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### Key Takeaways from the IPF Experts at the Pulmonary Fibrosis Foundation's PFF Summit

Narrator Open:

Welcome to CME on ReachMD. This activity, Key Takeaways from the IPF Experts at the Pulmonary Fibrosis Foundation Summit, is developed by Global Academy for Medical Education, accredited by Postgraduate Institute for Medicine, and supported by educational grants from Boehringer Ingelheim and Genentech.

This activity focuses on data from some of the key presentations given at the recent PFF meeting in Nashville.

Before beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Your host is Dr. Ashira Johnson.

Dr. Johnson:

I'm Dr. Shira Johnson. Today we are at the Pulmonary Fibrosis Foundation Summit in Nashville, Tennessee. We will be discussing the cytology, treatment and other important aspects of idiopathic pulmonary fibrosis.

Dr. Johnson:

Joining me now is Christine Garcia, Professor of Internal Medicine and a member of the Division of Pulmonary and Critical Care Medicine at the University of Texas Southwestern Medical Center. Welcome, Dr. Garcia. Thank you for joining us.

Dr. Garcia:

It's a pleasure.

Dr. Johnson:

Dr. Garcia, you have a special interest in some of the genetic aspects of interstitial lung diseases, including IPF. If a patient comes to you with a strong family history of pulmonary fibrosis, do you then recommend genetic testing?

Dr. Garcia:

Sure, I think that's a great question, and I think the answer lies in to how strong is that family history as well as what are the specifics about their family history and their personal diagnosis? Let me give you an example.

Dr. Johnson:

Please.

Dr. Garcia:

For a person who comes to me and they're in their 80s, they may say, "Oh, I have one other family member that I know of who had pulmonary fibrosis," and we'd go through the full description of how many individuals in the family, the medical history of parents, siblings, children, grandparents, aunts and uncles. And then I start asking at what age were people diagnosed with pulmonary fibrosis, and if this person in their 80s says, "Someone else in my family was diagnosed also in their 80s," then I would not pursue any genetic

workup, because we know pulmonary fibrosis, specifically IPF, has an increased incidence with age. We also know that there's an environmental risk, so perhaps that person and the other person were in the same home environment where they were all smokers or exposed to certain risk factors. So, if there's a few number of individuals or late-onset disease, I would not recommend genetic testing. Contrast that with some of the individuals who come and see me and they walk in and they say, "I know of 6 other family members who have died of this disease," and all of them were diagnosed, say, in their 50s or 40s, etc., for that group and that patient, in particular, I would suggest, "Well, let's find out what's going on here," and we would pursue a genetic workup.

Dr. Johnson:

Is there any other testing needed besides this genetic test at that time?

Dr. Garcia:

Sure. Well, it depends. If we send off the testing for genetics and it comes back with variants and a certain gene—for example, in the telomerase gene—then the next question would be: Have other people with pulmonary fibrosis been found to have this exact variant? For example, we know the arginine-865 histidine variant is one particular variant. It's now been described in multiple families across multiple continents—Canada, the United States and Brazil—and so, for that variant I would say, yes, the data is very strong that that variant is linked to this disease. It's also been linked to short telomere lengths. It's also been linked with a decrease in the protein activity of telomerase in cell studies, and so it depends on what the genetic results show. But if the results come back with an iffy result, a variant of unknown significance, then additional testing may be necessary to determine if that variant actually plays a role in the disease.

Dr. Johnson:

You also mentioned in your talk that there is evidence of worse outcomes for patients who have short telomere lengths. How does this impact your conversation with patients in the clinic?

Dr. Garcia:

So, at this point the testing that we do for telomere length and the testing that we showed, what I showed in the talk as well as our manuscripts, all of those fall under the umbrella of research testing, not CLIA-certified testing. So, actually, those results really don't have much impact on what we share with the patient.

Dr. Johnson:

So, how does the knowledge of genetic information influence your discussions with patients about their individual medical care?

Dr. Garcia:

That's a great question. So, basically, we follow the paradigm of clinical care that's outlined according to the American Thoracic Society, the ERS, and we go by specific clinical diagnoses. For those with a diagnosis of IPF that also has one of these telomere mutations, it's easy. We follow guidelines, and we present them with the options of starting FDA-approved antifibrotic medications. Pretty much, that's most of the patients that we see.

