

[Deepa]: Hello everyone and welcome to RareShare/Rare Genomics Institute second session of our podcast series, Ask the Expert. This podcast will focus on advances in Antisynthetase Syndrome from a clinical and research perspective.

My name is Deepa Kushwaha, and I am the Program Manager for Rare Genomics Institute, hosting today, will be Dr. Jimmy Lin, RGI's president. Dr. Lin, can you tell the listeners about RareShare/Rare Genomics Institute?

[Jimmy]: Happy to Deepa, the Rare Genomics Institute is a non-profit that was established four years ago to be able to help rare disease patients access top researchers and actually also find funding and connect to potential researcher help find for a cure. RareShare joined us last year, the RGI and RareShare is a platform, an online community where rare disease patients can talk to each other and we actually bring more experts to be able to add to that conversation so we're excited to work together as Rare Genomics and RareShare to hopefully provide some early answers and not all of them but to the millions and millions of people in the US and in the world affected by rare disease.

So this is the second one of our disease specific podcast that we're doing but also just want to let the listeners know we also have another set of podcast that we're in the middle of preparing that's general to all rare diseases such as 'Overcoming Financial Barriers' or 'How to Navigate the Medical System' So those podcasts are in preparation and stay tuned. They'll be coming.

One last thing before we start there's a quick disclaimer. We're going to be talking a lot about really new information and research level information and this is just for educational purposes. Definitely, this does not replace talking to your doctor. So before you act on anything, make sure you talk to your doctor. And ultimately, we also have provided a mechanism to ask questions so thanks for everybody from around the globe who ask questions and we'll try to get to as many as we can and the ones that we don't, we'll be able to hopefully find a way to provide answers afterwards and we'll be able to provide the link and responses on the RGI website as well as within the RareShare Antisynthetase Syndrome community forum

Alright, so without further ado, Deepa will introduce our experts.

[Deepa]: Thanks Dr. Lin, as mentioned today's segment will focus on helping patients living with Antisynthetase Syndrome, from a clinical and research perspective. We have a leading expert in the field, Dr. Fredrick Miller, joining us this afternoon. Dr. Miller is Chief of the Environmental Autoimmunity Group in the National Institute of Environmental Health Sciences at the NIH, Bethesda, Maryland USA.

He obtained his M.D. and Ph.D. from Case Western Reserve University and he went on to do medical residencies at Emory and Stanford and then he received training in rheumatology and immunology at the NIH. Dr. Miller oversees investigators in his group as well as others in national and international consortia that conduct a wide range of basic as well as clinical research on adult and juvenile autoimmune disorders. His work in the autoimmune disorders spans across three decades and has been

greatly involved in all the aspects including environmental risk factors, epidemiology, genetics, pathogenesis, evaluation and treatment of all the systemic autoimmune disorders.

Currently, he is leading a clinical trial at NIEHS to identify environmental risk factors leading to Anti-synthetase Syndrome.

Our next Panelist is another pioneer in the field of AS Syndrome; Dr. Lisa Christopher-Stine
Dr. Christopher-Stine is Director of the Johns Hopkins Myositis Center. She's also an Associate Professor of Medicine and Neurology. She is a rheumatologist and serves as an advisor to medical students in the Johns Hopkins School of Medicine College Advisory Program and she is also a board member of the Johns Hopkins IRB.

Dr. Christopher-Stine received her MD at Hahnemann University School of Medicine and she attained her Masters of Public Health from the Johns Hopkins Bloomberg School of Public Health.

Currently, her focus is on clinical research pertaining to inflammatory myopathies which is dealing with 1500 patients at John Hopkins Myositis center where she specifically characterizes unique phenotypes, novel therapeutic approaches and novel disease subsets. She is also undertaking an international effort to determine the most appropriate patient-driven outcome measures in inflammatory myopathies. Dr. Christopher-Stine and her colleagues have also discovered a novel autoimmune myopathy which is closely linked to statins and she is also studying their toxicity targeting indirectly or directly to autoimmune muscle injury and recently she's also started discovering the burden of calcinosis in adult dermatomyositis.

[Jimmy]: Well thank you. Thank you Dr. Christopher-Stine, Dr. Miller for joining us and we're really excited. Today we'll talk about all the different aspects of Antisynthetase syndrome. Thinking about causes, etiologies, symptoms, diagnosis driven and we're excited to start that conversation. So the fact that ground work is, what is Antisynthetase Syndrome, what are the kinds of this disease out there, what are some of the risk factors, can you help us there?

[Dr. Christopher-Stine]: Sure, I'll start with that. So the Antisynthetase Syndrome is a very long name of course. So it's called a syndrome because it's generally groups a bunch of clinical features together. So, when you ask how many different kinds of Antisynthetase patients or different kinds of syndromes, we can answer it a few ways, I think the first way I would answer that is that you could look at the antibodies or the immune system proteins that are targeted in this syndrome and you may have heard of anti-Jo-1 for example. We'll probably speak about the others as part of our discussion later in this podcast.

