SUPPLEMENT

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Panel Discussion: Can There Be a Biomarker for Sleepiness?

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Dr. Quan: It appears to me that there are two issues to consider when discussing the possibility for a biomarker for sleepiness. In one scenario, we are looking for something that will identify people who have an increase in sleep propensity. I'll just use that word, so that we can recognize that they are at risk for doing something dangerous. In the other scenario, we are looking for a biomarker that is associated with chronically-reduced sleep and then we associate that with some abnormality in their metabolic or their physiologic function, which can have implications for their personal health. I would like to ask the people on the panel if they think that this is a reasonable dichotomy, or if they think that perhaps there is something else we should be looking at?

Dr. Shaw: I definitely think it's a reasonable dichotomy. My expectation is that a biomarker for acute sleep loss is easier to find—easier to validate than the more chronic conditions. With that in mind, I think that a lot of people here in the audience are taking saliva samples when they do their sleep experiments. They use melatonin as a phase marker, and we really need to think about keeping these and preserving these. We need to encourage NIH to provide funding so that when somebody does discover a biomarker, a candidate biomarker, there are samples that can then be processed. The hard part is doing the experiment to begin with, in fact, even a study to evaluate these biomarkers. But it's doable once we start to succeed and have some candidates. Throwing these samples away is just a huge waste.

Dr. Naidoo: I agree that the dichotomy is acceptable—that you define sleepiness and sleep propensity differently. Rather than looking for a particular biomarker, I would think we should also consider looking for profiles—molecular profiles or behavioral profiles together, instead of a single biomarker for any one state.

Dr. Haeggström: I think that what is really interesting is to keep a clear boundary between what sleepiness does to operational capabilities and what sleepiness as a phenomenon is. I also think they require very different types of research. From my perspective, I am much more inclined to the first one—operational concept. But I think there should be a lot of thought and effort also put into what sleep really is because I don't think we know that.

Dr. Krueger: I would very much agree with that comment. Last night, I reflected on a comment made by Greg Belenky[a] when he was working at Walter Reed Army Hospital. He asked a general about whether he could study sleep. The general's response was that he wasn't interested whether or not his soldiers were sleepy; he was interested in whether or not they could perform. That's a valid concern under that condition. However, if you are a clinician and your patient's complaining of "sleepiness," you probably do not care as much about how they are performing, especially on the battle field, but you are more concerned about their quality of life and what sleepiness does to that. Very different biomarkers may be required. They are very different conditions. We do have to make choices, in terms of what our endpoint is, i.e., what our objective is. What's the goal of developing a series of molecules as biomarkers? For what purpose do you want to use them?

Dr. Church: I think one useful distinction is that if you have some pre-existing predisposition towards a particular type or flavor of sleep disorder, it may influence the kind of biomarkers that you could get out of, for example, saliva and the way you interpret them. Also, it may influence the kind of preventatives that you use in order to prevent your genetic destiny from becoming an actual accident someday.

Dr. Naidoo: In response to what Dr. Krueger said, I agree when people are talking about performance. However, we have been talking a lot about sleep and sleepiness, but we haven't discussed wakefulness and quality of wakefulness. When we think of wakefulness often we just describe it as a single state but it is probably not a single state. There could be types of wakefulness. I think a biomarker that could also reflect states of wakefulness may also be useful to address issues of sleep and sleepiness, and sleep drive.

Dr. Quan: To move this forward, I was wondering if we could ask for some input from both the panel and the audience about what steps we should take as a research community of sleep investigators to find either markers for the chronic state of sleep deprivation or sleep debt or need for sleep, and for the acute issue of trying to identify people who are at risk for some dangerous behavior as a result of being sleepy or drowsy?

Audience Member (Dr. Johns[b]): Can I just make a point that having a discussion like this is the first step. Having another discussion like this would be a good second step because I don't think we are going to solve the problems right here and now. This sort of discussion has not occurred in the past and we should have had it 20 years ago. There are many more things we need to discuss. So, can I suggest that we have some sort of regular, maybe not frequent, but regular discussion on this topic so that we can reach some consensus over a period of time, because it will not happen today?

