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Keys to Diagnosing & Managing Systemic Sclerosis Interstitial Lung Disease

Dr. Swigris:
Welcome. My name is Jeff Swigris, and I am a Professor and Pulmonologist in the Interstitial Lung Disease program at National Jewish Health in Denver, Colorado. Our educational activity, Systemic Sclerosis Interstitial Lung Disease, a Multidisciplinary Approach to Diagnosis, Treatment, and Longitudinal Management, is supported by an independent educational grant from Boehringer Ingleheim Pharmaceuticals Incorporated, and is provided through a collaboration between National Jewish Health, the nation's leading respiratory hospital based in Denver, Colorado, and its partners, Mount Sinai in New York City, and Jefferson Health in Philadelphia. These top institutions have formed the Mount Sinai, National Jewish Health Respiratory Institute in New York City, and the Jane and Leonard Korman Respiratory Institute, Jefferson Health, National Jewish Health in Philadelphia, Pennsylvania. These three organizations bring together leading expertise in diagnosing and treating all forms of respiratory illness and lung disease, including asthma, chronic obstructive pulmonary disease, interstitial lung disease, and bronchiectasis. This collaboration encompasses advanced research, clinical trials, and other programs to serve patients throughout the country in an unparalleled respiratory network. For our discussion today, I am joined by my colleagues, Dr. Maria Padilla, Professor of Medicine, and Director of the Advanced Lung Disease and Interstitial Lung Disease programs at the Mount Sinai National Jewish Health Respiratory Institute; Dr. Jesse Roman, Professor of Medicine, and the Chief Executive Officer of the Jane and Leonard Korman Respiratory Institute, and Enterprise Division Chief of Pulmonary, Allergy, and Critical Care Medicine at Jefferson Health; and Dr. Mehrnaz Maleki, Associate Professor of Medicine, and Director of the Rheumatology Clinic at National Jewish Health. Please join us as we discuss best practices for the diagnosis of scleroderma-related ILD and present multidisciplinary perspectives related to the treatment and longitudinal management of this rare disease.

David:
Summer of 2013, as I was encouraged to – we were used to traveling in the summer and having a good time, and I noticed that my skin was changing. I started getting these brown pigments all over my chest and my back. And one of my friends actually told me, "Hey, you probably want to check that." And I got really – I wasn't that concerned at that point. I was in pretty good shape. I was a very active snowboarder. I used to run 2 miles every day. So as I got back to the states, I started getting other symptoms. My hands were swollen every morning, they will hurt. My feet were swollen. I was having problems breathing. I was having problems just going up one flight of stairs. I was developing this really tense cough, and my work was getting to be a little bit difficult; just my day-to-day activities. So at that point it was when I started realizing I had something wrong. I finished my chemotherapy treatment at the end of 2015, and from that point on until now, my scleroderma has been on the remission. And all of the symptoms that were making me feel bad have been non-existent. Obviously, there are some that you cope with like arthritis, but the tightness in my skin that was really bad, you know, you feel constrained in your own skin. The painful numbness in your fingers, you know, those are pretty much non-existent. My actual pulmonary function capacity has been actually increasing a little bit, not very much, which is, you know, you don't get that. And at that point, I was feeling so inspired to continue to do what I needed to do. I started snowboarding again; not as I used to, but you know, everything with my limitation where I can actually do it. Everybody has a battle to fight at one point in your life. Mine was just started at 36. But that wasn't going to stop me from continuing to live where I can actually live a normal life with my family and my kids, so that's probably – don't stop your life. There is treatment.

Dr. Swigris:
Thank you for your attention for that. That's why we're here, right? We take care of patients like David. So, case 1; let's think about a case as we begin the symposium. A 36-year-old, Hispanic male, three months of exertional dyspnea, starts noticing his hands and feet are swollen. He called them "Mickey Mouse hands and feet." Seven months of white and blue fingers when it's cold. Thickening of the skin. And his doc says, "Well, this isn't right. Let's get a skin biopsy," and he's diagnosed with morphia, limited scleroderma. Past medical history – he really has none. There's really no contributory history in terms of his family history, social, environmental, or occupational history. He was a former smoker, quit a couple of years ago. On physical exam, by our esteemed rheumatologist, puffy hands and feet. She notices some palmar telangiectasia, periungual erythema, abnormal nail fold capillaroscopy, and sclerotic patches on the skin of the trunk, and some mild sclerodactyly. The pulmonic component of the second heart sound is normal, crackles at the lung bases on lung auscultation. Pulmonary function studies you see there; there's mildly reduced FVC, moderately reduced DLCO. And there's a problem with gas exchange. In Denver, he walks a pretty good distance of 1,430 feet, but the saturates from normoxia to 85%. Serologic examination you see there. High titer ANA in a homogeneous pattern and high titer SCL-7 antibody. Here are some slices through his high-resolution chest CT scan, and here we are at the aortic arch. There are a few subtle abnormalities that I won't point out in the interest of time, but as we go down, I think you can easily appreciate there is a lower zone predominant abnormality. There are a mixture of ground-glass opacities and reticular opacities. I think you can appreciate traction bronchiectasis at the bases. And if you look closely, this is really not an immediately subpleural process, is it? You see a little bit of subpleural sparing, and I think it's most evidenced in the right lung there. You see that rim of black or normal parenchyma between the pleura and the opacities. You can see a hiatal hernia there, thickened lower esophageal wall, and more of the same. So let's reflect on that case. You complete the evaluation, you do an echocardiogram, you look for esophageal motility and gastroesophageal reflux. As the physical exam would suggest with a normal P2, there's no pulmonary hypertension. Comprehensive lab evaluation showed no abnormalities of renal function. There is moderate esophageal dysmotility and moderate reflux, and you decide to treat. What's the best treatment option? 1,000 mg of I.V. Solu-Medrol daily for three consecutive days? Combination nintedanib and pirfenidone? Combination lisinopril and sildenafil, mycophenylate and mofetil? Or daily oral cyclophosphamide? You'll find in your syllabus an infographic, so one sheet that's going to cover, you know, give a 30,000-foot view of scleroderma ILD. And the way that I like to think about ILD as a pulmonologist, is there will be patients coming to me who already have scleroderma, and then we find out that they have interstitial lung disease. There are patients with ILD who, on further investigation, are found to have systemic sclerosis. And then there are patients who present to us with unexplained dyspnea, and we actually find that they not only have systemic sclerosis, but the ILD manifestation, as well. The key point that we want to get across is that these patients are complex. Right? It takes an interdisciplinary, multidisciplinary approach to their diagnosis, to therapeutic decision-making, and to their longitudinal management. And that's what we're going to talk about this morning. To start things off, Dr. Maleki Fischbach will be up here to talk about epidemiology, and how to make the diagnosis of systemic sclerosis. Merhnaz?

