same electronic health record that I do in my office so that we can actually do those scores and track them over time on our rheumatoid patients. It's nice to see an improvement and a lot of patients when they're really, really sick, they get a 50% improvement with methotrexate. They're happy as a clam, because they're 50% better.

Dr. Eugene Huffstutter:

But they still have active disease that needs to be addressed or five years later, 10 years later they're going to have permanent joint deformities or permanent x-ray changes that are the things that correlate with long term disability. So I actually like to use another measure. I think it's nice for drug studies to show level improvement, so you show the drug actually works. But if you're really taking care of a patient, you want them to have low disease activity and you can define it. Even some physicians actually use patient reported outcomes like a RAPID, and I think that's really a better thing to document that the patient is doing well with their particular illness.

Moderator Dr. Charnot:

And can you describe this RAPID? I'm sorry, we're not familiar with that.

Dr. Eugene Huffstutter:

I'll have to look this one up, because I use these acronyms so frequently, I forget what they stand for. For instance, I mentioned CDI and SDI. So CDI is clinical index of disease activity. Help me out guys.

Dr. Kerrin Burte:

Clinical activity index. CDI.

Dr. Eugene Huffstutter:

And then the SDI.

Dr. Kerrin Burte:

Go ahead.

Dr. Eugene Huffstutter:

The SDI is-

Dr. Kerrin Burte:

I don't know, good question.

Dr. Eugene Huffstutter:

It actually is the same thing as a CDI, but it includes a measure, a more objective measure, like a sed rate or a CRP. And then the DAS score looks at tender and swollen joint counts and has a formula that actually looks at populations and it will give you a score that will represent remission, low disease activity, moderate or high disease activity. So those are all instruments that are used to monitor rheumatoids. The problem that, and these are great tools in looking at clinical trials, but they're not as good at tools in practice because my patients are messy. And what I mean by that is they have more than one problem.

Dr. Eugene Huffstutter:

They have osteoarthritis with their rheumatoid. They have fibromyalgia with their rheumatoid. They have diabetes and diabetic neuropathy. So when they will do a pain score, their pain score may be really high based on their diabetic neuropathy or their fibromyalgia or their osteoarthritis and not related to their rheumatoid arthritis. So that that's where the clinicians, the physician global, is very important. And when you get a score, it almost always needs to be an asterisk. And you look at the other diagnosis that these patients have. And if they're an M0579, they're zero positive rheumatoid. But if they've also got fibromyalgia, M79.7 or osteoarthritis M15.0. So if you're coding those and you see those other codes, recognize that these other measures may not be as valid.

Dr. Kerrin Burte:

This is Dr. Burte again, we use the RAPID3 form. I think Dr. Hofstetter was referring to its patient reported activity scale pain score and overall functional score, which can be affected by comorbidities like osteoarthritis, but also the joint count, I think is very important. How many specific joints still have active synovitis in them? And we try and use that functionally with other disease activity indicators like CRP and ESR, which are thrown off intermittently as well. So it's kind of a melange, it's a mixture. But I think that the swollen joint count is kind of important because of these comorbidities like fibromyalgia and osteoarthritis that throw off the patient reported outcomes.

Moderator Dr. Charnot:

Thank you. So if I could summarize this one, it seems like there's some agreement that some of the metrics used in some publications like the ACR20 and 50 may not be as useful constructs for measuring disease improvements or they are good for measuring improvements, but perhaps not disease activity. And so that's where we need, it sounds like we have a lot of other scales and metrics used for this

purpose. So given that you have these different metrics for disease activity and therefore measuring response, if we could then go back to question number two, using your definitions of improvement in disease activity and response, can we readdress this question regarding the rationale for prescribing TNF inhibitors as first line therapy and perhaps the statement then about one third of patients adequately responding to this class of treatments is inaccurate. And so if you could address that, that would be very helpful.

Dr. Bien-Wilner:

Can I first make a clarification. When we say first line, I think we mean not first line. We mean assuming the patient has failed a traditional first line therapy and is then going to be given a biologic. Is that correct?

Dr. Greg Niemer :

Yeah, that's helpful because when I first read that question, I was like, well, I don't use biologics as first line, if you traditionally think of, okay, first line treatment is methotrexate or DMARD. So yeah, I think the other issue with this question is, just like Gene said, is the use of the word adequately. I mean, if you look at some of the scores that typically are used more as the objective measurement in a rheumatology practice such as a CDI score or possibly a DAS, I mean, you're looking at remission rates with TNF blockers and other biologics too, in the one third range. So you're looking at getting one third of patients in remission and you compare that to DMARD therapy where the goal with DMARD therapy is to keep people functioning, but it was very uncommon that you ever saw a patient in remission from Plaquenil therapy or methotrexate, unless people had really mild disease.

Dr. Greg Niemer :

And those aren't patients that you're looking at using TNF blockers with anyway. So typically we're using TNF blockers or other biologics in people that have moderate to severe disease. In other words, that aren't controlled by traditional DMARD therapy. And so the chances of getting that group into remission are very small. So now we have biologics where the data shows that the remission rate is about a third. Now I would say if I'm looking at adequate response, and that means that patients are improved at least like if you would like to say a moderate disease activity score by a CDI or DAS, then you're looking at 70% of patients that have an adequate response, if that's how you define adequate. So again, everything changed with the biologics. It used to be that our goal with rheumatoid patients as clinicians, as rheumatologists, was to keep people functioning as long as possible.

