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2 populations, I think it's our responsibility to believe  
3 that and to take that information and use it  
4 clinically. But again, that requires a lot of work by  
5 the manufacturer.

6 But if it's done in a way that's consistent  
7 with how we understand sleep testing, then I think  
8 that's really our best bet. I mean, most of us, as you  
9 said earlier with the WatchPAT, don't go back to the  
10 raw data. We trust the tables and the graphs that are  
11 provided.

12 So if a similar output could be modeled there,  
13 I think that's sort of the entry for us as clinicians  
14 to look at nonconventional or unconventional sleep  
15 testing devices like these.

16 DR. DENNENY: Ofer, do you have any additional  
17 thoughts on that?

18 DR. JACOBOWITZ: So one problem of course is  
19 that we can't -- with the flood of applications and  
20 devices, we cannot as clinicians become experts in a  
21 thousand different devices and apps.

22 But certainly we need to understand the basis

1 of the algorithm and its potential pitfalls as well as  
2 benefits. I think that that is very important, to have  
3 a more robust description of the algorithm so that at  
4 least we can -- and obviously validation studies.

5 DR. DENNENY: Craig?

6 DR. KIRSCH: So --

7 DR. DENNENY: I'm sorry. Doug first.

8 DR. KIRSCH: So I think what I'll say is a  
9 couple of things. Number one, Raj, as you point out,  
10 you know, you have the ability to review the raw data  
11 of a WatchPAT device.

12 But it's the algorithm that's really been  
13 determined to be the predictor of validation, not the  
14 human eye, right?

15 So I do in fact review the data on those tests  
16 just to make sure that the test validity looks good  
17 enough. But in the end, over-scoring the algorithm  
18 doesn't -- is difficult to do because it has been  
19 validated based on the algorithm.

20 I'm not sure I need to understand how the --  
21 what the algorithm of the WatchPAT is, Ofer. But what  
22 I feel is that it has been validated enough for me to

1 be comfortable that you've gotten there.

2 And so, I think, you know, one option is to  
3 publicly open your validation and say, yes, I'm valid  
4 against a gold standard of some kind. I think the  
5 alternative is to say, well, here's my algorithm.

6 This is how it works. Is that going to make  
7 you feel more comfortable with it? If it hasn't been  
8 validated, the answer is not really, right? And the  
9 company's not going to be super excited about releasing  
10 its algorithm.

11 So in the end, you're really going to be  
12 forced to rely upon some sort of validation study that  
13 makes us comfortable enough. It's why we are so  
14 comfortable with the tonometry. It's because there are  
15 200-plus studies that say that tonometry is correlated  
16 with PSG-based AHI.

17 DR. DENNENY: Craig?

18 DR. FEIED: Well, I maybe understood the  
19 question slightly differently because I agree  
20 wholeheartedly if there are validation studies that are  
21 convincing, statistically convincing and clinically  
22 convincing, then we can accept it and otherwise we



1 really cannot.

2 But I was -- I thought this might be more  
3 about how do you deal with the different formats in  
4 which the data is presented and the different kinds of  
5 data that you might not be familiar with, the PAT, and  
6 the patient comes in with this thing and here's their  
7 reading. And they assure you that it's validated or  
8 maybe you look in the literature and it's validated.

9 But you haven't seen it before and these new  
10 things are coming at your every few weeks. And well,  
11 all I can say is welcome to the new world because, you  
12 know, that's sort of how it is now, new stuff and we  
13 can't keep up. And I don't think anybody can.

14 DR. DENNENY: Okay. Bakul, did you have any  
15 comments on that?

16 MR. PATEL: Not really. But I think -- I  
17 think Craig is absolutely right. I think the way we  
18 look at, you know, everyone understanding these studies  
19 and understanding what does validation look like, I  
20 think there's going to be a lot of black boxes as we  
21 move forward.

22 And the question is how do we understand. You

1 know, so Doug, when you talked about the basis of the  
2 algorithm, I think it's great to the know the basis of  
3 the algorithm.

4 But when you think about AI and you have deep  
5 machine learning, it's going to be really hard to sort  
6 of take what a machine has learned and then further  
7 explain it. I think there's work being done in that  
8 world to sort of explain that.

