Talking Sleep Season 4

Episode 6

March 25, 2022

Phenotyping in Obstructive Sleep Apnea

Dr. Allan Pack, guest

Episode Transcript

DR. KHOSLA: Thank you for joining us for Talking Sleep, a podcast of the American Academy of Sleep Medicine. I'm your host, Dr. Seema Khosla, medical director of the North Dakota Center for Sleep in Fargo.

Today, we're exploring some of the science behind obstructive sleep apnea with researcher and clinician Dr. Allan Pack.

DR. PACK is editor-in-chief of the journal SLEEP and the John Miclot professor of medicine at the University of Pennsylvania. He was the founding director of the Center for Sleep and Circadian Neurobiology and the Division of Sleep Medicine at Penn. Dr. Pack's research focuses on the genetics of sleep and sleep disorders. Thanks for joining us today, Dr. Pack.

DR. PACK: Well, thank you for inviting me.

DR. KHOSLA: So we want to talk today about your research into OSA phenotyping and how it may help us to provide more personalized treatment for our patients. So what exactly is OSA phenotyping?

DR. PACK: Yeah, I think the concept that we need to get across is the whole idea that sleep apnea is a very heterogenous disorder. And if you think about it that way, not every patient's identical, there's different symptoms, different consequences and so on. And the idea is that you need to understand the heterogeneity, that people are different, and you need to understand it in multiple dimensions. As I mentioned, the symptom dimension, people have different symptoms.

People have different clinical presentations. People have different risk factors for the disease and people have different consequences, and that can be assessed in terms of different physiology, different molecular changes and so on. So the whole idea is that it's heterogeneous and you're going to try to understand the heterogeneity of the endo/phenotypes, but you're going to try to understand it in multiple dimensions.

DR. KHOSLA: So how exactly do we accomplish this? I mean, how do you phenotype a patient?

DR. PACK: Well, what you need to do is you need to start with how are they different, right, and then what is the relevance of these differences? And people have looked at that in different ways, right? So you need to assemble a very large group of people, patients with a lot of information, and then typically you don't assume that you know what the differences are. You let the data speak for itself. And what you do is things like cluster analysis. And you say, are there different subgroups here? And what cluster analysis identifies is people who, they're quite close together, but they're very different from the next group. And so you're trying to minimize the differences within a cluster and maximize the differences between clusters. Now, you can do that with physiological measures. You can do that with symptoms. You can do that with molecular measures. And then once you establish these differences and the relevance then you can translate the findings you have and translate them into the clinic so that you say, I'm giving you a tool to work out which particular subtype of sleep apnea you're working on. So is the research is broad trying to identify subtypes. Once you identify the subtypes and you come up with measures of them, then you want to translate that into the clinic.

DR. KHOSLA: Oh, so outline for me what are the major OSA phenotypes?

DR. PACK: Well, so people would look at it in different ways, ok. So the thing that we've we basically focused on a lot is symptom subtypes. And we started out with probably in 2014, we had developed what's called the Icelandic Sleep Apnea Cohort in Iceland with our good friend Thorarinn Gislason who had about 900 people, something like that, where we have very extensive questionnaires and then when we did the cluster analysis, what we did is we found

there were three distinct subtypes. And the subtypes were people whose major complaint was disturbed sleep with normal Epworth scores, a group of people who were minimally symptomatic, they woke up feeling refreshed, they weren't sleepy even though they had, you know, significant sleep apnea. And then there was a group of people who were excessively sleepy. Now the excessively sleepy group had a very high Epworth, 15.6. It was in the narcolepsy range. They fell asleep, driving and so on. That's what you think of with sleep apnea, an excessively sleepy person. That was only 44% of the total. And you see three very distinct subtypes, and then the question is why? Why is that? How do they benefit from treatment? Do they benefit differentially? And as a relevance of these so-called subtypes, symptomatic subtypes in terms of other consequences?

The first thing we did is we found these three subtypes, and I should point out, it wasn't explained by severity of disease. They had severe sleep apnea. Their AHIs were identical in the three different subtypes, almost identical. It wasn't explained by severity, they were all in the 33 to 34 range. And so it wasn't explained by severity, and it wasn't explained by sleep apnea. It was something that responded differently to the same challenge or the same disease. And you responded from a symptomatic point of view in a different way. And then you know, the question then is, okay, you find them in Iceland is, can you replicate that? And that's very important so that you end up showing that, you know, this is pretty reliable, if I could do it in other areas.