Dr. Greg Niemer :

But there was a steady decline in these patients and there's high rates, long term, of inflammatory eye disease and lung disease and increased rates of lymphomas and mortality rates that were similar to a lot of malignancies. So that's what we were dealing with prior to treatment. And now we're looking at opportunities to have 30% of those patients in remission without, I mean, it's very uncommon with patients that are treated with biologics, that long term you're going to see increased rates of cardiovascular disease or lymphomas or lung disease or inflammatory eye disease. We've cut those rates significantly with these new treatments. So again, that word adequate, I think is inadequate.

Dr. Bien-Wilner:

This is Dr. Bien-Willner, I want to follow up with this efficacy revision and I have a very specific follow up to that statement or question, follow up to that statement. So I would say, I will ask the panel based on

evidence that you're aware of, or your experience in treating these patients, patients who failed to respond to the first biologic, be it a TNF alpha inhibitor or one of the other biologics, if they switched to a second line biologic, what kind of response do you typically see? Do you expect those patients to respond to another biologic if they fail that first biologic?

Dr. Kerrin Burte:

This is Dr. Bird. I think each time you have a failure of a biologic, the blooms off the rose a little bit, it goes maybe from 70 to 50% for a second biologic. I don't know if the others would agree with me or with that or not. And I'm not sure we know how to decide do we do more TNF inhibitors or other mechanisms of action. Because I've seen conflicting reports whether you should switch mechanisms of action, T-cell blockers, biosix inhibitors, or stick with a second TNF inhibitor. But that the rate of response is not as adequate, but still more than this one third, I think.

Dr. Greg Niemer :

is Dr. Niemer, again, I think that's a difficult. I mean, I certainly have had, and I think actually data also shows if I have someone say for instance on a TNF blocker and they don't respond at all and you switch therapy and you can still capture and achieve a very high rate of response. So again, I think it's very patient dependent and a lot of it has to do with like Dr. Huffstutter said, how long the patient has had rheumatoid. Because the further along the timeline you get with patients having very active disease, then I think you start, you do start seeing a decline in response. And that's why it's imperative to try to get patients on the best treatment for them as soon as possible.

Dr. Greg Niemer :

And that's kind of where the whole treat to target approach came about with treating rheumatoid arthritis. Because a lot of times I think rheumatologists weren't, they weren't on a protocol as far as, okay, let's go three months, three to six months in this medication and let's then assess with some type of objective evidence how the patient's responding and then make a change. Because if you go too long before making that change, then I think your response rate does drop off. I personally, I think if you can make changes more quickly, then your chance of getting a robust response to medication is much greater.

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. I want to clarify something that you may ask in your question and that is you phrased it that you have a patient, you start them on a biologic, let's say a TNF and they don't respond. Then what are the odds of moving on? Well, it's a little more complicated than that in that some patients will be on something and will respond initially, and then they'll lose response. Some patients won't respond at all, they'll just have nothing. And then some people will develop an intolerance to the medication. And so you don't really know if they're TNF driven or that particular way of blocking TNF is the right way to go with those patients. So you may want to cycle them through a different one, because I've had patients that can tolerate one TNF medicine and not another and vice versa. So trying to define that lack of response is not a simple yes or no thing because patients can initially respond.

Dr. Eugene Huffstutter:

But we recognize that these are agents that don't cure the disease. They try to control the disease. So the mechanism for the immune system losing tolerance and being active and destroying joints and affecting the lungs and eyes and the other manifestations of rheumatoid arthritis, that problem with the

immune system is still present. We're just blocking one particular mechanism if we're blocking TNF or if we're blocking IL-6 or there are other ways to deal with this, for instance, blocking T-cells or B-cells. So that I think it's nice to have freedom to look at these individuals and watch and see how they respond so that you can kind of make that determination. Is it an intolerance? Do you think that TNF is still a driving cytokine with them, so you want to try another one that may be better tolerated or not have that particular side effect?

Moderator Dr. Charnot:

Thank you. That's very helpful clarification, because it sounds like we're looking at two different issues here with the TNF inhibitors. I'm sorry, this is Dr. Charnot-Katsikas, in that one case it's a matter of response, but also there's this issue of intolerance and perhaps some of the other TNF inhibitors will have a better tolerance profile. And if that's a correct statement, please do confirm that. And also, if I may follow that up with, to date, is there any indication or any way to tell which patients will have an intolerance or are there any markers that help you make those decisions?

Dr. Eugene Huffstutter:

This is Dr. Hofstetter. Not for intolerance. And again, it's an individual thing. For instance, you can have a randomized trial and you don't really see any difference in tolerance with their individual variations that we don't quite understand in individual patients where they will handle one medicine and not another and vice versa. So I think that's why we still call it practicing medicine because it is kind of learning our individual patients, what it's like to walk in their shoes and what their particular aspirations are and what risks they're willing to take to go in remission.

Dr. Bien-Wilner:

Can I ask a follow up? This is Dr. Bien-Willner. So obviously we're considering, this is MolDX and we're talking about policies for laboratory tests, particularly molecular laboratory tests. So if you should have a laboratory test that could identify a patient that would not respond to one of the very many biologic agents, so first, would you use that test if it was only for one of the many biologic agents? Or under which considerations would you use it? And two, if you chose not to use such a test, to advise on not using one of the many specific biologic agents, what would be the, based on evidence or your experience, what would be the potential harm to those individuals who do not get that test rendered?