Dr. Fischbach:
Good morning, everyone. I think I'm the only rheumatologist here, so I'm not as used to early hours like you guys. You all look full of vim and vigor, so I'm good to go. So let's talk about epidemiology. As you can see, the prevalence of this condition has a quite wide range for incidence and prevalence, and what do you think this can be? I think it's because we have underdiagnosed patients in many areas of the board. If you're not familiar with something, you cannot recognize it. And perhaps that was the purpose of this conference. Systemic sclerosis has higher rates in United States than Australia compared to Japan and Europe. African-Americans are more affected compared to Caucasians. They also have more severe disease; more interstitial lung disease. Females more affected than males around three to four. And in general, in the U.S., we have 100,000 people affected by systemic sclerosis. So another question: ILD may develop in any patient with systemic sclerosis. All of the following are clinical features and factors that increase risk for scleroderma ILD except? Great. So let's talk about different phenotype of this condition. So, we have something called scleroderma sine scleroderma. We have that term in rheumatology quite often, like myositis sine myositis. So these are the patients that do not have cutaneous manifestation, but they have the rest of the manifestation like GI dysmotility, Raynaud's phenomenon, ILD, pulmonary hypertension. Limited cutaneous systemic scleroderma, formerly known as CREST syndrome, which is the abbreviation of calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasia. Normally, the involvement are distal to elbow and knee. Diffuse cutaneous systemic scleroderma, we use Rodnan skin score system to assess the extent of skin involvement, and scleroderma overlap syndrome that is overlapped with different conditions like rheumatoid arthritis, myositis, Sjogren's, and systemic lupus erythematosus. So we rheumatologists really like our serology. And we use it for diagnosis, as well as anticipating the disease manifestation. For example, nuclear ANA, anti-centromere antibody, and anti-TH/TO they are more involved with limited disease in PAH, although it doesn't mean they don't get ILD. Anti-TH/TO also can give you ILD, but we – they have more limited disease and we always have to look for PAH. Scl-70, anti-topoisomerase 1, topoisomerase 3, RNP 1, 2, 3 they cause diffuse disease and more ILD. Again, it doesn't mean they don't have pulmonary arterial hypertension. RNP 3 has severe ILD. In overlap, we use myositis panels like PM/Scl anti-Ku that is overlapped with myositis. SSAA, which is overlapped with Sjogren's. Antiphospholipid anti-Sm overlap with lupus and it's not there, but anti-CCP overlap with rheumatoid arthritis. We use ACR/EULAR criteria of 2013, which improved quite a bit from the previous criteria. It has three