There are a couple of subsets that I just want to highlight, though. For example, there may be someone who comes to us with a family history of pulmonary fibrosis and we discover one of these mutations. Another family member may come with the similar symptoms, as it often happens that they'll be the first case or the proband, and then as he tells his family members or she tells her family members, siblings, cousins, etc. say, "Oh, I've been short of breath for a number of months or years," and they come for testing as well. If we discover one of these rare mutations and we know that it's likely to be pathogenic, which means it probably causes the disease, if we find that all the individuals in the family with pulmonary fibrosis share the same one, then, at this point, my personal recommendation is that we do not need to pursue surgical lung biopsies given the risks of that, and we try to get them on the FDA-approved antifibrotic medications.

Dr. Johnson:

What would you say are the most important takeaway messages from your talk today?

Dr. Garcia:

Well, I would say that the number one takeaway message is that over the last 10 years we've made just tremendous strides in understanding the genetics of this disorder. It's really opened up our eyes in terms of the driving mechanistic pathways for certain patients. And I think the excitement is now we need to focus on these different subsets of patients and figure out what are the best therapies for them. What can we do to improve their life, the quality of life and the length of life? We do this research really to help the next generation, the next 10, 20, 30 years. We don't know where it's going to lead.

I would also add that patients sometimes come to me and they are so worried, especially family members, of their potential risk for this devastating disease, and I remind everyone that there is so much for us to still understand about the genetics. For example, for pathogenic variants and the most common gene, the TERT gene, we know that approximately 50% of people will end up with pulmonary fibrosis. I know that's a devastating statistic, but the flipside is that 50% will not end up with pulmonary fibrosis. And what we need to

know as scientists and clinicians is what determines that additional risk, because if we could figure that out, we could protect people from developing pulmonary fibrosis. We know that environmental effects definitely affect the risk, and so when I do these family draws where I go in people's homes and we draw everyone in the family, I tell everyone, "We don't know the genetic risk. That's why you're on our top list to study. But I can tell every teenager here you cannot smoke because you have a family history of pulmonary fibrosis. You have to protect your lungs. You have to be careful what you're exposed to."

Dr. Johnson:

Thank you for being with us today. I appreciate your time.

Dr. Garcia:

Thank you.

Dr. Johnson:

I'm joined now by Dr. Victor Thannickal, Professor of Medicine and the Ben Vaughan Branscomb Chair of Medicine in Respiratory Disease at the University of Alabama at Birmingham. Doctor, thank you for being with us today.

Dr. Thannickal:

Thank you.

Dr. Johnson:

Can you tell us whether IPF is actually a disease of aging, and if so, why?

Dr. Thannickal:

Yes, I think there is a greater appreciation that IPF is, in fact, a disease of aging, as you said. The diagnosis of IPF is made in the mid 60s, and it's rare for a patient to be diagnosed with IPF before the age of 40. And there is, in fact, an exponential increase in both the incidence and prevalence of IPF with each decile of age.

Dr. Johnson:

What does the latest research tell us about how the aging process itself causes or contributes to this disease?

Dr. Thannickal:

So, aging is a very complex phenotype. As you know, aging increases the susceptibility to a number of diseases of the lung and other organ systems, Alzheimer's, kidney disease, heart disease, and IPF as well as an entity known as senile emphysema seems to be more common in the elderly population. So IPF, in particular, has certain features of aging and what we like to think of as geroscience, which is the biology of aging and how it informs disease processes that are operating in age-related diseases, and there are a number of these so-called aging phenotypes or hallmarks that we are now trying to target for therapy.

Dr. Johnson:

Is there anything that individuals can do to alter the aging process, or offset its effects to minimize the risk for IPF, and if not, also change the natural course of the disease by doing so?

Dr. Thannickal:

So, there is active research being conducted by the National Institute on Aging to look at interventions that may prolong not only lifespan but, more importantly, health span so that individuals can live longer and healthier lives. So, the number of diseases of aging that we have to deal with this aging population is also going to be a challenge for healthcare workers and also has some very profound socioeconomic impact. Until we get interventions that improve lifespan, I think looking into interventions in specific age-related diseases that have these so-called aging hallmarks may be the best way to combat those diseases of aging.

Dr. Johnson:

Does the emerging data about the role of aging help us in developing new treatments that might be more effective for IPF?

Dr. Thannickal:

So, that's what my laboratory and several others around the world are looking at. We are specifically interested in a class of drugs known as senolytics, so we know that with aging there's accumulation of senescent cells in various tissues. That's been demonstrated again in diseases such as Alzheimer's, and also in IPF. So, the idea is that these senescent cells acquire an apoptosis-resistant phenotype, and they also secrete a number of mediators that are cytotoxic and that impair the regenerative capacity of other cells within tissues, so the idea is to get rid of these senescent cells with drugs that can kill these, selectively kill, the senescent cells. And we have to do more work to determine what the best senolytics are and what is safe to use. I don't think we understand quite yet whether, in fact, this is a safe strategy, because there are arguments that senescent cells may actually have beneficial roles in different processes such as wound healing, and it's a tumor suppressor mechanism, but I think if you can target senescent cells and prevent the SASP cytokines

and mediators causing injury to the surrounding tissues, that could be beneficial long-term.