9 But it's not there yet. And that's going to  
10 be the critical part as we move forward is like how do  
11 we take what the machine learns and then tell somebody.  
12 It's like you going to school for, you know, however  
13 many years that you went to and then explaining that  
14 this is what I learned in, you know, a page or two.

15 That's the challenge we are facing and, yes,  
16 the challenge about will docs actually know how to  
17 interpret or understand that basis, it's going to get  
18 complicated over time.

19 DR. DENNENY: Doug, are you on to speak?  
20 Ofer?

21 DR. JACOBOWITZ: Oh, thank you. So maybe we  
22 can -- maybe we can comment about something similar to

1 what was in the previous panel is that what are the --  
2 what are the important features of a home sleep apnea  
3 testing device that's available to the consumers.

4 DR. DENNENY: And that's a different question.

5 DR. JACOBOWITZ: That's a different question?

6 DR. DENNENY: Yes.

7 DR. JACOBOWITZ: I'm sorry. That's why I  
8 asked.

9 DR. DENNENY: So I wanted to move a little bit  
10 toward the validation. We've spoken about validation.  
11 Are we going to expect all these device manufacturers  
12 to validate against a sleep study -- against a CPAP or  
13 some other device?

14 Is that reasonable? You've seen, in your  
15 talk, 40 on one. There'll probably be thousands of  
16 these. Are they all going to spend the money to  
17 validate against CPAP or some other -- some other  
18 standard? Is that reasonable for the FDA to ask?  
19 Craig, you want to --

20 DR. FEIED: Do you mean -- do you mean -- do  
21 you mean validating against polysom?

22 DR. DENNENY: Right.

1 DR. FEIED: Polysom, because you said CPAP.

2 DR. DENNENY: Oh, I'm sorry.

3 DR. FEIED: So it was just a slip there.

4 DR. DENNENY: I'm sorry. I'm on to the  
5 management. Let's stick with the diagnosis first.

6 DR. FEIED: Well, I think really there seem to  
7 be several pieces to this. And we saw them in the  
8 slides that you showed. One of the questions is what  
9 is the risk that we're dealing with.

10 Another part is what is the claims -- what are  
11 the claims that are being made. If there are claims  
12 being made that are associated with a risk, perhaps  
13 it's just a risk of keeping people away, steering  
14 people away from a traditional pathway.

15 You know, if I put an app out that told you to  
16 drink -- take St. John's wort of cancer, people will do  
17 it, you know? And they'll die. There's a real problem  
18 with diverting people away from therapies that are  
19 effective.

20 And so, yes, I think if claims are going to be  
21 made, then the app, like any device, should be  
22 validated in a way that we can accept and that we can

1 believe in and that the recommendations or the  
2 interventions.

3 But in this case, we're talking about  
4 diagnostic and not necessarily telling people we're  
5 leaving out at this moment how it tells you to sleep  
6 earlier and proper yourself up on more pillows and put  
7 marbles on the back or an orange underneath your  
8 shoulders, those kinds of things.

9 We're talking about the diagnosis. So that  
10 diagnosis, if it's not being used to guide or withhold  
11 treatment is irrelevant. But if it's being used to  
12 guide or recommend or to not recommend treatment, then,  
13 yeah, it must be validated against polysom because  
14 that's our current gold standard.

15 DR. DENNENY: And some of these would be, I  
16 would think there'll be monitoring devices going  
17 forward as well. And that's additional to that  
18 question. Doug, did you have a comment on this one?

19 DR. KIRSCH: Yeah. I mean, I think I touched  
20 on it in my talk. I mean, I feel home sleep apnea  
21 testing is one step away from what we already view as  
22 the gold standard to validate based on home sleep apnea

1 testing, to me strikes as somewhat concerning based on  
2 the fact that in reviewing many home sleep apnea tests,  
3 there are sufficient errors in review and scoring that  
4 they're liable to be -- they're tricky at best.

5           You've removed a bunch of signals that help us  
6 make a diagnosis. And so, it would strike me that  
7 polysomnography would be a better validation tool than  
8 home sleep apnea testing.

9           DR. DENNENY: Ofer?

10           DR. JACOBOWITZ: So I don't know. I mean, I  
11 think that possibly home sleep apnea testing,  
12 especially if done over multi-night, may be as useful.