hallmark of fibrosis of the skin and organs, also antibodies we already talked about, and vasculopathy like Raynaud's phenomenon and pulmonary arterial hypertension. Good sensitivity and specificity total score of 9 or more is classified as definite systemic sclerosis. These are the common symptoms: fatigue, stiff joints, loss of strength, pain, sleep difficulties, and skin discoloration. Let's talk about the skin. Maybe this is the best one for pulmonologists because they give us lots of information; different manifestations of skin. So we saw my patient, David. So she – he came to us with pruritus and edema, and that was his first manifestation. But by the time he got to us, he had sclerodactyly. There is a way to look for sclerodactyly; just look at distal DIP, and if they loss the wrinkles, that's very mild sclerodactyly, and then sclerosis, digital tip ulcer, loss of hair in acral area, and dry skin. I have some pictures. So this is pitting of the tip of the fingers. We always look at tip of the fingers. If you don't treat it, they can get ulceration. Calcinosis cutis, this is calcium deposit. We sometimes use x-ray of the hands; very simple test to prove that. Lipoatrophy, my patient David had that on his back, and actually responded to Cellcept, and it's completely normal. Telangiectasias, that's maybe the best one. The patient enters your room and they have red spots on their face and on their tongue, lips, and palms. And this salt and pepper appearance because of hypopigmentation and depigmentation. So that edema was pre-scleroderma manifestation. Another pre-scleroderma manifestation is Raynaud's phenomenon. Before they have anything else, years before, they may have Raynaud's. How do we know that Raynaud's is important? So, if somebody is in their 20s and 30s and have Raynaud's with cold, and anxiety, and nothing else, that's primary Raynaud's phenomenon. But if their 40 or 50 years old, suddenly becomes severe Raynaud's and whitening instead of blue and purple, that's the more sign that this can be something of connective tissue disorder. Then we have capillaroscopy. We have fancy machines like, you know, microscope, but they also have a small, cheap one you can buy from Amazon. So they have decreased capillary numbers, capillary dilatation, capillary dropout, and hemorrhage. They have also increased thromboembolic disease. GI dysmotility is another good one. If the patient has difficulty swallowing, and by meaning GI, it's not just esophagus; they even have issues with their stomach and their colon, they have problem moving their bowels. Of course, reflux, chronic esophagitis, and stricture formation, Barrett's esophagitis, and pulmonary microaspiration is another good one because this is something perhaps we can prevent that can make their long manifestation worse. This is Dave. So if your gastroenterologist calls and sees a watermelon in patient's stomach that means they are more prone to having acute GI bleeding. This is a sign – a risk factor for GI bleeding. Cardiac involvement; so, my esteemed colleague, Dr. Padilla, is going to elaborate on that more. But we have double-issue group 1 PAH. In PAH group, we also have PVOD and PCH. Why it's important to think about that, another issue if you don't know something, if you're not familiar with something, we cannot think of it. PVOD and PCH is important because if you treat them with vasodilator like garden variety PAH, they can develop pulmonary edema or even cause them to die. We also have group 3 that is hypoxia driven, and group 4 that is related to thromboembolic disease. Another good thing about cardiac manifestation and pulmonologists, imagine if you look at a CT scan of the chest and you see pericarditis or pericardial effusion. This all is a possibility of CTD, connective tissue disorder, and especially scleroderma. When they did autopsies on these patients, up to 80% of them had pericardial disease. So scleroderma is a cardiac disease. They also had patchy myocardial fibrosis. This is a pathological hallmark of the disease, and that can cause problems with arrhythmia, conduction defect, coronary vasospasm is also likely. Imagine Raynaud's for coronary arteries, and systolic and diastolic dysfunction. Joint maybe for pulmonologists, if you do something we call prayer sign where they cannot get their hands together, that means they have contractures. Very interesting feature is acroosteolysis, the resorption of the distal phalanx of the hands; again, a hand x-ray tells us a lot of things. Tendon friction rub, if they have it, it's with high mortality, so even joints can help us to predict the outcome. And frank inflammatory arthritis is rare, but they have some clinical arthritis; they have the morning stiffness and other issues related to inflammatory arthritis. Everybody knows scleroderma renal crisis, again it can cause pulmonary edema, microangiopathic hemolytic edema with schistocytes, glomerulonephritis very rare and sometimes associated with ANCA, elevated albumin, elevated creatinine, and hypertension. Neuropathy, you heard from my patient that he had numbness and tingling. The skin gets tight and presses on the nerves, so kind of like carpal tunnel, and it can happen in any part of the body. Myopathy. Myopathy – imagine the skin is so tight and press on the muscles so CK will go up. It doesn't have to be inflammatory myositis. Headaches, seizure, stroke, radiculopathy, enthesitis, myelopathy; again, when you have fibrosis, you have extra collagen and this can happen. Lots of genitourinary issues, erectile dysfunction, vaginal dryness, constriction, and dyspareunia. Lung cancer. So, colleagues in 2010, they did a study and they realized that the longer the patient has the scleroderma, the higher the chance of lung cancer. In RNA preliminaries 1 and 3 is higher chance for developing lung cancer, has higher chance. This is RNP 1 and 3, so which we see in diffuse scleroderma with ILD. Hematologic cancer, myeloproliferative, esophageal cancer obviously because of Barrett's esophagitis and oropharyngeal carcinoma. And I'm not going to talk about the lungs; there are better people here. Thank you so much for listening to me. I hope you learned something about the systemic aspect of sclerodermal lung disease. Thank you.

Dr. Swigris:
Thank you, Mehrnaz. And now, Dr. Roman is going to talk to us about therapeutic treatment options for scleroderma ILD. Jesse?

Dr. Roman:
Thank you, sir. Good morning, everyone. Now that you are fully awake and you're experts in the epidemiology and manifestations of the