In general, the syndrome itself can be comprised of many things which can include interstitial lung disease and myositis and then various other clinical features and some patients express all of them.

Some patients only express clinically lung disease and so the syndrome is generally defined as the presence of one of those anti bodies that we find in the blood as well as at least one clinical feature of this syndrome and many people really like to see more than one. As far as the antibodies that we see, there are currently eight known antibodies; anti-JO-1, PL-7, PL-12, EJ and OJ and those five are clinically testable in specialty laboratories at least in the United States and some places in Europe as well, as well as Asia.

And the other antibodies are more rare and generally not as often tested in a clinical laboratory at least in the United States and that would be anti-KS, anti-ZO and anti-HA. They are the rare of the anti-bodies because of fewer people seem to express those.

[Jimmy]: Well thank you for that great answer. So the antibodies for the patient, when they first get started, what are the first symptoms and do we know about causes about that or prognosis of Antisynthetase Syndrome?

[Dr. Miller]: Yeah this is Fred Miller and again I thank everyone for participating today and for the opportunity to talk about some very important and possibly growing problem in our population. So in terms of risk factors for the development of these diseases, we don't know too much about that and this is one of the reasons we're doing this study right now at the NIH which involves Dr. Stine at Hopkins and many other centers where we're trying to understand by comparing patients with the Antisynthetase Syndrome with other myositis patients and with healthy controls, what it is that could have induced these diseases. So the study is ongoing right now and patients who are interested in this can call our recruitment office 1-800-411-1222. It's called the Myo-Risk study.

Some hints as to what maybe causing these diseases come from other investigators with the hint that perhaps cigarette smoking maybe a risk factor in certain individuals that have these certain genetic backgrounds. There are also risk factors and the major genetic risk factor at least in Caucasians is the HLA-8.1 haplotype as it's called. The HLA genes are genes that are important to immune responses to different environmental agents. HLA stands for human leukocyte antigen, and these genes are particularly preserved in a number of different Caucasian populations. They are relatively frequent and these are not really abnormal genes that people have but their variations, there are different spellings of this gene and the spelling that seems to be a risk factor for the Antisynthetase Syndrome is the HLA-DR3 is one of the primary ones. Part of the 8.1 haploid type.

Another possible risk factor has been identified by some Spanish investigators where they looked at a number of individuals and found the occupations relating to exposure to dust, certain gasses or fumes may also be a risk factor. And in fact, so it's probably a combination of these genetic risk factors and certain environmental risk factors that together result in these diseases.

[Jimmy]: Well thank you for that and the question is – I mean there are two questions that's related to this. Number one is, how is this related to interstitial lung disease or other lung involvement unless you have one particular color from British Columbia in Canada, thinking about 60% that she's red and have lung involvement and 40% without and how does it make a difference whether it involves the lung or not? Is it difference of severity due to that?

[Dr. Christopher-Stine]: Sure, so this is Dr. Lisa Christopher-Stine and so interstitial lung disease is often seen in combination with the Antisynthetase Syndrome, it need not to be clinically present however so for reasons unclear with some patients with these antibodies that are known as the Synthetase antibodies don't express lung disease. If you look at what's estimated in the medical literature, the prevalence of interstitial lung disease across all myositis patients, not just the Antisynthetase subsets but myositis itself ranges anywhere depending on how the study is done from 20 to 78% but if you look specifically at the Antisynthetase patients, that estimate of lung disease is more likely to be anywhere from 67 to as much as 100% in some studies depending on the way they were done.

So having a Synthetase antibody enriches the possibility of having lung disease. I think the second part of that question was, how does that make the disease different or more severe and I think in fact having lung disease can increase the severity of the disease. It's one of the complications that well certainly treatable in many cases is something that concerns us in at risk for morbidity and mortality.

[Jimmy]: Well thanks for that, so besides lung disease. Also it seems like there are some connections with polymyositis or dermatomyositis or Reynaud's Syndrome, what's the relationship of those diseases with Antisynthetase Syndrome?

[Dr. Miller]: Alright, so as Dr. Lisa Christopher-Stine said, Asynthetase Syndrome has many different aspects to it and they include not only the presence of one of these eight antibodies but also myositis, either poly or dermatomyositis, lung disease, arthritis or joint pains, arthralgias. Mechanic's hands is cracking and scaling of the fingers that look like a car mechanic actually but they can really occur in patients that don't do any mechanic work, Reynaud's phenomenon where the hands can become change colors in the cold or when with emotional distress and some patients have fevers as well. About a third of the patients roughly speaking, develop the myositis before the—and some of the other symptoms before the lung disease. About a third develop them all these number of these symptoms all at the same time. And about a third developed the lung disease first before the myositis and other symptoms and it appears that the different antibodies have slightly different frequencies have some of these features too. So the Jo-1 patients for example which is the most common form of Antisynthetase Syndrome tend to have more muscle disease, myositis, mechanic's hands and arthralgias; that joint pains or arthritis, inflammation of the joints and the non-Jo-1 patients tend to have more fevers and the interstitial lung disease.