Dr. Johnson:

Can you tell us a little more about the role of senolytics in IPF?

Dr. Thannickal:

Yes, so there are some recent data from our laboratory and other groups that have shown that there is an accumulation of senescent cells within the IPF lung, and these senescent cells may be detrimental to the tissue regenerative response to injury and even in the homeostasis of tissues such as the lung, so I think the idea is to get rid of these senescent cells through these drugs that could act as senolytic compounds and with the understanding that these cells do accumulate in the lung, and specifically in IPF getting rid of these so-called bad cells that are senescent could be beneficial to the lung's regenerative capacity.

Dr. Johnson:

Thank you very much for being our guest today.

Dr. Thannickal:

Thank you.

Dr. Johnson:

I'm speaking with Sonye Danoff, Associate Professor in the Division of Pulmonary and Critical Care Medicine and Co-director of the Hopkins Interstitial Lung Disease Clinic at Johns Hopkins School of Medicine in Baltimore. Thank you for joining me.

Dr. Danoff:

It's my pleasure.

Dr. Johnson:

Dr. Danoff, the approach to treating IPF has changed dramatically in the recent months because of the approval of two new drugs. What are the issues that make clinical trials for IPF treatment particularly challenging?

Dr. Danoff:

When one establishes a clinical trial, it's important to think about which patients are actually being selected for the trial because the results of the trial may actually be affected by whether a patient's natural history would have been to be stable or whether it would have been to progress.

The other issues that come up are how we actually determine whether a drug is effective in a clinical trial, and this is based on the choice of endpoints. So, in the clinical trials that I discussed today, the endpoint was actually a change in pulmonary function, specifically a change in forced vital capacity. Now, while that is something that's easy to measure, it's not something which has real clinical meaning to most of our patients. So, as we look at clinical trials, we have to balance whether the endpoint is relevant to the patients who we're caring for.

Dr. Johnson:

So, in your view, how is the management of IPF changing now that there are new therapies available?

Dr. Danoff:

In terms of therapy, the presence of nintedanib and pirfenidone obviously has been a rather significant change in the landscape. Over the 25 years before the approval of nintedanib and pirfenidone, there were many clinical trials, and we had reached a point where there had been many negative clinical trials, which I think had created a level of nihilism. The really robust trials that were done with nintedanib and pirfenidone showed firstly that you could carry out a very effective clinical trial with very good patient enrollment, large patient enrollment, and both of the studies really had very similar results, that being the reduction in the rate of decline of lung function. Now, clearly, that is very different from curing a disease or making a patient better, but I think that as a first step towards treating our patients and improving quality of life and length of life, this is an important first step.

Dr. Johnson:

Now, I also understand that there are some adverse side effects that occur with these drugs. How do you manage this in your clinical practice?

Dr. Danoff:

We know that the benefits of pirfenidone and nintedanib are relatively modest with reductions in the rates of decline of lung function. So, for nintedanib, the most common side effect is actually diarrhea, which in clinical trial occurred in up to 65% of patients. This obviously is a very important side effect, and there has been a lot of effort towards providing patients with education about the potential for the side

effect, strategies for minimizing the side effect, therapeutics for reducing the side effect, and so that they can continue on therapy in a way that allows them to be safe and comfortable. The major side effect that's associated with pirfenidone are two-fold. The first are upper GI symptoms, such as nausea and/or loss of appetite, and this is often associated with weight loss. The second is a sun-related rash, which can be problematic for people who spend a lot of time out in the sun. And again, really there has been a very concerted effort to identify strategies to minimize these side effects and to help patients think about how to avoid the development of side effects like the sun-related rash.