Dr. Greg Niemer :

So, this is Dr. Niemer. I think if you're to look at are these, I think, the first thing is, would a test be helpful? And if you're able to say, okay, this would be a patient that may respond better to a TNF blocker, this may be a patient that would not respond well to a TNF blocker. I think that that would be very helpful. And because, like I said, we're almost on a clock when we're treating these patients. Since data shows the patients that are well controlled from the initiation of their symptoms to about six months out from there, those patients do much better, long term, and you have a greater chance of getting them in a remission.

Dr. Greg Niemer :

If you're able to pinpoint, if you're able to at least take out one of the biologic classes from the get go, then that could save you a lot of time and it could greatly benefit the patient long term. As far as a negative for not, I guess another way of saying it is, if you don't have this class of testing, then you could

prolong the time period where you have a patient under control and you have some form of control by six to 12 months. In a life cycle of a rheumatoid patient, that can be pretty significant.

Dr. Kerrin Burte:

This is Dr. Bird. I agree, yeah, just that it would be nice to cut down the amount of time that I spend telling patients that we're doing this by trial and error, going from TNF to T-cell blocker to IL-6 blocker. And if we could go straight to one, assuming the test was very pretty high, positive, predictive value and not super expensive, of course, that would be great.

Dr. Bien-Wilner:

This is Dr. Wilner again, I just want to add one, just to clarify one part of that question for that last response. So I just heard that, yes, if you had a test that could select with a good positive, predictive value, which agent the patient may respond to, that that would be of value. But I want to clarify, what if the test only identified one of the many classes and only informed you on that one class? Would you still consider that to be a useful test?

Dr. Eugene Huffstutter:

So, this is Dr. Huffstutter. I agree with my two colleagues. I think it would be useful. We as rheumatologists always want more data. I mean, it's like the pathologist who does an autopsy and demands more tissue. We can never get enough of knowledge about that particular patient and their immune system. So for instance, if I had to pick one, an agent that, or a test that would say this particular class of drugs will not work or is unlikely to work in a rheumatoid patients, I would pick the TNFs because there are five agents there. And I've got particular payers that demand failing two of those agents before I can use something else. And they may require a minimum of three month trial and sometimes a six month trial before I'm able to move on to a different agent.

Dr. Eugene Huffstutter:

So in a particular patient, they may go a year on a drug that it would be predicted to not help them while their immune system is still active, while they're having continued joint pain, joint destruction, et cetera. So if I could do a blood test to say, this is, and again, if the test is accurate so that you could depend on those results and say, you really would not benefit or this patient would be unlikely to benefit from this class, especially it were the TNF since there are five agents there, I think that would be valuable.

Dr. Greg Niemer :

Yeah, this is Dr. Niemer. I would agree with that.

Dr. Kerrin Burte:

This is Dr. Burte. I agree also.

Moderator Dr. Charnot:

And to clarify, this is Dr. Charnot-Katsikas, in terms of differentiating, as opposed to providing a class level probability of response in terms of differentiating within that class some of the various agents, is that something that you see as valuable? Or would a class level information suffice at this point?

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. I mean, it would be great if you could say, well, this TNF, because it has the FC portion of antibodies is not going to work, but this one that doesn't have this particular molecular structure could work. The more precision we can get, the more exact we can predict how a patient would do, the better. But if you can say, look, it doesn't look like TNF is a major cytokine for this individual, you're better off moving on to different classes, that also would be helpful. I think the mantra here is the best, most precise information we can have to individualize that patient's care. We want.

PART 2 OF 4 ENDS [00:46:04]

Dr. Bien -Wilner:

If I could just another high-level summary questions, Dr. Bien-Wilner, again. So earlier you guys all agreed that the primary method you all use in determining the appropriate biologic is based on specific information from that patient, whether they would be compliant with a dosage or the method of delivery of the drug or other comorbidities and side effect profiles of the drugs. I guess what I would like, what I want to ask you all is what is the relative value between the individual considerations that you mentioned earlier? And I believe are your primary decision making processes. And this last question, which is if you had information for only one drug, and let's say that information was that a patient wouldn't respond to a TNF alpha, what is the relative value of those two sort of competing thoughts and how often would information realistically from such a test, not only just then give you information, because obviously we don't pay for, for tests that just give you information. We pay for tests that have clinical utility.

Dr. Bien-Wilner:

By that specifically, meaning that the results of the test would actually change your management of the patient. So with that in mind, again, that we're looking for things that have utility, how often would it, what's the relative importance of such a test in the global overall perspective in selecting a biologic therapy?

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. I think it would be very valuable because that would, as I said, I've got, Medicare is not one of these, but I've got payers that demand two TNF failures. So if I could say on the front end, look, the drugs that are your preferred drugs are predicted not to help these people, I could at least go on to look at. And sometimes it is nuances that, that you mentioned before, but look at the other agents that are available to me outside the TNF class and say, okay, of these drugs, what would best fit what I think this patient needs to control their rheumatoid arthritis. Therefore, you can save a lot of visits. You can say these drugs are incredibly expensive, so you could potentially save one year's worth of TNF drug from a patient, and also probably improve their outcomes because you are more likely to get them on a therapy that would work and control their disease better.

Dr. Eugene Huffstutter:

From a practical standpoint, or from a monetary standpoint, it could be very valuable and that's not accounting for the just personal aspects of the patient missing work and loss. I know there are, there are methods to calculate all of that, but I think just from a monetary standpoint of paying the pharmacy bill, the cheapest drug is always the best, most effective drug. The one that's going to work in the patient

and the sooner you can get to that and cut to the chase and find the drug that's going to work for a patient, the better it is for everybody payers included.