It's now been replicated by us both in a large clinical cohort that we collected internationally. It was replicated by us and a Korean genomic cohort, a population cohort. It was replicated by us in the Sleep Heart Health Study. The Canadian National Biobank replicated it, that was independent of us. It was replicated in a Hispanic study in the U.S. It was replicated in a clinical cohort in Chile and a clinical cohort in France.

Now, having said, they replicated, the optimal number of clusters varied. The Iceland thing was three distinct clusters. At some places we found four. At some places we found five. For example, the Sleep Heart Health Study we're found the same basic three as Iceland, but we found

another group that had moderate sleepiness. And so the same three basic ones were always there and we're developing a tool that we can give clinicians that they can then assign people into one of these three distinct subtypes. So it's been pretty well replicated and it's pretty clear that you have these distinct, these distinct symptomatic subtypes.

Now, the idea that people could have sleep apnea and not be sleepy is not new, right? In fact, in the original Terry Young classic paper, the Wisconsin Sleep Cohort paper published in New England Journal in 1993, she distinguished between what she calls sleep apnea, you know AHI over 15 wherever it was and what she called sleep apnea syndrome where you had the AHI and you were sleepy. So that was recognized very early on in our field that there were people out there in the population you could find who had sleep-disorder breathing, but they weren't symptomatic. The fact that you can present with insomnia that's also been recognized…talk of a co-morbid insomnia with sleep apnea. So the symptom cluster idea basically gives a framework that you can assign people into these different classes and you can think about it.

Now, if you look at treatment benefit from the point of view of symptoms, it's not surprising that the minimally symptomatic group don't benefit that much is still significant. Their Epworth is normal, it’s like seven. They have a slight reduction, a significant reduction, but the changes are very small, whereas in the excessively sleepy group on CPAP, they go from 15.6 to 10 or something like that and they got a high reduction in Epworth. And so the symptomatic benefit varies between the groups.

The other thing that we did is we asked the question is there other differences between these people and these different symptom subtypes? And we look to the Sleep Heart Health Study, whereas you know, your cardiovascular outcome data, and what we were able to show and that was it was excessively sleepy group that had the cardiovascular risk. There was no increased cardiovascular risk in the insomnia group or in the minimally symptomatic group. It was only in the excessively sleepy group. And that's very important because the excessively sleepy people were excluded, as you know, from the recent large, randomized trials.

DR. KHOSLA: Well, that's exactly it, right? The AHRQ report, you know, they looked at the trials that excluded sleepy people.

DR. PACK: Right. Oh, no, absolutely. And you know, and, you know, and it's hotly debated about A, you know, was that appropriate? And, B, you know, how do you deal with it? So the data we have in the Sleep Heart Health study said it was only the excessively sleepy people that had the increased cardiovascular risk. Now, again, we're not the first group of people ever to say that. You know, this previous paper by Kapur, who showed that in the Sleep Health Heart Study, the association between sleep disordered-breathing and hypertension was only found in sleepy people. It wasn't present in non-sleepy. That's one thing. Virend Somers did a study where people, he'd study them, he did sleep studies one months after they'd had an MI, and then he followed them over time. Almost all were not treated. And what he found was that there was a difference in reinfarction rates in the people who were excessively sleepy compared to those who weren't. So the same idea is there. So it's out there in other areas. The fact that the excessively sleepy subtype is an increased risk for cardiovascular events was replicated in the Chilean study, the Labarca and Gonzalo study that was published recently in CHEST. It was not replicated in the French study that came out in the Blue Journal. They did not find that in the excessively sleepy. But, you know, as they acknowledge and we wrote a letter, I mean, it's a very challenging in clinical cohorts because, you know, there's referral bias. I mean, minimally symptomatic people who people thought had a cardiovascular risk, they snored, they got a sleep study. So, so, so, you know, so, so I don't think it excludes that. And I think the majority of the evidence, both in our own work and in our previous work, is excessive sleepiness is like a symptomatic biomarker, if you like, for cardiovascular the risk.