Dr. Shaw: I would like to make a brief comment. I think there are multiple ways to go. I think we have to try to find devices like this balance,[1] which is brilliant, and potentially can be put in the field very quickly is a great way to go; identifying biomarkers, some kind of analyte that can be extracted from an easily accessible fluid. The problem with looking at saliva is that you cannot do it in the field. But ultimately, we need to do discovery. It has to happen. I would submit that we need to study people who have been sleep deprived for 24 hours. We know, unequivocally, that the majority of humans that are kept awake for 24 hours are sleepy and impaired. Let us find biomarkers that are associated with that condition. Then we can start talking about individuals that might not be as impaired as others. However, until we find things to look at, we are not going to make any progress. We are just going to debate the meaning of sleep propensity and drowsiness, and no progress is going to be made at all.

Dr. Haeggström: I have one comment. I think that during these last 24 hours, we have been talking a lot about how sleepy somebody is right now. However, I think we have been talking very little about predicting how sleepy somebody will be in an hour or five hours from now. Previously, I attended a talk where it was said, "It doesn't matter if I can predict how sleepy you are at one millisecond from now because you can't do anything about it." This is the third issue which I would like to add to my earlier comments, that is the ability to predict sleepiness. At least from an operational point of view, this kind of predicting is valuable.

Audience Member: I would like to ask a question about vulnerability in children. We have been talking most of the time today about adults, but we know that particularly some groups of children, in deprived environments especially, are under-slept. This affects their lifelong health and perhaps their learning capacities. I am wondering if there might be practical markers of behavior, appetite or whatever that we could offer parents to encourage them to get the little kids more sleep, even in a day-care center, because we are talking about, essentially, setting lifelong opportunities.

Dr. Church: I can say from personal experience that this is one of those diseases that people blame the victim. Throughout my education and my daughter's education, we have had chalk thrown at us and been sent out of the room. It took us about six months, with physicians helping, to convince the school that my daughter was not just lazy or staying up late at night playing video games or something like that. So, sometimes branding works against you and sometimes it actually helps you to identify what you need to do. Of course, this is complicated by the fact that our school system is not set up for teenage waking circadian rhythms anyway. I think that even before we get to medical treatments of various sorts, there is a need for getting societal treatment.

Dr. Quan: With respect to that question and what Dr. Shaw mentioned, if you actually had an analyzer or something that you could mark a person that is not getting enough sleep, even as a little kid, then you could tell the parent "Your child, according to this test, is low on sleep; you need to do something about this, otherwise there are some ramifications as the child grows up." The challenge for us, I think, is to identify what such an analyte or biomarker might be. Potential fluids that might be analyzed include saliva and urine. Unfortunately, our speaker from Italy could not make it, but their group are doing tests on exhaled breath, which is exactly what a breathalyzer does.[2] All of these potential biological fluids, you might say, are out there for possible analysis to determine if there is something measurable related to sleepiness.

Dr. Naidoo: I would like to add to Dr. Shaw's suggestion. I know it is difficult to get large numbers of subjects to be sleep deprived, but we have hundreds of thousands of people who we know have a complaint of sleepiness—these are the sleep apneics. I know there are confounds because of co-existing conditions. However, I think we should in some organized fashion use this huge pool of subjects that we know have different levels of sleepiness. If anyone has suggestions on how we could all work together, I think that would be great.

Dr. Haeggström: I have a comment. I think in most of the presentations here, data were presented from sleep deprived subjects and allowed to have recovery sleep. However, people do not like to stay awake because it is unpleasant. What if you do not sleep deprive subjects? Rather, in the lab, you give them a very nice king-sized bed and turn the test the other way around. You test how well they recover and try to identify your markers in that way. Of course, you make the implicit assumption that the same markers that respond to this recovery would also respond to when you deprive. It might be easier to get people to sleep in a bed for small amounts than to stay awake.

Audience Member: My question for the panel is this. If you look at existing legislation, Maggie's law in New Jersey, Senator Moore's bills here in Massachusetts, any of the other states that have proposed drowsy-driving legislation, the ACGME intern guidelines, the Federal regulations in the number of industries, the focus has largely been on work hours, hours of service, possibly hours of rest, but no other metrics targeted at people who may be sleepy or operating in the potentially sleepy state. Based on your expert opinion, can you suggest, maybe short of a biomarker, other metrics that might be good to use in legislation, laws, policy, standard operating procedures, for people to evaluate when someone probably should not be working or operating?