Dr. Bien-Wilner:

Can I Follow up, this is Dr Ben Wilner again. So obviously we write policy for Medicare and not for private payers. Does the focus only on Medicare patients, again, discussing the relative value of how you determine what the appropriate biologic is, does your answer change when you only have with Medicare beneficiaries, where there may not be an unnecessary requirement for picking one biologic over another, because we're basing the determination on some sort of evidentiary process?

Dr. Eugene Huffstutter:

No. This Dr. Huffstutter again. It's more important to have it for you because you don't demand that I try anything first. You don't have a formula that says you must first fail these. It's more important for your patients because I can be a better physician to your patients because I can use my judgment to take care of them the best way I know possible.

Dr. Greg Niemer :

Yeah, and I would say we, and you were talking about how do you stratify these things? We talked to about certain situations where maybe you wouldn't use one class of biologic versus another. I would say that if I saw a hundred rheumatoid patients and we're putting them on biologics, then maybe 10 of them or less that I would say, okay, I shouldn't use this medication because of this preexisting condition or this certain situation. The vast majority of our patients are patients that we could look at and say, okay, well we could start them on three or four of the different classes of biologics. At that point, a lot of times your decision making is, I don't want to say it's throwing noodles against the wall because it's not that random, but it's not like you're going on in a lot of other objective evidence to say that this class of biologic is significantly better than another. Having this is an added part of your arsenal to be in that decision making would be very helpful.

Moderator Dr. Charnot:

I have a follow up to that. This is our Dr.Katsikas so you know we hear what you're saying, that having some additional information from some kind of a test that might provide some problem information about predicting response to these biologics might be useful, but in terms of test characteristics required for your confidence in such a test to do so, we haven't quite addressed that and so the question really that I have is about use of a test that may predict a response or lack of response to biologics and a high, positive, predictive value. What are we looking at in terms of defining response in that case? Right. We talked about ACR 2050 and how those may not be sufficient definitions of response. What would you like to see to give you confidence in a test that would be able to do something like this?

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. A test that would confidently rule out one of the classes of biologics from working. What would we want to see in that test besides excellent sensitivity and specificity sorts of things? Is that what you're asking?

Moderator Dr. Charnot:

The question is, you mentioned, you'd like to see a high, positive, predictive value for such a test, but, but what would be the comparator used there or the definition used? So would it be an ACR value or would it be some other markers of disease, remission or response? You mentioned there are so many that can be used. So how would we basically determine if the test is really good? What would we use to determine response?

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. That's a great question. I think you can actually do it analogous to you're looking at a drug trial. Again, the ACR 2050s and 70s were developed to show drugs work. What you're trying to do is show a test works, and you can use that same analogy. I mean, ideally I would like for you to give me a blood test to say, okay, if you use this drug, you're going to get this patient remission, or you're going to get this patient in the low disease activity. We are not there yet to my understanding. Nobody is able to tell us which drug to use, but they are testing and I'm going to depend on you to think about that. But if you could do a test to say, look I know that the ACR guidelines say the first biologic should be a TNF and that's probably because the first one came out and last century, 1998, so that we're very familiar with safety and efficacy because they've been around so long.

Dr. Eugene Huffstutter:

But if you could say, look, when you looked at this class of, or these group of rheumatoids and we did this test and in the test that it predicted they wouldn't respond. They really got a low response for an ACR 20, 50, or 70. That is useful information. I'm sorry if I gave you the feeling that ACR 2050 or 70 is not valuable. It's extremely valuable. It shows us an amount of improvement, but it's not a be all and end all to following patients. We want our patients to improve. Absolutely. But we also want that improvement to get to a level so that they have low or minimal disease activity.

Dr. Eugene Huffstutter:

So, and some patients an ACR 50 is quite adequate because they already started out with disease activity that wasn't really high, but in someone who's got 30 swollen and tender joints, you've really got to treat those patients aggressively to get their disease in remission. So in response to your question, I think you can look at a test to show, Hey, it predicts that the ACR 20, 50s and 70s are not really good with that. Maybe other agents do and in fact, what I think would be even better is on the patients that had this test and it showed that a TNF may not work. If they had data to show that other mechanisms did, then, like I said, we've saved the system a lot of money.

Dr. Burte:

Dr. Burte. -which measure I would leave that to the academics. Which measures the best to, which clinical measures the best to develop the test. That would be the most helpful. I don't know the exact answer. 28 rapid. I think it's an academic, a question for academics.

Dr. Greg Niemer :

I'd like to revisit-

Moderator Dr. Charnot:

Would ACR, oh, I'm sorry. Just one quick follow up to this one. Would ACR suffice, I guess, is really the question or would it be ACR plus some additional disease activity metrics so that you'd like to see albeit there could be a variety of those.

Dr. Greg Niemer :

So let me make sure that I understand this. So you're saying, okay, you have a, say for instance, you have a predictive test and you find that predictive test correlates so that if the test shows that the patient would not be a good responder to a certain class and you follow those patients for a year and you find that its predictive value is great and showing that those patients don't respond, that's what you're talking about, just, okay. What is your test going to be that you would check? Is that right?

Moderator Dr. Charnot:

Right. So are you using, are you using a response measure that's basically the ACR 20 or 50, or do you need, is that sufficient as a response measure or, is it not? Do you need that, albeit it has its own value, plus some other measure of disease activity or response to a properly assess a test?