The reason they were excluded in these clinical trials is a couple of things. So the first thing is they took the view it was unethical. IRBs take the view as unethical, some IRBs, to randomize people into no treatment for three years who are excessively sleepy. You have an increased risk of car crashes and so on. Some people like Sanjay Patel have argued it's not unethical. You can do that. Even if it's ethical, the question is, is it feasible? I mean, if you talk to a patient who's very symptomatic and you say look, I'd like you to go into this clinical trial, you may not get

treated for 3 years, are you going to agree? And so so many patients are not going to agree or the physicians are not going to agree. So it's not a question just of ethics. It's a question of feasibility. And and the APPLES study, which was six months…remember to do cardiovascular outcomes, you're probably talking three, five years…the APPLES study was six months. And they could not get people recruited into no treatment in the APPLES study from sleep practices, it just didn't happen. And they had to recruit people from the population. And what happened was you know, 78% of the people in the APPLES study were recruited from advertisements in the general population.

DR. KHOSLA: Oh, wow. That's high.

DR. PACK: Right? No, I mean, that's the only way that you got it done. And the problem with that is what we know, not surprisingly, is that these subtypes exist in clinical cohorts. They exist and in population cohorts. But the prevalence of the minimally symptomatic group is higher in population-based cohorts. So you can recruit people like that. They snore. There may be witnessed apneas, they're symptomatic, they're willing to go into these clinical trials and that's the issue. So so so basically what happened is the SAVE study excluded people who had Epworths over 15 but even though you could go in if you had an Epworth of 12 or something that the average Epworth score in the SAVE study I think was seven and a half or something like that. The Spanish study with the myocardial infarctions excluded people with Epworths over ten, as did the Kaiser study.

So all of these studies excluded excessively sleepy people and in fact we just published a paper just came out in SLEEP with our colleagues in Western Australia where we looked at consecutive patients in the so-called Western Australia Sleep Health Cohort with Bhajan Singh and Nigel McArdle, and they recruited every patient for a period of years into this cohort and we could look at that cohort and we could say what percentage of patients they had in that cohort would have qualified for these these large randomized trials. And the answer was somewhere around 5 or 10%. So, so most of the patients the patients that were in these trials are not the patients that we see clinically. And it's very important to realize that. These trials do not prove

that sleep apnea does not benefit cardiovascular disease. What it proves is, is that if you take people who minimally symptomatic and you randomized into CPAP, and as a result they're very low CPAP adherence, I mean, adherence in these trials is terrible and people who are only partially or asymptomatic don't benefit. That's why these trials, that's the question these trials answer. They do not answer the question as to whether the patients we see clinically who are excessively sleepy are going to benefit from CPAP in terms of cardiovascular risk. The answer to that is unknown.

DR. KHOSLA: So then can phenotypes change over time?

DR. PACK: Well, that's a great question. We don't know that. And that's a weakness of the thing. I mean, we can certainly look at that in the Sleep Heart Health Study because most of them were not treated. And that's something we are planning to do to look and see if you're a, an asymptomatic person now and you're back in ten years are you still an asymptomatic person. We don't know the answer to that but that's very that as a very important question. And it's something we need that we need to determine. Actually, we've shown we can replicate it. And certainly we've shown the differential benefit in treatment, which, you know, and we talked about the cardiovascular risk, but whether the symptoms subtypes can vary over time, it’s still an open question.

DR. KHOSLA: So let's take a short break. And when we come back, we'll talk about how phenotyping can help us provide personalized treatment. You're listening to Talking Sleep from the American Academy of Sleep Medicine.

AD BREAK: It's time to go “back to sleep” at SLEEP 2022. The annual meeting of the Associated Professional Sleep Societies is returning in person June 4-8 in Charlotte, North Carolina. Register, view the preliminary program and learn more at sleepmeeting.org.

DR. KHOSLA: Welcome back to Talking Sleep. Our guest today is Dr. Allan Pack, researcher, clinician and editor in chief of the journal Sleep. So tell me about your work in Iceland. I mean, why Iceland?