13           Again, polysomnography is a gold standard only  
14 because it was first. It's not because it's better  
15 necessarily. It's just what we have as the original.  
16 So I would argue possibly home sleep apnea testing can  
17 also be of benefit if used on multiple nights.

18           DR. DENNENY: Raj?

19           DR. DEDHIA: Yeah. I think polysomnography  
20 should be the gold standard. One of the challenges  
21 with home sleep apnea tests, as was again mentioned  
22 earlier, was the failure to accurately identify central

1 sleep apnea. As a surgeon, I can tell you that once a  
2 month I get a patient who was inappropriately diagnosed  
3 with obstructive sleep apnea by a WatchPAT or something  
4 else when in fact it's central sleep apnea. I'm sure  
5 that my dentist colleagues would agree with that.

6 And the problem is they get treated with an  
7 expensive therapy like an oral appliance or a dangerous  
8 therapy like surgery and for the wrong diagnosis. So  
9 this to me is a real clinical concern.

10 So I would say that it's a screening tool for  
11 patients that are going to be undergoing dental or  
12 surgical therapy. CPAP, it's okay because even CPAP  
13 treats central sleep apnea half the time correctly. So  
14 it's less of a concern with PAP therapy.

15 But I think when we're talking about  
16 alternatives, it's really important to make sure you  
17 have something more accurate.

18 DR. DENNENY: Okay. So now to the question  
19 you were looking at, what parameters would you like to  
20 see these devices measure, including any new  
21 parameters? If we're looking into the future, we may  
22 be able to measure things that aren't well-measured

1 now. Raj, you want to start with that?

2 DR. DEDHIA: Yeah. I came up with five things  
3 that I thought should be measured. This has to do  
4 mostly with from home sleep apnea testing. Total sleep  
5 time, which we've talked about. Perhaps a proxy of  
6 that would be total recording time, but at least some  
7 estimate of sleep.

8 Oximetry I think is crucial. An ODI4 -- so if  
9 you have oxygen, you can get an ODI4. You can get a  
10 T90. You can get an O2 nadir. Those three I think are  
11 very pertinent when we're talking about patient risk.

12 Position, time supine, non-supine as well as  
13 the associated AHI or whatever index you want to use, I  
14 think that's important for patient treatment selection.  
15 Those with uniquely positional sleep apnea have an  
16 option called positional (ph) therapy.

17 And then snoring, percent time over 40, which  
18 is what the WHO uses, or 45 decibels I think is an  
19 important metric.

20 And the fifth one was from talks about how  
21 many nights. I think two nights of -- I mean, these  
22 DHDs, these digital health devices are great because



1 you can do multi-night.

2 So I think why not make it at least two nights  
3 of testing, so get at least say 10 hours between the  
4 two nights I think would give me some confidence as a  
5 clinician interpreting the data.

6 DR. DENNENY: Ofer?

7 DR. JACOBOWITZ: So are you asking what is the  
8 -- what's the minimal or what's the optimal set of --

9 DR. DENNENY: I'm asking you what would you  
10 like measured --

11 DR. JACOBOWITZ: What would I like?

12 DR. DENNENY: -- if that could be one item or  
13 if you want 20 items or some items that isn't even  
14 usable now. We're looking at the future here.

15 DR. JACOBOWITZ: Right. So clearly we'd also  
16 want to have something that either is a surrogate or a  
17 fairly direct measure of actual sleep. So, you know,  
18 actigraphy can obviously overestimate sleep, for  
19 example, in insomniacs.

20 But that could be a -- you know, a simply and  
21 readily available measure. And obviously with other  
22 technologies that are in development or will be

1 available, then sleep time would be very, very useful.

2 DR. DENNENY: Okay. Doug?

3 DR. KIRSCH: Certainly, Raj, I'd echo some of  
4 the suggestions that you made. I think, you know, if  
5 we're looking forward, one of the things is that there  
6 is some data looking not just at AHI but, you know,  
7 AHI, as has been evidenced in some of the earlier  
8 panels, is a crude metric in some ways.

9 It's just a numeric count of how many apneas.  
10 It doesn't talk about the length of those apneas. It  
11 doesn't talk about the depth of the desaturation  
12 associated with those apneas.