I think that for every patient it needs to be an individual conversation, because firstly, the decision to take a therapeutic agent is one that balances risk and benefit. Some patients may prefer not to accept the risks related to taking a specific therapeutic, if it doesn't seem appropriate to their goals and their stage of disease. For patients who do decide that they want to take a therapeutic agent, we talk about the side effects and about how that might influence their life, the life that they have chosen for themselves. So, I think I mentioned that for patients who spend a lot of time out in the sun—I'm from the Mid-Atlantic where people sail a lot—when people are out on the water sailing a lot, it's very difficult to manage the sun protection just because of the intensity of sunlight in that area. Similarly, people who spend a lot of time in areas where there is a lot of bright sunshine—people who live in Florida or the Southwest—it may be more difficult for them to manage the side effects related to the sun sensitivity. They really would not be able to tolerate the risk of developing diarrhea. And so we have these discussions. We talk about the fact that side effects can be managed. And for each patient, again, the approach to minimizing side effects is very individualized, so for some people it may simply be adjusting what they're eating before they take their medication or the timing of their medication, or it may be altering another medication. Perhaps a patient has previously had issues with constipation and has been on a stool softener and we just simply need to stop that medication in order to normalize the bowel movements. So, for each of these there is a very important connection between the patients and the providers, and I think that it needs to be an ongoing conversation because side effects can develop over time and the management needs may change over time.

Dr. Johnson:

So, now that these drugs are approved by the FDA and, of course, you're using them in your clinical practice, can you comment at all on what you are seeing in terms of changes of the FVC, improvement on lifestyle, things that make you feel like we are on the right track and this is certainly improving the quality of life for these patients?

Dr. Danoff:

These medications have been available for a little over 2 years, and so most patients have only been on medication for a relatively short period of time unless they started on medication as a part of a clinical trial. I think that what we found is that the presence of medications has created a greater sense of hope for our patients, because at one stage we could help them with nonpharmacological therapy, things like pulmonary rehab, oxygen therapy, making sure other comorbidities were treated, which we continue to do now, but this provides another opportunity for the patients. I think it's a bit early to really have a strong sense of these being disease-changing therapies. I think that these are a really important first step and that because we have shown that such clinical trials are possible, feasible, that there is strong patient and provider participation, I think it's going to lead to more clinical trials, and I think that that is already obvious, because there are many, many other new therapies that are in trial currently, so I have a great hope for our patients moving forward that there will be even more personalized, individualized therapies available for our patients.

Dr. Johnson:

Thank you very much for the work you've done in this area and also for being a part of education for ReachMD today.

Dr. Danoff:

Well, thank you for inviting me.

Dr. Johnson:

For our last conversation, I'm joined by Dr. Gregory Cosgrove, Chief Medical Officer of the Pulmonary Fibrosis Foundation in Chicago and Associate Professor of Medicine at National Jewish Health at the University of Colorado in Denver. Dr. Cosgrove, it's a pleasure to speak to you today.

Dr. Cosgrove:

Thank you for having me.

Dr. Johnson:

So, we've been talking with some of your colleagues, and we've learned a lot about the approved therapies for IPF that came out recently. What could you tell us about other drugs currently in the pipeline?

Dr. Cosgrove:

Well, what we've learned over the past 10 to 15 years is that the fibrotic process, whether it be in the lung or elsewhere, is complex. We

understand that because now we're starting to dissect the different pathways that may be involved in the fibroproliferative process, so that complexity leads to incredible opportunities, because there are, perhaps, many different areas in which we can intervene and target to hopefully decrease the fibroproliferative process as occurs with the two approved therapies, or in combination or in isolation, perhaps other pathways may significantly alter the process. Ultimately, the hope is to identify a cure, whether that's a single agent or perhaps multiple agents working together to interrupt several different pathways. That really is the exciting aspect of drug development in pulmonary fibrosis right now. It is important to move as quickly as we can for the obvious reasons with the serious toll that the disease takes on patients, but overall, the incredible interest after the identification of the first two approved therapies has led to an onslaught of several other companies that are interested and have really been committed to the field.

Dr. Johnson:

So, where do you see this going in the future, say the next 3 to 5 years?

Dr. Cosgrove:

I can tell you where I'd like to see it go.

Dr. Johnson:

Tell us.

Dr. Cosgrove:

Which is integrating all the aspects of the community, meaning the excellent science done through the National Institutes of Health and many prominent institutions throughout the country, coordinating that with the Pulmonary Fibrosis Foundation as well as the patient community, BioPharma, and so that it's an organized approach to identify the best, safest, and most efficient ways to identify therapies for patients. And the ultimate goal would be to identify a cure, but if we can further decrease the progression of the disease and also identify ways in which we can assist in the symptoms that plague many patients, such as cough, breathlessness and fatigue, they are all unique and important targets.