DR. PACK: Well, the reason we got to Iceland was I'm very interested in the genetics. Right. And I was reading these papers in science and because, you know, that time you were doing family-based linkage studies and they said they had DNA and loads of people in Iceland and they could trace them all the way back to the 11th century. Because they had all the marriage records, they put them into databases. They built what they called a genealogy. And a company got going there called Decode Genetics that was going to take advantage of that. And then the genetic strategy changed to genome wide association study. It's got a big advantage for clinical research, particularly for genetic research and sleep apnea.

Iceland is not a big country. I mean, 380,000 people live in Iceland, three quarters of them live in the capital city, Reykjavik. They do home studies in five different places around the island. And then if have moderate to severe sleep apnea, and an AHI over 15 and you want to go on CPAP, you need to go to Reykjavik and meet Dr. Gislason and his team at the University of Iceland Hospital. He's the only person who can prescribe CPAP in Iceland. So it means that every single person in Iceland who's going on CPAP sees Dr. Gislason and you capture the whole country essentially. And Dr. Gislason was trained as a Ph.D. in epidemiology in Sweden. As far as he's concerned, every patient he sees is a research subject and they all fill out these extensive questionnaires. We built databases so that we get the sleep study data, that's the genetic data and so on. And the Icelandic population are very, very supportive of the research. You don't have to reimburse them for conducting research. That's not part of the culture. And you get participation rates of over 90%. And then the other thing you have is you have a single EHR for the whole country, so you can track these people, what happened to them through the EHR because it's a kind of nationalized health system and so on. So there's substantial advantages to and we've had an NIH grant now in Iceland for over ten years and we've built a very collaborative program with Dr. Gislason, we've published a large number of papers together and we're still continuing to do that. So it's been a very productive collaboration.

DR. KHOSLA: So you mentioned your clinical tool that you are developing to identify these OSA phenotypes. So so does this help us figure out who needs treatment and what kind of

treatment? You know, like patients who maybe have high loop gain, should they not use an oral appliance?

DR. PACK: Yeah, well, that's a whole different story. So so I don't think we'd be whether people are going to benefit. I mean, you're right. We need to look at the severity of these symptom subtypes and find out if you switch, then, you know, you would need to treat people. If it turns out that the minimally symptomatic is a very stable thing…there's a real question. If they're not going to benefit a lot from a symptomatic point of view and they're not going to benefit from a cardiovascular point of view, the real question is to whether they treat it. Some people would argue they don't. What you're getting at, though, is, again, the other way to think about endo/phenotypes. And this the Andrew Wellman work with Scott Sands and Danny Eckert and they basically have pushed the idea that there's different physiological risk factors. There's four risk factors. There's what you mentioned, high loop gain. There's a collapse of all the upper airways. There's arousal threshold, how rapidly you wake up, your CO2 levels go up, you know, you have a high arousal threshold or a low arousal threshold. And then the final one is the muscle responsiveness. There's negative pressure that builds up in the upper airway if you have apnea, and that simulates a reflex that increases activity of upper airway dilator muscles. So there are these four different so-called endo-phenotypes, physiological phenotypes. Now when they initially described them, they're very complicated protocols, right. So they were to have the so-called CPAP drops, you'd have a catheter down there to measure the pressure in the upper airway, you'd have an EMG measuring genioglossus activity and so on.

And they were able to document, you know, it's hard to do in controls because you need events and drop the CPAP pressure. And then they went from that, which was a fairly cumbersome…it was a research thing that never been applied clinically to the argument that you could extract the data from sleep study regular sleep study data, you can extract these four basic things. And that's why the story gets a little murky. You know, is the extraction, the way it works, is based on a very simple model of ventilatory control. And then you're basically parameterize them all and you end up being able to estimate these four different variables, right? And then the published papers, as you've indicated high loop gain, intraoral devices and so on.

Now there are people like me who say it's a bit premature. I mean, I just think it's a very interesting idea, it's premature. And here's why I believe that. First of all, Magdy Younes has written an article in Clinics in Chest Medicine saying, look, this model that's been used is pretty primitive. It's making a lot of assumptions and some of them are untenable, you know. Magdy's shown, for example, that arousal is not a single phenomenon. You've got different intensities of arousal. And as you know, he's able to estimate intensity of arousal on a scale of one to nine. Some people tend to have very intense arousal, some people not. And that's not taken care of in the model. So the model treats arousal as a single entity. And it's not. There's variation intensity. That's the first thing. So there's questions about the simplicity of the model.