disease, let's talk a little bit about the treatment. One of the things you realize is that I only have a few minutes to tell you about how to treat scleroderma-related ILD or systemic sclerosis ILD. And unfortunately, that time will be more than enough. And the reason is, we don't really have a tremendous toolset for the treatment of this condition. But I will finish with a few promising agents that might be very helpful in the near future. So first, a question: Your patient presents with new onset CREST syndrome manifesting as scleroderma distal to the elbow, sclerodactyly, telangiectasia, esophageal dysmotility, and anti-centromere antibodies, the risk for progressive ILD is? High, or low, or no risk? Okay? And the answer to that is really on this slide that says antibody status rather than the extent of scleroderma is most informative relative to the risk for ILD. So if you have patients with nuclear ANA or anti-TO antibodies or Slc-70, they have a higher risk of progressive of ILD, as opposed to the bottom where you have the anti-polymerase or the anti-centromere antibodies, which may have problems related to other organs, but less with ILD. Not that you cannot have it, but in essence, the extent of their skin disease, for example, may not be sufficient for you to judge where they're heading with interstitial lung disease. Now, we want to study pulmonary fibrosis and we want to treat it because we recognize that it pretends a worse outcome. So if you look on the left of your slide, the lower your FVC, the more extensive fibrosis on your CT scan, the worse your outcome, as you see on the bottom slide. And so people have been looking for targets for intervention. And in the area of scleroderma, we understand that there is inflammation, that there could be tissue injury, there is vascular damage to endothelium, there's immunity with activation of B and T cells, macrophages, and ultimately affecting the fibroblasts and promoting fibrosis. So, as you can imagine, there are a lot of chemokines and cytokines and other cells, and cells that are potential targets for intervention, but people have focused on the inflammatory immunity component of this process. And so here are some of the drug therapies that can be used; cyclophosphamide, mycophenylate mofetil or Cellcept, nintedanib, low-dose prednisone, and of course others have used azathioprine and rituximab as reasonable alternatives to the above. One of the points I want to highlight today that is not just about treating the interstitial lung disease; that there is much we can do with these patients. First of all, by having the correct diagnosis and avoiding procedures that are not important. Number two, are they hypoxemic or not? That will enhance survival for progressive fibrosing lung disorders. Do they need a prescriptive exercise program? Do they need to be part of a pulmonary rehabilitation program? Have they had their immunizations? Do we have the appropriate diet? Have we evaluated them for the appropriate comorbidities? Do they have sleep disorder breathing? Can they engage in behavioral changes to avoid reflux and microaspirations? All of those are equally important as the drugs that we start these patients on for their chronic lung disease. Now, many of you are familiar with the scleroderma study. It was a double-blind randomized placebo-controlled trial that treated patients with oral cyclophosphamide versus placebo. These patients had moderate restrictive lung disease, a DLCO that was over 30%, they have some inflammation by BAL, and they were given cyclophosphamide at 2 mg/kg per day versus placebo for one year, and followed for a second year. Only 13 centers were involved. And what you can see here is a comparison between the placebo on the blue line and cyclophosphamide, and there is some modest improvement on the adjusted at 15%. Now, notice that the Y-axis does not start at 0, so it's really like 4 to 3, maybe 5% which is statistically significant, but not always necessarily clinically significant, but this was sufficient for us to continue or start using cyclophosphamide more often in the care for these patients. But clearly with this slide, you realize much more needs to be done. Now these days, people like to use mycophenylate, and this comes from another study, also a double-blind randomized trial where they used oral cyclophosphamide versus Cellcept. So these patients were already on baseline therapy, and then were treated with cyclophosphamide or mycophenylate. And half and half almost were strategized or randomized to this therapy, and there was no difference. And what this data suggested, again, very similar change in FVC, but what this study suggested is that one or the other could have a similar effect. And since mycophenylate is a little better tolerated for these patients and has less consequences as long as you follow them appropriately, many people have moved on to use mycophenylate for the management of these patients. Now of course we talked about immunity. And you can't go without talking about the potential effect of autologous hematopoietic stem cell transplantation, which has been tested, and it seems to increase the mortality of these patients early on, but it may confer long-term benefit. It is modest. And of course, in these patients who don't do well who continue to progress despite your best management, they should be considered for lung transplantation. And today we know that the outcomes of those patients is no different than the outcomes of patients with other lung disorders after the procedure. But more recently, people have been more interested in the fibroblasts. Just like we've learned in idiopathic pulmonary fibrosis, that is more of a non-inflammatory process and more of a fibrogenic process, this idea of activation of fibroblasts trans – bio-fibroblasts transdifferentiation in excessive production of connective tissue matrices like collagen, people have targeted this. And one of the drugs that has been targeted is nintedanib. Now, I don't think you can see this, but you remember this SENSCIS trial published in New England Journal of Medicine just earlier this year where they looked at over 800 patients; 500+ were randomized to nintedanib versus placebo. Many of these patients were already on a therapy. In fact 48% were on Cellcept already, but they added on top of their therapy nintedanib as an antifibrotic agent. And what they found was very similar to the data that you might remember related to idiopathic pulmonary fibrosis when nintedanib was approved back in 2014 and 2015. And in the upper left panel up there, what you see is a bigger drop in adjusted FVC in the placebo group versus the experimental group, and of course the common decrease in FVC, as you see over time in a period of 52 weeks, but a slower decline with nintedanib. So nintedanib again does not improve the condition, does not make you feel better, does not reverse or cure the fibrosis; it slows down the decline, but much better than what we've seen without it. And that's important. Now one other important thing, as you remember from looking at this

paper is that many people are concerned about the adverse effects of nintedanib, and many of these adverse effects are usually gastrointestinal, but as you can see on this list, they were very similar in both groups. So I would not withhold this drug considering they may have worse side effects than not using it at all. That is not the case; at least by this trial. I'm going to leave you with this slide because I think this is a promising slide about what's going to happen in the future. I've talked to you about the potential targets for intervention, immune cells like microphytes and lymphocytes, the epithelium; we think about the epithelium as being chronically injured causing dysfunction and increased production of profibrotic agents like transforming growth factor beta that ultimately affects the fibroblasts. You have fibroblast transdifferentiation, excessive production of extracellular matrices, contraction, and scar tissue. Now every red thing that you see up there is just an example of some of the experimental drugs that are being trialed in different phase trials. Some of them are already in phase 3, some of them are just awaiting data collection. But it's important to know that we believe, or the panel believes, that in the next 5 to 10 years, there will be other agents that will be equally safe, and perhaps even more effective than what we have today. Thank you.