[Jimmy]: Thanks for that. There's little questions from a particular patient about, I think I'll group two questions together about cause and prognosis, so Jenifer from Wisconsin asked about, is there a link with Antisynthetase Syndrome with fibromyalgia and then Charlotte from north Dakota asked about in terms of prognosis if Antisynthetase patients is in remission, can they stay in remission indefinitely or could it come out of remission, what is the prognosis. So I'm bunching two patient's questions there about cause and about prognosis.

[Dr. Christopher-Stine]: So if you could just repeat the first part of question, tell me about the cause again?

[Jimmy]: Is it linked to fibromyalgia?

[Dr. Christopher-Stine]: Yes, so I'll go out there to save it. I don't know that I have seen or certainly haven't done myself conclusive studies that fibromyalgia is linked to this particular incident. There are certainly studies in cousins to this disease and other autoimmune disease. Lupus and fibromyalgia is an overlap, in my personal experience, examining patients, while I am impressed with the fact that patients may report more muscle pain than I think we really are traditionally taught is associated with these diseases, true diagnosable fibromyalgia with specific tender points, I don't actually see a particular uptake in that versus the general population for example. I have not seen that link; I also do not think that fibromyalgia would be causal for this syndrome. Having sad that certainly, anything can overlap. I do think that fibromyalgia-like state do occur with chronic sleep deprivation and some patients with auto immune disease have extraordinary fatigue and if they are oxygen dependent, may or may not have difficulties with sleep, so it's a potential—I could theorize that somebody who had fibromyalgia type symptoms might in fact have those muscle pains from perhaps sleep deprivation.

The second point of the question was?

[Jimmy]: Prognosis, if it goes into remission, could someone stay in remission indefinitely? What are some things that could cause you trigger so they come out of remission?

[Dr. Christopher-Stine]: Sure, so again, I don't – you'll hear this thing a lot, because it's a rare disease I don't know that there's a large population studies to know this. What I can say in caring for a lot of patients with the Antisynthetase Syndrome is that I absolutely have seen people go into full remission. Sometimes even the most severe disease actually does regress. That means [Inaudible 0:17:58] being that I may not see patients with severe scarring in their lung completely reverse. Generally, that tends to be a bit more irreversible. Having sad that, patients with severe muscle disease or even those who have severe lung disease can absolutely have some reversal and in some cases, really full remission on medication and I would say that remission, I generally think about in two categories. Remission on medication and remission without medication and the former so being in remission meaning there are no clinical symptoms that I can see evident. Not infrequently but it requires immunosuppressant medications and sometimes lifelong. Patients always say, "How long will I be on these meds?" I say, "I really think that we can't say lifelong because we have new discoveries every few years then we get better at what we do so it may not be necessarily truly lifelong" But I'll say an extended period of time.

And then there is the minority but it does happen where patients can get off all immunosuppressants. What does that and how to predict that is an interest of mind. I truly can't tell you with any certainty in my own experience what may predict that. One thing for sure seems to be earlier diagnosis. So the earlier you're treated in general in my experience, the better your response. Not a perfect correlation but that's one hypothesis.

And then the other thing I would say is the longer you are in remission, the longer you are likely to stay in remission. And I think finally that question also included the topic of what makes one come out of remission and again, experience tells me that this disease like many others, Rheumatoid Arthritis, Systemic Lupus, it seems to be some trauma or insult to the immune system and that could be something as simple as viral illness, a common cold may trip the immune system for reasons unclear.

Autoimmunity is an aberrant immune response. Our immune systems don't work quite the way they should so maybe when we have to call them into help for something like a viral illness or surgery or even an emotional trauma, I have seen instances of all three of those things take people out of a remissive state, in remission state and then have re-expression of their disease and the final comment I'll make is that it can go back into remission and that I usually tell patients while we celebrate successes and I do think the longer one is in remission, the more exciting that is and it's generally less likely to come out of remission.

The reality is that autoimmune diseases undulate. There is this idea of flare and suppression of such and where you can have disease quiet for a long time and for reasons unclear, it flares. Patients often blame themselves or try to figure out a trigger and despite what I told you sometimes there is no discernable trigger and it's just the way the disease seems to be patterned.

[Jimmy]: Thank you for that.

[Dr. Miller]: I agree with everything that Lisa said here, I might just add that one feature that we've seen particularly related to the Antisynthetase Syndrome is that it tends to be a disease that does recur and thus flare so to speak, whenever medications are tapered too rapidly and that's probably the most common cause of flare in our experience is that they, the doctors or the patients together decide that they will decrease the dosage of either the Prednisone or some of the other agents that they're taking and then the case of the Antisynthetase Syndrome, these are patients that you have to be very careful and slow about tapering medications because they do tend to flare very frequently when you do this.