Dr. Greg Niemer :

Yeah. I think a lot of the studies, again, Dr. Niemer, I think a lot of the studies are being done now, more emphasis is being put on test such as a CDI or a DAS in assessing disease activity. Those are also easier to do. All you need is some, is as a test has been validated as far as something predicting disease activity and whichever one is well validated and is easy to measure. I think that's what you go with.

Moderator Dr. Charnot:

Thank you. I'm sorry. I think, I think Dr. Wilner had a question as well.

Dr. Bien-Wilner:

I just had a clarifying question. Earlier we discussed using the more broad efficacy measures that patients who fail a biologic and are placed on a second biologic have a depreciating return. I think numbers like 50% and then 30% on successive biologics were discussed. I just wanted to clarify, is there any difference to that moving within versus between different classes of biologics that you're aware of?

Dr. Kerrin Burte:

This is Dr. Burte. By tradition or because we had nothing better, we would sometimes switch between mechanism of action, hoping that if someone wasn't responsive to a TNF blocker, they'd respond to an IL6 inhibitor or to a T-cell activation inhibitor or BCL inhibitor. I'm not as confident in that as I've recently seen that maybe I've seen journal articles that do not support that. Sometimes you're just as helpful if you switch between the second and third TNM inhibitor, instead of switching between mechanistic classes. I wonder what the others, if they agree with that?

Dr. Greg Niemer :

This is Dr. Niemer. I think a lot of times when biologics come out on the market, the first study is looking at that biologic versus methotrexate and that's kind of the underhanded pitch. That's the slow pitch that oftentimes the biologics will do much better. Now, the second, the next phase will come out, usually are, or over with okay, patients that have failed a biologic already. It's a good question, and I'm not sure if it's significant, as far as the differences that you can see as far as staying within the same class versus going without going outside of the class. I think a lot of TNF blockers show that patients that have say, for instance, you know, failed one TNF blocker, that they have a relatively good response rate with their product. You can say the same thing with another mechanism of action and patients that have failed

TNF blockers. I'm not sure if there's necessarily a significant difference in response rates and going outside of the class versus staying within the class.

Dr. Eugene Huffstutter:

Dr. Huffstutter. I think that there're studies to kind of show both ways. I think getting back to your original question, like I said, like you were asking is if you really had an agent that would predict a non-response, then you would want to stay away from that class and do something else. I think it depends on what the data shows. If the data is pretty good for instance with TNFs and all the TNFs, you would probably stay away from that class or at least your first agents would be choosing a different mechanism of action. I think that could, as I said, save the patient's time and money and the system time and money.

Dr. Greg Niemer :

Yeah. This is Dr. Niemer again. I think that's true because if you look like I was talking about, if you, off a TNF blocker does a study saying that, okay, patient has to fail one TNF block and this new TNF blocker showed an ACR 50, and that looks, I mean, that's a good score, but that still means 50% of the patients didn't have, didn't meet that criteria. So you've got a lot of potential to capture patients in a different way. That's why something like a test that could help narrow your decision making a little bit could be helpful.

Dr. Bien-Wilner:

Add one last sort of thought or question on this matter. Obviously one concern we would have is if you would have information that the patient would not respond to a specific class, what is the likelihood that it would respond to a different class when all the information you have is that it won't respond to a specific class? I think one concern was just raised, which is if the data don't suggest that you do better switching between classes than within classes, that sort of suggests that the number of patients that respond by switching classes because they don't respond to a class because of a biologic signal to an entire class may be not significant. Any thoughts or question or response to that?

Dr. Greg Niemer :

Yeah, I would say, and this is Dr. Niemer, that again, if you're, if the data that you are, that you are collecting and the response rates, if we had a chance of having response rate 90% on a drug, then I could see where that argument would make sense. But since we're talking about response rates, especially if we're looking at the studies of ACR 2015 and 70, if you take that into consideration, the number of patients that don't respond to treatment, that's where you get this high variability of patients that respond to one class than another. You can't really, you can't adjudicate that from the way that the studies are set up and the response rates that we receive. I could say of my patients that I follow at the end of the day, gosh, you know, much greater.

Dr. Greg Niemer :

I don't have an exact percentage, but it'd be higher than 70% of patients will have a significant response to something. It's very uncommon for us to see a patient or they don't respond to anything because we at all these different options available to us. Thankfully, most of our patients have some type of response if you're carrying out your argument saying, okay, well, the patients aren't going to do that much better on a different class of drug. That would mean that we would have a large percentage of our

patients that don't respond to anything. And that's not true. Most of our patients respond. It just takes us a while sometimes to get there. And again, that's what we're trying to narrow down.

Dr. Bien-Wilner:

Thank you. I think that's great feedback. I would ask if you have any other than personal experience, if you know of any evidence to that effect, I think that would be very helpful to us as well.

Moderator Dr. Charnot:

Great. Thank you all. So, moving on. Some of our, we're kind of bouncing around a little bit, but this has been a very, very fruitful discussion. And so we've addressed some of the questions down the sequence here. And so in terms of biomarkers and evidence around bio markers, and that's sort of what we've been addressing all of this time. Are you aware of any evidence for biomarkers for this purpose to help guide targeted therapy selection?