Dr. Swigris:
Thank you, Jesse, for that wonderful overview. And now, Dr. Padilla is going to talk to us about strategies for the longitudinal management of these patients.

Dr. Padilla:
Thank you, Jeff. Good morning, everyone. It's truly a pleasure to be here and discussing this very challenging problem. And we are grateful to Jeff, to Mehrnaz, and to Jesse for outlining the challenges that we face in taking care of a patient with scleroderma. This multiorgan disease indeed requires a village for us to treat these patients. The specialists that you have listed there are all impacting in the care of our patients. The longitudinal care of these patients requires that we look at things that are going to improve the survival that we have heard, and also to improve the quality of life of our patients, such as David, for the future. So we see here that the cause of death in systemic sclerosis has changed over the last decades. Most of it is because we have found some treatment for diseases such as renal involvement that no longer poses the threat that it did in the beginning of the study that you see conducted here. However, if you look at this, the lung involvement in systemic sclerosis is the cause of death in over 60% of our patients that will die. And mostly this represents the interstitial lung disease that we've been talking about in mostly pulmonary fibrosis, but also pulmonary arterial hypertension. So if we are looking at these two comorbidities, these are where we need to concentrate and try to make advances or at least screen our patients early enough so that we can implement some of the new therapies that are coming in the future, participate in clinical trials to improve this. Here we see the impact of these comorbidities or these manifestations in the survival in patients with scleroderma. If a patient has no pulmonary manifestations in the predominant manifestation of their disease or other organs, you see that they have a 10-year survival of about 84%. This drops significantly if you have interstitial lung disease, where that survival is about 58%. However, if they have pulmonary arterial hypertension, something that potentially treatable in this state, that is dramatically down to about 27% survival at the same age. So if we think of our patient who is 36, and this does not look like a good prospect if he develops any of these manifestations, about 20% of our patients with scleroderma will have a combined pulmonary fibrosis and pulmonary hypertension. And we have heard about the risk factors for ILD in systemic sclerosis worth repeating, and for us to keep these risk factors in mind so that we can screen our patients appropriately. And all patients should be screened in a systematic way so that we can potentially intervene early in the manifestations. How do we start the screening process in our patients? How do we follow them longitudinal? As pulmonologists, we depend on the pulmonary function studies to give us an insight into the disease. We know that the rate of loss of vital capacity is greatest in those first five years, so two to four years after we have made that diagnosis. The rate of loss continues over a period of time, but it's not as dramatic in the first one. So it becomes very important to investigate these patients in very short intervals in the initial period of their disease. We also know from pulmonary function studies that they are associated with decreased survival. So if you drop your forced vital capacity by greater than 10% over one year or you drop your diffusing capacity by greater than 15% at 24 months from your diagnosis, this marks our patient as to having a decreased survival. Pulmonary function also helps us to become more aware of the potential of other complications that we see, so that if we look at the ratio between the forced vital capacity and the diffusing capacity, particularly in those patients who don't have a lot of fibrotic disease, it may trigger you to start thinking of pulmonary hypertension and to investigate this patient in this fashion. Another tool that we have for evaluating patients for these – in these manifestations is the high-resolution CT scan. Every patient with inter – with scleroderma should have a CT scan because you can't depend on the vital capacity to be the guide as to when you have interstitial lung disease or not. So when we look at the CT scan, we look at the degree of involvement because that too is reflected in their PFT. So we can go from minimal involvement to very extensive involvement with more than 30 to 40% of our parenchyma is involved with the interstitial process. So if we combined the PFTs and the CT scan, we can stratify our patient into extensive disease, or limited disease. And we do that by looking at the extent of the CT scan involvement and, if it's greater than 20% and your forced vital capacity is less than 70%, by definition, you have extensive disease. And if it's less than that, then you have limited disease. And the importance of this is that this classification based on CT scan and forced vital capacity has been shown – has been demonstrated to have an impact on survival. So if you do have extensive disease,