[Dr. Christopher-Stine]: That's an excellent point; I would absolutely echo that in our experience as well.

[Jimmy]: Thanks for that, and what if the disease is not treated well and what are some of the chronic [inaudible 0:21:52], so tell me the things that could happen if their disease is not controlled well?

[Dr. Miller]: I'll just, well I guess I'll answer that first, of course every bouts of inflammation in myositis syndromes tends to leave a little bit of damage, our scarring or fibrosis associated with it and that is irregardless of what tissue it's in and as we've discussed, the Antisynthetase Syndrome tends to have a lot of different organ systems involved. The skin if dermatomyositis is a part of this, lungs as we mentioned and the muscle. Sometimes the joints as well.

And so each time that there's an inflammatory process going on there, at least for a certain period of time, even if that eventually comes under control, it often leaves some damage or some scarring or some fibrosis behind and that scarring really cannot itself be directly changed. And so there's a little bit of that probably as a result of almost every bout of disease activity that can resolve in problems in breathing or some weakness or some skin fibrosis that you sometimes get. So that's certainly one of the outcomes that can occur with chronic disease here that's why of course one should try to be diagnosed early, one should get on top of the inflammation very quickly and one should often maintain the anti-inflammatory drugs for some time before really tapering them off to be sure that patients are in remission before they are tapered completely off.

[Jimmy]: Right. We have two questions related to symptoms of it. We have questions from Australia, from Queensland, Paul from Australia talks about, that he has a burning sensation in his body, his blood is boiling hot, is this common for people with Antisynthetase Syndrome, and now we have another question from Stephanie from Florida, talked about, there's with the muscle loss, can this muscle loss be reversed through exercise, weight bearing exercise or other mechanisms?

[Dr. Christopher-Stine]: I'll try to take a stab at that one, so I would say that the – it's a curious question about burning. Again, I don't have a conclusive answer, I'm curious to know if Dr. Miller has some thought on this. A couple of things that come to my mind when I hear patients talk about a burning sensation, I would say it's not necessarily always in the context of the Antisynthetase Syndrome. But I do see patients with more often the dermatomyositis version where there's a rash present as well as muscle involvement; they tend to feel hot. Their skin can sometimes feel hot to the touch to them or even underneath where I can't really feel it. So perhaps it's a localized inflammatory response in the skin that patients feel a burn. There is another phenomenon I have seen in which patients sort of developed this deep muscle pain/burn and I have seen evidence on imaging, on MRI when the fascia which is the covering of the muscle, not the muscle itself but it's the overlying connective tissue on top of the muscle. That can become inflamed particularly in dermatomyositis. Either with or without the Antisynthetase Syndrome and patients can sometimes talk about a burning sensation. So, that's my thought on burning, I don't know if Dr. Miller wants to chime in on anything else.

[Dr. Miller]: I agree, I see those two things and of course these patients with this diseases, this Antisynthetase Syndrome also tend to have fevers and it isn't described whether there's a fever or not but that often can have the sensation of kind of a burning sensation throughout the whole body. A little different in the usual fever sometimes but other than that I don't have another explanation. Of course something else could be going on as well that could be the result of this.

[Dr. Christopher-Stine]: And I think the other question was about exercising can...

[Jimmy]: Muscle loss.

[Dr. Christopher-Stine]: Muscle loss.

[Jimmy]: Yeah muscle loss, how do you help with muscle loss and muscle wasting?

[Dr. Christopher-Stine]: I think there are two types of ways I categorize muscle loss. Some people look at their size or their arms and they say, "Boy they're visibly atrophied", they've gotten smaller and sometimes that's a result of truly having an atrophic muscle where the muscles gotten small as a disease has progressed and inflammation has caused that. if you look on imaging studies again, if we can look at an MRI of people's muscles, two things we see are smaller muscles or atrophic muscles and sometimes we actually see normal muscle size but something called fatty infiltration or fatty replacement where overtime, a muscle that's damaged gets absolutely replaced by fat and seems to be again a chronic consequence of chronic inflammation. At least it's our current thinking, at least to my knowledge that while muscle cells are terminal when they are dead and the muscle cell individually dies and the term for that is necrosis.

When the muscle cell itself dies, it doesn't itself get regenerated, however, looking at a broad picture and on a more macroscopic rather than a microscopic level, if you look at the patients themselves, the two things I've seen are, the patients can indeed increase their muscle bulk again. I'm not an exercise expert although some of our colleagues in Sweden have done some beautiful work showing that exercise is absolutely indicated as long as there's no other contraindication or reason a doctor has said not to exercise. It's indicated for this disease, at least after the acute phase, sometimes it's very difficult of course to exercise when the disease is first at the onset of the disease. But before, where we use to tell people rest your muscles, don't exercise. In fact, that's been fully I think reversed and to the point where even the scientific literature bears that out that with time and use people build muscle and perhaps that's recruiting other healthy muscle to step in and perhaps it is actually bulking up some of those muscles that aren't completely dead but rather just a little bit smaller that require some muscle building.