Dr. Greg Niemer :

Well, I guess I'll start on this one. I'm aware of early evidence. And honestly, this is an area where I haven't had a lot of personal experience because the testing at this point, unfortunately, is not covered well by insurance. I know that some of the studies have not been extremely large, but certainly I know at this point, there are some studies that have, have been published that are showing a correlation between the results, say for instance, a test that checks to see if a patient would respond well to a TNF blocker, and whether those patients do well clinically going on TNF blockers. So yes, we early at-

Dr. Kerrin Burte:

This is Dr. Burte, provide some detail.

Moderator Dr. Charnot:

Go ahead.

Dr. Kerrin Burte:

In preparation for this, I saw one article where they were checking kind of protein levels, trying to predict with protein levels and genetic markers who might respond to a biologic. It wasn't a simple answer. It was a grouping of a number of genetic markers and protein markers that might predict. It wasn't a very simple answer. But I haven't seen anything that's like a simple one or two biomarkers that might be predictive of response to a biologic.

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. I'm aware of a blood test that does predict whether someone will, and I guess this is the double negative, so it will predict non-response to TNFs. And I think to answer that you have to really look at their data and see what happened to the patients. For instance, did they have patients who got this test who were put on TNFs? What's their likelihood for getting a response, however, it's measured.

Dr. Eugene Huffstutter:

And I think all of these can be useful measurements? Or if they skipped the TNFs and went to another mechanism, how did they respond? And you could kind look at their response compared to a group of patients that were just methotrexate non-responder. I know you're looking at different studies, but if you look at the TNFs, I know that they said there's a third that get an adequate response. Well, that's the delta between the placebo, which is methotrexate in most cases and your biologics, and we usually look at 60, 40, 20, and usually the placebo is 30, 20 10. So there's a 30% difference or delta between the placebo arm and the active competitor arm, which in most cases is statistically significant. So I think it just depends on what the data shows and I must confess to you, I'm not familiar with their, this predictive data.

Dr. Eugene Huffstutter:

I am familiar with the concept and the concept is wonderful and fabulous, but, and I know I'm filled with cliches, but my next cliche is the devils in the details. So what do the details show? How predictive is this test for non-response to TNF? Do they have patients that were given the blood test, started on a TNF, and then what is their response compared to put on other agent? I think that it would be nice to have a test that works. I just don't know. I'm not familiar enough to say that there's one out there right now.

Moderator Dr. Charnot:

Right. Thank you. So it sounds like there are a few studies and regarding some biomarker testing, but these are small studies and really, it's hard to nail that there is a significant level of robust evidence regarding such biomarker testing for predicting-

PART 3 OF 4 ENDS [01:09:04]

Moderator Dr. Charnot:

Regarding such biomarker testing for predicting targeted therapy selection. Would that be an accurate statement?

Dr. Greg Niemer :

This is Dr. Niemer. Yeah. I think that the early studies certainly look promising, and so you always want to follow-up with larger studies. And I think that's what's happening now, is that studies are enrolling with larger populations to try to verify, and I guess confirm the early studies. And if that's the case, if those studies show and confirm the earlier studies, then I think you've got your answer, and that certainly being able to use a marker like this to target your treatment. I mean, they're similar to being able to focus someone who's [inaudible 01:09:47] positive and treating their cancer. That's something that would significantly improve that patient's outcome and get you to the right place more quickly.

Dr. Greg Niemer :

So yeah, if there's confirmed evidence showing that there's positive predictive value of predicted outcomes, then yeah. I think that's when you've got your answer, something that's clinically relevant would help in decision making not just giving more information.

Moderator Dr. Charnot:

Thank you. And regarding some of these new tests, technologies, biomarkers, as far as you're aware, does the literature support their use in only limited situations or populations with rheumatoid arthritis?

Do you see ... Where do you see their greatest utility? Is there a subpopulation or a specific clinical situation that's more focused within this disease state?

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. I think it would be for that next step. I mean, most rheumatologists who are going to use a traditional DMARD first, and if they're not doing well, that's kind of the next step where you would want to look at that. You want to look at patients that still have active disease despite traditional DMARDs or triple therapy. And I must confess that I'm not as well versed on this aspect of the literature as I should be. Maybe there is data out there that supports it. I just, we didn't have a live ACR meeting this year. I must confess, I'm not sure I feel as comfortable about saying I'm current with the literature or not. I know you sent a fairly extensive bibliography of things to review that frankly overwhelmed me.

Dr. Eugene Huffstutter:

So that being said, I think that... and I know you depend on us for answers here. And I think that if we could look at peer review journals and you could see that there's enough data there to show that this is a good test that predicts non-response. And it also shows that in this subset of patients that may not respond to a TNF, we can offer them other therapies. Because if the same subset of patients don't respond to IL-6 or blocking TNFs or whatnot, then I think the previous questioner is spot on, in that it doesn't serve any value. But if we can show that in patients that these drugs or this test predicts non-response, and we are able to use other our modalities and these patients go into remission, I think that's, it's a valuable tool and it can save us some time.

Moderator Dr. Charnot:

Right. Thank you.

Dr. Eugene Huffstutter:

Yeah. There's one other question that you had sent. This is Dr. Huffstutter again. I thought it was really interesting talking about literature and blood tests versus synovial tests. I know that there is some literature, mostly from Britain. And I think that that shows that the Brits really do have a stiff upper lip because they did synovial biopsies in fingers of patients with rheumatoid arthritis, and really had some nice predictive value about how they were able to do that. I'll frankly will tell you in my practice, I will never be able to convince any of my rheumatoids to get a synovial biopsy of their fingers. And so therefore the test will not have any utility in my office.