you see here that the curves dramatically separate. This is a tool that we all have available; we have our PFTs and we have our CT scan because all these patients are presented in this way. So here we have another comorbidity that dramatically impacts our patients with systemic sclerosis, and we should be looking for this on every patient. And that is the manifestation of pulmonary hypertension. And you can see here that there are many factors or underlying pathogenic mechanisms by which patients with scleroderma develop pulmonary hypertension. We certainly heard that there is a vasculopathy. There is an inflammation of these vessels, and that leads to the development of systemic sclerosis. We see also that fibrosis can lead to the development of pulmonary hypertension, and the longer the fibrosis is there, the greater the risk of this patient eventually developing pulmonary hypertension. We heard also that this is a procoagulant disease and that there is in situ thromboses in a number of patients, and they under-recognize pulmonary venocclusive disease as also a factor of development of pulmonary hypertension. You can see here nicely outlined or suspected by the presence of thickening of the septal findings that you have there and also by the presence of what looks like curly beelines, the typical findings of pulmonary venocclusive disease. So if you have this type of CT scan, please think about this possibility because the management of that patient with pulmonary hypertension may be different than the usual one. These factors, including the presence of myocardial disease that can also lead to the development of a pulmonary hypertension in our patients that are perhaps the reasons why it is difficult to treat pulmonary hypertension in scleroderma. And that the outcomes in this treatment is not as robust as they are in the patients who have idiopathic pulmonary arterial hypertension. But it may also be because we detect pulmonary hypertension in our patients with scleroderma at a more advanced state. Usually they're in class 3 or 4 when we make a diagnosis. And obviously at that time, the potential interventions are not there. So how do we then follow these patients or suspect it? Certainly we have some factors that we know are associated with increased risk of developing pulmonary hypertension, and they are outlined here so that if you have a patient with that, then you, by all means, please send them for the echocardiogram. If you find some findings on your echocardiogram that make you suspect that indeed the patient has pulmonary hypertension, please proceed to your right heart cath. You should always do a right heart cath before instituting therapy in these patients because of the many factors that are important in making the diagnosis of pulmonary hypertension and assessing the degree of pulmonary hypertension and then intervening with the proper medication. I think that the right heart cath also helps you finding those other causes of pulmonary hypertension that come directly from the heart, from the dysfunction of the left ventricle. And those patients you are going to treat differently than you treat those that have the pulmonary hypertension alone. So – and it's important that, at the time of right heart cath, we do some challenges, and that we do hemodynamic monitoring in these patients. So how, in general, do we – what is the longitudinal assessment of these patients? So, for sure, a baseline evaluation should include the echocardiogram, the PFTs as we have discussed before, and also the CT scan for these patients. And it's important that longitudinally, we follow these patients early on at the onset of their disease with frequent PFTs every three to four months for the first three years or so. And then that we can spare – that we can space it out. And again, our CT scan, because it also helps us detecting some of the comorbidities such as lung cancer that these patients should have, then we follow them approximately every 12 months or so. And the 6-minute walk we use to guide some need for oxygen in these patients. So all of these things are done, and we see here that some of the important things in the longitudinal assessment of our patients are recapped here. And remember the phenotype that we're looking for in those patients who develop ILD, remember that fibrosis does matter, and that ILD and pulmonary arterial hypertension are truly a dismal comorbidity to manifestation of this disease. So the message is please screen and detect early, and intervene. Because I think that, as outlined before, the future of this disease may be improving and these comorbidities can go the way of the renal one where we are going to be seeing them lower. Thank you very much for your attention.

Dr. Swigris:
Thank you, Maria. Now we're going to have a discussion up here, just sort of an out-loud back-and-forth. To frame our discussion, let's talk about a case. So, consider a 70-year-old gentleman, former smoker, who presents with three years of exertional dyspnea and dry cough. He's noted blue-ing – what he describes as blue-ing of his fingers that began two years ago and has been intermittent ever since. Not terribly bothersome, just something that he noticed. His past medical history is significant for coronary artery disease, gastroesophageal reflux, and hyperlipidemia. He's a former 20-pack-year smoker, but he quit 10 years ago. He served in Vietnam, and was exposed to Agent Orange. His family history is noncontributory. There is a history of celiac disease in a sister. His primary care provider ordered a chest radiograph to evaluate his dyspnea. Chest radiograph was found to be abnormal, and he was referred to a pulmonologist. That pulmonologist performed pulmonary function studies and ordered a high-resolution CT scan. Pulmonary function studies revealed a forced vital capacity 68% of the predicted value, and a DLCO also 68% of the predicted value. The high-resolution CT scan showed clear evidence of a fibrosing interstitial pneumonia manifesting as a lower-zone predominant reticular abnormality with some ground-glass opacities, as well. No definitive honeycombing. Cardiac evaluation reasonable in a 70-year-old who presents with exertional dyspnea was negative. Because of the abnormal CT scan, he was referred for surgical lung biopsy. Here are slices of the CT scan, which show here in the lower zones peribronchovascular ground-glass opacities with fine reticular pattern. Traction bronchiectasis is fairly prominent as we go down through the bases. Of note on this slice, which shows his heart anteriorly and spine posteriorly, we see an air fluid level in the esophagus, which is a small clue to the possibility of esophageal dysmotility. And as we see at the extreme spaces, again fine reticular pattern, ground glass, traction bronchiectasis, subpleural sparing so a fine rim of normal-appearing lung