Integrating the science is really the next phase more directly into development, and that would be through the genetics and genomics initiatives where perhaps we can directly target specific pathways perhaps using the genetic code to tell us would a patient be more likely than not to respond to a specific therapy, or just as importantly, which therapies might they be more predisposed to have side effects which might obviate the potential benefits of drug. that is a more complicated approach because you have to integrate the basic science into the clinical sciences and research science, but it may lead to a much more efficient way in which we can treat patients and hopefully identify therapies that are clinically "targeted" for your specific problem. Even though the whole group might represent fibrosis, there are likely subgroups that respond differently, and perhaps, more advantageously for patients. So, that would be the hope that over the next several years the tremendous groundwork that's been done with human genome project and now specifically utilizing resources where there are cohorts of patients with pulmonary fibrosis, much like the registry where we are collecting those data, the clinical data as well as the ability to sequence their DNA and collaborate with others to use that effectively to help patients is really the next few years and the steps forward in my opinion.

Dr. Johnson:

So, what would you say is the most important takeaway messages from your talk today, thinking both of the patient population and the researchers that are here?

Dr. Cosgrove:

I think it's probably my last slide where I emphasized the importance of collaboration, and it really needs to be a group effort, that we all have the same mission to help patients live longer and better lives with pulmonary fibrosis, and we need to capitalize on the assets of each major stakeholder, whether they are a patient, a researcher, a clinician, BioPharma, the NIH, so that it's a coordinated effort, and in doing so I think we can decrease the delay in diagnosis, increase the likelihood of identifying more important therapies moving forward.

Dr. Johnson:

Would you like to comment on any work that's been done or what you see for the future in terms of prevention of this disease or prevention of progression of the disease?

Prevention is a very important aspect of the disease, and it's been difficult because patients often have symptoms for 2 or 3 years before they are diagnosed, and so awareness is the first step, perhaps, to better make physicians and patients aware that this is a possibility. So, it's typically in individuals that are older; average age of onset is mid 60s. Often times there is an association with smoking. But we are learning a lot more about the environmental impact on your lungs, and so, that is part of our awareness campaign.

More recently, with the advent of the genetic consortia that are identifying perhaps at-risk genes that predispose patients and/or families, that may lead to an opportunity for us to tailor based on a genetic predisposition to identify, monitor patients much the same it's



done with other screening, say breast cancer screening or at-risk families that have additional risk factors that might predispose them in the future. And we can obviate those risks, probably not decrease them to zero, but we can decrease it so that the likelihood of progression, as you mentioned, might be minimized. That's really the hope. I don't think we are quite to the level of understanding as to the impacts of genetics right now, but through coordinated efforts perhaps with the patient registry where the generous donation of data where patients can volunteer and then we can follow them longitudinally, those data and their participation are what will allow us to better understand the risk factors and then counsel patients in the future with more confidence as to better pathways for prevention and/or risk reduction for progression of their disease.

Dr. Johnson:

Could you tell us a little more about the registry and how that enters into the work that you're doing?

Dr. Cosgrove:

The Care Center Network and Patient Registry is kind of the centerpiece of our scientific investment right now. It's a major undertaking with 40 centers across the United States in which patients can volunteer to donate their clinical information, meaning how the disease affects them, their symptoms, the way in which they are diagnosed, as well as the CAT scan imaging that's been performed as part of their diagnostic evaluation, and lastly, a biorepository where they donate blood, and in doing that it's a collection of information which to this point has not been done as longitudinally in the past. It was a one-shot observation in most studies, which is fabulous information, but longitudinally, if we follow patients over years and we continue to accumulate those data, we get a better understanding as to how the disease is impacting them, the course of the disease over time. And integrating that now with the genetics if they do donate their blood, we can understand if there are minor abnormalities in their genetic code that might predispose them or predict they have a slower course or a more rapid course, so that can feed back into our initiative of educating patients and perhaps providing tailored care for them. Unless we have that cohort of individuals and continue to expand the registry, we won't have a sufficient number of patients to make strong recommendations to help physicians care for those patients, help the scientists better understand the basic mechanisms of what is causing the fibrosis, and lastly, the ability to perhaps perform clinical trials where we can intervene and effectively evaluate therapies to treat pulmonary fibrosis in the future.

Dr. Johnson:

Thank you very much for being with us today.

Dr. Cosgrove:

Thank you. I appreciate the opportunity.

Dr. Johnson:

I want to thank our faculty for helping us better understand the emerging science of idiopathic pulmonary fibrosis, the new approaches to its treatment and what the future might hold for clinicians and their patients.

For ReachMD, I am your host, Dr. Shira Johnson, at the Pulmonary Fibrosis Foundation Summit. Thank you for joining us.

Narrator Close:

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