[Jimmy]: Great, let's all shift over to talk about treatments. So, many of our listeners are interested in terms of whether there are any new treatments for Antisynthetase Syndrome, what are some of the things that you see that are most exciting that potentially could be helpful for the disease.

[Dr. Miller]: Well I think I'll start with that one I guess and Lisa please add your thoughts. The traditional approach of course for all myositis syndromes is to start with steroids but I think one of the changes in our thinking is to be more aggressive early on in the diagnosis and is particularly true for the Antisynthetase Syndrome and to add additional medications even from the very beginning of the disease and traditional medications here would be things like methotrexate, mycophenolate cyclosporine, tacrolimus and IV Cytoxan especially when there's lung involvement.

We recently completed the study of rituximab in myositis generally and found that the Antisynthetase patients that we had in that city did particularly well, responded better in fact in some ways than some of the other patients so, I think rituximab is what's beginning to attack B cells. It's another, it's relatively new, still not approved treatment for myositis but is one that I think is very helpful in patients with Antisynthetase Syndrome and I would use it though after probably trying some of the other more standard approaches. One of the questions was also talking about, even more novel treatments asking about stem cells and gene therapy. And in fact, stem cell treatment, autologous stem cell treatment. That means using your own stem cells, taking them out of the bone marrow or the peripheral blood, wiping out your immune system so to speak and then growing up and giving those cells back to you to try to reset the immuno-stat that some people have said has been tried and it is sort of a last ditch approach because there are many risk of course when you wipe out the immune system with the drugs that are needed to do that and so that there are deaths associated with this relating to infections and problems like that. But there are few reports of some cases where in fact patients have gone into remission as a result of this type of treatment and there is an ongoing study right now by Dr. Richard Burt actually at North Western University in Chicago looking at stem cells in myositis.

A useful source here is a website entitled 'ClinicalTrials.Gov' and if you put in the term myositis, you can see all the different studies that are ongoing in myositis and that's a useful site to look at. The other area that was asked about was gene therapy. And again, we're very early in gene therapy of muscle

diseases as we are for most other diseases. However, Dr. Jerry Mendell in Columbus, Ohio has been doing the study using a gene therapy of a protein called follistatin which actually is a protein that inhibits the function of a protein called myostatin which tends to block down muscle growth in inclusion body myositis. And the idea here is you can block down the inhibitors of muscle growth that will allow muscles to regrow and reform and increase the function in the patients. So we're all waiting anxiously to see the results of that study because of course if it works in inclusion body myositis, it could work in other muscle diseases as well.

[Dr. Christopher-Stine]: I would agree with that. I would say, echo everything that Dr. Miller said. One other thought and again there's little data to back this up but we have seen some and there's some Japanese investigators that have reported their experience positively as well with IVIg. So every once in a while, we add that on as an adjunctive therapy to other immunosuppressants; IVIg doesn't suppress the immune system as much as it modulates or that changes it and I think we're not fully clear on all the ways that IVIg works so that's one option. We've had some luck with tacrolimus as have investigators in Pittsburgh cohort of mine said as patients where they follow a large number of patients with interstitial lung disease.

So tacrolimus, which is another immunosuppressant, has been helpful for us as well. I do think the data from the large rim study that rituximab in myositis, study that Dr. Miller mentioned which showed that anti-Jo-1 patients in particular responded well is very encouraging. It may suggest that there are some medications that are more appropriate for each subset of the disease and these are rare diseases so they are harder to see patterns but as we aggregate patients into larger trials, I think we'll get a better sense for this.

And I will also just make the comment that I have never really seen as much excitement from the pharmaceutical industry as I have in the last five years regarding enthusiasm, interest for novel targets for thinking about these diseases. They don't necessarily name the Antisynthetase Syndrome perse but often they'll put that under the umbrella of dermatomyositis and polymyositis with lung disease. Patients can have dermato or polymyositis with concomitant lung disease and have a different antibody so sometimes there are overlaps with different antibodies that are not Antisynthetase antibodies that look clinically similar but one with Antisynthetase Syndrome would benefit in a trial such as that.

So, I know that I have personal interest in this particular subset of patients and novel therapies and I as Dr. Miller, I'm sure has also seen, we are seeing more and more interest in the pharmaceutical industry for what was previously really flying very low on the radar so I have high hopes that we'll see some more novel therapies come to the market in the coming years.

[Jimmy]: Well thank you for that. My additional question is because many of our patients are – because it's such a rare disease and patients often don't get to see a physician that specializes or has this knowledge specific about Antisynthetase Syndrome, any suggestions on people who potentially live in areas that are none within academic centers or might not have direct access to experts. What would you recommend them do, potentially with their physicians or what other sources, do you have any recommendations there?