Dr. Kerrin Burte:

Yeah. This is Dr. Burte. I agree if you could test the drug versus the bug, almost like a culture and sensitivity use the synovia against the different biologics. That would be the most direct summary way to predict response. But I agree with Dr. Huffstutter, I don't think I would get many to agree to that procedure.

Dr. Greg Niemer :

Yeah. That data's been out. I know University of Michigan released some data on synovial biopsies gosh, like 10 years ago. And it's not being done because it's just not clinically feasible. To get our patients to do that it would be extremely difficult. And so if you had a blood option that even if it wasn't quite as good as doing a synovial biopsy, then you're good. The blood option at least is going to be able to be used clinically.

Moderator Dr. Charnot:

Thank you. It sounds like there's definite consensus there fact that we'd have a direct measure of disease activity perhaps, but that's just not something that we're willing to do in the United States, at least not at this point. So thank you all for that. If I could ask a follow-up question related to, if we go back, to sort of the biomarker approach and we talked about how perhaps a good population would be certainly after you've used your DMARD therapy. And then if a patient is not doing well on those to then, as you're considering alternate therapies that maybe a biomarker test would be useful in that scenario. I guess my question about that is, would that be the branch point at which you would consider use of such a test, assuming such a test is proven to be clinically valid and useful, or would it be once you've attempted the first TNS or biologic? And so if you could just elaborate maybe a little bit more on that, that would be helpful.

Dr. Greg Niemer :

Yeah, I think, and this is Dr. Niemer. I don't think the literature at this point really gives you the answer as far as, and from my understand the study so far, nothing has been designed to show when you use this test specifically. I think that you could certainly argue that if a perfect scenario, when you're looking at putting someone on a biologic treatment, if you're able to narrow your options essentially by 50%, almost 50% is the number of TNF markers that are on the market. That would be a reasonable place to use it. Now you will probably have physicians that would prefer to start with one by biologic or one TNF block say, "Hey, I'm going to start with TNF blocker", but then if the patient doesn't respond in three months, then you do the test.

Dr. Greg Niemer :

I think you could argue both ways. And to me, the purest way or place for it to be used is with when you're making that first decision of which biologic to use. The thing is if one of these markers comes on the market, a lot of patients that have rheumatoid arthritis obviously have already been on several biologics. So they're going to be used in that realm as well. So, I don't think you could say, well, this test can only or should only be used in this scenario, because if you're looking at a rheumatoid patient, who's... you're deciding what to do with their first biologic. I think that's a reasonable place to use it. This marker comes on the market and they've already been on a couple of different biologics, and you're trying to decide which one you use next. You could use it there too. So again, I'm not sure if I'm ready, and I don't think that the data would really dictate where you would kind of pigeonhole this type of markers' use.

Dr. Eugene Huffstutter:

This Dr. Huffstutter. I also have some concerns because we're dealing with patients, we're dealing with biologic systems, and if you start them on a medicine, does that alter what you're measuring? So, I mean, is the best time to actually do this when they're first diagnosed with rheumatoid arthritis, does methotrexate alter the results of the test or does leflunomide or one of the other DMARD, does starting a biologic alter the test? I think it just depends on what the data shows. If they can show that it's in patients who are newly diagnosed with rheumatoid, that you get your best predictive results, then maybe that's when it needs to be done. I like to maybe put it later on because as was pointed out by one of the other directors, you want the test to be practical.

Dr. Eugene Huffstutter:

You want it to be useful. You want it to change what you're doing. You don't want it to be an intellectual exercise. So since we're all going to try disease modifying agents first, then I don't think it needs to be done before any treatment is done. Although, it depends on what the data shows with the predictability of the test. I think a more logical time would be down at a branch point when you're trying to decide where do I go from here? And what would indicate the most likelihood of using this test to guide my therapy? So I had mentioned before methotrexate or other DMARD failures is where I would ideally like to use it, but just because someone has been started on a biologic because of insurance reasons or whatnot, if the test shows that it's still valid to use, then it would be nice to have.

Dr. Eugene Huffstutter:

Because they may have a mandate to try second TNF. But if you can do the test to say, look, they're not responding to this first one. And the data shows that they're probably not respond to second one, you save three to six months of therapy, pain with the patient disease progression, et cetera., and can move on to hopefully find some, a more effective therapy.

Moderator Dr. Charnot:

Thank you. That's very helpful. And it sort of provides us with your clinical thinking as you might approach something like this, should it be available and should be evidence support its use. And that's exactly what we're looking for. So we have basically about 15 minutes left allotted for this discussion. I guess, before we continue, are there specific things you'd like to address that we haven't already discussed related to this topic? So I want to open it up to the three of you, perhaps there's a question that we should have asked or something that we should have considered so far. I'd like to hear your thoughts at this point.

Dr. Eugene Huffstutter:

This Dr. Huffstutter, I'll start out with this. And I'll reiterate the comment that I made earlier. I really believe that rheumatoid arthritis is a different disease in different people and the comorbidities are very important considerations. I think when you're analyzing the data of the tests, and I'm sure that there'll be people who are developing tests that will present their data, but I would ask them who they define as rheumatoid arthritis patients. Do they mandate that they're seropositive, that is rheumatoid factor positive or CCP positive or whether their ANA is positive or do they include what a lot of clinicians do, any inflammatory arthritis you'll...? And the codes can help you with this. If they allow code for M0579, then that's seropositive rheumatoid arthritis. If it's something like M0609, then it's seronegative rheumatoid arthritis.