13 And as you work towards deeper learning of  
14 some of these data sets, I think that there has been  
15 some early published data that there are combinations  
16 of length and desaturation that could be evaluated just  
17 beyond a pure AHI, but give you a better sense of how  
18 severe someone's apnea is, not just based on a numeric  
19 count of times that they stopped breathing.

20 In addition, I would still want to have, as  
21 best we could, a measure or surrogate measure of sleep,  
22 position, oxygen saturation, et cetera.

1 DR. DENNENY: Okay. Craig, any thoughts?

2 DR. FEIED: Well, since we seem to be in  
3 fantasy land, you know, since the smartphones today  
4 can't do this kind of stuff and we can hook sensors up  
5 to them, but I'm just going to go right where I want to  
6 be.

7 First of all, I'd like to have not a surrogate  
8 measure of sleep, but an actual measure of sleep. I'd  
9 like to have EEG and that's actually possible and  
10 feasible today at home.

11 And I think especially with machine learning,  
12 we know that there are -- there is software out there  
13 that can do automatic spindle detection and deep sleep  
14 staging and can do it as well as inter-operator  
15 concordance in a sleep lab.

16 So I'd like to see that in my device. And I'd  
17 also like to see mass spectrometer in there. And I'd  
18 like ambient exhaled air and I'll get my end-tidal CO2.  
19 So I'll see my respiratory rate from that. and I think  
20 there's a lot of evidence that a lot of the  
21 physiological disturbances that occur with sleep apnea  
22 are reflected very quickly in the chemical makeup, the

1 chemical fingerprint of what's exhales. So there's  
2 where I want to be.

3 DR. DENNENY: Any other big wishes now that  
4 you've heard his? Anyone else? Okay. So next, one of  
5 the things that I think most of the public is very  
6 sensitive to, and I assume we are as well, and it's on  
7 the slides that you talked about, Bakul, and also the  
8 ones Dr. Nandkumar sent to me, is cybersecurity.

9 With people hacking into this, that and the  
10 other for money, I mean, there's certainly the  
11 propensity that someone would go off the ranch and try  
12 to hack into these devices.

13 So my question is what level of security can  
14 be mandated by the FDA or what is necessary or adequate  
15 to maintain safety and validity of the data you get  
16 with these devices? And is it a real concern to you?  
17 So why don't you start, Craig? We'll start at the  
18 other end this time.

19 DR. FEIED: Well, you know, my personal worry  
20 and my personal nightmare is that I'll have a sleep-  
21 related device near my bed and that while I'm asleep,  
22 somebody will hack into it and change my vote in the

1       upcoming election.  But --

2                 DR. DENNENY:  On your sleep device?

3                 DR. FEIED:  My sleep device, you know, it'll  
4       say something to me or somehow sway my --

5                 DR. DENNENY:  Oh, hypnotism.  Okay.

6                 DR. FEIED:  -- sway my thinking.

7                 DR. DENNENY:  Okay.

8                 DR. FEIED:  But, and that, maybe I shouldn't  
9       joke about that because, you know, probably somebody  
10       out there would love to do that.

11                But yes, security is a big, big, big, big  
12       problem.  And when you have closed loop-types of  
13       devices that are going to actually do something -- so  
14       people approached me about helping them with an open  
15       source artificial pancreas.

16                You know, there's been a lot of work in this  
17       field.  And some of the early self-experimenters wanted  
18       to connect their sensor -- their glucose sensor up to  
19       their insulin pump with a smartphone in between.

20                And the question was is it feasible and can it  
21       be made safe and what would the algorithms be.  And the  
22       only thing that I can think is, oh my God, you know,

1 hackers will get in. If you have three devices  
2 wirelessly talking to each other, I don't believe it's  
3 going to be possible to keep hackers out because there  
4 are gaps and holes everywhere.

5           And so, I'm very, very worried about that and  
6 I would hope that our uses of the data would be -- that  
7 there would be built-in statistical analyses to help us  
8 have confidence in the data that we do receive and that  
9 we also wrap it with all the security that we can. As  
10 new threats emerge, we'll have to be continually  
11 adjusting that.

12           DR. DENNENY: Doug?

13           DR. KIRSCH: I think, as the concern has been  
14 raised with implantable devices and things that are  
15 wirelessly connected and implanted in the human body, I  
16 think that we ought to be equally concerned with apps  
17 and other devices that are externally being used to  
18 test us in a variety of ways.