parenchyma between the visceral pleural and the opacities, and no definitive honeycombing. The surgical biopsy indeed showed a fibrosing interstitial pneumonia that the pathologist read as a pattern of usual interstitial pneumonia with fibroblastic foci and all the usual features, including microscopic honeycombing, but there were so-called NSIP-like areas scattered throughout. And that always raises a question about how to approach a patient with these pathological abnormalities. Because UIP was present, he was diagnosed with idiopathic pulmonary fibrosis. The pulmonologist at the outside believed there was no systemic autoimmune disease or significant exposure to account for the pulmonary fibrosis, so indeed the diagnosis of IPF was made, and he was started on an antifibrotic, pirfenidone. The patient then was referred to an interstitial lung disease center, where he was able to be evaluated in a multidisciplinary fashion by rheumatology and pulmonology. So the rheumatologist elicited a bit more history. This blue-ing of the fingers was actually slam-dunk consistent for Raynaud's phenomenon. The rheumatologist also identified some subtle exam findings, including an abnormal nail fold capillaroscopy and some subtle puffy fingers. When we think about the diagnostic criteria for systemic sclerosis, those three things gave him 8 points. And remember, a 9-point total gives us a diagnosis of systemic sclerosis, so 8 points there. He has interstitial lung disease, which is another 2 points. And then serological evaluation was performed, which had not been done at the outside; he had an elevated anti-RNA polymerase 3, an elevated ANA in a nucleolar pattern, and a negative anti-centromere antibody. And the rheumatologist and interstitial lung disease physician conferred together and came up with a clinical summary diagnosis of systemic sclerosis. So we're dealing with scleroderma-related interstitial lung disease. This slide shows pulmonary physiology over time. So before the surgical lung biopsy, recall FVC and DLCO were each 68% of the predicted value. After pirfenidone was put on, he actually continued to lose lung function with his FVC sliding down from 3.25 to 3.15 liters. After the correct diagnosis of systemic sclerosis was made, and scleroderma ILD was confirmed, pirfenidone was stopped and he was started on daily oral cyclophosphamide. And over the next six months, you can see that pulmonary physiology actually improves. So FVC climbed to 73% of the predicted value, and DLCO climbed up to 75% of the predicted value. Here are side-by-side comparisons of pre-cyclophosphamide images on the left and post-cyclophosphamide images from a similar slice on the right. And you can see there's dramatic improvement in the ground-glass and even the reticular opacities. There are areas of traction bronchiectasis, and there is definitely significant fibrosis remaining, but you can see pretty impressive improvements in the ground-glass and reticular opacities throughout the lower zones of the lungs. The question that I would pose to Jesse first, and I would like Maria to chime in, is: How should we think about therapy moving forward in a patient like this? Jesse, do you have thoughts? And there's no right answer to this, so –

Dr. Roman:
Sure, no. I have to agree that there is no right answer. I want to emphasize one thing, Jeff, and that is that it took this patient to go to his center that knows about this to get the right answer. And there is good data for IPF, for example; that the longer it takes for you to get to the right place, the higher your mortality. Because it's not about just the treatment; it's about getting the right diagnosis and preventing things that perhaps are not helpful. So in this case, I started getting worried about the use of cyclophosphamide after a year because of complications and so forth. So in this case, depending on how the PFTs are doing, and so forth, I would switch to mycophenylate and I would add nintedanib because of the data. So I'm tackling the immune response and I'm tackling the fibrotic response.

Dr. Swigris:
Maria, what do you think?

Dr. Padilla:
Jesse, that's wonderful. And again, no right answers. But I think that in a patient who is continuing to improve on immunotherapy, there is a rationale for continuing that before adding things. I think that you should wait until the patient stops responding to an antifibrotic agent when it's obvious that their fibrosis is the predominant manifestation of the disease and the predominant problem that needs to be attacked. So I would not add it immediately but would wait.

Dr. Roman:
Yeah, that's why I mentioned the concept of a year. Actually, how is the increase in changes in other complications from cyclophosphamide? Is that very much of an issue after a certain amount of time?

Dr. Fischbach:
So, in the old days, they were using oral cyclophosphamide for a very, very long time. And there was high risk of bladder cancer. Nowadays, we do I.V. cyclophosphamide, at least in my practice, and we do it six months is like the patient you saw, David, who has had chemotherapy. He had such a rapid disease, that we did eight months. We followed the urinalysis; no blood in the urine. And now – then we transition to Cellcept. So I think we cannot do cyclophosphamide indefinitely because if you do it, bladder cancer will come, and again that's a big comorbidity.

Dr. Padilla:
…also the bone marrow suppression.

Dr. Fischbach:
Absolutely. Bone marrow cancer, and other things if they're in the childbearing age with problems with infertility, so it's a very heavy-duty medication, but in David's case, we did it for eight months instead of six.

Dr. Swigris:
I do want to make sure we're just all on the same page. You know, there is no head-to-head trial of mycophenylate versus nintedanib, right? So it's expert opinion, it's shared decision-making, it's looking at your individual patient and the situation that he or she presents in terms of your therapeutic decision-making. But you're not going to find in the literature mycophenylate versus nintedanib, which one is better? Should they be added? Or should you use monotherapy? With respect to that, let's say we have a patient with very severe skin disease. Okay? And Jesse and Maria decide this patient also has ILD and they're going to put him on nintedanib. Mehrnaz, how should we think about the skin disease in a patient like that? So, severe skin disease, pretty severe ILD, goes on – is on nintedanib and comes in to see you?

Dr. Fischbach:
So, just back to the trial. So 48% of the patients that were on nintedanib, they were on mycophenylate mofetil as a baseline. So we don't know what is the synergic effect of this medication or one comes first. Perhaps decreasing inflammation can help the antifibrotic effect. But we, in rheumatoid arthritis, we treat ILD at times separate from joint because Cellcept is a good medication. It doesn't do much for the joints. We can't add rituximab to Cellcept, so we have to address the joints. If the joint problem is mild, we can do hydroxychloroquine. So I would say if Maria and Jesse want to do nintedanib, I may add Cellcept because that works good for the skin or IVIg or other medications.