Dr. Eugene Huffstutter:

And so is the data supportive in these different subsets of rheumatoids. And so I know the question was brought up, where would you position this? Well, their seropositivity may be important in differentiating the response. So you may want to look at that carefully and ask those kind of questions is what types of rheumatoids were they looking at? What were their age group, what are the comorbid conditions that assisted in these patients? Because maybe having diabetes affects the blood test in some way. Because as I pointed out, our patients that we see in practice are messy. They have multiple comorbid conditions and I can't refuse treatment, say come back when you only have one thing wrong with you, because I have to address the entire patient and coordinate my care with their other physicians and coordinate that with their other disease processes.

Moderator Dr. Charnot:

Thank you. That's a great point. I'm sorry, was that Dr. Hofstadter?

Dr. Eugene Huffstutter:

Yes. Ma'am.

Moderator Dr. Charnot:

Yes, yes. Thank you, we definitely appreciate that comment. And it certainly provides an additional point of critical evaluation for these types of tests as they start to come down the pike. Anything else we should have, or should ask or should address before we wrap up?

Dr. Kerrin Burte:

This is Dr. Burte. I'm just curious, maybe others know, where is this test? What is it measuring or intersecting? Is it a genetic test or a biomarker or?

Moderator Dr. Charnot:

Yeah. Thank you. So we're not really addressing one specific test. The point here is to sort of address the literature around the evidence for use of a type of biomarker test that might help predict a choice of therapy or response to therapy for these patients. So, we're not really looking at one specific test and we could... Some of the literature that's available does consider testing in this regards that is a combination of biomarkers, like routine laboratory tests of inflammation. Let's say with some genetic markers and maybe some patient specific factors, to demographic types of factors, things like that and putting it all together. But we're not really, the point of today was to address how such a test would be useful to you, if at all.

Moderator Dr. Charnot:

But just again, looking at the literature, we do have some of these sort of combinatorial tests that are, have been published to date. So the point being that they are including patient demographics and patients' labs of inflammation in addition, or on top of some of these genetic markers, and to what degree does the combination provide the added value over some of these things as you already use them in your clinical practice? So that is certainly a question as well.

Dr. Greg Niemer:

I would hope that's a differentiation. Yeah. I would just hope the differentiation is sharp. I'm sure such a test will be expensive. And we all dream for tests like that, so that it can differentiate a responder from a non-responder, but I would just hope that it's a clear cut thing. There are other combination markers that are available, a summary of 10, 11 different biomarkers, IL-6 too. It can be measured in the blood that at a certain number level, it suggests these people are still active and more likely to have erosive damaging disease that had never found to be terribly helpful above and beyond the other clinical measures that we have. Hopefully it would be that it would be decisive. That would be my wish.

Dr. Eugene Huffstutter:

This is Dr. Huffstutter. Thank you for the clarification for this, because again, I felt really inadequate discussing some of the literature that talks about the derivation of some of these markers. This is a tough nut to crack. Let me tell you, because as was previously mentioned, we have some tests that are

combination of different biomarkers. And two of the biomarkers that they actually measure are TNF and IL-6, and these absolute blood levels are not predictive of whether they'll respond to a TNF agent or an IL-6 drug. So what drives these immune systems is incredibly complicated. I'm really looking forward to someone smarter than I am figuring out how the immune system works to predict a response to a particular drug.

Moderator Dr. Charnot:

That's actually a very poignant point that you just made. And I'd like to, to ask a clarifying question or even as a follow-up, if you have evidence literature to support that where these you have these combinatorial tests as you just mentioned with TNS blockers, or IL-6 that are measuring these biomarkers, but somehow those are not predictive of response to some of these biologic therapies. I think that would be something useful for us as well in our consideration. So if that's something that you can provide to us, we'd be certainly appreciate it.

Dr. Eugene Huffstutter:

Yeah. This is Dr. Huffstutter. The name of the test that, comes by different name, is the multimodal, the commercial name for it is a Vectra DA, and it takes 18 different products. And I've talked to the company and it's a very valid measure of how active their disease is. And they've gotten some new data to show that with, if you can include some data about the patients and in terms of smoking history or whatnot, they can give you an absolute predictor for cardiovascular risk and disease. But in terms of predicting a response to particular therapy, they'll tell you that it has not been shown to adequately reflect that. And I think it goes to, and I mentioned this earlier, what happens in the synovin with the joint lining can be very different than what happens in the peripheral blood.

Dr. Eugene Huffstutter:

And so that's where I think would be really interesting to see what they're measuring and how good their correlation with the different markers that they're measuring, how good that is in predicting or predicting a non-response or a response. I think the proof is going to be in the pudding. And I'm really looking forward to becoming more familiar with this literature.

Moderator Dr. Charnot:

Thank you for providing that information. That's certainly helpful to us. Yeah. So we certainly agree and we have a lot of information. I think this discussion has been incredibly fruitful and I just want to thank our subject matter experts and panelists for your preparation and discussion response to these questions. I think we've certainly learned a significant amount from your thought process and how you practice. We will certainly follow up by email with you. And with that, I want to just provide one last moment to ask either our panelists or any of our medical directors for any final comments or follow up questions or we wrap up this session. Hearing none, I want to thank you all for your participating in this CAC. We certainly appreciate your time and input. And with that, we will adjourn the predictive testing to guide targeted therapy selection in rheumatoid arthritis. Thank you all and have a great rest of your day.

PART 4 OF 4 ENDS [01:29:33]