Dr. Krueger: I think the complexity of the situation is going to make it very difficult to translate it into law because people perform poorly, for example, if they have a cold. There are all kinds of different infectious diseases. Your performance goes down, your attention deteriorates and you get sleepy sometimes. It varies over the course of the disease, so we can easily develop biomarkers to see if you have a disease but the sleepiness and sleep varies depending on where you are in the disease and who you are. So, it wouldn't help much in that case. Yet we know that if you're sick and driving your car you are not going

to be doing as well as if you are well. Employers sort of know this because they tell you to stay home if you are sick. The list goes on, and there are all kinds of non-infectious diseases that we know that are associated with sleepiness which then can lead to worse performance. So, I don't know how you can translate this complexity into law. Law has to be crystal clear otherwise it is not fair. It is a difficult situation.

Dr. Quan: I think it's going to be task specific. In other words, a truck driver drives a truck so that is a specific task. An airline pilots flies a plane. That is another specific task. For a physician, the task is a little bit more complex because it involves a lot more cognitive processing and decision making. Nevertheless, it may be that you would have to find a specific biomarker for the specific type of task that you want to test. But what, then, defines a person being able to work or do the task, or not do the task? I do not think it is an all-or-none. For example, there is a specific level for alcohol that defines legal intoxication. Obviously, there are people who can drive above the limit reasonably well, perhaps better than some people who are below the limit. However, somebody has determined that above a certain limit, for most people the risk is too great to allow people to drive, and then that defines the law. This is basically almost arbitrary in a way because, as you know, the alcohol limit in some states is 0.10 and other places it's 0.08. It could be even lower in other countries. There are some complexities, obviously, and there is a distinction between what you make as a legal decision versus the science behind the decisions.

Audience Member: I just want to make a follow up. Just so you know, as it stands now, lawmakers generally do take an all-or-nothing approach when they deliberate about sleepiness. That is to say, after you work a certain number of hours, that is it. The other thing that they often mention is that if there is proof that you actually fell asleep behind the wheel or whatever, that is good enough. So, they are taking this all-or-nothing approach. The challenge to the research community is to figure out how to perhaps translate a medium, happy medium in between those extremes.

Audience Member: This question is directed to Dr. Krueger. I am impressed by your bottom-up model. It is both informational and inspirational. The animal model you are using is a nocturnal animal. Do you think of any diurnal animal model that can serve the same purpose?

Dr. Krueger: Yes, I can think of two. One would be the daego, which is a diurnal rodent. And, of course, the other one is the fruit fly.

Dr. Shaw: I think Dr. Krueger is right. You need to study the fly. And, actually, if you look at the micro-array experiments that have been published on the fly modulated by sleep and wakefulness, a lot of the genes that are identified are derived from the whole heads of the flies, their eyes included.

Dr. Krueger: With the mouse or fly you have a lot of genetic information. More in the fly than you do in the mouse, and you really need that genetic information to test the hypotheses. Even though the data I showed for cortical column sleep are from rats, the data really should replicate that in mice. But it would be very hard to get a mouse trained to sit still and sleep unrestrained, as would be necessary for that type of experiment. However, an electronic microchip has been developed, so it may be possible to do these experiments in free-roaming animals, but the technological challenges are considerable.

Audience Member (Dr. Czeisler[c]): My question, or my comment, is really directed toward what Dr. Church presented and when he was talking about the potential individual genetic differences in susceptibility to sleep loss and the HLA DQB1 story. It reminds me of the Pro 355 polymorphisms. The group in Surrey has shown that individuals who have this particular polymorphism are much more vulnerable to being awake for an extended duration during the biological night. They make several fold more errors in cognitive testing when they're trying to stay awake at night in an adverse circadian phase, having been awake all day. So, I think this brings another dimension into the framework that I was suggesting at the beginning of this meeting yesterday. We were trying to look at the effect of chronic exposure to restricted sleep and its potential effects on the cardiovascular system, the immune system, and consolidation of memory. This is in contrast, as emphasized by Dr. Shaw, to the acute effects of 24 hours of wakefulness. Trying to find biomarkers of each of those is maybe quite different. However, I think that Dr. Church has now brought in the other perspective of looking at inter-individual vulnerability to each of those situations. Because, it may be really a combination of having a particular genetic background and then being exposed to either chronic sleep restriction or acute sleep deprivation that makes a particular individual much more vulnerable than someone else.