[Dr. Christopher-Stine]: I would say my bias there is that if it all possible to at least get one second opinion at a tertiary care center. I think when you have a rare disease, that's where the beauty of having expertise at a place like the National Institute of Health, John Hopkins, University of Pittsburgh, all of these centers they have large cohorts of patients where we see them every day. The reason that I suggest at least a second opinion if it all possible, if travel is possible, and certainly I know that the National Institute of Health can sometimes offer patients that normally would maybe not have the resources to travel to be seen there under certain protocols.

At our institution, I believe that we do help provide often some guidance to local physicians that may have no experience or very little experience in seeing this. So I think that be who you to try your best to get to a tertiary care center. If that is not an option, and you still have some resources to travel, the other thing I think is important is to attend program such as the Myositis Association Annual Patient Conference. Best in valuable for patients where they learn from other patients, they learn from physicians and other providers who provide talks on these types of topics and I think you just really—the world becomes a little smaller when you can talk to people who have been n your circumstances including physicians and other patients.

And then finally, while I think the web can serve as a source of information. I also think there has to be caution there because some of the information that patients bring to me and I find my patients have incredibly good health literacy. They know their disease very well. I still think that there's a lot of misinformation so I would be somewhat cautionary. So again, my long answer shortened would be try your best to get to a center that has experience to at least get one opinion if you can be followed there. That's preferable, the model that most of us follow is to give our opinion, have the patient go back to their local treating physician to be seen in the interim appointments and then come back maybe perhaps twice yearly or three times yearly for follow up to make sure that things are going the way that we expect them to go and then to manage if there is an issue outside of that but I really can't recommend in stronger terms a rare disease such as the Antisynthetase Syndrome to seek out medical providers who have experience of this disease.

[Jimmy]: Great. Wow, that definitely a great advice there. And for patients who do already have Antisynthetase Syndrome and want to participate in research or trials, how do they find out about it, I think Dr. Miller has mentioned a website but how do they found out about it and then how can they be involved?

[Dr. Miller]: Well I thought some of the suggestions that Lisa was making are good ones. I agree that the web has some good information and then has some areas that probably are not as reliable. I think reliable sites are the Clinicaltrials.Gov site that I mentioned which is sponsored by the National Library of Medicine, part of the US Government that collects reliable information from all the different studies that are going on around the world actually and then list by topic those that are ongoing and those that have completed and those of even being planned to begin soon so, they share the of information there. As was mentioned, I think that the Myositis Association which is the world's largest patient support group centered in the Washington Area here but also an international organization and its absolute reach is another very good source for information and the TMA, as it's abbreviated, has a wonderful site

also that talks a lot about these diseases and where one can go to get some more information about them. There are also books that the Myositis Association sponsored that also are very valuable for getting some information about these diseases as well. And I think going to the tertiary and sometimes quaternary referral centers, they were mentioned where experts have seen lots of these patients have a lot of experience is also useful on resource.

[Jimmy]: Great, thank you so much. Some of our patients, we have a patient in Florida and another patient in Canada asking about lifestyle changes or dietary changes that they can make to alleviate their disease, are there suggestions that you will make to such patients in terms with their lifestyle that would be helpful for their disease?

[Dr. Christopher-Stine]: I think probably physicians are the least schooled in giving this advice which is probably some of the most important advice that we have to give. I often teach my students and well, students themselves know this and I tell people in the public that physicians in general are not well-trained on diet, about four hours I think I had of nutrition in four years of medical school so everything that we read I believe that we read in our own. I think there's a lot of interest in this idea of how diet modulates the immune system, the leaky gut idea of having perhaps an immune response beginning in the gut and I think that while this is very preliminary, there is provocative thought that what we put in our bodies which makes sense is important and may in fact either provoke or dampen down our immune response.

There are a lot of guides out there as far as diet and I don't think any of them have been scientifically vetted but a lot of nutritionists tried this idea of an anti-inflammatory diet. I have not seen that adequately researched well and often the medical literature to recommend such a thing but I don't recommend necessarily against it.

Lifestyle, a few things that I recommend to my patient for sure if you have the rash of dermatomyositis; sun exposure is quite important. Certainly Dr. Miller is an expert on this and has shown this but we believe that even the exposure to excessive sun certainly between the hours of 10 and 2 but any sun exposure without sun protection can turn the disease on. I've actually seen it spawn the disease back not only with regards to skin but actually muscle. So I think UV light is a very important environmental trigger to try to avoid and then finally, I think it's just to really take good care of yourself so it would be the sound advice that we would give any patient which would include making sure that you can to the extent that you are able to reduce the stresses in your life. I have on occasion ask my patients to take a leave of absence from their work to see how important it is that how much their work is contributing to their illness in any way. While ably, we should all be productive members of society in ways that we can. There are times that certain professions do seem to aggravate the disease and even taking a short break or temporary break to see if indeed that's true or perhaps maybe that's actually helpful that your work is helpful in helping your disease.