Dr. Swigris:
So a key point there is, you know, this is input from the rheumatologist. So we as pulmonologists need to lean on the rheumatologists and remind ourselves this is a systemic disease; we need to be looking out for other organ involvement, lean on and involve our colleagues from other subspecialties to help us with the management. And as pulmonologists, we sometimes end up being sort of the primary care docs, right? Maria, can you speak to how you – when a patient comes in who is recently diagnosed, and they – let's say you start them on therapy for their ILD, what is the – when is the next visit? When is sort of the first visit after initiating therapy? When should that occur? And what kind of testing would you do in that patient?

Dr. Padilla:
It's a very good question. And I think that what's important is the monitoring of your patient very closely so that you can look for the potential toxicity of the medication that you have decided to start, so that that revisit should happen at a very short interval. And I would say that any place between one and two months after you have initiated therapy would be appropriate. The interval between visits can be then extended, but the frequency of lab monitoring to prevent the toxicity of the disease and to make sure that no other problem has arisen should be done at periodic intervals. Do not refill a prescription without having had seen your labs and everything else on these patients because these drugs that we are utilizing are indeed potentially toxic.

Dr. Swigris:
Jesse, maybe time for one more question. So, there once was a time when it seemed like no transplant center would think about transplanting a patient with scleroderma-related ILD. Now, it seems like some centers are opening up to that option. Do you have thoughts, Jesse? Or what would be a trigger for you to potentially send a patient to a transplant center?

Dr. Roman:
Well, in contrast to the previous days where we waited until the patient was ready for the transplant, it's nice to send these patients early so they can have a communication with the transplant doc and make a decision whether this is the right thing for them or if there are pre-starting conditions that will prevent them from having a transplant, and that is out of the question at some point. So early communication, early referral; not necessarily for listing, but for communication, is important to me. The second point I would make is that if they're slowly deteriorating despite your best efforts, and particularly when the is so low that they're starting – you're starting to be concerned for oxygen supplementation, that is certainly a key to consider this. The final point I want to make is that one of the biggest concerns about transplant in these patients is esophageal dysmotility, because reflux and microaspirations is a big deterrent for lung transplantation rejection, but big centers who do a lot of patients will actually handle that surgically, as well. Maria, what would you think?

Dr. Padilla:
I agree with you. I think that the survival of our patients with scleroderma after lung transplant is similar to that for other indications. So that the earlier that you have a patient communicate with a transplant center, the more the benefit accrues to the patient. They participate in pulmonary rehab so that they can remain as fit as possible during the waiting period. Some of them even get additional

therapies that may then extend the period before that transplant occurs. But the communication is critical. Let the transplant center say you're too early for us, okay? And come back in six months, come back in a year, but at least you don't send the patient when it's obvious to everyone that the patient is in dire need for a transplant, and other things can happen fast enough for that particular patient. So, I agree with you, Jesse.

Dr. Swigris:
Great. Thank you, panel. Now I'd like to summarize. Patients with – ultimately diagnosed with scleroderma ILD can present in various ways. Recall you might have patients who have definitive systemic sclerosis and then develop exertional dyspnea, and they're found to have interstitial lung disease. You might have a patient who has known interstitial lung disease who, on careful examination, or maybe after the development of features over time, are found to have systemic sclerosis. And then there are patients who might present with unexplained dyspnea and they're found to indeed have systemic sclerosis and interstitial lung disease. And those diagnoses are made concomitantly. Because of the challenges in making the diagnosis and in the longitudinal management, interdisciplinary evaluation is key; both in terms of making the correct diagnosis and following patients over time. There are now a handful of therapies that are available to these patients, and so with those choices comes several nuances. And we would urge you to get familiar with the data that the trials of these agents showed us, and manage expectations. Specifically, if you're talking about nintedanib, recall lung function did not improve in patients exposed to nintedanib. In contrast to cyclophosphamide and mycophenylate where FVC actually climbed in comparison with placebo. So nintedanib slowed disease progression. There are subtle differences in the cohorts of those trials, but know the data, be transparent with your patients so that you can, together, make the best decision about drug therapy. Don't forget other therapeutic maneuvers, including keeping these patient's vaccinations up to date. Look for the need for supplemental oxygen and prescribe it if indicated. And our opinion is that every patient with systemic sclerosis and related interstitial lung disease should enroll in pulmonary rehabilitation; that includes those with combination interstitial lung disease and pulmonary hypertension. The longitudinal evaluation like the diagnosis is interdisciplinary. Of course it's going to vary based on the manifestations and the risks for both interstitial lung disease and pulmonary hypertension. In general, patients with scleroderma-related ILD should be seen quarterly or thereabouts. And that evaluation should include a history, examination, spirometry, diffusing capacity, an assessment of their functional capacity – we use a 6-minute walk test, and an assessment of supplemental oxygen needs. And, in general, we would say these patients need high-resolution CT scans every 12 to 15 months or so. If not, only to look for the extent of lung fibrosis, to screen for lung cancer, which we know the incidence is elevated in these patients. I thank you very much for attending. We are happy to stay up here for 5 to 10 minutes and answer questions. If you have questions that you'd like to ask any of the panel members up here, feel free to come up. And we thank you very much for your attention and your attendance.