Dr. Shaw: I think this is really important information to have, but we know that some people are sensitive to alcohol and other people are not. There are polymorphisms of the alcohol dehydrogenase genes. Yet, if you get pulled over by a police officer and you have a blood-alcohol of 0.08, he is not going to let you off the hook if you have the polymorphism that lets you metabolize alcohol faster. So, we can test for biomarkers in different patient populations to see how well they hold up and identifying people who are at risk is great, but finding a biomarker that allows us to actually do research requires that we actually do discovery.

Audience Member (Dr. Czeisler): I'm not arguing against it. I'm just saying that there are other situations besides being pulled over by the police. So, if you have a particular genetic background, working 30-hour shifts twice a week as a resident physician might not be the best situation for you to be in. For another example, chronically restricting your sleep to five hours per night may put you at a five-fold increased risk of cardiovascular disease if you have one particular genetic background. In contrast, if you have another genetic background, it might not expose you to that risk.

Dr. Quan: And that's something, perhaps, that the personal genome project ultimately would be able to shed information on, correct?

Dr. Church: Right. I mean, in principle, any test paradigm that can be non-invasively and easily worked out, and applied to the core could be studied in that manner and correlated with the genetics. Back to the being pulled over by the police for possible alcohol intoxication, that is current practice. The current practice could change if our biomarkers inform it and if there is really a difference in susceptibility to different alcohol levels in terms of your performance. That could be reflected

in the law. You might still measure the alcohol levels, but you might have on your license what level is right for you.

Audience Member (Dr. Balkin[d]): Actually, I was going to say something very much along the same lines that Dr. Church just said. The reason we do not do what Dr. Shaw suggested is we did not have the ability to do it. In the military, our strategy is going to be measuring sleep with actigraphy over long periods of time, probably for years at a time. Essentially, we will have sleep histories of soldiers for their entire time in the military. In terms of performance, which is what the military is interested in, this is going to serve as input to a model based on Borbely's two-process model of slow wave sleep—although to a large extent it seems to work for prediction of performance of sleepiness as well. We have modeled the performance of many students and soldiers, and there are significant individual differences in their abilities to withstand the effects of sleep loss, i.e., their resilience to sleep loss. We can always tweak the parameters of our model to very nicely fit any individual, which means that the factors that we have in the model work very well. What we do not have are the factors that determine individual differences. If we can determine a genetic factor that describes or reflects resilience to the effects of sleep loss, it would be something that could be put into these performance-prediction models. It would increase their utility exponentially. I would also like to mention that in the military, we probably would not ever actually select people for jobs based on it (their innate resilience to the effects of sleep loss). Rather, we would use these models to make informed decisions regarding administration of interventions—caffeine, modafanil, amphetamine, or whatever. Also, I would like you to think about the fact as we put actigraphs on soldiers, that this data, as we measure performance, would be sort of a natural experiment. We will be able to take the information that we learn from these soldiers' sleep and performance and feed it back into the model. We will not only learn things about individuals, but the relationship among sleep, circadian rhythms, and performance in general.

Dr. Haeggström: While Dr. Balkin was talking, I was thinking that now you can see ads every now and then encouraging you to have your LDL-HDL level measured. I don't know the number of people who have this done, but some people do. I wonder if it would it be possible to similarly say "Be a conscientious citizen and go and test your sleep curve." People will then have their sleep curve recorded. They already have many credit cards anyway so it would be easy to store the information. That would allow them to know it. It would allow them to be tested if they feel a little bit drowsy.

Audience Member: I had a question of Dr. Church. How does one get access to the data? What is the access route? Do I go to NIH and say I'm going to work on this? Do I come and say, "Here's an idea," and now let's take it to NIH?

Dr. Church: So, if it involves a change in their behavior or anything put into their body that is out of the ordinary, then it would require a new IRB protocol. Whether or not it involves a new IRB protocol, their participation is voluntary. It does not require NIH involvement but I would urge you to try to think creatively about ways that you can use natural behavior, realizing that it not the perfect double-blind clinical trial. Go to personalgenomes.org and then contact Jason Vogue, who's the director of community. He will get back to you about the exact protocol.

Dr. Quan: Are there any other comments from the audience or the panel? If not, I thank you all for coming and participating.

FOOTNOTES

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REFERENCE

1. Forsman P, Wallin A, Haeggström E. Vallidation of a posturographic approach to monitor sleepiness. *J Biomech* 2010;43:3214-6.
2. Carpagnano GE. Exhaled breath analysis and sleep. *J Clin Sleep Med* 2011;7(5):Supplement S34-S37.

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