So I would say get plenty of rest, drink a lot of water, eat well and eating well probably includes decreasing sugar content, watching obviously to maintain a neutral weight and this is important for patients with myositis because it is difficult to maneuver one's body when they have excessive weight.

[Inaudible 0:42:47] it's an extra burden on the body in general but for patients with myositis, this can be quite significant. It also can hurt joints as well being overweight or obese. So, I guess it's really just sound lifestyle advice which we give to anyone with the caveat that the sun exposure is much more important in our dermatomyositis subset of patients.

[Dr. Miller]: I'd agree with that and as it turns out, our mothers and grandmothers were right what they've told us what's hard is what we should be doing. And I would certainly echo all of the things that Dr. Lisa Christopher-Stine just said. I think additional things based on preliminary data, we really don't have good data here so we're doing this based on general recommendations and other areas of medicine that certainly is smoking, if you are smoking, certainly stopping smoking is probably a very important part of this and I've seen a few examples of that actually improving patient's disease.

Exercise, maintaining weight, between blood pressure, avoiding stress, trying to maintain and enhance those close personal relationships that you already have or developing those if you don't have those because being part of community I think is a very important part of our welfare as humans overall.

And of course the diet question's a very important one but there's remarkably little information that really has been studied in this area and it's a really big area that needs investigation. Since we're learning more and more about the microbiome now, there's organisms that we co-exist with in our gut and on our skin and other areas. And our diet clearly affects these and we really need to know more about this but I think a very diet, Mediterranean type diet; probably low in fat, low in sugar are good ideas. Thinking about anti-oxidants, I'm thinking about omega 3s are all reasonable things to do in the absence of any specific information that can help us in these areas.

[Jimmy]: Great, there are actually some questions, there's a question from Cleveland, Australia, and also a question from Dublin, Ireland talking about in terms of life expectancy. What's the change in life expectancy for patients with the disease and then we also have another, Lisa from Dublin, Ireland asking about being on a drug and her disease stabilizing and then the doctors doesn't want to take her off and she's wanting to be off of it and she want to know how taking medication would potentially affect her life expectancy as well. So talk about that, I know you mentioned about tapering the drug is going to be important but, talk about life expectancy and the effects of this disease to prognosis there?

[Dr. Miller]: I think I guess I'll start on that. We've done some studies in the past that have suggested that this syndrome is one that has results in a shorter life expectancy than other types of myositis, this studies relate to information collected about 30 years ago when we weren't as good in diagnosing and treating this diseases and I haven't seen any recent information that really has allowed us to expound upon or make more accurate. That information I think, these are serious diseases, it's particularly the lung disease, it's probably the part of the syndrome, it is the most serious and that causes most of the doubts related to the Antisynthetase Syndrome but we really don't have good predictors. I think some of the data that's been both we and others have created which is incomplete and based on small numbers would suggest that certain factors such as older age, certainly the development of cancer which rarely occurs in this syndrome and this syndrome generally is a protector for the development of cancer but there are some cancer cases that do occur I think, severe disease that the time of onset and

difficult to treat disease, the presence of fevers and Reynaud's for example all tend to be poor prognostic factors but again, there's a lot of individual variation here that makes us very hard to have crystal balls that let us really predict an individual case, how people are going to fair overtime and the very important thing is to really be sure that we have a careful and a complete assessment by an educative physician in this area so that all the disease activity and damage can be assessed and all the organs and optimally treated to minimize the long term effects of the disease.

In terms of the medications, it is true that all the medications that we use have potential side effects blocking down the immune system is dangerous in its absolute sense and can increase the risk of infections and other problems but of course it's the balancing act that we all have to play in this game and there are no free rides here. We really have to think about the pros and cons of all the approaches that we take and optimize that balancing act as much as we can.

[Jimmy]: Final question before I give you time for closing thoughts, there's a lot of excitement at least in the US and somewhere around the world about precision medicine and personalized medicine and also like these diseases, I know there's a lot of non-genetic markers for Antisynthetase Syndrome but I love to simply hear out of your thoughts in terms of going forward, there's emphasis on precise medicine precision medicine and then how that potentially could be helpful for patients with Antisynthetase Syndrome and if any of those genetic discoveries coming out and the genome, where in the microbiome could be potentially helpful in understanding this disease.

[Dr. Christopher-Stine]: So I would say that we are on the cusp of knowing or trying to know the answer to that question. I think it's a little premature but I think the exciting part is that previous genomics technology such as something called Whole-Exome Sequencing where we're trying really to look at the active art of a person's genetic makeup. Trying to figure out the way it works used to be extraordinarily expensive. And while it's not inexpensive, it is becoming more available to do these studies as the pricing does decrease. So I think with time, when accessibility will be able to answer some of these questions. The way I would envision those answers to help the patient and help the physician, would be the idea that when one walks into our office, we have a way of personalizing their treatment regimens so it would be wonderful to know why one person is a methotrexate responder where the same person who has almost identical characteristics as far as age, race, similar age, same race, same gender, maybe even same antibody clinically look similar one as a responder to a medication and one is not.