19           I don't think this is something that can be  
20 ignored. I'm not sure I have an answer to what level  
21 that security is. That's probably someone far smarter  
22 than me. But what I will say is the more security, the

1 better from my perspective for any of our health apps  
2 or health-related data.

3 DR. DENNENY: Ofer?

4 DR. JACOBOWITZ: Yeah, and potential  
5 additional concern is obviously causing devices to  
6 overheat or explode, especially those that contain  
7 batteries.

8 So hacking can also be physically dangerous,  
9 not just privacy. And I don't have a comment about the  
10 level of security. But it should be high.

11 DR. DENNENY: Raj?

12 DR. DEDHIA: Yeah, I'll just agree with the  
13 panelists. From the other end of it, I would say with  
14 what's going on with Facebook, I think just to be  
15 completely explicit about what information will be  
16 captured by the devices and then be available, I think  
17 make sure that's clear and the FDA can I'm sure mandate  
18 that in some way, particularly if there's a pathologic  
19 label to it.

20 You know, OSA patient, you know, this patient,  
21 now if insurance of anybody else gets a hold of that, I  
22 think that's a concern. So I think just those things

1 can be hopefully regulated by the FDA.

2 DR. DENNENY: Bakul, could you tell us kind of  
3 what could -- what can the FDA do as far as mandating  
4 security of these devices? I know it's clearly in your  
5 mind because it was on your slides and it's in the  
6 Cures. So --

7 MR. PATEL: So there's -- I'll talk about two  
8 things. I mean, we have currently -- we have two  
9 guidances today on cybersecurity. One is the  
10 premarket, what we expect people to design in security  
11 into all their products. And the second one is about  
12 post-market, what to do when you are exposed to a  
13 cybersecurity threat.

14 I think at a very high level, I'll just  
15 describe it very briefly. I think nobody could argue  
16 that we want cybersecurity to be addressed and designed  
17 then and not an after-the-fact thought, right? So  
18 that's a premarket guidance.

19 The post-market guidance is about recognizing  
20 that no matter how big of a fortress you build, you'll  
21 always have some threat and vulnerability that will be  
22 exposed to you. So how do you have -- how do you sort



1 of have a mechanism in place?

2 So that goes to the capabilities of the  
3 organization to sort of react -- observe, monitor,  
4 react and lock down and make sure that you have the  
5 right bandwidth to sort of do that in a very quick way  
6 to minimize the progression of the threat. So that's  
7 the fundamental thought that we have.

8 I mean, so if I were take that one step  
9 higher, I think about there has to be processes and  
10 capabilities in an organization. And then, there has  
11 to be product level security that needs to be thought  
12 about. And you can layer that, layer the same sort of  
13 concepts on privacy as well.

14 But that's what we are trying to get towards  
15 is like have the right methods, have the right  
16 resources, have the right infrastructure and have the  
17 right methods to identify, communicate and resolve  
18 issues or at least, you know, monitor them to the area  
19 -- to this area of cybersecurity so that can be  
20 proactively, you know, headed off.

21 DR. DENNENY: Well, I've got one more question  
22 before we open it up to the floor. And this is a

1 pretty broad one.

2 What are your greatest concerns and/or hopes  
3 with the proliferation of digital health products in  
4 the management of sleep-disordered breathing or sleep  
5 apnea? Doug, I'll let you start off since you gave our  
6 excellent talk to begin with.

7 DR. KIRSCH: Certainly from a hope  
8 perspective, I think -- as I think I pointed out  
9 briefly in my talk, there is a very large population of  
10 patients who have sleep apnea today that are not being  
11 tested either due to access or due to cost.

12 And the idea of a broader available assessment  
13 option will lead to improvement in a number of ways, as  
14 we've talked about treating sleep apnea leads to  
15 improved quality of life, reduced motor vehicle  
16 accidents and improved health.

17 So I think there is a lot of hope on the  
18 horizon for improving our ability to test and hopefully  
19 to then treat a larger number of patients with sleep  
20 apnea, or specifically obstructive sleep apnea.

21 I think the concern that I have and that I  
22 think has been raised at times on this panel is broadly















































































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I, BENJAMIN GRAHAM, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

April 28, 2018

DATE

\_\_\_\_\_  
Benjamin Graham