The second concern is the reliability of these estimates has not really been shown. I think it's premature to be applying them. We need to know that if I study you tonight and I show you're somebody with a high loop gain, if I study you in a week or two weeks are you still somebody with a high loop gain? How reliable are these measures? I think that's very important before we start applying it clinically.

And then thirdly, we should be able to validate that, right? I mean, you could measure arousal threshold in other ways. You can measure loop gain in other ways. And we should show that the measures we would gain from these techniques line up. There's a very good agreement between that and the gold standard measure. So I argue with all my team, I mean, I ask them when they present, you know, how your reliability data going? How's the validation going? And I do think that's really important.

While that's going on, the Nox Medical in Iceland, nothing to do with me, but the company in Iceland that makes sleep study equipment. They've licensed that technology and they're working on it. And one of the things they pointed out is that the system, the whole idea falls apart if people open their mouths, right. So you're basically looking at nasal pressure. The input to the model is nasal pressure signals, that's the ventilatory measure, essentially. And if you open your mouth, you know, that's not going to work. And they actually had a presentation in Rome last week at the Rome World Sleep Meeting where they're showing that they can get a ventilatory

measure from well-applied inductance plethysmography belts. They're working on the belt signal and trying to say we can overcome that problem with the mouth opening.

So my view of that whole world is it's very interesting. I think there's potential there but they've got to address is the model too simple. They've got to address reliability. They've got to address some of the technological challenges and they should show the validation. And I believe that any conclusion that we should be using this at the moment clinically is premature. I think we've got to get that basic information down. We know we're dealing with reliable measures. We know that they measure what they think they measure, and then we can start thinking about applying them clinically. Now, what Nox has made available, but it's only if you use Nox equipment and that's a bit of a challenge, right. So Nox has built a whole system. If you use Nox equipment, you can upload your data into a website and it will spit out these measures for you. So I think, you know, we're just got ahead of ourselves. At least that's my view, I think it's interesting, but I don't think we're at a point that you can personalize therapy based on this. I believe we've got to do a lot more homework.

DR. KHOSLA: Well, and so that's interesting. Because we had chatted about personalized medicine and personomics and the search for sleep-related biomarkers. And so when we talk about biomarkers, is this sort of the idea of identifying people with sleep apnea or is it a way to follow it over time? I mean, what is the purpose of them?

DR. PACK: Right. No, I know. I think that's a great question. So I think one of the one of the things is that we've now got a tremendous different technologies that we're happy to talk about that to identify different approaches to assessing things in blood that could be potential biomarkers. And then the question is, what's the use cases? There was a workshop that was conducted, it was published in SLEEP, actually, Janet Mullington is the first author, between the NHLBI, the National Heart, Lung and Blood Institute, the NIH, and the Sleep Research Society and it talks about the use cases, right? And basically, there's three different use cases that you can think about. So the first thing would be, could you get a blood test to assess who's likely to have

sleep apnea? Right. Could I do a routine blood test and say, yeah, you're likely to sleep apnea and you would move down that path. So that's the first use case, case identification.

The second use case is really following efficacy of therapy, right? I mean, we published a paper a number of years ago with Terri Weaver looking at how is the CPAP use in the X axis and on the Y axis the percent of people who went from being sleepy to not being sleepy. And what you find is you find people with three hours of use, so it isn't huge, but 30% of people normalized in 3 hours of therapy. And the other end, there was a group of people, even with 7 hours, they didn't normalize. So it's pretty clear that people may respond to CPAP in different ways. And at the moment we looked at hours of use and we tend to think about as, you know, the same the same hours of use and that's likely to vary. Some people may do very well on low numbers and some people may need very high numbers to do well. And so that's the second use case. Could you come up with, I think like a hemoglobin A1C to us and you got an objective measure of efficacy, a therapy that you could apply. So that's the second use case.