So the beauty would be to have that types of personalized approach. So then instead of using the dart board approach as I call it where we're sure to throw in the darts hoping that we've thrown the darts before we're pretty good at hitting the bulls eye because we've seen it before. Not everything responds the same and therefore, it would be nice to have that kind of precision. And then the other way I could envision genomic data to be of help would be it to predict the clinical phenotype, in other words, the way that the person will express this disease so we talked about the fact that some people have more severe lung disease, some people have cancer. Some people have more severe arthritis or skin disease. So I think if we were ahead of the game and we knew the more likely expression of the disease beyond just the antibody and what we know today, we might be more pre-emptive and be able to make more informed decisions earlier in the game to help prevent complications later on.

[Dr. Miller]: I would agree with all those things. That's been one of my interests to try to understand the genetic basis for these diseases and I formed an international consortium called the Myositis Genetics Consortium in fact to try to do that. There were about 2,000 patients now in these studies and have done whole genome analyses through genome wide association studies as their call and found that in fact there are some of the same genes, there are risk factors for other autoimmune disease are also risk factors for certain types of myositis and I think that following along these findings, and going into more depth and to understanding how the different types of myositis have not only different presentations but also different genetic and environmental risk factors will ultimately help us understand perhaps why this diseases come about as well as why some respond better or not so well to certain different types of medications. I think the hope is actually to prevent the development of some of these diseases if we know the genes and the environmental risk factors that come together that cause them. It's possible that we could keep them away from each other and actually prevent these diseases from occurring in the first place.

[Jimmy]: Wow, that's a great hope. What if we can imagine a world where this disease can be prevented before it starts? That's an amazing beautiful picture Dr. Miller. So the close –I want to give you a little bit just some time with what are your closing thoughts you want to leave to our listeners about the disease. So with Dr. Miller any closing thoughts that you would provide or advice you would give to our listeners?

[Dr. Miller]: Yes, like Dr. Lisa Christopher-Stine, I'm very optimistic about the current and future possibilities here. We live in an era where there are just incredible, technical advances and our capabilities of doing a lot of different studies to help us understand that way genetic and environmental risk factors but also mechanisms for disease. And we are finally getting the handle on understanding some of these in different types of patients that we have. Also the international community has come together through a lot of international groups to allow us to work together in myositis and to aggregate adequate numbers of patients to be able to do some of these studies and these rare diseases.

The pharmaceutical companies are also becoming more interested since we've now standardized some of the ways to measure disease activity and damage in these diseases which I think has been one of our inhibitors before. And so there's great I think interest and hope that we'll also see a lot more clinical trials going on here.

So from a combination of understanding more about the genetics, the mechanisms of the disease, the types of myositis, having large numbers of patients available to do these studies and having the pharmaceutical industry more involved, I think there's great potential for understanding a lot more about these diseases and I say not only curing them but also ultimately potentially preventing them.

[Dr. Christopher-Stine]: I'm really very grateful for the opportunity to participate today, I say that I'm in the business of hope and I think that I'm privileged to care for wonderful people and I think that there is a lot of hope on the horizon for these illnesses. I think that what was once quite formidable, we are slowly making good advances to allow people to live their lives either with the disease or hopefully not expressing even the symptoms of the disease. I would echo Dr. Miller's wonderful sentiment that we'd

love to live in a world where they were completely preventable and I don't think that is not a reality. I think that that's absolutely possible. Hopefully, within my lifetime of practicing medicine so I'd also just like to say that I think that there is power and knowledge and that I was very impressed with the quality of the questions that were posted. This is a group who cares about themselves, cares about each other and I think that this is a wonderful step in having a community, people locally but certainly having to reach out to a community worldwide such as this one and having resources such as RareShare which I feel very privileged to be associated with to help disseminate information to empower you. I think as a patient, the most important part of your health care is to be up-to-date and be on top of your own health care.

So, I think we have a very bright future with a lot of interest and I am very fortunate, I feel very privileged to practice medicine at a time like this.

[Jimmy]: Thank you so much both Dr. Miller and Dr. Christopher-Stine, we really appreciate good time and more importantly your work and research day in and day out serving patients in advancing science. Well we really thank you for that and also, being able to be so open to the questions of the patients have. And we do strive on RareShare.org to help you provide a lot of goods, information that scientifically to be accurate and provide links and we'll be doing that and we're starting to do that with this podcast and be able to hopefully help this community to be able to access some of the latest research, some of the experts so that we can know and we'll all fight this disease together.

Thank you once again and this podcast will be available on the internet as well as transcripts in the next few weeks and then we also have some of the questions that we didn't get to on the RareShare platform and then we have some discussion there. We look forward to further interactions with you. So this is going to be the end of the podcast, thank you very much.

[Dr. Miller]: Than you it's an honor to be a part of this.

[Dr. Christopher-Stine]: Thank you so much.