The third use case would be can you use it prognostically, right? I mean, there are papers out there you know, from the hypertension literature that from that resistant hypertension trial in Spain, where they took the high responders and the non-responders and showed there were different biomarkers in the two groups. So could you use the information to predict who's going to show a big benefit from blood pressure? Could you do it to predict who's going to get increased diabetes risk? Could you do it to predict who's going to get cardiovascular events? And so that said, the third use case is prognostication. So it's case identification, assessment of efficacy and prognostication, and all of them, I think, are possible. And what we're going to need is much larger studies than the ones that have been done. But the technology's out there to be able to assess, the so-called, all the different "omics." And in the currently release, just released last December, in the new national plan for sleep research the number one priority is developing, for sleep research, is developing biomarkers for sleep disorders.

DR. KHOSLA: So you know, we've had a lot of discussion about the pitfalls of the AHI. So what do you think the future of sleep medicine looks like? I mean, you've kind of hit on the ORP…what does it look like to you?

DR. PACK: Yeah, no, I agree with that. I think that pure AHI, I mean, I think the European report about AHI is pretty negative. And the Sleep Research Society one, the one that Malhotra was the first author on, that is a more balanced report. I mean, the AHI makes intuitive sense. I mean, you're talking about a disorder where you believe people stop breathing or their breathing declines during sleep. So imagine the number of times that happens. It's quite relevant, right? So the AHI has clinical relevance. The fact that now the argument against is, well, it doesn't really predict the outcomes But as I've indicated, sleep-disordered breathing is very heterogenous. And some people don't know about outcomes. Why would the AHI be that predictive? Right. I think we try to think about that. There's no single measure going to come out that is going to predict stuff. Now, having said that, people are now working on new metrics. And I think this is an exciting area, new metrics that you can obtain from the sleep study. The ORP is one. I'll talk about that in a minute. And then there's two there's two metrics that are pushed to be related to cardiovascular risk, so-called hypoxic burden. You look at the total amount of hypoxic drops, the areas and so on, and that comes across the night and you come up with total hypoxic burden. And in the Sleep Heart Health and the MrOS study, hypoxic burden is associated with cardiovascular mortality. So that's one measure that has some real potential.

A second measure is the heart rate response either to arousal or the heart rate response to events. What happens is people, when they have an arousal, the heart rate goes up. But the magnitude of the increase in heart rate, even at a fixed intensity of arousal, varies between people. It is sort of a measure of sympathetic [response], right. You have an event, you have an arousal, you get a sympathetic surge, your heart rate goes up. And that varies between people. We did a study with that and the twins study we did, we showed it was very reproducible from night to night, but it varied between people. And we also showed because it was twins, it was heritable. So there's genes involved in determining the heart rate response to arousal. And there's a recent paper showing the heart rate response to arousal in non-sleepy people. Again, it was done in the Sleep

Heart Health and MrOS, I think. And it showed that there was a relationship between heart rate response to arousal and cardiovascular events and also cardiovascular mortality overall. But when he did the the analysis, and divided people into sleepy people and non-sleepy people, it was only found in the non-sleepy. And that was because the sleepy people got big reactions because they're sleepy.

And so so there's these two very interesting metrics coming along. And again, I don't think we should start, you know, throwing every AHI out the door and get rid of all the great science we've done using the AHI and the epidemiology. We need to think about it carefully. We need to be thoughtful about what we're doing. Constructive and not just jumping around. And I do think that we again, we need more data. How can you calculate these metrics easily? How reliable are they? All of the basic stuff we just talked about. And then we need to look at it not only in a population-based cohorts, but in clinical cohorts. So there's a good deal of work to be done to establish them.

The ORP, it's a terrible name, actually. And it's a very clever thing, but I'm not sure it's branded that well, the odds ratio product, you say to people, what do you study? Odds-ratio product. How would you know it has anything to do with sleep? But that is a very clever measure. It's a continuous measure of sleep quality. Right. I mean it's every 3 seconds and the scale is like zero to four, something like that. And, and the lower the number, the deeper the sleep. And so you I mean, it's not just looking at Delta, it's looking at all the different bands simultaneously, and it's giving you a measure of sleep quality and the high numbers you lose sleep quality, the low numbers, you could deep sleep and you can look at it across the night and it's really good and again, we've done studies in the twins with that. You can see that it varies between people, even if you looked at standard sleep staging. You find people with deeper, you know, N3 compared to other people, again, it's heritable. It tends to be an, you know, an individual response. So it's a very, very cool measure that gives us a way of objectively measuring sleep quality.

We've applied that technology with Magdy to this question of the symptom subtypes. We tried to say, was it the case that the symptom subtypes had differences in the quality of the sleep right.

And could we define that. When we did that, what we found was, well, you know, it's not surprising I suppose was the group that was different was the disturbed or the insomnia group. They had poorer sleep quality in every stage of sleep. They had poor quality sleep across the night. They weren't that sleepy during the day. We did not find differences at the moment in what we looked at between the minimally symptomatic and the excessively sleepy group. Certainly the disturbed sleep group were a group of people with sleep apnea who had poor sleep quality. Now some of them say the insomnia is due to the sleep apnea. Right. I mean, they're not because they're up dancing. They wake up and they have poor sleep quality. And on CPAP, that insomnia goes away. Other ones, you know, they have insomnia. And it just happens to be there along with their sleep apnea and it and it doesn't improve with CPAP. So I think the ORP is another very, very helpful measure in terms of thinking of a sleep quality. It gets us beyond the traditional staging of sleep and acknowledges the side that misses, you know, another dimension which is the quality of that particular stage.

DR. KHOSLA: No, you're exactly right. I'm wondering how your how your tool is going to fit into all of this.

DR. PACK: Well, I think what you know, I think what's going to happen here is you're going to have a number of different tools. You're going to have a tool that allows you to define them into a symptom subtype and that might be helpful in terms of the way you're thinking about it. We're hoping that by an app or something. The Epworth on its own is not sufficient. I mean, in people they may have normal Epworths, but they're still complaining of feeling sleepy several times a week. So it takes more than just the Epworth. The Epworth's the biggest single contributor to the thing, right. We've got a write-up that's just come out in CHEST pointing that out, that it's going to take, you know, more than just the Epworth to do it. And then you define these different symptom subtypes. I think where we're going to be going is we've got these new tools coming along that we can analyze the PSG from and it's going to provide a lot more information. One of the challenges and I do I brought this up at the in the Rome meeting where they had they had a symposium on ORP. The ORP is now owned by Cerebra, right. So if you want go ORP you have to get Cerebra equipment. If you want to get the Andrew Wellman physiological phenotypes,

you need to get Nox equipment. It's not a good place. You know, the new measures are owned by somebody and you have to use their equipment. It's not a good place to be.

And, Ali [Azarbarzin], you know, he's I don't think it'll be successful, but he's trying to patent hypoxic burden. Now, I don't think that's going to happen because it's published. So how can you patent something that's already in a public domain? But that's what's happening. These tools these new exciting tools tend to be patented. They tend to be given to companies for license income and it's not going to be a great place for our field to be that the new tools that can move us forward. Yeah, you have to have one equipment to get that, you have to have another equipment to get this. And I do think the Academy needs to think about that. How do we move beyond that because it's not helpful.

DR. KHOSLA: So any final thoughts?

DR. PACK: No, I think my final thoughts would be that this is a very exciting time to be in this OK. I think the ideas that are being pushed here on sleep apnea in terms of different symptoms subtypes, in terms of different different physiology, different molecular biomarkers. You know, it's a wonderful era to be in and I do think we can create a whole new world for sleep medicine based on a much more personalized approach.

It's a work in progress and I think we've got to be careful as we go along to make sure it's available to people, we can move this along as fast as we can. At the same time, I believe that these approaches, it's the same for everything, right. Whether using hypersomnia or whether you got insomnia it's the same basic idea that this idea of personalized heterogeneity is changing medicine in every area. And I think we're in a very fortunate place in sleep that we've got a lot of patients we can phenotype them very well. And we got a lot of sleep centers there. And I do think we can move this along in a fairly rapid way. So I think it's a very exciting time to be in this field.

DR. KHOSLA: Well, thank you for your work in this important area. The era of personalized medicine is here I hope your research will allow us to offer patients more personalized treatments.

Thanks for listening to Talking Sleep, brought to you by the American Academy of Sleep Medicine. For more podcast episodes, please visit our website at aasm.org. You can also subscribe through your favorite podcast service. And if you enjoyed this episode, please take a moment to leave a rating or review. For more feedback or suggestions email us at podcast@aasm.org. I hope you'll join us again for more Talking Sleep. Until next time this is Seema Khosla, encouraging you to sleep well so you can live well.